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Brief Report

A Case Series of Concomitant Falls and COVID-19 Infection Among Older Adults

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ABSTRACT

Introduction. Few studies have examined the hospital course and patient outcomes among elderly trauma patients with COVID-19 and traumatic fall-related injuries. This study aimed to describe patient characteristics and hospital outcomes for older adults who sustained fall-related injuries and were concurrently infected with COVID-19.

Methods. A retrospective chart review was conducted for patients aged 65 years and older who were admitted to a single Level 1 trauma center with fall-related injuries between March 3, 2020 and March 3, 2021.

Results. Of the 807 patients who presented with fall-related injuries during the study period, 16% (n = 128) were tested for COVID-19, and 17% (n = 22) of those tested positive. After excluding one patient, 21 patients were included in the analysis. Common comorbidities among these patients included hypertension (86%, n = 18), dyslipidemia (57%, n = 12), and diabetes (43%, n = 9). Upon admission, 62% (n = 13) of patients exhibited respiratory symptoms such as cough, shortness of breath, and hypoxemia, while approximately 24% (n = 5) were asymptomatic for COVID-19 at presentation. Complications included unplanned intensive care unit or operating room visits (29%, n = 6). COVID-19-related complications included acute hypoxic respiratory failure (67%, n = 14) and pneumonia (43%, n = 9). In-hospital mortality was 19% (n = 4).

Conclusions. During the height of the COVID-19 pandemic, 17% of elderly patients admitted to a single Level 1 trauma center for fall-related injuries were concurrently infected with COVID-19. These patients experienced a high frequency of complications and in-hospital mortality. Therefore, COVID-19 should be recognized as a severe and potentially lethal comorbidity among older adults who sustain fall-related injuries.

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INTRODUCTION

Among older adults, falls are a leading cause of injury and hospitalization.[1] In 2018, approximately 28% of older adults in the U.S. reported falling, which resulted in 950,000 hospitalizations and about 32,000 deaths.[1] With the worldwide spread of COVID-19, new challenges emerged in treating older adults, particularly since a study conducted in Wuhan, China, found that older age is an early predictor of poor prognosis and increases the odds of in-hospital mortality for COVID-19 patients.[2]

Additionally, older adults may present with different symptoms than younger populations due to immunosenescence, comorbidities, and nutritional status.[3] While younger individuals typically present with respiratory symptoms, some research suggests that falls and other atypical symptoms of COVID-19 are more prominent among older adults.[4-8] However, none of these studies have specifically examined the hospital course and outcomes of elderly trauma patients with COVID-19 and traumatic fall-related injuries.[9]

A study conducted at our institution compared the characteristics of elderly patients admitted with traumatic fall-related injuries before and during the COVID-19 pandemic.[9] The findings indicated that despite differences in comorbidities, injury patterns, complications, and discharge locations, the frequency of falls was similar across the COVID-19 and pre-pandemic periods.[9]

This study extends that analysis by focusing specifically on COVID-19 positive patients from the previous study.[9] It aimed to analyze patient characteristics and hospital outcomes among older adults who were COVID-19 positive and presented with fall-related injuries at a Level 1 trauma center during the height of the pandemic.

METHODS

After obtaining Institutional Review Board (IRB) approval, we used the trauma registry at an American College of Surgeons-verified Level 1 trauma center to identify patients 65 years and older who experienced fall-related injuries during the first phase of the COVID-19 pandemic (March 3, 2020 through March 3, 2021). The first patient with confirmed COVID-19 at our facility was reported on March 13, 2020.[10] Medical charts were reviewed to determine if these patients with fall-related injuries were concurrently positive for COVID-19.

A retrospective review of the trauma registry and patient medical records was conducted. Variables abstracted included patient demographics (e.g., age, gender, comorbidities), living environment before the fall, and pre-injury medication. The mechanism of injury was categorized into one of the following groups: same-level fall, fall from height, or fall from unspecified height. Injury details included the Injury Severity Score (ISS), Glasgow Coma Scale score (GCS), and type of injury. Additional data collected included intake vitals, initial labs, and COVID-19 symptoms, such as cough, shortness of breath, and hypoxemia. Information on ICU admission and duration, mechanical ventilation and duration, hospital length of stay, COVID-19-specific treatments, complications, discharge details, and mortality also was gathered.

Statistical Analysis. Statistical Analysis System® (SAS) software, Version 9.4 (SAS Institute Inc., Cary, NC) was used for data analysis. This study aimed to characterize trends, injury patterns, and outcomes of people 65 years and older who experienced a traumatic fall. Patients' socio-demographic characteristics were summarized using descriptive statistics. Means and standard deviations were presented for normally distributed, skewed, or ordinal scaled parameters. Qualitative variables were reported as absolute numbers and relative frequencies.

Likelihood ratio chi-square and Fisher's exact tests were used for 2x2 and RxC contingency tables to test the association and agreement between COVID-19 periods and all categorical and nominal variables.

The Kolmogorov-Smirnov normality test assessed whether continuous variables were normally distributed. For normally distributed outcome variables, paired t-tests and independent t-tests were utilized. For non-normally distributed outcome variables, the Wilcoxon or Hodges-Lehmann method was used for a robust nonparametric estimator of the population's location parameter. This approach estimates parameters based on the "pseudo-median," closely related to the population median. All statistical tests were considered significant at $p \leq 0.05$.

RESULTS

Of the 807 patients who presented with fall-related injuries during the study timeframe, 16% (n = 128) were tested for COVID-19. Among those tested, 17% (n = 22) were positive. One patient was excluded from the analysis due to being a member of a vulnerable population, resulting in a total of 21 patients included in the analysis. Most patients were White (91%, n = 19), male (52%, n = 11), and lived at home or independently prior to falling (67%, n = 14; Table 1). The average age at presentation was 83 ± 6.7 years. The most common comorbidities were hypertension (86%, n = 18), dyslipidemia (57%, n = 12), and diabetes mellitus (43%, n = 9).

Approximately 33% (n = 7) of patients sustained injuries in a rural location, and 24% (n = 5) were transferred from an outside hospital (Table 2). The average time to presentation was approximately seven hours. The mechanism of injury for most patients involved same-level falls (62%, n = 13), while a smaller proportion experienced falls from height (24%, n = 5) or unspecified falls (14%, n = 3). Patients were minimally injured, with an average Glasgow Coma Scale (GCS) score of 14.5 ± 0.9 and an average Injury Severity Score (ISS) of 8 ± 4.1. The most common injuries were lower extremity fractures (48%, n = 10), followed by soft tissue injuries (24%, n = 5) and rib fractures (24%, n = 5).

On admission, 62% (n = 13) of patients had respiratory symptoms such as cough, shortness of breath, and hypoxemia (Table 3). Less commonly encountered symptoms included altered mental status or confusion (29%, n = 6), fever or chills (14%, n = 3), weakness (14%, n = 3), and diarrhea (5%, n = 1). Approximately one-fourth of patients (24%, n = 5) were asymptomatic for COVID-19 at presentation. Notably, 33% (n = 7) of patients were previously diagnosed with or known to have COVID-19 at presentation.

Average vital signs were normal except for a slightly elevated average systolic blood pressure (Table 3). Only three patients were tested for alcohol levels, none of which were positive. Abnormal glucose readings (76%, n = 16), abnormal hemoglobin results (67%, n = 14), and abnormal creatinine values (52%, n = 11) were common.

Approximately 43% (n = 9) of patients required immobilization or traction for their fall-related injuries (Table 4). Repair or replacement procedures of the lower extremity were also relatively common (29%, n = 6). COVID-19-related medical treatments included therapeutic anticoagulants (71%, n = 15), corticosteroids (57%, n = 12), antiviral agents (52%, n = 11), and antibiotics (52%, n = 11; Table 4). Oxygen therapy was utilized for 71% (n = 15) of patients.

Table 1. Demographics and comorbidities among COVID-19 positive older adults admitted with fall-related injuries.

Measures	All Patients (N = 21)
Age	83 ± 6.7 years
Gender	
Male	52% (11)
Female	48% (10)
Race	
White	91% (19)
Black/African American	5% (1)
Asian American	5% (1)
Living environment	
Home or independent living	67% (14)
Nursing home	24% (5)
Skilled nursing facility	10% (2)
Comorbidities	
Hypertension	86% (18)
Dyslipidemia	57% (12)
Diabetes mellitus	43% (9)
Dementia	38% (8)
Coronary artery disease (CAD)	38% (8)
Mental or personality disorder	38% (8)
Chronic renal failure	33% (7)
Atrial fibrillation	24% (5)
Chronic obstructive pulmonary disease (COPD)	24% (5)
Cerebral vascular accident (CVA)	19% (4)
Congestive heart failure (CHF)	19% (4)
Peripheral arterial disease (PAD)	10% (2)
Alcohol use disorder	5% (1)
Pre-injury medications	
Aspirin	67% (14)
Lipid-lowering agents	62% (13)
Beta-blockers	43% (9)
Diuretics	43% (9)
Antihypertensives	38% (8)
Inhalers	24% (5)
Insulin	19% (4)

*Presented as % (number) or mean ± standard deviation

Table 2. Injury characteristics among COVID-19 positive older adults admitted with fall-related injuries.

Measures	All Patients (N = 21)
Transfer	24% (5)
Rural location	33% (7)
Time to hospital presentation, days	0.3 ± 0.6
Mechanism of injury	
Same-level falls	62% (13)
Falls from height	24% (5)
Unspecified falls	14% (3)
Injury Severity Score (ISS)	8 ± 4.1
Glasgow Coma Scale (GCS)	14.5 ± 0.9
Abbreviated Injury Scale (AIS)	
Head	3 ± 0.0
Chest	3 ± 0.9
Abdomen	3 ± 0.0
Extremity	3 ± 0.4
Head injury	
Subdural hemorrhage	5% (1)
Loss of consciousness	5% (1)
Thoracic injury	
Rib fractures	24% (5)
Pneumothorax/hemopneumothorax	5% (1)
Spinal injury	
Cervical fracture	5% (1)
Lumbar fracture	5% (1)
Extremity injury	
Lower extremity fracture	48% (10)
Femur fracture	38% (8)
Upper extremity fracture	5% (1)
Soft tissue injury	24% (5)

*Presented as % (number) or mean ± standard deviation

Table 3. Admitting symptoms, vitals, and laboratory results among COVID-19 positive older adults admitted with fall-related injuries.

Measures	All Patients (N = 21)
Previously diagnosed with COVID-19	33% (7)
Symptoms of COVID-19	
Respiratory symptoms	62% (13)
Altered mental status and/or confusion	29% (6)
Asymptomatic	24% (5)
Fever and/or chills	14% (3)
Weakness	14% (3)
Diarrhea	5% (1)
Admitting vitals	
Heart rate beats per minute	90 ± 24 .5
Systolic blood pressure	137 ± 24.8
Diastolic blood pressure	78 ± 16.6
Mean arterial blood pressure	98 ± 17.1
Temperature, degrees Celsius	37 ± 0.6
% oxygen saturation	95 ± 2.8
Respiratory rate, breaths per minute	19 ± 5.4
Tested for alcohol	14% (3)
Alcohol above legal limits	0% (0)
Initial laboratory results	
Abnormal hemoglobin (<12 or >16 g/dL)	67% (14)
Abnormal glucose (<70 or >99 mg/dL)	76% (16)
Abnormal creatinine (<0.57 or >1.11 mg/dL)	52% (11)
Abnormal platelets (<150 or >400 x 103/uL)	38% (8)
Abnormal INR (<0.9 or >1.2)	24% (5)
Abnormal lactic acid (<0.5 or >2.2)	14.3% (3)
Abnormal PTT (<25 or >36.5 seconds)	14.3% (3)

*Presented as % (number) or mean ± standard deviation
Abbreviations: INR, international normalized ratio; PTT, partial thromboplastin time

Table 4. Management and COVID-19 treatment methods among COVID-19 positive older adults admitted with fall-related injuries.

Measures	All Patients (N = 21)
Imagining studies (e.g., CT scan, US, MRI)	100% (21)
CT exam conducted	76% (16)
Positive FAST exam	0% (0)
Placement (e.g., packing and immobilization)	43% (9)
Immobilization/traction of neck	19% (4)
Immobilization/traction of back	5% (1)
Immobilization/traction of upper extremity	5% (1)
Immobilization/traction of lower extremity	14% (3)
Measure and monitor	86% (18)
Extracorporeal or systemic assistance and performance	10% (2)
Medical and/or surgical procedures (repair, replacement)	57% (12)
Lower bone	29% (6)
Skin	5% (1)
Upper bone	5% (1)

Table 4. Management and COVID-19 treatment methods among COVID-19 positive older adults admitted with fall-related injuries. *continued.*

Measures	All Patients (N = 21)
Subcutaneous and fascia	5% (1)
Lower joints	10% (2)
Vasculature	14% (3)
Urinary systems	19% (4)
COVID-19 drug-based treatment	
Therapeutic anticoagulant	71% (15)
Corticosteroids	57% (12)
Antibiotics	52% (11)
Antiviral	52% (11)
Convalescent plasma	38% (8)
Diuretic	19% (4)
Bicarbonate	5% (1)
Inotrope	5% (1)
None	14% (3)
COVID-19 non-drug-based treatment	
Oxygen requirement	71% (15)
Non-invasive positive pressure ventilation	14% (3)
Hemodialysis	10% (2)
Mechanical ventilation	10% (2)
Vapotherm® (heated and humidified high flow nasal cannula)	10% (2)
Proning (turning on abdomen)	5% (1)
None	29% (6)

*Presented as % (number)

Complications included unplanned visits to the intensive care unit (ICU) or operating room (29%, n = 6; Table 5). COVID-19-related complications included acute hypoxic respiratory failure (67%, n = 14) and pneumonia (43%, n = 9). Half of the patients (52%, n = 11) required ICU admission, and one patient (5%) required mechanical ventilation. Most patients were discharged to skilled nursing facilities (38%, n = 8) or home (23%, n = 5). In-hospital mortality was 19% (n = 4), with two patients dying from cardiac arrest and two from respiratory arrest. All deaths were attributed to COVID-19 infection.

Table 5. Complications and hospital course among COVID-19 positive older adults admitted with fall-related injuries.

Measures	All Patients (N = 21)
Overall complications	
Unplanned intensive care unit/operating room visit	29% (6)
Cardiac arrest with CPR	10% (2)
Myocardial infarction	10% (2)
Arrhythmia	5% (1)
Atrial fibrillation	5% (1)
Shock (hypovolemic, cardiogenic, or neurogenic)	5% (1)
None	29% (6)
COVID-related complications	
Acute hypoxic respiratory failure	67% (14)
Pneumonia	43% (9)
Cardiovascular (e.g., exacerbation of HFrEF, cardiac arrest, atrial fibrillation, MI)	19% (4)
Encephalopathy	10% (2)
Septic shock	5% (1)
None	29% (6)
Transfusion of packed red blood cells	33% (7)
PRBC units	3 ± 2.3
Intensive care unit admission	52% (11)
ICU length of stay, days	6 ± 4.1
Mechanical ventilation	5% (1)
Mechanical ventilation days	1 ± 0.0
Comfort care	19% (4)
Hospital length of stay, days	8 ± 7.2
Discharge location	
Skilled nursing facility	38% (8)
Home with services	14% (3)
Home	10% (2)
Inpatient rehab	10% (2)
Hospice	10% (2)
In-hospital mortality	19% (4)

*Presented as % (number) or mean ± standard deviation
Abbreviations: HFrE, heart failure with reduced ejection fraction; MI, myocardial infarction; PRBC, packed red blood cells; ICU, intensive care unit

DISCUSSION

The elderly population has been disproportionately affected by the COVID-19 pandemic due to pre-existing conditions and the natural effects of aging.[3] This demographic also experiences a high rate of falls, increasing the risk of serious injury.[1] During the height of the COVID-19 pandemic, we found that 17% of elderly patients admitted for fall-related injuries who were tested for COVID-19 were infected.

Most of these patients experienced lower extremity and femoral fractures. Common comorbidities included hypertension, dyslipidemia,

and diabetes mellitus, which are known risk factors for severe COVID-19 complications.[2-4,11] The interplay among falls, COVID-19, and patient comorbidities had not been examined prior to this study.

Respiratory symptoms such as cough and shortness of breath were the most reported COVID-19 symptoms, consistent with existing literature.[6-11] Non-respiratory symptoms included altered mental status or confusion, while weakness and diarrhea were less common. Another study found that one in five hospitalized older adults presented with fever, cough, and shortness of breath,[12] while 30% of patients aged 70 and older did not exhibit typical symptoms.[7] Additionally, 28% of those with fall-related injuries also presented with delirium.[7]

Notably, only 16% of patients with fall-related injuries were tested for COVID-19 in our study. Previous studies suggest that delayed diagnosis due to asymptomatic or atypical presentations can lead to rapid spread, particularly in long-term care facilities.[12,13] Testing only patients with cardinal COVID-19 symptoms risks misidentifying older adults who present with atypical symptoms such as falls.

In-hospital mortality for this study was 19%, higher than the 4% mortality rate from our previous study during the same period.[9] These patients were symptomatic on admission, presenting with fall-related findings and COVID-19 symptoms such as hypoxia, dyspnea, fever, and cough. Studies have shown that the odds of 30-day mortality are three times higher for patients presenting atypically compared to those with typical symptoms.[8,14] Additionally, patients with atypical symptoms were more likely to be frail and have a higher risk of delirium and falling, though no difference in 30-day mortality was observed between groups.[8]

Limitations. The generalizability of this research may be limited due to the use of data from a single institution, a small sample size, and a retrospective study design that relies on the accuracy of the trauma registry and medical charts. Additionally, patient history may be subject to recall bias, particularly if there was a delay in presentation following the injuries. Some patients may not have been appropriately identified as having COVID-19 due to the lack of testing for asymptomatic patients and the limited availability of testing kits early in the pandemic. Notably, information regarding COVID-19 vaccination status was not assessed in this study, as vaccines only became available starting December 11, 2020, partway through the study period.[15]

CONCLUSIONS

To our knowledge, this is the largest single-institution study in the U.S. to describe this concomitant presentation. Our findings suggest that elderly fall patients admitted with COVID-19 experienced a high frequency of complications and in-hospital mortality compared to rates at our institution during the same period. Therefore, it is important to recognize COVID-19 as a severe and potentially lethal comorbidity among older adults with fall-related injuries.

REFERENCES

[1] Moreland B, Kakara R, Henry A. Trends in nonfatal falls and fall-related injuries among adults aged ≥65 - United States, 2012-2018. MMWR Morb Mortal Wkly Rep 2020; 69(27):875-881. PMID: 32644982.
[2] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020; 395(10229):1054-1062. PMID: 32171076.
[3] Chen Y, Klein SL, Garibaldi BT, et al. Aging in COVID-19: Vulnerability, immunity and intervention. Ageing Res Rev 2021; 65:101205. PMID: 33137510.
[4] Nabors C, Sridhar A, Hooda U, et al. Characteristics and outcomes of patients 80 years and older hospitalized with Coronavirus Disease 2019 (COVID-19). Cardiol Rev 2021; 29(1):39-42. PMID: 33136582.
[5] Gawronska K, Lorkowski J. Falls as one of the atypical presentations of COVID-19 in older population. Geriatr Orthop Surg Rehabil 2021; 12:21514593219966619. PMID: 33680533.
[6] Knopp P, Miles A, Webb TE, et al. Presenting features of COVID-19 in older people: Relationships with frailty, inflammation and mortality. Eur Geriatr Med 2020; 11(6):1089-1094. PMID: 32734464.
[7] Hunt C, Olcott F, Williams G, Chan T. Failing the frail: The need to broaden the COVID-19 case definition for geriatric patients. Clin Med (Lond) 2021; 21(6):e604-e607. PMID: 34642166.
[8] van Son JE, Kahn ECP, van der Bol JM, et al. Atypical presentation of COVID-19 in older patients is associated with frailty but not with adverse outcomes. Eur Geriatr Med 2023; 14(2):333-343. PMID: 36749454.
[9] Zayat MN, Vander Griend MA, Flesher N, et al. Falls among older adults during the COVID-19 pandemic compared to a pre-pandemic period: A case-control study. Am Surg 2023: 31348231180919. PMID: 37285470.
[10] Tucker H. KWCH12. 2020. https://www.kwch.com/content/news/Welsey-Medical-Center-doctor-confirms-first-coronavirus-case-in-Wichita-568770071.html. Accessed June 30, 2024.
[11] Karlsson LK, Jakobsen LH, Hollensberg L, et al. Clinical presentation and mortality in hospitalized patients aged 80+ years with COVID-19: A retrospective cohort study. Arch Gerontol Geriatr 2021; 94:104335. PMID: 33476754.
[12] Kerr AD, Stacpoole SR. Coronavirus in the elderly: A late lockdown UK cohort. Clin Med (Lond) 2020; 20(6):e222-e228. PMID: 32912964.
[13] Blain H, Rolland Y, Benetos A, et al. Atypical clinical presentation of COVID-19 infection in residents of a long-term care facility. Eur Geriatr Med 2020; 11(6):1085-1088. PMID: 33025500.
[14] Pop-Vicas A, Haleem A, Osman F, et al. Risk factors and mortality for atypical presentation of COVID-19 infection in hospitalized patients - Lessons from the early pandemic. WMJ 2021; 120(2):94-99. PMID: 34255947.
[15] U.S. Department of Health and Human Services. 2022. https://www.hhs.gov/coronavirus/covid-19-vaccines/index.html#:~:text=December%2011%2C%202020,the%20prevention%20of%20COVID%2D19. Accessed June 30, 2024.

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Brief Report

Breast Biopsy Notification Preferences and Health Literacy

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ABSTRACT

Introduction. Communication of breast biopsy results varies and does not always meet patient expectations. This study aimed to determine how patients previously diagnosed with breast cancer preferred to receive their biopsy results, including preferences for communication methods, the type of medical professional delivering the results, and wait time. Additionally, we evaluated how health literacy might affect these preferences.

Methods. English-speaking female patients who had previously been diagnosed with breast cancer were surveyed at a breast surgery clinic in Wichita, Kansas. The survey included the Brief Health Literacy Screen (BHLS), questions on how they received their biopsy results, and their preferences for receiving results. Participants were classified as having adequate or inadequate literacy based on their BHLS responses and a scoring system from previous research.

Results. The study included 101 participants. Overall, 64% preferred in-person communication, 40% preferred to hear from their primary care physician, 36% from their surgeon, and 56% wanted results within 24 hours. There was no statistically significant difference in preferences based on health literacy, including communication method (p = 0.44), type of medical professional (p = 0.56), and wait time (p = 0.38).

Conclusions. Most participants preferred to receive biopsy results indicating a breast cancer diagnosis in-person, regardless of their health literacy. While it may be sufficient to call a patient with benign biopsy results, it is recommended to offer an in-person discussion for cancer diagnoses, respecting the patient's preference.

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INTRODUCTION

More than one million patients undergo breast biopsies annually in the U.S.[1] There is considerable variability in how results are disclosed, and patient preferences are not always met.[2-4] Age, race, internet access, and marital status have previously been identified as factors associated with how patients prefer receiving their breast biopsy results.[2,5]

Inadequate health literacy, limiting a patient's ability to read, understand, and act on healthcare information,[6] affects approximately one-third of Americans and is associated with patients' preferences for receiving other cancer biopsy results.[7-10] It is unknown if health literacy is associated with result disclosure preferences among patients who have undergone breast biopsies. This research sought to determine if health literacy is associated with notification preferences among patients who have undergone breast biopsy procedures.

METHODS

Female patients 18 years and older who were diagnosed with breast cancer within the last five years were eligible to participate in this study between May 10 and August 31, 2021. Non-English-speaking patients and those requiring a legally authorized representative were excluded. Eligible participants were invited to complete a paper survey by their nurse during an office visit with their breast surgeon. No financial compensation or other incentives were offered. This study was approved by the Institutional Review Boards (IRB) at the University of Kansas Medical Center and Ascension Via Christi Hospitals.

Collected demographic information included age, race, ethnicity, highest education level, and internet access.[11] Health literacy was assessed using the Brief Health Literacy Screen (BHLS), a validated three-question measure.[12] Each response was assigned a score from one to five. A score of three or less on any question, or a cumulative score of nine or less, was defined as "inadequate health literacy."[10,12]

Participants reported how they received their biopsy results and their preferences, including the modality (e.g., telephone, patient portal, in-person, U.S. mail), provider (e.g., primary care provider, radiologist, nurse, breast surgeon), and wait time to receive results (e.g., within 24 hours, 1-2 days, 3-5 days, 5-7 days).[2,5] Participants ranked the importance of several factors, such as receiving results as soon as they were available, from someone they knew, or from a specialist who could better explain the results.[5]

Study data were collected and managed using REDCap® electronic data capture tools hosted at the University of Kansas Medical Center.[13,14] SAS 9.4 was used for all data analyses. Chi-square tests were used to examine the association between preferred biopsy result disclosure characteristics and demographic variables, health literacy level, and highest patient priority.

RESULTS

Of the 103 surveys returned, 101 were completed. Most participants reported being 60 years or older (72%, n = 73) and White (73%, n = 74; Table 1). Almost one-third (30%, n = 31) had inadequate health literacy.

Most participants reported receiving their results over the telephone (50%, n = 47) or in-person (46%, n = 44; Table 2). Among participants with inadequate health literacy, 64% (n = 18) received biopsy results in-person, compared to 27% (n = 26) with adequate health literacy (p = 0.059). Most respondents preferred to receive results in-person (64%, n = 59). Of these, 71% (n = 42) received results in-person, while 25% (n = 15) received results via telephone.

The highest reported first priorities of respondents were receiving results as soon as they were available (68%, n = 65), receiving results from a breast specialist (20%, n = 19), or from their primary care physician (11%, n = 11). There were no differences in preferences for how results were delivered, the type of clinician who delivered the results, or the wait time to receive results based on participants' health literacy (Table 3).

Table 1. Demographic information of respondents.

Variable	%	Frequency
Age (years)		
18 to 29	0%	0
30 to 39	1%	1
40 to 49	6%	7
50 to 59	19%	20
60 to 69	25%	26
70 to 79	37%	38
80 to 88	8%	9
Race and ethnicity		
White	73%	74
Black or African American	5%	6
Asian	4%	5
Hispanic or Latino	7%	8
Other	7%	8
Education		
Not completed high school	8%	9
High school	29%	30
College/university	42%	43
Graduate school	18%	19
Internet access		
Yes	85%	86
No	13%	13
Missing	2%	2
Distance from breast surgeon's office		
10 miles or less	34%	34
11 to 25 miles	44%	44
26 to 50 miles	15%	15
Greater than 50 miles	7%	7
Missing	1%	1
Time since biopsy results received		
Less than 1 month ago	27%	27
1 to 3 months ago	7%	7
4 to 6 months ago	1%	1
7 to 9 months ago	3%	3
9 to 11 months ago	1%	1
12 or more months ago	59%	58
Missing	3%	4

Table 2. Notification experiences vs. preferences of survey respondents.

Notification Variable	How Actually Notified	Notification Preference	p-value
Notification method			<0.0001
In the clinic, face-to-face	46% (44)	64% (59)	
Telephone	50% (47)	33% (31)	
E-mail	1% (1)	1% (1)	
Secure online portal	1% (1)	0% (0)	
U.S. mail	1% (1)	0% (0)	
Passive notification	0% (0)	1% (1)	
Missing	7% (7)	8% (9)	
Clinician communicating results			<0.0001
Radiologist	13% (13)	18% (16)	
Primary care provider	38 % (36)	40% (36)	
Primary care provider's nurse	6% (6)	3% (3)	
Radiologist's nurse	1% (1)	1% (1)	
Breast specialist	36% (34)	36% (32)	
Missing	8% (8)	13% (13)	
Wait time for results			0.02
Within 24 hours	20% (17)	56% (52)	
1 to 2 days	40% (34)	39% (36)	
3 to 5 days	27% (23)	3% (3)	
5 to 7 days	11% (10)	1% (1)	
Missing	16% (17)	8% (9)	

Table 3. Notification preferences and health literacy.

Preference Variable	Health Literacy		p-value
	Adequate	Inadequate	
Modality preference			0.44
In the clinic, face-to-face	60% (39)	74% (20)	
Over the telephone	36% (24)	25% (7)	
E-mail	1% (1)	0% (0)	
Passive notification	1% (1)	0% (0)	
Missing	7% (5)	12% (4)	
Provider preference			0.56
Radiologist	18% (11)	18% (5)	
Primary care provider	39% (24)	44% (12)	
Primary care provider's nurse	3% (2)	3% (1)	
Radiologist's nurse	0% (0)	3% (1)	
Breast specialist	39% (24)	29% (8)	
Missing	12% (9)	12% (4)	
Wait time preference after biopsy			0.38
Within 24 hours	56% (37)	55% (15)	
1 to 2 days	36% (24)	44% (12)	
3 to 5 days	4% (3)	0% (0)	
5 to 7 days	1% (1)	0% (0)	
Missing	7% (5)	12% (4)	

Two participants added comments about their experiences. One wrote,

> *"One thing that was traumatizing for me is I was told by the biopsy radiologist (at the appt, when I had no support) that it was most likely cancer. To have this news delivered... when I was alone, was awful. Truly one of the hardest parts of my whole treatment."*

Another participant reported, *"It is nerve-wracking being here today, waiting for results w/o knowing pos or ng. —this [was] one week post."*

DISCUSSION

Most participants reported that their biopsy results were delivered as they preferred. However, many who preferred an in-person discussion received their results over the phone. Patient preferences may depend on whether the biopsy results are benign or cancerous. A survey of patients before receiving their breast biopsy results suggested that most (~70%) preferred receiving results over the telephone.[5] This sample included patients who eventually received both positive and negative results. In comparison, patients who received positive results only were more likely to prefer face-to-face communication: a prior survey of breast cancer survivors reported that 50% would have preferred face-to-face results,[2] while 64% of participants in this study preferred face-to-face communication.

When cancer diagnoses are disclosed in-person rather than over the phone, conversations tend to be longer and more often include discussions of treatment options, which increases patient satisfaction.[3] In-person conversations may also allow more involvement of patients' partners in initial discussions, enhancing satisfaction with treatment decision-making.[15] Despite the increasing trend of sharing biopsy results over the phone, it remains crucial to follow best communication practices.[4]

As expected, the most important factor for most participants was a speedy turnaround.[2,5,10,16,17] Interestingly, nearly 60% of participants who prioritized quick results also preferred in-person communication. Virtual visits may facilitate these face-to-face discussions more quickly for those with cancerous results.

More participants with inadequate health literacy reported receiving their diagnosis in-person compared to those with adequate health literacy. Providers may have sensed that in-person notification could benefit some patients based on perceived understanding or other factors. A follow-up study could poll providers to identify factors influencing the choice of in-person diagnosis versus other modalities. One-third of participants had low health literacy, which can make navigating a breast cancer diagnosis and treatment challenging. Future research could explore why patients with different levels of health literacy have varied diagnosis experiences.

Limitations. Most participants were White, older than 60 years, and highly educated, which limits the generalizability of this study.[18,19] All participants had a positive biopsy result and were diagnosed with cancer; therefore, the findings may not be applicable to all patients who receive a breast biopsy result, including those with negative biopsies. The survey did not include questions about the availability of a partner, family member, or other support person when the patient was notified of the positive result. Additionally, online patient portal utilization in Wichita is lower than the national average, which may limit the generalizability of findings about modality preferences.[20] Finally, participants were surveyed up to five years after diagnosis, potentially introducing recall bias.

CONCLUSIONS

Surveyed patients preferred to receive their breast biopsy results in-person and as quickly as possible, regardless of health literacy. While prior surveys of patients before receiving their biopsy results indicated a preference for telephone communication, this study of patients diagnosed with breast cancer after a positive biopsy suggests that, when delivering bad news, patients should be offered an in-person appointment whenever possible. With the increased availability of telehealth, virtual visits may allow patients to benefit from in-person communication of a cancer diagnosis while minimizing wait times. Further studies should explore how providers or nurse navigators decide which patients may benefit from an in-person appointment, why patients with lower health literacy are more likely to have an in-person appointment, and how to increase patient satisfaction with specific modalities (e.g., in-person, phone) logistically, including the involvement of a partner or trusted support person.

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REFERENCES

[1] Dahabreh IJ, Wieland LS, Adam GP, Halladay C, Lau J, Trikalinos TA. Core needle and open surgical biopsy for diagnosis of breast lesions: An update to the 2009 report [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Sep. Report No.: 14-EHC040-EF. PMID: 25275206.

[2] Attai DJ, Hampton R, Staley AC, Borgert A, Landercasper J. What do patients prefer? Understanding patient perspectives on receiving a new breast cancer diagnosis. Ann Surg Oncol 2016; 23(10):3182-3189. PMID: 27306904.

[3] Figg WD, Smith EK, Price DK, et al. Disclosing a diagnosis of cancer: Where and how does it occur? J Clin Oncol 2010; 28(22):3630-3635. PMID: 20606078.

[4] McElroy JA, Proulx CM, Johnson L, et al. Breaking bad news of a breast cancer diagnosis over the telephone: An emerging trend. Support Care Cancer 2019; 27(3):943-950. PMID: 30088139.

[5] Brazeal HA, Holley SO, Appleton CM, Lee MV. Patient preferences for breast biopsy result notification. Breast 2018; 24:448-450. PMID: 29105892.

[6] Ad Hoc Committee on Health Literacy for the Council on Scientific Affairs. Health literacy: Report of the Council on Scientific Affairs. JAMA 1999; 281(6):552-557. PMID: 10022112.

[7] Williams MV, Parker RM, Baker DW, et al. Inadequate functional health literacy among patients at two public hospitals. J Amer Med Assoc 1995; 274(21):1677-1682. PMID: 7474271.

[8] Kutner M, Greenberg E, Jin Y, Paulsen C. The health literacy of America's adults: Results from the 2003 National Assessment of Adult Literacy. Washington, DC: US Department of Education. National Center for Education Statistics 2006; 2483. ERIC Number: ED493284.

[9] Morreale MK, Moore TF, Kim S, Uphold HS, Mabunda LM, Harper FWK. Preferences for notification of imaging results in patients with metastatic cancer. Patient Educ Couns 2020; 103(2):392-397. PMID: 31466880.

[10] Saraswathula A, Lee JY, Megwalu UC. Patient preferences regarding the communication of biopsy results in the general otolaryngology clinic. Am J Otolaryngol 2019; 40(1):83-88. PMID: 30472134.

[11] NIH Office of Research on Women's Health. NIH Inclusion Outreach Toolkit: How to Engage, Recruit, and Retain Women in Clinical Research, Office of Management and Budget (OMB) Standards. 2021. https://orwh.od.nih.gov/toolkit/other-relevant-federal-policies/OMB-standards. Accessed August 26, 2022.
[12] Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. Fam Med 2004; 36(8):588-594. PMID: 15343421.
[13] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[14] Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software partners. J Biomed Inform 2019; 95:103208. PMID: 31078660.
[15] Palmer-Wackerly AL, Krieger JL, Rhodes ND. The role of health care provider and partner decisional support in patients' cancer treatment decision-making satisfaction. J Health Commun 2017; 22(1):10-19. PMID: 27967332.
[16] Lang EV, Berbaum KS, Lutgendorf SK. Large-core breast biopsy: Abnormal salivary cortisol profiles associated with uncertainty of diagnosis. Radiology 2009; 250(3):631-637. PMID: 19244038.
[17] Choudhry A, Hong J, Chong K, et al. Patient preferences for biopsy result notification in an era of electronic messaging methods. JAMA Dermatol 2015; 151(5):513-520. PMID: 25831475.
[18] United States Census Bureau. QuickFacts: Sedgwick County Kansas. 2021. https://www.census.gov/quickfacts/sedgwickcountykansas. Accessed August 26, 2022.
[19] United States Census Bureau. Labor Force Participation by Level of Education. 2020. https://www.census.gov/library/visualizations/2020/comm/labor-force-by-education.html. Accessed August 26, 2022.
[20] The Office of the National Coordinator for Health Information Technology. Individuals' use of online medical records and technology for health needs. 2018. https://www.healthit.gov/sites/default/files/page/2018-03/HINTS-2017-Consumer-Data-Brief-3.21.18.pdf. Accessed August 26, 2022.

Keywords: biopsy, large core needle, breast neoplasms, health literacy, truth disclosure

KANSAS JOURNAL of MEDICINE

Brief Report

Do Technical Implementations Help Physicians: An Evaluation of a New Procedure Documentation Tool on Provider Efficiency in the Electronic Health Record

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ABSTRACT

Introduction. Provider time spent in the electronic health record (EHR) continues to increase, adding stress to an already demanding field. This study quantified the impact of a new EHR procedure documentation tool designed to reduce charting burden.

Methods. This retrospective cohort study was conducted at the University of Kansas Health System and involved ambulatory physicians from all hospitals who were granted access to a new procedural documentation tool. Data on time spent per chart and clicks per chart per office visit were gathered from the hospital's EHR system. The cohort also completed a survey regarding their self-perceived efficiency in the EHR and charting burden.

Results. The procedure documentation tool was used for 68% (25/37) of eligible procedures at one-month post-implementation. There was no significant difference in minutes per chart between the group that used the tool and the group that did not, although the group using the tool had lower charting time (median difference [MD] = 5.517; 95% CI, -0.283 to 13.317; p = 0.066). A similar trend was seen with clicks per chart, with an MD of 4 (95% CI, -3 to 11; p = 0.25).

Conclusions. While the difference was not significant, this study achieved its goal of quantifying the impact of a health information technology (HIT) project and indicates the need for further examination of how to quantify future projects. It lays the groundwork for future evaluation of similar tools and studies. ***Kans J Med 2024;17:100-102***

INTRODUCTION

Burnout among physicians is a significant issue, with the prevalence among physicians rising or remaining steady despite interventions.[1,2] One of the perceived leading causes of burnout is poorly designed electronic health record (EHR) systems.[3] As a result, many EHR vendors and health information technology (HIT) teams have attempted to introduce functionality and features to reduce physician charting burden. Despite these interventions, burnout remains high with about 50% of physicians citing too much EHR time as a leading factor for their burnout and dissatisfaction.[4]

Reduced charting time has been associated with reductions in burnout and improvements in efficiency.[5] Prior research has done little to define efficiency quantitatively. Methods have included the number of standard tools (such as order sets) used, self-report efficiency, and amount of time in the EHR.[6,7] Sinsky et al.[8] have proposed seven core EHR use measures, which include total EHR time, work outside of work, time on encounter note documentation, time on prescriptions, time on inbox, teamwork for orders, and undivided attention.

While there is literature on the impact of EHR implementation on efficiency for physicians and the transition between EHR systems, little information is currently available on the effect of upgrades or add-on features to an EHR.[9,10] HIT teams at hospitals often implement upgrades or additional features to ease the charting burden or make more tools available. However, it is unknown whether these upgrades achieve their goal.

We aimed to use one of the seven core EHR measures, encounter note documentation, to identify the effect of a new procedure documentation tool on physician charting efficiency at the University of Kansas Medical Center (KUMC). Additionally, we sought to create a framework for future evaluations of similar tool implementations.

METHODS

Study Design. The author conducted this retrospective cohort study at KUMC from July through September 2020, with approval from the KUMC Institutional Review Board (IRB). The study aimed to evaluate the impact of a new procedure documentation tool on provider charting efficiency. The tool, developed by Epic Systems, an EHR company, was optimized by the KUMC team, including physician informaticians, clinical content experts, and information technology professionals. The study period spanned four weeks before implementation of the tool through four weeks post-implementation. Physicians had the option to use the tool for documenting in-office procedures but were not required or prompted to do so.

The study comprised two parts: a retrospective database extraction and a physician survey. For the database extraction, the EHR automatically collected and stored data on physician time spent in each patient's chart. The survey, conducted four weeks post-implementation, involved a convenience sample of family physicians, and assessed their efficiency and satisfaction with the EHR. Survey data were collected and managed using REDCap electronic data capture tools hosted at KUMC.[11,12]

Participant Eligibility Criteria. All physicians practicing at the KUMC family medicine department were eligible, except those contracted through an outside vendor. Written consent was obtained from all survey participants.

For database extraction, chart information was anonymously extracted for physicians performing eligible procedures, including bladder catheterization, endometrial biopsy, colposcopy, laceration repair, nail removal, foreign body locations, cast application, suture removal, incision and drainage, skin lesion biopsy, skin tag, nerve block, tendon sheath, spirometry, vasectomy, ultrasound guidance, botulinum toxin injection for migraines, cardiovascular stress testing, and skin tag removal.

Outcome Measures. The primary measure was the minutes spent charting per encounter. Secondary measures included the number of clicks per encounter and survey questions assessing tool efficiency and EHR use. These survey questions were rated on a 5-point Likert scale

(Strongly Agree, Agree, Neutral, Disagree, Strongly Disagree) and were created by the authors. The survey items were adapted from internal IT evaluations and reviewed by two institutional physician informaticists to ensure they met the study's goals.

Statistical Analyses. IBM® SPSS (Statistical Package for Social Sciences; Armonk, NY), version 29, was used for these analyses. Normality of data was assessed using the Shapiro-Wilk test. Means were compared using Student's t-test or the Mann-Whitney U test. Survey responses were analyzed qualitatively.

RESULTS

Database Results. The procedure documentation tool was adopted by 68% (25/37) of eligible physicians in the family medicine department one-month post-implementation, indicating broad but not universal adoption. The Shapiro-Wilk test for normality of distribution was statistically significant for minutes spent in chart ($p < 0.001$) and clicks per encounter ($p < 0.001$), suggesting that neither sample was normally distributed. Therefore, the Mann-Whitney U test was used to compare the distribution differences between the samples.

There was no significant difference in the mean rank of minutes spent in the chart per encounter between the group that used the tool and the group that did not. The median minutes per chart for those not using the tool was 17.3, while for those using the tool, it was 10.5 (Figure 1). The median difference in minutes spent charting per encounter between the tool users and non-users was 5.5 (95% CI, -0.28, 13.3; U = 160; p = 0.066).

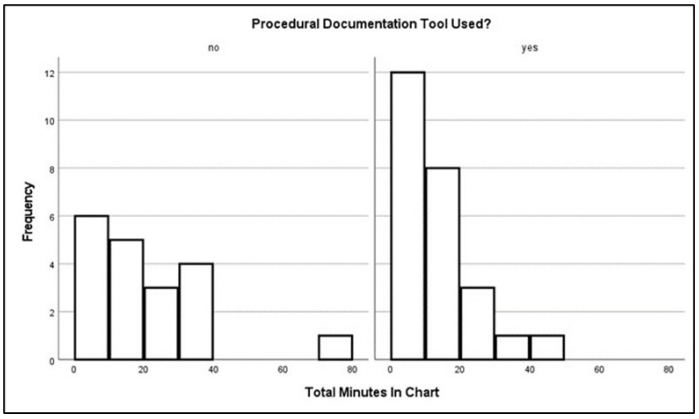

Figure 1. Histogram distribution of minutes spent per charting encounter.
Note: When comparing groups who used the procedural documentation tool against those who did not, there was no statistically significant difference between total minutes in chart (p = 0.066). Although, there was a trend for the procedural documentation tool to have fewer minutes spent in the chart.

There was no significant difference in the mean rank of clicks per charting encounter between the two groups. The median number of clicks per chart for charts that used the procedural documentation tool was 22, while for charts that did not use the tool, it was 23 (Figure 2). The median difference in the number of clicks was 4 (95% CI, -3 to 11; U = 189; p = 0.25).

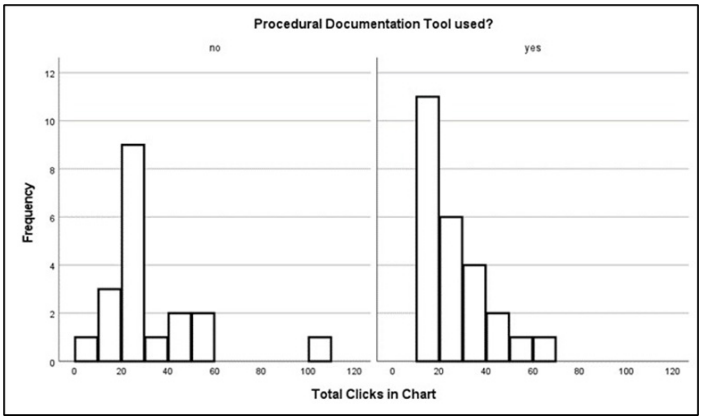

Figure 2. Histogram distribution of clicks per charting encounter.
Note: When comparing groups who used the procedural documentation tool against those who did not, there was no statistically significant difference between total clicks in chart (p = 0.25). Although, there was a trend for the procedural documentation tool to have fewer clicks in the chart.

Survey Results. There was a 22% response rate (13/59) to the survey among the physicians in the department. Among the 13 participants who responded, 8 (62%) used the tool frequently to complete their workflows, and 10 (77%) felt that it allowed them to complete their workflows more efficiently (Table 1). Additionally, 11 respondents (85%) considered themselves highly proficient users of the EHR system. Only one respondent felt less efficient in using the EHR system after the tool's implementation compared to before.

Table 1. Most physicians used the procedure documentation tool at the follow up and found it to have a positive effect on their workflow.

	No. (%)		
Survey Questions on Efficiency	**Agree**	**Disagree**	
I feel I am a highly proficient user of the EHR system.	11 (79%)	3 (21%)	
I feel comfortable using tools and the EHR in general.	14 (100%)	0 (0%)	
I feel I am efficient in my use of the EHR system.	10 (71%)	4 (29%)	
Since its implementation, I am using the procedure documentation tool often to complete my workflows.	8 (62%)	5 (38%)	
The procedure documentation tool has allowed me to complete my workflows more efficiently compared to before it was implemented.	11 (85%)	2 (15%)	
I feel that I am more efficient in my use today of the EHR system than I was two months ago.	10 (79%)	3 (21%)	
I am satisfied with my experience in the EHR system.	12 (86%)	2 (14%)	
	Bothers Me	**Is Not a Problem**	**Is Only a Problem Sometimes**
Spending time in the EHR outside of normal business hours	9 (64%)	1 (7%)	4 (29%)

Note: List of items delivered in the qualitative survey and percentage responders, divided based on agreement with the statement.

DISCUSSION

This retrospective cohort study evaluated the change that a new procedure documentation tool had on provider charting efficiency. This new tool was not associated with a statistically significant effect on charting time per encounter or clicks-in-chart per encounter, with p-values of 0.06 and 0.25, respectively. However, it did show a potentially clinically significant effect on charting efficiency for providers, as the tool was associated with a decrease in time in the chart by up to 10 minutes per encounter.

These findings are consistent with those of Sinsky et al.,[8] proposing that time per encounter is one core measure that affects happiness in the EHR. Time per chart can significantly affect charting experience and burnout among physicians and further measures should be taken to help reduce charting burden.

Mostly self-reported highly proficient users responded to the survey and felt that it improved their workflow. Highly skilled users of the EHR may have benefitted more from the tool implementation than lower-skilled users, who would require more training or time to achieve an equal benefit.

Although the method showed value in determining the change in charting time, the value of the tool was undercut by a lack of utilization. The method is valuable on its own as the health informatics team can utilize the process we developed to understand the impact of future tools on charting experience. This information will greatly improve planning, execution, and retrospective evaluation of future IT tools.

Limitations. Limitations of this study include the small department size (59 total physicians), low survey response rates (22%), and the short time frame over which the data was evaluated (one month prior to tool implementation and one month after tool implementation). Only 37 eligible procedures occurred, insufficient for definitive conclusions. The low response rate was likely due to physician survey fatigue and the lack of monetary incentives.[13] Additionally, a non-validated scale was used to gauge physician insights on the tool, which can limit the reliability of the results. Although Likert scales are well-known, the specific questions and response options need validation.[14] Using a fully validated tool would improve the study. Additionally, leveraging the Cosmos database, which pools encounters from 256 million patients, could significantly enhance the study's power.

Next Steps. Next steps for the project include implementation of the analysis method on a tool with high utilization rates for a more accurate evaluation. Another step is to find other implementations to which the method can be applied and re-evaluate the procedure documentation tool in the family medicine department at one year. This would let us determine if more familiarity with the tool leads to more effective utilization. A future evaluation would be combined with an evaluation with the System Usability Scale, a reliable, validated scale used as a part of usability engineering to determine an assessment of usability.[15,16] An alternative is to evaluate the tool in a subset of physicians who were already familiar with the procedure documentation tool and compare it to a subset who did not use the tool at all. Another step is to evaluate the quality of the procedure notes between the physicians who used the tool and those that did not. This would evaluate if the notes met billing standards necessary for reimbursement purposes.

CONCLUSIONS

This retrospective cohort study found no statistically significant difference in physician charting burden after implementing a new procedure documentation tool. However, it indicated the potential for interventions to reduce physician charting burden. The study quantified the impact of a HIT project on physician charting burden, laying the groundwork for evaluating future tools and identifying necessary future studies to assess the impact of HIT on physician charting experience.

REFERENCES

[1] Shanafelt TD, Hasan O, Dyrbye LN, et al. Changes in burnout and satisfaction with work-life balance in physicians and the general US working population between 2011 and 2014. Mayo Clin Proc 2015; 90(12):1600-1613. PMID: 26653297.
[2] Shanafelt TD, West CP, Sinsky C, et al. Changes in burnout and satisfaction with work-life integration in physicians and the general US working population between 2011 and 2017. Mayo Clin Proc 2019; 94(9):1681-1694. PMID: 30803733.
[3] Kroth PJ, Morioka-Douglas N, Veres S, et al. Association of electronic health record design and use factors with clinician stress and burnout. JAMA Netw Open 2019; 2(8):e199609. PMID: 31418810.
[4] Linzer M, Poplau S, Babbott S, et al. Worklife and wellness in academic general internal medicine: Results from a national survey. J Gen Intern Med 2016; 31(9):1004-1010. PMID: 27138425.
[5] Robinson KE, Kersey JA. Novel electronic health record (EHR) education intervention in large healthcare organization improves quality, efficiency, time, and impact on burnout. Medicine (Baltimore) 2018; 97(38):e12319. PMID: 30235684.
[6] DiAngi YT, Stevens LA, Halpern-Felsher B, Pageler NM, Lee TC. Electronic health record (EHR) training program identifies a new tool to quantify the EHR time burden and improves providers' perceived control over their workload in the EHR. JAMIA Open 2019; 2(2):222-230. PMID: 31984357.
[7] Melnick ER, Dyrbye LN, Sinsky CA, et al. The association between perceived electronic health record usability and professional burnout among US physicians. Mayo Clin Proc 2020; 95(3):476-487. PMID: 31735343.
[8] Sinsky CA, Rule A, Cohen G, et al. Metrics for assessing physician activity using electronic health record log data. J Am Med Inform Assoc 2020; 27(4):639-643. PMID: 32027360.
[9] Zandieh SO, Abramson EL, Pfoh ER, Yoon-Flannery K, Edwards A, Kaushal R. Transitioning between ambulatory EHRs: A study of practitioners' perspectives. J Am Med Inform Assoc 2012; 19(3):401-406. PMID: 21875866.
[10] Haidar YM, Moshtaghi O, Mahboubi H, et al. Association between electronic medical record implementation and otolaryngologist productivity in the ambulatory setting. JAMA Otolaryngol Head Neck Surg 2017; 143(1):20-24. PMID: 27583577.
[11] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2):377-381. PMID: 18929686.
[12] Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019; 95:103208. PMID: 31078660.
[13] Cunningham CT, Quan H, Hemmelgarn B, et al. Exploring physician specialist response rates to web-based surveys. BMC Med Res Methodol 2015; 15:32. PMID: 25888346.
[14] Schatz M, Zeiger RS, Chen W, Yang S-J, Stanford RH, Garris CP. A Comparison of the psychometric properties of the Mini–Rhinitis Quality of Life Questionnaire and the Rhinitis Control Assessment Test. Am J Rhinol Allergy 2012; 26(2):127-133. PMID: 22487290.
[15] Peres SC, Pham T, Phillips R. Validation of the system usability scale (SUS): SUS in the wild. Proceedings of the Human Factors and Ergonomics Society Annual Meeting 2013; 57(1):192-196.
[16] Brooke J. SUS: A quick and dirty usability scale. 1996; 189-194.

Keywords: electronic health record, burnout, professional, efficiency

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Case Report

A Case Report of a Successful Treatment of Ipilimumab Plus Nivolumab (IPI-NIVO)-Induced Sialadenitis with Coconut Oil

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INTRODUCTION

Ipilimumab-plus-nivolumab (IPI-NIVO) immunotherapy is increasingly used to treat various cancers, including advanced melanoma. Ipilimumab, a cytotoxic T-lymphocyte associated protein 4 inhibitor, enhances the immune response against cancer cells by allowing the primary T-cell costimulatory receptor, cluster of differentiation 28, to bind freely to cluster of differentiation 80 ligands on antigen-presenting cells.[1] Nivolumab, a monoclonal antibody, binds to programmed cell death protein 1 (PD-1), a cell-surface protein on T-cells. Normally, PD-1 binding to programmed cell death ligand 1 (PD-L1) on antigen-presenting cells prevents autoimmunity, but tumors exploit this mechanism to evade immune detection. Nivolumab inhibits PD-L1 binding to PD-1, exposing the tumor to a stronger immune response.[2]

Both medications can cause autoimmune side effects, such as rash, altered thyroid function, vitiligo, pneumonitis, hepatitis, and colitis. The rate of these adverse events increases from 27.3% for ipilimumab alone and 16.3% for nivolumab alone to 55% with combined therapy. Although adverse effects of these medications are common, immunotherapy-induced sialadenitis is rare, occurring in only 0.03-0.05% of patients on IPI-NIVO.[3]

Coconut oil has been used for oral health for centuries, notably in the practice of "oil pulling" found in ancient Ayurvedic texts.[4] Some studies suggest it reduces salivary bacterial counts, though results are mixed and often at high risk for bias.[4-6] Despite its widespread use on the Indian subcontinent, research supporting coconut oil for xerostomia and mucositis is limited.

This report discusses a metastatic melanoma patient with IPI-NIVO-induced sialadenitis complicated by xerostomia and mucositis who was successfully treated with coconut oil oral rinses.

CASE REPORT

A 59-year-old male with metastatic melanoma began treatment with IPI-NIVO soon after diagnosis. He completed four cycles of ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) every three weeks, followed by 11 cycles of nivolumab alone (3 mg/kg) every four weeks. After the ninth cycle, the patient presented with dry mouth, rawness, erythema, and pain in the oral mucosa, bilateral parotid gland swelling, and nodules near the parotid glands. He also reported extreme sensitivity to salty foods and toothbrushing, requiring dietary adjustments, but had no pain without these triggers.

These symptoms, consistent with sialadenitis complicated by xerostomia and mucositis, remained stable after the 10th cycle of immunotherapy. Both the xerostomia and mucositis were of "grade 2" severity based on the National Cancer Institute's Common Terminology Criteria for Adverse Events.[7] As he did not exhibit life-threatening symptoms like colitis or pneumonitis, corticosteroids were not initiated, and no dose reductions were made.

After the 11th cycle, the patient began using Biotene® toothpaste, which partially alleviated his dry mouth and oral mucosa rawness. Before the 12th cycle, he started using coconut oil as an oral rinse two to three times daily on his daughter's advice, which significantly relieved his symptoms. This treatment subjectively improved the flexibility, color, and moisture of his oral mucosa, reduced xerostomia, and enhanced his quality of life. The patient continued these rinses during his remaining treatments, with progressive improvement and no recurrence of symptoms. He did not require corticosteroids or dose reductions throughout the process.

DISCUSSION

While immunotherapy-induced sialadenitis was the leading suspicion in this case, there was concern that the palpable nodes might indicate progressive metastatic melanoma. To confirm the diagnosis, the patient underwent a fine needle aspiration (FNA) biopsy of his right mandibular lymph node. Pathology revealed a mixed population of benign lymphocytes, consistent with lymphoepithelial sialadenitis (Figure 1). This diagnosis is significant, as IPI-NIVO immunotherapy is known to cause sialadenitis in only 0.03% to 0.05% of patients.[3]

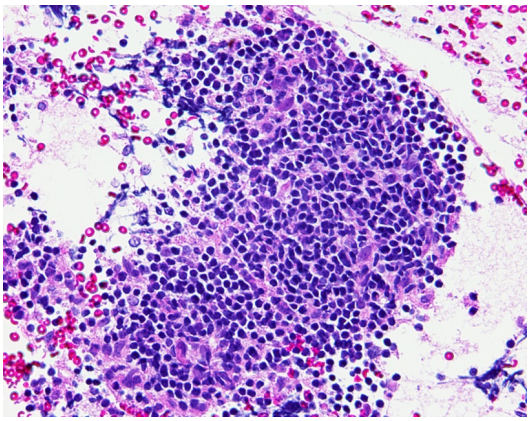

Figure 1. Mixed population of reactive lymphocytes, fine needle aspiration biopsy, 200X original magnification, hematoxylin-eosin.

Despite its rarity, sialadenitis and resultant sicca symptoms can significantly impact quality of life, making it crucial for practitioners to monitor for this side effect. While literature suggests that patients may recover with systemic or topical sialagogues such as pilocarpine,[8] systemic corticosteroids like prednisone,[9] or temporary discontinuation of immunotherapy,[10] this patient showed significant improvement using coconut oil alone.

The patient's positive response to coconut oil highlights an important consideration for providers: using nonpharmacologic therapies as first-line treatment for sicca symptoms induced by ipilimumab and nivolumab can spare patients from systemic sialagogues or corticosteroids, which have their own adverse effects. Additionally, coconut oil use may prevent delays in completing immunotherapy, which, although

unlikely to impact treatment outcomes significantly, can cause notable distress for patients.[11]

Given the case-based nature of this report and resultant lack of any control, it is unclear whether the patient's symptoms may have improved over time without the use of coconut oil. Further, some patients may still require systemic corticosteroids, topical or systemic sialagogues, and/or delays before their next immunotherapy cycle to alleviate symptoms of sialadenitis, xerostomia, and mucositis induced by immunotherapy. However, given the case patient's significant response to coconut oil use, this therapy and/or similar oral lubricants should be considered as useful adjuncts for managing these symptoms.

ACKNOWLEGEMENTS

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REFERENCES

[1] Tarhini A, Lo E, Minor DR. Releasing the breaks on the immune system: Ipilimumab in melanoma and other tumors. Cancer Biother Radiopharm 2010; 25(6):601-613. PMID: 21204754.
[2] Rendon A, Rayi A. Nivolumab. Treasure Island, FL: StatPearls Publishing. 2024 Feb 28. PMID: 33620870.
[3] Carreau NA, Pavlick AC. Nivolumab and ipilimumab: Immunotherapy for treatment of malignant melanoma. Future Oncol 2019; 15(4):349-358. PMID: 30334646.
[4] Pavithran VK, Krishna M, Kumar VA, Jaiswal A, Selvan AK, Rawlani S. The effect of oil pulling with pure coconut oil on streptococcus mutans: A randomized controlled trial. Journal of Indian Association of Public Health Dentistry 2017; 15(3):200-204. doi: 10.4103/jiaphd.jiaphd_29_17.
[5] Woolley J, Gibbons T, Patel K, Sacco R. The effect of oil pulling with coconut oil to improve dental hygiene and oral health: A systematic review. Heliyon 2020; 6(8):e04789. PMID: 32923724.
[6] Siripaiboonpong N, Matangkasombut O, Pengcharoen H, Boonchaiyapluk B, Rujiraprasert P, Srithanyarat SS. Microbiological effects of virgin coconut oil pulling in comparison with palm oil pulling as an adjunctive oral hygiene care for patients with gingival inflammation: A randomized controlled clinical trial. J Indian Soc Periodontol 2022; 26(1):58-63. PMID: 35136318.
[7] U.S. Department of Health and Human Services. National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed July 31, 2024.
[8] Glavina A, Tadina A. Sicca symptoms and sialoadenitis as immune-related adverse events of nivolumab treatment in renal malignancy. MOJ Clin Med Case Rep 2023; 13(1):21-23. doi: 10.15406/mojcr.2023.13.00429.
[9] Takahashi S, Chieko X, Sakai T, Hirose S, Nakamura M. Nivolumab-induced sialadenitis. Respirol Case Rep 2018; 6(5):e00322. PMID: 29686875.
[10] Warner BM, Baer AN, Lipson EJ, et al. Sicca syndrome associated with immune checkpoint inhibitor therapy. Oncologist 2019; 24(9):1259-1269. PMID: 30996010.
[11] Frosch ZAK, Jacobs LM, O'Brien CS, et al. "Cancer's a demon": A qualitative study of fear and multilevel factors contributing to cancer treatment delays. Support Care Cancer 2023; 32(1):13. PMID: 38060063.

Keywords: sialadenitis, immunotherapy, xerostomia, mucositis, coconut oil

KANSAS JOURNAL of MEDICINE

Case Report

What's the Leading Point? A Benign Polypoid Mass Behind the Trouble

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INTRODUCTION

Adult intestinal intussusception occurs when one segment of the bowel telescopes into an adjacent segment. It is a rare condition that is difficult to diagnose due to nonspecific gastrointestinal symptoms. While obstruction and bowel ischemia can occur, only 1% of small bowel obstructions in adults is the result of intussusception.[1] Unlike pediatric cases, most adult intussusceptions are secondary to an identifiable pathology, typically an organic lesion such as a neoplasm, acting as a leading point. Imaging modalities, particularly abdominal computed tomography (CT), are essential for confirming intussusception, although ultrasonography also plays a diagnostic role.

Treatment usually involves surgical resection of the affected bowel segment due to the high risk of structural anomalies and malignancy. This paper presents the case of a patient who came to our clinic with refractory, chronic iron deficiency anemia. He was ultimately found to have a benign polypoid mass that had ulcerated in the setting of chronic entero-enteric intussusception.

CASE REPORT

A 67-year-old male with a history of iron deficiency anemia of unclear etiology, diverticulitis, non-Hodgkin's lymphoma (marginal B-cell), and chronic, rate-controlled atrial fibrillation presented to gastroenterology for further evaluation of his anemia. His surgical history included a partial colectomy 11 years prior for complicated diverticulitis and a cholecystectomy. The patient denied taking anticoagulants or nonsteroidal anti-inflammatory drugs. He had no significant alcohol, tobacco, or drug use.

Over the past seven years, the patient reported some dark stools but denied melena and hematochezia. Records from the six months prior to presentation showed mild anemia with a hemoglobin level ranging from 11.0 to 12.9 g/dL. He received two doses of intravenous iron during that time. A CT scan one-month prior revealed intussusception of the terminal ileum, presumed to be due to a leading lymph node effect (Figure 1).

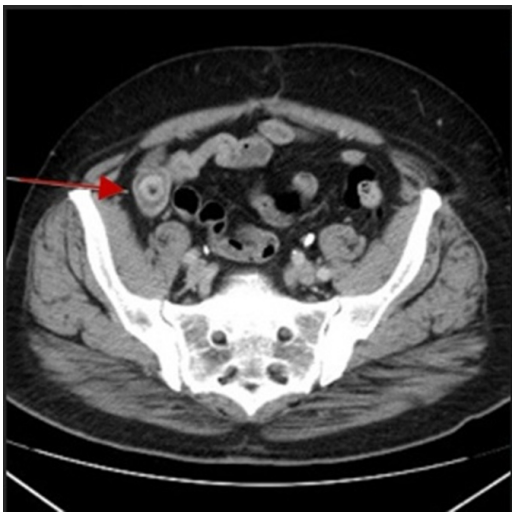

Figure 1. Computed tomography (CT) abdomen showing intussusception of the terminal ileum.

An esophagogastroduodenoscopy and colonoscopy were performed. The esophagus, stomach, and duodenum appeared normal. The colonoscopy showed small, non-bleeding internal hemorrhoids and five sub-centimeter sessile polyps resected from the sigmoid colon, hepatic flexure, and transverse colon. A left-sided surgical anastomosis was also noted. Due to unremarkable findings, the patient underwent a small bowel follow-through (SBFT) and capsule endoscopy. Additional testing included tissue transglutaminase antibody screening, which was negative.

SBFT (Figure 2) and capsule endoscopy (Figure 3) revealed an ulcerated polyp or mass protruding into the lumen of the distal small bowel. A repeat abdominal CT three months after presentation showed resolution of the previously noted intussusception in the distal ileum. Due to a strong suspicion of gastrointestinal pathology as the cause of his progressive anemia, the patient underwent an exploratory laparotomy, resulting in the discovery and resection of a 3 cm ulcerated polypoid mass in the ileum. Pathology revealed an intraluminal pedunculated, exophytic 2.9 cm benign polypoid mass with features consistent with chronic prolapsed/intussuscepted bowel wall tissue, mucosal surface ulceration, mucosal and submucosal granulation tissue formation, and mild chronic inflammation (Figure 4).

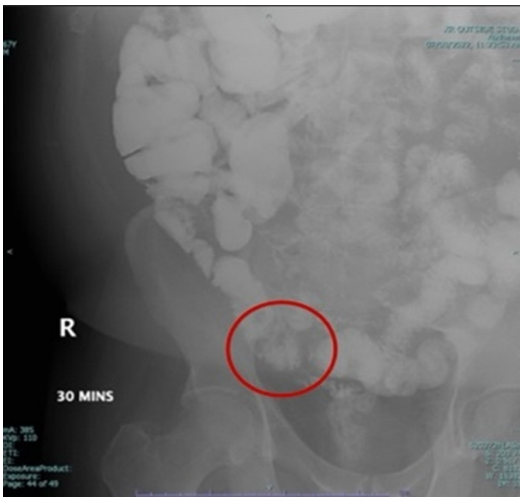

Figure 2. Small bowel follow-through showing transition point in the right lower quadrant.

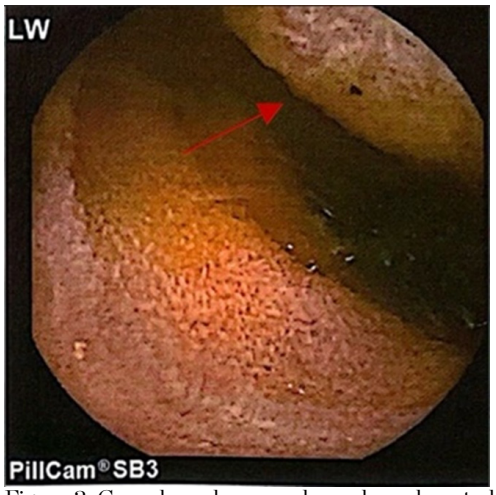

Figure 3. Capsule endoscopy showed an ulcerated polyp or mass protruding into the lumen of the distal small bowel.

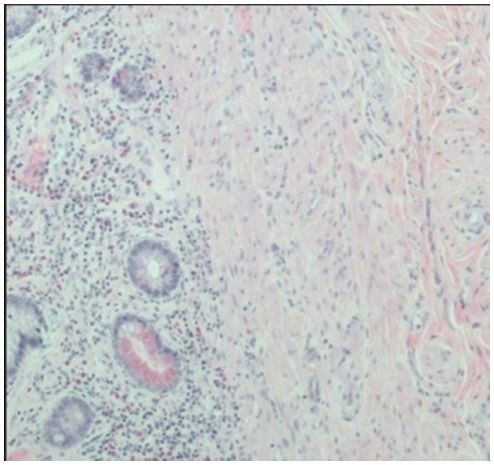
Figure 4. Biopsy showing features consistent with chronic prolapsed bowel wall tissue, with mucosal surface ulceration, mucosal and submucosal granulation tissue formation.

The patient was readmitted to the hospital seven days after the exploratory laparotomy with symptoms of partial small bowel obstruction, which resolved with conservative management. Follow-up iron studies showed improvement from his prior baseline.

DISCUSSION

Bowel intussusception occurs when a segment of the bowel, along with part of its mesentery, telescopes into the lumen of an adjacent segment. While common in children, adult intussusception is rare, accounting for only 5% of all cases.[1] Clinical presentation in adults varies and can include colicky abdominal pain, nausea, vomiting, GI bleeding, abdominal distension, and changes in bowel habits. Intussusception is typically classified by location, etiology, and the presence or absence of a lead point.

When classified by location, benign organic lesions are more frequently associated with entero-enteric intussusception, while malignancies are more common in large bowel intussusception. Differential diagnoses for causes of intussusception include malignancies such as gastrointestinal stromal tumors (GIST), neuroendocrine tumors, leiomyomas, and other small intestine cancers, as well as conditions like leading lymph node effect, arteriovenous malformations, ulcers, celiac disease, and other small bowel pathologies.[2,3] In 70 - 90% of adult cases, leading points are formed by organic lesions such as inflammatory bowel disease (IBD), Meckel's diverticulum, vascular anomalies, post-operative adhesions, and benign or malignant lesions.[4]

Ultrasound can be useful in diagnosing intussusception in both children and adults, showing the characteristic target or doughnut sign in the transverse view and the pseudo-kidney sign in the longitudinal view. However, CT is currently considered the most sensitive radiologic method to confirm intussusception, with a reported diagnostic accuracy of 58 - 100%.[1] Unlike ultrasound, CT is not affected by gas in the bowel lumen and can help determine the cause, locate the lead point, rule out obstruction, and evaluate for complications. Characteristic CT features include a target or sausage-shaped soft-tissue mass with a layering effect and mesenteric vessels within the bowel lumen.[5]

Due to non-specific symptoms, the diagnosis of adult intussusception is often delayed and typically confirmed through surgery. Given the high proportion of malignant lesions as leading points in adults, surgery remains the treatment of choice.[1] Preoperative reduction with barium or air is not recommended due to potential complications such as perforation, intraluminal seeding, and venous tumor dissemination.[3,6]

In our case, pathology revealed a segment of ileum with a benign 2.9 cm polypoid lesion characterized by marked fibromuscular proliferation, prolapse-type changes, ulceration, and features of chronic mucosal injury, with no evidence of neoplasm. Polypoid lesions, which can be neoplastic or benign, more frequently originate from the mucosa but also can develop from the submucosa. Their etiology is largely unknown, but they most commonly occur in the stomach, followed by the small bowel, with peak incidence in the sixth and seventh decades of life. In the small bowel, they usually present as intussusception or obstruction.[7] Polypoid lesions also can ulcerate, cause GI bleeding, and result in anemia.[8] Differential diagnoses for benign polypoid masses include inflammatory myofibroblastic tumors, GIST, and inflammatory polyps related to IBD.

CONCLUSIONS

In conclusion, adult intussusception is a rare and challenging diagnosis in patients with anemia and/or obstruction. Diagnosis is often missed due to non-specific symptoms. In most cases, a pathologic mass acting as a leading point can be identified with abdominal CT, which not only distinguishes the presence or absence of a lead point but also helps determine the mass's location to guide management. Benign lesions are more common in entero-enteric locations, and treatment typically involves formal resection of the involved bowel segment. Therefore, it is important to consider benign polypoid masses in the differential diagnosis of lesions causing small bowel intussusception and in patients with non-specific symptoms such as anemia and abdominal pain.

REFERENCES

[1] Marinis A, Yiallourou A, Samanides L, et al. Intussusception of the bowel in adults: A review. World J Gastroenterol 2009; 15(4):407-411. PMID: 19152443.
[2] Carvalho A, Leitão P, Pinheiro J, et al. Small bowel intussusception in 2 adults caused by inflammatory polyps. Radiol Case Rep 2017; 12(4):710-714. PMID: 29484055.
[3] Akbulut S. Intussusception due to inflammatory fibroid polyp: A case report and comprehensive literature review. World J Gastroenterol 2012; 18(40):5745-5752. PMID: 23155316.
[4] Baleato-González S, Vilanova JC, García-Figueiras R, Juez IB, Martínez de Alegría A. Intussusception in adults: What radiologists should know. Emerg Radiol 2012; 19(2):89-101. PMID: 22200965.
[5] Begos DG, Sandor A, Modlin IM. The diagnosis and management of adult intussusception. Am J Surg 1997; 173(2):88-94. PMID: 9074370.
[6] Eisen LK, Cunningham JD, Aufses AH Jr. Intussusception in adults: Institutional review. J Am Coll Surg 1999; 188(4):390-395. PMID: 10195723.
[7] Harned RK, Buck JL, Shekitka KM. Inflammatory fibroid polyps of the gastrointestinal tract: Radiologic evaluation. Radiology 1992; 182(3):863-866. PMID: 1535909.
[8] Kim YH, Blake MA, Harisinghani MG, et al. Adult intestinal intussusception: CT appearances and identification of a causative lead point. Radiographics 2006; 26(3):733-744. PMID: 16702451.

Keywords: intussusception, capsule endoscopy, ileal neoplasm

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Case Report

Anchoring Bias: A Cautionary Tale of Point-of-Care Ultrasound and Cardiac Tamponade

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INTRODUCTION

Cardiac tamponade is a hemodynamic condition where the accumulation of pericardial contents, typically a pericardial effusion, leads to significantly increased intrapericardial pressure. This pressure decreases diastolic filling and ultimately progresses to a life-threatening decrease in cardiac output.[1] Electrocardiographic abnormalities may include reduced voltage, sinus tachycardia, and electrical alternans (alternating QRS voltage). A chest x-ray may show an enlarged cardiac silhouette.[2] When there is high clinical suspicion for cardiac tamponade, echocardiography is the primary diagnostic modality for initial evaluation.[2,3]

Prompt diagnosis is crucial for improved outcomes in cardiac tamponade due to the rapid progression of hemodynamic compromise. Adding a bedside ultrasound protocol to standard care allows for a rapid evaluation that can enhance the assessment of differential diagnoses.[4] The bedside point-of-care ultrasound (POCUS) exam is a valuable adjunct for diagnosing tamponade. However, it is essential to recognize that while POCUS is quick and non-invasive, it also can leave clinicians vulnerable to cognitive bias and diagnostic errors.[5]

CASE REPORT

A 51-year-old female weighing 44 kg with a three-week history of congestion, cough, and dyspnea presented to the emergency department (ED) due to worsening symptoms and lethargy. Her past medical history included end-stage renal disease on hemodialysis (HD), cerebral vascular accident, deep vein thrombosis with subsequent pulmonary embolism and inferior vena cava filter placement, chronic pericardial effusions with pericardial windows, aortic insufficiency, regular tobacco use, and warfarin use. She had missed HD two days prior due to malaise but underwent HD the following day.

During transport to the ED via emergency medical services, she received a 1 L fluid bolus. On initial assessment in the ED, she was hypoxic, hypotensive, and drowsy but oriented. Fluid overload from missed dialysis was suspected as the cause of her presentation. Nephrology was consulted and arranged for HD and/or continuous renal replacement therapy. An electrocardiogram showed a low voltage QRS, prompting the ED physician to perform a POCUS, revealing a large pericardial effusion without tamponade. Cardiology was consulted and ordered a stat transthoracic echocardiogram, which confirmed no tamponade physiology. Cardiothoracic surgery was consulted, and a computed tomography (CT) thorax without contrast was ordered for operative planning. The hospitalist admitted the patient to the intensive care unit.

Sepsis was considered as a potential cause for her hypotension, so blood cultures were obtained, and she was started on broad-spectrum antibiotics and a norepinephrine drip. Another 1000 mL fluid bolus was given. A chest x-ray indicated right upper lobe consolidation, suggesting an infectious infiltrate or possibly a central obstructing mass. The subsequent CT thorax scan identified pneumonia as the likely cause, ruling out an endobronchial obstructing lesion, and noted cardiomegaly with a large pericardial effusion, recommending cardiothoracic surgery consultation for a pericardial window.

Shortly after the CT scan, upon returning to her ED room, the patient became cyanotic, unresponsive, apneic, and bradycardic. Cardiopulmonary resuscitation (CPR) was initiated, and the ED physician performed a blind pericardiocentesis during the first pulse check, obtaining 25 mL of fluid. CPR resumed, the patient was intubated, and return of spontaneous circulation was achieved after 10 minutes. An emergent pericardial window in the operating room was then planned.

The anesthesiology team, including two critical care-trained anesthesiologists, evaluated the patient and performed a POCUS exam, showing a persistent massive pericardial effusion without tamponade. To stabilize the patient for transport to the operating room, a pericardiocentesis under ultrasound guidance was performed, removing approximately 75 mL of fluid without significant hemodynamic improvement.

The patient underwent a pericardial window via a mini thoracotomy through the fifth intercostal space on the left. During the procedure, she experienced asystole, responsive to direct cardiac compression. Intraoperative transesophageal echocardiogram revealed left ventricular hypokinesis with an ejection fraction of <20%, severe tricuspid regurgitation, severe pulmonary hypertension, sustained bowing of the intra-atrial septum into the left atrium, and a concentric pericardial effusion. Upon opening the pericardium, 200 mL of fluid were removed.

Following surgery, the patient was transferred to the intensive care unit, intubated, and on high doses of multiple inotropes. Despite these efforts, her neurological status did not improve. Goals of care were discussed with her family, and the decision was made to designate her as "Do-Not-Resuscitate." She passed away 14 hours after initial presentation. Initial blood cultures taken in the ED later returned positive, indicating bacterial sepsis secondary to pneumonia, which may have contributed to her outcome.

DISCUSSION

Guidelines from the American Heart Association, American College of Cardiology, American Society of Echocardiography, and European Society of Cardiology label echocardiography as the first-level diagnostic tool in the evaluation of pericardial pathology.[6] It is essential for physicians to understand the physiologic and echocardiographic distinctions between a large pericardial effusion and cardiac tamponade, as each diagnoses will lead to vastly different paths of clinical management and acuity.

The intrapericardial pressure (IPP) is proportional to the pericardial fluid volume and the stiffness of the pericardial sac – the latter otherwise can be described as inversely proportional to the compliance.[5] Normal IPP is lower than normal intracardial pressures; under normal circumstances, IPP does not exert influence on cardiac filling. Tamponade physiology will be seen when the IPP does impact cardiac filling. In other words, the detrimental hemodynamic effects of a pericardial effusion will be exerted due to increased IPP's, which depends on the rate of rise of the effusion and pericardial compliance. It is not necessarily impacted by the size of the effusion.[5,7] The pericardial sac can stretch to accommodate for an increase in intrapericardial fluid, but this increase in pericardial compliance will occur gradually.[3] The aforementioned physiology is the foundation for understanding the echocardiographic findings.

The earliest echocardiographic sign of tamponade is right atrial collapse during end-diastole and beginning of systole. It also is referred to as right atrial inversion or invagination (RAI).[3,5] Of all the chambers of the heart during the cardiac cycle, the lowest pressure is found in the right atrium during systole, approximately 3 - 5 mmHg.[6] The invagination of the right atrial wall is a passive response to the relative pressure on each side of the wall.[8] As IPP increases and exceeds right atrial pressure, the wall will collapse. Although echocardiographic sensitivity and specificity vary for RAI as a sign of tamponade, their values increase as the RAI increases in duration, especially when it is greater than one-third.[5,6,8] The optimal views for RAI visualization are the subxiphoid long-axis view and the apical four-chamber view.[5,6] In our case, the basic POCUS exam was looking for obvious pathology that might have been treatable via needle or medication; valvular pathology and gradients were formally assessed in the operating room with transesophageal echocardiography.

The echocardiographic sign of tamponade that carries the highest specificity is diastolic right ventricular collapse, also referred to as right ventricular inversion (RVI). The severity of tamponade correlates to the duration of RVI.[5] This finding follows the same physiological principle previously mentioned: chamber collapse simply reflects the relation of IPP to intracardiac pressures. The presence of RAI and RVI are dependent on intrinsic right heart pressures, and these signs may be absent in conditions such as pulmonary hypertension and tricuspid regurgitation.[7] The lack of any right-sided chamber collapse carries a 90% negative predictive value.[3]

The echocardiographic views for visualizing RVI are the apical four-chamber view, subxiphoid long-axis view, and the parasternal long-axis view[5]; in the parasternal long-axis view, RVI can specifically be appreciated with M-mode echocardiography, as it shows the most compliant right ventricle outflow tract.[7] Respirophasic variations in inferior vena cava diameter and mitral and tricuspid inflow velocities serve as surrogate measurements for assessing cardiac tamponade with the utilization of echocardiography. Although outside of the scope of this article, there is a review[6] that addresses this topic in-depth.

Septic shock and sepsis-related cardiogenic shock diagnoses also can be supported through ultrasound. Sepsis-related cardiogenic shock reports moderate depression in the left ventricular systolic function and normal left ventricular end-diastolic volume.[9] Using ultrasound for diagnosing septic shock allows for identifying characteristics of pleural effusion and the type of effusion based on the echogenicity pattern, or septa or empyema.[10] In our case, we could not rule out septic shock as a diagnosis because of the bacterial sepsis secondary to pneumonia that was identified after the patient expired. Additionally, the patient suffered cardiac arrest with return of spontaneous circulation after initial pericardiocentesis by the ED provider. Before a different diagnosis could be identified, and due to the emergent nature of the case, the patient was sent to the operating room for the pericardial winder via mini thoracotomy.

Just as clinical signs and symptoms do not serve as sole diagnostic indicators for cardiac tamponade, neither do ultrasonographic findings. As with all aspects of medical decision making, the physician incorporates clinical suspicion, maintains an evolving differential diagnosis, and incorporates all diagnostic measurements. While POCUS can serve as a powerful adjunct to the clinical examination, it should not be used as a substitute for or as equivalent to a comprehensive echocardiogram.[11] The cardiac POCUS exam has many protocols established, and it is intended to allow for rapid evaluation of reversible causes of shock, improve accuracy of diagnosis, and condense a differential diagnosis.[12]

One unique characteristic of this case report is that the patient underwent three variations of treatments for a pericardial effusion within a two-hour period. The patient underwent a blind pericardiocentesis, an ultrasound-guided pericardiocentesis, and a surgical pericardial window (a partial pericardiectomy) – none of which demonstrated a significant improvement in the patient's clinical status. While ultrasound-guided pericardiocentesis procedural methodology is beyond the scope of this article, Flint and Siegel[13] and Hatch et al.[14] go into a systematic, stepwise description.

This case report represents an example of anchoring bias – the tendency to place undue focus on a case's starting point, without adequate adjustment for new information. Anchoring bias occurs when there is not an adjustment to a differential diagnosis as new data emerges, possibly contradicting the initial presumptive diagnosis.[15] Despite the POCUS exams lacking evidence of tamponade physiology, and despite lack of improvement in hemodynamic stability post-procedures, the working diagnosis remained as shock secondary to cardiac tamponade. A large pericardial effusion in conjunction with a patient presenting in shock does warrant cardiac tamponade on a differential; however, lack of improvement following appropriate treatment should prompt re-evaluation of the diagnosis. Additionally, because the patient had a history of chronic pericardial effusions, anchoring bias may have played a large part in the treatment route. In this case, there were interdisciplinary discussions about whether the clinical picture and cardiac arrest were secondary to cardiac tamponade.

POCUS has gained wide acceptance among acute care physicians, as it facilitates the rapid diagnosis of several life-threatening conditions, potentially leading to changes in clinical decision-making.[11] In

this era of POCUS-driven care, it is imperative to remain cautious of anchoring bias to avoid incorrectly narrowing a differential diagnosis.

REFERENCES

[1] Fadl SA, Nasrullah A, Harris A, Edwards R, Kicska G. Comprehensive review of pericardial diseases using different imaging modalities. Int J Cardiovasc Imaging 2020; 36(5):947-969. PMID: 32048125.
[2] Azarbal A, LeWinter MM. Pericardial effusion. Cardiol Clin 2017; 35(4):515-524. PMID: 29025543.
[3] Wann S, Passen E. Echocardiography in pericardial disease. J Am Soc Echocardiogr 2008; 21(1):7-13. PMID: 18165123.
[4] Jones AE, Tayal VS, Sullivan DM, Kline JA. Randomized, controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of nontraumatic hypotension in emergency department patients. Crit Care Med 2004; 32(8):1703-1708. PMID: 15286547.
[5] Alerhand S, Carter JM. What echocardiographic findings suggest a pericardial effusion is causing tamponade? Am J Emerg Med 2019; 37(2):321-326. PMID: 30471929.
[6] Alerhand S, Adrian RJ, Long B, Avila J. Pericardial tamponade: A comprehensive emergency medicine and echocardiography review. Am J Emerg Med 2022; 58:159-174. PMID: 35696801.
[7] Appleton C, Gillam L, Koulogiannis K. Cardiac tamponade. Cardiol Clin 2017; 35(4):525-537. PMID: 29025544.
[8] Gillam LD, Guyer DE, Gibson TC, King ME, Marshall JE, Weyman AE. Hydrodynamic compression of the right atrium: A new echocardiographic sign of cardiac tamponade. Circulation 1983; 68(2):294-301. PMID: 6861307.
[9] Jardin F, Brun-Nay D, Auvert B, Beauchet A, Bourdarias JP. Sepsis-related cardiogenic shock. Crit Care Med 1990; 18(10):1055-1060. PMID: 2209030.
[10] Tullo G, Candelli M, Gasparrini I, Micci S, Franceschi F. Ultrasound in sepsis and septic shock - from diagnosis to treatment. J Clin Med 2023; 12(3):1185. PMID: 36769833.
[11] Douflé G, Teijeiro-Paradis R, Morales-Castro D, et al. Point-of-care ultrasound: A case series of potential pitfalls. CASE (Phila) 2022; 6(6):284-292. PMID: 36036054.
[12] Seif D, Perera P, Mailhot T, Riley D, Mandavia D. Bedside ultrasound in resuscitation and the rapid ultrasound in shock protocol. Crit Care Res Pract 2012; 2012:503254. PMID: 23133747.
[13] Flint N, Siegel RJ. Echo-guided pericardiocentesis: When and how should it be performed? Curr Cardiol Rep 2020; 22(8):71. PMID: 32572594.
[14] Hatch N, Wu TS, Barr L, Roque PJ. Advanced ultrasound procedures. Crit Care Clin 2014; 30(2):305-329, vi. Epub 2013 Dec 4. Erratum in: Crit Care Clin 2014; 30(4):xi. Barr, Laurel [added]; Roque, Pedro J [added]. PMID: 24606778.
[15] Beer L, Golub L, Smith DT. Diagnostic reasoning and decision making. In: McKean SC, Ross JJ, Dressler DD, Scheurer DB, editors. Principles and Practice of Hospital Medicine, 2e. McGraw Hill; 2017.

Keywords: point-of-care testing, ultrasonography, case reports, bias

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KANSAS JOURNAL of MEDICINE

Case Report

Central Venous Thrombosis Presenting with an Unknown Etiology: A Case Report

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INTRODUCTION

Central venous thrombosis (CVT), a blood clot in the dural venous sinuses of the brain, is a rare condition, accounting for less than 1% of all strokes. Despite its rarity, CVT carries a mortality rate of 5.5 - 18% even with treatment.[1] This case report highlights a patient with this potentially fatal condition who presented with only a headache and no neurological deficits. Clinicians should maintain a high index of suspicion for CVT, even in patients without traditional hypercoagulable risk factors.

CASE REPORT

A 43-year-old woman with a history of ocular migraines presented with a three-day history of waxing and waning headache, nausea, and vomiting. Her primary concern was that the headache differed in character and intensity from her usual ocular migraines. The headache was so debilitating that she was unable to complete her normal activities. It was severe, frontal, and associated with photophobia, phonophobia, nausea, and vomiting. Despite taking acetaminophen and ibuprofen at home, she experienced only mild relief. A few weeks prior, she and her daughter had a viral illness with conjunctivitis and vomiting. Differential diagnoses included migraine, intracranial mass, dural venous thrombosis, viral illness, hypertensive emergency, electrolyte abnormality, thyroid dysfunction, and pregnancy.

Upon presentation to the emergency department (ED), her vitals were notable for elevated blood pressure at 177/111 mmHg, a heart rate of 100 beats per minute, a respiratory rate of 16 breaths per minute, room air oxygen saturation of 97%, and a temperature of 36.6°C. Initial and repeat neurological examinations were reassuring, with no focal deficits. Cranial nerves II through XII were intact, sensation and motor function were equal, and gait was normal. She was treated with intravenous fluids, prochlorperazine, diphenhydramine, ketorolac, and magnesium for symptom management. A complete blood count (CBC), comprehensive metabolic panel (CMP), thyroid-stimulating hormone (TSH), magnesium, and phosphorus levels were ordered, all of which were unremarkable. There was no leukocytosis, electrolyte imbalance, or thyroid dysfunction contributing to her headache. A point-of-care urine pregnancy test (UHCG) was negative, and an infectious workup, including a respiratory viral panel, also was negative.

Given that the headache differed in character and intensity from her typical migraines and was unrelieved by home medications, a non-contrast head computed tomography (CT) was ordered immediately upon presentation. The CT was notable for an asymmetric hyperdensity of the left transverse and sigmoid sinus, raising concern for CVT (Figure 1). Additionally, there was a left peritentorial hyperdensity suggesting an adjacent thrombosed vein. A subsequent CT venogram with contrast confirmed an acute central venous sinus thrombosis involving the left transverse, sigmoid, and jugular sinuses (Figure 2). The patient was started on a heparin drip, and neurology was consulted. After evaluation, she was admitted to the neurology service for further assessment of the underlying cause of the CVT.

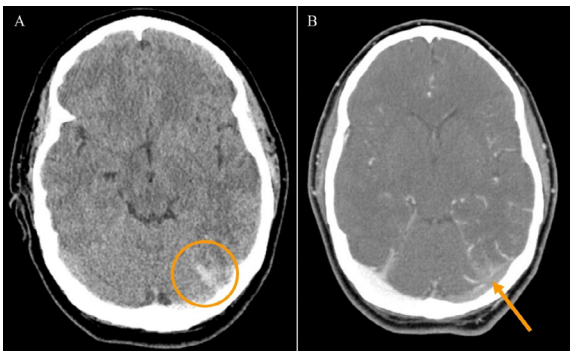

Figure 1. (A) CT head without contrast showing abnormal asymmetric hyperdensity involving the left transverse (orange circle) and sigmoid sinus. (B) CT venogram head with contrast showing acute CVT propagating from the sinus confluence through the left transverse (orange arrow) and sigmoid sinus.

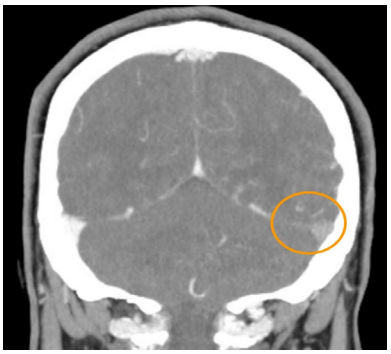

Figure 2. CT venogram with contrast head showing asymmetric filling defect in left transverse sinus (orange circle).

The following day, a repeat non-contrast head CT showed stable findings, and she was transitioned from heparin to apixaban. During her admission, hypercoagulable labs and additional imaging were conducted to investigate the cause of the thrombus. Tests for beta-2-glycoprotein and cardiolipin antibodies, factor 2 mutation, factor V Leiden mutation, protein C and S deficiencies, antithrombin III deficiency, lupus anticoagulant, and homocysteine levels were all negative. A CT of the chest, abdomen, and pelvis with contrast also was negative for malignancy. Upon discharge, the patient was instructed to continue anticoagulation with apixaban and to follow up with magnetic resonance imaging (MRI) with and without contrast.

Three months later, MRI showed significant recanalization of the sinuses. At her follow-up appointment with neurology, she was advised to discontinue apixaban, begin aspirin, and stay up-to-date with her annual SARS-CoV-2 vaccinations.

DISCUSSION

The cerebral sinuses are made up of the superficial and deep venous system that eventually drain into the internal jugular vein.[2] The superior sagittal and cavernous sinus are the major portions of the superficial venous system; and the deep system consists of the straight, transverse, and sigmoid sinuses. Multiple venous sinuses are involved in most patients diagnosed with a CVT.[2,3] Involvement of the straight sinus and deep venous system is more likely to present with altered consciousness or confusion.[3] Our patient was involved of her transverse and sigmoid sinuses. This is one potential reason why she remained alert and oriented with no change in mentation upon arrival to the ED.

The described patient presented with a headache worse and different in character from her typical migraines without papilledema or stroke-like symptoms. The clinical presentation of CVT is variable and somewhat dependent on the size of thrombus, sinuses affected, presence of collateral flow, and acuity of onset. About 40% of CVT patients present with stroke-like symptoms within 48 hours of symptom onset.[1] Persistent and/or progressively worsening headache is the most common presenting symptom, seen in 80 - 90% of cases, and can uncommonly be the only presenting symptom.[1-3] A case series of CVT presenting with isolated headache found that while the character of headache was not uniform, it tended to be severe, progressive, continuous, and different from the patients' usual migraines.[4] Papilledema has been reported in up to 85% of patients with acute or subacute onset and 100% of patients with chronic onset CVT.[2,3]

CVT is most common in women, comprising approximately 70% of cases, and is strongly associated with oral contraceptive use and pregnancy. However, numerous other prothrombotic risk factors have been implicated.[1,3] Median age of those affected is 30 to 41 years.[3] Rarely, there have been cases of CVT reported in patients without preexisting co-morbidities and a negative coagulation workup as in our patient. In several cases, an acute viral illness preceded the CVT by about seven days.[5] The SARS-CoV-2 virus has been identified in several previously healthy patients as a suggested agent for the creation of a hypercoagulable state. The virus' tropism for the ACE2 receptor on endothelial cells leads to endothelial damage and excessive clot formation.[6,7]

Another suggested mechanism of acute viral infection leading to CVT is the generation of a cytokine storm with subsequent endothelial damage and a prothrombotic state.[8] Adenovirus, one of the leading causes of conjunctivitis, is one virus capable of creating a cytokine storm.[9] Bacterial and fungal infections of the head and neck, including orbital cellulitis, paranasal sinusitis, and otitis media/mastoiditis, can also precede CVT.[1,10] Our patient lacked prothrombotic risk factors, but was endorsing viral symptoms, including conjunctivitis a few weeks prior to her ED presentation. Overall mortality is 5.5 - 18%, with severe or permanent disability in 6 - 10% of surviving patients.[1] Most patients have a favorable prognosis after treatment.[1,3]

Neuroimaging is considered the gold standard diagnostic tool and is required for formal diagnosis and CVT localization.[2] CT is the initial imaging modality of choice for most patients with non-specific neurological symptoms, primarily due to how rapidly it can be acquired.[11] Findings on CT include hyperattenuation of the affected venous sinus, dense clot sign, and indirect signs such as cerebral edema, mass effect, and hemorrhage.[2,11] However, Cumurciuc et al.[4] and Timóteo et al.[12] noted that non-contrast CT examination was normal in 40% of patients, who presented with isolated headache, but ultimately had a CVT. This finding suggests that CT and MRI venogram should be considered to evaluate for filling defects in patients presenting with severe headache and an initial negative workup. These imaging modalities may show evidence of collateralization to bypass the occluded segment(s).[13]

Although 57 - 86% of treated patients make a full recovery, mortality is still as high as 18%.[1] Potential risk factors for increased mortality include age (infancy or elderly), altered mental status, GCS <9, coma, ICH, malignancy, deep vein thrombosis, and hyperglycemia.[1] The ultimate cause of death for patients diagnosed and treated for a CVT are herniation, status epilepticus, and pulmonary embolism.[1]

CONCLUSIONS

CVT often occurs in the presence of hypercoagulability, malignancy, or viral illness. Due to an unremarkable hypercoagulable and malignant work up, etiology of our patient's CVT is unknown and suspected to be related to viral illness. It is important for ED providers to consider CVT for patients presenting with a headache and normal neurologic exam.

REFERENCES

1 Ranjan R, Ken-Dror G, Sharma P. Pathophysiology, diagnosis and management of cerebral venous thrombosis: A comprehensive review. Medicine (Baltimore) 2023; 102(48):e36366. PMID: 38050259.
2 Idiculla PS, Gurala D, Palanisamy M, Vijayakumar R, Dhandapani S, Nagarajan E. Cerebral venous thrombosis: A comprehensive review. Eur Neurol 2020; 83(4):369-379. PMID: 32877892.
3 Luo Y, Tian X, Wang X. Diagnosis and treatment of cerebral venous thrombosis: A review. Front Aging Neurosci 2018; 10(2). PMID: 29441008.
4 Cumurciuc R, Crassard I, Sarov M, Valade D, Bousser MG. Headache as the only neurological sign of cerebral venous thrombosis: A series of 17 cases. J Neurol Neurosurg Psychiatry 2005; 76(8):1084-1087. PMID: 16024884.
5 Kallel N, Saidani A, Kotti A, et al. Coronavirus disease 19 (COVID-19) and Cerebral venous sinus thrombosis (CVST): A case series and review of the literature. Clin Case Rep 2022; 10(8):e6143. PMID: 35957796.
6 Bolaji P, Kukoyi B, Ahmad N, Wharton C. Extensive cerebral venous sinus thrombosis: A potential complication in a patient with COVID-19 disease. BMJ Case Reports 2020; 13:e236820. PMID: 32784243.
7 Abdulgayoom M, Abdelmahmuod E, Elfaki A, Halabiya MA. Cerebral venous sinus thrombosis as an unexpected complication of COVID-19 pneumonia. Cureus 2021; 13(7):e16498. PMID: 34430113.
8 Asif R, O' Mahony MS. Rare complication of COVID-19 presenting as isolated headache. BMJ Case Rep 2020; 13(10):e239275. PMID: 33122242.
9 Solano D, Fu L, Czyz CN. Viral conjunctivitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. 2023 Aug 28. PMID: 29262100.
10 Korathanakhun P, Petpichetchian W, Sathirapanya P, Geater SL. Cerebral venous thrombosis: Comparing characteristics of infective and non-infective aetiologies: A 12-year retrospective study. Postgrad Med J 2015; 91(1082):670-674. PMID: 26499451.
11 Dmytriw AA, Song JSA, Yu E, Poon CS. Cerebral venous thrombosis: State of the art diagnosis and management. Neuroradiology 2018; 60(7):669-685. PMID: 29752489.
12 Timóteo Â, Inácio N, Machado S, Pinto AA, Parreira E. Headache as the sole presentation of cerebral venous thrombosis: A prospective study. J Headache Pain 2012; 13(6):487-490. PMID: 22592865.
13 Barboza MA, Mejías C, Colin-Luna J, Quiroz-Compean A, Arauz, A. Intracranial venous collaterals in cerebral venous thrombosis: Clinical and imaging impact. J Neurol Neurosurg Psychiatry 2015; 86(12):1314-1318. PMID: 25589781.

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Review

Pigmented Villonodular Synovitis: A Critical Review

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INTRODUCTION

Pigmented villonodular synovitis (PVNS), also recognized as tenosynovial giant cell tumor (TGCT) or giant cell tumor of the tendon sheath (GCTTS), represents a benign, but locally aggressive neoplastic process that involves the synovial lining of joints. PVNS, TGCT, and GCTTS are essentially identical in clinical presentation and histology. This disease process likely occurs along a spectrum of severity; however, it is typically categorized into a local or diffuse form. Localized disease is often considered to comprise a well circumscribed soft tissue mass involving only a portion of the synovium; in diffuse disease, an ill-defined soft tissue mass is observed with involvement of most or all the joint synovia. The proliferation of synovial tissue and inflammation that occur with this condition most often presents with swelling, pain, decreased range of motion, and stiffness. This can produce rapid destruction of the articular cartilage and lead to early osteoarthritis (OA).

Believed to be the first reported case of TGCT, Chassaignac in 1852 described a nodular lesion of the synovial membrane of the flexor tendons in the fingers. This was originally thought to be a neoplastic process given its growth pattern and capacity to erode surrounding bone and joint tissue, as well as a high recurrence rate after resection. However, that assumption was brought into question in 1941 when Flandry et al.[1] and Tyler et al.[2] described this disease as an inflammatory process and proposed the term pigmented villonodular synovitis. More recent studies demonstrating clonal chromosomal aberrations have established the pathogenesis as neoplastic in origin.[3,4]

Etiology

In 2006, West et al.[5] provided a breakthrough in understanding the etiology and pathogenesis contributing to PVNS by confirming that translocations involving 1p11-13 are present in most patients with PVNS and demonstrated that colony stimulating factor-1 (CSF-1) is the gene located at this chromosome breakpoint. West et al.[5] found that 23 of 30 patients with TCGT and 5 of 8 patients with PVNS had a CSF-1 translocation, but only 2 - 16% of the tumor cells carried the translocation and expressed CSF-1. This suggests that only a minority of cells are neoplastic and that the majority of intratumoral cells are reactive, non-neoplastic cells, recruited by the local overexpression of CSF-1. A better understanding of the molecular pathways involved with PVNS has led to potential targets for medical management of this disease. Further understanding may generate future molecular targets for medications.

Clinical Presentation and Natural History

PVNS can be found throughout the body, but it is usually the large joints that are chiefly involved.[6,7] Of the large joints, the knee is the most frequently affected by a significant margin. In a study of 237 consecutive patients with a PVNS diagnosis, Xie et al.[7] demonstrated that 74% of cases involved the knee, 18% involved the hip, 3% involved the ankle or wrist, and 1% involved the shoulder or elbow. Rare locations for PVNS include the temporomandibular joint (TMJ) and the spine.[8,9] Localized PVNS in the knee can present in any area of the synovial tissue, however, most lesions will arise in the suprapatellar pouch, or Hoffa's fat pad.[10] For diffuse disease, lesions are predominantly found intra-articularly and mainly affect the knee.[6,7,10] Patients typically present in the third to fifth decades of life with an insidious onset of joint pain, swelling, and stiffness. Recurrent hemarthroses may also occur.[6,11] Rarely patients may present with mechanical symptoms. For superficial locations, a soft mass may be palpable on exam. Occasionally, a history of localized trauma may be reported. Gender predominance has varied in the literature. Initial radiographs often are normal in the early stages of disease, and with nonspecific symptoms, patients may be symptomatic for extended periods of time before diagnosis. One study found a mean delay from symptom onset to diagnosis to be 55 months.[12] This demonstrates the importance of considering PVNS in the differential for patients who present with joint swelling and/or joint pain.

PVNS may become symptomatic, thus limiting the activity and function of patients. The localized form typically is considered less aggressive than the diffuse type, and greater success has been observed when treating localized disease. In contrast, the diffuse type tends to be more aggressive, having a more rapidly destructive course, resulting in a poorer prognosis. While the continued presence or recurrence of PVNS in any joint can lead to cartilage destruction, this is more apparent in the hip joint. The progression of cartilage destruction and lytic lesions on both sides of the joint ultimately leads to significant arthritis.[11]

Diagnosis

Accurately diagnosing PVNS often is challenging as patients typically present with nonspecific symptoms of joint pain and swelling, and the prevalence of PVNS is low compared to other conditions that result in identical presenting symptoms. Patients routinely are misdiagnosed with other conditions, such as rheumatologic disorders, trauma, meniscus injuries, or infection, prior to a diagnosis of PVNS. Flandry et al.[13] found that only 17% of patients were correctly diagnosed with PVNS prior to referral. In general, PVNS should be considered in the differential in any inflammatory arthritis. If patients do not respond to initial treatment, more diagnostic workup should be considered to rule out PVNS.[14]

Multiple imaging modalities are frequently used to help diagnose PVNS, while excluding other conditions to narrow the diagnosis. Radiographs often are the first imaging study obtained (Figure 1). In most cases, radiographs reveal nonspecific features including soft tissue swelling, joint effusion, degenerative joint disease, or a normal appearance.[15-18] Well defined erosions with relative preservation of joint

space may be noted in early phases of the disease. Cystic lesions, often symmetric on either side of the joint line in a non-weight-bearing region of the joint, or at the capsular insertion site, without calcification, may be suggestive of PVNS. With progression of the disease, joint space narrowing may occur concentrically, especially when involving joints with minimal volume capacity such as the hip.[5,17]

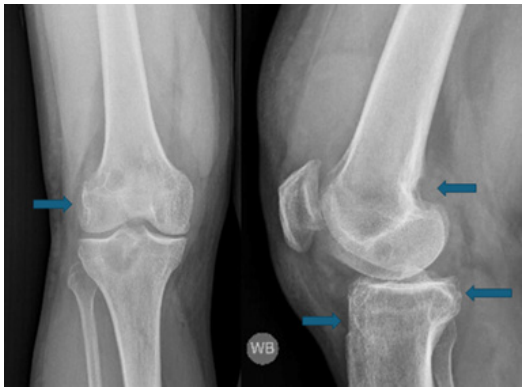

Figure 1. X-ray of right knee demonstrating pigmented villonodular synovitis. Anterior-Posterior (Left) and Lateral (Right) views demonstrating multiple erosions in the lateral femoral condyle and proximal tibia, large joint effusion, and degenerative changes.

Magnetic resonance imaging (MRI) often is the imaging study of choice to further evaluate a patient with nonspecific symptoms of joint pain, intermittent swelling, and possible mechanical symptoms. Not only can an MRI assist in ruling out more common etiologies for these nonspecific symptoms at presentation, but there are pathognomonic features present on MRI which highly suggest PVNS as the diagnosis (Figure 2). The signal characteristics observed on MRI reflect the histological composition of the diseased tissue, particularly the hemosiderin deposition, lipids, fibrous stroma, and inflammatory cells. This is represented as nodular masses with heterogeneous low signal intensity on both T1 and T2 weighted sequences with blooming artifact. This "blooming artifact," which is most characteristic of PVNS, is best appreciated on gradient echo sequences and represents the increased signal dropout from the presence of hemosiderin. MRI also plays an instrumental role in determining localized versus diffuse forms, as well as the extent and specific location of the lesion. This information is important for treatment strategy and possible surgical planning.[15,18,19] Although MRI can be extremely helpful in suggesting the diagnosis of PVNS, histologic confirmation with a tissue biopsy remains the gold standard.

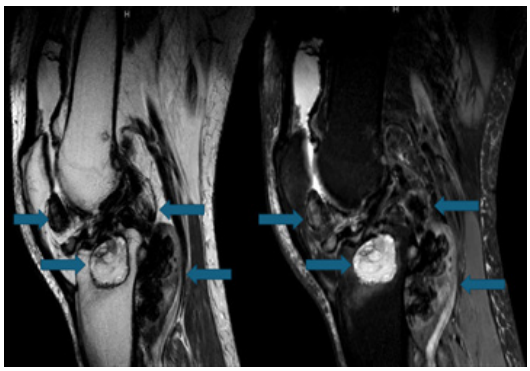

Figure 2. MRI of right knee demonstrating pigmented villonodular synovitis. T1 (Left) and T2 (Right) sagittal sequences showing nodular masses diffusely in both the anterior and posterior compartments of the knee with heterogenous low signal intensity. A large joint effusion and large tibial cyst are also noted.

Management

Surgical

Localized PVNS. Numerous treatment regimens exist in the management of localized PVNS, including observation with serial imaging, open excision, arthroscopic excision, or combined arthroscopic and open excision. With advancements in arthroscopic techniques, arthroscopic partial synovectomy is considered the preferred surgical option. The primary aim of surgical management is to resect all the diseased synovium to prevent local recurrence and reduce the risk of OA. Much of the current literature focuses on treatment outcomes for the knee as this is the most involved joint. Multiple studies involving surgical treatment of the knee have demonstrated excellent results. A systematic review performed by Auregan et al.[20] demonstrated low recurrence rates of disease (8.7% and 6.9%) and low complication rates (<1% and 0%) with no significant differences between open synovectomy and arthroscopic synovectomy, respectively. A more recent case series by Patel et al.[10] similarly demonstrated no significant difference in recurrence rates between open and arthroscopic synovectomy, respectively (8.7% vs 9.1%). Additionally, excellent functional results are likely to be observed after surgical treatment. Dines et al.[21] showed a mean post-operative Lysholm score of 95.4 for patients treated with arthroscopic synovectomy at least five years of follow-up. All patients had full range of motion of their knee and had no concerns of pain, locking, clicking, or swelling. Despite low recurrence rates with arthroscopic treatment, concern for recurrence exists, principally with posterior based lesions. This is a result of the technically challenging nature of an arthroscopic posterior synovectomy due to anatomical blind spots when viewing this space from an anterior portal. However, newer arthroscopy techniques have been described to help visualize the knee's posterior compartment.[22] In localized disease of the posterior compartment of the knee in 10 patients who underwent arthroscopic synovectomy, Shekhar et al.[23] demonstrated no recurrence of disease or symptoms and a mean International Knee Documentation Committee subjective score of 85 post-operatively. For surgeons with less arthroscopy experience, an arthroscopic assisted mini open partial synovectomy can be considered as a safe alternative. Georgiannos et al.[24] compared an arthroscopically assisted mini open technique to an all-arthroscopic technique and found similar post-operative Lysholm scores, as well as recurrence rates between the techniques.

Treatment efficacy in other joints with localized PVNS have not been as well studied to date as the knee. However, available studies have demonstrated similar results to that found for arthroscopic treatment of lesions in the knee.[25-27] In a recent large multicenter database study by Mastboom et al.[28] on localized PVNS of large joints, they demonstrated no significant difference in recurrence rates on multivariate analysis when comparing arthroscopic to open treatment. A lesion size of >5 cm was found to result in a significant increase in recurrence of disease.

Overall, both open and arthroscopic excision of localized PVNS lesions produce good to excellent outcomes with low recurrence and

complication rates. Initial treatment with arthroscopy, however, may tend to be favored in many cases with an experienced arthroscopist as lower rates of morbidity, pain, and stiffness may be associated with arthroscopic compared to open treatment.

Diffuse PVNS. Best treatment practices for diffuse PVNS of large joints remain controversial. Higher rates of disease recurrence are routinely reported despite varying surgical treatment options when compared to treatment of localized disease. In a meta-analysis by Mollon et al.,[29] they demonstrated that patients with localized PVNS treated surgically had a recurrence rate of 7% compared to 28% in patients treated surgically with diffuse disease. Several studies have sought to determine the efficacy of arthroscopic versus open versus a combined approach with results having varied significantly throughout the literature. Regardless of treatment approach, complete resection is required to reduce the likelihood of recurrence. Patel et al.[10] demonstrated in 102 patients treated operatively for diffuse PVNS of the knee, a significantly higher rate of recurrence with arthroscopic treatment compared to open synovectomy (83.3% vs 44.8%). It also was noted that most complications occurred in patients who underwent an open procedure. In contrast, multiple case series have demonstrated good to excellent results following arthroscopic treatment for diffuse PVNS of the knee, with low recurrence and complication rates reported at final follow up.[30,31] It is important when performing an arthroscopic synovectomy for diffuse disease to utilize multiple accessory portals. The advantages of performing an isolated arthroscopic synovectomy include minimizing post-operative stiffness, shorter rehabilitation period, and fewer wound complications.[32] Other comparison studies have demonstrated no significant difference in recurrence rates between arthroscopic and open synovectomy. A systematic review by Auregan et al.[20] for diffuse PVNS of the knee found no significant difference in recurrence rates between arthroscopic compared to open synovectomy (16.1% vs 22.6%), with a significant difference in complication rates which favored arthroscopy (0 vs 19%). A more recent meta-analysis by Chandra et al.[33] demonstrated a 1.56 times higher rate of recurrence for diffuse PVNS of the knee when treated arthroscopically compared to an open approach. Some surgeons have performed a combined arthroscopic and open approach which has demonstrated potentially more promising results for diffuse disease. Mollon et al.[34] demonstrated a recurrence rate of 13% in 15 patients with good to excellent outcomes in all patients treated with combined arthroscopic and open synovectomy for diffuse disease. Colman et al.[35] compared a series of patients treated with combined arthroscopy and open synovectomy to patients treated with just arthroscopy or open synovectomy alone and found that recurrence rate for the combined group was significantly lower at 9% compared to 62% and 64%, respectively.

Again, limited data are available for treatment outcomes of PVNS involving other large joints. Nazal et al.[26] reported on a small series of five patients with diffuse type PVNS of the hip treated with arthroscopic synovectomy. No recurrence of disease was reported, and outcome scores were lower than patients treated arthroscopically for localized disease, however, this was not significantly different. Byrd et al.[25] reported good to excellent outcomes in patients treated arthroscopically for PVNS of the hip. The mean Harris Hip Score (HHS) improved from 62 pre-op to 89 post-op (scores <70 poor, 70 - 80 fair, 80 - 90 good, 90 - 100 excellent). Three of these patients had diffuse PVNS with a mean improvement of 38 points in the HHS. A systematic review by Siegel et al.[27] evaluating patients with PVNS of the foot and ankle treated with either open or arthroscopic synovectomy demonstrated a recurrence rate of 21% which is comparable to the results for other joints in the literature. However, the complication rate was higher than that seen in other joints at 24%. One explanation for the increased complications in treatment of the foot and ankle may be related to the poorer blood circulation compared to other large joints which may impact the healing potential. Additionally, there is a tendency to perform an open rather than arthroscopic procedure which may trend towards an increase in the complication rate.

Radiation

Radiation therapy either alone or as an adjuvant therapy following operative treatment may be considered in an attempt to reduce recurrence rates of disease. Results have been mixed, and the side effect profile of radiation must be considered as well. O'Sullivan et al.[36] published one of the earlier reports on utilizing external beam radiation in patients with PVNS. In this study the recurrence rate was 7% which is comparable or better than other studies in the literature. Additionally, most patients experienced good to excellent functional outcomes. Similar results were found by Chien et al.[37] in patients with diffuse PVNS of the knee treated with open synovectomy followed by moderate radiation dose therapy in which the recurrence rate was 8.3% compared to 57% in patients treated with open synovectomy alone. These results, however, were not reproducible for their patients treated with arthroscopic synovectomy. Sun et al.[38] compared outcomes of patients with PVNS of the hip who underwent arthroscopic synovectomy to those who underwent arthroscopic synovectomy plus adjuvant radiotherapy. They found that hip outcomes scores and Visual Analog Scale pain scores were comparable between the two groups and no patients who underwent adjuvant radiotherapy converted to total hip arthroplasty (THA) compared to 38% in the group without radiotherapy. Despite some promising results, caution must be taken when considering this adjunct as radiation is not a benign therapy. Radiation induced sarcoma or significant wound complications can develop.[37,39] It is unknown whether the potential benefit of radiation therapy following synovectomy outweighs its potential complications in the treatment of a benign process.

Medical Management

With significant advances in molecular biology and an improvement in the understanding of underlying molecular pathways involved in various conditions, medicines are being developed to act specifically on these targets. The discovery of overexpression of CSF-1 as the etiology which chiefly contributes to the development of PVNS, has provided a molecular target for potential medical management of this condition.

Pexidartinib. Pexidartinib acts as a CSF-1 receptor inhibitor, thereby restricting PVNS growth.[40-42] In a phase three randomized

clinical trial[41] (ENLIVEN study) of 120 patients (61 receiving pexidartinib, 59 receiving Placebo) with symptomatic, advanced PVNS in which surgery was not recommended, patients who received pexadartinib demonstrated improved outcomes of their disease compared to placebo. The overall response rate of the disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) was 39% in the pexidartinib group compared to 0% for placebo at 25 weeks. Additionally, the pexadartinib group demonstrated a significant improvement in physical functioning compared to placebo.[41] Given these notable benefits, this became the first FDA approved drug specifically for the treatment of PVNS. Despite significant benefits, adverse events occurred in 98% of patients who received pexidartinib with the most common event being hair color changes. Grade three (severe) or four (life-threatening) adverse events did occur in 44% of patients, which were often increases in liver enzymes. Serious hepatotoxic side effects were experienced by eight people taking pexidartinib, however, three people recovered after discontinuing the medication.[41] As a result, this medication is currently only available in the U.S. via the Risk Evaluation and Mitigation Strategy (REMS) Program.[40]

Patients considered candidates for this medication are predominantly those with inoperable diffuse disease or in which surgical resection would be associated with worsening function and would likely cause severe morbidity.[41,43] This medication is available as an oral capsule, with a recommended dosage of 250 mg twice daily.[44,45] Continued use of pexidartinib is indicated until evidence of either disease progression or drug toxicity occurs. Ongoing monitoring via frequent liver testing is required.[40-42] Studies evaluating outcomes following operative management with adjuvant medical therapy have yet to be performed.

Imatinib. Imatinib acts as an inhibitor of macrophage colony stimulating factor (M-CSFR) activation of non-neoplastic PVNS cells.[46] Most commonly utilized for chronic myeloid leukemia and gastrointestinal stromal tumors, the effect of imatinib on PVNS was first reported on a single patient. Blay et al.[46] first reported the use of imatinib in a patient with PVNS with promising initial results from a case report demonstrating complete remission by the fifth month after starting imatinib. The course of treatment was interrupted a few months later with observed disease relapse, but a second complete remission was documented shortly after re-introducing imatinib.[46] In a study of 62 patients with PVNS, Verspoor et al.[47] demonstrated an overall response rate of disease based on RECIST of 31% in those taking imatinib. Additionally, symptom improvement was found in 78% of patients.

Use of this medication is reserved for those with symptomatic recurrence of PVNS following surgery, or in instances where surgical re-excision would detrimentally affect function.[46-48] It is available as an oral tablet, with recommended dose of either 100 mg, 400 mg, or 600 mg once daily. Optimal treatment duration has yet to be elucidated. Continued use is indicated without progression of disease or evidence of drug toxicity. The most common adverse effects are edema, muscle cramping, musculoskeletal pain, abdominal pain, nausea, vomiting, diarrhea, rash, or fatigue.[47,48]

Salvage. The goal of treatment in patients with PVNS is to reduce symptoms, improve clinical outcomes, minimize recurrence rates, and decrease the risk of cartilage and soft tissue destruction that leads to early OA and ultimately worsening pain and function. Total joint arthroplasty can be considered as a salvage option for significant recurrent disease with associated degenerative changes and if all other options have failed.[49,50] While data are limited, some promising results have been observed following hip and knee arthroplasty in patients with PVNS.[51,52] Houdek et al.[51] presented a series of 48 patients with PVNS who underwent total knee arthroplasty (TKA). The local recurrence rate of disease was 13%. They found that patients who had undergone at least two procedures to remove PVNS from the knee were significantly more likely to have recurrence following TKA. The overall 10-year revision free survival rate was 80%. Revisions were most performed for tumor recurrence and component loosening. The complication rate of 52% is notably higher compared to patients who undergo TKA for primary OA with most complications being related to joint stiffness.[51] Casp et al.[53] also demonstrated a significantly increased rate of stiffness in patients with PVNS who underwent TKA compared to a control matched cohort of patients with primary OA (6.8% vs 4.7%), although the overall rates were significantly lower than the previously mentioned study. The infection rate also was found to be higher at two years at 3.3% in patients with PVNS compared to 1.5% in the OA group, although rates of ER visits, hospital readmission, revision TKA at two years and death at one year were not found to be significantly different between the matched groups.[53]

Despite a paucity of literature, results of THA in patients with hip PVNS are encouraging. Xu et al.[54] compared 19 patients with PVNS who underwent a THA to matched controls and found no significant difference between groups with respect to revision rates and HHS at final follow-up. Additionally, there was no evidence of recurrence of disease in the PVNS cohort.[54] Tibbo et al.[11] also demonstrated good outcomes in 25 patients with PVNS who underwent THA. Only one patient was noted to have disease recurrence, which was determined at 24 years post-operatively. However, a high complication rate was noted in this study, which was most commonly aseptic loosening. All patients with aseptic loosening were noted to have uncross-linked polyethylene components. In contrast, all patients with highly cross-linked polyethylene liners did not demonstrate any loosening for a survivorship free of revision at 10 years of 100%. The mean HHS at final follow-up was 78, significantly improved from pre-operative scores.[11] Overall, the available literature demonstrates good outcomes in patients with PVNS who undergo total joint arthroplasty as a salvage option for treatment. However, surgeons should remain cautious about complications, as this has routinely been found to be higher in this patient population.

Summary

PVNS represents a benign neoplastic process that involves the synovial lining of joints, most commonly affecting the knee when involving the large joints. This disease process occurs along a spectrum of severity, divided into localized and diffuse forms. The proliferation of synovial tissue and inflammation that occurs with this condition may present with swelling, pain, and stiffness. These non-specific symptoms, as well as the limited occurrence of this disease process, often leads to a delay in

initial diagnosis and treatment. Advanced imaging with MRI is helpful in suggesting a diagnosis of PVNS, but histology is necessary to confirm the diagnosis.

Best management practices for the treatment of PVNS have yet to be elucidated at this time and may vary depending on the extent of the disease. Both arthroscopic and open synovectomy have been found to be effective for the treatment of localized disease, with a potential preference to arthroscopic synovectomy given low complication rates and good functional outcomes after the procedure. Controversy remains for diffuse disease treatment as outcomes have varied amongst studies. Medical therapy with pexidartinib or imatinib may be considered as stand-alone therapy, an adjunct therapy to surgery, or for patients who are not surgical candidates. More investigation is required to optimize their effect while minimizing the side effect profile. If these methods fail to treat the disease process, promising results have been observed with total joint arthroplasty in patients who develop severe or recurrent disease and progress to significant OA, although a higher rate of complications has been observed compared to total joint arthroplasty for primary OA.

REFERENCES

[1] Flandry F, Hughston JC. Pigmented villonodular synovitis. J Bone Joint Surg Am 1987; 69(6):942-949. PMID: 3597511.
[2] Tyler WK, Vidal AF, Williams RJ, Healey JH. Pigmented villonodular synovitis. J Am Acad Orthop Surg 2006; 14(6):376-385. PMID: 16757677.
[3] Nilsson M, Höglund M, Panagopoulos I, et al. Molecular cytogenetic mapping of recurrent chromosomal breakpoints in tenosynovial giant cell tumors. Virchows Arch 2002; 441(5):475-480. PMID: 12447678.
[4] Sciot R, Rosai J, Dal Cin P, et al. Analysis of 35 cases of localized and diffuse tenosynovial giant cell tumor: A report from the Chromosomes and Morphology (CHAMP) study group. Mod Pathol 1999; 12(6):576-579. PMID: 10392632.
[5] West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci U S A 2006; 103(3):690-695. PMID: 16407111.
[6] Ottaviani S, Ayral X, Dougados M, Gossec L. Pigmented villonodular synovitis: A retrospective single-center study of 122 cases and review of the literature. Semin Arthritis Rheum 2011; 40(6):539-546. PMID: 20884045.
[7] Xie GP, Jiang N, Liang CX, et al. Pigmented villonodular synovitis: A retrospective multicenter study of 237 cases. PLoS One 2015; 10(3):e0121451. doi: 10.1371/journal.pone.0121451. PMID: 25799575.
[8] Roguski M, Safain MG, Zerris VA, et al. Pigmented villonodular synovitis of the thoracic spine. J Clin Neurosci 2014; 21(10):1679-1685. PMID: 24938389.
[9] Wang DD, Luo HY, Guo CB, Meng JH. Clinical and immunohistochemical analysis of diffuse tenosynovial giant cell tumour of the temporomandibular joint. Int J Oral Maxillofac Surg 2020; 49(7):882-888. PMID: 32014315.
[10] Patel KH, Gikas PD, Pollock RC, et al. Pigmented villonodular synovitis of the knee: A retrospective analysis of 214 cases at a UK tertiary referral centre. Knee 2017; 24(4):808-815. PMID: 28442184.
[11] Tibbo ME, Wyles CC, Rose PS, Sim FH, Houdek MT, Taunton MJ. Long-term outcome of hip arthroplasty in the setting of pigmented villonodular synovitis. J Arthroplasty 2018; 33(5):1467-1471. PMID: 29352684.
[12] Ma X, Shi G, Xia C, Liu H, He J, Jin W. Pigmented villonodular synovitis: A retrospective study of seventy-five cases (eighty-one joints). Int Orthop 2013; 37(6):1165-1170. PMID: 23503697.
[13] Flandry F, Hughston JC, McCann SB, Kurtz DM. Diagnostic features of diffuse pigmented villonodular synovitis of the knee. Clin Orthop Relat Res 1994; (298):212-220. PMID: 8118978.
[14] Willimon SC, Busch MT, Perkins CA. Pigmented villonodular synovitis of the knee: An underappreciated source of pain in children and adolescents. J Pediatr Orthop 2018; 38(8):e482-e485. PMID: 23503697.
[15] Al-Nakshabandi NA, Ryan AG, Choudur H, et al. Pigmented villonodular synovitis. Clin Radiol 2004; 59(5):414-420. PMID: 15081846.
[16] Friedman T, Chen T, Chang A. MRI diagnosis of recurrent pigmented villonodular synovitis following total joint arthroplasty. Hss j 2013; 9(1):100-105. PMID: 24426852.
[17] Gouin F, Noailles T. Localized and diffuse forms of tenosynovial giant cell tumor (formerly giant cell tumor of the tendon sheath and pigmented villonodular synovitis). Orthop Traumatol Surg Res 2017; 103(1s):S91-s97. PMID: 28057477.
[18] Murphey MD, Rhee JH, Lewis RB, Fanburg-Smith JC, Flemming DJ, Walker EA. Pigmented villonodular synovitis: Radiologic-pathologic correlation. Radiographics 2008; 28(5):1493-1518. PMID: 18794322.
[19] Lin J, Jacobson JA, Jamadar DA, Ellis JH. Pigmented villonodular synovitis and related lesions: The spectrum of imaging findings. AJR Am J Roentgenol 1999; 172(1):191-197. PMID: 9888766.
[20] Aurégan JC, Klouche S, Bohu Y, Lefèvre N, Herman S, Hardy P. Treatment of pigmented villonodular synovitis of the knee. Arthroscopy 2014; 30(10):1327-1341. PMID: 24999007.
[21] Dines JS, DeBerardino TM, Wells JL, et al. Long-term follow-up of surgically treated localized pigmented villonodular synovitis of the knee. Arthroscopy 2007; 23(9):930-937. PMID: 17868831.
[22] Moran J, Miller MD, Schneble CA, Yalcin S, Katz LD, Medvecky MJ. Arthroscopic synovectomy for tenosynovial giant cell tumor/pigmented villonodular synovitis in the posterior knee using the posterior trans-septal portal technique. JBJS Essent Surg Tech 2022; 12(1). PMID: 35685235.
[23] Shekhar A, Patil SS, Dixit C, Tapasvi SR. Localized pigmented villonodular synovitis of posterior compartment of the knee. J Orthop Surg (Hong Kong) 2017; 25(3):2309499017727923. PMID: 28847242.
[24] Georgiannos D, Boutsiadis A, Agathangelidis F, Papastergiou S, Karataglis D, Bisbinas I. Arthroscopically-assisted mini open partial synovectomy for the treatment of localized pigmented villonodular synovitis of the knee. A retrospective comparative study with long-term follow up. Int Orthop 2017; 41(5):925-930. PMID: 27866235.
[25] Byrd JW, Jones KS, Maiers GP, 2nd. Two to 10 Years' follow-up of arthroscopic management of pigmented villonodular synovitis in the hip: A case series. Arthroscopy 2013; 29(11):1783-1787. PMID: 24209675.
[26] Nazal MR, Parsa A, Gibbs JS, Abraham PF, Martin SD. Mid-term results of arthroscopic synovectomy for pigmented villonodular synovitis of the hip. Arthroscopy 2020; 36(6):1587-1598. PMID: 32061973.
[27] Siegel M, Bode L, Südkamp N, et al. Treatment, recurrence rates and follow-up of tenosynovial giant cell tumor (TGCT) of the foot and ankle-A systematic review and meta-analysis. PLoS One 2021; 16(12):e0260795. PMID: 34855875.
[28] Mastboom MJL, Staals EL, Verspoor FGM, et al. Surgical treatment of localized-type tenosynovial giant cell tumors of large joints: A study based on a multicenter-pooled database of 31 international sarcoma centers. J Bone Joint Surg Am 2019; 101(14):1309-1318. PMID: 31318811.
[29] Mollon B, Lee A, Busse JW, et al. The effect of surgical synovectomy and radiotherapy on the rate of recurrence of pigmented villonodular synovitis of the knee: an individual patient meta-analysis. Bone Joint J 2015; 97-b(4):550-557. PMID: 25820897.
[30] Cheng YH, Lin YH, Tseng IC, Chan YS. A case series of intra-articular diffuse pigmented villonodular synovitis of the knee: Prognosis of complete synovectomy under arthroscopic surgery. J Orthop Surg (Hong Kong) 2021; 29(2):23094990211022042. PMID: 34114516.
[31] Keyhani S, Kazemi SM, Ahn JH, Verdonk R, Soleymanha M. Arthroscopic treatment of diffuse pigmented villonodular synovitis of the knee: Complete synovectomy and septum removal-midterm results. J Knee Surg 2019; 32(5):427-433. PMID: 29727868.
[32] Chang JS, Higgins JP, Kosy JD, Theodoropoulos J. Systematic arthroscopic treatment of diffuse pigmented villonodular synovitis in the knee. Arthrosc Tech 2017; 6(5):e1547-e1551. PMID: 29354472.
[33] Chandra AA, Agarwal S, Donahue A, Handorf E, Abraham JA. Arthroscopic versus open management of diffuse-type tenosynovial giant cell tumor of the knee: A meta-analysis of retrospective cohort studies. J Am Acad Orthop Surg Glob Res Rev 2021; 4(12). PMID: 34882586.
[34] Mollon B, Griffin AM, Ferguson PC, Wunder JS, Theodoropoulos J. Combined arthroscopic and open synovectomy for diffuse pigmented villonodular synovitis of the knee. Knee Surg Sports Traumatol Arthrosc 2016; 24(1):260-266. PMID: 25308157.

[35] Colman MW, Ye J, Weiss KR, Goodman MA, McGough RL, 3rd. Does combined open and arthroscopic synovectomy for diffuse PVNS of the knee improve recurrence rates? Clin Orthop Relat Res 2013; 471(3):883-890. PMID: 22996360.
[36] O'Sullivan B, Cummings B, Catton C, et al. Outcome following radiation treatment for high-risk pigmented villonodular synovitis. Int J Radiat Oncol Biol Phys 1995; 32(3):777-786. PMID: 7790264.
[37] Chien JC, Wei YP, Chen CY, et al. Long-term functional outcomes of diffuse pigmented villonodular synovitis of knee: The role of adjuvant radiotherapy. Medicine (Baltimore) 2021; 100(12):e23794. PMID: 33761628.
[38] Sun H, Ju XD, Huang HJ, Zhang X, Wang JQ. Clinical outcomes of endoscopic synovectomy with adjuvant radiotherapy of pigmented villonodular synovitis of the hip: A case series of single center. BMC Musculoskelet Disord 2022; 23(1):192. PMID: 35236301.
[39] Bickels J, Isaakov J, Kollender Y, Meller I. Unacceptable complications following intra-articular injection of yttrium 90 in the ankle joint for diffuse pigmented villonodular synovitis. J Bone Joint Surg Am 2008; 90(2):326-328. PMID: 18245592.
[40] Palmerini E, Longhi A, Donati DM, Staals EL. Pexidartinib for the treatment of adult patients with symptomatic tenosynovial giant cell tumor: Safety and efficacy. Expert Rev Anticancer Ther 2020; 20(6):441-445. PMID: 32297819.
[41] Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): A randomised phase 3 trial. Lancet 2019; 394(10197):478-487. PMID: 31229240.
[42] Van De Sande M, Tap WD, Gelhorn HL, et al. Pexidartinib improves physical functioning and stiffness in patients with tenosynovial giant cell tumor: Results from the ENLIVEN randomized clinical trial. Acta Orthop 2021; 92(4):493-499. PMID: 33977825.
[43] Spierenburg G, van der Heijden L, van Langevelde K, et al. Tenosynovial giant cell tumors (TGCT): Molecular biology, drug targets and non-surgical pharmacological approaches. Expert Opin Ther Targets 2022; 26(4):333-345. PMID: 35443852.
[44] Benner B, Good L, Quiroga D, at al. Pexidartinib, a novel small molecule CSF-1R inhibitor in use for tenosynovial giant cell tumor: A systematic review of pre-clinical and clinical development. Drug Des Devel Ther 2020; 14:1693-1704. PMID: 32440095.
[45] Monestime S, Lazaridis D. Pexidartinib (TURALIO™): The first FDA-indicated systemic treatment for tenosynovial giant cell tumor. Drugs R D 2020; 20(3):189-195. PMID: 32617868.
[46] Blay JY, El Sayadi H, Thiesse P, Garret J, Ray-Coquard I. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). Ann Oncol 2008; 19(4):821-822. PMID: 18296418.
[47] Verspoor FGM, Mastboom MJL, Hannink G, et al. Long-term efficacy of imatinib mesylate in patients with advanced tenosynovial giant cell tumor. Sci Rep 2019; 9(1):14551. PMID: 31601938.
[48] Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer 2012; 118(6):1649-1655. PMID: 21823110.
[49] Tan YC, Tan JY, Tsitskaris K. Systematic review: Total knee arthroplasty (TKA) in patients with pigmented villonodular synovitis (PVNS). Knee Surg Relat Res 2021; 33(1):6. PMID: 33632334.
[50] Yoo JJ, Kwon YS, Koo KH, Yoon KS, Min BW, Kim HJ. Cementless total hip arthroplasty performed in patients with pigmented villonodular synovitis. J Arthroplasty 2010; 25(4):552-557. PMID: 19356895.
[51] Houdek MT, Scorianz M, Wyles CC, Trousdale RT, Sim FH, Taunton MJ. Long-term outcome of knee arthroplasty in the setting of pigmented villonodular synovitis. Knee 2017; 24(4):851-855. PMID: 28552192.
[52] Lin W, Dai Y, Niu J, Yang G, Li M, Wang F. Pigmented villonodular synovitis does not influence the outcomes following cruciate-retaining total knee arthroplasty: A case-control study with minimum 5-year follow-up. J Orthop Surg Res 2020; 15(1):388. PMID: 32894157.
[53] Casp AJ, Browne JA, Durig NE, Werner BC. Complications after total knee arthroplasty in patients with pigmented villonodular synovitis. J Arthroplasty 2019; 34(1):36-39. PMID: 30266323.
[54] Xu C, Guo H, Bell KL, Kuo FC, Chen JY. Pigmented villonodular synovitis does not influence the outcome following cementless total hip arthroplasty using ceramic-on-ceramic articulation: A case-control study with middle-term follow-up. J Orthop Surg Res 2018; 13(1):294. PMID: 30458820.

Keywords: synovitis, pigmented villonodular, giant cell tumor, orthopedics, radiotherapy

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Review

Foot-strike Hemolysis: A Scoping Review of Long-Distance Runners

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ABSTRACT

Objective. To investigate the role that foot-strike hemolysis plays in sports-related anemia in marathon and ultramarathon runners.

Data Sources. PubMed, Embase, Cochrane, Grey literature.

Study Selection. Inclusion criteria consisted of human studies with runners completing a sanctioned race of marathon distance or greater, with outcomes measured by pre- and post-race hematological assessments.

Data Extraction. Three independent reviewers systematically extracted data from selected studies. Data included age, sex, height, weight, best marathon time, and pre- and post-race outcomes for complete blood count, reticulocyte count, and iron studies. The evaluation of potential bias was conducted using the Methodological Index for Nonrandomized Studies (MINORS) criteria.

Data Synthesis. The literature search yielded 334 studies, of which nine met the inclusion criteria, encompassing data from 267 runners. The majority (88%, 236 out of 267) were male, with a weighted mean age of 37 years (SD 8.2). The reticulocyte count demonstrated a 16% increase between pre- and post-race measurements, although still within normal limits, while haptoglobin levels were reduced by 21%. Hemoglobin, hematocrit, and RBC count values remained within accepted normal limits.

Conclusions. Changes in reticulocyte count and haptoglobin levels suggest transient foot-strike hemolysis; however, hemoglobin and hematocrit levels did not change notably. It is unclear whether these associations are influenced by differences in runner demographics, running experience, or race characteristics. Further studies should evaluate hemolytic changes while matching participants by demographic characteristics, level of running experience, and specific marathon course characteristics. Additionally, research should analyze whether intravascular hemolysis occurs at race distances shorter than 42.2 km. ***Kans J Med 2024;17:119-125***

INTRODUCTION

In endurance runners, sports-related anemia has been described as commonplace. Various mechanisms are known to contribute to sports-related anemia, the most common of which is due to hemodilution secondary to a training-dependent increase in plasma volume.[1] Additional explanations for sports anemia include metabolic injury, exercise-induced oxidative stress, iron deficiency, gastrointestinal bleeding, hematuria, and direct mechanical injury to red blood cells (RBCs) due to repetitive and forceful impacts of the feet with the ground, known as foot-strike hemolysis.[1]

Foot-strike hemolysis, also known as march hemoglobinuria, was first described by Kast in 1884, detailing a 19-year-old man who developed gross hemoglobinuria after a prolonged period of marching.[2] Further studies have demonstrated exercise-induced intravascular hemolysis, conventionally diagnosed by an increased concentration of free hemoglobin in serum, decreased haptoglobin level, and reticulocytosis, as well as markers of cytolysis such as elevated levels of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and unconjugated bilirubin.[3]

Sports anemia is generally transient and typically resolves within one to three months after discontinuing intensive exercise.[4] However, about 8% of elite athletes will develop frank anemia, defined as a hemoglobin concentration below 14.0 g/dL in males and 12.0 g/dL in females.[5] The precise contribution of foot-strike hemolysis to the development of sports anemia in long-distance runners has yet to be concretely defined. No systematic or scoping reviews have been published examining the current body of literature concerning this phenomenon to better determine the role, if any, that foot-strike hemolysis plays in sports-related anemia.

The goal of this scoping review was to quantitatively analyze the current available literature to summarize the existing body of literature surrounding foot-strike hemolysis and evaluate the hematologic effects following long distance runs of 42.2km (26.2 miles, the marathon distance) and greater.

METHODS

Search Strategy and Study Selection. Three independent authors (A.G., N.L., and N.D.) performed a scoping review of the literature following the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR) guidelines (Figure 1).[6] The review was registered with the Prospective Register of Systematic Reviews (PROSPERO; [CRD42023454879]), and no similar meta-analyses or systematic reviews were identified. Databases utilized included PubMed, Embase, Cochrane, and a review of the grey literature. The electronic database search was performed through December 2023. The keywords used in the search, combined with the following Boolean operators included: "Foot strike hemolysis" OR "March hemoglobinuria" OR "Sports anemia" OR "Exercise-induced hemolysis" OR "Foot strike anemia". No filter was used during the database searches. All studies included were published, peer-reviewed articles. There were no specific timeline constraints regarding these publications. Appendix 1 provides further specific details regarding the location of PRISMA-ScR checklist items in the manuscript (appendix is only available online at journals.ku.edu/kjm).

Eligibility Criteria. All searches were extracted, and duplicate search results were discarded. Abstracts of each of the search results were screened to determine relevance. Articles were further excluded based on the following criteria: (1) non-English text, (2) full-length text

not available, (3) non-human study, (4) athletes did not run marathon length race (42.2 km) or longer, and (5) no pre-run and post-run hematological measurements. Studies that did not meet any of the exclusion criteria were included in the scoping review.

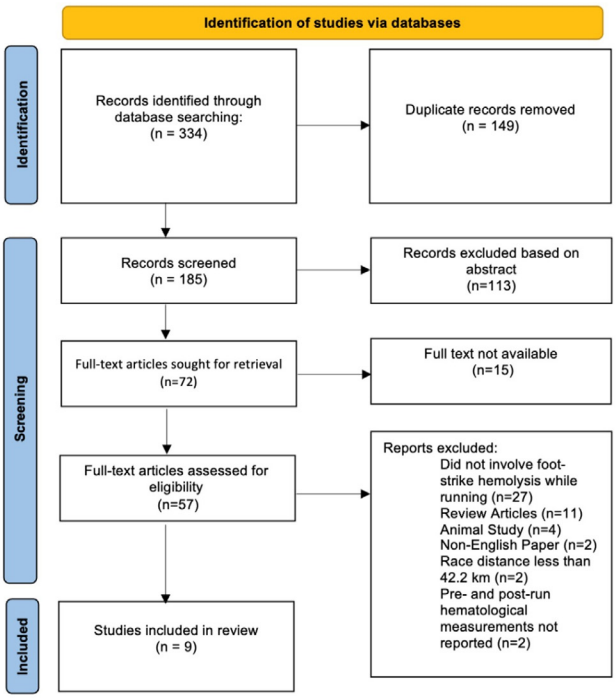

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for studies included in scoping review.

Data Extraction. Data were extracted systematically from each selected study by a team of three independent reviewers (A.G., N.D., and N.L.). Data was cross-checked by each reviewer to limit bias and ensure accuracy. The outcomes sought during the data extraction phase consisted of a comprehensive set of data including demographic data, pre-race, and post-race outcomes. Demographic data included age, sex, height, weight, and best marathon time. Pre-race and post-race outcomes included a complete blood count, reticulocyte count, haptoglobin, and iron studies.

Risk of Bias Assessment. Potential bias was evaluated using the Methodological Index for Nonrandomized Studies (MINORS) criteria by two independent reviewers (A.G. and N.D). The MINORS is a validated instrument to assess the quality of non-randomized studies using a score between 0 and 16 (> 12 = high quality; 8 - 12 = intermediate quality; <8 = low quality) for noncomparative studies.[7] In the case of discrepancies in scoring, a third independent reviewer (N.L.) was utilized.

Statistical Analysis. Aggregate data from each study were summarized using weighted means and standard deviations for pre- and post-race follow-up measures. Weighting was based on sample size per study. Data also were summarized by race distance. Primary outcomes included hemoglobin, haptoglobin, and reticulocyte count.

RESULTS

The results of the comprehensive literature are displayed in Figure 1. A total of 334 studies were initially identified. After removing duplicate records, 185 remained. Another 15 were excluded due to unavailability of full-text articles. This process left 57 full-text articles to be assessed. Of these, 48 were excluded, resulting in nine studies being included in the review. The nine included studies consisted of a total of 267 runners. A summary of the characteristics of the studies included is presented in Table 1.

Most runners included in the study were male (n = 236), with a mean age of 38 years. The runners' mean best marathon time was 220 minutes. Race distance varied from study to study. Three studies examined races of marathon distance (42.2 km), three examined races between 42.2 km – 160 km, and two studies examined a one day and six-day ultra-marathon race, respectively. The overall average race distance was 54.4 km.

Baseline, follow-up and change in lab values were summarized as weighted means and are shown in Table 2. Change in lab values revealed three large increases: 45% increase in the ferritin level (ng/mL), from 93 at baseline to 135 at follow-up; 38% increase in platelet count (n*10^9/L), from 241 to 332; and a 16% increase in reticulocyte count (n*10^9/L), from 1.33 to 1.54. Two large decreases in lab values were observed: 28% decrease in the serum iron level (ug/d), from 103 at baseline to 74 at follow-up; and a 21% decrease in the haptoglobin level (g/L) 1.18 to 0.93. Despite changes in both reticulocyte count and haptoglobin level, hemoglobin levels, hematocrit, and RBC counts remained within accepted normal limits. The hemoglobin level increased by 1.1%; hematocrit by 0.2%; and RBC count by 1.7%, from 4.82 10^6/uL to 4.90 10^6/uL.

Table 3 summarizes the weighted mean change by race length. Race length varied by study, with the largest sample from 42.2 km race with 190 runners; only one runner was represented in the 160 km race. Weighted mean change also varied considerably; however, a few possible linear trends were observed: lab values for hemoglobin (g/dL) appeared to decline as length of race increased: from .30 increase at 42.2 km to a 1.50 decrease for the six-day race. Similarly, hematocrit (%) declined from a 1.43 increase down to 5.0 decrease. Conversely, ferritin (ng/mL) appeared to increase as race length increased: from 16 at 42.2 km to 129 for the six-day race. Lab values for both reticulocyte count (10^9/L) and haptoglobin (g/L) remained steady, regardless of race length.

Results of the bias assessment from MINORS are shown in Table 4. Reviewers found that all nine studies included in the analysis were of intermediate quality, with Score (Quality) ranging from 9 to 12. Studies lacked blind evaluation of the study endpoints (Q5) and power analyses to determine study size (Q8).

Table 1. Study characteristics.

Author	Year	Type of Study	Race Setting	Mean C°	Race Distance (km)	Total Runners	Mean Age	Sex (Male, Female)	Outcome Measures	Main findings
Chiu[1]	2015	Case Series	Taipei, Taiwan	26.8	100	25	47	(25,0)	Blood counts, free plasma hemoglobin, IL-6, TNF-alpha, Hs-CRP, EPO, and iron panel, 1 week before, immediately after, and 24 hours post-race	Hemoglobin rise immediately post-race, no changes in RDW, haptoglobin decrease immediately post-race with return to baseline at 24 hours, ferritin increase immediately post-race and 24 hours post-race
Davidson[12]	1987	Before-after	UK	11	42.2	135	32.7	(110,25)	Red cell, leukocyte, and platelet parameters, and haptoglobin 30 min pre-race and within 5-min post-race	Significant decrease in haptoglobin, RBC, Hgb, and an increase in ferritin and WBC count.
Fallon[8]	2002	Case Series	Colac, Australia	16	6 days	8	47	(7,1)	Red cell and reticulocyte parameters 30 minutes prior to race, each day of the 6-day race, and immediately post-race.	Haptoglobin decreased on day 1, elevated on day 3-6. Hemoglobin decrease day 2-6, Increase in percentage of reticulocytes with high RNA content
Kratz[9]	2006	Case Series	Boston, MA	21.1	42.2	32	49	(27,5)	Blood counts, reticulocyte counts, WBC differentials, platelet parameters, 36 hours before and immediately after race	Increase in WBC, hematocrit, and RBC count post-race. Increased hemoglobin and reticulocyte count. Elevated RBC fragments.
Lijnen[13]	1988	Case Series	Belgium	9.2	42.2	23	24.6	(23,0)	Blood counts, lactate, urine tests 8h, 2 h, and 5 minutes pre-race, and 12 h, 36 h, and 7 days post-race	LDH and myoglobin concentration increased, Haptoglobin decreased immediately and 12 hours post-race
Lippi[5]	2012	Case Series	n/a	7	60	18	42	(18,0)	Pre- and post-race hematological testing, creatine kinase (CK), albumin, AST, LDH	No statistically significant variations in hemoglobin, RBC count, and hematocrit. Haptoglobin and MCV significantly decreased, RDW increased.
Liu[11]	2018	Case Series	Taipei, Taiwan	20	24 hours	19	45	(19,0)	Blood counts, hemolysis markers, iron panel, and viscoelastic properties 1 week pre-race and immediately post-race	Haptoglobin, RBC count, plasma free hemoglobin decreased significantly. Reticulocyte and ferritin increased post-race.
Sanchis-Gomar[7]	2016	Case Report	Indoors	n/a	160	1	37	(1,0)	Blood counts, muscle and liver markers, iron metabolism, electrolytes, and metabolic markers 3 days before and 0, 24 and 48 hours postexercise	Increased post-exercise serum CK, AST/ALT, Bilirubin, Hemoglobin. RBC decline at 48 hours, increased ferritin at 24 and 48 hours.
Yusof[10]	1985	Case Series	Badwater Basin, CA	55	216	6	53.8	(6,0)	Hematocrit, hemoglobin, leukocyte count, EPO, protein, urinalysis, 1-hour pre-race, at 21, 42, 84, 126 km, and immediately after the race	Hemoglobin increased after 42 km compared with 216-km level. Haptoglobin decreased during the initial 84 km. Spectrins reduced throughout the race.

Table 2. Baseline and follow-up weighted means including laboratory values.

Variable	n	Baseline	Follow-up	Change	%
		$Mean_{wgt}$ (SD)	$Mean_{wgt}$ (SD)	$Mean_{wgt}$	Change
Height (m)	185	1.73 (0.06)	--	--	
Weight (kg)	216	68.14 (7.51)	--	--	
Best marathon time (min)	210	219.41 (34.24)	--	--	
Hemoglobin (g/dL)	267	14.17 (1.06)	14.33 (0.97)	0.16	+1.13
Hematocrit (%)	132	44.01 (2.43	44.09 (2.88)	0.07	+0.18
RBC (10^6/uL)	267	4.82 (0.34)	4.9 (0.35)	0.07	+1.66
MCV (fl)	244	90.3 (4.05)	90.49 (4.10)	0.20	+0.21
MCH (pg)	244	30.41 (1.52)	30.32 (1.58)	-0.09	-0.30
MCHC (g/dL)	244	33.77 (0.77)	33.47 (0.89)	-0.33	-0.89
RDW (%)	238	11.76 (0.82)	12.16 (1.97)	0.46	+3.40
Reticulocyte count (n*10^9/L)	59	1.33 (0.42)	1.54 (0.47)	0.21	+15.79
Platelet count (n*10^9/L)	193	240.98 (52.99)	331.83 (63.72)	90.84	+37.70
Haptoglobin (g/L)	214	1.18 (0.49)	0.93 (0.50)	-0.26	-21.19
Iron (µg/d)	53	103.23 (36.93)	73.92 (34.04)	-29.31	-28.39
Ferritin (ng/mL)	78	93.43 (69.82)	135.04 (104.62)	41.60	+44.54

% Change = [(Follow-up – Baseline)/Baseline] * 100
Normal lab values by sex:
- Hemoglobin: 13.6 - 16.9 g/dL for males; 11.9 - 14.8 g/dL for females.
- Hematocrit: 40 - 50% for males; 35 - 43% for females
- Red blood cell count (RBC): 4.2 - 5.7 * 10^6/microL for males; 3.8 - 5.0 * 10^6/microL for females
- Mean corpuscular volume (MCV): males and females, 82.5 - 98 fL
- Mean corpuscular hemoglobin (MCH): males and females, 27.6 - 33.3pg.
- Mean corpuscular hemoglobin concentration (MCHC): males and females, 32.5 - 35.2 g/dL
- Red blood cell distribution width (RDW): males and females, 11.4 - 13.5%.
- Reticulocyte count: 16 - 130 * 10^9/L for males; 16- 98 * 10^9/L for females.
- Platelet count: 152- 324 *10^3/microL for males; 153- 361 *10^3/microL for females
- Haptoglobin: males and females, 50-220 mg/dL or 0.5-2.2 g/L
- Iron: 65 to 176 µg/dL for males; 50 to 170 µg/dL for females
- Ferritin: 12–300 nanograms per milliliter (ng/mL) for males; 12–150 ng/mL for females

Table 3. Weighted mean change by race length.*

Variable	Race Length						
	42.2 km	60 km	100 km	160 km	216 km	24-hour race†	6-day race†
Population (n)	190	18	25	1	6	19	8
Weighted mean change							
Hemoglobin (g/dL)	0.30	0.10	0.40	-0.60	-0.48	-0.50	-1.50
Hematocrit (%)	1.43	-0.57	0.90	-2.20	-2.00	-1.43	-5.00
RBC (10^6/uL)	0.14	-0.07	0.10	-0.23	-0.18	-0.17	-0.53
MCV (fl)	0.49	-1.43	0.40	0.00	-0.58	-0.50	-0.50
MCH (pg)	-0.17	0.00	0.30	0.10	0.26	-0.30	0.40
MCHC (g/dL)	-0.55	0.50	0.20	0.20	0.58	-0.17	0.60
RDW (%)	0.59	0.07	0.00	-0.30	0.00	0.07	-0.50
Reticulocyte count (10^9/L)	0.20	0.00	0.00	0.00	0.00	0.20	0.30
Reticulocyte count (10^9/L)	99.54	0.00	38.30	-48.00	0.00	0.00	0.00
Haptoglobin (g/L)	-0.41	-0.30	0.38	0.00	-0.23	-0.50	1.00
Iron (ug/dL)	0.00	0.00	-54.10	6.00	0.00	15.67	-63.10
Ferritin (ng/mL)	16.00	0.00	42.80	52.70	0.00	36.33	129.00

Note: RBC, Red blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red blood cell distribution width.
*Values represent differences calculated between baseline and follow-up weighted means
† 24-hour and 6-day races were time-based rather than distance-based races.

Table 4. MINORS criteria assessment of bias.

Author (Year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Score (Quality)
Chiu (2015)[1]	2	2	2	1	0	2	1	0	10 (Intermediate)
Davidson (1987)[8]	2	0	2	1	0	2	2	0	9 (Intermediate)
Fallon (2022)[9]	2	1	2	2	0	2	1	0	10 (Intermediate)
Kratz (2006)[10]	2	2	2	2	0	2	2	0	12 (Intermediate)
Lijnen (1988)[11]	2	2	2	2	0	2	2	0	12 (Intermediate)
Lippi (2012)[5]	2	1	2	2	0	2	2	0	11 (Intermediate)
Liu (2018)[12]	2	1	2	1	0	2	1	0	9 (Intermediate)
Sanchis-Gomar (2016)[13]	2	0	2	1	0	2	2	0	9 (Intermediate)
Yusof (1985)[14]	2	1	2	2	0	2	2	0	11 (Intermediate)

Rating per question: 0 = not reported, 1= reported but inadequate, 2= reported and adequate
Score (Quality): >12 = high, 8-12 = intermediate, < 8 = low
Q1: Clearly state aim
Q2: Inclusion of consecutive patients
Q3: Prospective collection of data
Q4: Appropriate endpoints
Q5: Unbiased assessment of endpoints
Q6: Appropriate follow-up period
Q7: Loss to follow-up less than 5%
Q8: Prospective calculation of study size

DISCUSSION

The sport of running has surged in popularity over the past decade, with races attracting 108 million participants across 70,000 events in 2019.[17] The COVID-19 pandemic has further amplified the sport of running, with runners increasing their mileage and number of runs per week significantly.[18] Given this rise in popularity, understanding the mechanisms by which sports anemia occur is integral for effective treatment and prevention, helping to avoid injury and improve running performance.

Our study findings provide valuable insights into the potential effects of foot-strike hemolysis on marathon runners. Hemolysis is primarily indicated by a decreased haptoglobin level, which was evident in this study. Haptoglobin is a molecule whose function is to complex with free hemoglobin when intravascular destruction of erythrocytes occurs, allowing for the recycling of both the hemoglobin and iron intrahepatically.[19] In the present study, haptoglobin levels were reduced by 21% between pre- and post-race weighted means. In most cases, despite a reduction in the haptoglobin level suggestive of intravascular hemolysis, clinically apparent hemoglobinuria did not occur.

Evaluation of RBC Parameters. An increase in the mean reticulocyte count was found, consistent with the human body's physiologic response to RBC breakdown, although mean values were still within normal levels. Variability in the reticulocyte count has been noted as commonplace. Increased red blood cell turnover has been described following various race distances, including short training runs, marathons, ultramarathons, and triathlons.[9] One theory for reticulocyte response variability is that present-day shoe materials have attenuated the severity of foot-strike hemolysis, thus leading to a diminished reticulocyte response.[3] Telford et al.[20] described reticulocyte levels that were 29% higher in runners training with hard-soled shoes running 429 km in 18 days, compared with a matched control group of soft-soled shoes. The lack of significant clinical effects or critical changes to the haptoglobin level and reticulocyte count may be attributable to pre-race physiologic adaptations. The average runner in the systematic review had a best marathon time of 220 minutes and was running an average of 54.4 km per week prior to the study. This appreciable training stimulus likely allows for the attenuation of substantial effects to the body, as these well-trained athletes had already reached a stable erythropoietic response.[5]

The study participants' mean hemoglobin level increased slightly from 14.17 to 14.33 g/dL, a 1.1% increase, with hematocrit also increasing slightly but remaining within normal limits. The pre-race hemoglobin of ~14 g/dL is evidence that the average runner in the study did not begin their respective race with traditionally defined anemia. The lack of significant change after undergoing an endurance race may be attributable to physiologic adaptations. However, it is plausible that hemoconcentration contributed to the increase of these values, as dehydration is commonplace in endurance running races.[21] In general, exhaustive endurance exercise initially causes volume contraction due body fluid loss, with subsequent volume expansion between 6 - 25%. The mechanism of this volume expansion is not entirely known but is likely due to activation of the renin-angiotensin-aldosterone (RAAS) system along with the osmotic regulation of vasopressin. In most cases, labs were taken immediately after the race, likely prior to the body's ability to recover from dehydrative effects.[19] Chiu et al.[1] looked at anemia in male 100 km ultramarathon runners. An analysis of hematological parameters immediately post-race as well as 24 hours post-race found mean hemoglobin levels of 14.7 ± 0.8 and 13.6 ± 0.8, respectively.

The foot-strike hemolysis phenomenon can be additionally supported by the increased red blood cell distribution width (RDW). RDW is a routine measure of variability in the size of circulating erythrocytes. RDW commonly is increased in nutritional deficiencies, such as iron, B12, and folate deficiency. Hemolysis results in reticulocytosis due to the body's attempt to compensate for erythrocyte losses. Due to the size disparity between reticulocytes and mature erythrocytes, RDW typically is elevated in cases of reticulocytosis.[22]

Evaluation of Iron Stores. The evaluation of iron and ferritin level changes is complex due to various factors influencing these parameters. It is well known that long-distance running can lead to depletion of iron stores. Some reasons for this include hemolysis, hematuria, sweating, and inflammation stimulating hepcidin production.[23] Because the intestinal absorption of iron is low (heme iron showing 15 - 25% absorption, with nonheme iron showing only 2 - 5% absorption), iron deficiency is common.[24] In the present study, iron levels were substantially reduced by 28%, from 103.23 ug/dL to 73.92 ug/dL. Ferritin levels, on the other hand, increased by 44.5% from 93.43 ng/mL to 135.04 ng/mL. In many cases, ferritin levels are decreased in trained individuals due to increased iron turnover and cell destruction from running. However, as stated previously, the effects of hemoconcentration likely play a role in the increased levels seen.[25] In addition, runners who already were taking iron supplementation prior to the study may have artificially elevated levels of ferritin. Despite substantial changes in iron levels, clinical manifestations associated with these changes were not present.

Oxidative Stress. Several confounding factors exist that may play a role in erythrocyte injury as it relates to physical exercise. Exercise-induced oxidative stress has been noted to occur in several athletic non-traumatic endeavors such as swimming, cycling, and rowing.[5] One of the primary mechanisms of this process relates to increased oxygen uptake into skeletal muscle which facilitates the generation of reactive oxygen species (ROS) and free radicals. Factors contributing to this increased ROS production include cellular pH changes, body temperature alterations, and catecholamine production.[26]

Limitations. The study has several limitations. First, the lack of quantitative research on foot-strike hemolysis limits the ability to make generalizable conclusions and impacted heterogeneity. Much of this variability can be attributable to intrinsic race characteristics, including race surface and conditions, which may significantly affect the amount of hemolysis.

Another limitation is the variability in runner demographics. Many runner characteristics have not been described in previous studies, including experience, hydration status, and nutrition. Additionally, some argue that new shoe technology has significantly reduced the

hemolytic effects of repeated foot striking.[5]

Another limitation is the lack of statistical evaluation for pre-post differences. We chose not to conduct such tests, as there is a potential bias in utilizing pre-post mean differences. This bias may stem from lack of control group, along with differences in measurement, and study design. While a standardized mean score might account for differences in measurement, there is no control group for comparing these calculations. Therefore, an inherent correlation between the pre- and post-test data exists, which may result in biased outcomes.[27] Future studies may want to consider utilizing MA-CONT, a more robust way to analyze continuous outcomes.[28]

Lastly, studies like Yusof et al.[14] discuss that exercise-induced hemolysis is more prominent in the early stages of an endurance race, likely secondary to preferential removal of older red blood cells via splenic filtration rather than intravascular hemolysis. Unfortunately, few studies have examined early race RBC damages due to the logistical challenges of conducting such research.

CONCLUSIONS

Changes in reticulocyte count and haptoglobin suggest a transient foot-strike hemolysis, though hemoglobin and hematocrit did not change notably. These findings may be attributable to dehydration, advances in shoe technology, or physiological adaptations in endurance athletes. Future studies should evaluate hemolytic changes while matching participants by demographic characteristics, level of running experience, and specific marathon course characteristics as well as investigating intravascular hemolysis distances shorter than 42.2 km.

REFERENCES

[1] Chiu YH, Lai JI, Wang SH, et al. Early changes of the anemia phenomenon in male 100-km ultramarathoners. J Chin Med Assoc 2015; 78(2):108-113. PMID: 25456038.
[2] Kast A. Ueber paroxysmale hämoglobinurie durch gehen. DMW - Deutsche Medizinische Wochenschrift 1884; 10(52):840-842. doi:10.1055/s-0028-1143431.
[3] Lippi G, Sanchis-Gomar F. Epidemiological, biological and clinical update on exercise-induced hemolysis. Ann Transl Med 2019; 7(12):270. PMID: 31355237.
[4] Wouthuyzen-Bakker M, van Assen S. Exercise-induced anaemia: A forgotten cause of iron deficiency anaemia in young adults. Br J Gen Pract 2015; 65(634):268-269. PMID: 25918331.
[5] Lippi G, Schena F, Salvagno GL, Aloe R, Banfi G, Guidi GC. Foot-strike haemolysis after a 60-km ultramarathon. Blood Transfus 2012; 10(3):377-383. PMID: 22682343.
[6] Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for Scoping Reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med 2018; 169(7):467-473. PMID: 30178033.
[7] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): Development and validation of a new instrument. ANZ J Surg 2003; 73(9):712-716. PMID: 12956787.
[8] Davidson RJ, Robertson JD, Galea G, Maughan RJ. Hematological changes associated with marathon running. Int J Sports Med 1987; 8(1):19-25. PMID: 3557778.
[9] Fallon KE, Bishop G. Changes in erythropoiesis assessed by reticulocyte parameters during ultralong distance running. Clin J Sport Med 2002; 12(3):172-178. PMID: 12011725.
[10] Kratz A, Wood MJ, Siegel AJ, Hiers JR, Van Cott EM. Effects of marathon running on platelet activation markers: Direct evidence for in vivo platelet activation. Am J Clin Pathol 2006; 125(2):296-300. PMID: 16393676.
[11] Lijnen P, Hespel P, Fagard R, et al. Indicators of cell breakdown in plasma of men during and after a marathon race. Int J Sports Med 1988; 9(2):108-113. PMID: 3384515.
[12] Liu C-H, Tseng Y-F, Lai J-I, et al. The changes of red blood cell viscoelasticity and sports anemia in male 24-hr ultra-marathoners. J Chin Med Assoc 2018; 81(5):475-481. PMID: 29133160.
[13] Sanchis-Gomar F, Alis R, Rodríguez-Vicente G, Lucia A, Casajús JA, Garatachea N. Blood and urinary abnormalities induced during and after 24-hour continuous running. Clin J Sport Med 2016; 26(5). PMID: 26222342.
[14] Yusof A, Leithauser RM, Roth HJ, Finkernagel H, Wilson MT, Beneke R. Exercise-induced hemolysis is caused by protein modification and most evident during the early phase of an ultraendurance race. J Appl Physiol 2007; 102(2):582-586. PMID: 17284654.
[15] Adeli K, Raizman JE, Chen Y, et al. Complex biological profile of hematologic markers across pediatric, adult, and geriatric ages: Establishment of robust pediatric and adult reference intervals on the basis of the Canadian Health Measures Survey. Clin Chem 2015; 61(8):1075-1086. PMID: 26044509.
[16] Van den Bossche J, Devreese K, Malfait R, et al. Reference intervals for a complete blood count determined on different automated haematology analysers: Abx Pentra 120 Retic, Coulter Gen-S, Sysmex SE 9500, Abbott Cell Dyn 4000 and Bayer Advia 120. Clin Chem Lab Med 2002; 40(1):69-73. PMID: 11916274.
[17] Andersen JJ. The state of running 2019. RunRepeat. November 3, 1970. https://runrepeat.com/state-of-running. Accessed February 24, 2024.
[18] DeJong AF, Fish PN, Hertel J. Running behaviors, motivations, and injury risk during the COVID-19 pandemic: A survey of 1147 runners. PLOS ONE 2021; 16(2). PMID: 33577584.
[19] Shaskey DJ, Green GA. Sports haematology. Sports Med 2000; 29(1):27-38. PMID: 10688281.
[20] Telford RD, Sly GJ, Hahn AG, Cunningham RB, Bryant C, Smith JA. Footstrike is the major cause of hemolysis during running. J Appl Physiol 2003; 94(1):38-42. PMID: 12391035.
[21] Armstrong LE. Rehydration during endurance exercise: Challenges, research, options, methods. Nutrients 2021; 13(3):887. PMID: 33803421.
[22] May JE, Marques MB, Reddy VVB, Gangaraju R. Three neglected numbers in the CBC: The RDW, MPV, and NRBC count. Cleve Clin J Med 2019; 86(3):167-172. PMID: 30849034.
[23] Buratti P, Gammella E, Rybinska I, Cairo G, Recalcati S. Recent advances in iron metabolism: Relevance for health, exercise, and performance. Med Sci Sports Exerc 2015; 47(8):1596-1604. PMID: 25494391.
[24] Koikawa N, Nagaoka I, Yamaguchi M, Hamano H, Yamauchi K, Sawaki K. Preventive effect of lactoferrin intake on anemia in female long distance runners. Biosci Biotechnol Biochem 2008; 72(4):931-935. PMID: 18391460.
[25] Suedekum NA, Dimeff RJ. Iron and the athlete. Curr Sports Med Rep 2005; 4(4):199-202. PMID: 16004828.
[26] Yavari A, Javadi M, Mirmiran P, Bahadoran Z. Exercise-induced oxidative stress and dietary antoxidatnts. Asian J Sports Med 2015; 6(1). PMID: 25883776.
[27] Cuijpers P, Weitz E, Cristea IA, Twisk J. Pre-post effect sizes should be avoided in meta-analyses. Epidemiol Psychiatr Sci 2016; 26(4):364-368. PMID: 27790968.
[28] Papadimitropoulou K, Riley RD, Dekkers OM, Stijnen T, le Cessie S. MA-cont:pre/post effect size: An interactive tool for the meta-analysis of continuous outcomes using R Shiny. Res Synth Methods 2022; 13(5):649-660. PMID: 35841123.

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Letter to the Editor

Comment on "Drug-Induced Lupus Following mRNA COVID-19 Vaccination and Monoclonal Antibody Infusion for Treatment of COVID-19 Infection"

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To the Editor:

We would like to share ideas on "Drug-Induced Lupus Following mRNA COVID-19 Vaccination and Monoclonal Antibody Infusion for Treatment of COVID-19 Infection."[1] This case study describes a patient who had the Moderna mRNA COVID-19 vaccine, monoclonal antibody infusion, and further immunization before developing drug-induced lupus (DIL). The report describes the patient's appearance, diagnostic process, and course of therapy, emphasizing the difficulties in identifying DIL because there are no clear guidelines. There are some methodological issues with the case, despite the fact that it offers insightful information about how DIL manifests after vaccination. The study does not address the precise methods by which the patient's monoclonal antibody infusion and COVID-19 vaccination may have caused DIL, nor does it go into possible drug interactions with the patient's underlying medical history.

A more comprehensive analysis of the literature on DIL in relation to COVID-19 vaccinations and monoclonal antibody infusions would also be beneficial to the report. A more thorough examination of prior DIL cases following vaccination may help to clarify the risk factors and consequences related to this condition. The long-term effects of DIL in this patient, such as the possibility of recurrence or the requirement for further monitoring, also are not included in the study. In order to improve clinical practice and patient care, future research should concentrate on clarifying the pathogenesis of DIL in relation to COVID-19 immunization and monoclonal antibody therapy.

The report also fails to address how genetic predisposition to DIL after vaccination may be a result of immunization. Future research should take into account the possibility that genetic sensitivity to drug-induced autoimmune reactions contributes significantly to the development of DIL. Furthermore, the impact of DIL on the patient's long-term prognosis and quality of life is not discussed in the report. In order to better support patients who suffer this uncommon adverse event, health care personnel may find it helpful to understand the psychological and social ramifications of DIL. Research should go further in the goal of creating individualized strategies for managing DIL that take into consideration each patient's unique risk factors and response to treatment.

In summary, even though the case report offers insightful information about the diagnosis and treatment of DIL following vaccination, there are certain methodological flaws and room for development. The pathogenesis of DIL in relation to COVID-19 immunization and monoclonal antibody therapy should be clarified in future studies. Genetic variables that predispose people to DIL also should be investigated, as should the long-term effects of this condition on patients' quality of life. Health care professionals can better understand and manage drug-induced lupus in the context of developing medicinal solutions by addressing these limitations and concentrating on these future directions.

REFERENCES

1 Nguyen T, Wanjala S, Akkawi AR, Rowe K, Malik B. Drug-induced lupus following mRNA COVID-19 vaccination and monoclonal antibody infusion for treatment of COVID-19 infection. Kans J Med 2024; 17:36-38. PMID: 38694172.

Author Response

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Thank you for the thoughtful and detailed review of our manuscript titled "Drug-Induced Lupus Following mRNA COVID-19 Vaccination and Monoclonal Antibody Infusion for Treatment of COVID-19 Infection." We appreciate the opportunity to clarify our intent and address the points raised.

The primary purpose of our case report was to raise awareness about a rare and concerning phenomenon that has yet to be widely reported. Our patient's case, involving the development of drug-induced lupus (DIL) associated with the administration of the Moderna mRNA COVID-19 vaccine and a monoclonal antibody infusion, was particularly noteworthy due to the short timeframe and the lack of other contributing factors. Our intent was not to provide an exhaustive explanation of the mechanisms of DIL but to highlight a potential adverse effect of COVID-19 vaccination and monoclonal antibody therapy that warrants further investigation.

We carefully considered all the patient's medications and health status. The patient was on a limited number of medications, and there were no changes in his health or medication regimen other than receiving the COVID-19 vaccine and monoclonal antibody infusion within a short period. This temporal association suggests a possible link that deserves attention in case there are other following cases that share a similar timespan.

We acknowledge the reviewer's suggestion for a more comprehensive analysis of the literature. However, it is important to note that there are currently very few studies that adequately can explain this phenomenon, as well as DIL in general. The rarity of this occurrence and the limited data available underscore the need for further research, which our case report aimed to encourage.

Our goal in publishing this case report was to present a potential concern and a rare adverse event to the medical community, thereby

encouraging more research and investigation into this area. By sharing our findings, we hope to contribute to a growing body of knowledge that will ultimately lead to a better understanding of DIL and its associations with COVID-19 vaccination and monoclonal antibody therapy.

We agree that research should go into individualized strategies for managing such illnesses. For this patient, his symptoms had entirely resolved as seen in his three-month follow-up without any residual symptoms, further suggesting the self-resolving nature of DIL. For the psychological and social ramifications of this event, we agree that this aspect would have been a valuable addition to this paper. At his three-month follow-up, our patient was concerned about this phenomenon reoccurring. After further reassurance and explanation, he understood what we believed might have caused it, and it did not lead him to reject future vaccinations. He continued to receive his age-appropriate vaccinations and further recommended COVID-19 vaccinations one year later.

In conclusion, while our report did not delve into the detailed pathogenesis of DIL, it serves as a crucial step in raising awareness and prompting further scientific inquiry. We believe that highlighting such cases is essential for advancing medical knowledge and improving patient care. To our knowledge, there are no published data on DIL associated with the COVID-19 vaccine and monoclonal antibody, as this phenomenon is not well documented. Although there are multiple case reports and series suggesting the COVID-19 vaccine may induce systemic lupus erythematosus, there remains no discussion on the self-limiting diagnosis of DIL potentially linked to the vaccine and monoclonal antibody infusion.[1-4] We hope this paper raises awareness, fosters discussion, and encourages further research on this possible phenomenon. Our goal in reporting this case was to help physicians and patients gain a deeper understanding of this remarkable and lifesaving vaccine technology. Thank you once again for your valuable feedback.

REFERENCES

[1] Lemoine C, Padilla C, Krampe N, et al. Systemic lupus erythematous after Pfizer COVID-19 vaccine: A case report. Clin Rheumatol 2022; 41(5):1597-1601. PMID: 35294664.

[2] Voisin O, Priollet P. Systemic lupus induced by messenger RNA vaccination. Mayo Clin Proc 2022; 97(7):1398-1399. PMID: 35787868.

[3] Shah S, Danda D, Kavadichanda C, Das S, Adarsh MB, Negi VS. Autoimmune and rheumatic musculoskeletal diseases as a consequence of SARS-CoV-2 infection and its treatment. Rheumatol Int 2020; 40(10):1539-1554. PMID: 32666137.

[4] Peng K, Li X, Yang D, et al. Risk of autoimmune diseases following COVID-19 and the potential protective effect from vaccination: A population-based cohort study. EClinicalMedicine 2023; 63:102154. PMID: 37637754.

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