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*Brief Report*

# EValuation of Acute and Early Phase P2Y12 Inhibitor DE-escalation After PerCutaneous Intervention (EVADE PCI)

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## ABSTRACT

**Introduction.** Aspirin and an oral P2Y12 inhibitor are recommended for one year after percutaneous coronary intervention (PCI) in patients with acute coronary syndromes. While ticagrelor or prasugrel, more potent P2Y12 inhibitors, are preferred over clopidogrel, de-escalation often is based on provider judgment. This study compared cardiovascular outcomes and bleeding risks between patients who remained on ticagrelor or prasugrel (unchanged group) and those de-escalated to clopidogrel within 30 days of PCI.

**Methods.** The authors analyzed data from patients admitted between June 2014 and December 2022 for acute coronary syndromes requiring PCI who received an oral P2Y12 inhibitor within 72 hours of admission. The primary outcome was a composite of all-cause mortality, urgent revascularization, stent thrombosis, stroke, and major bleeding at one year. Secondary outcomes included the individual components of the composite outcome. Statistical analyses included chi-square tests, Student's t-tests, or non-parametric equivalents, as appropriate.

**Results.** A total of 210 patients met the inclusion criteria, with 149 remaining on unchanged P2Y12 therapy and 61 undergoing de-escalation. There was no statistically significant difference in the composite outcome between the unchanged and de-escalated groups (n [%]: 25 [17] vs. 6 [10]; $\chi^2$ [1, N = 210] = 1.658, p = 0.198). Additionally, secondary outcomes, including all-cause mortality, urgent revascularization, stent thrombosis, stroke, and major bleeding, did not differ significantly between groups.

**Conclusions.** A composite outcome of all-cause mortality, urgent revascularization, stent thrombosis, stroke, and major bleeding at one year was similar between patients who continued ticagrelor or prasugrel and those de-escalated to clopidogrel within 30 days of PCI. Larger studies are needed to confirm these findings and assess the optimal timing for therapy adjustments.

## INTRODUCTION

An oral purinergic receptor type Y subtype 12 (P2Y12) inhibitor is recommended in combination with aspirin for one year after percutaneous coronary intervention (PCI) in patients with acute coronary syndromes.[1,2] Studies comparing the efficacy of oral P2Y12 inhibitors suggest that ticagrelor or prasugrel provides better outcomes than clopidogrel, as clopidogrel undergoes extensive first-pass metabolism, exhibits greater pharmacokinetic and pharmacodynamic variability, and provides less platelet inhibition.[3-7] Despite these findings, clopidogrel often is prescribed due to cost, adherence concerns, or an increased risk of bleeding.[8-14]

De-escalation of P2Y12 inhibitor therapy occurs when a patient initially receives ticagrelor or prasugrel after PCI and later is switched to clopidogrel. The timing of de-escalation requires balancing ischemic and hemorrhagic risks. Current expert consensus defines de-escalation timing as acute (<24 hours), early (1-30 days), and late (>30 days).[8] Previous trials indicate that late-phase de-escalation to clopidogrel does not adversely affect clinical outcomes one-year post-PCI.[15-22]

Studies report an in-hospital P2Y12 inhibitor de-escalation rate of 5-23% among patients with acute coronary syndromes undergoing PCI.[13,23-29] This suggests a preference for ticagrelor or prasugrel at initial treatment, with de-escalation occurring post-discharge once patient factors such as cost, adherence, or bleeding risk are identified.[8-14] However, there is limited published outcome data on in-hospital de-escalation. One expert panel provides guidance on how to de-escalate P2Y12 therapy but does not specify timing,[8] while two consensus statements classify de-escalation as potentially safe and effective but acknowledge limited supporting data.[30,31] Various guidelines differ on guided versus unguided de-escalation, with some suggesting platelet function testing for select patients, though it is not routinely recommended.[31]

We designed a retrospective cohort study to compare acute and early-phase P2Y12 inhibitor de-escalation to unchanged therapy following PCI in patients with acute coronary syndromes.

## METHODS

**Study Design.** This retrospective cohort study, conducted at a comprehensive cardiac hospital, compared cardiovascular outcomes and bleeding risks between patients de-escalated to clopidogrel within 30 days of PCI and those who remained on their initial P2Y12 inhibitor therapy. The study was approved by the hospital's Institutional Review Board (IRB) and classified as minimal risk.

**Patient Selection.** Patients were included if they were ≥18 years old, admitted to a comprehensive cardiac hospital for an acute coronary syndrome requiring PCI between June 2014 and December 2021, received an oral P2Y12 inhibitor within 72 hours of admission, and continued dual antiplatelet therapy (DAPT) at discharge.

Exclusion criteria included initial P2Y12 therapy with clopidogrel; thrombocytopenia on admission (platelet count $<50\times10^9$/L); death within 24 hours of admission; pre-admission DAPT or chronic anticoagulation therapy; allergy to clopidogrel, prasugrel, ticagrelor, or aspirin; history of intracranial or gastrointestinal bleeding within the past year and planned coronary artery bypass graft within 30 days post-PCI.

Patients in the de-escalated group received at least one dose of ticagrelor or prasugrel and were switched to clopidogrel within 30 days post-PCI. The unchanged group remained on ticagrelor or prasugrel throughout treatment.

**Outcomes.** The primary outcome was a composite of all-cause mortality, urgent revascularization, stent thrombosis, stroke, and major bleeding at one-year post-acute coronary syndrome. Secondary outcomes included the individual components of this composite measure.

**Data Collection.** Collected data included:

- Patient demographics (name, age, sex, weight)
- Hospital admissions (June 2014-December 2022)
- Medical history (hypertension, diabetes, dyslipidemia, smoking, myocardial infarction, prior coronary artery bypass graft)
- Diagnosis codes for unstable angina, ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, stent thrombosis, and stroke
- Baseline clinical characteristics (ejection fraction, initial platelet count, allergies to P2Y12 inhibitors or aspirin, culprit lesions, number of vessels treated, stent type)
- P2Y12 inhibitor therapy details (name, dose, route, frequency, administration date/time, therapy changes)
- Mortality data and transfused packed red blood cells
- Major bleeding events (defined as transfusion of ≥2 units of packed red blood cells within 24 hours)

Because the hospital's standard protocol includes aspirin 81 mg with a P2Y12 inhibitor, aspirin administration was not specifically recorded.

**Standard Hospital Procedures.** During the study period, patients received a loading dose of prasugrel or ticagrelor once their coronary anatomy was confirmed, followed by maintenance therapy. No standardized protocol existed for de-escalation timing, so patients could have been switched to clopidogrel at any point during their admission.

**Data Analysis.** A power calculation was performed based on a prior study evaluating a composite outcome of cardiovascular death, urgent revascularization, stroke, and bleeding, which reported event rates of 13.4% in patients who switched DAPT after 30 days and 26.3% in those who remained on unchanged DAPT.[15] Assuming similar event rates, a sample size of 298 patients was required to achieve 80% power with an alpha of 0.05.

Patients were selected in reverse chronological order until the target sample size was met. Discrete variables were analyzed using the Chi-squared or Fisher's exact test, as appropriate, while continuous variables were assessed using a Student's t-test or Wilcoxon rank sum test, depending on data distribution. Statistical analyses were conducted using SigmaPlot 14.5®.

## RESULTS

Of the 313 patients screened, 210 met the inclusion criteria for analysis (unchanged DAPT: n = 149; de-escalated DAPT: n = 61; Figure 1). The study population was predominantly male (131/210, 62%) with a median age of 62.5 years (interquartile range [IQR]: 54-69.25). At presentation, 53% (112/210) of patients had a non-ST-elevation myocardial infarction (NSTEMI), and 95% received ticagrelor as the initial P2Y12 inhibitor.

In the de-escalation group, there was a significantly higher proportion of smokers (n [%]: 30 [49] vs. 50 [34]; $\chi^2$[1, N = 210] = 4.48, p = 0.034) and patients with diabetes (n [%]: 29 [47] vs. 47 [32]; $\chi^2$[1, N = 210] = 4.796, p = 0.029) compared to the unchanged DAPT group. Additionally, the de-escalation group had a significantly longer hospital stay (median [IQR]: 3.2 [2.5-4.6] vs. 2.7 [2.1-4.1] days; p <0.023). No other baseline characteristics differed significantly between groups (Table 1).

Among the 61 patients in the de-escalation group, therapy de-escalation occurred at a median of 1.26 days (IQR: 0.73-2.6) post-PCI.

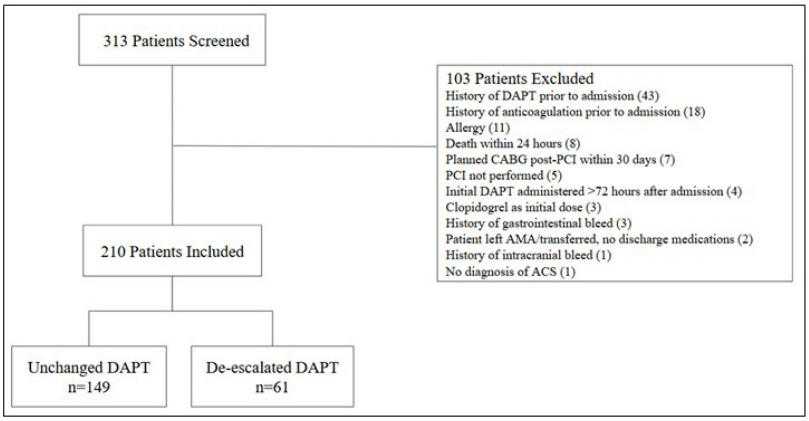


**Figure 1.** Patient criteria. DAPT, dual antiplatelet therapy; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention, AMA, against medical advice; ACS, acute coronary syndrome.

In patients presenting with acute coronary syndrome and undergoing PCI, there was a composite outcome rate of 14.8%, with no significant difference between the de-escalated and unchanged DAPT groups (n [%]: 6 [9.8] vs. 25 [16.8]; $\chi^2$[1, N = 210] = 1.658, p = 0.198).

Although there was a numerical decrease in all-cause mortality (1 [2%] vs. 13 [9%]; $\chi^2$[1, N = 210] = 3.492, p = 0.062) and major bleeding (1 [2%] vs. 8 [5%]; $\chi^2$[1, N = 210] = 1.468, p = 0.226) in the de-escalation group, these differences were not statistically significant.

Similarly, there were no significant differences between the de-escalated and unchanged DAPT groups in stent thrombosis (0 [0%] vs. 1 [1%]; $\chi^2$[1, N = 210] = 0.411, p = 0.521), urgent revascularization (4 [7%] vs. 11 [7%]; $\chi^2$[1, N = 210] = 0.044, p = 0.833), or stroke (0 [0%] vs. 1 [1%]; $\chi^2$[1, N = 210] = 0.411, p = 0.521).

## DISCUSSION

There was a 14.8% risk of major adverse cardiovascular events, with no statistically significant difference between patients receiving de-escalated and unchanged DAPT. Compared to unchanged DAPT, the de-escalation group showed a trend toward lower all-cause mortality and major bleeding. To the authors' knowledge, this is the first study to evaluate the one-year risk of major adverse cardiovascular events following in-hospital, acute-phase P2Y12 inhibitor therapy de-escalation after PCI without platelet function testing guidance.

Previous studies assessing P2Y12 inhibitor de-escalation at or after discharge found similar rates of major adverse cardiovascular events compared to no de-escalation, with most patients in these studies receiving prasugrel post-PCI.[13,26,32,33] Our study, which primarily evaluated ticagrelor as the initial antiplatelet therapy, found no difference in major adverse cardiovascular events. Unlike prior trials, we excluded patients on chronic anticoagulation or pre-admission DAPT to better isolate the effects of de-escalation.[33] Despite differences in study populations and designs, our findings reinforce that early de-escalation to clopidogrel may be a safe alternative to more potent P2Y12 inhibitors.[13,26,32-34]

**Table 1. Clinical characteristics.**

| Characteristic | De-escalated DAPT N = 61 | Unchanged DAPT N = 149 |
|---|---|---|
| Age, mean (SD) | 60 (13) | 63 (11) |
| Sex, male | 32 (52) | 99 (66) |
| Medical history | | |
| Hypertension | 44 (72) | 98 (66) |
| Diabetes* | 29 (47) | 47 (32) |
| Dyslipidemia | 46 (75) | 102 (69) |
| Current smoker* | 30 (49) | 50 (34) |
| History of CABG | 3 (5) | 8 (5) |
| EF, median (IQR) | 55 (45-60) N = 39 | 44 (40-55) N = 99 |
| Presenting condition | | |
| Unstable angina | 1 (2) | 1 (<1) |
| NSTEMI | 38 (62) | 74 (50) |
| STEMI | 22 (36) | 74 (50) |
| Initial antiplatelet, Ticagrelor* | 58 (95) | 142 (95) |
| Hospital LOS, median (IQR)* | 3.2 (2.5-4.6) | 2.7 (2.1-4.1) |
| In-hospital mortality | 0 (0) | 5 (3) |
| Culprit lesion | | |
| Left main | 0 (0) | 8 (5) |
| Left anterior descending | 0 (0) | 8 (5) |
| Left circumflex | 17 (28) | 29 (19) |
| Right coronary artery | 23 (38) | 63 (43) |
| Venous graft | 1 (2) | 3 (2) |
| Number of vessels treated | | |
| 1 | 50 (82) | 120 (81) |
| 2 | 11 (18) | 25 (17) |
| 3 | 0 (0) | 4 (3) |
| Stent type | | |
| Drug-eluting stent | 60 (98) | 149 (100) |

*Statistically significant p <.05
Data presented as numbers (%), unless otherwise stated.
DAPT, dual antiplatelet therapy; SD, standard deviation; CABG, coronary artery bypass graft; EF, ejection fraction; LOS, length of stay; IQR, interquartile range; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

Current guidelines recommend aspirin with a potent P2Y12 inhibitor after coronary stent placement while suggesting de-escalation for patients at increased bleeding risk.[1,2] However, the safety of de-escalation in the acute early phase remains uncertain. Prior studies have assessed de-escalation after 30 days post-PCI and found no significant difference in ischemic events. Our study is unique in evaluating the safety and efficacy of de-escalation within 30 days of stent placement, providing updated evidence on early de-escalation strategies in acute coronary syndrome patients post-PCI.[13,33,34]

Patients with diabetes and a history of smoking have an increased risk of platelet hyperreactivity and thrombotic events.[35-37] Previous studies have found no significant difference in outcomes between de-escalation and standard P2Y12 inhibitor therapy in diabetic patients.[38,39] Additionally, smoking may influence the pharmacokinetics and pharmacodynamics of clopidogrel.[40] In our study, 47% (29/61) of patients in the de-escalated group and 32% (47/149) in the unchanged group had diabetes, while 49% (30/61) and 34% (50/149), respectively, were current smokers. Notably, our study found a trend toward improved composite outcomes in the de-escalation group. This hypothesis-generating subgroup analysis raises questions about the influence of social history and comorbidities on platelet hyperreactivity post-PCI.

**Limitations.** Due to the retrospective nature of this study, the sample size was small and did not achieve the calculated power, increasing the risk of a type II error. A larger sample size would be needed to draw more definitive conclusions. The study also is limited by the assumption of aspirin administration and adherence to P2Y12 inhibitor therapy, as compliance was not directly assessed.

Additionally, the reasons for de-escalation remain unknown, and data on de-escalation after hospital discharge were not collected. No platelet function assays were performed, as they are not guideline-recommended.[31] As a result, patients who were non-responders to clopidogrel could not be identified, limiting the study's external validity.

Furthermore, outcomes for patients who were readmitted to outside hospitals were not captured. While some studies have used more comprehensive bleeding definitions, this study defined major bleeding as requiring transfusion of two or more units of packed red blood cells within 24 hours.

## CONCLUSIONS

De-escalation of P2Y12 therapy from prasugrel or ticagrelor to clopidogrel within 30 days of PCI did not statistically impact one-year outcomes of all-cause mortality, urgent revascularization, stent thrombosis, stroke, and major bleeding. Further randomized controlled trials are needed to strengthen these findings.

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*Keywords: Dual antiplatelet therapy, percutaneous coronary intervention, acute coronary syndrome, clopidogrel, ticagrelor*

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*Case Report*

# Bruised and Bleeding: A Case Report of Acquired Hemophilia A

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## INTRODUCTION

Acquired hemophilia A (AHA), also known as acquired factor VIII deficiency, is a rare bleeding disorder with an incidence of up to eight cases per million per year, based on data from European and Canadian populations.[1-3] It results from the development of autoantibodies against factor VIII,[4-6] leading to spontaneous bleeding, most commonly in the skin, muscles, soft tissue, or mucous membranes.[6] Unlike inherited hemophilia, AHA occurs in individuals without a personal or family history of bleeding disorders. Approximately 50% of cases are idiopathic, while the remaining cases are associated with underlying autoimmune conditions, pregnancy, medications, or malignancy.[7]

AHA predominantly affects the elderly, with incidence increasing with age and a median onset in the mid-to-late 70s.[2,3,8] Here, we report the case of an elderly male diagnosed with AHA. He presented with a right thigh hematoma and severe anemia (hemoglobin 3.9 g/dL) following a fall at home three weeks prior. Due to the rarity of AHA, this factor VIII deficiency disorder was not initially considered in the differential diagnosis for adult anemia, leading to a delayed diagnosis and treatment.[1,7]

## CASE REPORT

An 82-year-old male was brought to the emergency department from his assisted living facility with a one-week history of fatigue and pallor. On admission, his hemoglobin was critically low at 3.9 g/dL, and he had a healing right lower flank bruise from a fall three weeks prior. His vital signs were stable, and initial labs showed thrombocytosis (platelets 586,000/uL) and an elevated reticulocyte count (13.9%). Lactate dehydrogenase was slightly elevated (333 U/L, reference: 81-234 U/L), but haptoglobin, total bilirubin, and direct/indirect antiglobulin tests were normal. Two units of packed red blood cells (pRBCs) were transfused.

The patient had a history of moderate dementia (type unspecified), depression, Type 2 diabetes, chronic iron-deficiency anemia, degenerative joint disease, chronic obstructive pulmonary disease (from prior tobacco use), and a remote history of surgically resected bladder cancer. No personal or family history of bleeding disorders or prior significant bleeding events were reported. His home medications included donepezil, sertraline, metformin, ferrous sulfate, and ibuprofen. He denied hematochezia, hematuria, hemoptysis, or hematemesis, though staff noted dark stools from iron supplementation.

A computed tomography (CT) scan of the abdomen and pelvis revealed nodular thickening of the urinary bladder, raising suspicion for malignancy. Initial differentials included occult gastrointestinal (GI) bleeding, nutritional deficiency, and hemolytic anemia. Hemolysis was deemed unlikely due to normal bilirubin and antibody levels, and nutritional deficiencies were considered less likely given ongoing iron supplementation and stable weight. Gastroenterology and hematology/oncology were consulted. Esophagogastroduodenoscopy was unremarkable, and colonoscopy was deferred due to poor bowel preparation. The patient received folate, pantoprazole, and a short course of vitamin B12, while iron supplements were temporarily held to monitor for melena. Donepezil and sertraline were continued inpatient.

Despite six pRBC transfusions over four days, the patient was unable to maintain a hemoglobin >7.0 g/dL. By Day 4, frank melena developed, and subcutaneous hematomas appeared in dependent areas (upper and lower back/buttocks). Coagulation studies revealed a significantly prolonged activated partial thromboplastin time (aPTT) of 97 seconds, with normal prothrombin time (PT) and international normalized ratio (INR). Prednisone (1 mg/kg) was initiated.

On Day 6, bleeding diathesis studies confirmed AHA, with severe factor VIII deficiency (<0.5% activity; normal 63-117%) and an FVIII inhibitor titer of 2.4 Bethesda Units (BU). The patient required four additional pRBC transfusions and received recombinant activated factor VII (rFVIIa) from Days 7-9, after which melena resolved and hemoglobin stabilized at 8.5 g/dL. However, over the following days, hemoglobin declined, and subcutaneous hematomas expanded (Figure 1).

By Day 14, another transfusion was required, along with rFVIIa administration on Days 14-15 and intravenous immunoglobulin (IVIG) on Day 15. Hemoglobin initially stabilized at 7.8 g/dL but fell to 6.0 g/dL by Day 18, with melena progressing to significant hematochezia. Despite further transfusions and rFVIIa, the patient succumbed to internal bleeding, severe anemia, and hypovolemic shock on Day 19 (Figure 2).

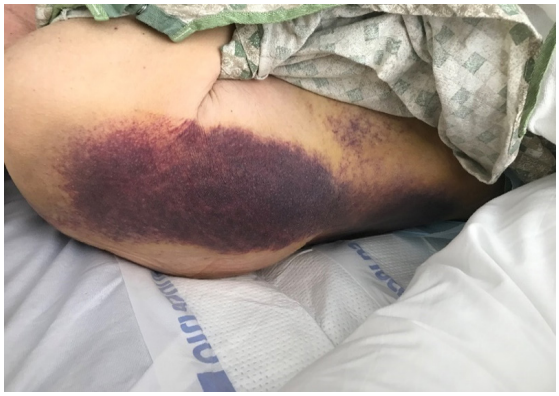

**Figure 1.** Subcutaneous hematoma on Day 10.

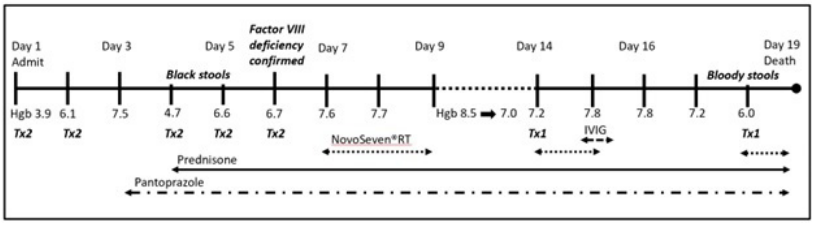


**Figure 2.** Timeline of key events, including hemoglobin levels, clinical symptoms, and treatments provided to patient during his 19-day hospitalization.
Note: Hgb, hemoglobin (normal range 14.0-18.0 mg/dL); T, Transfusion; NovoSeven® RT, coagulation Factor VIIa, recombinant; IVIG, intravenous immunoglobulin.

## DISCUSSION

Over the past few decades, there has been a slight uptick in the incidence rate of AHA secondary to greater awareness of AHA and/or underdiagnosis in previous studies.[1] Nevertheless, the true incidence is likely underestimated since AHA often is not considered on the differential for bleeding in an elderly patient,[6] possibly due to a higher propensity of GI bleeds in this population coupled with the higher likelihood of using non-steroidal anti-inflammatory drugs and anticoagulants. AHA was not included in the initial differential diagnosis in this case. Instead, our initial working diagnosis was lower GI bleed, possibly from a colorectal cancer or diverticular bleed, given patient's age, history of dark stools, no recent colonoscopy per assisted living staff, and history of iron deficiency anemia. As such, gastroenterology was consulted first rather than hematology. This resulted in diagnostic and treatment delays, and ultimately a fatal bleed 19 days after initial presentation despite aggressive treatments.

The hallmark of AHA is an isolated prolongation of aPTT, with normal PT and platelet count in patients with no personal or family history of bleeding disorders.[6] Though our patient met criteria for AHA, the prolonged aPTT was initially overlooked as a lab error. Due to low suspicion for AHA, the aPTT was not initially repeated, subsequently delaying diagnosis and treatment by six days. Delayed diagnosis of AHA is common since clinicians often do not have a high index of suspicion for an acquired bleeding disorder, coupled with misinterpretation of lab results.[9] One retrospective study reported the median time to diagnosis from onset of bleeding was 14 days.[10] Patients on anticoagulation therapy further confound diagnosis and delay treatment.[10] Delayed diagnosis have been associated with poorer treatment outcomes and higher mortality rates.[10,11]

The mainstay of AHA treatment involves immunosuppressive therapy and blood products. Prednisone was started on Day four due to initial concerns for non-immune hemolytic anemia. Recombinant Factor VIIa was started on Day seven following AHA diagnosis. This two-pronged treatment approach served to eradicate autoantibodies and circumvent the neutralized FVIII, thus controlling bleeding. Hemoglobin stabilized within one day of starting recombinant FVIIa; however, by Day 14, rebleeding occurred with a drop in hemoglobin. Bleeding recurrence after initial response to therapy is common: the European Acquired Haemophilia Registry reported bleeding recurrence in 25% of cases, with a median time to bleeding recurrence of 14 days.[11] Our patient was restarted on recombinant FVIIa, as well as treated with IVIG and solumedrol, in addition to ongoing prednisone. His hemoglobin once again stabilized for four days; however, by Day 18, our patient developed melena, transitioning to frank blood and expired hours later.

Despite optimal treatment, fatal bleeding occurs in up to 10% of AHA cases.[2,8,11] Collins and colleagues reported bleeding was the cause of death in 9.1% of cases at a median of 19 days,[2] similar to the timeline of our patient. Eradication of autoantibodies is challenging, and patients may repeatedly bleed during the weeks to months of treatment required to eliminate the autoantibodies.[12] The addition of cyclophosphamide may have improved our patient's outcome since the combination of prednisone and cyclophosphamide has been shown to achieve complete remission with undetectable inhibitor levels more often than with prednisone alone.[13] However, in our case, we suspect an underlying malignancy was driving autoantibody production. Without treating the neoplasm, autoantibody eradication would have been difficult. Our patient had a history of bladder cancer with CT imaging during his admission concerning for bladder cancer recurrence. Unfortunately, he was too critically ill to initiate cancer treatment. Sallah and colleagues found that over 50% of cancer patients with AHA were unable to achieve undetectable factor VIII inhibitor levels despite immunosuppressive treatment and died from bleeding within two months of AHA diagnosis.[9]

Most hemorrhagic deaths associated with AHA occur within the first few weeks after initial presentation as observed with our patient.[4,6,7] Resuming the patient's home sertraline and donepezil may have contributed to our patient's predisposition for ongoing GI bleeding. Selective serotonin reuptake inhibitors (SSRI) use has been associated with increased risk of bleeding, particularly in the GI tract.[14,15] SSRI-related bleeding likely is underreported due to limited awareness among patients and physicians of this increased risk of bleeding.[14] Serotonin is needed for primary platelet activation and aggregation.[15,16] SSRIs reduce storage of serotonin in platelet granules.[15] Diminished serotonin storage in platelets may interfere with platelet aggregation, and subsequent hemostasis.[16] Taken together, continuing home sertraline may have exacerbated bleeding in our patient who already was predisposed to elevated bleeding risk from advanced age and an underlying bleeding disorder. Acetylcholinesterase (AChE) inhibitors, including donepezil, have been implicated in increased risk for bruising and bleeding.[17-20] A recent ex vivo study examining human platelet activation found donepezil inhibited platelet activation, and posited that drugs inhibiting AChE may promote bleeding.[21] It remains unclear if continuing our patient's home donepezil may have contributed to his fatal bleed.

## CONCLUSIONS

Important teaching points from this case include the following: AHA should be on the differential when considering an elderly patient with bleeding due to the potential for a life-threatening bleed. Physicians need a high index of suspicion for this acquired bleeding disorder along with careful interpretation of laboratory results. More awareness is needed regarding the increased risk of bleeding with commonly used medications, particularly in patients with an underlying bleeding disorder.

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KANSAS JOURNAL of MEDICINE

*Case Report*

# Diagnostic Challenges in Neurosarcoidosis: A Complex Case of an Elderly Patient with a History of B-cell Lymphoma

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## INTRODUCTION

Sarcoidosis is a multisystem inflammatory disease of unclear etiology. It presents with non-caseating granulomatous lesions, primarily in the mediastinal lymph nodes as bilateral lymphadenopathy, but it can affect any organ system.[1] The disease has a genetic association, with a higher incidence in African Americans than in Whites (34 vs. 11 cases per 100,000). The pulmonary system is involved in 60-65% of cases, while extrapulmonary sarcoidosis occurs in 25-30% of cases.[2]

Neurosarcoidosis (NS) is a form of sarcoidosis that affects the cranial and peripheral nerves, brain, spinal cord, leptomeninges, and muscles. It can present with facial nerve palsy, optic neuritis, aseptic meningitis, and lesions in the brain or spinal cord. Severe complications occur in 5-10% of patients, including focal neurological deficits, hydrocephalus, encephalopathy, psychosis, peripheral neuropathy, and myopathy.[3] Diagnosing NS is challenging due to its nonspecific and varied presentation. Between 30% and 70% of patients exhibit neurological symptoms at initial diagnosis, and about half of them also have systemic sarcoidosis.[4] NS can present either in isolation or alongside systemic sarcoidosis.[5,6] Given its significant morbidity and an overall mortality rate of 5-20%,[3,7,8] NS should be considered in the differential diagnosis of patients with unexplained neurological symptoms.

There is no specific diagnostic marker for NS, but the following criteria aid diagnosis:

a. Radiological evidence of non-caseating granulomatous inflammation with compatible clinical presentation.
b. Pathological confirmation of systemic sarcoidosis via biopsy.
c. Nervous system biopsy consistent with NS, with or without systemic involvement.[9]

Diagnostic tests, including ophthalmologic exams, chest X-rays, angiotensin-converting enzyme (ACE) levels, and contrast-enhanced magnetic resonance imaging (MRI), provide supportive evidence. Extensive blood work is necessary to rule out alternative diagnoses such as infections or malignancies, including tests for vitamin deficiencies, toxins, serum tumor markers, and relevant serologic or blood cultures. Despite newer therapeutic options, corticosteroids remain the first-line of treatment.[8]

We present a case of NS in an elderly patient with a history of B-cell lymphoma but no systemic involvement.

## CASE REPORT

A 72-year-old female with history of diffuse large B-cell lymphoma (DLBCL), mitral valve prolapse, Addison's disease, and hypothyroidism was admitted to the hospital with delirium, confusion, lower extremity weakness, and urinary incontinence. She had been diagnosed with stage 4B DLBCL five years prior and had undergone six cycles of R-CHOP chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). She had been in remission for the past two years and was receiving routine follow-up care from her primary care physician and oncologist. The patient also had residual bilateral leg numbness, attributed to chemotherapy-induced peripheral neuropathy.[10]

Three months before this admission, she had been hospitalized for similar symptoms, including bilateral lower extremity weakness and urinary incontinence. Given her medical and oncologic history, an extensive workup was performed, including a complete blood count (CBC) with differential, peripheral blood smear, comprehensive metabolic panel (CMP), thyroid panel, urinalysis with reflex culture, and cerebrospinal fluid (CSF) analysis. Laboratory results were within her baseline values, and CSF cytology was inconclusive. Flow cytometry was negative for malignant cells. Extensive antibody screening for inflammatory, paraneoplastic, and autoimmune diseases also was negative. However, an elevated ACE level was noted, while serum calcium, vitamin D, and parathyroid hormone (PTH) levels were unremarkable. Urinalysis was positive for leukocyte esterase and nitrites, and urine cultures grew *Escherichia coli* (*E. coli*), confirming a urinary tract infection.

Imaging studies, including a computed tomography (CT) scan of the chest, abdomen, and pelvis, showed no lymphadenopathy or other masses. A non-contrast MRI of the spine revealed an extensive abnormal signal from T5/6 to the conus medullaris of the central spinal cord, raising concerns for syringomyelia, acute myelitis, or a neoplastic process. A contrast-enhanced MRI of the cervical, thoracic, and lumbar spine demonstrated intramedullary enhancement at T9-T10, consistent with acute myelitis, along with degenerative disc disease and spinal stenosis at C5/6. MRI of the brain showed mild T2/FLAIR hyperintensities in the supratentorial white matter, predominantly periventricular. The differential diagnosis included chronic microangiopathy, transverse myelitis, demyelinating disease, and migraine vasculitis. The patient was treated with intravenous glucocorticoids and ceftriaxone for five days. Given her improvement and preference, a spinal cord biopsy was deferred. The urinary tract infection resolved with antibiotics, and she was discharged to a rehabilitation facility for lower extremity strengthening.

One month later, she was readmitted with recurrent urinary incontinence and lower extremity weakness. MRI of the lumbar and thoracic spine showed an interval increase in enhancement within the thoracic spinal cord from T9-T11, with an associated syrinx from T4-T5, raising suspicion for an intramedullary mass. CSF cytology and flow cytometry remained negative. Given the possibility of central nervous system (CNS) relapse of DLBCL, a bone marrow biopsy was performed. A spinal cord biopsy was again recommended but deferred. A

multidisciplinary team discussion was held, and the patient opted for a therapeutic trial of radiotherapy. She received 10 cycles of external beam radiation (total dose: 3,000 cGy) to the thoracic spine. Due to her history of Addison's disease and prior responsiveness to systemic steroids, she also was treated with dexamethasone in addition to hydrocortisone. By the sixth cycle of radiation, her lower extremity weakness showed partial improvement, but urinary incontinence persisted. Repeat urinalysis was negative for infection. After completing radiation, she was transferred to inpatient rehabilitation on a three-week dexamethasone taper.

During rehabilitation, she developed dysuria, and urine cultures were positive for *E. coli* and *Proteus vulgaris*. She was treated with a seven-day course of cefdinir. Shortly thereafter, she was transferred back to acute care due to fever, worsening leg weakness, and thrombocytopenia. Brain MRI showed scattered diffusion abnormalities in the right posterior frontal and occipital lobes, along with microvascular infarcts and patchy leptomeningeal enhancement restricted to the right occipital lobe. Repeat thoracic spine MRI showed persistent T2 signal changes but decreased craniocaudal enhancement compared to prior imaging. Urine cultures revealed multi-drug-resistant *E. coli*, and meropenem was initiated based on culture sensitivities.

A repeat bone marrow biopsy was performed, which showed no evidence of lymphoma but revealed non-necrotizing granulomatous inflammation. This prompted a broader differential diagnosis, including infectious, rheumatologic, and neoplastic causes. Further workup included bronchoscopy with bronchoalveolar lavage (BAL), urine and blood cultures, CSF studies, and serologic testing. BAL was negative for malignancy, organisms, acid-fast bacilli, *Histoplasma* antigen, and *Pneumocystis jirovecii*, showing only a reactive lymphoid infiltrate. QuantiFERON® Gold testing for tuberculosis was negative. CSF studies ruled out viral, fungal, and bacterial infections. Antibody panels for paraneoplastic syndromes, vasculitis, and autoimmune diseases were negative. A CT angiogram of the chest ruled out pulmonary embolism but showed findings consistent with severe acute lung injury, including ground-glass opacities, septal line thickening, and varicoid bronchial dilation, suggesting diffuse alveolar damage.

After ruling out CNS lymphoma, infections, and autoimmune conditions, a diagnosis of NS was made. This was based on the presence of chronic granulomatous inflammation in the bone marrow, pancytopenia, persistent T2 signal changes in the thoracic spinal cord (T9-T11), and abnormal brain MRI findings. The patient was transferred to the intensive care unit due to worsening respiratory distress and hypoxia. She was intubated, mechanically ventilated, and started on intravenous methylprednisolone (1,000 mg for three days), followed by prednisone (60 mg daily). Despite aggressive treatment, she developed septic shock requiring vasopressors. On day five, she succumbed to refractory shock and cardiopulmonary arrest.

## DISCUSSION

NS exhibits considerable variability in outcomes, influenced by several critical factors. These include the severity and extent of disease, the specific neuroanatomical sites involved, and the timeliness of presentation and diagnosis.[3]

In the presented case, the patient's symptoms of lower extremity weakness and urinary incontinence were nonspecific. NS can manifest as spinal cord lesions and peripheral nerve involvement. Approximately 5-10% of patients with sarcoidosis initially present with neurological symptoms.[7] Notably, patients with cranial nerve involvement are more likely to receive an early diagnosis and have better outcomes. This contrasts with the current case, where peripheral neuropathy was the presenting feature. A study of 54 patients with NS found that certain clinical presentations correlated with better outcomes.[11] For example, patients with cranial neuropathies (except for bilateral optic neuritis), myelopathies, seizures, and headaches had a higher likelihood of favorable responses to treatment. In particular, most patients with facial nerve palsy or hearing loss showed either complete resolution or significant improvement.[11]

Serologic tests commonly used in diagnosing sarcoidosis include ACE, adenosine deaminase, serum amyloid A, and soluble interleukin-2 receptor. In this case, the patient had an elevated ACE level, while all other tests were negative. However, the diagnostic utility of ACE remains controversial. A meta-analysis reported a sensitivity of 76% and specificity of 80%, suggesting that while serum ACE levels may assist in diagnosing and assessing disease activity in sarcoidosis, isolated ACE measurements should be interpreted with caution.[12]

The differential diagnosis of noncaseating granulomas is broad and includes infectious, malignant, autoimmune, and toxic etiologies, as well as sarcoidosis. Diagnostic tests such as blood cultures, BAL, viral screening, flow cytometry, neoplastic and paraneoplastic antibody panels, and inflammatory markers can help narrow the differential.[13] In this case, an extensive workup was largely unremarkable. The presence of noncaseating granulomas, elevated ACE levels, and radiological findings ultimately supported the diagnosis of NS.

Primary central nervous system lymphomas (PCNSL) are aggressive malignancies, almost always due to DLBCL.[14] While 40% of DLBCL patients experience relapse or refractory disease, only 2-5% have CNS involvement, making such relapses rare but often devastating.[15,16] Moreover, the variable radiological features in immunocompetent versus immunocompromised patients further complicate diagnosis.[17] Although tissue biopsy remains the gold standard, radiological findings and CSF studies can be useful in cases where biopsy is not feasible.[18] Given the patient's spinal cord involvement, a trial of radiation therapy was considered.

A 2020 study examined the time to diagnosis in patients with sarcoid-associated myelopathy. Among those without a prior sarcoidosis diagnosis, the median time from symptom onset to NS diagnosis was five months. However, delays varied significantly, ranging from 1 to 50 months, depending on MRI findings.[11] Regarding disease outcomes, 52% of patients experienced moderate to severe disability. After one year, 50% showed improvement, 26% worsened, and 24% remained stable.[10] This variability in time to diagnosis highlights its potential impact on prognosis, as delayed treatment may contribute to disease progression.

## CONCLUSIONS

Both NS and CNS lymphoma can present with similar neurological deficits, creating significant diagnostic challenges.[19] Additionally, both conditions can have nonspecific radiological findings, further complicating differentiation. This case underscores these challenges, particularly given the patient's history of DLBCL, which has the potential to progress to CNS lymphoma. While bone marrow biopsy, radiological findings, and clinical presentation can aid in diagnosis, prognosis remains poor despite advancements in diagnostic techniques.

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*Keywords: Neurosarcoidosis, B- cell Lymphoma*

KANSAS JOURNAL of MEDICINE

*Case Report*

# Epstein-Barr Virus (EBV) Induced Hemophagocytic Lymphohistiocytosis (HLH) with Granulomatous Hepatitis

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## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of immune hyperactivation that can result in severe multiorgan failure and death. This disease has classically been described in the pediatric setting but over the past decade has garnered more notoriety in adult populations. The true incidence rate in adults is unclear and suspected to be underdiagnosed.[1] A retrospective cohort study conducted from 2006 to 2019 in the United States found over 16,000 non-elective admissions for HLH and observed an increasing rate of HLH diagnoses during this time period which could be attributed to increased awareness.[2] In clinical practice, early recognition and diagnosis of HLH is critical, as mortality is high without timely intervention to control the immune response. Making the diagnosis of HLH can be difficult as its presentation can mimic other disease processes in the presence of confounders such as sepsis.[3]

In this case report, we discuss an adult patient who initially presented with jaundice and acute liver injury, requiring hospitalization with extensive multidisciplinary workup before revealing a diagnosis of HLH secondary to acute Epstein Barr Virus (EBV) infection. Acute liver injury has a broad differential diagnosis, and this case illustrates the exceptional difficulty providers encounter in making the diagnosis of HLH.

## CASE REPORT

A 34-year-old male with no significant medical history presented to his primary care physician with sore throat, malaise, intermittent fever, nausea, vomiting, and jaundice. A positive MonoSpot™ test raised suspicion for a viral illness. Abdominal ultrasound revealed marked hepatosplenomegaly, with a spleen measuring 17.6 cm (normal range: 12-14 cm in adult males).[4] He was referred to the hospital for further evaluation.

On admission to the emergency department, he was afebrile but tachycardic, with palpable hepatosplenomegaly. Laboratory tests showed leukocytosis (WBC 13.4 K/µL, 85% neutrophils), anemia (Hb 7.5 g/dL), elevated liver enzymes (ALT/AST 258/249 U/L), hyperferritinemia (3,926 ng/mL), and marked hyperbilirubinemia (total bilirubin 39.4 mg/dL). Serum creatinine and platelet counts were within normal limits. A computed tomography (CT) scan of the abdomen and pelvis confirmed hepatosplenomegaly with punctate calcified granulomas in the spleen.

After transfer to our tertiary care hospital, repeat labs showed a further hemoglobin (Hb) decline to 6.3 g/dL. He received a transfusion of packed red blood cells and N-acetylcysteine for suspected EBV-induced acute liver injury. Minutes after starting the transfusion, he developed fever, tachycardia, and dyspnea, necessitating a rapid response activation and intensive care unit (ICU) transfer. The transfusion was stopped, and his symptoms resolved, but his Hb dropped further to 5.0 g/dL, with worsening hyperbilirubinemia (total bilirubin 47.7 mg/dL, direct bilirubin 26.4 mg/dL) and acute kidney injury (creatinine 2.57 mg/dL, up from 0.8 mg/dL baseline). Additional labs showed hypertriglyceridemia (538 mg/dL), hypofibrinogenemia (71 mg/dL), and elevated LDH (725 U/L). Hematology initiated high-dose steroids (methlyprednisolone 1 mg/kg divided twice daily) and plasmapheresis for suspected autoimmune hemolytic anemia (AIHA), leading to Hb stabilization at 7.5 g/dL.

Infectious diseases and gastroenterology were consulted. Empiric ceftriaxone (2 g IV daily) and doxycycline (100 mg PO twice daily) were started for suspected tick-borne illness. EBV serologies revealed positive capsid IgG, capsid IgM, and early antigen antibodies, with negative nuclear antigen antibody and an EBV PCR of 16,300 copies, confirming acute EBV infection. Tests for viral hepatitis, syphilis, HIV, parvovirus B19, and tick-borne illnesses were negative. A direct Coombs test was positive for C3, suggesting cold agglutinin syndrome, which was corroborated by an elevated cold agglutinin titer (1:128, normal <1:32). However, hemolysis markers (haptoglobin and indirect bilirubin) were normal.

A bone marrow biopsy and repeat peripheral smear showed trilineage hematopoiesis with 1% blasts, and hemophagocytosis in neutrophils and monocytes on the smear, though not in the marrow biopsy. A liver biopsy revealed granulomatous hepatitis with fibrin-ring granulomas, cholestasis, scattered EBV-positive lymphoid cells (Figure 1), and sinusoidal hemophagocytosis, supporting a diagnosis of EBV-induced HLH. IL-2 receptor was markedly elevated at 7,611 pg/mL (RR 175-852 pg/mL).

The patient remained on high-dose steroids with clinical improvement, allowing discontinuation of antibiotics. Etoposide and rituximab were considered but deferred as his condition improved on steroids alone. He required only two plasmapheresis treatments, and his hemoglobin stabilized without further transfusions. He was discharged on hospital day seven with an eight-week dexamethasone taper and prophylactic trimethoprim-sulfamethoxazole (80/400 mg PO daily).

At discharge, his hemoglobin was 8.4 g/dL, total bilirubin had decreased to 4.4 mg/dL, and ferritin was 745 ng/mL. Two months post-discharge, EBV PCR was negative, and liver and renal function had normalized. By the end of his steroid taper, ferritin had declined to 355 ng/mL. Follow-up positron emission tomography (PET)/CT imaging at 10 weeks showed significant improvement in hepatosplenomegaly, and he had returned to his baseline health.

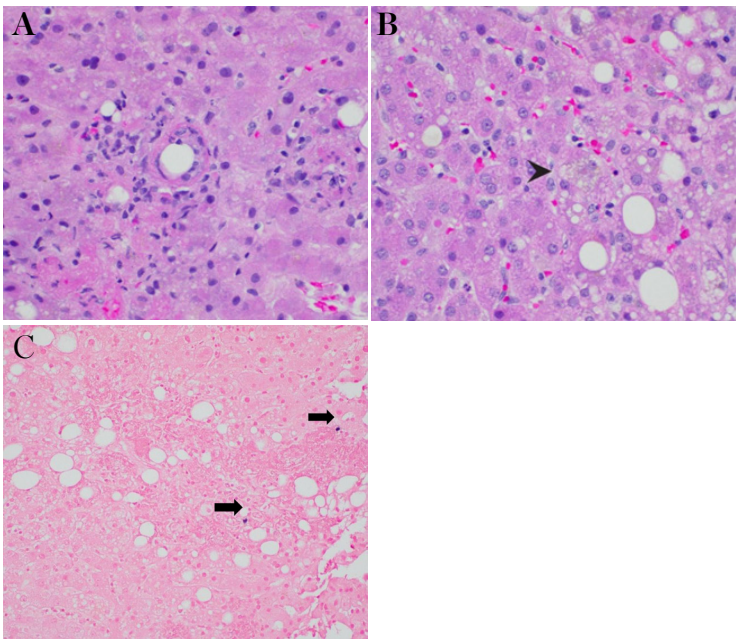


**Figure 1.** Liver core biopsy histopathology. A) Fibrin ring granuloma characterized by a central fat droplet surrounded by a ring of fibrin and epithelioid histiocytes (400X magnification, hematoxylin and eosin (H&E) stain). B) Hepatocellular cholestasis (arrowhead) and hemophagocytosis within sinusoids (400X magnification, H&E stain). C) In situ hybridization for Epstein-Barr virus (EBV) shows scattered positive lymphoid cells (200X magnification).

## DISCUSSION

HLH is a syndrome of immune hyperactivation caused by various triggers depending on the patient population. It is characterized by dysregulated activation of T cells and macrophages, leading to a cytokine storm, systemic inflammation, multiorgan dysfunction, and cytopenias. Clinically, HLH often mimics sepsis, most triggered by infections or hematologic malignancies. Previously considered primarily a pediatric disease, increasing literature has highlighted its occurrence in adults. Adult HLH carries a high mortality rate, potentially greater than in pediatric cases, with estimates ranging from 20% to 40%. Given its severity, early diagnosis and treatment are critical.[5-8]

Diagnosing HLH in adults is challenging due to its overlap with other conditions. While pediatric HLH often is linked to genetic mutations (familial/primary HLH), adult HLH typically arises from an underlying disease (secondary/reactive HLH).[5,7] Common triggers include infections, malignancies, and autoimmune disorders, with immune checkpoint inhibitors and chemotherapy also implicated.[5,9] A 2014 study of 2,197 adult HLH cases found infections responsible for 50.4% of cases, with hematologic malignancies accounting for 44.6%.[6] Among infections, viruses were the most frequent triggers (34.6%), with EBV being the most common (15%).[6]

EBV-related HLH occurs when the virus infects B cells, requiring cytotoxic immunity for viral clearance. Failure of this mechanism can lead to uncontrolled viremia and excessive cytokine activation.[10] Patients with underlying immune deficiencies, such as X-linked lymphoproliferative disease types 1 and 2, are at higher risk for EBV-induced HLH.[10,11]

The most widely used diagnostic criteria come from the *HLH-2004* study, which requires either a molecular diagnosis or at least five of the following eight criteria: fever, splenomegaly, cytopenias (affecting ≥2 lineages), hypertriglyceridemia, hemophagocytosis on bone marrow histology, decreased NK cell activity, hyperferritinemia, and elevated soluble IL-2 receptor levels.[12,13] However, these criteria were originally developed in pediatric populations, raising concerns about their applicability to adults, who are more likely to develop HLH from secondary causes. Comorbid conditions such as diabetes and hyperlipidemia also may affect laboratory markers, reducing diagnostic specificity.[14] Consequently, HLH in adults often is considered a diagnosis of exclusion, leading to delays in care and worse outcomes.

In this case, the patient met five *HLH-2004* criteria (splenomegaly, fever, hypertriglyceridemia/hypofibrinogenemia, hyperferritinemia, and elevated soluble IL-2). Although bone marrow biopsy did not confirm HLH, hemophagocytosis was present in both the peripheral blood smear and liver biopsy, alongside fibrin-ring granulomas and EBV-positive lymphoid cells, findings consistent with active EBV infection, a known HLH trigger.[15]

Given the limitations of *HLH-2004* criteria in adults, alternative diagnostic tools have been proposed.[2,14] The HScore, developed in *Arthritis & Rheumatology*, assesses nine clinical and laboratory parameters to estimate the probability of HLH. Our patient had an HScore of 219, corresponding to a 96% likelihood of HLH.[16]

Additionally, a retrospective study at MD Anderson reviewed 61 cases of confirmed adult HLH and found that only 21% met *HLH-2004* criteria, though many had incomplete workups.[17] To improve diagnostic accuracy, researchers expanded the *HLH-2004* criteria from 8 to 18 variables while maintaining the requirement that at least five be met for diagnosis.[17] New criteria included renal failure, elevated liver enzymes, coagulopathy, hypoalbuminemia, and increased LDH. Applying this expanded system, our patient met 10 of 18 criteria.

Current HLH treatment strategies are largely derived from pediatric studies (*HLH-94*[12] and *HLH-2004*[13]), which emphasize etoposide and steroid therapy, with hematopoietic stem cell transplantation (HSCT) for refractory cases. Cyclosporine was initially included in induction therapy, but subsequent studies failed to show additional benefit.[13] No major clinical trials specifically guide adult HLH treatment, leading to therapeutic uncertainty.

In this case, the patient responded rapidly to steroids and plasmapheresis, which were initiated for suspected autoimmune hemolytic anemia rather than HLH.[18] By the time HLH was confirmed, etoposide was deferred. Although rituximab is sometimes used for EBV-HLH in cases of high viremia, it was unnecessary here.

Despite increasing recognition, adult HLH remains difficult to diagnose due to its nonspecific presentation and overlap with other conditions. The *HLH-2004* criteria lack specificity in adults, and some diagnostic tests (e.g., soluble IL-2 receptor) are costly and time-consuming. Although alternative markers like glycosylated ferritin and IL-18 have been explored, no large-scale trials have validated their utility. Refining diagnostic strategies, especially for adult and EBV-associated HLH, remains a critical need.

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*Keywords: critical care, hemophagocytic lymphohistiocytosis, EBV*

KANSAS JOURNAL of MEDICINE

*Case Report*

# Hypertensive Crisis Following Co-ingested Tobacco, Marijuana, and Red Wine: A Case Report

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## INTRODUCTION

Monoamine oxidase (MAO), an enzyme found in the stomach, intestines, and liver, metabolizes tyramine as well as other monoamines, including dopamine and norepinephrine (NE). For most individuals, consuming tyramine-rich foods, such as red wine, dark chocolate, hard cheeses, and fermented foods, does not pose a problem. However, hypertensive crises following excessive tyramine ingestion are well-documented, particularly in patients taking monoamine oxidase inhibitors (MAOIs) for depression.[1]

When MAO is inhibited, tyramine enters systemic circulation and is taken up by nerve terminals via the NE uptake pump, displacing NE from intracellular stores. The resulting surge of NE in the bloodstream leads to increased blood pressure.[1] Since MAO also metabolizes NE, its inhibition allows unchecked NE accumulation, potentially triggering hypertensive emergencies.

We report a case of debilitating dizziness episodes culminating in a hypertensive emergency in an older woman. No definitive cause of her hypertensive crisis was identified; however, the temporal and repeated association of symptoms with red wine ingestion suggested possible MAO inhibition. In the absence of relevant case reports, we explore whether chronic cannabis and tobacco use may have contributed to insidious inhibition of monoamine oxidase-A (MAO-A), the primary isoform in the gut and liver.

## CASE REPORT

A 72-year-old Caucasian woman with a history of well-controlled mild hypertension, hypercholesterolemia, depression, and prediabetes presented for an office visit due to worsening episodes of dizziness and nausea. She had high health literacy, was medication-compliant, and had a BMI of 17.8. Her medications included sertraline 50 mg, atorvastatin 40 mg, and amlodipine 2.5 mg. She engaged in moderate physical activity weekly, followed a low-sodium Dietary Approaches to Stop Hypertension (DASH)-compliant diet, and consumed approximately 12 ounces of wine once per week. She had a 40-pack-year smoking history, reporting "10 smokes/day," later revealed to be hand-rolled cigarettes containing both tobacco and marijuana.

The patient had been on amlodipine 2.5 mg daily for years. Two years prior, she discontinued amlodipine and simultaneously stopped smoking, but when she resumed smoking, she required the reintroduction of amlodipine. Her dizziness began approximately nine months before admission, initially positional and associated with recumbency and physical therapy for left hip osteoarthritis. During a telehealth visit, she was diagnosed with benign paroxysmal positional vertigo (BPPV) and advised on maneuvers to alleviate symptoms. Her dizziness resolved within a month without intervention, and her blood pressure (BP) increased from low levels. Three months later, she underwent a left hip replacement, completed post-operative therapy, and was able to walk up to three miles. Despite ongoing intermittent dizziness, nausea, and epigastric discomfort, a trial of proton-pump inhibitors was declined in favor of dietary adjustments and probiotics, which did not alleviate symptoms.

Her dizziness worsened significantly following a weekly social event where she consumed 350 mL (11 ounces) of red wine. She awoke with dizziness, nausea, and dry heaves, remaining bedridden for two days. The dizziness was described as profound disequilibrium and instability rather than vertigo. A second episode followed after reducing wine intake to 125 mL (4.2 ounces). In response, she maintained a food diary, reduced dairy intake, and tried over-the-counter remedies for her symptoms. Concerned about hypotension, she discontinued amlodipine without checking her BP at home. Upon evaluation the next day, her BP was normal, but it subsequently increased to ~150/80 mmHg, the highest she recalled. Amlodipine was restarted.

Four days later, she reported nearly five weeks of persistent dizziness, primarily occurring after wine consumption. Examination revealed intact cranial nerves and a normal ENT and cardiovascular exam. Lateral nystagmus was provoked but did not reproduce symptoms, making BPPV unlikely. Her BP was 162/90 mmHg, decreasing to 122/72 mmHg on retake, and no medication adjustments were made. One week later, she returned with profound ataxia and disequilibrium, describing a need to hold onto walls while ambulating but denying vertigo or orthostatic symptoms. She was alert, oriented, and had no neurological deficits. Her BP readings were 164/86 mmHg sitting, 162/100 mmHg standing, and 182/106 mmHg supine.

Due to concerns for hypertensive emergency and possible cerebrovascular accident (CVA), she was sent to the emergency department (ED). While hospitalized, she disclosed for the first time that she regularly smoked "spliffs" (hand-rolled cigarettes with equal parts tobacco and cannabis), about 10 per day. Imaging (computed tomography angiography and magnetic resonance imaging) was negative for CVA. Her BP improved to ~150/70 mmHg with an increase in amlodipine to 5 mg. She abstained from smoking during hospitalization, and urine drug testing was positive only for tetrahydrocannabinol (THC).

At discharge, she was advised to continue amlodipine 5 mg and to reduce or cease smoking. She fully discontinued smoking within 10 days post-discharge, with a negative cannabinoid screen after four weeks. Her nausea and abdominal discomfort resolved following smoking cessation, with no further adverse events. Table 1 shows the timeline of events.

**Table 1. Timeline of events.**

| Time | Dizziness | Amlodipine (mg) | Blood Pressure (mm Hg) | |
|---|---|---|---|---|
| | | | Office | Home |
| Month -28 to -10 | absent | 2.5a | 130/80 | 129/80 |
| Month -9 | moderate | 2.5 | n/a | 115/78 |
| Month -8 to -1 | absent | 2.5 | 121/77 | 124/80 |
| Week -3 | severe | 2.5 | n/a | n/a |
| Week -2 | severe | 2.5 | n/a | n/a |
| Week -1 | mild | 0b | 122/72 | 137/83 |
| **Admission** | moderate | 2.5 | 182/106 | 151/92 |
| Week +1 | absent | 5 | 138/78 | 128/80 |
| Week +2 | absent | 5 | n/a | 129/81 |
| Week +3 | absent | 5 | n/a | 124/80 |
| Month +1 | absent | 5 | 122/66 | 127/78 |

Note: Office blood pressure (BP) represents single or averaged double measurements; home BP is an average of 7 to 244 measurements. n/a = not available
(a) Amlodipine was discontinued by patient during 10-week smoking cessation; reinstated after resuming smoking and BP increased from 124/78 mmHg to 136/82 mmHg
(b) Amlodipine was discontinued by patient for 10d following severe dizziness; reinstated after home BP showed increase

## DISCUSSION

Given the lack of a clear etiology, pheochromocytoma was considered but deemed unlikely due to the patient's response to amlodipine and symptom association with red wine. MAO inhibition was not initially suspected, as her medication list lacked known inhibitors. However, after learning that she rolled her own cigarettes with tobacco and cannabis, we explored the possibility that MAO-A inhibition resulted from these substances.

Cigarette smokers have long been known to have 20-30% lower MAO-A activity than non-smokers.[2] The irreversible MAO-A inhibitor, 1,4-benzoquinone, was recently identified as a component of tobacco smoke that appears in physiological relevant concentrations.[3] Irreversible inhibition persists until new MAO-A is synthesized, on the order of weeks. Loose tobacco (used in self-rolled cigarettes) inhibits MAO-A more than factory-made cigarettes due to higher tar concentrations.[4] Simultaneous alcohol and cannabis use increases systemic THC levels, potentially exacerbating these effects.[5] Finally, chronic drug administration causes a change in the dose-response curve that describes inhibition of MAO,[6] allowing lower doses of inhibitors to cause the same degree of inhibition. The combined influence of loose tobacco, heavy cannabis use, and alcohol likely impaired MAO-A activity, increasing susceptibility to tyramine's sympathomimetic effects. Normally metabolized by MAO-A in the gut and liver, tyramine can accumulate when MAO is inhibited, leading to norepinephrine release and dangerous hypertensive episodes.[1] Elevated plasma tyramine levels have been linked to essential hypertension, and individual responses vary widely, with some experiencing extreme blood pressure spikes after dietary tyramine exposure.[7]

The patient had a long history of drug use without recent changes in frequency or source, raising the question of why hypertensive emergencies occurred now. Age-related factors, such as the natural increase in systolic blood pressure and reduced hepatic/renal function, may have contributed to prolonged drug effects. Moreover, MAO inhibition can be progressive, with time-dependent accumulation leading to increased sensitivity.[6]

Prodromal symptoms, including unexplained gastrointestinal discomfort, may have been early signs of tyramine accumulation. Although dizziness was initially attributed to BPPV, home monitoring showed hypotensive episodes, suggesting a complex interplay between tyramine and blood pressure regulation.

**Clinical Implications:**

- MAO inhibition should be considered in atypical hypertensive cases, especially in patients using tobacco, cannabis, and alcohol.
- Primary care physicians should be aware of increasing cannabis use among older adults. Daily or near-daily use is now more common than alcohol use in the U.S., and cannabis-related emergency visits among the elderly have risen sharply.
- A non-judgmental approach to substance use history can help uncover hidden risk factors. The patient underestimated the cardiovascular risks of smoking and cannabis, only recognizing them after a health crisis.

While this case strongly suggests MAO inhibition as the underlying mechanism, the absence of direct MAO activity measurements remains a limitation. The patient provided written informed consent for this report.

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*Keywords: Cannabis, tobacco use, tyramine, monoamine oxidase*

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*Case Report*

# A Case of Tumor-to-Tumor Metastasis: Breast Carcinoma Metastatic to Oncocytic Carcinoma of Thyroid

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## INTRODUCTION

Tumor-to-tumor metastasis is a rare and intriguing oncologic phenomenon in which one tumor metastasizes to the parenchyma of a separate primary tumor, which may be benign or malignant.[1] This occurrence adds complexity to cancer biology, challenging our understanding of tumor behavior, metastatic pathways, and diagnostic considerations.

In this case report, we present an instance of tumor-to-tumor metastasis involving breast carcinoma metastasizing to an oncocytic carcinoma of the thyroid. This case highlights the diagnostic challenges, clinical implications, and therapeutic considerations associated with this rare phenomenon.

## CASE REPORT

A 63-year-old female was initially diagnosed with hormone receptor-positive invasive ductal carcinoma of the left breast in 2008. In December 2009, she underwent a left breast excisional biopsy, which revealed a 1.5 cm, moderately differentiated invasive ductal carcinoma with a 20% micropapillary component. The tumor was estrogen receptor (ER) positive (70%), progesterone receptor (PR) positive (7%), and human epidermal growth factor receptor 2 (HER2) negative, with an antigen Kiel 67 (Ki-67) proliferation index of 23%. Surgical margins were positive, and peritumoral lymphatic invasion was present.

In January 2010, she underwent a left breast lumpectomy, which showed no residual carcinoma. One sentinel lymph node was excised and found to contain multiple micrometastases. Her pathologic stage was T1cN1mi (T1c: tumor >1 cm but ≤2 cm; N1mi: micrometastases in axillary lymph nodes, measuring 0.2-2 mm). She completed adjuvant chemotherapy with four cycles of docetaxel and cyclophosphamide, radiation therapy to the left breast and regional lymph nodes, and six years of tamoxifen.

The patient was lost to follow-up for several years but re-established care in July 2023. At that time, she was found to have a slightly elevated cancer antigen (CA) 27.29 level. A positron emission tomography (PET) scan in September 2023 (Figure 1) revealed hypermetabolic mediastinal lymphadenopathy, sclerotic osseous metastases with mild fluorodeoxyglucose (FDG) uptake, and an avidly hypermetabolic, enlarged, nodular right thyroid gland. A bone biopsy of the right inferior pubic ramus confirmed metastatic carcinoma positive for cytokeratin 7 (CK7) and GATA-binding protein 3 (GATA3), consistent with breast origin. Due to the decalcified and crushed nature of the bone biopsy, biomarker analysis could not be performed.

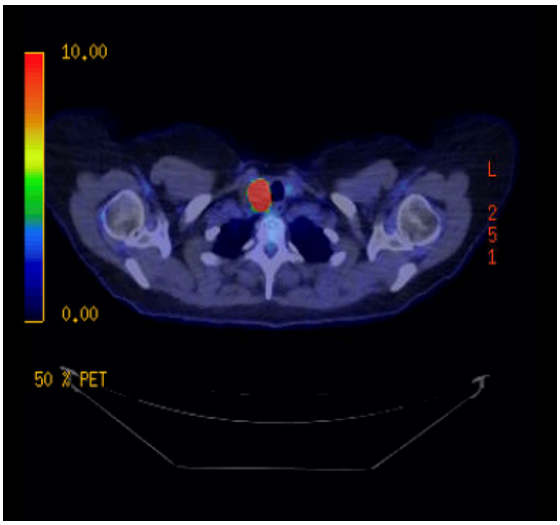


**Figure 1.** PET scan revealing avidly hypermetabolic right thyroid nodule.

Given her hypermetabolic mediastinal lymphadenopathy, an endobronchial ultrasound-guided fine needle aspirate (FNA) of the 11R lymph node was performed, revealing metastatic carcinoma positive for ER, GATA3, mammaglobin, and gross cystic disease fluid protein 15 (GCDFP15), and negative for thyroid transcription factor 1 (TTF1), consistent with metastatic breast carcinoma.

In November 2023, a thyroid ultrasound showed a right mid-thyroid hypoechoic nodule measuring 3.0 × 2.0 × 2.0 cm with a solid composition, categorized as TI-RADS 4 (suspicious, 5-80% malignancy). An ultrasound-guided right thyroid biopsy revealed follicular-patterned thyroid tissue without nuclear features of papillary thyroid carcinoma, leading to a differential diagnosis of thyroid follicular nodular disease or follicular neoplasm. A repeat FNA of the thyroid nodule was reported as atypia of undetermined significance. Afirma genomic sequencing classified the nodule as suspicious, with an estimated 50% risk of malignancy. *BRAF* p.V600E, *RET/PTC1*, and *RET/PTC3* mutations were not detected. She subsequently underwent a right hemithyroidectomy.

**Pathology Findings.** Gross examination revealed a 2.9 × 2.1 × 1.7 cm encapsulated follicular-patterned neoplasm (Figure 2). Hematoxylin and eosin (H&E)-stained sections showed an encapsulated oncocytic follicular neoplasm without nuclear features of papillary thyroid carcinoma. Foci of neoplastic follicular tumor cells were present within CD31-positive and D2-40-negative vascular spaces, confirming angioinvasion. Thus, a diagnosis of encapsulated angioinvasive oncocytic carcinoma of the thyroid was made.

Focally, involving <10% of the total nodule, was a distinct population of epithelial cells with non-oncocytic cytoplasm and a more ductal-glandular architecture. Immunohistochemistry demonstrated that these cells were strongly positive for GATA3 and ER (>95%) but negative for TTF1 and PAX8, consistent with metastatic breast carcinoma. In contrast, the adjacent oncocytic follicular epithelial cells were positive for TTF1 and PAX8 but negative for GATA3 and ER. The metastatic breast carcinoma was PR-negative and showed HER2 2+ expression by immunohistochemistry, with a nonamplified fluorescent

in situ hybridization (FISH) result.

A final diagnosis of metastatic ER-positive mammary carcinoma to an encapsulated angioinvasive oncocytic carcinoma of the thyroid was rendered. The patient was started on an aromatase inhibitor (AI) and a cyclin-dependent kinase (CDK) 4/6 inhibitor, along with a bisphosphonate for bone metastases.

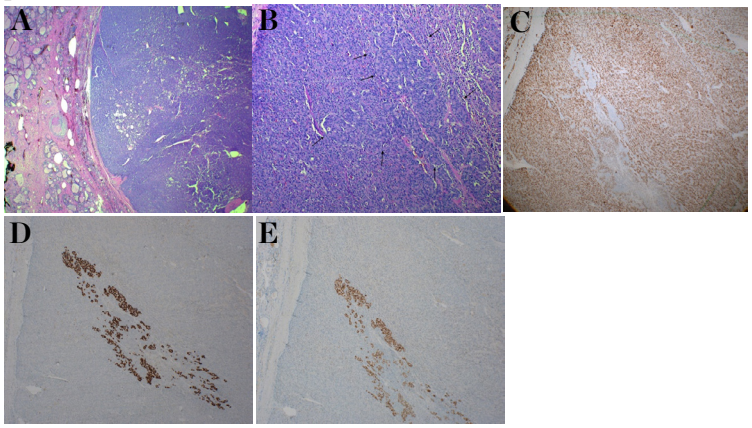


**Figure 2.** Metastatic breast carcinoma to an encapsulated angioinvasive oncocytic carcinoma of thyroid. A) H&E sections showed an encapsulated follicular neoplasm. B) Medium power shows a subtly distinct population of cells within the follicular neoplasm. Arrows pointing out foci of metastatic breast carcinoma. C) The second population of cells are negative for the thyroid marker PAX8 with the surrounding follicular neoplasm cells labeling as PAX8 positive. D) GATA3, and E) Estrogen Receptor (ER) are both positive in the breast carcinoma foci while the recipient thyroid neoplasm is negative for these markers.

## DISCUSSION

Thyroid oncocytic carcinoma, also known as oxyphilic or Hürthle cell carcinoma, is a distinct subtype of thyroid cancer characterized by oncocytic (Hürthle) cells, which exhibit abundant eosinophilic granular cytoplasm.[2] This case represents the first reported instance of mammary carcinoma metastasizing to thyroid oncocytic carcinoma, highlighting a rare and clinically significant phenomenon: tumor-to-tumor metastasis.

Tumor-to-tumor metastasis should not be confused with a collision tumor, in which one tumor non-hematogenously invades an adjacent tumor.[3] In contrast, tumor-to-tumor metastasis is a true hematogenous process, where circulating tumor cells from a primary malignancy travel through the bloodstream and lodge in the microvasculature of a secondary tumor.

Despite its rich vascularization, the thyroid gland is an uncommon site for metastatic spread, possibly due to its high arterial flow rate. A retrospective study by Moghaddam et al.[4] found metastatic carcinoma in only 0.46% of thyroid cancer specimens, underscoring the rarity of thyroid metastasis. However, the thyroid is among the most frequently reported recipients of tumor-to-tumor metastases,[5] suggesting that thyroid tumors may create a microenvironment conducive to metastatic colonization.

Among the 150 documented cases of tumor-to-tumor metastasis in the English-language literature, 29 involved a thyroid tumor as the recipient neoplasm.[6] It is possible that disruptions in vascular architecture and alterations in blood flow within thyroid neoplasms facilitate the extravasation of circulating tumor cells, leading to the formation of metastatic deposits.

The "seed and soil" hypothesis, first proposed by Stephen Paget in 1889, suggests that the microenvironment of the host tissue (the "soil") plays a crucial role in determining the metastatic potential of circulating tumor cells (the "seeds").[7] In tumor-to-tumor metastasis, the recipient tumor's microenvironment may serve as a supportive niche for metastatic cell survival and proliferation.

Several mechanisms may contribute to this phenomenon:

- Chemotactic and homing signals: The recipient tumor may secrete cytokines, growth factors, and extracellular matrix components that attract circulating tumor cells, promoting their migration and infiltration.
- Immune evasion: Metastatic tumor cells may evade immune surveillance within the recipient tumor, enabling them to establish metastatic foci undetected.[8]
- Immunosuppressive microenvironment: Both the primary and secondary tumors may produce immunosuppressive factors, creating a tumor-permissive niche that fosters metastatic cell survival and proliferation.

Recognizing tumor-to-tumor metastasis is critical for guiding treatment decisions, as primary and metastatic tumors often have distinct biological behaviors and may not respond to the same therapies. Understanding each tumor's characteristics can inform:

- Chemotherapy and targeted therapy selection, ensuring treatments address both malignancies appropriately.
- Surgical intervention planning, where the presence of aggressive metastatic disease may necessitate prompt intervention, while a low-grade localized tumor may allow for delayed treatment.[9]
- Accurate biopsy interpretation, preventing misdiagnosis of metastatic deposits as primary malignancies.

## CONCLUSIONS

This case contributes to the existing literature by documenting a unique instance of breast carcinoma metastasizing into oncocytic carcinoma of the thyroid gland. By expanding our understanding of tumor metastasis dynamics and the diagnostic challenges associated with tumor-to-tumor metastasis, we aim to improve patient outcomes and refine therapeutic strategies for similar clinical scenarios.

Increased awareness of tumor-to-tumor metastasis can prompt clinicians to consider this phenomenon in patients with multiple tumors or unexpected histological findings, ensuring comprehensive patient evaluation and appropriate management.

Overall, tumor-to-tumor metastasis is a multifaceted process driven by complex interactions between tumor cells and the host microenvironment. Elucidating the underlying mechanisms could provide valuable insights into tumor biology, potentially leading to novel therapeutic strategies that disrupt metastatic dissemination and improve patient outcomes.

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*Case Report*

# Phenotypic Heterogeny of Hereditary Angioedema Within a Single Family

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## INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant disorder characterized by episodic angioedema, affecting approximately 1 in 50,000 people.[1] It is most caused by mutations in the *SERPING1* gene, which encodes the C1 esterase inhibitor (C1-INH) protein. Less commonly, HAE results from gain-of-function mutations in the *F12*, *PLG*, or *ANGPT1* genes, leading to increased bradykinin activity.[2]

C1-INH plays a critical role in regulating the complement system, bradykinin formation, coagulation factors, and the fibrinolytic protease plasmin.[3] Deficiency or dysfunction of C1-INH leads to unregulated bradykinin production and excessive C4 consumption, resulting in angioedema. These biochemical markers help distinguish HAE from other forms of angioedema (Table 1).

While most *SERPING1* mutations involve deletions, duplications, or indels, over 748 variants have been identified, including missense, splice-site, and nonsense mutations.[4] Missense mutations, which alter a single amino acid, are generally associated with milder symptoms.[4] However, HAE severity can vary even among affected family members, and genotype-phenotype correlations remain unclear.[1,4] The lack of definitive associations between specific mutations and clinical presentation limits the ability to predict disease severity based on genetic findings.

This case report highlights the genotypic and phenotypic variability of HAE within a family, providing additional insights into this rare disease and underscoring the importance of comprehensive evaluation and monitoring of affected relatives.

**Table 1. Angioedema subtypes and complement levels.[5]**

| | C4 Level | C-INH Level | C1-INH Function | C1q Level |
|---|---|---|---|---|
| HAE Type I | Low | Low | Low | Normal |
| HAE Type II | Low | Normal-High | Low | Normal |
| HAE with normal C1-INH- levels | Normal | Normal | Normal | Normal |
| Acquired C1-INH deficiency | Low | Low | Low | Low |
| ACE-I angioedema | Normal | Normal | Normal | Normal |
| Idiopathic angioedema | Normal | Normal | Normal | Normal |

Adapted with permission from Bernstein, Severity of Hereditary Angioedema, Prevalence, and Diagnostic Considerations, 2018. Permission to use adapted table obtained from author.

## CASE REPORT

We present a 40-year-old male proband, the father of three children: a 14-year-old daughter (Daughter A), a 5-year-old daughter (Daughter B), and a 7-year-old son. Three of these family members have a clinical diagnosis of HAE, though with differing characteristics. Daughter A has a different mother than Daughter B and the son.

The proband was diagnosed with Type II HAE in his teens, characterized by absent C4 protein, a normal C1 esterase inhibitor level, and reduced C1 esterase inhibitor function. He experiences episodic angioedema and has a family history of HAE; his father died from the disease, though specific genetic mutations were not identified. Genetic testing of the proband revealed a pathogenic *SERPING1* p.Arg466Cys heterozygous mutation. He is managed prophylactically with short-acting (icatibant) and long-acting (lanadelumab) kallikrein inhibitors.

Daughter A (14 years old) tested positive for the same *SERPING1* mutation, but her laboratory results were inconclusive, and she remains asymptomatic post-puberty (Table 2). She keeps icatibant on hand for acute attacks and was advised to avoid estrogen-containing contraceptives, which can increase the frequency and severity of HAE attacks.[6]

Daughter B (5 years old, half-sister of Daughter A) also tested positive for the *SERPING1* p.Arg466Cys heterozygous mutation, with similarly inconclusive lab results (Table 2). However, she has experienced extremity and abdominal angioedema, and therapeutic intervention is pending.

The son (7 years old) tested negative for mutations in *SERPING1*, *F12*, *PLG*, and *ANGPT1*, with normal lab results (Table 2). He has never exhibited symptoms of HAE, consistent with his wild-type *SERPING1* genotype.

**Table 2. Complement protein quantity and levels of function of proband and offspring.**

| | | **C4** (normal levels) | **C1 esterase inhibitor level** (normal levels) | **C1 esterase inhibitor function** (normal levels) |
|---|---|---|---|---|
| **Father** | 2016 | <8 mg/dL (10-49) | 59 mg/dL (19-37) | <10% (<41 abnormal) |
| Type II HAE | | | | |
| | | | | |
| **Daughter A** | 2019 | 9.0 mg/dL (10-49) | 90 mg/dL (19-37) | 55% (41-67 equivocal) |
| Not typed | 2021 | <8 mg/dL (10-49) | 41 mg/dL (19-37) | 55% (41-67 equivocal) |
| | 2023 | <8 mg/dL (10-49) | 26 mg/dL (19-37) | 50% (41-67 equivocal) |
| | | | | |
| **Daughter B** | 2019 | 14 mg/dL (10-49) | 92 mg/dL (19-37) | 84% (>67) |
| Not typed | 2021 | <8 mg/dL (10-49) | 39 mg/dL (19-37) | 43% (41-67 equivocal) |
| | 2023 | <8 mg/dL (10-49) | 16 mg/dL (19-37) | 55% (41-67 equivocal) |
| | 2024 | 3 mg/dL (10-34) | 54 mg/dL (21-39) | 90% (>67) |
| | | | | |
| **Son** | 2019 | 16 mg/dL (10-49) | 35 mg/dL (19-37) | 87% (>67) |
| | 2022 | 34 mg/dL (10-49) | 40 mg/dL (19-37) | >90% (>67) |
| | 2023 | 24 mg/dL (10-49) | 31 mg/dL (19-37) | 106% (>67) |

## DISCUSSION

While the reason for the vastly different phenotypic presentations in this male proband and his two affected children remains unclear, they are not unique. One study described four family members with the *SERPING1* p.Met1Val missense mutation in exon 2, each exhibiting wide variation in the severity and frequency of HAE attacks.[6] Environmental and epigenetic factors, including hormonal and inflammatory signals, have been proposed to explain these variations.[4,7] For example, HAE attacks have been linked to an imbalance of pro- and anti-inflammatory cytokines.[7] Additionally, Cancian et al.[8] reported that HAE due to C1-INH deficiency tends to be more severe in females and can worsen after puberty.

Environmental influences, epigenetic modifications, pro-inflammatory states, and hormonal factors may contribute to the differing phenotypic presentations observed in this family.

In conclusion, we report a case of a male proband with Type II HAE and the variable phenotypic expressions of his offspring. This highlights the importance of early genetic screening and close monitoring of all family members for potential disease manifestation over time.

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