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WHAT'S INSIDE: ORIGINAL RESEARCH • CASE STUDIES • COMMENTARY

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TABLE OF CONTENTS

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Intra-Operative Experience using Magnetic Resonance Imaging (MRI) Based Patient Specific Cutting Guides during Total Knee Arthroplasty

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ABSTRACT

Background. The incidence of malalignment in total knee arthroplasty (TKA) using conventional instrument has been reported as high as 25%. A relatively new TKA system involves the use of a preoperative magnetic resonance image (MRI) to obtain accurate implant placement more consistently. For broad acceptance of this new technique, it is crucial to analyze the initial intra-operative experience. The specific aim of this study was to evaluate the initial intra-operative experience of a single surgeon using this new technique.

Methods. A total of 15 knees (12 patients: 6 female and 6 male) were reviewed from TKA procedures using the selected manufacturer's patient specific cutting guides between January 2011 and April 2013 at a single institution. Patient demographic and specific parameters and intra-operative alterations of component positioning were recorded and evaluated.

Results. The preoperative plan was able to predict correctly the size of the implanted femoral component in 87% (n = 13) and tibial component in 80% (n = 12) of the cases. However, 60% (n = 9) of cases required additional intra-operative corrections on femoral resection, and 73% (n = 11) required an additional 2 - 4 mm correction on the tibial proximal resection. Twenty percent (n = 3) required additional tibial varus/valgus correction, but there were no tibial slope corrections for any of the 15 cases.

Conclusions. The initial intra-operative experience of a single surgeon using current patient specific cutting guides for a selected manufacturer to align femoral and tibial components during TKA has raised some concerns. We agreed with previous studies that caution should be taken when using patient specific cutting guides without supportive data. The findings of this study provided additional evidence to contest the accuracy of patient specific cutting guides with respect to the initial experience of an orthopaedic surgeon who is trained in total joint replacement. The results provided more evidence to assist orthopaedic surgeons in the decision of whether to use these patient specific systems versus conventional TKA methods. ***KS J Med 2016;9(2):22-26.***

INTRODUCTION

Total knee arthroplasty (TKA) is one of the most common orthopaedic procedures performed and repeatedly has been associated with highly successful outcomes.[1-3] Post-operative knee function and knee pain scores have improved substantially following TKA.[4-10] Surgical techniques and component designs continue to expose inherent limitations that affect long-term outcomes and implant survival. Many elements have been implicated in influencing the long-term success of any TKA procedure. Proper mechanical alignment and stability of femoral and tibial components are two of these critical factors.[11-15] Varus/valgus alignment within 3° of neutral is necessary to prevent abnormal stresses across the weight bearing surfaces of the implants.[16-20] Thus, accuracy of component alignment and component sizing in TKA are essential for the longevity of a joint replacement.

The incidence of malalignment has been reported as high as 25%, even in facilities that are considered high volume centers.[21-22] Therefore, there exists a demand for innovation in TKA to obtain accurate implant placement more consistently. The use of patient specific cutting guides is one of the newer technologies being utilized during TKA procedures. This technique utilizes preoperative magnetic resonance imaging (MRI) to analyze both the normal and abnormal anatomy to construct a three-dimensional representation of the knee. These data are used to produce custom patient specific cutting guides for both the femur and tibia. These cutting guides are designed to result in more accurate bone cuts for acceptable mechanical alignment and soft tissue balancing without the intra-operative reliance on fixed anatomical landmarks that often are distorted secondary to chronic arthritic changes (i.e., osteophytes). Additionally, the MRI-based system allows the predetermination of implant sizes for both the femur and tibia prior to the operation. Decreased cost, blood loss, operative time and total amount of required instrumentation also have been reported as proposed benefits.[23-29]

Several studies have reported controversial experiences and variable outcomes when utilizing this technique.[24,25,30-33] For broad acceptance of this new technique in TKA procedures, it is crucial to analyze the initial intra-operative experience of using patient specific cutting guides in TKA. Therefore, the specific aim of this study was to evaluate the initial intra-operative experience of a single surgeon using the selected manufacturer's patient specific cutting guides to align femoral and tibial components during TKA.

METHODS

Institutional Review Board approval was obtained for the study. This retrospective study reviewed the initial intra-operative experience of a single surgeon (the principal investigator) during a consecutive series of TKA performed using a single manufacturer's (BioMet, Inc, Warsaw, IN) patient specific cutting guides. Preoperative assessment included documentation of gender, age, body mass index (BMI), and deformities in the knee. A total of 15 knee arthroplasties (12 consecutive patients: 6 female and 6 male) who had the procedure performed between January 2011 and April 2013 by the

principal investigator in a single institution were included.

The inclusion criterion was the principal diagnosis of osteoarthritis undergoing primary TKA. Patients with a history of trauma and/or a history of surgery on the operative knee were included as long as there was no retained hardware. Since the production of the patient specific cutting guides is dependent on the quality of the preoperative MRI, it was determined that the presence of hardware may interfere with the generation of accurate guides. The exclusion criterion was pre-operative planning where patient specific cutting guides were not utilized in any manner.

Preoperative planning for the MRI technique was performed as described by the manufacturer's protocol. Prior to surgery, each patient obtained a sagittal MRI of the operative lower extremity from the hip to the ankle. The MRI imaging data was provided to the cutting guide manufacturer who was responsible for the custom fabrication of the femoral and tibial cutting guides. The surgeon was provided with a virtual three-dimensional representation model of each patient's arthritic knee and the specialized computer software necessary for preoperative planning. The cutting guide manufacturer generated specialized disposable cutting guides for each patient (Figure 1). These cutting guides are used to determine accurate pin placement with standard resection instrumentation. Scheduling of the operation was made once the patient specific cutting guides were provided by the manufacturer.

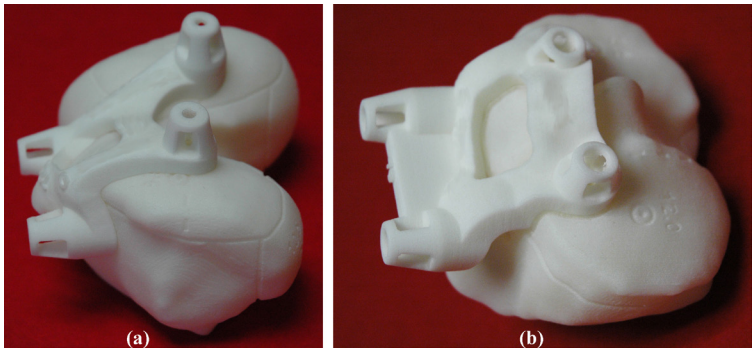

Figure 1. Custom cutting guides: (a) femoral cutting guide, (b) tibial cutting guide.

Each surgery was performed through a traditional medial parapatellar approach under tourniquet control. Once bony exposures were achieved and prior to any revision or resection of bone, the patient specific cutting guides were placed as manufacturer guidelines direct. The manufacturer stated that the placement of the guide should achieve a "glove fit" (i.e., the guide perfectly matches the contour of the bone). The guide was pinned after appropriate placement (Figure 2b). These initial steps were performed in similar fashion for both the femur and the tibia. In each of the operations, the femur was addressed first. After the femoral patient-specific cutting guide was pinned in place, the guide was removed and replaced with the conventional cutting guide (Figure 2c). Then, all cuts of the distal femur were performed in the standard fashion of a conventional TKA technique. Next, the surgeon evaluated femoral component size, femoral anterior-posterior translation, femoral proximal-distal translation, and femoral component rotation. A record was made of any bony cuts that had to be redone after the initial cut with the customized cutting guide. The size of the implanted components for both the femur and tibia also were recorded.

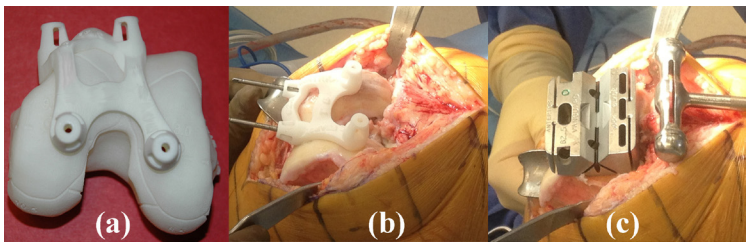

Figure 2. Femoral cutting procedure: (a) femoral cutting guide model, (b) placement of femoral cutting guide, (c) placement of conventional cutting guide.

With respect to femoral anterior-posterior translation and femoral proximal-distal translation, a revision of the initial cuts of 2 mm or greater was defined and recorded. The absolute amount of the revision cut was recorded. When evaluating femoral rotation, a revision was required if the rotation was not within the accepted literature value of greater than 3° of neutral mechanical axis.[34-37] The absolute amount of the revision was recorded.

A similar procedure was performed on the tibia as described for the femur, including placement of patient specific cutting guide, pinning, and replacement of the cutting guide with the conventional tibial cutting block. Following completion of the initial bone cuts, the tibial trial component was placed. Component placement was evaluated for appropriate tibial component size, tibial slope, tibial rotation, and tibial proximal-distal translation. With respect to tibial proximal-distal translation, a revision of the initial cut of 2 mm or greater was defined and recorded. A record was made of any bony cut that had to be revised after the initial cut, as determined by the placement of the patient specific cutting guide. The absolute amount of the revision cut was recorded.

After completion of revision bone cuts, both the femoral and tibial trial components were placed. Soft tissue balancing of the knee was evaluated. The femoral and tibial component sizes selected were recorded and compared to the component sizes determined by the preoperative MRI. Procedural blood loss and tourniquet time were recorded.

Data collection involved a chart review of the preoperative, operative, and postoperative notes documented by the orthopaedic surgeon, specifically in regards to the component sizes, revision cuts, and intra-operative complications, to evaluate the initial intra-operative experience with these patient specific cutting guides to align femoral and tibial components during TKA.

RESULTS

A total of 15 knees (12 patients) met the inclusion criteria, 8 knees (53%) were in females and 7 knees were in males (47%). Table 1 summarizes the demographic profile of the patients. The mean age was 58 years (range: 43 - 72 years) and the mean BMI was 32.4 kg/m2 (range: 19.8 - 42.0 kg/m2). The average tourniquet time was 56 ± 9 minutes, and the mean blood loss was 88 ± 34 mL.

Table 1. Profile of the twelve patients.

	Mean	SD	Range
Age (years)	58	9.8	43-72
Weight (kg)	91.8	24.5	47.6-127.5
Height (cm)	167.6	10.6	154.9-182.9
BMI (kg/m^2)	32.4	7.4	19.8-42.0
Tourniguet time (minutes)	56	9	42-70
Estimated blood loss (mL)	88	34	50-150

The preoperative plan correctly predicted the size of the implanted femoral component in 87% (13 of 15) and the tibial component in 80% (12 of 15) of the cases. However, a total of 9 (60%) of the 15 cases required additional corrections on femoral resection: four (27%) of the cases the femoral distal cut had to be redone to remove an additional 3 mm of femur, five (33%) of the cases the femoral rotation had to be redone to rotate 2 - 5° externally, and two (13%) of the cases required a femoral anterior-posterior correction of an additional 2 mm (one of the knees required both femoral rotation correction and femoral anterior-posterior correction, and one of the knees required both femoral distal cut correction and femoral rotation correction; Table 2). Of the total 15 TKAs, 11 (73%) cutting guides proposed for tibial proximal resections were not acceptable and had to be corrected by the removal of an additional 2 - 4 mm of bone. Only three knees (20%) required tibial varus/valgus correction, and there were no tibial slope corrections in all 15 cases (Table 2).

There were no surgical intra-operative complications including bleeding, wound complications, arterial or venous thromboembolic disease, vascular injury, neural deficit, ligament injury, instability, stiffness, fracture, infection, osteolysis, or implant loosening during any of the cases.[38]

DISCUSSION

The use of patient specific cutting guides that utilize preoperative MRI to align femoral and tibial components during TKA was introduced as an alternative technology with the potential benefit of improving overall component sizing, alignment, and reducing outliers.[39-41] These patient specific cutting guides are designed to promote more accurate bone cuts for acceptable mechanical alignment and soft tissue balancing. These cutting guides also diminish the intra-operative reliance on fixed anatomical landmarks that are often distorted secondary to chronic arthritic changes (i.e., osteophytes). Decreased costs, blood loss, incidence of fat embolism, and operative time also have been reported as proposed benefits.

Table 2. Inaccuracy of patient specific cutting guides in TKA.

	Femur				Tibia			
Subject #	Distal Cut	Rotation	Anterior-Posterior	Size	Proximal Cut	Varus/ Valgus	Slope	Size
1								
2					X			X
3	X							X
4					X			
5	X				X			
6		X			X			
7					X			X
8					X			
9	X				X			
10			X			X		
11		X		X	X			
12					X			
13		X	X	X	X			
14		X				X		
15	X	X			X	X		
Total	4 (27%)	5 (33%)	2 (13%)	2 (13%)	11 (73%)	3 (20%)	0 (0%)	3 (20%)
Overall correction	9 (60%)				14 (93%)			

Unlike the conventional system, the custom-fit TKA does not require the use of intramedullary alignment rods.[39-41] One of the other proposed benefits of this system includes the ability to plan a patient's component size preoperatively which decreases the number of instrument trays required and improved overall operating room efficiency. Concerns regarding this technology, however, exist. It does not allow the surgeon to intra-operatively assess the alignment of their resections, nor check the accuracy of the bone cuts for acceptable mechanical alignment and soft tissue balancing. If adjustments are required, additional instrument trays must be utilized.

Several studies have questioned the proposed cost-efficiency of this technology as to whether the suggested increase in operating room efficiency will offset the costs of additional preoperative imaging and fabrication of the cutting blocks.[26,42,43] Certainly, this is a legitimate concern for which this study does not provide an answer. The main objective of this study was to illustrate the initial experience of an experienced surgeon with a selected manufacturer's patient specific cutting guides during TKA. The results demonstrated that these custom-fit devices were not able to provide accurate implant placement, which is in contrast with the body of literature concerning the use of these custom-fit devices.

Bali and colleagues[30] prospectively studied 32 TKAs performed in 29 patients with MRI-based custom cutting guides. The system they used, however, provided slotted cutting

guides that do not require the use of standard instrumentation. Their results showed that 29 of the 32 knees had a mechanical axis restored to within 3° of neutral, and they concluded that this technology can be used safely in most cases of osteoarthritis of the knee. Our findings did not agree with their results. The cause of this discrepancy may lie in differences in the design of the custom cutting guides. Depending on the manufacturer, most recent guides can be used to determine pin placement for use with standard resection instrumentation, or may serve as the actual cutting guides slots. Although these different guide systems were not compared side-by-side, these differences in the design of patient specific cutting guides could potentially create the discrepancies in the accuracy of component alignment and sizing. Each patient specific system is either Computed Tomography (CT) or MRI-based. Proponents of CT-based systems claim component alignment is achieved more accurately with CT-based systems since CT technology generally is considered superior to MRI in regards to evaluating bony anatomy.[44] Recently, however, a CT-based system developed by a major orthopaedic implant company was recalled for general use, contributing to the uncertainty of which of these patient specific systems should be advocated.

Ng and colleagues[23] retrospectively reviewed 569 TKAs performed with patient-specific positioning guides and 155 with manual instrumentation by two surgeons. They used the same patient specific guide system as in this study, and reviewed long leg radiographs to evaluate mechanical alignment. Their results revealed that 91% of knees were aligned within 3° of a neutral mechanical axis and concluded that this technology can improve a surgeon's ability to obtain a neutral mechanical axis. Two of the authors, however, were consultants for and have research funded by the manufacturer which could serve as a potential for bias.

On the other hand, Nam and colleagues[45] performed a non-randomized retrospective review of 41 knees (37 patients) who received a TKA using an imageless computer-assisted surgery (CAS) system, and 41 knees (38 patients) who received a TKA using the same MRI based systems as this study. Their results demonstrated that patient specific cutting guides did not obtain the same degree of overall mechanical and tibial component alignment accuracy as a CAS technique.

There are limitations to this study including the small sample size, which prevented applying tests of significance due to a low power. The low number of procedures performed was unavoidable because the primary surgeon abandoned this specific system as the early outcomes were not satisfactory. In addition, only one selected patient specific system was evaluated, thus these outcomes may not be applied to other systems. Nevertheless, the outcomes were valuable because this study contributed to the available literature on the initial experience with one particular patient specific guide system. We also did not attempt to address the cost of this custom-fit technique, but rather evaluated our initial experience for total knee replacements. Furthermore, we did not determine long-term functional outcome, as the primary surgeon corrected all resections intra-operatively using the conventional instrument.

CONCLUSION

The overall findings of this study illustrated the concerns encountered during the initial intra-operative experience of a single surgeon with a selected manufacturer's patient specific cutting guides to align femoral and tibial components during TKA. This study demonstrated that one current patient specific cutting guide did not provide the proper alignment for femoral and tibial components during TKA. This study agreed with Stronach and colleagues[46] that caution should be taken when using the selected manufacturer's patient specific cutting guides without supportive data.

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CONFLICT OF INTEREST STATEMENT

This study did not receive any external support for this research project. The authors did not receive any payments, other personal benefit, or commitments or agreements that were related to the research. No benefits of any form were received directly or indirectly.

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Keywords: total knee arthroplasty, instrumentation, magnetic resonance imaging

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Two Cases of Autoimmune Hepatitis Presenting with *Pneumocystis jiroveci* Pneumonia

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INTRODUCTION

Pneumocystis jiroveci pneumonia (PJP) is a respiratory disease that causes high morbidity and mortality among immunocompromised and HIV patients.[1] In the United States, it remains the most common Acquired Immunodeficiency Syndrome (AIDS) defining illness. Though PJP can be life threatening, it is a treatable infection, so a rapid and accurate diagnosis is essential. Clinically, these patients present with nonspecific respiratory symptoms and signs suggestive of pulmonary infection such as cough, fever, dyspnea, hypoxemia, and an abnormal chest x-ray. PJP prophylaxis is considered the standard of care for patients with CD4 counts of less than 200 cells/mm.[2] PJP formerly occurred in 70 - 80% of HIV patients; however with prophylaxis and PJP treatment, the associated mortality has decreased to 20 - 40%.[2-3]

Approximately 90% of PJP cases occurred in patients with CD4+ counts of less than 200 cells/mm.[2] Other factors that are associated with increased risk for PJP include previous episodes of PJP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, or higher plasma HIV RNA.[4-5] Patients with a history of oropharyngeal candidiasis should receive chemoprophylaxis against PJP.[3,4] Trimethoprim-sulfamethoxazole is the recommended prophylactic agent and one double-strength tablet (160 mg - 800 mg) daily is the preferred regimen.[2] The diagnostic test of choice for PJP pneumonia is fiberoptic bronchoscopy with bronchoalveolar lavage and identifying the organism either by direct visualization with stains or by polymerase chain reaction (PCR). Prognosis for the patient depends on underlying comorbidities and immunological status.[6]

Autoimmune hepatitis is a chronic disease that can occur in patients of all ages and all ethnicities.[7] However, it is seen most commonly in females between 40 - 50 years old. A diagnosis of autoimmune hepatitis usually is made and characterized by clinical signs and symptoms, laboratory abnormalities, the presence of antibodies, and the concentration of serum globulin. Some of the most common symptoms include fatigue, icterus, abdominal discomfort, abdominal distension, dark urine, pale stools, and pruritus. Physical exam findings may include splenomegaly, ascites, hepatomegaly and epigastric tenderness.[8]

Characteristic laboratory findings in patients with autoimmune hepatitis can include an increase in bilirubin and abnormal liver enzyme levels.[8] Patients with autoimmune hepatitis also may have circulating serum antibodies, which can include anti-nuclear antibodies (ANA) and anti-smooth-muscle antibody (ASMA). It is also possible to see other antibodies such as anti-liver/kidney microsomal antibodies (ALKM-1), anti-liver cytosol antibodies (ALC-1), anti-double-stranded DNA (anti-dsDNA) and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). On occasion, anti-mitochondrial antibodies also may be found in association with all of the above.[8-9] The clinical manifestations range from asymptomatic to fulminant hepatic failure. Symptomatic patients with autoimmune hepatitis who are untreated have high mortality rates. The initial treatment for autoimmune hepatitis usually consists of immunosuppression with steroids sometimes combined with azathioprine.[10] The 10-year survival for treated patients is 90% and includes patients with advanced cirrhosis.[9]

Two separate cases of documented autoimmune hepatitis are presented. Both patients were admitted to the hospital with severe upper respiratory infectious symptoms and were diagnosed with *pneumocystis jiroveci* pneumonia. PJP is most common in patients with HIV/AIDS and patients diagnosed with cancer, but it is rare to find it in patients with autoimmune hepatitis.[11]

A literature search using PubMed revealed an article discussing PJP pneumonia and alcoholic liver disease.[12] A literature search on PJP pneumonia patients with severe liver disease revealed one article about liver transplant patients who developed PJP, suggesting possible prophylaxis for such patients.[13]

CASE REPORT

Table 1 discusses two patients with PJP pneumonia.

Table 1. Two cases of PJP pneumonia.

	Patient 1	Patient 2
Gender	Female	Male
Age	58 years old	31 years old
Admitted for:	Hypoxemic respiratory failure, syncope, right pleural effusion, productive cough for 1 week	Recurrent jaundice, extreme fatigue, fever, dry cough, progressive abdominal distension, 20 lb weight gain since last discharge 3 weeks prior
Past medical history:	Breast cancer, hepatic encephalopathy, obesity, autoimmune hepatitis diagnosed 4 months prior	Alpha-1 antitrypsin deficiency (diagnosed 2 weeks prior), esophageal varices, hypertension
Past surgical history:	Multiple paracenteses and thoracenteses; bilateral breast reduction	
Social history:	Former smoker	Former alcohol drinker; stopped 3 weeks prior

	Patient 1	Patient 2
Home medications	Prednisone 20 mg daily for 4 months Azathioprine 100 mg daily for 4 months Furosemide Lactulose Rifaximin	Prednisone for 16 days
Vital signs upon admission:	99.1F, 83/49 mmHg, 94 bpm, 30 rpm on mechanical ventilation	100.4F, 129/73 mmHg, 110 bpm, 16 rpm on room air
Physical exam:	Lungs: Diffuse crackles and rhonchi Abdomen: soft, mildly distended, decreased bowel sounds	Scleral icterus Lungs: clear to auscultation bilaterally Abdomen: soft, distended with ascites, diminished bowel sounds Extremities: anasarca Integument: jaundice Neurological: mild asterixis
Pertinent laboratory work:	WBC: 15,840 µL INR: 1.9 PTT: 32 seconds AST 89 U/L ALT: 43 U/L Alkaline phosphatase: 179 UL Albumin: 2.7 g/dL Total bilirubin: 7.1 mg/dL	WBC: 35,000 µL INR: 3.2 PTT: 49 seconds AST 192 U/L ALT: 167 U/L Alkaline phosphatase: 320 UL Albumin: 2.7 g/dL Total bilirubin: 15.8 mg/dL Antinuclear antibody titer: 1:80 Anti-smooth muscle antibody: 30 Liver biopsy: PAS diastase-resistant droplets Alpha-1 antitrypsin phenotype: SZ
Model for End-Stage Liver Disease Score	26	30
Child-Pugh Classification	Class C	Class C
(1-3)-β-d-glucan (BG) assay:	Positive with > 500 pg/mL	Positive with > 500 pg/mL
Pneumocystis by PCR:	Positive x 2 376 DNA copies/mL and 208 DNA copies/mL	Positive > 1000 DN copies/mL
Procalcitonin on admission:	4.64 µg/L	
Outcome:	Expired due to multiorgan failure	Stabled, discharged home

Patient 1 was transferred to our facility and required mechanical ventilator support for worsening hypoxemic respiratory failure. She was started on broad spectrum antibiotics and norepinephrine secondary to shock. She had a near complete opacification of the right lung from a pleural effusion (Figure 1). Fiberoptic bronchoscopy of the left upper and lower lobes showed purulent secretions in the left main stem and trachea. Thoracentesis showed straw-colored fluid.

She remained thrombocytopenic and coagulopathic. Throughout her hospitalization, she required transfusions of platelets and cryoprecipitate. Her (1-3)-β-d-glucan (BG) assay, performed on two different occasions, was positive with > 500 pg/mL. Her pneumocystis by PCR was positive on two different occasions. The first sample, obtained from a bronchoalveolar lavage in the left upper lobe, was positive with 376 DNA copies/mL. The second sample was taken from the left lower lobe of the bronchoalveolar lavage and was positive for 208 DNA copies/mL. Organisms were seen on cytology preparation. She also grew candida albicans in her lavage. All other cultures were negative. Despite all supportive efforts, she expired due to multi-organ failure.

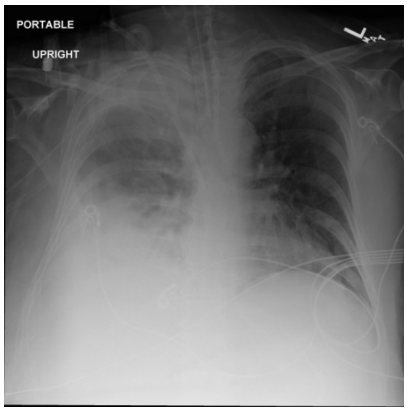

Figure 1. Chest radiograph demonstrated a right pleural effusion.

Patient 2 was admitted to the same hospital sixteen days prior for worsening jaundice, symptoms of upper respiratory infection, fevers, fatigue, nausea, vomiting, frequent nosebleeds, and intermittent joint pain primarily in his hands, knees, ankles, and shoulders. At that visit, he was placed on prednisone and evaluated for liver disease. His laboratory evaluation showed antinuclear antibody (ANA) positive at 1:80 with anti-smooth muscle antibody positive at 30. A transjugular liver biopsy was done and the pathology demonstrated PAS diastase-resistant droplets. He also had an alpha-1 antitrypsin phenotype of SZ.

A chest radiograph (Figure 2) and a representative slice of computed tomography (CT) of his chest (Figure 3) demonstrated interval development of discrete pulmonary nodules in the mid lung zones bilaterally since his last chest x-ray from the previous admission. The pulmonary mass on the right measured 3.5 cm and the pulmonary mass on the left measured 4.0 cm. A CT of his abdomen and pelvis demonstrated a liver with a slightly nodular contour, ascites, splenomegaly, and varices (Figure 4).

He was started on broad spectrum antibiotics. A paracentesis drained 2.7 liters of ascites fluid. His (1-3)-β-d-glucan (BG) assay test was greater than 500 and he was started on micafungin while awaiting further results. Fiberoptic bronchoscopy with bronchoalveolar lavage was positive by PCR for PJP at greater than 1000 DNA copies/mL. His antibiotics were switched to trimethoprim-sulfamethoxazole to treat the infection. He began to improve with a decreasing WBC count. Once his liver failure stabilized and his infection was resolving, he was discharged with instructions to continue trimethoprim-sulfamethoxazole treatment for 21 days then remain on a prophylactic dose for PJP.

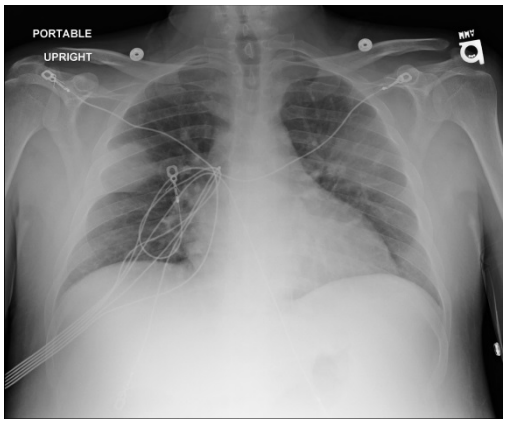

Figure 2. Chest radiograph demonstrated bilateral lung masses.

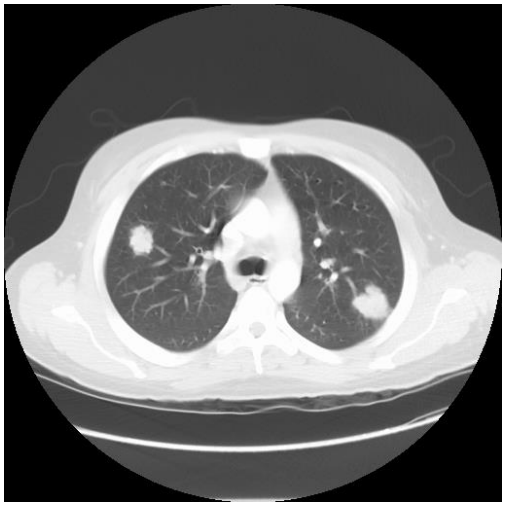

Figure 3. A representative slice of CT scan of the chest demonstrated pulmonary nodules.

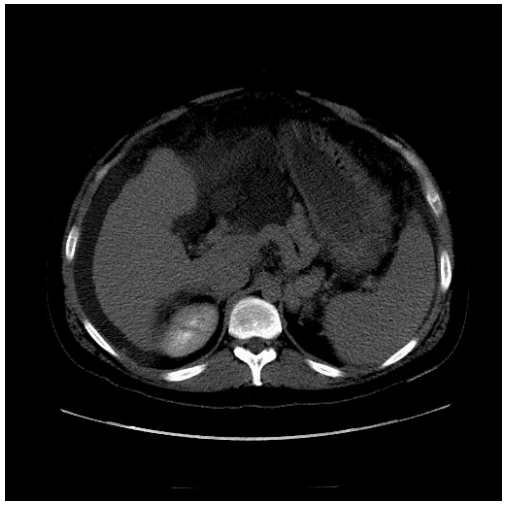

Figure 4. A representative slice of the CT scan of the abdomen demonstrated a nodular contour of the liver.

DISCUSSION

It is rare to diagnose PJP in patients with liver disease, as it is most commonly found in patients with HIV or AIDS. While patient 2 had known alpha-1 antitrypsin deficiency, his biopsy and clinical situation were more consistent with acute autoimmune hepatitis as the main driver of his current liver disease and decompensation. The occurrence of *pneumocystis jiroveci* pneumonia in cases with autoimmune hepatitis is very rare.

The incidence of PJP can be due to the administration of corticosteroids causing immunosuppression or to liver cirrhosis. Typically, shorter periods of treatment with immunosuppressive medications would not be associated with opportunistic infections. However, liver cirrhosis also is considered an immunocompromised state that can lead to a variety of infections as well and infection is directly responsible for approximately 30% of deaths in cirrhotic patients.[14-15] Cirrhosis will cause a systemic immune dysfunction which can decrease the ability to clear cytokines, bacteria and endotoxins from circulation. The liver contains reticuloendothelial cells which are central to clearing bacteria.[14] Additionally, patients with cirrhosis have decreased neutrophil mobilization and phagocytic activity. The level at which this happens can vary with the severity of liver disease.[14,16] Since PJP can be life-threatening, prompt diagnosis and treatment is imperative. It is felt that the "two hits" of liver failure with immunosuppression was sufficient to place these patients at risk for PJP infection with shorter periods of treatment with immunosuppression than is usually considered significant.

The use of corticosteroids is a risk factor for PJP.[17] In a large consecutive series of 116 patients without AIDS, patients with their first episode of PJP were analysed. Systemic corticosteroid therapy was administered to most of these patients the month before the onset of PJP. While it was not suggested that administration of corticosteroids is the only contributor to the development of PJP, PJP prophylaxis should be considered in patients where prolonged systemic corticosteroid therapy is prescribed.[18] An anti-inflammatory effect usually is obtained by administering 0.1 - 0.3 mg/kg per day of prednisone. However, higher dosages are required (ranging from 1 - 2 mg/kg/day) to produce faster immunosuppressive action.[19]

To treat autoimmune hepatitis, the standard therapy from clinical trials is prednisone or prednisolone at 30 - 60 mg/day alone or a lower steroid dose (20 - 30 mg/day) in combination with azathioprine (1 mg/kg/day).[9] Both are equally effective in the management of the patients with severe autoimmune hepatitis. Corticosteroids act rapidly on the immune system by interfering with cytokine production and inhibition of T-lymphocyte activation. The steroid dose is tapered over six-weeks to three-months to a maintenance dose of 15 mg/day or less. Most patients will have normalized aminotransferases within 6 - 12 weeks. Monitoring the response toward treatment includes serial aminotransferase and immunoglobulin measurement, and should be continued beyond normal laboratory results. A liver biopsy is recommended at the time of diagnosis because many patients have established cirrhosis at presentation.[7]

It may be beneficial for patients with autoimmune hepatitis who have contracted PJP to undergo prophylactic treatment for PJP with trimethoprim-sulfamethoxazole (one double strength 160 mg - 800 mg tablet daily), which is the recommended first line treatment for PJP in HIV-infected patients.[20] Once the prophylactic treatment is initiated, it is recommended to continue for life.[2] HIV-infected patients without PJP prophylaxis have a significantly higher mortality with the effect being most pronounced in those with the lowest CD4 counts. There are no studies to prove that the effect is similar to those with autoimmune hepatitis.[21] However, PJP unrelated to HIV can occur in immunosuppressed patients having malignancy or on immunosuppressive agents.[22-23]

Physicians should be aware that PJP is a possibility in patients who are receiving steroids or other immunosuppressive therapy, have a malignancy, or suffer from liver cirrhosis. The best way to decrease mortality in patients who have PJP but do not have HIV would be to identify them quickly and start prophylactic PJP therapy.[22,24,25] Prophylaxis for HIV patients is indicated when there is a CD4 count of less than 200 cells/mm.[2,21] A study performed in the UK suggested multiple steps to ensure proper treatment for PJP, including enhanced surveillance to characterize any additional groups of patients who may be at risk, increasing basic knowledge on *pneumocystis jiroveci* epidemiology, and ensuring adherence to current guidelines.[26]

One possibility for the increase in diagnosis of PJP is diagnostic bias, improved diagnostic methods, particularly the PCR method, which are more sensitive than previous methods.[26-27] There also has been an increase in number of renal transplants and hematological malignancies over the past decade; however, the increase for PJP was far greater than both of these factors combined. Thus the overall increase in PJP diagnosis cannot be explained solely on these factors.[26] Another reason that can explain the increase in PJP pneumonia is that patients are not receiving appropriate prophylactic therapy, which can lead to an increase in transmission.[26] Finally, another possibility could be that patients are living longer on immunosuppressive regimens, giving opportunistic organisms a longer period of time to infect.

For the two patients reported here, the process of their disease and the reason that they contracted with PJP are unknown. These patients most likely suffered from PJP with shorter courses of immunosuppression than usually is described, because of the second hit of immunosuppression due to cirrhosis. Perhaps the cirrhosis is a larger contributor to immunosuppression than once believed. Thus, with people living longer with cirrhosis, considerations of prophylaxis against opportunists when additional immunosuppressants are added may be warranted.

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Keywords: pneumocystis pneumonia, autoimmune hepatitis

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CASE REPORT

Ludwig's Angina Caused by Tongue Piercing

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INTRODUCTION

Body piercing is an ancient practice and common sites include the ear, nose, eyebrow, nipples, genitalia, tongue and lips. The tongue is the second most popular piercing site in the western world and its popularity is increasing rapidly.[1] This procedure occasionally can be complicated by Ludwig's angina which is a rapidly progressive necrotizing cellulitis of the floor of the mouth involving the submandibular and sublingual spaces.[2] It was first described by German physician, Dr. Wilhelm Friedrich von Ludwig, in 1836.[3] Its life threatening complication is airway obstruction. The mortality rate without treatment is around 50%, but with early diagnosis and aggressive management the mortality rate can be reduced to 8%.[4-6] This case report discusses the anatomical basis, diagnosis, and treatment of Ludwig's angina with an emphasis on early diagnosis and aggressive management.

CASE REPORT

A 39-year-old white male presented with tongue pain, neck swelling and trismus which developed one day after having a tongue piercing. He denied drooling, dyspnea, or stridor and had no smoking or alcohol history. On physical examination, he was not in respiratory distress and was not toxic in appearance. He was febrile with a temperature of 101 degrees, a pulse rate of 92 beats per minute, blood pressure of 135/85 mmHg, and a respiratory rate of 16 breaths per minute with an oxygen saturation of 99% on room air. The patient had limited ability to open his mouth with swelling and redness of the floor of the mouth, and his tongue was pierced but without swelling or redness. He had submandibular and sublingual induration and swelling, along with cervical lymphadenopathy. A presumptive diagnosis of Ludwig's angina was made based on patient history and physical examination. His white blood cell count was high at 14,000 cells/mcL with an elevated C-reactive protein. Blood cultures were negative. Computed tomography scan of the face and neck showed swelling of the tongue and floor of the mouth which was consistent with Ludwig's angina by imaging combined with clinical history (Figure 1). The patient was treated with intravenous piperacillin/tazobactam, clindamycin, and dexamethasone. The patient responded well to this treatment regimen and did not require intubation. During the hospital stay, the patient never complained of dyspnea and his oxygen saturation remained around 98 - 99% at room air. He was discharged on oral antibiotics after three days of monitoring.

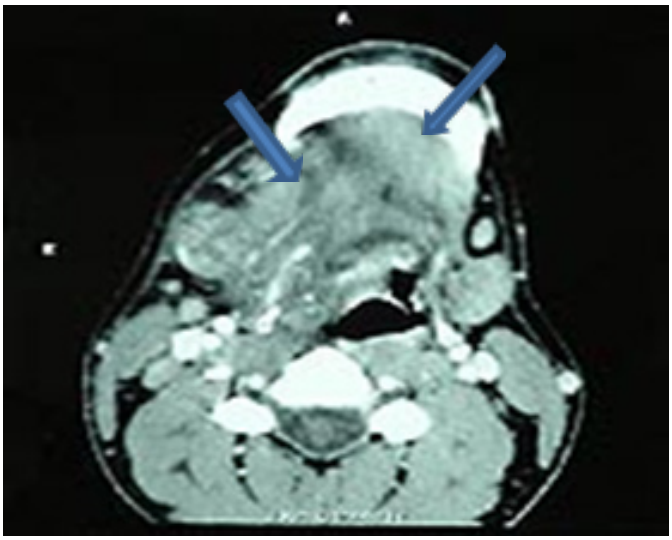

Figure 1. CT of the neck revealed thickening and inflammation of tongue, and floor of the mouth, compression of hypopharynx due to swelling of right lateral pharyngeal space.

DISCUSSION

The risk factors of Ludwig's angina are dental procedures, dental caries, an immunocompromised state, such as diabetes, alcoholics, immunosuppressive medications, HIV, and oral procedures including tongue and lip piercing.[7,8] Odontogenic infections account for the majority of cases.[9] The most commonly cultured organisms include Staphylococcus, Streptococcus, Peptostreptococcus, and Bacteroides species.[9] The precise statistics on the prevalence of tongue piercing and associated bacterial infection are not known. In a survey of college students, 47 of 454 (10.4%) respondents reported having their tongues pierced.[10] In a German registry of patients with head and neck piercings, 92 of 273 (33.7%) reported having their tongues pierced.[11]

The typical presentation of Ludwig's angina includes swelling, pain, and protrusion of the tongue.[12] Induration, swelling, erythema, and pain of the submandibular tissues also are common manifestations. Systemic symptoms will include fever, chills, and dysphagia. In severe cases, stridor, dyspnea, tachypnea, drooling, and sepsis can occur. Stridor and drooling raise the concern of imminent airway compromise due to elevation and posterior displacement of the tongue. Immediate nasal fiberoptic evaluation should be performed when imminent airway obstruction is

suspected.[12,13] Blind oral or nasotracheal intubation is contraindicated due to the risk of laryngospasm or abscess rupture. If fiberoptic-assisted intubation fails, then a cricothyrotomy and tracheostomy can be performed, which was not required in this patient.[13]

The management of Ludwig's angina is largely dependent on clinical judgment and experience. Traditionally, airway management with endotracheal intubation or surgical intervention with tracheostomy was pursued given the high mortality rate, but recently treatment has evolved from aggressive airway management to more conservative therapy.[13-15] The patient should undergo close observation on a specialized airway unit with serial clinical airway assessments. Imaging modalities, antibiotic therapy, surgical skills, and clinical experience are the key factors behind this change in practice. Conservative management includes early intravenous antibiotics and close airway observation.[15] Larawin et al.[16] retrospectively studied a total of 103 patients with deep neck space infections from 1993 to 2005. Ludwig's angina was the most commonly encountered infection, seen in 38 (37%) patients. Thirteen (34%) patients were managed successfully with medical therapy and only four (10%) patients required a tracheostomy.

Antibiotics should cover both gram positive and gram negative organisms in addition to anaerobes.[16-18] A combination of penicillin, clindamycin, and metronidazole is commonly used. Some authors recommend the addition of gentamycin and certain case reports have advocated the use of intravenous steroids. In these reports, corticosteroid administration helped to avoid the need for more aggressive airway management. To date, there are no randomized controlled trials that demonstrate the efficacy of corticosteroids in patients with Ludwig's angina.[19,20]

From our clinical experience we propose early intravenous broad spectrum antibiotic use and close airway observation (oxygen saturation, respiratory rate, and serial fiberoptic laryngoscopy) in a high dependency unit (HDU) or an otorhinolaryngology ward. Initial airway assessment is based on respiratory rate, oxygen saturation, and findings on fiberoptic laryngoscopy. After the initial clinical assessment and airway decision, patients should undergo CT scanning of their neck and thorax for further evaluation of detailed airway and deep neck spaces. Any abscess or collection cavity should be drained, along with removal of the piercing. Intravenous antibiotics is continued for 48 - 72 hours, then switched to oral antibiotics for 14 days along with outpatient follow-up with otorhinolaryngology.

CONCLUSION

We recommend conservative management of Ludwig's angina in selective cases, provided that early antibiotic therapy is initiated and any abscess is drained. Our review suggested that this is the preferred approach, as compared with previous invasive maneuvers. Both piercers and their clients should be aware of this potential complication, and standardized infection prevention and control practices should be adopted to reduce the risk. Health care professionals should obtain a history of tongue piercing in unexplained cases of infective endocarditis, brain abscess and intraoral infections for which piercing may be a risk.

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Keywords: Ludwig's angina, edema, tongue, body piercing

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CASE REPORT

Gastric Variceal Bleeding Secondary to Splenic Vein Thrombosis: A Case of Left-Sided Portal Hypertension

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INTRODUCTION

Gastric varices are found most frequently in patients with portal hypertension.[1] While gastric varices bleed less than esophageal varices, bleeding from gastric varices is often more severe and life threatening. A less common but significant cause of gastric varices is due to isolated left-sided portal hypertension (LSPH).[2] We present a case of bleeding gastric varices secondary to LSPH caused by a splenic vein thrombosis (SVT).

CASE REPORT

A 71-year-old male presented to his local emergency department after several black stools, dizziness, and an episode of syncope. His medical and surgical history included coronary artery disease with multiple stent placements, a pacemaker placement, and warm autoimmune hemolytic anemia diagnosed a month prior to presentation. An esophagogastroduodenoscopy (EGD) at this outside facility revealed what was thought to be a gastric ulcer along with two gastric polyps. The polyps were biopsied and the patient was sent home to follow-up with a colonoscopy a few days later.

The patient presented to our hospital, a regional referral center, the following evening and was admitted due to persistent symptoms of dizziness and dark stools. An abdominal exam was unremarkable for any tenderness to palpation or organomegaly. His blood pressure was 97/75 mmHg, pulse rate was 114 bpm, hemoglobin level was 5.9 g/dL, platelet count was 65,000/μL, lactic acid was 3.2 mmol/L, lactate dehydrogenase was 326 U/L, and liver function tests were unremarkable. On day two of hospitalization, a Technetium-99m red blood cell scan failed to localize any active bleeding, however, a repeat EGD revealed a large amount of hematin material and non-bleeding gastric varices in the gastric fundus consistent with isolated gastric varices type 1 (IGV1) by Sarin classification (Figure 1).[1] No endoscopic therapy was done. An abdominal ultrasound showed a patent portal vein but body habitus precluded the visualization of the splenic vasculature. An abdominal computed tomography angiography (CTA) scan on hospital day three showed a splenic vein thrombosis and a small superior splenic infarction. Surrounding structures, including the pancreas, appeared normal. The patient underwent an uncomplicated splenectomy on hospital day five and was sent home on hospital day nine. He was to follow-up with his primary care provider 14 days after his splenectomy to receive pneumococcal, Haemophilus, and meningococcal vaccines.

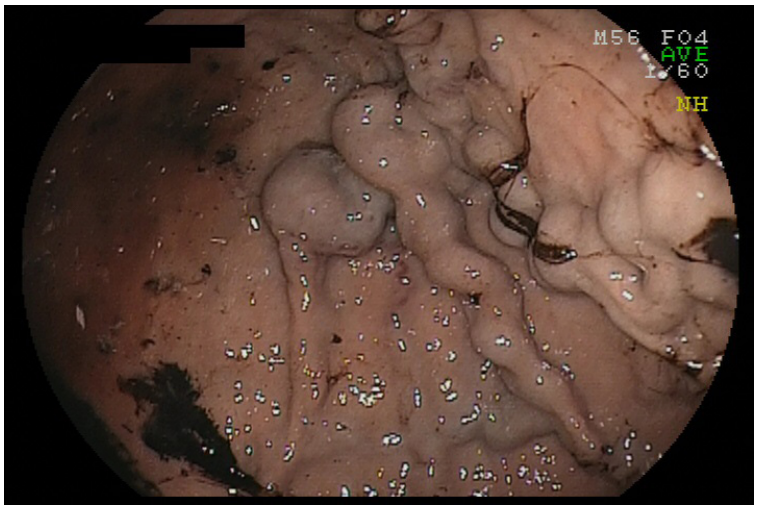

Figure 1. Isolated gastric varices in the gastric fundus.

DISCUSSION

LSPH is a less common, but significant cause of gastric varices that arises from any process that blocks blood flow through the splenic vein.[3,4] Blockage results in left-sided venous hypertension forcing splenic blood to back up through collaterals, commonly the short gastric veins, forming varices in submucosal gastric vessels. Obstruction is usually intravascular due to a SVT, however, less common causes of splenic vein compression by nearby organs, tumors, and other processes have been documented. SVT most commonly is due to disease processes in the pancreas because it lies directly anterior to the splenic vein. Acute and chronic pancreatitis account for 60% of SVTs and pancreatic malignancies account for 9%.[5]

Most patients with LSPH secondary to SVT are asymptomatic and an SVT is found incidentally on imaging for other reasons.[6-9] Symptomatic patients, such as ours, usually present with GI variceal bleeding (45 - 72%)[5,10] and abdominal pain (25 - 38%).[5,10,11] Splenomegaly is a variable finding and was not found in our patient. In a meta-analysis of patients with pancreatitis induced SVT, splenomegaly was only present in 51.9% of patients,[12] however, some studies suggest it is closer to 71%.[10] Ascites is rarely found as a presenting sign in LSPH.[13] Laboratory values can vary depending on the underlying etiology of the SVT, however, low hemoglobin suggests variceal bleeding. Nonetheless, a constellation of signs and symptoms should be

considered. This was especially important with our patient who already had low hemoglobin secondary to hemolytic anemia.

Doppler ultrasonography (US) is a common preliminary test to evaluate for SVT in patients with symptomatic LSPH. While fairly sensitive and specific (93% and 83%)[14,15] for finding portal vein thrombosis, the anatomic location of the splenic vein often makes it difficult to evaluate its patency, as was the case with our patient.[15] In patients whose treatment likely will require splenectomy, more comprehensive imaging allowing visualization of the entire portal system, such as computed tomography (CT) or magnetic resonance imaging (MRI), is more favorable.[16] In patients where pancreatic malignancy is suspected to be the cause of SVT, such as patients without a history of pancreatitis, endoscopic ultrasound (EUS) is used frequently because of its superiority to US and CT in diagnosing small pancreatic lesions and visualizing vascular invasion.[17,18]

Once the diagnosis of gastric varices caused by SVT-induced LSPH has been made, treatment is based on whether the varices ever have bled. In patients with active bleeding, intravariceal cyanoacrylate injection is the first line therapy to achieve hemostasis when available.[19] Other methods include banding or injection of a sclerosant. Once hemostasis is achieved or in patients with refractory bleeding, splenectomy is the treatment of choice,[3,8,12,20-23] because rebleed rates without it range from 4 - 17%.[7,8,24] Two studies have shown a 0% rebleed rate after splenectomy for previously bleeding gastric varices caused by LSPH.[5,6] Cyanoacrylate injection can be used as definitive therapy in other types of gastric varices, but due to the amount of collateral connections between the stomach and splenic vein, splenectomy is favored in cases of varices due to SVT. Splenic artery embolization can be used as an alternative to splenectomy in high-risk surgical patients, however, splenic abscesses can occur in up to 7% of patients following the procedure.[25] Further studies are needed to confirm the efficacy of embolization for first line therapy.[3,26] In the absence of any previous bleed, current literature suggests against prophylactic splenectomy.[8] Heider et al.[8] showed a bleeding rate of only 3.8% in patients with pancreatitis-induced SVT followed conservatively over 34 months.

Patients who undergo functional or surgical splenectomy require pneumococcal, Haemophilus, and meningococcal vaccines 14 days prior to the procedure. If urgent splenectomy is required, as was in our patient, vaccines should be administered at least 14 days following the procedure.[27] Studies with the pneumococcal vaccine suggest this timing allows for subsequently higher antibody concentrations.[28-30] Revaccinations are required and should be administered in accordance with the Infectious Diseases Society of America (IDSA) recommendations for vaccination of patients with asplenia.[27]

Prognosis is largely dependent on the underlying etiology of the SVT. Treatment effectiveness often is evaluated by assessing for recurrence of bleeding, however, this is difficult because a large proportion of the patients have an underlying malignancy and their life expectancy is short.

Our case highlights the importance of accurate diagnosis and work-up of gastric varices caused by LSPH. It reminds physicians of the different causes of LSPH and what diagnostic and therapeutic approaches are available for addressing gastric varices caused by LSPH secondary to SVT.

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Keyword: gastric varices, splenic vein, venous thrombosis, portal hypertension

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Pancytopenia: A New Manifestation of *Mycoplasma pneumoniae*

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INTRODUCTION

Mycoplasma pneumoniae initially was identified in 1944 as the pleuro-pulmonary like organism found in the sputum of patients with primary atypical pneumonia.[1,2] It is a common pathogen responsible for upper and lower respiratory infections in young adults and school-aged children.[1,3-5] It usually has a self-limited course characterized by cough, headache, and fatigue.[6] Respiratory infections including bronchitis, bronchiolitis, community-acquired pneumonia, and tracheobronchiolitis are common presentations.[1,6,7]

Extrapulmonary manifestations have been described in 25% of *Mycoplasma pneumoniae* cases and they usually manifest in the presence or absence of lung infection.[2] The presence of multiple extrapulmonary manifestations is considered a poor prognostic factor. These manifestations include neurological, hematological, cardiac, gastrointestinal, or dermatologic findings.[1-3,5-9] Hematological manifestations include hemolytic anemia, thrombocytopenic purpura, and disseminated intravascular coagulation.[2] When accompanied by respiratory disease, extrapulmonary manifestations tend to occur three or more days after the onset of respiratory disease and may last up to three weeks after resolution of the respiratory illness.[1,2]

We describe the first known adult case of *Mycoplasma pneumoniae* presenting with pancytopenia.

CASE REPORT

A previously healthy 23-year-old Asian female presented during mid-winter with a ten-day history of diarrhea and fever. She denied any other symptoms except for occasional cough of clear sputum. Her blood pressure on admission was 90/54 mmHg and her temperature was 101.2°F. Her physical exam was unremarkable. The white blood cell count was 1.1 K/uL with an absolute neutrophil count of 940 K/uL and absolute lymphocyte count of 90 K/uL. Hemoglobin was 9.2 g/dl with a mean corpuscular volume of 81.6 fL and platelet count 100 K/uL. Aspartate transaminase and alanine transaminase were elevated at 74 and 116 U/L, respectively. Erythrocyte sedimentation rate (ESR) was 23 mm/hr and C-reactive protein (CRP) was less than 0.5 mg/dL. A chest x-ray revealed bilateral infiltrates, greater on the right side. Cultures of blood and sputum also were negative.

Respiratory virus panel PCR for influenza A subtype H1 and H3, influenza B, RSV subtype A and B, adenovirus, rhinovirus, parainfluenza virus 1, 2, and 3, and human metapneumovirus were negative. Urine *streptococcus pneumoniae* and *legionella pneumophilia* group 1A and *Histoplasma* urine antigen were negative. Stool culture and studies for ova and parasites, occult blood, *clostridium difficile* toxin B PCR, *giardia* antigen, shiga toxin 1 and 2 also were negative. Direct Coombs test was positive with a low haptoglobin at 3 mg/dL (normal: 36 - 195), elevated lactate dehydrogenase at 680 U/L (normal: 98 - 192), elevated schistocyte count, and normal reticulocyte count indicative of autoimmune hemolytic anemia. Vitamin B12, iron panel, thyroid-stimulating hormone, and folate levels were insignificant. Ferritin level was elevated at 1528 ng/ml (normal: 11 - 307). Glucose-6-phosphate dehydrogenase (G6PD), pyruvate kinase level, and hemoglobin electrophoresis were normal. Disseminated intravascular coagulation (DIC) panel was negative.

Bone marrow aspirate revealed complete and nondysplastic erythroid and myeloid maturation; megakaryocytes were absent. Flow cytometry showed no increase in blasts and no immunophenotypic evidence of lymphoma. Leukemia flow panel was negative. Bone marrow karyotype had no clonal abnormality noted.

Mycoplasma pneumonia IgG and IgM levels were positive at 40,218 mg/dL and 1.23 mg/dL, respectively (reference range 0.00 to 1.09). *Chlamydia*, parvovirus B19, and hepatitis serology were negative. Polymerase chain reaction (PCR) was negative for other causes of autoimmune hemolytic anemia, such as cytomegalovirus, Epstein-Barr virus, in addition to HIV 1 and 2 antibodies.

Cerebrospinal fluid studies, including cell count, bacterial, acid-fast bacillus, viral and fungal culture, immunofixation, enterovirus, and herpes simplex virus PCR were negative. West Nile IgG and IgM antibodies, Venereal Disease Research Laboratory test, and cryptococcal antigen also were negative. C3 and C4 complement in blood were low. No blood parasites noted.

The patient was treated with 500 mg azithromycin for one day followed by 250 mg for four days. She showed improvement with resolution of symptoms, infiltrates, and neutropenia. A repeat complete blood count five days after completion of therapy revealed a white blood count of 5.7 K/uL, hemoglobin of 8.6 g/dl, and a platelet count of 192 K/uL.

DISCUSSION

Mycoplasma pneumoniae infections traditionally involve the respiratory tract, manifesting a wide variety of symptoms ranging from productive cough to severe pneumonia. Extrapulmonary manifestations involving almost all organ systems have been reported. Narita classified the pathogenesis of extrapulmonary manifestations into three categories that are not always mutually exclusive.[10] The direct type is mediated by inflammatory cytokine released locally by bacterial cell membrane. The indirect type is based on immune modulation and cross-reaction between human cells and bacterial cell components[10] where cross-reactivity of anti-*Mycoplasma pneumoniae* antibodies causes immune-mediated damage.[3] For instance, IgM autoantibodies directed against red blood cells have been proposed as the cause of cold-agglutinin hemolytic anemia. Moreover, central nervous system complications have been thought to result from autoantibodies against glucocerebrosidase.[7] Finally, the third type is a vascular occlusion where bacterium induces vasculitis and/or thrombosis.[10] The described extrapulmonary manifestations can be classified on the basis of the proposed pathogenesis as shown in Table 1.[11,12]

Table 1. Extrapulmonary manifestations classified by proposed mechanisms.

Extrapulmonary Manifestations	Direct Type	Indirect Type	Vascular Occlusion
Cardiovascular	• Endocarditis • Pericarditis	• Kawasaki Disease • Myocarditis	• Aortic Thrombus • Cardiac Thrombus
Dermatological		• Erythema Multiforme • Stevens-Johnsons Syndrome • Urticaria	
Digestive System	• Early Onset Hepatitis	• Late Onset Hepatitis	• Pancreatitis
Hematological/ Hematopoietic		• Autoimmune Hemolytic Anemia • Hemophagocytic Syndrome • Infectious Mononucleosis • Thrombocytopenic Purpura	• Disseminated Intravascular Coagulation • Splenic Infarct
Neurological	• Aseptic Meningitis • Early Onset Encephalitis	• Acute Cerebellar Ataxia • Guillain-Barre Syndrome • Late Onset Encephalitis	• Psychological Disorders • Striatal Necrosis • Stroke • Thalamic Necrosis

This report is the first known to describe pancytopenia in an adult as an extrapulmonary manifestation of *Mycoplasma pneumoniae* infection. Some cases reported leukocytosis with white blood cell count ranging from 26,000 to 56,000/mm^3 and rarely leukopenia with white count of 3,800/mm.[3,9,13,14] Some reports suggested a transient suppression of T-lymphocytes especially CD4+ T cells, and the immune system as a whole by unknown mechanisms.[1] Hemophagocytic lymphohistiocytosis (HLH) also was reported as a manifestation of *Mycoplasma*,[15] but the clinical presentation and bone marrow evaluation in our patient did not point to HLH.

The patient was of Chinese origin. Her last visit to Asia was a few months before presentation. *Mycoplasma* extrapulmonary infections from Asia have been reported, especially the southeast region. For instance, a similar case of mycoplasma pneumonia infection presenting with neutropenia, thrombocytopenia, and acute hepatitis was reported in a Taiwanese child in 2004,[13] but no cases have been reported in adults. Proposed ethnic differences may account for the differences in distribution and manifestations between the western communities and Southeast Asia; such as the presentation of Kawasaki disease, infectious mononucleosis, and *Mycoplasma* infection.[10] There might be a link between the ethnicity of this patient and her presentation with pancytopenia in the setting of *Mycoplasma* pulmonary infection. The underlying mechanism causing extrapulmonary manifestations and, in particular, bone marrow suppression needs to be elucidated further. Genetic and/or environmental factors might play a role in the clinical features of *Mycoplasma*. A few reports of *Mycoplasma* in HIV positive patients have been mentioned, however, no definite conclusion was reached concerning whether immunosuppression alters the incidence or severity of mycoplasma infection.[2]

Our patient received a five-day course of azithromycin and recovered. Supportive treatment also might be a reasonable approach, whereby antibiotics and steroids are given on individual basis.[1] Moreover, immune-modulatory therapeutics is entertained based on the hypothesis of an immune-mediated role in the pathogenesis of this infection.[2]

CONCLUSION

Despite the increasing knowledge about extrapulmonary manifestations of *Mycoplasma*, more research is needed in the areas of pathogenesis, epidemiological differences, host factors, and management. This case raised awareness and suspicion of possible *Mycoplasma pneumonia* infection in patients with bone marrow suppression and community acquired pneumonia especially in patients of Asian descent.

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Keywords: pancytopenia, mycoplasma pneumoniae

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CASE REPORT

Hydroxychloroquine-Induced Erythema Multiforme in a Pregnant Female

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INTRODUCTION

Hydroxychloroquine (HCQ) is a disease-modifying antirheumatic drug that is used commonly as an immunomodulatory agent in the treatment of rheumatic diseases. It is considered a relatively safe drug. It is a pregnancy class C drug; however, years of retrospective and prospective clinical experience has shown that its administration does not lead to fetal teratogenicity.[1-5] Rarely, it can lead to retinal toxicity that can be prevented and detected by periodic ophthalmologic examinations.[3] The most common cutaneous adverse reaction of HCQ is skin hyperpigmentation or a typical cutaneous drug eruption. However, it also can cause rare and more significant dermatoses, such as erythema multiforme (EM) or erythema annulare centrifugum.[4] Erythema multiforme is an acute, self-limiting mucocutaneous hypersensitivity syndrome. Approximately 66% of patients who develop EM possess the HLA-DQB1*0301 26 allele, which is present in only 31% of healthy subjects.[6] We present a severe case of EM induced by HCQ in a pregnant patient.

CASE REPORT

A 20-year-old pregnant African-American female presented to the rheumatology clinic at 16 weeks of gestation for the evaluation of an elevated antinuclear antibody level, a malar rash, and concern for undiagnosed systemic lupus erythematosus (SLE). The patient met the American College of Rheumatology (ACR) classification criteria for SLE based on malar rash, painless oral ulcers, alopecia, strongly positive ANA of titer > 1280 speckled pattern, photosensitivity and arthritis which confirmed the diagnosis of SLE.[7] The patient also had positive SSA and SSB (anti-Ro and anti-La) antibodies. Hence, HCQ therapy was initiated as an immunomodulatory agent to manage the SLE and prevent its potential complications for the patient and the fetus.

A few days later, the patient presented to the emergency department with a painful, erythematous macular exanthem predominantly over the anterior and posterior aspects of her torso and upper extremities. Additionally, she had tense and flaccid bullae bilaterally on her breasts and chest. The patient had no evidence of mucosal involvement, although she developed vesicles on her cutaneous lips, forehead, and cheeks. Subsequently, she was admitted for further evaluation and pain management, with rheumatology and dermatology inpatient consultations.

During her hospitalization, the patient developed target lesions on her palms and upper extremities consistent with EM (Figures 1 and 2). The patient underwent a skin biopsy that confirmed the diagnosis (Figure 3). Infectious serologies and cultures, including those for herpes simplex virus (HSV) and *Mycoplasma pneumoniae*, were negative. She was not on any other medicine except HCQ. Due to the concern for potential toxic epidermal necrolysis in bullous lesions, the patient initially was started on intravenous immunoglobulin for four days. She was transitioned to oral prednisone, 40 mg daily, with a slow taper after skin biopsy confirmed diagnosis of EM. After initiation of prednisone therapy, her skin lesions improved with resolution of erythema and pain. She was discharged in stable condition on a steroid taper with resolving skin lesions.

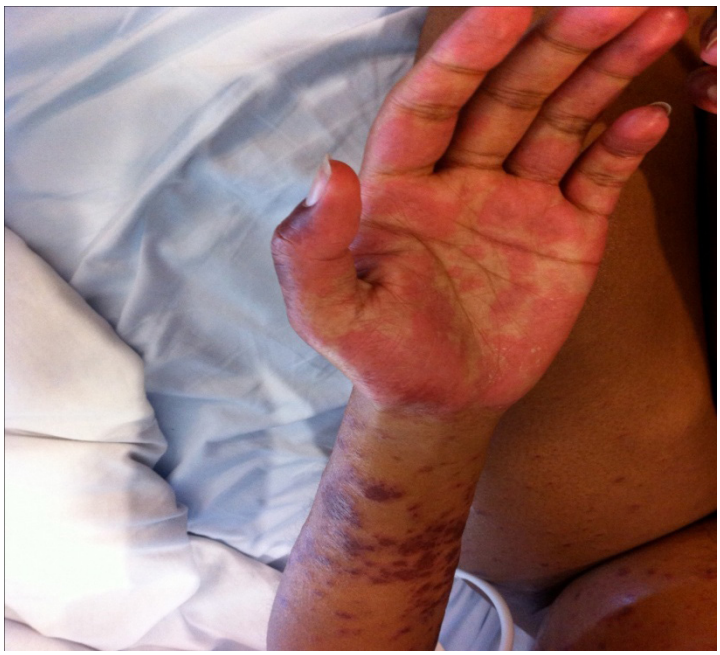

Figure 1. Diffuse, scattered erythematous macules coalesced into patches with islands of sparing on acral surface of left palm.

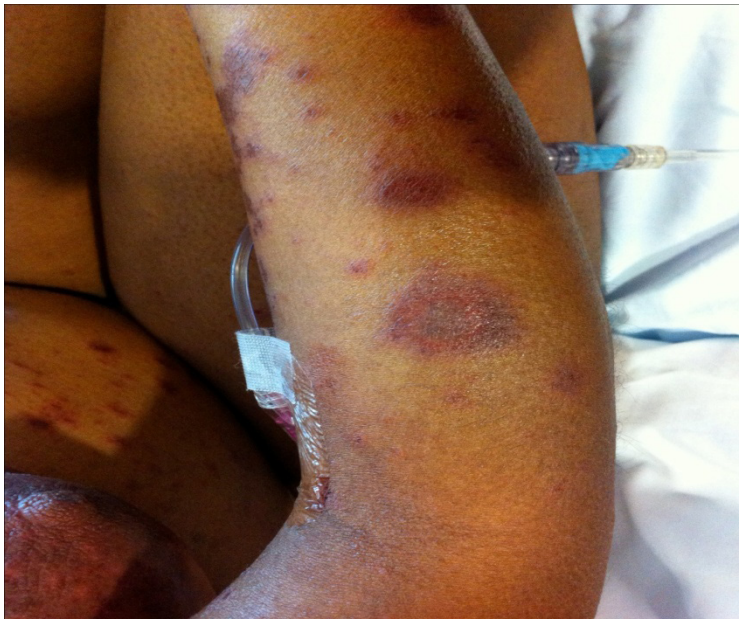

Figure 2. On day two, lesions began to form characteristic "typical" targetoid lesions including two concentric rings surrounding a central area of bullae and/or necrosis.

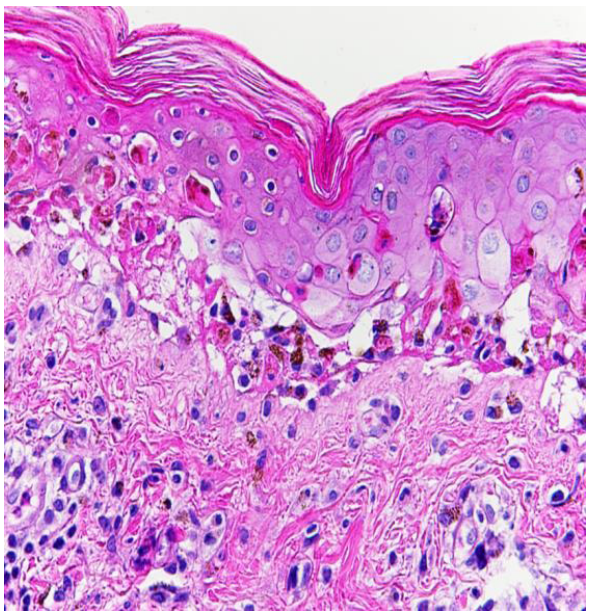

Figure 3. Skin biopsy demonstrated vacuolar interface lymphocytic dermatitis with ballooned and apoptic keratinocytes in the spinous layer, melanoderma and a normal corneum. Viral inclusions, deep dermatitis, eosinophils, and neutrophils were absent. Direct immunofluorescence was non-reactive for IgG, IgA, IgM, and C3.

DISCUSSION

Erythema multiforme, in its purest form, is an acute, self-limited but potentially recurrent skin disorder.[8] It is observed predominantly in young adults, rarely in childhood, and has a slight male preponderance but no racial bias. Austrian dermatologist Ferdinand von Hebra first described this condition in 1860.[9] The clinical hallmark of EM is the abrupt onset of typical target lesions forming within the first 24 hours. There may or may not be mucosal involvement. Clinically, the typical targets exhibit three distinct circles or "zones." The innermost circle often initially is dusky and followed centripetally by two other concentric rings. The central circle subsequently may develop into a bulla and/or crust later in the course of the disease. Additionally, atypical targets may be predominant, especially early in the course of the disease. Usually, there are only two different zones and there is generally a poorly defined border (< 3 cm in diameter).

Development of EM has been associated with herpes simplex virus (HSV) or *Mycoplasma pneumoniae* infections.[10] Rarely (<10% of cases), it is caused by drugs such as NSAIDS, sulfonamides, penicillin, antiepileptics, and antibiotics. According to the Medicines Control Agency, there have been four reports of EM since 1964 related to hydroxychloroquine use.[11] There is a single case report in the literature describing a case of erythema annulare centrifugum related to the use of hydroxychloroquine.[12] In addition, there is a report of acute generalized exanthematous pustulosis.[13] Furthermore, it is recognized that hydroxychloroquine can exacerbate psoriatic skin lesions,[14] an effect thought to be related to inhibition of epidermal transglutaminase activity.[15]

Most importantly, EM is to be differentiated from acute disseminated epidermal necrolysis, which includes Stevens–Johnson syndrome (SJS), toxic epidermal necrosis (TEN) and the SJS/TEN overlap.[16] In our case, there was a definite predilection for atypical targets upon the patient's presentation to the emergency room. The differential diagnosis was EM, SJS, and TEN. Our patient had no mucosal involvement, a variable that essentially is mandatory when diagnosing a patient with SJS or TEN. Also, the skin biopsy was consistent with EM, which ruled out the possibility of SJS, TEN, or bullous SLE. To the best of our knowledge, this is the first case of erythema multiforme due to hydroxychloroquine in a pregnant patient.

For clinicians, it can be a daunting task to make a clear and concise diagnosis when a patient presents with an abrupt onset of painful, blistering, and/or exfoliative skin lesions. First and foremost, a thorough history must be obtained. Medications and the duration or timing of exposure to medications are important when gathering the patient's history. One also must conduct a comprehensive review of systems and tests to rule out potential infectious etiologies that could cause an EM eruption, including but not limited to HSV or *mycoplasma pneumoniae*. Next, obtain a thorough physical examination of the patient's skin, including the mucosal surfaces of the ocular, oropharyngeal and genital surfaces. Skin biopsy for both permanent and frozen sections may differentiate between SJS/TEN, EM, bullous LE, or a bullous drug eruption. Even then, the diagnosis often cannot be made on pathology alone, hence the importance of the role a detailed history and physical examination play in securing an accurate diagnosis.

CONCLUSIONS

Overall, hydroxychloroquine has a minimal and acceptable side effect profile. It can be used in pregnancy, but its potential serious cutaneous side effects including SJS, TEN and EM should be considered prior to initiation. This extraordinary case highlights promising new medical management of medication-induced erythema multiforme with intravenous immunoglobulin and underscores the value of prompt diagnosis and supportive care. Prognosis reportedly is better for patients transferred promptly to a burn unit or intensive care unit.[17] For unknown reasons, our patient was treated in the general medicine unit. In an age of increasing patient poly-pharmacy, it is of paramount importance to consider all medication-induced side effects, both common and severe.

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Keywords: erythema multiforme, hydroxychloroquine, pregnancy, systemic lupus erythematous

KANSAS JOURNAL of MEDICINE

Bad Weed: A Case of Prolonged Psychosis Secondary to Synthetic Cannabinoids

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INTRODUCTION

Synthetic cannabinoid (SC) use has gained in popularity over the last decade in part due to ease of obtainability, perceived safety, and the ability to avoid detection on routine urine drug tests.[1] Once thought as a "legal high", users generally believe the effects and risks of SC to be similar to cannabis, if not safer. Although sparse, the medical literature has been increasing with reports of severe psychosis associated with SC use.[1-7] However, little is known about the duration of the effects. We report a unique case of prolonged psychosis after chronic use of SC.

CASE REPORT

An 18-year-old male presented to the emergency department (ED) with his parents after exhibiting bizarre behavior. In the ED, he presented with delusional thinking (e.g., government agents spying on him, mother poisoning his food), hearing voices, and responding to internal stimuli. His parents reported that symptoms started approximately two months prior after the patient relapsed and began smoking "K2" (a SC). He was admitted to the inpatient psychiatry unit and started on risperidone 1 mg twice daily.

He had experienced a similar episode eight months prior resulting in a 12-day hospitalization, considered to be secondary to chronic SC and marijuana use. He was treated and discharged on olanzapine and lithium. However, lithium was discontinued secondary to elevated thyroid stimulating hormone and olanzapine was discontinued a few months later due to continued stability and concerns regarding weight gain. He had no previous psychiatric history aside from mild chronic anxiety. Family history included a sibling with substance use disorder and mother with anxiety disorder. There was no family history of any psychotic disorder (e.g., schizophrenia).

On his admission, physical examination and baseline laboratory results (complete blood count, metabolic panel, and thyroid stimulating hormone) were unremarkable, including a urine drug screen which was negative. Blood alcohol level was not done at that time. He subsequently admitted to smoking "K2" chronically over the last two years. On day two of hospitalization, risperidone was increased to 4 mg/day with the addition of benztropine for extrapyramidal side effects. Over the next five days, he markedly improved and discharge planning was in process. However, on day seven, his psychosis returned accompanied by severe paranoia and an intense fear of dying. Risperidone was increased to 5 mg/day. Over the next eight days, his symptoms waxed and waned with periods of improvement followed by bizarre behavior including agitation, running into walls, and head banging requiring physical restraints. During one episode, he experienced diaphoresis, muscle rigidity, elevated temperature (37.8°C) and tachycardia (pulse 145). Throughout these periods of agitation, he was administered haloperidol (which resulted in a dystonic reaction), fluphenazine, or chlorpromazine along with lorazepam. Subsequently, risperidone was increased to 6 mg/day. Both magnetic resonance imaging and electroencephalogram were performed to rule out any acute intracranial pathology or epileptic activity; however, both studies were negative.

On day 15, divalproex sodium was started. It was switched three days later to lithium 600 mg/day due to elevated liver function tests. Shortly after starting lithium, the patient achieved sustained improvement without evidence of psychosis or agitation. He was discharged on day 26 taking risperidone 6 mg/day and lithium carbonate 600 mg/day.

DISCUSSION

Treatment of SC intoxication or toxicity can be challenging for clinicians due to the unknown effects of these agents. The most common active ingredient in SC is JWH-018, although products such as "K2", "Spice", and others may contain a blend of different SC (JWH-073, JWH-175 or similar).[8] The potency of SC is considered to be higher than tetrahydrocannabinol (THC) due to its full agonist effects on marijuana CB1 receptor compared to THC which is a weak partial agonist.[8,9]

Common symptoms of SC use include euphoria, anxiety, irritability, and tachycardia.[8] However, increasing reports of psychosis and paranoia are emerging in the literature.[1-7] A dose-response effect is theorized, meaning the heavier the use of SC, the more likely that psychotic effects will occur.[8]

Unfortunately, duration and treatment of psychosis secondary to SC remains unclear. Most case reports described psychosis as acute in onset, with symptoms resolving within 24 hours to one week requiring only supportive care.[1,3,5,6] However, in our patient, symptoms continued for almost one month. Only two case series were found describing psychosis lasting greater than two weeks in duration.[3,7] Van der Veer et al.[7] reported a case series of three patients all requiring

at least two-weeks of hospitalization following SC use. Their patients were treated with haloperidol or risperidone for their psychotic symptoms, and all patients had some psychotic symptoms present on discharge. Moreover, Hurst[3] reported psychotic symptoms lasting five months in three previously healthy males aged 21-25 after using SC. Treatment of their symptoms was not discussed.

There are no treatment recommendations for SC intoxication. Treatment of psychosis from SC commonly has been treated with haloperidol, olanzapine, or risperidone, while benzodiazepines are used regularly for supportive care for acute agitation and restlessness.[2,5-7] The majority of case reports or series of patients experiencing psychotic symptoms with SC are less than 30 years of age, which coincides with the usual age of onset of thought disorders such as schizophrenia.[2-5,7] SC may unmask symptoms of schizophrenia and this cannot be ruled out in our patient. Long term follow-up with our patient was needed to differentiate between a primary thought disorder versus substance induced psychotic disorder.

Our patient admitted to heavy SC use. Thus, we did not test specifically for the presence of SC. A few immunoassays have been developed to test for major metabolites of JWH-018.[10,11] However, testing in the urine is difficult due to the constantly changing composition of SC. Clinicians may consider urine testing for SC in patients presenting with psychosis though these tests are not routinely available at most medical centers. Samples generally have to be sent to an outside laboratory, resulting in delayed results, especially in the ED setting. Most often, clinicians will rely on patient or collateral information of SC use and utilize clinical judgment regarding SC consumption.

The long lasting presence of psychotic symptoms in our patient was concerning. This case highlighted the unknown risks, dangers, and treatment challenges in patients using SC. With the increasing popularity of SC among adolescents and young adults, further research is needed to determine behavioral, cognitive, psychological, and long-term effects of SC. Additional research and literature to describe the effects of SC can educate the public and health-care professionals about its dangers.

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Keywords: cannabis, cannabinoids, psychotic disorders

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COMMENTARY

Care Variation in the Treatment of Acute Coronary Syndrome Patients in India vs the United States

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INTRODUCTION

Controlling healthcare costs and expanding coverage have been the central domestic policy priorities of the Obama administration. While the Affordable Care Act will provide an avenue for insurance coverage to millions of previously uninsured Americans, it fails to address many of the fundamental problems perpetuating the ever-increasing strain healthcare costs place on the government, businesses, and the individual American citizen.

The United States healthcare system is the most expensive in the world. National healthcare expenditures top an estimated 17.9% of gross domestic product (GDP) and are expected to continue their trend upwards to 19.6% of GDP by 2021, with per capita spending double that of our European peers.[1] As the largest driver of the country's increasing debt, soaring costs in the health sector necessitate national and state governments to take drastic measures to meet their bottom lines through a combination of restrictions to Medicaid eligibility, increased taxes, as well as cuts to public education and other state programs.[2] Soaring medical expenditures and evidence that our high national investment is not producing the overall health results expected from such spending, signal that change is necessary if America is to rein in healthcare costs while improving the quality of care administered.

As the democratic process has stymied attempts for broader health reform, the necessary change required must come from within the existing system if American healthcare is to be transformed into something that is both self-sustaining and high performing for society as a whole. Developed nations around the world have found ways almost universally to deliver effective healthcare to their citizenry for a fraction of the United States' annual costs, however, successful models exist even in developing nations such as India.[3] As a developing nation with a nominal per capita income of only $1,500 and average "out-of-pocket" costs sitting at 60% of healthcare expenditures, ensuring access to medical treatment to a population over 1.2 billion starts with lowering the costs inherent with providing care to the masses.[4] In response to this huge demand for quality, cost-effective healthcare, many Indian hospitals have found ways to drive down the costs associated with healthcare to levels less than a fifth of those reported by hospitals in the United States.[5] In doing so, these institutions have expanded their impact in a country with so much need by increasing the quantity of care they provide for each healthcare dollar received.

Variation in the care provided between physicians and institutions leads to increased costs if the procedures ordered do little to improve the outcome of the care provided.[6] In fact, care variation and uneven adherence to evidence based standards in the treatment of many complex episodes of care, has led to cost differences reaching 50% between institutions in the US. More efficient care delivery to under-insured or non-insured patients, the largest contributors to overall health expenditures, could save the United States an estimated 300 billion dollars per year.[6]

In studying the care pathway for chest pain patients at hospitals in India and the US, differences between the provided care were determined. These findings, as well as more general observations from each institution, provided input into ways in which Indian hospitals have reduced the costs associated with care. Chest pain was chosen as it is an area that is evidence-based and has a high incidence rate, which also makes it a large contributor to the overall healthcare dollars spent. Due to the strong evidence backing specific treatment protocols in high-risk and STEMI acute coronary syndrome (ACS) patients, there is usually little variation in the care of patients on this end of the spectrum, setting up a control of sorts for the comparison. There is, however, a large variation in the care of those patients falling into lower risk categories, providing a suitable population in which to compare how these cost saving measures potentially impact the treatment path of these patients.

Through cumulative observational experiences at CARE and Osmania Hospitals, private and public respectively, in Hyderabad, India and at the University of Kansas Hospital (KUHA) in the United States, care-tracks for the treatment of low, medium, and high-risk chest pain patients were established. These tracks were designed to reflect the actual care provided, rather than stated treatment process maps at each institution. All observed patients were documented in terms of age, sex, time and day of arrival, chief complaint, onset of chest pain, risk factors (including diabetes, hypertension, hyperlipidemia, diabetes, family history of coronary artery disease, smoking, aspirin use in last seven days, and prior stenosis), as well as electrocardiogram (EKG), troponin, and two-dimensional echocardiogram (2D ECHO) results. These patients were followed to document the labs, procedures, and ongoing treatment decisions ordered throughout their hospitalization. Data concerning chest pain patients in the Clinical Throughput Unit (CTU) at the KUHA were obtained. The CTU is an outpatient observational unit that serves as an extension of the ER and supplements the observational data gathered separately at KUHA.

KUHA and CARE are accredited institutions by The Joint Commission and The National Accreditation Board for Hospitals & Healthcare Providers, its Indian equivalent, respectively, that have built their reputation on excellence in cardiac care. As a high-performing, cost-conscious Indian hospital, CARE provides an excellent

contrast to KUHA. Osmania General Hospital was included to obtain a more holistic view of the Indian healthcare system.

COMPARISONS

Clinical information from 38 patients presenting to CARE hospital in June 2014 and 257 patients to KUHA for complaints of chest pain was gathered and used to draw conclusions on the care of this patient population at each institution. Of these 257 patients at KUHA, 10 were direct observations made over the course of a week's time in May 2014, with the remaining clinical data obtained through a review of hospital medical records from November 2013 to May 2014. These clinical encounters were used to construct process maps reflecting the typical care pathway for chest pain patients presenting to KUHA and CARE, as detailed in Figures 1 and 2 respectively.

At KUHA, EKG screening and blood work for bedside troponin were performed on all 257 patients presenting to the emergency room (ER) with complaints of chest pain, with the exception of two patients in which EKG data could not be found. Patients with significant EKG changes, defined as ST-elevation, ST-depression, or T-wave inversion in two contiguous leads and positive troponin after this initial testing, were admitted for conventional angiography, with a sped-up process occurring for ST-elevated individuals that sometimes bypassed troponin screening in the emergency room. Those individuals without definitive ST segment elevation on EKG or positive troponin, but with other non-specific EKG changes were admitted to cardiology for ongoing care management. Additionally, patients who could not be ruled out for ACS with a single EKG and troponin, largely those with intermittent or ongoing pain of less than six hours onset, the amount of time it takes troponin to rise following a myocardial infarction (MI), were sent to the outpatient CTU unit for observation with serial EKG and troponin taken at six-hour intervals. The majority of patients undergoing observation received three or four troponin draws, average of 3.4 for CTU patients prior to leaving the unit. From the CTU, upwardly trending troponin or significant EKG changes were an indication for conventional angiography.

In the absence of these findings, the vast majority of patients were sent for thallium or exercise ECHO stress testing, which determined whether conventional angiography was performed or the patient was discharged with outpatient follow-up. In lieu of stress testing, a minority of lower-risk patients underwent cardiac computed tomography angiography (CCTA) evaluation if a non-ACS cause for the patient's symptoms was suspected.

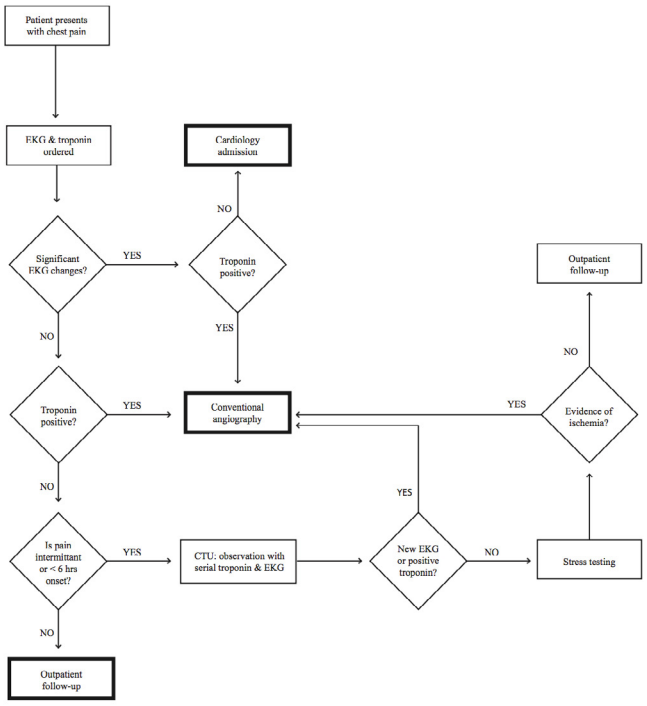

Figure 1. The University of Kansas Hospital observed chest pain protocol.

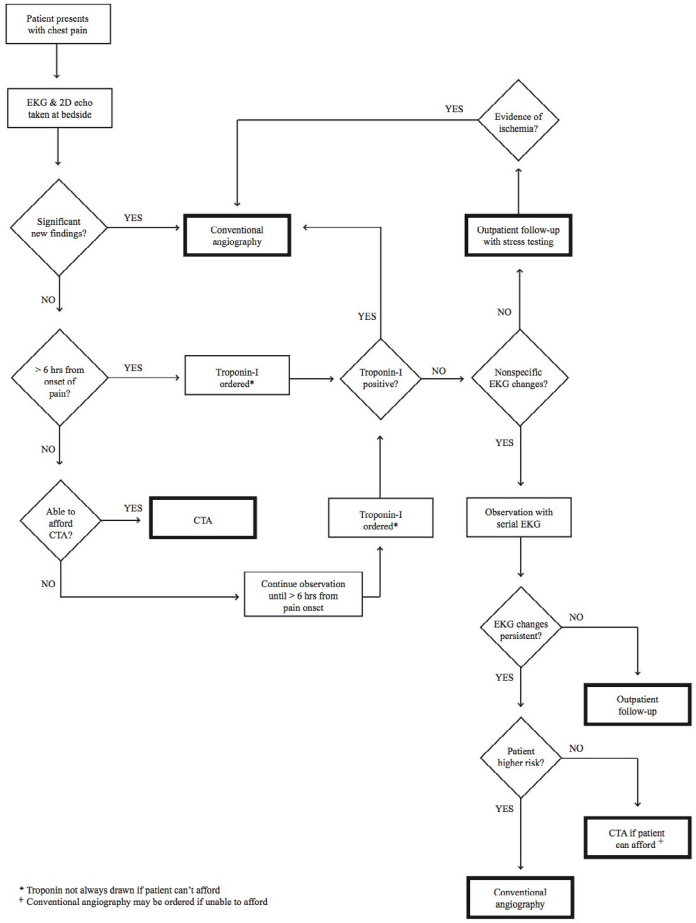

Figure 2. CARE Hospital observed chest pain protocol.

Patients presenting to CARE Hospital with complaints of chest pain quickly underwent EKG and resting ECHO evaluation, with interpretation by cardiologists, at the bedside. ST-segment elevation and new ST-depression or T-inversion accompanied with a bundle branch block, regional wall motion abnormalities on ECHO, or longstanding hypertension and diabetes were indications for the patient to be admitted straight to the heart catheter lab for conventional angiography. With two exceptions due to cost concerns in lower-risk patients, individuals who did not meet these criteria had troponin drawn once six hours had passed since the onset of their symptoms.

In a single instance, computed tomography angiography (CTA) was offered to a patient with atypical pain of one-hour onset with the means to afford this procedure instead of continuing observation until this six-hour threshold had been reached. A positive troponin draw resulted in a planned catheterization in all four observed cases. Three of these patients sent for conventional angiography following positive troponin had new nonspecific EKG changes at admission, while the fourth, who had a history of coronary artery disease without new EKG changes, was sent to the heart catheter lab after he remained symptomatic overnight. Chest pain patients with negative troponin values and without EKG changes were discharged for outpatient follow-up, repeat EKG, and stress testing in two to three days' time at the CARE cardiology clinic, while those with nonspecific EKG findings were kept for observation and serial EKG at two hour intervals. Persistent EKG changes, specifically ST-depression or T-wave inversions, resulted in either conventional angiography or CTA procedures depending on the patient's perceived risk level and ability to afford a CTA. A patient planned for a CTA may receive conventional angiography instead due to patient cost concern or higher risk features, such as elevated calcium scores, determined during the pre-CTA work-up.

DISCUSSION

Contrary to hospitals in the United States, the private Indian healthcare system has developed in an environment of chronic underfunding from the Indian government whose healthcare expenditure per capita in 2013 was only $61.[7] According to the Indian judicial system, every hospital in India is mandated to provide timely care to all individuals regardless of their ability to pay. In practice, however, this is not always the case. While CARE hospital has foundational money set aside for the treatment of non-paying patients, doctors, especially those seeing entry level patients, have to be very cognizant of the costs associated with the medical care provided. Many of the doctors at CARE expressed frustrations that the government does not realize that providing emergency care requires money for equipment and resources, money that is not refunded to the hospital fully from the government. In a country where the majority of citizens are unable to afford medical care, private hospitals are under pressure to keep costs down and to balance the care of these patients with paying patients. This is achieved at CARE through the utilization of a "hub and spoke" healthcare structure through which patients with the ability to pay and those requiring urgent care are referred from more rural clinics to centrally located hospitals where specialists and expensive equipment are concentrated.

In comparing KUHA and CARE, there were several differences noted in the care of patients presenting with chest pain at each institution. At CARE Hospital, troponin is used in a more focused and deliberate manner. Instead of using troponin in tandem with EKG to rule-in ACS in each chest-pain case, CARE first relies on 2D bedside echocardiography (ECHO) and EKG screening to catch high-risk ACS patients who require immediate catheterization. In using 2D-ECHO in place of an immediate troponin draw, CARE replaces lab work with imaging that has little additional per-use costs associated with it. Patients without significant EKG or ECHO findings will receive troponin lab work, but only after six hours from their reported onset of pain to insure that troponin levels have had sufficient time to show up in the blood. No patient observed at CARE received serial troponin draws, despite that being the stated treatment plan for one patient prior to his care ultimately being shifted to GI, which stands in stark contrast to standard protocol at KUHA. It is clear that CARE uses troponin testing in an effort to maximize the clinical usefulness of a single troponin draw per patient to cut down on the need for additional laboratory testing. Additionally, in sending patients to the heart catheter lab directly upon significant EKG findings, or nonspecific changes supported by ECHO, CARE cut back on much of the standard testing that is a part of the full-workup for these patients at KUHA prior to conventional angiography.

These differences in protocol do not come without clinical implications for patients who present with chest pain to each institution. At both KUHA and CARE, EKG is the first priority followed by troponin or ECHO, respectively. Although EKG is recognized as the first-line diagnostic tool for the detection of cardiac abnormalities, this testing is insensitive, yielding normal findings in 6-7% of ACS patients and non-diagnostic results in 50% of acute myocardial ischemia cases.[8] Troponin and ECHO testing are utilized in an attempt to bridge this gap, but each has its limitations. Troponin has proven to be a useful diagnostic test for myocardial infarction detection, however, while positive enzyme values strongly correlate with increased morbidity and mortality, non-elevated values far from rule out the presence of smaller episodes of ACS induced ischemic episodes that are predictive for future cardiac events.[9]

Troponin testing is positive in 5% of "low risk" patients and only 40% of patients that require revascularization procedures.[9] Likewise, while 2D resting ECHO screening is useful in visualizing regional wall motion abnormalities (RWMA) that develop within seconds of coronary artery occlusion, without stressing the heart, it is limited in its ability to assess the presence of smaller occlusions

or ischemic events.[10] Echocardiography has the advantage of detecting cases of ACS before EKG or troponin changes occur, however, it cannot differentiate between alternate causes of motion abnormalities such as left and right bundle branch blocks, which are a significant cause of false positives with this diagnostic tool. It also has the added benefit of providing prognostic information of the expectations for recovery following revascularization in cases of suspected hibernating myocardium through the measurement of end-diastolic wall thickness and left ventricular filling patterns.[11] Parato et al.[10] supported the role of EKG as the mainstay in ACS detection, especially in low-risk cases, but also demonstrated the value of a combination approach, one which utilizes the strengths of each diagnostic modality in making the prompt, accurate diagnosis of ACS.

Given the stated limitations, KUHA may be over-utilizing troponin testing, especially in patients that have recorded positive values already and will continue to have elevated levels for several weeks. In combining troponin testing with increased use of ECHO, KUHA may be able to replace some of the more costly laboratory testing with this proven imaging technique that requires minimal additional per-screening costs. Under existing payment structures within the American healthcare system, however, evaluation with ECHO involves a large charge markup. Effective use of ECHO also requires physicians trained in using and interpreting the results from this technology and is more time consuming. While CARE has trained cardiologists doing this screening in their emergency room, not all emergency medicine physicians at KUHA, who largely function on their own in the initial work-up of chest pain patients, are competent in utilizing this imaging modality. There are signs, however, that this may be changing. With bedside ultrasonography recently added to the list of core competencies expected from Emergency Medicine residency graduates, and with increasing numbers of ultrasonography fellowship trained emergency physicians entering the marketplace, it is not unreasonable to expect that this initial imaging could be performed without the added involvement of cardiology which increases the associated costs.

A potential concern from the pathway observed at both hospitals is the volume of patients undergoing catheterization. A recent meta-analysis by Stergiopoulos et al.[12] found no significant difference in the outcomes of stabilized non ST-elevated patients receiving either percutaneous coronary interventions or medical management for their known coronary artery disease. Given the costs and risks associated with these procedures, a prompt review of the indications for catheterization in non ST-elevated individuals is needed, in particular those receiving this intervention on the basis of positive stress testing and history of coronary artery disease.[12]

Outside of measures directly related to patient care, there were many ways that CARE Hospital reduced the costs related to each patient encounter. While the hospital was kept clean and secure, very little was spent on patient luxuries that are taken for granted in the United States. Individual rooms, which included a small TV, were provided only to patients that could afford to pay for them, otherwise patients were kept in wards with privacy provided through curtaining. Families were allowed in patient care areas for only an hour each day, which allowed the units to avoid congestion and maximize space utilization in this set-up. Additionally, while the hospital environment was kept at a comfortable temperature, it was achieved less through the utilization of air conditioning, although it was available if required, and more through the extensive use of fans and window shading in most units. Each of these areas represented measures that reduce patient costs without substantially impacting outcomes.

Unlike in the United States, patients in India keep track of their own healthcare records following their discharge. As a result of this practice, recording clinical impression, ongoing care plan, and discharge notes for low-risk chest pain patient encounters required "catching" the patient while they were present in the ER prior to their discharge. Additionally, as a hospital having built its reputation on cardiac care and that served as the "hub" in the organization's "hub and spoke" set-up, 70% of cardiac patients seen in the ER at CARE Hospital were higher-risk referrals from outside clinics, which added to the difficulty of gathering an adequate number of low-risk patient encounters. For these reasons, attention focused away from tracking all risk-category chest pain patients in the hospital to harder to observe lower-risk patients in the emergency room. Ultimately, the total volume of lower-risk cases collected likely did not reflect the entire range of clinical presentations screened at CARE, making construction of a process map that included every decision point impossible; however, no process map is broad enough to encompass every presentation. Ideally, pairing the care pathway observed at each hospital with patient risk to healthcare outcome analysis would have been more meaningful. This objective was hindered by the fact that quality outcome data are not mandated by the Indian government, and CARE, along with most private hospitals in India, do not track this information, as doing so requires additional administration and costs. Retroactive analysis of these data also is prevented in a system where medical records leave with the patient at the time of discharge.

In the end, the clinical time spent at Osmania Government Hospital did not prove to be a useful comparison to care in the United States. The healthcare system in India consists of a mixture of public and private allopathic institutions as well as alternative healthcare practitioners. Public hospitals are set up as a place where those living below the poverty line can come to receive medical care free of cost. However, with government investment in the public healthcare sector only totaling 1% of GDP, these institutions lack the resources to provide effective care to the masses that show up to their door.[7] The clinics are overwhelmed; one cardiologist sees 50 patients during their two hour clinic time, important medical equipment goes unfixed when it breaks down,

the heart catheter lab equipment was down during the entirety of my week stay, and large sections of the hospital go without any degree of cleaning. In fact, several patients had been waiting in the cardiology ward for a month for their planned percutaneous transluminal coronary angioplasty procedures due to equipment failures. The lack of consistency in care observed as a result of these factors makes comparison of care at Osmania to KUHA a fruitless exercise.

CONCLUSION

Protocols for chest pain patients at the University of Kansas Hospital in the United States and CARE Hospital in India were produced through clinical observation and compared. Notably, CARE Hospital places a much stronger reliance on 2D resting ECHO, bypassing immediate troponin testing prior to catheterization in ST-segment elevated individuals or those displaying new ST-depression or T-inversion accompanied with a bundle branch block, longstanding hypertension and diabetes, or regional wall motion abnormalities on ECHO. Additionally, as an institution facing tight budget constraints as a result of the socioeconomic and political realities of providing healthcare in India, CARE has found successful ways to reduce their operational costs in areas that do not have a negative impact on the quality of care administered.

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