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An Atypical Source of Persistent Fungemia in the Intensive Care Unit

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 63-year-old
Final Diagnosis: Deep vein thrombosis • septic shock
Symptoms: Hematemesis • respiratory failure
Medication: —
Clinical Procedure: —
Specialty: Critical Care Medicine • Infectious Diseases • General and Internal Medicine

Objective: Unknown etiology

Background: Candidemia is a common complication of critically ill and immunocompromised patients, with more than 50% associated mortality. Typical etiologies include valvular vegetations, intra-abdominal fluid collections, and central venous catheters. Treatment often entails surgical excision, but anticoagulation may be sufficient.

Case Report: Our case was a 63-year-old woman with diabetes mellitus, left hip osteoarthritis status after hemiarthroplasty, and alcohol use disorder, admitted to the Intensive Care Unit with diabetic ketoacidosis (DKA) and hemorrhagic shock from an upper gastrointestinal bleed. Complicating her course was the development of *Candida* species fungemia. An extensive workup including transthoracic echocardiography, computed tomography of the chest, abdomen, and pelvis, ocular examination, and hip aspiration was unrevealing in determining the etiology. Despite early line removal and appropriate antifungal therapy, the fungemia persisted. A broader evaluation revealed a venous thromboembolism, which ultimately was thought to be the source. Subsequent initiation of anticoagulation and continued antifungal therapy led to clearance of blood cultures with overall clinical improvement.

Conclusions: In critically ill patients at higher risk for development of venous thromboembolism, septic thrombi should be considered in the differential diagnosis when evaluating for source control in a patient with fungemia.

Keywords: Candidemia • Shock, Septic • Thrombophlebitis

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Background

Candida is part of the normal skin, vaginal, and gastrointestinal flora [1]; it typically will not cause infection unless the normal flora or the host antifungal defense response had been disrupted. For example, antibacterial agents allow for fungal overgrowth on mucosa or skin versus modifying the integrity of the skin by intravascular access devices [1]. Invasive candidiasis encompasses a variety of conditions, including candidemia, disseminated candidiasis, deep organ involvement, endocarditis, and meningitis [2]. The pathogenesis of invasive candidiasis is likely multifactorial, including gut translocation in immunocompromised patients and those with a history of abdominal surgery, as well as the formation of biofilms on central venous catheters [3-5]. While acknowledging the pathogenesis and its associated risk factors, predisposing factors include renal failure, antibiotic exposure, diabetes, pancreatitis, and prolonged intensive care unit (ICU) stay, with a peak incidence at around day 10 [2]. Once in the bloodstream, seeding can occur in several locations, including heart valves, brain, retina, kidney, and skin. Less common areas of seeding are the liver, spleen, muscle, and, rarely, vascular thrombi. We describe a patient who developed *Candida* thrombophlebitis in the right internal jugular vein after admission to the ICU.

Case Report

Our patient was a 63-year-old woman with alcohol use disorder, type 2 diabetes mellitus, hypertension, and chronic pancreatitis complicated by a pseudocyst, who was admitted to the ICU for mixed hemorrhagic/distributive shock in the setting of acute gastrointestinal bleed and diabetic ketoacidosis. On presentation to an outside hospital, she was reportedly lethargic with declining responsiveness, hypothermic to 32.4°C, and hypotensive with a blood pressure of 52/33 millimeters of mercury (mmHg). Initial laboratory test results revealed hemoglobin of 13 grams/deciliter (g/dL), glucose greater than 1500 milligrams/deciliter (mg/dL) with a beta-hydroxybutyrate greater than 22.50 millimoles per liter (mmol/L), creatinine of 3.55 mg/dL (with a baseline of 0.7-0.8 mg/dL), blood urea nitrogen (BUN) of 101 mg/dL, bicarbonate of 5 mmol/L, and pH of 7.01 on arterial blood gas. Her outside hospital course was complicated by large-volume hematemesis requiring 2 units of packed red blood cells, intubation for airway protection, and subsequent placement of a right internal jugular vein central line. She was then started on insulin and pantoprazole drips, given 1 dose of 2 g of intravenous (i.v.) ceftriaxone, and transferred to our hospital for further management.

On arrival at our hospital, she was afebrile, tachycardic to 120 beats per minute (bpm), maintaining a mean arterial pressure of 90/60 mmHg with a norepinephrine infusion at 0.3 microgram/kilogram/minute, and vasopressin infusion at 0.03 units/minute. Initial laboratory test results on arrival revealed a pH of 7.21 with a bicarbonate of 22 mmol/L based on arterial blood gas. Her glucose was 902 mg/dL, anion gap of 28 mmol/L with a potassium of 3.7 mmol/L, a BUN of 84 mg/dL, and a creatinine of 2.47 mg/dL. Other pertinent laboratory test results included a lipase of 69 units per liter (U/L), C-reactive protein of 262 milligrams per liter (mg/L), sedimentation rate of greater than 120 millimeters per hour (mm/h), undetectable ethanol, hemoglobin of 15 g/dL with platelets of 165 000 per cubic millimeter (cu mm), and white blood cell count of 3300 per cu mm. Given her degree of critical illness, an infectious diseases workup was initiated after obtaining blood, sputum, and urine cultures. A chest X-ray showed increased bilateral lower lung predominant patchy opacities. She remained on norepinephrine, vasopressin, and insulin drips and was started on broad-spectrum antimicrobial coverage with piperacillin/tazobactam.

On hospital day 1, her blood cultures returned positive for *Candida* species in 2 of 2 samples, thus she was started on micafungin 100 mg i.v. daily for undifferentiated *Candida* fungemia. Those cultures later speciated to *C. albicans*, which continued to grow on blood cultures obtained on hospital days 1-3. On hospital days 5 and 7, her blood cultures grew *C. glabrata* despite remaining on micafungin therapy during this time. An attempt at source control involved a line holiday with the removal of the arterial line and right internal jugular vein central line shortly after finding positive blood cultures. The workup for fungemia source consisted of a transthoracic echocardiogram without evidence of vegetation or new valvular regurgitation. Computed tomography (CT) with i.v. contrast of the chest revealed bilateral lower lobe consolidations with air bronchograms, extensive bilateral peribronchovascular mixed ground-glass consolidations with associated tree-in-bud nodularity, and airway thickening. CT of the abdomen and pelvis with i.v. contrast showed diffuse hepatomegaly with severe hepatic steatosis but no intra-abdominal fluid collections. The ophthalmologic exam was negative for intra-ocular lesions. Given her history of left hip hemiarthroplasty, plain films were obtained, and an attempted hip aspiration was unsuccessful, neither of which were consistent with hardware infection. Several days after the initial investigation, with persistently positive blood cultures, upper and lower extremity duplexes were obtained, ultimately revealing a deep vein thrombus (DVT) in the right internal jugular vein (**Figure 1**); no other clots were found. She was subsequently started on a heparin drip with clearance of both the clot and blood cultures in the following 2 days. At the recommendation of the Infectious Disease team, she remained on fluconazole for a total of 4 weeks after clearance of blood cultures. The right internal jugular clot was treated with a planned 3 months of enoxaparin (given renal dysfunction) for provoked DVT. She stayed in the hospital for a total of 31 days, 10 days

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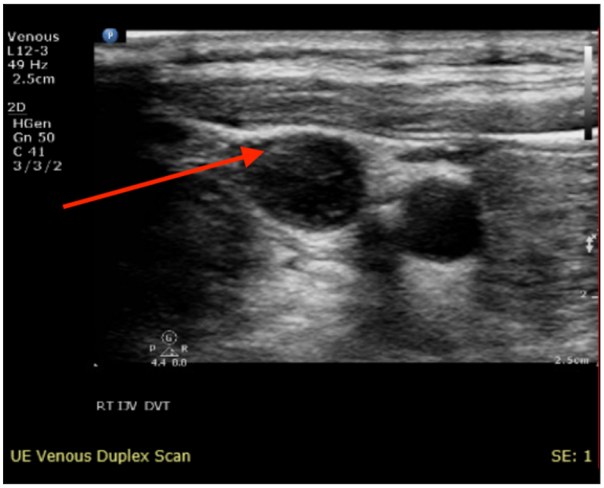

Figure 1. Right internal jugular, with compression. Arrow pointing to hyperechoic area in RIJ referring to clot in question.

in the general medicine ward after ICU transfer, and recovered to a point of stability for discharge to a skilled nursing facility.

Discussion

Invasive candidiasis is often fatal unless caught early and treated appropriately. Complicating a prompt diagnosis is the variety of clinical presentations, low yield of blood cultures, and the time it takes for fungal speciation. The presentation can vary from fever and leukocytosis to overt septic shock and can be missed unless accessible to involved tissue, or positive blood cultures. Our case highlights the importance of broad work-up when it comes to diagnosis and the difficulties encountered when the location challenges the ability to obtain proper source control.

A study done in Europe found the incidence of ICU-acquired invasive candidiasis to be 7.07 episodes per 1000 ICU admissions [1]. However, there is limited literature on infected thrombi as a source of persistent fungemia, noting as of 2012 that there had only been 24 reports of well-documented cases in the 30 years prior [6]. In a case series of 46 patients with suspected CVC-related septic thrombophlebitis, a mere 5 (11%) cases were due to *Candida* [7]. Further investigation of prevalence based on species and a literature review of *Candida*-related septic thrombophlebitis by Caccese et al found that *C. albicans* was isolated in 19 of 25 cases, *C. glabrata* in 5 of 25 cases, and *C. krusei* in 1 case [6]. Determining the species is of importance due to the effect of treatment choice. *C. glabrata* and *C. krusei* infections have reduced susceptibilities to azoles (68% for non-albicans *Candida* vs 95.6% for *C. albicans*) [8]. In our case, empiric therapy with echinocandins was appropriate given the growth of both *C. albicans* and *C. glabrata,* but is the clinician had chosen azole therapy and the fungemia persisted, knowledge of the above could have aided in appropriate determination of the next steps.

Over the years, recommendations for the treatment of *Candida* thrombophlebitis have varied. In 1993, a published case report by Kelly et al describes a case of a septic clot in the innominate vein complicated by pulmonary embolism and candidemia. Initially, the patient was treated with local clot lysis, amphotericin B, and vancomycin, but the persistence of fungemia led to surgical excision. The author goes on to describe how surgical excision was the criterion standard for septic peripheral vein clots, but the question remained about the ideal treatment for septic central veins given the relative inaccessibility for surgical thrombectomy. It also mentions several other case reports of patients with septic central venous thrombophlebitis who were successfully treated by catheter removal, anticoagulation, and parenteral antibiotics [9].

Several years later, Sung-ching Pan and colleagues published a case report in 2005 describing a patient with *C. krusei* thrombophlebitis of the inferior vena cava with persistent fungemia, treated solely with intravenous caspofungin, resulting in successful clearance of cultures. Of note, anticoagulation was considered but deferred in the setting of prolonged partial thromboplastin time [10]. More recently, based on clinical practice guidelines published in 2016, recommendation begins with catheter removal, incision, and drainage or resection of the vein if feasible, followed by antifungal therapy with amphotericin B, fluconazole, or an echinocandin for 2 weeks. There is a brief mention of anticoagulation or thrombolytic therapy as a possible alternate, but data thus far are lacking to justify a recommendation [11].

Finally, the impact of this condition raises the question of whether prophylaxis is warranted. The EMPIRICUS trial looked at this exact question, assessing critically ill adults who were mechanically ventilated with known *Candida* colonization, evidence of organ dysfunction, recent broad-spectrum antibiotic exposure, at least 1 arterial or central venous catheter, and new-onset sepsis. They wanted to see if empiric coverage with micafungin would reduce invasive fungal infection-free survival at 28 days [12]. While reducing the number of newly developed invasive fungal infections, the study did not find that empiric therapy versus placebo improved survival at 28 days [12]. While the battle against invasive candidiasis continues to evolve, practitioners must consider less common alternatives when it comes to evaluation and treatment, acknowledging there may not be much to do in the way of prophylaxis.

Conclusions

Our case highlights a rare etiology of fungemia. The presence of appropriate risk factors and persistent fungemia despite the

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removal of lines, ruling out other sources of infection such as intra-abdominal fluid collection, and use of appropriate antifungals should prompt the clinician to assess rare sources of infection such as infected thrombi.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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