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***Candida albicans* Cervical Lymphadenitis in Patients Who Have Acute Myeloid Leukemia**

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Abstract

We describe two patients with acute myelogenous leukemia who developed cervical lymphadenitis and chronic disseminated infection due to *Candida albicans*. *Candida albicans* infection should be considered in leukemic patients with acute lymphadenitis. Evaluation for visceral dissemination is warranted even in the absence of fungemia.

Keywords

Acute myeloid leukemia; Disseminated candidiasis; Lymphadenitis

Introduction

Candida species are the most common cause of invasive fungal infection in humans. *Candida* infection in immunocompromised hosts is frequently life threatening.¹ The involvement of lymph nodes in patients with disseminated candidiasis has been described as a rare occurrence that accompanies visceral involvement.² Such a localized manifestation may be an early indication of dissemination. We describe two adult patients with acute myelogenous leukemia (AML) who rapidly developed lymphadenitis after chemotherapy-induced neutropenia. In both patients, *Candida albicans* was identified in lymph node tissue.

Case Reports

Patient A

A 63-year-old man with Crohn's disease who was being administered infliximab (100 mg every 2 months for 3 years) was recently diagnosed with AML. He underwent induction chemotherapy with 7 days of cytarabine and 3 days of daunorubicin. His subsequent hospital

course was complicated by febrile neutropenia, spontaneous splenic rupture, and abdominal compartment syndrome requiring exploratory laparotomy with splenectomy. One week after neutrophil recovery he developed a rapidly enlarging left-sided submandibular lymphadenitis (Figure 1A). Dental evaluation was normal. A computed tomography (CT) scan of the neck with contrast demonstrated an irregularly enhancing mass with central low density in the left submandibular region approximately 2.2×4.8 cm. Liver function tests were normal. Multiple smaller low-density masses were noted in the posterior triangle on the left and on the right. Although the right jugular vein was compressed, there was no evidence of intravenous thrombus (Figure 1B). He was empirically treated with ciprofloxacin and metronidazole for bacterial infection.

He underwent fine-needle aspiration (FNA) of the left submandibular mass under CT guidance 7 days after antibacterials were initiated. The aspirate showed no growth on bacterial, fungal, or mycobacterial cultures; initial cytology from FNA showed abundant hyphal forms strongly suggestive of *Aspergillus* species on Gomori methenamine silver (GMS) stain, Giemsa stain showed acute inflammation (Figure 1C, D). 1,3- β -D-glucan (Associates of Cape Cod, East Falmouth, MA) levels were followed-up twice weekly and reached a peak of 80 pg/mL (the threshold at our institution for positivity) a day after receiving intravenous albumin. The galactomannan index was 0.11. Because *Aspergillus* infection seemed unlikely given the nature of the presentation, the patient underwent a diagnostic excisional lymph node biopsy of the left submandibular node 6 days after the FNA. The tissue demonstrated extensive acute inflammation with fungal organisms suggestive of yeast infection. Neck CT also showed pulmonary nodules on several cuts, and further evaluation with a dedicated chest CT showed multiple bilateral areas of consolidation with adjacent ground glass. CT of the abdomen showed several low attenuation micronodules in the liver as well consistent with hepatosplenic candidiasis. *Candida species* was not isolated from the blood. Subsequently, polymerase chain reaction (PCR) of the lymph node with 28S ribosomal RNA and internal transcribed spacer regions were performed (University of Washington, Seattle, WA) for fungal species identification and ultimately demonstrated *Candida albicans*.³

Antibacterials were stopped and he was discharged home on fluconazole. He was readmitted within a week with worsening right-sided neck swelling. A neck CT with contrast demonstrated multiple necrotic or suppurative lymph nodes in the right posterior chain. A repeat FNA was obtained. Bacterial and fungal cultures were again negative. Cytology showed necroinflammatory debris with fungal organisms on methenamine silver stain (MSS) stain and PCR was again positive for *Candida albicans*. The patient was treated with fluconazole; levofloxacin and metronidazole were empirically added. The patient did well clinically. His lymphadenitis and pulmonary nodules have completely resolved at the 5-month follow-up examination.

Patient B

A 45-year-old man with no significant medical history was diagnosed with AML. He received induction chemotherapy with 7 days of cytarabine and 3 days of daunorubicin. On day 18 after induction chemotherapy he developed acute right-sided submandibular

lymphadenitis in the setting of prolonged neutropenia. One week before the diagnosis of AML, he had lost a crown on his right lower molar. Dental evaluation revealed a possible sinus tract on the lower right ridge of the mandible. He was treated with vancomycin, ceftazidime, and ampicillin/sulbactam. A CT scan of the neck with contrast revealed heterogeneous low-density edema centered around the right tonsillar region with mild to moderate deformity of the airway in the right tonsillar region with multiple prominent upper cervical lymph nodes. There was no evidence of jugular vein thrombosis (Figure 1). The soft tissue swelling quickly lead to airway compromise requiring intubation.

He underwent operative debridement of the right neck. Cultures of debrided tissue demonstrated *Candida albicans*. Mycobacterial and bacterial culture remained sterile. Micafungin was added to his antimicrobial regimen. Further CT imaging showed scattered nodular opacities in bilateral lung fields as well as low-density lesions in the spleen and liver suggestive of visceral dissemination of *Candida*. 1,3- β -d-Glucan levels were serially followed-up and peaked at 170 pg/mL, although fungemia was never documented.

He improved after debridement and neutrophil count recovery. His antimicrobial regimen was changed to amoxicillin-clavulanic acid and fluconazole for discharge home. Although a bone marrow biopsy specimen obtained more than 1 month after induction chemotherapy suggested complete remission, he relapsed within a few weeks. Although his *Candida* infection remained controlled on antifungal therapy, he underwent reinduction chemotherapy twice without success and died of refractory leukemia.

Discussion

We describe a clinical syndrome of cervical lymphadenitis caused by *Candida albicans* and subsequent disseminated candidiasis in two patients undergoing chemotherapy for AML. Salient features of the case include recent history of profound neutropenia after treatment for hematologic malignancy, the rapid progression of neck swelling, and the findings of visceral dissemination in the absence of documented fungemia. Although we cannot exclude a mixed infection that includes mycotic and pyogenic organisms, only *Candida albicans* was isolated despite repeated diagnostic aspirations/biopsies, and no bacteria were isolated. The noted absence of fungemia parallels the presentation of hepatosplenic candidiasis.

Cervical lymphadenitis ascribed to *Candida albicans* in a patient with leukemia was first reported in 1979 by Epstein and Tuazon.⁴ Although no evidence of dissemination was discovered in that patient, the investigative technology was limited. In 1985, Shenep et al published a case series of three pediatric patients with leukemia who developed mycotic cervical lymphadenitis after mucositis.⁵ In all cases described, cultures from a lymph node aspirate revealed *Candida albicans*. Further investigation for persistent fever with CT showed lesions characteristic of visceral candidiasis (splenic, hepatic, and pulmonary). The authors note that the appearance of cervical lymphadenitis after neutropenia and mucositis should alert the physician to the “possibility of systemic mycoses, potentially involving the deep organs.” Chao et al (1995) describe one adult male patient with leukemia who developed inguinal lymphadenopathy and persistent fever. After repeated biopsies, *Candida tropicalis* was ultimately isolated from the spleen and a lower extremity lymph node.⁶

Diagnosing disseminated candidiasis is of critical importance in immunocompromised hosts. Attributable mortality from *Candida* approaches 48% in some studies, and is significantly increased by delays of 24 to 48 hours in the initiation of appropriate therapy.⁷ Prompt diagnosis of invasive candidiasis in acute leukemic patients is hindered by the low diagnostic yield of clinical samples, difficulty in obtaining diagnostic samples of affected organs, nonspecific clinical presentation, and delay in the development of characteristic nodular lesions on imaging. This difficulty has been at least partly alleviated by the usage of 1,3- β -D-Glucan; however, the sensitivity of this test for proven or probable invasive fungal infection is 0.63 (95% confidence interval [CI], 0.44–0.79) and a positive predictive value of 0.79 (95% CI, 0.57–0.92).⁸ Similar performance were characteristics were reported by Koo et al⁹; however, their study underscored the difficulty in interpreting the assay in the presence of intravenous immunoglobulin, albumin as well as hemodialysis with cellulose membranes as these can lead to false positive result. For example, patient A had a borderline positive 1,3- β -D-Glucan one day after albumin administration which made this test difficult to interpret. In addition, sensitivity in patients with hematologic malignancies 0.51 (95% CI 0.36–0.66) or after hematopoietic stem cell transplantation 0.43 (CI 0.18–0.71) was lower than in other subgroups.

PCR has emerged as a possible adjunct diagnostic strategy to routine cultures for fungal infections. McMullan et al evaluated the use of Taqman real-time PCR to detect medically important *Candida species* in serum samples in a prospective trial of nonneutropenic adults in a single intensive care unit.¹⁰ Five hundred twenty-seven specimens were obtained from 157 patients, 23 participants were categorized as having proven *Candida* infection at the time of sampling. If a single episode of *Candida famata* candidemia was excluded, the estimated clinical sensitivity, specificity, and positive and negative predictive values of the assays in the trial were 90.9%, 100%, 100%, and 99.8%, respectively. Although those results are encouraging, there are questions concerning the feasibility of real-time PCR in clinical settings. In our patient, we used PCR in a different way: identification of yeast found on cytology. This test, along with a low clinical threshold to investigate for dissemination of *Candida* in the presence of lymphadenitis in patients with acute leukemia, may lead to earlier diagnosis and improved clinical outcomes for such patients.

Conclusion

We report two cases of rapid onset cervical lymphadenitis after chemotherapy-induced neutropenia. In both patients, *Candida albicans* was identified in lymph node tissue. *Candida* infection in immunocompromised hosts can be life threatening. Lymphadenitis may be an early indication of disseminated fungal infection. *Candida albicans* should be considered as a possible pathogen in an acute lymphadenitis among immunocompromised patients and evaluation for visceral dissemination is warranted even in the absence of fungemia.

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Figure 1.

(A) Photo of Patient A With Swelling in the Left Submandibular Area. (B) Computerized Tomography of the Neck With Intravenous Contrast of Patient A Demonstrating an Irregularly Enhancing Mass With Central Low Density in the Left Submandibular Region. (C) Gram Stain of the Cytology From Patient A Demonstrating Fibrous Tissue With Extensive Acute Inflammation, Scattered Atypical Cells and Foreign Forms Suggestive of Fungal Organisms. (D) Methenamine Silver Stain of the Cytology From Patient A Showing Fungal Forms. The Polymerase Chain Reaction was Positive for *Candida albicans*.