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Case Report

A Case of Multiple Myeloma Presenting as *Streptococcus pneumoniae* Meningitis with *Candida auris* Fungemia

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Abstract
Multiple myeloma (MM), a plasma cell neoplasm, has a typical presenting pattern consisting of bone pain, renal failure, anemia, and/or hypercalcemia. Even though MM is a cancer that impairs the immune system, rarely is a systemic infection the first sign of disease. In this case report, our patient presented with altered mental status due to meningitis and was later diagnosed with MM. Furthermore, we display a case of a rare but emerging and serious fungus, *Candida auris*, that the patient developed during his inpatient stay. This is the first such record of *C. auris* in an MM patient.

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Introduction

Plasma cells in multiple myeloma (MM) proliferate uncontrollably, producing a monoclonal variant of an immunoglobulin. Among other harmful effects, these plasma cells damage their progenitor environment – the bone marrow – creating dysfunctional immune system cells that predispose the patient to bacterial, viral, and fungal infections. Most infections occur after three or more months following diagnosis and after initial chemotherapy, although some occur earlier [1]. Here we present a case of *Streptococcus pneumoniae* meningitis that prompted the diagnosis of MM. This patient's subsequent infection with *Candida auris* was most likely a result of a depressed immune system due to underlying MM. *C. auris* has a relatively novel appearance in several locations globally. This fungus generally arises in those with compromised immune systems and often is acquired in hospital settings, resistant to multiple drugs, and misidentified with other Candida species, making diagnosis and treatment difficult [15].

Case Report

A 72-year-old male with a history of hypertension and alcohol abuse was brought to the Emergency Department (ED) by his coworkers after developing an acute change in mental status and unsteady gait. He had a history of meningitis twelve years prior, which was treated accordingly, and had been in relatively good health until about a week earlier when, according to his wife, he began acting oddly.

On examination in the ED, the patient was febrile (T 38.3°C) and tachycardic (HR 121 bpm). Imaging of the head and chest were unremarkable for acute abnormalities or processes. Laboratory results revealed a left band shift without leukocytosis (WBC 6.2 × 10^3/μL). On physical exam, the patient was displaying the classic triad of meningitis (fever, nuchal rigidity, altered mental status), and a lumbar puncture was performed. Cerebrospinal fluid (CSF) analysis revealed increased total protein (>300 mg mg/dL), WBC (275/mm^3), and neutrophils (95%), and decreased glucose (3.93 mg/dL). The patient was admitted to the intensive care unit (ICU) with septic shock secondary to meningitis and immediately started on intravenous ceftriaxone, vancomycin, and dexamethasone. Blood and CSF cultures speciated to *Streptococcus pneumoniae*, and the patient completed two weeks of intravenous antibiotic therapy with ceftriaxone 2 grams every twelve hours for meningitis.

Further investigation ensued to understand why this patient had developed recurrent meningitis. The only immediately identifiable risk factor for meningitis was his alcoholism; there was no evidence of a predisposing infection in the previous months, and both an HIV 4th Generation test and ANA screen were negative. Early in his admission, the patient was noted to have an elevated total protein (9.9 g/dL), low albumin (1.9 g/dL), mild anemia (Hgb 12.2 g/dL), and elevated serum creatinine (1.3 mg/dL). With an unprovoked pneumococcal infection and lab tests suggestive of an underlying multiple myeloma, further work up was performed. Immunofixation and immunoglobulin quantitative tests showed an increased monoclonal gammopathy. The patient's IgG and β2-microglobulin levels were elevated, at 5,154 mg/dL and 3.58 mg/L respectively. No suspicious osseous lytic lesions were found on skeletal survey, and serum calcium remained within normal limits. A bone marrow biopsy was performed, showing hypercellular bone marrow and monoclonal IgG lambda restricted plasma cells, confirming the diagnosis of MM.

The patient was transferred to acute rehab to recover from neurological deficits secondary to meningitis. About three weeks into his rehab admission, the patient developed fevers and leukocytosis. He was transferred back to the inpatient medical floor and started on broad-spectrum antibiotics for sepsis of unknown source. Blood cultures grew *Candida auris* (identification confirmed by the New York State Department of Health), and he received a two-week course of antifungal therapy with intravenous micafungin 150 mg daily. Subsequent cultures were negative. The start of chemotherapy treatment for MM was significantly delayed until his active infections resolved.

After adequate treatment of the fungal infection, the patient was started on induction chemotherapy for multiple myeloma with the CyBorD regimen (cyclophosphamide, bortezomib, and dexamethasone), which was later changed to lenalidomide, bortezomib, and dexamethasone. He attained complete remission and has been without any recurrent infections since his diagnosis with *C. auris* candidemia.

Discussion

Multiple myeloma is a plasma cell malignancy characterized by the proliferation of plasma cells producing an abundance of a monoclonal immunoglobulin. This excess of a singular immunoglobulin causes the antibody-dependent humoral arm of the immune system to function poorly. In addition to increasing the number of defective immunoglobulins, MM suppresses functional immunoglobulins as well as various innate and adaptive immune system cells and their subsequent responses. Without functional antibodies, opsonization of pathogens cannot occur; these microorganisms, specifically polysaccharide encapsulated bacteria, go unrecognized in the body. Patients with MM are more susceptible to bacteremia secondary to *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and other such encapsulated organisms. A study by Twomey et al. affirmed that patients with MM demonstrated a higher incidence of severe infection when compared to healthy patients in the same age group [2].

A study by Chapel and Lee showed a higher incidence of first infection in the first three months after diagnosis of MM was made. If reinfection was taken into account, 75% of all serious infections were made after three months, after initial chemotherapy. Most of these infections were bacterial and respiratory or urinary in nature [1]. There are few instances, such as the case presented here, where an infection with a polysaccharide encapsulated organism was the presenting sign of multiple myeloma. This case report along with other similar case reports should serve as a cautionary tale for physicians to be more vigilant of patients developing severe bacterial infection with no known risk factors. Suspicion should be high for a patient presenting with severe infection and any other symptom such as leukopenia, acute renal disease, bone pain, and a history of several bacterial infections.

Not much research concerning *C. auris* and MM is available. Several virulence factors that *C. auris* uses to invade and cause blood infections are shared with *C. albicans*, its distant relative. We will attempt to bridge the normal defense mechanisms against *C. albicans* to those of *C. auris* and explore why these mechanisms are defective in MM.

TGF-B is produced in excess by myeloma cells and has a myriad of effects on suppressing the immune system as well as ensuring myeloma survival. One of these effects is the inhibition of the T cell's entrance into an IL-2 autocrine proliferation pathway, which hinders proper maturation and further cytokine secretion [3]. Dendritic cells (DCs) allow proper recognition, phagocytosis, and presentation of various fungal species to T cells [4]. It has been shown that in stable and progressive MM disease, TGF-B or IL-10 or both decrease CD-80, a costimulatory

molecule for T cells expressed by DCs [5]. Muc10 is a glycoprotein on the surface of plasma cells that can diminish the response of dendritic cells to produce proper stimulatory effects to T cells. The DCs in turn produce a high amount of IL-10 and low IL-12 which in turn diminish their ability to trigger protective Th1 cells [6]. Myeloma cells can also produce IL-6, a cytokine that inhibits Th1 differentiation from CD4 cells [7].

Lymphocytes in general are affected in this disease. Regarding T cells, there is an abnormal Th1/Th2 ratio in MM [8]. Signaling molecules such as CD28, CD152, CD3zeta, p56lck, ZAP-70, and PI3-k in both CD4 and CD8 cells of MM patients were demonstrated to be decreased [9]. A study showed that Th17 cells, which is an important T cell population responsible for preventing candida mucosal invasion, are reduced and functionally impaired in the peripheral blood in an MM patient [10]. A suppression of CD19 B-cells causes a polyclonal hypoglobulinemia especially in the early and late stages in MM [11]. B cells can also be suppressed by the inhibitory effects of TGF-B [12].

The mechanism by which a well-functioning immune system protects itself against *C. albicans* is through recognition and binding of pathogen-associated molecular patterns (PAMPs) through the innate arm of the immune system. Innate immune system cells have pattern recognition receptors that can bind PAMPs. After recognizing PAMPs, they elicit an effective inflammatory response by calling anti-fungal effector cells, neutrophils, and monocytes to the site of infection. Binding of beta-glucan of *C. albicans* by the dectin-1 receptor on DCs induces Th17 lymphocytes that secrete Il-17 [13]. Depending on the type of DC, subsets of Th1, cytotoxic lymphocytes, or Th17 cells are generated as a response [14]. Phagocytes prevent Candida species from causing bloodstream infections, and a disability in their function causes systemic candidiasis [11]. Conclusively, quantitative and qualitative shortcomings of Th1, Th17, DCs, neutrophils, and to a lesser extent B cells, all come together to provide an environment for an array of Candida infections.

C. auris is an emerging fungal threat to hospitalized patients, the highest concentrations of which have been in the regions of New York and New Jersey, according to the CDC [15]. Comparing annotation sequencing of the *C. auris* genome to other Candida species, 1,988 orthologous proteins with functional annotations were found. It is demonstrative that *C. auris* has many of the same virulence factors as other Candida species. It shares with *C. albicans* a group of virulence factors such as oligopeptide transporters, mannosyl transferases, secreted proteases, and genes involved with biofilm formations. Mannosyl transferases coordinate the synthesis of glycan, important cell wall units in Candida species, and play a role in immune recognition and host cell adherence. These enzymes were conserved in an isolate of *C. auris* with many orthologs of Candida species. It also contains ABC (ATP binding cassette) transporters, which are drug efflux pumps orthologous with *C. albicans*. However, the genetic annotation showed that *C. auris* employs slightly different proteins for other types of host cell adhesion [16]. Since *C. auris* and *C. albicans* share similar cell wall components and enzymes, it is probable that they evoke similar immune responses mediated by similar immune cells. Taking this information one step further, it is likely that the same defects seen in immune cells in MM that allow systemic candidiasis from *C. albicans* also allow the process of invasion of *C. auris* in one with MM.

This case report along with other similar case reports suggest that patients who present with sepsis caused by encapsulated bacteria may require further evaluation for underlying immunodeficiency. Meningitis in particular has been the presenting symptom of MM in a handful of cases. A summary table of bacterial syndromes as the first feature of MM can be found in the paper published by Naderi et al., which reported only five instances of meningitis as the manifestation of MM [17]. Myeloma patients may also be prone to infection by fungi,

such as the emerging *C. auris*. The regional prevalence of this fungus along with a patient's impaired immune system and extended hospital stay may predispose one to such life-threatening fungal infections. The timely evaluation and treatment of patients suspected of having MM is crucial, as a major delay in diagnosis has been associated with a negative impact on the disease course.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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Author Contributions

Dr. Samra provided the concept for and research behind this case report and drafted the manuscript. Mr. Noginsky provided research for the discussion of this case report and drafted the manuscript. Dr. Nielsen provided information on the pharmacologic treatment in this case and evaluated and edited the manuscript. Dr. Kalavar supervised the patient's treatment and the final development of this case report. All authors have read and approved the final manuscript.

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