CASE REPORT

Disseminated Cryptococcal infection in an immunocompetent host mimicking plasma cell disorder: a case report and literature review

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Key Clinical Message
Cryptococcosis is a potentially fatal fungal infection caused mainly by Cryptococcus neoformans (CN) species and it rarely infects immunocompetent hosts. The outcomes are better only if the condition is suspected and diagnosed early and treatment is instituted.

Keywords
Cryptococcus gattii, Cryptococcus neoformans, immunocompetent, polyclonal plasma cell proliferation.

Introduction
Cryptococcus is an encapsulated yeast found worldwide and, with its dynamic nomenclature encompassing nearly 40 recognized species, has four clinically important serotypes according to revised classification:
• Cryptococcus neoformans: serotypes A and D
• Cryptococcus gattii: serotypes B and C.

Cryptococcus neoformans is an opportunistic yeast found commonly in the droppings of wild birds, often pigeons, and continues to remain a cause of significant morbidity and mortality primarily in immunocompromised hosts. The vast majority of infected individuals are HIV positive, are transplant recipients, or have other form of suppressed T-cell mediated immunity [1].

The other major serotype, C. gattii, is endemic in parts of Africa and Australia and is capable of causing disseminated infections in immunocompetent hosts. Disseminated cryptococcosis is defined by either a (1) positive blood culture or (2) positive culture from at least two different sites.

Because of the yeast’s well-known affinity for the immunocompromised host, the infection largely remains undiagnosed until later in the course of illness when it involves an unusual host or infects an atypical organ system of the body, such as abdominal cavity, mesothelial membranes, or bone marrow [2]. We report a chronic, disseminated cryptococcal infection in an immunocompetent host which primarily involved the bone marrow and mimicked a plasma cell dyscrasia.

Case Presentation
A 79-year-old gentleman of Chinese ethnicity, with a past medical history significant for COPD and stable ischaemic heart disease, was found to have bicytopenia on a routine full blood count prior to a hernia repair. He was noted to have a normocytic, normochromic anaemia with decreased reticulocyte response and leukopenia. A bone marrow aspirate revealed mild dysplastic changes in all three lineages along with plasmacytosis Fig. 1A. Trephine showed increased number of CD 138 + plasma cells Fig. 1B. Flow cytometry confirmed the presence of two different populations of plasma cells which were nonclonal and had an unremarkable CD 45 positive, CD 38 bright, CD 138 positive, CD 56 negative, and CD 117
negative phenotype (Fig. 2). There was also no evidence of blasts or a clonal lymphoid infiltrate in the bone marrow.

Within a month of hernia repair, the patient was admitted with dyspnoea and fever of 1 week’s duration. He was anemic and leukopenic and was treated for possible neutropenic sepsis with pneumonia, mild congestive cardiac failure, and acute infective exacerbation of COPD. Cultures from blood, urine, stool, and sputum and TB PCR and AFB smears were negative and chest X-ray showed bilateral pleural effusions with focal consolidation in bilateral midzones. Initially, he responded to a carbapenem antibiotic as well as transfusion support during this period.

Serum electrophoresis and immunofixation (IFE) showed no conclusive evidence of a monoclonal paraprotein, although the initial serum IFE detected faint bands at IgM and lambda lanes and urine IFE at lambda lane. His serum M-band and skeletal survey were negative and serum calcium was normal. Flow Cytometry of peripheral blood demonstrated polyclonal, circulating lymphoplasmacytoid cells while a CT scan of neck/chest/abdomen/pelvis revealed mild splenomegaly and small volume lymphadenopathy involving retroperitoneal, left para-aortic, and right paratracheal lymph nodes. HIV serology was negative. Repeat Bone Marrow studies were deferred for later, in view of his ongoing illness and recent steroid therapy for acute exacerbation of COPD.

During his inpatient stay, the patient developed another fever and was covered with broad-spectrum antimicrobials. Chest X-ray showed bilateral pleural effusions. Pleurocentesis drained bloody pleural fluid which prompted bronchoscopic evaluation. Connective tissue disease workup was unremarkable and BAL studies were negative for malignancy and tuberculosis. The BAL, however, showed atypical plasma cells and fungal elements, the morphology of which was suggestive of a mixture of Candida and Cryptococcus (Fig. 3). Serum cryptococcal antigen was however negative, however. Meanwhile, the patient became hypotensive and was admitted to the Intensive Care Unit (ICU) for inotropic support. In addition to GCSF, he was treated with intravenous Amphotericin B for a presumptive diagnosis of disseminated cryptococcosis. Amphotericin was later changed to IV Ambisome due to worsening renal function. His pericardial effusion was largely stable and cryptococcal involvement was considered but pericardiocentesis deferred. BAL cultures eventually grew CN which was sensitive to fluconazole, therefore, Ambisome was changed to IV Fluconazole.

Despite aggressive management in the ICU, the patient continued to deteriorate and finally passed away. After the BAL had detected fungus, his bone marrow biopsy specimen done earlier was reexamined. A GMS stain of the marrow revealed two large cells containing GMS-positive yeast-like structures identical to those detected in BAL which was later confirmed to be CN via PCR (Fig. 4). Therefore, a diagnosis of chronic disseminated CN infection with pleural and pericardial effusion, lymph node, lung and bone marrow involvement was reached.

**Discussion**

Cryptococcosis is a fungal infection which kills more than half a million people every year worldwide. The genus *Cryptococcus* is a heterogeneous group of encapsulated yeast with two main species affecting humans: *Cryptococcus neoformans* [CN] and *Cryptococcus gattii* [CG] [3].

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**Figure 1.** Bone Marrow Studies. (A) Bone Marrow Aspirate showing plasmacytosis. The plasma cells are of normal morphology with no plasmablastic features. (B) Bone Marrow Trephine Biopsy, CD138 ×200, Normocellular marrow showing increased number of plasma cells with no granulomas seen.
Figure 2. Flow Cytometry. (A) The plasma cells are CD 19 dim and CD 56 negative (malignant plasma cells are CD56 positive). (B) The plasma cells are strongly positive for CD 45 and CD 38. (C) The plasma cells exhibit no light chain restriction which demonstrates that they are polyclonal. Note that there are two subpopulations of cytoplasmic lambda light chain-expressing plasma cells. (D) The plasma cells are of intermediate side scatter.

Figure 3. BAL left lower lobe of lung, GMS ×600: Macrophage containing intracellular fungal yeast forms with morphology of Cryptococcus.

Figure 4. GMS staining on Bone Marrow Trephine. BM trephine biopsy, GMS ×600: Review of bone marrow slides shows very few foamy cells, probably macrophages, containing intracellular fungal yeast forms.
These two species exhibit numerous differences in geographical distribution, ecological niches, molecular characteristics, and host predilections [4].

*Cryptococcus neoformans* is universally distributed and is isolated from various natural sources with particularly high concentrations occurring in avian faeces, guano, and soil. In contrast, *CG* is geographically restricted to tropical and subtropical regions and is commonly found on Eucalyptus trees [5, 6]. *Cryptococcus neoformans* is responsible for the majority of cryptococcal infection in immunocompromised hosts [4]. In contrast, *CG* affects mainly immunocompetent individuals [7].

The organism is inhaled as aerosolized droplets via the respiratory tract and, depending upon the host’s immune status, may cause a variety of symptoms. These may range from asymptomatic pulmonary infections to potentially life-threatening CNS infections [8]. Some of the other sites of hematogenous dissemination may include skin, bones, joints, kidneys, adrenal gland, spleen, and prostate.

In terms of serologic diagnosis, Cryptococcal antigen testing is nearly 100% sensitive and 96–99.5% specific when performed on serum and 96–100% sensitive and 93.5–99.8% specific when performed on CSF, in the appropriate clinical setting [9]. Cultures from blood,
sputum, and CSF are usually diagnostic. The drug of choice for initial therapy in disseminated, non-neural cryptococcosis in patients without HIV remain amphotericin B, with or without flucytosine [9] Amphotericin B has a rapid onset of action and often leads to clinical improvement more rapidly than either intravenous or oral fluconazole.

Histologic evaluation of tissues is an alternative method of detecting fungal organisms and remains a strong adjunct to microbiologic culture for diagnosis. It is usually suspected on Hematoxylin & Eosin (H&E) stains and then confirmed with direct visualization via specific stains for fungus, commonly GMS or PAS, in tissue and cytology specimens [10]. This patient had a negative serum cryptococcal antigen, likely due to an inability to mount an immune response secondary to protracted fungal infiltration of the bone marrow. His initial BAL cytology revealed a mixture of Candida and Cryptococcus, BAL culture was positive for Cryptococcus and PCR identified CN species. A reassessment of bone marrow trephine revealed GMS positive yeast identical to those in BAL.

Bone marrow cryptococcosis is a well-recognized manifestation, although relatively infrequent, in patients with Acquired Immunodeficiency Syndrome (AIDS) and is very rarely reported in immunocompetent hosts [11, 12]. Peripheral blood cytopenia and granulomatous inflammation with necrosis is the most commonly reported bone marrow morphology [13]. However, this patient’s bone marrow aspirate and trephine revealed plasmacytosis (10% of nucleated cells). Flow cytometric immunophenotyping showed a polyclonal plasma cell proliferation [14, 15]. Therefore, the polyclonal plasma cell proliferation was likely reactive to disseminated CN infection.

The etiology of plasmacytosis can be broadly classified into clonal and polyclonal causes. Clonal plasmacytosis is diagnosed based on the detection and quantification of a monoclonal protein and the presence or absence of target organ damage as defined by the WHO 2008 criteria [16]. Polyclonal plasmacytosis is a common finding in a variety of benign and malignant disease states. It is noteworthy that polyclonal plasmacytosis occurs in malignant disorders where plasma cells are not a component of the malignant clone. [17] An overview of the differential diagnoses for reactive plasmacytosis is presented in (Fig. 5). Table 1 summarizes the clinicopathological findings in selected cases of reactive plasmacytosis.

In conclusion, we present a case of disseminated cryptococcal infection in an immunocompetent host which manifested with marked plasmacytosis in the blood and marrow. To our knowledge, this is the first report of disseminated cryptococcosis mimicking a plasma cell dyscrasia. This case underscores the importance of considering fungal infection as a differential diagnosis for reactive plasmacytosis even in immunocompetent hosts, given the significant implications for management.

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Conflict of interest
The authors declare no conflict of interest.

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