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Trends in Internal Medicine

Invasive Fungal Infection of the Bone Marrow by Cryptococcus neoformans in a Young Person Living with HIV

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Keywords
Cryptococcus neoformans, Cryptococcus gatti, HIV, Fungal Infection.

Background
One of the most frequent systemic mycoses occurring in immunocompromised patients is cryptococcosis, a disease caused by *Cryptococcus neoformans* or *Cryptococcus gatti*; these ubiquitous, saprophytic, opportunistic fungi cause invasive infection frequently involving the lungs and central nervous system [1,2]. We report the case of a young lady with newly diagnosed HIV (human immunodeficiency virus) infection who additionally presented with uncommon hematological manifestations of cryptococcal disease comprising extensive bone marrow (BM) involvement and cytopenias.

Presentation
A 27-year-old South African lady consulted the emergency department complaining of a non-productive cough, dyspnea and night sweats for 2 weeks' duration; no other pertinent symptoms. At presentation her general examination was remarkable for pallor and tachypnea (respiratory rate: 26 breaths per minute), and systemic examination revealed nuchal rigidity and bilateral scattered pulmonary crepitations; no other pertinent signs. The overall clinical impression was that of a young lady with symptomatic anemia, a respiratory tract infection and meningitis.

Diagnostic Workup
A full blood count showed a severe normocytic anemia and moderate thrombocytopenia, and the differential white cell count confirmed a lymphopenia; normal absolute neutrophil count (Table 1). Microscopic examination of the peripheral blood film demonstrated a leukoerythroblastic picture (1% metamyelocytes, 1% myelocytes and 3% erythroblasts) and confirmed a true thrombocytopenia with no red cell fragmentation.

Table 1: Laboratory Tests and Results.

Laboratory test	Result	Reference range
White cell count	7.20×10^9/L	3.90 – 12.60
Hemoglobin (HB)	5.5 g/dL	12.0 – 15.0
Mean cell volume	95.7 fL	78.9 – 98.5
Platelet count (PLT)	59×10^9/L	186 – 454
Neutrophil count	5.47×10^9/L	1.60 – 8.30
Lymphocyte count	0.79×10^9/L	1.40 – 4.50
CD4 T-cell count	112 cells/µL	332 – 1642
HIV viral load	5641 copies/mL	
Cryptococcal antigen	Blood – Positive Cerebrospinal fluid – Positive	
Microbial culture	Blood – Positive Organism – *Cryptococcus neoformans*	

Subsequently, a serological diagnosis of HIV was also established. Further investigations (Table 1), including a diagnostic BM biopsy (Figure 1) additionally revealed disseminated fungal infection with *Cryptococcus neoformans*. The anemia and thrombocytopenia were attributed to multifactorial etiologies, including the effects of untreated HIV infection and displacement of hematopoiesis by granulomatous inflammation (Figure 1); disseminated intravascular coagulation, neoplasia, hemophagocytic lymphohistiocytosis and other opportunistic infections were not detected.

Table 2: Pharmacologic Agents.

Drug group	Drug name	Dosage	Frequency	Route	Duration
Analgesics	Paracetamol	1g	4 times daily	Oral	2 weeks
	Tramadol	50mg	3 times daily	Oral	2 weeks
Antifungals	Amphotericin B	50mg	Once daily	Intravenous	2 weeks
	Fluconazole	800mg	Once daily	Oral	8 weeks
Antibiotics	Co-trimoxazole	960mg	Once daily	Oral	Ongoing

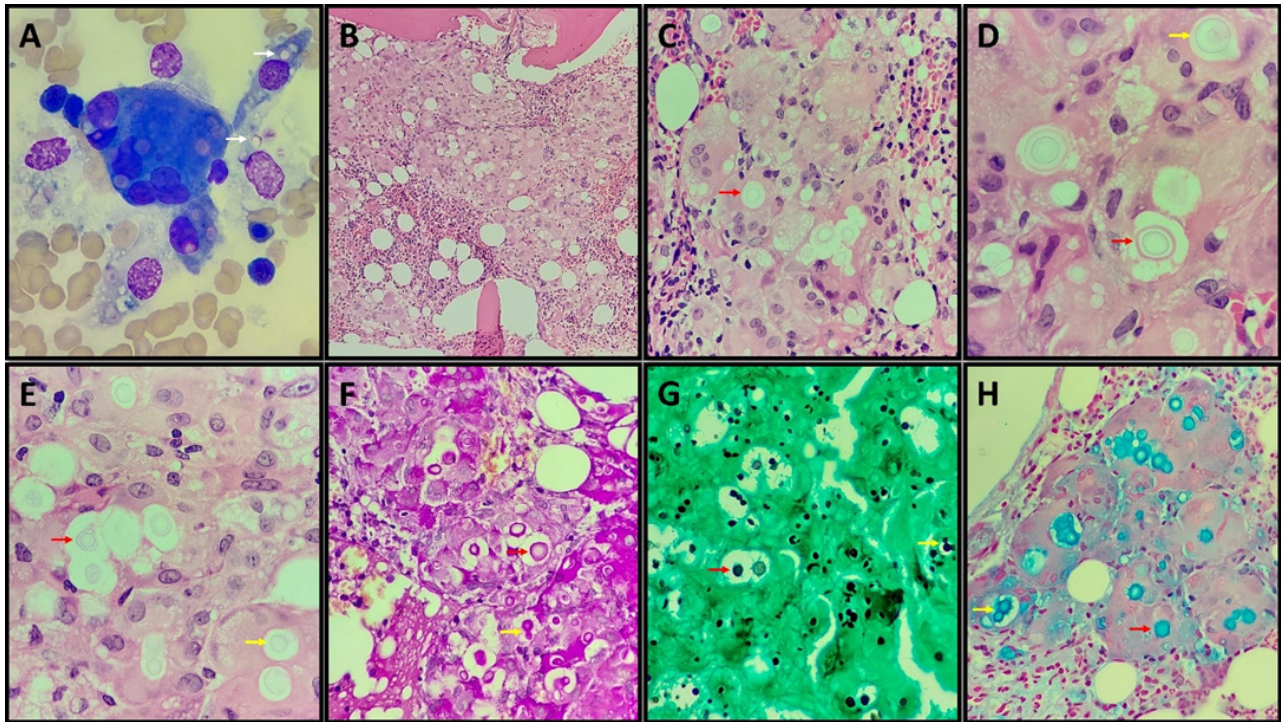

Figure 1: Bone Marrow Morphology.
Macrophages with intracytoplasmic fungal pathogens (Figure 1A; white arrows; BM aspirate; May-Grünwald-Giemsa; 100× objective). Effacement of BM architecture by focally extensive granulomatous inflammation (Figure 1B; trephine biopsy; Hematoxylin and Eosin (H&E); 10× objective). Macrophages containing large-sized, spherical yeast cells with thick, refractile capsules (Figure 1C-E; red arrows; trephine biopsy; H&E; Figure 1C: 40× objective; Figure 1D-E: 100× objective) and narrow-based budding (Figure 1D-E; yellow arrows; trephine biopsy; 100× objective). Special stains (Figure 1F: Periodic acid-Schiff; Figure 1G: Grocott's Methenamine Silver; Figure 1H: Alcian Blue) highlight *Cryptococcus* species (Figure 1F-H; red arrows; 40× objective) including budding forms (Figure 1F-H; yellow arrows; 40× objective).

Management

Supportive and specific in-patient therapeutic interventions involved blood product transfusions (red cell concentrate; target HB 7-8 g/dL), analgesics, antifungals and prophylactic antibiotics (Table 2); initiation of anti-retroviral therapy (ART) was deferred due to concerns for the potential development of immune reconstitution inflammatory syndrome. After 2 weeks of management at a tertiary facility, control of the acute infection was established as evidenced by a favorable clinical response, and the patient was referred to a regional hospital closer to her residence with an ongoing treatment plan including initiation of ART, maintenance therapy with fluconazole and continuation of co-trimoxazole prophylaxis. Subsequent out-patient assessment 16 weeks after initial presentation indicated improvement of key clinical and hematological parameters (HB 8.1 g/dL, PLT 154 × 10^9/L).

Discussion

Overall, this case demonstrates a rare pathologic entity evidenced by multi-system, fungal infection including extensive BM involvement, occurring in a young person living with HIV. In > 95% of cases, the aforementioned disease, cryptococcosis, is caused by the opportunistic pathogen *Cryptococcus neoformans* [3]. Infected people frequently present with subacute meningitis and are predominantly immunocompromised, especially HIV-infected individuals with a CD4 T-cell count of < 200 cells/mm^3 and/or World Health Organization clinical stages 3 and 4 of acquired immunodeficiency syndrome (AIDS). Importantly, it is the second commonest cause of death in AIDS patients worldwide (after tuberculosis); 30%-60% of AIDS patients with cryptococcosis die within 1 year [4-6]. The fungus can infect any organ system but pulmonary disease, meningitis and disseminated infection and are the commonest clinical manifestations [7]. Involvement of the BM is rare and occurs in < 10% of cases with disseminated disease [3,4,8,9].

Learning Points

- Disseminated fungal infection should prompt further investigations to exclude immunodeficiency, particularly HIV infection.
- Clinicians must consider the BM as a possible site of cryptococcal infection when selecting appropriate diagnostic investigations in such cases. Accordingly, the presence of cytopenias and a leukoerythroblastic picture should prompt a diagnostic BM biopsy.
- Careful morphological assessment of macrophages within both the BM aspirate and trephine biopsies is emphasized; multiple sections of the hematoxylin and eosin-stained trephine biopsy should be examined at high magnification to reveal the key morphological details of the fungal pathogens such as size, the capsule and budding.
- Not only do the relevant histochemical stains highlight the extent of fungal BM infiltration, they also enable species identification; besides staining with Periodic acid-Schiff and Grocott's Methenamine Silver, Alcian blue is also of diagnostic value for confirming *Cryptococcus* species [6,10,11].

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