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Case Report

Neuromeningeal cryptoccocosis revealing IgA-λ multiple myeloma

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ABSTRACT

Cryptococcosis is an opportunistic fungal infection that is commonly associated with an immune-compromised state. Cases of cryptococcosis have rarely been reported in patients with multiple myeloma (MM). However, cryptococcosis as a presenting symptom of MM has never been reported. We presented here a case of neuromeningeal cryptococcosis in a patient without underlying diseases, who has revealed IgA-λ MM. Early detection and treatment of cryptococcosis are essential to reduce morbidity.

1. Introduction

Cryptococcosis is an opportunistic infection due to capsulated basidiomycetous yeast genus *Cryptococcus* found in the environment [1,2]. Two species *Cryptococcus neoformans* and *Cryptococcus gattii* are mainly responsible for human disease. It is the third most common invasive fungal infection after candidiasis and aspergillosis and continues to be a source of morbidity and mortality among immunocompromised hosts [3]. High mortality in Cryptococcosis approximately up to 20% is seen in immunosuppressive conditions [3].

It usually occurs in patients infected with the human immunodeficiency virus (HIV) [1,2,4]. Although, it is increasingly reported in non-HIV immunocompromised hosts such as solid organ transplantation, systemic lupus erythematosus, malignancy, sarcoidosis cirrhosis and prolonged treatment with corticosteroids [1,3]. Approximately 20% of patients who have cryptococcosis without HIV infection, have no apparent underlying disease or risk factor. A potential association with polymorphisms in immunoglobulin genes and mannose binding protein gene and infection is reported in patients without apparent immunosuppression [3,4]. Cases of cryptococcosis have been rarely reported in patients with multiple myeloma (MM) [5]. However, cryptococcosis as a presenting symptom of MM, has never been reported. We report a case of neuromeningeal cryptococcosis in a patient without any apparent underlying conditions, who was consequently diagnosed with IgA- λ MM.

2. Case

A 63-year-old man with a history of Biermer anemia, who has been suffering from chronic headache for 2 months with associated asthenia, anorexia, and deterioration of his general condition. Three weeks after the beginning of the headaches, the patient developed morning and postprandial jet vomiting and a fever of 38.5 °C. Physical examination showed an asthenic patient, oral trush, bilateral VI nerve paralysis, and bilateral hearing loss and was hospitalized (day 0). The laboratory data revealed increased levels of C-reactive protein (34 mg/l), sedimentation rate (65 mm/hour), and fibrinogen (4.37 g/l) and a low Hb (11 g/dl) and lymphopenia (850/mm3). A CT-cerebrum sinuses as well as a cerebral MRI were performed and were both normal. Fundoscopy showed bilateral papillary edema (stage I). Lumbar puncture on day 0 showed a CSF pressure of 35 cm H2O, a pleiocytosis of 60/mm3 (80% lymphocytes), low glucose of 0.3 mmol/l, and increased protein of 0.69 g/l. Direct examinations with Ziehl Neelsen and Gram were negative.

India ink stain of the CSF showed encapsulated yeasts (Fig. 1). Culture on Sabouraud medium was positive after 3 days of incubation at 37 °C (**Fig. 2**). Species identification and antifungal susceptibility were performed respectively by Vitek® 2 YST-ID and AST-YS08 cards. *Cryptococcus neoformans* was identified and was susceptible to amphotericin B, fluconazole and flucytosine. Latex agglutination assay (PastorexTM Crypto Plus) was positive in both serum and CSF with a titer of 1/10,000 and 1/1000, respectively. A diagnosis of cryptococcal meningitis was

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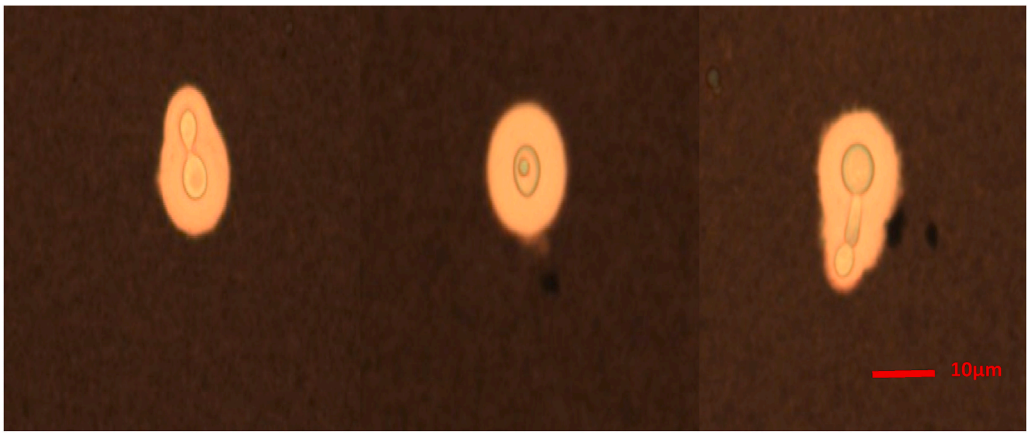

Fig. 1. Direct examination of the centrifugation pellet of CSF (×40 objective) with India.

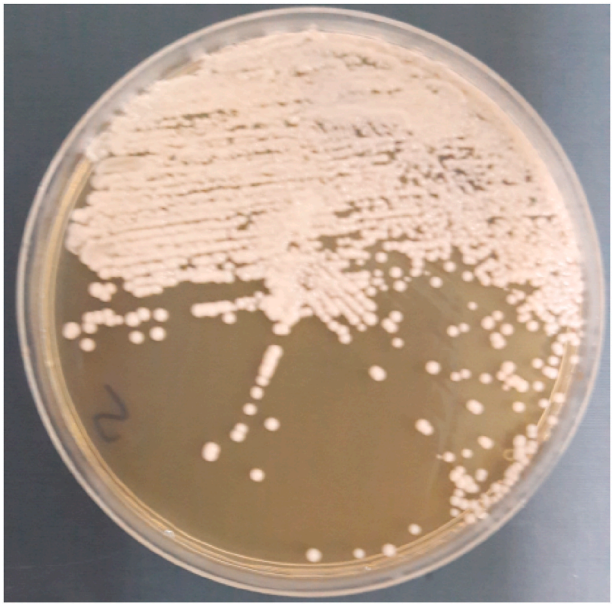

Fig. 2. Culture of *Cryptococcus neoformans* on Sabouraud medium showing beige mucous colonies after 3 days of incubation at 37 °C.

made. Blood, sputum and urine cultures were negative for *Cryptococcus*.

To investigate potential underlying immunodeficiency, the following tests were performed: HIV 1 and HIV 2 serology was negative; thoraco-abdominopelvic CT was normal; serum protein electrophoresis showed hypoalbuminemia of 33.3 g/l and hypogammaglobulinemia of 4.9 g/l and immunofixation of serum and urine proteins showed an IgA λ peak (Fig. 3). The concentration of serum-free light chains showed λ light chains of 400 mg/l (reference range: 5.71–6.3 mg/l) with κ/λ ratio of 0.05 (reference range: 0.26–1.65). Myelogram showed a dystrophic plasmocytosis of 12%. Beta2 microglobulin was increased to 3.82 mg/l (reference range: 0.8–3 mg/l). The CD4 T cell count was 245/mm3 with CD4/CD8 ratio of 1.5.

The patient was treated with amphotericin B-deoxycholate (0.7 mg/kg/day) and flucytosine (100 mg/kg/day) starting on day 0, with repeated lumbar punctures to lower the CSF pressure under 20 cmH2O. The duration of induction treatment was 21 days and resulted in sterilisation of the CSF and a decrease of antigen titers in both CSF and blood to 1/10. Clinically, the headache disappeared, but no improvement was seen in his bilateral hearing loss and loss of vision. Consolidation treatment was started at day 22, with fluconazole 800 mg/day for 12 weeks, followed by maintenance therapy with fluconazole 200mg/day for six months with good outcome.

3. Discussion

Only few reports of cryptococcosis in patients with MM have been noted which is most likely due to the fact that cell-mediated immunity is relatively intact even though humoral immunity is significantly deficient [5]. Table 1 summarizes all reported cases of cryptococcosis with underlying MM [5–10]. We noticed that all of the cases developed cryptococcosis at a late stage of the disease after chemotherapy, prolonged high dose corticosteroids, or stem cell transplantation, reducing CD4 cell counts and inversion of CD4/CD8 ratio [5,6]. However, cases of neuromeningeal cryptococcosis in patients with a CD4 count greater than 200/mm3 have been reported [1,11]. In our case, neuromeningeal cryptococcosis occurred in an apparently healthy patient allowing the discovery of MM. He didn't take any immunosuppressive medication and his CD4 cell count was 245/mm3.

Environmental factors such as prolonged and regular contact with animals, especially pigeons, are risk factors of cryptococcosis [4,11]. Only later at our patient's resumption of interrogation, we discovered that his son was a breeder of pigeons in the garden of the house, likely the source of infection in our patient.

Cr Ag may be detected by latex agglutination, enzyme immunoassays, or lateral flow assay [3]. In patients with cryptococcal meningitis, the sensitivity and specificity of latex agglutination is 93%–100%, and 93%–98%, respectively which is significantly better than India ink staining and CSF cytology in the early diagnosis of neuromeningeal cryptococcosis [3,12].

CSF culture on Sabouraud medium after 48–72 hours' incubation at 30 °C–35 °C in aerobic conditions give white to cream colonies that may turn orange tan or brown after prolonged incubation [3]. It usually takes 1 or 2 weeks to be positive but should be held for up to 4 weeks, particularly for patients receiving antifungal treatment [1,3].

According to the IDSA guidelines, the treatment of choice for induction therapy is intravenous deoxycholate amphotericin B with flucytosine for at least 2 weeks [13,14].

We presented here the first case of neuromeningeal cryptococcosis revealing IgA- λ MM in an early stage. Our case highlights the importance to consider *Cryptococcus* among the etiologies of meningitis in immunocompetent patients if more common etiologies are excluded.

Declaration of competing interest

There are no conflicts of interest for any authors.

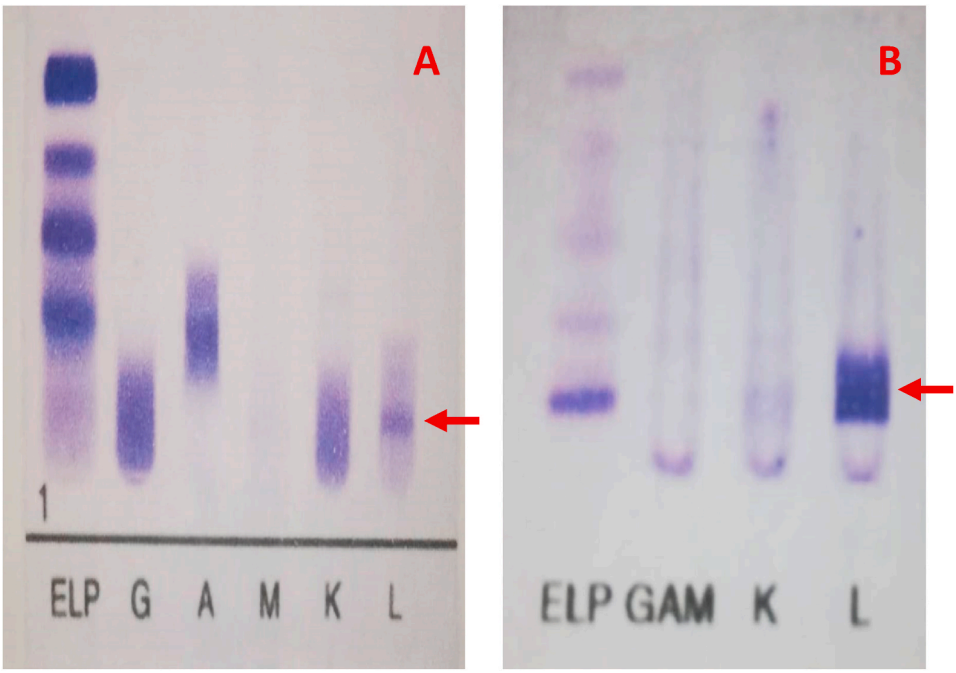

Fig. 3. Electrophoresis immunofixation of serum protein (A) and urine protein (B) revealing an IgA λ peak.

Table 1
Overview of cases reporting cryptococcosis with MM.

Author/year [reference]	age/sex	Type of myeloma/Treatment	Cryptococcal infection	Diagnosis	Outcome
Current case	63 years/ M	IgA-λ MM/None	Meningitis	India ink CSF (+) CrAg in serum 1/10,000 (+) and in CSF 1/1000 (+)	Survived
Mendpara SD 2002 [5]	42 years/ F	IgG-κ type MM stage III B/chemotherapy, corticosteroids, autologous SCT	Meningitis	India ink CSF (+) CrAg in CSF 1/512 (+)	Survived
Fickweiler W. 2009 [6]	61 years/ F	MM/chemotherapy, corticosteroids, autologous SCT	Cerebellitis	India ink CSF (+) + CSF culture (+)	Survived
Ludovic Suner 2014 [7]	77 years/ F	IgA-λ MM stage III/chemotherapy, corticosteroids	Disseminated in bone marrow	Bone marrow histopathologic examination (fungal cells) +India ink CSF (+) + CrAg in serum (+)	Died
Richard A. Ferraro 2016 [8]	64 years/ M	IgG-κ MM/chemotherapy, corticosteroids	Invasive sinusitis	biopsies of sinuses (+) CrAg in serum 1/64 (+)	Survived
Stella J. Bowcock 2017 [9]	75 years/ F	MM/chemotherapy, corticosteroids	Meningitis	CrAg in CSF 1/1280 (+) and in serum 1/ 640 (+)	Died
	79 years/ M	IgM MM/chemotherapy, corticosteroids	Fungemia	blood culture (+)	Died
Shuku Sato 2019 [10]	62 years/ F	IgG-λ type MM stage III/chemotherapy, corticosteroids	Meningitis + Fungemia	India ink CSF (+) CrAg in CSF and serum (+) blood and CSF cultures (+)	Died

MM: multiple myeloma, **SCT:** Stem cell transplantation, **CSF:** cerebrospinal fluid, **CrAg:** cryptococcal antigens.

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