Case Report

Neuromeningeal cryptococcosis revealing IgA-λ multiple myeloma

Latifa Mtibaa a,*, Imen Beji b, Manel Ayoub c, Nawel Baccouchi a, Souha Hannechi b, Zied Aouni c, Rym Abid b, Chakib Mazigh c, Riadh Battikh b, Boutheina Jemli a

a Laboratory of Parasitology-Mycology, Military Hospital of Tunis, 1008, Monfleury, Tunis, Tunisia
b Department of Infectious Diseases, Military Hospital of Tunis, 1008, Monfleury, Tunis, Tunisia
c Biochemistry Department, Military Hospital of Tunis, 1008, Monfleury, Tunis, Tunisia

ARTICLE INFO

Keywords: Cryptococcosis
Cryptococcus
Multiple
Myeloma

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 pleocytosis 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 fluocytosine. 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

* Corresponding author.
E-mail addresses: mtibaalatifa@yahoo.fr (L. Mtibaa), imenbeji92@gmail.com (I. Beji), manelayouhbmpit@gmail.com (M. Ayoub), nawelbaccouchi@gmail.com (N. Baccouchi), souha_hannachi@yahoo.fr (S. Hannechi), aouni_zied@yahoo.fr (Z. Aouni), abid_rym@yahoo.fr (R. Abid), chkouba.mazigh@gmail.com (C. Mazigh), battikh.riadh@gmail.com (R. Battikh), bjemli@yahoo.fr (B. Jemli).

https://doi.org/10.1016/j.mmcr.2021.02.005
Received 26 November 2020; Received in revised form 16 February 2021; Accepted 17 February 2021
Available online 23 February 2021
2211-7539/© 2021 The Authors. Published by Elsevier B.V. on behalf of International Society for Human and Animal Mycology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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/d) 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 [3]. 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 fluocytosine 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.
Table 1
Overview of cases reporting cryptococcosis with MM.

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

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

References

[1] M. El Fane, L. Badaoui, A. Ouладlaksen, M. Solqi, L. Marih, A. Chakib, et al., La cryptococcosse au cours de l’infection à VIH Journal de Mycologie Médicale, 2015, https://doi.org/10.1016/j.jymerm.2015.09.008.

[2] S. Chadli, M. Aghrouch, N. Taqarort, M. Malmoussi, Z. Ouagari, F. Moustaoui, et al., Cryptococcosse neuroméningée chez des patients infectés par le VIH au Centre Hospitalier Régional d’Agadir (région Sous-Massa, Maroc), J. Mycolog. Med. (2017), https://doi.org/10.1016/j.jymerm.2017.10.006.

[3] E.K. Mazica, J.R. Perfect, Cryptococcus, Infect. Dis. Clin. 30 (2016) 179–206, B. Bégoua, J.-B. Andonaba, S. Bamba, V. Konégré, B. Diallo, A. Traoré, La cryptococcosse: une étiologie potentielle d’ulcération faciale, J. Mycolog. Med. 24 (2014) e185-e188.

[4] S.D. Mendpara, C. Ustun, A.M. Kallah, F.M. Mazzella, P.A. Bilotou de, Cryptococcosse meningitis following autologous stem cell transplantation in a patient with multiple myeloma, Bone Marrow Transplant. 30 (2002) 259–260, https://doi.org/10.1038/sj.bmt.1703346.

[5] W. Fickweiler, M.J.H. Aries, R.H. Enting, E. Vellenga, J. De Keyser, Cryptococcosse cerebellitis after chemotherapy and autologous stem cell re-infusion in a patient with multiple myeloma, J. Neuror. 256 (2009) 145-146, https://doi.org/10.1007/s00415-009-0127-8.

[6] Ludovic Suner, Stéphanie Mathis, Disseminated cryptococcosis in bone marrow, Blood 123 (2014) 3070, https://doi.org/10.1182/blood-2014-01-553941.

[7] Richard A. Ferraro, Jana Ivanidze, Elizabeth Margolskee, Hamilton Tsang, Theresa Sconomiglio, S. Yuliya, et al., Invasive granulomatous cryptococcal sinusitis in an adult with multiple myeloma, Clin. Imag. 41 (2016) 65-68.

[8] Stella J. Bowcock, Kawai Yip, Kali Majumder, Mustafa Atta, M. Mansour Ceesay, Cryptococcose disséminée chez un patient Immunocompétent, J. Mycolog. Med. 25 (2017) 687, https://doi.org/10.1111/bjm.14496.

[9] Shuku Sato, Emiko Kambe, Yotaoru Tamai, Disseminated cryptococcosis in bone marrow, J. Mycolog. Med. 24 (2013) 260, https://doi.org/10.1016/j.jymed.2012.08.016.

[10] B. Elkhilhal, A. Hanaoui, L. Ghfir, A. Moustachi, S. Aoufi, M. Lyagoubi, Cryptococcosse disséminée chez un patient Immunocompétent, J. Mycolog. Med. 25 (2015) 208–212.

Fig. 3. Electrophoresis immunofixation of serum protein (A) and urine protein (B) revealing an IgA λ peak.
[12] Mariana Guarana, Jose Ernesto Vidal, Marcio Nucci, Cryptococcosis in patients with hematologic diseases, Current Fungal Infection Reports 12 (2018) 187–194, https://doi.org/10.1007/s12281-018-0332-y.

[13] J.R. Perfect, W.E. Dismukes, F. Dromer, et al., Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America, Clin. Infect. Dis. 50 (2010) 291–322.

[14] Andrés F. Henao-Martínez, Daniel B. Chastain, Carlos Franco-Paredes, Treatment of cryptococcosis in non-HIV immunocompromised patients, Curr. Opin. Infect. Dis. 31 (2018), https://doi.org/10.1097/QCO.000000000000454, 000–000.