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Review Article

Cryptococcosis: Unusual Presentation in A Patient Suffering of Acute Lymphoblastic Leukemia; Case Report and Review of The Literature

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Abstract:

Cryptococcosis is a disseminated fungal disease especially described in HIV patients, although in other non-HIV hosts such as those with other immunosuppression's were also described. Cryptococcus neoformans has been reported to be isolated from blood cultures in around 20% of patients with cryptococcosis being correlated with poor prognosis.

We report a case of HIV negative patient suffering from acute lymphoblastic leukemia (ALL) CD20+, treated with GATLA 2020 AYA protocol that developed disseminated cryptococcosis. Liposomal amphotericin was initiated to treat the fungal disease. However, despite antifungal therapy the patient died within 5 days. Literature on invasive fungal infections in ALL cases is also reviewed, with particular attention to cryptococcosis.

Key words: cryptococcosis; leukemia; all; neutropenia

Introduction

Cryptococcosis is an important opportunistic infection, that uncommon before the AIDS epidemics, most associated with malignancies and immunosuppressive treatments. Nowadays, it affects mainly people with human immunodeficiency virus (HIV/AIDS), being associated with cryptococcosis in about 80% of cases worldwide [1, 2]. However, it can also occur in haematological and oncological malignancies, those on biological therapies, solid organ transplant (SOT) and haematological stem cell transplant [3].

Cryptococcal infection occurs primarily by inhalation of propagules from environmental reservoirs [4]. This fungus can cause deadly meningitis and fungemia in immunocompromised patients such as those with advanced HIV (AIDS), T cell defects, inborn errors of immunity, malignancy, transplant recipients, and cancer patients [5-8]. Pulmonary cryptococcosis show single or multiple nodules. Milliar pattern that mimics TB, may be also present. Rare appearances include calcification, cavitation, bilateral bronchopneumonia and mass-like appearances [4].

Cryptococcosis is caused primarily by two fungal species, Cryptococcus neoformans and C. gattii. These species were initially distinguished by their antigenic diversity [9]. The encapsulated yeast form of C. neoformans is the most common cell type clinically observed [10, 11]. Cryptococcus is diagnosed from different samples, being the most important cerebrospinal fluid (CSF), blood culture and biopsy of cutaneous skin lesions from disseminated cutaneous impact [12, 13].

Hematological malignancies, such as leukemia and lymphoma, were reported to be risk factors for suffering of fungal infections [14]. The current approach for treating acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) incorporates the combination of potent chemotherapeutic agents and targeted molecular therapies. The

involvement of the CNS by oncohematological disease and the low concentration of chemotherapy drugs in the CSF, requires the use of intrathecal chemotherapy for treatment, which includes high doses of local corticosteroids in the CNS. Patients undergoing treatment for acute leukemia are at risk of life-threatening complications, either from the disease itself or from the therapy [15-19].

Here we report a fatal case of patient with ALL, HIV negative, suffering from cryptococcosis. This patient was also treated with rituximab for his leukemia. Besides, the literature on invasive fungal infections during and after rituximab therapy in ALL cases is also reviewed, with particular attention to cryptococcosis.

Case Report

A 27-year-old man native from Santiago del Estero, Argentina, presented cervical adenomegaly, asthenia, progressive adynamic, fever and headache and was started on treatment with amoxicillin and corticosteroids in December 2022. In February he consulted due to epistaxis, bony pain, night sweats, weight loss, fever, and headache. Laboratory analysis revealed Hto 20%, Hb: 5.9 g/dl, platelets 87000, white cells 56000 with 80% of immature cells and was diagnosed with ALL. Abdominal magnetic resonance imaging showed splenomegaly and globular kidney bigger in size. In March he was admitted to the Hematological Unit in our hospital. Blood count results were: total white cells: 146000, blasts 83%, lymphocytes 4%, neutrophis 10%, platelets 38000/mm. Chemotherapy treatment consisted on GATLA 2020 AYA protocol administration was started: cyclophosphamide (1780 mg), MESNA (712 mg), cytarabine (133 mg), 6-mercaptopurine (106 mg), intrathecal metotraxate (15 mg), dexamethasone (4 mg) and rituximab (670 mg) due ALL-CD 20+. Serology for HIV was negative and positive for Chagas disease. As a routine in all neutropenic patients, galactomannan test was performed. In this patient all consecutive results were negative. The patient persisted neutropenic and febrile. He was under antibiotic therapy with Bactrim and piperazilin-tazobactam. Caspofungin prophilaxis was administrated due vincristine. Due to headache and persistence of fever, lumbar puncture was conducted, blood and urine were collected for mycological studies. An Indian ink smear revealed the presence of encapsulated yeast compatible with Cryptococcus species. Serology for detection of cryptococcal glucuronoxylomannan capsule antigen performed with lateral flow (IMMY-2701 Corporate Center Dr Noman OK 73069, USA) in serum and CSF showed positive results being titles higher than 1/1000 in both. Growth of mucoid cream whitish colonies were observed in Sabouread from blood and CFS at 28 C. Microscopic examination showed no pseudohyphae production and rounded small capsulated cells. Identification from the colonies were analyzed by mass spectrometry in MALDI-TOF that matched with C. neoformans. On March 16th the patient was started on liposomal amphotericin B (3 mg/kg once daily). Results of blood analyses, drugs and treatment are listed in table 1. The patient worsened his status and was transferred to ICU. Despite antifungal therapy, the patient had a septic shock and died after 5 days, on April 8th.

	March 2nd	**March 5th**	**March 8th**	**March 11th**	**March 18th**	**March 30th**	**April 2nd**	**April 4th**
Leucocytes	92.78	104.76	8.2	8.0	7.8	0.79	0.71	0.49
Neutrophils	6.00	2.10	2.5	2.83	0.49	0.44	0.33	0.22
Hemoglobulin	8.4	---	8.2	8	7.8	8.6	7.7	7.3
Platelets	32	28	38	31	35	34	14	20
Chemotherapy	Alopurinol Omeprazol	Alopurinol Omeprazol Meprednisone Benadryl	Alopurinol Omeprazol Meprednisone Benadryl Preinduction GATLA AYA 2020	Metronydazole Cotrimoxazole Caspofungin	GATLA AYA 2020 Fase 1. A	GATLA AYA 2020	GATLA AYA 2020	GATLA AYA 2020
Antifungal Treatment	ND	ND			AMBL	AMBL	AMBL	AMBL
Serial galactomannan	ND	ND	negative	negative	negative	negative	negative	
Serum LF	ND	ND		>1/1000				
CSF LF	ND	ND		>1/1000				
Indian **CSF** Ink	ND	ND		positive				
Culture	ND	ND		*C. neoformans*				
Blood culture	ND	ND		*C. neoformans*				
Urine culture	ND	ND		negative				
Urine LF	ND	ND		negative				

Table 1: Summary of laboratory results and treatments.

Discussion

Clinical manifestations of CNS cryptococcosis include headache, fever, cranial neuropathy, alteration of consciousness, lethargy, memory loss, and meningeal irritation signs [20]. Pulmonary infection is usually asymptomatic [21-22] being single or multiple nodules the most common radiological appearances in pulmonary cryptococcosis [23]. Disseminated cryptococcosis with CNS involvement is a common presentation [24]. Some of these symptoms were reported in our case, with the detection of yeasts in blood and cerebrospinal fluid. The classical virulence factors of C. neoformans include capsule formation, and melanin pigment production [25-26]. Other organs that may be involved include skin, prostate, eyes, bone, and blood. In the respiratory tract there are many

clinical manifestations, ranging from asymptomatic colonization of the airway or nodule to a life- threatening fungal pneumonia [20].

Invasive fungal infection (IFI) is relatively common in patients with hematological malignancies and could be attributed to host defense impairment due to intensive cytotoxic chemotherapies, hematopoietic stem cell transplantation, ablative radiation therapy, and the use of immunosuppressive agents. The most frequently reported infections in

ALL patients were bacterial pneumonia and sepsis, whereas fungal infections are less common but increasing [27-28].

Candida spp. and Aspergillus spp. have been the leading cause of IFI in these populations, more common seen in refractory patients than in those who achieve remission, suggesting a crucial role of the immune system reconstitution [27, 29]. However, other opportunistic fungi like Fusarium spp. or Mucorales are also involved [4]. On the other hand, cryptococcosis seems to be relatively rare in patients with hematological malignancies. The SEIFEM-2004 study it was observed only 8 cryptococcosis cases among 11,802 patients showing a low incidence of 0.07% [30]. Limited data are available about cryptococcosis related to ALL. Cases of cryptococcosis in acute leukemia patients have been published since middle 1950. For example, between 1956 and 1972 41 cases of cryptococcosis were reported in USA. Since then, more cases of cryptococcosis have been found, including those with AML and ALL, although AML, ALL, HIV-negative patients related to cryptococcosis remain uncommon, compared with those HIV patients [4, 31-34]. Cell-mediated immunity plays a central role in preventing and controlling infection caused by Cryptococcus sp [1, 35]. Some evidences indicate a role for humoral immunity [36], including the action of B-1 B-cells for resistance to C. neoformans infection [37]. This observation suggests that these patients, because the cellular immunity is more preserved in the early stage of the disease, may be less likely to develop Cryptococcus infections. However, when the underlying disease progress, significant CD4 depletion might occurs explaining the risk of suffering opportunistic for infections, as it happens in HIV patients in which the risk of cryptococcosis rises rapidly when the CD4 lymphocyte count drops below 100/L [2, 20].

Rituximab is a chimeric human/mouse monoclonal antibody against CD20. In the case reported here, the patient match with B-lineage ALL, and presented positive CD20 antigen, which is targeted by rituximab, drug that was administrated, as is suggested by other authors, that improve the outcome of such patients [38, 39]. Besides, rituximab was reported to be effective administered in combination with the standard transplant conditioning regimen of cyclophosphamide and total body irradiation for adult patients with ALL [39]. The prevalence of infection complicating rituximab monotherapy has been reported to be 30%, with bacterial infections accounting for 19%, viral infections for 10%, and fungal infections for as little as about 1% of all the infections [40]. A summary of cases using rituximab and fungal infections has been given in Table 2.

Disease	Treatment	Fungi isolated	Hu	Reference
ALL	Fludarabine cyclophosphamide rituximab	Cryptoccocus neoformans	Cryptoccocus neoformans	[41]
ALL	Doxorubicin cyclophosphamide vincristine prednisolone (CHOP)	C. neoformans	AMBL-fluconazole	[42]
Idiopathic Thrombocytopenic purpura	Prednisone rituximab	Aspergillus Niger	Voriconazole clarithromycin	[43]
Non-Hodgkin lymphoma	cyclophosphamide, antithymocyte globulin body irradiation rituximab	A. fumigatus	Itraconazole Voriconazole	[44]
Non-Hodgkin's lymphoma	cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) rituximab	Candida albicans	Fluconazole Voriconazole	[45]
B cell lymphoma	CHOP rituximab	C. krusei, C. tropicalis, C. parapsilopsis	AMBL fluconazole	[46]

Table 2: Incidence of fungal infections in patients with rituximab treatments.

Conclusion

we assume that the patient might have a latent infection that was reactivated through the immunosuppression triggered by the onset of ALL and chemotherapy, and C. neoformans disseminated via the bloodstream including CNS involvement. Report cases in non-HIV patients suffering from this disease to make aware for the early suspicion and prompt adequate therapy.

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