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LETTER TO EDITOR

Disseminated Cryptococcosis in a Patient with CD40 Ligand Deficiency

Ugo Françoise[1] · Emmanuel Lafont[1] · Felipe Suarez[2,3] · Fanny Lanternier[1,4,5] · Olivier Lortholary[1,3,4,5,6]

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To the editor,

Cryptococcosis is a severe invasive opportunistic fungal infection, occurring in patients with acquired cellular immunodeficiencies such as advanced HIV (human immunodeficiency virus) disease, solid organ transplantation (SOT), lymphoid malignancies, and solid cancers [1, 2]. The production of autoantibodies anti-IFN-γ and anti-GM-CSF also promotes this infection. Rare primary immunodeficiencies (PID) have been associated with cryptococcosis, particularly idiopathic CD4 lymphopenia, hyper IgE syndrome (STAT3 deficiency), STAT1 gain-of-function mutation, interleukin-12 receptor beta1 deficiency (IL12-Rβ1), and CD40L-deficiency [3].

Hyper-IgM (HIGM) syndromes are characterized by decreased plasma levels of IgG and IgA with a normal-to-increased IgM plasma level due to immunoglobulin class-switch recombination deficiency. Patients with HIGM present with recurrent upper and lower respiratory tract infections with primarily encapsulated bacteria as in severe humoral defects, but interestingly have a lower incidence of *Haemophilus* carriage and infection when compared to Bruton's disease. Patients with X-linked HIGM (CD40L deficiency) and autosomal recessive HIGM due to CD40 deficiency present with combined humoral and cellular immunodeficiency. Most patients with CD40L-deficiency are diagnosed before the age of 4, following an inaugural opportunistic infection, especially *Pneumocystis jirovecii* pneumonia (PCP). Patients with HIGM are also at increased risk of *Cryptosporidium* associated-sclerosing cholangitis, which is the first cause of death among those patients [3, 4].

Clinical expression, diagnostic, and therapeutic management of cryptococcosis vary according to the patient's immune status. Guidelines have been published for the main at-risk groups [1, 2]. However, as CD40L-deficiency remains a rare disease, no large-scale studies and no specific guidelines exist for this population.

We report the case of a 26-year-old patient with cryptococcal meningoencephalitis associated with CD40L-deficiency syndrome. At 3 months of life, this patient developed a PCP. CD40L gene sequencing showed homozygous mutation c.156G > A(p.Lys52lys) on exon 1). T lymphocytes from a patient were incubated with the FITC-conjugated specific CD40L antibody and analyzed in a flow cytometer (Pr C. Picard, Center for the Study of Primary Immunodeficiencies, Necker-Enfants Malades University Hospital). Results showed no expression of CD40L on the T cell surface from the patient. Those investigations led to the diagnosis of CD40L-deficiency syndrome. Life-long immunoglobulin replacement therapy and trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis was initiated. At the age of 26, he moved into a new apartment and engaged in a thorough cleaning of his balcony littered with pigeon droppings. A few days later, unusual headaches appeared with nausea and visual disturbance. Fifteen days later, headaches worsened, confusion, altered verbal fluency, and diplopia appeared. He was admitted in an infectious disease department. On clinical examination, he had no fever, no meningeal stiffness, no photophobia or phonophobia, but binocular diplopia was noted. Initial blood tests

Ugo Françoise and Emmanuel Lafont contributed equally to this work.

✉ Emmanuel Lafont
emmanuel.lafont@aphp.fr

✉ Olivier Lortholary
olivier.lortholary@aphp.fr

1 Department of Infectious Diseases and Tropical Medicine, Université de Paris Cité, Necker-Enfants Malades University Hospital, Centre d'Infectiologie Necker-Pasteur, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

2 Department of Haematology, Université de Paris, Necker-Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France

3 French National Reference Center for Primary Immune Deficiencies (CEREDIH), Necker-Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris, (AP-HP), Paris, France

4 Institut Pasteur, National Reference Center for Invasive Mycoses and Antifungals (NRCMA), Paris, France

5 Molecular Mycology Unit, CNRS UMR 2000, Institut Pasteur, Paris, France

6 INSERM UMR 1163, Imagine Institute, Université de Paris Cité, Sorbonne Paris Cité, Paris, France

were normal. The cerebrospinal fluid (CSF) analysis showed elevated protein level (0.72 g/l) with hypoglycorrachia (CSF glucose level = 2.1 mmol/l, serum glucose level = 6.1 mmol/l, CSF/serum glucose ratio = 0.34), and pleocytosis (28 leukocytes/mm^3, 80% of lymphocytes). CSF opening pressure was elevated (25 cm H_2O, normal < 15). The CSF cryptococcal antigen level was 1:2560 and 1:1280 in the serum. Concentrated CSF stained with India ink showed encapsulated yeasts. CSF and blood cultures grew *Cryptococcus neoformans*. CT-scan did not show any pulmonary involvement. Cerebral MRI was normal. Dilated fundus examination revealed bilateral papilledema. Enlarged blind spots were observed on visual field tests. Lancaster red-green test revealed bilateral involvement of the 6th cranial nerves. The patient was treated with 3 mg/kg/day of liposomal amphotericin (L-AmB) and 100 mg/kg/day of flucytosine (5FC). Iterative evacuating lumbar punctures (LP) were performed every 48 h, until normalization of intracranial pressure and disappearance of symptoms (a total of 17 LP). Sterilization of CSF was obtained after 4 weeks of L-AmB plus 5FC, and fluconazole was introduced at 800 mg/day for 8 weeks. Then, fluconazole 200 mg/day was prescribed as maintenance therapy. At last follow-up (in October 2021, after 24 months of treatment), the patient was free of symptoms, without any sequelae, and still treated by fluconazole prophylaxis.

We performed a literature review on PubMed, from 1990, Jan. 1 to 2021, Jul. 15, with the following keywords: "Cryptococcosis"' and "Hyper-IgM immunodeficiency syndrome". A total of 15 cases were found, including 9 (60%) with cryptococcal meningoencephalitis, and 6 (40%) extra-neurological cryptococcosis. Every patient is a man suffering from X-linked HIGM (CD40L deficiency).

Clinical characteristics, treatment, and outcome of the 6 patients with HIGM-associated extra-neurological cryptococcosis are described in Table 1. The main presentation of the 6 HIGM patients with non-neurological cryptococcal infections was fever, polyadenopathy (4/6), and pneumonia (2/6). This lymph node tropism is noteworthy, as such forms remain rare in HIV-infected patients. No death was observed among these patients.

Clinical characteristics, treatment, and outcome of the 11 patients with HIGM-associated cryptococcal meningoencephalitis (including the present case) are described in Table 2. At diagnosis of cryptococcosis, median age was 8 years old (range 2–26); X-linked HIGM diagnosis was already known for 73% of the patients. The initial presentation was fever (46%), subacute headache (55%), and diplopia (27%). Most patients had a high fungal load (36% had positive blood cultures; 18% had at least 3 organs infected). Sixty-four percent of patients presented at least one clinical sign of high intracranial pressure (HICP), but CSF opening pressure was measured for only 36% of the patients. Regarding anti-fungal treatment, three patients received L-AmB or amphotericin B deoxycholate plus 5FC for the induction phase, six received

Table 1 Characteristics of 6 patients with extra-neurological cryptococcosis and CD40-L deficiency between 1990 and 2021 after literature review

Characteristics	Age (y)*	Sex	Country	Known immune deficiency	Ig therapy*	Time to diagnosis**	Clinical presentation*	Positive cultures	Spinal fluid analysis	Relapse/death
Tabone et al. *Pediatr Infect Dis J* 1994	3	M	France	Yes	Yes	NA	Fever, adenopathy, hepatomegaly	Lymph node	Normal	No/No
Levy et al. *J Pediatr* 1997	NA	M	Europe	NA	NA	NA	NA	NA	NA	NA
Levy et al. *J Pediatr* 1997	NA	M	Europe	NA	NA	NA	NA	NA	NA	NA
Lee et al. J *Acta Cytol* 2001	11	M	South Korea	Yes	Yes	2 weeks	Fever, adenopathy, hepatomegaly	Lymph node	No	No/No
Jo et al. *Korean Med Sci* 2002	11	M	South Korea	Yes	Yes	NA	Adenopathy, hepatomegaly, splenomegaly	Lymph node	No	No/No
Acker et al. *J Pediatr* 2017	10	M	USA	Yes	Yes	6 months	Scalp lesion, adenopathy	Scalp biopsy	Normal	No/No

Ig immunoglobulins, *M* male, *NA* not available, *USA* United States of America, *y* years

*At cryptococcosis diagnosis; **time from start of symptoms to cryptococcosis diagnosis

Table 2 Characteristics of 11 patients with cryptococcal meningoencephalitis and CD40-L deficiency between 1990 and 2021 after literature review

Characteristics	Age (years)*	Sex	Country	Known immune deficiency	Ig*	Time to diagnosis**	Clinical presentation*	HICP	Positive cultures	Relapse/death	Time from diagnosis to death
Iseki et al. *Acta Paediatr* 1994	2	M	Japan	No	No	3 months	Fever, adenopathy, hepatomegaly	NA	CSF, BM, lymph node	Yes/Yes	44 months
Winkelstein et al. *Medicine* 2003	NA	M	USA	NA	NA	NA	NA	NA	CSF	NA/No	-
de Górgolas et al. *Scand J Infect Dis* 2005	27	M	Portugal	Yes	Yes	5 days	Fever, headache, vomiting, neck stiffness	Yes	CSF	No/No	-
Malheiro et al. *BMC Res. Notes* 2014	19	M	Portugal	Yes	Yes	2 weeks	Headache, vomiting, diplopia	Yes	CSF	No/No	-
Mitsui-Sekinaka et al. *J Allergy Clin Immunol* 2015	6	M	Japan	Yes	Yes	NA	NA	NA	CSF	NA/Yes	NA
Mohanty et al. *Indian J Pathol Microbiol* 2018	3	M	India	No	No	1 month	Fever, rash, adenopathy, hepatomegaly	NA	Blood, CSF, urine, sputum	No/No	-
Pacharn et al. *Asian Pac J Allergy Immunol* 2018	12	M	Thailand	Yes	Yes	NA	Fever, headache, meningeal syndrome	NA	Blood, CSF	Yes/No	-
Pacharn et al. *Asian Pac J Allergy Immunol* 2018	8	M	Thailand	Yes	Yes	NA	Fever, headache	NA	CSF	No/No	-
Suzuki et al. *J Mycol Med* 2019	5	M	Brazil	Yes	Yes	Several weeks	Confusion, diplopia	NA	Blood, CSF	No/Yes	26 days
Romani et al. *Frontiers* Immunol 2021	22	M	Italy	Yes	Yes	2 weeks	Headache	Yes	CSF	No/No	-
Our case-report	26	M	France	Yes	Yes	3 weeks	Headache, confusion, diplopia	Yes	Blood, CSF	No/No	-

BM bone marrow, *HICP* high intracranial pressure, *Ig* immunoglobulin replacement therapy, *M* male, *NA* not available

*At cryptococcosis diagnosis; **time from start of symptoms to cryptococcosis diagnosis

fluconazole (mean = x mg/d) for the consolidation phase, and four patients received fluconazole as secondary prophylaxis. Finally, only two of the reported patients received optimal antifungal treatment as recommended by various guidelines [1, 2]. There was only one diagnosis of post-infectious inflammatory response syndrome (PIIRS), which improved with the addition of corticosteroid therapy (Romani et al., see Table 2). Two relapses were reported. The mortality rate of patients with HIGM-associated cryptococcal meningoencephalitis (CM) was 27%. These patients were younger than others who survived (mean age of 4.3 versus 13 years old), and time to diagnosis were longer. Therefore, we hypothesized that mortality affects only the smallest patients, because of more challenging CM diagnosis among young children.

Among these 3 patients, no intracranial opening pressure was available at diagnosis. Only one received fluconazole as secondary prophylaxis. One died because of uncontrolled HICP at day 26 of hospitalization, and one died after disseminated cryptococcosis relapse.

In comparison, 1-year mortality after HIV-associated cryptococcal meningitis is estimated at 20% in North America and 30% in Europe [1].

There are no specific guidelines for management of HIGM-associated cryptococcal meningoencephalitis. However, considering high mortality among HIGM patients, considering our experience as a reference center for both PID and invasive fungal infections, we propose to follow guidelines for main at-risk populations [1, 2]. As HICP is the main cause of death in the case of AIDS-associated cryptococcal meningoencephalitis, CSF opening pressure should always be checked if cryptococcosis is suspected, and controlled at days 7 and 14 if cryptococcal meningoencephalitis is confirmed. HICP is defined as ICP > 20 cm H_2O. CSF drainage should be managed in first-line by repeated evacuating lumbar punctures if ICP > 25 cm H_20, even if cerebral MRI or dilated fundus examinations are normal [5]. ICP may be reduced to a critical threshold of 20 cm H_2O. Antifungal treatment should be prescribed as follows: (1) induction phase with 3 mg/kg/day of L-mab L-AmB and 100 mg/kg/day of 5FC until sterilization of the CSF mycological culture, (2) consolidation phase with 12 mg/kg/day of fluconazole during 8 weeks, and (3) maintenance therapy with 6 mg/kg/day of fluconazole for life.

Since lack of evidence for main at-risk populations, high risk of expected adverse event, and very low risk of PIIRS in HIGM patients, we do not recommend to use adjunctive corticosteroid therapy during cryptococcal meningoencephalitis in HIGM patients.

Allogeneic hematopoietic stem cell transplantation should be considered. We also propose to systematically check cryptococcal anti-genemia every 6 months in patients with CD40L-deficiency, as it is now commonly accepted in the HIV severely immunocompromised patients [1].

This report highlights the rarity (11 cases) and the severity (27% of death) of cryptococcal meningoencephalitis among patients with CD40L-deficiency. Given the absence of specific recommendations, guidelines for main at-risk populations should be followed [1, 2].

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Declarations

Additional Declarations for Articles in Life Science Journals that Report the Results of Studies Involving Humans and/or Animals: Not applicable.

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Consent to Participate Not applicable.

Consent for Publication The patient has consented to the submission of the case report to the journal.

Conflict of Interest The authors declare no competing interests.

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