

Cryptococcal meningitis in a child with hyperimmunoglobulin E syndrome

Garty B-Z, Wolach B, Ashkenazi S, Weismart Y, Rachmel A, Nitzan M.
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A 13-year-old boy with hyperimmunoglobulin E (hyper-IgE) syndrome presented with headache, blurred vision, photophobia and bilateral papilledema due to cryptococcal meningitis. Treatment with amphotericin B, and S-fluorocytosine for several weeks and repeated lumbar punctures did not reduce the intracranial pressure, and a myeloperitoneal shunt was performed. The child was maintained on fluconazole for an additional six months. Patients with hyper-IgE syndrome are at increased risk of opportunistic fungal infections such as cryptococcal meningitis.

**B.-Z. Garty¹, B. Wolach²,
S. Ashkenazi², Y. Weisman²,
A. Rachmel², M. Nitzan²**

¹Kipper Institute of Pediatric Allergy and Immunology, Departments of Pediatrics, ²Children's Medical Center of Israel, Beilinson Medical Campus, Petah Tiqva, ³Sapir Medical Center, Kfar Saba, Sackler Faculty of Medicine, Tel Aviv University, Israel

B.-Z. Garty, Kipper Institute of Pediatric Allergy and Immunology, Department of Pediatrics, Children's Medical Center of Israel, Beilinson Medical Campus, Petah Tiqva 49202, Israel

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Hyperimmunoglobulin E (hyper-IgE) syndrome is characterized by recurrent skin and lung infections, coarse facies, dermatitis, and elevated serum IgE levels (1, 2). Although most infections in this syndrome are caused by *Staphylococcus aureus*, other bacteria have also been implicated (1). Occasionally, fungal infections occur in hyper-IgE syndrome; these are caused mainly by *Candida albicans* and *Aspergillus* (1); cryptococcal infections are uncommon. We report a patient with hyper-IgE syndrome who developed *Cryptococcus neoformans* meningitis.

Case report

A 13-year-old boy was admitted because of a two-week history of headache, vomiting, blurred vision, photophobia, and short episodes of blindness. Past medical history included lung infections, otitis media, salmonella sepsis, furunculosis, and staphylococcal "cold" abscesses. Since the age of six months, he had had an eczematous rash, mainly on the face. Extensive immunologic investigations at the age of five years including immunoglobulins, complement, number and function of B and T lymphocytes, NBT test and phagocytic functions were within normal range except for IgE 22000 IU/ml (normal, up to 100 IU/ml); and slightly reduced neu-

trophil chemotaxis (40% of normal control). In view of the clinical and the laboratory features, hyper-IgE syndrome was diagnosed.

On admission, physical findings were temperature 36.7°C, pulse rate 45/min, blood pressure 140/90 mmHg, and respiratory rate 28/min. Symmetrical narrowing of visual fields, bilateral papilledema, acne-like eruption on the nose and cheeks, and purulent otitis were also found. There were no signs of meningeal irritation.

Laboratory findings were as follows: erythrocyte sedimentation rate 18 mm/hr; white blood cells (WBC) $7.8 \times 10^9/L$ (73% neutrophils, 18% lymphocytes, 8% monocytes, and 1% eosinophils). Hemoglobin, platelets, blood chemistry (SMA-18), urinalysis, chest radiograph, purified protein derivative (PPD) test, cultures of blood and urine were normal. Brain CT scan showed mild dilatation of the lateral ventricles. Lumbar puncture (LP) opening pressure was 600 mmH₂O (normal, up to 200 mmH₂O). Cerebrospinal fluid (CSF) examination showed $27 \times 10^6/L$ WBC, (65% mononuclear cells); protein 0.15 g/L and glucose 2.6 mmol/dl. India ink staining of the CSF was positive for capsulated yeasts. CSF culture was negative for bacteria or tuberculosis, but grew *Cryptococcus neoformans*. Latex agglutination test for cryptococcal antigen was positive in the CSF (1/2048) and in the serum (1/10 000).

The child was treated with amphotericin B 0.5 mg/kg/day, 5-fluorocytosine 120 mg/kg/day, cefuroxime 100 mg/kg/day, and dexamethasone 10 mg/day. Despite initial clinical improvement and normalization of the pulse and blood pressure, signs of increased intracranial pressure reappeared. Repeated LPs caused temporal reduction of the intracranial pressure, but without long-standing results. Therefore, on the fourth week of hospitalization, a myeloperitoneal shunt was inserted. 5-Fluorocytosine was stopped after six weeks, and amphotericin B administration was changed to every other day for an additional six weeks. The corticosteroids were tapered off over 12 weeks. When all these medications were discontinued, fluconazole 100 mg/day was instituted for an additional six months. Repeated CSF cultures were negative. Cryptococcal antigen titer in the CSF decreased to 1/512 and in the serum to 1/1024.

Discussion

Our patient had the typical clinical and laboratory findings of hyper-IgE syndrome, including markedly elevated serum levels of IgE, coarse facies, eczema, recurrent skin infections, and staphylococcal "cold" abscess. Although *Candida* infections are relatively common in hyper-IgE syndrome (1), only four cases of systemic cryptococcal infection have been reported (3–5). The first was a 29-year-old woman with cryptococcal colitis and chronic draining perirectal cryptococcal abscess whose disease resembled Crohn's disease (5). She recovered after surgical drainage and treatment with amphotericin B and fluorocytosine for 10 weeks. Another patient, a 31-year-old man, presented with hematemesis due to esophageal cryptococcosis and recovered after six weeks of treatment with amphotericin B and fluorocytosine (4). One 3-year-old boy developed cryptococcal meningitis and was treated with amphotericin B and fluorocytosine for six weeks. He had a relapse of the cryptococcal meningitis six months later and received another course of treatment and was then maintained on fluconazole for several months (3). A fourth patient with hyper-IgE syndrome and cryptococcal meningitis was also reported (3).

Cryptococcus neoformans is a saprophyte which usually evokes only minimal inflammatory response in human tissues. Although anticryptococcal antibodies can develop during infection, the role of these in host defense is unknown (6), and their presence does not seem to improve the ingestion of *Cryptococcus neoformans* by phagocytes (7). In contrast, a heat-labile factor present in the serum, possibly complement, appears to enhance opsonization (7).

The lack of complement in the CSF may contrib-

ute to the organism's survival in the central nervous system (8). However, cell-mediated immunity is apparently the major defense mechanism against infection due to cryptococcus (7, 9, 10). Propensity to cryptococcal infection has been observed in individuals with altered cell-mediated immunity, including patients with lymphoma, leukemia, or sarcoidosis, or patients on corticosteroid treatment (6). Impaired cell-mediated immunity has also been identified in patients with cryptococcal infection with no known underlying disease (6). Effective killing of cryptococcal organisms by the host requires the participation of neutrophils, activated macrophages, natural killer cells, and sensitized T lymphocytes (11).

Prolonged increased intracranial pressure, sometimes leading to optic atrophy and blindness, is characteristic of cryptococcal meningitis (6, 12, 13) and was also seen in our patient. Initial antifungal treatment and repeated LPs were not effective, and the installation of a myeloperitoneal shunt was required. Relapse of cryptococcal meningitis may occur up to 29 months after discontinuation of treatment (14), although usually it occurs within 12 months (15). To reduce the risk of relapse, prolonged antifungal therapy is recommended (16). Therefore, we maintained our patient on fluconazole for several months despite an apparently complete recovery.

Our patient demonstrates that in addition to a propensity for staphylococcal infections, there is increased risk of unusual fungal infections, such as cryptococcal meningitis, in hyper-IgE syndrome.

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