Vertebral Aspergillosis in a Patient with Autosomal-Dominant Hyper-IgE Syndrome

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We present a report of an autosomal-dominant hyper-IgE syndrome patient with vertebral aspergillosis. Early diagnosis and antifungal therapy with surgery are crucial for improving the outcome of this aggressive condition.

CASE REPORT

An 8-year-old boy was admitted for a mass in the neck with numbness in the right upper extremity. He had no fever, night sweating, weight loss, or fatigue. At presentation, the patient appeared malnourished but had no facial abnormalities. Marked growth retardation was noticed (height, 113 cm; weight, 19 kg (both less than the third percentile [1])). His medical history included a delay in primary tooth shedding, recurrent oral ulcers, and pulmonary infections of unidentified etiology. Vital sign measurements were within the normal ranges. On physical examination, a 4-cm by 3-cm soft mass was palpable in the right nuchal region, without tenderness or ulceration. His neurological functions were normal except for right extremity numbness. Blood tests showed elevated white blood cell (WBC) counts (10.4 × 10⁹/liter; normal range, 4 × 10⁹ to 10 × 10⁹/liter) with an increase in the percentage of eosinophils (14.2%; normal range, 0.5% to 5%), a high erythrocyte sedimentation rate (ESR; 90 mm/h; normal range, 0 to 5.2 mg/liter), and an elevated C-reactive protein (CRP) concentration (52.7 mg/liter; normal range, 0 to 15 mg/liter). The results of the tuberculin skin test and blood test for antituberculin antibody were negative. Magnetic resonance imaging (MRI) confirmed a 4-cm by 3.5-cm by 3-cm mass located in the cervical spine at the level of the C6/C7 vertebrae (Fig. 1D). We further considered that the patient was malnourished and had eosinophilia, recurrent oral ulcers, and pulmonary infections, and we performed additional immunological tests. We found an increased immunoglobulin E level (IgE, 3,370 IU/ml; normal range, 0 to 100 IU/ml), while other blood tests, including those for C3 and C4 complement components, antineutrophil cytoplasmic antibodies, extractable nuclear antigens, and antibodies related to systemic lupus erythematosus, all showed negative results. Consequently, hyper-IgE syndrome (HIES) was diagnosed. The diagnosis was confirmed by identification of a hot spot mutation (at nucleotide 1145; G to A, R382Q) by sequencing of the signal transducer and activator of transcription 3 (STAT3) gene.

A second surgical debridement of the abscess in the infected cervical vertebrae and internal fixation with fusion were performed in the fourth week after the first surgery. Fungal hyphae were detected on histological examination of the surgical specimen (Fig. 2), and the culture grew A. fumigatus. Five weeks after the second surgery, the patient gradually improved, and the WBC count, ESR, and CRP returned to normal. However, at the sixth week, the patient’s parents refused further examination or therapy for financial reasons. The patient was discharged and died approximately 1 month later.

Autosomal-dominant hyper-IgE syndrome (AD-HIES) is a primary immunodeficiency disorder characterized by recurrent staphylococcal infection of the skin and lungs and an extremely high serum IgE level. It is caused by a heterozygous dominant negative mutation in STAT3 (2, 3). The major immunological
consequences observed in AD-HIES patients are defects in T-helper 17 cell differentiation and development of antibody repertoire in response to immunization. Because of immunodeficiency, fungal infections, including mucocutaneous candidiasis and pulmonary aspergillosis, are common in patients with AD-HIES (4). However, to our knowledge, cases of AD-HIES with vertebral aspergillosis have not been reported in the literature.

Our patient presented with a paraspinal “cold” aspergillosis abscess (infections that lacked the features of typical inflammation, including redness and warmness [5]), which may have resulted from hematogenous dissemination from the space-occupying lesion in the left hilus pulmonis (arrow). Therefore, we believe that pulmonary aspergillosis in patients with AD-HIES should be aggressively treated to avoid dissemination.

Vertebral aspergillosis occurs primarily in severely immunocompromised hosts, such as patients with severe prolonged neutropenia, those who have received hematopoietic stem cell transplants or solid organ transplants, those with advanced AIDS, and those with chronic granulomatous disease or other primary immunodeficiency disorders (6, 7). Vertebral aspergillosis is one of the most common invasive fungal infections, with up to 58% mortality (8). Early diagnosis is crucial in improving the prognosis. Current methods for diagnosing invasive aspergillosis include assessment of clinical symptoms and radiological features, mycological examination via microscopy and culturing, and histological examination of biopsy material. Nonculture techniques include antigen and antibody detection and molecular methods such as PCR. Histological and pathological evidence from tissue biopsy specimens or resection material is considered the gold standard for diagnosing invasive aspergillosis. However, the required processing time and low sensitivity are limiting factors for this method. On the other hand, molecular approaches such as PCR have high sensitivity and specificity (6), but their clinical implication is yet to be established.

Treatment of vertebral aspergillosis involves antifungal therapy and surgery. Voriconazole has been recommended for Aspergillus osteomyelitis and nervous system aspergillosis (9). Pediatric patients typically require higher concentrations of voriconazole than do adults, and the optimal dose for pediatric patients remains controversial. The Infectious Diseases Society of America (IDSA) recommend a 6-mg/kg loading dose, administered intravenously every 12 h for 1 day, followed by an intravenous dose of 4 mg/kg every 12 h or an oral dose of 200 mg every 12 h (9). However, Soler-Palacin et al. (10) found that for patients aged 5 years and older, the median intravenous dose needed to achieve therapeutic levels was 15 mg kg\(^{-1}\) day\(^{-1}\). Surgery is generally required when there is evidence of spinal cord (nerve root) compression or vertebral bony destruction (7, 9).

In conclusion, vertebral aspergillosis in patients with AD-HIES is rare. An early definitive diagnosis remains a clinical challenge, and a high index of suspicion is required. Voriconazole combined with surgery is recommended for the management of this aggressive condition.

REFERENCES


