Invasive multifocal cryptococcal airway disease in a teenager with hypogammaglobulinaemia

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Abstract

Cryptococcosis is an invasive, opportunistic, fungal infection that predominantly effects the respiratory tract and central nervous system in immunocompromised patients. It is classically associated with defects in cellular immunity such as acquired immunodeficiency syndrome. Here we describe a case of life-threatening laryngitis, endobronchitis and pneumonia due to Cryptococcus neoformans in a teenager with hypogammaglobulinaemia. To the best of our knowledge, no previous cases of laryngeal cryptococcosis have been reported in the paediatric population.

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Invasive multifocal cryptococcal airway disease in a teenager with hypogammaglobulinaemia

Authors

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Abstract

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Main Text

To the Editor,

Introduction

Cryptococcosis is an invasive fungal infection caused by encapsulated environmental yeasts of the Cryptococcus genus. Infections are primarily caused by two species: *Cryptococcus neoformans* and*Cryptococcus gattii* . These pathogens have a predilection for infecting the lungs and the central nervous system (CNS), particularly in immunocompromised patients. (1)

The lungs are the main portal of entry for cryptococci into the body, with inhaled airborne cryptococcal spores and small desiccated yeast cells depositing throughout the respiratory tree, resulting in either asymptomatic colonization or infection. Respiratory cryptococcosis predominantly affects the parenchyma and pleura, with endobronchial and upper airway infections much less commonly.(2) Disseminated cryptococcosis is classically associated with cell-mediated immunodeficiencies such as advanced human immunodeficiency virus (HIV) infection or following solid organ transplant. (3)

Here we describe a case of life-threatening laryngitis, endobronchitis and pneumonia due to *C. neoformans* in a teenager with hypogammaglobulinaemia.

Case

A fifteen-year-old male was admitted to hospital following a one-month history of productive cough and haemoptysis. A two-week course of oral amoxicillin-clavulanic acid had been trialled as an outpatient, with no improvement in his symptoms.

His past medical history was significant for hypogammaglobulinaemia and bronchiectasis. He developed hypogammaglobulinaemia at two years of age, following a treatment course of rituximab for refractory thrombocytopenic purpura. He had recurrent severe lower respiratory tract infections throughout his childhood, likely secondary to his antibody deficiency, and was diagnosed with bronchiectasis of his right middle lobe and bilateral lower lobes aged seven. His only regular medication was weekly subcutaneous immunoglobulin replacement. There was no history of immunosuppressive medication use. His immunisations were up to date. He was known to be HIV negative, well nourished, and in good health prior to this illness. His sputum samples during previous LRTIs isolated multi-drug-resistant *Haemophilus influenzae.*

On presentation he was afebrile with normal oxygen saturations and an unremarkable clinical examination. Blood tests on admission were normal. Chest x-ray showed new confluent consolidation in the right middle lobe. He was commenced on intravenous (IV) cefuroxime and oral doxycycline. IMAGE 1

However, his symptoms progressed over the first week of his admission to include dysphonia and odynophagia, with worsening haemoptysis.

A computed tomography scan of the chest was performed which revealed a soft tissue mass abutting the oblique and horizontal fissures of the right lung. Endobronchial obstruction was seen throughout the right middle lobe with complete obstruction of the lateral segmental bronchus. Small airways disease manifested by tree-in-bud formation was present within aerated portions of the remainder of the right middle lobe. Notably, a markedly dilated and thick-walled trachea was evident, with multiple lesions visibly arising from its internal lumen. IMAGE 2

Given his clinical progression and imaging, he underwent a laryngotracheobronchoscopy.

During induction of anaesthetic the patient rapidly developed complete airway obstruction and could not be conventionally intubated or ventilated by bag-mask. Otorhinolaryngologists were able to secure an endotracheal airway using a ventilating bronchoscope. Extensive papillomatosis-like lesions were visualised occluding his larynx. These were visible down his respiratory tract to beyond the carina. Grossly, they resembled recurrent respiratory papillomatosis (RRP) secondary to a human papilloma virus infection (HPV). They were extremely friable and actively bleeding. He proceeded to undergo debulking of the laryngeal papilloma-like lesions to create a stable airway.

Budding, encapsulated yeast were visualised on microscopic review of multiple samples taken during endoscopy. A heavy growth of C*ryptococcus neoformans* complex was reported after 48 hours of incubation. Serum cryptococcal antigen showed a high titre of 1:640. Histological examination of tissue samples also revealed cryptococcosis and did not show evidence of RRP. HPV DNA was not detected on PCR. He was commenced IV amphotercin B and fluconazole.

Intracranial imaging was unremarkable. While there was no clinical concern for meningitis, cerebrospinal fluid (CSF) samples taken prior to and during antifungal treatment. These did not show evidence of cryptococcal CNS disease.

His immune function was re-evaluated during this admission, but tests were in keeping with his previous results. Lymphocyte subsets showed a low CD4 T-Cell count of 315 (500-1600 cells/uL) and a very low CD19 B-Cell count of 42 (80-600 cells/uL). CD8 and CD3 cells were within normal ranges. Immunoglobulin G (IgG) was within normal ranges while immunoglobulin A (IgA) and immunoglobulin M (IgM) were completely absent.

Repeat endoscopy after five days of anti-fungal medication demonstrated minimal recrudescence of the obstructing lesions and almost complete resolution of airway lesions after two weeks of treatment. He was discharged home within four weeks of his first laryngotracheobronchoscopy to complete a six-months course of fluconazole.

Discussion

Cryptococcal disease involving the larynx has been reported infrequently in adult patients, but to our knowledge there are no previous reported cases of laryngeal cryptococcosis in children. (4)

Pathogenic cryptococci have characteristic virulence factors that contribute to infections, most notably polysaccharide capsules which facilitate immune system evasion. In vitro studies demonstrate the requirement of antibody or complement mediated opsonisation of the capsule for successful phagocytosis and destruction of cryptococci. Although there are case reports of cryptococcal disease in adults and children with antibody related immune-deficiencies, cryptococcosis is not a widely recognised complication of hypogamoglobulinaemia. (5)

This patient had longstanding hypogammaglobulinaemia. He had limited native B-cell function, and all his circulating immunoglobulin was derived from weekly subcutaneous infusions of pooled-donor IgG. He was unable to receive or produce IgM or IgA. His CD4 count was below the lower limit of normal but well above the threshold associated with severe cryptococcal disease in HIV positive patients.

Conclusion

This case demonstrates a significant cryptococcal airway and parenchymal respiratory infection in a paediatric patient with a humoral immunodeficiency. Cryptococcosis should be considered as a cause of severe respiratory infections in immunocompromised patients, including those without defects in cellular immunity.

Acknowledgement Clinical details and images provided with written consent from the patient and family.

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