Chronic necrotizing pulmonary aspergillosis in an immunocompetent, obese 10-year-old boy

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Chronic necrotizing pulmonary aspergillosis is a rare form of pulmonary aspergillosis. It is usually seen in middle-aged or elderly patients with underlying chronic lung disease or mild immunodeficiency, and has been only rarely encountered in children. Clinical presentation is variable and usually involves constitutional symptoms of several months' duration as well as respiratory symptoms. We present a previously well, immunocompetent, obese 10-year-old boy with cough and mild hemoptysis lasting for a couple of days and a round pulmonary infiltrate on chest radiograph. Further diagnostic investigations revealed the histopathological features of chronic necrotizing pulmonary aspergillosis in excised lung tissue, and *Aspergillus fumigatus* was isolated in lung tissue culture. This is one of the youngest described patients with this semi-invasive form of aspergillosis.

Key words: aspergillosis, children, CNPA, obesity.

Aspergillus species are environmental molds whose spores can reach the respiratory tract by airborne transmission, causing a wide range of pulmonary diseases in humans. There are four main syndromes, which are influenced by the host's immune status and lung function and structure; these are invasive pulmonary aspergillosis, chronic necrotizing pulmonary aspergillosis (CNPA), aspergilloma and allergic bronchopulmonary aspergillosis[1,2]. These conditions may coexist or may progress from one to another, reflecting the possibility that the *Aspergillus*-related syndromes represent a spectrum of the same disease rather than separate entities[3,4].

Case Report

A previously well 10-year-old boy, an urban dweller, presented with cough and mild hemoptysis lasting for a couple of days. On physical examination his height was 158 cm (>P97), and he weighed 60 kg, with a body mass index of 24.1 kg/m^2 (P97), which put him in the obese range. On lung auscultation, right-sided crackles were noted, and the chest X-ray (CXR) revealed a round infiltrate in the right upper lobe (RUL). The levels of inflammatory markers (C-reactive protein, erythrocyte sedimentation rate) and the white blood cell count were within reference ranges on repeated measurements. He was treated with azithromycin for presumed atypical pneumonia, and the symptoms ceased, but repeated CXR remained unchanged. Workup for tuberculosis and echinococcosis was negative. Routine investigations revealed no underlying defect of humoral or cell-mediated immunity, and a nitroblue tetrazolium (NBT) dye test showed normal neutrophil response. A chest computerized tomography (CT) scan demonstrated a round lesion in apical and posterior segments of the RUL with an air-meniscus sign and absence of postcontrast enhancement (Fig. 1). Pleural thickening was noted, associated with fibrotic bands extending from the lesion toward the thoracic wall. Bronchoscopy did not reveal any anatomical abnormalities, and there were no histological

changes in the biopsy specimen of the segmental bronchus. Direct microscopic examination and microbiological culture of bronchoalveolar lavage (BAL) fluid were negative, but fungal antigen testing of the BAL sample detected *Aspergillus* antigen (galactomannan 2.45 pg/ml; cutoff ≥0.5 pg/ml). Serum IgG antibodies to *Aspergillus* were positive (96 U/ml; cutoff 70 U/ml), while serum IgM antibodies to *Aspergillus* and galactomannan were negative. Because of the worsening of hemoptysis, and in order to determine the nature of the lesion, a surgical exploration and resection of the affected posterior segment of the RUL was performed. Histology revealed suppurative bronchiolitis and bronchitis, bronchiectases and small abscess cavities, and extension of mixed inflammatory infiltrate in the adjacent pulmonary parenchyma with incipient fibrosis. Some large bronchiectases with empty lumina were located just beneath the thickened, fibrotic pleura (Fig. 2), but no cavity corresponding to aspergilloma was found. Grocott's staining demonstrated fungal elements in some of the small cavitary lesions and also invading lung parenchyma, but without angioinvasion (Fig. 3). These histological changes were regarded as diagnostic of CNPA. Mycological culture of an excised lung tissue sample yielded *A. fumigatus*. Postoperatively, the boy received a 6-week treatment with voriconazole (200 mg bd) in order to treat presumed remaining infection of lung parenchyma. He is well after 2 years of follow-up.

Discussion

CNPA, also called semi-invasive or subacute invasive aspergillosis, is an indolent, cavitary infectious process in the lung parenchyma secondary to local invasion by *Aspergillus* spp., usually *Aspergillus fumigatus*, with a slowly progressive clinical course. It is an uncommon manifestation of aspergillosis and usually affects individuals with underlying chronic lung disease or mildly immunosuppressive conditions such as diabetes mellitus or alcoholism[1]. Also, an immunogenetic defect comprising a mutation in the mannose-binding lectin gene as well as a possible dysfunction of the CD40-CD40L axis may compromise the immune response against *Aspergillus* in patients with CNPA[5,6]. Typically, patients are in the 4th-6th decades of life[7,8]. A literature search revealed case reports of chronic pulmonary aspergillosis in three boys with chronic granulomatous disease diagnosed after open lung biopsy[9], and in an 8-year-old girl with old pulmonary tuberculosis[10]. We found only one report of CNPA in a previously healthy child (a 7-year-old girl), originally described as invasive primary aspergillosis of the lung with cerebral metastasis by Conen et al., but later classified as CNPA by Binder et al.[11,12].

The clinical symptoms of CNPA are often insidious and include chronic cough, sputum production, hemoptysis and constitutional symptoms such as fever, malaise, fatigue and weight loss of 1-6 months' duration. The range of severity can be from extremely mild to severe, and occasionally may present as asymptomatic disease[1,2,6,13]. The chest radiograph and chest CT scan usually show areas of focal consolidation or indolent mass-like lesions with or without cavitation and pleural thickening, predominantly in the upper lung lobes[14,15]. These radiological findings tend to progress over weeks to months[1]. However, in immunocompetent patients without preexisting lung lesions it can present as a single nodule or mass with or without an air-meniscus sign, or as a localized consolidation. These lesions cannot be reliably differentiated from a malignant neoplasm or the lesions of other chronic infections on CXR or CT scans[8,15].

Aspergilloma may have similar presenting symptoms to those of CNPA. Therefore, it is sometimes difficult to distinguish these two conditions on clinical grounds alone, particularly if a previous chest radiograph is not available[7]. In CNPA, there is a local invasion of the lung tissue and a preexisting cavity is not needed, although a cavity with

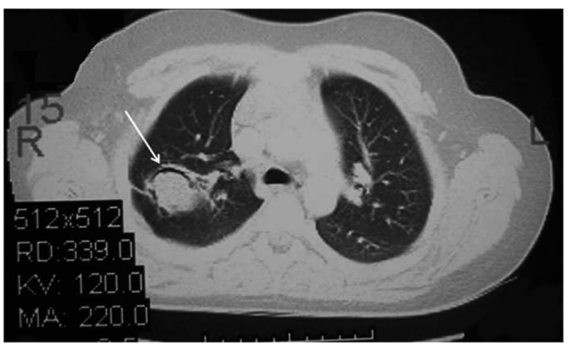

Fig. 1. CT scan showing round opacity with air-meniscus sign (arrow) and fibrotic bands extending from the lesion toward the lateral thoracic wall.

a fungal ball may develop in the lung as a secondary phenomenon due to destruction by fungus[1]. Some authors speculate that aspergilli may cause blockage of a normal bronchus by mucus, followed by infection, weakening of the bronchial walls and dilatation[11]. Also, aspergilloma can invade the cavity wall, causing local parenchymal destruction, so that a fungus ball may be seen in nearly 50% of patients with CNPA[11]. As these entities may coexist or progress from one to another, they represent a part of the spectrum of *Aspergillus* overlap syndromes[3].

Moreover, there is substantial overlap between the serological markers in these two entities, as almost all patients with either of these conditions have elevated levels of IgG to *Aspergillus*. Cultures of sputum and tissue samples obtained during bronchoscopy may be positive for *Aspergillus* spp. in both CNPA and aspergilloma[7].

Definitive diagnosis of CNPA requires a histological demonstration of *Aspergillus* hyphae invasion of lung tissue, which does not occur in aspergilloma. Histopathological hallmarks of CNPA are necrosis of lung tissue, acute or chronic inflammation of the cavity wall and presence of hyphae morphologically consistent with *Aspergillus* spp[2,8]. Pleural thickening, as assessed by imaging and histopathological study, is common in both CNPA and aspergilloma[7]. However, despite the differences between these two disorders, complete distinction may be difficult histologically.

The mainstay of treatment for CNPA is antifungal therapy. Orally administrated voriconazole or itraconazole is preferred to parenteral therapy, except in cases of severe disease where initial therapy with intravenous amphotericin B or voriconazole is recommended[16]. Surgery is reserved for patients who do not respond to initial medical management and have adequate pulmonary reserve and acceptable operative risks[1,17]. Aspergilloma requires either no therapy or surgical resection in case of recurrent hemoptysis[16]. Data on the long-term survival of patients with CNPA are still scarce, and there is a wide range of reported mortality rates (varying from 10% to 40%)[2], with mortality usually the result of a comorbid condition[13].

Our patient had symptoms of pulmonary disease only—cough and hemoptysis of short duration—and had no obvious constitutional symptoms, or elevated levels of inflammatory markers. The child also had no history of previous lung disease. However, this could be argued given the fact that there were no previous CXRs available and histopathology findings revealed chronic changes, namely bronchiectases and incipient fibrosis. We considered him immunocompetent since he had experienced no serious infections in the past, and routine tests revealed no signs of humoral or cellular immunodeficiency.

On the other hand, it is worth considering whether his obesity might have played a role as a contributing factor in the pathogenesis of CNPA. The available evidence suggests that obesity may result in an altered immune surveillance and impaired host defense, and the

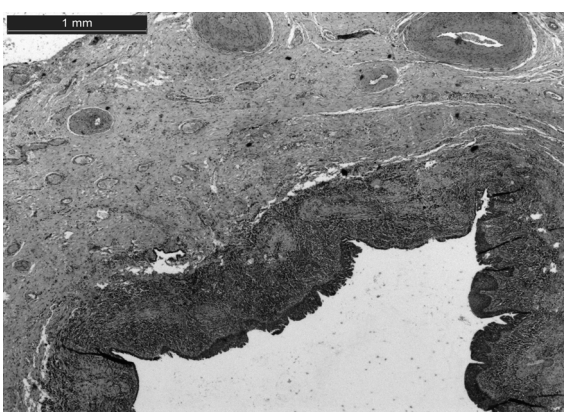

Fig. 2. Large bronchiectases with focal squamous metaplasia of the epithelium located just beneath the fibrotic, markedly thickened pleura (HE stain, 2.5 ×).

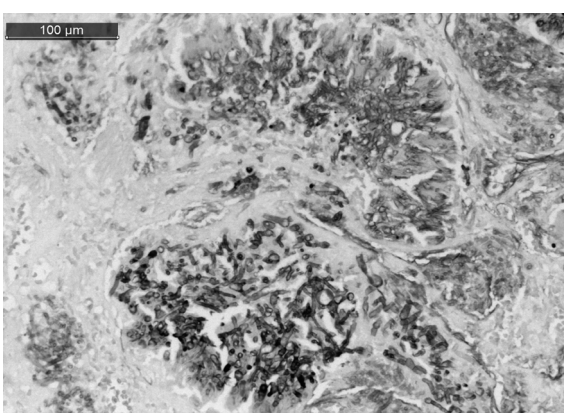

Fig. 3. Characteristic *Aspergillus* hyphae involving several small bronchiectatic cavities in lung parenchyma (Grocott's methenamine silver fungus stain, 200 ×).

incidence of both nosocomial and community-acquired infections is increased in obese individuals[18]. Even in childhood, an excess of body fat can lead to a reduction in upper airway diameter due to the mechanical effect on soft tissues, increased collapsibility of the airways and reduced lung compliance. These mechanisms may cause an increased susceptibility to serious respiratory infections[18].

To our knowledge, our patient is one of the youngest reported patients with CNPA. The case underscores the fact that this form of pulmonary aspergillosis can affect an otherwise seemingly healthy child, with no antecedent history of clinically apparent lung disease or apparent immunodeficiency, and present with somewhat obscure symptoms. Sometimes it may be difficult to distinguish between CNPA and aspergilloma based on radiological and clinical parameters. In this case study, the surgically resected material was crucial for establishing the definitive diagnosis of the solitary pulmonary nodule through histopathology.

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