Case report

Granulomatous response to invasive pulmonary aspergillosis in an immunotherapy-naive host, a maladaptive response?

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A B S T R A C T

Pulmonary aspergillosis causes a wide spectrum of disease, ranging from asymptomatic airway colonization to severe invasive disease, contingent on the host's immune status and underlying pulmonary anatomy. The invasive form of aspergillosis is a rare occurrence in the immunocompetent population. Nevertheless, patients with a compromised innate immune response are at greatest risk. We present a case of a patient with known Crohn's disease who developed invasive pulmonary aspergillosis. His clinical picture was further complicated by an uncommon immune response characterized by the development of granulomas encasing the *Aspergillus* forms found on his lung biopsy, likely representing a maladaptive response, possibly related to the effects of his granulomatous disease in the lungs. He was successfully treated with antifungal therapy and video assisted thoracoscopic surgery with placement of thoracostomy tube drainage for a parapneumonic effusion. We will discuss the factors leading to his atypical presentation and clinical outcome.

1. Introduction

Aspergillus fumigatus infection causes a wide range of respiratory manifestations ranging from asymptomatic pulmonary colonization to severe invasive pulmonary aspergillosis (IPA). The disease presentation depends strongly on the host's immune status, as well as the patient's pulmonary anatomy [1]. Invasive aspergillosis is infrequently seen in patients with preserved immune function. However, uncommon infections should always be considered in patients who present with an atypical clinical picture or who do not respond appropriately to the accepted first line of therapy. We present the case of an immunomodulatory therapy-naïve patient with history of Crohn's disease and a pneumonia with an atypical presentation.

2. Case

A 59-year old male with a history of Crohn's disease (CD) requiring partial colectomy 8 years prior to presentation and treated only intermittently with mesalamine and lost to follow up with gastroenterology for 6 years, prediabetes and peripheral arterial disease, presented to his primary care physician's office for several weeks of minimally productive cough, low-grade fever and shortness of breath, associated with subjective weight loss. He was not receiving any immunosuppressive or immunomodulating therapies for CD at that time. His initial laboratory testing revealed a white blood cell count of 45,000/μl as well as a creatinine of 3.1mg/dl, increased from a normal baseline. He was admitted to the hospital for further evaluation of leukocytosis. On admission, he was febrile to 39.4° Celsius, tachycardic at 130 beats per minute, and tachypneic at 38 respirations per minute. Given his respiratory picture, chest imaging was obtained and demonstrated bilateral multifocal airspace disease right greater than left involvement (Fig. 1). Intravenous ceftriaxone and azithromycin were initiated for presumed community acquired pneumonia. After 5 days without a significant improvement in his clinical condition, antibiotic coverage was broadened to vancomycin and piperacillin/tazobactam. Routine sputum cultures, acid-fast bacilli stain and cultures, urinary *Legionella* and *Streptococcus pneumoniae* antigen tests, and blood cultures from the day of admission remained negative. His respiratory status remained unchanged despite escalation in his care. A bronchoscopy done on day 9 of hospitalization yielded purulent material from all examined fields. Routine and fungal cultures from bronchial washings grew *Aspergillus fumigatus* and *Candida albicans* (the latter was deemed a contaminant). Intravenous voriconazole was started and other antimicrobials were discontinued.

Extensive immunodeficiency workup to rule out immunodeficiency including HIV test, serum complement levels and 24-hr urinary protein
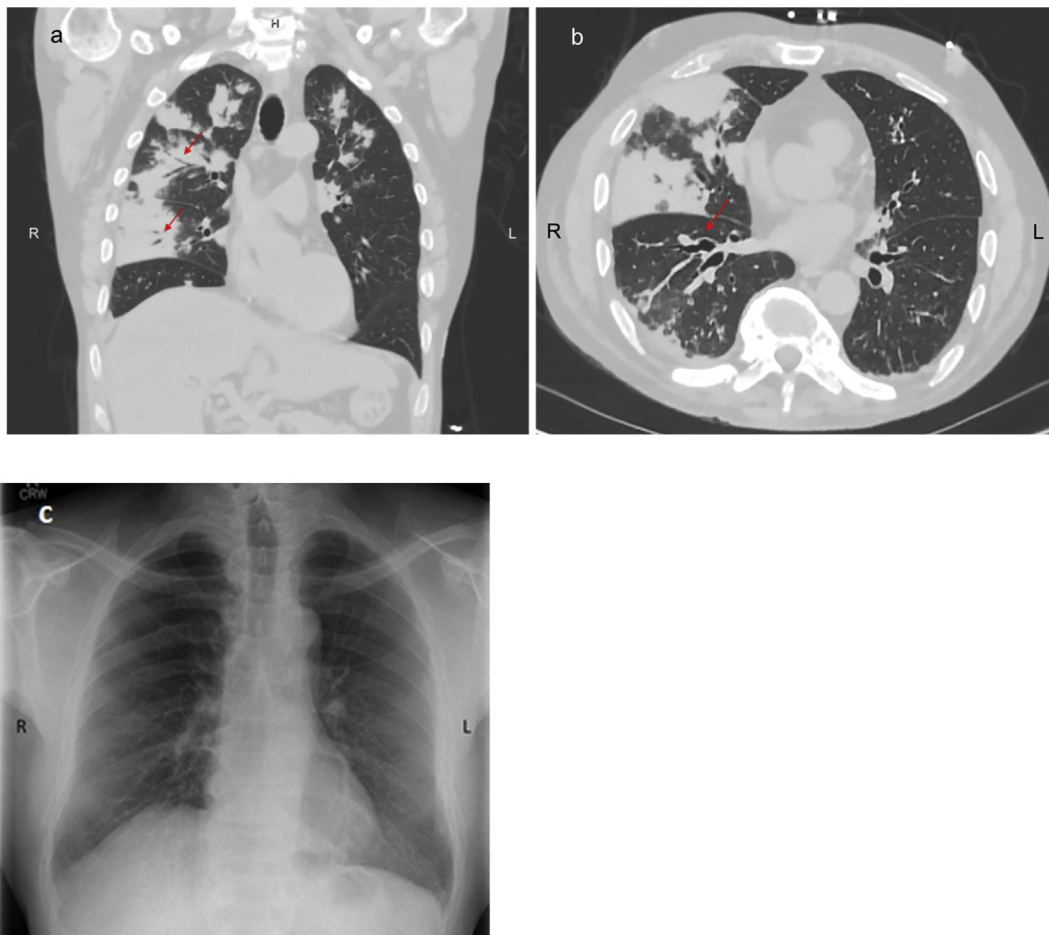
Fig. 1. a) Coronal chest CT: bilateral airspace opacities with predominant right sided involvement. Air bronchograms can be appreciated in right superior and right middle lobe (arrows). b) Transverse plane chest CT: predominant right middle lobe airspace disease. A small air bronchogram can be appreciated in the posterior portion of the middle lobe. There is bronchiectasis in the right inferior lobe (arrow). Trace right pleural effusion can also be appreciated. c) Last known Xray from 3 years prior to presentation.
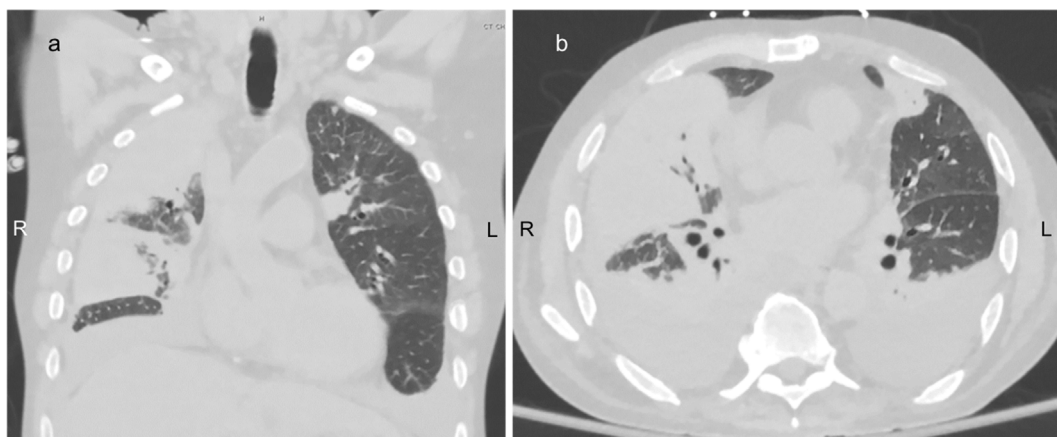

Fig. 2. a) Coronal chest CT showing worsening bilateral pleural effusions and worsening right sided pulmonary consolidation. b) Transverse plane chest CT demonstrating moderate sized bilateral pleural effusions. Bilateral parenchymal involvement can be appreciated with air bronchograms on the right side.

excretion was unrevealing. After starting voriconazole, his laboratory parameters initially improved; however, his respiratory status deteriorated due to worsening parapneumonic effusions and parenchymal infiltrates (Fig. 2). He underwent video-assisted thoracoscopy and pleural biopsy with thoracostomy tube placement for drainage of the parapneumonic effusion. Pathology results were consistent with pulmonary parenchyma and invasion with *Aspergillus* hyphae within necrotizing

granulomas (Fig. 3), and pleural fluid analysis was consistent with exudative effusion without empyema. His tube thoracostomy was removed after 5 days when drainage seized. He continued to improve and was discharged with a 12-week-course of oral voriconazole (200mg every 12 hours). Follow-up after 12 weeks of antifungal therapy showed complete resolution of his symptoms as well as resolution of acute kidney injury. Repeat chest imaging showed marked improvement,
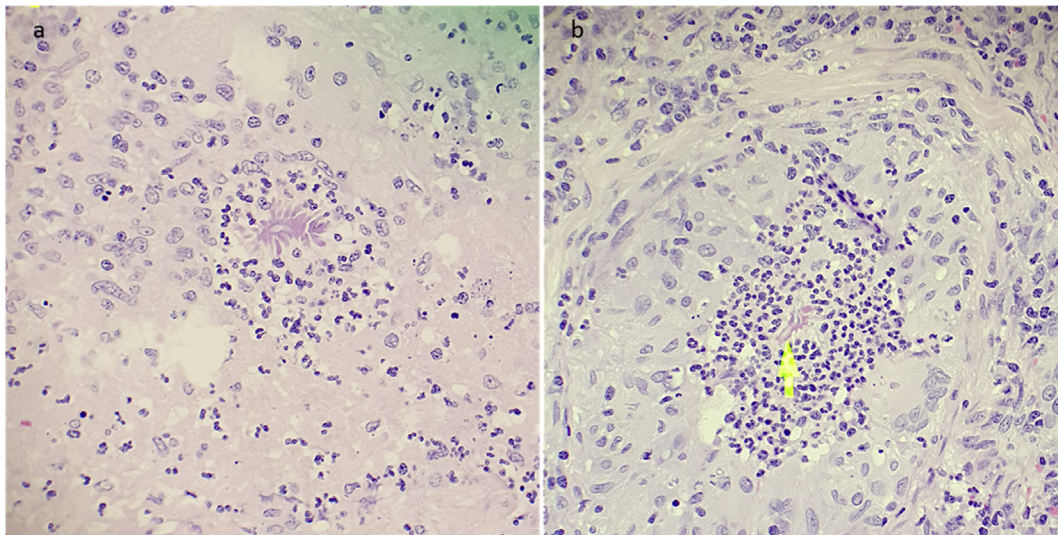
Fig. 3. a and b: HE stains of a lung parenchymal biopsy demonstrating organized necrotizing granulomas surrounding fungal forms. A multicellular infiltrate can be appreciated.
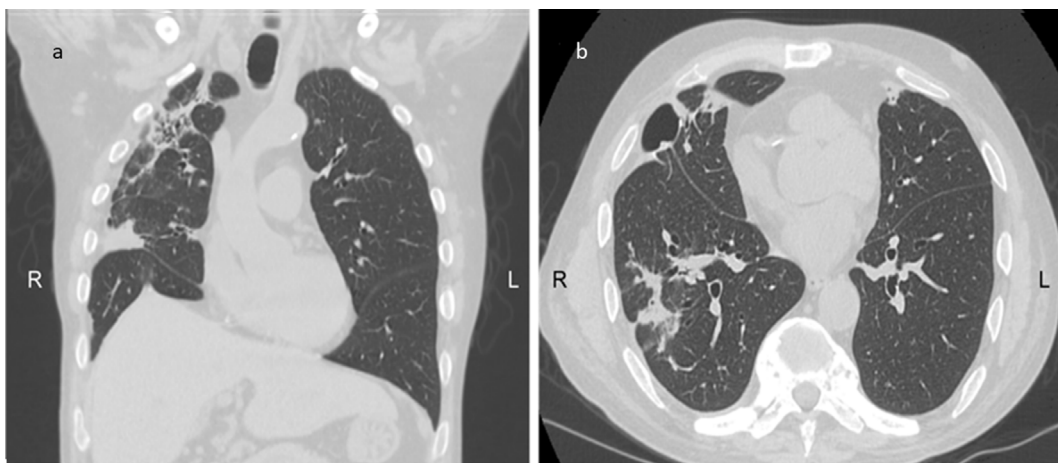

Fig. 4. a and b: Coronal and sagittal views of chest computed tomography done after 12 weeks of treatment. Complete resolution of parenchymal infiltrates representing resolution of airspace disease can be observed. There is lung scarring present as well as right diaphragmatic tenting seen in the coronal view. Some residual effusion can be see in the right side on the coronal view in the interlobar fissure. On the sagittal view a bulla can be appreciated in the anterior right side.

albeit with residual scarring (Fig. 4).

3. Discussion

Aspergillus fumigatus is one of the most ubiquitous saprophytic fungi in the environment and its small and robust sporulation allows wide airborne distribution [2]. Initially, *A. fumigatus* was considered a relatively innocuous pathogen. However, the increased incidence in infection in immunocompromised patients has disclosed this mold's potential to cause severe, life-threatening invasive and angioinvasive disease. When the immune system is compromised or there is a pre-existing anatomical or physiological pulmonary dysfunction, *A. fumigatus* can infect and disrupt the involved tissue and lead to invasive disease [3]. The immunobiology of inflammatory bowel disease has been a topic of extensive research in recent years. Abnormal inflammatory responses to bacterial pathogens have been reported in CD which are related to several factors such as: abundant tumor necrosis factor-alpha (TNF-α) production, diminished polymorphonuclear infiltration and decreased interleukin (IL) formation and release (IL-8, IL-1β) [4]. Nevertheless, opportunistic fungal infections in the absence of targeted biologic therapy remain rare.

Pulmonary manifestations of aspergillosis depend principally on the host. The gamut includes pulmonary aspergilloma, chronic necrotizing aspergillosis, IPA, and allergic bronchopulmonary aspergillosis (or ABPA) [1]. Invasive pulmonary aspergillosis is the typical presentation in immunocompromised patients; commonly characterized by neutropenia, hematological malignancy, chemotherapy, prolonged high-dose steroid use or hematopoietic stem-cell and solid organ transplantation [1,5,6]. It is well established that profoundly immunocompromised patients are at risk for IPA. Recent data have described cases of invasive fungal infections in patients with milder degrees of immunosuppression, such as patients with chronic lung disease, low-dose steroid use and critical illness [7,8] The entity in these patients is termed chronic necrotizing aspergillosis, a slowly progressive yet locally aggressive presentation.

In immunocompetent individuals, the inhaled *Aspergillus* conidia (or spores) are initially targeted by the innate immune system [3,9]. The initial tier of a host's defense encompasses the respiratory anatomical mucus barrier and the alveolar macrophages. These phagocytes are able to recognize fungal wall and other cellular components and impede fungal penetrance [3]. Following the initial breach in the immune system, dendritic cells activate the T-cell adaptive immune response, which in turn differentiate into Th1 cells generating an *Aspergillus*-specific T-cell response [10,11]. Th1 cells are associated with the

secretion of IL-2 and the promotion of cytotoxic T-cell proliferation, ensuring a robust secondary immune response [12]. Failure of the host's innate immune system to eliminate the fungal spores results in germination into invasive hyphae and the development of fungal- and inflammation-induced alveolar surface damage and further dissemination into adjacent structures [13]. Additional local cytokine release and proliferation of polymorphonucleated cells also contribute to loco-regional damage.

The absence of a consistent and reliable immune response increases the risk of invasive fungal infections manifold, particularly in patients with an underlying malignancy, recent chemotherapy requirement or hematopoietic stem-cell transplant recipients [14].

Published data on the immune response in inflammatory bowel disease (IBD)—mainly CD and ulcerative colitis—clarify the abnormal innate immune system in this disease. Moreover, patients with IBD may have a small yet significant risk for severe infections, such as IPA [4]. The immune response in CD is characterized in part by an increased production in interferon-gamma, (IFN-γ), TNF-α and IL-2 by activated macrophages, both of which participate in recruitment of T-cells and perpetuation of chronic inflammation [3,15]. The interrupted neutrophilic and phagocytic responses in CD, as demonstrated by defective chemotaxis and cellular dysfunction, may play a role in the initiation and progression of IPA in our patient. Furthermore, the characteristic increase in in both INF-γ and TNF-α, coupled with decreased macrophage autophagy of patients with CD, may lead to ineffective lysis of *Aspergillus* conidia and explain the development of granulomas in our patient [16]. Furthermore, it is totally possible than a milder form of a more obscure neutrophilic disease that was not tested in our patient (I.e. chronic granulomatous disease) coexists with his IBD, accounting for an abnormal immune response to aspergillus and his development of IPA.

Lung manifestations of CD involve both small and large airways. Bronchial inflammation with or without the presence of bronchiectasis is the most common feature in CD. Although, subclinical evidence of inflammation on examination of bronchial alveolar lavage fluid is also reported [17–19]. Other parenchymal manifestations are bronchiolitis obliterans syndrome, parenchymal nodule formation and alveolar consolidation. Of interest, several cases of granuloma formation within the lung parenchyma in patients with CD are described in the literature [20,21]. These reported histopathological findings are similar to our case. Atypical infections in CD-affected patients are also described, representing an additional diagnostic and therapeutic challenge [22]. Invasive aspergillosis in patients with CD is not an unknown pathology in those treated with immunosuppressive therapy—mainly long-standing high-dose steroids or TNF-α-blocking agents, such as infliximab [15,23,24]. To our knowledge, this is the first case of IPA with a granulomatous response to *Aspergillus* reported in an immunotherapy-naïve patient with CD.

As demonstrated by Stamatiades et Al. [25], other fungal infections have been reported in patients with IBD, the most common of which is gastrointestinal colonization of Candida. Reports of invasive mucormycosis, histoplasmosis, blastomycosis, *Penumocystis jirovecii* infections, and coccidioidomycosis as well as cryptococcosis also exist in IBD patients [25–27]. The most common risk factor predisposing to fungal infections in IBD is the use of anti-TNF-α agents. Use of corticosteroids and other immunomodulators has also been identified as an important risk factor. Furthermore, our case directly contradicts most studies that have found that prior or current use of anti-TNF-α agents is a required risk factor for the development of invasive fungal disease. Of note, these studies have specifically excluded patients with invasive aspergillosis due its rarity amongst patients with IBD. One explanation for the low incidence of IPA in patients with IBD is the need for a defective alveolar epithelium that allows for the mold to invade [25]. As we have hypothesized above, this also explains how IPA could have developed in our patient if we consider the possibility of pulmonary granulomas disrupting the alveolar epithelium and allowing for *Aspergillus* invasion.

Mortality rates of invasive aspergillosis remain high, ranging from 50% to 90%; however, these estimates were reported in patients with neutropenia and hematopoietic stem-cell transplant recipients [1]. The mortality data in healthy individuals is unknown given the extreme rarity of this scenario. Once IPA is suspected, prompt initiation of an appropriate first-line antifungal agent—voriconazole—is essential. A 12-week course of antifungal therapy is recommended, with transition to an oral regimen after the first week and once the patient is able to tolerate oral medications [28]. Our patient completed 12-weeks of voriconazole with radiographic and clinical improvement. He required video assisted thoracoscopy for tissue diagnosis and assessment of invasiveness of the disease as well as thoracostomy tube placement due to worsening of the parapneumonic effusion after initiation of antifungal therapy. This initial deterioration was most likely related to heightened inflammatory response caused by increased exposure to *Aspergillus* antigens secondary to the death of its conidia after the start of antifungal therapy.

4. Conclusion

Invasive aspergillosis is a severe disease associated with high mortality rates in the immunocompromised population. It is uncommon in individuals without immunocompromising conditions or structural lung disease. *Aspergillus fumigatus* does not typically cause granulomas as an immune response. Our case denotes how maladaptive immune mechanisms, characteristic of CD, can generate an abnormal respiratory immune cascade, potentially causing a granulomatous response. Further investigation is warranted to elucidate how the immune system in patients with CD interacts with *Aspergillus*, as well as to identify other at-risk groups for the development of IPA.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmcr.2018.05.017.

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