Idiopathic CD4 lymphocytopenia with giant cell arteritis and pulmonary mucormycosis

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ABSTRACT

Idiopathic CD4 lymphocytopenia (ICL) is characterized by a low CD4+ lymphocyte count in the absence of HIV or other underlying etiologies. We report a case of a 57-year old man with ICL and giant cell arteritis (GCA) who developed pulmonary mucormycosis, which, to our knowledge, is the first report of these occurring in a patient with ICL. Abnormally low total lymphocyte or CD4+ cell counts occurring in patients with autoimmune disorders should alert clinicians to the possibility of ICL. Immunosuppressive treatment should be used with caution in this context.
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1. Introduction

Idiopathic CD4 lymphocytopenia (ICL) is a rare, heterogeneous disorder defined by repeated measurements of the CD4 T lymphocyte count less than 300 cells/μL or less than 20 percent of total T lymphocytes in the absence of HIV infection or other etiology known to cause low CD4 cell counts [1,2]. Patients with ICL often also have a deficiency in CD8 T cells, B cells, and/or NK cells [1,3]. In published reports, ICL has been noted to occur in association with malignancies, and autoimmune disorders. Diagnosis of ICL is commonly made in the setting of opportunistic infections such as Cryptococcus and non-tuberculous mycobacteria [4]. The most commonly reported co-occurring malignancy is non-Hodgkin's lymphoma [4]. Associations with a number of autoimmune disorders have been reported, including Sjogren's syndrome, sarcoidosis, and psoriasis [4]. Because of reports of ICL co-occurring with autoimmune diseases and because some ICL patients have positive antinuclear antibodies (ANAs), ICL may have an underlying autoimmune etiology [4,5].

ICL was first described in 1989 in case reports of severe opportunistic infections and CD4 lymphocytopenia in HIV-negative patients in the U.S. and abroad. In 1992, the CDC named and defined the disease and assembled a task force that reviewed the 230,179 reported AIDS cases. From this, 47 patients with ICL were identified, 40% of which had AIDS-defining illnesses, 53% had conditions that were not AIDS-defining, and only 6% were asymptomatic [3]. Furthermore, there is no evidence of transmissibility of ICL among sex partners, children, blood donors [3]. To date there has been no evidence that ICL has a viral etiology [6].

We report an unusual case of a patient with ICL and uncontrolled diabetes who was diagnosed with giant cell arteritis (GCA), prescribed prednisone, and subsequently developed pulmonary mucormycosis.

2. Case

A 57-year-old Caucasian man with past medical history significant for type 2 diabetes mellitus and stage V chronic kidney disease presented to an outside hospital (day 0) with a severe headache and proximal muscle weakness. Temporal artery biopsy was diagnostic for GCA, and clinical exam was consistent with polymyalgia rheumatica. He was treated with prednisone at a dose of 60 mg daily.

Two weeks later he was admitted to our hospital (day 14) because of a worsening headache. Complete blood count with differential revealed a white cell count of 9.1×10^3/μL and lymphocyte count of 430/μL; flow cytometry was ordered to further evaluate this lymphopenia. His headache improved, and he was promptly discharged. Flow cytometric analysis was resulted after discharge and showed a lymphocyte count of 240/μL, CD4 count of 60/μL, CD8 count of 120/μL, and a CD4:CD8 ratio of 0.5; the patient was advised to follow up with his primary care physician, and

appropriate prophylaxis was initiated. Based on review of CBC results, the patient had lymphopenia prior to initiation of prednisone, but flow cytometry was never performed at outside institutions. Western blot and PCR performed at our institution confirmed that he was HIV-negative.

Four days later (day 18) he re-presented with fever and weakness. During this hospitalization he experienced severe right-sided chest pain, and decreased breath sounds were appreciated at the right apex. A chest radiograph showed a right upper lobe opacity (Fig. 1), and a subsequent computed tomography (CT) scan of the chest showed a rounded area of airspace opacity in the right upper lobe with central cavitation and surrounding ground glass halo (Fig. 2), an appearance consistent with angioinvasive fungal infection. Additionally, (1,3)-beta-D-glucan was elevated at 166 pg/mL. Therefore, he was started on liposomal amphotericin B (5 mg/kg QD). Subsequent right upper lobe biopsy revealed broad, irregular, ribbon-like pauciseptate hyphae with wide angle branching, consistent with mucormycosis (Fig. 3). Culture of tissue from this specimen isolated *Rhizopus* species. He was transitioned to oral posaconazole 300 mg daily, with liposomal amphotericin B overlap for one more week. Prednisone was tapered over the next four weeks. Repeat flow cytometry during this admission revealed a CD4 count of 154/μL, CD8 count of 144/μL, and CD4:CD8 ratio of 1.1.

This patient's management was complicated by active bleeding from multiple sites; he was anticoagulated with heparin due to prior deep venous thrombosis. Surgical debridement was considered because of evidence suggesting this improves survival in patients with mucormycosis [7]; however, this patient was a poor surgical candidate and chose to proceed with medical management alone.

3. Discussion

Pulmonary mucormycosis is acquired by inhalation of fungal spores belonging to Zygomycetes of the order, Mucorales, specifically Mucoromycotina. *Rhizopus arrhizus* is the most common offending agent. However, a variety of other organisms, including *Cunninghamella bertholletiae*, *Rhizomucor pusillus*, and others can all cause a similar clinical disease state. Infections caused by these organisms can rapidly progress to infarction and necrosis of surrounding tissue. Diabetes mellitus is the strongest risk factor, as the infecting Rhizopus organisms thrive in the setting of diabetic ketoacidosis, although the more common presentation of mucormycosis in diabetic patients is rhino-orbital-cerebral [8]. Other risk factors include hematologic malignancies, treatment with glucocorticoids, hematopoietic stem cell and solid organ transplants, iron overload, and AIDS. Mucormycosis has not previously been described in the setting of ICL. Treatment of

mucormycosis typically involves liposomal amphotericin B followed by oral posaconazole step down [9]. IV posaconazole is used in patients who do not respond to or cannot tolerate amphotericin B. Additionally, urgent surgical debridement is recommended. Survival for mucormycosis remains poor; survival is worst for disseminated mucormycosis, followed by gastrointestinal, pulmonary, and rhino-orbital-cerebral. Surgery and antifungal therapies significantly improve survival [7,8].

Fig. 2. Computed tomography (CT) imaging of the chest 10 days after admission showing evidence of angioinvasive fungal infection. The image reveals a rounded area of airspace opacity in the right upper lobe with central cavitation and surrounding ground glass halo.
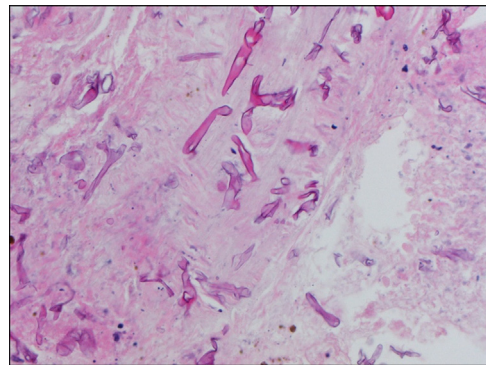
Fig. 3. Right upper lobe lung biopsy. The H&E stained, paraffin embedded section demonstrates necrotic lung tissue with broad, irregular, ribbon-like pauciseptate hyphae with wide angle branching, consistent with mucormycosis (400× magnification).
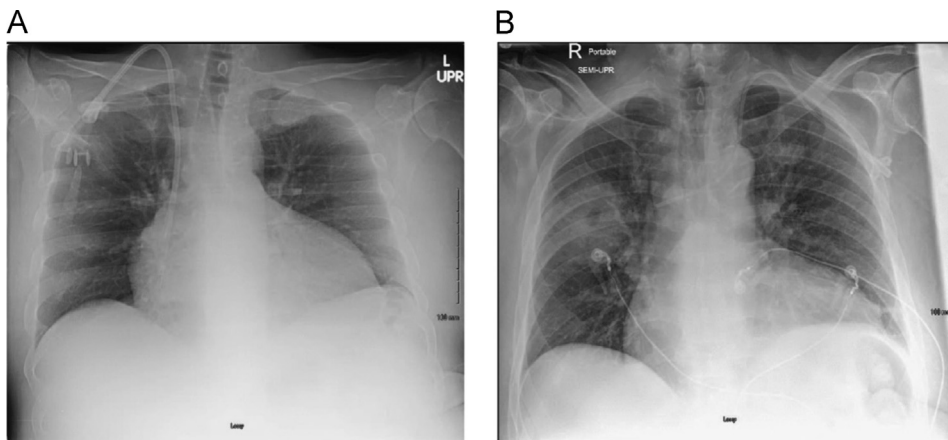
Fig. 1. Chest X ray, AP view. (A) On admission. (B) 10 days after admission following complaint of right-sided chest pain and accompanying decreased breath sounds over right upper lung field.

A recent meta-analysis of 258 ICL case reports since 1989 demonstrated that 87.6% of ICL patients had at least one opportunistic infection, with the most common being Cryptococcus, mycobacteria, Candida, and varicella zoster virus (VZV) [4]. Malignancies were found in 18% of patients, with the most common being lymphoma, squamous cell carcinoma of the skin, and Kaposi's sarcoma. Lastly, autoimmune diseases were seen in 14%, with Sjogren's syndrome, sarcoidosis, and psoriasis being the most common. They also found that the mean initial CD4 count was 142.6/μL, CD8 count 295/μL, and the CD4:CD8 ratio 0.6. The analysis also demonstrated that ICL has a male predominance (1.8:1). None of the patients analyzed in this study had GCA or mucormycosis. A low CD8 count (< 180/μL) is often seen in ICL, including our patient, and is associated with higher risk of opportunistic infection and associated death [10]. Our patient was at an increased risk of mucormycosis due to ICL, uncontrolled diabetes, and use of prednisone for GCA.

Evidence for possible etiologies of ICL is scarce. A viral etiology was initially suspected, but this has not been replicated [6]. Some studies have demonstrated evidence of increased activation and turnover of CD4 cells; excess CD4 apoptosis may be due to over-expression of Fas/FasL [11]. Another theory is that an inflamed, leaky gut allows more microbes to get through gut wall, as evidenced by the observation of elevated LPS in ICL patients [12]. Defective CXCR4 expression by T cells [13] and defects in the CD3-TCR pathway have also been suggested [14]. Lastly, there is also evidence of auto-immune etiology; one case report described a patient with auto-antibodies selective to CD4+ cells, which is consistent with the many reports of comorbid autoimmune conditions in ICL [15]. There are no sufficient treatments for ICL; treatment is aimed at preventing and treating opportunistic infections and other comorbidities.

Conflict of interest statement

None.

Acknowledgments

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