Eosinophilic pneumonia as a presentation of occult chronic granulomatous disease

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Abstract: We present a case of invasive pulmonary aspergillosis (IPA) in a previously healthy young woman who presented with what initially appeared to be an acute eosinophilic pneumonia. A second lung biopsy taken after treatment with steroids showed invasive Aspergillus with associated necrotizing granulomas, a pattern commonly found in chronic granulomatous disease (CGD). Both siblings, and by extrapolation, the patient, were actually found to have CGD. A review of the literature revealed other cases of presumed immunocompetent patients with IPA with presentations and lung histopathology similar to that of our patient.

We conclude that chronic granulomatous disease presenting in the adult may be more common than previously assumed, and that patients previously presumed immunocompetent, but with granulomatous invasive pulmonary aspergillosis, may have chronic granulomatous disease. Furthermore, and most devastatingly in this case, the presentation may simulate a recently described steroid responsive acute lung disease, acute eosinophilic pneumonia.


Case report

A white female aged 23 yrs developed sudden onset of dyspnoea, dry cough and fever approximately 12 h after working in a yard with compost on July 3, 1994. She was seen in consultation by a pulmonologist after 2 days of persistent symptoms. When she presented to the office she was febrile to 38.3°C (101°F). Her physical examination was significant for bibasilar rales. A complete blood count (CBC) revealed a white blood count (WBC) of 13,000 cells·µL−1 with 10% eosinophils. Her room air oximetry was 93% but dropped to 87% with walking. Her chest radiograph revealed diffuse bilateral alveolar infiltrates (fig. 1). The patient was immediately...
admitted to hospital and underwent bronchoscopy. The airways were unremarkable. The bronchoalveolar lavage (BAL) differential revealed 67% eosinophils. A transbronchial biopsy demonstrated a well-preserved alveolar architecture with extensive eosinophilic infiltration. No granulomas were seen. Grocott-methanamine stains for fungus were negative. Gram stain, bacterial cultures, fungal and acid-fast bacillus (AFB) smears and cultures on both BAL fluid and the transbronchial biopsy specimens were negative. Her erythrocyte sedimentation rate (ESR) was 130 mm·h⁻¹. A hypersensitivity pneumonitis screen revealed positive precipitins for *Aspergillus niger* and *A. flavus*. Her serum immunoglobulin (Ig) E levels were greater than 5,000 (normal range 15–40) international units (IU)·mL⁻¹. The differential diagnosis included AEP vs hypersensitivity pneumonitis. The patient was begun on 40 mg of i.v. methylprednisolone every 6 h. Within 24 h she had defervesced, her room air oximetry improved from 86 to 90%, and her chest radiograph exhibited significant improvement (fig. 2). She was discharged on 60 mg of prednisone·day⁻¹ after 3 days in the hospital.

Her medical history was significant for childhood recurrent furunculoses and hyper-IgE (200–5,000 IU·mL⁻¹) beginning at age 4 yrs. Immunological examination revealed no specific diagnosis, although the possibility of Job’s syndrome, or a variant, had been entertained. The infections cleared when treated with dicloxacillin but promptly recurred when the drug was discontinued. The patient was placed on chronic dicloxacillin until age 10 yrs and thereafter remained asymptomatic on no medication. From ages 10–23 yrs, the patient remained very healthy and was visiting her family in Connecticut while on summer vacation from her medical school in Grenada. She had no history of smoking, previous pneumonias or asthma, or exercise intolerance. There was no history of intravenous drug abuse and she had no human immunodeficiency virus (HIV) risk factors. She was on no medication at the time of presentation.

The patient was seen in follow-up on July 12 1994, 1 week after starting corticosteroid treatment and reported feeling well. She was afebrile and her physical exam was unchanged. A repeat chest radiograph on July 14 1994 revealed decreased but persistent infiltrates. A reduction of her prednisone was begun but she developed a fever, recurrent dry cough, and dyspnoea. A diagnosis of tropical eosinophilia was entertained but stool cultures and smears were negative, as were microfilarial titers. She was placed back on her original dose of 60 mg prednisone·day⁻¹ but her symptoms persisted. A chest radiograph on July 25 1994 revealed worsened infiltrates with a nodular appearance. Open lung biopsy was discussed with the patient but she deferred at the time. Her steroid dose was increased to 120 mg prednisone·day⁻¹ and then changed to methylprednisolone and her symptoms improved. A repeat chest radiograph on August 3 1994 revealed further progression of her infiltrates (fig. 3). A chest computed tomography (CT) scan on August 4 1994 revealed diffuse interstitial and nodular alveolar infiltrates with confluence (fig. 4). A sputum culture from August 1 1994 revealed *Aspergillus fumigatus.*

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Fig. 2. – Chest radiograph from July 7 1994. Note significant clearing of infiltrates.

Fig. 3. – Chest radiograph on August 3 1994 revealing worsening bilateral infiltrates, despite prednisone, now with a moderate nodular appearance.

Fig. 4. – Computed tomography scan of chest performed on August 4 1994 revealing diffuse interstitial and alveolar infiltrates with confluence.
The patient was admitted to the Yale New Haven Hospital (YNHH) for thoracoscopic open lung biopsy on August 6 1994. On admission she was alert without apparent distress. Her temperature was 38.9°C, respiratory rate 22 breaths·min⁻¹, cardiac frequency 140 beats·min⁻¹, and blood pressure 120/70 mmHg. The CBC revealed a WBC of 13,700 cells·µL⁻¹ with 77% segmented neutrophils, 18% bands and 0% eosinophils. Her room air arterial blood gas (ABG) was pH 7.51, partial pressure of carbon dioxide (Paco₂) 4.9 kPa (37 mmHg), partial pressure of oxygen (Pao₂) 10.9 kPa (82 mmHg), and 97% haemoglobin saturation. Blood and sputum cultures were obtained and she was begun on amphotericin B (0.6 mg·kg⁻¹ after a test dose) and oxacillin. The thoracoscopic examination on August 7 1994 revealed a diffusely diseased and fibrotic right lung with multiple small nodules. Histology (figs. 5 and 6) showed necrotizing suppurative granulomas with septate hyphae throughout the parenchyma. Most of the granulomas were not centred on either bronchioles or vessels although on silver stain, rare bronchioles did have identifiable hyphae within them. This was confirmed by elastic stains to highlight vessels and bronchi. The amphotericin B was increased to 1.0 mg·kg⁻¹. On August 8 1994 the patient developed worsening infiltrates, episodes of hypotension, and hypoxaemia. She developed progressive hypoxaemia and hypercapnoea and died early in the morning of August 10 1994. No autopsy was performed.

One year later, the patient’s 17 yr old sister presented with cough, fever, and general malaise. A chest radiograph revealed a cavitary right upper lobe cavitary lesion with an air-fluid level as well as an ill-defined infiltrate in the right middle lobe. She was placed on clindamycin for presumed aspiration pneumonia and her WBC fell from 12,000 to 8,000 cells·µL⁻¹. She and her 21 yr old brother were subsequently tested for NBT and superoxide generation at the Mount Sinai Medical Center in New York city. Neither had any superoxide hyperglobulinaemia and the NBT test showed no reduction. Her brother showed a modest hyperglobulinaemia with an IgG of 1761, IgA of 260, IgM 43, and IgE of 2554 IU·mL⁻¹. Both siblings, and by extrapolation, the deceased sister, were diagnosed with an autosomal recessive form of CGD. Both siblings of the patient are now on trimethoprim/sulfamethoxazole DS b.i.d. and are receiving subcutaneous injections of gamma interferon 50 mg·m⁻² three times weekly.

**Discussion**

The case described above depicts IPA in an adult with CGD who was previously assumed immunocompetent. The features of this patient’s presentation and her course are similar to other cases in the literature in which presumed immunocompetent individuals initially present with hyper-IgE, eosinophilia (of blood, tissue, or BAL), often after massive exposure and then, either simultaneously or subsequently, develop an IPA characterized by suppurative granulomas within the parenchyma of the lung [9–14].

The salient features of these similar cases extracted from the literature are summarized below and in table 1. Ricker et al. [9] described a case similar to ours in which an 11 yr old boy presented with cough and infiltrates 8 h after playing in a compost pile. Acute eosinophilic pneumonia was diagnosed by BAL. No bacteria, fungi, or viruses grew from blood or BAL cultures. Corticosteroid therapy was begun resulting in immediate improvement and he was discharged on the eighth hospital day only to return 3 days later with fever, tachypnoea and worsening infiltrates on chest radiograph. Open lung biopsy revealed necrotizing granulomas with septate branching hyphae and subsequent autopsy revealed nearly confluent granulomas containing fungal hyphae. *Aspergillus fumigatus* was cultured from both BAL fluid and lung. A NBT test was reported as normal.

Meeker et al. [12] described the outcome of two brothers, aged 32 and 19 yrs, who both developed low grade fevers and chills within 2 weeks after unrolling 1 yr old hay. Both presented with interstitial nodular infiltrates. BAL from the older brother demonstrated no organisms on smear, remained culture negative, and revealed only 3% eosinophils on the differential. He exhibited spontaneous improvement both symptomatically and radiographically over 2 weeks. Bronchoscopy with BAL performed on the younger brother revealed 34% eosinophils and open lung biopsy demonstrated suppurative-type granulomas with hyphae characteristic of *Aspergillus* spp.
YOCUM et al. [13] described a case of a 37 yr old woman who developed persistent fever, malaise, and dry cough after bagging mouldy oats. On presentation 3 weeks later she was noted to have bilateral interstitial fibronodular infiltrates. A transbronchial biopsy revealed consolidation of parenchyma with infiltrates of plasma cells, lymphocytes, and a "moderate number" of eosinophils. Numerous granulomas were identified throughout the lobule with branching septate hyphae characteristic of Aspergillus fumigatus within the necrotic centres of the granulomas. Aspergillus fumigatus was cultured from the BAL. The patient received 6 days of antituberculous therapy. Her temperature began to diminish, but after the results of her bronchoscopy were known, the cough recurred. While reported as a hypersensitivity reaction, the histology is not consistent with that interpretation, but rather, in conjunction with the history, indicates a self-limited infection.

COOPER et al. [11] described the case of a 33 yr old man who developed IPA of both the pericardium and lung. No discernible immunological defects were detected despite extensive testing. Biopsy specimens from his lung showed "granuloma" formation.

Finally, ZUK et al. [14] reported the case of a previously healthy gardener aged 34 yrs who presented with a 5 day history of dry cough, fever, and dyspnoea. A chest radiograph revealed bilateral basal infiltrates. A bronchoscopy on day 7 of his hospitalization failed to demonstrate organisms. His condition deteriorated and at autopsy his lungs were diffusely involved with suppurative granulomas with giant cells. Fungal hyphae were present within the giant cells.

Two important questions are generated by the comparison of our case to those described. Firstly, did any of these presumably immunocompetent patients with IPA actually have CGD? Although some of these patients were acutely treated with steroids, and cases of invasive aspergillosis developing after steroid therapy de novo or for hypersensitivity-related Aspergillus disease are certainly well-described (if uncommon, especially after short courses of steroids), most of the patients described herein did not require steroids for invasion. In addition, every one of these patients had suppurative granulomas as a response to the Aspergillus invasion. The histopathology of this form of IPA has been described commonly only for CGD in which Aspergillus bronchopneumonia has been noted with some frequency [8, 15, 16]. KELLY et al. [8], in a retrospective examination of IPA in patients without major risk factors, suggested that Aspergillus bronchopneumonia with suppurating granulomas is sufficiently distinctive to suggest CGD when no other risk factor is present. Although most cases of CGD are manifest before age 3 yrs, a recent retrospective analysis suggests that CGD first presenting in adults may be more common than previously assumed [1]. In that study, four of the 11 patients with CGD had a normal or near normal NBT test. Diagnosis was possible only on quantitative measurement of superoxide production in the granulocytes. Of note, two of the 11 patients died from complications of the CGD, one at age 23 yrs (the same age as our patient) after contracting a fulminate Aspergillus pneumonia.

The second question generated by our case is whether Aspergillus is at least one of the undefined antigens responsible for AEP. Our patient, on initial presentation, fulfilled essentially all the diagnostic criteria of ALLEN [12]. In that study, four of the 11 patients presenting in adults may be more common than previously assumed [1]. In that study, four of the 11 patients with CGD had a normal or near normal NBT test. Diagnosis was possible only on quantitative measurement of superoxide production in the granulocytes. Of note, two of the 11 patients died from complications of the CGD, one at age 23 yrs (the same age as our patient) after contracting a fulminate Aspergillus pneumonia.

These cases suggest a common overall pattern associating massive exposure to Aspergillus spp., a hypersensitivity response with eosinophilia, and the development of eosinophilic pneumonia and CGD.
of IPA with necrotizing suppurative granulomas. We propose that: 1) previously reported cases of invasive pulmonary aspergillosis in presumed immunocompetent adults may have been, in fact, invasive pulmonary aspergillosis in adults with chronic granulomatous disease; 2) Aspergillus species may represent at least one of the so far unidentified antigens responsible for acute eosinophilic pneumonia; and 3) acute eosinophilic pneumonia is, by definition, a diagnosis of exclusion, and infectious aetiologies, especially (but not exclusively) fungal, should be continuously pursued after corticosteroid treatment is initiated.

References