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Adalimumab-linked adult asthma and CEP

**Chronic cough and an atypical peripheral pattern on chest imaging: A case report
secondary to suspected drug onset**

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ABSTRACT

Introduction:

Chronic eosinophilic pneumonia (CEP) is an uncommon interstitial lung disease with nonspecific symptoms that is a diagnostic and treatment challenge. The exact pathology is unknown and putatively involves a complex inflammatory cascade associated with the abnormal accumulation of eosinophils. Our patient had a history of adult-onset asthma after initiating TNF-inhibitor therapy. CEP coexisting with asthma has been reported, but never linked to the use of a TNF-inhibitor---as we report here.

Case Study:

A 36-year-old prisoner with a history of psoriasis presented with progressive worsening dyspnea, pleuritic chest pain, and cough. His symptoms started 2-months prior while taking adalimumab, a TNF-inhibitor, for the treatment of psoriasis.

Results:

His initial workup revealed 26.9% eosinophils on CBC, elevated IgE levels on BAL, and bilateral lung opacities on imaging. The patient's symptoms and eosinophilia improved markedly after starting corticosteroids. Based on these findings, the patient was ultimately diagnosed with CEP.

Conclusion:

To our knowledge, this is the first case of asthma and CEP in a patient taking adalimumab (a TNF-inhibitor). Our patient likely had eosinophilic asthma phenotype, which works through the Th2 cell pathway. His psoriasis, which is primarily a Th1 cell pathway disease, likely masked his asthma most of his life. Once on adalimumab, the Th1 response was suppressed and the Th2 pathway was unmasked---revealing itself clinically as asthma. The events that led to the diagnosis of asthma were unknown. However, his symptoms began after starting adalimumab and may explain the chronic pulmonary changes and the possibility that this drug indirectly caused CEP.

Key Words

Case Reports, Control/Management, Diagnostics, Therapy, Immunopathogenesis

INTRODUCTION

Chronic eosinophilic pneumonia (CEP) is an uncommon interstitial lung disease with nonspecific symptoms, including progressive dyspnea and nonproductive cough. The diagnosis and treatment is especially challenging, considering that the final diagnosis is dependent on the response to treatment. The exact etiology is unknown, but suspected to involve a complex cascade of inflammatory processes related to the abnormal accumulation of eosinophils.

Herein, we present the case of a 36-year old man who developed adult-onset asthma after starting adalimumab, a TNF-inhibitor, for the treatment of psoriasis. He continued to demonstrate progressive dyspnea and cough until his clinical symptoms abated after the initiation of corticosteroids. This improvement coincided with his laboratory and imaging findings, suggesting a possible association between CEP and TNF-inhibitors.

CASE STUDY

The patient is a 36-year-old Caucasian male who was sent to the hospital from a federal prison for dry cough, pleuritic chest pain, and a two-month history of dyspnea that had worsened over the last two weeks. He denied subjective fevers, night sweats, weight loss, hemoptysis, or exposure to sick contacts.

His past medical history includes psoriatic arthritis controlled with adalimumab, which was started two years prior to this presentation. Two months following his first treatment, he was diagnosed with asthma and was prescribed albuterol and mometasone inhalers for daily control. The inhalers initially provided symptomatic relief; however, they eventually became less

effective. No childhood history asthma or allergic rhinitis was noted. Furthermore, he was not on any other medications, including NSAIDs or methotrexate, or herbal supplements. He has a 15-pack year smoking history and a history of methamphetamine use, both of which he had stopped 10 years prior to this hospitalization. Family history included a mother with rheumatoid arthritis and asthma. A CXR in prison showed changes from the year prior, suggesting active pulmonary tuberculosis (TB).

RESULTS

In the emergency department, aside from a blood pressure of 140/80 mm Hg, the patient had normal vital signs. On auscultation, he had bilateral wheezes with increased fremitus and dullness to percussion in the upper lung zones. His CBC showed a white blood cell count of 14,400/ μ L with 26.9% eosinophils and moderately elevated absolute eosinophilia that measured 4020 eosinophils/ μ L. Serum IgE was over 1000 IU > mL. His urine toxicology screen was also negative.

An initial CXR performed on presentation revealed increased bilateral upper lung zone opacities (Figure 1). High-resolution computerized tomography (HRCT) of the thorax with contrast demonstrated bilateral patchy opacities, fibrosis, and bronchiectasis, predominantly affecting the mid-to-upper lung zones (Figure 2). Accordingly, he received azithromycin and ceftriaxone for community acquired pneumonia. He was sent to the medical floor with TB precautions and his sputum was induced for acid-fast bacilli (AFB) testing. Skin prick testing was not available at the facility and pulmonary function testing was not performed.

Given three negative AFB tests, sputum and blood cultures, lack of clinical improvement with the initial treatment regimen, and the radiological findings, a bronchoscopy with bronchoalveolar lavage (BAL) was performed. On BAL, the major airways were friable and erythematous. His left and right lungs measured at 59% and 44% eosinophils, respectively. BAL IgE was 544 IU/mL (normal <114 IU/mL) and serum IgE was >1000 IU/mL (normal 150-300 IU/mL). Serum and BAL galactomannan assays, markers used to diagnose invasive aspergillosis, were also negative. Thin prep slides of the bilateral BAL showed alveolar macrophages with scattered eosinophils (Figure 3).

Our diagnosis included the exclusion of pulmonary diseases such as TB and allergic bronchopulmonary aspergillosis (ABPA). Offending toxins and drugs such as methotrexate, non-steroidal inflammatory drugs, and antibiotics, were also excluded. The high eosinophilia count in serum and BAL, radiological findings, and response to corticosteroid treatment collectively strongly suggested the diagnosis of CEP. Marked clinical improvement was seen after initiation of corticosteroids (initial dose of 125 mg of methylprednisolone I.V. x 1, then 60 mg I.V. Q8H x 2 d) with an eosinophilia decrease from 4020 eosinophils/ μ L (moderate) to 750 eosinophils/ μ L (mild). The patient was thereafter discharged on prednisone 60 mg P.O. daily x 2 weeks. A 2-week followup appointment with a pulmonologist was arranged; however, because he was incarcerated, we were not allowed to review the medical decisions that were made following discharge and thus unable to assess his progress.

Final diagnosis of CEP was based on exclusion and supported by many factors, including peripheral opacities of the mid-upper lung zones on imaging, high eosinophil count on BAL,

high peripheral blood eosinophilia (26.9%), and positive response to corticosteroid treatment. Pertinent negative findings included unremarkable toxicology, acid fast bacillus (AFB), and Galactomannan assays (in both peripheral blood and BAL). The diagnosis was further bolstered given the absence of recent administration of medications known to induce eosinophilia, such as NSAIDs, methotrexate, or antibiotics.

DISCUSSION

Clinical Discussion

CEP was first described by Carrington CB *et al.* in 1969, as a chronic variant of Löffler's syndrome, in a patient with a history of asthma and allergic rhinitis who exhibited dyspnea, fever, and peripheral eosinophilia.¹ CEP is mostly seen in the fourth decade of life with up to half of affected patients having a positive history of atopy, including asthma and rhinitis.²

A detailed history and physical exam are crucial in the diagnosis of CEP, which partially relies on the exclusion of other eosinophilic processes. Considerable overlap exists between the symptoms of acute eosinophilic pneumonia (AEP) and CEP. Common findings include BAL with $\geq 20\%$ eosinophilia, high IgE levels, and lung biopsy with edema and eosinophilic infiltrates. A dramatic response is seen to corticosteroids in both diseases, although relapses rarely occur in AEP after appropriate treatment. Peripheral eosinophilia, atopic disease, and asthma are usually absent in AEP. It has been suggested that CEP manifests several months before the diagnosis,³ whereas in AEP, the symptoms appear within 2-3 days.⁴ Both diseases feature nonspecific clinical symptoms, including cough, fever, dyspnea, weight loss, wheezing, night sweats, chest pain, and occasional hemoptysis.

Allergic bronchopulmonary aspergillosis (ABPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are among the most common misdiagnoses in patients with CEP. EGPA manifests with systemic necrotizing vasculitis, extravascular granulomas, and neuropathy, which are usually absent in CEP.⁴⁻⁶ ABPA resembles CEP as both present with asthma, migratory pulmonary infiltrates, and high IgE levels.^{2,5} However, central bronchiectasis and circulating precipitins directed against *Aspergillus fumigatus* favors the diagnosis of ABPA.

No evidence has confirmed a direct correlation between CEP and TNF-inhibitors such as adalimumab. However, there is a link between TNF-inhibitors and asthma. One case study reported a 51-year-old female that developed asthma-like symptoms after receiving adalimumab.⁷ Asthma may be induced by TNF-inhibitors via the suppression of T-helper 1 (Th1) cells, which are active in rheumatologic diseases.⁸ The T-helper 2 (Th2) cytokine pattern is active in atopic diseases, resulting in elevated levels of IgE. Furthermore, the Th2 response is inhibited by Th1 cytokines. Several cases of bronchospasm following the administration of adalimumab have been cited.⁷⁻⁹

Our patient likely had eosinophilic asthma phenotype¹⁰, which works through the Th2 cell pathway. However, because he also had psoriasis, primarily a Th1 cell pathway disease, his asthma was likely masked most of his life. Upon starting adalimumab for psoriasis, the Th1 response was suppressed and the Th2 pathway was unmasked revealing itself clinically as asthma. Several case reports link adalimumab to asthma, pulmonary eosinophilia, and interstitial lung disease in those with rheumatologic conditions.¹¹ A growing compendium of cases suggest that TNF-targeted therapies potentially predispose to pulmonary complications, including

asthma-like symptoms, chronic pneumonitis, chronic pneumonitis/fibrosis, SLE-like reactions, and exacerbations of underlying lung disease.¹²⁻¹⁴ One case report even suggests the link between TNF therapy and acute necrotizing eosinophilic myocarditis.¹⁵

In our case, the events that led to the diagnosis of asthma were unknown, but it is unlikely the patient harbored latent asthma. His symptoms began after starting adalimumab and may explain the chronic pulmonary changes with the possibility that this drug may have induced eosinophilic inflammation. Like most eosinophilic pulmonary diseases, toxin or drug-induced CEP resolves with removal of the offending agent. Our patient's symptoms improved with the discontinuation of adalimumab and the initiation of corticosteroids.

Radiologic Discussion

Classic characteristics suggestive of CEP on CXR and HRCT include consolidative opacities that are bilateral, peripheral, non-segmental, and upper lobe predominant.¹⁶ This pattern, otherwise known as “photographic negative” of pulmonary edema or the “reverse batwing” sign, is present in less than a third of cases but is not specific for CEP.³ Furthermore, most presentations do not fit classic findings. As such, the radiological presentation of CEP can mimic non-eosinophilic lung diseases with similar presentations (TB, organizing pneumonia, and sarcoidosis) and other eosinophilic lung diseases such as AEP, ABPA, drug-induced eosinophilic pneumonia, EGPA, and Löffler's syndrome.

The most common finding for CEP on CXR and HRCT is a patchy consolidation with upper lobe involvement in a third to half of patients.² Acute TB and ABPA can present similarly on imaging. Notably, acute pulmonary TB usually presents with other findings not present in CEP,

including one or more cavitory lesions, nodules, pleural effusions, and hilar or mediastinal lymphadenopathy. Similarly, sarcoidosis was unlikely based on lack of definitive bilateral hilar adenopathy on CXR and lack of nodules cysts, or significant bronchial wall thickening on HRCT. Fibrosis was present in our case but this is neither sensitive nor specific for sarcoidosis.

The CXR demonstrated bronchial wall thickening and widening in a parallel configuration (colloquially described as the “tram track” sign). This is frequently seen in ABPA. HRCT demonstrated mild bronchiectasis as opposed to the widespread proximal bronchiectasis and bronchial wall thickening seen in ABPA. An acute process, such as AEP, results in diffuse opacities and bilateral pleural effusions; patterns not consistent with this case presentation.¹⁷

The sole reliance of imaging to diagnose CEP can be a challenge, especially since most cases do not demonstrate a classical presentation. The location and pattern of opacifications seen on CXR in combination with HRCT can help the radiologist provide a meaningful differential for the clinician.

Pathologic Discussion

The exact pathogenesis of CEP is unknown, but is thought to involve a complex cascade of inflammatory processes. The main cytokine that has been identified is interleukin-5 (IL-5), which acts to induce the production and inhibit apoptosis of eosinophils.¹⁸ These cells accumulate in the lungs, causing damage to the parenchyma. Beninati *et al.* demonstrated a role for HLA-DR expression in pulmonary eosinophils, as opposed to peripheral blood eosinophils, to explain a possible target for immune pathogenesis in the lung parenchyma.¹⁹ The histological findings of CEP include interstitial and intra-alveolar exudates of eosinophils and histiocytes in

more than 65% of patients, organizing pneumonia in 25% of patients, eosinophilic microabscesses, intra-alveolar necrosis, sarcoid-like granulomas, Charcot-Leyden crystals, and occasional organizing pneumonia.³ This patient's lung cytological studies demonstrated eosinophilic alveolitis with cytoplasmic vacuolization intermixed with macrophages, fibrosis, and fibroblast plugs, which are features consistent with eosinophilic pneumonia (Figure 3).

CONCLUSION

The diagnosis of chronic eosinophilic pneumonia (CEP) is challenging as it accounts for less than 5% of all interstitial lung diseases.²⁰ The final diagnosis is dependent on the exclusion of other eosinophilic pulmonary diseases, as well as supporting clinical, radiological, pathological, and chemical evidence, and the response to treatment. Less than 10% of patients recover without medical treatment. A complication of CEP is irreversible fibrosis and rarely death from respiratory failure.¹

Symptomatic improvement may occur within 24-48 hours of initiation of corticosteroids and corresponding radiographic clearing usually occurs ~2 weeks. Most patients require prolonged or lifelong therapy and relapse is common if corticosteroids are discontinued within the first six months of therapy.²¹ Treatment with omalizumab, a recombinant humanized monoclonal antibody against IgE, can be considered as an alternative to prolonged corticosteroid therapy or in corticosteroid intolerance.²² First shown to be successful in CEP in 2012, omalizumab is indicated in those with elevated IgE, severe persistent asthma, and positive skin prick test to allergens.²² Omalizumab has been suggested to have a pro-apoptotic effect on eosinophils, which can aid in the treatment of refractory CEP. Given that IL-5 has a strong role in eosinophilic

syndromes, mepolizumab, a humanized anti-IL-5 antibody, may potentially provide therapeutic benefit although further studies are needed.^{22, 23}

In conclusion, the diagnosis CEP may be challenging, but recognizing the unique features of this disease may provide early symptomatic relief and prevent unnecessary diagnostic measures. This case points to a possible indirect relationship between TNF-inhibitors and CEP. Studies demonstrating the link between TNF-inhibitors and asthma are ongoing, but the correlation between CEP and asthma has been established.

Declaration of interests

The authors declare no conflicts of interest, financial or otherwise.

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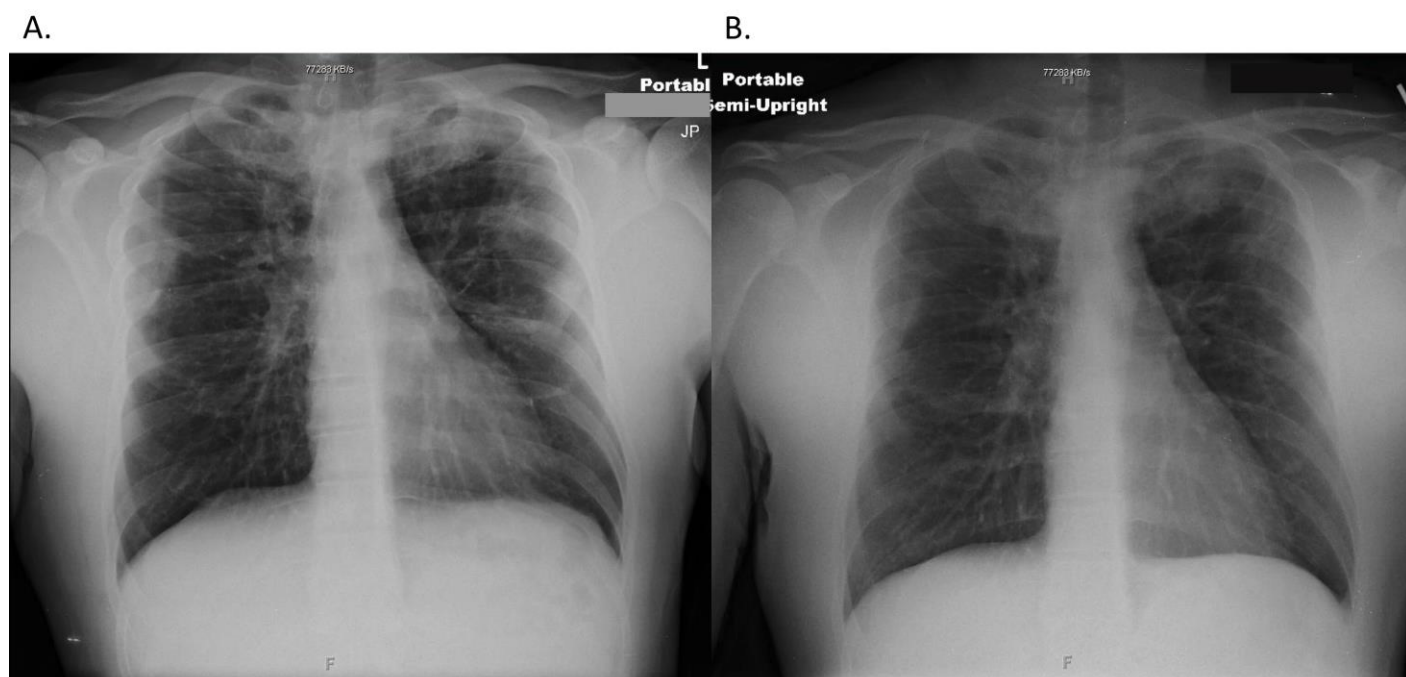


Figure 1

Figure 1. (A) Bedside chest radiograph (day 1) showing a mild increase in perihilar opacities consistent with bronchiolitis or asthma. Note the involvement of the upper lobes. This is a classic radiograph of a “photograph negative” of pulmonary edema. **(B)** Bedside semi-upright chest radiograph (day 4) showing a mild improvement following the administration of corticosteroids.

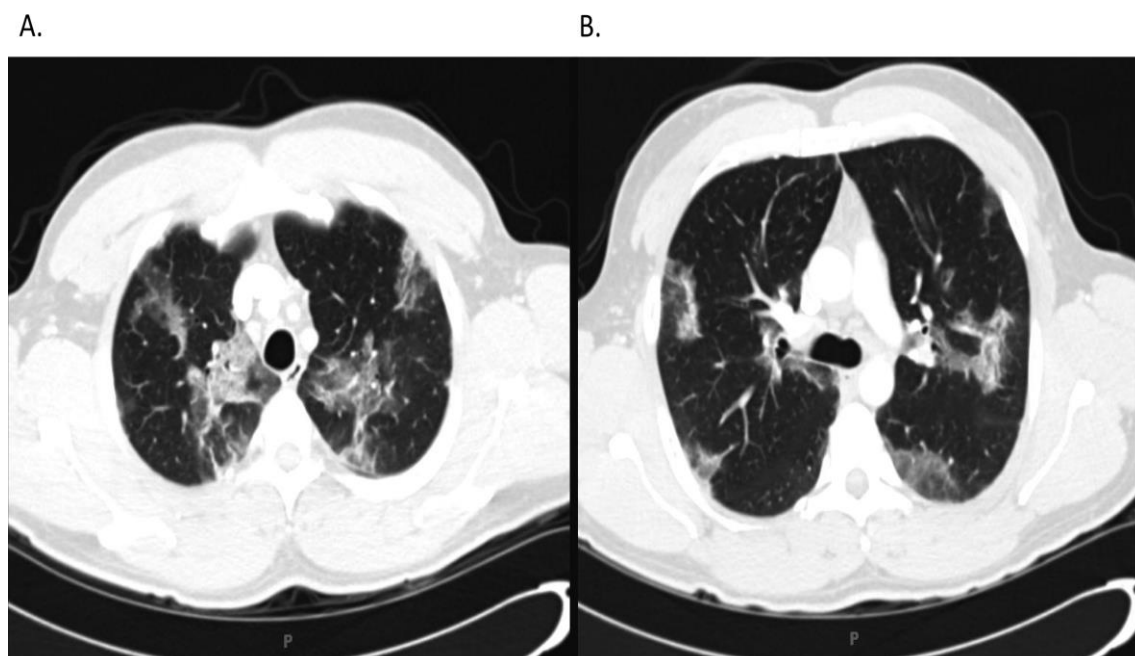


Figure 2

Figure 2. (A-B) High resolution axial contrast-enhanced CT thorax (lung window) demonstrates patchy opacities and/or fibrosis bilaterally, accompanied by a mild bronchiectasis most notable in the mid-to-upper lung zones. These findings appear to be chronic, but they may also reflect a superimposed pneumonic process.

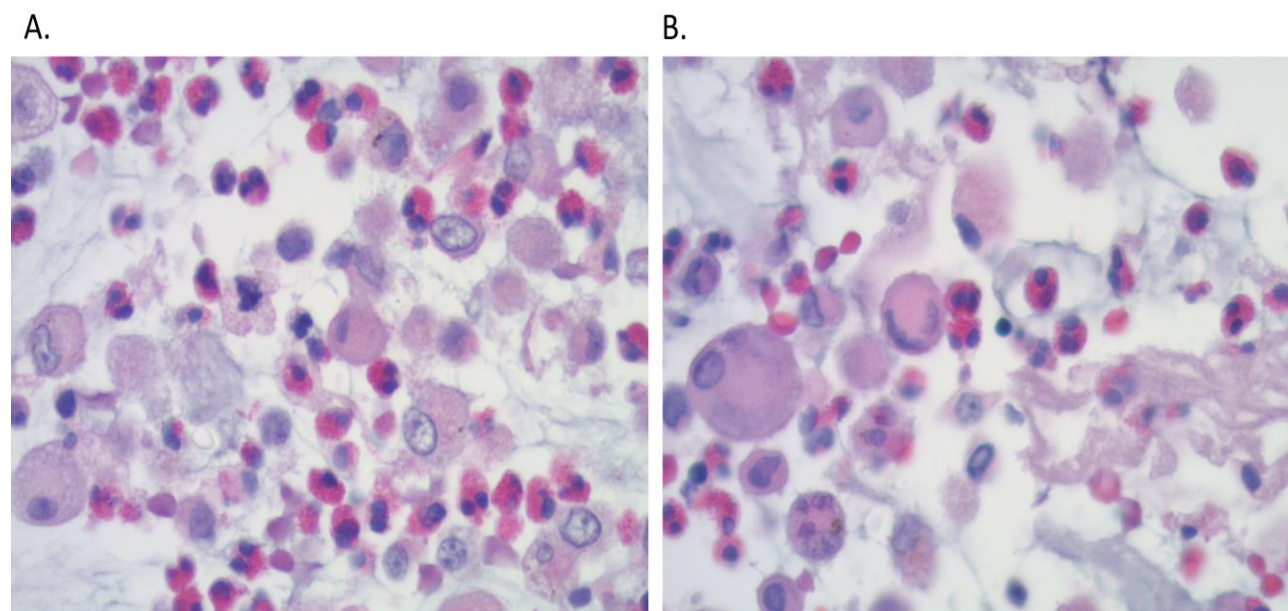


Figure 3

Figure 3. (A-B) Thin prep slides of a left and right bronchoalveolar lavage showing alveolar macrophages with scattered eosinophils. More than two-thirds of patients with CEP display diffuse infiltrate of eosinophils with variable numbers of histiocytes, fibrin and proteinaceous material.³