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Idiopathic Chronic Eosinophilic Pneumonia, a Rare Differential Diagnosis

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ABSTRACT

Eosinophilic pneumonia remains a rare clinical diagnosis, and one not often seen in clinical practice. Eosinophilic pneumonia can present with acute presentations, such as in Löeffler's syndrome in which patient develops low-grade fever, and respiratory symptoms such as dyspnea, non-productive cough or haemoptysis. These respiratory manifestations of Löeffler's syndrome are typically self-limiting and only last for about 1 to 2 weeks. On the other hand, eosinophilic pneumonia can also present with subacute or chronic presentations, such as in chronic eosinophilic pneumonia (CEP), where symptoms are usually present for several months before a clear diagnosis is made. Patients with CEP commonly present with weight loss, low-grade fever, drenching night sweats and an initial dry cough which later turns productive of mucoid sputum. However, in some cases, severe acute respiratory distress syndrome (ARDS) and severe hypoxaemia have also been reported. Although rare, eosinophilic pneumonia should be considered in the differential diagnosis of pulmonary and peripheral blood eosinophilia.[1] Long-term corticosteroids therapy remains the treatment of choice, resulting in prompt treatment response and resolution of symptoms. In this case, we would like to present the case of a 51-year-old patient who presented with characteristic clinical and radiological features of CEP, as well as the presence of abundant eosinophils and Charcot-Leyden crystals in bronchoalveolar lavage (BAL).

CASE REPORT

A 51-year old carpenter initially presented with one-week history of shortness of breath on exertion and an initial dry cough that later turned productive of green sputum. He is a non-smoker with no previous underlying lung disease. On arrival at the Emergency Department, he was saturating at 93% on air and his physical examination revealed few crepitations at both lung bases. His initial arterial blood gas (ABG) on admission showed type 1 respiratory failure with pH 7.43, pCO_2 5.45, pO_2 7.62, HCO_3^- 26.7 and base excess of 3.0. His admission blood showed not only a mildly raised white cell count (WCC) of $11.7x10^9$/L with neutrophil count of $8.0x10^9$/L but also an eosinophilia of $1.2x10^9$. Over the course of an hour he then gradually desaturated and had increasing oxygen requirements of up to 4L/min. His chest radiograph showed clear lung fields. In view of his ongoing hypoxaemia and increasing oxygen requirements, a d-dimer test was performed and returned negative, ruling out pulmonary embolism (PE). Other than that, various tests such as sputum acid-fast bacilli (AFB), HIV serology, atypical pneumonia screen and flu swabs have all returned negative. A HRCT of the chest was later performed and reported to be evidence of focal ground glass opacities in apical segments of both lungs (figure 1). He was then treated with 7-day course of antibiotics according to trust policy for community acquired pneumonia (CAP).

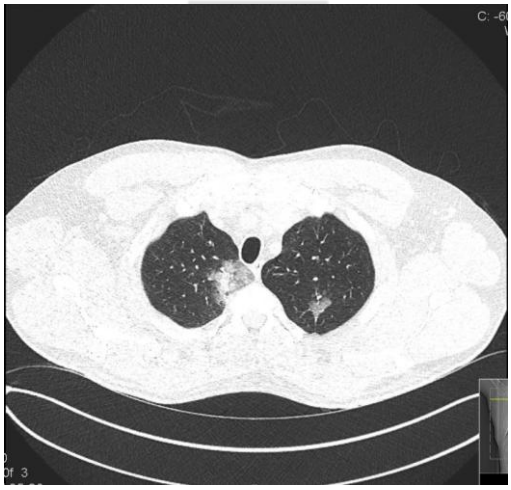

FIGURE 1. HRCT performed on first admission showing focal area of ground glass opacities noted in apical segments of both lungs. There was also a couple of small volume pre-tracheal lymph nodes present, with no evidence of mass lesions or nodules. The rest of the lung parenchymal attenuation is normal.

A week after discharge the patient was readmitted, presenting with non-resolving symptoms and a widespread bilateral expiratory wheeze. He denied having any weight loss, night

sweats, or haemoptysis and his sputum cultures have all returned negative for AFB. However, his full blood count (FBC) on second admission showed a worsening eosinophilia of $3.2x10^9$/L and a raised white cell count of $13x10^9$/L. His chest radiograph revealed a new rounded opacity in the right upper lobe apex with no cavitary changes despite completing 7-day course of antibiotics (figure 2).

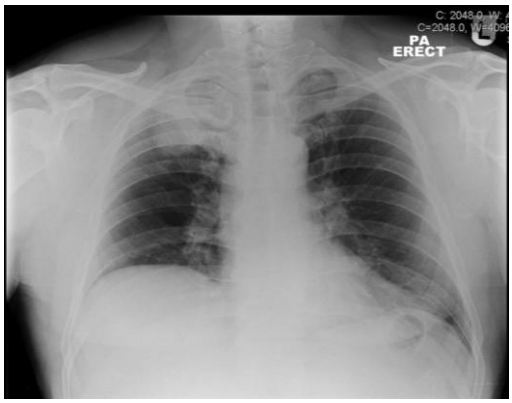

FIGURE 2. Chest radiograph performed after 7 days of antibiotics treatment, showing a new rounded opacity in the right upper lobe apex with no cavitary changes. The rest of the lungs and pleura are clear.

Due to recent hospitalization, he was then started on intravenous (IV) tazocin to cover for hospital-acquired pneumonia (HAP). Despite IV tazocin treatment, his eosinophil count continued to rise and peaked at $6.2x10^9$/L. A CT chest, abdomen and pelvis was also performed, which showed multifocal areas of patchy consolidation and ground glass changes in the lung apices, worse compared to that on first admission (figure 3).

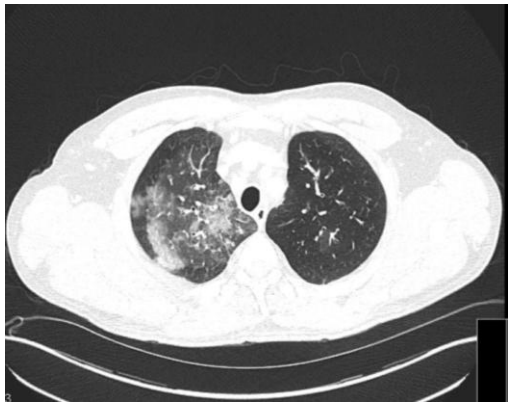

FIGURE 3. CT chest performed on second admission showing multifocal areas of patchy consolidation and ground glass change involving upper lobes bilaterally but more on the right

side. There is also mild bronchial wall thickening with early bronchiectatic changes mainly in the upper lobes.

Other than that, he was also found to be weakly positive for perinuclear anti-neutrophil cytoplasmic antibody (pANCA) IgG, which however seroconverted to a negative result on subsequent measurements. He was also tested negative for PR3/MPO ELISA and galactomannan. His serum IgE was found to peak at 2,078 kunits/L. A BAL was performed on the second admission, and approximately 7mls of cloudy colourless fluid was obtained. Microscopic examination of the bronchial washing later revealed a marked excess of eosinophils, greater than 10% of the total cells present with the presence of Charcot Leyden crystals (figure 4 and 5). Charcot Leyden crystals are produced from the breakdown of eosinophils. They stain purplish-red on trichome stain and appear as paired hexagonal pyramids joined at the bases. They consist of lysophospholipase, an enzyme synthesized by eosinophils.[2]

The presence of Charcot Leyden crystals gave us a broad differential diagnosis including fungal infections such as Aspergillus fumigatus, parasitic infections such as schistosomiasis, Ascaris and Strongyloides, drugs and toxins related, and autoimmune conditions such as Churg Strauss syndrome.[1] However, the specimen from bronchial washing was not only tested negative for microscopy, culture and sensitivity (MC&S) but was also negative for all other pathogens such as Strongyloides, Schistosoma, toxoplasma, filarial and fungal infections. Although these findings were in keeping with Churg Strauss Syndrome, it was deemed unlikely that the patient indeed suffers from eosinophilic granulomatosis with polyangiitis (EGPA) as he did not have symptoms suggestive of sinusitis or asthma. Hence, a differential diagnosis of eosinophilic pneumonia was considered.

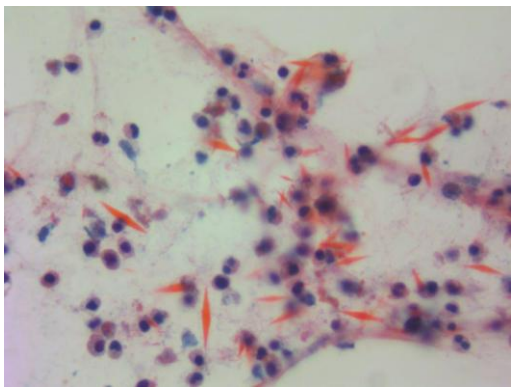

FIGURE 4. Bronchial washing Charcot-Leyden crystals.

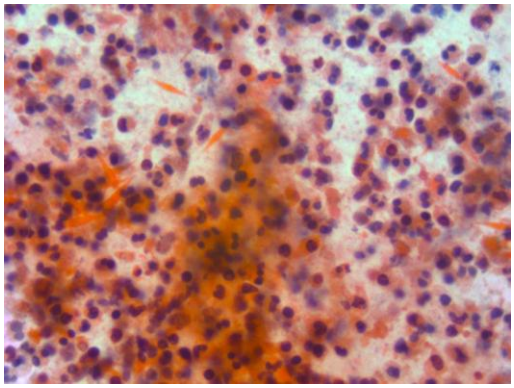

FIGURE 5. Charcot-Leyden crystals.

TREATMENT AND FOLLOW-UP

After excluding all the possible infectious causes to his symptoms, he was then started on both prednisolone 40mg once daily and inhaled beclomethasone and formoterol (Fostair®).

1-month post discharge the patient was reviewed in outpatient clinic. He appeared well with no respiratory symptoms, and his chest was clear on auscultation. A respiratory function test showed normal values of FEV_1 2.98 (83% predicted); FVC 3.49 (79% predicted) and ratio of 85%.

However, 10 days after discontinuing his prednisolone, he then re-attended Emergency Department presenting with another episode of symptoms relapse and hypoxia, with pO_2 of 7.02. He was then again restarted on prednisolone 60mg and was advised to continue with corticosteroid treatment for at least 6 months. When reviewed in outpatient clinic again, his repeat chest radiograph showed a resolution of the previous consolidation with clear lung fields (figure 6). The patient also reported a full resolution of his respiratory symptoms, and his eosinophilia has also improved, with eosinophil count of $0.3x10^9$/L.

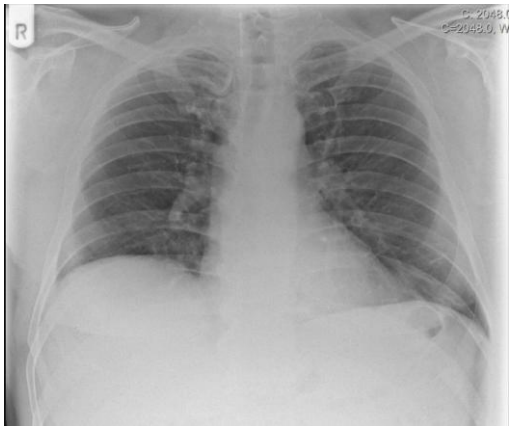

FIGURE 6. A repeat chest radiograph following commencement of corticosteroid treatments, showing clear lung fields and costophrenic recesses.

DISCUSSION - INVESTIGATION FOR CEP

The association between eosinophilia and pulmonary infiltrates was initially identified by Löffler in 1932. Later in 1969, Liebow and Carrington subsequently described the term eosinophilic pneumonia as an umbrella term to include all disorders characterised by eosinophilic infiltration of the lungs, with or without blood eosinophilia.[1]

The exact role of eosinophils in the pathogenesis of various eosinophilic pneumonia remains unclear. In parasitic infections such as strongyloidiasis, eosinophils play a vital role in eradicating the infectious offending pathogen; however, in conditions like allergic bronchopulmonary aspergillosis (ABPA) and asthma, eosinophils accumulate in the lungs due to immune hypersensitivity and act as the prominent driver for further tissue injury. There are a number of aetiology that are known to trigger pulmonary eosinophilic syndromes, such as parasitic infestations in tropical pulmonary eosinophilia, as well as some commonly used drugs including clarithromycin, ibuprofen, and diclofenac in drug-or toxin-induced eosinophilic pneumonia. However, in some cases such as idiopathic eosinophilic pneumonia, the culprits causing such syndromes are poorly recognized.[1]

Idiopathic eosinophilic pneumonia can present with either acute or chronic manifestations.[3]Chronic eosinophilic pneumonia (CEP) occurs predominantly in middle-aged women and can occur in conjunction with asthma in more than 50% of the cases.[4,5]There are no clearly established criteria for the diagnosis of CEP but the diagnosis can be based on the presence of classical respiratory symptoms of more than 2 weeks duration, pulmonary infiltrates on chest radiography, alveolar and/or peripheral blood

eosinophilia and a prompt response to corticosteroids treatment.[4,6]BAL of >25% eosinophils is highly suggestive of CEP. The diagnosis of CEP is crucial as less than 10% of cases resolve spontaneously. If untreated, CEP can progress to irreversible pulmonary fibrotic changes.[7] We, therefore, suggest that CEP should be considered in patients with bilateral lung consolidation and peripheral blood eosinophilia, and BAL should be considered as the gold-standard investigation to confirm the diagnosis.

DISCUSSION - MANAGEMENT OF CEP

A case report published by Fox and Seed described three cases of chronic eosinophilic pneumonia, all of which have unknown aetiology. All of these patients were found to have chest radiographs evident of widespread shadowing bilaterally, as well as blood eosinophilia. In two of these three cases the patients present with at least 6-week history of progressive dyspnoea, malaise, and weight loss. Similar to our patient, one of the patients in Fox and Seed's report was initially treated with combined antibiotics for lower respiratory tract infection but continued to deteriorate both clinically and radiologically. All of the patients in Fox and Seed's case report underwent open lung biopsy, all of which revealed both interstitial and intra-alveolar eosinophilic pneumonia with vasculitis and bronchiolitis obliterans. Electron microscopy also revealed eosinophilia and the presence of eosinophilic granules within macrophages. One patient recovered spontaneously, while the two other had drastic improvement of their clinical symptoms and radiological clearance after treatment with oral prednisolone. These patients were given oral prednisolone for at least 6 months. However, similar to our patient, one patient from Fox and Seed's report suffered both symptoms and radiological relapse only five months after steroid withdrawal.[8]

An article published by Ono et al. suggested although both acute and chronic eosinophilic pneumonia was shown to have excellent response to corticosteroids treatment, the risk of relapse during steroid weaning is very high.[3,5]A long-term follow-up of 12 CEP patients over an average of 10.2 years showed that only 2 out of 12 patients were able to successfully discontinue their high-dose steroid therapy at 1 and 3 years respectively, without demonstrating a clinical relapse of their symptoms for at least 6 years. For the remaining of the patients, a large proportion relapsed, some on more than one occasions. These relapses were found to have occurred either when corticosteroids therapy was completely discontinued, or even during tapering of steroids doses. Once corticosteroids treatment was recommended in these patients, they again responded with the same dramatic improvement in

their symptoms. However, this improvement is generally only sustainable until the steroids dose was again decreased, leading to a pattern of remission and recurrence of symptoms.[4]

The long-term use of corticosteroid therapy can lead to significant side effects such as development of cushingoid habitus, osteoporosis, growth suppression and hyperlipidaemia.[9,10]In 2012, Shin YS et al explored the option of treating CEP with anti-IgE therapy.[5]Anti-IgE antibody was one of the most novel and striking discovery in allergy field. It not only is capable of down-regulating the expression of high-affinity IgE receptors (FcεRI) in inflammatory cells but is also able to rapidly reduce the levels of circulating free IgE.

Both patients in their case report were diagnosed with CEP and were initially treated with systemic corticosteroids. However, they both suffered recurrent pulmonary and peripheral eosinophilia after reduction of oral steroid doses. Anti-IgE therapy was later started in these two patients and the result was that anti-IgE therapy when administered once every two weeks for ten cycles successfully induced remission of respiratory symptoms with no further evidence of both peripheral eosinophilia and eosinophilic infiltration on radiological imaging for at least 15 months.[5] Despite studies showing successful treatment of CEP with anti-IgE therapy, the data on this still remains very limited.[5,11]

In our case, our patient presented with an episode of symptoms relapse and hypoxia only 10 days after discontinuing prednisolone treatment. When restarted on prednisolone 60mg, he again responded with dramatic improvement of his symptoms. The treatment with corticosteroids was maintained for at least 6 months, resulting in both radiological and clinical resolution of his symptoms.

Although high-dose corticosteroids still remain as the mainstay treatment for CEP, there are no consensuses on the duration or doses of corticosteroids treatment. Most authors recommend an initial dose of 0.5 to 1mg/kg/day of prednisolone with a gradual tapering of doses over a six to twelve-month period. As previously discussed, relapses occurring during and after weaning of corticosteroid doses are observed in up to 50% of the patients. Relapses in these patients remain responsive to corticosteroid therapy, and up to half of patients affected by CEP will require long-term corticosteroid treatment. Therefore, it is advisable to recommend preventative measures to reduce the risks of corticosteroid-induced osteoporosis.[12]

CONCLUSION

The patient in our case report presented with clinical features typical of CEP. Unfortunately, the diagnosis of CEP was overlooked on the first admission despite peripheral eosinophilia and HRCT findings suggestive of CEP, resulting in multiple hospital admissions. Although the correct diagnosis was eventually made, we strongly suggest that CEP should be considered in patients with bilateral lung consolidation and peripheral blood eosinophilia, and BAL should be carried out in order to confirm the diagnosis. Other than that, prompt treatment with corticosteroids is also crucial as untreated CEP can lead to irreversible pulmonary fibrotic changes.[7]

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FINANCIAL / NON-FINANCIAL DISCLOSURES:

The authors have reported that no potential conflicts of interest exist with any authors, companies or organisations.

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