A 77 year old male with peripheral eosinophilia, pulmonary infiltrates and a small pleural effusion

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Abstract. – The presence of peripheral eosinophilia with lung infiltrates poses a diagnostic challenge for the clinician. The differential diagnosis includes a wide spectrum of diseases. In some of them (for example vasculitis, lymphoma) eosinophilic pneumonia represents just another "symptom" and not the final diagnosis. A thorough diagnostic procedure is required to examine all related clinical entities in order to establish a firm diagnosis. In particular, Idiopathic Chronic Eosinophilic Pneumonia (ICEP) is a rare disorder. In the majority of cases, it is characterized by peripheral eosinophilia, lung infiltrates, bronchoalveolar lavage eosinophilia (above 25%), exclusion of other possible causes and last but not least an impressive improvement under steroid therapy. Relapses are common but they do not seem to be related with ICEP associated mortality.

Key Words:

Chronic eosinophilic pneumonia, Bronchoalveolar lavage.

Case History

A 77 year old male patient was referred to our Clinic because of non productive cough for a period of two months. The patient reported deterioration regarding coughing when he was lying in the supine position. He also complained of constitutional symptoms such as anorexia and fatigue but no fever.

In his past medical history a cholecystectomy was reported and the patient was on no medication.

He was a non-smoker and had not travelled abroad recently. He was currently retired and worked as a truck-driver in a transport company. He had no domestic pets.

Physical examination revealed normal vital signs. There was no clubbing, cervical or axillary lymphadenopathy, skin lesions or joint swelling.

Auscultation of the lungs revealed diminished breath sounds bilaterally but no wheezing.

The biochemical profile was normal, except-GT: 103 IU/L. Otherwise renal, liver functions were within normal limits. Total blood count revealed peripheral eosinophilia (absolute number 1260/mm^3). The exact CBC was as follows: Ht: 39,2%, WBC: 7330/mm^3, PLT: 34,2000/mm^3. ESR was 86).

Pulmonary function test showed a restrictive pattern (TLC: 56% predicted) without an obstructive component or evidence of small airway disease (FEV$_1$: 81%, FVC: 72%. FEV$_1$/FVC: 84%, FEF25-75%: 91%). The patient was not able to cooperate for the estimation of DLco.

Levels of total IgE were increased (102 IU/ml).

On admission, patient's chest radiograph was (CXR) characterized by extensive infiltrates mainly involving the upper/middle lung zones (Figure 1).

On HRCT (Figures 2a, b, c) there was a diffuse consolidative pattern (with air-bronchogram in some areas). The areas of consolidation were more extensive on the left lung, patchy in distribution, involving both the central and peripheral lung. Also, the upper/middle zone predominance of the disease was confirmed. A minimal left pleural effusion and a lower paratracheal lymph node (short axis diameter about 1 cm) were also found.

No bronchiectasis or atelectasis was identified.

What is Your Differential Diagnosis?

What Are Your Next Steps in the Diagnostic Procedure?

The long standing course of the disease, the absence of fever and the presence of cough predominating is against infectious causes by common pathogens. The differential diagnosis of a diffuse consolidative pattern with upper zone predomi-
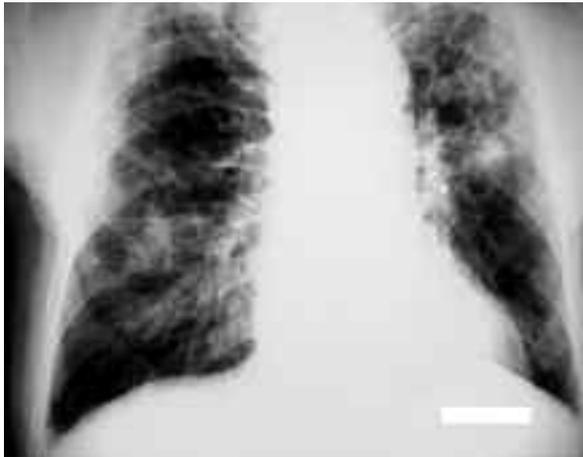
Figure 1. Extensive infiltrates mainly involving the upper/middle lung zones.

nance includes: chronic eosinophilic pneumonia, extrinsic allergic alveolitis (no allergen exposure was identified), Non Specific Interstitial Pneumonia (NSIP) (the lower parts of the lung are usually more involved, no history or signs of a collagen vascular disease), Cryptogenic Organizing Pneumonia (COP), Desquamative Interstitial Pneumonia (the patient was a non smoker though), "alveolar" sarcoidosis, Churg Strauss syndrome (no history or clinical features compatible with asthma), neoplastic causes (bronchoalveolar carcinoma, pulmonary lymphoma), tuberculosis.

Of course, the presence of peripheral eosinophilia narrows significantly the differential list and is the driving force for the next diagnostic interventions. In other words the main priority is to establish if the peripheral eosinophilia is related with the pulmonary infiltrates. So, bronchoalveolar lavage was performed. The results were: total cell number: 25×10^4 /ml, macrophages: 39%, lymphocytes: 7,4%, eosinophils: 28%, neutrophils: 24%. No neoplastic or atypical cells were observed. Transbronchial biopsy (TBNA) was also performed (LB$_3$). The histology showed extensive infiltration by lymphocytes and eosinophils in the alveolar septa and lumen. Again, no signs of granuloma, vasculitis or malignancy were identified.

After the establishment of the eosinophilic nature of the infiltrates, the next step was to ex-
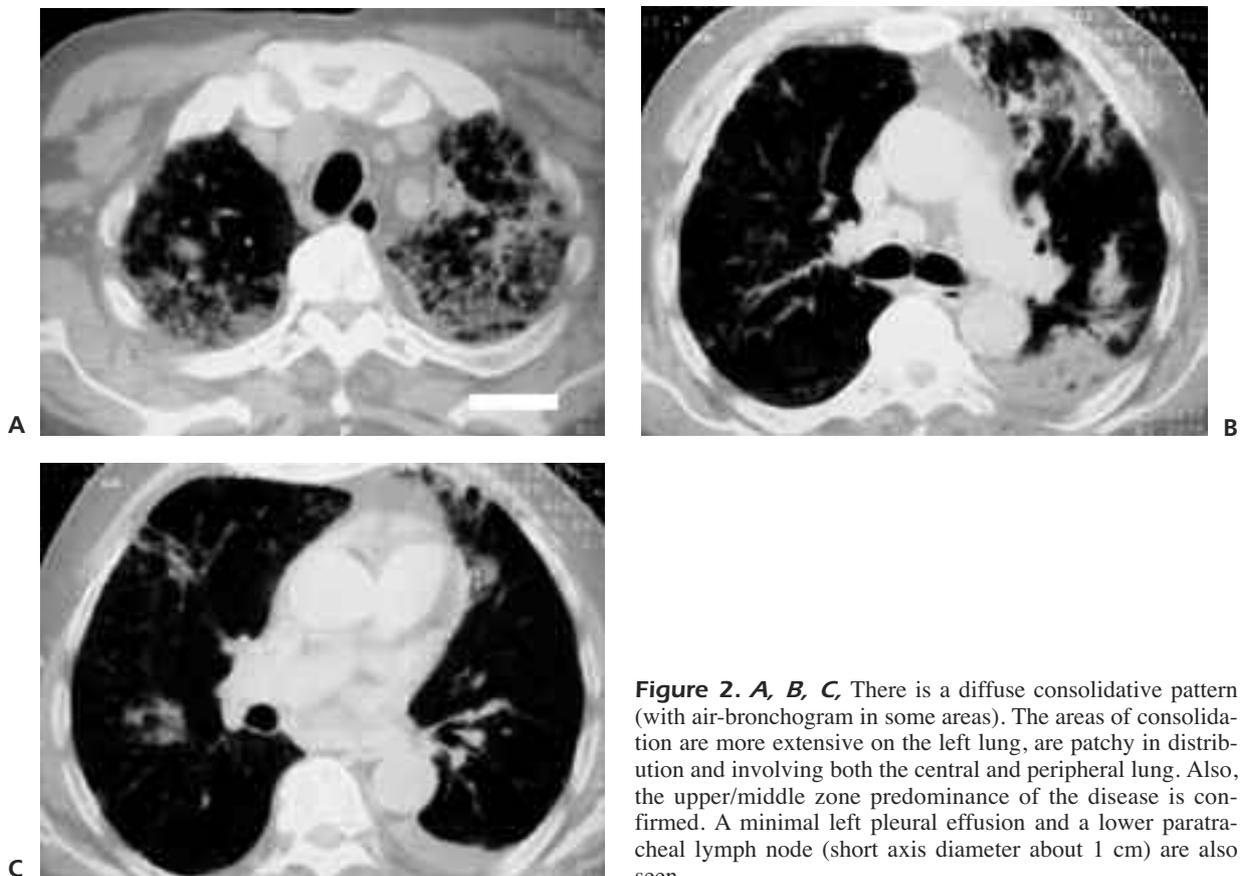

Figure 2. A, B, C, There is a diffuse consolidative pattern (with air-bronchogram in some areas). The areas of consolidation are more extensive on the left lung, are patchy in distribution and involving both the central and peripheral lung. Also, the upper/middle zone predominance of the disease is confirmed. A minimal left pleural effusion and a lower paratracheal lymph node (short axis diameter about 1 cm) are also seen.

clude a possible underlying cause of the peripheral eosinophilia. Washings (as well as sputum samples) were examined for the presence of Nocardia, Fungi and acid fast bacilli. All results were negative including cultures. Antiechinococcal antibodies were negative.

Sputum and washings cytology analysis were negative for malignancy. The examination of stools and bronchial washings were negative for the presence of parasites.

In a patient with peripheral eosinophilia and lung infiltrates Churg Strauss syndrome (as well as other vasculitides as Wegener's granulomatosis) are within the differential list. Of course, the absence of history or clinical features compatible with asthma is strongly against this diagnosis. Moreover, the patient didn't present any extrapulmonary symptoms that could imply the presence of a systemic disease as angioitis or collagen vascular disease. The laboratory results for ANA, rheumatoid factor, p-ANCA, c-ANCA were negative. There is a well known relation between eosinophilic pneumonia and the presence of vasculitis or rheumatoid arthritis. These considerations should be taken seriously into account in the process of differential diagnosis.

Regarding the possibility of allergic bronchopulmonary aspergillosis (ABPA) there was no history of asthma or cystic fibrosis. Also, there was no central bronchiectasis or fleeting infiltrates and the serologic panel (including precipitins and specific anti-IgE antibodies against *Aspergillus*) were negative.

The patient during hospitalization was complaining for a severe discomfort sensation in the upper abdomen. A gastroscopy and colonoscopy were performed to exclude the possibility of an underlying malignancy (mainly gastric lymphoma) that could explain the peripheral eosinophilia and the symptoms of the patient. Both examinations were negative.

CT examination of upper/lower abdomen was normal.

Regarding eosinophilic pneumonias, the protracted course of the disease excluded diagnoses as simple eosinophilic pneumonia, acute eosinophilic pneumonia. There were no systemic symptoms to support the diagnosis of idiopathic hypereosinophilic syndrome. The microscopic examination of a peripheral blood smear revealed no abnormality (no eosinophil or lymphocyte clonality). Finally, the patient was on no medication, so a drug related disease is also excluded.
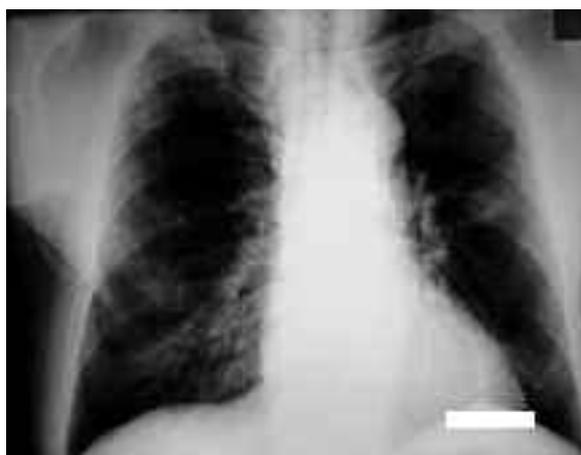

Figure 3. Significant improvement after 3 days of steroid therapy.

Therefore, the diagnosis of idiopathic chronic eosinophilic pneumonia (ICEP) was established.

Steroids were administered at an initial dose of 40mg prednisolone/day (0.5 mg/kg/day). After three days (Figure 3) the patient reported a significant improvement regarding his cough, appetite and fatigue. This was parallel with the striking improvement in his CXR. Steroid treatment continues until now (3 months after initiation) with a gradual decrease. The patient exhibited no signs of relapse and is under monthly observation (Figure 4). Remarkably, six days after the initiation of steroids, peripheral eosinophils fell to the absolute number of 40/mm^3 and ESR dropped to 29.

Figure 4. No relapse after 2,5 months (tapering phase).

Brief Review (Table I)

Idiopathic Chronic Eosinophilic Pneumonia (ICEP) was first described by Carrington in 1969[1]. It is a diagnosis of exclusion. All possible causes of peripheral and lung eosinophilia should be examined before the establishment of the diagnosis.

Its etiology is unknown. It has been described in women after radiation for breast cancer[2,3].

It is a rare disease[4]. Although no age group is exempted, it is extremely rare in childhood and usually peaks in the fifth decade. Women are affected twice as often as men. Usually (90%), the patients are non or former smokers[5-7]. The majority of patients in a series[6] were non smokers, suggesting that smoking may be "protective" in some manner.

The disease has a gradual onset and is characterized by cough, dyspnea and constitutional symptoms as fever, anorexia, fatigue, night sweats and sometimes weight loss[8]. In one third to one half of cases, there are asthma like symptoms[9].

Findings at physical examination are poor and non specific as diminished breath sounds, crackles, wheezing. It must be emphasized that ICEP is limited to the lungs. Any signs of extrapulmonary manifestations (hematuria, arthropathy, mononeuritis multiplex, skin nodules) must lead the diagnostic procedure to systemic diseases as vasculitides or collagen vascular disease. It must be stressed though that even rare, there are several cases showing a connection between eosinophilic pneumonia and rheumatoid arthritis (RA)[10-12]. Sometimes eosinophilic pneumonia can even precede the clinical manifestations of RA[13]. Also, a relation with vasculitis is known[14].

Total blood count reveals peripheral eosinophilia (frequently greater than $1000/mm^3$) in the majority of cases (90%). In about 50% of cases elevated levels of IgE are found. Other non specific findings include elevated ESR, CRP[6].

Imaging features consist of bilateral opacities (consolidation or ground glass attenuation) with an upper/middle zone predominance. The peripheral/subpleural distribution of the lesions (photographic negative of pulmonary edema) was considered characteristic of the disease[15] but actually is observed in about 25% to 50% of cases[5,16]. Furthermore, there are other clinical entities that can present with this radiographic appearance as Cryptogenic Organizing Pneumonia[17], sarcoidosis[18], drug induced pulmonary toxicity, NSIP. In our patient there was no subpleural distribution of the findings but the upper zone predominance was characteristic of the disease. Migration of the infiltrates although highly suggestive of eosinophilic pneumonias, is present in about 25% of patients[6,19] and can also be seen in COP. Mediastinal adenopathy, although a non specific finding, was present in our case. It can be present in up to 50% and its presence does not rule out ICEP[20]. The enlarged lymph nodes are smaller than 1.0 to 1.5 cm, otherwise further diagnostic testing is needed (TBNA, mediastinoscopy)[6,21]. Pleural effusion is uncommon and if present of minimal size (as in our patient).

Pulmonary function tests show a restrictive pattern with a reduction in diffusion capacity. An obstructive pattern can be seen in case of concurrent bronchiolitis or asthma. Arterial blood gases usually demonstrate a mild to moderate hypoxemia.

On histology gross eosinophilic infiltration of the interstitium and alveolar lumen is seen, while other inflammatory cells may participate (lymphocytes, neutrophils, plasma cells). Areas of Organizing Pneumonia may be identified[5]. In most cases, biopsy is not needed for the establishment of the diagnosis.

Regarding diagnosis, it is of great importance to demonstrate bronchoalveolar lavage (BAL) eosinophilia above the threshold of 25%[6], keeping in mind that BAL eosinophilia just proves the eosinophilic nature of the lung lesions. Fas mediated apoptosis seems to be suppressed in BAL eosinophils resulting in prolonged survival within the lung parenchyma[22]. Thus they have the chance

Table I. Learning points.

- In a patient with peripheral eosinophilia and pulmonary infiltrates a bronchoalveolar lavage (BAL) is mandatory to establish the probable relation
- BAL eosinophilia above the threshold of 25% establishes the diagnosis of eosinophilic pneumonia
- An extensive work up is required to confirm probable underlying diseases or establish the diagnosis of idiopathic chronic eosinophilic pneumonia (ICEP)
- The peripheral distribution of infiltrates in ICEP although characteristic they are neither pathognomonic nor frequently identified (25% of cases). So, the lack of this distribution pattern should not discourage the physician from the diagnosis
- The presence of mediastinal lymphadenopathy (short axis diameter below 1 cm) is frequently found (approximately 50%) and does not rule out ICEP
- The clinical and radiographic improvement under steroids is impressive. If this is not the case the diagnosis should be reconsidered

to prolong their toxic effect which is reflected by the high levels of Eosinophilic Cationic Protein (ECP), Eosinophilic Derived Neurotoxin (EDN) found in bronchoalveolar lavage fluid (BALF)[22]. A BALF hyperglobulinemia can be identified and specifically the levels of IgA are correlated to the levels of ECP. May be the former plays a role in the degranulation of eosinophils[23].

Recruitment of eosinophils in the lung parenchyma is not fully understood. Th2 cytokines interleukin 4 (IL-4), IL-5, IL-13, as well as IL-6, IL-10 are increased in BALF regarding the affected lung areas. IL-5 is not elevated in the non-affected areas as well as in serum[24]. Thymus and activation-regulated chemokine (TARC) plays an important role in the recruitment of Th2 cells. The reduction of TARC is followed by a reduction in IL-5 and eosinophil levels in the lung, emphasizing its significance in the pathogenesis of the disease[25]. Chemokine CCL5, formerly known as Regulated on Activation, Normal T Expressed and Secreted (RANTES) and eotaxin, also seem to play an important role in the recruitment of eosinophils in the lung[26-28].

In order to reach to a specific diagnosis of ICEP the patient must have a compatible clinical history (protracted course, fever, cough, asthma-like symptoms, no severe respiratory insufficiency), a compatible radiographic appearance. Last but not least other possible causes of peripheral and/or lung eosinophilia must be excluded after thorough investigation. Inevitably, since the term Idiopathic is included, the diagnosis of ICEP is one of exclusion (Table I).

Response under oral steroid therapy is impressive[29]. 40 mg/day of prednisolone is usually sufficient. In our patient there was a clear improvement in his CXR within 3 days, concurrently with an improvement in his symptoms. Full blood count and ESR returned to normal within six days. This dramatic response is considered characteristic for ICEP[1,6]. It can also be seen (although usually not to this extent) in cases of COP. Steroid therapy, with tapering doses, is maintained for a minimum of 6 to 12 months. There is no consensus for the dosing and duration of treatment. These parameters are individualized regarding the response of each patient. Some patients have to receive a small dose of steroids indefinitely. In such cases the problem of steroid induced osteoporosis must be examined and the steroids must be titrated to the minimum dose that keeps the patient symptom free. The rate of relapses is quite high (50%)[6]. Thankfully,

the relapses (if treated properly with an increase in steroid dosing) do not seem to influence survival. Since eosinophil is an extremely toxic cell[30,31], a delay in the initiation of treatment can lead to fibrosis[32]. There is controversy regarding the role of inhaled steroids. They must be administered in cases of concurrent asthma although it is not clarified if they have an oral steroid sparing effect or if they act protectively against the onset of relapses[6,9,33]. Development of asthma after the onset of ICEP has been reported. Some patients develop persistent small airway disease even in the absence of clinical or radiological signs of relapse. Our patient's spirometry after three months continues to be within normal limits.

In our case the presence of striking peripheral eosinophilia led the differential diagnosis towards ICEP. Usually ICEP presents at an earlier age (fifth decade) and fever is a frequent symptom (absent in our patient). The protracted course practically excluded diagnoses such as acute eosinophilic pneumonia (average age of presentation 30 years, usually no peripheral eosinophilia) and simple pulmonary eosinophilia. The absence of systemic symptoms and negative serology tests was against vasculitides and collagen vascular disease. There was no history of asthma to support the diagnosis of Churg-Strauss syndrome or ABPA. BAL confirmed the eosinophilic nature of the lung infiltrates. The clinical and imaging context was compatible with ICEP and the exclusion of other causes of eosinophilia established the diagnosis.

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