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Manifestation peculiarities of idiopathic chronic eosinophilic pneumonia

Research Article

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Abstract: Chronic eosinophilic pneumonia is a rare interstitial lung disorder, which causes diagnostic difficulties. Often the disease is diagnosed correctly after several weeks or months following initial presentation. The aim of the study was to prospectively evaluate peculiarities of manifestation of idiopathic chronic eosinophilic pneumonia (ICEP), which may allow to improving early diagnosis. Twenty patients with ICEP were involved in this investigation. The cases of acute eosinophilic pneumonia and cases of chronic eosinophilic pneumonia of known origin were excluded. To define archetypal signs of the idiopathic chronic eosinophilic pneumonia, 3 comparable groups were selected. They were the group of 50 patients with community-acquired pneumonia (COP); the group of 21 asthmatic patients with COP, and the cluster of 10 patients with morphologically confirmed cryptogenic organizing pneumonia (OP). Clinical and radiological manifestation of ICEP was similar to COP and cryptogenic OP manifestation. We have found that chest pain; fine rales and pleurisy were unrepresentative for ICEP. However, blood eosinophilia was typical sign of ICEP and wheezing was a frequent observation. Usually ICEP patients had relative mild clinical symptoms and moderate increased C reactive protein (CRP) level even in cases of multiple pulmonary infiltrates. In conclusion, in cases of not typical pneumonia course, i.e. non-resolving or recurrent pulmonary infiltrates; relative mild clinical symptoms and moderate increased CRP level with multiple pulmonary infiltrates; blood eosinophilia and/or signs of airway obstruction eosinophilic pneumonia should be suspected and bronchoalveolar lavage and/or bronchoscopic lung biopsy performed.

Keywords: *Asthma • Eosinophilic pneumonia • Infectious pneumonia • Organizing pneumonia*

1. Introduction

Eosinophilic pneumonia is defined as a pathological condition characterized by infiltration of the lung parenchyma by eosinophils that may or may not be accompanied by an excess of these cells in the peripheral blood. Usually eosinophilic pneumonia is manifested as peripheral opacities on chest X-ray and various levels of blood eosinophilia [1]. Eosinophilic pneumonia is associated with several causes (e.g., parasites invasion, drug-induced, systemic collagen-vascular disorders) and the clinical presentation of the disease is variable [2-6]. Etiologically eosinophilic pneumonia may be divided into known cause and

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unknown cause (idiopathic). In the developing world, pulmonary infiltrates with eosinophiles usually represent parasitic infection; in the developed countries, it more commonly represents drug-induced, connective tissue disease or idiopathic disease [7]. Furthermore this disorder is divided into acute eosinophilic pneumonia (up to 1-2 weeks) and chronic eosinophilic pneumonia [8,9].

Bronchoalveolar lavage (BAL) and/or bronchoscopic lung biopsy are the main diagnostic methods of eosinophilic pneumonia [10-12]. Eosinophilic pneumonia is a rare interstitial lung disorder, which causes diagnostic difficulties. Generally it is the most difficult to diagnose chronic eosinophilic pneumonia. Usually, chronic eosinophilic pneumonia is presented with obvious clinical symptoms such as cough, dyspnea or fever. However, the disease is diagnosed correctly after several weeks or months following initial presentation [12-18].

Thus a very important question from the clinical practice point of view is which of simple respiratory clinical and radiological symptoms allow suspecting eosinophilic pneumonia, especially in general practice, and when bronchoscopy is necessary.

There are few publications in medical literature to clinical manifestation of idiopathic chronic eosinophilic pneumonia (ICEP). It is impossible to perform large prospective studies in ICEP because it is rare, even if it were possible to perform national collaborative studies [19].

In 1997, the Clinic of Chest Diseases, Allergology and Radiology of Vilnius University the launched a study of interstitial diseases. The aim of this study was to evaluate prospectively clinical symptoms, the diagnostic role of bronchologic methods, course of the interstitial diseases and other related issues [20-24]. The aim of this particular part of the study was to evaluate peculiarities of manifestation of ICEP, which may allow improving early diagnosis.

2. Material and Methods

2.1. Patients

The study population consisted of 20 consecutive patients with idiopathic chronic eosinophilic pneumonia for the first time diagnosed between 1997 and 2008 in the Centre of Pulmonology and Allergology of Vilnius University Hospital *Santariškių klinikos*. The diagnosis was based on duration of respiratory symptoms for more than 2 weeks; pulmonary infiltrates; alveolar eosinophilia; exclusion of any known cause of eosinophilic lung disease [25].

Table 1. BAL fluid cells and blood IgE concentration of the patient with idiopathic chronic eosinophilic pneumonia.

Parameter	Meaning
BAL macrophages, %	43±26
BAL lymphocytes, %	13±9
BAL neutrophils, %	10±16
BAL eosinophils, %	34±27
BAL total cells, 10^6 L	842±800
Blood IgE, U/L	572±647

BAL – bronchoalveolar lavage. IgE – immunoglobulin E. Results presented by average ± standard deviation

Pulmonary tissue eosinophilia was diagnosed by means of bronchoalveolar lavage in 15 patients, transbronchial biopsy in 1 patient, and both in 4 patients. BAL fluid cells and IgE concentration in the patient with idiopathic chronic eosinophilic pneumonia are presented in Table 1. The cases of acute eosinophilic pneumonia and cases of chronic eosinophilic pneumonia of known origin (for example: collagen-vascular disease, drug-induced, parasitic or fungal infection, including *Aspergillus*) were excluded. 4 patients in this group had bronchial asthma; they were diagnosed earlier. Bronchoalveolar lavage and bronchoscopic lung biopsy were performed the way we comprehensively described in previous publications [20,21]. All patients were treated with corticosteroids and responded well to therapy. However, three patients (all non-asthmatic) had several relapses of their symptoms and pulmonary infiltration according to the chest X-ray.

To define characteristic signs of the ICEP, 3 comparable groups were selected. Diseases with the symptoms of allusive signs of the chronic eosinophilic pneumonia were selected for comparison [26-28]. The first group was composed of 50 accidentally selected consecutive patients with radiographically confirmed hospital treated community-acquired pneumonia (COP); the second group consisted of 21 consecutive asthmatic patients with previously diagnosed disease, who had caught hospital treated COP between 1997 and 2008. Ten patients were incorporated into a third comparable cluster. This cluster, which had morphologically confirmed organizing pneumonia (OP), was diagnosed in our Center during the same time period. OP was diagnosed as was described earlier [29]. Patients with OP of known etiology (associated with blood or collagen-vascular diseases, adverse drug reaction and likewise) were excluded. The patients with adjacent disorder (e.g. haemathological, kidney diseases), which may influence the manifestation of our study of diseases were also excluded.

Table 2. Demographic data and duration of disease before diagnosis establishment of the patients of the study.

Parameter	ICEP	COP	Asthmatics with COP	Cryptogenic OP
Number of patients	20	50	21	10
Male/female*	7 (35)/13 (65)	25 (50)/25 (50)	5 (24)/16 (76)	6 (60)/4 (40)
Age, years**	45 (16–67)	50 (18–94)	68 (18–83)	52 (22–79)
Nonsmokers/smokers	19/1	39/11	18/3	8/2
Disease duration, weeks**	6,5 (2–46)	1 (1–9) $^{+}$	2 (1–8) $^{+}$	5 (2–9)

*ICEP – idiopathic chronic eosinophilic pneumonia, COP – community-acquired pneumonia, OP – organizing pneumonia. *Data presented in absolute numbers and percents (brackets), **data presented in median, maximum and minimum values (brackets). $^{+}$ $p < 0,001$ between ICEP and other groups*

Table 3. Complaints and auscultation data of the study patients.

Parameter	ICEP	COP	Asthmatics with COP	Cryptogenic OP
Fever, %	65	96 *	86	80
Cough, %	80	96 *	100 **	90
Dyspnoea, %	55	34	95 **	40
Chest pain, %	0	40 *	5	30 **
No rales, %	20	18	0 **	60 **
Wheeze, %	70	16 *	95 **	0 *
Fine rales, %	10	72 *	48 **	40

*ICEP – idiopathic chronic eosinophilic pneumonia, COP – community-acquired pneumonia, OP – organizing pneumonia. * $p < 0,001$ between ICEP and other groups, ** $p < 0,05$ between ICEP and other groups*

2.2. Methods

All patients were examined at the Centre of Pulmonology and Allergology of Vilnius University Hospital *Santariškių klinikos*, with written agreement for invasive examinations. Lung biopsy samples were examined at the National Centre of Pathology. Statistic data was processed at the Department of Mathematical Statistics of Vilnius Gediminas Technical University.

Demographic data and disease duration of the study patients before diagnosis establishment are shown in Table 2. Investigation of complains, blood, chest X-ray and respiratory function tests were performed for all patients.

Statistical data processing was performed by SPSS 15.0 programme. Data of different groups were compared according to *Mann-Whitney-Wilcoxon* test. Correlation was evaluated by the *Pearson* correlation coefficient.

3. Results

Patients with ICEP had minimum complaints in comparison to the patients from other groups (Table 3). None of them had chest pain. Lung auscultation revealed wheezing, rarely – fine rales. More often wheezing was found only in asthmatic patients with COP. Presence of wheezing correlated with the sense of the shortness of breath ($r = 0,42$, $p < 0,001$) and duration of the disease ($r = 0,23$, $p < 0,05$).

A large number of the blood eosinophils were the sole laboratory finding that distinguished ICEP patients from all other groups (Table 4). The number of blood eosinophils correlated with duration of the disease ($r = 0,2$, $p < 0,05$), but did not correlate with BAL fluid eosinophils.

Patients with ICEP more often had multiple lung infiltrations than patients with COP, but this difference was not statistically significant. However, patients with COP more often had infiltration of the adjacent lung segments (in one or adjacent lobes), compared to the CIEP patients, who had infiltration in the distant lung segments or lobes. This feature was characteristic for cryptogenic organizing pneumonia as well. Discrete lung infiltrations were revealed on the lung computer tomography scans. None of the CIEP patients had pleurisy (Table 5). These patients and asthmatic patients with COP often had epithelial and mucus plugs in bronchi revealed on the bronchoscopy. Sometimes these plugs were seen on lung computer tomography scans. Presence of the epithelial and mucus plugs had correlation with sense of dyspnoea ($r = 0,53$, $p < 0,05$) and a number of blood eosinophils ($r = 0,32$, $p < 0,05$). However, there were no significant differences in lung function indices between groups (Table 5). Forced expiratory volume in 1 second (FEV_1) correlated with oxygen partial pressure (PO_2) ($r = 0,8$, $p < 0,01$) and dioxide partial pressure (PCO_2) ($r = 0,79$, $p < 0,01$) indices.

Table 4. Blood tests data of the study patients.

Parameter	ICEP	COP	Asthmatics with COP	Cryptogenic OP
Leucocytes, 10^9 L	10,5 (6–23)	9,9 (2–26)	7,9 (3–23)	9,2 (5–21)
Eosinophils, 10^9 L	1,5 (0,01–10,2)	0,1 (0–1,3) *	0,1 (0–1,4) *	0,15 (0,04–0,5) *
Eosinophils, % L	14 (0–73)	1 (0–15) *	1 (0–19) *	2 (0–6) *
CRP, mg/L	47 (5–74)	100 (1–392) **	23 (3–212)	79 (1–112)
PO_2, mm Hg	61 (40–81)	60 (49–83)	61 (43–80)	58 (47–72)
PCO_2, mm Hg	39 (34–44)	38 (30–52)	38 (32–44)	39 (32–45)
SO_2, %	92 (76–97)	92 (83–98)	92 (80–95)	92 (81–96)

*ICEP – idiopathic chronic eosinophilic pneumonia, COP – community-acquired pneumonia, OP – organizing pneumonia. CRP – C reactive protein, PO_2 – oxygen partial pressure, PCO_2 – dioxide partial pressure, SO_2 – oxygen saturation. Results presented in median, maximum and minimum values (brackets). * $p < 0,001$ between ICEP and other groups, ** $p < 0,05$ between ICEP and other groups*

Table 5. Chest X-ray and spirometry tests data of the study patients.

Parameter	ICEP	COP	Asthmatics with COP	Cryptogenic OP
Single infiltration, %	60	76	76	60
Multiple infiltrations, %	40	24	24	40
Pleurisy, %	0	24 **	14	10
FVC, % pred. *	92 (50–111)	102 (71–142)	102 (47–130)	86 (55–117)
FEV_1, % pred. *	74 (46–105)	99 (60–137)	77 (46–123)	86 (54–118)
FEV_1/FVC, % *	75 (52–95)	79 (52–98)	72 (39–95)	81 (78–83)

*ICEP – idiopathic chronic eosinophilic pneumonia, COP – community-acquired pneumonia, OP – organizing pneumonia. FVC – forced vital capacity, FEV_1 – forced expiratory volume in 1 second. *Meanings presented in median, maximum and minimum values (brackets). **$p < 0,05$ between ICEP and others group. Pred. – predicted*

4. Discussion

We prospectively examined data of complaints, physical, blood, radiographic and respiratory function examination of 20 patients with idiopathic chronic eosinophilic pneumonia. Results were compared to community-acquired pneumonia and cryptogenic organizing pneumonia patients' data. The main results of the study are as follows; the clinical and radiological manifestation of ICEP was similar to COP and cryptogenic OP manifestation. We have found that chest pain; fine rales and pleurisy were unrepresentative for ICEP. However, blood eosinophilia was a typical sign of ICEP along with wheezing. Usually ICEP patients had relative mild clinical symptoms and a moderate increase in CRP levels even in the cases of multiple pulmonary infiltrates.

ICEP is a rare disorder, the exact prevalence remains unknown. Most published scientific studies are retrospective. Study groups usually consist of ten to thirty patients [13,25,30]. In children eosinophilic pneumonia is a more rare cause of lung disease. Several months of illness may continue before the correct diagnosis [31]. We have described previously the case of chronic eosinophilic pneumonia, which was diagnosed after 10 months of the disease onset, though a patient suffered from four relapses after initial manifestation [14]. In 50 percent of ICEP patients of this study the proper diagnosis was established later than after 2 months.

Chronic eosinophilic pneumonia should be differentiated from acute eosinophilic pneumonia, which is characterized by acute onset and short (usually up to 1 week) duration. It may be presented with mild symptoms and soft pulmonary infiltrates (*Loeffler* syndrome), or with acute respiratory distress syndrome [5,32]. Our experience shows that acute eosinophilic pneumonia with respiratory distress syndrome is a very rare disorder among our population. We have had only one such patient during the study period (not included in this study).

Clinical symptoms (cough, fever, dyspnoea) of our ICEP patients were similar to those described by previous authors [13,30]. We compared ICEP symptoms with symptoms of the similar pulmonary disorders. So we had found that chest pain and fine rales on lung auscultation were unrepresentative for ICEP. However, chest pain and fine rales are common symptoms of community-acquired pneumonia [26,33], but relapse is exceptional. As in other studies [12,34], patients with ICEP had moderate increased C reactive protein (CRP) level. While levels of CRP in community-acquired pneumonia may vary [35,36], we found that its level was significantly higher than in ICEP patients. CRP level in asthmatic patients with COP were not higher than of

ICEP patients and lower than in non-asthmatic patients with COP. It is likely, that severity of their condition (and hospitalization) was determined not only by pneumonia itself, but also exacerbation of asthma. However, the duration of pneumonia was not longer than usual.

Idiopathic chronic eosinophilic pneumonia is presented equally with single or multiple pulmonary infiltrates. Intensity of the infiltrates varies from ground glass to consolidation [37,38]. There was no pleurisy case in our ICEP group. Chronic eosinophilic pneumonia may be present with pleural effusion [39], but it is not a characteristic sign [37,38,40]. However, parapneumonic effusion is common for infectious pneumonia [26,33,41].

Relatively long duration of the disease (assumptive COP), i.e. the time for resolving of pulmonary infiltrates, may help to suspect chronic eosinophilic pneumonia (or organizing pneumonia as well). Duration of the disease of our study ICEP patients was significantly longer than of asthmatic and non-asthmatic patients with COP. There is no clear time definition of any resolving and slowly resolving pneumonia, but re-investigation based on specific individual condition is recommended [42].

Chronic eosinophilic pneumonia should always be distinguished with organizing pneumonia and tuberculosis [17,28]. Precise differential diagnosis between ICEP and other diseases was out of the scope of our study. The main purpose was to find signs, which allow suspecting that patient has non-infectious pneumonia. When the disease is suspected, further diagnostic pathway usually is simple – bronchoscopy with BAL and/or bronchoscopic lung biopsy. Previous authors [28] showed that distinction between high-resolution computed tomography findings in chronic eosinophilic pneumonia and bronchiolitis obliterans with organizing pneumonia can be made with confidence in only a small percentage of cases. Moreover, relapses occurred in more than half of the patients with cryptogenic OP [43].

About one third of ICEP patients have bronchial asthma [25]. Marchand et al. found that asthma was relatively severe and worsened after the diagnosis of ICEP. However the presence of asthma was associated with fewer relapses of ICEP, possibly due to the long-term inhaled corticosteroids in asthmatics [19]. In agreement with this finding we found that all three patients of our study who experienced several severe relapses were non-asthmatic.

In line with other authors [13,30,44] there was a finding of high blood eosinophilia and increased immunoglobulin E concentration. Pathogenesis of ICEP is still unclear. Idiopathic eosinophilic pneumonia may be recognized as an eosinophil-induced lung injury, and modulation of eosinophil accumulation and activation may be important in the pathophysiology of idiopathic eosinophilic pneumonia [45]. Eosinophil accumulation in the lungs in chronic eosinophilic pneumonia patients seems to be due to the selective migration of Th_2 lymphocytes to the lungs in response to an unknown trigger. Th_2 lymphocytes release increased amounts of interleukin 5 and other cytokines resulting in eosinophils migration to the lung [10,45,46]. Activation of the defensin-linked immune system suggests that inhaled antigen(s) may be involved in the pathogenesis of chronic eosinophilic pneumonia [47].

Due to reduced apoptosis (programmed cells death) eosinophils accumulated in the alveolar space and interstitium [48]. We have not found a correlation between blood and BAL fluid eosinophils count, possibly due to different eosinophils survival time in the blood and in the lungs, and heterogeneity of lung damage as well. Eosinophils released several tissue damaging mediators (e.g. eosinophilic cationic protein) [49,50]. They cause desquamation of airway epithelium cells and the formation of epithelium mucous plugs in bronchi, which may induce or worsen existing bronchial obstruction [16].

Relapses are the main complication during the course of chronic eosinophilic pneumonia. They may manifest as increasing blood eosinophilia, worsening of airway obstruction or new pulmonary infiltrates [30]. ICEP may progress to lung fibrosis [51].

There are certain limitations to our study. ICEP, cryptogenic OP and asthmatic patients with COP groups were relatively small. However, these disorders are rare themselves. Wheeze and airway obstruction in ICEP patients were found more often than other authors [13,30,34] reported. These differences may be due to natural variation in overall small groups in different studies. Alternatively, it is possible, that in some of our patients ICEP was first manifestation of Churg-Strauss syndrome, which will manifest in the future. Solans *et al*. [52] reported that of 32 cases of Churg-Strauss syndrome in all patients but one asthma symptoms preceded vasculitis development by between 6 months and 29 yr (mean 9 yr). So a careful follow-up of ICEP patients is essential.

In conclusion, it should be said that although idiopathic chronic eosinophilic pneumonia manifested clinically and radiologically similar to community-acquired pneumonia and cryptogenic organizing pneumonia, our study shows that there are some differences which allow suspecting chronic eosinophilic pneumonia. In the cases of non-typical pneumonia course, i.e. non-resolving or recurrent pulmonary infiltrates; relative mild clinical symptoms and moderate increased CRP level with multiple pulmonary infiltrates; blood eosinophilia and/

or signs of airway obstruction eosinophilic pneumonia should be suspected and bronchoalveolar lavage and/or bronchoscopic lung biopsy performed.

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