Clinical Characteristics of 20 Patients with Chronic Eosinophilic Pneumonia: A 6-year Retrospective Study

Yang Xu
Chinese PLA General Hospital

Zhanbo Wang
Chinese PLA General Hospital

Zhaorui Zhang
Chinese PLA General Hospital

Yu Dai
Chinese PLA General Hospital

Qiang Zhu
Chinese PLA General Hospital

Zhixin Liang (✉ liangzx301@126.com)
Chinese PLA General Hospital

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Abstract

**Background:** Chronic eosinophilic pneumonia (CEP) is a rare disease and there are few systematic studies on the disease. We summarized the clinical and pathological data of CEP to improve the understanding of the disease, as well as to reduce misdiagnosis and mistreatment.

**Methods:** The data of patients pathologically diagnosed as CEP in PLA General Hospital between May 2013 and May 2019 were collected, and the clinical manifestations, imaging characteristics, pathological features, treatment and prognosis were retrospectively analyzed.

**Results:** There were 20 patients with CEP, including 6 males and 14 females. The average age at the time of diagnosis was 47.0 ± 10.2 (22-83) years, and the average course of disease was 15.5 ±11.5 (2-72) months. The main clinical manifestations were cough, dyspnea, expectoration, and shortness of breath, and often accompanied by fever, weight loss, and asthenia. 19 patients had elevated peripheral blood eosinophils, with the proportion of eosinophils ranging from 5.3-64.7%, and the absolute value of eosinophils ranging from 0.72-14.43×10^9/L. 18 patients had increased proportion of eosinophils in bronchoalveolar lavage fluid (BALF), ranging from 12-67%, with an average of 46%. The main imaging features were patchy shadows, consolidated shadows, and ground glass shadows. The histological examination of bronchial mucosal biopsy indicated eosinophilic infiltration in submucosal tissues and the pulmonary biopsy indicated a large number of eosinophils infiltration in alveolar cavity and septum as the main pathological changes of CEP. All of 20 patients were treated with glucocorticoid, and one of them relapsed during follow-up.

**Conclusions:** The onset of CEP is insidious and the clinical manifestations are lack of specificity. Eosinophils increase in peripheral blood and BALF in most of CEP patients. The typical image is peripheral and subpleural distribution of lung infiltrates. The diagnosis of CEP depends on pathology, and glucocorticoid therapy is effective.

**Background**

Eosinophilic lung diseases (ELD) are a group of diseases characterized by different degrees of eosinophilic lung infiltration with or without increased eosinophils in the peripheral blood [1]. Chronic eosinophilic pneumonia (CEP) is a type of ELD first reported by Carrington in 1969 [2]. Due to the lack of specificity in the symptoms, signs and imaging manifestations of CEP, clinicians are inexperienced in the diagnosis and treatment of CEP, and thus these diseases are prone to missed diagnosis and misdiagnosis. CEP is a rare disease with unknown etiology, mostly reported in the form of individual case report, and there are few systematic studies on the disease. The data of 20 patients pathologically diagnosed as CEP in the Respiratory Department of PLA General Hospital between May 2013 and May 2019 were collected, and their clinical manifestations, imaging characteristics, pathological features, treatment and prognosis were retrospectively analyzed and summarized to improve the understanding of the CEP.
Methods

Setting

This study was performed at Chinese PLA General Hospital, a tertiary-care hospital in Beijing with more than 3400 beds and 200 thousand inpatients per year. The hospital provides medical service for both the military and the public.

Patients and design

20 patients who were pathologically diagnosed as CEP between May 2013 and May 2019 in the Respiratory Department of PLA General Hospital were included in the study. The clinical data of 20 patients with CEP were collected, analyzed and summarized; these data included general information, clinical symptoms and signs, laboratory examination, imaging examination, pulmonary function examination, bronchoscopy, cytological classification of bronchoalveolar lavage fluid, pathological examination, treatment and prognosis. All the records were checked twice by two researchers respectively to avoid mistakes.

Statistical analysis

SPSS software, version 20.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. The data conformed to normal distribution and are presented as the mean ± standard deviation.

Results

General conditions

In total, 20 patients pathologically diagnosed as CEP in Respiratory Department of PLA General Hospital between May 2013 and May 2019 were enrolled, including 6 males and 14 females, with a male-to-female ratio of 1:2.3. The age at the time of diagnosis was 22–83 years, with an average age of 47.0 ± 10.2 years. The course of disease varied between 2 months and 6 years, and the average course was 15.5 ± 11.5 months. 10 patients had a history of allergic diseases, of which 8 had a history of bronchial asthma before CEP diagnosis, 4 had allergic rhinitis or sinusitis and 8 had a history of drug or food allergy. With regards to misdiagnosis, among the 20 cases, 10 cases were misdiagnosed as pulmonary infection, 4 cases were misdiagnosed as pulmonary tuberculosis, 4 cases were misdiagnosed as bronchial asthma and 2 cases were misdiagnosed as pulmonary tumors (Table 1).


| Variable                      | patients with CEP(n = 20) |
|-------------------------------|---------------------------|
| Age (yr), mean ± SD (range)   | 47.0 ± 10.2 (22–83)       |
| Gender                        |                           |
| Male                          | 6                         |
| Female                        | 14                        |
| Course (mo), mean ± SD (range)| 15.5 ± 11.5 (2–72)        |
| Allergic diseases             |                           |
| Bronchial asthma              | 8                         |
| Allergic rhinitis or sinusitis| 4                         |
| Misdiagnosed diseases         |                           |
| Pulmonary infection           | 10                        |
| Pulmonary tuberculosis        | 4                         |
| Bronchial asthma              | 4                         |
| Pulmonary tumors              | 2                         |
| Symptoms                      |                           |
| Cough                         | 18                        |
| Dyspnea                       | 18                        |
| Expectoration                 | 10                        |
| Shortness of breath           | 9                         |
| Chest pain                    | 2                         |
| Hemoptysis                    | 1                         |
| Fever                         | 10                        |
| Weight loss                   | 4                         |
| Asthenia                      | 4                         |
| Skin urticaria                | 2                         |
| Night sweats                  | 1                         |
| Nausea                        | 1                         |
| Signs                         |                           |
Variable | patients with CEP(n = 20)
---|---
Moist rales and scattered wheeze. | 12
Lymphadenectasis | 1
Hepatosplenomegaly | 1

**Clinical manifestations**

The clinical symptoms of 20 patients with CEP were lack of specificity, and the common symptoms included cough (18/20 cases), dyspnea (18/20 cases), expectoration (10/20 cases), shortness of breath (9/20 cases), chest pain (2/20 cases), hemoptysis (1/20 cases), fever (10/20 cases), weight loss (4/20 cases), and asthenia (4/20 cases). Individual cases had night sweats, dry mouth and eyes, skin urticaria, nausea and other manifestations. More than half of the patients (12/20 cases) had wheezing and moist rales on auscultation of the lungs, while extrapulmonary signs included lymphadenectasis and hepatosplenomegaly were uncommon (Table 1).

**Laboratory examination**

A total of 19 patients (95%, 19/20 cases) had elevated peripheral blood eosinophils, with the proportion of eosinophils ranging from 5.3–64.7%, and the absolute value of eosinophils ranging from 0.72–14.43 × 10⁹/L. Among them, 12 patients (63.2%, 12/19 cases) had mild elevation of peripheral blood eosinophils, 5 patients (26.3%, 5/19 cases) had moderate elevation of eosinophils and 3 patients (15.8%, 3/19 cases) had severe elevation of eosinophils. In addition, 12 patients (60%, 12/20 cases) had elevated peripheral blood platelets, 9 patients (45%, 9/20 cases) had elevated C-reactive protein, 10 patients (50%, 10/20 cases) had elevated ESR and 12 patients (60%, 12/20 cases) had elevated IgE. There were no significant abnormalities in G test, GM test, tuberculosis-related examination and tumor-related examination in all patients.

**Arterial blood gas and pulmonary function examination**

All 20 patients underwent arterial blood gas analysis; 10 patients had hypoxemia and 10 patients had normal arterial blood gas. All 20 patients underwent pulmonary function tests, including 7 patients with restrictive ventilatory dysfunction, 6 patients with mixed ventilatory dysfunction, 5 patients with obstructive ventilatory dysfunction, 12 patients with decreased diffusion function and 2 patients with no obvious abnormalities in pulmonary function.

**Imaging findings**

Chest CT was performed in all 20 patients. 4 patients had unilateral distribution of pulmonary lesions and 16 patients had bilateral distribution. The lesions were mainly distributed in the periphery or subpleura (Fig. 1M and N). The main lesions were patchy shadows (Fig. 1A) in 12 cases, consolidated shadows (Fig. 1D) in 6 cases, and ground glass shadows (Fig. 1G) in 2 cases. Some patients had atypical lesions,
including one case with nodular shadows (Fig. 1I), one case with cavitary changes (Fig. 1K) and one cases with pleural effusion.

**Bronchoscopy and bronchoalveolar lavage**

All 20 patients underwent bronchoscopy, including 8 cases with congestion and edema of bronchial mucosa (Fig. 2A and B), 2 cases with local chronic inflammatory changes (Fig. 2C), 2 cases with granular or nodular protrusions of endotracheal membrane (Fig. 2D and E) and 8 cases without obvious abnormalities under bronchoscopy. All 20 patients underwent bronchoalveolar lavage, of which 18 patients had increased proportion of eosinophils in BALF, ranging from 12–67%, with an average of 46%.

**Pathological examination**

All 20 patients were confirmed as CEP by pathological examination. 12 cases underwent bronchoscopic biopsy, of which 10 cases demonstrated chronic bronchial mucosal inflammation with massive eosinophil infiltration (Fig. 3A and B), some cases showed eosinophilic abscess formation (Fig. 3C and D), and some cases had Charcot-Leyden crystals (Fig. 3D). Percutaneous lung biopsy was further performed in the other 10 cases (including 8 cases with no obvious abnormality under endoscopy and 2 cases with chronic mucosal inflammation by endoscopic biopsy). The histological examination of 10 cases indicated that there were various degrees of chronic inflammatory cell infiltration in the alveolar cavity and interstitium, and obvious eosinophil infiltration was observed (Fig. 3E and F). In addition, eosinophilic abscess formation (Fig. 3G and H) and Charcot-Leyden crystals were identified in some cases (Fig. 3H). Moreover, one patient with pleural effusion underwent puncture and drainage of pleural effusion fluid at the same time and fluid cytology examination also showed a large amount of eosinophil infiltration (Fig. 3I).

**Treatment and follow-up**

Glucocorticoid therapy was recommended and the starting dose of prednisone was 1.0 mg/kg-1 d-1 in all 20 patients. Intravenous methylprednisolone (dose equivalent to prednisone 1.0 mg/kg-1 d-1) was administered for 1–2 weeks after diagnosis; after reexamination of pulmonary imaging for improvement, oral methylprednisolone tablets (dose equivalent to prednisone 0.5 mg/kg-1 d-1) were given, and one tablet was reduced every two weeks. When the hormone was reduced to the maintenance dose (equivalent to 15 mg of prednisone), reduced one tablet per month and the total course of treatment was > 6 months. In 17 patients, the symptoms improved after 2–3 days of hormone treatment; in 16 patients, the proportion of eosinophils in peripheral blood decreased to normal after 3–5 days of hormone treatment, and the chest imaging improved in 14 patients after 1 week of treatment (Fig. 1B and E). In addition, the symptoms of all 20 patients improved after 2 weeks of hormone therapy, and the chest imaging improved significantly in 4 weeks (Fig. 1C, F, H, J, L and N). After 1–2 years of follow-up, 19 patients did not relapse; one patient discontinued medication by himself without following medical advice and was re-admitted later. Hormone therapy was given again and the condition improved.
Thereafter, the patient insisted on treatment for half a year and no recurrence occurred after 2 years of follow-up.

Discussion

ELDs are a group of diseases characterized by varying degrees of eosinophilic pulmonary infiltration or increased peripheral blood eosinophils [1]. ELDs can be classified into three categories according to whether there are clear pathogenic causes and vascular lesions [3]. The first category is ELDs with unknown pathogenic causes, including simple pulmonary eosinophilia, acute eosinophilic pneumonia, chronic eosinophilic pneumonia and idiopathic hypereosinophilic syndrome. Second category is ELDs with clear pathogenic causes, including parasitic infection, drug allergy and allergic bronchopulmonary aspergillosis. The third category is ELDs with vascular lesions, including allergic vasculitis and allergic eosinophilic granulomatous vasculitis.

CEP is a type of ELD of unknown etiology, and was first reported by Carrington in 1969 [2]. The epidemiology indicates that CEP is a rare disease with an incidence of < 1/100,000 [4], mostly reported in the form of individual case report, and there are few systematic studies on the disease. We summarized the clinical and pathological data of 20 patients pathologically diagnosed as CEP to improve the understanding of CEP, as well as to reduce misdiagnosis and mistreatment. In our study, the average age of 20 patients with CEP was 47.0 ± 10.2 years and the ratio of male to female was 1:2.3, which means that middle-aged women are more susceptible to CEP. The course of disease ranging between 2 months and 6 years, with an average course of 15.5 ± 11.5 months, which means CEP has a subacute or chronic onset. In our study, 50% patients had the history of allergic diseases, most commonly bronchial asthma, followed by allergic rhinitis and sinusitis, and CEP may be closely related to allergic diseases. 85% cases in our study were non-smokers, if smoking may play a protective role in the pathogenesis of CEP needs further investigation.

CEP has lack of specificity in the symptoms, and the main clinical manifestations were cough, dyspnea, expectoration, and shortness of breath, and often accompanied by fever, weight loss, and asthenia. CEP is mainly confined to the lung and respiratory tract, but also has mild extrapulmonary manifestations, such as pericardial effusion, arthralgia, neuropathy, nonspecific skin manifestations and abnormal liver function, which are easily confused with allergic eosinophilic granulomatous vasculitis or idiopathic hypereosinophilic syndrome [5, 6]. The symptoms of CEP are atypical and can be misdiagnosed as pneumonia, tuberculosis and lung cancer [7–9]. If there is antibiotic-refractory “pneumonia”, or “asthma” with poor therapeutic effect of inhaled hormones, or “tuberculosis” without improvement in anti-tuberculosis treatment, it is necessary to be vigilant against CEP.

In the present study, 95% patients had elevated peripheral blood eosinophils, with the proportion of eosinophils ranging from 5.3–64.7%. Therefor, the elevated peripheral blood eosinophils contribute to the diagnosis of CEP [10]. There were also a few patients with no elevation of eosinophils in peripheral blood, thus the patients with normal proportion of eosinophils in peripheral blood could not be excluded from
CEP. CEP may have non-specific anemia, increased platelets, C-reactive protein and erythrocyte sedimentation rate. Elevated serum IgE level was observed in some cases, suggesting the presence of allergic factors in some CEP patients.

Hypoxemia can occur in the acute phase of CEP. Among 20 patients, 10 patients had mild hypoxemia and 2 patients had carbon dioxide retention, which indicated that the infiltration of eosinophils in the lung had an impact on the respiratory physiology of patients. The main changes of pulmonary function in CEP are restrictive ventilation disorder and diffuse hypofunction, obstructive ventilation disorder may occur in patients with asthma, and some patients develop mixed ventilation dysfunction in later stage. After treatment, pulmonary function improved rapidly. Recent studies have revealed that reduced lung CO diffusivity is a significant predictor of disease subclinical activity and recurrence in CEP patients [11].

The lesions in the pulmonary imaging of 20 cases are bilateral, non-migratory with clear boundaries, and mainly distributed in the periphery or subpleura. The most common lesions were patchy shadows, followed by consolidation and ground glass shadows. Some cases had atypical changes, such as nodular shadows, atelectasis, cavity formation, and pleural effusion. The image manifestations of CEP are diverse and can be misdiagnosed. To some extent, the peripheral and subpleural distribution of lung infiltrates may contribute to the diagnosis of CEP.

Bronchoscopic examination of the 20 patients identified that congestion and edema of bronchial mucosa were the most common manifestations. Granular or nodular protrusions could be observed in the endotracheal membrane of few patients [12], which were caused by CEP invading the airway. In our study, 90% patients had the increased proportion of eosinophils in BALF, ranging from 12–67%, with an average of 46%. The proportion of eosinophils in BALF was increased in some patients without obvious abnormal changes under bronchoscopy, which reflected the important value of bronchoscopy alveolar lavage in the diagnosis of CEP. It has been reported that it is suggestive of CEP when the proportion of eosinophils in BALF is > 25% [13]. In our study, the proportion of eosinophils in BALF was < 25% in some cases, and the pathology of pulmonary puncture indicated CEP; thus the demarcation of 25% for the diagnosis of CEP may be stringent.

If the patient is suspected of CEP and the differential diagnosis is difficult, bronchial mucosal biopsy and pulmonary biopsy are recommended. The histological examination of bronchial mucosal biopsy indicated eosinophilic infiltration in submucosal tissues and pulmonary biopsy indicated a large number of eosinophils infiltration in alveolar cavity and septum as the main pathological changes of CEP [14, 15]. Aggregation of eosinophils and necrosis form an ‘eosinophilic abscess’ [16], and Charcot-Leyden crystals also can be found in some cases. The clinical and image manifestations of CEP are complex and diverse, and the diagnosis of CEP will be confirmed by pathology.

Glucocorticoid is the most effective drug for CEP [17]. There is no unified standard for the dosage and course of glucocorticoid therapy. It has been suggested that the initial dose of glucocorticoid therapy is prednisone 0.5-1 mg kg⁻¹ d⁻¹. There is a possibility of recurrence of CEP during the course of hormone reduction or after withdrawal. It was also reported that when the hormone was reduced to 15 mg, it was
easy for the disease to reoccur, thus the process of hormone reduction should be cautious. Previous retrospective studies demonstrated that the disease recurrence was prone to increase in < 6 months treatment. In our study, the initial dose of glucocorticoid treatment in 20 patients was methylprednisolone (dose equivalent to prednisone 1.0 mg/kg-1 d-1), intravenously used for 1–2 weeks. After chest imaging improved, oral methylprednisolone tablets (dose equivalent to prednisone 0.5 mg/kg-1 d-1) were used and gradually reduced to a minimum maintenance dose of 15 mg, and the total course of treatment was > 6 months. The overall therapeutic effect is good and can be recommended.

In recent years, there were a few case reports of successful treatment of CEP by suplatast tosilate due to intolerance of hormone therapy [18]. Suplatast tosilate is mainly used to treat asthma and allergic rhinitis, which can reduce IgE synthesis by inhibiting the production of interleukin-4 by T cells. It has also been reported that Omazu monoclonal antibody has a significant effect in the treatment of CEP [19–21]. Omazu monoclonal antibody is a new anti-IgE antibody used in asthma and other allergic diseases. The therapeutic mechanism of suplatast tosilate and Omazu in the treatment of CEP needs further study. Previous studies have reported that eosinophils play an important role in the occurrence and development of CEP and there are targeted drugs for eosinophil recruitment, eosinophil activation and eosinophil apoptosis induction [22, 23]. However, whether these drugs can be used in the treatment of CEP requires further investigation.

**Conclusion**

CEP is a rare disease and lack of typical clinical manifestations. If patients have respiratory symptoms lasting for > 2 weeks, increased eosinophils in BALF and/or peripheral blood, and chest imaging with non-segmental patchy shadows and solid shadows under subpleural or in the peripheral of the lung, the possibility of CEP should be considered. Because the clinical and image manifestations of CEP are complex and diverse, in cases with difficult diagnosis, CEP can be confirmed by pathology. Glucocorticoid is the most effective treatment for CEP, and the dose and time course of hormone therapy should be individualized. New monoclonal antibodies against eosinophilic inflammation can also provide a novel direction for the treatment of CEP, and actively investigating the etiology and pathogenesis can provide new ideas for diagnosis and treatment of CEP.

**Abbreviations**

CEP
chronic eosinophilic pneumonia; BALF:bronchoalveolar lavage fluid; ELD: eosinophilic lung diseases

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Chinese PLA General Hospital ethics committee (S2020-301).
Consent for publication

The patients provided written informed consent for publication.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

YX and ZBW made substantial contributions to analyze and interpret the patients’ data, and YX was a major contributor in writing the manuscript. ZXL made substantial contributions to conception and design. ZRZ and QZ performed the bronchoscopic examination. ZBW performed the pathological examination. DY made contribution to acquisition of imaging data. All authors read and approved the final manuscript.

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Figures
Figure 1

Pulmonary CT of chronic eosinophilic pneumonia. In case 1, pulmonary CT (A) showed scattered patchy shadows in both lungs. One-week after treatment with glucocorticoid, reexamination CT scan (B) showed
that patchy shadows were reduced. One-month after treatment with glucocorticoid, reexamination CT (C) showed that patchy shadows largely disappeared. In case 2, pulmonary CT scan (D) showed local pulmonary consolidation in the left lower lobe. One-week after treatment with glucocorticoid, reexamination CT scan (E) showed that the consolidation was reduced. One-month after treatment with glucocorticoid, reexamination CT scan (F) showed that the consolidation was further improved. In case 3, pulmonary CT scan (G) showed ground glass opacities in the left upper lobe. One-month after treatment with glucocorticoid, reexamination CT scan (H) showed that the ground glass opacities were completely absorbed. In case 4, pulmonary CT scan (I) showed scattered nodular shadows in both lower lungs. One-month after treatment with glucocorticoid, reexamination CT scan (J) showed that the nodular shadows largely disappeared. In case 5, pulmonary CT scan (K) showed a hollow lesion in the dorsal segment of the lower lobe of the right lung. One-month after treatment with glucocorticoid, reexamination CT scan (L) showed that the hollow lesion was absorbed. In case 6, pulmonary CT scan (M) showed multiple patches and solid changes in both lungs. The lesions were mainly distributed under subpleural and peripheral of the lung. One-month after treatment with glucocorticoid, reexamination CT scan (N) showed that the lesions of both lungs were reduced.
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Figure 2

Bronchoscopy of chronic eosinophilic pneumonia. A: Bronchoscopy revealed edema of the bronchial mucosa in the posterior segment of the upper lobe of the right lung and obstruction of the lumen with white necrosis; B: Bronchoscopy revealed hyperemia of the bronchial mucosa in the right middle segment, with scattered white membranous secretions on the mucosal surface; C: Bronchoscopy revealed chronic inflammatory changes locally in the bronchial mucosa, with multiple carbon deposition; D: Bronchoscopy revealed congestion and edema of the bronchial mucosa in the dorsal segment of the left lower lobe, with diffuse nodular protrusions on the mucosal surface; E: Bronchoscopy revealed diffuse granular protrusions on the mucosal surface of the left lower lobe bronchus; F: Reexamination bronchoscopy of Fig. 2E after one-month glucocorticoid therapy revealed a marked decrease in diffuse granular protrusions.
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Figure 3

The pathology of bronchoscopic biopsy and pulmonary biopsy of chronic eosinophilic pneumonia. A: Bronchoscopic pathological examination revealed chronic inflammation of respiratory epithelial mucosa with acute inflammation and granulation formation, and edema of the lamina propria with massive eosinophil infiltration. (Magnification×100); B: Bronchoscopic pathological examination revealed chronic inflammation of respiratory epithelial mucosa with acute inflammation and granulation formation, and edema of the lamina propria with massive eosinophil infiltration. (Magnification×200); C: Bronchoscopic biopsy revealed eosinophilic abscess formation with localized Charcot-Leyden crystals. (Magnification×100); D: Bronchoscopic biopsy revealed eosinophilic abscess formation with localized Charcot-Leyden crystals. (Magnification×200); E: Pulmonary biopsy showed local interstitial fibrous proliferation and acute and chronic inflammatory cell infiltration, and a large number of eosinophils infiltration in alveolar cavity and interstitium. (Magnification×100); F: Pulmonary biopsy showed local interstitial fibrous proliferation and acute and chronic inflammatory cell infiltration, and a large number of eosinophils infiltration in alveolar cavity and interstitium. (Magnification×200); G: Pulmonary biopsy revealed eosinophilic abscess formation with localized Charcot-Leyden crystals. (Magnification×100); H: Pulmonary biopsy revealed eosinophilic abscess formation with localized Charcot-Leyden crystals.
(Magnification×200); I: Cytological examination of pleural effusion fluid in chronic eosinophilic pneumonia. Cytological examination of pleural effusion fluid suggested a marked increase in eosinophils, up to 30%. (Magnification×400). Hematoxylin-eosin staining. Arrows indicate eosinophils and double arrows indicate Charcot-Leyden crystals.
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