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Hypereosinophilic obliterative bronchiolitis with an elevated level of serum CEA: a case report and a review of the literature

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Abstract. – A 44-year-old man presented with chronic, persistent cough and occasional wheezing. Airflow obstruction, blood eosinophilia and a remarkable elevated level of serum carcinoembryonic antigen (CEA) were found. Radiographic and pathological studies confirmed eosinophilic bronchiolitis. There was no evidence of neoplasms by extensive examinations. After a protracted oral steroid therapy, the blood eosinophil count, the serum CEA level and the lung lesions were all improved in parallel, whereas fixed airflow obstruction remained. This case was diagnosed as a new distinct syndrome, hypereosinophilic obliterative bronchiolits. Serum CEA and blood eosinophil cell count served as good markers of the disease condition for this syndrome.

Key Words:
Eosinophilic lung disease, Eosinophilia, Asthma, Obliterative bronchiolitis, Carcinoembryonic antigen.

Introduction

Eosinophilic lung disease shows a diverse spectrum of pulmonary disorders characterized by an increase in blood and/or lung eosinophils, idiopathic or secondary to different etiologies. It can be suspected based on either the finding of pulmonary disease with blood eosinophilia, bronchoalveolar lavage eosinophilia, or lung tissue eosinophilia on lung biopsy[1]. Eosinophilic bronchiolitis was first report in Japan, 2001[2]. Recently, Cordier et al[3] introduced a new syndrome as hypereosinophilic obliterative bronchiolits (HOB), defined by marked eosinophilia, persistent airflow obstruction and direct signs of bronchiolitis on radiographic study. We describe a case of chronic cough resembling the above characteristics and diagnosed as HOB.

Case Presentation

A 44-year-old man presented on September 14, 2012 with chronic, persistent cough and occasional wheezing. He had a history of allergic rhinitis over 10 years. As for lifestyle, he did not smoke. He kept no pets and had been employed as a cook for 20 years. Three months before his visit, the patient had had recurrent "asthma attacks" with mucous sputum, paroxysmal dyspnea and wheezing. The chest thin-section computed tomography (CT) showed diffuse ill-defined centrilobular nodules in both the upper lobes and the right middle lobes. He was diagnosed as "military tuberculosis" in a local tertiary hospital and received anti-tuberculosis therapy for 2 months. A follow-up chest CT demonstrated no radiological remission, and moreover, the patient's dyspnea intensified. Thus he was referred to our hospital.

On admission, his oxygen saturation at rest was 87% (on room air), and he was quite exhausted and had to keep a sitting position due to dyspnea and cough. There were wheezing and end-inspiratory rales in all lung lobes, with noncardiac murmur. Results of laboratory tests showed a white blood cell count of 8.63×10^9/L with a remarkable increasing eosinophil level, 2.31×10^9/L (26.81%), erythrocyte sedimentation rate of 6 mm after 1 hour, a total serum immunoglobulin E of 156 IU/mL, and a serum carcinoembryonic antigen (CEA) of 29.9 ng/mL. No bacteria or fungi were present on direct sputum

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smear or culture. Tuberculin skin test and interferon- release assay for *Mycobacterium tuberculosis* infection were negative, as were stool analysis for parasites and galactomannan testing for moulds. There was no positive finding when screening for rheumatoid factor, antinuclear antibody, anti-extractable nuclear antigen antibodies, antineutrophilic cytoplasmic antibodies and cold agglutination test.

Pulmonary function studies showed obstructive impairment that first-second forced expiratory volume (FEV_1) was 1.64 L (41% predicted), forced vital capacity (FVC) of 3.58 L (73% predicted) and a ratio of FEV_1 to FVC was 46%. High-resolution (HR) CT revealed bilateral diffuse poor-defined centrilobular nodules with some V-shaped or Y-shaped opacities, but no lesions in the interstitial areas (Figure 1A). Because of the unusual elevated level of serum CEA, [18F]-fluoro-2-deoxy-D-glucose positron emission tomography/CT scan was performed and the result ruled out pulmonary adenocarcinoma or other occult malignancies.

Bronchoscopy was performed on hospital day 3. Bronchoalveolar lavage fluid (BALF) cultures for bacteria and fungi were negative, and there was no evidence of *Mycobacterium Tuberculosis* either on BALF smears or by DNA-PCR test. A transbronchial lung biopsy (TBLB) from the right lower lobe disclosed prominent eosinophilic infiltration in bronchiolar submucosal region and adjacent alveolar tissue, which was pathologically consistent with eosinophilic bronchiolitis (EB) (Figure 2).

The patient received nebulized budesonide (1000 μg twice daily) since the date of admission, and intravenous methylprednisolone (MP, 40 mg once daily) was initiated immediately after the bronchoscopic examination. After the treatment, symptoms improved dramatically. Cough and dyspnea decreased in several days. A remarkable fall in both of blood eosinophil count and serum CEA titre was observed, as 0.34×10^9/L (4.44%) and 23.3 ng/mL, respectively. At the same time the patient took a second spirometric test, which also revealed improvement in FVC (4.28 L, 90% predicted), FEV_1 (2.43 L, 63% predicted), and FEV_1/FVC % (57%). Then the dose of MP was tapered by 4mg every other week and inhaled formoterol/budesonide took placed of nebulized budesonide. The clinical conditions of the patient came to complete remission and he was discharged.

He has been followed up as an outpatient for 28 months. The blood tests for eosinophil count and serum CEA level, and the spirometric test results show at Table I. When the dose of MP was prescribed as 12 mg once daily, a repeated chest HRCT scan showed obvious improvement in the shadows in the lung fields (Figure 1B), as well as lung function (FVC, 5.18 L; FEV_1, 3.57 L; FEV_1/FVC %, 69%). A "tight control" step-down strategy was carried out as an oral MP tapering dose of 4 mg every two months. While on 8mg alternate day of MP, he complained of recurrent dry cough and both of blood eosinophil cell count and serum CEA titre were slightly elevated as 0.83×10^9/L and 6.5 ng/mL, respectively. Transient increase in MP dose of 20 mg daily for 5 days and 12 mg daily for subsequent 2 weeks resulted in clinical manifestation and hematology test improvement. The oral corticosteroid therapy

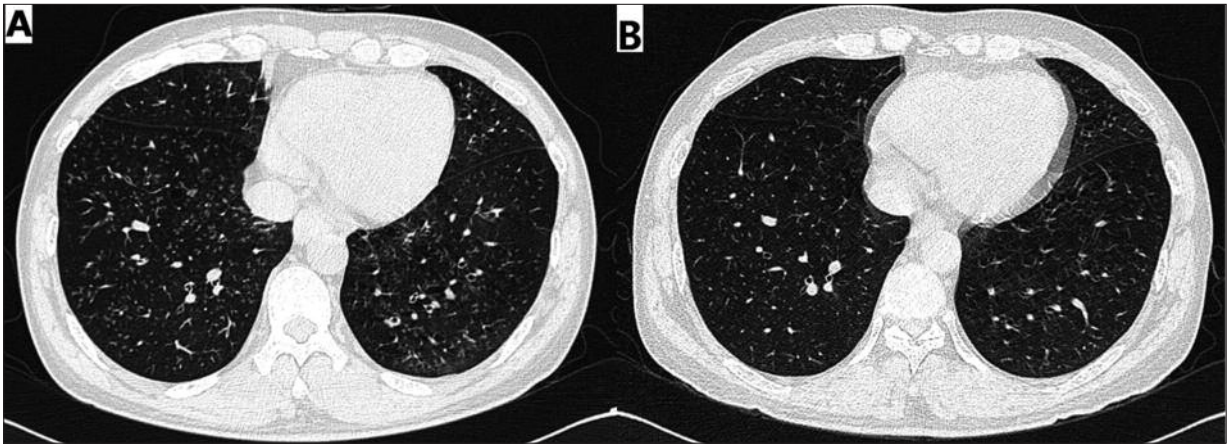

Figure 1. Radiographic findings: ***(A)*** on admission: diffuse poor-defined centrilobular nodules with some V-shaped or Y-shaped opacities in the both lung fields; ***(B)*** after oral steroid treatment: improvement of nodules and opacities.

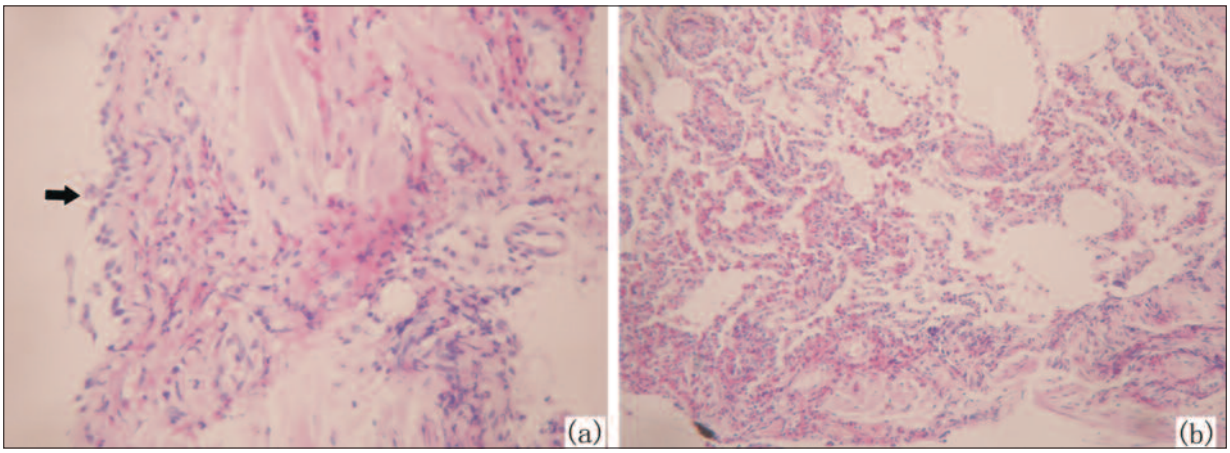

Figure 2. Pathological findings: ***(a)*** rich eosinophilic infiltrate in the bronchiolar submucosa region (the black arrow shows the epithelial layer of the bronchiole, HE staining × 200); ***(b)*** prominent eosinophilic infiltrate within adjacent alveoli (HE staining × 100).

has been prolonged until now, with inhaled corticosteroids and inhaled long-acting bronchodilators. At the last visit, the patient still received oral MP therapy with a dose of 8 mg per day, and airflow obstruction remained on pulmonary function test.

Literature Review

A literature search was performed in the electronic databases of PubMed with the term "eosinophilic bronchiolitis" from 1965 to December, 2014. One hundred and seventy-four papers were found in total, and after reviewing 7 isolated case reports of eosinophilic bronchiolitis (EB)[2,4-9] and 1 case series report of hypereosinophilic obliterative bronchiolitis (HOB)[3] were enrolled. Here, we collated the clinical files of the EB patients and analyzed as a case series (Table II).

Demographic Characteristics and Related Risk Factors

All patients were Asian, six from Japan and one from Taiwan. The disease appeared to occur more often in the middle ages (range 22-62 year-old, median age 46 year-old), without significant gender difference. Five patients had a history of bronchial asthma, and the rest showed airway hyperreactivity on lung function test. Sinusitis was the most common comorbidity (three out of seven patients).

Clinical Manifestations

Exertional dyspnea (six out of seven patients), productive cough (five out of seven patients) and recurrent wheezing (four out of seven patients) were the major symptoms expect for case 4. Typical asthma attacks had recurred in several cases until the patients showed ineffective response to

Table I. Changing of spirometric tests, eosinophil cell count and serum CEA level at admission (September, 2012), 2 weeks, 1 month, 2 months, 4 months, 6 months, 12 months and 28 months after methylprednisolone therapy (September, October, November, 2012; March, October, 2013; and January, 2015, respectively).

	09/15/12	09/28/12	10/08/12	11/05/12	01/10/13	03/12/13	10/15/13	01/14/15
Eos, 10^9/L	2.31	0.34	0.27	0.11	0.04	0.06	0.83	1.01
Eos, %	26.81	4.44	3.10	1.10	0.44	0.80	11.10	14.8
CEA, ng/ml	29.9	23.3	17	4.1	3.1	2.6	6.5	7.7
FVC, liters	3.58	4.28	–	5.18	5.05	5.10	–	4.86
FEV_1, liters	1.64	2.43	–	3.57	3.45	3.40	–	2.69
FEV_1/FVC, %	46	57	–	69	68	67	–	55
MP, mg/d	40	40	20	12	8	8/4	8*	8

Abbreviations: Eos: eosinophil; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; MP: methylprednisolone; 8/4: 8 mg/d and 4 mg/d alternatively; 8*: 8 mg every other day.

Table II. Clinical characteristics of patients with eosinophilic bronchiolitis (EB) reported in the previous studies.

Case Age Sex	Symptoms	History of atopy and/ or asthma	Serum Eos $\times 10^9$/L (%)	BALF Eos (%)	Total IgE (IU/ml)	Method of biopsy	Initial treatment	Outcome	Year Author
1 46 M	Dyspnea, wheeze, cough	- (Airway hyperreactivity +)	6.84 (57.0)	91	1548	Surgical (VAT)	Oral PSL 40 mg/d	Recurrence when OCS tapering	2001 Takayanagi[2]
2 23 M	Dyspnea, wheeze, cough	Hay fever (Airway hyperreactivity +)	1.74 (29.0)	32.2	350	Surgical (VAT)	Oral PSL 30 mg/d with ICS	Recurrence when OCS tapering	2003 Nakagome[4]
3 62 F	Dyspnea, cough	+; allergic rhinitis	1.11 (18.5)	Not tested	48	Surgical (VAT)	MP 80 mg/d iv.drip Later oral PSL with ICS	Recurrence when OCS tapering	2004 Nagata[5]
4 50 F	Chest shadow	+; eosinophilic sinusitis (surgery)	1.18 (15.9)	Not tested	655	Surgical (VAT)	Hydrocortisone iv.drip, later oral PSL 30 mg/d	No recurrence	2006 Tsuburai[6]
5 42 M	Dyspnea, cough	+; chronic sinusitis	1.68 (23.6)	91.4	122	Surgical	Oral PSL 30 mg/d	Recurrence when OCS tapering	2006 Morimoto[7]
6 56 F	Dyspnea, wheeze, cough	+; chronic sinusitis	2.9 (35.4)	68.7	411	TBLB	Oral PSL 40 mg/d with ICS	No recurrence	2010 Fukushima[8]
7 22 F	Dyspnea, wheeze, cough	+ (possible occupational)	No count available (47.0)	12	5700	Surgical	Pulse MP 1 g/d × 3 d; omalizumab 450 mg every 2 wks	Improved	2014 Wang[9]

Abbreviations: Eos: eosinophil; PSL: prednisolone; MP: methylprednisolone; ICS: inhaled corticosteroids; iv.drip: drip intravenous infusion; OCS: oral corticosteroids; VAT: video-associated thoracoscopic lung biopsy; TBLB: transbronchial lung biopsy. *Note:* all data enrolled were the maximum values in the clinical courses.

the standard treatments of asthma involving inhaled corticosteroids and inhaled long-acting bronchodilators. The mean duration from the onset to the diagnosis of EB was 3 years (range 3 months to 8 years). No patient presented eosinophilic-related, extra-respiratory, systemic manifestations. No clinical evidence of infections including virus, bacteria (especially *Mycobacterium tuberculosis*), molds and parasites were apparent at diagnosis. Case 1 and case 3 were diagnosed as diffuse panbronchiolitis (DPB) and had been receiving erythromycin therapy for 3 years and 1 year, respectively. However, serum eosinophilia was disclosed before medication. The others were not taking any drugs with possible iatrogenic eosinophilia outcome.

Laboratory Findings

Serum eosinophilia were observed in all the patients with a mean count of 2.58×10^9/L (range $1.11\text{-}6.84 \times 10^9$/L), while the BALF eosinophil count ranged from 12% to 91.4%. Sputum cytology study of three patients demonstrated abundant eosinophils in the airway secretion. C reactive protein was elevated in four patients with the maximum value of 50 mg/L. Two patients (case 1 and case 7) had a remarkable level of total IgE, but IgE specific to *Aspergillus fumigatus* was negative in all patients. Systemic immunology testing included antinuclear antibodies (positive in case 6 with a low titre) and antineutrophil cytoplasmic antibodies (all negative). Thus, no patient met the diagnostic criteria of allergic bronchopulmonary aspergillus (ABPA), connective tissue disease or systemic vasculitis. It is notable that case 4 had a significantly increased serum level of CEA (102.5 ng/ml) and, then, decreased after oral steroid therapy, compatible with the variation trend of blood eosinophil count.

Radiographic Findings

Centrilobular nodules as the direct sign of bronchiolitis were predominant abnormalities on CT in all patients. Thickening of bronchi on CT imaging was apparent in five patients, and atelectasis was discerned in case 4, both indicating chronic bronchitis with airway remodeling.

Pathological Findings

Lung specimens were obtained by surgery in six patients and transbronchial lung biopsy in one patient. The major features included massive eosinophil infiltration on the bronchiolar walls (all patients) with accumulation of eosinophils, plasma cells and lymphocytes within the bronchiolar lumina (four out of seven patients). The minor features included fibrous thickening of bronchioles (three out of seven patients), Charcot-Leyden crystals (two out of seven patients), eosinophil infiltration within the peribronchial region (two out of seven patients) and mucous plug at the bronchus (case 4). The above features were pathologically distinguished with the other bronchiolitis entities.

Spirometric Findings and Follow-Up

Irreversible airflow obstruction was the major disorder at diagnosis of EB in six patients (lung function test results were not available in case 7). Except case 7, systemic corticosteroid therapy, initiated at a dose of 30 mg-100 mg per day (prednisolone equivalent), resulted in a marked improvement in the clinical symptoms, radiographic findings and lung function, as well as the serum eosinophil count. However, the respiratory symptoms recurred during oral corticosteroid tapering in four patients, and one patient (case 3) remained airflow obstructive limitation after 2-year treatment with the FEV_1 to FVC ratio of 57%. For case 7, omalizumab was initiated because of rapid lung function deterioration and unusual elevated total IgE despite five courses of pulse methylprednisolone therapy at a dose of 1 g/day for successive 3 days.

Discussion

We have described a patient with eosinophilic bronchiolitis, persistent obstructive airflow limitation and elevated serum CEA titre. Bronchiolitis is an inflammatory process mainly centered in and around bronchiolar regions, with a sparing of a considerable portion of the other parenchymal structures[10,11]. The best way to establish a diagnosis of bronchiolitis is definitely a lung biopsy, but our patient refused the suggestion of thoracoscopic lung biopsy. However, we were still able to figure out the predominant lesion due to the correlation between HRCT manifestations and pathologic changes. Muller and Miller[12] classified the CT features of bronchiolitis into 3 patterns: 1) ground-glass attenuation and consolidation, 2) low attenuation and mosaic perfusion, and 3) centrilobular nodules and branching lines. The latter pattern corresponds pathologically to

the plugging of small airways or dilated bronchioles, which was characteristic in the radiographic imaging of the present case.

Adult bronchiolitis is less common and comprises a heterogeneous group of disorders which often manifest relatively chronic clinical course, impaired pulmonary function (obstructive and/or restrictive) with the aforementioned radiographic findings but nondiagnostic[10,11]. Etiologically, it is categorized as secondary and idiopathic or primary [13]. Secondary bronchiolitis is most common in almost all causes of pulmonary infections, hypersensitivity disorders such as bronchial asthma, ABPA, Churg-Strauss syndrome, the whole spectrum of smoking-related disorders, and neoplasms. While idiopathic or primary bronchiolitis is nonrelated to identifiable origins, most of which are defined pathologically and used in clinical diagnosis, for instance, cryptogenic constrictive bronchiolitis, DPB, bronchiolitis obliterans syndrome, cryptogenic organizing pneumonia (COP), etc. In the present case, according to the direct sign of bilateral diffuse centrilobular nodules without lung parenchymal involvement, a disorder located in the bronchioles was considered. Since there were no evidence of infections, connective tissue diseases, systemic vasculitis, or neoplasms, and the patient had no history of smoking, this disorder did not appear to relate to the above etiologies. In addition, he showed significant airflow limitation and had a poor response to the standard treatment for asthma, which made an impression that the bronchilitis was not secondary to chronic asthma. On the other hand, eosinophil-rich infiltrate on the histopathological examination was found higher than expected in typical cellular bronchiolitis; peribronchiolar fibrosis, granulomatous inflammation and foamy macrophages infiltrate in the bronchiolar lumina were absent, differentiating from constrictive bronchiolitis, COP and DPB, respectively[11]. Thus, an initial diagnosis of primary eosinophilic bronchiolitis was made.

The previous EB cases[2,4-9] share the following common characteristics: (1) asthmatic-like symptoms that response ineffectively to standard asthma treatment; (2) diffuse centrilobular nodules on CT imaging; (3) predominant eosinophil infiltration within the bronchiolar region on pathological examination with serum eosinophilia; (4) a prolonged oral corticosteroid therapy appeared to be necessary for correlation of airflow obstruction. Obviously, our patient resembles the previous EB cases in the aspects of radiographic and histological findings, whereas he did not have a history of bronchial asthma, and systemic corticosteroid plus inhaled therapy did not normalize the lung function. Therefore, the present case should be distinguished from pathological eosinophil bronchiolitis with asthma.

As mentioned above, Cordier et al[3] recently reported a series of cases termed as hypereosinophilic obliterative bronchiolits (HOB). This new syndrome is defined by: (1) blood hypereosinophilia > 1.0×10^9/L and/or BAL eosinophilia > 25%; (2) persistent airflow obstruction not improved by a prolonged course of inhaled bronchodilators and corticosteroids (200 ug/d of beclometasone or equivalent); and (3) characteristic direct signs of bronchiolitis on HRCT imaging and/or at lung biopsy. Its definition overlaps some features of EB, without emphasizing past illnesses (like atopy or asthma), or present symptoms (especially severe, chronic cough). Whether EB and HOB belong to the same spectrum of conditions require further studies.

HOB invokes the differential diagnosis of "severe asthma" easily, the concept of which is recently clarified as "asthma which requires treatment with high dose inhaled corticosteroids plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy" by The European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force[14]. From a pathological point of view, small bronchi and bronchioles may be involved in chronic asthma, specifically in a severe and persistent pattern. However, widespread centrilobular nodules are rarely observed in patients with asthma. There was supporting evidence in the study by Wenzel et al[15]. They described 10 patients with clinically severe asthma with radiographic lesions, and only one case demonstrated a tree-in-bud pattern on CT scan. Certainly, radiographic study plays an important role in differential diagnosis between HOB and severe asthma. In the present case, the clinical picture met the diagnostic criteria of HOB, and the patient's symptoms paralleled the CT findings with a long-term oral corticosteroid treatment. It is reasonable to consider that our case belongs to this distinct syndrome.

The unique information from the present case is the paralleled changing between serum CEA and blood eosinophil count. Serum CEA titre elevation is most often observed in the malignancies; yet in some benign inflammatory conditions

of respiratory or gastrointestinal tract, the titre may be slightly elevated, usually less than 10 ng/ml. Tsuburai et al[6] reported a case of eosinophilic bronchiolitis and sinusitis. Overexpression of CEA was found by immunohistochemistry in the mucous plugs and bronchial epithelial cells, as well as the sinus, resulting in the elevated serum level. Like the present case, both the clinical symptoms and the serum CEA level were improved by oral steroid therapy. From this point of view, serum CEA level appeared to be a good marker of the disease condition.

Conclusions

We described a case of hypereosinophilic obliterative bronchiolits with an elevated level of serum CEA. A long-term oral steroid treatment was effective and necessary for the clinical, radiographic and functional improvement. For the present case, serum CEA titre and blood eosinophil cell count were considered as good markers of the disease condition.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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