Fatal anaphylaxis in the presence of eosinophilic pneumonia in an asthmatic patient. A case report

Man Liang¹, Ananda Sunnasseet¹, Liu Yan¹, Na Zheng¹, Luo Zhuo¹, Zhang Haidong²*, Liu Liang²

Abstract: Eosinophilic pneumonia (EP) is a rare allergic syndrome. It has been subdivided into two types including acute eosinophilic pneumonia and chronic eosinophilic pneumonia. The pathology of EP is usually characterized by diffuse eosinophilic granulocyte infiltration in the lungs. We present the unusual case of a 39-year-old woman who died unexpectedly in hospital. She had a previous history of asthma and repeated hospital admissions. A fatal asthmatic attack was initially opined as the cause of death but autopsy disclosed that she died of anaphylactic shock in the presence of EP. Microscopic examination of organs and tissues showed eosinophilic granulocyte infiltration not only in the lungs, but also in the splenic sinuses, gastric mucosa and at the injection site on the skin of the dorsum of the hand. Patients with EP very rarely show eosinophilic granulocytes infiltration in locations other than the lungs. Her hypersensitive diathesis, injection infusion of a combination of a traditional Chinese drug and western drug and the presence of EP were together contributed to anaphylaxis and death.

Key words: Eosinophilic pneumonia, Anaphylactic shock, Eosinophilic granulocyte, Forensic pathology

Eosinophilic pneumonia (EP) is an allergic syndrome classified as either ‘acute eosinophilic pneumonia’ (AEP) or ‘chronic eosinophilic pneumonia’ (CEP) depending on the symptoms a person is experiencing. The majority of patients affected are middle-aged females, especially those with a hypersensitive diathesis. The incidence of AEP is estimated to be 9.1 per 100,000 person-years (95% confidence interval, 4.3-13.3), and death in these cases is usually due to respiratory failure [1]. Few individuals die of CEP [2].

Although a few clinical and epidemiological studies have been carried out [3], case reports and research articles concerning EP in forensic medicine are scarce. Patients with EP usually have a hypersensitive diathesis and they are more prone to anaphylaxis. We present this unusual case of unexpected death due to anaphylactic shock in the presence of EP after intravenous infusion of drugs regimen.

Case report

A 39-year-old Chinese woman who had a previous history of bronchial asthma, experienced dyspnea and tachypnea she was rushed and to a clinic found in her vicinity. Two weeks prior to this episode, she had been taking some cephalosporin antibiotic, aminophylline and a compound traditional Chinese medication called ‘Shuanhuanglian’, but she was not relieved.
At the clinic, she was treated with an intravenous infusion of 5% glucose solution containing 30 mL of ‘Shuanghuanglian’ and 10 mg of dexamethasone. Subsequently, she became pale, unconscious, and a weak pulse and shallow breath were noted. Cardiopulmonary resuscitation was attempted by the immediate personnel and 1 mg of adrenalin hydrochloride was given intramuscularly, but her response was not obvious.

With the help of emergency physicians, however, vital signs were restored, breathing and cardiac rhythm became stable and she was taken to a better equipped hospital. However, she died shortly after reaching the hospital. As no proper diagnosis could be given, the case was referred for forensic autopsy. Her medical records mentioned several admissions to hospital during the last two years for episodes of severe cough, occasional fever and night sweats, and a diagnosis of exacerbation of asthma was always made. She was successfully treated with corticosteroids, bronchodilators and antipyretics on every occasion.

**Autopsy findings**

Autopsy was carried out 3 days after death. External examination was unremarkable except for therapeutic scars. On internal examination, the upper airway was not edematous. A large amount of clear yellow liquid was noted in the trachea. About 60 ml of pale yellow liquid was collected from the left and right thorax altogether.

Adhesions were present on the visceral pleura of both lungs. The left and right lung weighed 563 g and 606 g respectively and the cut surfaces showed congestion, edema and focal hemorrhage. Large amount of mucus was present in the bronchus and bronchioles. Blood vessels in the brain and in the meninges were dilated and congested. The heart weighed 277g and no abnormalities of the coronary arteries were seen. Gross examinations of other organs were unremarkable.

**Histological findings**

Inflammatory cells, especially eosinophilic granulocytes, were found in the mucosa and submucosa of the trachea, bronchi, intratracheal and alveolar spaces (Fig. 1). Also, sporadic eosinophilic granulocyte infiltration was found in the submucosa of the laryngopharynx. Hypertrophy and hyperplasia of the mucus glands were noticed. Fusion of the pulmonary alveoli gave an emphysematous-like appearance.

Vessels in the myocardial interstitium were dilated and congested and a large number of eosinophilic granulocytes were also present. Focal eosinophilic granulocyte infiltration was observed in the subepithelium of the esophagus, and the blood vessels showed dilation and congestion.

Eosinophilic granulocytes were also seen at the portal tracts of the liver lobules, in the splenic sinuses, in the mucosa of the gastric fundus, in the intestinal subepithelium and at the injection site in the skin of the dorsum of the hand.

**Laboratory examinations**

Blood biochemistry results showed the following table (Table 1).

<table>
<thead>
<tr>
<th>Blood biochemistry</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgE</td>
<td>609 IU/mL (Normal Values 2-258 IU/mL)</td>
</tr>
<tr>
<td>Tryptase</td>
<td>26 ng/mL (Normal Values&lt;11.5 ng/mL)</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>11.2 g/dL</td>
</tr>
<tr>
<td>Platelet</td>
<td>290,000/mm³</td>
</tr>
<tr>
<td>WBC</td>
<td>12,900/mm³</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>77%</td>
</tr>
<tr>
<td>Monocytes</td>
<td>1%</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>14% (absolute count 2206/mm³)</td>
</tr>
<tr>
<td>Absolute Basophils</td>
<td>0%</td>
</tr>
<tr>
<td>ESR</td>
<td>161mm</td>
</tr>
</tbody>
</table>

**Table 1 Blood biochemistry results**

Blood sugar, urea, serum creatinine, liver function tests and urine microscopy were within normal limits.
Discussions

AEP is characterized by marked symptoms of fever, dyspnoea and hypoxemia. The disease is rapidly progressive (taking less than 1 month to develop) [4-6]. Very high numbers of eosinophils may be present in bronchoalveolar lavage (BAL) fluid and lung biopsy can reveal large numbers of eosinophils in the alveoli [7, 8].

Peripheral blood eosinophilia (eosinophil>6%) is the main finding which is accompanied by elevated serum total IgE level in two third of the patients. Chest radiograph and HRCT may show air-space consolidation, diffuse ground glass attenuation, septal lines and pleural effusions.

The criteria currently proposed for diagnosis of AEP are: (1) acute onset of symptoms, usually <7 days; (2) fever; (3) bilateral infiltrates on chest radiograph; (4) severe hypoxemia with PaO₂ <60 mmHg, and/or an alveolar-arterial gradient >40 mmHg; (5) pulmonary eosinophilia with >25% eosinophils in BAL fluid; (6) no history of hypersensitivity to drugs, no evidence of infection, and no other known cause of eosinophilic lung disease [15, 16].

However, Tazelaar et al. found that the duration of symptoms ranged between 1 and 30 days and exceeded 7 days in 7 patients. Thus, the diagnostic criteria of AEP should include duration of symptoms for up to 1 month [17]. A milder form of AEP without respiratory failure should also be taken into account.

CEP means that pulmonary eosinophilic infiltrates have a protracted course, persisting for several weeks or months, and even lasting more than 1 year if left untreated [9, 10]. Most patients are middle-aged and approximately 50% have asthma, which is usually of adult onset [11, 12]. The cause is usually unknown, hence the use of the term ‘cryptogenic pulmonary eosinophilia’ to describe the condition.

The clinical presentation is usually insidious with malaise, fever, night sweats and weight loss, which are often marked. Respiratory symptoms consist of dyspnoea, a dry cough and occasionally wheezing. Eosinophilic granulocytes counts often rise and infiltration is widespread in the lungs. Pathologically, there is infiltration of the interstitial tissues with predominantly eosinophils, but also with small and large mononuclear cells [13].

In approximately two thirds of patients, the chest radiograph shows a characteristic pattern of quite extensive air-space consolidation which is peripherally distributed [14]. The radiographic appearances together with a typical clinical picture and blood eosinophilia are usually sufficient to make the diagnosis.

There are no established diagnosis criteria for CEP. Diagnosis is usually based on the association of:

(1) respiratory symptoms of usually more than 2 weeks duration;
(2) alveolar and/or blood eosinophilia (expertises propose: alveolar eosinophilia 40% at bronchoalveolar differential cell count; blood eosinophilia 1000/mm³);
(3) pulmonary infiltrates with usually a peripheral predominance on chest imaging;
(4) exclusion of any known cause of eosinophilic lung disease [18].

In our case, the decedent was a middle-aged female with a typical history of bronchial asthma and because of her hypersensitive diathesis she was prone to allergies and anaphylaxis. The microscopic findings showed a large quantity of eosinophilic granulocytes in the mucosa and submucosa of the trachea, and bronchi and in the intratracheal and alveolar spaces. Also, blood biochemistry showed a high eosinophil count, increased ESR, a rather low hemoglobin level and an increased platelet count.
Taken together, the medical history, blood biochemistry and histological findings strongly suggested a diagnosis of eosinophilic pneumonia. Since the symptoms, such as dyspnoea and tachypnea, were present for more than 2 weeks, the decedent was assumed to have had CEP. However, no signs of respiratory failure were noted from the time of intravenous injection up to the agonal stage, and since the incidence of AEP is estimated to be 9.1 per 100,000 person-years, and very few individuals die of CEP [1, 2], it is rather unlikely that eosinophilic pneumonia was a direct cause of death but it definitely contributed to the patient’s demise.

Blood IgE and tryptase levels were increased, which highly suggests the presence of an allergic reaction. Tryptase is mainly released by mast cells, but other immune cells such as basophils and myeloblasts can also produce this enzyme. Eosinophil production of tryptase has not been described, and the lack of correlation between peripheral blood eosinophil counts and serum tryptase levels suggests that eosinophils are not the only source of the elevated serum tryptase in patients [19, 20].

Figure 1. Eosinophilic granulocytes infiltration in the mucosa and submucosa of the trachea, bronchi, intratracheal and alveolar spaces

Furthermore, besides the pulmonary symptoms, histopathological examination revealed eosinophilic granulocyte infiltration in the myocardial interstitium, the portal tracts of the liver lobules,
the splenic sinuses, the mucosa of the gastric fundus, and the injection site in the skin on the dorsum of the hand. Extra pulmonary infiltration of these immunity cells is commonly seen during anaphylaxis [21].

In the clinic, the traditional Chinese drug ‘Shuanhuanglian’ was administered in combination with dexamethasone.

The main ingredient of the medicinal drug ‘Shuanghuanglian’ is baicalin, which is a kind of flavonoids compounds. Baicalin has significant bioactivity including bacteriostasis, diuresis, anti-inflammatory and anti-allergy effects.

‘Shuanghuanglian’ has been used extensively in clinical practice. Some reports described that mixture of traditional Chinese medicine injection (TCMI) and pharmaceuticals increase the possibility of allergy as the number of drug particles add up significantly [22].

In our case, the dosage and way of administering this drug were according to protocol. The decedent was given a mixed injection of dexamethasone and shuanghuanglian, which induced a severe allergic reaction. Circulatory failure followed and she lost consciousness. This situation is typical of anaphylactic shock. The decedent had CEP and adding to her hypersensitive diathesis made her much more prone to allergies and anaphylaxis. The cause of death was attributed to anaphylactic shock in the presence of CEP.

As usual, during a forensic investigation, consideration should be given to the history, clinical data, presentation of the disease, radiological evaluation, and pathological findings. Distinguishing between eosinophilic pneumonia and other diseases is also important when dealing with similar complicated cases.

A differential diagnosis should include simple pulmonary eosinophilia (Löffler syndrome), allergic bronchopulmonary aspergillosis (APBA), drug reaction, parasitic infection, Churg-Strauss syndrome, cancer lymphagenesis and monaryaspergillosis [24].

Blood tryptase levels should always form part of the investigation in suspected cases of anaphylactic death. Features in the clinical history suggesting a general reaction should be considered before deciding between asthma and anaphylaxis as the cause of death.

References