Hypereosinophilic syndrome with pulmonary and cardiac involvement in a patient with asthma

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IDIOPATHIC HYPEREOSINOPHILIC SYNDROME is characterized by prolonged eosinophilia without an identifiable underlying cause and multiple-organ dysfunction, most frequently involving the heart, the central or peripheral nervous system and the lungs. We describe a case in which a patient with asthma who had idiopathic hypereosinophilic syndrome with pulmonary involvement presented with symptoms of pulmonary embolism and left ventricular thrombus.

Case

A 50-year-old nonsmoking white woman with bronchial asthma was admitted to hospital for reassessment of her recurring dry cough, chest tightness and wheezing. She reported a family history of asthma and a personal history of mild, persistent asthma and bronchospasm after viral upper respiratory tract infections for 20 years, without regular therapy.

In the years before the current admission, the patient had been admitted twice to hospital, for 6 and 7 days respectively, with symptoms of dry cough, chest tightness and wheezing diagnosed as asthma and confirmed by means of spirometry. During each admission she had been given inhalation therapy with bronchodilators and steroids to relieve her symptoms and discharged home. An unexplained elevation of her eosinophil count (> 4.00 × 10^9/L) had been noted incidentally during each stay.

In a third admission, 5 months before the current one, the patient had presented with dry cough, chest tightness, wheezing and chest pain. During that stay the arterial blood gas values revealed hypoxemia and hypocapnia (partial pressure of oxygen [PO2] 64.3 mm Hg and partial pressure of carbon dioxide [PCO2] 32.5 mm Hg), and a ventilation-perfusion scan indicated an intermediate probability of bilateral pulmonary microemboli. Subsequent Doppler ultrasonography of her legs was negative for deep vein thromboses, and protein C, protein S and anti-thrombin III levels were normal. Peripheral blood smears showed a markedly elevated eosinophil count (> 6.00 × 10^9/L) and an isolated IgE elevation (948 [normally < 240] µg/L). The patient reported no personal or family history of deep vein thrombo-sis or pulmonary embolism, but additional questioning revealed that, 10 years earlier, she had been investigated for dyspnea and had had an unidentified left ventricular mass detected incidentally on an echocardiogram that was presumed to be a thrombus. At that time she had declined thromboectomy and had not received other treatment or anticoagulation therapy and was lost to follow-up. During this third admission she was given heparin intravenously for 5 days and then oral warfarin therapy at discharge.

At the current admission the patient returned for reassessment of her lung disease. Her respiratory symptoms (shortness of breath, wheezing, dry cough and chest tightness) had gradually returned over the last 5 months, and she was unable to control them with her bronchodilators, which she used irregularly. She was afebrile and normotensive, but there was tachycardia (pulse 118 beats/min and regular), and her conjunctiva were hyperemic (diagnosed as scleritis at a later ophthalmologic consultation). Rhonchi were heard throughout her chest. In addition, her affect was flat, and she described symptoms of depression; a psychology consultation confirmed that her mood was low and that she was anxious.

Pulmonary function tests revealed a mild obstructive and moderate restrictive pattern (forced expiratory volume in 1 second [FEV1] 46%, forced vital capacity [FVC] 55%, ratio of FEV1 to FVC 72, mean maximum flow 38%, peak expiratory flow 53%, diffusing capacity of the lung for carbon monoxide [DLCO] 46% and DLCO adjusted for alveolar volume [DLCO/VA] 86%). Arterial blood gas values showed hypoxemia and hypocapnia (PO2 50.7 mm Hg, PCO2 32.3 mm Hg, pH 7.44, bicarbonate 22.9 mmol/L and oxygen saturation 87.7%). Chest radiography revealed bilateral hilar enlargement due to vascular engorgement (Fig.1).

Additional testing revealed that the total leukocyte count was normal (10.7 × 10^9/L) but that the eosinophil count was elevated (4.40 × 10^9/L [40.9% in the differential leukocyte count]). The erythrocyte sedimentation rate was elevated (50 mm/h), as was the serum IgE level (2527 µg/L). The creatinine kinase (CK) level and CK MB fraction were normal, and urinalysis, tests for rheumatological markers (rheumatoid factor, C-reactive protein, antinuclear antibodies and antineutrophil cytoplasmic autoantibody) and thyroid function tests yielded unremarkable results.
An electrocardiogram revealed nonspecific ST-segment and T-wave changes. Similar to echocardiography findings 10 years earlier, transthoracic echocardiography showed an enlarged left ventricle containing a large, floating mass, later interpreted on a transesophageal echocardiogram to be a left ventricular thrombus (Fig. 2). Doppler echocardiography revealed an increased pulmonary artery pressure of 35 mm Hg. A CT scan of the thorax showed bilateral infarcts, appearing as segmental band shadows. A ventilation-perfusion scan showed bilateral subsegmental perfusion defects consistent with those seen on the scan performed 5 months earlier. The patient was judged to have intermediate probability of a pulmonary embolus. Doppler ultrasonography of the lower extremities and pelvis did not reveal its source. A CT scan of the head appeared normal.

A diagnosis of asthma, pulmonary embolism and left ventricular thrombus was made, and the patient was given a bronchodilator (salbutamol) and warfarin. Investigations to look for causes of the eosinophilia (e.g., parasitosis, immunodeficiency and malignant disease) included stool microscopy, tumour marker assays (for carcinoembryonic antigen and cancer antigen (CA) 125, CA 19-9, CA 15-3 and CA 72-4), mammography, gastroduodenoscopy, bronchoscopy, abdominopelvic ultrasonography, and vaginal and pelvic examination; all yielded normal findings. Aerobic, anaerobic and fungal cultures of sputum and bronchoalveolar lavage fluid did not yield any organisms. Gram and acid-fast staining of bronchoalveolar lavage fluid yielded negative results for bacteria, but the percentage of eosinophils was more than 60% in the differential leukocyte count. Transbronchial and bronchial mucosal biopsies demonstrated submucosal eosinophilia (Fig. 3). Bone marrow aspiration biopsy revealed the percentage of eosinophils to be greater than 90% among other cells seen, but no other abnormality.

Because of the patient’s peripheral eosinophilia lasting longer than 6 months, the multiple-organ dysfunction and the exclusion of other causes of eosinophilia, a diagnosis of hypereosinophilic syndrome (HES) was made. The oral anticoagulant therapy was stopped, and oral therapy with the steroid deflazocort (60 mg/d) and the cytostatic agent hydroxyurea (1000 mg/d) was begun. Within 15–20 days the blood eosinophil count decreased, to 0.60 × 10⁹/L (6% on differential leukocyte count), and the patient was discharged home.

Five months later, during another hospital admission because of an episode of bronchospasm, the patient’s peripheral blood eosinophil count was found to be further decreased (0.02 × 10⁹/L) and the count in bone marrow aspirate had dramatically dropped, from 90% to 8%. Results of repeated tests for malignant disease and the primary causes of eosinophilia were again negative. Transthoracic echocardiography revealed that the cardiac thrombus was still present. She was given high-dose inhalation fluticasone therapy (2000 µg/d) and discharged home. The hydroxyurea therapy was continued. The oral deflazocort therapy was tapered over the following 3 months to a maintenance dose of 15 mg/d and then stopped within a few months. Her depression and anxiety required treatment with haloperidol and citalopram.

Two years after the HES was diagnosed, the patient’s left ventricular thrombus was still present. Atrial fibrillation (pulse 170 beats/min) and left ventricular failure developed, probably owing to reduced stroke volume and high pulmonary arterial pressures due to pulmonary vascular involvement.

Comments

This case is significant because it fulfills all of the main criteria of HES, but it involved a patient with a left ventricular thrombus and asthma, which may or may not have been related to the HES. The case is also unique because of the pulmonary involvement mimicking pulmonary embolism.

HES was first described in 1968, by Hardy and Anderson.1 The incidence of the syndrome is unknown. However, most district hospitals serving areas of about

Fig. 1: Chest radiograph on admission, showing hilar enlargement due to vascular engorgement.

Fig. 2: Transthoracic echocardiogram, showing large thrombus in left ventricle.
200,000 population can expect to see 1 or 2 new cases each year. In reported cases, HES affects white people more often than black people, and men 9 times more often than women, although the severity of the syndrome does not differ between the sexes. Any organ system may be involved, but cardiopulmonary and neurologic dysfunction are the usual causes of illness and death. The most serious involvements are endomyocardial fibrosis, myocardial infarction, left or right ventricular insufficiency and restrictive cardiomyopathy.

The basic pathology of HES is the sequestration of eosinophils in organ tissues or systems. Eosinophil-derived neurotoxin, eosinophil cationic protein and major basic protein are enzymes released by eosinophils that cause endothelial damage and promote fibrosis, thrombosis and infarction.

Pulmonary involvement can be seen in 40%–60% of cases. The most common respiratory symptom is chronic, persistent cough. The lung involvement results in nocturnal cough, productive sputum, wheezing and dyspnea, which raises the suspicion of bronchial hyperreactivity. Patients may be misdiagnosed as having asthma. However, pulmonary function tests typically reveal no airflow limitation. Although bronchospasm has been noted to occur in HES, sporadic cases of asthma have been reported to accompany HES. Pulmonary involvement may also be secondary to congestive heart failure or emboli originating from right ventricular thrombi or may reflect primary eosinophilic infiltration of lung parenchyma. Bronchoalveolar lavage may recover a large number of eosinophils in HES patients. In our patient, a cause of pulmonary embolism (e.g., deep vein thrombosis or a right ventricular mass) was not identified. Most cases of pulmonary embolism present with right ventricular involvement. However, our patient had left ventricular involvement. In HES, symptoms resembling those of pulmonary embolism usually result from the margination of a large number of eosinophils in the lung vasculature. This “thrombus,” which is subsequently detected clinically, is not therefore a true thrombus but rather an eosinophilic accumulation. We believe that this is what happened in our patient. The Task Force on Pulmonary Embolism of the European Society of Cardiology does not include HES as a risk factor for pulmonary embolism. Asthmatic symptoms may result from these marginalized eosinophils interfering with gas exchange and promoting mucus secretion.

When cardiac involvement occurs (in more than 60% of patients with HES), the most common finding is endomyocardial fibrosis. Thrombus may involve atrioventricular valve leaflets. Progressive scarring, especially on the posterior mitral valve, can most often be seen preventing its movement. Although cardiac involvement is best diagnosed by means of endomyocardial biopsy, this technique can have a high morbidity and mortality and be difficult to perform. Instead, a noninvasive procedure such as transesophageal echocardiography is valuable for detecting thrombus formation. Significant arrhythmia with chronic heart failure is often found in the late stages of HES, as happened in our case.

Neuropsychiatric symptoms are common in HES owing to involvement of the central nervous system. They often present as a loss of intellect, depressed mood and poor coordination. Although our patient’s CT head scan appeared normal, her neuropsychiatric symptoms may have resulted from microvascular eosinophilic occlusions originating from the left side of the heart. Peripheral neuropathy is also common in HES but was not experienced by our patient. Adie’s syndrome (pupillotonia), keratoconjunctivitis sicca and scleritis are the main forms of ocular involvement. Our patient did experience hyperemic conjunctivas and scleritis.

The differential diagnosis of hypereosinophilia includes malignant disease, parasitosis and other infections. Eosinophilic bronchitis is a common cause of chronic cough, occurring in up to 13% of patients with that symptom. However, eosinophilic bronchitis greatly differs from HES because it is not associated with peripheral

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**Fig. 3: Bronchial mucosa, with eosinophils (arrows) under bronchial epithelium (hematoxylin and eosin stain, magnification ×100).**
blood eosinophilia, or accumulation of eosinophils in bone marrow or in visceral organs, including the heart.

Eosinophilic leukemia is also in the differential diagnosis of HES, but we ruled it out in our case because of the patient’s long survival time of 10 years since her cardiac thrombus was detected, because she responded well to therapy and because atypical formation or blastic transformation of eosinophils was not detected.

Other conditions to be considered in the differential diagnosis of HES are chronic eosinophilic pneumonia and Churg–Strauss syndrome (a major cause of vasculitis associated with eosinophilia). An elevated IgE level can be found in either of these conditions. However, the former condition is limited to the lungs and characterized by peripheral pulmonary infiltrations, whereas HES typically occurs in more central organs and involves multiple viscera. Also, unlike in chronic eosinophilic pneumonia, the administration of cytotoxic agents (e.g., hydroxyurea, vincristine and alkylating agents) with or without steroids can provide long-lasting results in HES, causing pulmonary eosinophil infiltrates to gradually disappear. Although vasculitis is not a predominant feature of HES as it is with Churg–Strauss syndrome, patients with HES may exhibit pathological evidence of vasculitis. Churg–Strauss syndrome may involve similar organs to those affected by HES; however, the absence of renal involvement and the presence of bone marrow findings in our patient helped to distinguish HES from it.

Although anticoagulant therapy is not recommended in HES patients by some, because it has no effect on preventing further thrombosis, others encourage its use in HES patients with pulmonary embolism or another thrombotic process. In our case, we prescribed therapy with steroids and hydroxyurea after stopping the anticoagulant therapy of 6 months’ duration. Although the steroids and hydroxyurea did not appear to resolve the cardiac thrombus, the patient’s eosinophil counts in peripheral blood and bone marrow, as well as her respiratory symptoms, remained improved. Combinations of steroids and cytotoxic agents, interferon-α and bone marrow transplantation are other treatment strategies for HES that have been used with varying degrees of success.

In summary, HES can present nonspecifically, with multiple cutaneous, immunologic, ocular, rheumatologic and gastrointestinal manifestations. Physicians should consider HES in the differential diagnosis of patients presenting with scintigraphically demonstrated pulmonary embolism and blood eosinophilia. Although, as in our case, other comorbidities such as asthma can mask the accurate diagnosis of HES with pulmonary involvement, early diagnosis often leads to the most appropriate management.

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References


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