

CASE REPORT

Childhood Idiopathic Hypereosinophilic Syndrome: Report of a Case

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Idiopathic hypereosinophilic syndrome (HES) is a disease characterized by persistent elevation of blood eosinophils and diffuse organ infiltration by mature eosinophils. Specific criteria for idiopathic HES include an absolute eosinophil count (AEC) in the peripheral blood greater than $1,500/\text{mm}^3$ persisting for at least 6 months, and the presence of signs or symptoms of organ involvement without evidence of known causes.¹ Parasitic, allergic or other recognized causes of eosinophilia must be excluded.² Idiopathic HES is generally observed in middle-age adults with male predominance and a peak age of onset in the fifth decade,^{2,3} and has only rarely been reported in children. To our knowledge there has been no case report of childhood idiopathic HES in Taiwan.

We describe a 15-year-old girl presenting with symptomatic idiopathic HES, who responded well to treatment with prednisolone alone. Here we also review the prognostic factors, clinical characteristics, diagnosis and management of idiopathic HES in children.

SUMMARY We described a 15-year-old girl who presented with persistent fever, bilateral flank pain, and worsening dyspnea. The peripheral blood cell count showed remarkable eosinophilia at the time of admission. Severe pleural effusion with eosinophilic infiltrations as well as pericardial effusion were noted thereafter. Bone marrow examination disclosed markedly increased eosinophils. Bilateral ectasia of the renal pelvis was found in an ultrasonographic study of the kidneys. Spiking fever and progressive shortness of breath persisted despite treatment with empiric antibiotics for infection. Based on the clinical course and histological findings, a tentative diagnosis of idiopathic HES was made. After treatment with oral prednisolone daily (1 mg/kg/day) for one week, there was a rapid improvement in her clinical condition. She was discharged a few days later and the steroids were withdrawn gradually when she was asymptomatic. The absolute eosinophil count (AEC) was monitored during follow-up. At 3 weeks, the AEC had fallen from $8,060/\text{mm}^3$ to $4,792/\text{mm}^3$ and it further fell to $1,591/\text{mm}^3$ at 5 months, and to $855/\text{mm}^3$ at 8 months during follow-up. There is no evidence of any other organ involvement until now. The clinical manifestations, diagnosis and management of idiopathic HES in children are also reviewed.

CASE REPORT

A 15-year-old girl was referred to our hospital because of worsening shortness of breath and persistent high fever under the impression of acute pyelonephritis despite treatment with empiric antibiotics. There was no history of bronchial asthma and nasal allergy or any relevant traveling history regarding worm infestation.

On admission, her pulse rate was 122/minute, regular blood

pressure was 88/59 mmHg, respiratory rate was 36/minute and body temperature was 38.9°C. Physical examination revealed tachycardia, tachypnea, dyspnea, and mild lethargy. Moist rales were heard bilaterally in the lower parts of the pulmonary fields. Bilateral percussion pain over the costovertebral angles

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was also present.

A leukocytosis was found ($19,700/\text{mm}^3$) with eosinophils being responsible for 34% of the total leukocyte population. Her absolute eosinophil count (AEC) was $8,060/\text{mm}^3$. Serum creatinine kinase was 223 IU/l (normal 10-130 IU/l) with a muscle-brain fraction of 10% of the total creatinine kinase isoenzymes (normal 0-2%). Throat, urine, stool and parasites examinations were all negative. Serum immunoglobulins, except IgE (920 IU/ml), and complement factors were normal and antinuclear antibody (ANA) was negative. Serum eosinophilic cationic protein (ECP) was $23.4 \mu\text{g/ml}$ (normal $< 8 \mu\text{g/ml}$). Urine analysis showed pyuria (wbc, 8-10/HPF).

On the chest radiograph, a diffuse infiltrative shadow was observed bilaterally in the lower parts of the pulmonary fields. The cardiothoracic ratio was 45%. Renal ultrasound disclosed bilateral ectasia of the renal pelvis and an abdominal ultrasound uncovered moderate accumulation of ascites and mild hepatomegaly. Blood smears revealed significantly increased eosinophils without any signs of hemoparasites. Serial stool examinations for parasites were also negative.

Septic shock was considered initially owing to temporary consciousness changes, hypotension, prolonged capillary refilling time (> 3 seconds), and dyspnea. The symptoms and vital signs improved gradually following treatment with fluid resuscitation and intravenous inotropic agent (Dopamine) administration. Although her general condition was under control with inotropics and empiric antibiotic therapy, low grade fever and dyspnea still persisted, and even deteriorated on the fifth day of admission. The chest radiograph



Fig. 1 Chest radiograph reveals bilateral large pleural effusions, diffuse pulmonary infiltrates, and cardiomegaly (the cardiothoracic ratio is about 60%).

showed bilateral large pleural effusions and cardiomegaly (Fig. 1). The cardiothoracic ratio had increased to 60%. Two-dimensional echocardiography revealed a minimal accumulation of pericardial effusion (Fig. 2). Electrocardiography showed sinus tachycardia and mild ST elevation on lead V_2 - V_6 , I, II, and aVL. Cytologic analysis of pleural fluid revealed a significant eosinophilic infiltration (leukocyte count, $56/\mu\text{l}$, neutrophil, 25%, lymphocyte, 64%, eosinophil, 11%). Conversely, identical analysis of the

cerebrospinal fluid was normal without eosinophils. Bone marrow aspirates showed that 30% of the cells belonged to eosinophilic series; no blast cells were seen (Fig. 3).

On the basis of clinical manifestations, eosinophilia without a recognizable cause, a tentative diagnosis of idiopathic HES was made. She was then started on oral prednisolone (1 mg/kg/day). The symptoms and signs improved promptly within two days. The

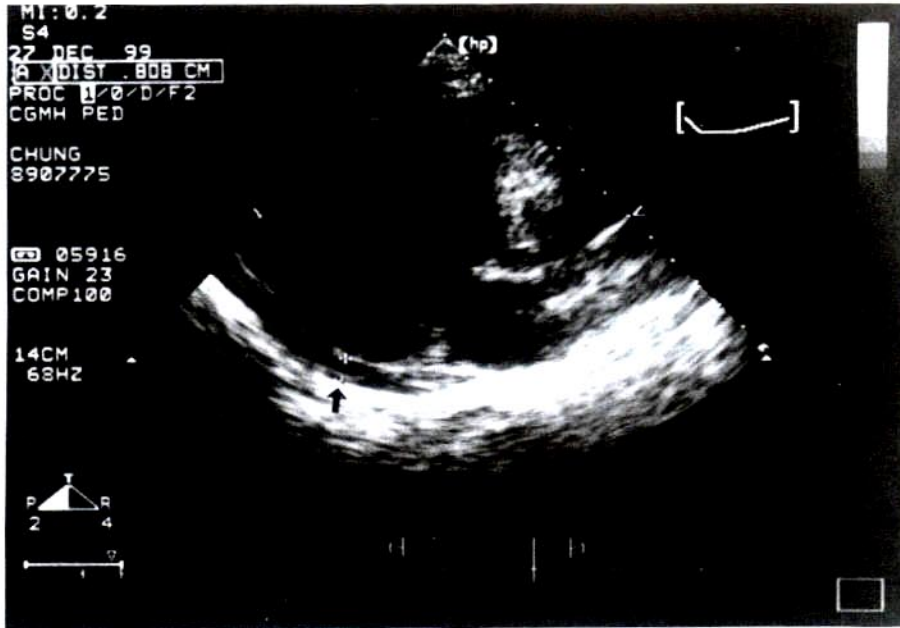


Fig. 2 Two-dimensional echocardiography demonstrates small amount of pericardial effusion (solid arrow) without obvious ventricular wall thickening.

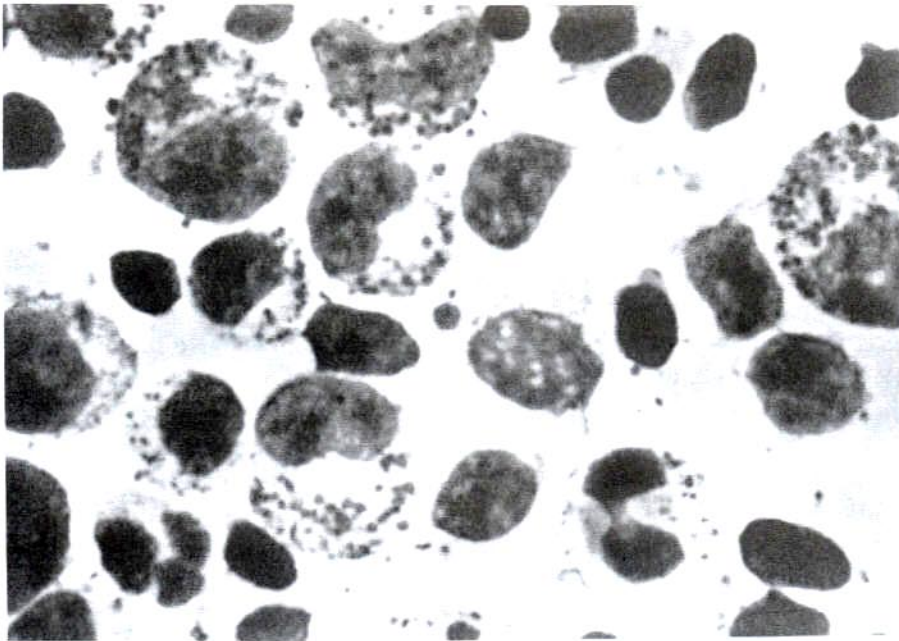


Fig. 3 Bone marrow aspirates showing 30% of cells belonging to eosinophilic series; no blast cells were seen (H & E, original magnification $\times 200$).

pleural and pericardial effusions decreased within a few days of treatment with prednisolone, and completely disappeared within one week. She was discharged a few

days later. After her dramatic clinical improvement the steroids were gradually withdrawn and finally stopped after two weeks. The absolute eosinophil count (AEC) was

monitored during follow-up. At 3 weeks, AEC dropped from 8,060/ mm^3 to 4,792/ mm^3 and further fell to 1,591/ mm^3 at 6 months, and 855/ mm^3 at 8 months tested in our

outpatient clinic. There was no evidence of any other organ involvement during the subsequent follow up.

DISCUSSION

Eosinophilia is commonly associated with allergic disorders, drug reactions, cutaneous diseases, and malignancies, particularly Hodgkin's disease and the non-Hodgkin's lymphomas. It is also found in vasculitis syndromes, myelogenous leukemias, necrosis of tissues following radiation, parasitic infestations, specific bacterial and viral infections, and immune deficiency disorders.² In addition, it may be uncovered in the idiopathic hypereosinophilic syndrome (HES).

The term idiopathic HES was actually first used in 1968,⁴ with defining criteria proposed in 1975.¹ As previously described, the diagnosis is often one of exclusions as there is no specific diagnostic test for idiopathic HES. Idiopathic HES has been described in all races. No family has been described with two or more affected members. In addition, idiopathic HES is more common in men than in women (by a 9:1 ratio) and tends to occur between the ages of 20 and 50 years, although some cases have been noted in children.^{1,2,5} Signs and symptoms of idiopathic HES have been described in several reviews⁵⁻⁷ and are variable, including fatigue, cough, dyspnea, myalgias, fever, skin rash, and "incidental" findings. Organ involvements include hematologic (100%), cardiovascular (58%), neurologic (54%), skin (56%), and pulmonary (49%).⁵

This etiology of idiopathic HES is unknown and authors have hypothesized as an autoimmune,⁷ malignant,⁸ and an exaggerated response to an initial eosinopoietic

stimulus. The factors that influence eosinophil production are, however, becoming clearer. Eosinophilia may be induced by interleukin-3 (IL-3), granulocyte-macrophage cloning-stimulating factor (GM-CSF), IL-4, and IL-5. IL-5 is specific for the eosinophil/basophil lineage, and is probably the principal regulator.^{9,10} The increased eosinophil production in idiopathic HES may be related to an intrinsic bone marrow defect or failure of peripheral tissue to inhibit the eosinophil response.⁷ However, no antigen has been identified. Hypothetical causes include abnormal responses to IL-5 or over production of IL-5, defects in receptors on eosinophil progenitor cells, abnormal proliferative responses leading to additional cell divisions, and abnormalities on feedback signals from tissues to regulatory cells.⁵

Over 50% of patients with idiopathic HES suffer from cardiac involvement leading to cardiac dysfunction, which is the leading cause of death in both children and adults.¹¹ It, therefore, follows that the endocardial surface is the main target organ damaged in patients with idiopathic HES, presumably due to the direct toxic effect of a major basic protein and other eosinophil-derived products on this cell layer. Pathologically, endocardial necrosis is found initially, followed by fibrin deposition and fibrosis.⁶ Thus, intracavitary fibrin clots result in outflow restriction or valve dysfunction.¹² Under these circumstances, clinical manifestations can include increased pulmonary and systemic venous pressure due to ventricular failure and systemic infarctions due to fibrin emboli. Our patient presented with mild cardiac involvement including myocarditis and a small accumulation of pericardial effusion leading to temporary cardiac dysfunction. No ventricular wall thickening or

thrombosis was found by echocardiography.

Neurologic involvement is also in found over 50% of patients with idiopathic HES. The neurologic complications may be divided into three types: primary central nervous system dysfunction, cerebrovascular accidents owing to systemic emboli, and peripheral neuropathy. Nevertheless, there was no neurologic manifestation in our patient.

Approximately 50% of patients with idiopathic HES suffer from pulmonary involvement. Pulmonary manifestations mainly include symptoms of cough and dyspnea, which may result from eosinophilic infiltration of pulmonary tissue as well as from congestive heart failure or pulmonary emboli. Clinical findings in children specifically include dyspnea, cough, pneumonia, pleural effusion, and pulmonary edema. Pulmonary findings in our patient included pulmonary edema and bilateral marked pleural effusions with eosinophilic infiltrations.

Cutaneous involvement is also seen in over 50% of the cases.⁵ Erythematous, pruritic papules and nodules of the trunk and extremities, urticaria, and angioedema have been described. Splenic, hepatic, ocular, and gastrointestinal involvements are also reported in about 20-40% of individuals.⁵ Mild hepatomegaly was noted in our patient.

Renal lesions are very rare. A review of renal changes in children² correlated proteinuria and hematuria clinically with postmortem changes of enlarged kidneys and renal infiltration with eosinophils. Still, bilateral pelviectasis with pyuria was uncovered in our patient under the impression of acute pyelonephritis without positive

results from bacterial urine culture.

The differential diagnosis of idiopathic HES includes several conditions associated with eosinophilia, such as allergic disorders, parasitic infestations, neoplastic disorders, and so forth.² Most eosinophilic syndromes are limited to specific organs, such as eosinophilic pneumonia or eosinophilic gastroenteritis, and characteristically do not extend beyond their own target organ, and hence lack the multi-organ involvement often found with idiopathic HES. These distinct eosinophilic syndromes, therefore, can usually be separated from idiopathic HES. Eosinophilic syndromes with multi-organ involvement mainly include idiopathic HES, eosinophilic leukemia, Churg-Strauss syndrome, and the autoimmune lymphoproliferative syndrome (ALPS). Eosinophilic leukemia is characterized by pronounced and persistent eosinophilia with immature forms, either in the peripheral blood or bone marrow; more than 5% blast forms in the bone marrow and tissue infiltration by immature cells of predominantly eosinophilic type.^{2,13} There were no blast cells in our patient's blood smear and bone marrow aspirates. Churg-Strauss syndrome is characterized by peripheral blood hypereosinophilia, systemic necrotizing vasculitis, mononeuropathy or polyneuropathy, and a preceding history of bronchial asthma. No neurologic involvement and asthma history were disclosed in this case. Autoimmune lymphoproliferative syndrome (ALPS) is a rare, newly recognized, defective lymphocyte apoptosis disorder and is characterized by lymphadenopathy, splenomegaly, pancytopenia, autoimmune phenomena, expansion of double-negative T lymphocytes (TCR $\alpha\beta$ ⁺, CD4⁻ CD8⁻), and eosinophilia.¹⁴ The defect in this

disorder involves the Fas-Fas ligand cell death pathway which contributes to the lymphoproliferation as well as eosinophilia.¹⁵ No lymphadenopathy or splenomegaly or pancytopenia or autoantibodies were found in this patient.

The diagnosis of idiopathic HES requires that eosinophilias of identifiable etiologies be excluded. These include eosinophilia eliciting parasitic infestations that are caused by helminthic parasites. However, some tissue- or blood-dwelling helminthes can not be detected by serial stool examinations like filarial infections, trichinosis, strongyloidiasis and particularly in children with visceral larva migrans caused by *Toxocara canis*, a round worm from the household dog. However, infection of *Toxocara canis* is very rare in Taiwan. Serologic tests for the specific parasites were not available in our hospital.

In patients with eosinophilia that lack evidence of organ involvement, specific therapy is not necessary. Such patients with apparently benign hypereosinophilia do not require any therapeutic interventions. Symptomatic patients with idiopathic HES usually respond well to corticosteroid therapy. Treatment with hydroxyurea, vincristine, alkylating agents, α -interferon, and cyclosporin may slow the disease progress or reduce relapses.^{5,16} Untreated, many of these patients progress toward severe Loeffler's fibroblastic endocarditis with heart failure caused by valvular damage and restrictive heart failure.¹⁶ Cardiac surgery such as valve replacement may be necessary.

In summary, since the definition of idiopathic HES is not etiologic but rather empiric, diverse disorders, characterized by a dys-

regulation in eosinophil dynamics resulting in sustained eosinophilia, have been grouped under this entity. The heterogeneity of patients with idiopathic HES ranges from those with favorable prognostic features containing increases in IgE, angioedema, and corticosteroid-responsive eosinophilia, to those with unfavorable prognostic factors including pronounced leukocytosis, congestive heart failure, myeloblasts in peripheral blood, splenomegaly, increased vitamin B₁₂ levels, abnormal leukocyte alkaline phosphatase activity, and cytogenetic abnormalities.¹ Our patient presented sustained eosinophilia for more than 6 months, myocarditis with pericardial effusion, pulmonary edema with bilateral massive pleural effusions, and remarkable eosinophilia without recognized causes in the bone marrow and peripheral blood.

Although the mortality of patients with idiopathic HES is high, early identification and aggressive treatment can result in significant clinical benefit and improved prognosis in children with this syndrome.

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