

PEDIATRIC HYPEREOSINOPHILIC SYNDROME (HES) DIFFERS FROM ADULT HES

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The idiopathic hypereosinophilic syndrome (HES) developed in a 15-year-old boy who presented with colitis, cough, rash, and hepatitis. Molecular analysis failed to demonstrate the Fip1-like1-Platelet Derived Growth Factor Receptor α chain (FIP1L1-PDGFRA) mutation described in adult patients with HES. There are significant clinical differences between the pediatric and adult presentations of HES. (*J Pediatr* 2005;146:134-6)

Idiopathic HES is a rare disorder characterized by eosinophilia $>1500/\text{mm}^3$ for longer than 6 months, no evidence of known causes of eosinophilia, and evidence of organ involvement.¹ Virtually any organ can be involved with HES. This disorder commonly occurs between 20 and 50 years of age and is more common among males than females. We report a case of pediatric HES, describe our patient's clinical outcome, and highlight differences between pediatric and adult HES based on a literature review.

CASE REPORT

A 15 year-old Caucasian male presented with abdominal pain, diarrhea, and a 10-lb weight loss. Colonoscopy revealed neutrophilic infiltration of the colonic mucosa with crypt abscesses in the epithelium and lamina propria consistent with chronic active colitis. Stool was positive for *Clostridium difficile* toxin, attributed to chronic minocycline use for acne, and was negative for ova and parasites. A complete blood count revealed an absolute eosinophil count of 1890 (normal $<400/\text{mm}^3$). The patient was treated with metronidazole and was asymptomatic for 6 months. He then developed a nonproductive cough, night sweats, and a diffuse pruritic, papular rash. Computed tomography of the chest showed small peripheral pulmonary nodules and ground glass opacities. A complete blood count revealed an absolute eosinophil count of 52,000/ mm^3 . Additional lab studies revealed an IgE level of 8561 (7-110 U/mL), alkaline phosphatase of 1149 (50-280 U/mL), γ -glutamyl transpeptidase of 193 (0-50 U/mL), serum tryptase of 4.7 (1.9-13.5 $\mu\text{g/L}$), and B12 level of 475 (221-700 pg/mL). Ultrasonography of the liver showed a diffusely abnormal parenchymal pattern with echogenic linear radiating bands of density and dilated bile ducts in the left lobe. Echocardiography was normal. Molecular analysis of the patient's peripheral blood for the Fip1-like1-Platelet Derived Growth Factor Receptor α chain (FIP1L1-PDGFRA) fusion tyrosine kinase associated with HES in 9 of 16 adults² was negative.

Open lung biopsy showed patchy interstitial and intra-alveolar inflammation with a predominance of eosinophils. Skin biopsy showed acute neutrophilic folliculitis with perivascular dermatitis with eosinophils. Neither biopsy revealed evidence of vasculitis. Bone marrow biopsy demonstrated a hypercellular marrow with predominantly eosinophils and no blasts, consistent with idiopathic HES. No bone marrow mastocytosis or morphologically abnormal mast cells were noted. Karyotype was normal. Physical exam at that time was significant for erythematous, pruritic papules on the skin, a normal cardiac exam, no splenomegaly, and no neurologic abnormalities.

The patient was started on prednisone 60 mg orally daily. One week later his absolute eosinophil count was 110/ mm^3 . Tapering prednisone to <10 mg orally daily led to consistent recurrence of eosinophilia and symptoms. Therapy with imatinib mesylate (Gleevec, Novartis, Basel, Switzerland) starting at 100 mg orally daily and increased to 300 mg orally daily was not effective in controlling eosinophilia in the absence of prednisone.

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|---------------|---|-----|----------------------------|
| FIP1L1-PDGFRA | Fip1-like1-Platelet Derived Growth Factor Receptor α chain | HES | Hypereosinophilic syndrome |
|---------------|---|-----|----------------------------|

Table I. Demographic information, presenting symptoms, and organ system involvement of 38 cases of pediatric HES

| | Number | Percent |
|-------------------------|--|---------|
| Age | Mean = 8.2 years Range = 1–16 years | |
| Sex | | |
| Male | 21 | 55.3 |
| Female | 17 | 44.7 |
| Presenting symptoms* | | |
| Fever | 20 | 58.8 |
| Arthralgias | 8 | 23.5 |
| Fatigue | 8 | 23.5 |
| Rash | 8 | 23.5 |
| Cough | 7 | 20.6 |
| Neurologic symptoms | 6 | 17.6 |
| Dyspnea | 6 | 17.6 |
| Diarrhea | 5 | 14.7 |
| Abdominal pain | 4 | 11.8 |
| Vomiting | 4 | 11.8 |
| Headache | 4 | 11.8 |
| Sore throat | 4 | 11.8 |
| Organs involved | | |
| Heart | 27 | 71.0 |
| Lungs | 21 | 55.3 |
| Skin | 13 | 34.2 |
| Nervous system | 10 | 26.3 |
| Gastrointestinal | 8 | 21.0 |
| Associated with ALL | 14 | 36.8 |
| Chromosomal abnormality | 7 | 18.4 |

ALL, acute lymphoblastic leukemia.

*Data not available for 4 patients.

DISCUSSION

A search of the literature for “pediatric hypereosinophilic syndrome” or “child hypereosinophilic syndrome” revealed 38 cases reported in the English language (Table I).^{1,4-23} Pediatric HES has only a slight male predominance (55.3% male vs 44.7% female), whereas adult HES is reported to be more common among males than females, in a ratio of 9 to 1.¹ In the adult literature, the frequencies of symptoms found on presentation are: fatigue (26%), cough (24%), dyspnea (16%), rash (12%), and fever (12%).³ We found that fever (58.8%), arthralgias (23.5%), and rash (23.5%) were more common presenting symptoms in pediatric cases. Of note, headache and sore throat were not uncommon presenting symptoms (11.8% each). As with adults, involvement of the cardiovascular system is the major source of morbidity and mortality.

Pediatric HES is commonly associated with chromosomal abnormalities, including trisomy 8 and a translocation involving the *abl* oncogene.⁵⁻⁹ In almost 40% of reported cases, pediatric HES has been associated with acute leukemia, especially acute lymphoblastic leukemia.^{4-6,10-12} The goal of therapy in patients with HES is to lower the eosinophil count

Table II. Treatment, response, and morbidity/mortality of 38 cases of pediatric HES

| Treatment* | Number | Percent | Response to treatment‡ |
|------------------|--------|---------|--|
| Corticosteroids | 28 | 84.8 | 11/28 responded as monotherapy or in conjunction with hydroxyurea, cyclophosphamide, vincristine, methotrexate, and/or cyclosporin |
| Vincristine | 9 | 27.3 | 4/9 responded in conjunction with prednisone, hydroxyurea, and/or 6-MP |
| 6-mercaptopurine | 4 | 12.1 | 1/4 responded in conjunction with vincristine |
| Hydroxyurea | 3 | 9.1 | 2/3 responded in conjunction with prednisone and vincristine |
| ACTH | 3 | 9.1 | 2/3 responded as monotherapy |
| Busulfan | 2 | 6.1 | 0/2 responded as monotherapy |
| Methotrexate | 2 | 6.1 | 1/2 responded in conjunction with prednisone and cyclosporine |
| Cyclophosphamide | 2 | 6.1 | 1/2 responded in conjunction with prednisone |
| Cyclosporin | 2 | 6.1 | 1/2 responded in conjunction with prednisone and methotrexate |
| Interferon-α | 1 | 3 | 1/1 responded as monotherapy |
| Outcome† | | | |
| Alive | 15 | 41.7 | |
| Expired | 21 | 58.3 | |

ACTH, adrenocorticotropic hormone; 6-MP, 6-mercaptopurine.

*Data not available for 5 patients.

†Data not available for 2 patients. Numbers reported are at the time of publication. Of the 21 expired patients, no data were available for 3 patients in regards to survival time. The mean length of survival was 10.6 months from the time of diagnosis in the remaining 18 patients (range 0.5-42 months).

‡Response defined as patient alive at time of publication.

and prevent organ dysfunction. Corticosteroids are the initial treatment of choice. For children unresponsive to steroids, agents such as hydroxyurea, vincristine, mercaptopurine, and, recently, interferon-α have been used^{13,14,30} (Table II).

Monoclonal anti-IL-5 antibody therapy may be an important therapeutic option, although it has not yet been tested in pediatric HES.²⁷⁻²⁹

A novel tyrosine kinase created by the fusion of the FIP1L1 and PDGFRA genes has been recently described in patients with HES.² This fusion protein is the result of an interstitial deletion on chromosome 4 and is a target of the tyrosine kinase inhibitor imatinib mesylate. Thus, a positive therapeutic response to imatinib is likely if this fusion protein is identified, although patients have responded to imatinib even if no fusion protein is identified. Patients with the FIP1L1-PDGFR gene are likely to have the myeloproliferative variant of HES, as opposed to the lymphoproliferative (eg, T-cell clone overproducing interleukin-5 leading to eosinophilia) or otherwise unclassified forms of the disease.²⁶ No pediatric case with the FIP1L1-PDGFR fusion gene has been reported to date.

Long-term prognosis has not been reported in pediatric HES. However, information was available for 36 of the 38 cases we reviewed; 15 patients were reported to be alive at the time their cases were published, whereas 21 had expired. Of these 21 patients, no data were available for 3 patients regarding survival. The mean length of survival was 10.6 months (range 0.2-42 months) from the time of diagnosis in the remaining 18 patients. In the adult HES population, with earlier diagnosis and intensive follow-up, the survival of HES patients has improved over the years. In 1975 Chusid et al reported a mean survival of 9 months and a 3-year survival of 12%.¹ In a series of 40 patients with HES published in 1989, an 80% survival at 5 years and a 42% survival at 15 years was reported.²⁴

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