

Case Report

Large T-cell lymphoma in a 13-year-old girl with hyperimmunoglobulinemia E syndrome

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Large T-cell lymphoma was diagnosed in a 13-year-old girl with hyperimmunoglobulinemia E syndrome (HIES). Her past medical history included severe dermatitis, recurrent pneumonia, urinary tract infections, mucocutaneous herpetic infections, fungal skin infections, and staphylococcal sepsis. The diagnosis of HIES, based on the clinical features and a serum IgE level of $>20\,000$ IU/ml, was established when the girl was 6 years old. This is the eighth case of lymphoma in a patient with HIES reported in the English-language medical literature. HIES has not usually been considered a predisposing factor for malignancy, but in view of the rarity of HIES and the young age of the patients, this association seems to be more than coincidental. A link between lymphoma and Epstein–Barr virus (EBV) infection in patients with HIES has been proposed. Serological tests for EBV in our patient were positive 6 years prior to the development of the lymphoma; however, examination for EBV DNA in the lymph node biopsy failed to detect EBV in the tumor.

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Hyperimmunoglobulinemia E syndrome (HIES) is a rare immunodeficiency disorder characterized by recurrent staphylococcal infection involving the skin, lungs and other organs, and high serum IgE levels (usually >5000 IU/ml). Eczema and coarse facies are common findings. Dental and skeletal abnormalities, including prolonged retained primary teeth, craniosynostosis, and osteopenia with fracture after minor trauma, have also been reported (1,2). Males and females are equally affected. The disease occurs occasionally in individuals of successive generations, suggesting an autosomal dominant inheritance with variable penetrance (3). Recently, linkage analysis identified a gene for HIES on chromosome 4 (1).

The specific immunologic defect in HIES has not been clarified. The elevated IgE is considered to be an epiphenomenon, as are the abnormal neutrophil chemotaxis and diminished antibody response which are found in some patients (4). Several investigators reported a cytokine imbalance in patients with HIES, with relative

deficiency of interferon- γ and over-expression of interleukin-4 (5–7).

The prevalence of malignancies in patients with several immune deficiencies is markedly elevated. HIES, however, has not generally been considered as a predisposing factor for malignancy (8), although the association was noted (2). We report on a girl with HIES and large cell lymphoma and review the reports of malignancy in HIES.

Case report

The 13-year-old girl was born at term, weighing 3.5 kg. Her parents, healthy Muslim Arabs, are first-degree cousins. Three of her six siblings died 25–30 years ago during infancy; two of them probably had HIES. One brother with severe failure to thrive had recurrent abscesses, recurrent pneumonia and eosinophilia, and died of septicemia at age 18 months; the second brother had severe dermatitis, recurrent abscesses and eosinophilia, and died at age 20 months; the third sibling

had complex congenital heart disease and died at age 8 months. Three other siblings are healthy.

The patient's past medical history included severe chronic dermatitis; recurrent pneumonia, sometimes occurring with eosinophilia; bronchiectasis; recurrent urinary tract infections; recurrent mucocutaneous herpes infections; recurrent herpetic keratitis; and chronic tinea capitis and corporis caused by *Microsporum canis* and staphylococcal sepsis. She had chronic eczematous lesions on the trunk and limbs, depigmentation, and multiple scars. She also suffered from severe pruritus that was poorly controlled by topical anti-fungal medications and anti-histamines. At 6 years of age, the diagnosis of HIES was established on the basis of the clinical features and a serum IgE level of $>20\,000$ IU/ml. The results of immunologic tests at 10 years of age are shown in Table 1. The patient received long-term treatment with cloxacillin and ketoconazole, and occasionally also acyclovir.

At 13 years of age the patient was hospitalized because of general deterioration, fever, weight loss, and lymphadenopathy in the neck, axilla, and inguinal region. Findings on physical examination included severe wastage, dry skin with fissures, hyper- and hypo-pigmentation, an erythema marginatum-like rash, and lichenification. Bilateral enlarged hard lymph nodes were palpable in the posterior cervical triangle, axillae, and inguinal area. Heart sounds were normal. Breath sounds were decreased and crackles were heard over the right lung. The abdomen was swollen with hepatomegaly and splenomegaly. Clubbing of fingers and onychomycosis were present.

Laboratory tests showed hemoglobin 8.5 g/dl, white blood count $18\,800/\text{mm}^3$ (neutrophils 29%, lymphocytes 21%, monocytes 15%, eosinophils 35%), and platelets $490\,000/\text{mm}^3$. Serum electrolytes were within the normal range. Serum iron was 10 $\mu\text{g}/\text{dl}$, aspartate aminotransferase 88 μI , alanine aminotransferase 136 μI , gammaglutamyltranspeptidase 54 μI , and lactate dehydrogenase 2,155 μI . Tests were negative for hepatitis A immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies, antibodies to hepatitis B surface antigen, and hepatitis C antibodies. The titer for herpes simplex virus was 1:512; for varicella zoster virus, 1:2; for cytomegalovirus IgG, 1:160; for Epstein-Barr virus (EBV) viral capsid antigen IgG, 1:1,024; and for EBV IgM, 0. Six years previously, EBV serology gave an EBV IgM titre of 1:32 and an EBV viral capsid antigen IgG titre of 1:1,024. Serologic analysis for human immunodeficiency virus (HIV) was negative.

Chest X-ray revealed bilateral infiltrates. Abdominal computerized tomography scan showed

hepatomegaly and multiple round nodules in the liver and spleen. Bone marrow aspiration was not diagnostic.

Cervical lymph node biopsy revealed large T-cell lymphoma. EBV DNA was not found in the biopsy specimen.

The patient's condition deteriorated further before chemotherapy was initiated. Severe coagulopathy and thrombocytopenia developed, and blood cultures grew coagulase-positive *Staphylococcus*. Despite intensive supportive treatment and administration of broad-spectrum antibiotics, she died a few days after admission.

Discussion

HIES, first described by Davis et al. (9) in 1966 as Job's syndrome, is a well-known clinical syndrome, but the exact immune defect is not yet clearly understood. Some inherited immune deficiencies are known to predispose patients to malignancy. The calculated prevalence of cancer in Wiskott-Aldrich syndrome is 1000-fold higher than in immunocompetent children (10), and the calculated prevalence of gastric carcinoma increases 50-fold in common variable immunodeficiency (11). Approximately 35% of patients with X-linked lymphoproliferative syndrome develop lymphoma (12). Malignancy is common also in ataxia telangiectasia (8). Iatrogenic immune suppression, HIV infection, and autoimmune diseases are also associated with increased risk for malignancy (8). HIES has not usually been considered to be a factor predisposing patients to malignancy (8).

The malignancies in immunodeficient hosts demonstrate a peculiar preponderance of non-Hodgkin lymphomas, which accounts for $\approx 65\%$ of all cases of malignancy in children with immunodeficiency (8). The mechanism underlying this susceptibility remains unclear. Some researchers have suggested that chronic stimulation by viral antigens (especially EBV), promoted by inadequate neutralizing antibody, creates conditions favorable to oncogenic transformation (8).

Eight cases of lymphoma have been reported in patients with HIES (including our patient) (13–19) (Table 2). The male to female ratio seems to be equal, and the mean age at diagnosis of malignancy was 19 years (range 7–46 years). Most cases were fatal. One of the patients, a 46-old man with B-cell lymphoma, underwent allogeneic stem cell transplantation and died 6 months afterwards as a result of interstitial pneumonitis (19). Other malignancies (vulvar cancer and liver tumor) have been reported in two patients with HIES (20,21).

Table 1. Immunologic findings of a 13-year-old girl with hyperimmunoglobulinemia E syndrome and lymphoma

Parameter	Result	Normal range/control
Immunoglobulins		
IgG	1,880 mg/dl	650–1,350 mg/dl
IgA	360 mg/dl	70–280 mg/dl
IgM	185 mg/dl	80–250 mg/dl
IgE	>20,000 IU/ml	<100 IU/ml
IgG ₁	1,450 mg/dl	400–1,000 mg/dl
IgG ₂	146 mg/dl	140–550 mg/dl
IgG ₃	96 mg/dl	15–150 mg/dl
IgG ₄	60 mg/dl	2–90 mg/dl
Complement		
C3	177 mg/dl	150–220 mg/dl
C4	29 mg/dl	20–32 mg/dl
CH50	60%	40–200%
Functional antibodies	–	–
Anti-diphtheria	0.02 IU/ml	>0.1 IU/ml
Anti-tetanus	0.03 IU/ml	>0.1 IU/ml
Lymphocytes		
CD3	74% 1,160/mm ³	60–85% 1,300–4,700/mm ³
CD4	33% 518/mm ³	50–70% 800–2,800/mm ³
CD8	40% 630/mm ³	25–45% 600–1,800/mm ³
CD16	5% 80/mm ³	3–15% 45–700/mm ³
CD19	16% 250/mm ³	5–18% 75–800/mm ³
CD4/CD8	0.8	1.1–2.5
<i>In vitro</i> response to mitogen stimulation	–	Control
PHA	10,300 c.p.m.	26,000 c.p.m.
PWA	1,660 c.p.m.	11,440 c.p.m.
Con A	5,200 c.p.m.	10,200 c.p.m.
<i>In vitro</i> responses to antigen stimulation*	–	
SAC	1.6	15.6±2.2
Candidin	1.1	15.2±1.8
NK activity (ratio 50:1)†	26.4	23.6
Polymorphonuclear function	–	
Chemotaxis	Normal	–
Phagocytosis and bacterial killing assay	Normal	–

*Stimulation index.

†Against the K-562 cell line.

Con A, concanavalin A; c.p.m., counts per minute; NK, natural killer cells; PHA, phytohemagglutinin; PWA, pokeweed mitogen; SAC, *Staphylococcus aureus* cowan I.

A previous infection with EBV may predispose HIES patients to the development of lymphoma (13,18), as observed in patients with X-linked lymphoproliferative disease and acquired immunodeficiency syndrome (22). In our patient, positive serology to EBV was noted 6 years prior to the development of the lymphoma; however,

EBV DNA was not found in the lymph node biopsy.

It appears that the susceptibility to malignancy, specifically in HIES, may be a result of chronic polyclonal stimulation of B cells in combination with the T-cell abnormalities that exist in these patients, as was also noted in our patient. Our

Table 2. Reports of hyperimmunoglobulinemia E syndrome and lymphoma

Author/reference	Gender of patient	Age of patient	Diagnosis	Symptoms sign	Outcome
Lin et al. (13)	M	10 years	Hodgkin's lymphoma	Neck mass for 3 months	Fatal
Bale et al. (14)	F	10 years	Histiocytic lymphoma of brain	Lethargy, right-sided weakness, increased intra-cranial pressure, intra-cranial mass	Fatal
Einsele et al. (15)	F	24 years	Non-Hodgkin's lymphoma	Sub-mandibular lymph node enlargement	Fatal
Kowalchuk (16)	?	24 years	Hodgkin's lymphoma	Pneumonia	Recovery
Bukeley & Sampson (17)	M	19 years	Hodgkin's lymphoma	NA	NA
Gorin et al. (18)	M	7 years	Burkitt's lymphoma	Emesis, loss of appetite, abdominal mass	Fatal
Nester et al. (19)	M	46 years	Large B-cell lymphoma	Cervical lymphadenopathy	Fatal*
Present case	F	13 years	Large T-cell lymphoma	Weight loss, lymphadenopathy	Fatal

NA, data not available to the authors.

*Underwent allogeneic stem cell transplantation.

patient had both B- and T-cell abnormalities, including: a elevated level of IgE; polyclonal hypergammaglobulinemia; a low level of functional antibodies (she received diphtheria-pertussis-tetanus immunizations); a diminished response to antigen stimulation and, to a lesser degree, to mitogen stimulation; and a relatively low number of CD4 cells (Table 1). These immunologic abnormalities may have laid the groundwork for oncogenic transformation.

Based on the present data we assume that patients with HIES are prone to malignant lymphoma at an early age. It is still unclear if this tendency is related to EBV infection. Screening of patients with HIES for EBV infection may further our understanding of this issue.

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