

CLINICAL REPORT

Hyper-IgE Syndrome with Widespread Premalign Oral Papillomas Treated with Interferon α 2b

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We report a case of a 7-year-old girl with hyperimmunoglobulin-E syndrome presenting with widespread oral papillomas which were tested for human papilloma virus DNA and had shown to be at high/intermediate risk group for malignancy. She had elevated levels of IgE, recurrent sinopulmonary infections, atopic-like dermatitis, peripheral eosinophilia and defective neutrophil chemotaxis. Interferon alfa 2b therapy and chemoprophylaxis with sulfamethoxazole-trimethoprim was given. Although the papillomas partially improved with the treatment, sinopulmonary infections continue to occur. **Key words:** Hyperimmunoglobulin-E syndrome; Human Papilloma Virus; immunodeficiency; interferon; oral papillomas.

(Accepted December 17, 2004.)

Acta Derm Venereol 2005; 85: 433–435.

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Hyperimmunoglobulin-E syndrome (HIES) is a primary immunodeficiency state that is characterized by markedly increased levels of IgE, recurrent cutaneous and systemic pyogenic infections, atopic-like dermatitis, peripheral eosinophilia and defective neutrophil chemotaxis (1). We report here a case of HIES with widespread premalign oral papillomas, partially responding to interferon (IFN)- α 2b.

CASE REPORT

A 7-year-old girl presented with widespread papillomas on her tongue, inner lips, buccal mucosa and gingiva in



Fig. 1. Oral papillomas on the inner lips (a) and tongue (b). Note the verruca vulgaris lesion at the third finger.

October 2002. She had had recurrent otitis media, pneumonia and sinusitis in the previous 2 years. She had a history of furuncles on her neck, scalp and axillae until she was 6 months of age and swelling of her lips following consumption of some foods.

At admission, she had eczematous, excoriated, secondary infected papules and plaques on her axillae, lumbosacral area, forearm flexural areas, and around her neck and lips (Figs 1 and 2). She had xerosis and

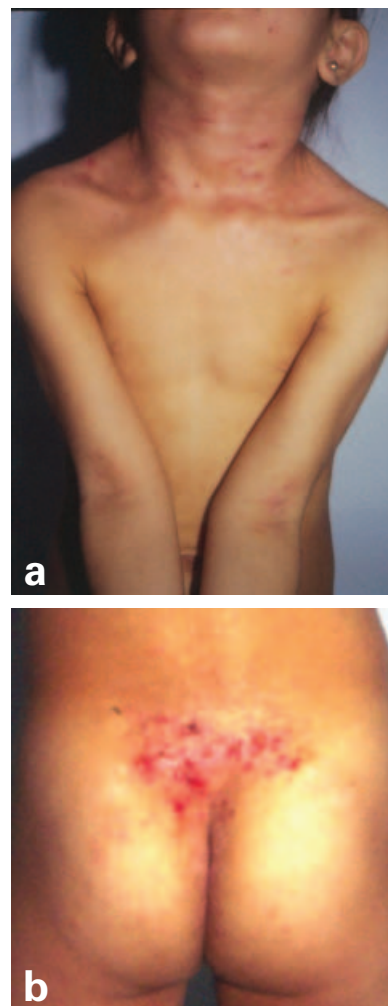


Fig. 2. Eczematous lesions on the neck and flexural areas (a) and secondary infected and excoriated lesions in the lumbosacral area (b).

pruritus. Besides her oral papillomas, she had several verruca vulgaris lesions on her hands.

Several biopsy specimens were taken from oral mucosa, one of which was examined histopathologically and revealed oral papilloma; the others were tested for human papilloma virus (HPV) DNA by HC2 HPV DNA test (Digene Corporation) according to the manufacturer's instructions. Two risk groups (low and high/intermediate risk groups) can be differentiated by this test and in our case the high/intermediate risk HPV types group (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) was found to be positive, while the low risk HPV types group (6, 11, 42, 43, 44) was found to be negative. Laryngoscopic examination showed no papillomas on the larynx.

Serum biochemistry and the complete blood count were normal, except for the white blood cells: 16250/ μ l, with 62.9% neutrophils, 18.2% lymphocytes, and 11.4% eosinophils. She had a high level of IgE (19600 U/ml) and a slightly decreased level of IgM: 40.4 mg/dl (normal: 45–250 mg/dl), while her IgG, IgA, C3 and C4 levels were within normal ranges. As for cellular immunity, CD19 lymphocytes were increased: 36% (normal: 11–16%). CD3 (48%, normal: 60–85%) and CD8 (17%, normal: 19–48%) lymphocytes were slightly decreased; CD4, CD56, CD45 levels were within normal ranges. Cutaneous response to candida and tuberculin was absent. The nitroblue tetrazolium test was 7% (normal: 15%). She had defective polymorphonuclear chemotaxis with neutrophil chemotaxis index being 1.4 (normal: 2). Because of the high levels of IgE, parasite and parasite eggs were searched for in stool and the prick test (inhalant) was performed; all these investigations were negative. Anti-HIV was negative.

As the patient complained of swelling of the lips following consumption of some foods, a skin scratch prick test was performed and reactions to cacao (+++), cheese (++), egg (++), watery yoghurt (+++) and tomato (+) were obtained.

She was hospitalized and treated with systemic antibiotics, antihistamines, local corticosteroids and emollients. As for her oral papillomas, some of the lesions were treated with laser ablation followed by adjuvant IFN- α 2b, 3×10^6 IU/m²/dose, subcutaneously three times a week.

The patient has been followed for 17 months. In the first month of the treatment her eosinophil count increased up to 54.8%, then slowly decreased to 5.4% during her follow-up correlated with clinical improvement to the treatment while the IgE level fluctuated between 14000 and 24300 IU/ml, showing no significant change. CD19 lymphocytes decreased to 22% and CD4 level changed between 19 and 29% (normal: 29–59%); CD3, CD8, CD45, CD56 lymphocytes stayed at normal levels. Decreased levels of IgM continued (27.6–40.4%), while there was an increase in IgG and IgG1 fraction

(IgG=1950 mg/dl, normal: 460–1600 mg/dl; IgG1=1210 mg/dl, normal: 206–657 mg/dl).

She had pneumonia at admission, and during the follow-up period she had relapsing otitis, sinusitis and pneumonia. She developed anaemia and inguinal lymphadenopathies.

The pathological examination of the total excision of an inguinal lymphadenopathy showed non-specific changes with reactive follicular hyperplasia. A punch biopsy performed from the gluteal lesions revealed eczematous changes with diffuse parakeratosis, colonization of bacteria, acanthosis and slight spongiosis. Clinical and radiographic dental examination was normal. Measured bone density was normal.

DISCUSSION

HIES was first described by Davis-Schaller-Wedgewood in 1966 (1), then further defined and clarified by Buckley et al. in 1972 (2). HIES is a rare primary, complex, multi-system immunodeficiency disorder which lacks distinctive laboratory tests and set-up criteria. The diagnosis is based upon several immunological, non-immunological and clinical features such as markedly elevated IgE (10 times the normal limit has been suggested as a diagnostic level), marked eosinophilia in blood and/or sputum, defective neutrophil chemotaxis and depressed cell-mediated immunity to ubiquitous antigens (2, 3), all of which were present in our patient. Positive immediate wheal and flare reactions to a variety of food, inhalant, bacterial and fungal antigens can also be seen (3). Only reactions to some foods with the scratch test were found to be positive in our patient.

Coarse facial features and skeletal abnormalities (hyperextensible joints, scoliosis, osteopenia) are the defined non-immunological features (2, 3) but were absent in our case. However, the facial features can develop progressively and become universal by late adolescence (2).

Clinical features that can be seen are: severe infections of the skin and lower respiratory tract from infancy; cold abscesses; non-specific, excoriated, papular and pustular eruptions (3–5). The papulopustular eruption can be the initial eruption and the earliest clue to the diagnosis in infancy (5). Patients have little or no respiratory allergy and IgE is normal in non-affected relatives (3). There are reported cases of malignancies (2, 3). As for our patient although she had a history of furunculosis, we only observed impetiginized eczema during her follow-up, and although the cold abscesses have been said to be pathognomonic of HIES, they are not essential to the diagnosis (2). However, she had recurrent pneumonia and upper respiratory tract infections which continued to occur in spite of IFN therapy and chemoprophylaxis with oral sulfamethoxazole-trimethoprim.

The distribution of the dermatitis, high levels of IgE and recurrent bacterial infections of the skin and sinopulmonary tract (mostly the lung involvement) help to distinguish it from atopic dermatitis (4–6).

Heck disease (focal epithelial hyperplasia) is a benign infection of the oral mucosa caused by HPV infection which can easily be confused with papillomas or condylomas. However, HPV 13 and 32 are the most common types associated with this disease which are benign types of HPV (7). Moreover the disease tends to be familial (7). HPV 13 and 32 could not be determined in this patient but we used oral mucosa biopsies and detected positivity for the high/intermediate risk group.

There are reported cases of HPV infections in immunocompromised patients but only one case of HIES with multiple papillomas in the literature has been found (8). As the papillomas were widespread and showed high risk group for malignancy, IFN therapy was preferred and although they improved with this treatment, smaller and decreased numbers of new lesions continue to occur.

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