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CASE REPORT

Hyperimmunoglobulin E syndrome with Sjogren's syndrome in a child

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We describe a case of hyperimmunoglobulin E syndrome (HIES) associated with Sjogren's syndrome (SS) in a 10-year-old boy and provide a brief review of the literature. Although seen in adults, SS occurring after a primary immunodeficiency disease such as HIES has not previously been reported in a child.

Hyperimmunoglobulin E syndrome (HIES) is a primary immunodeficiency disorder characterised by recurrent sino-pulmonary infections, cutaneous abscesses and chronic eczematous dermatitis.[1,2] The syndrome is also associated with coarse facies, growth restriction, osteoporosis, eosinophilia and auto-immune disorders.

Sjogren's syndrome (SS) is characterised by dry eyes, dry mouth and parotid enlargement, in the presence of specific auto-antibodies.[3] It is termed primary SS when it is not associated with any other immunological disease. Secondary SS is associated with systemic lupus erythematosus (SLE), mixed connective tissue diseases and other auto-immune conditions. We describe a case of HIES associated with SS, a previously unreported association in children.

Case report

A 10-year-old boy presented with recurrent boils, oral candidiasis, mild eczematous lesions and cervical lymphadenopathy. He had a history of recurrent chest and skin infections including bronchopneumonia, recurrent boils, cutaneous abscesses, pharyngitis, purulent conjunctivitis and balanoposthitis from the age of 6 years. His height was 122 cm (<3rd percentile, z-score -2.53) and his weight 22 kg (<3rd percentile, z-score -2.41). Respiratory examination revealed bilateral crackles with no other systemic pathology detected clinically.

Investigation revealed a haemoglobin concentration of 9.1 g/dl, a total white cell count of 14.2×10^9/l, polymorphs 70%, lymphocytes 18%, eosinophils 12%, a platelet count of 375×10^9/l and an erythrocyte sedimentation rate of 41 mm/1st h. A chest radiograph revealed features of bronchopneumonia. The results of liver and renal function tests were normal. *Staphylococcus aureus* was grown in pus from the cutaneous abscesses, and a throat swab culture grew *Candida albicans*. Fine-needle aspiration of a cervical lymph node showed smear positivity for mycobacteria, which were later confirmed by the polymerase chain reaction to be *Mycobacterium tuberculosis* complex. HIV enzyme-linked immunosorbent assay was negative. Lymphocyte subset flow cytometry showed a normal pattern for CD3 (52%), CD4 (32%), CD8 (22%) and CD19 (10%). Immunoglobulin analysis revealed an IgG level of 1 280 mg/dl (normal range 1 124±235 mg/dl), IgA 170 mg/dl (normal range 131±60 mg/dl) and IgM 84 mg/dl (normal range 79±33 mg/dl). The IgE level was 1 776 IU/ml (normal <51 IU/ml). The patient's neutrophil phagocytic function, evaluated by the nitroblue tetrazolium test and complement assays (C3, C4 and CH50), was normal. HIES was suspected because of the recurrent respiratory infections, cutaneous staphylococcal abscesses, chronic eczematous dermatitis, eosinophilia and high IgE level. The patient also had tuberculosis and growth restriction.

The patient responded to vancomycin and aminoglycosides, prescribed on the basis of the culture report, fluconazole and antituberculosis drugs (isoniazid, rifampicin, ethambutol and pyrazinamide). Co-trimoxazole was added as prophylaxis. He was followed up as an outpatient.

Six months later, he presented with painless bilateral parotid gland swelling, dryness of the mouth and dysphagia. Photophobia and intermittent blurred vision were also present. Ophthalmologic evaluation documented dryness of the eyes. Rose-Bengal staining of the cornea suggested superficial erosions. Unstimulated salivary flow measurement was suggestive of a dry mouth (0.7 ml in 15 minutes). Schirmer's test showed a positive result with <5 mm wetting of a filter paper strip in 15 minutes. Rheumatoid factor and antinuclear antibody were positive, anti-double stranded DNA was negative, anti-Ro/SSA was positive, and hepatitis C serology was negative. Salivary gland biopsy was not performed as consent could not be obtained.

Discussion

Abnormal chemotaxis, deranged lymphocytic function and altered cytokine response are implicated in the pathophysiology of recurrent infections in HIES.[1] Several auto-immune diseases, including systemic lupus erythematosus (SLE), have been reported in association with HIES. Lymphomas have also been associated with the condition. Vernal conjunctivitis associated with HIES is well described.[2]

SS is an ill-defined disorder and rarely encountered in children.[3] The diagnostic criteria for SS in children are poorly validated.[4] Secondary SS, more frequent than the primary variety, is associated with SLE, mixed connective tissue diseases and extremely rarely juvenile idiopathic arthritis and cutaneous scleroderma syndrome.[3,4,5] Our patient did not have any pre-existing auto-immune disease. We

diagnosed the case as primary SS according to American-European consensus criteria.[6] The presence of dry eyes and mouth for 3 months, reduced unstimulated salivary flow and a positive Schirmer's test in the presence of auto-antibody anti-Ro (SSA) with exclusion of other secondary causes established the diagnosis of primary SS.

Two distinct genetic variants of HIES have been described, namely autosomal recessive HIES (AR-HIES) and HIES with STAT3 mutation.[7,8] The immunopathogenesis of STAT3 deficiency is still a matter of debate, and T-helper 1 (Th-1)/Th2 cytokine imbalance has been suggested as a causative factor.[9] In one report of a case in an adult, where primary SS followed HIES diagnosis, the authors proposed the Th2 cytokine as the predominant mechanism.[10] Cimaz *et al.* reported a series of 40 children from European centres with primary SS, but none of them had associated HIES.[11] To the best of our knowledge, HIES co-existing with primary SS has not been previously reported in children.

Sjogren's syndrome is an ill-defined disorder and rarely encountered in children.

References

1. Leung DY, Geha RS. Clinical and immunologic aspects of hyperimmunoglobulin E syndrome. Haematol Oncol Clin North Am 1988;2:81-100.
2. Frohn A, Weidle EG, Seelhorst A, et al. Eye involvement in hyperimmunoglobulin E syndrome. Kiln Monatsbl Augenheilkd 1990;197:432-435.
3. Cassidy JT, Petty RE. Overlap syndromes. In: Cassidy JT, Petty RE, Lindsley CB, Laxer RM , eds. Textbook of Pediatric Rheumatology. 4th ed. Philadelphia: Elsevier Saunders, 2005:482-491.
4. Deprettere AJ, Van Acker KJ, De Clerck LS, et al. Diagnosis of Sjogren's syndrome in children. Am J Dis Child 1988;142:1185-87.
5. Rocha G, Kavalec C. Sjogren's syndrome in child. Can J Ophthalmol 1994;29:234-237.
6. Vitali C, Bombardieri S, Jonsson R, et al. European Study Group on Classification Criteria for Sjögren's Syndrome. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-558.
7. Freeman AF, Holland SM. Clinical manifestations, etiology, and pathogenesis of the hyper IgE syndromes. Pediatr Res 2009;65(5 Pt 2):32R-37R. [http://dx.doi.org/10.1203/PDR.0b013e31819dc8c5]
8. Freeman AF, Holland SM. Clinical manifestations of hyper IgE syndromes. Dis Markers 2010;29:123-130.
9. Freeman AF, Holland SM. The hyper IgE syndromes. Immunol Allergy Clin North Am 2008;28:277-viii. [http://dx.doi.org/10.1016/j.iac.2008.01.005]
10. Azuma N, Katada Y, Harada Y, et al. Case of primary Sjögren's syndrome with hypereosinophilia and elevation of serum IgE: measurements of serum IL-4, IL-5 and the IgG subclass [Article in Japanese]. Arerugi 2005;56:646-651.
11. Cimaz R, Casadei A, Rose C, et al. Primary Sjogren syndrome in the paediatric age: a multicentre survey. Eur J Pediatr 2003;162:661-665.