



Case report

Septic arthritis in a case of hyper-IgE syndrome

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ABSTRACT

Hyper-IgE syndrome (HIES) is characterized by recurrent skin and pulmonary infections (mainly bacterial), eczematous dermatitis and elevated serum IgE levels. Associated abnormalities in some patients include coarse facial features, failure or delay of shedding of primary teeth, recurrent fractures, hyperextensible joints, and scoliosis. Laboratory abnormalities include elevated total serum IgE levels, typically ranging from 1,000 to greater than 50,000 IU/ml and variable eosinophilia. The diagnosis of HIES is based upon the presence of suggestive clinical and laboratory findings. A definitive laboratory test is not commercially available at present. Management of patients with HIES is focused on skin care, prevention of infection, prompt and complete treatment of infections that do develop, and control of pulmonary complications.

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Artritis séptica en un caso de síndrome de hiperinmunoglobulinemia E

RESUMEN

El síndrome de hiperinmunoglobulinemia E (HIES) se caracteriza por infecciones recurrentes cutáneas y pulmonares (principalmente bacterianas), dermatitis eccematosas y elevados niveles séricos de IgE. Anomalías asociadas en algunos pacientes incluyen rasgos faciales toscos, fracaso o retraso de la caída de los dientes primarios, fracturas recurrentes, hiperlaxitud en las articulaciones y escoliosis. Anormalidades de laboratorio son niveles elevados de IgE total en suero, generalmente, de 1.000 a más de 50.000 U/ml y eosinofilia variable. El diagnóstico de HIES se basa en la presencia de característicos hallazgos clínicos y de laboratorio. Un test diagnóstico definitivo no existe en la actualidad. El manejo de los pacientes con HIES se centra en el cuidado de la piel, la prevención de la infección, el tratamiento precoz de las infecciones que se desarrollan y el control de las complicaciones pulmonares.

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Introduction

Hyperimmunoglobulinemia E (HIES) is a rare hereditary autosomal, dominant, disease, with incomplete penetrance, characterized by an alteration in the liberation of IFN γ by T lymphocytes, IgE overproduction and a faulty neutrophil chemotaxis.¹ Patients present itching and eczema similar to atopic dermatitis, frequent infections, particularly of the scalp due to *Staphylococcus aureus* and *Candida albicans*, pneumonia, ears, nose and throat infections, arthritis. Skin abscesses and facial and skeletal alterations (fractures, alterations in teething).² The diagnosis is carried out

clinically and through laboratory data. Treatment is based on the control of dermatitis with good skin hydration and avoidance of skin infections.

Case report

We present the case of a 9 year old girl with a history of atopic dermatitis, double dentition, adequately treated lung tuberculosis at the age of 6 and recurrent middle ear infections. She had no family history of rheumatic disease, inflammatory intestinal disease or psoriasis. She was under study at another hospital for presenting, for the previous two years, four episodes of recurrent monoarthritis, always of the left carpus, lasting 15 days each, with fever and empiric oral antibiotic therapy (amoxicillin-clavulanate) and non-steroidal anti-inflammatory drugs (ibuprofen), with no symptoms in the intercritical periods. Her laboratory results, which included general

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Figure.

laboratory analysis, rheumatoid factor, determination of antinuclear antibodies and HLA B27 typing, were normal or negative. She was sent to our department for the first time for the evaluation of a new episode of left carpal monoarthritis with an onset 10 days prior, accompanied by fever of 38.5 °C, without any cough nor other data of infectious origin. Physical examination showed a peculiar aspect of the face, with a prominent forehead, wide nasal bridge, skin lesions suggestive of allergy (and some evidence of scratching) on the arms and thighs, left carpal arthritis with limitation for flexion and extension (Figure) and 38 °C fever on the day se was hospitalized, with the rest of the systemic and neurological examination being normal.

Laboratory tests showed an elevation of acute phase reactants (ESR 86 mm/1.st h and CRP 37 mg/dl) and IgE (10,000 U/ml), with autoimmunity tests, (antinuclear antibodies, anti-citrullinated peptide antibodies), Mantoux, rheumatoid factor and arthritis serology (parvovirus B19, brucella, borrelia, etc.) negative. Hemogram and serum biochemistry were normal. There was no eosinophilia. Blood cultures, urine cultures and the detection of parasites and ova in excrement were negative. Skeletal x-rays (hands, feet, sacroiliac joints and thorax) only showed, as evidence of disease, the destruction of the left carpal scaphoid bone. Because of the lack of prior x-rays, we completed the study with a magnetic resonance of the left hand which showed the presence of synovial hypertrophic pannus in the distal radio ulnar joint, in the carpal region and the surface of the extensor side of the wrist, with signs of osteonecrosis and bone fragmentation of the carpal scaphoid and a pattern of non-specific marrow edema of the carpus and the metacarpal area.

Because there was no clear etiologic diagnosis of monoarthritis and there was data suggesting synovial and bone affection, we decided to perform a biopsy and culture with pathologic analysis of the left carpus, showing chronic synovitis with zones of acute synovitis and a culture positive to *S. aureus*, leading to the start of treatment with intravenous antibiotic according to the antibiogram, with cloxacillin for 3 weeks and then orally for another 3 weeks, with clinical improvement and normalization of analytical parameters (acute phase reactants). The point of entry of *S. aureus* was likely through the skin (through scratching). The study was completed by the Department of Immunology, with normal counts of CD3+, CD4+, CD8+ and CD19+ lymphocytes, determined by flow cytometry; IgA and IgM were normal, with elevated IgG and a descent of subclasses; an ELISA evaluation of the production of specific antibodies vs *Pneumococcal polysaccharides* was carried out, with an adequate response and normal cytokine production by mononuclear cultured cells (IL-4, IFN γ , IL-13) evaluated at a secretion level and

transcriptional message, and a reduction in the in vitro chemotaxis of neutrophils and a reduction in Nitro tetrazolium (NBT) by plate activated neutrophils. The family study was negative and up to the moment no signal or transcription activator 3 (STAT3) mutations have been analyzed for lack of technical capacity.

Currently, at the age of 11, she continues visiting our department as well as in Immunology and Rehabilitation (using a left carpus postural cast) as well as Orthopedics, without any new infectious complications. Although with deformity and a certain limitation of the left wrist, she can carry out all of her daily activities, received no medical treatment, although skin care has been insisted upon by maintaining an adequate hydration and through hygiene and dietary measures. The possibility of surgery in order to correct the joint deformity has not been ruled out for the future.

Discussion

HIES is associated to an increase in the serum levels of IgE.¹ Clinical characteristics include skin manifestations since early infancy; recurrent skin abscesses and pneumonia; skeletal abnormalities and minor trauma induced fractures, as well as retention of early dentition. Patients with this syndrome have characteristic facial and skeletal changes and suffer recurrent infections (mainly cutaneous, due to *S. aureus* and *C. albicans*) and dermatitis. In addition to elevated serum IgE, there are intermittent defects in chemotaxis of polymorphonuclear leukocytes and immune regulation.² Recently, an alteration in STAT3 has been identified as the cause of this syndrome. STAT3 is important in inducing signaling for several cytokines, hormones and growth factors, although the precise mechanisms that clarify why the skin, immunological and skeletal alterations occur are unknown.^{3,4} IgE serum levels are not related to the severity of disease; therefore, in infancy it can be very elevated and then be reduced with time until it reaches normal values. Clinic includes, in addition to skin affection, diverse infectious complications such as skin infections and pneumonia, characteristic facial appearance, bone abnormalities, fracture upon minimal trauma and alterations in dentition.

The diagnosis is based on clinical and laboratory data, finding an elevation of serum IgE (from 2,000 to 50,000 U/ml), peripheral eosinophilia (40%-50% of total leukocytes), an increase in IgG and a reduction in its subclasses, IgA, IgM and IgD, as well as normal complement.

Differential diagnosis includes atopic dermatitis, Wiskott-Aldrich syndrome and combined severe immunodeficiency. Patients with atopic dermatitis do not usually develop systemic infections (abscesses or pneumonias), but only superficial skin inflammation and, in addition, have no facial abnormalities or bone alterations. In Wiskott-Aldrich syndrome we find, in addition to thrombocytopenia and hematomas and a lack of abscesses, an elevation of IgE and eczema. In severe combined immunodeficiency, the skin rash is different from eczema in HIES and the immunological diagnosis is key.⁵

Treatment of HIES is based⁶ on controlling itching and dermatitis with the use of antihistamine, good skin hydration and topical steroids in the swollen, but uninfected areas of the skin. It is fundamental to prevent the appearance of a severe systemic infection through early diagnosis and treatment. Trimethoprim with sulphamethoxazole can be employed in patients with frequent and severe skin infections and possible lung complications must be controlled, such as pneumococci (which may even require surgery) and respiratory failure.

Recombinant IFN γ has been used in these patients with severe infection, based on the fact that IFN γ inhibits the synthesis of IgE

and improves neutrophil chemotaxis *in vivo*; it has been used in patients with severe infections such as lung aspergillosis. Other immunomodulating agents such as low-dose cyclosporine, rituximab, levamisole, cimetidine and ascorbic acid,⁷ have been used in a limited manner with variable results. Intravenous immunoglobulin has not shown effective results.⁸ Omalizumab, an anti-IgE antibody used in patients with severe asthma, blocks the liberation of histamine mediated by mast cell IgE, and has been used cautiously in these patients due to the elevated levels of IgE that are produced, but its use is not currently recommended.⁹

The main causes of death are infectious lung complications (aspergillosis, etc.) and lymphoma (usually with a poor prognosis).¹⁰ Pneumatocelle can be colonized by gram negative bacteria and fungi, leading to pneumonia, systemic infections and lung hemorrhage. Vascular invasion by fungi can cause mycotic aneurisms with hemorrhagic lung and other organ complications.

We present this case due to the importance of the differential diagnosis of monoarthritis in children and the relevance of synovial tissue biopsy as a helpful technique for diagnostic and therapeutic orientation in a case of recurrent chronic monoarthritis of an unclear etiology. It is important to keep the diagnostic suspicion of this syndrome in pediatric patients with moderate chronic dermatitis and recurrent foot infections in mind. It is necessary to start the search for early markers of disease that allow for the early identification of patients due to the fact that the prognosis depends on the age of the patient at the moment immunodeficiency is detected. Early onset of prophylaxis and therapy has shown to be an effective form

of preventing the early development of complications, especially pulmonary ones.

Disclosures

The authors have no disclosures to make.

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