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Review article

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Hyper-Ig E syndrome in adult patient: a clinical case and a review of the literature

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Abstract

Hyper-Ig E syndrome (HIES) includes a rare group of primary immunodeficiency conditions with frequently recurrent lung and skin infections. The respiratory system is affected by acute and chronic bronchitis, otitis, recurrent pneumonia, pneumocele, pleurisy, severe and prolonged sinusitis. Cutaneous manifestations are presented with "cold abscesses" and eczema/dermatitis. A pathognomic feature for the syndrome is the increased level of serum Ig E. The etiology of HIES still remains unclear. HIES occurs sporadically or is inherited - as an autosomal dominant HIES or autosomal recessive HIES. The type of inheritance determines the variable clinical picture of the syndrome. The pathogenetic diversity, the absence of specific clinical criteria as well as the presentation of few or minor symptoms in some patients complicate the diagnosis.

We report a clinical case of a sporadic hyper-Ig E syndrome in an adult man suffering from atopic dermatitis since childhood presented with recurrent bacterial, viral, fungal and protozoan infections of the respiratory tract, gastrointestinal tract, skin and mucosal surfaces. A brief review of the scientific literature is also included.

Key Words: Hyper-Ig E Syndrome, Job`S Syndrome, Jobs-Buckley Syndrome, Adult Patients, Ig E, Primary Immunodeficiency, Skin.

Introduction

HIES is a rare group of primary immunodeficiency conditions with multiorgan involvement and specific clinical and laboratory findings. The initial study of HIES began in 1966, when S. D. Davis, J. Schaller and R. Wedgewood described clinical cases of two girls with frequent respiratory infections, severe dermatitis and recurrent "cold" skin abscesses [1]. The presented syndrome-complex is called by the authors "Job`s syndrome" (Job is a biblical character whose body was covered with abscesses). R. Buckley et al. published a paper with detailed descriptions of this syndrome in two boys with high levels of Ig E and eosinophilia [2].

Two years later, H. R. Hill et al. found that Job and Buckley syndrome were essentially the same condition. Today, Job-Buckley syndrome is described as hyper-Ig E syndrome [HIES, Hyper-IgE syndrome, HIERIS (Hyper-IgE recurrent infection syndrome)] [3]. In the mid-1970s, the immunological abnormalities found in the syndrome led to its inclusion in the group of primary immunodeficiencies [4]. The etiology of HIES still remains unclear, suggesting that it is abnormal neutrophil chemotaxis due to decreased production or secretion of interferon-γ and impaired Th1/Th2-cytokine profile. These immunological alterations determine the impaired cellular immunity, the susceptibility to infections and the allergy-atopy predisposition of the affected patients. HIES occurs sporadically or is inherited - as an autosomal dominant HIES (AD-HIES) or autosomal recessive HIES (AR-HIES).

The type of inheritance determines the variable clinical picture of the syndrome. Thus, the autosomal dominant form lacks any immunological findings and is presented with a constellation of facial, dental, skeletal and connective tissue disorders, recurrent infections and eczema. There is no somatic involvement, but recurrent viral infections, neurological complications, autoimmune diseases, and neoplasia have been observed in the autosomal recessive form of the syndrome. Typical signs of HIES are eczema/atopic dermatitis, abscesses, pneumonia, mucosal candidiasis, high Ig E serum level and eosinophilia. HIES is specifically characterized by the appearance of atypical eczema/ atopic dermatitis in the first days after birth [5]. Seven main clinical findings with a specificity of >85% were identified, namely: abscesses of inter-

nal organs, other severe infections, pneumocele, candidiasis of the skin and nails, bone fractures without adequate trauma and a positive family history [18]. HIES is thought to be ubiquitous, with isolated reports of Caucasian race, Asian and African populations [9, 10]. HIES affects both sexes equally.

HIES has been shown to be due to mutations in the STAT3, DOCK8 and Tyk2-genes. In AD-HIES and sporadic types of syndrome, immune changes are caused by a heterozygous mission mutation or in-frame deletions STAT3. In the majority of patients with AR-HIES, a homozygous point mutation DOCK8 (dedicator of cytokinesis gene 8) was found, disrupting the synthesis of proteins that regulates the actin cytoskeleton. A distinctive feature of the AR-HIES is the recurrent, intense and difficult to control viral infections of the skin - HSV, VZV, HPV, Molluscum contagiosum virus. DOCK8 deficiency has been associated with the development of neoplasms during childhood and adolescence: squamous cell carcinoma at the sites of recurrent viral infections and Burkitt,s lymphoma [18].

Case report

We present a 47-year-old male with a known atopic dermatitis since childhood admitted with complaints of redness and itching of the skin of the face, trunk and limbs. The initial changes start from the skin folds of the body with gradual dissemination on the head, trunk and limbs. The patient associated the rash with the use of Zyrtec D, taken for chronic rhino-conjunctivitis. Given the patient,s complaints, multiple consultations with dermatologists and allergologists were conducted. The patient was diagnosed with polyallergy to house dust mites, mold, cats, dogs, wormwood, five species of grass, beech, birch pollen and decompound flowers. According to personal medical history, the patient suffers from frequently recurrent chordeoli, folliculitis, boils, herpes simplex labialis and chronic bronchitis.

In 2018, the patient was diagnosed with toxocariasis. Antiparasitic treatment with Albendazole was administered. In the same year, he was admitted to hospital due to dermatitis. A histological examination of the skin demonstrated subacute spongiform dermatitis. The conducted systemic therapy with corticosteroids, antihistamines, as well as local treatment with emollients and local corticosteroids has an unsatisfactory effect. In November 2020, the patient suffered from COVID-19 - induced pneumonia, followed by a significant worsening of the rash.

On the recommendation of a gastroenterologist, the patient's stool sampleswere examined and Candida spp was isolated. A systemic three-day treatment with antifungal drug was provided. In 2020, the patient underwent a screening test of antinuclear antibodies (ANA) and Anti-Centromere B so that a connective tissue disease could be excluded. In this case, such correlation with HIES was not established.

In 2021, laboratory and microbiological examinations have shown peripheral eosinophilia - 9.2%, increased levels of lactate dehydrogenase (LDH) - 823,0 IU/L, C-reactive protein (CRP) - 6,9 mg/L, Ig E - 7146.9 IU/ml (compared to 716 IU/ml in 2018), negative parasitological tests for borreliosis, helminths and Larva migrans. S. aureus is isolated from nasal, ear secretion and skin surface.

Cutaneous findings

The skin changes involved the face, neck, trunk, and lower and upper extremities (fig. 1-8). They are represented by symmetrical, well-defined, erythematous papules and extensive plaques, reaching size up to 20 cm in diameter, circumferentially affecting the limbs. Discrete desquamation is found (fig. 1, 2, 3). In somebody areas, linear excoriations and erosions covered with haemorrhagic crusts are observed. Peripheral enlarged lymph nodes were found cervically (along the left m. sternocleidomastoids), right supraclavicular, axillary, and in the inguinal regions. The lymph nodes are enlarged, painless, mobile, and non-fused with the surrounding tissue. A histological examination of a lesion of the left axilla (fig. 10) shows compact Orth hyperkeratosis, reduced stratum granulosum, irregular acanthosis, mild spongiosis mainly in the lower epidermal segment, moderate interstitial, and perivascular mixed inflammatory infiltrate with scarce number of neutrophils. The given histological picture corresponds to spongiotic dermatitis.

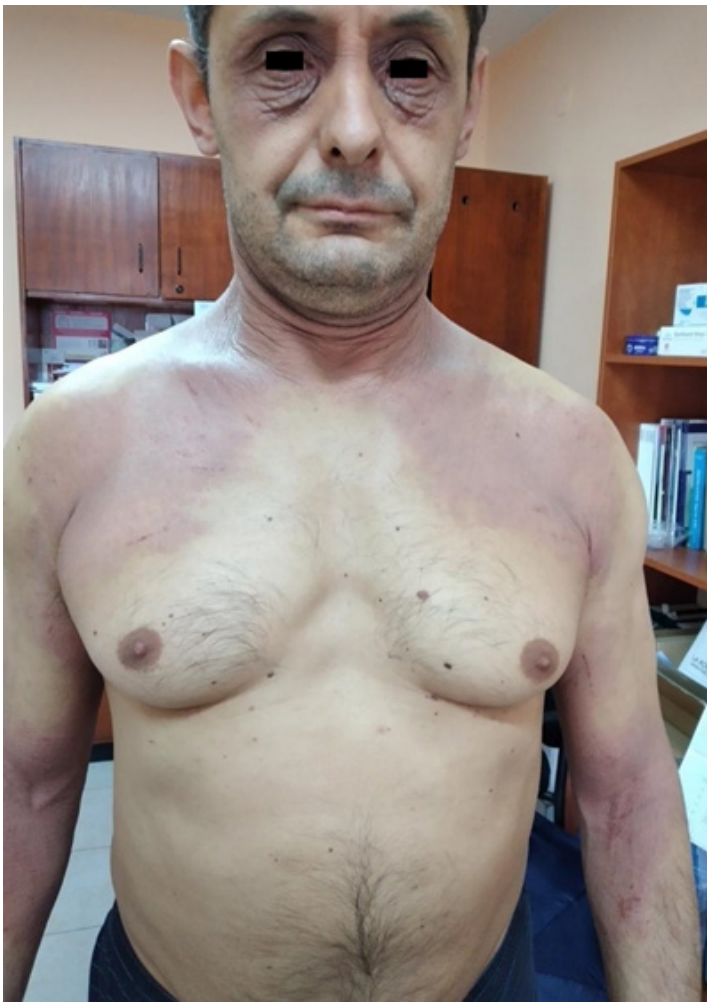
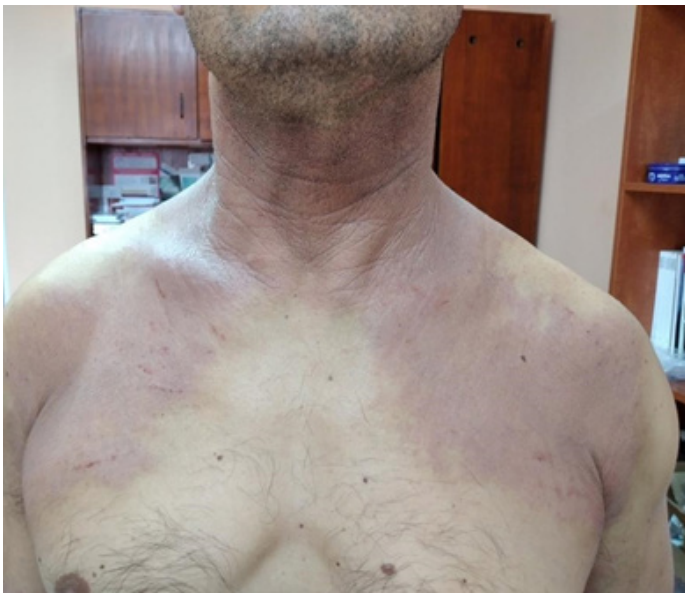


Figure 1



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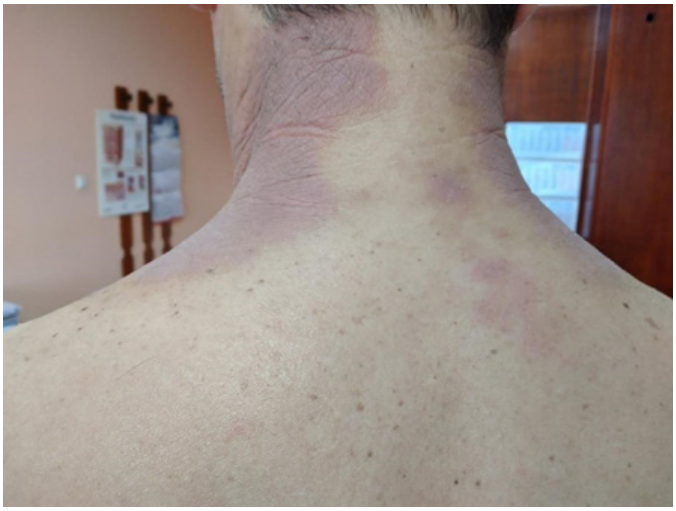

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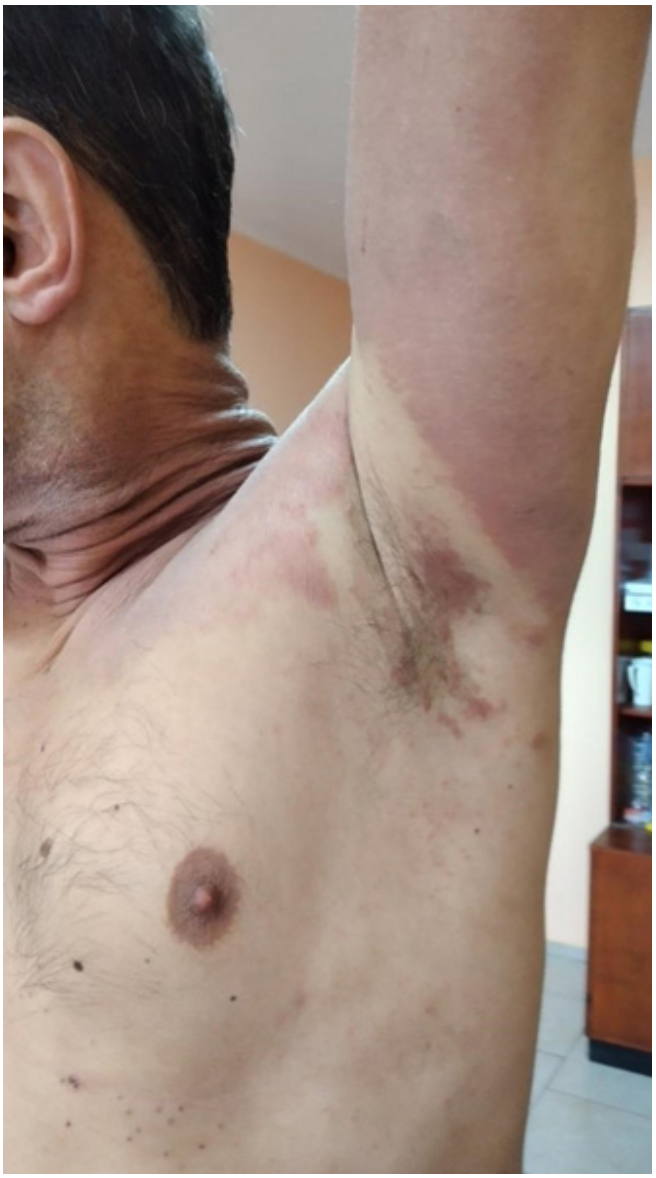

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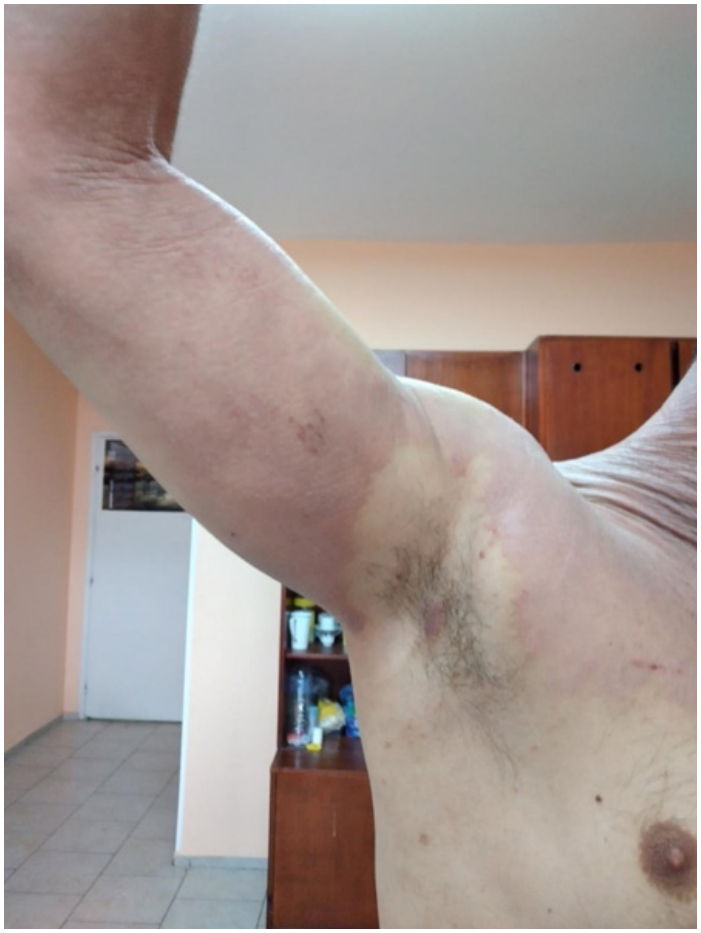
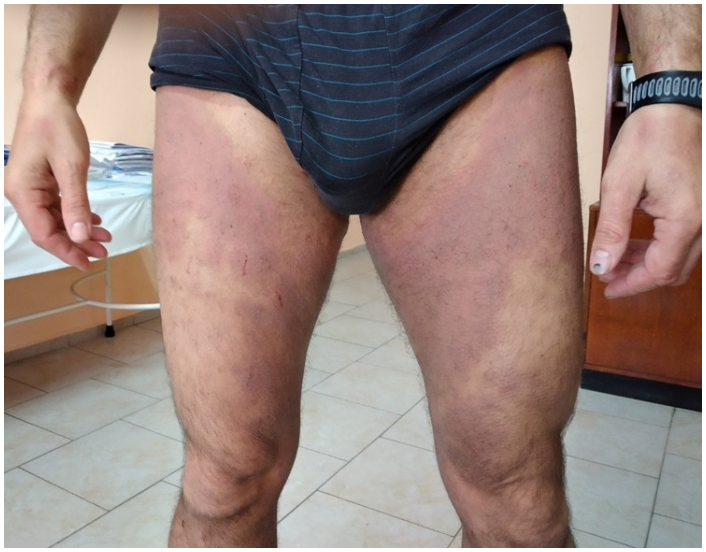


Figure 5



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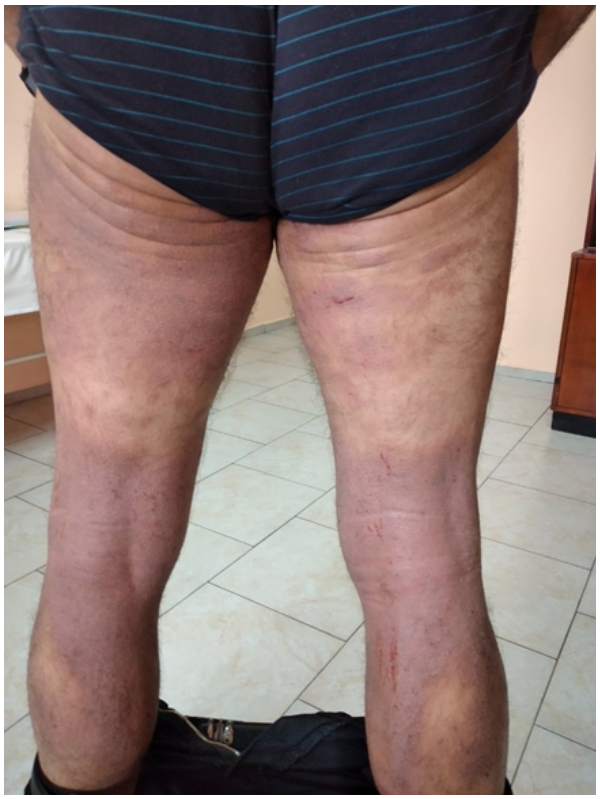

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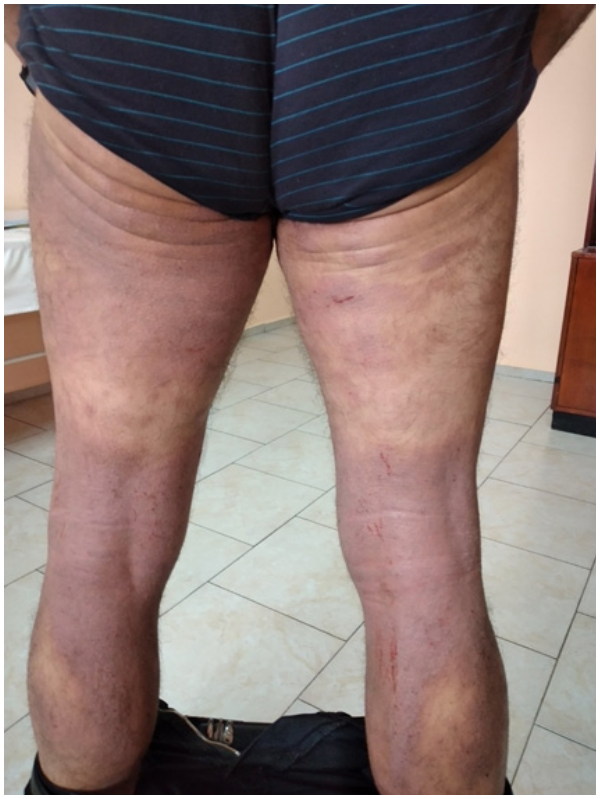

Figure 8

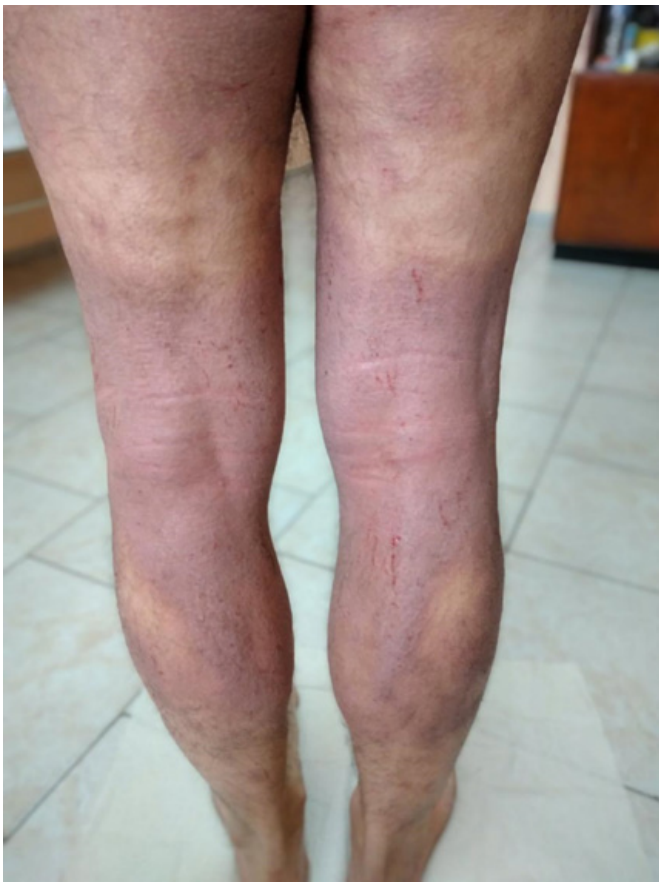

Figure 9

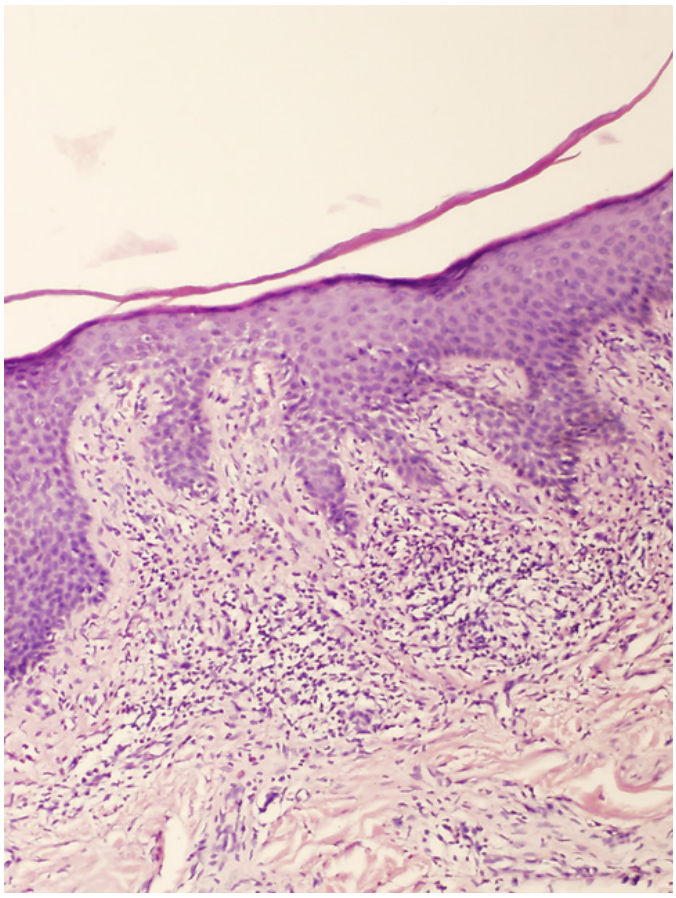

Figure 10

Fig. 1 - 9. The pathological changes involve the skin of the face (fig. 1), neck (fig. 2, 3), trunk and lower and upper extremities (fig. 1-9). They are represented by symmetrical, well-defined, erythematous papules and extensive plaques, reaching size up to 20 cm in diameter, circumferentially affecting the limbs (fig. 1, 4, 5, 6, 7). Discrete desquamation is found.

Figure. 10 Histopathological examination of axillary skin lesion Compact orthohyperkeratosis, reduced stratum granulosum, uneven acanthosis, mild spongiosis mainly in the lower epidermal segment, moderate interstitial and perivascular mixed inflammatory infiltrate with scarce number of neutrophils. The given histological picture corresponds to dermatitis.

The presence of a personal medical history of atopic dermatitis in childhood, polyallergy, recurrent bacterial and viral infections of upper respiratory tract, skin, eyes, a history of toxocariasis, gastrointestinal candidiasis, elevated Ig E with a tendency to increase, negative results for toxocariasis, elevated LDH level, elevated ANA and Anti-Centrome B Ab titer and dermatitis point to hyper-Ig E syndrome. The patient was treated with Methylprednisolone 40 mg/i.v./d., Desloratadine 5 mg/ p.o./bid, Allergosan 20 mg./i.m./d., Amoxicillin/Clavulanic acid 1 gr./p.o./bid. Local treatment included Hydrocortisone butyrate cream 0.1% and Clobetasol propionate 0.05%, bid. The patient underwent NB-UVB phototherapy 3 times a week for 1and a half month. A good therapeutic result was achieved.

Discussion

Autosomal dominant HIES (AD-HIES)

AD-HIES was discovered by B. Grimbacher et al. in a study of 30 patients and 70 of their relatives, in whom autosomal dominant inheritance, alteration in the immune homeostasis and changes in the maxillofacial apparatus, skeleton and connective tissue structures were found [6].

AD-HIES is caused by hypomorphic mutations in the signal transducer and the activator of transcription 3 (STAT3) gene leading to the classic multisystemic manifestation of the syndrome of dental, skeletal and connective tissue disorders [13, 14, 15]. The STAT3 mutation is responsible for defective, multiple cytokine signal transduction, including IL-6 and IL-22, leading to impaired Th17 function, explaining the predisposition to infections in the syndrome.

AD-HIES is presented with a classic triad of recurrent staphylococcal abscesses, recurrent upper respiratory tract infections and elevated serum level of Ig E [8]. Furunculosis and cellulitis can be observed in early childhood. "Cold" abscesses are pathognomic for the syndrome and are common in patients without antibiotic prophylaxis [18]. HIES occurs with frequent recurrent respiratory infections, often due to *Staphylococcus aureus*, including MRSA, less commonly *Haemophilus influenzae and Streptococcus pneumoniae.*

Pneumonia in HIES is typically complicated by lung abscesses, bronchiectasis, broncho-plural fistulas and pneumatocele. The presented broncho-pulmonary lesions are predisposing factors for colonization by opportunistic microorganisms such as *Pseudomonas aeruginosa and Aspergillus fumigatus* [18]. They cause chronic respiratory insufficiency - the most common cause of death in patients with HIES, followed by hemoptysis complicating lung abscesses and cystic lung diseases [18, 19]. In addition, affection of the upper respiratory tract could manifest as paranasal sinusitis, exudative otitis media, otitis externa, and mastoiditis [18].

A common association is the concomitant course of the syndrome with some fungal infections such as Candida albicans and other strains. There have been reports of infection with Pneumocystis jirovecii, Cryptococcosus spp., Histoplasmacapsulatum, Mycobacterium intracellulare, Nocardiaspp. as well as post BCG-vaccination complications [8, 18]. In AD-HIES, HSV infections are relatively rare [20]. The majority of the patients with AD-HIES possess some constitutional features such as coarse face, rough skin, deep-set eyes, a prominent forehead, prognathism, thick lower lip and auricles, a wide nose and increased interalar distance [22, 23, 24, 25], mid-face anomalies, arched palate [23] and a rare malformation - cranyosynostosis. AD-HIES is also characterized by oral and dental findings such as delayed loss of primary teeth, abnormal development of permanent teeth, severe dental caries with periapical abscess formation [25] and periodontitis [8, 26]. B. Grimbacher et al. report recurrent pathological bone fractures of the long bones, ribs and less commonly, the spine [8].

The ocular involvement includes extensive xanthelasmas, giant chalasias, undefined eyelid nodules, strabismus, retinal detachment with complicated cataracts (18). It has been shown that in AD-HIES there exists an increased risk of autoimmune diseases such as systemic lupus erythematosus [27, 28, 29], dermatomyositis [30] and membrane proliferative glomerulonephritis [31]. In addition, patients with AD-HIES are inclined to develop Hodgkin`s and Non-Hodgkin`s lymphoma [18]. I. Oztop et al. reported a comorbidity between AD-HIES and lung adenocarcinoma [32]. Coronary and aortic aneurysm, cerebral artery thrombosis and congenital patent ductus venosus have been identified [18].

Autosomal recessive HIES (AR-HIES)

AR-HIES was discovered in 2004 by E. Renner et al. [7]. It is caused by a mutation in Tyk2 gene. Tyk2 deficiency is responsible for impaired immune response of innate and acquired immunity due to defective cytokine signal transduction pathways which depend on INF-α, IL-6, IL-10, IL-12 and IL-23 [16, 17]. According to Q. Zhang et al. most patients suffer from recurrent otitis media, mastoiditis, sinusitis, pneumonia or bronchitis with bronchiectasis [33, 34]. In contrast to AD-HIES, in AR-HIES there is a predisposition to severe fungal and viral skin infections with HSV, VZV, HPV, Molluscumcontagiosum virus [35]. Detailed studies were conducted by M. D. Erlewyne-Lajeunesse in 2000 [36], B. Grimbacher et al. in 2005 [18)] A. F. Freeman and S. M. Holland in 2008 and 2009 [11, 12].

Laboratory findings

AD-HIES

A distinctive feature of HIES is the increased serum Ig E concentration exceeding 2000 U/ml and often - greater than 5000 U/ml. It was found that a value of 2000 U/ml is considered the cut-off point in establishing a definitive diagnosis [36]. The severity of the infection does not correlate with the level of serum Ig E [18, 37].

AR-HIES

In these patients, T-cell lymphopenia was detected with low counts of both CD4+ and CD8+ T cells, impaired T-cell expansion from activated peripheral blood mononuclear cells in vitro. Here, eosinophilia and elevated Ig E serum level is more pronounced [18].

Diagnosis

The diagnosis of HIES is made mainly by characteristic clinical findings, high serum IgE levels, eosinophilia and a positive family history [37]. B. Grimbacher et al. [5] offer a scoring system comprising both clinical and laboratory diagnostic criteria accepted by the National Institute of Health. The presented scoring system is a set of symptoms in the presence of which a result is obtained. The result indicates the probability of the patient being a carrier of the syndrome. With a value of over 40 the diagnosis is certain, a result between 20 and 40 means a possible diagnosis and a result below 20 – means it is unlikely.

Genetic testing

Genetic testing for STAT3 and/or DOCK8 is required in suspected cases [37]. Most of the patients with AD-HIES have heterogenous STAT3 mutations in the DNA-binding and Scr homology 2 - domains. All mutations are hypomorphic - missense or in-frame deletions.

Treatment

The main principle in HIES treatment consists in prevention and management of infections. Prolonged and regular use of systemic antibiotics and antifungals is essential to prevent the development of severe complications and parenchymal damage. Surgical treatment is undertaken in cases of lung abscesses, pneumocele and limited bronchiectasis [18]. Regarding cutaneous manifestations,

regular and long-term treatment with antibiotics and antifungals, is recommended. Skin abscesses are excised and drained. In severe cases of eczema, local emollients and corticosteroids are used in addition to antibiotic treatment. In dermatomycosis, onychomycosis, vaginosis and oral thrush - treatment with second-generation triazoles is effective. It is also effective in the treatment of invasive aspergillosis [18].

Long-term antimicrobial chemotherapy, including that against S. aureus, Thrimethoprime/sulfamethoxasole, semisynthetic penicillins, cephalosporins, significantly reduce skin abscesses and staphylococcal pneumonia. The use of immunoglobulins is controversial. A positive clinical outcome was observed as well as an improvement in neutrophil chemotactic function during prophylactic treatment with H2-receptor antagonists. Improvement in neutrophil phagocytosis and respiratory function has been reported upon application of sodium cromoglycate [18]. Some authors share positive therapeutic results in the treatment of skin complications with isotretinoine [36]. Good results have been demonstrated in stem cell transplantation [37].

Conclusions

We present a 47-year-old male with a sporadic hyper-IgE syndrome. HIES is a complex heterogenous group of primary immunodeficiency conditions manifested by a spectrum of variable clinical findings which have caused enormous diagnostic difficulties. To date, there are no specific clinical criteria, so the diagnosis is still based on the analysis of the disease, the patient`s life, family history, clinical manifestations of immune deficiency and the type of immune defect.

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ABBREVIATIONS

ANA- Antinuclear antibodies
AD-HIES - Autosomal dominant hyper-Ig E syndrome
AR-HIES - Autosomal recessivet hyper-Ig E syndrome
BCG - Bacillus Calmette-Guerin
CRP - C-reactive protein
HIES - Hyper-Ig E syndrome
HPV - Human Papilloma Virus
HSV - Herpes simplex virus
LDH - Lactate dehydrogenase
MRSA - Methicillin-resistant Staphylococcus aureus
NB-UVB - Narrow Band Ultraviolet-B
VZV - Varicella Zoster virus