



## Job's Syndrome With a Family History of Kawasaki Disease: A Case Presentation and Review of Literature

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### Abstract

**Background:** Job's syndrome or hyper-immunoglobulin E (IgE) syndrome (HIES) is an extremely rare primary immunodeficiency disease with an approximate annual incidence of less than 1/1 000 000. It is characterized by recurrent cold staphylococcal infections, unusual eczematous dermatitis, severe lung infections, and extensively high concentrations of the serum antibody IgE.

**Case Presentation:** A typical case of Job's syndrome with a family history of Kawasaki disease is presented in this study aiming at identifying the clinical features, investigational procedures, and management strategy, as well as evaluating the role of the ear, nose, and throat specialist and highlighting the probable relation between Job's syndrome and Kawasaki disease.

**Conclusions:** In general, early detection with proper care can prevent the progression of Job syndrome. In addition, the initiated treatment at the first signs of infection is mandatory for preventing long-term complications. There is a probable relation between Job and Kawasaki which requires more consideration.

**Keywords:** Job's syndrome, Kawasaki, Neck mass, Hyper-immunoglobulin E syndrome, Primary immunodeficiency

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### Introduction

Job's syndrome or hyper-immunoglobulin E (IgE) syndrome (HIES), which was first described in 1966, is a highly rare primary immunodeficiency disease, which develops due to mutations in STAT3 or DOCK8 genes (1). It is characterized by recurrent cold staphylococcal infections, unusual eczematous dermatitis, severe lung infections, and markedly increased levels of IgE (2). Although patients with Job's syndrome usually gather symptoms and signs, the literature sheds light on some cases that recognized unusual specific manifestations. Arora et al reported a case with an additional, not yet reported the finding of retinal detachment in a 15-year-old male child suffering from Job's syndrome (3). In another study, Singh et al demonstrated a case of a 13-month-old male child with complaints of pustular lesions on the neck, face, and upper chest. Physical examinations showed multiple pustular lesions associated with itching and abscesses around the neck, concentrated around the parotid region some of which had hemorrhaged and were crusted (2). Cruz-Portelles et al reported a case of HIES with one of the worst pulmonary sequels found in the literature (4). Similarly, Leonard et al presented a case report of a 22-year-old man with Job's syndrome complaining of back pain. He was found to have diffuse

large B-cell lymphoma involving his second lumbar vertebrae and spleen. Chemotherapy achieved complete remission after 4 cycles. In previous reports on lymphoma in Job's syndrome, patients were presented with extranodal disease and had poor outcomes. Lymphoma associated with Job's syndrome can achieve complete remission by appropriate chemotherapy and hematological support (5).

This study reports a case with characteristic and classical manifestations, but it is the first case of Job's syndrome with a family history of Kawasaki disease. There are many cross points in these two diseases, which motivate us to compare between them. In particular, no previous similar case has been so far published in this regard. Only about 250 Job's syndrome cases have been recorded worldwide (1). Due to its rareness, this case report seeks to spotlight clinical features, investigational procedures, and management strategies and to discuss the role of ear, nose, and throat (ENT) specialist. Another hypothesis was made concerning a proposed relation between Job's syndrome and Kawasaki disease.

### Case Report

A 10-year-old male child admitted to the pediatric hospital was referred to the ENT clinic with a complaint

of a cold mass in the left neck that started 20 days ago. It was associated with difficulty in swallowing, relentless pruritus, eczematous dermatitis, unproductive cough in the last two days, and a pain in his left knee with fever accompanied by normal appetite on the last day. His medical history started sequentially 15 days after his birth with eczematous dermatitis first, recurrent cases of pneumonia with pneumatoceles, recurrent oral candidiasis, and cyanosis after an effort or during fever, recurrent abscesses (2 episodes per year) in the face, neck, lower limbs and armpits, painful teeth and only one previous episode of acute sinusitis. The diagnosis of an autosomal dominant form of HIES was made 2 years ago based on clinical and laboratory findings. His surgery history included a right pneumatoceles eradication in February 2019 at the age of 9 years old, incision and drainage of a right pneumatocele filled with pus at the age of 18 months, and a repair of an inguinal hernia at the same age. His family history was also positive for hypothyroidism in the mother and Kawasaki disease was diagnosed in his 17 years old brother when he was 3 years old.

On physical examination, the skin showed the signs of widespread pruritic dermatitis, mainly at the face, neck, chest, and abdomen. The left neck mass was fluctuant without any pain, fever, or redness (Figure 1a). Retained primary teeth and other oral manifestations were noticed as well (Figure 1b). He had coarse facies (Figure 1c) although the ears and nose examination was normal. Finally, there was a noticeable joint hyper-extensibility in small joints (Figure 1d).

Laboratory feedback included hemoglobin of 12.1 g/dL, white blood cell count of 10 100 with 65% neutrophils and 26% lymphocytes, platelets of 250 000, *C-reactive protein*



**Figure 1. Job's Syndrome Features.** Note. (a) Pruritic eczematous dermatitis on the face and the cold neck mass was anterior to the left sternocleidomastoid muscle (2<sup>nd</sup> and 3<sup>rd</sup> neck levels), measured approximately (3×4) cm. (b) Oral manifestations included retained primary teeth, double rows of teeth with both primary and constant intermixed teeth, a high arched palate, erythematous mucosa, and caries. (c) Coarse facies with a prominent forehead, broad nasal bridge, deep-set eyes, and protruding pores. (d) Joint hyper-extensibility.

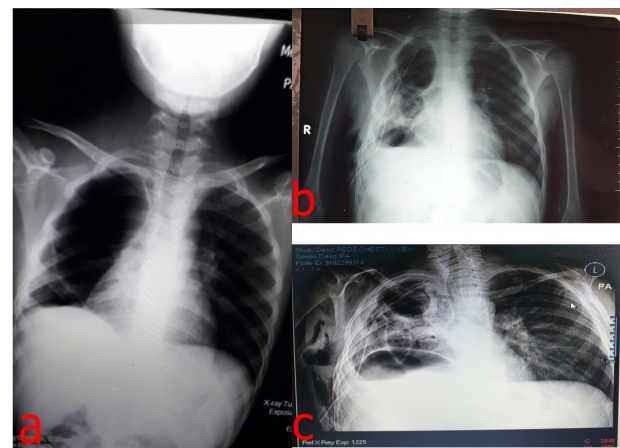
of 0.5, creatinine of 0.6, sodium of 137, potassium of 4.03, and IgE of 2500 IU/mL (RR: 10-179 IU/ML). A chest X-ray performed on admission was normal compared with two previous chest X-rays in March and April 2019 (Figure 2). Neck ultrasound demonstrated a well-defined mass filled with heterogeneous content below the left mandibular angle with the enhanced wall for blood supply that was measured (3×3.5×4) cm, align with an abscess. It also showed multiple lymphadenopathies, fusiform with central blood supply, and the largest ones are in the right neck (1.2×0.4) cm, left side (1.2×0.6) cm, right and left posterior triangles (1.6×0.7) cm and (1.2×0.6) cm, respectively.

Topical antibiotic and steroid creams, oral nystatin, ceftriaxone (IV), metronidazole (IV), and bath of ketoconazole were first used that showed an important improvement. On the 7<sup>th</sup> day of the treatment, a pus culture with methicillin-resistant *Staphylococcus aureus* was received with good sensitivity to vancomycin, gentamicin, amikacin, trimethoprim-sulfamethoxazole, and some other antibiotics while isolating no other germs. Skin lesions improved (Figure 3) and prophylactic treatment with trimethoprim-sulfamethoxazole was recommended accordingly.

## Discussion

HIES (formerly known as Job's syndrome) was first described in two girls by Devis et al in 1966, who named the disease after the biblical figure Job. In 1972, Buckley et al also described two boys with similar symptoms. These two syndromes (HIES and Job's syndrome) are thought to be the same and are under the broad category of hyper-IgE syndrome which is a rare immunodeficiency disorder, has inconstant expressivity, and is associated with multiple abnormalities (6).

There are two types of HIES, including autosomal-dominant and autosomal-recessive ones. The first type is



**Figure 2. Job's Syndrome Radiology.** Note. (a) Chest X-ray performed on admission was normal. (b, c) Chest X-ray performed on March and April 2019 showed multiple thin-walled cysts filled with air consistent with super-infection.



**Figure 3.** The Imporved Skin Lesions and Cold Abscess

caused by mutations in the signal transducer and activator of the transcription (STAT)3 gene, location 17q12 and might be familial or sporadic. This type is characterized by skeletal, connective tissue, recurrent pulmonary infections, and eczema (4,7). Inheritance usually follows this pattern. The other type is the autosomal-recessive one which is caused by the dedicator of cytokinesis (DOCK)8 mutations 9p24 or tyrosine kinase (TYK)2 19p13.2 mutations. It is presented with repeated viral and staphylococcal skin infections, frequent central nervous system anomalies, and vasculitis and shows a higher death rate, as well as a lack of tendency to pneumatoceles formation (8,9) although this pattern is infrequent.

The STAT3 gene provides instructions for making a protein that plays an important role in several body systems. In the immune system, a lack of effective STAT3 blocks the maturation of T cells, especially Th17 and other immune cells. The resulting immune system abnormalities make people with AD-HIES extremely susceptible to infections, especially the bacterial and fungal infections of the lungs and the skin. The STAT3 protein is also concerned with the formation of cells that build and break down the bone tissue, which might clarify the skeletal and dental anomaly characteristic of this case. IgE composition is normally reinforced by the Th2 cytokine *interleukin 4* (IL-4) and IL-13, and repressed by Th1 *interferon-gamma* and IL-12. The reduced production of INF- $\gamma$  by T cells has been demonstrated in HIES patients and is probably related to hyper-IgE (10).

FATED is a common mnemonic that is used to remind the symptoms, representing coarse **F**acies, cold staph **A**bscesses, retained primary **T**eeth, increased **I**gE, and **D**ermatologic problems. Patients with Job's syndrome usually gather symptoms and signs. Nearly they all have a history of pruritic, and eczematous dermatitis in early life. The sporadic occurrence of staphylococcal abscesses is common, and they are often referred to as cold abscesses because they become without any pain, heat, or redness. Chronic mucocutaneous candidiasis and onychomycosis are common as well (1).

Serious and repeated bacterial pneumonia is often recognized during infancy. The diagnosis is frequently delayed due to the lack of evident inflammatory signs contributing to the progress of the infection and pneumatoceles and bronchiectasis formation that predispose to secondary infections (11). Patients may also have recurrent bacterial arthritis and staphylococcal osteomyelitis at fracture sites, history of otitis externa, chronic otitis media, sinusitis, multiple caries, fissured tongue, and gingivitis or cervicofacial infection (1). The occurrence of malignant disease in HIES is higher, particularly non-Hodgkin's and Hodgkin's lymphoma (4). Diagnosis is made based on clinical findings, lab feedback containing mild to moderate eosinophilia in over 90% of patients, extremely high concentrations of IgE levels, and genetic tests (12). No definitive therapy is available in this regard. The mainstay of treatment is the monitoring of bacterial infections and it is typically longer than exemplary treatment because the disease responds more slowly than that of patients without HIES (1).

The goals of pharmacotherapy are to eradicate infections, reduce the morbidity rate, and prevent complications (1). The treatment focuses on skincare that is essential for eczema side-by-side with *S. aureus* infection prophylaxis, which is often given. During infections, although *S. aureus* is the most repeated germ announced as a cause of pneumonia, Gram-negative bacteria including *Pseudomonas* spp. and fungus have been often recognized as a cause of complications and death (11). Early incision and drainage followed by the intravenous administration of antibiotics are used for cutaneous infections (1). Thus, a surgical decision should be made in conditions of pulmonary complications. It is noteworthy that thoracic surgery can be complicated with a poor expansion of the residual lung after pulmonary cyst operation (4). Some studies mentioned the immunomodulation agents without clear results (13-15). Psychotherapy can be a successful management strategy for the severe psychological impact that can be imposed on children with excessive pruritus.

#### Point of View

The co-occurrence of Job's syndrome and Kawasaki disease in the same family (two brothers) motivated us to compare between them considering that no previous similar case has so far been published in this regard. There exist many cross points in these two diseases. Kawasaki and Job were first described in 1967 and 1966, respectively. Kawasaki primarily affects children younger than 5 years old while Job usually commences in infancy. Kawasaki causes inflammation in the walls of medium-sized arteries tending to affect coronary arteries. It is recognized as a leading cause of acquired heart disease in children. Serious complications include coronary artery dilatations and aneurysms (16). The vascular alterations of middle-sized arteries in Job's syndrome have been

observed, and coronary artery aneurysms have been described which may produce myocardial infarction (17). Kawasaki is occasionally called mucocutaneous lymph node syndrome because it also affects lymph nodes, skin, and the mucous membranes inside the mouth, nose, and throat (16). It should be noted that chronic mucocutaneous candidiasis is common in patients suffering from Job. Kawasaki's symptoms are, a rash on the main part of the body, swollen lymph nodes in the neck and perhaps elsewhere, irritability, swollen tongue, and joint pain. As mentioned earlier, a newborn eruption is normally the first appearance in Job. Staphylococcal cold abscesses with lymphadenopathy, oral manifestations, hyperextensibility, and recurrent arthritis are also possible (10). Nonetheless, the causes of Kawasaki remain unknown. Some researchers relate the disease to bacteria, viruses, or other environmental factors. Certain genes might make the child more likely to get it (16). Remember that HIESs have multiple genetic bases. Patients are highly susceptible to bacterial, viral, and fungal infections. Undoubtedly, it is highly recommended to search more in the literature and make some hypotheses about this proposed relation.

#### Authors' Contribution

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#### Conflict of Interest Disclosures

There is no conflict of interests.

#### Ethical Statement

This study was approved by the Ethics Committee of Damascus University of Medical Sciences.

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#### Informed Consent

The child's mother signed the informed consent for participating in the study.

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