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Clinical improvement in Job syndrome following administration of co-trimoxazole, omalizumab and inhaled tobramycin

Abstract

Established treatment regimens for the autosomal dominant hyperimmunoglobulin E syndrome, denominated Job syndrome, are lacking. Thus, Job syndrome still exerts a dramatic impact on patients' quality of life. Our aim was to present safety and effectiveness of a regimen including co-trimoxazole, omalizumab and inhaled tobramycin in Job syndrome. A 26-year-old woman diagnosed with Job syndrome since infancy through sequencing revealing G342D mutation in STAT3 gene was initiated in the above mentioned treatment regimen; she was followed for 6 months, and to date, none recurrent pulmonary or skin infection was noticed. Furthermore, a considerable improvement in skin lesions was observed. A combination of anti-IgE and longitudinal use of inhaled antibiotics seems well-founded in Job syndrome.

Key words: Job syndrome, recurrent infections, omalizumab, inhaled antibiotics

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Introduction

A 26-year-old woman, never smoker, presented to our department with cough, yellow sputum and localized left chest pain. Chest radiograph revealed consolidation in the left lower lobe and a fluid-filled cavity in the middle lobe. She denied the presence of fever, night sweats or weight loss. She had a medical history of Job syndrome diagnosed during infancy based on compatible genetic (G342D mutation in STAT3 gene) and clinical (recurrent lower respiratory and skin infections in need of repeated hospitalizations with several courses of empirical antimicrobial agents) findings.

Material and methods

Physical examination findings

Physical examination revealed the following vital signs: blood pressure of 110/70 mm Hg; heart rate, 85 beats/min; temperature, 36,8°C and oxygen saturation, 97% on room air. Lung auscultation revealed crackles mainly on left side while heart and abdomen examination results were unremarkable. There were no palpable lymph nodes. Clubbing was present, as well as extensive skin lesions on the upper limbs and hyperextensibility of finger joints.

Diagnostic studies

The complete blood and metabolic panel revealed elevated white blood cells (WBC) (16,1 K/μL) with neutrophilic predominance on admission (62%) and eosinophilic predominance on discharge (40%) and elevated c-reactive protein (22,33 mg/dL). Urinalysis and electrocardiogram were normal. Chest computed tomography (CT) showed cystic bronchiectatic lesions in the right upper lobe combined with a fluid-filled cavity within the middle lobe and consolidation in the left lower lobe (Figure 1). The patient underwent conventional bronchoscopy with the presence of purulent bronchial secretions bilaterally and hemorrhagic mucosa in the middle lobe. Culture of washing for common pathogens was

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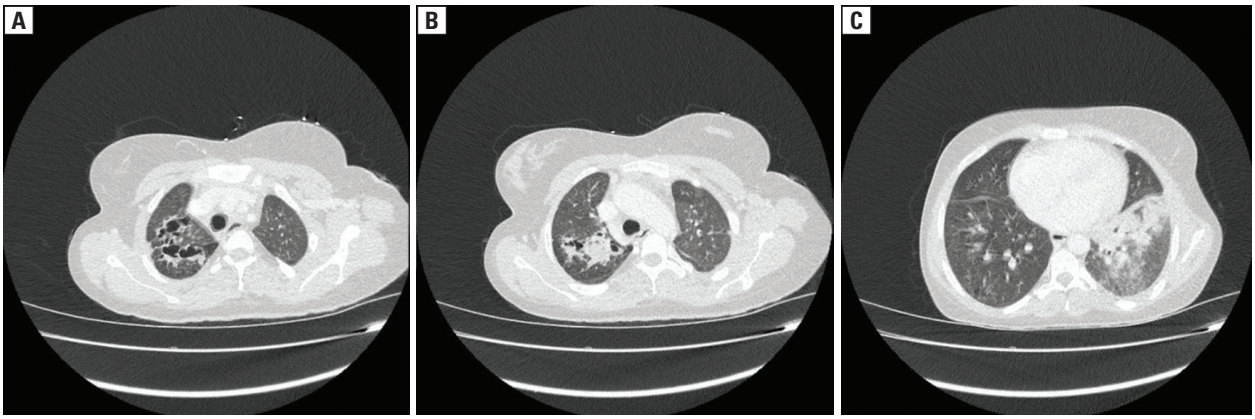

Figure 1. Chest computed tomography showed cystic bronchiectasis in the right upper lobe (**A**), a fluid-filled cavity in the middle lobe (**B**) and consolidation in the left lower lobe (**C**)

positive for Methicillin-resistant *Staphylococcus aureus* (MRSA) infection and negative for mycobacterium infection. Cytological examination of washing was negative for malignancy. Pulmonary function tests showed bronchodilator reversibility (PRE: forced expiratory volume in 1 second [FEV_1] / forced vital capacity [FVC]: 83%, FEV_1 of 1.65 L [59% of predicted] and FVC of 2 L [63% of predicted] — POST: FEV_1/FVC: 87%, FEV_1 of 1.8 L [68% of predicted] and FVC of 2.06 L [66% of predicted]). Skin prick test was positive for mixed fungus, *Tilia tomentosa* and *Candida*. Moxifloxacin and linezolid were administered for ten days based on antibiogram. An improvement on chest radiogram performed four weeks later was obvious. This was the sixth hospitalization for our patient within the previous year attributed to pneumonia following multiple hospitalizations since infancy due to recurrent lower respiratory or skin infections.

Clinical course

The patient was admitted with recurrent pneumonia in setting of diagnosed Job syndrome since infancy. Genetic confirmation of the disease had been conducted through sequencing revealing G342D mutation in STAT3 gene. Recent laboratory examination had revealed remarkably elevated serum IgE levels >30 000 IU/mL and eosinophilia (31% WBC count: 9.27 K/μL). During her last hospitalization, the patient was treated with antimicrobial therapy based on antibiogram, as part of symptomatic management of recurrent respiratory infections observed throughout the clinical course of syndrome. Considering multiple hospitalizations and extensive post-infectious structural abnormalities of lung parenchyma, multidisciplinary approach yielded a therapeutic regimen including biological anti-IgE agent and longitudinal antibiotics on a chemoprophylactic basis as the optimal strategy. In particular, the patient was commenced on co-trimoxazole, omalizumab and inhaled tobramycin. Established evidence has shown that co-trimoxazole is a safe and effective substitution to penicillins and has anti-MRSA coverage [1]. Furthermore, omalizumab, a monoclonal anti-IgE, has been shown closely related to a decline in serum IgE with symptomatic improvement especially in atopic conditions [2–4]. Eventually, inhaled antibiotics have emerged as a new option for specific groups of patients, including patients with bronchiectasis, combining high drug concentrations directly to the site of infection and concomitantly minimizing systemic absorption and potential side effects. Co-trimoxazole was administered orally in prophylactic dosage three times a week, omalizumab in dosage adjusted by the patient's weight and baseline IgE once a month subcutaneously and inhaled tobramycin 300 mg twice a day. The woman was followed for 6 months, with no recurrent respiratory or skin infections. Furthermore, a considerable improvement of skin lesions was observed (Figure 2). To the extent of our knowledge, this is the first time that combination of anti-IgE and longitudinal use of inhaled antibiotics is proposed in Job syndrome.

Discussion

Hyperimmunoglobulin E syndrome is a rare primary immunodeficiency disorder characterized by eczema, skin abscesses, recurrent staphylococcal infections of the skin and lungs, pneumatocele formation, candidiasis, eosinophilia, and elevated serum levels of IgE [5]. It was

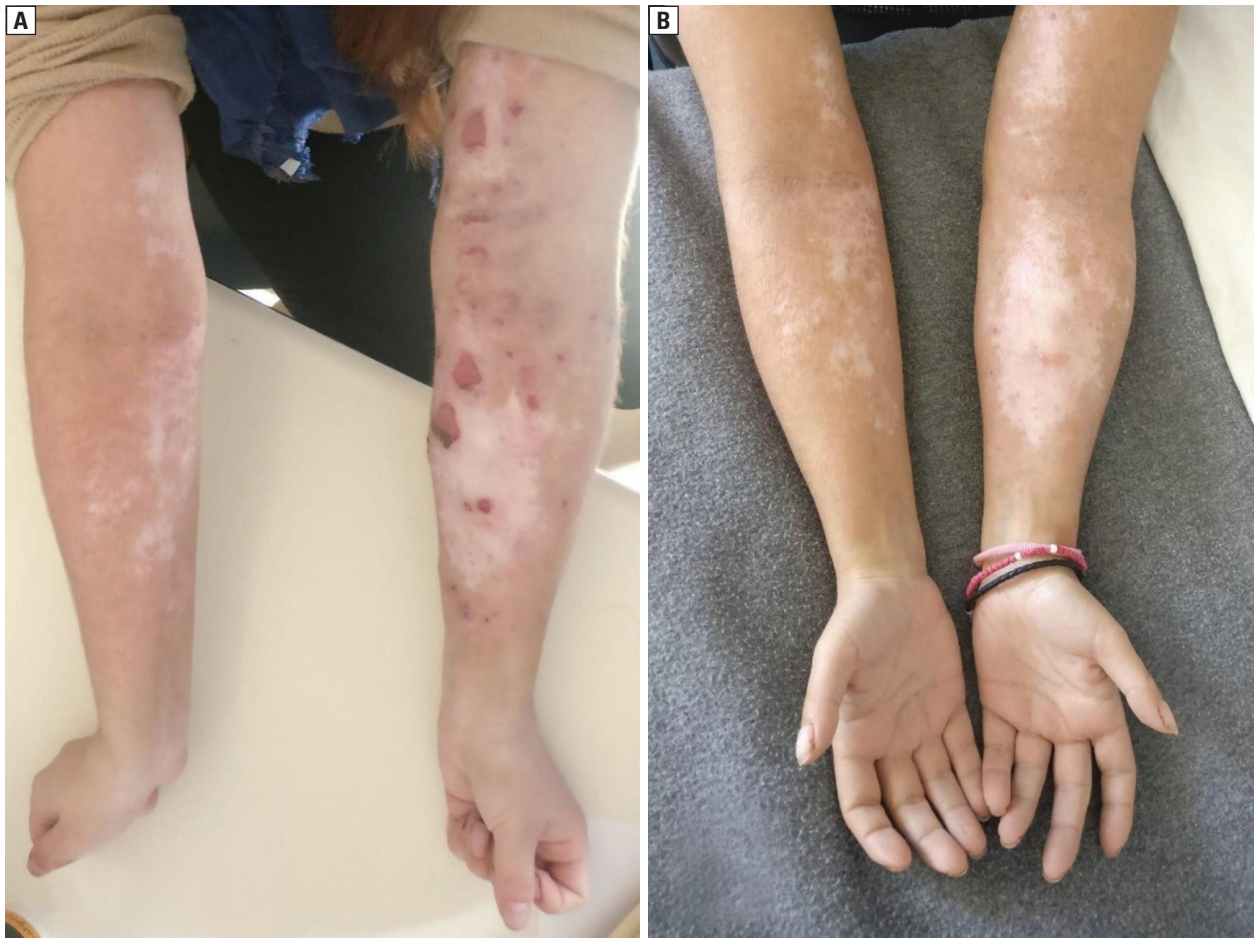

Figure 2. Improvement of skin lesions following administration of omalizumab for 6 months

first described as "Job syndrome" by David *et al*. in 1966 in two patients with eczema, recurrent pulmonary infections and cold lung abscesses and was later associated by Buckley *et al*. in 1972 with increased serum immunoglobulin E levels [6]. Job syndrome is classified as the autosomal dominant hyper-IgE syndrome, in which patients have abnormalities in different systems, including the immune system, connective tissue, skeletal and vascular structures [7]. It is attributed to a mutation in the STAT3 gene in more than two-thirds of cases (70%) with the etiology of the rest cases remaining unclear [8]. Clinical signs of immunological features include recurrent skin and pulmonary bacterial or candidiasis infections. *Staphylococcus aureus* is the predominant pathogen resulting in follicular skin lesions or recurrent lung abscesses, bronchiectasis and pneumatoceles. *Streptococcus pneumoniae* and *Haemophilus* are observable less frequently, while *Aspergillus* and *Pseudomonas* are usual cause of chronic colonization of bronchiectasis. The main laboratory diagnostic feature is an increase in serum IgE levels of more than 2000 IU/mL. Eosinophilia is observed in more than 90% of the patients while WBC count can be normal, elevated or reduced in number [9]. The established treatment is the long-term, sometimes consecutive, use of antibiotics by adapting the administration of antimicrobial agents to opportunistic infections occurring in affected patients, and in selected cases, applying surgical procedures during abscess development. In order to overcome purely symptomatic treatment applied for the moment, biological treatment with monoclonal antibodies or combination of biologics and antibiotics could be an optimal strategy. Further studies towards this direction are greatly anticipated.

Conflict of interest

None to declare.

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