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Case Report

Autoimmune/autoinflammatory syndrome induced by adjuvants after multi-component meningococcal serogroup B vaccination in a 7-year-old girl: a case report

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ABSTRACT

Background. Vaccines, which make it possible to be protected from many life-threatening infectious diseases, have been used safely and effectively for years. Most vaccines used today contain a variety of adjuvants and exogenous proteins. Severe reactions, in addition to transient and self-limiting mild reactions, mostly caused by these components, have been reported. The effects of vaccine adjuvants on the pathogenesis of immune-mediated diseases are still under investigation. The syndrome called Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) has been defined in the literature.

Case. We found a novel mutation of autoinflammatory diseases in the genetic analysis of our patient. The patient developed symptoms of prolonged fever, rash, arthritis and serositis after multicomponent serogroup B meningococcal (Bexsero®) vaccination, without a previously known rheumatic disease. In the presence of clinical findings in our patient, the diagnostic criteria of ASIA syndrome were met.

Conclusion. To the best of our knowledge, this is the first case report of a patient diagnosed with the autoinflammatory disease with a novel mutation after Bexsero® vaccination. We consider that genetic examinations will be useful in patients with a systemic vaccine reaction in the presence of ASIA when diagnostic criteria are met.

Key words: vaccines, cryopyrin-associated periodic syndromes, ASIA syndrome, adjuvants, autoimmune diseases.

Vaccines, an indispensable public health measure, are very effective in preventing infectious diseases.[1] The multicomponent meningococcal serogroup B vaccine (4CMenB), Bexsero® (GSK Vaccines Srl, Siena, Italy) is the first vaccine approved to prevent the invasive disease caused by Neisseria meningitides serogroup B. The vaccine contains aluminum hydroxide in addition to its active ingredients.[2]

In general, there is a fear of reactions to vaccine components and that vaccines may trigger the development of various diseases.[1] Most of the adverse effects that develop after 4CMenB vaccination have been reported to be general disorders and administration site conditions. Suspected immune-mediated and/or neurological diseases are less common, but Kawasaki disease, Henoch-Schoenlein purpura, Juvenile idiopathic arthritis, myositis, vasculitis, epilepsy, paralysis, Guillain-Barre syndrome have been reported.[3]

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Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) was first reported in 2011. The presence of 2 major or 1 major and 2 minor criteria is sufficient for diagnosis. (Table I).[4]

In recent years, as a result of a better understanding of the natural immune system regulation, immune activation pathways and in consequence of genetic studies, the number of diseases included in the group of autoinflammatory diseases has increased.[5]

We found a novel mutation in the NLRP12 gene in the genetic analysis of our patient who had no known disease other than seasonal allergic rhinitis before, who developed symptoms of prolonged fever, rash, arthritis and serositis after Bexsero® vaccination, and who met ASIA diagnostic criteria. Here, we presented the difficulties in the differential diagnosis and treatment of our patient in the light of the literature.

Case Report

A 7-year-old girl was admitted to our emergency service with the signs of a rash, redness in the eyes, pain and swelling in her ankles and the complaint of high fever for 3 days. The Bexsero® vaccine had been administered 3 days ago. The patient had no known diseases except for seasonal allergic rhinitis and occasionally used antihistamines for the rhinitis. No previous side effects were observed in the patient, who was vaccinated according to the national vaccination schedule. Her mother was followed up with the diagnosis of Hashimoto's thyroiditis, and there were no additional features in her family history. On physical examination, her body weight was 24 kg (SDS: 0.06, Percentile: 52.39) and her height was 132 cm (SDS: 1.8, Percentile: 96.41). Her axillary temperature was 38.3^{0}C, pulse 150 beats per min, respiratory rate was 28 breaths per min, arterial blood pressure was 90/65mmHg. Her general condition was moderate, and widespread skin lesions compatible with erythema multiforme, bilateral non-purulent conjunctivitis and periorbital heliotrope rash were observed. Breathing sounds decreased in the base of the lungs on auscultation. On palpation, the liver was 3 cm below the costal margin. Swelling and warmth in the ankles were present (Fig 1). Her laboratory examination results were as follows; Leukocytes (WBC) 17300 (4000-10000)/μL, Neutrophils (NEU) 16200 (2000-6000)/

Table I. Diagnostic criteria for Autoimmune/inflammatory syndrome induced by adjuvants.

Major criteria	• Exposure to external stimuli (infection, vaccine, silicone, adjuvant) before clinical manifestations
	• The appearance of "typical" clinical manifestations
	Myalgia, myositis, or muscle weakness
	Arthralgia and/or arthritis
	Chronic fatigue, unrefreshing sleep, or sleep disturbance
	Neurological manifestations (especially associated with demyelination)
	Cognitive impairment, memory loss
	Pyrexia, dry mouth
	• Removal of inciting agent induces improvement
	• Typical biopsy of involved organs
Minor criteria	• The appearance of autoantibodies or antibodies directed at the suspected adjuvant
	• Other clinical manifestations (ie, IBS)
	• Specific HLA (ie, HLA DRB1, HLA DQB1) Progression of an autoimmune disease (ie, MS, SS)

HLA: human leukocyte antigen, IBS: irritable bowel syndrome, MS: multiple sclerosis, SS: systemic sclerosis.

μL, Lymphocytes (LYM) 1000 (1500-3500)/ μL, Eosinophils (EOS) 200 (0-500)/μL. CRP 375.80 (0-5) mg/L, erythrocyte sedimentation rate 91 (0-20) mm/h and procalcitonin was 0,98 (0-0.5) ng/ml. She was lymphopenic because her lymphocyte count was below 1500/ μL, but lymphocyte subsets and Ig G,A,M,E values were within normal reference ranges for her age. House dust, cat, grass/cereal for specific IgE values were <0.10 kU/L. Other laboratory findings planned to assess systemic involvement were: Creatine phosphokinase (CPK): 30 (0-145) U/L, CK MB: 0.6 (0.6-6.3) ng/ml, HS-TROPONIN I: 106.6 (8.4-18.3) ng/L. C3:1.65 (0,9-1,8) g/L, C4: 0.372 (0,1-0,49) g/L. HS-TROPONIN was high and other parameters were within normal range. On abdominal ultrasound (USG) hepatosplenomegaly with 43mm and minimal abdominal fluid; on neck USG, reactive lymph nodes smaller than 1 cm were observed. Minimal pleural effusion on the right was seen on chest radiography. The transthoracic echocardiography revealed 1-2. 1st-degree tricuspid regurgitation, 1st-degree mitral insufficiency and a 5-6 mm mild pericardial effusion adjacent to the right ventricle. Coronary arteries were evaluated as normal. These findings were compatible with pancarditis. She was hospitalized with pre-diagnoses of atypical Kawasaki disease, vaccine reaction, sepsis, and connective tissue disease. Oral cetirizine dihydrochloride and empirical intravenous (iv) cefotaxime treatment was initiated for the patient. TORCH, Ebstein

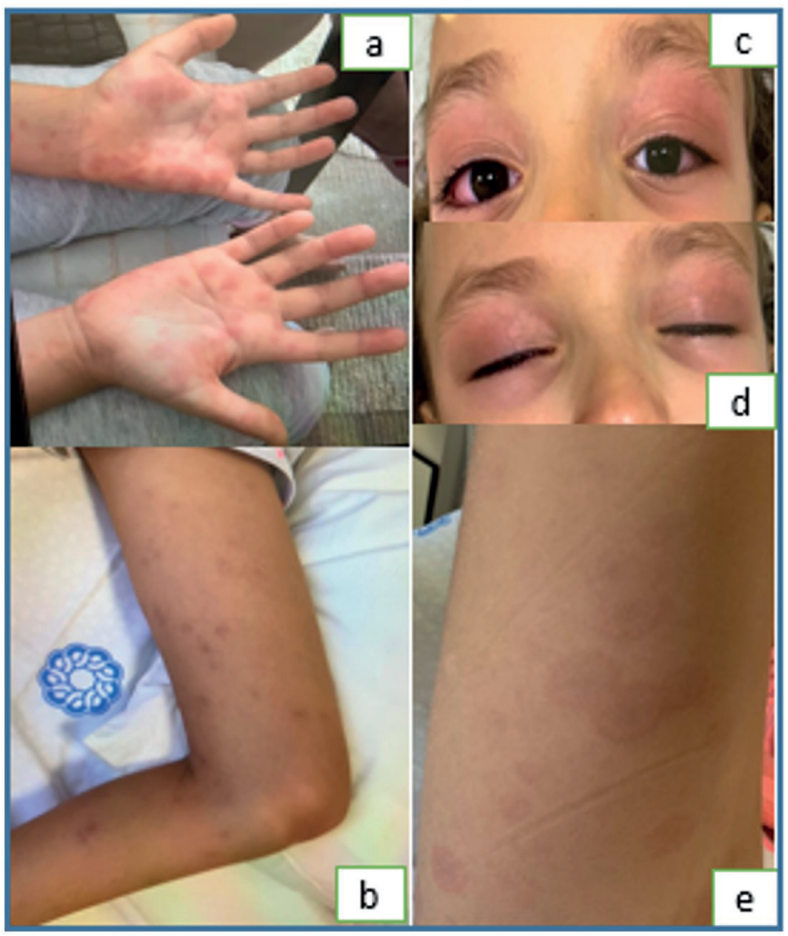

Fig. 1. Skin and occular findings of our patient.

a, b. Maculopapular erythema in the palm and lower extremities,

c. Nonpurulent conjunctivitis, **d.** Heliotrope rash, **e.** Erythema multiforme.

barr virüs (EBV), Human immunodeficiency virus (HIV) and Brucella serological test results of the patient were negative. Cefotaxime treatment was discontinued on the 4th day because no growth was found in blood, urine and throat cultures. In the follow-up, mild hypoalbuminemia (3.14 g / dL) developed along with microscopic hematuria and proteinuria. Antinuclear antibody (ANA) pattern was spotted and positive with a titer over 1/100. A genetic panel was run for autoinflammatory diseases due to clinical findings. Anti-extractible nuclear antigens (ENA) antibodies (Anti nRNP / Sm, Anti Sm, Anti SS-A, Anti SS-B, Anti Scl 70, Anti CENP-B, Anti Nucleosome, Anti Histone, Anti Jo1, Anti Ribosomal P, Anti PM-Scl) was negative. With a serum sickness-like reaction, atypical Kawasaki and autoinflammatory disease pre-diagnosis, the patient was started on intravenous (IV) methylprednisolone 2 mg/kg on the 5th day of hospitalization. Her fever dropped dramatically after the first dose of steroid therapy. Acute phase reactants and leukocytosis regressed over time. On the 4th day of the steroid treatment of the patient who clinically recovered, the CRP value decreased to 19.30 mg/L and the procalcitonin value was normal. Hypoalbuminemia and urine tests improved. Control laboratory test results were: WBC 24300 (4000-10000)/μL, NEU 13900(2000-6000)/μL, LYM 8600(1500-3500)/μL, EOS 100(0-500)/μL, HGB 11.7 (12-16) g/dL, HCT 34%, PLT 1212000(150000-450000) /μL. It was thought that neutrophilia and thrombocytosis developed secondary to steroid treatment. The steroid dose was reduced to 1mg/kg/day. Control echocardiography showed mild left ventricular hypertrophy and minimal mitral insufficiency. The antiaggregant dose of aspirin (5mg/kg/day) treatment was initiated for the patient. The patient, whose control laboratory findings, active complaints and skin findings improved, was discharged on the 8th day of admission to continue outpatient follow-up. Steroid (1mg/kg/day) and aspirin (100 mg/kg/day) treatment was discontinued within two weeks and the patient had no active complaints at her follow-up control. Genetic analysis revealed pathogenic heterozygous p Lys695Arg (c.2084A>G) mutation in the 10th exon of the MEFV gene; Possibly pathogenic, heterozygous novel p.Val151GlnfsTer41 (c.451_452delGT) mutation in exon 3 of NLRP12 gene and heterozygous, of unknown clinical significance p.Arg860Trp (c.2578C>T) mutation in exon 6 of NLRP12 gene. Informed consent was received from her family.

Discussion

Diseases with a rash accompanying fever are common in children. The most common causes are infections, collagen tissue diseases and drug reactions.[6] Possible infectious causes were primarily excluded in our patient, who was accompanied by symptoms of rash, arthritis, serositis and fever that continued for three days after vaccination. We considered the pre-diagnosis of a serum sickness-like reaction (SSLR) in our patient, who had a clinic compatible with serum sickness, because complement levels were found to be normal.

SSLR is a systemic hypersensitivity reaction which generally occurs secondary to drugs. The characteristic symptoms, which begin within 1-2 weeks after exposure to the causative agent, are rash, fever, polyarthralgia and/or polyarthritis. It is differentiated from serum sickness with the absence of immune complexes in the circulation and normal complement levels.[7]

After vaccination, the onset of the findings in the patient was shorter than three days and her clinic did not improve with time. Due to these reasons, we ruled out the diagnosis of SSLR.

Juvenile dermatomyositis disease, which was mentioned in the preliminary diagnosis due to the finding of heliotrope rash and muscle weakness, was excluded because of the absence of additional dermatological findings, normal CPK values and the development of acute clinical findings after vaccination. In addition, although ANA positivity was detected in our patient, the diagnosis of other collagen tissue diseases was excluded because the ENA profile

was negative and the clinical findings were not sufficient for diagnosis.

Kawasaki disease (KD) is a systemic vasculitis that is most commonly seen in males between the ages of six months and five years, and mostly involves the middle and small arteries. The presence of fever lasting five days or longer and at least 4 of the following clinical findings: changes in the periphery of the extremities, polymorph exanthema, bilateral conjunctival congestion, changes in the oropharyngeal mucosa, and cervical lymphadenopathy are necessary for the diagnosis. In addition to the fever criterion, atypical KD is also mentioned in patients with lung and gastrointestinal system involvement that do not meet all the diagnostic criteria.[8]

In our patient, fever lasting more than five days, diffuse maculopapular rash, serositis, non-purulent conjunctivitis were findings compatible with KD. However, oropharynx involvement, pathological cervical lymphadenopathy, coronary artery involvement, were not observed in our patient. However, the diagnosis of atypical Kawasaki with the detection of pleural effusion and free fluid in the abdomen remained among the possible diagnoses.

Studies also support that vaccines induce autoinflammatory diseases, especially in genetically susceptible individuals. Severe exacerbations of chronic rheumatic diseases have frequently been reported in the literature following vaccination. Based on this, ASIA syndrome has been defined.[9-12] Sarcoidosis, Sjögren's syndrome, undifferentiated connective tissue disease, silicone implant incompatibility syndrome, and immune-related adverse events are defined as classic examples of ASIA. These disorders have been described after an adjuvant stimulus (silicone implantation, drugs, infections, metals, vaccines, etc.) among genetically predisposed individuals, which induce an hyperstimulation of the immune system resulting in the production of autoantibodies, eventually leading to the development of autoimmune diseases.[12]

However, the presence of ASIA syndrome is still debated in studies due to the lack of syndrome-specific diagnostic criteria and evidence for the triggering role of adjuvants in this syndrome. Also, the time between antigen exposure and the development of ASIA syndrome is unclear. A recent study reported that this time ranged from 2 days to 23 years.[4]

In the presence of clinical findings developing 3 days after vaccination in our patient, 2 major diagnostic criteria of ASIA syndrome were met. Although there was no family history and recurrent complaints, genetic analysis was planned for the patient with suspected autoinflammatory disease. In the treatment plan for possible diagnoses, we preferred IV methylprednisolone and oral cetirizine dihydrochloride treatments, since there were no contraindications for any disease and this is a common treatment method. At the end of two weeks of treatment, the patients clinical and laboratory findings improved. During her follow-up, a significant mutation in the NLRP12 gene was detected in her genetic analysis.

To date, only 62 patients with NLRP12 mutations were reported in a 2020 review. Therefore, a comprehensive description of the phenotypic variations associated with this mutation is lacking. Similar to our patient, the main symptom reported in the cases was fever (93%), while other findings were rash, urticaria, myalgia, polyarthralgia/arthritis, abdominal pain (41-62%).[13]

In a different study involving 246 children with periodic fever of unknown cause, NLRP12 mutation was identified in 15 patients as a result of next-generation sequencing analysis. The age of the first autoinflammatory disease-related fever attack has been reported to vary between 2 months and 13 years. While short-term corticosteroid therapy was found to be effective in the treatment of attacks in most patients, it has been reported that canakinumab (anti-interleukin-1p antibody) was successfully used in a severe case.[14]

Familial cold autoinflammatory syndrome-2 (FCAS2) is an autoinflammatory disease characterized by recurrent rash, fever, urticaria, arthralgia and myalgia in which autosomal dominant mutations are detected in the NLRP12 gene. In most patients, exposure to cold is a trigger for attacks. Although the age of onset varies from the first to middle ages of life, the clinical symptoms are also quite heterogeneous.[5]

In our case, there was no history of a periodic finding and cold exposure was not a triggering factor. A definitive diagnosis was made in our patient with the help of the genetic tests planned as a result of the presence of non-specific but multisystemic findings occurring after vaccination.

As a result, to the best of our knowledge, no autoinflammatory disease diagnosed with a novel mutation after Bexsero® vaccination in children has been reported in the literature. The differential diagnosis of rash and prolonged fever findings accompanied by systemic findings is not always easy, as in our patient. It is beneficial to use genetic tests for autoinflammatory diseases in suspected cases, even if it is the first attack. In this way, the genetic variations and phenotype relationships of rare autoinflammatory diseases will become apparent in time.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: OA, SA, OGB, NU, OK; data collection: OA, TÇ; analysis and interpretation of results: OA, SA, GA, ÖKB; draft manuscript preparation: OA, SA, TC, SA. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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