Mashhad University of Medical Sciences (MUMS)

Reviews in Clinical Medicine

Clinical Research Development Center Ghaem Hospital

Autosomal Recessive Agammaglobulinemia in Juvenile Idiopathic Arthritis: A Case Report

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ARTICLE INFO

Article type
Case report

Article history
Received: 22 Sep 2019
Revised: 30 Oct 2019
Accepted: 22 Jun 2020

Keywords
Agammaglobulinemia
Immunoglobulins
Juvenile Idiopathic Arthritis

ABSTRACT

The B lymphocyte developmental blocks agammaglobulinemia, leading to peripheral B cell depletion and plasma immunoglobulin reduction. Agammaglobulinemia is a rare yet severe disease since it is presented with recurrent sinopulmonary and skin, central nervous system, bone, and joint infections. The onset of the disease is reported to be at the age of six months. Associations have been reported between arthritis and immunodeficiency disorders, such as agammaglobulinemia and common variable immunodeficiency (CVID). This study aimed to present the case of a 3.5-year-old female with a three-month history of the swelling of the left knee, mimicking oligoarticular juvenile idiopathic arthritis. After the initiation of immunosuppressive treatment, the patient developed large, tender, erythematous lesions on the inguinal region bilaterally, which developed to ecthyma gangrenosum due to Pseudomonas. The patient's mother also reported recurrent episodes of infections since the patient was a one-year-old infant. Subsequent to the immunological examinations and laboratory tests, the patient was diagnosed with autosomal recessive agammaglobulinemia due to low serum immunoglobulin concentration and the absence of peripheral B cells. Primary immunodeficiency conditions (particularly agammaglobulinemia) and CVID should be considered in children with arthritis and recurrent infections. Moreover, immunological analysis should be performed prior to treatment in these children.

Please cite this paper as:
Zare Feizabadi A, Malek A, Ahanchian H. Autosomal Recessive Agammaglobulinemia in Juvenile Idiopathic Arthritis: A Case Report. Rev Clin Med. 2020;7(2): 75-77.

Introduction

Agammaglobulinemia is a rare form of primary immunodeficiency disorder, which is characterized by the lack of peripheral B cells and significant reduction of immunoglobulin concentrations due to the early arrest of B cell maturation in the bone marrow (1). Agammaglobulinemia is classified as X-linked agammaglobulinemia and autosomal recessive agammaglobulinemia; the former accounts for 85-90% of the cases and is induced by the mutations of the Bruton tyrosine kinase (BTK) gene on the X chromosome, which is responsible for B cell maturation (2, 3). The latter accounts for an equal occurrence of 10-15% of the remaining cases in both genders and is caused by the deficiencies in the pre-BCR complex or signaling proteins. Both forms of agammaglobulinemia have similar clinical manifestations. (4)

After the age of six months, when maternal antibodies subside gradually, the patients develop serial bacterial infections with Streptococcus pneumoniae, Moraxella catarrhalis, and Haemophilus influenzae, which affect the respiratory tract (sinusitis, pneumonia, and otitis media), skin, central nervous system, gastrointestinal tract (giardiasis), bones, and joints (5).

Juvenile idiopathic arthritis (JIA) may occur in patients with primary immunodeficiency disorders, including agammaglobulinemia and common variable immunodeficiency. Intravenous immunoglobulin is considered to be the only ap-

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propriate treatment for these patients (6, 7).

This study aimed to present the case of a patient with severe and repeated episodes of infection accompanied by JIA presentation.

Case report

A 3.5-year-old female patient was referred with the swelling of the left knee without erythema and three months of limping before referral. She was admitted to Rheumatology Department of Akbar Hospital, affiliated to Mashhad University of Medical Sciences in Mashhad, Iran in October 2018.

The patient had no history of trauma, and the physical examination revealed the swelling of the left knee and reduced range of motion. In addition, the muscle atrophy of the left lower limb was observed due to immobility. All the other joints were normal in the examination and had a normal range of motion. The complete blood count and other laboratory tests (ANA, Anti-ccp, RF, and PPD) were also normal. The sonography results showed effusion in the left knee, and bone marrow aspiration was also performed, showing normal cellularity.

Based on the left knee arthritis, which prolonged for more than six weeks, and joint effusion, the patient was diagnosed with oligoarticular JIA. Treatment started with nonsteroidal anti-inflammatory drugs (ibuprofen syrup: 10 mg/kg/dose; TDS), methotrexate (10 mg/m2/week; intramuscular), and low-dose prednisolone tablets (5 mg daily).

About 20 days after the methotrexate treatment, the patient was returned to the hospital with walking difficulty. Initially, the physicians suspected JIA flare-up; however, the physical examinations of the patient indicated diffuse perineal and inguinal erythema with tenderness. Therefore, she was admitted again, and during hospitalization, the erythema progressed to ecthyma gangrenosum with the focal necrosis of the tissue (Figure 1).

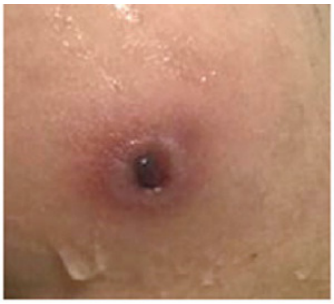

Figure 1. Ecthyma Gangrenosum

In addition, the results of sonography showed the thickness of the skin and subcutaneous tissue, and the patient was subjected to broad-spectrum antibiotics, including meropenem (30 mg/kg/dose three times a day) and vancomycin (15 mg/kg/dose four times a day).

Since the wound culture was positive for Pseudomonas aeruginosa, treatment was administered with intravenous anti-pseudomonas antibiotics, including amikacin (10 mg/kg/dose three times a day) and meropenem (30 mg/kg/dose three times a day for 15 days), which were administered consistently. Moreover, the surgical debridement of the necrotic tissues was performed, and the patient was discharged with the prescription of oral fluoroquinolone.

After the review of the medical history and infections of the patient, her parents reported episodes of sinusitis and upper respiratory tract infections since the patient was a one-year-old infant. In addition, the parents stated that she had been admitted to a hospital two years before with fever, cough, and severe respiratory distress. At that time, the chest X-ray and echocardiography had shown severe pericardial effusion, tamponade, and a fungal-shaped mass in the right atrium. Sternotomy was also performed on the patient to surgically remove the cardiac mass, and the pericardial window was also developed. The pericardial fluid culture was negative, and cytopathology showed acute inflammatory fluid with no atypical cells. Furthermore, cardiac mass pathology indicated a blood clot (white and red blood cell sediments with fibrins). Based on the medical history of the patient, the physicians suspected immunodeficiency, and the results of the immunological evaluation revealed extremely low serum immunoglobulin levels (IgG: 304 mg/dl, IgA: 2 mg/dl, IgM: 1 mg/dl, IgE<0.1 mg/dl), and the circulating CD19+ lymphocytes were estimated at 0.3% (Table 1).

Table 1. Immunological Examinations

Test	Result	Unit	Reference Range
Isohemagglutinin			
Anti-A	Negative		
Anti-B	Positive		
Blood Group and RH	A Positive		
IgG Serum	304	mg/dl	453-916
IgA	2	mg/dl	20-100
IgM	1	mg/dl	19-146
IgE (CLIA)	<0.1	IU/ml	<81
HBsAb (CLIA)	72.28	mlu/ml	<20 Non-immune >20 Immune
HIV Ab (1+2) (CLIA)	0.36	Index	<0.9 Non-reactive 0.9-1.1 Borderline >1.1 Reactive
CD3	79.5	% Lymph	30-70
CD4	27.7	% Lymph	22-58
CD4/CD8	0.5	*% Lymph*	1-4
CD19	0.3	*% Lymph*	9-30
NBT Activated	98%		>95%

As a female, the status of the patient showed low immunoglobulin levels and the absence of circulating B cells, which led us to the diagnosis of autosomal recessive agammaglobulinemia. Since the disease was associated with JIA in our patient, treatment with monthly intravenous immunoglobulin was initiated to maintain the protective levels of serum immunoglobulin, prophylactic antibiotics, and prohibition of the attenuated vaccines.

Discussion

Agammaglobulinemia is characterized by extremely low levels of immunoglobulins, with the heritage pattern of either X-linked or autosomal recessive. In these conditions, peripheral B cells reduce due to the arrest in their maturation pathway. Autosomal recessive agammaglobulinemia should be suspected when the patient has a family history consistent with this pattern of inheritance, when a female patient has agammaglobulinemia or when the mutation of the BTK gene cannot be identified in a male patient with agammaglobulinemia. Both types of the disorder have the same clinical and laboratory properties and treatment method. The patients often present with repetitive infections (e.g., pneumonia, sinusitis, diarrhea, conjunctivitis, cellulitis, meningitis/encephalitis, sepsis, hepatitis, septic arthritis, and osteomyelitis) after the age of six months when maternal immunoglobulins disappear from the bloodstream (8). The causative pathogens are mostly encapsulated; such examples are Streptococcus pneumoniae, Haemophilus influenzae type B, Streptococcus pyogenes, and Pseudomonas, which affect the respiratory tract, skin, bone, joints, and central nervous system. On the other hand, Campylobacter, Giardia, and Salmonella species often infect the gastrointestinal tract, while enterovirus affects the central nervous system.

Aseptic arthritis has been detected in approximately 10-30% of hypogammaglobulinemia cases; the association of autoimmune arthritis disorders (e.g., rheumatoid arthritis, JIA, and spondyloarthritis) with this condition has also been reported in several studies (9). Arthritis is commonly classified as aseptic-oligoarthritis and monoarthritis (10).

In patients with primary immunodeficiency and JIA, it is considered typical not to have positive ANA and RF factors due to the lack of immunoglobulin synthesis similar to our patient (6). The levels of IgG, IgA, and IgM are also lower than 100 mg/dl or might even be undetectable. However, IgG levels may be within the range of 200-300 mg/dl, and CD19 may reduce significantly (8). The available treatment for this immunological disorder is intravenous immunoglobulin, along with prolonged antibiotic therapy and proscription of attenuated vaccines.

The evaluation of the case in the present study indicated the possible association between immune deficiency and rheumatoid disease. The patient was a female with recurrent infection (e.g., sinusitis) since infancy and a history of purulent cardiac tamponade requiring surgical pericardiectomy. She was admitted to the Rheumatology Department of Akbar Hospital due to chronic aseptic arthritis mimicking JIA. Following the JIA treatment initiation, the patient developed large perianal erythematous plaques due to Pseudomonas infection. Considering her gender, recurrent, severe infections, low levels of immunoglobulins, and CD marker of 0.3%, the patient was diagnosed with autosomal recessive agammaglobulinemia. The patient was discharged after intravenous immunoglobulin and prolonged antibiotic therapy. Furthermore, the avoidance of live vaccines was recommended.

Conclusion

According to the results, patients with recurrent or severe infections and aseptic arthritis who are unresponsive to treatment should be examined meticulously. In addition, they must be subjected to immunological examinations for the further investigation of their condition.

Conflict of Interest

The authors declare no conflict of interest.

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