Case Report *Iran J Ped Hematol Oncol. 2023, Vol 13, No 3, 222-224*

ORCHITIS and Chronic Granulomatous Disease

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Received: 27 March 2021 **Accepted:** 08 January 2023

Abstract
Chronic Granulomatous Disease (CGD) is a primary immunodeficiency disorder, which is almost always characterized by impairment of the function of leukocytes and generally presents with recurrent chronic relapsing bacterial or fungal infection. This study reported a three-year-old boy who was referred to the Pediatric Hematology and Oncology Center of Shohada Khalij-e-Fars general hospital, Bushehr with recurrent lymphadenitis, and orchitis, who suffered from this disease. Since confirmation of diagnosis, he is receiving Co-trimoxazole three times per week as prophylaxis, and the plan for him is hematopoietic stem cell transplantation (HSCT).
Key Words: Chronic Granulomatous Disease, Lymphadenitis, Orchitis.

Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder, which is known as a dysfunction of leukocyte's killing activities, this disease mostly presents with recurrent chronic relapsing bacterial or fungal infections. Unfortunately, this disorder finally leads to visceral abscesses, lymphadenitis, or tissue granuloma formation (1). Generally, CGD is caused by mutations in genes of protein-encoding subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which plays a main role in the respiratory burst phenomenon in the leukocytes for killing a few dangerous microorganisms (1).

Case Report

A three-year-old boy was referred to our Pediatric Hematology and Oncology Center with his chief complaints of progressive swelling, erythema, and pain in the right submandibular and mastoid region associated with past 7 days of intermittent fever (Figure-1). The patient physical examination also showed some tenderness, edema, and erythema adjacent to the cervical lymph nodes area. The patient was admitted to the pediatric ward at Shohada Khalij-e-Fars general hospital, Bushehr Iran for more evaluation and a therapeutic plan.

A review of the patient's past medical history showed he was admitted three times before for sepsis workup since three months old. The growth and development history of the patient was normal. In family history, the parents were relatives (second-degree consanguine) and the patient had a history of another sibling dead after sepsis without any confirmed pathologic agent, at about one and a half years of age. In our patient, lymph node sonography revealed inflammation in both lymph nodes. The lymph node drainage was done and the culture was sent, which was negative. The laboratory studies showed a shift to the left in leukocytosis while we saw elevated titers of both indices: ESR and CRP. The patient was admitted to the hospital for antibiotics therapy for at least 10 days with a combination of medications of; Clindamycin and Ceftriaxone intravenously. About 10 days later the patient get healthy perfectly and

discharged from our hospital. Unfortunately 2 months later to discharge, he was admitted again for swelling, erythema, and pain in the right-sided testis. The patient's physical examination also revealed these problems occurred in the vicinity of the right-sided testis while newly diagnosed inguinal lymphadenopathy. The vital sign was stable but he was febrile. Sonography of the scrotum and inguinal lymph node was accomplished and reported, there was an inflammation event around both testes that may suggest a testicular malignancy while the lymph node diameter was 20 *15 mm in size. All related laboratory studies were performed thereafter. Recent laboratory findings showed leukocytosis with a shift to the left and elevated ESR and CRP. Instantaneous Urologist consultation, requested for necessary emergency right-sided orchiectomy as soon as possible. After unilateral orchiectomy, histopathology evaluation showed the right testis tissue inflammation. A combination of antibiotics therapy was administrated and continued for 10 days (Clindamycin and Ceftriaxone intravenously) again concerning microorganism sensitivity.

However with the patient familial history and recurrent inflammation and sepsis, lymphadenitis, and orchitis, we finally considered whether the patient should be intended for primary immune system impairment, then in follow-up laboratory evaluation for our assumption, we assessed: IgA, IgG, IgM, IgE plasma level, tetanus and pneumococcal antibody titers. Fortunately, these were normal but Di Hydro Rhodamine DH titer (DHR) was significantly positive. After a thorough para-clinical assessment of our patient, we considered the disease, Chronic Granulomatous Disease (CGD) could be labeled on the patient and necessitated the patient to receive long-lasting Co-trimoxazole at least 3 times a week for prophylaxis purposes. Our plan was bone marrow transplantation and fortunately, his sister was a full-matched HLA member for bone marrow transplantation donation.

Figure 1. A 3-year-old patient with lymphadenitis in the submandibular and mastoid region

Discussion

CGD is caused by mutations in genes encoding protein subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, which plays a main role in the respiratory burst in leukocytes. Most patient who suffered from CGD has a mutation in the CYBB with X-liked genetic transmission, NCF1, NCF2, and CYBA with autosomal recessive genetic transmission (1). Respiratory bursts result in the production of oxygen-free radicals like superoxide ions, hydrogen peroxide, hypochlorite ions, and hydroxyl radicals. These oxygen-free radicals are needed for the phagocytosis process. Overall, a defective NADPH oxidase system causes patients with CGD to be predisposed to recurrent bacterial and fungal infections because of defection in neutrophils' ability to expose phosphatidylserine, which is a

recognition factor for phagocytic cells to clear apoptotic cell bodies (1, 2).

In addition to recurrent infections, patients the majority of the time developed sterile granulomas in the gastrointestinal tract, liver, lymphoid tissues, and skin, with no clinical evidence of infections (3, 4). In most CGD patients, the defective primary immune response to clearing the infections responsible for not adequate antimicrobial response, such as fungi, yeasts, Nocardia asteroid, Staphylococcus aureus, Escherichia coli, Nontyphoidal salmonella, Klebsiella pneumonia and Burkholderia cepacia (5, 6).

Long-term antibiotic and anti-fungal prophylaxis, hematopoietic stem cell transplant, interferon-gamma, and gene therapy are the different forms of therapies in CGD (7).

The resume in our patient is related to the familial history and recurrent inflammation presented as sepsis, for more evaluation of our patient we further send samples for whole exome sequencing, which reported the patient has a mutation in the CYBB with X-liked genetic transmission according to most patient with CGD who have mutations in their CYBB gene that encodes gp91phox, located at Xp21.1. CYBB mutation. This is the most frequent mutation with 65 percent in frequency. Overall, in all patients with recurrent infections and inflammation, they should be evaluated for primary or secondary immune deficiencies.

Conclusion

This study reported a three-year-old boy who was referred to the Pediatric Hematology and Oncology Center of Shohada Khalij-e-Fars general hospital, Bushehr with recurrent lymphadenitis, and orchitis, who suffered from this disease. Since confirmation of diagnosis, he is receiving Co-trimoxazole three times per week as prophylaxis, and the plan for him is HSCT.

Conflict of interest

The authors had no conflict of interest to declare.

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