Chronic necrotizing granulomatous skin lesions and MHC class I deficiency syndrome due to TAP2 deficiency

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Abstract

Major histocompatibility complexes class I (MHC- I) deficiency, also known as bare lymphocyte syndrome type 1 (BLS-1), is a rare autosomal recessively inherited immunodeficiency disorder with remarkable clinical and biological heterogeneity. Transporter associated with antigen processing (TAP) is a member of the ATP-binding cassette superfamily of transporters and consists of two subunits, TAP1 or TAP2. Any defect resulting from a mutation or deletion of these two subunits, adversely affects the peptide translocation in the endoplasmic reticulum, which is an important process for the proper assembly of MHC- I molecules.

To date, few patients with reduced cell surface expression of MHC-I molecules have been reported. Herein; we described two Iranian cases with 2 and 3 decades delayed diagnosis of chronic necrotizing granulomatous skin lesions due to TAP2 deficiency without pulmonary involvement; and then segregation analysis in family members was performed by PCR and Sanger sequencing among 10 members of their family and found three homozygous mutation in three asymptomatic patients.

Introduction

Human lymphocyte antigen (HLA) class I deficiency, also known as bare lymphocyte syndrome type 1 (BLS-1), was first identified in 1978 and is a rare autosomal recessively inherited immunodeficiency disorder with remarkable clinical and biological heterogeneity. BLS type 1 is characterized by severely deficient expression of HLA class I, whereas the defective expression of HLA class II is observed in BLS type 2, which the latter causes life threatening infections in early childhood [1].

HLA class I molecules, also called major histocompatibility complexes class I (MHC-I), appear on the surface of all nucleated human cells. They are heterodimer molecules that consist of a heavy chain or α subunit and a light chain called β 2-microglobulin. The α subunit contains the α 1, α 2, and α 3 domains. The peptide-binding site is formed by the α 1 and α 2 domains and binds to antigenic peptides with 8-10 amino acids that are derived from the proteasome by degradation of cytosolic proteins.

Endogenous proteins are processed proteolytically by the proteasome. Subsequently, the generated small peptides are transferred to the endoplasmic reticulum (ER) lumen by a transporter associated with antigen processing (TAP). TAP is a member of the ATP-binding cassette (ABC) superfamily of transporters and consists of two subunits, including TAP1 or TAP2. Any defect resulting from a mutation or deletion of TAP1 or TAP2 hampers the peptide translocation in the ER, which is an important process for the proper assembly of HLA class I molecules in the ER. Therefore, TAP defects result in attenuated expression of HLA class 1 molecules on the cell surface and impair the intracellular antigen presentation pathway [2–4].

In patients with TAP deficiency, the expression levels of MHC-I molecules on the cell surface are significantly lower (30–100-fold) than in normal hosts. As a result, these patients suffer from bacterial infections, including sinusitis, chronic respiratory tract inflammation, and granulomatous skin lesions.

The latter occurs in about 50% of patients. It is well understood that mutations in the TAP2 subunit cause more serious problems than mutations in the TAP1 subunit [4–6]. The disease is extremely rare and usually appears late in childhood, usually when they become adults. Their HLA genotype is homozygous, and their parents are usually first cousins [4]. Herein; we evaluated a genetic study of an Iranian family with MHC class I deficiency syndrome due to TAP2 deficiency. We first described the index case, and then we analyzed the sequencing of the patient, her parents, and also other family members.

Method

Study Participants

Ten members of an Iranian family were included in the study. Blood samples were taken for DNA analysis and the participants' genomes were sequenced.

Genotyping and Analysis

Samples were collected from the subjects after obtaining written informed consent. Genomic DNA was isolated from peripheral blood samples using the Exgene™ Blood SV kit (GeneAll Cat. No. 105-101 / 105-152), according to the kit's protocol.

Paired-end sequencing (2 × 101bp) was performed on the NextSeq2000 sequencer (Illumina, San Diego, CA). WES libraries were prepared and captured according to the Agilent Technologies Sure-Select protocol. The sequence data were mapped to the human reference genome (hg-19, NCBI37) using the Burrows-Wheeler Alignment (BWA) method. About 99% of the mapped reads were covered and the mean coverage of the target regions was ~75 times. Variants were identified with the Genome Analysis Toolkit, SAMtools, and the Picard Tools.

Variant validation: PCR and Sanger sequencing

Validation of TAP2 gene, single nucleotide deletion variant identified by whole-exome sequencing (WES) in the index patient, and segregation analysis in family members was done by PCR and Sanger sequencing. This specific primers pair designed for the test: F: 5'-CTGTGGCTCCTTGGGAAAAC-3', R: 5'-CAGCACCTGGAAGAGGAGAA -3'.

Results

Medical history of the index case

Patient II.2, the index patient, was a 46-year-old woman who was referred to our hospital, in February 2021, with a 20-year history of skin lesions involving the lower limb. Her medical history was unremarkable except for these chronic skin lesions on her right leg and foot. The lesions started on the right foot, which gradually grew larger and also increased in number [Figure 1]. The skin lesions were itchy papules and nodules on the right leg and foot, accompanied by right leg edema and foot

disfigurement. The patient was hemodynamically stable and complete blood counts, liver function tests, renal function tests, and comprehensive metabolic panels were unremarkable. Before the admission, skin lesion biopsies had been performed several times during the last years. The histopathologic examination showed hyperkeratosis, parakeratosis, acanthosis, and mild spongiosis of the epidermis. Dermis revealed a large area of necrosis centered on the deep dermis including thickened and hyalinized collagen fibers and some vessels. The necrotic area was surrounded by a granulomatous inflammation containing aggregates of histiocytes, Langhans type multinucleated giant cells, numerous lymphocytes, and plasma cells. Periodic acid Schiff (PAS), Ziehl Neelsen and modified acid fast staining were all negative. These findings were consistent with necrotizing granulomatous inflammation [Figure 2]. No microorganisms were detected and the patient had no documented evidence of tuberculosis or sarcoidosis. Differential diagnoses included deep mycosis, mycobacterial infections, and also mycetoma. The result of the polymerase chain reaction (PCR) of the MTB complex was negative. In addition, mycological and mycobacterial cultures were negative.

Six months, and then eight months of empirical anti-TB treatment were ineffective. After being diagnosed with sarcoidosis, she was treated with corticosteroids and methotrexate, but the lesions did not improve. Two years ago, the patient was diagnosed with probable deep mycosis and was given itraconazole and also a course of voriconazole which were not beneficial. The skin lesions continued to exacerbate periodically without responding to other treatments.

Based on history exacerbated numerous skin lesions on the right leg and foot accompanied by disfigurement, actinomycetoma, or eumycetoma was probably diagnosed for the patient. The empirical treatment consisted of amphotericin B deoxycholate, clindamycin, and co-trimoxazole were initiated. The patient had no respiratory signs and symptoms. Computed tomography of the chest revealed normal findings. Magnetic resonance imaging of the right foot was also normal with no evidence for osteomyelitis. After a few days, the exacerbating episode was diminished modestly with antibacterial therapy [Figure 3].

In connection with the long-lasting and non-healing chronic necrotizing granulomatous skin lesions over several years, possible underlying immunodeficiency was considered. Therefore, the immunological work-ups including flow-cytometry and also WES were performed. The patient was discharged 16 days after admission, taking co-trimoxazole double-strength tablets every 8 hours, clindamycin 600 mg every 8 hours, penicillin v every 6 hours, and terbinafine 500 mg every 12 hours. Laboratory data are shown (Table 1-4).

Table 1
Differential blood cell count of index case.

Laboratory test	Reference range	Result
WBC ($10^3/\mu\text{L}$)	4-10	7.8
Neutrophils ($10^3/\mu\text{L}$)	1.5-8	2.9
Lymphocyte ($10^3/\mu\text{L}$)	0.8-4.8	4
Monocyte	0.2-1	0.6
Basophil	0-0.2	0
Eosinophil	0-0.8	0.2
Hb (gr/dl)	12-14	10.9
MCV (fL)	80-100	87.2
PLT ($10^3/\mu\text{L}$)	140-450	278
WBC, White blood cells; PLT, Platelets; Hb, Hemoglobin		

Table 2
Flow Cytometry, whole blood.

Test	Result	Reference range
CD3%	67.7	62-87
CD4%	35.1	32-64
CD8%	38.6	18-35
CD19%	8.9	6-23
CD20%	10	5-22
CD56%	37.3	3-15
CD3 absolute count cells/ μL	2146	900-2400
CD4 absolute count cells/ μL	1113	430-1800
CD19 absolute count cells/ μL	282	110-570
CD20 absolute count cells/ μL	317	74-440
HLA-DR %	10.9	3-15
CD, cluster of differentiation; HLA, Human leukocyte antigens		

Table 3

Test	Result	Reference range	Method
HBs Ag index	0.59	Negative :<0.9 Equivocal:0.9-1.1 Reactive: ≥ 1.1	ECL
HBs Ab IU/L	15.6	Negative :< 9 Equivocal: 9-11 Reactive: >11	ECL
HIV (1-2) Ab	Negative	Negative	ECL
Diphtheria Ab (IgG) IU/mL	0.295	Basic immunization recommended: <0.01 Booster vaccination recommended: 0.01-0.1 Good immunity: >0.1	ELISA
Tetanus Ab (IgG) IU/mL	1.169	No immunity: <0.01 Immune protection is not ensured: 0.01-0.1 Adequate immune protection: > 0.1	CLIA
Anti-Streptolysin O	Negative IU/mL	< 200	Latex agglutination
Blood group and RH	A positive	-	-
Isoagglutinin Titer, Anti-A	Negative	> 1:8	Conventional Test Tube
Isoagglutinin Titer, Anti-B	1:8	> 1:8	Conventional Test Tube
Interferon-Gamma Release Assays	Positive	-	Quantiferon TB gold
HBs Ag, Hepatitis B surface <i>antigen</i> ; HBs Ab; Hepatitis B surface <i>antibody</i> ; HIV, <i>human immunodeficiency virus</i> ; ECL, Electrochemiluminescence; ELISA, Enzyme-linked immunosorbent assay; CLIA, Chemoluminescence immunoassay			

Table 4
Lymphocyte transformation test (LTT)

Test	Patient' SI	Control' SI	Normal range
LTT-PHA	6.5	4.9	≥ 3
LTT-BCG	3.5	3.2	≥ 2.5
LTT-DT	2	2.8	≥ 2.5
LTT- <i>Candida</i>	1.5	2.6	≥ 2.5
PHA, Phytohemagglutinin; BCG, Bacille Calmette-Guerin; DT, Diphtheria-Tetanus;			

WES of the index patient identified a homozygous frameshift deletion (NM_018833:c.983delC:p.A328Gfs*52) in the TAP2 gene that resulted in a truncated protein. According to the ACMG variant classification criteria, this mutation is categorized as pathogenic. This finding was validated by Sanger sequencing in the index patient. In addition, the genotypes of her parents, siblings, and her affected second cousin were evaluated. The pedigree and the genome sequencing of family members are shown [Figure 4, 5].

Parents and the patient family members

Patient I.4, index patient's second cousin, was a 61-year-old patient who has been developing hypopigmented ulcerative patches and plaques with itching, erythema, and severe edema involving lower limbs for 33 years ago with nodules around the nose [Figure 6]. Microscopic examination of the skin biopsies revealed hyperkeratosis, parakeratosis, spongiosis, and acanthosis of the epidermis. The dermis showed a dense infiltration of mixed inflammatory cells, including some multinucleated giant cells surrounding a large central area of necrosis. These findings were compatible with the necrotizing granulomatous reaction. Ziehl–Nielsen staining for acid-fast bacilli and PAS staining were negative. MTB PCR results were also found negative. Six months of empirical anti-tuberculosis treatment did not show positive results. Since TAP2 deficiency was proven for the index patient, this patient was also suspected of having MHC class I deficiency. WES test indicated the same homozygous mutation in the TAP2 gene. Hence, the patient had the same disorder as the index patient.

Patient II.2 had three brothers and three sisters. Sequence analyzes of brothers, including case II.4 (40 years old) and II.8 (28 years old) revealed a homogeneous mutation of TAP2 deficiency. Both cases were asymptomatic, except for a history of recurrent minor aphthous oral ulcers. Case II.6 (33 years old), one of the sisters of the index patient, was also found to have homozygous TAP2 deficiency but was completely asymptomatic. Case II.7 (31 years old), another sister of the index patient, was heterozygous for this mutation with no symptom. Case II.3 and II.5, sister and brother of patient II.2, represented the wild type of TAP2. Case I.2 (68 years old) and I.3 (60 years old), the father and mother of patient II.2, were heterozygous for this mutation and were also asymptomatic.

Discussion

Bare lymphocyte syndrome is an entity due to mutations in genes of human leukocyte antigen. To date, few patients with reduced cell surface expression of MHC-I molecules have been reported. On the other hand, MHC-II deficiency is also a rare autosomal recessive combined immunodeficiency which affects thymic epithelium and also both marrow-derived cells, leading to impaired antigen presentation, defective maturation and activation of CD4⁺ lymphocyte. Patients are susceptible to multiple severe infections including bacteria, fungi and also viruses and death in early childhood is common [7]. In contrast to severe MHC-II deficiency, these patients have characteristic clinical manifestations that are not usually life-threatening [8]. MHC-I deficiency is not often diagnosed because it is scarce and can remain asymptomatic for decades [9]. MHC-I molecules appear at variable levels on the surface of all nucleated cells in the body. Besides the role of presenting intracellular antigenic peptides to cytotoxic T lymphocytes, these molecules also have a significant role in modulating the activity of cells carrying MHC-I binding receptors, including natural killer (NK) cells and T cells [10, 11]. Hence, malignant or virus-infected cells that cannot express HLA class I molecules are killed by NK and T cells. It has also been suggested that diminished levels of HLA class I molecules in TAP-deficient patients lead to the attacking of self-cells by NK cells, a phenomenon called missing self-recognition [12]. Indeed, it seems that neutrophils are the main culprit in the pathogenesis of TAP deficiency due to chemo-attraction or activation resulting from inefficient pathogen clearance. In some cases, chronic cutaneous granulomatous lesions involving the skin have been described. No specific pathogens have been identified in these lesions. Although histopathology of sinuses and skin lesions may reveal necrotizing granulomatous inflammation, but this finding had not been identified in the lungs of TAP deficient patients [4].

Among patients with MHC type 1 deficiency, recurrent bacterial infections of the upper respiratory tract including sinusitis or otitis media, also nasal polyps have been reported. The infection may extend to the lower respiratory tract and cause bronchitis, pneumonia, and bronchiectasis. *Haemophilus influenza*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* are the most common organisms developing the infection [13, 14].

Cutaneous manifestations are necrotizing granulomatous lesions from a pustule or subcutaneous nodule, with progressive extension and also ulceration in an asymmetrical distribution over the legs, or hands, the former being more common. [6, 15, 16]. In a study by Zimmer et al., four patients developed facial lesions around and on the nose which were accompanied by septal perforation and destruction of the nasal cartilage [8]. The cousin of the index case had a skin lesion around the nose in midface. Mycobacteria, fungi, or other pathogens have never been identified in these lesions [4].

Infectious complications in the central nervous system can be misdiagnosed with granulomatosis with polyangiitis (formerly Wegener's granulomatosis) and make a challenging issue. Discrimination of this entity from other disease conditions including chronic granulomatous disease, common variable

immunodeficiency, granulomatosis with polyangiitis, sarcoidosis, mycobacterial infections, and cystic fibrosis is necessary [4].

Mutations in the TAP-2 subunit are associated with failure of MHC- I expression on cells leading to the abnormal selection of CD8+ T cells in the thymus. Decreased number of alpha/beta TCR-positive CD8 T cells were observed in patients with TAP deficiency. On the flip side, the patients represent a higher proportion of gamma/ delta-positive CD8+ T cells. Despite normal levels of NK cells, including CD3-CD56/CD16+ and also CD3-CD8+ NK cells in the patients, their function is abnormal [17]. However, flow cytometry is an important diagnostic tool for HLA class II deficiency. The absence of cellular and humoral immune responses to foreign antigens and inactivation of T cells are the most significant immunological feature of BLS type 2. In this disorder, although the total number of circulating T and B lymphocytes is normal, a decrease in CD4+ T lymphocytes is noted, which varies from patient to patient [18]. The complete absence of HLA-DR expression on B cells and monocytes is diagnostic [19].

Due to the low number of patients, there is no strong evidence of treatment. Bone marrow transplantation and also gene therapy have been treatment options for HLA II deficiency, but therapeutic options for HLA I deficiency are principally based on the prevention of infections [20]. The treatment includes antibiotic therapy for respiratory infections with or without chest physiotherapy. However, in addition to antibiotics, intravenous immunoglobulin may be useful in some patients [4]. For chronic sinusitis, sinus surgery is not recommended as it can exacerbate the condition and in cases of cutaneous lesions, local therapy can be helpful [4]. In a study by Law-Ping-Man et al. treatment with long-term chloroquine was used as an anti-inflammatory and also immunomodulatory agent (3.5 mg/kg/d), leading to persistence of the plaques without progression. Immunomodulatory treatment with interferon and immunosuppressive therapy, consisting of corticosteroids in combination with other agents such as azathioprine, cyclophosphamide, methotrexate, or cyclosporine is not recommended due to exacerbation of lesions and this type of therapy is contraindicated in TAP-deficient patients [4, 7, 21].

We presented two patients who developed chronic, slowly progressive granulomatous lesions one of them on the right lower limb and the other on the face and also lower limbs. The skin lesions of our patients were considered severe and not spontaneously healed. These two patients lack the other characteristic feature of this disorder, including recurrent bacterial infections of the respiratory tract with subsequent bronchiectasis. Our findings showed that TAP-deficient patients represented immunity against infections. It has been shown that MHC-I expression mainly occurs using TAP-dependent pathways, but there are also TAP-independent pathways that enable patients to have sufficient immunity against infections [22].

Declarations

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Figures

Figure 1

Papules and nodules on the right leg and foot with leg edema and also foot disfigurement.

Figure 2

Histopathologic examination revealed findings consistent with necrotizing granulomatous inflammation.

Figure 3

Improvement of exacerbating episode after antimicrobial therapy.

Figure 4

Genome sequencing of family members.

TAP2 Family

Figure 5

Pedigree of an Iranian family with TAP 2 deficiency.

Figure 6

Ulcerative patches and plaques with erythema, and edema of limbs and also nodules around the nose.