CASE REPORT
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New Presentation of CD27 Deficiency; Coronary Ectasia and COVID-19

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ABSTRACT

CD27 is a costimulatory receptor involved in the maturation of the innate and adaptive immunity. CD27, through interaction with CD70, plays a role in the control of Epstein-Barr virus (EBV) infection. CD27 deficiency leads to an immune dysregulation disease characterized by EBV susceptibility. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might put patients with primary immunodeficiency at risk for adverse outcomes.

Chromogenic in situ hybridization (CISH) study was performed to detect EBV in the lymphoma tissue. Genetic analysis of the patient was done with Whole Exome Sequencing and detected variant was confirmed with PCR-Sanger sequencing.

Here we report a 20-month-old boy with CD27 deficiency who developed lymphoma and coronary artery ectasia and had been infected with SARS-CoV-2. Clinical and laboratory findings

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were incompatible with atypical Kawasaki syndrome or multisystem inflammatory syndrome in children (MIS-C).

As CD27 deficiency is a rare immune defect, publishing clinical data about the identified patient(s) can shed light on our knowledge about the related phenotype and the spectrum of clinical manifestations associated with CD27 deficiency. Thus, our findings expanded the spectrum of manifestations beyond EBV infection, highlighting this unusual cardiac sequela that could be related to EBV infection, lymphoma, or an underlying disease.

Keywords: CD27 deficiency; COVID-19; Coronary ectasia; EBV-associated lymphoma; Multisystem inflammatory syndrome in children

INTRODUCTION

Inborn errors of immunity (IEIs), also referred to as primary immunodeficiencies, are a heterogeneous group of diseases presenting with increased susceptibility to infections, allergies, autoinflammation, autoimmunity, and malignancies. They comprise a constantly growing number of diseases with more than 450 genetic defects, classified into 10 main groups.[1,2] Immune dysregulation, characterized by a spectrum of autoimmune and inflammatory conditions, has been categorized by the International Union of Immunological Societies (IUIS) as an entity affecting the adaptive immune response.[2-4] One of the subgroups of immune dysregulation diseases in the IUIS classification is susceptibility to Epstein-Barr virus (EBV). These disorders are characterized by susceptibility to complications following infection with EBV, such as fulminant infectious mononucleosis, hemophagocytic lymphohistiocytosis, lymphoproliferation diseases, dysgammaglobulinemia, and lymphoma.[5,6]

Tumor necrosis factor receptor superfamily, Member 7 (TNFRSF7) or *CD27* gene is located at 12p13.31, and its encoded protein is expressed on naive and central memory T cells, memory B cells, plasma cells, and some subsets of natural killer (NK) cells.[7] Engagement of this costimulatory receptor by its ligand, CD70 (or TNFSF7), activates several signaling pathways and influences the function, survival, and differentiation of T, B, NK, and plasma cells.[8] The deficiency of CD27 (Lymphoproliferative syndrome-2, LPS2; OMIM 615122) in humans was first described by van Montfrans in 2012[9] and now more than 35 patients have been reported in the literature.[10,11] This disorder is characterized by lymphoproliferative disorders, hemophagocytic lymphohistiocytosis, lymphoma, hypo- or dysgammaglobulinemia, impaired antibody responses, and extreme susceptibility to EBV-associated disorders; Some patients can develop autoimmune manifestations, oral ulcers, and susceptibility to other herpes viruses.[10,12].

Since the COVID-19 pandemic, efforts have been made to identify predisposing and risk factors in a small proportion of patients who develop a critical or severe course of the disease. Thus, several studies have been conducted to explore if affected people with IEI have an increased risk for adverse outcomes. The rate of being affected by SARS-CoV-2 compared with the general population, and having a more severe clinical course can vary through different categories of IEI.[13-15] To the best of our knowledge, the spectrum of clinical manifestations in CD27-deficient patients affected by COVID-19 has not yet been reported in the literature.

Here, we discuss a new CD27-deficient patient with a history of COVID-19 infection who developed cardiac sequelae and lymphoma.

MATERIALS AND METHODS

Clinical Evaluation

The patient was diagnosed and registered[13,16] based on the published national guidelines of IEI. An extensive clinical and paraclinical investigation was accomplished during the patient's admission to local hospitals. Written informed consent was obtained according to the guidelines from the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (approval number: IR.TUMS.MEDICINE.REC.1398.564). The clinical diagnosis of IEI was made according to the criteria of the European Society for Immunodeficiencies (ESID).[17]

Immunologic and Laboratory Evaluation Method

The workup of the immune system was conducted according to the latest versions of the immunologic assay.[18] COVID-19 evaluation was accomplished by reverse transcriptase-polymerase chain reaction (RT-PCR), with a negative result for the cycle threshold (CT) >40 and a positive (detected) result for CT ≤40. The presence of EBV in the lymphoma block biopsy was demonstrated by chromogenic in situ hybridization (CISH) for the small RNA–encoding region (EBER) using the Epstein Barr Virus (EBER) CISH Detection Kit, Vitro Master Diagnóstica., Spain, according to the manufacturer's instructions.

Genetic Testing and Confirmatory Sequencing

As the first step, blood samples from the patient and his family were collected in EDTA-containing tubes as the first step. Then genomic DNA was extracted from whole blood using the Blood SV mini kit (GeneAll Biotechnology Co., Ltd., South Korea). For the next step, the sequencing of libraries was performed by high-throughput paired-end sequencing using the NovaSeq 6000 Sequencing System (Illumina Co., USA). Sequencing data were analyzed using the Genome Analysis Toolkit (GATK-v3.4.0), and detected variants were annotated by several public annotation databases as described previously.[19-21] Eventually, proper filtering and the interpretation of a short list of variants in terms of pathogenicity were performed based on the American College of Medical Genetics and Genomics (ACMG) guideline for variant interpretation.[22]

Validation of the detected *CD27* variant in the patient and confirmation of segregation in the family members were performed by PCR (sequence of the forward primer: 5′GCCACAATAGAGATTCTGCCTTC3′ and reverse primer: 5′GTATGCAAGGATCACACTGAGC3′) following Sanger sequencing using ABI 3500 Genetic Analyzer. The candidate variant was ultimately classified based on the ACMG guideline for the interpretation of sequence variants.[22]

RESULTS

The proband is a 20-month-old boy born to consanguineous Iranian parents without history of any immunodeficiency disorders in the family. He was the second of two children; his older brother is a healthy 5-year-old. His birth weight was 3100 g. His mother has a cardiac pacemaker, as she had obvious cardiac complications during the second child's delivery**.** His pedigree was compatible with an autosomal recessive disease (Figure 1A). He appeared healthy until 6 months, before his recurrent upper respiratory infections began. At the age of 1 year, the patient developed fever, rhinorrhea, and lethargy for a week. He was admitted to a local hospital due to improper response to outpatient treatments. Splenomegaly, anemia, and elevated levels of C-reactive protein (CRP), aspartate transaminase (AST), and alanine aminotransferase (ALT) were detected during his admission (Table 1). In order to investigate the prolonged fever and splenomegaly, a number of laboratory tests were performed, including the Coombs Wright test, 2-mercaptoethanol (2ME) Brucella agglutination test, purified protein derivative (PPD) skin test, rheumatoid factor, antinuclear antibodies, peripheral blood smear, and urine culture. All tests were normal. He was discharged in an acceptable condition after 5 days but returned with fever, splenomegaly, elevated AST, ALT, and lactate dehydrogenase levels due to a hepatitis of unknown origin. Serologic tests for herpes simplex viruses (I and II), cytomegalovirus (CMV), human immunodeficiency virus (HIV), and hepatitis B and C were negative but was positive for EBV immunoglobulin G. Anemia was still evident (Table 1). A bone marrow aspiration (BMA) was perfomed due to prolonged fever to rule out kala-azar or malignancies, but no abnormalities were found. The direct antiglobulin test was performed twice with negative results. Abdominopelvic ultrasound only revealed splenomegaly. Echocardiography illustrated the normal structure and function of the heart without any pleural or pericardial effusion. After 1 month, the patient was discharged in generally good health but with no definitive diagnosis.

After discharge, he experienced periodic fever and an increased titer of liver enzymes with lethargy and loss of appetite. At the age of 20 months, he was admitted again with persistent fever and restlessness since 10 days before hospitalization, with a splenomegaly since 6 months, several neck lymphadenopathy, a parotid lump, elevated level of liver enzymes, CRP, erythrocyte sedimentation rate (ESR), fibrinogen, and prohormone B-type natriuretic peptide (NT-proBNP, 246 pg/mL; normal range, 5-59 pg/mL). BMA showed normal results except for increased histiocytes. An abdominal ultrasound revealed splenomegaly with several enlarged lymph nodes. The neck ultrasound demonstrated

multiple reactive lymph nodes on both the right and left sides, with a maximum diameter of 33*****18 mm and 24***9 mm, respectively. Cardiac evaluations including echocardiography, electrocardiography, and CT angiography determined mild mitral regurgitation, tricuspid regurgitation, pulmonary insufficiency, good left ventricle ejection fraction, minimal pulmonary edema, and ectasia of coronary arteries [right coronary artery (RCA): 0.4 cm, left anterior descending (LAD): 0.36 cm, left main coronary artery *(*LMCA): 0.28 cm, and left circumflex **(**LCX): 0.28 cm).

Moreover, the Z score was calculated based on the patient's weight and height as follows: (RCA: 7.16, LAD: 7.62, LMCA: 1.62). Based on the Z score, RCA, and LAD, this patient had a large aneurysm. Consequently, intravenous immunoglobulin and aspirin were administered with suspicion of atypical Kawasaki disease. The fever subcided, and the sizes of coronary arteries decreased (RCA: 3.6 mm, LMCA: 2.7 mm, LAD: 2.9 mm, LCX: 2.9 mm). Thereupon, he was discharged with oral aspirin. A biopsy of the largest lymph node was performed after 1 month due to no change in the lymph node size. Hodgkin lymphoma, a mixed cellularity type, stage IIIBS, was diagnosed and confirmed by another pathology laboratory. A spiral CT scan of the neck and thorax with IV contrast revealed several cervical lymphadenopathies in the posterior cervical triangle, submandibular, and bilateral axillary areas. EBV PCR and CISH analysis for EBER in the lymphoma tissue were performed and were positive (Figures 1B and 1C). The viral load of EBV in the plasma was 514,056 copies/mL. The CMV tests were negative in both plasma and tissue. Considering the onset age of lymphoma, past medical history of the patient, high level of EBV viral load, and consanguinity of the parents, an underlying inborn error of immunity was suspected, and immunological and genetic evaluations were conducted (Table 1).

Whole-exome sequencing revealed a previously described pathogenic frameshift variant (homozygous c.18delC/p.Trp7GlyfsTer44) in the *CD27* gene [NM_001242.5, Minor allele frequency **(**MAF)=0]. Similar to the previous family with this mutation,[10] CD27 evaluation confirmed a decreased expression level of the corresponding marker in the patient's blood (0.17%) on the CD19 gate. Observing thePVS1 (as a null variant), PM2 (absent in population databases), PP3 (computational data) criteria, and also previous reports, the variant detected in our patient can be classified as a pathogenic variant. Further analysis by PCR-Sanger sequencing validated the homozygous status of the detected variant in the patient and showed the carrier status of his healthy parents and his healthy brother (Figure 1). This segregation analysis was consistent with an autosomal recessive pattern of inheritance.

The patient's lymphoma was treated with the combination of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and cyclophosphamide, vincristine sulfate, procarbazine hydrochloride, and prednisone (COPP) regimens. A decrease in coronary artery aneurysms was observed in the following months after taking aspirin and Plavix. He was on aspirin therapy for 8 months after the diagnosis of Kawasaki-like disease during the remission phase after chemotherapy. Six months after his diagnosis of lymphoma, he was admitted due to fever and a positive COVID-19 PCR, but without any other signs or symptoms of COVID-19 infection. Echocardiography revealed ectasia of the RCA (0.3 cm) and LAD (0.28 cm) arteries, mild mitral regurgitation, tricuspid regurgitation, and pulmonary edema. An elevated level of CRP, ESR, and AST with normal levels of ALT and alkaline phosphatase, anemia, leukopenia, and thrombocythemia were detected. His COVID-19 PCR test remained positive for a month, and eventually, he received supportive care for COVID-19 infection.

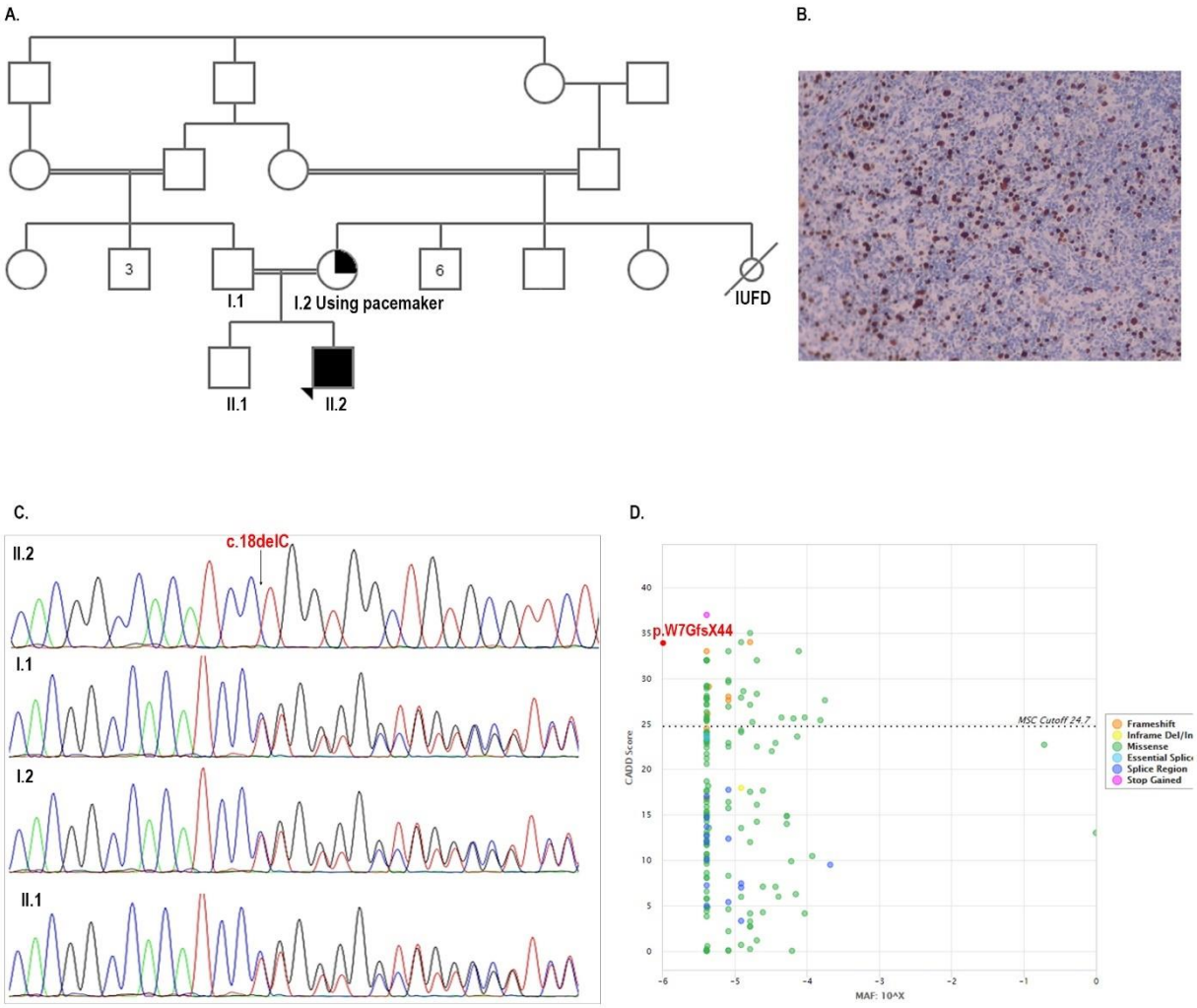

Figure 1. Pedigree of the patient (A). Epstein-Barr virus–encoded small RNA (EBER)-positivity for the lymphoma tissue is depicted (B). Sanger investigation of the variant detected in the family. The top panel confirmed the homozygosity of the patient for the c.18del variant in the *CD27* gene. The other panels demonstrate the heterozygosity of his father, mother, and brother, respectively (C). Correlation of combined annotation-dependent depletion (CADD) scores with allele frequencies for pathogenic CD27 mutation (red dot) and for CD27 variants (green dots) for missense mutations, blue dots for splice acceptor mutations, purple dots for splice donor mutations, pink dots for start losses, and brown dots for frameshift mutations) reported in the population databases (gnomAD: http://gnomad.broadinstitute.org) (D) MSC, mutation significance cutoff.

Table 1. Laboratory results

Age (months)	13.5	14.5	15	19	19.5	20	26	Normal range
AST (u/L)	58	262	173	106	73	52	54	<56
ALT (u/L)	50	239	79	69	40	19	30	<41
Bilirubin (Total)	-	1.2	0.92	1.37	-	0.6	0.55	<1.2
ALKP (u/L)	-	-	436	-	305	250	281	180-1200
CRP	+++	++	+	+	35	45	53	up to 10
ESR (mm/hr)	92	32	16	14	44	62	76	<15
RBC (10^6)	4.16	-	4.06	4.73	4.29	4.15	4.05	4.5-5-9
Hb (g/dL)	10	8.9	8.4	9.7	8.7	8.4	9.3	14-17.5
PLT (10^3/µL)	335	-	255	251	270	253	248	150-450
WBC (/µL)	8.8	14.1	8.6	9.6	8	8	1.7	4.4-11
Neutrophil (%)	-	-	45	46	45	40	75	-
Lymphocyte (%)	-	-	50	50	48	52	22	-
IgG (mg/dL)	-	-	-	-	-	866**		350-1000
IgM (mg/dL)	-	-	-	-	-	143**		40-140
IgA (mg/dL)	-	-	-	-	-	44**		19-220
IgE (IU/mL)	-	-	-	-	-	3**		<144
Anti-diphtheria Antibody	-	-	-	-	-	0.57**		0.1-1
Anti-tetanus Antibody	-	-	-	-	-	3.5**		1-5
CD3 (%)*	-	-	-	-	71**	76**		35-78
CD4 (%)*	-	-	-	-	37**	41**		22-62
CD8 (%)*	-	-	-	-	32**	39**		12- 36
CD4/CD8	-	-	-	-	1.15**	1.41**		1-3
CD16 (%)*	-	-	-	-	8.07**	7.89**		-
CD56 (%)*	-	-	-	-	1.66**	1.69**		-
CD19 (%)*	-	-	-	-	8.70 **	11**		3- 14
CD 20 (%)*	-	-	-	-	8.60**	-		3-15
FOXP3 (%)*	-	-	-	-	-	3.38**	26	2.15

**% of lymphocytes; **After IVIG treatment;* ALT: alanine transaminase; ALKP: alkaline phosphatase; AST: aspartate aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; g/dL: grams per deciliter; Hb: hemoglobin; IU/mL: international units per milliliter; mg/dl: milligrams per deciliter; mm/hr: millimeters per hour; PLT: platelets; RBC: red blood cell; u/L: units per liter; WBC: white blood cell.

DISCUSSION

This article describes a CD27-deficient patient who developed cardiac sequelae, lymphoma, and COVID-19 infection. EBV infection may be difficult to control in patients with monogenic immunodeficiency. Patients with several genetic defects, including mutations in *CD27*, *CD70*, *CD137*, *SH2D1A*, and *XIAP*, have a selective vulnerability to EBV with a high penetrance of developing related signs and symptoms.[5,23]

In a cohort of 33 CD27-deficient individuals, 94% exhibited EBV positivity at diagnosis.[10] Our patient was seropositive at the beginning of his unusual presentations. Thereafter, he developed EBV-positive mixed cellularity Hodgkin lymphoma. Lymphoma is one of the complications exhibited in patients genetically predisposed to severe EBV infection. The underlying mechanisms for developing lymphoma in these defects are not completely understood. However, it might be the result of a disability in controlling EBV infection or being unable to eradicate transformed cells regardless of EBV infection or a combination of these effects.[8,25] Thirty-nine percent of CD27 deficient patients experience lymphoma, with an average age of 7.8 years.[10,11]

Recurrent infections, including respiratory and skin infections, are common features of LPS2.[10] The presented patient experienced recurrent upper respiratory infections early in his life. Recurrent fever seems to be more prevalent in Iranian patients (4 out of 5 patients), whereas only one out of the 28 patients had periodic fever in a previously reported cohort of patients.[10]

Our patient presented with recurrent fever and long-term ectasia of the coronary arteries and was treated for suspicious or atypical Kawasaki disease. Kawasaki is an acute inflammatory disorder. Besides having a persistent fever for at least 5 days, it has 5 essential diagnostic criteria. Patients with fever but less than 4 criteria could be diagnosed with Kawasaki disease when coronary artery abnormalities are determined by echocardiography or angiography.[26] A quarter of untreated patients develop coronary artery complications. The exact etiology of Kawasaki disease is unknown; however, it has been suggested that a few viral pathogens trigger the development of Kawasaki disease. Furthermore some genetic causes have been defined as its etiology, such as *ITPKC*, *CASP3*, *BLK*, and *FCGR2A*. The pathophysiology of Kawasaki disease involves hyperactivation of the innate immune system, an immune response related to Th17, and inhibitory effects of T and B cell responses.[27]

Some patients with CD27 deficiency manifest autoinflammatory symptoms. This suggests a regulatory effect of CD27-CD70 signaling on immune responses. As an in vivo analysis of genetically modified mice showed, CD27-CD70 costimulation inhibits Th17 differentiation, resulting in suppressed Th17-mediated autoimmunity and inflammation. The most common autoinflammation presentation in CD27-deficient patients is stomatitis. Uveitis, fever, arthritis, and vasculitis were the next.[10] Based on these studies, the cause of coronary involvement in our patient might be his underlying disease (CD27 deficiency) or the EBV infection.

The age of onset of CD27 deficiency has been reported to range from 8 months to 22 years, and our patient is among the youngest to present with recurrent upper respiratory tract infections in childhood. Approximately half of the patients exhibited their first sign of the disease at the age of 5 years or older. The 7 asymptomatic patients out of 41 mutant individuals indicate reduced penetrance (about 82%) for the disease, even though this value might be overestimated because the disease seems to have age-related penetrance.[10,11]

Ghosh et al. reported that 50% and 21% of heterozygous carriers of CD70 and CD27 mutations, respectively, developed malignant events. They hypothesized that this difference between these two genes might be due to the different sample sizes of the two cohorts.[10] However, none of the first, second, or third relatives of our patient experienced malignancy.

It seems there is no phenotype-genotype correlation between the type and position of the mutation and the phenotype of the affected patient. For example, in the case of the C53Y mutation, which is the most common mutation detected in CD27 deficient patients, the disease can be fatal in the early years of life and, on the other hand, there is a report on asymptomatic adolescence at the age of 12 years.[10]

One may think that the loss of function of mutations (such as frameshifts) at the beginning of the gene are correlated with a more severe course of the disease. However, in a family segregating the c.18del mutation, located at the beginning of the gene, three half-siblings (with ages of 8, 16, and 20 years) homozygote for the variant did not develop any presentation of the disease.[11] These variable presentations in individuals and reduced penetrance of the disease with the same homozygous mutation can result from other genetic and environmental factors.

Management of LPS2 consists of routine screening for complications, treatment of malignancies, treatment of infections (particularly EBV and its consequences), antibody therapy for B-cell depletion, and allogeneic hematopoietic stem cell transplantation (HSCT). Besides, Ghosh et al. recommended performing HSCT from unrelated donors for heterozygous carriers because of their increased risk for malignancies. Our patient is

now on IVIG therapy, but we are considering HSCT for him because of the encouraging results from another conducted study.[10]

Our patient had a fever, elevated NT-proBNP, and CRP without other signs or symptoms of COVID-19 infection. He did not develop serious COVID-19 complications, although his RT-PCR remained positive for 1 month. In general, the EBV-susceptible group of IEI does not overlap with the increased adverse outcome of COVID-19; however, among the 19 IEI cases affected by COVID-19 in a cohort of 2754 patients, only 1 patient had CD70 deficiency (5.2%) who recovered without the need for intensive care.[13,26]

An early presentation of EBV-positive lymphoma could be a clue to an underlying IEI. Therefore, a careful workup, focused on the types of infectious and other complications, is warranted to establish a suspicion of an IEI in children affected by lymphoma. Many IEI type are rare; therefore, publishing precise clinical data about these patient(s) can shed light on our knowledge about the related diseases and the spectrum of clinical manifestations. In turn, this helps to improve early diagnosis of the disease and thus reduce damage to organs of affected individuals as well as improve therapies. Here, we expand the clinical spectrum of CD27 deficiency from EBV-associated lymphoma to coronary ectasia (atypical Kawasaki disease) and mild COVID-19 infection.

STATEMENT OF ETHICS

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Approval No. IR.TUMS.MEDICINE.REC1398.564).

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CONFLICT OF INTEREST

The authors have no conflict of interests to disclose.

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