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RESEARCH

New mutations and new phenotypes: a case of Major Histocompatibility Complex Class II Deficiency

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Abstract

Major Histocompatibility Complex Class II Deficiency is a rare primary immunodeficiency disease with autosomal recessive inheritance. It is characterized by the absence of Major Histocompatibility Complex Class II molecules on the surface of immune cells. In this article, we will present a four-month-old baby girl who presented with recurrent fever and progressive exacerbation of respiratory symptoms since a month ago. Relevant examinations suggested pancytopenia, a decrease in CD4 and CD3 ratio, and CD4/CD8 inversion, hypogammaglobulinemia, and diagnosis of hemophagocytic syndrome during treatment which all led to the consideration of the presence of immunodeficiency diseases, and the diagnosis of Major Histocompatibility Complex Class II Deficiency was made by peripheral blood whole-exon sequencing (WES). This case is remarkable in that it reveals features of hemophagocytic syndrome in a Major Histocompatibility Complex Class II Deficiency infant, most probably caused by cytomegalovirus, which rarely reported before, and the Major Histocompatibility Complex Class II Deficiency caused by a novel mutation site in the RFXANK gene which never reported, and it also describes the diagnostic and therapeutic course in detail. In addition, we have summarized the information related to Major Histocompatibility Complex Class II Deficiency triggered by mutations in the RFXANK gene to assist clinicians in early recognition and diagnosis.

Keywords Major Histocompatibility Complex Class II Deficiency · RFXANK gene · Mutation · Hemophagocytic syndrome

Abbreviations

MHC	Major Histocompatibility Complex
BLS	Bare lymphocyte syndrome
CIITA	Class II transactivator
RFX	Regulatory factor X
HSCT	Hematopoietic stem cell transplantation
POCUS	Point-of-care ultrasound

Introduction

Major Histocompatibility Complex (MHC) Class II Deficiency, also known as bare lymphocyte syndrome (BLS), is a severe combined immunodeficiency disease, which is a genetically heterogeneous disorder that is genetically regulated by defects in multiple trans-activating genes that regulate the expression of MHC II genes resulting in deficient expression of MHC II [1]. Although patients with MHC II deficiency have intact MHC II genes, defective regulation of MHC II gene expression results in defective constitutive and inducible expression of MHC II molecules on the surface of B cells, monocytes, and activated T cells in all patients [2]. MHC II molecules are heterodimeric (α/β) transmembrane glycoproteins that play key roles in the immune system such as the establishment of MHC II restricted CD4 + T lymphocytes mature repertoire in the thymus as well as foreign antigen presentation driving CD4 + T cells immune responses in the periphery [3]. The immune system suffers severe damage due to the lack of expression of MHC class II molecules,

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resulting in their inability to generate an adequate response to external antigens [4].

Four different regulators control the transcription of the currently known MHC II genes. These regulatory factors are caused by mutations in the genes encoding the heterotrimeric transcription factors RFX (including RFXANK, RFX5, and RFXAP) and the class II transactivator (CIITA) [5]. More than 85% of the children had mutations in the genes of the subunits of regulatory factor X (RFXANK, RFX5, RFXAP), a protein complex that binds to the MHC II promoter and activates transcription. The remaining patients had defects in class II transactivators (CIITA) that regulate MHC II antigenic constitutively and IFN-γ upregulation [6].

This report reveals a newly identified mutation in the RFXANK gene that triggers abnormalities in the primary histocompatibility complex class II. The study also notes that affected patients exhibit symptoms of hemophagocytic syndrome, thus deepening our understanding of this disorder's genotypic and phenotypic features. In addition, the report mentions the evaluation of patients using imaging counts such as CT and ultrasound techniques and summarizes the information related to Major Histocompatibility Complex Class II Deficiency triggered by mutations in the RFXANK gene.

Case presentation

Here, we present a female patient with MHC II deficiency due to a new mutation in the RFXANK gene. She was from a consanguineous family in southwest China and was their first child. There had been no similar illnesses in the family before this (Fig. 1). She was hospitalized for aspiration pneumonia after birth. One month ago, at the age of three months, she developed cough and wheezing, which led her to the local hospital, and the symptoms improved after three days of hospitalization. Twenty days ago, she was again admitted to a local hospital with a chief complaint of diarrhoea and intermittent fever, where she was treated with mechanical ventilation, antibiotics, and gammaglobulin, but her respiratory symptoms continued to worsen. She was urgently transferred to our hospital for further treatment.

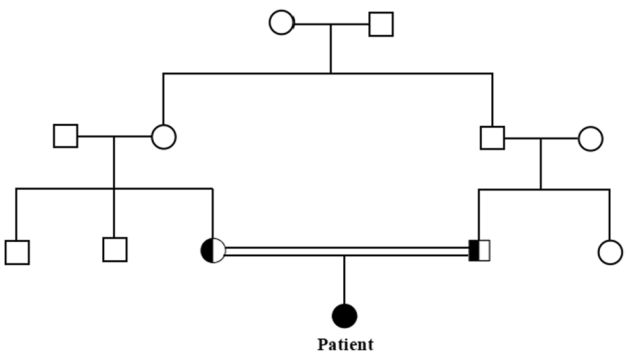

Fig. 1 Family tree diagram of the patient

At the time of admission, the child's transcutaneous oxygen saturation was 77%. The symptoms of respiratory distress included pale lips, cyanosis, nodding respiration, nasal agitation, and inspiratory triple concavity. The Initial chest CT (Fig. 2A) showed decreased transmittance and diffuse patchy hyperdensity in both lungs, confirming acute respiratory distress, and the child was placed on a constant-frequency ventilator to assist with the treatment. The initial ultrasound evaluation showed diffuse B-line predominance (Fig. 3A) and a markedly enlarged liver approximately 3–4 cm below the ribs. Hepatomegaly is initially considered to be due to severe infections As the child had been on antibiotics and a mechanical ventilator for a prolonged period, considering drug-resistant organisms and some opportunistic pathogens, anti-infective therapy with meropenem, sulfamethoxazole, and metagenomics next generation sequencing (mNGS) were performed. The child experienced severe hypoxemia (P_aO2 49 mmHg) and hypercapnia (P_aCO2 77.4 mmHg) within 7 h of admission and was switched to a high-frequency ventilator for assisted respiration. The next day, sputum sequencing revealed that the patient had a mixed infection with multiple bacteria, fungi, and viruses, including *Stenotrophomonas maltophilia*, *Candida parapsilosis*, *Clavispora lusitaniae*, *Human betaherpesvirus* 5, Human respiratory syncytial virus A, and Rhinovirus A. Based on the sequencing results, the decision was made to discontinue meropenem and switch to cefoperazone sulbactam sodium combined with sulfamethoxazole for intravenous infusion against infections and voriconazole for oral antifungal. In the following days, the patient's symptoms stabilized, but by the sixth day, the neutrophil count dropped sharply (0.18×10^9/L, normal range 0.6–7.5×10^9/L). It was decided to discontinue cefoperazone sodium sulbactam and replace it with piperacillin-tazobactam to be alert for hematologic abnormalities and adverse drug reactions. By day 7, the child's respiratory distress is better than before; with hypercapnia relieved (P_aCO2 42.2 mmHg), the mode was switched back to constant-frequency ventilation. From day 9 to day 14, the child again showed a change in condition, with intermittent fever occurring every day, and routine blood results showed marked elevation of ultrasensitive C-reactive protein (50.5 mg/L, normal range 0–10 mg/L) and interleukin 6 (265.8 pg/ml, normal range ≦ 7 pg/ml). On day 10, ultrasonography of the lungs (Fig. 3B) revealed extensive blurring of the pleural lines. Compared with the ultrasound examination on admission (Fig. 3A), there was an increase in the number of B-lines (Fig. 3B-1), signs of fragmentation (Fig. 3B-2), and substantial changes Fig (Fig. 3B-3), which are typical of inflammation in the lungs. On day 12, the child was successfully taken off the ventilator

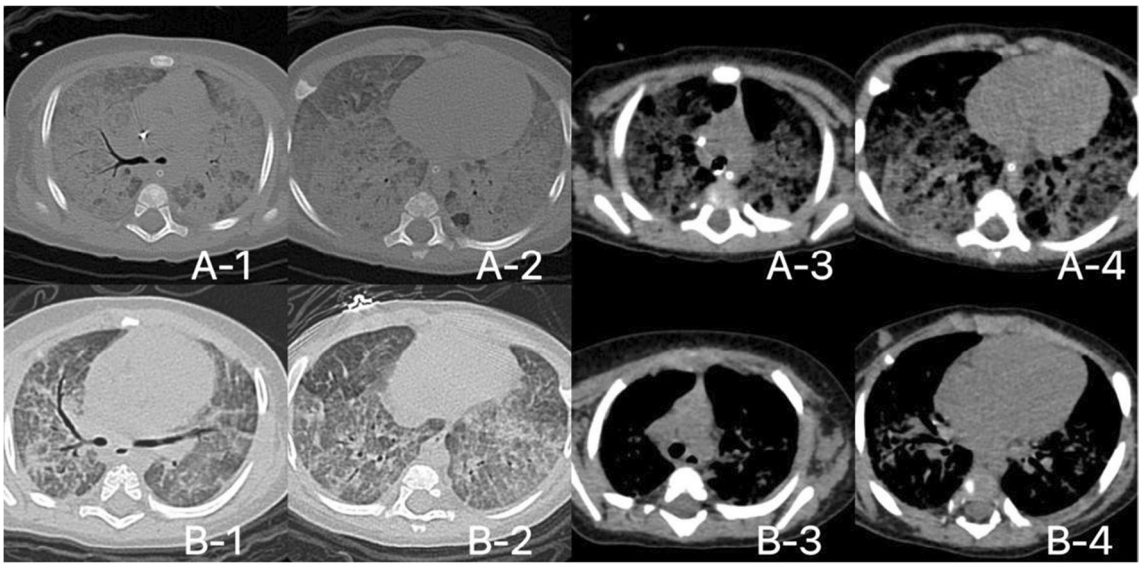

Fig. 2 The images shown in (**A-1**), (**A-2**), (**A-3**), and (**A-4**) are the chest CT on the day of admission showed diffuse flaky, patchy hyperdense shadows in both lungs, with scattered small patches of air retention and areas of ground glass density within them. The images shown in (**B-1**), (**B-2**), (**B-3**), and (**B-4**) are the chest CT after 4 weeks of treatment showed extensive ground-glass density shadows in both lungs with some solid lesions, which were more resorbed than before

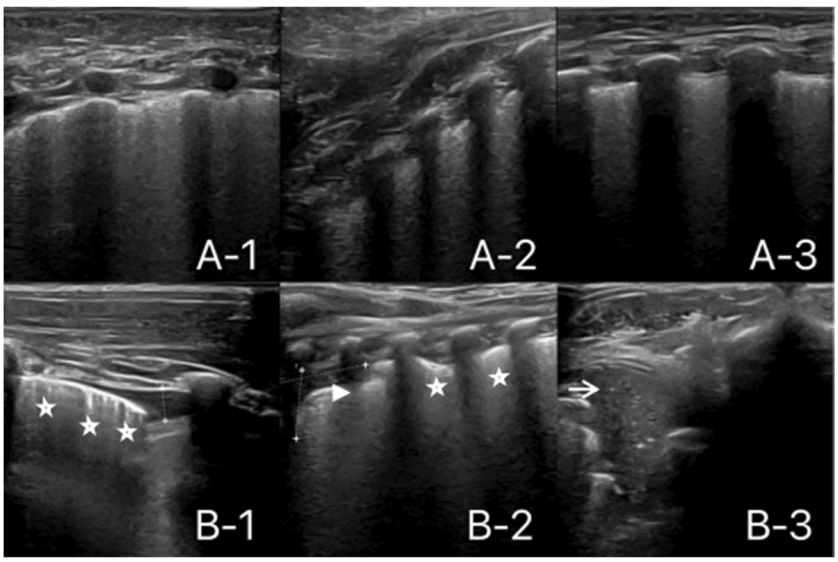

Fig. 3 The images shown in (**A-1**), (**A-2**), and (**A-3**) are ultrasound images of the lungs at the time of admission, showing a diffuse B-line distribution in the anterior (**A-1**), middle (**A-2**), and posterior (**A-3**) of the lungs. The images shown in (**B-1**), (**B-2**), and (**B-3**) are ultrasound images of lungs on day 10, showing thickening and blurring of pleural lines, extensive B-lines (star) (**B-1**), localized fragmentation signs in the anterior lungs (black triangle) (**B-2**), and large solid lesions are seen in the posterior lungs (right arrow) (**B-3**)

and switched to humidified high-flow nasal cannula oxygen therapy. Serum cytomegalovirus DNA was 2.14×10^5 copies/ml (normal range $< 5.00 \times 10^2$ copies/ml), so ganciclovir anticytomegalovirus therapy was added on day 13. Hemophagocytic syndrome was suspected due to the child's recurrent severe infections, pancytopenia (WBC 1.8×10^9/L, normal range $4.3–14.2 \times 10^9$/L; RBC 2.94×10^{12}/L, normal range $3.3–5.2 \times 10^9$/L; PLT 92×10^9/L, normal range $183–614 \times 10^9$/L), persistent fever, ferritin more significant than 500 (FER > 1650.0ng/mL), elevated triglyceride levels (TG 5.59 mmol/L, normal range 0–2.30 mmol/L), and plasma fibrinogen < 1.5g/L (FIB 1.22 g/L), and bone marrow smear on the 14th day showed hemophagocytes in the bone marrow, which finally confirmed hemophagocytic syndrome. Dexamethasone was soon infused, but etoposide was not, considering she receiving a powerful antiviral treatment and extreme weakness. By day 20, the child's oxygen saturation was gradually stabilized (transcutaneous carbon dioxide pressure monitoring TCPCO2 38 mmHg, transcutaneous oxygen pressure monitoring TCPO2 59 mmHg), and humidified high-flow nasal cannula was stopped instead of a nasal cannula. On the four weeks of treatment, the child was

reexamined with a chest CT, and the CT showed (Fig. 2B) that the patient's lung lesion area much reduced from the time of admission (Fig. 2A), suggesting that much of the inflammation had been resorbed, but that the substantial interstitial changes had increased from before. After 30 days of treatment, she was successfully discharged from the hospital; however, continuous oxygen inhalation via nasal cannula is still required. Cytomegalovirus amplification continues to rise in children after discharge from hospital, ineffective second-line treatment, enlarged and progressively ruptured left axillary lymph nodes (Fig. 4), and a positive blood test for tuberculosis and ultimately died 3 months after discharge from our hospital.

Due to the recurrent multiple pathogen infections, the tortuous nature of antibiotic therapy, and the young age and severity of the child's condition, we suspected that this young patient had a primary immunodeficiency disease. Laboratory findings (Table 1) showed pancytopenia; weakened immunity, mainly in the form of decreased IgA and IgM; and using flow cytometry to assess the cellular immunodeficiency of the child, a decrease in CD4 and CD3 ratio, an increase in CD8 ratio, and a reversal of CD4/CD8 observed, which further confirmed the presence of an immunodeficiency. In order to clarify the diagnosis, peripheral blood whole exome testing was completed with the consent of the family.

Whole exome sequencing data revealed that the patient's RFXANK gene underwent a mutation in the pure c.516 (exon7) dup (Fig. 5), resulting in MHC II deficiency. This mutation occurs at exon 7 of the RFXANK gene and results in a duplication of nucleotides at position 516 in the sequence of the gene. This further triggers a protein frameshift mutation starting at amino acid 173, which causes the 173rd amino acid encoded by the gene to shift from valine to cysteine and prematurely terminates the translation process of the protein after a subsequent extension of 8 amino acids. This mutation is a novel site that has not been documented to date.

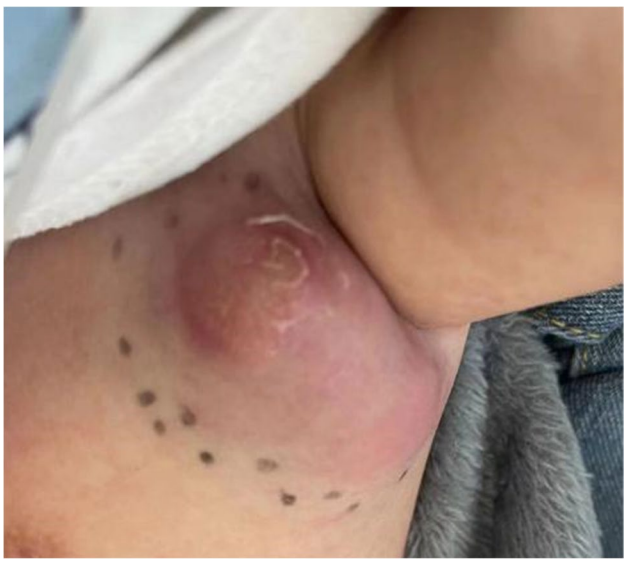

Fig. 4 A distinctive red mass is visible in the child's left axilla

Table 1 Laboratory tests features of the patient with the associated normal range

	Patient date	Normal range
Cell count		
WBC ($\times 10^9$/L)	1.80	4.3–14.2
RBC ($\times 10^{12}$/L)	2.94	3.3–5.2
PLT ($\times 10^9$/L)	92	183–614
Ig concentration		
IgG (g/L)	5.56	2.60–6.90
IgA (g/L)	< 0.04	0.08–0.57
IgM(g/L)	0.15	0.26–1.00
Immunophenotyping		
CD3 (%)	45.7	57.45–75.22
CD4 (%)	8.3	37.71–56.05
CD8(%)	35.0	12.61–25.08
CD4/CD8	0.24	1.62–3.77

Discussion

MHC Class II Deficiency is a rare primary autosomal recessive immunodeficiency disorder that was first described in the late 1970s. The distinguishing feature of this disease is the absence of MHC II molecules on the surface of immune cells [7]. Flow cytometry is a dependable method for ascertaining the lack of MHC II molecules expression; however, pinpointing the genetic anomaly is crucial for conclusive diagnosis and treatment [8]. Infection begins in the first year of life and usually involves the respiratory and gastrointestinal tracts. Severe malabsorption with failure to thrive ensues, often leading to early childhood death [9]. The most common infectious agents include intracellular (e.g. cytomegalovirus, Salmonella, and Cryptosporidium) and extracellular [8]. Treatment options for BLS type II are limited to either HSCT or continuous prophylactic therapy [10]. Nonetheless, HSCT in individuals with MHC II deficiency shows reduced survival rates in contrast to other types of primary immune deficiencies [11]. Damoiseaux and his team conducted an in-depth study of 35 patients with class II expression defects of the major histocompatibility complex. The results of the study showed that of the 23 patients who underwent HSCT, 10 managed to survive and make a full recovery, while 12 sadly passed away after transplantation, and these deaths could have been due to post-transplantation deaths, severe

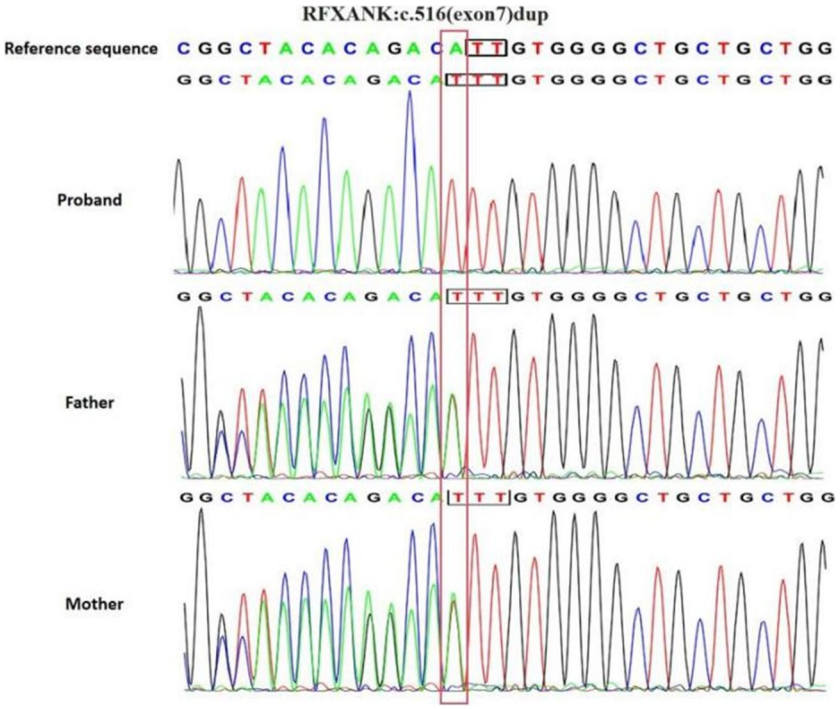

Fig. 5 A novel, pure-heterozygous mutation was identified in the RFXANK gene (NM_003721; exon 7; c.516(exon7)dup), which results in a frameshift mutation that leads to protein dysfunction. Sanger sequencing confirmed that the patient was pure heterozygous and that both parents (father and mother) were heterozygous carriers of the mutation. (In the illustration, the black line symbolizes guanine, the blue line represents cytosine, the red line represents thymine, and the green line is a symbol for adenine)

infections, or GVHD; of the 12 patients who did not undergo HSCT, 5 sadly passed away, and 7 are still alive, but all of them were accompanied by the development of respiratory and/or gastrointestinal and/or hepatic symptoms [12]. The patient in this case ended up not undergoing HSCT because she was still young, had multiple underlying diseases, and had a poor prognosis.

In addition, we chose the keywords "MHC II deficiency" and "bare lymphocyte syndrome" to conduct a detailed literature analysis of all MHC II deficiency patients reported in PubMed before April 2024 (Table 2). In total, in the course of our study, we succeeded in identifying 29 different patterns of variants in the RFXANK gene that were associated with 150 patients suffering from MHC II deficiency, with a significantly higher prevalence in children born from consanguineous marriages in 47 families with known family relationships (38/47); among 136 patients with known ethnicity, the highest rate was found in Algeria (47/136), which may be related to the high rate of consanguineous marriages in the region. It can also be found that most of the patients had begun to encounter repeated respiratory and gastrointestinal related sudden illnesses in infancy. From this case, we can observe that it coincides with most of the symptoms of MHC II deficiency caused by mutations in the RFXANK gene. The patient was born in a consanguineous family and experienced multiple respiratory and gastrointestinal infections from infancy. It also gives us a new direction to consider whether children born to consanguineous families with recurrent respiratory and gastrointestinal infections since infancy can be considered MHC II deficient in the first place.

Our patient suffered from severe pneumonia, acute respiratory distress syndrome, respiratory failure, megaloblastic infections, hypogammaglobulinemia, decreased IgA and IgM concentration, a decrease in CD4 and CD3 ratio, and CD4/CD8 inversion, which are common manifestations of immunodeficiency diseases. Then, the WES test clarified the patient's MHC II deficiency due to RFXANK gene mutation; meanwhile, during the treatment, the clinical symptoms of the haemophagocytic syndrome were finally diagnosed through the child's recurrent infections, recurrent fever, ferritin > 500, elevated triglyceride level, plasma fibrinogen < 1.5 g/L, bone marrow smear showing haemophagocytes, and haematopoietic cells, which is the second case of MHC II deficiency combined with hemophagocytic syndrome reported in the literature.

Haemophagocytic syndrome is often classified as primary (occurring in the presence of an underlying predisposing genetic defect in immune function) or as secondary (occurring in the absence of an underlying predisposing defect, typically in the setting of an infectious, malignant, or autoimmune trigger) [38]. Two autosomal recessive gene defects underlie 40–50% of primary (familial) cases worldwide: perforin, the major immune cytotoxic protein, and MUNC 13–4, a protein involved in exocytosis of perforin-bearing cytotoxic granules during apoptosis. Related autosomal recessive defects of secretory cytotoxic lysosomes—LYST 1 (Chediak-Higashi syndrome), Rab27A (Griscelli syndrome), and X-linked lymphoproliferative disorder—also carry a very high risk of fatal hemophagocytic lymphohistiocytosis [39]. Therefore, the aetiology of haemophagocytic syndrome in

Table 2 Information for patients with MHC II deficiency due to mutations in the RFXANK gene

Mutation of RFXANK	Year of publication	Case number	Ethnicity	Consanguinity	Sex	Age of onset (mo)	Initial symptoms	Reference
c.558T > A	2024	1	Saudi Arabian	-	F	24	Sinusitis, pneumonia	[13]
c.304G > T c.634C > T	2024	1		-	F	2	CMV retinitis, adrenal failure	[14]
c.565C > T	2023	1		+	M	6	Pneumonia, diarrhoea, autoimmune haemolytic anaemia, pulmonary haemorrhage	[14]
c.338-1G > C	2023	1	Iranian	+				[15]
c.232C > T	2022	1	Afghanistan	+	M	5	Respiratory insufficiency, diarrhoea, growth retardation, rhinovirus infection	[10]
c.271 + 1G > C	2021	2	Saudi Arabian	+	M		Recurrent otitis-media, cognitive symptoms/ Chronic diarrhoea, growth retardation, recurrent chest infections, thrush	[16]
c.337 + 1G > C	2020	1	China	-	M	7	Cough, shortness of breath	[17]
c.431T > C	2018	2	Egyptian	+	M/F	4/*	Pneumonia, prolonged diarrhoea, ear drainage, thrush/(-)	[8]
c.247_250delTCAG	2018	1	Egyptian	+	F	4	Pneumonia, prolonged diarrhoea, ear drainage	[8]
c.600delG	2018	1	Egyptian	+	M	4	Pneumonia, prolonged diarrhoea, thrush	[8]
c.495G > A	2018	1	Iranian	+	F	6	Pneumonia, prolonged fever, broad-spectrum antibiotic resistance	[18]
G > A in TGG codon for W188	2017	1	Iranian	-	M	4	Fever, prolonged diarrhoea, recurrent mouth ulcers, fail to thrive, developmental delays	[19]
c.362A > P	2017	1		+	F		Recurrent pneumonia	[20]

Table 2 (continued)

Mutation of RFX-ANK	Year of publication	Case number	Ethnicity	Consanguinity	Sex	Age of onset (mo)	Initial symptoms	Reference
c.469C > T	2015	1	Mexican	+	M	4	Respiratory infection, acute otitis media, diffuse rash	[21]
insTCAC.IVS4 + 1	2012	4	Kuwaiti		F/M/F/M	2/1/3/4	Pneumonia	[22]
AW188x	2012	2	Kuwaiti		M	5/3	Pneumonia	[22]
R212X	2003	1	Turkish	+				[23]
D121V	2003	1	Saudi Arabian	+				[23]
IVS4 + 5G > A	2003	1	Egyptian		F	18		[24]
c. IVS4 + 1G > C	2001	1	North African	+	M		Chronic diarrhoea, recurrent lung infections	[25]
p. E101X	2000	1	Turkish				Infections	[26]
p. R156X	2000	1	Italian				Infections	[26]
380delT 856-1G → Tsub	2000	1	French/Spanish				Infections	[26]
P. Q103X	2000	1						[27]
c.162delG	2023	5	Iranian	+				[15]
	2020	1	Iranian	+	M		Prolonged diarrhoea, fever, cough, vomiting	[28]
c.438 + 5G > A	2023	1	Iranian	+				[15]
	2016	1						[29]
c.362A > T	2023	1			F			[30]
	2014	1	Saudi Arabian		F	6	Pneumonia, infections	[31]
	2012	4	Kuwaiti		M/F/F/F	0/3/6/0	Pneumonia	[22]
p. L195P	2003	1						[32]
	2000	1						[27]
c.752delG26bp	2013	25	Tunisian					[3]
	2012	2	Tunisian	-	F	6	Pneumonia, diarrhoea	[33]
	2012	9	Algeria	8 + /1-	5F/4M			[34]
	2011	35	Algeria (25) Moroccan (4) Tunisian (6)					[12]
	2010	10	Moroccan	8 + /2-	7F/3M		Diarrhoea, recurrent respiratory infections	[35]
	2000	17	Algerian (12) Tunisian (3) Moroccan (1) Algerian/French (1)					[26]
	2000	1						[27]
	1999	2						[36]
	1998	3						[37]

children is unclear, and the presence of a well-defined immunodeficiency disease in children with recurrent infections from an early age may be secondary to haemophagocytic syndrome, as well as the fact that the children were born to consanguineous families, and the WES results suggest that the children have the potential for disease caused by the LYST mutation, making them potential candidates for the primary haemophagocytic syndrome as well.

Bedside the patient's condition was also skilfully evaluated with the help of Point-of-care ultrasound(POCUS). As a noninvasive diagnostic tool, POCUS is performed at the first time of admission and throughout the progress. It is now an essential component of the evidence-based management of many respiratory diseases, allowing the dynamic visualization of pulmonary pathology, and may also be helpful in rapidly identifying alternative diagnoses that require differentiated therapeutic approaches. Many studies have demonstrated its value in managing conditions such as pneumonia, acute respiratory distress syndrome, pleural effusion, and pneumothorax. Ultrasound plays a vital role throughout our evaluation of a patient's condition [40]. At the same time, POCUS is used in conjunction with CT technology to provide a more in-depth and dynamic picture of a child's disease progression; it also provides early diagnostic and prognostic assessment information, giving clinicians time to make the right decisions. For patients with impaired immune function, it explores a safer means of monitoring than X-rays; it provides new information and tools in diagnosis and identification. It is also a rapid detection technique for complications.

Due to the rarity of this disease, it is prone to underdiagnosis and misdiagnosis, while there is no uniform guideline or consensus on treatment. Our report adds genotypic and phenotypic profiles to such diseases, aiming to provide a reference for clinical diagnosis and treatment. Nevertheless, timely and effective identification of patients with Major Histocompatibility Complex Class II Deficiency and providing them with effective treatment remains a significant challenge for our future. We should accumulate more experience in identifying patients with Major Histocompatibility Complex Class II defects promptly and actively explore more effective methods for the treatment of Major Histocompatibility Complex Class II Deficiency which is an important future research direction.

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Author Contribution L.XT wrote the main manuscript text, L.B prepared Fig. 3 and provided materials and ideas for the article. All authors reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Posovszky C, et al. Persisting enteropathy and disturbed adaptive mucosal immunity due to MHC class II deficiency. Clin Immunol. 2019;203:125–33.
2. Wolf HM, et al. Residual expression of functional MHC class II molecules in twin brothers with MHC class II deficiency is cell type specific. Br J Haematol. 2001;115(2):460–71.
3. Ben-Mustapha I, et al. Clinical, immunological and genetic findings of a large Tunisian series of major histocompatibility complex class II deficiency patients. J Clin Immunol. 2013;33(4):865–70.
4. Reith W, Mach B. The bare lymphocyte syndrome and the regulation of MHC expression. Annu Rev Immunol. 2001;19:331–73.
5. DeSandro AM, Nagarajan UM, Boss JM. Associations and interactions between bare lymphocyte syndrome factors. Mol Cell Biol. 2000;20(17):6587–99.
6. Small TN, et al. Alternative donor SCT for the treatment of MHC class II deficiency. Bone Marrow Transplant. 2013;48(2):226–32.
7. Hanna S, Etzioni A. MHC class I and II deficiencies. J Allergy Clin Immunol. 2014;134(2):269–75.
8. El Hawary RE, et al. MHC-II deficiency among Egyptians: novel mutations and unique phenotypes. J Allergy Clin Immunol Pract. 2019;7(3):856–63.
9. Klein C, et al. Major histocompatibility complex class II deficiency: clinical manifestations, immunologic features, and outcome. J Pediatr. 1993;123(6):921–8.
10. Damoiseaux M, et al. Lessons learned from the diagnostic workup of a patient with the bare lymphocyte syndrome type II. Clin Immunol. 2022;235:108932.
11. Castano-Jaramillo LM, et al. Meta-analysis of hematopoietic stem cell transplantation in major histocompatibility complex class II deficiency. Pediatr Transplant. 2020;24(6):e13774.
12. Ouederni M, et al. Major histocompatibility complex class II expression deficiency caused by a RFXANK founder mutation: a survey of 35 patients. Blood. 2011;118(19):5108–18.
13. Alroqi FJ, et al. Novel presentation of Major Histocompatibility Complex Class II Deficiency with hemophagocytic lymphohistiocytosis. J Clin Immunol. 2024;44(3):73.

14. Ünsal H, et al. A large single-center cohort of bare lymphocyte syndrome: Immunological and genetic features in Turkey. Scand J Immunol. 2024;99(1):e13335.
15. Mousavi Khorshidi MS, et al. Clinical, immunological, and genetic findings in Iranian patients with MHC-II Deficiency: confirmation of c.162delG RFXANK founder mutation in the Iranian population. J Clin Immunol. 2023;43(8):1941–52.
16. Alharby E, et al. Progressive ataxia and neurologic regression in RFXANK-associated bare lymphocyte syndrome. Neurol Genet. 2021;7(3):e586.
17. Cai YQ, et al. A novel RFXANK mutation in a Chinese child with MHC II deficiency: case report and literature review. Open Forum Infect Dis. 2020;7(8):ofaa314.
18. Abolnezhadian F, Saeedi-Boroujeni A, Iranparast S. MHC Class II Deficiency with normal CD4+ T cell counts: a case report. Iran J Allergy Asthma Immunol. 2018;17(6):594–600.
19. Farrokhi S, et al. MHC class II deficiency: report of a novel mutation and special review. Allergol Immunopathol (Madr). 2018;46(3):263–75.
20. Shah RM, et al. Enterovirus-related immune reconstitution inflammatory syndrome (IRIS) following haploidentical stem cell transplantation in an MHC class II-deficient child. J Clin Immunol. 2017;37(5):419–21.
21. Clarridge K, et al. Major Histocompatibility Complex Class II Deficiency due to a novel mutation in RFXANK in a child of Mexican descent. J Clin Immunol. 2016;36(1):4–5.
22. Al-Herz W, et al. Major histocompatibility complex class II deficiency in Kuwait: clinical manifestations, immunological findings and molecular profile. J Clin Immunol. 2013;33(3):513–9.
23. Wiszniewski W, et al. Novel mutations in the RFXANK gene: RFX complex containing in-vitro-generated RFXANK mutant binds the promoter without transactivating MHC II. Immunogenetics. 2003;54(11):747–55.
24. Prod'homme T, et al. Splicing defect in RFXANK results in a moderate combined immunodeficiency and long-duration clinical course. Immunogenetics. 2003;55(8):530–9.
25. Lennon-Duménil AM, et al. Uncoordinated HLA-D gene expression in a RFXANK-defective patient with MHC class II deficiency. J Immunol. 2001;166(9):5681–7.
26. Wiszniewski W, et al. Founder effect for a 26-bp deletion in the RFXANK gene in North African major histocompatibility complex class II-deficient patients belonging to complementation group B. Immunogenetics. 2000;51(4–5):261–7.
27. Nagarajan UM, et al. Novel mutations within the RFX-B gene and partial rescue of MHC and related genes through exogenous class II transactivator in RFX-B-deficient cells. J Immunol. 2000;164(7):3666–74.
28. Abolnezhadian F, et al. A novel mutation in RFXANK gene and low B cell count in a patient with MHC class II deficiency: a case report. Immunol Res. 2020;68(4):225–31.
29. Sheikhbahaei S, et al. Gene mutations responsible for primary immunodeficiency disorders: a report from the first primary immunodeficiency biobank in Iran. Allergy Asthma Clin Immunol. 2016;12:62.
30. Ramanathan S, et al. Haploidentical CD3(+) TCR αβ/CD19(+)-depleted HSCT for MHC class II deficiency and persistent SARS-CoV-2 pneumonitis. J Allergy Clin Immunol Glob. 2023;2(1):101–4.
31. Abu-Arja RF, et al. Disseminated Bacillus Calmette-Guérin (BCG) infection following allogeneic hematopoietic stem cell transplant in a patient with Bare Lymphocyte Syndrome type II. Transpl Infect Dis. 2014;16(5):830–7.
32. Nekrep N, et al. When the lymphocyte loses its clothes. Immunity. 2003;18(4):453–7.
33. Guirat-Dhouib N, et al. Oral HPV infection and MHC class II deficiency (A study of two cases with atypical outcome). Clin Mol Allergy. 2012;10(1):6.
34. Djidjik R, et al. Clinical, immunological and genetic features in eleven Algerian patients with major histocompatibility complex class II expression deficiency. Allergy Asthma Clin Immunol. 2012;8(1):14.
35. Naamane H, et al. The 752delG26 mutation in the RFXANK gene associated with major histocompatibility complex class II deficiency: evidence for a founder effect in the Moroccan population. Eur J Pediatr. 2010;169(9):1069–74.
36. Nagarajan UM, et al. RFX-B is the gene responsible for the most common cause of the bare lymphocyte syndrome, an MHC class II immunodeficiency. Immunity. 1999;10(2):153–62.
37. Masternak K, et al. A gene encoding a novel RFX-associated transactivator is mutated in the majority of MHC class II deficiency patients. Nat Genet. 1998;20(3):273–7.
38. Al-Samkari H, Berliner N. Hemophagocytic Lymphohistiocytosis. Annu Rev Pathol. 2018;13:27–49.
39. Filipovich AH. Hemophagocytic lymphohistiocytosis and related disorders. Curr Opin Allergy Clin Immunol. 2006;6(6):410–5.
40. Liu J, et al. Lung ultrasonography for the diagnosis of severe neonatal pneumonia. Chest. 2014;146(2):383–8.