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CASE REPORT

Variable CD18 expression in a 22-year-old female with leukocyte adhesion deficiency I: Clinical case and literature review

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Key Clinical Message

Partial leukocyte adhesion deficiency type 1 (LAD-1) deficiency is extremely rare condition with milder infectious manifestation and immune system imbalance leads to increased risks of autoinflammatory complications, such as pyoderma gangrenosum, that can be triggered by trauma or pregnancy. In patients with spice-site ITGB2 variants, partial expression can occur due to different β2 integrin isophorms expression.

Abstract

LAD-1, OMIM ID #116920 is a rare, autosomal recessive disorder that results from mutations in the *ITGB2* gene that encodes the CD18 β2 integrin subunit.

According to the CD18 expression, LAD-1 is categorized as severe (<2%), moderate (2%–30%), or mild (>30%). Here, we describe a 22-year-old female, who presented with inflammatory skin disease and oral cavity, as well as respiratory tract infections during the first year of life. LAD-1 was diagnosed at the age of 2 years by low expression of CD18 (1%). Whole-exome sequencing identified homozygous c. 59-10C>A variant in the *ITGB2* gene. Despite severe phenotype, the patient survived to adulthood without hematopoietic stem cell transplantation and became pregnant at the age of 20 years, with pregnancy complicated by a pyoderma gangrenosum-like lesion. During her life, CD18 expression increased from 1% to 9%; at 22 years of age, 5% of neutrophils and 9% of lymphocytes were $CD18^+$. All $CD18^+$-lymphocytes were predominantly memory/effector cytotoxic T cells. However, revertant mosaicism was not being established suggesting that CD18 expression variability may be mediated by other mechanisms such as different β2 integrin isophorms expression.

KEYWORDS

CD18 expression, leukocyte adhesion deficiency, pregnancy, pyoderma gangrenosum

1 | INTRODUCTION

Leukocyte adhesion deficiency type 1 (LAD-1) is the most common form of LAD but is nonetheless extremely rare with about 450 unique cases described in the last half century.[1–5] Most cases of LAD-1 exhibit life-threatening symptoms. Patients often manifest with delayed separation of the umbilical cord, poor wound healing, leukocytosis, recurrent bacterial and fungal infections, periodontitis, sepsis, and other inflammatory conditions due to impaired polymorphonuclear neutrophils (PMN) migration.[6] Current treatment strategies for LAD-1 are limited. Antibiotic therapy is commonly used to prevent recurrent infections but usually has adverse side effects. Most patients with LAD-1 die in childhood due to recurrent infection and delayed wound healing; few patients survive to adulthood.

Mild- and moderate phenotype patients have better survival, though patients not undergoing hematopoietic stem cell transplantation (HSCT) have a high risk of non-infectious complications. Since LAD-1 is a rare disease, and partial deficiency is even more rare, non-infectious complications are mentioned only in few case reports and include malignancies, such as M7 acute myelocytic leukemia, diffuse large B-cell lymphoma,[7,8] autoimmune disorders,[9–11] and inflammatory complications, the most common of which is pyoderma-like skin lesions.[12–19]

Partial CD18 expression is usually associated with missense or splice site mutations in *ITGB2* gene.[2,5,20,21] Additionally, somatic revertant mosaicism was described in four unrelated patients, three or them from a single center, suggesting that it may be relatively common event for this disorder.[22,23]

Here, we report on clinical case of adult female with LAD-1 deficiency and variable partial expression of CD18 β2 integrin subunit. Some dermatological aspects and surgical treatment details were published before,[24] but in current report, we present the full clinical story since childhood to present days, genetic conformation of LAD I diagnosis and study of CD18 expression in different patient's age.

2 | CASE PRESENTATION

2.1 | Clinical history

The patient was the second child of the West-Ukrainian family, full-term, and vaginally delivered with a birth weight of 3350 g. Her umbilical cord fell off normally and the umbilical wound healed without features.

At 4 months, the patient presented with pneumonia and paronychia; at 5 months, she manifested atopic dermatitis, complicated by streptoderma, followed by abscess and keloid scars formation; and at 9 months, she had an episode of sepsis, stomatitis, mastitis, carditis, and furunculosis. Each of these presentations was accompanied by leukocytosis in the range of 17,000–25,000/mm^3 (normal range—5500–12,000/mm^3). Her clinical picture prompted an immunologic evaluation, and the absence of adhesion molecules CD18/CD11b on granulocytes was confirmed by flow cytometry at the age of 2 years, establishing the diagnosis of LAD-1.

Starting at 1 year of age, the girl had 1–2 annual episodes of bacterial skin infections with the formation of ulcers on the skin that took a long time to heal, recurrent aphthous stomatitis, bronchitis and upper respiratory tract infections, without life-threatening infections. Prescribed antibiotic prophylaxis was not followed carefully by patient's family. At the age of 14 years, the patient suffered from sepsis: septicemia, acute hematogenous osteomyelitis, periosteal phlegmon, and bilateral pleuropneumonia. She responded well to treatment with oral and intravenous antibiotics along with surgical management of some of skin lesions. Concentrations of serum immunoglobulins A, M, and G were normal during these events, but after her recovery from severe episode intravenous immunoglobulin was added to supplement antibiotic therapy. At the age of 17 years, she had a body mass index of 28.4 (height 163 cm, weight 75.5 kg). She suffered from chronic progressive periodontitis and periodically has mild pustular skin lesions.

At the age of 20 years, she become pregnant. At 8 weeks of gestation, a papule appeared on the patient's left leg that rapidly progressed to necrotic ulcerations with fever and leukocytosis (39,000/mm,^{3} normal range—4000–9500/mm^3) (Figure 1A,B). At 17 weeks, the papule evolved into a large ulcer on the front, medial, and lateral surfaces of the left thigh, with a purple and undermined edge, covered with necrotic tissues and fibrin, measuring 32 × 28 cm (Figure 1C). Skin biopsy was not performed because of the patient's lack of consent for this procedure, due to severe associated pain. Therefore, a clinical diagnosis of pyoderma gangrenosum (PG)-like lesion was established. Therapy was started with prednisolone 0.6 mg/kg daily and cyclosporine 4.6 mg/kg daily. During the first 3 weeks, the prednisolone dose was tapered to 0.15 mg/kg daily and cyclosporine dose was increased to 5.4 mg/kg daily because of low serum levels. The wound was dressed with an antimicrobial hydrofiber dressing and changed once a day because of the large amount of effusion and necrotic tissue. Additional therapy included physiotherapy, erythrocyte concentrate transfusion, and supplementation of albumin, vitamins, and minerals. The ulcer stabilized and pain reduction was achieved within the first few days of treatment. Thereafter, slight epithelialization appeared at all edges and the wound began to decrease and shrink to 24 × 27 cm in 3 weeks. During the follow-up visit at the 7th week of treatment, a further clinical improvement was observed with a reduction of the ulcer size to 15 × 21 cm and white blood cell count to 20,800/mm^3 (+22 week, Figure 1D,E). Cyclosporine and prednisolone dosing was further reduced to 3.8 mg/kg. Details of dermatological aspects and treatment were published in.[24]

Pregnancy resolved with the birth of a full-term baby boy with no health problems. After delivery, the woman continued to receive immunosuppression with glucocorticosteroids with a gradual decrease in dosing to prednisolone 10 mg/day and cyclosporine 100 mg twice daily. The

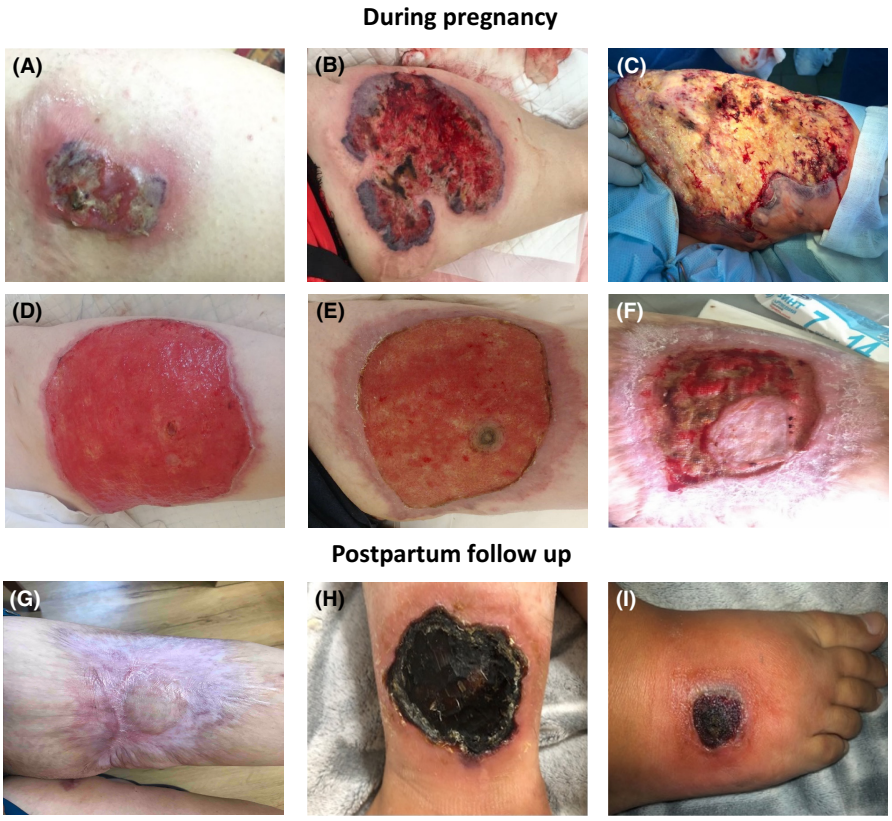

FIGURE 1 Evolution of the skin lesions on the left thigh within pregnancy. (A) Lesion on the left thing (+8 weeks of pregnancy); (B) disease progression, treatment with imipenem/cilastatin, linezolid, levofloxacin, ornidazole and fluconazole is unsuccessful (+8 weeks of pregnancy); (C) large ulcer on the front, medial, and lateral surfaces of the left thigh, covered with necrotic tissues and fibrin, before surgery (+17 weeks of pregnancy); (D–F) wound healing after surgery followed by cyclosporine and prednisolone treatment (+19–39 weeks of pregnancy); (G) scar after complete healing of wound on the left thigh 1 year and 8 months after baby delivery. (H, I) New foci of gangrenous pyoderma (2, 3) on the lower limbs.

main wound healed, but small new lesions have intermittently appeared on her extremities with slow healing during the past year, leading to adjustments in the prednisolone dosage (Figure 1F).

HSCT was considered as a treatment option in Ukraine. Unfortunately, related family donor was not identified. The beginning of the war in February 2022 forced the patient to move to Poland for further treatment. The wound on the left thigh healed, but new foci of gangrenous pyoderma (2–3) constantly appeared on the lower limbs with periodic healing and the appearance of new ones (Figure 1G–I). *Enterococcus faecalis* was cultured from the wound. The girl also had paronychia of the thumb, from which *Pseudomonas aeruginosa*, *Citrobacter youngae* were isolated. *P. aeruginosa* was also isolated from the throat and perianal area.

Leukocytosis is persistent (from 24,270/mm^3 to 12,230/mm^3). She received several courses of antbiotics, antivirals, and antifungals, the dose of glucocorticoids was increased, and she continued to receive cyclosporine and local treatment of wounds. Subsequently, cyclosporine was discontinued due to side effects from the kidneys.

The patient returned to Ukraine, further management is decided, taking into account the condition of the patient and the difficult external circumstances associated with the war and limited resources. She is currently receiving subcutaneous immunoglobulin, trimetoprim/sulfametoxazole, prednisolone 5 mg/day. It should be noted that the patient's child is currently 1 year and 8 months old. The boy is healthy.

2.2 | Laboratory findings (genetic testing and CD18 expression studies)

Whole-exome sequencing revealed homozygous variant NM_000211.5: c.59-10C>A in the *ITGB2* gene on chromosome 21 (NC_000021.8: g.46330297G>T). This variant is in the intronic region that is 10 bp upstream from exon 3, which was predicted to influence the alternative splicing at 3′ acceptor site. In fact, Cher et al. has shown by RT-PCR that this variant change has resulted in an alternative transcript with an insertion of 43 bp intronic sequence

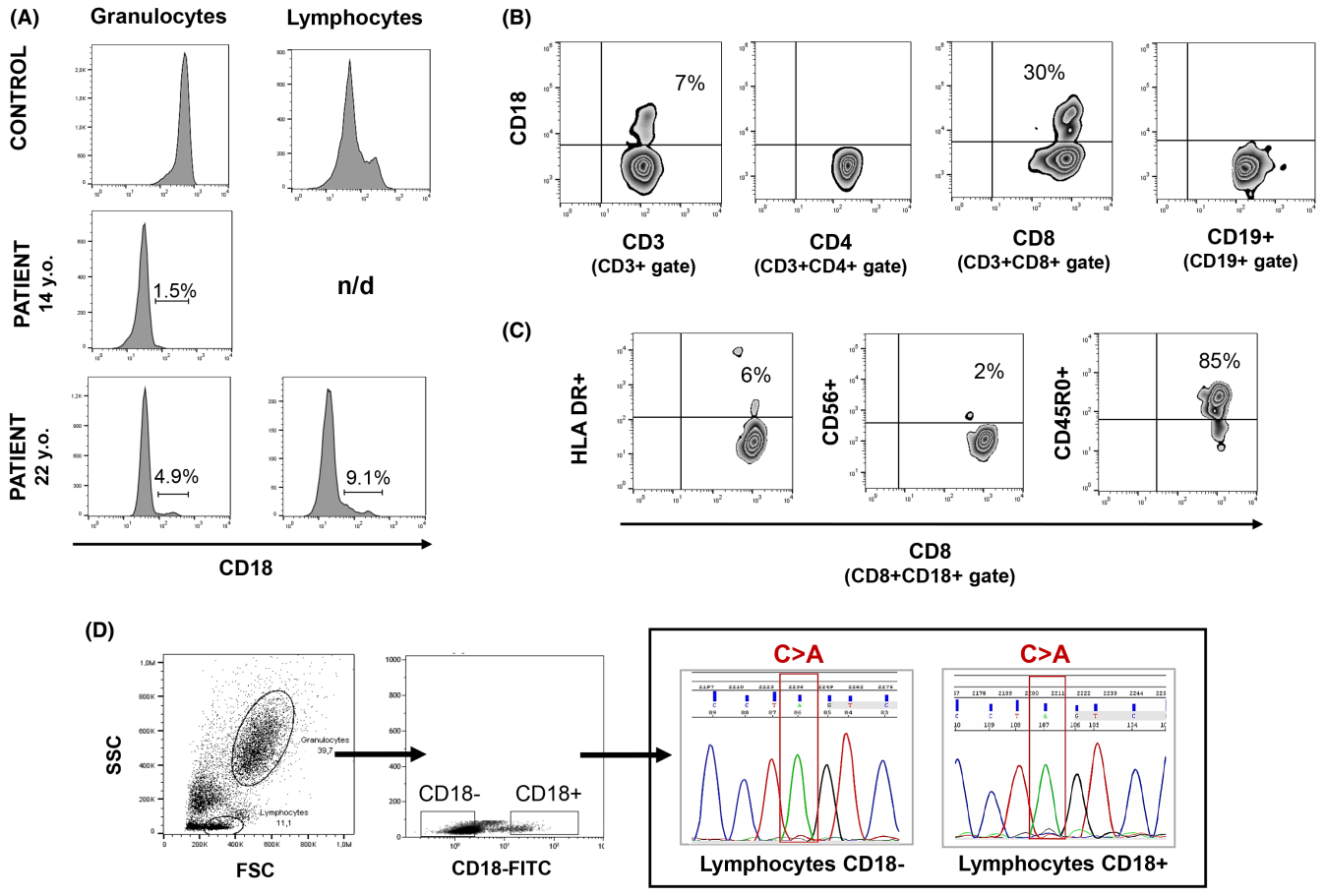

FIGURE 2 (A) CD18 expression on lymphocytes and neutrophils in different patient's ages; (B) all CD18$^+$ lymphocytes are CD3$^+$CD8$^+$ positive, about 30% of all CD8$^+$ T-cells were CD18$^+$; (C) CD3$^+$CD8$^+$ CD18$^+$ cells phenotype, expression of CD45R0, HLA DR and CD56, back gating and multigating techniques were used to assess coexpression of multiple cell surface markers on CD18$^+$ lymphocytes; (D) sequencing of sorted CD18b right and CD18 negative lymphocytes subsets. Both subsets are homozygous for c.59-10C>A.

that leads to premature termination. This variant has been reported previously in an LAD-I patient and shown to result in a premature stop codon (p.C19_V20ins11X12).[25]

At the moment of diagnosis at the age of 2 years and further with a re-examination at 14 years, CD18 expression on PMN was 1% and 1.5%, correspondently, which is consistent with severe LAD-1. However, the clinical picture did not match these results, such low expression would lead to more severe and frequent infectious episodes. For this reason, at the patient's age of 22 years, evaluation of CD18 expression on peripheral blood PMNs and lymphocytes were performed using flow cytometry and imaging flow cytometry. CD18-positive PMNs amounted to 4.9%. Unlike PMNs, lymphocytes demonstrated distinct $CD18^+$ populations in addition to the major CD18-dim peaks (Figure 2A). All positive $CD18^+$ lymphocytes were predominantly cytotoxic T cells, with a memory/effector phenotype (Figure 2B,C, for imaging flow cytometry—Figure S1A,B). Additionally, T-cell receptor repertoires were investigated. The TCR Vβ repertoire of both the $CD18^+/CD8^+$ and $CD18^-/CD8^+$ T cells was analyzed by flow cytometry using commercially available monoclonal antibodies specific for 24 Vβ subfamilies, covering more than 70% of all TCRVβ families. All of the TCR Vβ subfamilies were expressed without underrepresentation or overrepresentation in both $CD18^+/CD8^+$ and in $CD18^-/CD8^+$ cells (Figure S2A,B).

Somatic reversions of inherited mutations in inborn errors of immunity are typically associated with milder clinical phenotypes. Given that patient had survived into adulthood, we hypothesized that her $CD18^+$ cytotoxic T lymphocytes may have had somatic reversion, leading to her milder phenotype. Genomic DNA was obtained from sorted $CD18^+$ and $CD18^-$ lymphocytes the patient's peripheral blood. Mutation site–specific amplification and sequencing were performed. All of the $CD18^{-/+}$ clones from the patient were homozygous for c.59-10C>A (Figure 2D).

Because of the homozygosity of the inherited original mutation p.C19_V20ins11X12, neither gene conversion nor crossing over could be the mechanism.

3 | DISCUSSION

We describe a Slavic adult female LAD I patient with variable CD18 expression during her lifetime and whose pregnancy was complicated by a PG-like disorder. This is a highly unusual case, as we found only a single prior mention of non-complicated pregnancy and delivery in an LAD I deficient woman.[13] Since the average lifespan of patients with mild phenotype is about 40 years old,[3] pregnancy in this group of patients is possible, and it is important for clinicians to be aware of its potential complications.

PG is severe skin disorder that predominantly occurs in adult patients with systemic underlying conditions (autoimmune, malignancies etc.). Pediatric manifestations are uncommon and often associated with autoinflammatory disorders such as Pyogenic Arthritis, Pyoderma gangrenosum and Acne syndrome.[26] In some cases, pyoderma may occur with other, non-autoinflammatory primary immune deficiencies, such as chronic granulomatous disease[27] and LAD-1. PG in LAD I deficient patients is often characterized as PG-like disorder due to non-typical histology with reduced neutrophil infiltrations compared to classical PG.[16]

There are only 14 published cases of PG-like necrotic lesions in LAD-1 deficient patients (Table 1). All of them have mild to moderate disease severity and residual CD18 expression. PG presented as unique episodes in some patients and in others had a relapsing course. Often trauma is a trigger for PG. In this patient, there was no history of trauma and PG was associated with pregnancy. In otherwise healthy patients, PG is a rare pregnancy complication, with only 26 cases published with the majority occurring between the second trimester and postpartum.[28] Increased granulocyte colony-stimulating factor levels in pregnant woman can contribute to neutrophil activation and an aberrant inflammatory response. As some patients with mild to moderate LAD-1 deficiency can develop aberrant inflammation, we suspect that pregnancy in LAD-1 women may lead to an even higher risk of PG.

Patients with partial CD18 expression are present in almost in all published cohorts of LAD-1 deficiency (in an Indian cohort about 16% of all LAD-1 deficient patients had >2% of $CD18^3$). Usually these patients have mild to moderate phenotypes that correspond to partially functioning β-integrins. According to cohort studies that match partial CD18 expression with mutation type, missense or splice site mutations are prevalent in mild to moderate phenotype cohort (about 80%).[2,20] In addition, four unrelated patients with somatic reversion in distinct population of CD8 T-cells have been described, with only one TCRVb clone prevailed in the $CD8^+CD18^+$ T-cell subset.[22,23]

Due to severely diminished CD18 expression in childhood and the presence of a $CD8^+CD18^+$ T-cell subset, we suspected revertant mosaicism, but all $CD18^+$ lymphocytes carried the homozygous mutation, disproving this hypothesis. CD18 has 13 potential isoforms (https://www.uniprot.org/uniprot/P05107). As some patients with splice site mutations have partial CD18 expression, this may be related to alternative splicing. We suspect that CD18 isoforms that capable to binding monoclonal antibodies are present, and according to clinical course of the disease, these isoforms can be partially functional.

TABLE 1 Demographic, clinical, laboratory, and genetic characteristics of all reported LAD-1 patients with pyoderma gangrenosum-like disorder.

#	Country	Gender	Mutation	Age of diagnosis	CD18 expression (neutrophil)	Pyoderma manifestation	Trigger	Outcome	Other clinical data	Reference
1	Netherlands	Male	n/d	n/d	About 10%	Since 1st year	n/d	Resolved	Infections (pneumonia, otitis, sinusitis)	Kerkhof et al.[13]
2		Female	n/d	n/d	About 10%	Since 1st year	n/d	Fatal (28 years)	Pregnancy, healthy son, infectious	
3		Male	n/d	n/d	About 10%	7 years	n/d	Resolved	Infections and psoriasiform dermatosis	
4	UK	Female	n/d	5 years	Low (% not indicated)	4 years	n/d	Resolved	n/d	Bedlow et al.[14]
5	USA	Male	c. 314T>C:p. Leu105Pro (hom)	11 years	40%	Since 3 years	Trauma/ unknown	Resolved	Infectious episodes	Hinze et al.[17]
6	Israel	Female	n/d	n/d	1% (at the moment of pyoderma)	13 years	n/d	Resolved	HSCT in 12 m, healthy before 13 years old	Elenberg et al.[18]
7	USA	Male	p. Lys196Thr/p. Arg593Cys	3 years	Partial deficiency (% unknown)	11 years (relapsed, 20y history)	Trauma/ unknown	Resolved	Infections	Nord et al.[12]
8	India	Male	IVS10+4A>G	4 years	48%	Since 2 years	Trauma/ unknown	Resolved	Infections	Madkaikar et al.[19]
9		Female	IVS10+4A>G	11 years	65%					
10		Male	IVS10+4A>G	2 years	50%					
11		Male	IVS10+4A>G	16 years	19%					
12	Sweden	Male	Intron 14+1delG/ c.130A>C; p.Thr44Pro	15 years	9%	Since 3 years (relapsed)	n/d	Resolved	Rare infectious episodes	Vahlquist et al.[15]
13	USA	Female	n/d	18 m	5%–10%	9 years	Trauma	Resolved	n/d	Simpson et al.[16]
14	Ukraine	Female	p.C19_V20ins11X12 (hom)	1 years	1%–5%	20 years	Pregnancy	Treated	Infectious episodes	Current case, also published Opalińska et al.[24]

Abbreviations: Hom, homozygous; HSCT, Hematopoietic Stem Cell Transplantation; m, months; n/d, no data; y = years.

Although we excluded revertant mosaicism, we acknowledge the limitations of used laboratory methods range; therefore, even alternative splicing is the only possible explanation for partial CD18 expression, the presence of other isoforms in current case has not been experimentally proved.

4 | CONCLUSION

Partial LAD-1 deficiency is extremely rare disorder, that characterized mild or moderate clinical phenotype with reduced frequency and severity of infections, but these patients may still be at risk for autoimmune and autoinflammatory complications, the most common is PG-like skin lesions. In current case, somatic reversion as one of the mechanisms capable of explaining partial expression in a particular cell population has not been confirmed. Since the patient has a mutation at the splice site, partial CD18 expression might be caused by alternative splicing mechanisms. Given the "relatively mild" disease course, we suspect that production of partially functional CD18 isoforms that capable to binding monoclonal antibodies takes place.

AUTHOR CONTRIBUTIONS

Anastasiia V. Bondarenko: Conceptualization; investigation; resources; writing – original draft; writing – review and editing. **Oksana R. Boyarchuk:** Conceptualization; investigation; resources; writing – original draft; writing – review and editing. **Inga S. Sakovich:** Conceptualization; investigation; methodology; writing – original draft; writing – review and editing. **Ekaterina A. Polyakova:** Investigation; writing – review and editing. **Alexander A. Migas:** Investigation; writing – review and editing. **Aleksandra N. Kupchinskaya:** Investigation; writing – review and editing. **Aleksandra Opalinska:** Investigation; writing – review and editing. **Adam Reich:** Investigation; writing – review and editing. **Liubov Volianska:** Investigation; writing – review and editing. **Anna M. Hilfanova:** Investigation; writing – review and editing. **Fedir I. Lapiy:** Investigation; writing – review and editing. **Liudmyla I. Chernyshova:** Investigation; writing – review and editing. **Alla P. Volokha:** Investigation; writing – review and editing. **Dariia V. Zabara:** Investigation; writing – review and editing. **Mikhail V. Belevtsev:** Investigation; writing – review and editing. **Tatsiana V. Shman:** Investigation; writing – review and editing. **Lyudmila V. Kukharenko:** Investigation; writing – review and editing. **Mikhail V. Goltsev:** Investigation; writing – review and editing. **Tatsiana G. Dubouskaya:** Investigation; writing – review and editing. **Andrei Y. Hancharou:** Investigation; writing – review and editing. **Weizhen Ji:** Investigation; writing – review and editing. **Saquib Lakhani:** Investigation; writing – review and editing. **Carrie L. Lucas:** Investigation; writing – review and editing. **Olga V. Aleinikova:** Conceptualization; writing – review and editing. **Svetlana O. Sharapova:** Conceptualization; project administration; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was performed in line with the principles of the Declaration of Helsinki. Study was approved by the institutional review boards involved in all diagnostics and treatment procedures (Ukraine, USA, Poland, Belarus).

CONSENT TO PARTICIPATE

Informed consent forms were signed by the parents and by the patient after the age of 18 years old.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy. The patient consented to present data and images in a medical journal.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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