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RESEARCH

Deficiency of Adenosine Deaminase 2 Masquerading as Behçet's Disease: Phenotypic Mimicry with HLA-B*51 Positivity

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Abstract

Purpose Deficiency of adenosine deaminase 2 (DADA2) is a rare monogenic autoinflammatory disease resulting from biallelic loss-of-function mutations in *ADA2* gene. It has variable clinical manifestations, some of which can mimic Behçet's disease (BD). Herein, we present a family of three siblings diagnosed with DADA2, two of whom were initially misdiagnosed as BD based on clinical phenotype including positive human leukocyte antigen B51 (HLA-B*51).

Methods Gene mutational analysis was performed by whole exome (WES) and Sanger sequencing.

Results We reported two siblings presented with recurrent oral ulcers, fever, arthritis, and skin lesions, alongside elevated inflammatory markers and HLA-B*51 positivity, leading to an initial misdiagnosis of BD. Genetic testing later revealed a homozygous *ADA2* variant (c.139G > A p.Gly47Arg) in both siblings and their asymptomatic younger sister, confirming DADA2 diagnosis. Thereafter, we reviewed the literature to identify other patients misdiagnosed with BD but later found to have DADA2. This resulted in a cohort of 10 DADA2 patients, including our two reported siblings. The median time from symptoms onset to the final diagnosis of DADA2 was 7 years. All patients exhibited BD-like phenotype, except for uveitis, and 8 were HLA-B*51 positive, which likely contributed to the diagnostic confusion.

Conclusion These findings highlight the broad clinical spectrum of DADA2, which can resemble BD, and suggest that HLA-B*51 positivity in DADA2 may further complicate diagnosis. Clinicians should maintain a high index of suspicion for DADA2 in early-onset BD-like cases, particularly without uveitis, or a family history of similar symptoms. Further studies are warranted to explore HLA-B*51 role in DADA2 phenotype.

Keywords ADA2 deficiency · Behçet's disease · Rheumatic disease · Children · HLA-B*51 · Autoinflammatory

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Introduction

Deficiency of adenosine deaminase 2 (DADA2) is a rare autosomal recessive autoinflammatory disorder, first identified in 2014 [1, 2]. Since then, DADA2 cases have been reported at increasingly rapid pace, with an expected disease prevalence of ~ 1 in 222,000 individuals [3]. Considering the disease's mode of inheritance, the prevalence is expected to be higher in consanguineous populations like the Middle East.

This disorder arises from a deficiency in adenosine deaminase (ADA) 2, a key enzyme highly expressed in myeloid cells and secreted by activated monocytes, macrophages, and dendritic cells [4]. Under normal physiological status, ADA2 presents at low concentration but significantly increases during stress and inflammation [5]. ADA2 contributes to the process of monocytes differentiation into macrophages, promoting either the pro-inflammatory M1 macrophages, which drive inflammation and tissue damage, or the anti-inflammatory M2 macrophages [6]. Also, it catalyzes the deamination of extracellular adenosine and 2'deoxyadenosine into inosine and deoxyinosine, respectively [5, 6]. Furthermore, it has been proposed that ADA2 has a role in endothelial cell and hematopoietic cell development [1, 7].

Therefore, biallelic loss-of-function mutations in the *ADA2* gene result in decreased ADA2 activity/level, leading to the accumulation of extracellular adenosine due to reduced deamination process. It also impairs the monocyte differentiation, causing an overproduction of pro-inflammatory M1 macrophages and a reduction in anti-inflammatory M2 macrophages. This imbalance contributes to chronic tissue inflammation; a hallmark feature of DADA2 [1, 2]. Furthermore, accumulated extracellular adenosine in DADA2 patients can stimulate the formation of neutrophil extracellular traps (NETs), which induces NETosis and eventually results in high Tumor Necrosis Factor Alpha (TNF-α) production by activated macrophages [8].

Patients with DADA2 exhibit broad clinical spectrum with variable age of onset [9, 10]. Recently, an international multidisciplinary consensus statement for DADA2 patients have been released by the DADA2 Consensus Committee [11]. They categorized the disease presentation into four main phenotypes. The presymptomatic phenotype includes individuals who have no signs or symptoms of DADA2 but are identified through family screening or incidental genetic testing. The hematologic phenotype includes patients with mainly cytopenia, lymphoproliferation and/or large granular lymphocytosis. Patients with hypogammaglobulinemia, recurrent and/or opportunistic infections are classified under the immunodeficient phenotype [11].

The fourth group is the inflammatory and/or vasculitic phenotype, which includes patients with recurrent fever, elevated inflammatory markers, skin rash, stroke, vascular aneurysm, and/or infarction. Patients with this phenotype are often misdiagnosed as polyarteritis nodosa (PAN), or Sneddon syndrome. In fact, DADA2 was first described as a mimicker of PAN by two different groups [1, 2]. Subsequently, many patients previously diagnosed with PAN were screened and found to carry pathogenic *ADA2* mutations [12–15]. Moreover, some experts have suggested screening all pediatric PAN patients for DADA2, especially those with a family history of PAN or who have not responded to initial treatment [16].

Similar to childhood PAN, we believe Behcet disease (BD) is another systemic inflammatory condition that can present with features nearly indistinguishable from the inflammatory/vasculitic phenotype of DADA2. BD is a rare disorder of unknown etiology that typically manifests with recurrent oral and genital ulcers, uveitis, vascular thrombosis or aneurysm, erythema nodosum and various skin lesions [17]. BD is strongly associated with the HLA-B51 antigen, being the strongest genetic susceptibility factor discovered so far that presents in over 60% of BD patients [18–22]. However, it is important to note that the pathogenic role of HLA-B*51 in BD remains unclear, and evidence supporting its use as a diagnostic marker is lacking [18]. Furthermore, the prevalence of HLA-B*51 is significantly higher in the healthy population of countries along the Silk Road, the region where BD is most prevalent, suggesting that additional factors likely contribute to the development of BD [18, 20].

In this article, we reported a family of three siblings confirmed to have DADA2, two of whom were initially misdiagnosed with BD based on clinical phenotype, including positive HLA B*51 antigen. We therefore reviewed the literature to describe the clinical features of patients who were initially diagnosed with BD and later recognized as having DADA2.

Methods

Patients

The patients' clinical presentation and laboratory investigations are presented in the Results section. Sample collections were obtained from patients during their visits and follow-up at the pediatric rheumatology clinic for medical evaluation. Written informed consent was obtained from the patients' parents in accordance with King Abdulaziz Medical City (KAMC) protocol, following the Saudi Ministry of Health (MOH) guidelines and the ethical principles of the Declaration of Helsinki and its later amendments.

Genetic Studies

Genomic DNA was extracted from patients' whole blood using the QIAamp DNA Mini Kit (Qiagen, Germany) following the manufacturer's protocol. Whole-exome sequencing (WES) was then performed, targeting genes associated with monogenic autoinflammatory disorders. The identified homozygous *ADA2* variant was confirmed in the patient and her family members by Sanger sequencing. All genetic testing procedures were conducted as previously described in this article [23].

Results

The case study presents a family with three siblings from consanguineous parents, with no relevant family history of autoimmune or autoinflammatory conditions (Fig. 1).

The first daughter (A1) was referred to our clinic at the age of 4 years with a one-year history of recurrent, painful, non-scaring oral ulcers, occurring three times within that year. She also had bilateral, tender subcutaneous nodules on her lower limbs, which lasted for several weeks then resolved leaving hyperpigmented lesions. Additionally, she experienced recurrent episodes of low-grade fever at irregular intervals, along with migratory arthritis without significant morning stiffness. On examination, she had active arthritis in the left ankle joint and multiple hyperpigmented macules on her shins, with the rest of her physical examination being unremarkable. Initial investigations showed normal complete blood count (CBC) with differentials, unremarkable kidney and liver profile, but elevated inflammatory markers with C-reactive protein (CRP) of 64 mg/L (Normal range: < 8 mg/L) and erythrocyte sedimentation rate (ESR) of 65 mm/hr (Normal range: 0 – 20 mm/hr). Basic immunological workup, including immunoglobulin levels, antinuclear antibody (ANA), extractable nuclear antigen (ENA) panel, anti-neutrophil cytoplasmic antibodies (Anti-proteinase-3 and myeloperoxidase), and complement levels (C3 and C4), were all unremarkable (Table S1). Given the suspicion of BD, HLA-B*51 testing was performed and returned positive. Unfortunately, a skin biopsy was not performed because no fresh lesions were available at the time of presentation to our clinic.

The patient was initially started on Celecoxib (50 mg twice daily) and Colchicine (0.5 mg/day) with a presumed diagnosis of BD. She was followed regularly for nearly 2 years, during which her symptoms, including oral ulcers and arthritis, showed minimal improvement despite multiple increases in Colchicine dosage, reaching 2 mg twice daily. Subcutaneous (SC) Methotrexate (15 mg/m^2/week) was added, but it didn't fully improve her arthritis. At age 6, SC Adalimumab (20 mg every 2 weeks) was introduced, leading to dramatic improvement in her symptoms. Subsequently, Colchicine and Celecoxib were gradually weaned off.

During a follow-up visit, the patient's mother reported that her second daughter, a 4-year-old girl (A2), had been experiencing similar symptoms for about a year, including recurrent oral ulcers, arthralgia, skin rash, and episodes of low-grade fever. The patient's sister (A2) was brought to our clinic, and found to have livedo reticularis on the upper and lower limbs, as shown in Fig. 2. Otherwise, the remainder of her physical examination was normal. Her laboratory results were similar to her older sister's (A1), with mildly elevated inflammatory markers (CRP: 13 mg/L, ESR: 28 mm/hr) and positive HLA-B*51 antigen (Table S1). Initially, she was started on Colchicine (0.5 mg/day) with a suspected diagnosis of BD, but liker her older sister, she didn't improve

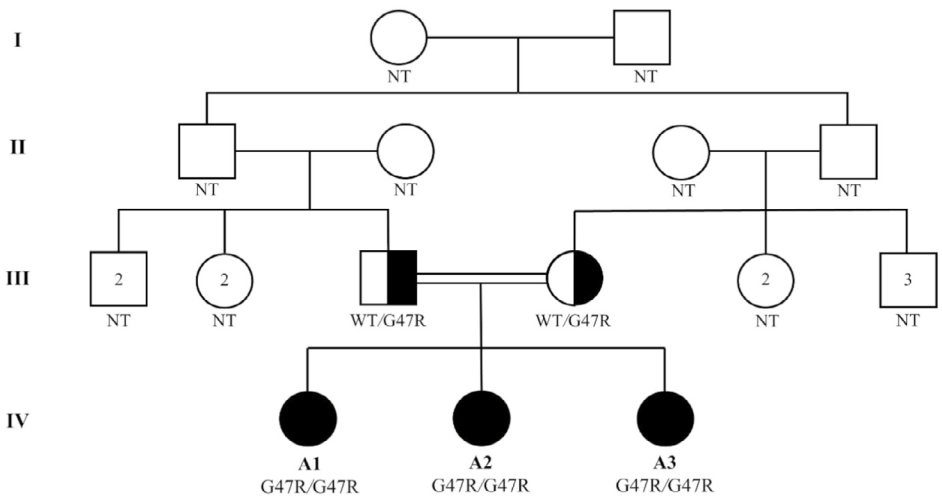

Fig. 1 Pedigree of the reported patients (A1, A2, and A3) with DADA2 disease carrying G47R homozygous mutations of *ADA2* gene

NT; not tested, WT: wild type.

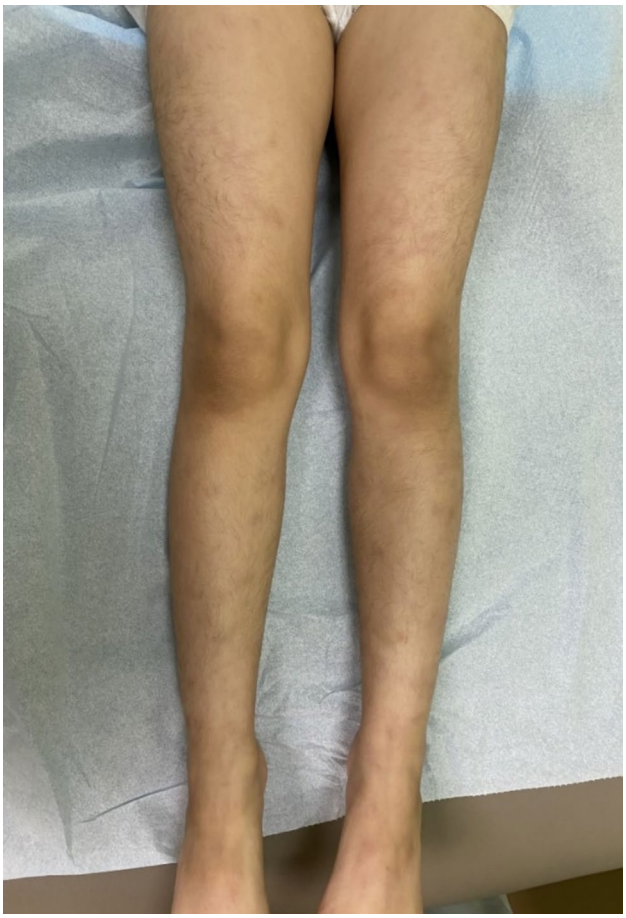

Fig. 2 Bilateral livedo reticularis rash over the lower limbs of patient A2

despite maximizing Colchicine dose to 2 mg every 12 h. Therefore, SC Adalimumab (20 mg every 2 weeks) was initiated, leading to the complete resolution of her symptoms and normalization of inflammatory markers.

Given the early onset of symptoms in both sisters, parental consanguinity, and poor response to initial therapies for BD, monogenic autoinflammatory diseases were considered. Subsequently, whole-exome sequencing (WES) was performed for the first patient (A1), revealing a homozygous pathogenic mutation in *ADA2*, c.139G > A p.(Gly47Arg). This variant results in an amino acid change from glycine to arginine at position 47 and has been previously reported as pathogenic in patients with DADA2 [1, 2]. According to the American College of Medical Genetics and Genomics (ACMG) guidelines, this variant is classified as Pathogenic (Class 1) based on the following evidence: (1) it is a well-established pathogenic variant in ClinVar (Variation ID: 120,304) and the Human Gene Mutation Database (HGMD); (2) it has been reported in multiple unrelated patients with DADA2; and (3) it is located in a critical functional domain of the ADA2 protein. In silico predictive tools, including SIFT, PolyPhen-2, and MutationTaster, consistently support the deleterious effect of this variant on protein function.

Following this, Sanger sequencing of *ADA2* gene was conducted to screen the rest of the family, including the second symptomatic sister (A2), who also tested positive for the same homozygous variant. Additionally, their youngest, asymptomatic sister was found to carry the same homozygous variant. As expected, the parents were heterozygous carriers of this mutation.

After identifying the same mutation in the youngest sister (A3), a 3-year-old girl, she was brought in for further evaluation. Her medical history and physical examination were normal, and her laboratory investigations, including inflammatory markers, were unremarkable (Table S1). A brain MRI (magnetic resonance imaging) and MRA (magnetic resonance angiography) were also performed, both of which were normal. We discussed with the parents the potential of starting her on anti-TNF therapy despite being asymptomatic, given that she carried the same pathogenic genotype causing DADA2 as her sisters. However, after careful consideration, the parents opted for close follow-up instead of initiating treatment at that time.

Discussion

DADA2 is a monogenic autoinflammatory disorder with broad and variable signs and symptoms, which can be categorized into three main phenotypes: vasculitis, hematologic abnormalities, and immunodeficiency [11]. This phenotypic variability often leads to diagnostic challenges, as DADA2 can mimic a wide range of other diseases depending on its predominant manifestations. For instance, in patients presenting primarily with hematologic abnormalities such as cytopenia, pure red cell aplasia, or lymphoproliferation, they may be misdiagnosed initially with Diamond-Blackfan anemia or Evans syndrome. Similarly, the immunodeficient phenotype of DADA2, characterized by hypogammaglobulinemia, recurrent infections, and/or lymphopenia, can overlap with conditions such as combined immunodeficiency, common variable immunodeficiency (CVID), or autoimmune lymphoproliferative syndrome (ALPS). Finally, the vasculitic phenotype that includes features like recurrent fever, livedo reticularis, and early-onset strokes, can mimic systemic vasculitis like PAN or monogenic lupus [11, 24–28]. These overlapping features underscore the importance of considering DADA2 in the differential diagnosis of patients with early-onset systemic inflammation, particularly when the clinical presentation does not fully align with classic diagnostic criteria for these conditions.

In this article, we reported a family of three siblings with genetically confirmed DADA2, two of whom were initially misdiagnosed with Behçet's disease (BD) due to the striking

overlap in clinical features, including recurrent oral ulcers, cutaneous lesions, and HLA-B51 positivity. We therefore reviewed the literature using the PubMed database, restricted to English-language articles, and identified eight additional DADA2 patients from five unrelated families [24–28], all of whom were initially labeled with BD before being found to carry pathogenic *ADA2* mutations (Table 1).

Both DADA2 and BD are complex conditions that can present with a range of overlapping symptoms, with the inflammatory manifestations being the major clinical feature of both diseases. As shown in Table 1, almost all the patients exhibited a combination of fever, livedo reticularis, cutaneous ulcers, arthritis/arthralgia, with symptoms typically beginning in early childhood. This early age of onset is a notable feature, as BD is more commonly diagnosed in adulthood or late childhood [17], whereas DADA2 often presents in the first decade of life, particularly in populations with a high prevalence of consanguinity, which increases the likelihood of autosomal recessive conditions. The median time from the onset of symptoms to reaching the final diagnosis of DADA2 was 7 years, underscoring the diagnostic challenges posed by the overlapping clinical features of these conditions. In addition to the clinical phenotype, we believe that the positivity of HLA-B51 (8/10) further contributed to the initial misdiagnosis of BD in these cases, as HLA-B51 is a well-established genetic susceptibility factor for BD [18–20]. This highlights the importance of considering genetic and molecular testing, particularly in pediatric patients with early-onset inflammatory symptoms and/or a family history of consanguinity, to differentiate between these clinically similar disorders.

Conversely, uveitis is rarely associated with DADA2 disease. In fact, it has been reported in only four cases of DADA2 [29–32]. This trend was also observed in Table 1 as none of the patients who were misdiagnosed with BD had uveitis, a hallmark commonly seen in BD patients [33]. We believe that the absence of uveitis could serve as a key clinical clue in differentiating between DADA2 patients presenting with a BD-like phenotype and those with true early-onset BD.

In general, the diagnosis of DADA2 is often challenging due to its broad spectrum of clinical manifestations including hematologic, immunodeficiency, inflammatory and/or vasculitic phenotypes [11]. Moreover, the absence of standardized diagnostic criteria and the limited availability of ADA2 enzyme activity tests in most centers complicate the process. The high costs and need for sending samples abroad for testing also contribute to these challenges [27, 34]. In such cases, genetic testing may be the only viable diagnostic option. However, it is time-consuming and may not always yield definitive results, which can to delays in managing those patients.

Once the diagnosis is confirmed, establishing a prompt and effective treatment plan is crucial for managing DADA2 patients, aiming to address its diverse clinical manifestations and minimize disease-associated morbidity and mortality. It involves a range of therapeutic options to control the symptoms and prevent disease progression. The international DADA2 Consensus Committee considers anti-TNF therapy as the treatment of choice for patients with inflammatory and vasculitic phenotype [11]. Lifelong anti-TNF therapy demonstrated a desirable effect in achieving remission and decreasing the risk for strokes and other vasculitic complications [11, 35]. As shown in Table 1, all the patients were started on TNF inhibitors except for three related individuals (E6, E7, and E8). The first patient (E6) passed away before reaching to the diagnosis, while the other two (E7 and E8) refused anti-TNF treatment as they became asymptomatic after starting Colchicine [27]. Allogeneic hematopoietic stem cell transplantation (HSCT) may emerge as a necessary intervention when having a severe form of the disorder such as bone marrow failure and refractory cytopenia [11]. A recent systematic review showed that among 25 patients who underwent HSCT, a complete resolution of the disease manifestations was reported in 22 cases [35].

Following the discussion of treatment options for symptomatic DADA2 patients, a significant clinical dilemma arises regarding whether anti TNF therapy should be started in all asymptomatic patients for stroke prevention. The DADA2 Consensus Committee was unable to provide a strong recommendation for treating such patients, advising only to consider it, likely due to the unpredictable nature of DADA2 and the lack of natural history data [11]. In the case of our asymptomatic patient (A3), her parents opted to delay starting the medication. For the past four years, she has been regularly monitored in the clinic, remaining stable with normal blood counts and inflammatory markers. Additionally, MRI/MRA scan was performed and did not identify any abnormalities. Until larger prospective studies provide clearer guidance, we believe the decision should be made collaboratively between the provider and the patient's family. Clinicians must carefully weigh the risks and benefits, balancing the need for indefinite therapy in an asymptomatic individual against the potential for a catastrophic event as the first manifestation of the disease.

Our study has several limitations to consider. First, the limited number of patients, particularly asymptomatic individuals like Patient A3, restricts our ability to generalize management recommendations for presymptomatic DADA2 cases. Second, while genetic testing confirmed the ADA2 variant, ADA2 enzyme activity was not assayed to confirm functional deficiency in multiple patients. Third, the role of HLA-B*51 in driving the BD-like phenotype remains unclear. Lastly, the retrospective nature of our

Table 1 Key characteristics of DADA2 patients initially misdiagnosed with Behcet's disease

Family/Patient	A1	A2	B3 [24]	C4 [25]	D5 [26]	E6 [27]	E7 [27]	E8 [27]	F9 [28]	F10 [28]
Age at disease onset	3y	3y	12y	8m	3y	5.5y	2.5y	?	3y	12y
Age at diagnosis	7y	5y	15y	15y	18y	10y	3y	37y	21y	23y
Sex	F	F	M	M	F	F	M	M	F	F
Consanguinity	+	+	+	-	-	+	+	+	?	?
Previous diagnosis	Behcet's	Behcet's	Behcet's	Behcet's	Behcet's	Behcet's	Behcet's	Behcet's	Behcet's	Behcet's
Origin	Saudi	Saudi	Turki	Italy	Romania	Iran	Iran	Iran	Turki	Turki
Fever	+	+	+	+	+	+	+	+	+	-
Erythema nodosum	+	+	-	+	-	-	-	-	+	+
Livedo reticularis	-	+	+	+	+	+	+	+	-	+
Oral ulcers	+	+	?	+	+	+	+	+	-	+
Genital ulcers	-	-	?	+	+	-	-	-	+	-
Arthritis/ Arthralgia	+	+	+	+	+	+	-	+	+	+
Neurologic	-	-	Headache, stroke	Stroke	-	Recurrent strokes	-	Headache	Vertigo	-
Ocular	-	-	Optic neuritis	-	-	-	-	-	3rd nerve palsy	-
Gastrointestinal	-	-	Abdominal pain, HSM, diarrhea	Intestinal vasculitis, portal HTN, HSP	Pancreatitis, HSP, colitis, perforation	-	-	-	Enlarged spleen	-
Hematologic	-	-	-	Anemia, neutropenia	Leukopenia, Neutropenia	High Plt	-	-	Leukopenia	Leukopenia
Other findings	-	-	Raynaud's, Pathergy +	HET (P268S) in *NOD2*†	Anti-dsDNA +	-	-	-	-	-
Immunological	-	Low IgA	Low IgM	?	Low IgG	-	-	Low IgM	-	-
High CRP	+	+	+	+	+	+	-	+	+	-
High ESR	+	+	+	-	+	+	-	+	+	-
HLA-B*51	+	+	+	+	+	+	+	+	-	-
Previous treatment	COL, MTX, NSAIDs	COL, MTX, NSAIDs	Steroid, COL, MSZ, INF, FFP	CAN, Thal, RTX, COL AZA, CyA, MTX, ETN	Steroid, COL, HCQ, ETN‡	AZA, Steroid, MMF	COL	COL	COL, CAN, AZA	COL

Table 1 (continued)

Family/Patient	A1	A2	B3 [24]	C4 [25]	D5 [26]	E6 [27]	E7 [27]	E8 [27]	F9 [28]	F10 [28]
ADA2 gene mutation	G47R Missense HOM	G47R Missense HOM	G47R Missense HOM	G47R Missense HOM	G47R Missense, A221Q fs*45 Comp. HET	G47R Missense HOM	G47R Missense HOM	G47R Missense HOM	c.973- 2A > G p.(?) splice site HOM	c.973- 2A > G p.(?) splice site HOM
Current treatment	Adal	Adal	ETN	Steroid	-	-	COL	COL	Adal	Adal
Outcome	Rem	Rem	Rem	Rem	Demise	Demise	Rem	Rem	Rem	Rem

†; The authors who originally described this patient proposed that part of the gastrointestinal manifestations observed in the patient could have been driven by a CD-like disorder due to the presence of this heterozygous variant (P268S) in *NOD2*

‡; This patient received only one dose of etanercept then passed away

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *HLA-B*51* human leukocyte antigen B51, *y* years, *m* months, *F* female, *M* male, *HSM* hepatosplenomegaly, *Ig* immunoglobulin, *COL* colchicine, *MTX* methotrexate, *NSAIDs* Nonsteroidal anti-inflammatory drugs, *MSZ* Mesalazine, *Adal.* adalimumab, *ETN* etanercept, *CAN* canakinumab, *AZA* Azathioprine, *RTX* Rituximab, *Thal* Thalidomide, *CyA* cyclosporin, *Rem.* remission, *FFP* Fresh frozen plasma, *HOM* homozygous mutation, *HET* heterozygous mutation, *Comp.* compound, *Plt.* platelets

analysis may introduce selection bias, particularly in identifying DADA2 cases initially misdiagnosed as BD.

In conclusion, DADA2 is an inherited disease associated with significant morbidity and mortality, and it can present with a wide range of clinical manifestations, including a Behcet's disease-like phenotype. The presence of HLA-B*51 in such patients may mislead clinicians and delay the diagnosis of DADA2, as highlighted in the reported cases. Physicians should consider alternative diagnoses to BD in cases of poor response to treatment, early age of symptom onset, or a family history of consanguinity and/or BD. Notably, none of the patients misdiagnosed with BD in our review had a history of uveitis, a common feature in BD. The absence of uveitis may serve as a useful clinical clue for identifying DADA2 in patients presenting with a BD-like phenotype. Finally, prospective studies are urgently needed to refine recommendations for monitoring and potentially treating presymptomatic DADA2 patients.

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Author Contributions Abdullah Almojali and Abdulrahman Alrahseed conceptualized and designed the study. Abdullah Almojali, Bushra Alharbi and Reem Alharbi collected of the patients' clinical information and wrote the manuscript. Fayhan Alroqi, Wafaa Alsuwairi, Jubran Alqanatish, and Abdulrhman Alrasheed supervised the entire research and revised the final manuscript. All authors have read and approved the final version of manuscript.

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

Declarations

Informed Consent The patients' parents have consented to the submission of the report to the journal.

Conflicts of Interest The authors declare no competing interests.

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