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Vasculitis associated with adenosine deaminase 2 deficiency: at the crossroads between Behçet's disease and autoinflammation. A viewpoint

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SUMMARY

Adenosine deaminase 2 deficiency (DADA2) is a rare monogenic vasculopathy caused by loss-of-function homozygous or compound heterozygous mutations in *ADA2*, formerly *CECR1* (*cat eye syndrome chromosome region 1*) gene. The DADA2 phenotype is widely heterogeneous, and patients may present with fever, weight loss, livedo reticularis/racemosa, digital ischemia, cutaneous ulceration, peripheral neuropathy, abdominal pain, bowel perforation, and portal or nephrogenic hypertension. More specific manifestations include early-onset ischemic or hemorrhagic stroke, mild immunodeficiency and hypogammaglobinemia, cytopenia, and vision disturbances. Herein, we present the case of a young male with vasculitis associated with DADA2. The presence of *HLA-B51* and the clinical features of this patient raised the question of similarities between *ADA2* deficiency, Behçet's disease, and *NOD2*-associated diseases. Treatment of this rare monogenic disease is challenging and based on small case series. The long-term experience of this patient proved the difficulties of prednisone tapering and the lack of satisfactory therapeutic strategies.

Key words: *Adenosine deaminase 2, vasculitis, NOD2 Behçet's disease, inflammatory bowel diseases, autoinflammatory.*

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INTRODUCTION

Adenosine deaminase 2 deficiency (DADA2) is a rare monogenic vasculopathy caused by loss-of-function homozygous or compound heterozygous mutations in *ADA2*, formerly *CECR1* (*cat eye syndrome chromosome region 1*) gene. The phenotype of DADA2 is widely heterogeneous, with a variable age of onset (1-3). The most common reported manifestations are recurrent fever, weight loss, livedo reticularis/racemosa, digital ischemia, cutaneous ulceration, peripheral neuropathy, abdominal pain, bowel perforation, and portal or nephrogenic hypertension. More specific manifestations include early-onset ischemic or hemorrhagic stroke, mild immunodeficiency and hypogammaglobinemia, cytopenia, and vision problems (4, 5). Treatment of this rare monogenic disease is challenging and based on small case series. Herein, we present the case of a young male with vasculitis associated with DADA2 with a unique genetic background linking this syndrome to Behçet's disease (BD) and *NOD2*-associated diseases.

CASE REPORT

A 22-year-old male patient was referred to the Rheumatology Unit of the University of Perugia due to the onset of rectal bleeding and consequent anemia. The patient is the first of two brothers, and his familial history is unremarkable. The clinical history of this patient began at the age of 8 months with a high fever and severe neutropenia. A bone marrow aspirate was performed, but no significant abnormalities were found. At the age of 3, neutropenia, fever, joint pain, diarrhea, and the subsequent appearance of nod-

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ular erythematous and purplish lesions on the lower limbs and buttocks occurred (Figure 1).

At the age of 7, the patient was hospitalized for acute abdominal pain and hepatomegaly. A liver biopsy documented Budd-Chiari syndrome. Moreover, a biopsy of the nodular erythematous lesions of the lower limbs demonstrated leukocytoclastic vasculitis. High-dose intravenous glucocorticoids (GC) were administered and slowly tapered off in about 18 months. Following GC reduction, abdominal pain, mouth ulcers, and vesicular lesions with necrotic evolution relapsed, leading to hospitalization and treatment with GC and high-dose intravenous immunoglobulins. Given the persistence of severe abdominal pain, 3 months later the patient underwent an intestinal video capsule and colonoscopy, showing the presence of ileal ulcers and granular colic mucosa. At that time, a BD diagnosis was formulated, and the patient started therapy with thalidomide in association with steroids with partial benefit and relapse at a dose of prednisone lower than 10 mg/day. For this reason, in November 2009, therapy with methotrexate was started with a poor response, and in June 2010, etanercept (ETN) was started, obtaining clinical remission for 1 year. In June 2011, he developed fever, arthralgias, asthenia, and abdominal pain requiring high-dose GC therapy. Nonetheless, recurrent episodes of severe abdominal pain, the occurrence of nodular skin lesions with ulcerative evolution, and the incapability of tapering the GC dosage led to switching from ETN to colchicine up to 2 mg/day, then cyclosporine 2.5 mg/kg/day, and finally azathioprine (AZA) 2 mg/kg/day without any significant improvement.

A second liver biopsy showed cirrhotic architecture with an inflammatory lymphohistiocytic and eosinophilic granulocytic infiltrate, severe vascular-based alteration associated with signs of chronic cholestasis, and features of inflammatory destructive cholangitis. More relevantly, the presence of significant neutrophilic infiltration of the periportal spaces was demonstrated. A skin biopsy of the nodular lesions confirmed a histological picture compatible with leukocytoclastic vasculitis; moreover, signs of vasculitis with granulocytic infiltrate and fibrinoid necrosis were found. In 2014, genetic investigations excluded the presence of an autoinflammatory disease, while the *NOD2* c.802 C>T (p.P268S) heterozygous missense variant was found. The autoantibody profile [including antinuclear (ANA), anti-extractable nuclear antigen, anti-double stranded DNA, antineutrophil cytoplasmic (ANCA), antiphospholipid, anti-citrullinated peptides, antimitochondrial, anti-smooth muscle antibodies, and rheumatoid factor] was persistently unremarkable. The presence of a homozygous *CECR1* mutation encoding for *ADA2* was discovered. For this reason, a diagnosis of DADA2 was suggested, and ETN was started again with an improvement in the clinical picture until a further worsening following the reduction of the steroid therapy to doses lower than 10 mg/day.

Therefore, the patient was treated with the anti-interleukin 1 (anti-IL 1) agent anakinra with an incomplete response (skin ulcers

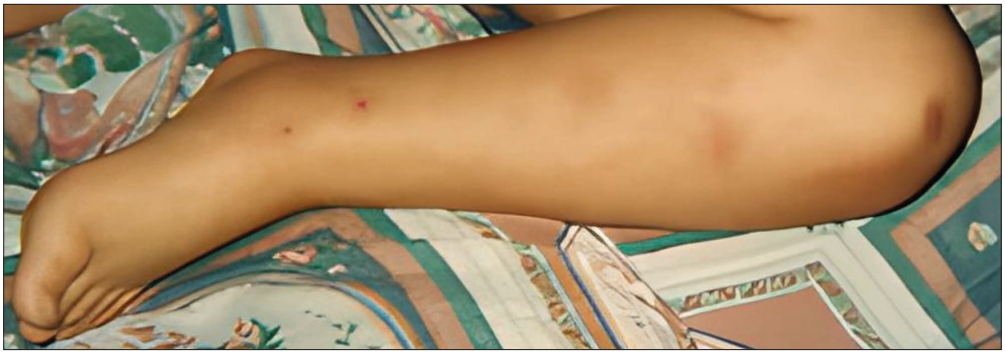

Figure 1 - Nodular erythematous and purplish lesions of the lower limbs.

and joint pain persisted), whereby the dosage was increased to 200 mg/day, obtaining an acceptable clinical response with a prednisone dosage maintained at ≥10 mg/day.
Nonetheless, the patient, who was 15 years old at the time, refused daily subcutaneous therapy. Thus, in February 2016, treatment with canakinumab (CAN) was started, and 28 monthly doses were administered in combination with hydroxychloroquine, with partial clinical response and the reappearance of symptoms upon reduction of steroid therapy to <10 mg/day. For these reasons, rituximab (RTX) was started in February 2020, according to the protocol for ANCA-associated vasculitis, with a satisfactory therapeutic response and clinical remission for about 1 year. Due to concerns related to RTX use during the SARS-CoV-2 pandemic, this treatment was discontinued, and the patient was treated solely with AZA with poor clinical response due to the occurrence of frequent abdominal pain attacks treated with high GC doses.
In September 2021, AZA was withdrawn, and, upon the reduction of the steroid therapy, gastrointestinal (GI) bleeding occurred with moderate anemia (hemoglobin 7.7 g/dL). An esophagogastroduodenoscopy showed no alterations, while a colonoscopy highlighted the presence of a solitary rectal ulcer. Therefore, in 2022, mesalazine therapy was briefly started without any efficacy. In October 2022, he was first referred to the Rheumatology Unit of the University of Perugia due to a worsening of general conditions with profuse asthenia, abdominal pain with rectal bleeding, and articular pain at the ankles and feet. The patient, significantly shorter than any other family member and with Cushingoid features (fatty hump between shoulders, rounded face, abdominal striae rubrae, height 159 cm, weight 82 kg, body mass index 32.44), presented with livedo racemosa of the lower limbs, medial perimalleolar rounded scars at the ankles (Figure 2), no swollen joints, and tender ankles. Laboratory tests demonstrated moderate microcytic hypochromic anemia [hemoglobin (Hb) 8.2 g/dL], slightly increased C-reactive protein (CPR) levels (0.7 mg/dL), and normal erythrocyte sedimentation rate. The antibody tests for ANA, anti-mitochondrion, anti-smooth muscle and anti-liver kidney microsomal antibodies were again unremarkable. A musculoskeletal ultrasound of the ankles revealed no sign of synovitis. A colonoscopy was performed and showed the presence of a lozenge-shaped ulcer of the rectum with a fundus covered in fibrin and hyperemia of the surrounding mucosa with similar alterations in the sigmoid colon. A histological examination of the lesions detected signs of active chronic

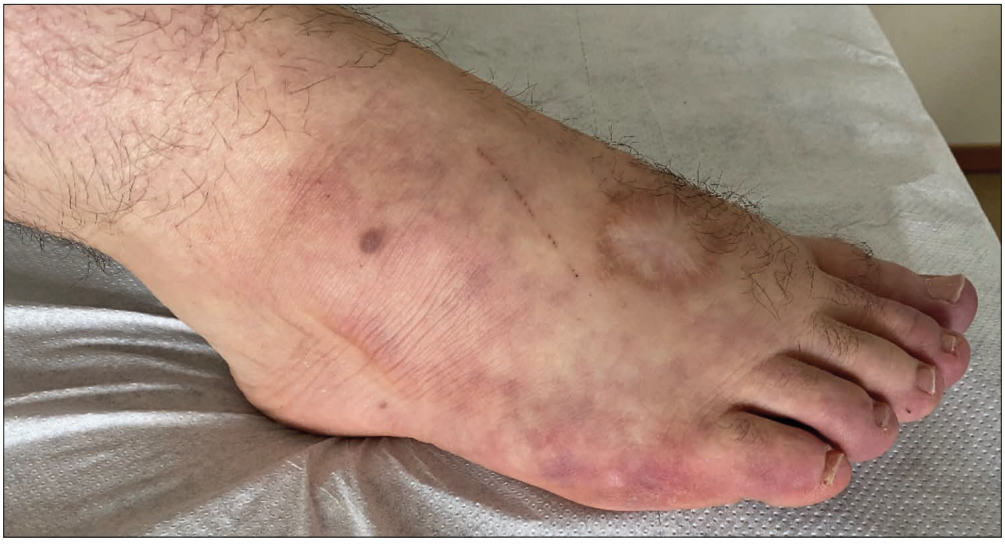

Figure 2 - Livedo racemosa and rounded scars due to previous polyarteritis nodosa-like lesions.

inflammation of the mucosa and fibrous-inflammatory material of the ulcer.
During hospitalization, the patient was treated with prednisone at a dosage of 0.5 mg/kg with considerable clinical efficacy (interruption of GI bleeding, Hb and CRP levels within the normal range). Further examinations, such as a positron emission tomography/computed tomography scan, were not performed given the prompt response to steroid therapy, the lack of evidence of systemic vasculitis and to avoid radiation exposure. Remission was obtained, and the patient is stable with a prednisone dose of 10 mg/day. Given the risk of having a heterozygous mutation, genetic screening was proposed to the brother as well as the parents, who refused to be tested.

DISCUSSION AND CONCLUSIONS

Adenosine deaminase 2 deficiency and Behçet's disease

The patient was diagnosed with DADA2-associated vasculitis due to the presence of a homozygous *CECR1* mutation, fever, livedo racemosa of the lower limbs, previous ischemic strokes, hepatosplenomegaly, portal hypertension, cutaneous polyarteritis nodosa, neutropenia and intestinal vasculitis. An intriguing feature of our patient is the fact that he was found to carry the *HLA-B51* allele, typically associated with BD. Specifically, BD is an inflammatory disease of unknown etiology with multisystemic involvement characterized by mucocutaneous, ocular, musculoskeletal, vascular, GI and central nervous system (CNS) manifestations (6). In particular, the typical clinical manifestation of BD is represented by the triad of oral and genital aphthosis and recurrent uveitis. Nonetheless, other cutaneous manifestations have been described, such as papulopustular or erythema nodosum-like lesions, thrombophlebitis, and skin ulcers (7). Despite the classic oral and genital localization of recurrent aphthous lesions, it is known that these lesions can be localized anywhere in the GI tract (8). Van Well et al. described 6 patients with DADA2 and BD-like phenotype (9); in particular, some of these patients presented with manifestations such as recurrent oral and/or genital aphthosis, folliculitis, erythema nodosum, and GI ulcerations. As far as we know, the patient herein is the first described in the literature with the presence of the *HLA-B51* allele. It is interesting to note that some similarities exist between DADA2 clinical expression in our patient and BD clinical manifestations, in particular in terms of mucocutaneous involvement. Another similarity between BD and DADA2 lies in the fact that both conditions are characterized by autoinflammatory, thrombotic and vasculitic aspects, as observed in our patient with fever, arthralgias, Budd-Chiari syndrome, and leukocytoclastic vasculitis.
Mucocutaneous lesions mimicking BD have been described in other monogenic autoinflammatory diseases (AIDs), including mevalonate kinase deficiency and haplotype insufficiency for A20. AIDs are characterized by abnormal activation of the innate immune system that manifests clinically with recurrent episodes of fever and other inflammatory systemic manifestations such as rash, arthritis, serositis, lymphadenopathy, CNS, and other organ involvement. It is known that vasculitic involvement can be a relevant feature in these diseases and sometimes represents the predominant aspect. This is particularly evident in DADA2, as well as in BD, which has been classified as a *variable vessel vasculitis* in the 2012 International Chapel Hill Consensus Conference since it can involve both arteries and veins of any caliber and location and, at the same time, as a multigenic AID with unknown etiology (6, 10). Whether this is a true association between BD and DADA2 or another additional aspect of the complex phenotype of DADA2 is yet to be determined. Human leukocyte antigen genotyping in DADA2 patients could be proposed, as could the adoption of a treatment strategy that targets both conditions.

Adenosine deaminase 2 deficiency and NOD2-associated diseases

NOD2, later renamed *caspase-activating recruitment domain 15* (*CARD15*) gene, encodes a protein essential for maintaining ho-

meostasis in the immune system. Pathologies associated with *NOD2* mutations include Crohn's disease (CD), Blau syndrome and *NOD2*-associated autoinflammatory disease (11, 12).

CD is a chronic inflammatory bowel disease strongly associated with *NOD2*/*CARD15*. A polymorphism commonly found in CD patients is the substitution of cytosine for thymine in exon 4 at position 802 of *NOD2* (c.802 C>T, p.P268S), the mutation found in our patient. The prevalence of this variant reaches almost 50% in CD patients compared to 18.6% in the general population (13). Furthermore, the presence of this mutation in heterozygosity is associated with a 2-4 times increased risk of developing CD compared to the rest of the population (14). The p.P268S polymorphism has been related to the presence of ileal lesions, stenosis of the intestinal lumen and the onset of the disease in subjects younger than 40 years of age (15). It could be possible that at least part of the GI clinical picture observed in our patients could have been driven by a CD-like disorder.

Other conditions linked to the *NOD2*/*CARD15* mutations are Blau syndrome and early-onset sarcoidosis (EOS), which respectively represent the familial form with autosomal dominant transmission and the sporadic form of a rare granulomatous autoinflammatory disease with early onset (before 4 years of age) characterized by the triad of symmetrical arthritis, dermatitis, and recurrent uveitis. The p.P268S variant has been found in some patients diagnosed with Blau syndrome/EOS, along with other mutations in the *NOD2*/*CARD15* gene (12, 16-18). Of note, Zhong *et al*. suggested that the p.P268S variant, which causes a *NOD2* loss-of-function, is less likely to be pathogenic among patients with Blau syndrome (19). More recently, Mao et al. found that Blau *NOD2* mutations precipitate a loss of canonical *NOD2* signaling *via RIPK2* and that this loss has two consequences: firstly, it results in defective *NOD2* ligand-mediated NF-κB activation and secondly, it disrupts *NOD2*-mediated cross-regulation, whereby *NOD2* downregulates concomitant innate toll-like receptor-responses (20).

Considerations on pathogenesis

The pathogenesis of DADA2 and its clinical heterogeneity can be explained by the involvement of multiple immune system actors. In fact, DADA2 is an atypical AID in which the causative gene is not involved in the classical pathway of inflammation but rather affects purine metabolism and cell signaling. Monocyte-macrophages have a central role in the pathogenesis of some clinical phenotypes of the disease, but other recently identified mechanisms contribute to the pleiotropic clinical features of DADA2 (21). A central role has recently been attributed to the dysregulation of the interferon (IFN) axis (both type I and II). Elevated levels of IFNγ have been found in the plasma of DADA2 patients, which could lead to proinflammatory macrophage differentiation (M1) and the release of tumor necrosis factor α (TNFα) (22). Additionally, an increase in immature $CD56^{+}$ natural killer (NK) cells, known as regulatory NK cells, characterized by low cytotoxicity but high production of cytokines including TNFα, was found in DADA2 patients. This cellular subset could play a role in some unique clinical features of DADA2, such as recurrent viral infections and macrophage activation syndrome (21).

Furthermore, an alteration in the myeloid dendritic cell subset with a significant increase in $CD16^{+}CD1c^{lo/-}$ cells was found in DADA2 patients. This subtype has a potent stimulatory effect on T cells and the production of proinflammatory cytokines and thus appears to play a role in maintaining the inflammatory state (23). A pathogenic role of neutrophils has been described through the generation of neutrophil extracellular traps (NETs) that may induce TNFα release by macrophages (24).

Regarding the adaptive immune system's involvement in the pathogenesis of the disease, DADA2 determines the reduction of helper and cytotoxic T lymphocytes. Furthermore, analysis of T cell transcriptomes in DADA2 shows hyperactivation of the IFN pathway (21). The most relevant effect of DADA2 is the alteration of B cell differentiation, which is compromised at various levels, with a reduction in memory cells and

plasma cells and an increase in immature B lymphocytes. The ability of B cells to undergo immunoglobulin class switches is impaired, and the response to various stimuli by naïve B cells is reduced. From a phenotypic point of view, all of this translates into hypogammaglobulinemia and an increased risk of infection (21, 22).

Considerations on treatment

To date, DADA2 treatment is based on the use of systemic steroids and conventional immunosuppressants. Indeed, due to the extreme rarity of this clinical condition, there is a lack of approved guidelines and randomized clinical trials (25). Our patient's clinical history highlights that high steroid doses are crucial for the control of disease flares, and a GC dose below <10 mg/day could not be achieved due to disease exacerbations. This led to the Cushingoid features of our patients and may represent a significant long-term burden for damage accrual.

Recently, several authors have proposed the use of biologic disease modifying antirheumatic drugs in the treatment of this disease. In particular, those with the most robust evidence in terms of clinical efficacy are anti-TNFα agents. These should be used as first-line therapy, having been shown to be effective in most clinical manifestations and in the prevention of stroke. Among the anti-TNFα agents, the one with the most robust evidence is ETN which was used in the treatment of 43 DADA2 patients, achieving complete clinical remission in 31 of them. Other anti-TNFα drugs successfully used for this disease include adalimumab, with complete remission reached in 12 of 16 treated patients, and infliximab, with remission induced in 7 of 13 patients. Long-term outcomes with anti-TNFα drugs are yet to be widely reported (1, 5, 26). Among the anti-IL 6 drugs, tocilizumab was used in only 4 patients, leading to a poor clinical response in only one of them (5, 27). Anti-IL 1 therapy (CAN and ANA) failed to control inflammation in DADA2 patients (25, 28).

From a literature review, only 3 patients with DADA2 have been treated with RTX (5, 27, 29). In these patients, the CD20 depletive therapy led to therapeutic failure or a non-satisfactory clinical response. In particular, one of these patients experienced an episode of cerebral ischemia during treatment with RTX (29). The only manifestation that appears to improve in DADA2 patients treated with RTX is autoimmune cytopenia, although data from randomized clinical trials are lacking (26).

As DADA2 does not act unequivocally on a single inflammatory pathway, a drug that acts pleiotropically is desirable (30, 31). The partial response shown in our patient to anti-TNF and anti-IL 1 drugs is in line with the evidence from the literature. We cannot provide a definite conclusion on RTX given the relatively short follow-up post-administration.

Most likely, even though anti-TNF drugs represent the therapeutic mainstay of DADA2, they are not effective in treating some clinical aspects of the disease, such as hematological manifestations. Thus, new therapeutic options, including anti-IFNγ antibodies, NET inhibitors and Janus kinase inhibitors, may expand the therapeutic armamentarium (21). Certainly, a better understanding of the immunological mechanisms underlying DADA2 is needed to identify the appropriate therapeutic strategy until gene transfer therapy proves consistent clinical efficacy (32).

Contributions

CP, conceptualization; AC, FT, data acquisition, writing-original draft preparation; AC, FT, GC, EB investigation and resources; AC, FT, CP. data curation; CP, GC, RG, EB, writing-review and editing; RG, supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no potential conflict of interest.

Patient consent for publication

The patient signed informed consent regarding publishing personal data and photographs.

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Availability of data and materials
Data and materials are available from the corresponding author upon request.

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