Infliximab as successful treatment option in a case of adenosine deaminase 2 deficiency

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SUMMARY

Deficiency of adenosine deaminase 2 (DADA2) is a recessively inherited autoinflammatory disease characterized by systemic inflammation and immunodeficiency. Infliximab proved to be favorable in the treatment of this condition. This case report is concerned with a DADA2 deficient patient treated with infliximab.

This is a rare case of DADA2 in a 32-year-old female patient. The patient was admitted with a clinical presentation of erythema, ulcers, and pruritus on both legs and ankles, accompanied by red ulcerative oral lesions, fatigue, malaise, and dizziness. The patient's genetic analysis was positive for DADA2. Treatment based on TNF-α inhibition was highly effective for this patient. We used laboratory testing and punch biopsy as differential diagnostic tools, where antinuclear antibody positivity, high prolactin levels, and high serum C-reactive protein were observed. The punch biopsy revealed both orthohyperkeratosis and parahyperkeratosis of the dermis, diffuse core fragments, plasma in the stratum corneum, and hypergranulous acanthosis.

DADA2 treatment is centered on tumor necrosis factor α suppression. Although high-dose systemic glucocorticoids can reduce inflammation in the initial stages of the disease, most patients have a resistant or relapsing response to tapering attempts. The prevalence of undiagnosed cases of autoinflammatory diseases is anticipated to diminish with the growing awareness of them.

Key words: *DADA2, infliximab, erythema, ulcers.*

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INTRODUCTION

The deficiency of adenosine deaminase 2 (DADA2), a condition inherited with a monogenic autoinflammatory pattern, is a systemic disease in children and, less frequently, in adults. Although DADA2 can present with broad-ranging symptoms such as strokes, medium-vessel vasculitis, hematologic disease, and immunodeficiency, its three main manifestations are vasculitis, immunologic manifestations, and hematologic features. In 2005, Zavialov et al. (1) performed the first purification of adenosine deaminase 2 (ADA2). The *ADA2* gene is located on chromosome 22q11.1. The first definition of DADA2 was made by two distinct groups in 2014 (2, 3). Here, we present the case of a patient who initially had erythema on her foot, which developed into ulcerative lesions over time and who was then diagnosed with DADA2.

The adenosine deaminase enzyme has 2 main isoforms in humans, which are ADA1 and ADA2. The major functional adenosine deaminase is ADA1, which is a 40-kDa monomer present in most human cells. The role of ADA1 is to reduce adenosine in intracellular space. Severe combined immunodeficiency disorder, whose molecular foundation was first and accidentally discovered by Gatti et al. in 1972, manifests when this enzyme is absent or depleted (4). Under physiological conditions, the ADA1 enzyme serves the primary role of preventing adenosine cytotoxicity. However, under stress, the ADA2 enzyme takes on a more important role in the prevention of adenosine cytotoxicity. The 57-kDa homodimer ADA2 enzyme is secreted into the extracel-

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lular space, and as previously mentioned, its functions are minimal under normal conditions. Under conditions of stress, altered temperature or pH, the ADA2 enzyme's supporting role can change, potentially increasing its function and significance (1).

CASE REPORT

A 34-year-old female patient with erythema, ulceration, and itching on her foot, in addition to bilateral pain on the tibia, was referred to our rheumatology polyclinic (Figure 1). Dermal lesions were compatible with polyarteritis nodosa (PAN), which we included in the differential diagnosis. Additionally, she experienced alopecia and red-ulcerative oral lesions. The patient also complained of constant fatigue, malaise, and dizziness, as well as lack of balance. She also had a pituitary adenoma as well as restless legs syndrome. Her laboratory evaluation revealed an antinuclear antibody positive result, elevated prolactin, and increased C-reactive protein levels (11.1 mg/L). The hematological evaluation of the patient was insignificant, whereas the remaining physical examination showed normal results.

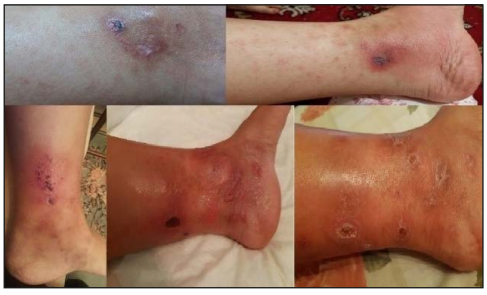

Figure 1 - Erythema and ulcers on the medial malleolus and distal tibia.

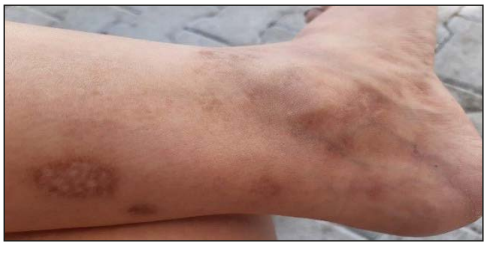

Figure 2 - The same lesions after treatment.

The punch biopsy, performed on the patient's medial left ankle, demonstrated orthohyperkeratosis and parahyperkeratosis of the dermis, widespread core fragments and plasma in the stratum corneum, and hypergranulous acanthosis. It additionally revealed vascular proliferation throughout the entire dermis, fibrinoid material in the vascular cells and walls, swollen endothelial appearance, thick vessel walls, core fragments, and neutrophils in the perivascular region. There was no periodic acid-Schiff positivity. The vascular processes, together with the clinical evaluation of the patient, suggested the presence of underlying vasculitis.

The patient was diagnosed with DADA2 after a genetic screening for the *ADA2* gene revealed the homozygous genetic alteration c281A>G(p.His94Arg). Following the diagnosis, the patient began treatment with 150 mg of azathioprine. Initial prednisone treatment was 60 mg daily, then progressively tapered to 5 mg daily. Infliximab was initially administered at a 300 mg (5 mg/kg), at 0-2nd and 6th week stages. The interval between the administrations was then increased to every 8 weeks. The treatment with infliximab is ongoing.

Infliximab is a murine-human monoclonal antibody that intercepts and neutralizes tumor necrosis factor α (TNF-α), a key inflammatory cytokine. After the treatment, her symptoms reduced, and she had no complaints (Figure 2).

DISCUSSION AND CONCLUSIONS

Due to the disease's late appearance (the patient's symptoms started when she was 32 years old), our case report is an uncommon instance of DADA2, as the condition is often only encountered in childhood (2). Compared to DADA2 diagnosed in childhood, DADA2 diagnosed in adults more commonly has a vascular phenotype and less frequently exhibits bone marrow failure. Adults with DADA2 vasculopathy have far fewer strokes but more severe dermal involvement. Both adults and children can experience the full range of DADA2

clinical manifestations, with adults being overrepresented in vasculopathy phenotypes (5).

The literature reports that adulthood-reported cases are more likely to present with ulcerative lesions, which are suggestive of vasculitis, especially PAN (6). Although the skin manifestations of PAN and DADA2 are similar, DADA2 shows an earlier age presentation and has a more severe progression (7). Regarding PAN and DADA2 treatment responses, non-anti-TNFα agents seem to be ineffective in patients with DADA2, whereas tocilizumab and rituximab have displayed controversial efficacy in PAN (7). This was also applicable to our case.

Regarding treatment response differences between child and adult-onset DADA2 patients, there are more resistant cases in the adult-onset disease group (8). Differently, our case showed an excellent response to treatment.

The patient experienced alopecia and some neurologic difficulties, including loss of balance, along with erythematous and ulcerative lesions and itching on both legs. Many cutaneous abnormalities, such as livedo reticularis, livedo racemosa, ulcers, maculopapular rashes, erythema nodosum, Raynaud's phenomenon, and digital gangrene, are indicative of DADA2 (2). Our patient was positive for the benign ADA2 variant homozygous c281A>G(p.His94Arg) during genetic testing; this variant is not one of the prevalent Turkish variants like Gly47Arg, which is also prominent among the Georgian-Jewish population (9).

TNF-α inhibition is the mainstay of DADA2 treatment; nevertheless, high-dose systemic glucocorticoids can reduce inflammation during the acute stage of the disease, but the majority of patients exhibit a refractory or relapsing response to tapering attempts (10). Anti-TNF drugs lessen inflammation, ischemic stroke risk, immune suppression signs, hepatosplenomegaly, and neutropenia symptoms. Additionally, vasculitis symptoms and autoinflammatory disorders are prevented and managed. The poor red blood cell and platelet counts are also improved by anti-TNF medications, which do not seem to be very helpful at reversing severe bone marrow abnormalities in DADA2 (5). While TNF-α inhibitors appear to have a very low impact on ADA2 enzyme activity levels, they are highly effective in patients with DADA2 (11). Hematopoietic stem cell transplantation can be used to treat patients who respond poorly to TNF-α inhibition. A study of 14 patients undergoing HSTC for DADA2 reported successful outcomes (12).

A wide range of clinical symptoms are associated with the *ADA2* gene, which has recently been identified as a possible cause of autoinflammatory diseases. To determine the precise function of ADA2 in the etiology of autoinflammatory diseases, more functional and clinical research is required. We can save many of these conditions from remaining undiagnosed by raising awareness of rare AIDs, especially among internists, rheumatologists, pediatricians, and neurologists.

Contributions

All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate

No ethical committee approval was required.

Patient consent for publication

Informed consent was obtained from the patient.

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Availability of data and materials

Data available from the corresponding author upon request.

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