Case Report

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Deficiency of adenosine deaminase 2 (DADA2) presented with bilateral renal subcapsular hematoma: a case report and literature review

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Introduction and importance: Adenosine deaminase 2 (DADA2) deficiency is a monogenic autoinflammatory disease caused by biallelic mutations in the ADA2 gene. Small- and medium-sized vessels may be involved and can cause various clinical symptoms, including features resembling polyarteritis nodosa (PAN). In this article, the authors discuss a unique case of DADA2 disease in which a patient presented with a bilateral renal subcapsular hematoma.

Case presentation: An 18-year-old female patient with a history of recurrent optic neuritis presented with a sudden onset of right flank pain as well as nausea, vomiting, weight loss, fever, and elevated arterial blood pressure. Comprehensive abdominal imaging revealed the presence of a bilateral renal subcapsular hematoma. A laboratory test revealed a positive ANA, negative C-ANCA and P-ANCA, and high ESR and CRP. This finding indicated the presence of systemic inflammation. The authors considered DADA2 based on the patient's clinical features and her family's history of autoimmune diseases. A genetic study of the patient revealed the presence of a homozygous ADA2 mutation at chromosomal position 22:17182609, which confirmed the presence of adenosine deaminase 2 deficiency.

Clinical discussion: The authors present a rare case of DADA2 disease successfully treated with immunosuppressive therapy. As the authors suspected of having known autoimmune diseases, the patient's clinical and laboratory results improved with corticosteroids and etanercept treatment, leading to notable remission. Under continuous CT imaging, the subcapsular hematoma shrank significantly over two months, decreasing from 8.3 to 5 cm in size for the right-sided hematoma and completely disappearing for the left-sided hematoma.

Conclusion: The clinical features of DADA2 may be fatal, but DADA2 may also be curable; therefore, early diagnosis and treatment are essential.

Keywords: ADA2 gene, bilateral renal subcapsular hematoma, case report, deficiency of adenosine deaminase, polyarteritis nodosa

Introduction

Adenosine deaminase type 2 (DADA2) deficiency is an inherited disease with an autosomal recessive pattern resulting from an ADA2 gene mutation or a CECR1 gene mutation (cat eye syndrome chromosome region, candidate 1). In 2014, DADA2 was first described by Elkan and colleagues and Zhou and colleagues in two separate articles[1]. Since DADA2 was first described, only ~200 cases have been reported[1]. The clinical manifestations of DADA2 vary among individuals of different ages[2]. Vascular involvement is commonly reported and is known as polyarteritis nodosa mimics (PAN mimics) disease. In this case, the most affected organs are the skin (e.g. erythema nodosum, Raynaud's phenomena, and ulcers), nervous system (e.g. stroke, seizure, and headache), kidney (e.g. renal infarcts), gastrointestinal tract (e.g. mesenteric ischemia), and eyes (e.g. retinal artery occlusion and optic neuritis)[3].

To the best of our knowledge, we report the first case of DADA2 with vascular involvement that presented with a bilateral renal subcapsular hematoma and closely mimicked polyarteritis nodosa. The patient's clinical and laboratory results improved after treatment with corticosteroids and etanercept.

Although DADA2 is an uncommon disease and is rarely discussed in the literature, biologic medications—tumor necrosis factor α inhibitors (TNF-α inhibitors), such as etanercept, infliximab, and adalimumab—have been reported to be the mainstays

HIGHLIGHTS

- Deficiency of adenosine deaminase type 2 (DADA2) is an inherited disease with an autosomal recessive pattern.
- The clinical manifestation of DADA2 varies in different individuals and ages.
- The clinical features of DADA2 may be potentially fatal but may also be curable.
- We report the first case of DADA2, which presented with bilateral renal subcapsular hematoma.

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of treatment for these patients[1]. TNF-α-based immunosuppressive therapy should be started as soon as possible to avoid serious consequences, such as neurological disorders (e.g. hemorrhagic and ischemic stroke), hypogammaglobulinemia, bone marrow aplasia, pure red cell aplasia (PRCA), neutropenia, and thrombocytopenia[1,2]. The presence of endothelial cell injury and activated myeloid cells is closely linked to DADA2 vasculitis. Consequently, TNF-α inhibitors are a good treatment option because they reduce systemic inflammation and endothelial damage[4].

This article describes the clinical characteristics, investigation, course of treatment, and prognosis of a rare case of DADA2, which could be potentially life-threatening if not treated at the proper time.

We complied with the recommendations in the Case Report Guidelines (CARE guidelines)[5].

Case presentation

An 18-year-old female patient presented to the emergency department complaining of a 3-day history of right flank pain. The pain was constant, gradual, and radiated toward the back. Her pain increased with lying in the supine position and during inspiration. Attempts to assume an upright posture were correspondingly impeded due to considerable pain. Nothing relieved the severe pain (rated 8/10 by the patient). She also had a history of nausea, followed by vomiting after each solid and liquid intake. Additional systemic manifestations included fever, chills, sweating, and palpitations. Furthermore, the patient experienced an unintentional weight loss of 5 kg in 2 weeks. The patient had a medical history of recurrent episodes of optic neuritis, with the most recent admission occurring 3 years prior.

Previous non-contrast MR images of the brain and spinal cord revealed hyperintense T2/FLAIR foci, with one localized in the centrum semioval and periventricular subcortical regions and the other demonstrating multiple bilateral regions in the periventricular and subcortical areas. The observed features on MRI suggest a propensity toward vasculitis, with a decreased likelihood of demyelinating disease. Consequently, the patient received steroids. Her doctors recommended a subsequent follow-up; however, the patient did not attend the scheduled follow-up visits. She had a medical history indicative of Raynaud's phenomenon and Livedo Reticularis, exacerbated by exposure to cold weather. In addition, the clinical profile encompasses joint pain, morning stiffness lasting more than 1 h, chronic fatigue, and myalgia. In addition, the patient's history revealed an abrupt loss of muscular tone in both the upper and lower limbs, resulting in falls and the dropping of objects. There was no history of oral or genital ulcers. The patient reported a persistently poor mood for more than 3 years. Her family history is noteworthy. Her maternal cousin had DADA2 at the age of 4. The father had juvenile idiopathic arthritis (JIA), and her mother developed rheumatoid arthritis at the age of 35. In addition, the patient's father and mother are consanguineous and are first cousins. There was no known history of allergies to any specific food or drug. Both the drug and surgical histories were unremarkable.

On examination, the patient was unwell, distressed, and in pain with tachycardia (120 bpm), tachypnea (22/min), a blood pressure of 160/100 mmHg, and an oxygen saturation of 96%. Upon physical examination, the patient was unwell, distressed, and in pain, exhibiting mild pallor without rash, ecchymosis,

Table 1

Laboratory results.

Laboratory test	Value	Normal values
Complete blood count		
WBC count	10.1×10^9/l	($4.5–11.0 \times 10^9$/l)
Hemoglobin	13.2 g/dl	12.1–15.1 g/dl
Hematocrit	44.4%	36–48%
Platelets	694 K/Ul	140–400 K/ul
Neutrophils	77.8%	40–60%
Lymphocytes	18.2%	20% to 40%
Monocytes	0.4%	2–8%
Eosinophils	0.3%	1–4%
Basophils	0.1%	1–5%
RBCs	5.14 million cells/mcl	4.2–5.4 million cells/mcl
Serum chemistry		
Na	139 mEq/ l	135–145 mEq/ l
K	3.9 mEq/l	3.5–5.5 mEq/l
BUN	8 mg/dl	6–24 mg/dl
Creatinine	0.71 mg/dl	0.6–1.1 mg/dl
Total Bilirubin	0.3 mg/dl	0.1–1.2 mg/dl
Direct Bilirubin	0.1 mg/dl	< 0.3 mg/dl
ALP	91 IU/l	44–147 IU/l
AST	39 IU/l	< 40 IU/l
ALT	21 IU/l	19 to 25 IU/l
Total Protein	7.4 g/dl	6 to 8 g/dl
Albumin	3.5 g/dl	3.4–5.4 g/dl
Coagulation profile		
PT	12.6 s	10–13 s
PTT	40.1 s	25–35 s
INR	0.96	1.0
Random blood sugar	104 mg/dl	< 140 mg/dl
Immunology		
P-ANCA	Negative	Negative
C-ANCA	Negative	Negative
ANA	Positive (1:80)	Negative (1:40 or less)
C3	173 mg/dl	75 to 175 mg/dl
C4	33 mg/dl	15 to 45 mg/dl
PCNA	Negative	Negative
Anti-CCP	Negative (2.8 u/ml)	Negative <20 u/ml
Rheumatoid factor	positive	Negative
dsDNA antibody	Negative	Negative
SmD1 antibody	Negative	Negative
SS-A	Negative	Negative
SS-B	Negative	Negative
Scl70	Negative	Negative
Jo-1	Negative	Negative
AMA M2	Negative	Negative
Nucleosome	Negative	Negative
Histone	Negative	Negative
CENP-B	Negative	Negative
PO	Negative	Negative
Urinalysis		
Protein	+ 1	Negative
Blood	+ 3	+ 2 or less
Culture	NO growth	NO growth
RBCs	Many	4 (RBC/HPF) or less
WBCs	(2–4)	(2–4)
Appearance	Turpid	Clear
Color	Straw	Yellow/straw
pH	Acidic (< 6)	4.6–8
Leukocytes	Negative	Negative

ALP, alkaline phosphatase; ALT, alanine transaminase; AMA, anti-mitochondrial antibodies; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; C3, complement component 3; C4, complement component 4; CCP, cyclic citrullinated peptides; CENP, centromere proteins; dsDNA, double-stranded deoxyribonucleic acid; INR, international normalized ratio; K, potassium; Na, sodium; PCNA, proliferating cell nuclear antigen; pH, potential hydrogen; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cells; Scl70, scleroderma antibody; SmD1, Smith; SS, Sjögren's-syndrome-related antigen; WBC, white blood cells.

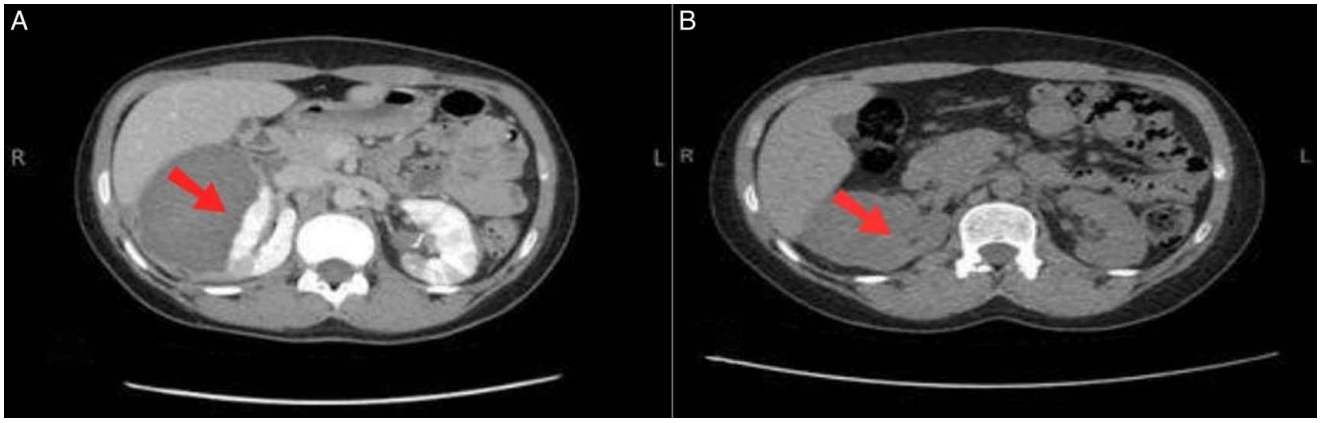

Figure 1. Abdominal CT scan shows a subcapsular hematoma in the right kidney in (A) and a substantial regression of the pathological condition after two months in (B).

purpura, or petechiae. Abdominal examination revealed tenderness in the right costovertebral angle. Pulmonary auscultation revealed clear lung fields, and the cardiac rhythm was regular.

Full investigations were performed; Table 1. Abdominal and urinary tract ultrasound examinations revealed a large liver measuring 17.5 cm with a normal echo texture. Ultrasound of the right kidney revealed an 11.4×5.7 cm subcapsular hematoma, exerting pressure on the renal parenchyma. In addition, there was an increase in the size of the vascularized hyperechoic component (clot). Ultrasound of the left kidney revealed a 2.6×0.6 cm subcapsular hematoma. Abdominal CT revealed a bilateral subcapsular hematoma measuring ~8.3×5.6 cm on the right side. (Fig. 1A). Furthermore, abdominal CT angiography revealed renal microinfarctions associated with the aneurysms. Non-contrast brain MRI revealed no acute intracranial abnormalities, such as infarction or hemorrhage (Fig. 2).

Owing to a strong family history of rheumatologic disease and a positive family history of DADA2, a genetic study was performed on the patient, which revealed the presence of a homozygous ADA2 mutation at chromosomal position 22:17182609. ADA2 is involved in cell division and proliferation and has a role in monocyte differentiation. All of the coding regions of ADA2 are susceptible to mutations linked to DADA2[2]. After DADA2 was confirmed by the presence of the ADA2 mutation, etanercept (50 mg subcutaneously once a week) was administered.

The patient was also diagnosed with stage II hypertension during admission, with a blood pressure reading of 160/100 mmHg. Subsequently, an angiotensin receptor blocker was prescribed. Two weeks after the intervention, there was an improvement in blood pressure (132/87 mmHg). A follow-up contrast abdominal CT scan demonstrated a significant reduction in the size of the right-sided hematoma (from 8.3 to 5 cm) and the complete disappearance of the left-sided hematoma. (Fig. 1B) Consequently, the urology consultation team recommended observation and follow-up of the patient, choosing not to intervene with the existing hematoma.

Discussion

We describe a patient who presented with renal subcapsular hematoma, weight loss of 5 kg, Livedo reticularis, Raynaud's phenomenon, arthritis, fatigue, myalgia, and high blood pressure. Although these characteristics are similar to those of polyarteritis nodosa (PAN), DADA2 was identified through genetic testing and family history.

A retrospective study identified 33 patients with DADA2 in India[6]. All of them presented with a manifestation of systemic vasculitis that mimics PAN, except one patient who presented with PRCA and two patients who were diagnosed by screening. Seventy-nine percent of patients showed neurological symptoms (over half of the patients had a stroke), and 73% showed skin involvement[6].

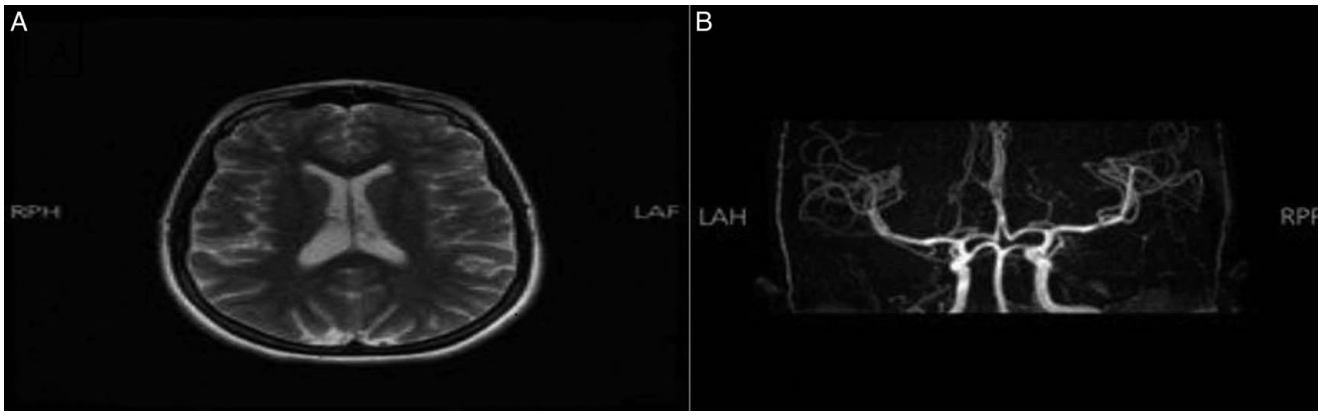

Figure 2. A non- contrast brain MRI reveals an absence of acute intracranial abnormalities in (A). There is no evidence of high-grade stenosis or aneurysmal dilatation in both anterior and posterior circulation in (B).

Furthermore, 55% of patients demonstrated constitutional symptoms. Among patients, 49% had renal system involvement, 46% had intestinal manifestations, 30% had joint involvement, and 17% had testicular pain. In addition to the wide range of manifestations, myocarditis, pancreatic infarction, end-organ ischemia, aneurysm of the vessel, and small bowel obstruction can occur[6].

Moreover, a systematic review conducted in 2021 included 378 patients with DADA2[7]. Skin manifestations were the most common feature in this patient, with a percentage of 67.9% (Livedo reticularis in 47.6% of patients). Other features were reported, including hematological disorders (56.3%), neurological manifestations (51%), immunological disorders (42.3%), joint involvement (35.4%), enlargement of the spleen and liver (30.6% and 23.5%, respectively), gastrointestinal symptoms (29.8%), and recurrent infections (18.5%)[7]. Myalgia, renal abnormalities, mouth ulcers, failure to thrive (FTT), ocular manifestations, and testicular symptoms were reported (17.9%, 17.7%, 11.9%, 9.5%, 7.6%, 3.4%, and 2.6%, respectively)[7].

Vascular involvement in DADA2 can affect various organs, such as the liver, spleen, kidneys, heart, and bowel[8]. An observational study of 60 patients with DADA2 showed bowel necrosis in 5 patients and abdominal vessel involvement in 8 patients (arteritis, aneurysms, and stenosis)[8]. Spleen infarcts were present in 4 patients, and renal infarcts were present in 13 patients. Only 4 patients had proteinuria, and 1 patient had hematuria. Most patients had been diagnosed with PAN before having a genetic study[8]. In a cohort study involving thirty DADA2 patients, systemic inflammation, vasculitis, and hypogammaglobulinemia were the most common presentations[9].

Conclusion

DADA2 deficiency has a wide spectrum of clinical manifestations. In this particular patient, DADA2 presented with bilateral renal subcapsular hematoma, which could be life-threatening if not treated at the proper time. Moreover, a better understanding of DADA2 may aid in its diagnosis, management, and improvement. Subsequent investigations into the role of ADA2 and the pathophysiology of DADA2 may enhance our understanding of this disease and facilitate prompt diagnosis.

Ethical approval

This study is exempt from ethical approval at our hospital.

Consent

Written informed consent was obtained from the patient for reporting this case and its associated images. The consent is available for review on request.

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Author contribution

Data collection: M.A.-G., J.Y., I.R., A.A., A.H.K., A.A.M.W. Writing the manuscript: M.A.-G., J.Y., I.R., A.A., A.H.K., A.A.M.W. Study concept or design: M.A.-G., J.Y., I.R., A.A., A.H.K., A.A.M.W. Review and editing the manuscript: M.A.-G., J.Y., I.R., A.A. , A.H.K., A.A.M.W.

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The authors declare no conflicts of interest.

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Data availability statement

Data sharing is available upon reasonable request.

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