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Early Onset Stroke, Polyarteritis Nodosa, and Livedo Racemosa

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CASE SUMMARY

History

A 25-year-old Caucasian woman was seen in the Dermatology Consult Clinic at the National Institutes of Health (NIH) Clinical Center for livedo racemosa.* She was born full term without complications to nonconsanguineous Caucasian parents. At 5 months of age the patient sustained right lacunar thalamic and parietal cerebrovascular accidents (CVA). At that time, she had an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and was noted to have reticulate erythematous patches on her extremities. Pertinent laboratory findings included a platelet count of 900 K/uL (162-380 K/uL) and negative antinuclear and anticardiolipin antibodies.

In the first year of life the patient also developed intermittent episodes of red, nontender papules, initially on her extremities and face, and later on the trunk, that were clinically diagnosed as cutaneous polyarteritis nodosa (PAN). Throughout childhood she experienced intermittent fevers, as often as 3-4 times a week, oral ulcerations several times each year, and chronic livedo changes on the skin. She also developed recurrent bacterial ear and sinus infections requiring frequent antibiotics, myringotomy and tympanostomy tubes. Immunologic evaluation revealed an immunoglobulin (Ig)G subclass deficiency for which she received intravenous immunoglobulin (IVIG). At age 13 she had syncopal episodes and was diagnosed with cardiomyopathy and long QT syndrome. At age 16, she began chronic treatment with prednisone after she developed left central retinal artery occlusion. The patient had multiple transient ischemic attacks during childhood and was prescribed multiple anticoagulants. She also developed progressive hepatosplenomegaly. A bone marrow biopsy

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*Patient was previously reported as part of the initial description of DADA2 syndrome by Zhou, Yang, Ombrello et al. (Early-onset stroke and vasculopathy associated with mutations in ADA2. *N Engl J Med* 2014;370:911-20)

at age 22 for persistent leukopenia revealed mildly hypocellular marrow. One week later she acutely developed garbled speech, lost the ability to ambulate, and became obtunded. She was on a stable dose of warfarin at the time and had no antecedent injury. Imaging revealed an extensive hemorrhage in the left hemisphere (Figure 1). The extensive infarct resulted in a dense right hemiparesis, right visual field deficit, and expressive aphasia.

Physical examination

The patient was a pleasant, alert, nonverbal young woman in a wheelchair noted to have right-sided hemiparesis. On her upper and lower extremities she had a patchy, erythematous, livedo racemosa-like pattern with thick branching. Approximately 20 small, erythematous nodules were also noted on the upper and lower extremities (Figure 2, A). There were no nail abnormalities.

Histopathology

A punch biopsy from a nodule on the left leg revealed destruction of the vascular wall of a medium-sized artery in the reticular dermis with fibrinous deposits, neutrophilic infiltrate, and surrounding dense lymphohistiocytic infiltrate consistent with vasculitis (Figure 3). A second biopsy from an area of livedo on the right forearm revealed dilated and thickened superficial vessels only.

Significant diagnostic studies

Ultrasound of the abdomen revealed moderate splenomegaly and cholelithiasis. Laboratory evaluation revealed elevated CRP, low immunoglobulins, pancytopenia, and elevated liver enzymes (Table I). Genetic testing identified compound heterozygous mutations (H112Q/G47A) in the *CECR1* (cat eye syndrome chromosome region, candidate 1) gene, encoding adenosine deaminase 2 (ADA2). Plasma ADA2 enzymatic activity was decreased (10.9 ng/ml) compared to controls (116.3 ng/ml) and her unaffected heterozygote parents (91.1 and 55.6 ng/mL).

Diagnosis

Deficiency of adenosine deaminase 2 (DADA2) resulting from compound heterozygous mutations in the *CECR1* gene.

Follow-up

Soon after diagnosis the patient suffered several episodes of massive hematemesis associated with Grade III esophageal varices from portal hypertension, requiring banding four times. Hepatic biopsy demonstrated hepatoportal sclerosis. Prednisone was increased from 10mg to 15 mg a day, etanercept was initiated at 50 mg subcutaneously once a week, and a splenorenal shunt was placed. Since that time, the patient has had resolution of cutaneous PAN symptoms, improvement of portal hypertension with no bleeding varices, and no additional CVAs. Livedo racemosa was unchanged (Figure 2, B and C).

DISCUSSION

In 2014 two groups simultaneously reported a new syndrome due to deficiency in ADA2 in the *New England Journal of Medicine*. Zhou *et al.*¹ described a cohort of 9 individuals who developed early-onset stroke, intermittent fevers, and systemic vasculopathy. Navon Elkan *et al.*² described 24 individuals from 10 families with a heritable form of cutaneous or systemic PAN. Genetic studies performed on affected individuals and unaffected family members identified recessively inherited mutations in the *CECR1* gene. Since the first description of DADA2, more than 50 cases have been reported.³⁻¹³

DADA2 is a multisystem syndrome with variable features of autoinflammation, vasculitis, and a mild immunodeficiency (Table II). Patients experience recurrent fevers with elevated inflammatory markers. Multiple cerebrovascular accidents may occur as early as infancy. Patients often develop hepatomegaly and splenomegaly. The development of portal hypertension is not uncommon, resulting in varices and placing patients at risk of hemorrhage. Splenomegaly can result in thrombocytopenia from splenic sequestration.

Livedo racemosa is the most consistent cutaneous finding in affected individuals and is most prominent on the extremities and trunk. Unlike the fine net-like pattern of livedo reticularis, in livedo racemosa the branches are broader and often are interrupted or incomplete. Livedo on the lower extremities may be more prominent upon standing. Erythematous nodules that clinically and histologically resemble cutaneous PAN and Raynaud's phenomenon develop in some patients.

The optimal management for DADA2 is unknown. All patients at the NIH have been started on anti-tumor necrosis factor (anti-TNF α) therapy: etanercept (n=14), adalimumab (2), and golimumab (1). Since initiation of anti-TNF α therapy, none of the 17 patients at the NIH have sustained an additional CVA. However, the natural history of DADA2 is not well-defined and long-term experience with anti-TNF α therapy in this patient population is needed.¹⁴ Cutaneous PAN has resolved with anti-TNF α therapy in the cohort treated at the NIH; however, livedo changes appear to be less responsive to therapy. One additional possible benefit observed with anti-TNF α therapy is improvement of portal hypertension.

CECR1 encodes ADA2, a secreted protein that degrades adenosine and 2'-deoxyadenosine. Mutations in *CECR1* result in decreased plasma levels and enzymatic activity of ADA2. ADA2 has been implicated in the development and differentiation of endothelial cells and leukocytes.¹ The primary source of ADA2 is monocytes and macrophages, and ADA2 is thought to be important for the differentiation of monocytes to macrophages.¹⁵ However, the exact mechanism by which loss of ADA2 function results in vasculopathy remains unclear. Based on genome-wide analysis on peripheral blood of affected individuals in which neutrophil-expressed genes were overexpressed, it has been hypothesized that vasculitis may in part be due to chronic activity of neutrophils, which express receptors for adenosine.¹¹

In conclusion, DADA2 is a newly described autosomal recessive syndrome characterized by recurrent fevers, early-onset CVA, livedo racemosa, PAN, and portal hypertension. Given the known association between livedo racemosa and CVA in the setting of Sneddon syndrome, it is interesting to speculate that some patients with this diagnosis may have a gene defect in

CECR1. As recognition of this disorder grows and additional affected individuals are identified, the clinical manifestations, natural history, and preferred therapy will continue to be better defined.

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ABBREVIATION AND ACRONYM LIST

ADA2	adenosine deaminase 2
Anti-TNFα	anti-tumor necrosis factor
CECR1	cat eye syndrome chromosome region, candidate 1
CRP	C-reactive protein
CVA	cerebrovascular accidents
DADA2	deficiency of adenosine deaminase 2
ESR	erythrocyte sedimentation rate
Ig	immunoglobulin
IVIG	intravenous immunoglobulin
NIH	National Institutes of Health
PAN	polyarteritis nodosa

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KEY TEACHING POINTS

- Deficiency in adenosine deaminase 2 is an autosomal recessive syndrome characterized by recurrent fever, early-onset stroke, livedo racemosa, PAN, and hepatosplenomegaly.
- Preliminary experience suggests anti-TNF α therapy may prevent further CVAs, improve cutaneous PAN, and improve hepatobiliary function, but further study is needed.
- Early identification and confirmation of mutations in the *CECR1* gene can potentially decrease morbidity from this disease by guiding selection of appropriate therapy early in the course of disease.

Fig 1. Neurologic sequelae of DADA2. A large hemorrhagic infarction involving the left cerebral hemisphere is seen on magnetic resonance imaging at the time of stroke symptoms at age 22.

Fig 2. Cutaneous manifestations of DADA2. **A**, On initial visit pink, firm, discrete nodules were present on the right upper extremity, consistent with cutaneous PAN. **B**, Examination at a follow up visit in June 2015 showed irregular, thick branching erythema on the right upper extremity and **(C)** violaceous, thick, branching livedo on the right lower extremity in a dependent position.

Fig 3. Histology of vasculitis in DADA2. **A**, Histopathologic examination demonstrated destruction of a medium sized vessel in the reticular dermis. **B**, Higher magnification revealed fibrinoid necrosis of the vessel with neutrophils and a dense lymphohistiocytic infiltrate surrounding the vessel. (**A** and **B** Hematoxylin-eosin stain; original magnifications: **A**, X4; **B**, X20.)

TABLE I

Laboratory assessment in patient with DADA2.

Laboratory test	Value	Normal range
White blood cell count	2.76 K/uL	3.98-10.04 K/uL
Hemoglobin	10.7 g/dL	11.2-15.7 g/dL
Platelet count	66 K/uL	173-369 K/uL
Serum IgG	577 mg/dL	642-1730 mg/dL
Serum IgA	50 mg/dL	91-499 mg/dL
Serum IgM	28 mg/dL	34-342 mg/dL
ESR	7 mm/hr	0-42 mm/hr
CRP	8.4 mg/L	<3.0 mg/L
Alkaline phosphatase	539 U/L	37-116 U/L
Alanine aminotransferase	123 U/L	6-41 U/L
Aspartate aminotransferase	86 U/L	9-34 U/L

CRP, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *Ig*, immunoglobulin,

TABLE II

Clinical manifestations of DADA2.

ORGAN	MANIFESTATION
Skin	Livedo racemosa, polyarteritis nodosa, Raynaud's phenomenon
Neurologic	Ischemic and hemorrhagic stroke in childhood, peripheral neuropathy
Gastrointestinal	Splenomegaly, hepatomegaly, hepatoportal sclerosis, portal hypertension with secondary varices
Hematologic	Variable cytopenia: lymphopenia > thrombocytopenia
Immunology	Immunoglobulin deficiencies, B cell deficiency
Cardiology	Prolonged QT interval