Dermatologic Features of ADA2 Deficiency in Cutaneous Polyarteritis Nodosa

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Polyarteritis nodosa (PAN) is a systemic vascular disease that is associated with poor prognosis. First described in 1866 by Küssmaul and Maier, it manifests as a systemic, necrotizing vasculitis of medium-sized arteries, affecting the peripheral nervous system, musculature, gastrointestinal system, kidneys, and the skin. A total of 25% to 60% of patients with PAN experience cutaneous symptoms.1

In contrast, cutaneous polyarteritis nodosa (cPAN) is a benign, rare form of PAN that for many years has been reported to be limited to the skin.2 It was first described by Lindberg2 in 1931 as a relapsing-remitting condition. It is not thought to exist in the current collection of antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides. In the current literature, cPAN has been referred to as a clinical syndrome that consists of (1) histopathologic confirmation of a necrotizing, nongranulomatous, medium-sized vessel arteritis; (2) cutaneous lesions, such as subcutaneous nodules, ulcers, and livedo racemosa; (3) absence of ANCAs; and (4) absence of systemic organ involvement with vasculitis.3

Recent discoveries have attributed an autosomal recessive mutation in the CERC1 gene as one of the genetic defects associated with cPAN.4,5 The CERC1 gene encodes for ADA2, a plasma protein that is essential for the development and differentiation of endothelial cells and leukocytes.4,5 Deficiency in ADA2 (DADA2) has a wide spectrum of clinical manifestations that can range from fatal vasculopathies to a more indolent cutaneous-limited disease. The most common clinical characteristics include cPAN, fever, livedo racemosa, lacunar strokes, hepatosplenomegaly with portal hypertension, Sneddon syndrome, and B-cell immunodeficiency (which encompasses cellular deficiency of B cells and hypogammaglobulinemia).4,5

The recent discovery of DADA2 has not only brought new insights into the molecular basis of cPAN but also has profound implications in its diagnosis and treatment. We describe 2 white siblings with an early-onset diagnosis of cPAN who were recently found to carry autosomal recessive novel compound heterozygote mutations in CERC1, leading to low levels of ADA2. Both siblings had persistent skin lesions in the setting of recurrent infections, the female sibling had significant B-cell immunodeficiency (identified several years after the original cPAN diagnosis), and the male sibling had a milder B-cell defect. We describe the dermatologic features of DADA2 in cPAN.

**IMPORTANCE** Mutations in the CERC1 gene associated with deficiency in the ADA2 protein (DADA2) have been implicated in the pathogenesis of cutaneous polyarteritis nodosa (cPAN) and early-onset vasculopathy. DADA2 is not only limited to cPAN and vasculopathy but also includes immunodeficiency that affects several cellular compartments, including B cells; however, some patients appear to have a more indolent, skin-limited disease.

**OBSERVATIONS** In this report, we describe 2 white siblings (female and male) with a history of cPAN with DADA2 as a result of novel compound heterozygous mutations inherited in trans in the CERC1 gene (c.37_39del[p.K13del] and c.984C>A[p.N328K]). The onset of disease was earlier in the female sibling than the male sibling although both were diagnosed as having cPAN in early childhood. The disease is associated with a more significant immunodeficiency and other systemic symptoms in the female than the male sibling.

**CONCLUSIONS AND RELEVANCE** These findings suggest a genetic cause of cPAN in some patients. Therefore, DADA2 should be considered in patients with cPAN, specifically in those whose conditions are diagnosed at an early age, regardless of their ethnicity, presence or absence of systemic symptoms, or a family history of the disease.

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Report of Cases

Case 1
An 18-year-old white woman presented with a history of persistent livedo racemosa of the lower extremities from the age of 2 years. She was the first child born at term after an uneventful pregnancy to nonconsanguineous white parents. Family history was negative for rheumatologic or genetic diseases. A diagnosis of cPAN was rendered at 4 years of age after the results of a thorough workup were negative for infectious disease and other underlying causes. Skin biopsy specimens revealed a medium-sized vessel, necrotizing arteritis. The patient’s symptoms fluctuated for years, and her lesions were treated with dapsone.

At 13 years of age, she presented with asymptomatic livedo racemosa on the lower extremities (Figure 1A and B) and systemic symptoms of fever, headaches, fatigue, nausea, and vomiting. Given the associated systemic signs and symptoms, the diagnosis of cPAN was reconsidered. A thorough diagnostic workup failed to reveal a coexistent underlying disease and was only significant for a B-cell immunodeficiency with decreased IgA and IgM. Skin biopsy specimens from an area of livedo on the leg revealed nongranulomatous, necrotizing arteritis of a medium-sized vessel, confirming the diagnosis of cPAN (Figure 1C). Histopathological analysis of a livedo area revealing nongranulomatous, necrotizing arteritis of a medium-sized vessel (hematoxylin-eosin, original magnification ×200).

Given the patient’s early age of presentation and the chronic and persistent course, whole exome sequencing was performed, which revealed compound heterozygous variations of uncertain significance in the CERC1 gene (c.37_39del [p.K13del] and c.984C>A [p.N328K]) that was confirmed by Sanger sequencing. The pathogenic nature of these genetic variants was confirmed by measuring ADA2 levels in plasma, which established DADA2, compared with healthy controls (total mean [SD] ADA2 levels: female sibling, 0.43 [0.11] U/L; mother, 4.87 [0.15] U/L; father, 5.29 [5.29] U/L; pediatric reference value, 27.00 [2.30] U/L; adult reference value, 12.90 [2.60] U/L; to convert ADA2 levels to nanokatals per liter, multiply by 16.667). The parents had decreased but not absent ADA2 levels consistent with each one having one heterozygous CERC1 mutation. Similar to the total ADA2 levels, the mean (SD) levels of enzymatic ADA2 were close to absent in the female sibling and decreased in the parents (female sibling, 0.23 [0.06] U/L; mother, 5.73 [0.04] U/L; father, 5.00 [0.14] U/L).

The patient never experienced a thrombotic event, and the results of her blood serologic tests, including a coagulation workup and ANCA studies, were within the reference ranges or normal. The genetic data in conjunction with the protein result and clinical phenotype confirmed a diagnosis of DADA2 for this patient. The patient is currently being treated with tumor necrosis factor α (TNF-α) inhibitors with improvement in symptoms but not complete remission. Therefore, alternative treatment strategies are being considered for this patient.

Case 2
This patient is the younger male sibling of case 1. He is an 11-year-old boy with a history of recurrent streptococcal throat infections since the age of 5 years. At 10 years of age, he developed subcutaneous nodules with overlying erythema on the lower extremities and feet (Figure 2A and B). Initially, these lesions were thought to represent erythema nodosum second-
ary to his recurrent infections. Apart from his recurrent throat infections, the patient was asymptomatic.

Given the persistent nature of his skin lesions and his family history of cPAN, a thorough workup was undertaken. The findings of his laboratory workup were unremarkable except for elevated anti-Dnase B titers (from his multiple and recurrent streptococcal infections). A biopsy specimen from a subcutaneous nodule on the right knee revealed nongranulomatous, necrotizing arteritis of a medium-sized vessel (Figure 2C), confirming a diagnosis of cPAN. Genetic and protein studies were pursued simultaneously with the female patient and revealed the same novel compound heterozygous mutation in the CERC1 gene, leading to a diagnosis of DADA2 for this second child.

**Discussion**

These cases represent 2 white siblings with novel mutations in CERC1 with a clinical phenotype of cPAN among other findings, confirming a diagnosis of DADA2. Autosomal recessive homozygous or compound heterozygous mutations in the CERC1 gene on chromosome 22q11 have been recognized as a cause of cPAN. Mutations in CERC1 occur in approximately 10% of persons of Georgian-Jewish ancestry in association with early-onset PAN, often familial.

ADA2 belongs to a family of ADA growth factors and is a secreted molecule that converts adenosine to inosine and 2’-deoxyadenosine to 2’-deoxyinosine. Because neutrophils express receptors to adenosine, ADA2 acts as a regulator for neutrophil activation. Deficient levels of ADA2 lead to marked upregulation of neutrophil-expressed gene transcripts. To date, there is genetic evidence of an endogenous anti-inflammatory feedback loop mediated by adenosine signaling. The net effect of ADA2 is to limit collateral damage during unregulated inflammation. These findings suggest that a possible mechanism for DADA2 is uncontrolled, chronic, and increased activity of neutrophils, leading to endothelial cell dysfunction. Additional studies have identified an extracellular ADA-related growth factor as an important mediator for the maintenance of vascular development and integrity. This finding is of significant importance for organ development and immune system signaling. According to recent discoveries, in the absence of ADA2, endothelial cells appear damaged and express inflammatory markers. This finding leads to the accumulation of proinflammatory cytokines, which consequently induces tissue injury. Although new theories to explain reasonable pathways for the development of DADA2 phenotype are currently arising, more research is needed to elucidate the exact pathophysiologic mechanism behind the disease, although some observations have already been made on the anti-inflammatory activity of adenosine. Nonetheless, the current evidence supports that DADA2 is a complex disease that compromises a variety of autoimmune, autoimmune, and immunodeficiency mechanisms.

The clinical features of DADA2 are characterized by a highly variable age at onset (ranging from 2 months to 59 years), severity, and organ involvement. Phenotypic variability is noted for the same genotype, suggesting that epigenetic variations and environmental influences are possible essential modifying factors for the disease (Table). Family history is negative in most cases. There appears to be a strong correlation with history of recurrent bacterial and viral infections. Initial presentation may include recurrent fevers and livedo racemosa in early childhood. In these cases, the presence of necrotizing vasculitis on biopsy specimens, although helpful for a diagnosis of cPAN, lacks sensitivity because patients can present with small-vessel leukocytoclastic vasculitis or peri-vascular T lymphocytes, without frank vasculitis.

The disease evolves over time, presenting in some cases with severe or fatal systemic vasculitis and multiple strokes that can occur at a very early age (<5 years). Other possible
associated systemic symptoms are listed in the Table. A subset of patients, especially those of middle age, can present with limited cutaneous manifestations, including subcutaneous nodules, purpura, livedo reticularis, livedo racemosa, Raynaud phenomenon, and ulcerations.4 6 9 In the most severe form of the disease, skin manifestations may also include digital necrosis and gangrene.4 6

Laboratory workup in most cases is unremarkable or can reveal a previously unrecognized variable severity immunodeficiency that is currently most evident in the B-cell lineage.4 6 The results of extensive studies for ANCA, antiphospholipid antibodies, hypercoagulability, autoimmune serologic findings, and imaging are frequently negative. Nonetheless, these tests are essential and have significant diagnostic utility to primarily exclude other causes, such as PAN. During febrile episodes, patients can have elevation of acute-phase reactants, which can be directly related with active vasculitis or a thrombotic event.

Therapeutic options for DADA2 are primarily based on case series and reports. Investigating the mechanism of DADA2 has been crucial for the development of new therapies for this otherwise potentially devastating disease. Because ADA2 is a secreted molecule, it is possible that recombinant ADA2 protein and administration of fresh-frozen plasma (which contains ADA2) may be beneficial, although this has not been proven. The most effective therapy to date, in a limited number of patients, has been hematopoietic cell transplantation.11 Because of its anti-inflammatory effects, anti–TNF-α agents are effective for this disorder,4 13 although this treatment is likely to be more effective when levels of TNF-α are elevated. Other therapeutic options include anti-interleukin 6-blocking agents (eg, tocilizumab), systemic corticosteroids, and other forms of immunosuppressive agents, all of which have led to variable results. Treatment should be based on a case by case basis primarily centered on the presentation and severity of the disease. Despite attempts to define specific classification criteria for adults and children, the diagnosis of cPAN remains challenging.3 Before these recent discoveries, cPAN occurring with systemic symptoms, immunodeficiency, and/or major organ damage was thought to either be a reactive inflammatory event or medication induced. The recent evidence confirms an underlying genetic cause of this disease, which should prompt a thorough evaluation for patients with cPAN irrespective of their age, ethnicity, family history, and presence or absence of systemic symptoms. In our opinion, a diagnosis of primary cPAN should be reserved for those patients in whom screening for DADA2 is unrevealing.

These findings provide an alert, specifically for the dermatology community, about the occurrence of a perhaps fatal disorder in patients with cPAN. Screening for the disease should include a basic immunodeficiency workup and measurement of ADA2 levels. Genetic studies and counseling should be performed when possible.

## Table. Clinical Spectrum of ADA2 Deficiency Disease

<table>
<thead>
<tr>
<th>System Involved</th>
<th>Presentation</th>
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<tbody>
<tr>
<td>General health</td>
<td>Fevers</td>
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<tr>
<td></td>
<td>Recurrent bacterial or viral infections</td>
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<tr>
<td></td>
<td>Myalgias and arthralgias</td>
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<tr>
<td>Skin</td>
<td>Livedo reticularis</td>
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<td></td>
<td>Livedo racemosa</td>
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<td></td>
<td>Ulcers</td>
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<td></td>
<td>Subcutaneous nodules</td>
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<td></td>
<td>Raynaud phenomenon</td>
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<td>Digit necrosis</td>
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<tr>
<td>Neurologic</td>
<td>Ischemic and hemorrhagic strokes</td>
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<td></td>
<td>Intracranial bleeding</td>
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<td></td>
<td>Peripheral neuropathy</td>
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<td>Liver</td>
<td>Hepatomegaly</td>
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<td>Portal hypertension</td>
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<tr>
<td>Immune</td>
<td>B-cell immunodeficiency (blood and bone marrow)</td>
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<td></td>
<td>Low IgM and IgA levels</td>
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<td></td>
<td>Lymphopenia or pancytopenia</td>
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</table>

Conclusions

Our findings confirm a genetic basis for cPAN in a subset of patients that is not limited to any specific ethnic group. DADA2 disease should be considered in all patients with cPAN, and screening should include measurement of ADA2 levels, basic immunodeficiency workup, and appropriate workup to exclude underlying organ damage when clinically apt. Additional immunologic studies should be pursued under the guidance of an immunologist. Identification of mutations in the *CECR1* gene can significantly expedite diagnosis and have profound implications for the early recognition and treatment of this recently recognized disease.
Dermatologic Etymology
Configuration

A cutaneous disease can be classified according to its configuration (Latin. configuration, configurations, configuration, formation). The configuration of skin disease may be described as follows:

- **Annular** (Latin. annulus, annuli, ring)¹ ²
- **Grouped** (French. groupe, cluster) + (Italian. gruppo, knot) + (Spanish. grupo, group) Note: Likely also German in origin from kruppaz, round mass.²
- **Arcuate** (Latin. arcuatus, arcuata, arcatum, bow-like, arched)³
- **Gyrate** (Greek. gyros, a circle) + (Latin. gyrus, gyri, circle, ring)² ³
- **Circinate** (Latin. circinatus, circinata, circinatum, rounded, circular)¹ ³
- **Polymorphic** (Greek. πολυμορφος, of many forms)³
- **Diffuse** (Latin. diffuses < dis, apart, + fundere, to pour)² ³
- **Coalescing** (Latin. comm., together + aescere to grow up coalesco, coalescer, to unite, grow together, become one in growth)² ³
- **Confluent** (Latin. confluentes, meeting place)³
- **Scarlatiniform** (Italian. scarlatinina, scarlet fever) + (Latin. forma, formae, form)¹
- **Crescentic** (Latin. cresco, crescere, to arise, come forth)² ³
- **Discrete** (Latin. discretus, discrete, separate)² ³

**NOTABLE NOTES**

**Herpetiform** (Ancient Greek. ἔρπειν, to creep, spread) + (Latin. forma, formae, form)² ³

**Linear** (Latin. linea, lineae, string, line)² ³

**Morbilliform** (Latin. morbillus, morbilli, measles) + (Latin. forma, formae, form)² ³

**Nummular** (Greek. νομιλος, customary, legal) + (Latin. nummulus, nummuli, coin)² ³

**Reticular** (Latin. reticulum, reticuli, small net)¹

**Striate** (Latin. stria, strie, furrow)¹

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