Clinical and pathological dermatological features of deficiency of adenosine deaminase 2: A multicenter, retrospective, observational study

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Dear Editor, Adenosine deaminase 2 deficiency (DADA2) is a monogenic autoinflammatory disease associated with *ADA2* mutations[1].

DADA2 diagnosis remains hard given its variable clinical presentation[2]. Although no tests are commercially available, serum ADA2 activity measurement can help secure the diagnosis which is confirmed by *ADA2* sequencing. Recently, Rama *et al*. proposed a decision tree for the genetic diagnosis of DADA2 based on prerequisites including among others, cutaneous manifestations. However, no study has specifically described DADA2's dermatological spectrum. Furthermore, pathological findings on skin biopsies have rarely been reported[1,3], and specific histological features remain to be determined. We conducted a multicenter retrospective study with assessment of clinical and pathological dermatological findings among 8 french DADA2 patients.

Cutaneous polyarteritis nodosa (cPAN) was defined as fibrinoid necrotizing vasculitis affecting the small arteries and arterioles(≥ 300µm) in the panniculus and dermal-subcutaneous junction as described by Ishibashi and Chen in a 4-stage process[4] with exclusion after clinicopathologic correlation of differential diagnoses particularly antineutrophil cytoplasmic antibody-associated vasculitis.

DADA2's main clinical features are presented in **Table 1** and detailed in **Supplemental Table 1**. Median age at first symptom was 9.5 [range 0.5-29] years, whereas median age at diagnosis was 25.5 [range 6-38] years.

Cutaneous manifestations (**Figure 1**) were the first symptoms of DADA2 in 3/8 patients. Livedo was observed in all cases and was of the racemosa subtype in 7/8 patients, with mostly a large pattern (6/8). It involved both legs and arms in all cases, extending to the abdomen or trunk in 3 cases. It was palpable in one patient. Other cutaneous manifestations included leg nodules (n=7, non-specific or erythema nodosum-like lesions), leg ulcers (n=3), Raynaud's phenomenon (n=2), "atrophie blanche" (n=2), digital necrosis (n=2), erythematous feet papules (n=1), and psoriasis (n=1).

Overall, 12 skin biopsies from 7 patients were reviewed (**Table 1 and Figure 1**). cPAN was identified in 4/7 patients. In patients n°3 and 4, skin biopsies revealed thrombosis of dermal and/or hypodermal

capillaries, without vasculitis. While subacute cPAN was also observed in skin biopsy from patient n°4, patient n°3 had only isolated thrombosis.

Here, we portrayed the dermatological spectrum of DADA2 patients thus contributing to its better recognition. Livedo was observed in all cases, was mostly racemosa, extensive with a large reticular pattern. Differentiating between DADA2 and antiphospholipid-negative Sneddon's syndrome (as in patient n°4) may be challenging since both may present with livedo and strokes[5]. While skin biopsies of DADA2 patients most frequently revealed vasculitis, 2 patients in our series showed capillary thrombosis such as in Sneddon's syndrome[5].

Importantly, 3/7 patients did not have vasculitis on skin biopsy. The site and depth of biopsy is probably important. Indeed, while we found non-specific features in 2 superficial biopsies of livedo without analyzable hypodermis, cPAN was more frequently identified in biopsies taken from nodules.

Overall, livedo racemosa with a large branch pattern, nodules or ulcerations in a context of neurovascular events, recurrent fever, low IgM levels and pediatric onset, are suggestive of DADA2. While cPAN on skin biopsy is suggestive of DADA2, its absence or the presence of thrombotic features does not exclude the diagnosis.

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Abbreviations and acronyms

DADA2: Adenosine deaminase 2 deficiency

cPAN: Cutaneous polyarteritis nodosa

CRP: C-reactive protein

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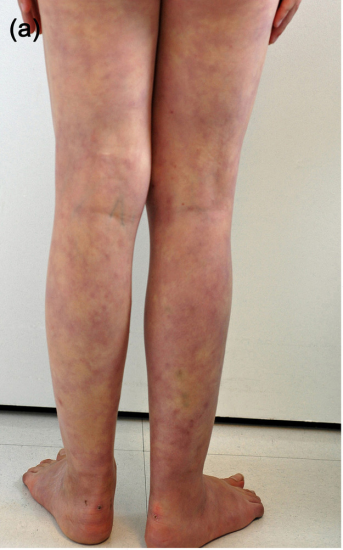
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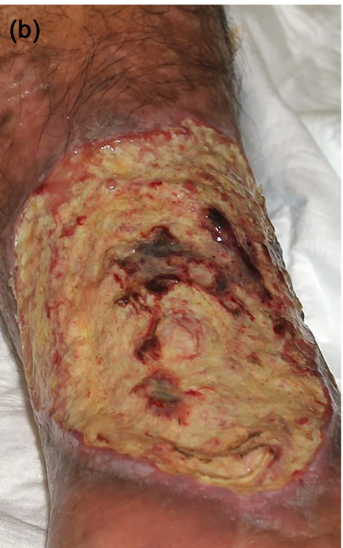
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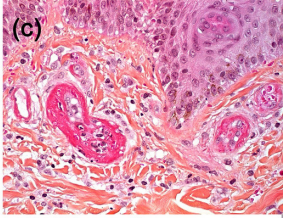
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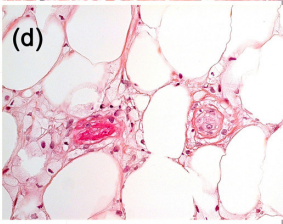
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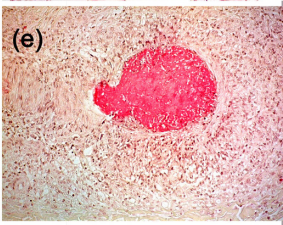
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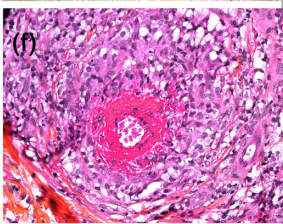
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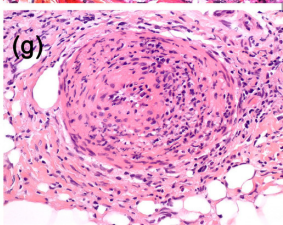
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Table 1. Main clinical and pathological skin features of the 8 French DADA2 patients

Patient/ Biopsy N	Skin manifestations	Extra-cutaneous manifestations	Site of biopsy	Thrombosis	Type of vessels	Vasculitis	Type of vessels	Other findings
1/1	-Livedo racemosa -Perimalleolar ulcers - Raynaud's phenomenon -"Atrophie blanche"	Recurrent fever, increased CRP level, abdominal pain, peripheral neuropathy	Leg ulcer	No	-	No	-	Pyogenic granuloma
2/1	-Livedo racemosa	Recurrent fever, arthralgia, myalgia, hepatitis	Livedo of the leg	No	-	No	-	Slight perivenular lymphocytic infiltrate in hypodermis
3/1	-Livedo racemosa -Leg nodules	Anemia, increased CRP level	Nodule of the leg	Yes	Hypodermal capillaries	No	-	
3/2	-Perimalleolar ulcers -"Atrophie blanche"		Livedo of an ankle	Yes	Dermal capillaries	No	-	
3/3			Livedo of the trunk	No	-	No	-	Non-specific inflammation
3/4			Nodule of an ankle	Yes	Dermal and hypodermal capillaries	No	-	
3/5			Nodule of the leg	Yes	Dermal and hypodermal capillaries	No	-	
4/1	-Livedo racemosa -Leg nodules -Digital necrosis -Raynaud's phenomenon -Erythematous feet papules	Recurrent fever, recurrent ENT infections, cerebral infarct, hypogammaglobulinemia	Livedo of the thigh (infiltrated zone)	Yes	Dermal and hypodermal capillaries	Subacute cPAN	Deep dermis medium-sized artery	-

5/1	-Livedo racemosa -Ulcerated leg nodules -Leg nodules -Psoriasis	Recurrent fever, increased CRP level, pericarditis, myocarditis, intestinal vasculitis, renal microaneurysm, peripheral neuropathy, TIA > death	Nodule of the leg	Yes	Deep dermis medium-sized artery	Acute cPAN	Deep dermis medium-sized artery	
6	-Livedo reticularis	Increased CRP level, ischemic strokes, hepatosplenomegaly, low IgM level, negative vaccinal serologies	No biopsy					
7/1	-Livedo racemosa -Leg nodules	Recurrent fever, increased CRP level, arthralgia, abdominal pain, hepato-splenomegaly, epilepsy	Nodule of the leg	No	-	Reparative cPAN	Deep dermis medium-sized artery	
7/2			Nodule of the leg	No		No	-	Septal panniculitis
8/1	-Livedo racemosa -Digital necrosis -Leg nodules	Recurrent fever, increased CRP level, Ischemic strokes, abdominal pain, psychosis, pericarditis	Nodule of the leg	No		Subacute cPAN	Deep dermis medium-sized artery	

CRP: C-reactive protein, ENT: Ear, nose, and throat; TIA: Transient ischemic attack, cPAN: cutaneous periarteritis nodosa, Definition of cPAN stages by Ishibashi and Chen: Acute : endothelial loss and fibrin thrombi with neutrophil infiltration without obvious internal elastic lamina disruption and medial fibrinoid necrosis; Subacute: mixed cell infiltrates showing a unique intimal target-like fibrinoid necrosis with fibrinoid leakage extending through the disrupted sites of the internal elastic lamina to the media; Reparative: intimal fibroblastic proliferation and perivascular neovascularization with predominant infiltrates of histiocytes and lymphocytes; Healed: minimal cellular inflammation with occlusive intimal thickening. Thrombosis was defined as complete occlusion of the vascular lumen by a cluster of fibrin