

# Congenital sideroblastic anemia associated with B cell immunodeficiency, periodic fevers, and developmental delay: A case report and review of mucocutaneous features

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## Abstract

This is a 40-year-old woman with sideroblastic anemia with B cell immunodeficiency, periodic fevers, and developmental delay syndrome, who has genital and extragenital lichen sclerosis on the abdomen and the upper back that have become erythematous and painful during febrile episodes. This report summarizes the published cases of sideroblastic anemia with B cell immunodeficiency, periodic fevers, and developmental delay and highlights associated mucocutaneous features.

## Keywords

Case report, sideroblastic anemia with B cell immunodeficiency, periodic fevers, and developmental delay, morphea, lichen sclerosis

## Introduction

Sideroblastic anemia with B cell immunodeficiency, periodic fevers, and developmental delay (SIFD) is a newly recognized condition characterized by severe microcytic anemia, pan-gammaglobulinemia, B-cell lymphopenia, and recurrent non-infectious febrile episodes with gastrointestinal symptoms.<sup>1</sup> Genotyping of individuals with SIFD revealed its association with an autosomal recessive mutation in the template-independent RNA polymerase *tRNA nucleotidyl transferase 1* (TRNT1), which is required for the maturation of cytosolic and mitochondrial transfer RNAs (tRNAs).<sup>2,3</sup> So far, mucocutaneous involvement was described in two cases presenting in one as brittle hair and in other as chronic ichthyosis, punctuated with eruptions of erythema and/or hypopigmentation. Skin biopsy of ichthyotic skin revealed a perivascular lymphohistiocytic infiltrate within the papillary dermis but lacked specific diagnostic features; electron microscopy showed small foci of fibrillar amyloid-like material. We report the first case of SIFD conclusively linked to genetic variants that presented with skin autoimmune phenomena in the forms of diffuse lichen sclerosis and morphea in addition to the classic features of this syndrome.

## Case report

The patient is a 40-year-old Caucasian female diagnosed with SIFD in 2017. The patient's sideroblastic anemia was diagnosed in infancy. Recurrent and frequent emergency department visits for fever and diarrhea in toddlerhood ultimately led to the diagnosis of hypogammaglobulinemia and treatment with intravenous immunoglobulin infusions (IVIG). Later in childhood, she was found to have moderate sensorineural hearing loss, retinitis pigmentosa, hypothyroidism, and osteoporosis. She was referred to dermatology in 2015 for evaluation of extensive indurated plaques. On

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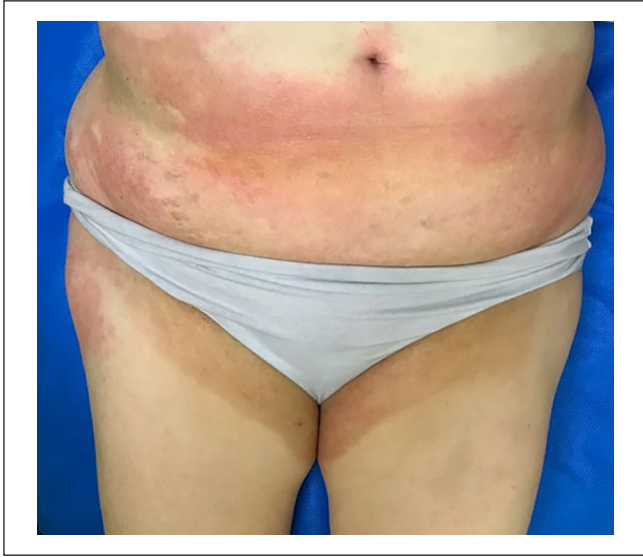
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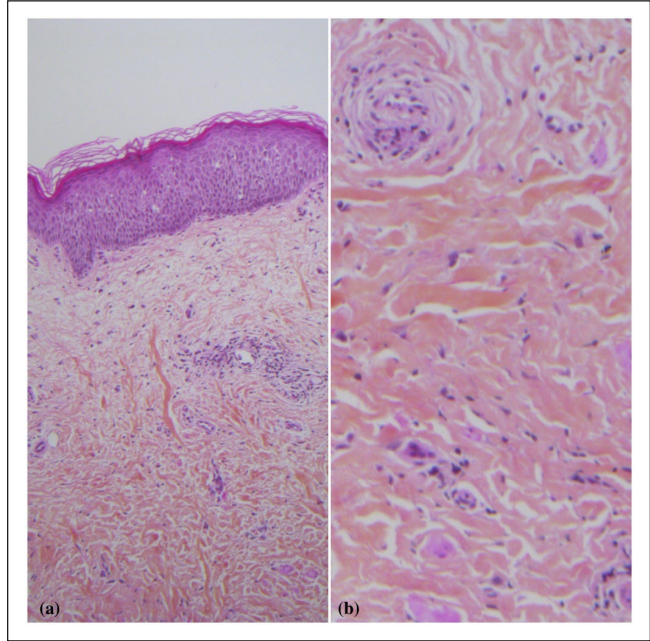


**Figure 1.** Image of extragenital lichen sclerosus showing diffuse lichenoid patches containing multiple wrinkled and atrophic areas on the lower abdomen and bilateral medial thighs.

examination, no dysmorphic features were noted. On patient's abdomen, flanks, back, and thighs confluent indurated plaque with hyper- and hypopigmentation and areas of epidermal atrophy were noted. These plaques would eventually become erythematous episodically (Figure 1). Two skin biopsies were performed from the abdomen and the vulva. The abdominal biopsy was consistent with lichen sclerosus et atrophicus (LSA), while the vulvar one showed morphea (Figure 2). Given the multiple comorbidities, the patient's skin conditions were treated with high-potency topical steroids. Because of the constellation of multiple rare manifestations clinically suggestive of SIFD, the patient was referred to medical genetics. A subsequent genotyping panel revealed heterozygosity for two pathogenic *TRNT1* variants (C.668T>C and C1057-7C>G) as well as incidental homozygosity for an HFE variant associated with hemochromatosis. Patient denied a family history of similar symptoms. Over the past 2 years, she repeatedly presented to the emergency room (ER) with painful erythematous patches overlying her LSA. The pain and the erythema resolve rapidly with the initiation of broad-spectrum intravenous (IV) antibiotics but the LSA lesions persisted.

## Discussion

SIFD was first described in 2013 by Wiseman et al.,<sup>1</sup> with a total of 12 cases identified from 10 families since then (Table 1). All reported cases were associated with *TRNT1* variants. *TRNT1* encodes CCA sequence-adding enzymes essential for the maturation of both nuclear and mitochondrial tRNAs. Loss of *TRNT1* function is fatal, while *TRNT1* variants can be disease related.<sup>5</sup>



**Figure 2.** HPS showing spongiotic epidermis with mild alteration of the papillary dermis (a) and thickened collagen in the dermis (b).

To our knowledge, this is the first case of SIFD in which autoimmunity and specifically autoimmunity affecting the skin has been observed. It is not surprising to observe autoimmune phenomena in immunodeficiency disorders. For example, the most common primary immunodeficiency among children and adults, variable immunodeficiency (CVID) disorder, is characterized by low immunoglobulin levels (IgG, IgA, and/or IgM) and poor response to vaccines,<sup>6</sup> with autoimmune conditions occurring in up to 25% of the patients.<sup>7</sup> In one study of 224 patients diagnosed with CVID, 17% presented initially with autoimmune symptoms only, while 2.3% of the patients developed autoimmune phenomenon later.<sup>8</sup> Although the mechanism by which autoimmunity occurs in CVID is poorly understood, mutations in the related receptor, transmembrane activator, and calcium-modulating ligand interactor (*TAC1*) have been implicated as well as increased serum levels of cytokines necessary for survival and maturation of B cells, for example, acidic protein rich in leucine (APRIL) and B cell-activating factor (BAFF).<sup>9,10</sup> Generally, CVID-associated autoimmunity occurs less often in males, and patients with autoimmune issues tend to develop fewer infections despite their higher tendency for enteropathy as in the present case.<sup>11</sup>

SIFD is a recently recognized condition that includes hypogammaglobulinemia as part of its classic disease phenotype. Like other primary immunodeficiency disorders, autoimmune phenomena may be associated. Further reports are needed to estimate the risk of autoimmune and neoplastic diseases in patients with SIFD.

**Table 1.** Congenital sideroblastic anemia associated with B cell immunodeficiency, periodic fevers, and developmental delay patient's characteristics.

Case	Age of presentation	Sex	Ethnicity	Skin findings	Other features	Reference
1	5 months	Female	South Asian	Ichthyosis, Erythema, hypopigmentation	Sensorineural hearing loss, pigmentary retinitis, nephrocalcinosis	Wiseman et al. <sup>1</sup> and Wedatilake et al. <sup>4</sup>
2	8 weeks	Male	South Asian	NR	Nephrocalcinosis	Wiseman et al. <sup>1</sup> and Wedatilake et al. <sup>4</sup>
3	3 h	Female	Caucasian	Brittle hair, recurrent oral ulcerations	Renal tubular Fanconi syndrome with chronic hypokalemia and hypophosphatemia.	Wiseman et al. <sup>1</sup>
4	1 month	Male	Caucasian	Brittle hair	Recurrent seizures fat malabsorption and nonspecific villous atrophy on small bowel biopsy, and avascular necrosis of the right femur, hypokalemia, adrenal hemorrhage	Wiseman et al. <sup>1</sup>
5	3 weeks	Male	Caucasian	NR	Recurrent seizures and communicating hydrocephalus with macrocephaly; exocrine pancreatic insufficiency; and splenomegaly	Wiseman et al. <sup>1</sup>
6	2 months	Female	Caucasian	NR	Progressive/generalized hypotonia and sensorineural deafness. dilated cardiomyopathy	Wiseman et al. <sup>1</sup>
7	7 months	Male	Hispanic	NR	Nystagmus and recurrent/severe seizures, hepatosplenomegaly	Wiseman et al. <sup>1</sup>
8	7 weeks	Female	Hispanic	NR	Sickle cell trait	Wiseman et al. <sup>1</sup>
9	2 months	Female	Caucasian	NR	Torticollis and bilateral sensorineural hearing loss. Nephrocalcinosis and significant hypercalciuria	Wiseman et al. <sup>1</sup>
10	6 months	Female	South Asian	NR		Wiseman et al. <sup>1</sup>
11	7 weeks	Male	Caucasian	NR	Pigmentary retinitis	Wiseman et al. <sup>1</sup>
12	1 month	Male	Caucasian	fragmented, brittle hair		Wiseman et al. <sup>1</sup>
13	2 weeks	Female	Caucasian	Brittle hair	Nystagmus and photophobia retinal dystrophy progressive cerebellar atrophy chronic gastritis, partial villous atrophy, hepatosplenomegaly, and pancreatic insufficiency recurrent seizures	Wedatilake et al. <sup>4</sup>
14	3 weeks	Male	Caucasian	NR		Wedatilake et al. <sup>4</sup>
15	Birth	Female	NR	NR	Massive hepatosplenomegaly. jaundice, multiorgan failure and evidence of intracranial hemorrhage.	Barton et al. <sup>3</sup>
16	Birth	Male	NR	Generalized purpuric skin rash	Penoscrotal hypospadias and microphallus, hydrops, hepatomegaly	Barton et al. <sup>3</sup>
17	2 weeks	Female	Caucasian	Morphea and extragenital Lichen sclerosus atrophicus	Recurrent seizure, sensorineural hearing loss, and pigmentary retinitis	Present case

NR: not reported.

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### Informed consent

The patient provided informed consent for publication of the case report.

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