Recurrent fevers, progressive lipodystrophy, and annular plaques in a child

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CASE SUMMARY

History

A 6-year-old Hispanic girl was referred to the National Institutes of Health (NIH) for evaluation of recurrent fever, rash, arthritis, lipodystrophy, and oral ulcers. She was born full-term, and her family history was unremarkable. On day 8 of life, she developed an erythematous lesion on the nose and was given the diagnosis of cellulitis. Over the next several months, rashes developed in other areas of her body; she had recurrent fevers and failure to thrive. Skin biopsies were initially interpreted as cutaneous involvement of acute myelogenous leukemia, and she received cytarabine, daunorubicin, and etoposide without response. Chemotherapy was discontinued due to worsening of the rash and development of a seizure. Radiation therapy was given for 22 days. Bone marrow biopsy results were unremarkable.

By 15 months of age, she had chronic diarrhea and abdominal pain, and laboratory testing showed elevated acute phase reactants (erythrocyte sedimentation rate 70 mm/h, C-reactive protein 68 mg/L). Treatment with tacrolimus, colchicine, and anakinra failed to elicit a response. Treatment with tocilizumab resulted in normalization of acute phase reactants, but worsening of both her skin rash and polyarthralgia. After each infusion of tocilizumab, she was unable to ambulate for about 5 days. At this point in her treatment, she tested negative for the *NLRP3* mutation.

By age 2 years, she had prolonged periods (up to 15 days) of continuous fever, rash, debilitating arthralgia, periumbilical pain, and oral ulcers. She exhibited speech delay and was below the 25th percentile in height and weight for her age. Prednisone at doses of ~1 mg/kg/d provided partial relief of her symptoms. At age 6 years, she had a lengthy hospital admission for fever and periorbital edema with a presumed diagnosis of periorbital cellulitis. The patient was enrolled in the NIH Natural History Protocol of Autoinflammatory Diseases (ClinicalTrials.gov Identifier: NCT02974595). The parents provided written informed consent.

Physical examination

The patient appeared small for her age with prominent cheekbones, sunken eyes, and a mildly protuberant abdomen. Tender, erythematous,

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Note: Drs Goldbach-Mansky and Montealegre Sanchez at the NIH are currently studying patients with autoinflammatory syndromes. Clinicians can refer interested patients to the NIH Patient Recruitment and Referral Office at 800-411-1222 or by e-mail to prpl@mail.cc.nih.gov.

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Abbreviations used:

CANDLE: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
NIH: National Institutes of Health
POMP: proteasome maturation protein
PSMB8: proteasome subunit β type 8

annular and arcuate, indurated plaques were present on the upper back, chest, and upper extremities, along with scattered, hyperpigmented, small nummular patches (Fig 1, *A* and *B*). There was asymmetric edema of the upper and lower eyelids with a violaceous hue without conjunctival erythema (Fig 1, *C*). The hands were small with tapered digits, loss of subcutaneous tissue, and joint swelling (Fig 1, *D*). There were 2 oval ulcers on the mucosal surface of the lips. Areas of lipoatrophy were appreciated on her face, upper extremities, fingers, and toes.

Histopathology

Histopathologic reevaluation of a skin biopsy from her right midback revealed an interstitial and perivascular dermal infiltrate composed primarily of atypical mononuclear cells with irregularly shaped nuclei with leukocytoclasis (Fig 2, *A* and *B*). A preponderance of cells stained with myeloperoxidase and CD163, signifying the myeloid lineage (Fig 2, *C*). There was also a perivascular distribution of CD123-positive plasmacytoid dendritic cells (Fig 2, *D*).

Significant diagnostic studies

Computed tomography scan of the cerebrum revealed bilateral calcification of the basal ganglia. Magnetic resonance imaging of the bilateral forearms showed myositis, fasciitis, and tenosynovitis. Cardiac magnetic resonance imaging was unremarkable. Mutation analysis revealed homozygous mutations in proteasome subunit β type 8 (*PSMB8*).

DIAGNOSIS

Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome.

FOLLOW-UP

The patient began treatment with the Janus kinase inhibitor baricitinib (2 mg/d) with some improvement, but continued to experience intermittent flares of rash, arthritis, and myositis. Her dose was titrated up to 6 mg/d, enabling discontinuation of prednisone and normalization of acute phase reactants. After 36 months of treatment with baricitinib, she remains in clinical remission but has experienced upper respiratory infections, BK viruria, and transient anemia, transaminitis, and thrombocytopenia. The patient also displayed dyslipidemia in the context of weight gain and hepatic steatosis.

DISCUSSION

The term CANDLE syndrome was first proposed in 2010 by Torrelo et al, in a series of 4 children with the clinical features of early-onset recurrent fevers, annular plaques, violaceous eyelid edema, failure to thrive, and lipodystrophy.[1] After the identification of the genetic basis of the syndrome, it was found that CANDLE shared the same origin as 2 hitherto considered independent entities: Nakajo-Nishimura syndrome and joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy syndrome.[2] These 3 conditions comprise a spectrum of overlapping clinical manifestations and are now called proteasome-associated autoinflammatory syndromes.[3]

Proteasomes are cylindrical structures found in the nucleus and cytoplasm of all eukaryotic cells and are responsible for degradation of ubiquitinated intracellular proteins from self or foreign origin.[4] Impaired proteasomal function leads to accumulation of damaged, misfolded, and oxidized proteins, which leads to cellular stress[5] and ultimately produces the type I interferon cytokine signature characteristic of CANDLE syndrome.[4] Interferon propagates inflammation by recruiting inflammatory cells and producing other proinflammatory cytokines and chemokines through the Janus kinase—signal transducer and activator of transcription signaling pathway.[6] The first identified and most frequently encountered gene[7] known to cause CANDLE syndrome is *PSMB8*; mutations in the gene can result in impaired incorporation of the β5i subunit into the immunoproteasome. Pathogenic mutations have since been discovered in genes encoding other proteasomal subunits, including *PSMB9*, *PSMB4*, and *PSMA3*, the latter 2 encoding constitutive components of the proteasome, as well as proteasome maturation protein (POMP), which controls proteasome assembly.[8,9] These mutations either hinder proteasome assembly or catalytic activity, ultimately disturbing proteostasis by the ubiquitin proteasome system.[10] The disease is autosomal recessive in patients with disease-causing *PSMB8* or *PSMB4* mutations and autosomal dominant in patients with *POMP* mutations. Digenic recessive inheritance might occur secondary

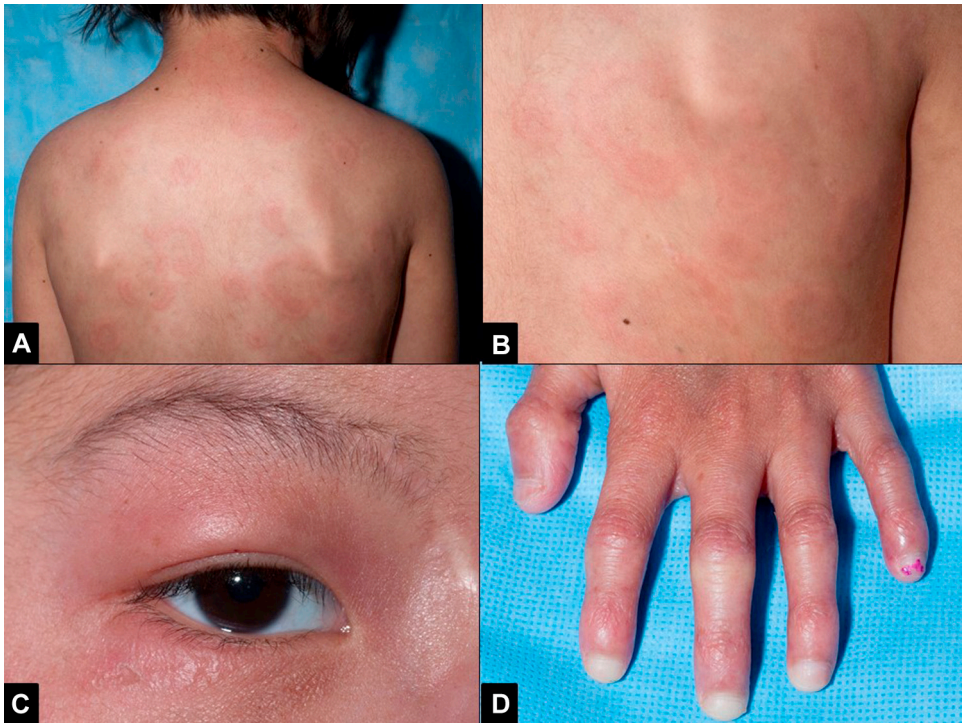

Fig 1. Clinical findings of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. **A**, Arcuate and annular, pink-to-violaceous plaques with indurated borders and hyperpigmented, purpuric central zones. **B**, Close-up view of annular, arcuate, and occasionally polycyclic plaques. **C**, Violaceous periorbital edema. **D**, Joint swelling with tapered, sclerotic digits, and nail bed pallor.

to monoallelic loss of function mutations in 2 different proteasome genes (ie, *PSMA3* and *PSMB8*, *PSMB4* and *PSMB9*, or *PSMB4* and *PSMB8*).[4,8] Autosomal dominant inheritance might also occur due to loss of function mutations (haploinsufficiency) of the gene coding the assembly protein POMP.

Histology

Skin biopsies of inflammatory plaques in CANDLE syndrome are characterized by a dense perivascular and interstitial polymorphous dermal infiltrate composed of immature myeloid cells, macrophages, plasmacytoid dendritic cells, and regulatory T cells ($CD25^+$, $FoxP3^+$). Plasmacytoid dendritic cells ($CD123^+$) are potent producers of type I interferon, the secretion of which recruits inflammatory cells, such as neutrophils and other myeloid cells.[11] Immature myeloid cells demonstrate large vesicular or kidney-shaped nuclei that stain with myeloperoxidase. A mixed-cell inflammatory infiltrate composed of neutrophils, eosinophils, and lymphocytes and karyorrhexis (without vasculitis) is often present as well.[1] Inflammation typically extends to the fat, manifesting as lobular panniculitis.[7]

Clinical features

Manifestations of CANDLE syndrome typically begin in the neonatal period with lymphadenopathy and failure to thrive.[6] Skin findings begin in infancy and include acral pernio-like lesions and annular erythematous to purpuric plaques (often with a raised, edematous pink border and a macular purpuric center). The annular plaques persist for several days and heal with purpura and postinflammatory hyperpigmentation.[6] Periorbital or, less commonly, perioral violaceous edema is an important clue to the diagnosis.[7] The combination of daily fevers and a characteristic rash with immature neutrophils is suggestive of the diagnosis of CANDLE syndrome.

Lipodystrophy may manifest on the face by 2 years of age but typically becomes more prominent later in childhood with progressive fat loss of the trunk and upper limbs (Table I). Increased abdominal fat and the presence of other features of metabolic syndrome (in the absence of peripheral fat deposition) suggest an effect of proteasome dysfunction on the development of metabolic syndrome and hepatic steatosis.[12] Late findings include contractures and muscle involvement manifesting as atrophy,

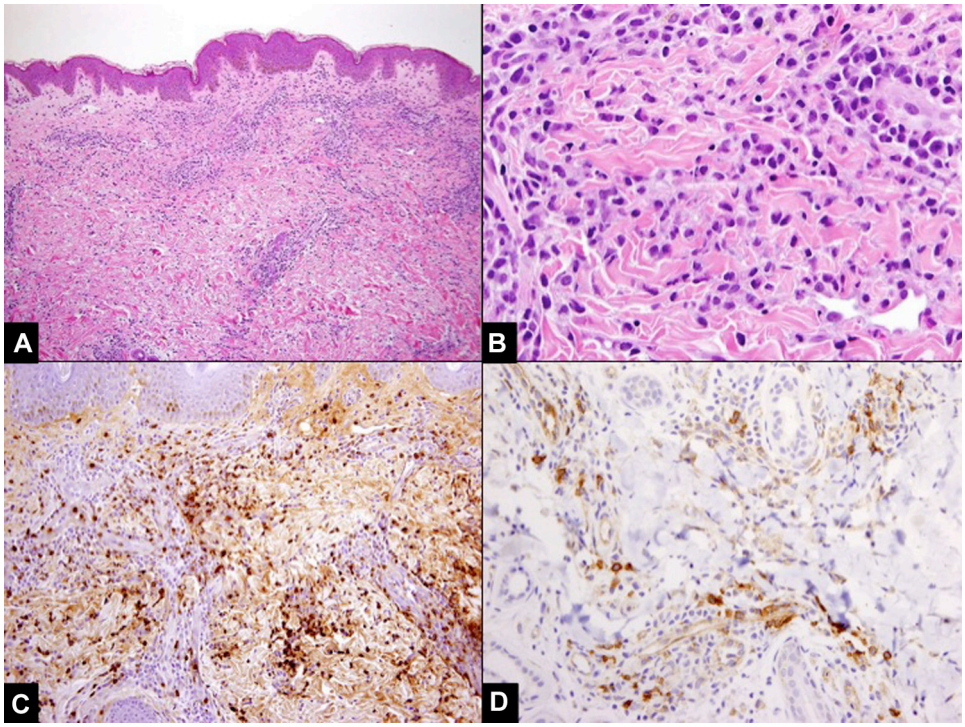

Fig 2. Histologic features of cutaneous eruptions in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. **A**, Superficial and deep dermal perivascular and interstitial mononuclear infiltrate. **B**, Leukocytoclasis without vasculitis is also evident. **C**, Myeloperoxidase stain highlights an atypical mononuclear infiltrate, confirming myeloid lineage. **D**, There are scattered $CD123^{+}$ plasmacytoid dendritic cells admixed in the infiltrate. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, 100×; **B**, 400×; **C**, myeloperoxidase immunohistochemical stain; original magnification: 200×; **D**, CD123 immunohistochemical stain; original magnification: 400×.)

myositis, and wasting.[2] Pulmonary hypertension has also been documented in CANDLE patients.[13] Hirsutism and acanthosis nigricans might be seen due to metabolic derangement and chronic steroid therapy.[7] Laboratory findings include anemia, elevated erythrocyte sedimentation rate and C-reactive protein, and transaminitis.[14] Brain imaging may reveal basal ganglia calcification.

Optimal management of CANDLE syndrome is unclear. Inhibition of interleukin 6 with tocilizumab has been found to provide modest improvement.[8] The Janus kinase 1/2 inhibitor baricitinib has shown promising results with improvement in clinical symptoms and cytopenias, inhibition of pathogenic interferon-associated signaling, and reduction of oral corticosteroid requirements. Montealegre Sanchez et al recently reported that 50% of CANDLE patients achieved clinical remission criteria while on bariticinib treatment.[15] The prognosis of CANDLE syndrome is variable, but left untreated, significant morbidity and mortality is common.[8] Fortunately, CANDLE syndrome has characteristic clinical and histologic features that begin at an early age that can aid in prompt diagnosis and intervention.

KEY TEACHING POINTS

- Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome is an autoinflammatory disorder characterized by recurrent fevers, progressive lipodystrophy, and failure to thrive. Cutaneous manifestations include violaceous eyelid edema, perniosis-like acral lesions, and annular erythematous plaques.
- CANDLE syndrome is caused by mutations in genes encoding proteins involved in assembly or function of the proteasome.
- The histopathology of CANDLE syndrome is distinct and demonstrates dermal infiltration of atypical myeloid cells, occasionally mimicking leukemia cutis.

Table I. Clinical manifestations of CANDLE syndrome

Organ system	Manifestation	Age of onset
Skin, hair, and nails	Acral perniotic lesions	Infancy only
	Annular plaques	Infancy
	Violaceous periorbital edema	Infancy
Musculoskeletal	Arthralgia	Infancy
	Lipodystrophy	Early childhood
	Digital swelling and deformation	Early childhood
	Contractures	Late childhood
	Prominent abdomen	Late childhood
	Myositis and muscle atrophy	Variable
	Chondritis and saddle nose	Variable
Neurologic	Basal ganglia calcification	Variable
	Lymphocytic aseptic meningitis	Variable
Constitutional	Failure to thrive	Infancy
	Recurrent fevers	Infancy
	Growth retardation	Infancy
	Lymphadenopathy	Variable
	Hepatosplenomegaly	Variable
Laboratory	Cytopenias (hemoglobin, platelets, ALC)	Infancy
	Transaminitis	Infancy
	Elevated acute phase reactants	Infancy
Metabolic	Insulin resistance and acanthosis nigricans	Late childhood
	Increase intra-abdominal fat	
	Dyslipidemia	
	Hepatic steatosis	
Cardiovascular	Arterial hypertension	Late childhood
	Pulmonary hypertension	Late childhood

ALC, Absolute lymphocyte count; *CANDLE*, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature.

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