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CASE REPORT

CANDLE syndrome: chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature—a rare case with a novel mutation

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Abstract We described herein a patient with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome and a novel mutation in *PSMB8* gene. This patient had multiple visceral inflammatory involvements, including rare manifestations, such as Sweet syndrome and pericarditis. A 3-year-old male, Caucasian, was born to consanguineous healthy parents. At the age of 11 months, he presented daily fever (temperature >40 °C), irritability, hepatomegaly, splenomegaly; and tender and itching, erythematous papular and edematous plaque lesions. Echocardiogram showed mild pericarditis. Skin biopsy revealed a neutrophil infiltrate without vasculitis suggesting Sweet syndrome. Mutational screening of *PSMB8* gene revealed homozygous c.280G>C, p.A94P mutation. He responded partially to high doses of oral glucorticoid and intravenous methylprednisolone. Colchicine, azathioprine, methotrexate, cyclosporine, and intravenous immunoglobulin were not efficacious. At the age of 3 years and 1 month, tocilizumab was administered resulting in remission of daily fever and irritability. However, there was no improvement of the skin tenderness and itching lesions.

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Conclusion: A new mutation in a CANDLE syndrome patient was reported with pericarditis and mimicking Sweet syndrome. The disease manifestations were refractory to immunosuppressive agents and partially responsive to tocilizumab therapy.

What is Known:

- *Proteasome-associated autoinflammatory syndromes (PRAAS) include four rare diseases.*
- *Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome was seldom reported.*

What is New:

- *We described a Brazilian patient with CANDLE syndrome possessing a novel mutation in the PSMB8 gene.*
- *This patient had multiple visceral inflammatory involvements, including rare manifestations, such as pericarditis and mimicking Sweet syndrome.*

Keywords CANDLE syndrome · Tocilizumab · Sweet syndrome · *PSMB8* gene

Abbreviations

ANA	Antinuclear antibodies
CANDLE	Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS	Cryopyrin associated periodic syndromes
CRP	C-reactive protein
ESR	Erytrocyte sedimentation rate
FMF	Familial Mediterranean fever
JAK	Janus kinase
JASL	Japanese autoinflammatory syndrome with lipodystrophy
JMP	Joint contractures, muscle atrophy, microcytic anemia and panniculitis-induced lipodystrophy
MKD	Mevalonate kinase deficiency
NNS	Nakajo-Nishimura syndrome
PRAAS	Proteasome-associated autoinflammatory syndromes
PSMB8	Proteasome subunit beta type 8
TRAPS	TNF receptor associated periodic syndrome
WBC	White blood cell

Introduction

The hereditary autoinflammatory syndromes are immunedysregulatory conditions caused by monogenic defects of innate immunity and are classified as primary immunodeficiencies; however, they are not usually associated with increased susceptibility to infections [1]. They manifest at early childhood with fever and disease-specific patterns of organ inflammation [1, 7].

Of note, proteasome-associated autoinflammatory syndromes (PRAAS) have been described under different terms in the past and include four acronyms with similar clinical, laboratory, and genetic features that comprise a spectrum of clinical severity [3, 11]. They are chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome (OMIM#256040); joint contractures, muscle atrophy, hepatomegaly, splenomegaly, microcytic anemia, and panniculitis-induced lipodystrophy (JMP) syndrome (OMIM#256040); Nakajo-Nishimura syndrome (NNS) (OMIM#256040); and Japanese autoinflammatory syndrome with lipodystrophy (JASL) (OMIM#256040) [10, 11].

Recently, CANDLE syndrome has been described as an early-onset autoinflammatory syndrome, characterized by recurrent fever, multiple skin lesions, specific facial phenotype, chronic anemia, increased acute phase reactants, and progressive lipodystrophy [5, 13, 14]. The majority of patients present with homozygous or compound heterozygous mutations in the proteasome subunit β type 8 (*PSMB8*) gene [4, 5, 8, 9, 11, 14]. Recently, it has been shown that CANDLE syndrome can also be caused by mutations in genes that encode other proteasome subunits, such as *PSMB4*, *PSMB9*, and *PSMA3* [2].

We described herein a Brazilian patient with CANDLE syndrome possessing a novel mutation in the *PSMB8* gene. This patient had multiple visceral inflammatory involvements, including rare manifestations, such as pericarditis and mimicking Sweet syndrome.

Case report

The patient is a 3-year-old Hispanic male born to consanguineous healthy mother and father. At the age of 11 months, he presented with daily fever (temperature >40 °C), irritability, hepatomegaly, splenomegaly, hands soft tissue edema; and tender and itching, erythematous papular nodular, pustular and edematous plaque lesions of the skin, suggesting acute febrile neutrophilic dermatosis (Sweet syndrome) (Fig. 1). The skin lesions affected the face, trunk, and upper and lower limbs. Facial features revealed thick lips, violaceous erythema of the eyelids and decreased fatty tissue of the face. His height and weight were below the third percentile. Laboratory tests showed progressive hypochromic microcytic anemia (hemoglobin 8.8 g/dL), leukocytosis (34.800/mm^3) with neutrophilia, and thrombocytosis (794.000/mm^3). Acute phase reactants were increased: C-reactive protein (CRP) was 285 mg/L (normal range 0–5) and erytrocyte sedimentation rate (ESR) was 64 mm/1st hour. Other exams showed elevated aspartate aminotransferase 87 U/L (normal 15–40), hypertriglyceridemia (183 mg/dL), while fasting glycemia and cholesterol levels were normal. The patient did not present hypergammaglobulinemia; however, high levels of IgA

Fig. 1 Clinical manifestations and genetic findings observed in a Brazilian patient with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. Nodular and pustular lesions and hands and fingers swelling at the age of 11 months

(139.5 mg/dL, normal 15.8–83.2) and IgM (267.4 mg/dL, normal 44–104) were found. Complement levels and lymphocyte immunophenotyping were normal. Immunological tests showed negative antinuclear antibodies (ANA), anti-double-stranded DNA, anti-Sm, anti-Ro/SSA and La/SSB, anti-RNP, and anticardiolipin autoantibodies. The serological tests for cytomegalovirus, toxoplasmosis, mononucleosis, rubella, parvovirus B19, HIV, HTLV 1/2, hepatitis A, hepatitis B, and hepatitis C were negative echocardiogram showed mild pericarditis. Bone marrow aspirate and ophthalmologic evaluation were normal. Skin biopsy revealed an inflammatory infiltrate with marked predominance of mature neutrophils and leukocytoclasis without vasculitis suggesting Sweet syndrome (Fig. 2a, b). Genetic screening for deficiencies of interleukin 1 (DIRA; OMIM#612852) and interleukin 36 (DITRA; OMIM#614204) receptor antagonists were negative. Genetic analysis by targeted sequencing of *PSMB8* gene (NM_148919.3) revealed the homozygous c.280G>C, p.A94P mutation (Fig. 3a), and the diagnosis of CANDLE syndrome was established (Goldbach-Mansky R, Translational Autoinflammatory Disease Section, National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, MD, USA). After that, prednisolone was started (1.0 mg/kg/day) with progressive tapering, resulting into a mild clinical improvement. Later on, he presented with high-temperature daily fever, hepatomegaly, splenomegaly, and diffuse recurrent skin eruptions that became purpuric with residual hyperpigmentation. Arthritis, muscle atrophy, joint contractures, and acanthosis nigricans were not observed. In the last 2 years, he received intravenous immunoglobulin (2.0 g/kg/month) for four consecutive months. This drug was discontinued due to cyanosis and chills during the last infusion. He was also treated with cyclosporine (5.0 mg/kg/day for 13 months), methotrexate (0.5 mg/kg/week for 2 months), colchicine (0.05 mg/kg/day), and azathioprine (2.5 mg/kg/day) without any apparent improvement of clinical manifestations. At this moment, hemoglobin was 8.4 g/dL, hematocrit 30.6 %, white blood cell count (WBC) 20.710/mm^3 (66 % neutrophils, 27 % lymphocytes, and 7 % monocytes), and platelets 709.000/mm^3. At the age of 3 years and 1 month, tocilizumab was administered (12 mg/kg, every 2 weeks, resulting three consecutive doses) simultaneously with prednisone (1.0 mg/kg/day), colchicine, and azathioprine, which resulted into the remission of daily fever and

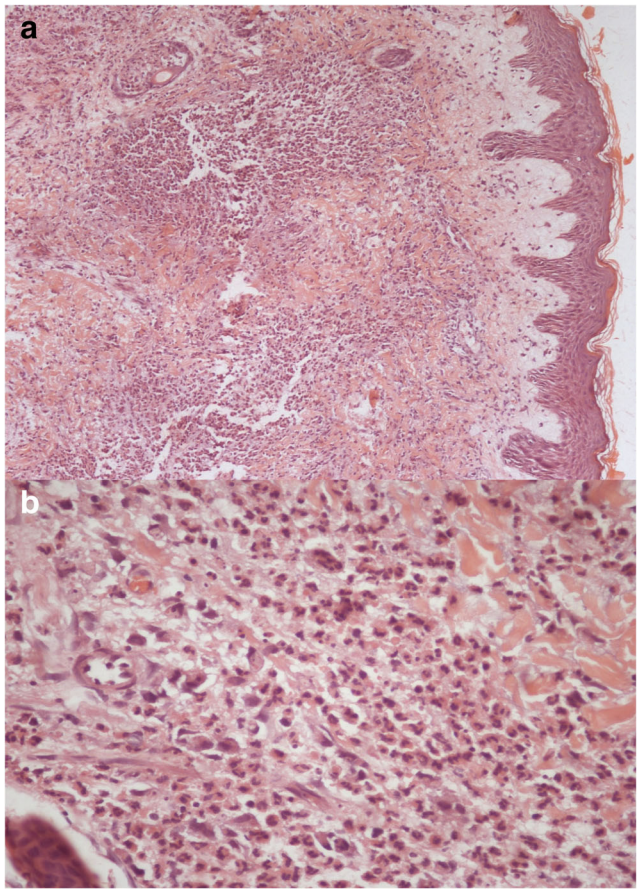
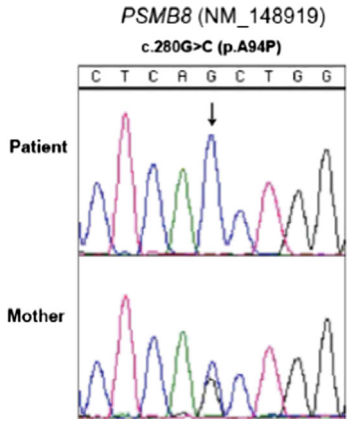


Fig. 2 **a** Skin biopsy reveals papillary dermal edema and a diffuse infiltrate of predominantly neutrophils (hematoxylin and eosin, ×40). **b** Mononuclear myeloid cells intermingled with mature neutrophils and leukocytoclasis. There is no evidence of vasculitis (Hematoxylin-eosin stain, ×400)



Gene	*PSMB8* (NM_148919.3)
Mutation	c.280G>C; p.A94P
Chromosomal	Chr6:32810734G>C
rsID	NA
dbSNP AF	NA
ESP6500 AF	0
ExAC AF	0
GERP score	4.09
Polyphen2	Probably Damaging
PROVEAN	Deleterious
SIFT	Damaging
Mutation Taster	Disease causing

Fig. 3 Genetic findings observed in a Brazilian patient with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. **a** Sanger sequencing electropherograms showing the *PSMB8* (*NM_148919.3*) c.280G>C, p.A94P mutation. The patient is homozygous and his mother is heterozygous for the *PSMB8* variant. **b** Genetic databases and prediction models show that the PSMB8 variant detected in the patient is novel and predicted to be damaging to the protein function. *AF* allele frequency, *ExAC* Exome Aggregation Consortium, which spans 61,486 unrelated individuals and includes the 1000 Genomes Pilot project and NHLBI Exome Sequencing Project (ESP6500)

irritability. However, there was no improvement of the skin tenderness and itching lesions, aside from the progression of the lipodystrophy (Fig. 4). Regarding the laboratory findings, we observed a decrease in WBC (12.660/mm^3) and platelets (445.000/mm^3), and in acute phase reactants: CRP was 0.4 mg/L and ESR 2 mm/1st hour. A slight raise on hemoglobin level was also evidenced (hemoglobin 9.9 g/dL) asides from the normalization of the liver enzymes levels. Considering the patient's lipid profile, we observed the maintenance of hypertriglyceridemia (172 mg/dL) and the development of hypercholesterolemia (total cholesterol 265 mg/dL, LDL cholesterol 226 mg/dL, and HDL cholesterol 28 mg/dL).

Discussion

We reported a rare case of a new proteasome-associated autoinflammatory disease (named CANDLE syndrome) with parental consanguinity and a novel mutation in *PSMB8* gene. Our patient presented with recurrent spiking fever, a variety of skin lesions, chronic anemia, and systemic inflammatory manifestations.

Of note, CANDLE syndrome occurs at early infancy with recurrent fever, skin manifestations, facial lipodystrophy, low weight and height, and protuberant abdomen due to increased intra-abdominal fat and hepatosplenomegaly, as observed herein [5, 12–14]. Our patient did not present joint contractures, especially in knees and hand joints, contrary to other CANDLE syndrome patients [12, 14]. To our knowledge, pericarditis has not previously been described in a CANDLE syndrome patient.

Importantly, we excluded infectious disease, malignancies and humoral and cellular primary immunodeficiencies syndromes, well-known causes of periodic fever in infants [7]. Other inherited autoinflammatory disorders with periodic fever and cutaneous manifestations, such as cryopyrin associated periodic syndromes (CAPS) (OMIM#607115/120100/191900), TNF receptor associated periodic syndrome (TRAPS) (OMIM#142680), familial Mediterranean fever (FMF) (OMIM#249100), and mevalonate kinase deficiency

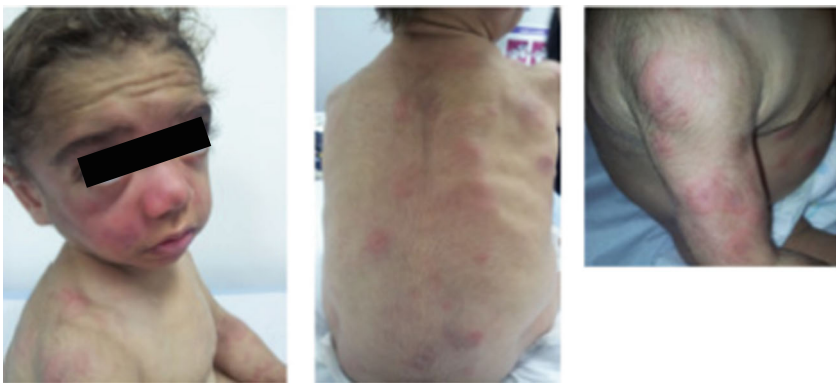


Fig. 4 Clinical manifestations observed in a Brazilian patient with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. Erythematous facial rash, nodules and plaques on the back and upper limbs; and areas of lipodystrophy on face, back and right arm, at the age of 3 years and 1 month

(MKD) (OMIM#260920), should also be considered in the differential diagnosis of CANDLE syndrome [5, 7, 13].

Laboratory abnormalities in CANDLE syndrome include non-specific chronic inflammatory alterations, such as chronic anemia, leukocytosis, thrombocytosis, and increased acute phase reactants. Elevated transaminases and triglycerides may also be found, as observed in the current case [10, 12, 13]. The finding of autosomal recessive mutations in *PSMB8* gene confirms the diagnosis of CANDLE syndrome [8, 9]. The homozygous p.A94P *PSMB8* variant detected in our patient has not been observed in any public genetic databases and is predicted to be pathogenic by several prediction tools (Fig. 3b). Moreover, the p.A92T variant, which is two amino acids earlier than our patient's, has previously been studied and it alters the conformation of the S1 substrate-specificity pocket [2]. An altered maturation of beta5i subunit of the immunoproteasome is also observed in HeLa cells transfected with A92T mutation [6]. Combined, these findings strongly suggest that the A94P variant detected in our patient is directly causing his phenotype.

CANDLE syndrome responds partially to high doses of oral glucorticoid and intravenous methylprednisolone [9]. Colchicine and immunosuppressive agents, such as azathioprine, methotrexate [11] and cyclosporine [5], and intravenous immunoglobulin were not effective in most of the patients [9], as was also evidenced in our patient. TNF-α inhibitors, IL-1 receptor antagonist, and anti IL-6 therapy have been reported with variable response [11]. However at present, a complete response was not observed with any of the medications used and they did not prevent the progression of lipodystrophy [11]. Because patients with CANDLE present with a type I interferon signature, it has been suggested that JAK inhibitors may ameliorate the clinical manifestations in these patients [9]. An ongoing study using a JAK inhibitor seems to improve the clinical manifestations of CANDLE syndrome [10].

In conclusion, a new mutation causing CANDLE syndrome was reported in a patient with pericarditis and mimicking Sweet syndrome. This patient was refractory to immunosuppressive agents. Tocilizumab therapy resulted into the remission of daily fever and irritability.

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Authors' contributions Acquisition of data: Cavalcante, Brunelli, Miranda, Novak, Malle, Aikawa, Jesus, and Silva.

Manuscript preparation: Cavalcante, Brunelli, Miranda, Novak, Malle, Aikawa, Jesus, and Silva.

Compliance with ethical standards This study was approved by the Local Ethics Committee of our University Hospital and a written informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no competing interests.

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