CANDLE Syndrome: A Recently Described Autoinflammatory Syndrome

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Summary: CANDLE syndrome (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) is a recently described autoinflammatory syndrome characterized by early onset, recurrent fever, skin lesions, and multisystemic inflammatory manifestations. Most of the patients have been shown to have mutation in *PSMB8* gene. Herein, we report a 2-year-old patient with young onset recurrent fever, atypical facies, widespread skin lesions, generalized lymphadenopathy, hepatosplenomegaly, joint contractures, hypertrglyceridemia, lipodystrophy, and autoimmune hemolytic anemia. Clinical features together with the skin biopsy findings were consistent with the CANDLE syndrome. The pathogenesis and treatment of this syndrome have not been fully understood. Increased awareness of this recently described syndrome may lead to recognition of new cases and better understanding of its pathogenesis which in turn may help for development of an effective treatment.

Key Words: autoimmune hemolytic anemia, CANDLE syndrome, fever, lipodystrophy

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CANDLE syndrome (chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) is a newly described autoinflammatory syndrome characterized by onset during the first year of life, recurrent febrile episodes, purpuric skin lesions, violaceous swollen eyelids, arthralgia, extremity contractures, delayed physical development, progressive lipodystrophy, anemia, and increased acute phase reactants.[1] As this is a newly described syndrome very few cases with typical clinical features have been reported in the literature. The diagnosis is further confirmed by skin biopsy findings of a characteristic atypical, mixed mononuclear, and neutrophilic infiltrate.[1,2] A genetic etiology possibly inherited in an autosomal recessive pattern was suggested with extended genetic studies. Most of the patients with CANDLE syndrome have been shown to carry mutations in *PSMB8*, a gene recently reported to cause JMP syndrome (joint contractures, muscle atrophy, and panniculitis-induced lipodystrophy) in adults.[2,3] There is no definitive treatment, yet some patients have been reported to benefit from steroids and nonsteroid anti-inflammatory drugs.

Herein, we present a 2-year-old patient who had the diagnosis of CANDLE while he was being investigated for his recurrent fever, widespread skin lesions, autoimmune hemolytic anemia, generalized lymphadenopathy, and hepatosplenomegaly.

CASE REPORT

A 2-year-old male, who was born to nonconsaguious healthy parents, first developed urticarial and papular skin lesions on the whole body when he was 4 months old. He had the diagnosis of cutaneous mastocytosis at that time, with remitting and relapsing erythematouse-purplish skin lesions from time to time. He had an operation for ventricular septal defect at 4 months of age. After 6 months of age, he had been hospitalized many times for recurrent noninfectious febrile episodes. At the age of 2 years, he was first consulted at our hematology clinic for investigation of anemia. On first evaluation, he was febrile, but otherwise appeared in good general health. His height and weight were below the third percentiles. Physical examination revealed a pallor skin with widespread eryhtematous-purplish skin lesions predominantly on the trunk, and also on extremities with 0.5 to 1 cm in size, violaceous swollen eyelids, atypical facies, microcephaly, generalized lymphadenopathy (bilateral cervical >1 cm, axillary >1.5 cm, inguinal >1.5 cm), protuberant abdomen, hepatosplenomegaly (liver and spleen 3 cm below costal margins), contractures in both knees, and lipodystrophy on face and extremities (Figs. 1, 2).

Complete blood analysis revealed normocytic normochromic anemia with hemoglobin of 8 g/dL, reticulocyte count of 4%, white blood cell count of 5.4×10^9/L, and platelet count of 214×10^9/L. Direct antiglobulin test was positive. The erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, and fibrinogen levels were elevated. The bone marrow aspiration examination revealed increased eythropoiesis with no evidence of atypical cells or hemophagocytosis. Other labarotory testing showed mildly increased liver enzyme tests and elevated triglycerides (212 mg/dL). Cytogenetic analysis from peripheral blood resulted in normal karyotype.

Thoracoabdominal computed tomography revealed mediastinal, para-aortic, and periportal multiple lymphadenopathies (the largest ones were ≤1.5 cm) and hepatosplenomegaly. Computed tomography of the brain was normal with no evidence of basal calcification. The ophtalmologic and auditory examinations were normal.

Presence of autoimmune hemolytic anemia with generalized lymphadenopathy and splenomegaly necessitated to consider the diagnosis of autoimmune lymphoproliferative syndrome (ALPS). Double-negative T cells were found to be elevated (6%). Pathologic specimens of excisional axillarly lymph node biopsy for diagnosis of ALPS or ALPS-related syndromes and also a skin biopsy from skin lesions were sent to a specialized pathology center for examination (National Cancer Institute Hematopathology, Bethesda). Axillary lymph node biopsy was resulted as reactive follicular hyperplasia. Tryptase and c-kit demonstrated a few scattered mast cells. CD20 and CD3 demonstrated appropriately situated B-cell and T-cell compartments. The T cells appear to be a mixture of $CD4^+$ and $CD8^+$ cells with no loss of CD4 or CD8,

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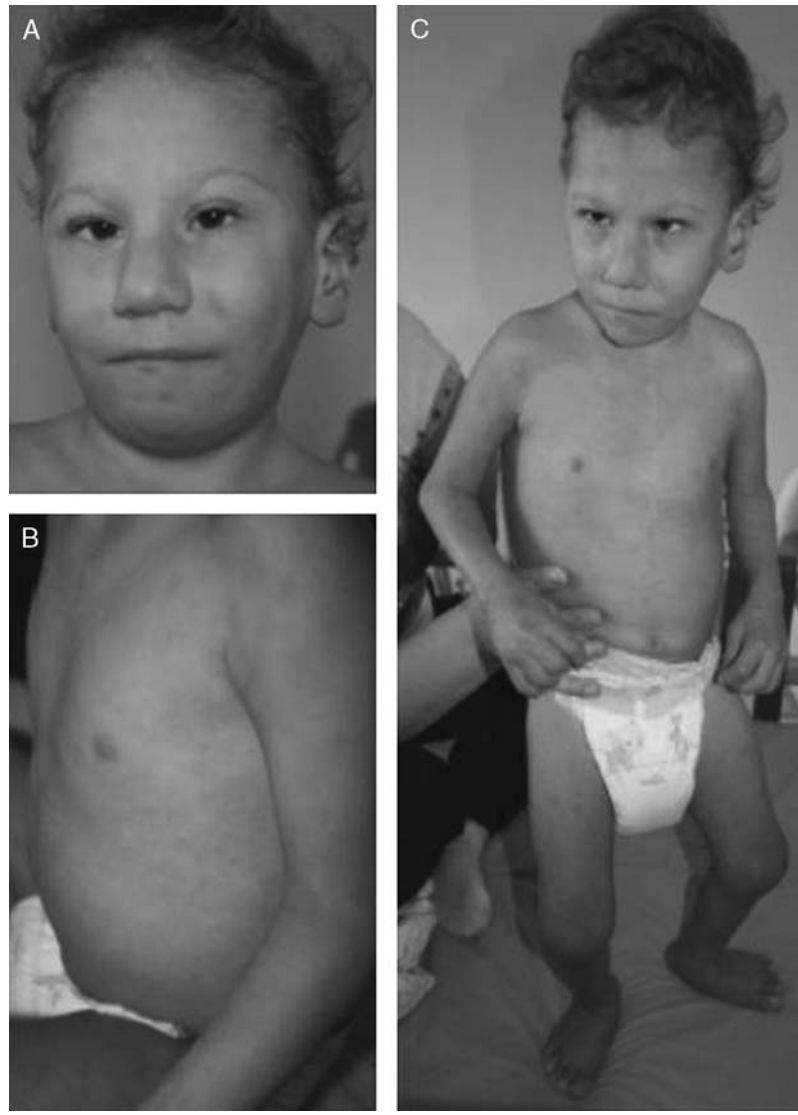

FIGURE 1. Images of the case. Atypical facies, lipodystrophy (A), skin rash (B), and contractures in the knees (C).

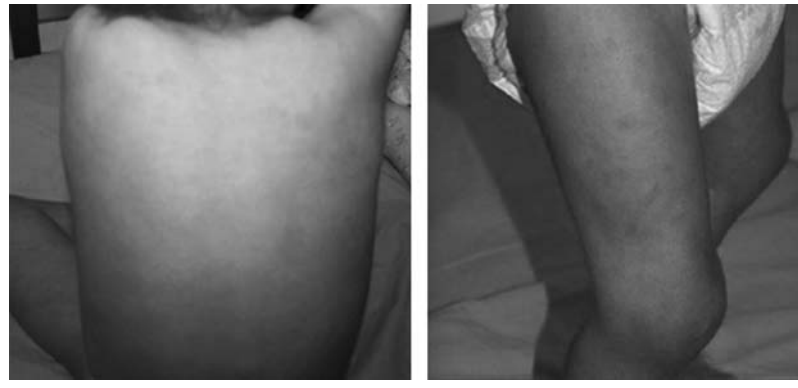

FIGURE 2. The images of the skin rash on trunk and limbs.

and they also appear to be positive for CD45RO. The skin biopsy revealed dermal mononuclear cell infiltrate with prominent apoptotic debris and papillary dermal edema. Mononuclear cells were positive for CD68 and myeloperoxidase. Most of the cells appeared to be negative for CD163 or chloroacetate esterase. CD123 was mostly negative. Tryptase and c-kit highlighted rare mast cells. The differential diagnosis in this case included histiocytoid Sweet syndrome, CANDLE syndrome, Crohn disease, Behçet syndrome, or rheumatoid arthritis according to the skin biopsy examination. Pathologic results together with the clinical and labarotory findings were consistent with the CANDLE syndrome. Genetic analysis for *PSMB8* gene revealed no mutation. Prednisolone with a dose of 1 mg/kg/d per oral and ibuprofen were started. Fever resolved in 24 hours. During the follow-up period, his lymph nodes, hepatosplenomegaly, hypertriglyceridemia, and autoimmune hemolytic anemia features disappeared. Prednisolone dose was tapered during follow-up. He has no complaints for a year.

DISCUSSION

Autoinflammatory conditions are multisystem diseases primarily resulting from perturbations in the adaptive immune system and characterized by recurrent fever episodes and systemic inflammation, which commonly involve the skin and joints. They may also have overlapping autoimmune disease characteristics.[2,4]

The patient presented here carries many of the characteristic features of this newly described autoinflammatory CANDLE syndrome. The CANDLE syndrome was originally described in 4 children having early-onset recurrent fevers, annular violaceous plagues, persistent low weight and height, lipodystrophy, hepatomegaly, and a range of visceral inflammatory manifestations in common.[1] The features of those 4 patients and our patient is shown in Table 1. Besides the clinical characteristics, a skin biopsy showing mononuclear intersititial infiltrate including immature neutrophils in the dermis and positivity for CD68 and MPO has been reported to be pathognomonic for CANDLE syndrome,[1,2] which was also present in our patient.

The occurrence of autoimmune hemolytic anemia together with hepatosplenomegaly and elevated double-negative T cells led us to consider the diagnosis of ALPS in this patient, but the examination of the lymph node biopsy was not consistent with this disease. The characteristic pathologic findings of ALPS include paracortical expansion due to infiltration by polyclonal TCR$\alpha\beta^+$ double-negative T cells accompanied by follicular hyperplasia and polyclonal plasmacytosis.[5] In our patient, the axillary lymph node biopsy was not consistent with ALPS. Moreover recurrent fever, early-onset skin rash, together with other features (elevated acute phase reactants, lipodystrophy, joint contractures) that are seen in our patient are main characteristics of CANDLE syndrome but they are not typical for ALPS.[5] Immune cytopenias including 3 lineages are also commonly seen in ALPS. Our patient did not develop immune neutropenia or thrombocytopenia. Early-onset disease is another important feature of CANDLE syndrome. Our patient developed skin rash at 4 months of age and had recurrent febrile episodes after 6 months of age. In ALPS, the average time for onset of clinical symptoms is reported to be 2 years.[6]

The presence of fever, in contrast, together with generalized lymphadenopathy and hepatosplenomegaly necessitated to exclude the possible underlying malignant diseases like leukemia or lymphoma in this patient. Examination of the bone marrow and lymph node biopsy ruled out these disorders. Taking into consideration the biopsy findings, the differental diagnosis included

TABLE 1. Features of Our Patient and the Other 4 Patients Reported by Torrelo et al[1]

Features	Patient 1*	Patient 2*	Patient 3*	Patient 4*	Our Patient
Early onset	+	+	+	+	+
Fever	+	+	+	+	+
Annular plaques	+	+	+	+	+
Eyelid violaceous swelling	+	+	+		+
Perioral swelling	+	+			
Ear and nose chondritis	+				
Low weight and height	+	+	+	+	+
Lipodystrophy	+	+	+	+	+
Prominent abdomen	+		+		+
Acanthosis nigricans and hirsuitism			+		
Lymphadenopathy	+				+
Hepatomegaly	+		+	+	+
Splenomegaly	+		+		+
Arthralgia/joint contracture	+	+	+		+
Conjunctivitis/nodular episcleritis	+	+			
Epididymitis	+				
Aseptic meningitis	+		+		
Parotitis			+		
Intersititial lung disease			+		
Nephritis			+		
Otitis			+		
Increased erythrocyte sedimentation rate and C-reactive protein	+	+	+	+	+
Anemia†	+	+	+	+	+
Increased platelet count	+			+	
Elevated alanine aminotransferase and aspartate aminotransferase	+	+	+	+	+
Increased triglyceride levels			+	+	+
Basal ganglia calcifications	+		+		

*The first 4 original cases published in the literature by Torrelo et al.[1]
†Generally microcytic, hypochromic. Autoimmune hemolytic anemia was present in patient 3 and in our patient.

histiocytoid Sweet syndrome, which is an acute febrile neutrophilic dermatosis characterized by fever, leukocytosis, and tender, erythematous, well-demarcated papules and plaques.[7] Our patient had persistent, nontender skin rash that was not relevant to the Sweet syndrome. The differential diagnosis of skin biopsy findings also included Crohn disease, Behçet disease, and rheumatoid arthritis but the clinical features of these diseases were not present in our patient.

After the original report of the CANDLE syndrome, a syndrome called JMP, diagnosed in 3 adult patients with joint contactures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy.[3] Those adult patients were shown to have mutation in the *PSMB8* gene. Later Liu et al,[2] screened 8 children diagnosed with CANDLE syndrome for mutation in the *PSMB8* gene and detected heterozygous or homozygous mutation in 7 of those children. They did not detect PSMB8 mutation in one of the patients, and suggested that there may be heterogeinity and also other genetic causes underlying CANDLE sydrome. Similarly in our patient, genetic analysis for *PSMB8* gene revealed no mutation, suggesting another possible genetic cause for this syndrome. Liu et al[2] also performed additional tests to those 8 patients, including serum cytokine levels, blood microarray profile and stat-1 phosphorylation, and concluded that interferon may be a key mediator of the inflammatory response and may present a therapeutic target.

In this report, we presented a patient with the newly described CANDLE syndrome. As this syndrome has fever, anemia, lymphadenopathy, and hepatosplenomegaly as presenting features, it must be included in the differential diagnosis of many hematological malignant or nonmalignant disorders. Almost all of the patients share the common clinical characteristics of early-onset disease with recurrent fever, violaceous skin rash, lipodystrophy, and persistent low weight and height. These features combined with other systemic features and typical histopathologic changes make the diagnosis and the genetic testing further confirms the diagnosis. The definition of new cases with this recently described CANDLE syndrome would allow better characterization of the disease leading to more definitive treatment modalities.

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