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A case of proteasome-associated auto-inflammatory syndrome with compound heterozygous mutations in *PSMB8*

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To the editor

Proteasome-associated auto-inflammatory syndrome (PRAAS) is caused by autosomal recessive mutations in the proteasome subunit β type 8 (*PSMB8*) gene. It includes Nakajo-Nishimura Syndrome (NNS),[1] Japanese Autoinflammatory Syndrome with Lipodystrophy (JASL),[2] Joint Contractures, Muscle Atrophy, Microcytic Anemia, and Panniculitis-Induced Lipodystrophy Syndrome (JMP)[3] and Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE).[4] Affected patients present with periodic fevers, rash, lipodystrophy, myositis, hyper-γ-globulinemia and autoantibodies at times.

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The case discussed was previously presented at the Arkansas Dermatology State Meeting in April 2012, the American Society of Dermatopathology in October 2012, and the American College of Physicians Internal Medicine Poster Competition at UAMS in October 2012.

We report a Hispanic male with a longstanding history of recurrent fevers and associated rash that has presented a diagnostic challenge over the past 19 years. During his infancy, extensive evaluations including multiple skin biopsies, a bone marrow biopsy and laboratory testing were inconclusive. The patient was lost to follow up since 2003. On physical examination in 2012, in addition to erythematous papules/nodules primarily on his upper and lower extremities, he was both physically and developmentally delayed and he had lipodystrophy on his face and upper body (Figure 1). Skin biopsies again revealed a dermal CD68 positive mononuclear infiltrate centering around unaltered adnexal structures. Subcutaneous lobules were atrophic with shrunken adipocytes. The epidermis was not involved and no vascular occlusion or leukocytoclasis was seen. Abnormal laboratory findings included elevated aldolase, CK, IL-6, IgG, IgM, IgE and Interferon-γ-inducible protein 10 (IP-10). Elevated ANA, ANCA, RF, CRP, TSH, ALT, and ALK were also noted. CT of the brain indicated basal ganglia calcification. An MRI of the upper thighs revealed patchy myositis. Based on the clinical presentations and laboratory findings, PRAAS was entertained. Direct DNA sequencing of *PSMB8* was performed at the National Institutes of Health, and the patient was found to be heterozygous for the known founder mutation p.T75M and a novel missense mutation p.A92T. Since his mother only carries the p.T75M mutation and his father died several years ago, it is unclear if the p.A92T mutation was inherited from his father or if it occurred de novo. Therefore the diagnosis of PRAAS is further confirmed by genetic testing.

Proteasomes are intracellular protease complexes that degrade polyubiquitinated proteins[5] and they are involved in cell cycle regulation, gene repair, NF-κB and IFN pathway activation.[4] Decreased proteasome activities caused by *PSMB8* mutations evoke an inflammatory response that involves activation of mitogen-activated protein kinase, upregulation of the interferon pathway and subsequent elevation of IL-6,IP -10 and/or IFN.[1] However, IL-1β and TNFα levels are normal. The table summarizes clinical symptoms, inflammatory disease manifestations and manifestations of organ damage that occurs with ongoing and longstanding inflammation.

Lack of effective treatment modalities contributes to a poor prognosis. Fever, skin lesions, and acute-phase reactant are responsive to oral glucocorticosteroids, but no therapy successfully halts the progression of the lipodystrophy and wasting. Inhibitors of IL-1, TNFα, and IL-6, show no or only temporary clinical improvement.[4] The immunoproteasome inhibitor bortezomib induces histiocytoid Sweet syndrome.[1] Since a JAK inhibitor tofactinib reduces upregulated STAT-1 phosphorylation in CANDLE patients, a compassionate study using the JAK 1/2 inhibitor baricitinib (Eli Lilly) is currently ongoing at the NIH (NCT01724580) and our patient is enrolled in the study.

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Acronyms and Abbreviations

CANDLE	Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature
IP-10	Interferon-γ- inducible protein 10
IFN	Interferon
JASL	Japanese autoinflammatory syndrome with lipodystrophy
JMP	Joint Contractures, Muscle Atrophy, Microcytic Anemia, and Panniculitis-Induced Lipodystrophy Syndrome
MAPK	mitogen-activated protein kinase
NF-κB	nuclear factor-κB
NNS	Nakajo-Nishimura Syndrome
PSMB8	human proteasome subunit β type 8 gene
PRAAS	proteasome-associated auto-inflammatory syndrome

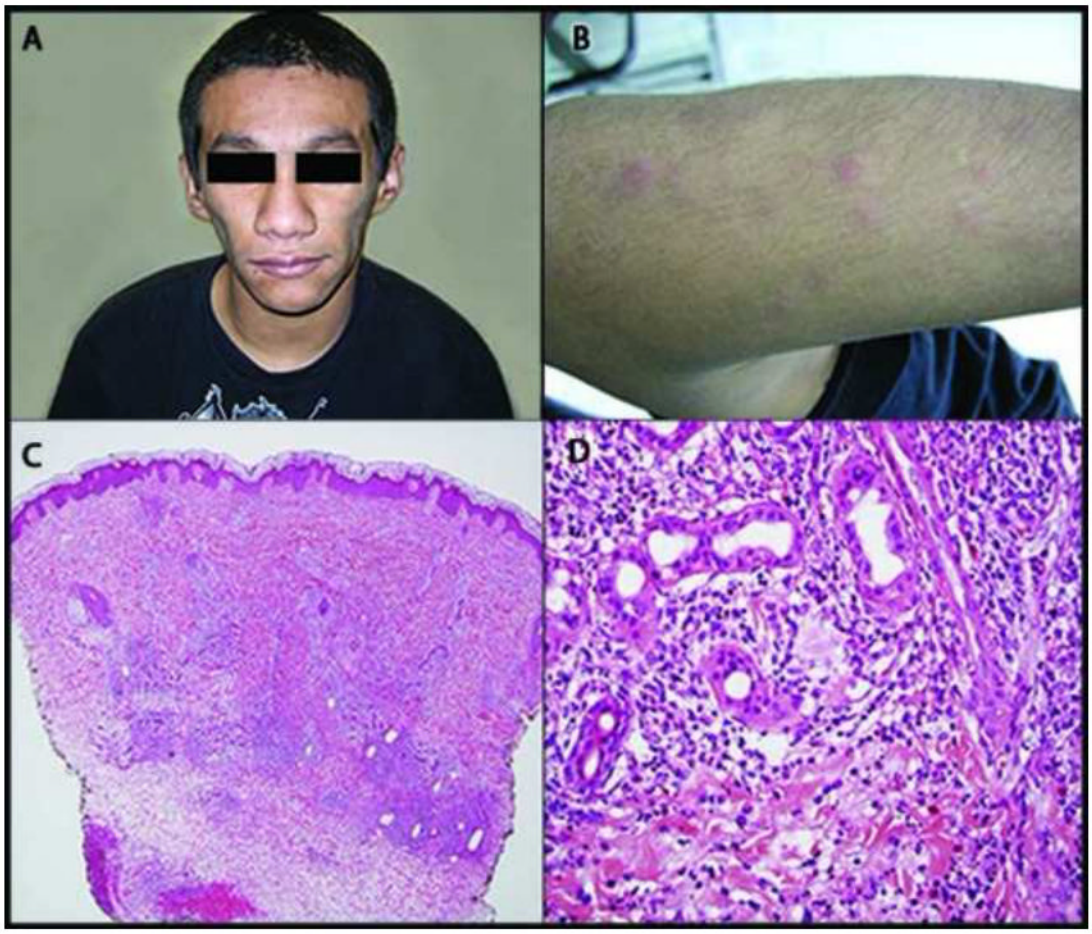

Figure 1.
Proteasome-associated auto-inflammatory syndrome. Clinical photograph demonstrates facial lipoatrophy (A). The patient displayed periodic presence of erythematous papules on extensor surfaces (B). Hematoxylin and eosin stain. Lower magnification demonstrates a perivascular, peri-eccrine, and interstitial mixed infiltrate most prominent in the mid to deep reticular dermis (C). On higher magnification, the infiltrate can be seen to be composed predominately of histiocytes and neutrophils, with admixed lymphocytes and eosinophils (D).

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Table

Summary of Clinical Presentations and Laboratory Findings of PRAAS

	Our patient	CANDLE syndrome (n = 9)	NNS (n = 7)	JASL (n = 3)	JMP (n = 3)
Clinical presentations					
Age of onset	3m	Early infancy	Infancy	1M or 3 Y	N/A
Recurrent fever	Yes	Yes	Yes	Yes	No
Arthritis	Yes	Yes	Yes	Yes	Yes
Skin eruptions	Erythematous nodules	Annular plaques Violacious eyelid	Heliotrope-like periorbital rash in 4/7 patients Nodular erythema in all 7 patiens	Nodular erythema	Erythematous maculopapular and nodules
Low weight and height	Yes	7/9	1/7	ND	
Low IQ	Yes	ND	1/7	1/3	Yes
Seizures	No	ND	ND	ND	Yes
Macroglossia	No	ND	ND	Yes	Yes
Anemia	Yes	8/9	6/7	ND	ND
WBC	Low nl range	Mild leukocytosis at early age and leukopenia later	ND	ND	ND
Inflammatory disease and autoimmunity					
Autoantibodies	↑↑ANA & ANCA	c-ANCA and ANA in 3/9 (two converted to normal)	ANCA, dsDNA and SS-A in 5/7	Undetectable	nl
Elevated ESR/CRP	Yes	Yes	Yes	Yes	Yes
Elevated CPK	Yes	ND	4/7	Normal	ND
Cytokine levels	↑↑ IL-6, nl TNFα, IL-1β, IP-10↑	↑ IL-6 and IP-10 in 3/9	↑↑ IL-6& IP-10, nl IFNγ.	↑ IL-6	↑ IFNγ, ↑ IL-6, ↑ IL-8
Hyper-γ-globulinemia	↑↑ IgE & G; nl IgA &D	Normal	7/7	↑↑ IgA & G 3/3	ND
Organs involved					
Lipodystrophy	Yes	Yes	Yes	Yes	Yes
Hepatomegaly	Yes	7/9	6/7	Yes	Yes
Splenomegaly	Yes	3/9			
Cardiac disease	No	ND	ND	2/3	ND
Hypertension	No	2/9	ND	No	ND

	Our patient	CANDLE syndrome (n = 9)	NNS (n = 7)	JASL (n = 3)	JMP (n = 3)
Myositis/muscle atrophy	Yes	Yes	Yes	Yes	Yes
Elevated LFTs	Yes	8/9	ND	ND	Yes
Dyslipidemia	No	6/9	4/7	No	Yes
Elevated TSH	Yes	2/9	ND	ND	ND
Basal ganglia calcification	Yes	2/6	6/7	2/3	3/3

Nl, normal; ND, not described