NEMO-NDAS: A Panniculitis in the Young Representing an Autoinflammatory Disorder in Disguise

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Abstract: A 15-month-old full-term boy of African descent with an asymptomatic sickle cell trait presented with episodes of transient erythematous subcutaneous nodules involving the entire body except the face, since 2 weeks of age. The skin lesions evolved to areas of lipoatrophy and hyperpigmentation. An initial skin biopsy, studied at a different department at 2 months, was initially misinterpreted as subcutaneous fat necrosis of the newborn, despite the lack of the typical radiated crystals and needle-shaped clefts characterizing that entity. At 4 months of age, he developed systemic inflammatory manifestations, including fever, a new rash, significant periorbital edema, and failure to thrive. An extensive workup showed leukocytosis, hypercalcemia, elevated inflammatory markers, hypertriglyceridemia, and transaminitis. A new skin biopsy of the eyelid was diagnosed as neutrophilic lobular panniculitis with necrotic adipocytes. An initial whole-exome sequencing did not identify any causative mutations, but a WES reanalysis focused on autoinflammatory disorders was requested based on additional clinicopathologic data and revealed a mosaic intronic mutation in *IKBKG* c. 671+3 G > C. This mutation encodes an mRNA missing exon 5 resulting in NF-kB essential modulator (NEMO) Δ-exon 5–autoinflammatory syndrome (NDAS). NEMO-NDAS is one of the systemic autoinflammatory diseases that may appear as an unexplained panniculitis in young children, who should be monitored for immunodeficiency and/or autoinflammatory diseases. The differential diagnosis of autoinflammatory disorders should be considered in such cases incorporating the use of the whole-genome/exome sequencing in the investigation. The inhibitor of kappa-B kinase regulatory subunit gamma (*IKBKG*) is located on chromosome Xq28 and encodes the NEMO, a critical molecule upstream of NF-kB activation.

Key Words: fat necrosis of the newborn, autoinflammatory diseases, SAIDs, NEMO

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INTRODUCTION

Systemic autoinflammatory diseases (SAIDs) are a heterogeneous group of disorders caused by dysregulation of the innate immune system resulting in severe systemic inflammation.[1] The use of the whole-genome/exome sequencing in the investigation of patients with suspected SAIDs has identified numerous genetic alterations. There are numerous monogenic disorders classified as autoinflammatory disorders by the latest report of the International Union of Immunological Societies.[2]

Pediatric neutrophilic panniculitis with lipodystrophy can be the initial presentation of SAIDs. The histologic diagnosis in this type of lesion is challenging, and this group of disorders is frequently misdiagnosed, sometimes with fatal consequences. In addition, the correct clinical and histologic characterization of the lesion is an important step to guide genetic and molecular studies.

In this article, we present the skin biopsy findings in a case of NEMO-deleted exon 5–autoinflammatory syndrome (NEMO-NDAS). NEMO is a regulatory subunit of the IKK multimeric complex, which acts as a negative regulator of NF-kB.[3] Only a few cases of NEMO-NDAS have been described, and the skin histological findings are not well characterized.

CASE PRESENTATION

A full-term boy of African descent with an asymptomatic sickle cell trait presented with episodes of transient erythematous subcutaneous nodules involving the entire body with episodes of periorbital inflammation and involvement of his head and scalp, since 2 weeks of age. The skin lesions evolved to areas of lipoatrophy and hyperpigmentation.

An initial skin biopsy from the left upper back taken at 2 months of age showed an extensive mixed inflammatory infiltrate in the deep dermis and subcutaneous fat, associated with prominent fat necrosis, lipophages, and focal calcification. The inflammation featured mainly histiocytes, giant cells, neutrophils, and lymphocytes, with rare eosinophils and plasma cells. These findings were interpreted (the initial biopsy was examined at a different department) as compatible with long-standing subcutaneous fat necrosis of the newborn.

At 4 months of age, the patient developed fever, a new rash, significant periorbital edema, and failure to thrive. An extensive blood workup was remarkable for leukocytosis, hypercalcemia, elevated inflammatory markers (CRP and ESR), hypertriglyceridemia, and

elevated liver enzymes. Abdominal ultrasound showed mild splenomegaly concerning infection. Antibiotic treatment was initiated, but cultures remained negative. A bone marrow biopsy revealed a normocellular marrow with maturing trilineage hematopoiesis, and the neutrophil oxidative burst activity measured by peripheral blood determined by flow cytometry was normal.

A new skin biopsy (performed at the UPMC Children's Hospital of Pittsburgh) of the eyelid lesion revealed heavy, mixed, predominantly neutrophilic inflammation of subcutaneous adipose tissue, with mild dermal perivascular and interstitial infiltrate, and it was diagnosed as neutrophilic lobular panniculitis with necrotic adipocytes (Figs. 1 and 2). An immunohistochemical stain for the complement membrane attack complex (C5b-9) was positive in the endothelium. The patient also showed similar extensive and predominantly neutrophilic inflammation in the liver and lymph node (data not shown). These histological findings were interpreted as evidence of a systemic inflammatory process, which includes autoinflammatory syndromes.

A whole-exome sequencing (WES) analysis did not identify any causative mutation. To the high clinical suspicion and the biopsy results supporting an autoinflammatory syndrome, a targeted reanalysis of the WES was performed, revealing a mosaic intronic mutation in IKBKG, which results in a mRNA missing exon 5, leading to a NEMO-deleted 5–autoinflammatory syndrome (NEMO-NDAS).

Baricitinib was started at 6 months, along a course of steroids. A few days later, the patient was admitted to the hospital with a fever and an increase in the abdominal cutaneous rash. Subsequently, high-dose adalimumab was initiated with a cessation of fever, substantial improvement of rash, and ability to wean steroids. On the last follow-up visit, at 15 months, he had some improvement in fevers, rashes, and inflammatory makers, but the patient has never been able to taper off steroids (tapering has precipitated fever/rash), and the liver enzymes have remained elevated.

DISCUSSION

This is a challenging and unique case presenting neutrophilic dermatitis, extensive panniculitis, and fat necrosis. An initial interpretation, rendered outside of the UPMC Children's Hospital of Pittsburgh, was "fat necrosis of the newborn," despite the absence of the characteristic radiated crystals or needle-shaped clefts seen in that entity.[4] However, the disease progressed with systemic inflammatory manifestations, including fever, increasing body rash, periorbital edema, failure to thrive, leukocytosis, hypercalcemia, hypertriglyceridemia, elevated inflammatory markers and liver enzymes.

An initial WES did not identify any causative mutations in our patient. The presence of neutrophilic panniculitis with fat necrosis, associated with a similar type of inflammation in the lymph node and liver, was the clue to request the targeted WES reanalysis focusing on the autoinflammatory disorders. This revealed a mosaic intronic mutation in IKBKG c. 671+3 G > C. This mutation encodes mRNA lacking exon 5 of NEMO, leading to NEMO-deleted 5–autoinflammatory

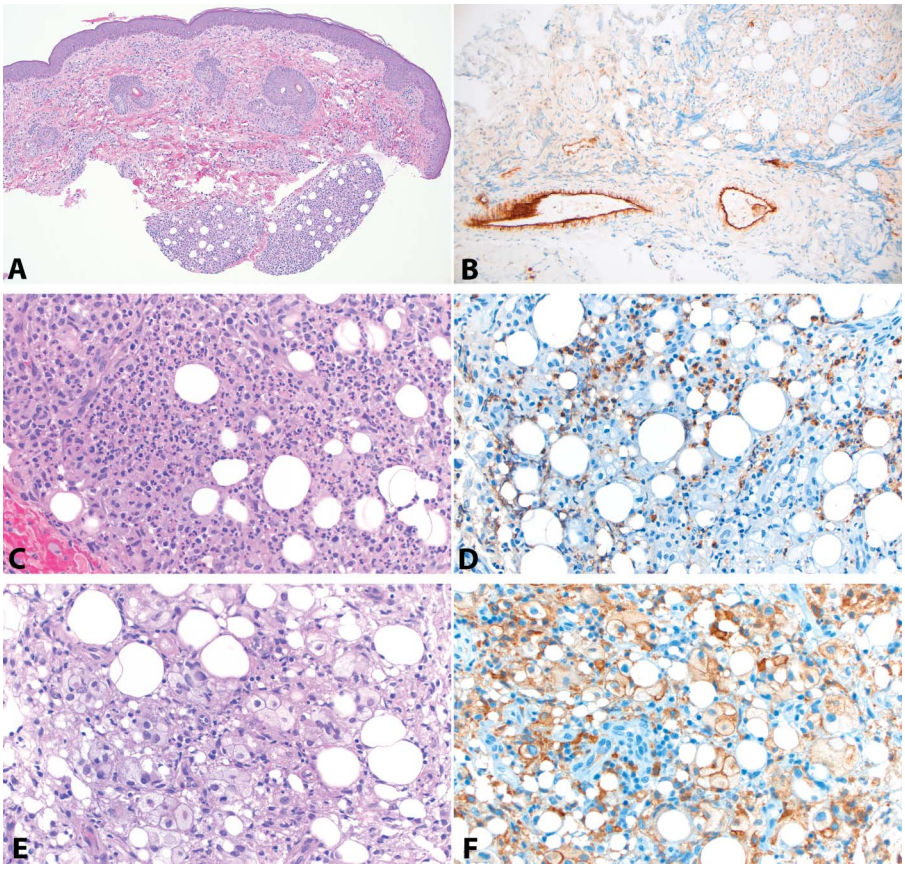

FIGURE 1. A, C, and E show the inflammatory areas at different levels and magnifications with H&E staining. B, D, and F show the immunohistochemical features studied. A, Low magnification of a lesional area showing an intense inflammatory infiltrate involving predominantly the subcutaneous adipose tissue in a pattern of lobular panniculitis (H&E; original magnification = ×100). C, Marked neutrophilic panniculitis (H&E; original magnification = ×400). E, Clusters of foamy macrophages between spared adipocytes (H&E; original magnification = ×400). B, Immunohistochemistry for C5b-9 with intense deposition in vascular endothelium (C5b-9 immunostain; original magnification = ×200). D, Immunohistochemistry for myeloperoxidase highlighting the numerous neutrophils in the inflammatory infiltrate (MPO immunostain; original magnification = ×400). F, Immunohistochemistry for CD163 showing the abundant macrophages infiltrating the adipose tissue (CD163 immunostain; original magnification = ×400).

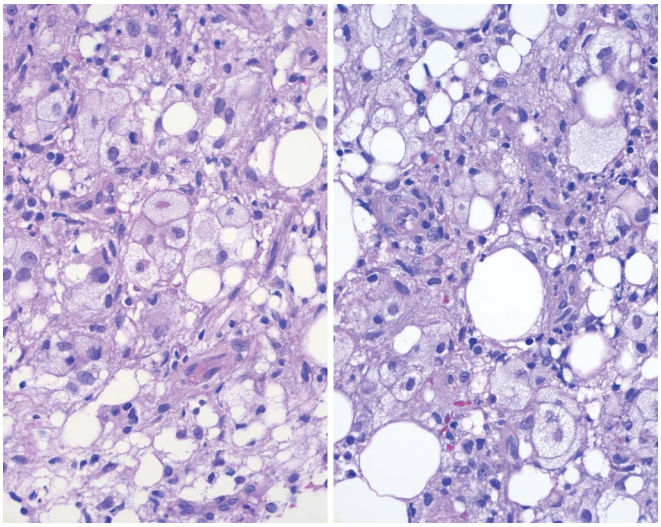

FIGURE 2. Two fields photographed at a high magnification showing macrophages with finely foamy cytoplasm forming clusters that surround occasionally preserved adipocytes in the subcutaneous adipose tissue. Note the lack of the typical crystals and needle-shaped clefts typically seen in fat necrosis of the newborn. This image should trigger a specific workup for autoinflammatory diseases (both photomicrographs show H&E staining; original magnification = ×600).

syndrome (NDAS). The genetic diagnosis of NEMO-associated diseases can be missed, especially with the presence of an IKBKG pseudogene (IKBKGP1). However, de Jesus et al[5] developed a screening bioinformatic tool to improve the sensitivity of discovering these splice site variants easily.

The IKBKG is located on chromosome Xq28 and encodes the NEMO which is known as NEMO.[6] NEMO functions as a negative regulator of the NF-kB pathway and a recruiter of catalytic subunits of the IKK complex.[7] NEMO mutations result in variable immune dysregulatory phenotypes. NEMO deletions and loss of function mutations are associated with immunodeficiency,[8] and mutations that cause NF-kB activation lead to a clinical spectrum of autoinflammatory states resembling Behçet disease.[9]

Our patient's mosaic mutation results in an alternative mRNA splicing and increased protein expression of NEMO lacking the domain encoded by exon 5, which can be seen in girls, although it is an X-linked disease. This mutation was described recently as NEMO-NDAS, which mimics chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE).[10] In another study, de Jesus et al reported 4 patients who have novel splice variants in IKBKG/NEMO with loss of exon 5. In contrast to patients harboring NEMO null mutation (loss of exons 4 to 10 of IKBKG gene) who demonstrate immunodeficiency, patients with NEMO spliced mutation (loss of exon 5 alone) exhibit systemic inflammation panniculitis and elevated interferon (IFN)-response gene score IRG-S.[11] Interestingly, deletion of NEMO exon 5 stabilizes the TBK1/IKKi complex and facilitates NF-κB activation. This explains the association between type I IFN–associated "autoinflammatory" manifestations and the related NF-κB nuclear translocation in NEMO-NDAS.[12]

CONCLUSIONS

A histological pattern of unexplained panniculitis with necrosis of adipose tissue in young infants does not necessarily indicate "fat necrosis of the newborn," especially if the clinical and laboratory manifestations are not characteristic of this condition. Neutrophilic panniculitis representing NEMO-NDAS may superficially mimic fat necrosis of the newborn. However, it is of the utmost importance to carry on a more in-depth histologic analysis, evaluation of the laboratory parameters, and detailed genetic testing, which may uncover other entities, such as autoinflammatory disorders, which should be incorporated into the differential diagnosis.[4,13]

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