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Infantile Onset Panniculitis With Uveitis And Systemic Granulomatosis: A New Clinicopathologic entity

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Abstract

We report four children with infantile onset lobular panniculitis, high fever, uveitis, and systemic granulomatous inflammation, recruited through the International Registry of Pediatric Granulomatous Arthritis (PGA)-. Neither *CARD15* nor *CIAS1* mutations were found. Despite immunosuppressive therapy, disease course was progressive. Response to anti-tumor necrosis factor (TNF) monoclonal antibody in 3 patients is of note.

Keywords

Panniculitis; Systemic Granulomatosis; Uveitis

Non-caseating epitheloid cell granulomas are likely the result of an exaggerated immune-inflammatory response against an unidentified antigen. They can be demonstrated in different chronic inflammatory conditions of which the classic example is sarcoidosis, and are distinguishable from infectious and foreign-body granulomas both histopathologically and biologically (1). In children, granulomatous inflammation is seen in immune deficiencies such as chronic granulomatous disease, systemic vasculitides, and inflammatory disorders such as Crohn disease.

The triad of granulomatous dermatitis, synovitis, and uveitis is characteristic of pediatric granulomatous arthritis (PGA) encompassing Blau syndrome--the familial form and early-onset sarcoidosis; the sporadic form; and that strongly associated with mutations in or near the NACHT domain of *CARD15* (2). The International Registry and DNA Repository of PGA have been established recently. By using non-restrictive inclusion criteria, the Registry aims to advance insight into the wide spectrum of pediatric granulomatous diseases both with and without the typical PGA triad (2).

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We report four children recruited through the registry who presented with infantile onset of widespread lobular panniculitis, panuveitis, arthropathy, and severe systemic illness. In all patients, granulomatous inflammation was demonstrated in involved organs and tissues.

Methods and Results

Four infants came to medical attention with prolonged high fever, systemic illness, and histologically documented lobular panniculitis. All patients had anemia and hepatosplenomegaly. With time, uveitis and arthritis became manifest, and granulomatous inflammation was demonstrated in a variety of organs and tissues (Table). Patient 4 showed hypercalcemia and hypercalciuria. For patient 1, disease course was progressive despite cortico-steroid and cyclosporine treatment, with pulmonary involvement and death from respiratory insufficiency at age 14. In patients 2, 3, and 4, treatment with anti-TNF monoclonal antibody allowed better disease control.

Histopathologically, all had numerous infiltrating histiocytes with lymphocytes and neutrophils in the subdermal fat, constituting a non-vasculitic, non-lipophagic, non-cytophagic lobular panniculitis. Patient 3 had diffuse histiocytic lobular panniculitis (Figure 1 A, B) and typical granuloma on followup biopsy documenting the evolving character of the process (Figure 1 C, D). Multiple granulomas composed of epitheloid cells, lymphocytes, and multinucleated giant cells were present in the liver (patient 1), synovium (patient 2), salivary gland, lymph node, colon (patient 3), dermis, and lung (patient 4). Immunohistochemical analysis showed histiocytes within a nodule and lymph node (patient 3) to be strongly positive for CD68, and negative for S100. Acid-fast and fungal stains were negative, as were cultures for bacteria, mycobacteria, and fungi.

Extensive investigations ruled out infections, pancreatic disease, α1-antitrypsin deficiency, autoimmune disease, complement deficiency, hemophagocytosis or neutrophil oxidase deficiency. At presentation, immunoglobulin levels and lymphocyte counts were normal in all patients. Patient 1 developed hypogammaglobulinaemia and lymphopenia at the age of 3 years possibly related to cortico-steroid treatment from a very young age (3). *CARD15* and *CIAS-1* gene analyses revealed no disease-associated mutations.

Discussion

These four infants have what appears to be a previously unrecognized syndrome consisting of febrile lobular panniculitis associated with arthritis, uveitis, and widespread granulomatous inflammation. Our patients showed a severe phenotype including significant visual impairment in 2 cases and widespread granulomatous inflammation with fatal outcome in one patient. The disease is not associated with a mutation in *CARD15*.

Panniculitis was chronic, recurrent, lobular, lymphohistiocytic, non-lipophagic, non-cytophagic, non-vasculitic, and in one instance with documented evolution to granuloma formation. Epitheloid giant cell granulomas were documented in subcutaneous fat tissue, dermis, synovium, salivary gland, lymph node, liver, colon, and lung parenchyma confirming the systemic nature of this disease. Hypercalcemia and hypercalciuria (as seen in patient 4) is a well-known feature of granulomatous disorders reportedly due to endogenous overproduction of 1,25-dihydroxy vitamin D3 by activated macrophages (4).

Panniculitis in children is uncommon and is a cardinal feature of a wide range of disorders from the relatively common erythema nodosum, to rare entities such as idiopathic relapsing febrile lobular panniculitis (historically known as Weber Christian disease) and fatal cytophagic histiocytic panniculitis (5). Histologically, panniculitis lesions can be predominantly septal (e.g. erythema nodosum) or lobular depending on the location of the

infiltrate (6). All our patients showed lobular histiocytic panniculitis and none showed vasculitis as with the lobular panniculitis of polyarteritis nodosa (5). Granulomas can be seen in septal panniculitides associated with tuberculosis, fungal infections, and Crohn disease but are rare in lobular panniculitides (5). In patient 4, histiocytic panniculitis exhibited granuloma formation at a later stage, underscoring the dynamic nature of the process as reported (6,7).

The very young age at onset of panniculitis in our patients, and the association with systemic features might raise suspicion of a cytophagic histiocytic syndrome within the spectrum of hemophagocytic disorders (5). However, a hemophagocytic syndrome was excluded by the absence of cytophagia and S100 staining in the subcutaneous tissue and absence of hemophagocytosis in bone marrow, liver, and lymph nodes. Although granulomas rarely can be observed in association with a hemophagocytic syndrome (8), widespread granuloma formation is not a characteristic feature of these disorders (9).

The similarity of this phenotype with pediatric granulomatous arthritis (PGA), a disease strongly associated with *CARD15* mutations and characterized by granulomatous uveitis and arthritis (2) is intriguing. Although the function of CARD15 is not yet completely understood, an uncontrolled pro-inflammatory state and/or an apoptosis defect may be involved in granuloma formation (10). One could postulate a defect in related proteins involved in pathways of inflammation and/or apoptosis to be involved in the present disorder. Although one of our patients had documented granulomas in the synovium (patient 2), the clinical presentation in all 4 cases differed from classic PGA by prominent panniculitis, early diffuse systemic involvement, and absence of mutation in *CARD15*.

Anti-TNF monoclonal antibody therapy has been used successfully in granulomatous inflammatory diseases including Crohn's and adult sarcoidosis (11). In our experience, the administration of anti-TNF agents allowed better disease control with tapering of systemic cortico-steroids. Failure to control uveitis, as reported elsewhere is of note (12).

Our report on four infants with lobular panniculitis, fever, and widespread granulomatous inflammation, underscores the complexity of the entities associated with panniculitis. We propose "Infantile Onset Panniculitis with Systemic Granulomatosis" as a new clinicopathologic entity and part of the spectrum of pediatric granulomatous inflammatory diseases.

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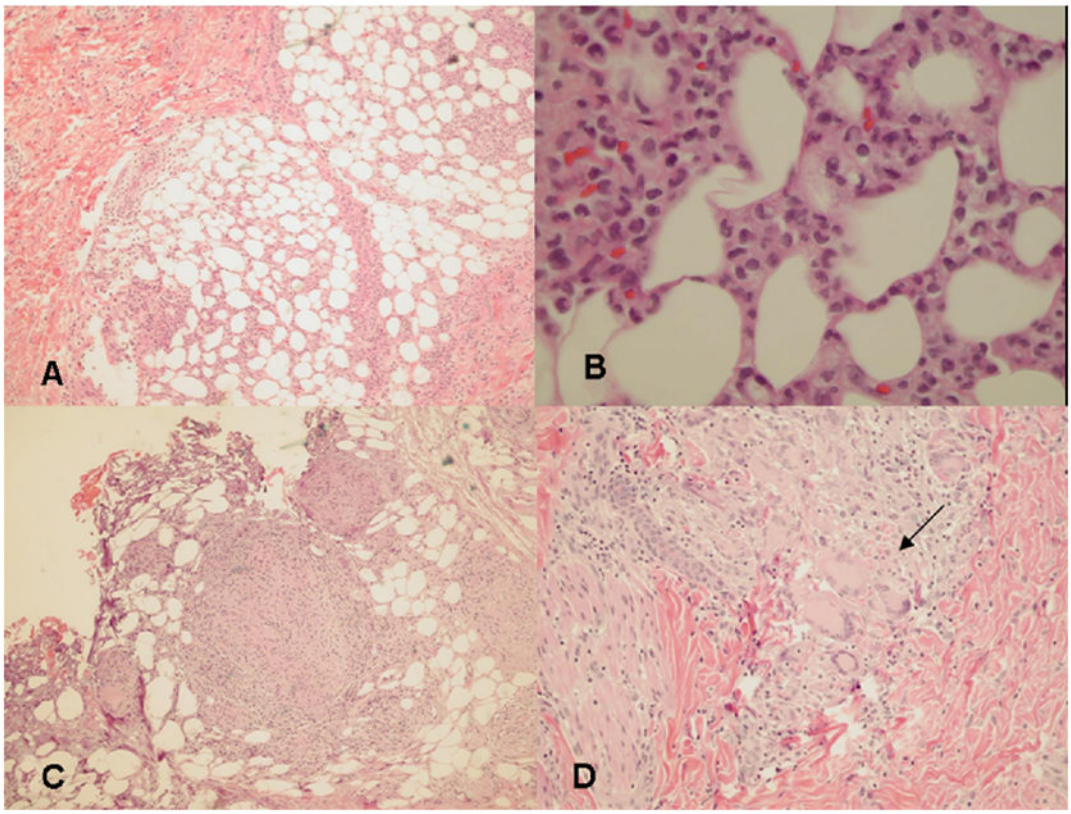

Figure.

A and B: Histopathologic features of histiocytic lobular panniculitis. A. Low-power view: a mostly lobular panniculitis. B. Higher magnification: dense infiltration with lymphocytes and histiocytes.

C and D: Later stage panniculitis lesion (patient 3). C. Low-power view: granulomas within the fat lobule. D. Higher magnification: numerous lymphocytes, epitheloid cells, and multinucleated giant cells (arrow) in a granuloma extending into the dermis. (A, B, C and D, Hematoxylin-eosin stain; magnifications A, C × 20, B × 60, D × 40).

Table

Clinical, laboratory and pathologic manifestations, and CARD15 analysis in 4 patients

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Age at onset	6 weeks	12 months	1 week	4 months
Painful panniculitis	+	+	+	+
Fever	+	+	+	+
Hepatosplenomegaly	+	+	+	+
Anemia, Thrombocytopenia	+ +	+ –	+ +	+ –
Serum Level of angiotension converting enzyme (ACE)	Normal	Increased	Normal	Increased
Uveitis	Panuveitis, retinal detachment	Panuveitis	Anterior uveitis, optic nerve edema	Anterior uveitis
Arthritis	Oligoarticular	Polyarticular + tenosynovitis	Oligoarticular	Polyarticular + tenosynovitis
Lipoatrophy	+	–	–	–
Epitheloid cell granulomata	Liver	Dermis, synovium	Lymph node, salivary gland, colonic submucosa, subcutaneous fat	Dermis, lung
CARD15 mutation	No	No	No	No
Treatment	Cortico-steroids, cyclosporine, IGIV	Cortico-steroids, MTX, TNF-antagonists	Cortico-steroids, IGIV, TNF-antagonists	Cortico-steroids, colchicine, cyclosporine, soluble TNF receptor, thalidomide
Course	Respiratory failure and death	Response to anti-TNF MoAb	Moderate response to anti-TNF MoAb	Response to anti-TNF MoAb