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CASE REPORTS

Exacerbation of Skin Lesions During Fever in a Patient With Chronic Infantile Neurologic Cutaneous Articular Syndrome

S. Aboín-González,[a] I. Aldanondo-Fernández de la Mora,[a] C.R. García-Acebes,[a] R. Carrillo-Gijón,[b] A. Harto-Castaño,[a] and P. Jaén-Olasolo[a]

[a]Servicio de Dermatología and [b]Servicio de Anatomía Patológica, Hospital Ramón y Cajal, Universidad de Alcalá de Henares, Madrid, Spain

Abstract. Chronic infantile neurologic cutaneous articular (CINCA) syndrome is a serious chronic systemic inflammatory disease that presents at a young age and that is characterized by skin, joint, and central nervous system disease. Skin symptoms are the first to appear, in the form of a longstanding nonpruritic urticarial rash, with exacerbations coinciding with episodes of fever, arthritis, and enlarged lymph nodes. The findings of biopsy of skin lesions are extremely variable but characterized by perivascular neutrophilic infiltrate. With the discovery of mutations in the *CIAS1* gene, which encodes a protein known as cryopyrin, this entity has been classified as one of the cryopyrin-associated autoinflammatory diseases, along with familial cold urticaria and Muckle-Wells syndrome. This discovery has also made available new therapeutic options. We present the case of a boy diagnosed with CINCA syndrome who presented with an outbreak of painful skin lesions and fever. These lesions were thought to be an exacerbation of underlying lesions during an episode of fever.

Key words: chronic infantile neurologic cutaneous and articular syndrome, neonatal onset multi-inflammatory disease, neutrophilic dermatitis, cryopyrin.

SÍNDROME CINCA: PRESENTACIÓN DE UN CASO CON EXACERBACIÓN FEBRIL DE SUS LESIONES CUTÁNEAS

Resumen. El síndrome CINCA (*Chronic Infantile Neurologic Cutaneous Articular Syndrome*) es una grave enfermedad inflamatoria sistémica crónica, de instauración temprana, que se caracteriza por afectación cutánea, articular y del sistema nervioso central (SNC). La clínica cutánea en forma de exantema urticariforme no pruriginoso es la primera en aparecer, siendo más o menos permanente con exacerbaciones que coinciden con brotes de fiebre, artritis y adenopatías. La biopsia de las lesiones cutáneas es muy variable, aunque destaca un infiltrado neutrofílico perivascular. El descubrimiento de mutaciones en el gen CIAS1, que codifica una proteína llamada criopirina, ha permitido añadir esta entidad al espectro de las enfermedades autoinflamatorias asociadas a criopirinas, junto con la urticaria familiar por frío y el síndrome de Muckle-Wells, implicando además nuevas opciones terapéuticas. Presentamos el caso de un varón diagnosticado de síndrome CINCA que presentó un brote de lesiones cutáneas dolorosas y fiebre, interpretándose éstas como una exacerbación de sus lesiones habituales durante un episodio febril.

Palabras clave: CINCA (*Chronic Infantile Neurologic Cutaneous Articular Syndrome*), NOMID (*Neonatal Onset Multi-Inflammatory Disease*), dermatitis neutrofílica, criopirina.

Introduction

Chronic infantile neurologic cutaneous articular (CINCA) syndrome, also known as neonatal onset multi-inflammatory disease (NOMID), is an early onset, chronic, persistent inflammatory disease that generally presents in neonates. It is characterized by skin, joint, and central nervous system (CNS) symptoms. Skin symptoms are the first to appear—generalized rash that is typically urticarial and nonpruritic. The rash presents exacerbations that coincide with episodes of fever, enlarged spleen, enlarged lymph nodes, and arthritis.[1-3]

The existence of familial cases of this syndrome suggests a possible genetic basis to the disease, and mutations in the *CIAS1* gene have recently been described.[4,5] We report a new case of a patient diagnosed with CINCA syndrome, with special reference to the remarkable skin symptoms

Correspondence:
Sonsoles Aboín González
Servicio de Dermatología
Hospital Ramón y Cajal Universidad de Alcalá de Henares
Carretera de Colmenar Viejo, km 9,400
28034 Madrid, Spain
asonsoles@hotmail.com

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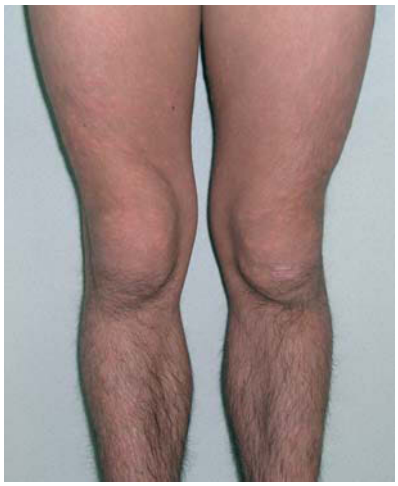

Figure 1. Patellar hypertrophy.

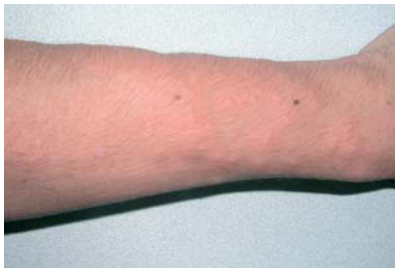

Figure 2. Edematous erythematous plaques.

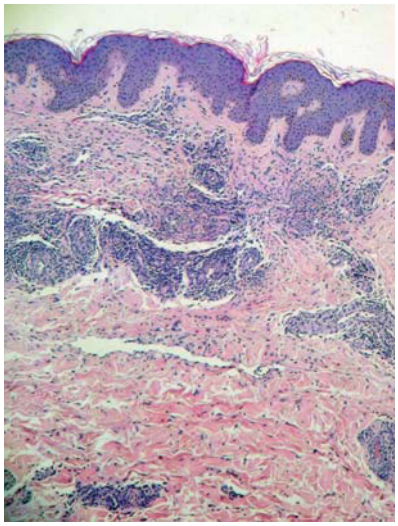

Figure 3. Biopsy of the lesions on entering the emergency department (hematoxylin–eosin, ×20): panoramic view of the lesion with dense patchy neutrophilic infiltrates in the superficial dermis, accompanied by dense mixed perivascular infiltrate affecting the superficial and deep vascular plexuses.

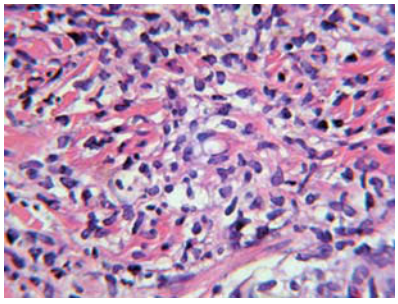

Figure 4. Biopsy of the lesions in the emergency department. Detail of the image shown in Figure 3 (hematoxylin–eosin, ×100): neutrophilic infiltrate.

and analysis of the rest of the clinical manifestations. Finally, we discuss the etiology and treatment of this syndrome.

Case Description

The patient was a 19-year-old man who had been diagnosed with CINCA syndrome since infancy; the diagnosis was based on the following clinical findings:

1. Cutaneous. Neonatal-onset recurring urticarial rash.
2. Neurologic. Episodes of headache and stiff neck consistent with aseptic meningitis.
3. Sense organs. Optic neuritis, uveitis, bilateral papillitis, and conductive deafness.
4. Joints. Chronic arthritis mainly affecting the knees, with hyperplasia of the patella (Figure 1), and intermittent acute arthritis of the ankles and metacarpophalangeal joints.

The patient also presented repeated episodes of high fever, enlarged lymph nodes, and splenomegaly. He also presented a peculiar phenotype, with a prominent forehead, receding nose and depapillated tongue, short limbs with short fingers and toes, and clubbed proximal interphalangeal joints.

He visited the emergency department in January 2004 due to an episode of painful lasting skin lesions unlike those normally presented by the patient; the lesions were accompanied by high fever. The patient had suspended treatment with corticosteroids the previous day due to acute gastroenteritis. The lesions consisted of highly edematous erythematous plaques, with surface pseudovesicles. They were located on the arms, forearms, legs, thighs, torso, neck, and ears, and hot and painful to the touch (Figure 2).

Laboratory workup revealed leukocytosis with high neutrophil counts (13.5×10^9 leukocytes/L, with 83% neutrophils) and microcytic anemia (hemoglobin, 10.6 g/dL; mean corpuscular volume, 60.4 fl; hematocrit, 33%). A presumptive diagnosis of Sweet syndrome-like neutrophilic dermatosis was made and a skin biopsy was performed that showed dense, patchy neutrophilic infiltrates in the superficial dermis, accompanied by a dense perivascular mixed inflammatory infiltrate that affected the superficial and deep plexuses (Figures 3 and 4). Biopsies of the urticarial lesions usually presented by the patient were then taken, and these revealed a predominately neutrophilic interstitial inflammatory infiltrate in the superficial and deep dermis (Figure 5).

Response to oral corticosteroids was rapid and the patient's condition was subsequently managed with nonsteroidal anti-inflammatory drugs (NSAIDs) until treatment was initiated in March 2005 with anakinra (interleukin-1 receptor antagonist) at a dosage of 100 mg/d, subcutaneously.

This treatment has since been maintained and shows a good clinical response in the skin, joints, and CNS, with reduced episodes of urticarial lesions, headache, stiffness of the neck, and joint swelling.

Discussion

CINCA syndrome, also known in the literature as NOMID, is a rare, chronic, persistent multisystemic inflammatory syndrome that appears in childhood. It was described by Prieur and Griscelli[6] in 1981 as an entity separate from juvenile rheumatoid arthritis and was named CINCA syndrome in 1987.[1] Hassink and Goldsmith[7] later called this entity NOMID.

The syndrome is characterized by a cutaneous rash, chronic polyarthritis, and neurologic involvement, often accompanied by fever, enlarged lymph nodes, and splenomegaly; several systems may become affected during the course of the disease.[1,6,7] Skin symptoms are the first to appear and usually manifest at the neonatal stage or in the first months of life.[1] The disease persists throughout the life of the patient and usually consists of a generalized nonpruritic urticarial rash that presents exacerbations during episodes of fever, enlarged lymph nodes, hepatosplenomegaly, and arthritis.[1,3] The morphology and histologic characteristics of the lesions, however, are highly varied and have not been studied systematically. Skin biopsies have shown findings ranging from nonspecific inflammatory abnormalities[2] to urticarial vasculitis of the small and medium vessels of the dermis.[8] The common denominator among these heterogeneous histologic findings is a predominately neutrophilic perivascular infiltrate. Our case report is of interest due to the highly inflammatory Sweet syndrome-like skin lesions. However, these lesions do not match the typical characteristics of Sweet syndrome, particularly in terms of the histology findings. In Sweet syndrome, histology findings are characterized by a diffuse, dense neutrophilic inflammatory infiltrate, occasionally with lymphocytes and eosinophils, located in the superficial dermis. Findings also include marked edema of the papillary dermis, and this can lead to subepidermal vesiculation. In our patient, although the inflammatory infiltrate contained abundant neutrophils, it was more polymorphic and was also located in the deep dermis; no edema was observed in the papillary dermis. We believe that these skin lesions presented by our patient may be considered to be an exacerbation of his usual lesions, which appeared during a febrile episode—as suggested in the literature.[3]

The joint and neurologic symptoms affect the patient's quality of life. Joint symptoms are a consistent finding in all patients with CINCA syndrome,[1,6] predominately in the large joints (knees), and range from arthralgia[1] to asymmetric deforming arthropathy,[9] with premature ossification of the patella and the epiphysis of the long bones and excess bone growth leading to hyperplasia of the patella. Practically all patients suffer progressive neurologic deterioration[1] as a result of the recurring aseptic meningitis. Headaches, vomiting, convulsions, and occasional mental retardation have been reported. The sense organs (eyes and ears) may also be affected and patients may present anterior and/or posterior uveitis and abnormalities of the optic nerve, even leading to blindness. Auditory symptoms may include conductive deafness.[1]

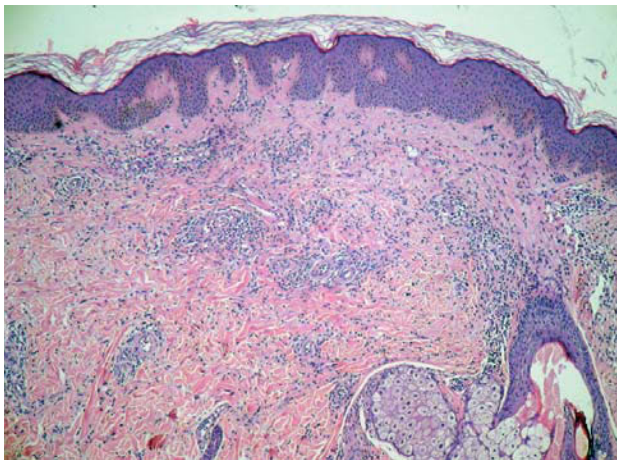

Figure 5. Biopsy of the usual lesions (hematoxylin–eosin, ×20): predominately neutrophilic interstitial inflammatory infiltrate in the superficial and deep dermis.

Patients with CINCA syndrome show characteristic morphological abnormalities such as a prominent forehead, low nasal bridge, drumstick fingers, shortened hands and feet, etc.

Analyses typically show a microcytic or hypochromic anemia, or anemia of chronic disease that does not respond to iron, leukocytosis with predominance of neutrophils and eosinophils, and an increased number of platelets and acute-phase reactants.

The pathogenesis of CINCA syndrome is not fully understood, though the occurrence of familial cases suggests that the disease may have a genetic basis.

Systemic autoinflammatory diseases have recently been reported in which activation of innate immunity is inadequate. These diseases include cryopyrin-associated systemic autoinflammatory diseases, which cover CINCA syndrome, Muckle-Wells syndrome (characterized by fever, urticarial rash, arthritis, conjunctivitis, and neurosensory deafness), and familial cold urticaria (similar to Muckle-Wells syndrome except that the urticaria is triggered in response to cold and that deafness does not develop).[4,5,10-12] These 3 diseases are considered to form a continuous spectrum of the same disorder with different phenotypic expressions[12] associated with autosomal dominant mutations of the *CIAS1* gene, located on chromosome 1.[13] CINCA

syndrome is considered to be the most severe disease of this spectrum.

The *CIAS1* gene is expressed in neutrophils, chondrocytes, and monocytes, and encodes a protein known as cryopyrin or NALP3—a component of the cytoplasmic protein structure called the inflammasome. This protein complex plays an important role in the inflammatory response by favoring—in response to the mutation of *CIAS1*—the synthesis of Interleukin-1β (IL-1β) and other proinflammatory cytokines, thanks to the activation of caspase 1 and nuclear factor κB.[4,5,10,14,15]

It has been suggested that the severity of the symptoms and the response to treatment of diseases associated with the *CIAS1* gene may be affected by the type of underlying genetic mutation,[11] together with other genetic and environmental factors.

In CINCA syndrome, most *CIAS1* mutations are de novo mutations, leading to sporadic clinical presentation. These mutations are only detected in 50% of patients clinically diagnosed with CINCA syndrome, suggesting genetic heterogeneity.[5]

Different drugs such as NSAIDs, oral corticosteroids, and immunosuppressants (azathioprine and methotrexate) have been used to treat the syndrome, but many of them are less than satisfactory. The recent discovery of the main role of *CIAS1* and the protein it encodes (cryopyrin) in increasing production of different proinflammatory cytokines, including IL-1β, has provided a new treatment option consisting of blocking the IL-1β receptor. The new drug that performs this function, anakinra, leads to clinical improvement and improved results in laboratory analysis in patients with CINCA syndrome,[15,16] regardless of the existence of mutations in *CIAS1*.[17]

Conflicts of Interest

The authors declare no conflicts of interest.

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