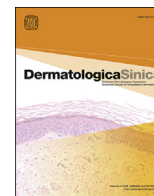


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## CASE REPORT

### A rheumatoid arthritis patient with chronic recurrent annular neutrophilic dermatosis: Are we dealing with a new type of rheumatoid arthritis-associated dermatosis?

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## ABSTRACT

Neutrophilic dermatoses comprise a heterogeneous group of disorders, which are characterized by inflammatory skin lesions that share a common histopathological feature, intense inflammatory infiltration consisting primarily of neutrophils, with no evidence of vasculitis. We describe a 75-year-old man with rheumatoid arthritis, who presented with erythematous edematous plaques. The histopathological findings indicated neutrophilic dermatosis; however, the patient was afebrile and without an elevated white blood cell count or systemic involvement. We think that the most suitable expression for this variant with clinical manifestations different from those of classical Sweet syndrome is “chronic recurrent annular neutrophilic dermatosis,” as introduced by Christensen et al.<sup>1</sup>

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## Introduction

The term “chronic recurrent annular neutrophilic dermatosis (CRAND)” was first used by Christensen et al<sup>1</sup> in 1989 to refer to the skin lesions of two patients who had chronically recurring outbreaks of generalized annular erythematous, edematous cutaneous plaques with histopathological findings suggestive of Sweet syndrome, but without fever or systemic signs and symptoms.

## Case Report

We describe a 75-year-old man with a 10-year history of rheumatoid arthritis (RA) who presented to our clinic with recurrent outbreaks of edematous, infiltrated, annular, erythematous plaques with a violaceous center. The lesions first appeared ~3 years before admission, were located on the patient's trunk, arms, legs, neck,

and scalp (Figures 1A–1C), and lasted for 3 weeks. The family history was negative for similar conditions. Upon admission, the patient was afebrile, and did not have malaise, myalgia, or lymphadenopathy. He had been taking nonsteroidal anti-inflammatory drugs for RA for 10 years. A complete blood count revealed anemia of chronic disease, and the results of routine biochemical testing were normal. His C-reactive protein level was 81 mg/L (reference range, 0–5 mg/L) and erythrocyte sedimentation rate was 71 mm/h (reference range, <20 mm/h). Chest radiography revealed sequelae of tuberculosis in both pulmonary apices. Abdominal ultrasound showed a solid intravesical bladder mass. The histopathological findings of a biopsy of the mass were consistent with papillomatous hyperplasia. Serological testing for evidence of infection with hepatotropic viruses, human immunodeficiency virus, and syphilis was negative. No other serological testing was performed. The patient was negative for the tumor markers prostate-specific antigen, carcinoembryonic antigen, and cancer antigen-19.9, and his stool was negative for occult blood. Serum immunoelectrophoresis findings were also normal. Together with the patient's physical examination and history, the clinical assessment was negative for an underlying malignancy, and no additional investigations for the presence of an underlying malignant tumor were performed.

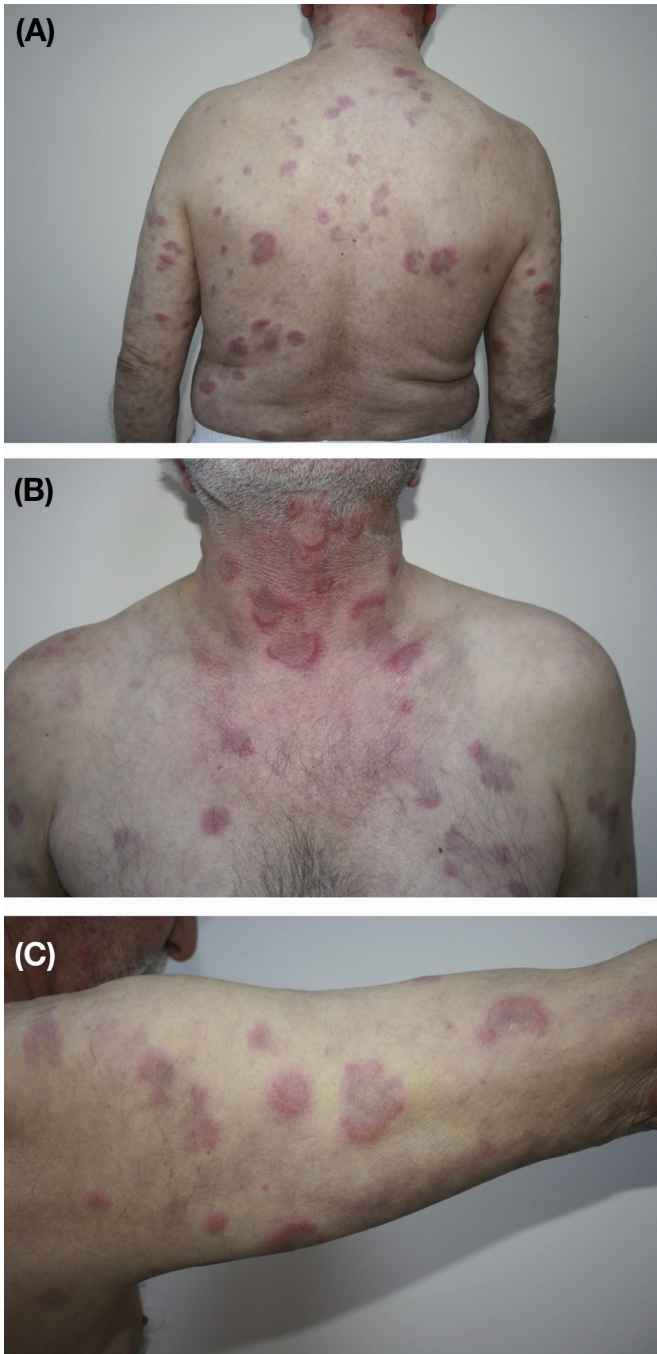
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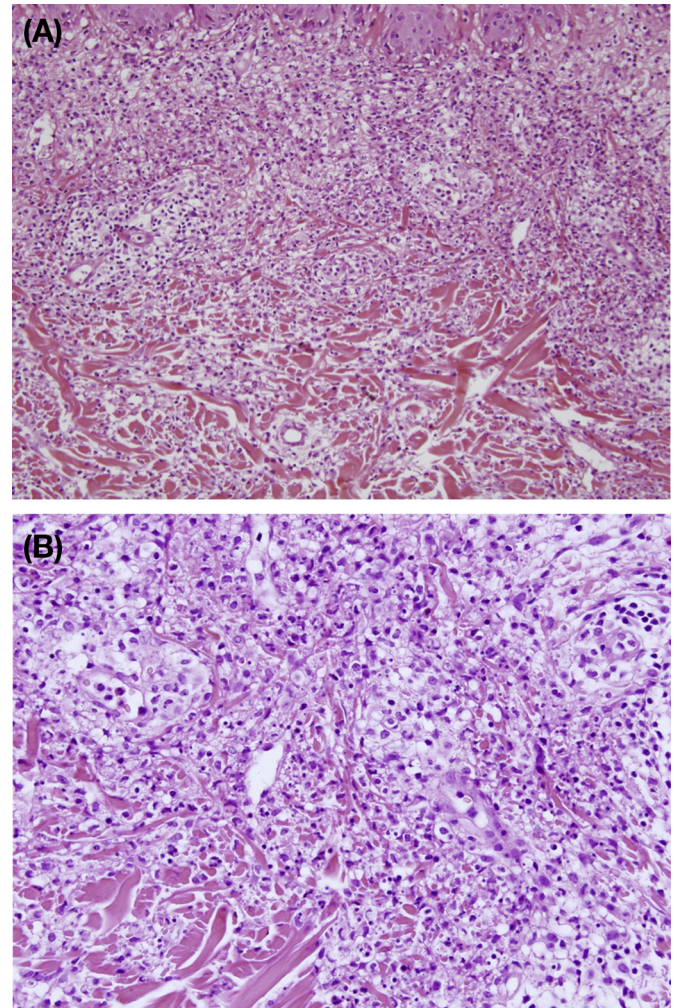
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**Figure 1** (A) Erythematous, edematous, annular plaques with violaceous center located on the trunk; (B) annular erythematous, edematous lesions located on the upper trunk and neck; (C) reddish-violaceous annular lesions on the arms.

A skin biopsy specimen showed neutrophilic infiltrate in the upper and mid-dermis, as well as leukocytoclasia. No vasculitis was observed (Figures 2A and 2B). Colchicine and dapsone, which inhibit neutrophil chemotaxis, were used to treat the infiltrate. However, because of the patient's low hemoglobin level and the occurrence of diarrhea, they were discontinued. The lesions were attributed to poorly controlled RA, and the patient was referred to a rheumatologist, who prescribed methylprednisolone (10 mg/d) and methotrexate (10 mg/wk) for 2 months. The lesions gradually disappeared. However, the patient stopped taking the methylprednisolone and methotrexate because he was worried about the side



**Figure 2** (A) Edema and intense neutrophilic inflammatory infiltrate in the dermis (hematoxylin–eosin  $\times 200$ ); (B) perivascular neutrophil predominant dense infiltrate and leukocytoclasia (hematoxylin–eosin  $\times 400$ ).

effects. Two weeks after the treatment was stopped, the lesions reappeared. At a 6-month follow-up visit, the patient complained of severe arthralgia and widespread lesions involving his entire body. He again refused systemic treatment with methylprednisolone and methotrexate.

## Discussion

In 1989, Christensen et al<sup>1</sup> reported two patients with chronically recurring outbreaks of generalized annular erythematous, edematous plaques. The histopathological findings were consistent with Sweet syndrome; however, the patients presented without fever or other findings characteristic of Sweet syndrome. Christensen et al<sup>1</sup> regarded these two cases as a unique entity because of the annular lesions and the absence of systemic manifestations, and used the descriptive term “chronic recurrent annular neutrophilic dermatosis” for the condition, instead of considering it to be a variant of Sweet syndrome.

Romero Aguilera et al<sup>2</sup> reported four cases that manifested as afebrile recurrent outbreaks occurring over a course of several years. The clinical appearance and histopathological features of the skin lesions of all four patients were suggestive of Sweet syndrome, but none of the patients at any time developed leukocytosis or



neutrophilia. However, these authors considered this presentation to be a variant of Sweet syndrome and not a separate entity.

Cabanillas et al.<sup>3</sup> reported a patient with a 6-month history of generalized painful annular erythematous, edematous plaques. The patient did not present with fever or leukocytosis, but did have neutrophilia and an elevated erythrocyte sedimentation rate. The lesions improved after a course of oral prednisone, and the patient only had occasional mild recurrences. The authors considered their case to resemble more closely Christensen et al.'s<sup>1</sup> CRAND instead of being a variant of Sweet syndrome.

Koguchi et al.<sup>4</sup> described a case of figurate erythema that was histopathologically characterized by neutrophilic infiltration. It was successfully treated with potassium iodide. The authors thought that their case could be considered to be a variant of CRAND.

In 2014, Mir-Bonafé et al.<sup>5</sup> reported a novel case of CRAND associated with RA, as in our patient. They obtained a successful outcome using dapsone plus colchicine to prevent additional recurrences over a 2-year follow-up period.

CRAND is a very rare condition; to the best of our knowledge, only five cases have been reported to date. Since no association has been found with drugs, infections, or systemic illness, its etiology remains unknown.<sup>5</sup> It is clinically characterized by recurrent outbreaks of indurated annular plaques with erythematous borders and a violaceous center. Fever, generalized symptoms such as malaise and myalgia, leukocytosis, and neutrophilia are absent. The histopathological findings include neutrophilic infiltration in the mid and upper dermis, leukocytoclasia, and no signs of vasculitis.<sup>4,5</sup>

The one case of RA-associated CRAND reported by Mir-Bonafé et al.<sup>5</sup> did not appear to manifest flare ups of CRAND linked to exacerbations of RA. We initially thought that the exacerbations of the lesions of our patient were associated with poorly controlled RA, and the rheumatologist who saw the patient prescribed systemic methotrexate and methylprednisolone. The lesions disappeared 2 weeks after the start of treatment and reappeared after the cessation of treatment. We observed that the appearance of the lesions was associated with worsening arthralgia.

RA skin manifestations can be either specific or nonspecific. The specific manifestations include subcutaneous nodules (classical rheumatoid nodules, accelerated rheumatoid nodules, or rheumatoid nodulosis), rheumatoid vasculitis, granulomatous dermatitides (interstitial granulomatous dermatitis or palisaded neutrophilic granulomatous dermatitis), and neutrophilic dermatosis (pyoderma gangrenosum, Sweet syndrome, rheumatoid neutrophilic dermatitis, neutrophilic dermatitis of the dorsal hands, syngenic sterile arthritis, pyoderma gangrenosum, acne syndrome/synovitis, acne, pustulosis, hyperostosis, osteomyelitis syndrome).<sup>6</sup>

RA-associated neutrophilic dermatosis has been linked to mutations in the genes regulating innate immunity, which can induce inflammasome-mediated neutrophil recruitment.<sup>7,8</sup> Sweet syndrome is rarely seen in patients with RA, and is characterized histopathologically by a neutrophilic infiltrate in the superficial derma

and clinically by the sudden onset of fever, an elevated white blood cell count, and erythematous, tender skin lesions.<sup>9</sup> Rheumatoid neutrophilic dermatosis presents with papules, erythematous plaques, nodules, and urticarial lesions with typical symmetric distributions on the joints, extensor surfaces of the extremities, and the trunk. Histopathological findings include neutrophilic infiltrate in the dermis without vasculitis.

The lesions of our patient most closely resembled those of patients with Sweet syndrome, except for the recurrent and annular nature of the lesions and absence of constitutional signs and symptoms such as fever and myalgia. We included rheumatoid neutrophilic dermatosis in the differential diagnosis, but our patient's lesions were edematous plaques instead of polymorphic lesions or pustules, and were distributed widely instead of confined to the joints or extensor surfaces of the extremities.<sup>10</sup>

In conclusion, we described a rare case of a patient with RA who developed a neutrophilic dermatosis with an atypical, chronic, and recurrent presentation. We think that "CRAND," a descriptive term first used by Christensen et al.,<sup>1</sup> to be the most appropriate name for this dermatological manifestation accompanied by clinical findings different from those of classic Sweet syndrome. We suggest that this is a new entity of RA-associated neutrophilic dermatosis, presenting as recurring lesions that worsen with the exacerbation of RA.

Additional studies of large series of similar cases can help us clarify whether or not CRAND is a new type of RA-associated neutrophilic dermatosis.

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