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Received: 18 May 2022 | Revised: 24 February 2023 | Accepted: 5 March 2023

DOI: 10.1111/cup.14425

CASE STUDY

JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Rheumatoid neutrophilic dermatosis under treatment with the interleukin-6-receptor-antagonist sarilumab in a patient with seropositive rheumatoid arthritis

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: 413490537

Abstract

Skin manifestations may arise as adverse events following the use of novel drugs. We report a case of a patient with seropositive rheumatoid arthritis who developed a rheumatoid neutrophilic dermatosis (RND) under treatment with the interleukin-6-receptor-antagonist sarilumab. The skin lesions developed 2–3 days after the first injection. RND presents with asymptomatic, symmetrical fixed urticarial-like papules, plaques, and nodules, localized typically on the extensor surfaces of the forearms and hands. After discontinuing the medication, the nodules in our patient disappeared within a month.

KEYWORDS
IL-6, neutrophils, rheumatoid arthritis, RND

1 | INTRODUCTION

Rheumatoid neutrophilic dermatosis (RND) is a rare skin manifestation. We report a novel case of RND connected to IL-6-receptor-antagonist sarilumab treatment in a patient with seropositive rheumatoid arthritis (RA).

2 | CASE REPORT

A 60-year-old woman came to our outpatient clinic in October 2020 with skin eruptions she developed 18 months ago. She suffered from seropositive ("rheumatoid factor"/RF-positive and "anti-mutated citrullinated vimentin antibody"/MCV-AK-positive) RA. RA was first diagnosed in 2007; her current Larsen score was 3. She also suffered from secondary Sjögren syndrome with xerophthalmia ("antinuclear antibody"/ANA-positive). Her current medication included the IL-6-receptor-antagonist sarilumab, which she received every 2 weeks. Previous medication included methotrexate, cyclosporine, tocilizumab, rituximab, and oral prednisolone.

She presented with red and skin-colored hard nodules and blisters on her hands and arms. The lesions on the fingers appeared in a linear formation (Figure 1). She did not report any pain or pruritus. As a possible trigger, the IL-6-receptor-antagonist sarilumab was suggested because the skin lesions developed 2–3 days after the first injection with sarilumab, which she first received 18 months before presentation.

The medication was then stopped, and two skin biopsies were taken, one from the finger and one from the forearm.

Histopathology revealed a dense neutrophilic infiltrate involving the whole dermis, with collagen degeneration. Dense neutrophilic perivascular infiltrates and endothelial swelling without leukocytoclasia were found. The biopsy from the finger additionally showed subepidermal vesiculation, with neutrophils and plasma cells in the blister. PAS, Giemsa, Fite, and Ziehl-Neelsen stains were negative for microorganisms (Figures 2–4). The diagnosis of RND was made.

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FIGURE 1 Clinical presentation of the forearm and the hand. She presented with red and skin-colored hard nodules and blisters. The lesions on the fingers appeared in a linear formation.

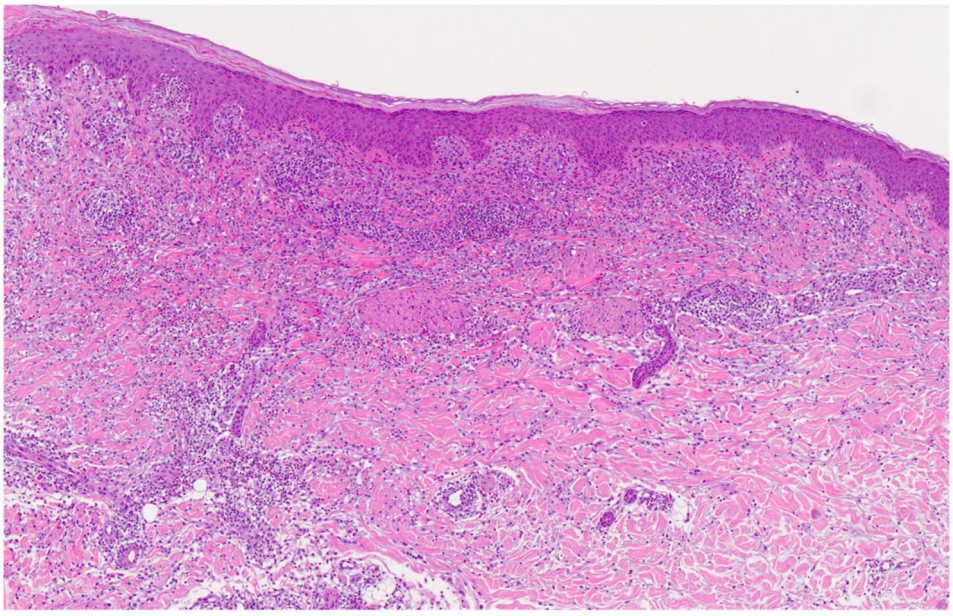

FIGURE 2 Skin biopsy of the forearm stained with H&E showing a heavy neutrophilic infiltrate involving the entire dermis and collagen degeneration. Original magnification ×50.

The patient was later treated with the JAK1/3-inhibitor tofacitinib. The nodules vanished within a month, and no new nodules appeared under JAK inhibition.

3 | DISCUSSION

Ackerman first described RND, a rare cutaneous manifestation of seropositive and seronegative RA, in 1978.[1] RND presents with symmetrical fixed urticarial-like papules, plaques, and nodules, localized typically on the extensor surfaces of the forearms and hands, rarely with vesiculobullous lesions. It is usually observed in patients with severe, prolonged, seropositive RA. Other symptoms, such as pruritus or pain, are not reported. Lesions can be refractory to topical and systemic treatment. However, they can also resolve with the improvement of RA.[2,3] Women are affected twice as often as men (2:1).

The clinical differential diagnoses include Sweet syndrome, Behçet disease, pyoderma gangrenosum, and bowel bypass syndrome. Sweet syndrome is the most challenging differential as a result of the similar clinical and histopathologic presentations.[2] Systemic symptoms such as fever, malaise, and arthralgias indicate Sweet syndrome, on the other hand RND is typically asymptomatic.[2] Regarding the histopathological findings, rheumatoid nodules are a common differential diagnosis. But rheumatoid nodules show palisading granulomatous inflammation with an inner central necrotic area, an intermediate area with palisading macrophages, and a surrounding zone of perivascular granulation tissue with infiltrative inflammatory cells.[3] When subepidermal blistering is reported, linear IgA dermatosis or bullous lupus erythematosus should be further considered.

RND is mainly characterized by a dense dermal neutrophilic infiltrate, which can even form microabscesses in the papillary dermis, endothelial swelling, and leukocytoclastia without vasculitis. Sometimes

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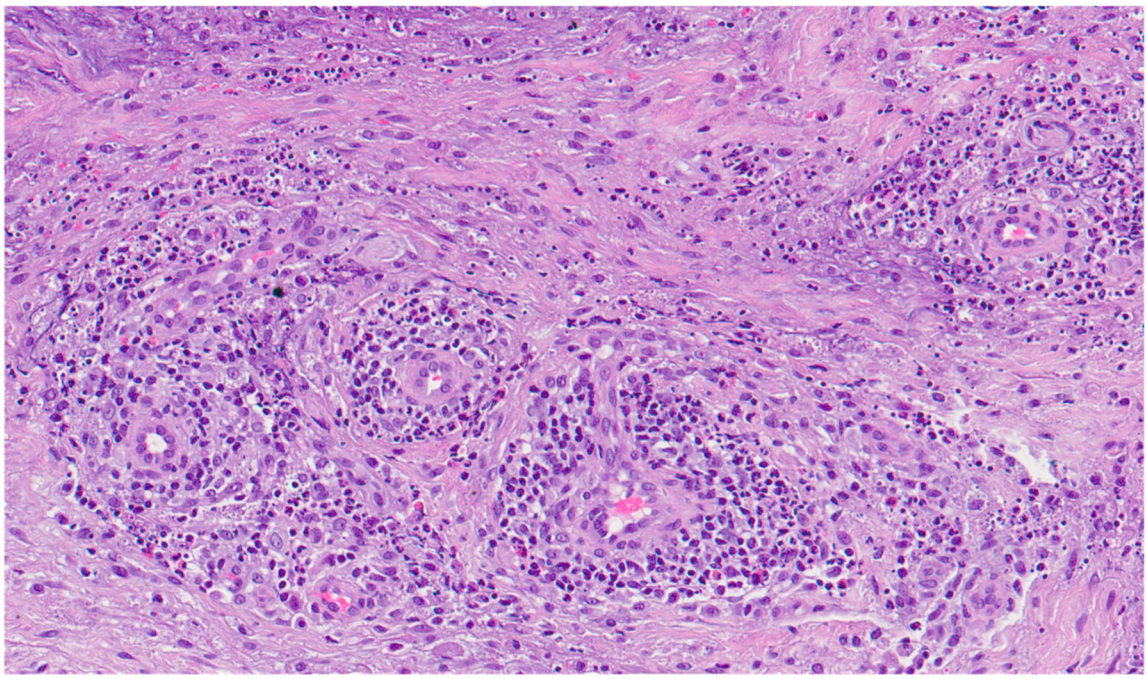

FIGURE 3 Skin biopsy of the finger stained with H&E showing dense neutrophilic perivascular infiltrates and endothelial swelling without leukocytoclasia. Original magnification ×150.

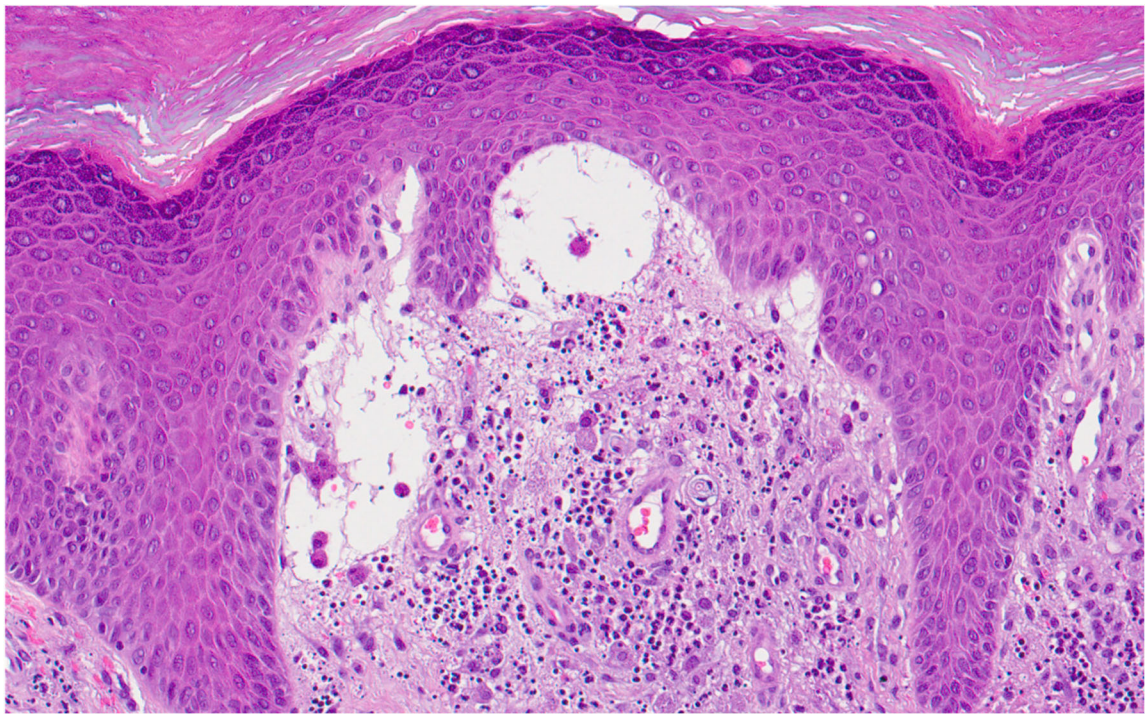

FIGURE 4 Skin biopsy of the finger stained with H&E showing subepidermal blistering with neutrophils and plasma cells. Original magnification ×150.

even intraepidermal spongiosis leading to vesiculation may be present, like in our case.[3] Table 1 shows the histopathological findings in published RND cases – since the review of cases by Brown et al in 2001.

The underlying pathogenesis remains to be elucidated. Immune complex activation via IL-6 and IL-8 has may play an etiopathogenic role.[14,15] Whether the RA or the therapy with sarilumab triggered the

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TABLE 1 Histopathological findings in published RND cases.

Author	RA	Histopathological findings
Brown et al[2]	Seronegative	Heavy neutrophilic infiltrates involving the entire dermis. Leukocytoklasia without vasculitis.
Rodwan et al[4]	Seronegative	Multiple foci of necrosis and mixed inflammatory infiltrate composed mainly of neutrophils. No evidence of vasculitis.
Zuk et al[5]	Seropositive	Dense neutrophilic infiltrate with histiocytes, multinucleated giant cells and neutrophils locally forming microabscesses with leukocytoclasis within the vessel wall.
Kubota et al[6]	Seropositive	Neutrophilic dermal infiltrate and leukocytoclasis without vasculitis.
Kaur et al[7]	Seropositive	Subepidermal pustule with neutrophils and nuclear dust scattered around the vessels and between collagen fibers in the upper dermis and mid dermis, but without vasculitis
André et al[8]	Seropositive	Dermal neutrophilic infiltrate with leukocytoclasis without vasculitis and large amounts of extravascular fibrin deposits.
Edgerton et al[9]	Seropositive	Diffuse superficial and deep dermal neutrophilic infiltrate with leukocytoclasis, marked papillary dermal edema, and focal epidermal ulceration. No histologic evidence of vasculitis was identified.
Lu et al[10]	Seropositive	Subepidermal and intraepidermal vesicles filled with numerous neutrophils. Extensive neutrophilic infiltrate with prominent leukocytoclasis was observed throughout the dermis. Mild endothelial swelling was noted, but no vasculitis.
Kreuter et al[11]	Seropositive	Subepidermal blisters with a superficial dense infiltrate of neutrophils, but no signs of vasculitis.
Yamamoto et al[12]	Seronegative	Cellular infiltrates composed of lymphocytes and neutrophils with nuclear dusts in the upper dermis.
Gay-Crosier et al[13]	Seronegative	Dense neutrophilic infiltrate with edema in the superficial dermis, an intraepidermal abcess of neutrophils reaching the stratum corneum, nonspongiotic adjacent epidermis and a mixed neutrophilic mononuclear infiltrate in the deep dermis.

RND in our patient is unclear. The fact that the patient suffered from RA for decades without developing RND earlier favors the latter argument.

ACKNOWLEDGMENTS

This study was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – 413490537. Open Access funding enabled and organized by Projekt DEAL.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Jost M, Schwarz T, Wehkamp U, Bohne A-S, Drerup K. Rheumatoid neutrophilic dermatosis under treatment with the interleukin-6-receptor-antagonist sarilumab in a patient with seropositive rheumatoid arthritis. *J Cutan Pathol*. 2023;50(8):734-738. doi:10.1111/cup.14425

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