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ACCELERATED NODULOSIS IN RHEUMATOID ARTHRITIS PATIENT TREATED WITH METHOTREXATE: A CASE REPORT AND CLINICAL INSIGHTS

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ABSTRACT – *Background:* Rheumatoid arthritis (RA) can manifest with extra-articular involvement affecting various organs and systems. The skin is the most commonly involved organ, with the classic manifestation being subcutaneous rheumatoid nodules (RNs), typically found in pressure-exposed areas of the skin. Accelerated nodulosis (AN) is considered a paradoxical effect of methotrexate (MTX) therapy and must be distinguished from classic RNs.

Case report: We report one diagnosed clinical case of seropositive RA patients who, during MTX therapy, experienced the rapid onset of RNs in multiple and unusually exuberant sites, and four suspected cases.

Conclusions: The development of unusually large RNs and/or their rapid appearance in multiple sites during MTX therapy, particularly in patients with low to moderate disease activity, should raise clinical suspicion for AN.

KEYWORDS: Subcutaneous accelerated nodulosis, Rheumatoid arthritis, Rheumatoid nodules, Methotrexate.

BACKGROUND

Rheumatoid arthritis (RA) can manifest extra-articular involvement affecting various organs and systems. The skin represents the most commonly involved organ, with the classic manifestation being subcutaneous rheumatoid nodules (RNs), observed in approximately 25% of seropositive RA patients.

The most frequent sites for RNs development include the fingers, elbows, Achilles tendon, and generally any pressure-exposed areas of the skin. Recently, rheumatoid nodules have also been described in the lungs, kidneys, and liver within the same seropositive RA patients[1]. Typically, RNs develop in patients with long-standing, seropositive RA and high disease activity levels.

Methotrexate (MTX) remains the cornerstone in the treatment of RA, yet rare paradoxical adverse effects, such as accelerated nodulosis (AN), pose both a diagnostic and therapeutic challenge. While isolated cases have been reported, comprehensive case series are scarce. Furthermore, only two cases of AN in patients affected by Systemic Lupus Erythematosus (SLE) with joint involvement, including Jaccoud's arthropathy, treated with MTX have been reported[2].

A peculiar aspect of AN is its onset during MTX therapy, a phenomenon extensively reported in the literature[3-6], with an incidence ranging from 8% to 11.6% in patients treated with MTX[3]. This condition is considered a paradoxical effect of MTX therapy and must be distinguished from classic RNs, primarily due to therapeutic implications. In most cases, suspending MTX leads to improvement or regression of the nodules[5,7]. AN has also been observed during treatment with other immunosuppressive drugs, such as leflunomide, azathioprine, and anti-TNF agents – infliximab, certolizumab – but the pathogenesis remains unclear[8].

We report one diagnosed clinical case of seropositive RA patients who, during MTX therapy, experienced the rapid onset of rheumatoid nodules in multiple and unusually exuberant sites, and four suspected cases.

CASE REPORT

We describe the case of a 55-year-old male, employed as a public administration worker and an active smoker.

Diagnosis: At 43 years of age, he was diagnosed with seropositive rheumatoid arthritis (RA) (Rheumatoid Factor [RF]: 150 IU/mL, Anti-Citrullinated Protein Antibodies [ACPA]: 300 IU/mL).

Treatment: The patient started on methotrexate (MTX) 15 mg/week as monotherapy, achieving good disease control (Erythrocyte Sedimentation Rate [ESR]: 10 mm/h, C-Reactive Protein [CRP]: 3 mg/L, Disease Activity Score-28 [DAS28]: 2.6). After approximately 10 years of stable MTX therapy 15 mg/week as monotherapy, the patient developed multiple subcutaneous nodules in rapid succession over the II-III-IV metacarpophalangeal (MCP) joints of the right hand and along the course of the right Achilles tendon. Notably, the patient's disease activity remained well-controlled, with regular inflammatory markers (ESR and CRP within normal range).

Clinical Management: The patient underwent surgical excision of the nodules.

Histopathological Findings: Histological examination revealed findings consistent with rheumatoid nodules (Figure 1).

In Table I, we report the clinical patterns of four suspected cases of accelerated nodulosis in rheumatoid arthritis patients on methotrexate therapy.

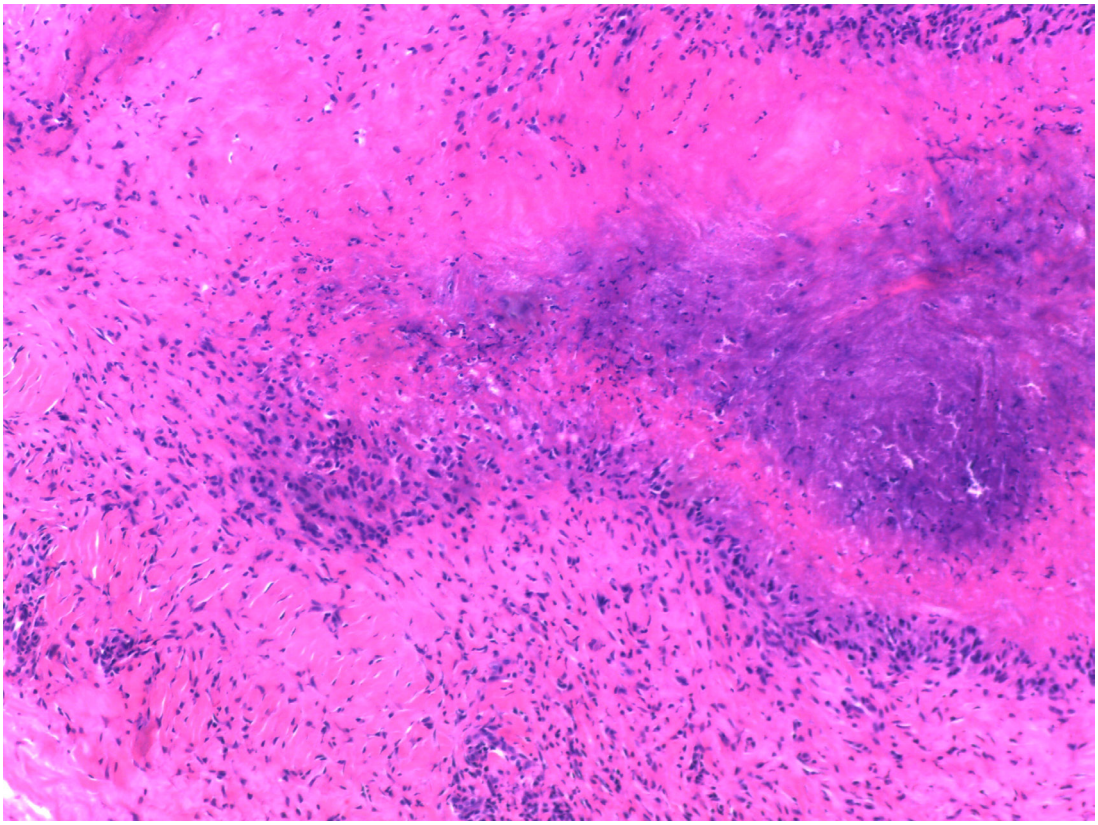

Figure 1. Histological examination.

Table 1. Clinical patterns of four suspected cases of accelerated nodulosis.

Case	Age/Sex	Occupation/ Smoking Status	RA Diagnosis (Age)	Serology (RF, ACPA)	Disease Activity (ESR, CRP, DAS28)	MTX Therapy (Duration/Dose)	Nodule Location	Management
1	60/M	Farmer, Smoker	45	RF: 300, ACPA: 600	ESR: 50, CRP: 30, DAS28: 4.1	10 years, 20 mg/week	Fingers, right Achilles tendon, large nodules on elbows	Refused surgical removal and biopsy
2	83/M	Former construction worker, Ex-smoker	53	RF: 200, ACPA: 250	ESR: 34, CRP: 20, DAS28: 3.9	15 years, MTX 10 mg/week + Sulfasalazine 500 mg × 4/day	Bilateral large subcutaneous nodules on elbows	Refused surgical removal and biopsy
3	70/M	Former farmer, Smoker	50	RF: 100, ACPA: 300	ESR: 35, CRP: 20, DAS28: 3.7	8 years, 15 mg/week	Fingers	Refused surgical removal and biopsy
4	65/M	Former plumber, Smoker	55	RF: 100, ACPA: 300	ESR: 38, CRP: 15, DAS28: 4.1	5 years, 10 mg/week	Large subcutaneous nodules on elbows	Refused surgical removal and biopsy

M: male. F: female. RA: rheumatoid arthritis. RF: rheumatoid factor. ACPA: Anti-Citrullinated Protein Antibodies. ESR: Erythrocyte Sedimentation Rate. CRP: C-Reactive Protein. DAS28: Disease Activity Score-28. MTX: methotrexate.

All patients were male smokers or ex-smokers, a well-known risk factor for rheumatoid nodulosis. Disease activity was moderate across all cases (DAS28 ranging from 3.7 to 4.1). MTX therapy duration varied from 5 to 15 years, with doses ranging from 10 to 20 mg/week. Nodules predominantly affected fingers, Achilles tendon, and elbows, with elbows being a common site. None of the patients consented to surgical excision or biopsy, except the index case.

DISCUSSION

AN, during MTX therapy, tipically arises in patients undergoing long-term treatment with this drug. However, cases of early onset, even after a few months of therapy, have been reported[3]. Interestingly, a similar condition, although sporadic, has been observed with other therapeutic agents, including tocilizumab, leflunomide, azathioprine, and anti-TNF-α therapies[9-12].

Unlike classic rheumatoid nodules (RNs), AN is often observed in patients with well-controlled disease activity or moderate disease activity, even in the absence of active synovitis. The nodules tend to appear rapidly, are generally smaller, and preferentially affect fingers, feet, elbows, and knees[3,5]. From a histological perspective, no differences have been identified between the two forms of nodulosis. The pathogenesis of AN remains poorly understood. A genetic study has shown a significant correlation between AN and the 2756GG genotype of the methionine synthase reductase gene[13]. Additional risk factors include heavy smoking, male gender, and the HLA-DRB1 0401 haplotype[9]. Another hypothesis suggests that MTX may inhibit the adenosine A1 receptor, leading to increased formation of multinucleated giant cells[14].

Pharmacological therapy for AN is often unsatisfactory. Various treatments have been attempted, including hydroxychloroquine, colchicine, D-penicillamine, sulfasalazine, and rituximab. Among these, rituximab appears to have shown the most promising results[15]. However, discontinuation of MTX remains the most effective therapeutic strategy to date to control AN

Our cases show some key findings, highlighting two particularly noteworthy observations:

1. In three of our patients, large rheumatoid nodules appeared on the elbows. This presentation is rare even in conventional rheumatoid nodulosis (RNs) but is even more exceptional in AN, where nodules are typically described as small. Our observations challenge this notion and suggest that MTX may induce a paradoxical effect severe enough to produce abnormally large nodules, which are rarely documented in clinical practice or literature.
2. Multisite and rapid nodule development in one patient (case #2). In this patient, nodules developed simultaneously in multiple sites – including the elbows, finger joints, and Achilles tendon – and in rapid succession. This multisite presentation is highly unusual and further supports drug-induced pathogenesis rather than being merely a manifestation of disease activity.

However, our cases confirm several previously described characteristics of AN: a) Male predominance; b) Association with smoking habits; c) Rapid onset and progression of nodules. While the occurrence in patients with moderate (DAS28 >3.2 <5.1) and low disease activity (DAS28: 2.6) contrasts with classic RNs, which are typically associated with high disease activity.

The incomplete follow-up in the suspected cases is the major limitation of this case series. Unfortunately, we were unable to observe the clinical evolution of the nodules following MTX discontinuation, as patients did not return for follow-up visits. This limitation underscores the challenges in long-term monitoring of such cases and highlights the need for further longitudinal studies to better understand the natural history and therapeutic outcomes of AN.

CONCLUSIONS

In conclusion, the development of unusually large rheumatoid nodules and/or their rapid appearance in multiple sites during MTX therapy, particularly in patients with low to moderate disease activity, should raise clinical suspicion for AN. When such nodules are observed, genetic testing—where available—should be considered, including the screening for the HLA-DRB1 0401 haplotype. These tests may provide valuable insights into genetic predispositions and help better understand the pathogenesis of AN. Even in the absence of definitive diagnostic confirmation, discontinuing MTX therapy should be strongly considered when nodules present with these atypical characteristics. Early recognition and timely intervention are crucial to prevent further complications and to guide appropriate therapeutic adjustments. Clinicians must remain vigilant for this paradoxical adverse event, as accelerated nodulo-

sis remains underdiagnosed and underreported. Further multicentric studies and long-term follow-ups are essential to clarify the optimal management strategies and to better define the pathophysiological mechanisms underlying this phenomenon.

This case report serves as a reminder of the importance of clinical observation and individualized patient care in managing rheumatoid arthritis and its rare complications.

Conflict of Interest:
The authors have no funding and conflicts of interest to disclose.

Data Availability:
All data generated or analyzed during this study are included in this published article.

Authors' Contributions:
P. Scolieri: Conceptualization, Clinical Investigation, Data Collection, Writing – Original Draft, Literature Review, Visualization and data curation.
C. Marrese: Conceptualization, Clinical Investigation, Data Collection, Writing – Original Draft, Literature Review, Visualization and data curation.
A. Migliore: Literature Review, Writing – Review & Editing, Supervision.
N. Buzzelli: Clinical Investigation, Data Collection.
A. Paglionico: Literature Review, Writing – Review & Editing.
S. Priori: Clinical Investigation, Data Collection.
A. Bakacs: Clinical Investigation, Data Collection.
V. Bruzzese: Conceptualization, Clinical Investigation, Data Collection, Writing – Original Draft, Literature Review, Visualisation and data curation, Writing – Review & Editing, Supervision.

Informed Consent and Ethics Statement
Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. All personal data have been anonymized to protect patient privacy.

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