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Accelerated rheumatoid nodulosis effectively treated with JAK-inhibitors: A description of 2 cases and review of literature

Calvisi SL[1]*†; Farina N[1]†; Baldissera E[1]; Boffini N[1]; Cariddi A[1]; Tomelleri A[1,2]; Cinalli S[3]; Matucci-Cerinic M[1]; Dagna L[1,2]

[1]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy.

[2]School of Medicine, Vita-Salute San Raffaele University, Milan, Italy.

[3]Department of Pathology, ASST Valtellina and Alto Lario, Sondrio, Italy.

[#]Equal Contribution.

***Corresponding Author: Calvisi SL**

Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy.

Email: calvisi.stefania@hsr.it

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Abstract

Rheumatoid Nodules (RN) are the most common extra-articular manifestation of rheumatoid arthritis (RA), while Accelerated Rheumatoid Nodulosis (ARN) is a rare event potentially triggered by immunosuppressive therapies. ARN management is not standardized: removing the causative drug towards an alternative treatment is the most common implemented strategy. Recently, Janus Kinase inhibitors (JAKi) have attained a crucial role for disease control in multidrug-resistant RA patients. Herein, we describe two cases of extensive subcutaneous and pulmonary ARN associated with tocilizumab and etanercept therapies, both resolved after a swap to filgotinib monotherapy. We also provide a narrative literature review, supporting the usefulness of JAKi in controlling this difficult-to- treat complication.

Keywords: Rheumatoid arthritis; Rheumatoid nodules; JAK inhibitors.

Introduction

Rheumatoid Nodules (RN) are detected in 20-30% of Rheumatoid Arthritis (RA) patients [1] and may present as Classic Rheumatoid Nodules (CRN), rheumatoid nodulosis, or Accelerated Rheumatoid Nodulosis (ARN) [2,3]. ARN has been reported in patients treated with conventional synthetic or biologic disease- modifying antirheumatic drugs (cs/bDMARDs) such as Methotrexate (MTX) [3-5], Leflunomide (LFN) [6], azathioprine [7], anti-TNFα agents [8-14], and anti-interleukin-6 therapies [15,16]. The term "accelerated" refers to the rapid onset and progression or to the extension of pre-existing nodules. The interval between the starting of the culprit drug and the development of nodules ranges from weeks to years and is unrelated to cumulative drug dosage. ARN often occurs in patients whose arthritis is in remission, unlike CRN.

CRN are usually located subcutaneously in areas of external pressure (e.g., elbows) but may also form in internal organs under mechanical stress (e.g., lungs, heart, larynx, liver, eyes, meninges, bladder), causing local damage. In ARN, the nodules are smaller but clinically similar to those seen in CRN, and they tend to develop on extremities (e.g., hands, feet) [2]. Pathologically, RN in ARN and CRN share similar granulomatous features [17,18] and risk factors [5,19-21]. Regional inflammation due to local trauma contributes to CRN pathogenesis [1], whereas ARN is primarily related to ongoing medications [4-16,19,20]. RN are associated with more severe systemic disease, particularly in ARN, a condition often symptomatic and occasionally life-threatening [21].

While CRN treatment is typically unnecessary, surgical removal may be required in cases of infection or local mass effects. ARN generally resolved by discontinuing the precipitating drug, sometimes with additional therapies [5,15,16,22-25]. This report describes two cases of subcutaneous and pulmonary ARN efficaciously treated with Janus Kinase inhibitors (JAKi) and

reviews seven other cases in which JAKi were successfully employed [26-32].

Case series

Case 1

In February 2024, a 62-year-old woman with a 16-year history of seropositive erosive RA, and a carrier of the HLA-DRB1*0401 allele, presented with the rapid onset of multiple subcutaneous nodules on her feet, with no prior history of RN. Physical examination revealed indurated, tender, erythematous subcutaneous nodules on the lateral margins of both feet, ranging from one to several centimeters in size. Ultrasound (US) imaging showed mixed, lobulated, inhomogeneous, hypoechoic, and non-compressible masses near the bone surfaces, with a central anechoic area and diffuse peripheral Doppler signals (Figure 1a). MRI confirmed typical RN features: low signal on T1-weighted and high signal on T2- weighted images, hyperintense STIR sequences, and reactive edema in surrounding adipose tissue (Figure 1b). The patient had previously been treated with LFN, sulfasalazine, MTX, certolizumab pegol, upadacitinib, and baricitinib, all discontinued due to inefficacy or toxicity. Tocilizumab was initiated two months before the ARN developed, achieving arthritis remission. ARN induced by tocilizumab was diagnosed, and treatment was swapped to filgotinib monotherapy. Six months later, RN had reduced in size and number, US inflammation had resolved, and arthritis remained in remission.

Case 2

In November 2022, a 64-year-old woman with a one-year history of seropositive non-erosive RA, a tobacco smoker, and a carrier of the HLA-DRB1*0401 allele, was evaluated for inflammatory arthritis in her wrists. She had been on LFN and low-dose methylprednisolone, with previous treatments of hydroxychloroquine and MTX proving ineffective or intolerable. Etanercept was prescribed, but after three months, she reported a dry cough and chest pain despite arthritis improvement. A chest CT scan revealed multiple parenchymal and subpleural lung nodules, 0.5-1.8 cm in diameter, some with central air excavation and peripheral enhancement (Figure 2a). No extra-pulmonary RN were present. A lung biopsy confirmed the presence of RN (Figure 2b). Lung ARN was diagnosed, and etanercept was discontinued, replaced with filgotinib monotherapy. Six months later, the lung nodules had decreased in size and excavation had resolved, with arthritis still in remission.

Discussion

ARN is a subset of RN affecting patients undergoing conventional and biologic disease-modifying anti- rheumatic drugs (c-bDMARDs) therapies for RA. The first description concerning MTX-ARN dates back to 1986 [36], and subsequently ARN was reported in association with multiple c-bDMARDs [4-16]; suggesting the definition of "immunomodulatory agents induced nodulosis" [20].

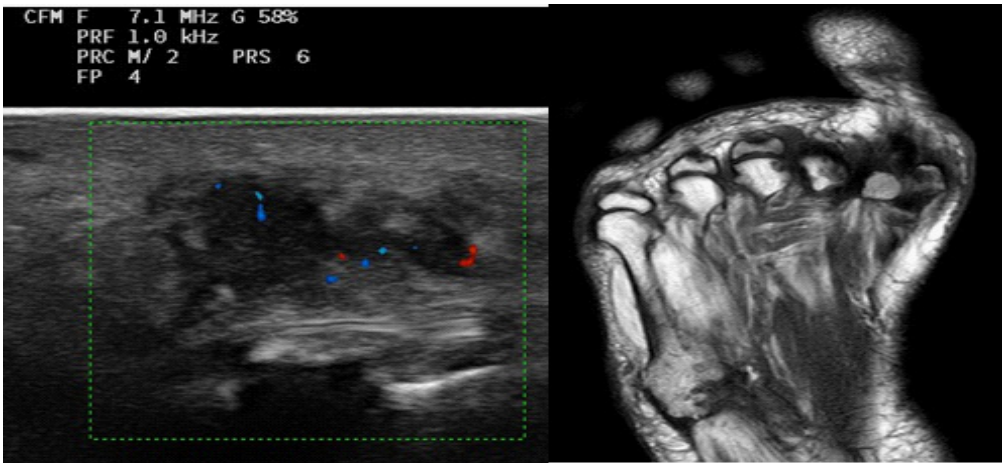

Figure 1: Ultrasound of the feet (a) showing non-homogeneous hypoechoic non-compressible masse close to the bone surface, with a central anechoic area and diffuse peripheric Color Doppler signal. MRI of the feet (b) showing a non-homogeneous lesion of approximately 23x20 mm, adjacent to the fifth metatarsal bone, with high signal on T2 images.

In our case series, we described two patients with RA who developed ARN shortly after starting biologic bDMARDs – one on tocilizumab and the other on etanercept. Both patients exhibited extensive and complicated nodular lesions, including tissue damage and infection. Notably, neither patient had a history of RN, but both had a genetic predisposition (HLA-DRB1*0401 allele), one was an active smoker—both factors known to increase the risk of ARN [5,19-21]. Despite these risk factors, the development of ARN appeared to be directly related to their bDMARD therapy, as discontinuing these treatments led to significant clinical improvement, strengthened by the swap to JAKi. These findings support the emerging role of JAKi as an efficacious therapeutic option in ARN, consistent with the limited literature on JAKi use in ARN and RN [26-32].

Our review of the literature identified seven published cases of JAKi use in ARN and RN, all of which reported favorable outcomes (Table 1).

These cases, like ours, involved patients with RA who were previously treated with c-bDMARDs (MTX, LFN, anti-TNF agents), highlighting the potential of JAKi as an alternative treatment for ARN. Interestingly, all but one patient were women – despite women being less predisposed to RN formation – suggesting a possible gender influence on JAKi response in RN, most were RF and ACPA positive, with four presenting pre-existing nodules. Our cases add to this body of evidence, providing further support for the efficacy of JAKi in ARN, especially filgotinib, which selectively inhibits pathways involved in

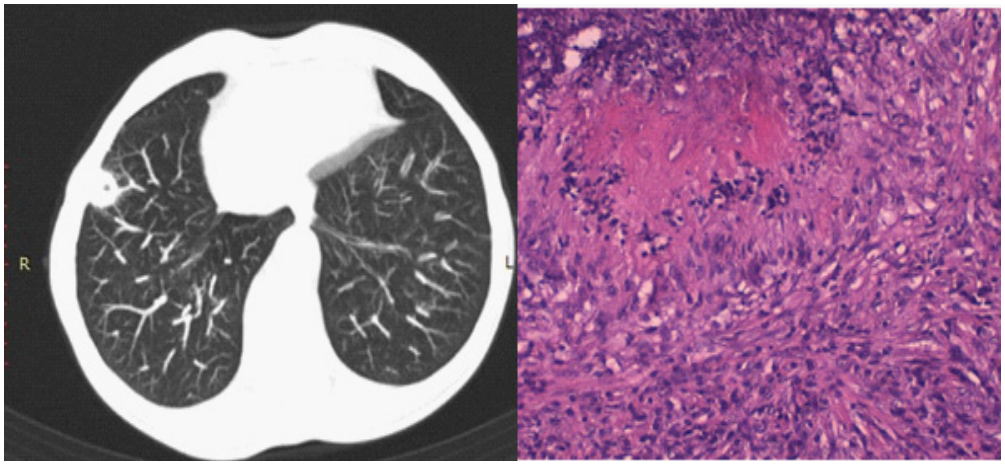

Figure 2: Computed tomography of the chest **(a)** showing a subpleural pulmonary nodule in the right lung with cavitation. Histology of lung biopsy **(b)** with hematoxylin and eosin stain (HE: 20X) showing a rheumatoid necrotizing non-caseous granuloma rimmed by lymphocytes and histiocytes in a palisade arrangement with perilesional tissue infiltration.

Table 1: Results of literature research inherent to cases of rheumatoid nodules treated with Janus Kinase inhibitors.

Article	Venerito [26]	V-Mendez [27]	Kondo [28]	Filipescu [29]	Iinuma [30]	Her [31]	Liu [32]
Publication year	2019	2020	2021	2021	2022	2024	2024
Age/sex	45, F	58, F	75, F	63, F	70, F	70, M	46, F
Disease duration*	1 y	3 y	10 y	17 y	1 y	-	1 y
Therapies/ duration	MTX/12 m	MTX / 4 y LFN / 3 y ADA/ 3 y	SSz-Tacr/ 1 y ETN / 9 y	MTX/ 6 y, SSz/ 1 y, LFN/ 2 y	IFX/ 6 m	SSz-steroid/ -	MTX/ 1y
Combined treatments	-	-	-		MTX 1y	-	LFN 1 y
Predisposing factors	RF/ACPA positivity	RF/ACPA positivity	RF/ACPA positivity	RF/ACPA positivity	-	RF/ACPA positivity	RF/ACPA positivity
Site of nodules	lung	hands/feet	lung	lung	hands	lung	lung
Preexisting nodules	yes, lung	yes, sc	no	yes, hands	yes, hands	no	no
Type of nodules	RN	ARN	ARN	ARN	ARN	RN	ARN
Symptoms	no	pain, loss of function, deformities	cough, haemoptysis	fever, dyspnea	pain	cough, dyspnea	no
Histology	-	RN	RN	RN	RN	RN	RN
Treatment	stop MTX start BARI	stop ADA, start BARI	stop ETN start ABA, IVCYC and then TOFA	stop LFN, start HCQ, CyS and then BARI	stop MTX/ IFX start FILGO	stop SSz start TOFA	stop MTX/LFN start BARI
Outcome/time	resolution/4 m	resolution/ 2 y	resolution/-	improvement/ 2 y	reduction in size/ 6 m	reduction in size/ 1 y	reduction in size/ 3-6 m

ABA: Abatacept; ACPA: Anti-Citrullinated Protein Antibodies; ADA: Adalimumab; ARN: Accelerated Rheumatoid Nodulosis; BARI: Baricitinib; CyS: Ciclosporine; FILGO: Filgotinib; HCQ: Hidroxicloroquine; IFX: Infliximab; IVCYC: Intravenous Cyclophosphamide; LFN: Leflunomide; m: Month; MTX: Methotrexate; RF: Rheumatoid Factor; RN: Rheumatoid Nodule; SSZ: Sulfasalazine; sc: Subcutaneous; Tacr: Tacrolimus; Tofa: Tofacitinib; y: year. *Disease duration before RN or ARN diagnosis.

RN development [34,35]. The use of JAKi, including filgotinib in monotherapy, appeared to be effective and well-tolerated, with rapid resolution of both subcutaneous and pulmonary nodules, as observed in our patients.

Our review also emphasized the variability of pulmonary ARN, which occurs between <0.4%-32% of RA patients, depending on the method for diagnosis [36]. Pulmonary nodules in ARN are typically asymptomatic unless complications arise, such as hemoptysis, pleural effusion, or pneumothorax, due to cavitation or pleural involvement. In our case, the clinical presentation, characterized by subpleural cavitated nodules, prompted early intervention to prevent serious complications. The use of filgotinib in this setting, though not previously reported in the literature, proved benefit in managing pulmonary nodules, further underscoring its potential place in ARN treatment.

The results from both our case series and the literature review suggest that JAKi, particularly filgotinib, may represent a viable treatment option for ARN. Given the lack of data on JAKi-induced ARN and the apparent protective effect of JAKi against systemic RA manifestations, further studies are needed to clarify their employ in ARN and other extra-articular complications of RA.

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