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BRIEF REPORT

Sonographic findings from inflammatory arthritis due to antisynthetase syndrome

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Abstract

Inflammatory arthritis is a common feature of antisynthetase syndrome. Ultrasonography is able to characterize important features of bone and tendon pathology but has not been evaluated in this setting. We review the sonographic findings in a series of patients with antisynthetase syndrome and inflammatory arthritis. A retrospective chart review was performed of patients with antisynthetase syndrome-associated inflammatory arthritis who had undergone ultrasound imaging for joint pathology. Seventeen sonographic assessments of eight patients were included. Synovial hypertrophy was seen in all eight patients, with active Doppler signal present in six patients (13 of 17 ultrasound locations). Tendon involvement was common, with tenosynovitis in seven patients (11 of 17 ultrasound locations). Erosions were present in five patients. Musculoskeletal ultrasound showed significant joint pathology including proliferative synovitis and tenosynovitis. This may be severe and associated with erosive disease. Further systematic studies are needed to better understand the articular involvement of antisynthetase syndrome.

Key points

- *Marked inflammatory change—with proliferative synovitis, tenosynovitis, and erosions—can be seen in selected patients with antisynthetase syndrome (ASyS).*
- *Inflammatory arthritis from ASyS can be severe and erosive in the absence of RF and ACPA and can be refractory to immunosuppressive therapy used to manage the myositis and interstitial lung disease.*
- *Systematic sonographic evaluation of patients with ASyS is needed to further evaluate pathology and treatment response of inflammatory arthritis.*

Keywords Antisynthetase syndrome · Inflammatory arthritis · Inflammatory myopathy · Ultrasonography

Introduction

Among the idiopathic inflammatory myopathies (IIM), the antisynthetase syndrome is a distinct subgroup. Antisynthetase syndrome (ASyS) is characterized by varying degrees of inflammatory myopathy, arthritis, mechanic's hands, interstitial lung disease, fever, and Raynaud's phenomenon [1]. The hallmark of this disease is the presence of autoantibodies directed against the aminoacyl-tRNA synthetases (ARS), with each antibody seemingly associated with varying degrees of disease expression and severity. To date, seven ARS antibodies are recognized (Jo-1, PL7-, PL-12, EJ, OJ, Ks, Zo, Ha), with Jo-1 as the most commonly found antibody in IIM.

The major manifestations of myositis, arthritis, and interstitial lung disease can occur at onset or later in the disease course. Among the extra-muscular manifestations of ASyS, less attention has been drawn to the joint involvement, even though approximately 70% of patients develop arthralgia or arthritis during the course of their disease [2–4]. Polyarthritis may be the initial manifestation often leading to an initial diagnosis of rheumatoid arthritis [5, 6]. In fact, 445 of 636

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(64%) ASyS had polyarticular, symmetrical arthritis from disease onset in the American and European Network of Antisynthetase Syndrome (AENEAS network) [2]. Additional diagnostic complexity is created by the presence of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), which can be found in ASyS and may lead to more prominent and severe arthritis [7–9]. Recently, multicenter collaborations have characterized aspects of arthritis and its clinical presentation in the context of ASyS [2, 4]. There is a growing appreciation of the contributions of joint involvement in this disease [10].

Ultrasonography has become an important imaging modality to evaluate inflammatory arthritis in rheumatoid arthritis and related diseases [11–13]. Sonographic evaluation of the synovium has been shown to correlate with pathology, specifically in regard to synovial vascularity and pro-angiogenic gene expression [14]. In ASyS-associated arthritis, there have been no published studies using musculoskeletal ultrasound to evaluate joints, with a scarcity of anatomic descriptions of articular disease. We therefore sought to describe eight cases of ASyS-associated arthritis evaluated with ultrasonography to highlight pathologic changes seen.

Patients and methods

This is a retrospective case series of patients with ASyS-associated inflammatory arthritis, who were referred for evaluation and treatment of symptomatic joints at the Johns Hopkins Musculoskeletal Ultrasound and Injection Clinic between November 2014 and May 2018. Each patient was evaluated by one examiner (JA). We identified and reviewed the medical records of those patients with ASyS-associated arthritis with available sonographic imaging of their joints. All patients were consented for participation in the longitudinal myositis cohort study approved by the Johns Hopkins Institutional Review Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Ultrasound assessments Symptomatic joints ($n = 17$) were assessed in each patient based on clinical need. Studies were carried out using a GE Logiq e (GE, Fairfield, CT, USA) with 12 L linear phased array transducer or hockey stick probe. For each joint region scanned, standard orthogonal views of symptomatic areas were obtained. The images were then reviewed by JA and JM, assessing for the presence/absence of joint pathology (synovial hypertrophy, Doppler enhancement, effusion), tendon pathology (tenosynovitis, enthesopathy), and bone changes (erosions). Definitions for ultrasound pathology are as described by OMERACT [15].

Results

Demographics

Eight patients with ASyS-associated arthritis were included in this study [Table 1]. They ranged in age from 28 to 57 years (44.8 ± 11.6 years), and 75% were female. Five patients had anti-Jo-1 antibodies, two had anti-PL-12 antibodies, and one had anti-EJ antibodies. Anti-Ro antibodies were present in four patients in addition to the antisynthetase antibodies. This was further characterized in three patients, of whom two had anti-Ro52 antibodies, and one patient had both anti-Ro52 and anti-Ro60 antibodies. RF was present transiently in low titer in one patient at the onset of the disease, though this was negative with subsequent testing. ACPA was initially negative in one patient but later was positive at 28.8 units (< 20 units). ACPA was otherwise negative in all other patients.

Three patients presented with arthritis as one of the initial manifestations of disease, and this was associated with concurrent muscle, lung, and/or cutaneous involvement in each patient. In this small cohort, no patient presented with isolated arthritis at the onset. Arthritis developed 6.8 ± 4.4 years later in the remaining five patients, often as immunosuppression directed at inflammatory myopathy and/or interstitial lung disease was tapered. All patients in this cohort developed clinically relevant myopathy and interstitial lung disease; 63% ($n = 5$) developed Raynaud's phenomenon, and 63% ($n = 5$) developed cutaneous disease. One patient developed overlap psoriasis 6 years after the diagnosis of ASyS.

Five patients never used tobacco products. Two were former smokers (1 pack-year and 14 pack-years) who had quit at least two decades before the diagnosis of ASyS. One patient actively uses tobacco products, estimated at 0.25 packs per day with a 12 pack-year history.

In the three patients with arthritis at initial presentation, there was symmetric involvement of the large (knees, hips, elbows) and small (hands, wrists, ankles, feet) joints. Later onset of arthritis was polyarticular, commonly involving the small joints of the hands, wrists, ankles, and feet. Shoulders and knees were also commonly involved with a later presentation. The patient with overlap psoriasis never developed dactylitis, DIP, or axial disease.

Ultrasound findings

The most frequently imaged joint was the hand (including MCPs, PIPs). In order of decreasing frequency, the other joints assessed included the wrists, feet, ankles, elbows, and knees [Table 2].

Table 1 Patient demographics and clinical variables

Patient ID	1	2	3	4	5	6	7	8
Age at diagnosis	56 F	51 M	57 M	37 F	30 F	46 F	28 F	53 F
Antibodies	Jo-1	Jo-1	Jo-1, RF, ACPA	Jo-1, Ro52	Jo-1, SSA	PL-12, Ro52	PL-12, Ro52, Ro60 RF	EJ
Duration of ASyS at the onset of arthritis	5 years	6 years	0 years	0 years	2 years	7 years	0 years	14 years
Duration of arthritis at time of US	1 year	2 years	3 years	3 years	2 years 5 years	2 years	7 years	2 months
IS at time of US	MMF, Pred (20 mg)	MTX	MTX, RTX, Pred (10 mg)	RTX, MMF	AZA AZA, MTX	AZA, Pred (20 mg)	AZA, Pred (7.5 mg), IVIG	AZA, LFN, Pred (20 mg)
Other IS prior to US	Pred, AZA, MMF	MTX	Pred AZA, MMF, IFX, RTX	Pred, AZA, MTX, MMF, RTX	Pred, HCQ, AZA, MTX	Pred, HCQ, AZA, ADA, RTX	Pred, HCQ, MMF, ADA, Toci, Aba	Pred, HCQ, AZA, LFN
Organ manifestation at ASyS onset								
Arthritis	–	–	+	+	–	–	+	–
Muscle	+	+	+	+	+	–	–	+
ILD[a]	+	+	+	–	+	+	+	+
Skin	+[b]	–	–	–	–	–	–	+[c]
Raynaud's phenomenon	–	–	–	+	+	+	+	–
Fever	+	–	–	–	–	–	–	–

ASyS antisynthetase syndrome, *IS* immunosuppression, *ILD* interstitial lung disease, *US* ultrasound,

Aba abatacept, *ADA* adalimumab, *AZA* azathioprine, *HCQ* hydroxychloroquine, *IFX* infliximab, *LFN* leflunomide,

MTX methotrexate, *MMF* mycophenolate mofetil, *Pred* prednisone, *RTX* rituximab, *Toci* tocilizumab

[a] Evaluated by chest CT and pulmonary function testing

[b] Gottron's papules, mechanic's hands, periungual erythema, and shawl sign

[c] Mechanic's hands

Table 2 Ultrasound findings

Patient	Location	Gray scale	Doppler	Effusion	Tenosynovitis	Enthesopathy	Erosion
1	Hand	+	+	+	–	–	+ (MCP)
	Wrist	+	+	+	–	–	+ (wrist)
2	Hands	+	–	+	+ (finger extensors)	–	+ (MCP)
3	Hands	+	+	+	+ (finger flexors)	–	+ (MCP)
	Wrist	+	+	–	+ (wrist extensors)	–	–
4	Hand	+	+	+	+ (wrist extensors, finger flexors)	–	–
	Wrist	+	+	+	+ (wrist extensors, finger flexors)	–	–
5	Hand (a)	+	–	+	–	–	–
	Hand (b)	+	–	+	–	–	–
	Wrist (b)	+	–	+	+ (wrist extensors)	–	–
6	Wrist	+	+	–	+ (wrist extensors)	–	–
	Elbow	+	+	–	–	–	–
7	Hand/wrist	+	+	+	+ (extensor carpi ulnaris, finger flexors)	–	–
	Foot/ankle	+	+	+	–	+ (decreased echogenicity of peroneus and Achilles tendons)	+ (MTP)
	Knee	+	+	+	–	+ (decreased echogenicity of patellar tendon)	–
8	Hands	+	+	+	+ (finger flexors)	+ (tendinitis with Doppler of finger extensor at PIP with enthesophyte)	+ (MCP)
	Wrists	+	+	+	–	–	–

PIP proximal interphalangeal joint, *MCP* metacarpophalangeal joint, *MTP* metatarsophalangeal joint; a, US at 2 years of arthritis duration; b, US at 5 years of arthritis duration

Synovial hypertrophy was present in all eight patients and was present in all 17 sonographic assessments of symptomatic joints [Fig. 1a]. Active Doppler enhancement was present in 76% ($n = 13$) of imaged joint locations [Fig. 1b]. Effusions were present in 71% ($n = 12$) and involved large and small joints [Fig. 1c]. Tendon evaluation showed marked tenosynovitis of the finger flexors or wrist extensor tendons in seven patients [Fig. 1d, e]. Tendinopathy was also seen in two cases, showing decreased echogenicity and tendon thickening at the patellar, peroneal, and Achilles tendons. Thickening of the extensor tendons at the fingers, with and without Doppler enhancement, was also seen.

Erosions and bony cortical irregularities were seen in five patients involving 35% ($n = 6$) of assessments [Fig. 1f]. Erosive disease most commonly involved the hands ($n = 4$) followed by the wrist ($n = 1$) and foot ($n = 1$). One patient developed erosive disease within the first year of musculoskeletal symptoms, though the overall ASyS disease duration at that time was 6 years. There was no difference between duration of disease based on the presence of erosions. Three of five patients with anti-Jo-1 antibodies had erosive disease, with erosive disease also seen in one patient with anti-PL-12 and one patient with anti-EJ antibodies. While half of this cohort ($n = 4$) had anti-Ro antibodies, these antibodies were only present in one of five patients with erosive disease.

Discussion

In the eight patients included in this study, a variety of pathologic findings were seen, usually with marked inflammatory changes despite active immunosuppressive treatment for their myositis. We found proliferative synovitis often with active Doppler enhancement, prominent tenosynovitis of the hand and wrist, tendinitis, effusions, and erosions. These findings resemble features seen in patients with rheumatoid arthritis and involve similar joints [12, 16, 17].

Clinically, the inflammatory arthritis of ASyS has been confused with rheumatoid arthritis [10, 18–21]. As described in one cohort, patients with early arthritis typically presented with a symmetric polyarthritis, and a later presentation of these symptoms was more likely to be oligoarticular or asymmetric [2]. Rheumatoid factor and ACPA can also be found in IIM, occurring in 10–15% of patients [7–9]. There is a suggestion that the presence of RF and ACPA increases the prevalence of early joint involvement and aggressiveness of disease [5, 7, 9, 10, 22]. Other studies, however, have suggested that RF and ACPA do not increase the prevalence of erosions [7]. The timing of articular involvement may be more relevant than these serologies, as the AENEAS cohort showed that early arthritis was associated with a higher prevalence of erosions, independent of serology [2]. Similar studies have also found no difference in risk of erosive disease in patients with

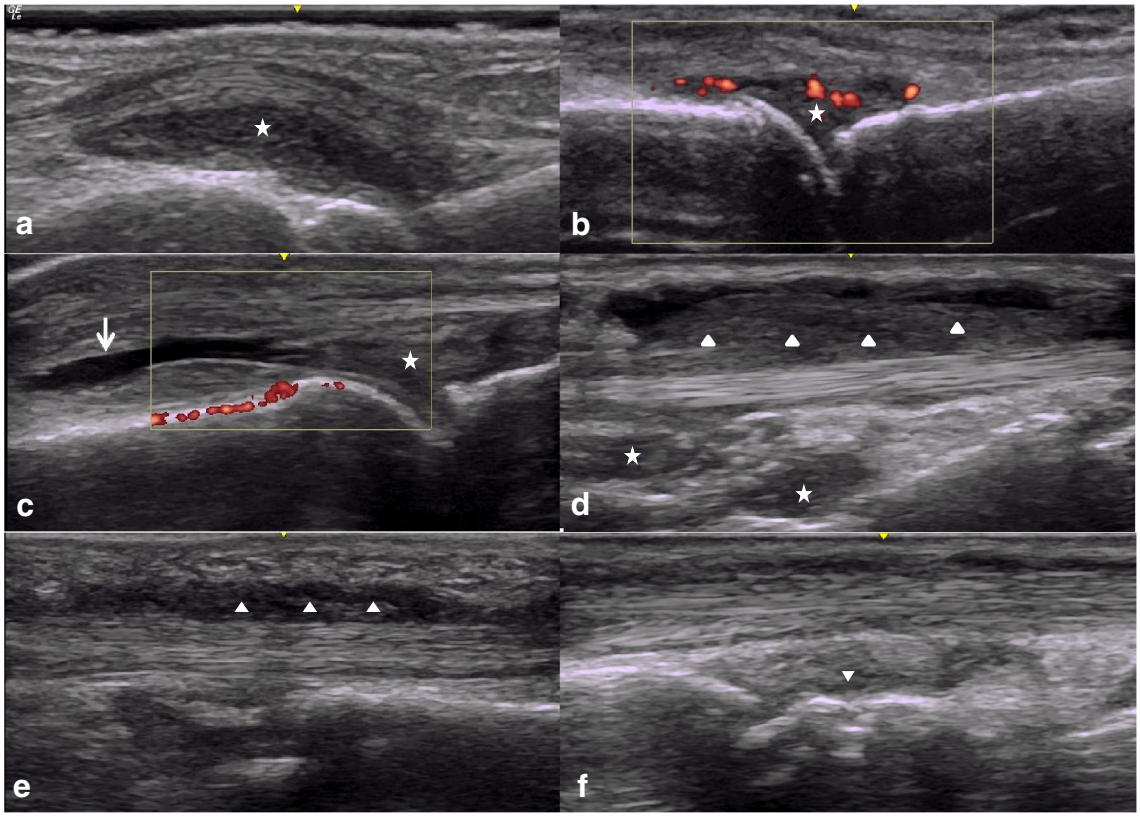

Fig. 1 Ultrasound images from patients with antisynthetase syndrome. **a** Marked synovial hypertrophy at an MCP joint (star); **b** synovial hypertrophy with Doppler enhancement at an MCP (star); **c** effusion at proximal recess of MCP joint (arrow) with synovial hypertrophy (star); **d** hypoechoic collections within extensor tendon at wrist comprising tenosynovitis (arrowheads), with synovial proliferation at radiocarpal and midcarpal joints (star); **e** hypoechoic collections within the finger flexor tendon sheath (arrowhead); **f** step down deformity (erosion) of carpal bone (arrowhead)

positive RF or ACPA [8]. In our cohort, only one patient had a persistent RF or ACPA, which indicates that ASyS antibodies alone can associate with such aggressive presentations.

The coexisting autoantibodies more commonly present in our cohort were anti-Ro antibodies, occurring in 50% of patients. Other studies have similarly shown a high prevalence of anti-Ro antibodies in ASyS, occurring in 52–66% of patients [23]. While larger studies have shown that anti-Ro52 antibodies do not increase the risk of joint complaints, these antibodies have been associated with a higher prevalence of erosions and increased risk of progressive joint deterioration [24]. Our center has previously shown that anti-Ro52 antibodies are also associated with earlier arthritis [25].

ASyS can lead to significant joint damage and disability. One patient in our cohort, a 26 years old woman with PL-12 antibodies, required extensive synovectomy, arthroplasty, and tendon transfer along with bilateral hip replacements within 4 years of disease onset. We also saw active inflammation despite the use of strong immunosuppressive regimens, often when muscle, skin, and lung disease had stabilized.

For most patients, prednisone and azathioprine were used at the time of initial evaluation reflecting the prevalence of concurrent pulmonary disease. However, most of the selected patients required additional immunosuppressive therapies for their joint disease over time. Seven patients were treated with rituximab, and three patients required anti-TNF therapy for arthritis. One patient had inflammatory arthritis that was refractory to treatment with adalimumab, tocilizumab, abatacept, and rituximab but eventually responded to tofacitinib. Our series, however, may be depicting the more severe end of the spectrum of joint involvement, as patients referred for clinical ultrasound had severe or persisting joint pain with need for diagnostic clarity or therapeutic intervention. Nevertheless, this hints to the potential aggressiveness of the articular disease.

Overall, the joint disease in ASyS appears to bear many similarities to rheumatoid arthritis; however, it is still not clear whether similar biological pathways may be involved. Given the multisystem involvement that accompanies ASyS and the therapeutic implications, a heightened awareness of this condition as a mimicker of seronegative or seropositive RA needs to be considered. In patients with early polyarthritis, a positive ANA and the presence of Raynaud's phenomenon may suggest the need for further evaluation of ASyS, as the onset of muscle and pulmonary involvement may be delayed by

21 months and 41 months, respectively, following the onset of arthritis [5].

Despite the retrospective nature and small numbers of our study, we demonstrate the characteristics of the joint disease in ASyS and the anatomic compartments involved using ultrasound. Although inflammatory arthritis and arthralgia are commonly present in the setting of ASyS, this component may often be overlooked in light of more urgent organ involvement (e.g., lung). Joint activity, however, should not be neglected as it can lead to structural damage and be further cause for disability. In this regard, further systematic evaluation is needed to further our understanding of articular pathology and treatment response in ASyS.

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Compliance with ethical standards

All patients were consented for participation in the longitudinal myositis cohort study approved by the Johns Hopkins Institutional Review Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Disclosures None.

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