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Original article

Increased incidence of spondyloarthropathies in patients with Takayasu arteritis: a systematic clinical survey

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ABSTRACT

Objectives: Takayasu arteritis and Spondyloarthritis are two distinct inflammatory diseases that affect the same age periods. Increasing number of reports on co-incident Takayasu arteritis-spondyloarthritis cases in literature raised the hypotheses about their association. The purpose of this study is to evaluate the incidence of spondyloarthropathy spectrum diseases in Takayasu arteritis patients.
Methods: Detailed clinical and demographic features of Takayasu arteritis patients were recorded and all were screened meticulously for the presence of spondyloarthropathy features following recommendations of Assessment of SpondyloArthritis international Society. Patients were questioned for inflammatory back pain, enthesitis, uveitis, inflammatory bowel disease, peripheral arthritis, and investigated accordingly with HLA-B27, plain X-rays and sacroiliac magnetic resonance imaging.
Results: A total of 69 Takayasu arteritis patients (65 female, 94.2%) were enrolled. After detailed investigation, 14 (20.3%) Takayasu arteritis patients fulfilled the Assessment of SpondyloArthritis international Society criteria for Spondyloarthropathy. Two of 14 (14.2%) spondyloarthropathy patients were positive for HLA-B27. Type 1 and type 2 Takayasu arteritis were more common in patients with diagnosis of both Takayasu arteritis and spondyloarthropathy than those without spondyloarthropathy. Most of patients with diagnosis of both these diseases required biologic therapies than patients with diagnosis of Takayasu arteritis alone (64.3% vs 29.1%, $P = 0.014$) due to refractory Takayasu arteritis.
Conclusion: Our results suggest a significant association between Takayasu arteritis and spondyloarthropathy. Possible shared genetic or immunopathogenic processes may explain this association, which merits further investigations.

1. Introduction

Takayasu arteritis (TA) is a rare granulomatous large vessel vasculitis which primarily affects aorta and its major branches causing stenosis, occlusion, dilatation and aneurysm formation. TA is a very rare disease with a per million population incidence of 2.6 in the United States, 0.8 in Sweden, 1–2 in Japan [1,2]. The annual incidence of TA in Turkey was estimated as 1.11 to 3.3/million, while the prevalence was estimated as 12.8 to 33/million [3,4]. Women are predominantly affected with an age of onset of ≤ 40 years [5,6]. Clinical manifestations are determined by the affected vessels and degree of inflammation [7]. Although the etiology of TA is unknown, genetic factors and cell-mediated autoimmunity are thought to play an important role in the pathogenesis of TA [8,9].

Spondyloarthritis (SpA) represents a group of inflammatory diseases characterized by enthesitis and subchondral inflammation affecting primarily axial (sacroiliac and spinal) and peripheral joints with additional extra-articular manifestations. SpAs have strong genetic influence; with HLA-B27 is the most prominent one. The estimated prevalence of SpA is as high as 1–2% in general population, although the frequency varies in different ethnic backgrounds [10]. In a nationwide study, the prevalence of SpA in Turkey was estimated as 0.46% [11].

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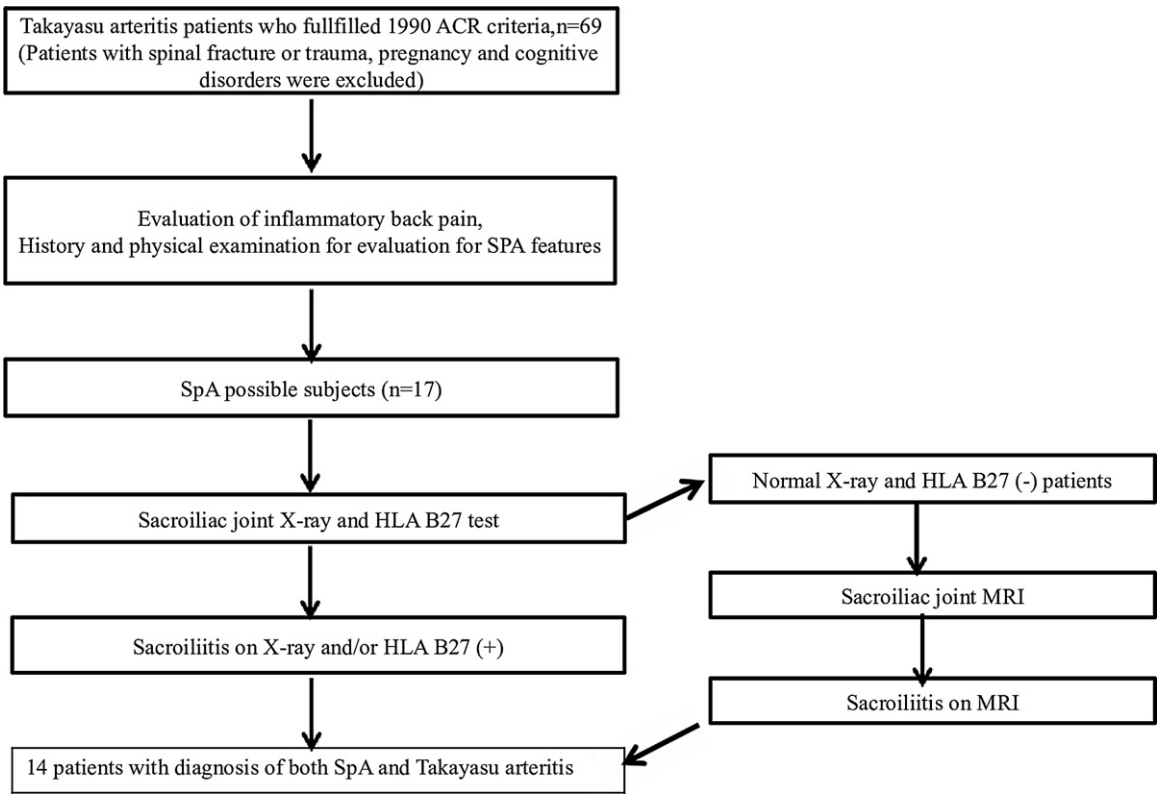

Fig. 1. Summary of the study SpA:Spondyloarthritis,MRI:Magnetic resonance imaging.

TA is a very are disease, and co-existence of TA and SpA is even rarer. Although there are many case reports on co-incidence of ankylosing spondylitis (AS) and TA since 1960's [12–14], no comprehensive study investigated the frequency of this association. A common pathophysiological background, especially a genetic mechanism or immunopathogenetic process can confirm the association of SpA and TA, and this association is probably not co-incidental [15]. In addition to this association, TA and psoriatic arthritis, ulcerative colitis, Crohn's disease or the association of these diseases with each other have also been shown.

Our hypothesis (clinical experience) is that TA and SpA association is more common than general assumption. The purpose of this study is to investigate the frequency of SpA spectrum diseases in patients with TA and define clinical features of patients with diagnosis of both TA and SpAs.

2. Methods

All TA patients admitted to two adult rheumatology clinics between April 2017 and April 2018 were included. All patients were fulfilled 1990 American College of Rheumatology (ACR) Classification Criteria for Takayasu arteritis [16]. ACR criteria include five clinical and one imaging criteria; age at disease onset $\leq$ 40 years, bruit over one or both subclavian arteries or the abdominal aorta, difference of at least 10 mmHg in systolic blood pressure between the arms, claudication of the extremities, decreased pulsation of one or both brachial arteries, arteriographic narrowing or occlusion. Diagnosis of TA requires at least three of six criteria. Those patients with spinal fracture or trauma, pregnancy and cognitive disorders were excluded from study. Demographic variables, TA disease features, co-morbidities, baseline and follow up radiographic findings, medical and surgical therapeutic interventions were recorded. The angiographic involvement pattern was categorized according to definition of Numano et al. [17]. The study was approved by the local ethics committee and informed consent was obtained from all participants.

Detailed evaluation including history and physical examination was performed in all patients in order to identify characteristics that suggest the presence of SpA; back and/or hip pain, history of uveitis, kyphosis, scoliosis, motion limitation of spine (lateral, anterior, posterior) and hip, history of arthritis (mono/oligo/polyarthritis) and enthesitis, diagnosis of inflammatory bowel disease (IBD) and psoriasis/psoriatic arthritis and osteoporosis, family history of SpA, IBD and psoriasis. Patients with back-hip pain longer than 3 months further evaluated with the following parameters to characterize inflammatory back pain (IBP); age at onset < 40 years, insidious onset, improvement with exercise, worsening with rest, and pain at night with improvement upon getting up. At least 4 of the following 5 parameters required to identify IBP [18].

HLA-B27 analysis and sacroiliac joint (SIJ) X-rays were performed in all patients with suspected SpA. The SI joint abnormalities were graded from 0 (normal) to 4 (total ankylosis) according to 1996 New Yok criteria. Patients regarded as positive for radiographic sacroiliitis if the score $\geq$ grade 2 bilaterally or $\geq$ grade 3 unilaterally [19]. Patients with grade 0, 1 and unilateral grade 2 sacroiliitis were further evaluated with SI magnetic resonance imaging (MRI). Sacroiliac MRI images and SIJ x-rays were assessed by a radiologist (MU) who blinded to clinical characteristics and SIJ x-ray images. T1-weighted, short tau inversion recovery (STIR) without contrast enhancement and T2-weighted sequences with fat suppression were used. Active inflammatory lesions (subchondral bone marrow edema/osteitis, synovitis, enthesitis, and capsulitis) and structural changes (subchondral sclerosis, bone erosion, fat metaplasia, bony bridges and ankylosis) were evaluated on MR images. The ASAS definition was used to define active sacroiliitis. Active sacroiliitis should include; bone marrow edema (BME) on STIR or on T2-weighted images with fat suppression in subchon-

Table 1
Characteristics of patients with Takayasu arteritis.

Characteristics	
Female, *n* (%)	65 (94.2)
Mean age at onset of TA symptoms, years	33.5 ± 14
Mean age at diagnosis, years	36 ± 13.5
Mean age of patients, years	43.4 ± 13.3
Number of patients ≤ 40 years at TA diagnosis, (%)	50 (72.5)
Claudication of extremities, *n* (%)	23 (33)
Decreased brachial artery pulse, *n* (%)	39 (56.5)
Blood pressure difference > 10 mmHg, *n* (%)	35 (50.7)
Bruits over subclavian or aorta, *n* (%)	31 (45)
Arteriogram abnormality	59 (85)

dral or periarticular bone marrow and at least two BME lesions on the same slice, or one lesion in the same quadrant on at least two consecutive slices should be observed [20,21]. ASAS criteria were used for diagnosis of SpA. Details of assessment is presented in (Fig. 1).

All statistical analyzes were performed with the Statistical Package for the Social Sciences (SPSS) 15.0 software (SPSS Inc., Chicago, IL). Descriptive values are presented by mean (Standard Deviation, SD) or median (range) and categorical variables as percentages. Comparison of categorical and continuous variables of SpA (+) and SpA (-) patients with TA were performed with Chi^2 and Mann–Whitney U tests respectively. *P*-values ≤ 0.05 were considered as statistically significant.

No specific external funding was dedicated for this study.

3. Results

Total 69 TA patients (65 female, 94.2%) were enrolled. Mean age of patients were 43.4 ± 13.3 years. Age at onset of symptoms and age of diagnosis were 33.5 ± 14 and 36 ± 13.5 years, respectively (Table 1). Hypertension and renal artery stenosis were the most common co-morbidities associated with TA (37.7% and 15.9%, respectively, (Table 2). Except coronary artery disease, comorbidities were similar between TA + SpA group and TA without SpA group (Table 2). Fatigue, weight loss and fever were the most common constitutional symptoms respectively (Table 3). Weak pulses (56.5%), asymmetric blood pressure between arms (50.7%), bruits (45%), headache and carotidynia (40%) were other frequent sign and symptoms. The frequency of clinical symptoms and findings were mostly similar between TA patients with/without SpA (Table 3). The most commonly affected organ systems were respiratory, cardiovascular, renal and neurologic systems. Typical arteriographic findings (85%) and age at disease onset before 40 years (72.5%) were two most frequent ACR criteria for TA. Type V was the most common angiographic involvement pattern (43.5%). At the time of evaluation 15 patients (21.7%) were receiving anti-TNF treatment while 16 (23.2%) patients were on tocilizumab treatment. SpA related clinical and imaging features were given in Table 4.

Table 3
Clinical symptoms and findings in patients with Takayasu arteritis.

Symptoms/Findings	TA + SpA (n = 14)	TA without SPA (n = 55)	*P*
Fever	5 (35.7)	15(27.3)	0.53
Weight loss	6 (42.9)	15(27.3)	0.25
Fatigue	14 (100)	39 (70.9)	0.021
Carotidynia	7 (50)	21 (38.2)	0.42
Raynaud phenomena	0	8(14.5)	0.12
Back pain	8 (57.1)	13 (23.6)	0.015
Syncope	2 (14.3)	9 (16.4)	0.85
Headache	5 (35.7)	23 (41.8)	0.8
Vision impairment	1 (7.7)	8 (14.5)	0.51
Dyspnea	2 (14.3)	14 (25.5)	0.37
Angina	2 (14.3)	6 (10.9)	0.72
Palpitation	4 (28.6)	21 (38.2)	0.5
Erythema nodosum	0	1 (1.8)	0.61

All values are presented as *n* (%).

Table 4
Musculoskeletal findings and spondyloarthropathy related features in patients with Takayasu arteritis.

Symptoms/Findings	*n* = 69 (%)
Chronic back pain	28 (39.4)
IBP	17 (23.9)
Peripheral arthritis	5 (7.2)
Enthesitis	5 (7.2)
Uveitis	4 (5.8)
Psoriasis	3 (4.3)
Erythema nodosum	3 (4.3)
Crohn's disease	2 (2.9)
Ulcerative colitis	2 (2.9)
Family history of SpA	4 (5.8)
Family history of psoriasis	3 (4.3)
Sacroiliitis (grade ≥ 2 X-ray)	8 (11.6)
MRI sacroiliitis	4 (5.8)

All values are presented as *n* (%). IBP: inflammatory back pain; MRI: magnetic resonance imaging; NSAIDs: non-steroidal anti-inflammatory drugs; SpA: spondyloarthritis.

While 28 patients (39.4%) had chronic back pain, 17 (24.6%) of them had inflammatory back pain. According to ASAS criteria 14 of 69 (20.3%) TA patients were diagnosed as SpA. HLA B27 was positive in two of 14 (14.2%) SpA confirmed patients. ASAS definition and clinical characteristics of SpA suspected patients were described in Table 5. Seven of 14 TA-SpA patients fulfilled the modified New York criteria for AS, but two of them had co-existent psoriatic arthritis and finally five patients classified as AS. Four patients with co-morbid IBD and three patients with co-morbid psoriasis had had other SpA features. Remaining two patients were classified as peripheral SpA and undifferentiated SpA.

SpA was diagnosed prior to TA in 9 patients and age at onset of back pain was 26.4 ± 9.7 years. Mean age, age at onset of TA symptoms and age at diagnosis of TA, were lower in SpA (+) patients than SpA (-) patients but did not reach statistical significance. Type 1 and 2 TA was more common (50%) in SpA (+) and type 5

Table 2
Co-morbidities observed in patients with Takayasu arteritis.

Co-morbidities	All patients (*n* = 69)	TA + SpA (*n* = 14)	TA without SpA (*n* = 55)	*P*
Diabetes mellitus	5 (7.2)	1 (7.1)	4 (7.3)	0.98
Hypertension	26 (37.7)	6 (42.9)	20 (36.4)	0.65
Coronary artery disease	4 (5.8)	3 (21.4)	1 (1.8)	0.005
Congestive heart failure	1 (1.4)	1 (7.1)	0	0.046
Renal artery stenosis	10 (14.5)	0	10 (18.2)	0.084
Chronic kidney disease	2 (2.9)	1 (7.1)	1 (1.9)	0.29
Asthma	3 (4.3)	1 (7.1)	2 (3.6)	0.56
Hepatitis B infection	2 (2.9)	1 (7.1)	1 (1.8)	0.28
IBD	4 (5.8)	4 (28.5)	0	0.004
Psoriasis	3 (4)	3 (21.4)	0	< 0.005

All values are presented as *n* (%). SpA: spondyloarthropathy; IBD: inflammatory bowel disease.

Table 5
Takayasu arteritis patients with inflammatory back pain, and their SpA associated clinical features.

Case #	Age	Sex	TA type	IBP	Arthritis	Enthesitis	Uveitis	Ps/ PsA	IBD	NSAİD response	Family Hx SPA	HLA-B27	CRP	X-ray	MRI	Ax SpA[a]	Per SpA[a]	AS[b]	Final SpA type
1	21	F	2b	+	-	-	-	-	-	+	-	-	17	+	+	+	-	+	AS
2	25	F	4	+	-	-	-	-	+	+	+	-	34	+	np	+	-	-	IBD SpA
3	27	F	5	+	-	-	+	-	+	+	-	-	15	-	+	+	-	-	IBD SpA
4	28	F	2b	+	-	-	+	+	-	+	-	+	9	-	-	+	-	-	PsA
5	30	F	3	+	+	-	-	+	-	+	-	-	21	+	np	+	+	+	PsA
6	31	F	5	+	-	-	-	-	-	+	-	-	4	-	-	-	-	-	-
7	32	F	4	+	+	+	-	-	+	-	+	-	18	-	-	-	+	-	IBD-SpA
8	35	F	2a	+	+	+	-	-	-	+	-	-	14	-	-	-	+	-	perSpA
9	35	F	1	+	-	-	-	-	-	+	-	-	20	+	np	+	-	+	AS
10	37	F	1	+	+	-	-	-	-	+	+	-	18	+	+	+	+	+	AS
11	41	F	5	+	-	-	-	-	+	+	-	-	29	-	+	+	+	-	IBD SpA
12	47	F	5	+	-	-	-	-	-	+	-	-	2	-	-	-	-	-	-
13	51	F	2b	+	-	-	-	-	-	+	-	+	13	-	-	+	-	-	uSpA
14	51	F	5	+	-	-	-	-	-	+	-	-	6	-	-	-	-	-	-
15	55	F	5	+	-	+	+	+	-	+	-	-	8	+	np	+	+	+	PsA
16	58	M	1	+	-	+	-	-	-	+	+	-	40	+	np	+	+	+	AS
17	59	F	3	+	+	+	+	-	-	+	-	-	85	+	np	+	+	+	AS

AxSpA: axial spondyloarthritis; PerSpA: peripheral spondyloarthritis; F: female; IBD: inflammatory bowel disease; M: male; MRI: magnetic resonance imaging; np: not performed; NSAID: non-steroidal anti-inflammatory drugs; Ps: psoriasis; PsA: psoriatic arthritis; SpA: spondyloarthropathy; TA: Takayasu arteritis; uSpA: undifferentiated SpA; CRP: C-reactive protein (*n*: 0–5 mg/L).

[a] Patients who met ASAS classification criteria for axial and peripheral SpA.

[b] Patients who met modified New York criteria for ankylosing spondylitis.

was more common (49.1%) in SpA (-) patients ($P = 0.041$). TA-SpA classified patients required more biologic therapies than non-SpA patients (64.3% vs. 29.1%, $P = 0.014$) due to refractory TA. Used biologic drugs were anti-TNFs in eight, tocilizumab and rituximab in two and ustekinumab in one. Seven of nine TA-SpA patients underwent remission with anti-TNFs and one patient was doing well with tocilizumab. One TA patient with psoriatic arthritis showed very resistant disease and underwent remission with ustekinumab.

4. Discussion

We observed remarkably high incidence of IBP and SpA in patients with TA (24.6% and 20.3%, respectively). In our study, age of onset of IBP symptoms was before the age of TA diagnosis (26.4 ± 9.7 vs. 36 ± 13.5 years). Nine patients had the diagnosis of SpA before the diagnosis of TA (three AS, three IBD, two psoriasis related SpA and one undifferentiated SpA).

TA is a very rare disease worldwide and its incidence is about 1 in per million [1,22]. SpA has a prevalence of 1-2% in worldwide [11]. In literature TA and AS association was presented as single case reports or case series [12–15]. This association was first reported in 1966 by Paloheimo et al. [12]. In a very recent French multicenter retrospective study, 14 patients with co-incident TA and SpA were reported. Subtypes of SpA were ankylosing spondylitis ($n = 11$), psoriatic arthritis ($n = 2$), and synovitis, acne, pustulosis, hyperostosis and osteitis syndrome ($n = 1$). HLA-B27 was positive in 3 cases, negative in 9, and unknown in 2. Thirteen SpA patients were diagnosed before the diagnosis of TA [13]. In other retrospective study from China [14], 1.04% of AS patients had TA and 6 of 470 cases of TA (1.27 %) reported to have AS. All these patients were initially diagnosed as AS, then found to have TA years later. Our findings were further supported these two studies. Again, in a recently published multicenter retrospective study from South Korea, sacroiliitis was present in 7.1% of TA patients and like our findings type 2 was more common in patients with sacroiliitis [23].

SpAs are chronic inflammatory joint diseases associated with HLA-B27. More than 90% of AS patients and 50-70% of other forms of SpAs are positive for HLA-B27 [24]. In above mentioned study, HLA-B27 was positive in 3 cases, negative in 9, and unknown in 2 [13]. In consistent with these reports, only two SpA patients in our study had HLA-B27 and interestingly none of AS patients was positive for HLA-B27. This interesting finding suggests that TA associated SpA might have a different pathophysiologic mechanism and HLA-B27 doesn't have a major role in pathogenesis of these patients.

In despite to extremely low prevalence of TA and 0.46% prevalence of SpA in Turkey, we reported highest coexistence of these two diseases in literature. This may be due to design of our study. This is the first study that prospectively and comprehensively evaluated prevalence of SpA in TA patients. When this high ratio of coexistance is considered, it is not easy to claim that the association of TA and SpA is incidental. While the main reason for this association is not clear, many factors may be responsible. Chronic inflammation in AS may be responsible for extra-articular manifestations. Aortitis, mitral valve disease, conduction abnormalities, aortic insufficiency and cardiomyopathy are among the cardiovascular complications of AS. Arterial inflammation in TA is a consequence of the balance between pro- and anti-inflammatory cytokines. Various pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-6, IL-12 and IL-18 are involved in granuloma formation in large vessels. It has been clearly demonstrated that granuloma formation in giant cell arteritis (GCA), including other granulomatous large vessel vasculitides involves Th1-related cytokines (IL-12, IFN-γ) and Th17-related cytokines (IL-6, IL-17 and IL-23) [25]. In aortic biopsies of TA patients, neutrophilic infiltrations have been demonstrated in vascular lesions [26]. Th17 cells support neutrophils in vascular inflammatory sites by secreting IL-17A, and IL-23 induces differentiation and stabilization of Th17 cells [27]. A recent study showed IL-17A expression in aortic tissue biopsies of active TA patients [28]. Increased Th17 activity evidenced by serum IL-17A and IL-23 in TA offers new perspectives on pathogenesis of TA.

Cyclooxygenase (COX), TNF-α, and IL-17 are main mediators involved in the pathogenesis of SpA. IL-17 synergizes and induces expression of a number of pro-inflammatory cytokines, including TNF-α, and acts in a positive feedback loop to increase the production and effects of IL-17. As a consequence of these interactions, IL-17 creates a strong clinical effect as much as TNF-α [29,30]. IL-17, IL-23 and IL-22 are essential for SpA and act together. IL-23 is responsible for stabilization and differentiation of the IL-17 cells and IL-22 for induction of osteogenesis after the resolution of inflammation [31].

Recently, anti-TNF treatment has been placed on the agenda in TA patients as a treatment option. Interestingly in literature

there are case reports of TA developing after initiation of these agents [32–34]. In these case reports two of three patients with SpA developed TA and the other one developed aortitis after treatment with anti-TNF agents. This paradoxical effect may be due to the presence of different pathophysiologic pathways in a subgroup of patients with TA. Majority of patients with diagnosis of both TA and SpA in our study were also on anti-TNF treatment. Infliximab and etanercept treatments showed positive results in resistant TA patients [35,36]. TNF antagonists are also an important treatment option in ankylosing spondylitis [37]. Targeted biologic therapy response patterns of both diseases together with involvement of above mentioned common pathogenetic pathways further explain their association. In our study, TA and SpA coexistence were found in 20.3% of patients, which is the highest rate that has been ever reported up to now. We made a meticulous investigation of all SpA related features (clinical, laboratory, genetic and imaging) in TA which may cause this higher frequency observed.

Our study has some limitations. Because patients were assessed under treatment, many SpA findings may have been masked and true frequency of TA and SpA association might be higher than we found. We did not perform cytokine studies, which may help to clarify pathogenetic pathways, involved in these two diseases. Although number of subjects is well enough to show an association, further analyzes with subtypes of SpAs and TA clinical presentations could not been performed.

Disclosure of interest

The authors declare that they have no competing interest.

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