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# Takayasu's arteritis: associated inflammatory diseases

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**Key words:** Takayasu's arteritis, ankylosing spondylitis, inflammatory bowel disease, Behçet's syndrome

## ABSTRACT

**Objective.** Case reports and series suggest that Takayasu's arteritis (TAK) can co-exist with other inflammatory disorders. We conducted a formal study to look specifically at the frequency of such inflammatory disorders in a large cohort of TAK followed by a single tertiary centre.

**Methods.** There were 238 patients registered with a diagnosis of TAK. Of these, 19 died, 18 were lost to follow-up and 3 did not wish to respond to our questionnaire. The remaining 198 (175 F/23 M) patients were called back at the outpatient clinic. A standardised form sought whether the patient was also diagnosed with inflammatory bowel disease (IBD), ankylosing spondylitis (AS), Behçet's syndrome (BS), autoimmune or any other inflammatory disorder. The presence of skin-mucosa lesions, inflammatory eye disease and inflammatory back pain were also specifically sought for.

**Results.** We identified 37 (19%) patients with inflammatory bowel disease (n=12, 6%), ankylosing spondylitis (n=15, 8%) or Behçet's syndrome (n=10, 5%). Thirteen (6.5%) patients had systemic or localised autoimmune disease and 9 (4.5%) miscellaneous inflammatory diseases. Among the 139 patients without any concomitant disease, inflammatory back pain (n=49, 35%) was the most common feature, followed by recurrent oral ulcer (n=20, 14%) erythema nodosum (n=17, 12%), arthritis (n=12, 9%) papulopustular lesions (n=8, 6%) and uveitis/scleritis (n=6, 4%). Only 64 patients (32%) did not have any concomitant disease/condition or specific clinical feature.

**Conclusion.** TAK does co-occur with IBD, AS and less frequently with BS in about 1/5 of the patients, at least in a hospital setting. There is no clear temporal pattern. The high prevalence of inflammatory back pain in the dorsal spine in TAK needs further scrutiny.

## Introduction

Takayasu's arteritis (TAK) is a large-vessel vasculitis, with an unknown aetiology (1). It mainly affects the aorta and its main branches as well as the proximal portions of pulmonary, renal and coronary arteries. The vessel inflammation consists of mononuclear cell infiltrations and granulomas, resulting in narrowing or aneurysmal formation of the affected vessels (2). It has a female predominance, with a female/male ratio ranging from 1.2-29.0/1 (3). Although it has been considered to be more common in Far East countries, it has a worldwide distribution (4). A study from the northwest part of Turkey have found an annual incidence rate for TAK to be 0.34/100000/year that is considerably high for such a rare disease (5).

Several articles have previously reported that TAK could co-exist with various chronic inflammatory disorders (6-8). Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are the most frequently reported associated diseases (9). Ankylosing spondylitis (AS) (10), sarcoidosis (11), psoriasis (8), rheumatoid arthritis (RA) (12), Behçet's syndrome (BS) (13) and antiphospholipid syndrome (14) are among the other reported associations, while whether these are associations or mere concomitant presence is not known. Data at hand are based mainly on case reports or series.

We conducted a formal study to look specifically at the frequency of association of such chronic inflammatory/autoimmune disorders in a large cohort of patients with TAK followed at a single tertiary centre.

## Material and methods

There were 238 (207 F/ 31 M) patients registered with a diagnosis of TAK at the Rheumatology Department of Cerrahpasa Medical Faculty, Istanbul University-Cerrahpasa, between 1977 and December 2015. The diagnosis of TAK

Competing interests: none declared.

was based on the finding of typical homogenous arterial wall thickening on conventional, computed tomography or magnetic resonance angiography and confirmed by a rheumatologist (ES).

Among the registered 238 TAK patients, 19 (8%) had died and 18 (8%) were lost to follow-up. 3 (1%) patients did not wish to respond to our questionnaire. The remaining 198 patients were called back to the outpatient clinic for an interview and for a physical examination. The patients who could not come to our clinic were evaluated by phone or e-mail.

A standardised form (Supplementary appendix) sought whether the patient had been also diagnosed by a specialised physician with IBD, AS, BS, psoriatic arthritis, psoriasis, amyloidosis, uveitis, RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SS), inflammatory myositis, small vessel vasculitis, or any other autoimmune or inflammatory disorder.

Patients with IBD were diagnosed as UC or CD if they had relevant findings in the endoscopic examinations confirmed by an expert gastroenterologist (AFC).

AS patients had to fulfill the radiologic 1984 modified New York criteria (15) The presence of inflammatory back pain (dorsal or lower or both) was specifically sought by using the Assessment of SpondyloArthritis international Society (ASAS) criteria (16).

BS patients had to fulfill the International Study Group criteria for the diagnosis of BS (17). Additionally, all patients were asked for the presence of skin-mucosa lesions such as recurrent oral ulcers (at least 3 in a year), genital ulcers, erythema nodosum and papulopustular lesions, and arthritis.

Patients were examined by the same ophthalmologist (DU) for the assessment of uveitis, scleritis, episcleritis and vasculitis. Echocardiography findings including the presence of pulmonary hypertension, aorta insufficiency and left ventricular hypertrophy were noted. In addition to the self-reported information, patient charts and all medical documentation available such as hospitalisation reports, imaging studies

and blood work were used as a source of information. We noted the patient demographic and clinical characteristics such as gender, age at TAK and associated disease diagnosis, current therapies and involved vessels. Finally, all information collected was grouped as:

- a) Any diagnosis compatible with IBD, AS or BS;
- b) Any diagnosis compatible with a systemic or localised autoimmune disease such as SLE, RA and SSc, etc.;
- c) Any diagnosis compatible with a miscellaneous inflammatory disease or condition such as sarcoidosis, amyloidosis, etc.;
- d) Any presence of a specific individual clinical feature ascribed to extra-intestinal involvement of IBD, SpA/AS or BS such as inflammatory back pain, arthritis, oral and genital ulcers, erythema nodosum, papulopustular lesions and inflammatory eye involvement.

The evaluation period of the study was completed in June 2016.

The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from patients and the ethics committee of Cerrahpasa Medical Faculty approved the study (211396/2016).

We used descriptive statistics for the demographic and clinical characteristics. Mean  $\pm$  SD or median (IQR) was given when appropriate. The frequencies may not sum to exactly 100% since some patients may belong to more than one group.

### Results

One hundred and ninety-eight (173 F/25 M) patients were evaluated. Of these, 158 (80%) were evaluated by face-to-face interviews, 38 (19%) were questioned by phone and 2 (1%) by e-mail (Fig. S1). Ninety-four (48%) of these patients had been hospitalised at least once during their follow up. The median follow-up time from diagnosis to the evaluation period was 8 years (IQR: 4–13 years). Table I displays the characteristics of all included patients.

#### Associated diseases or conditions

Pie chart shows distribution of all studied patients (Fig. 1). There were 37 pa-

**Table I.** Demographic and clinical characteristics of the included 198 patients.

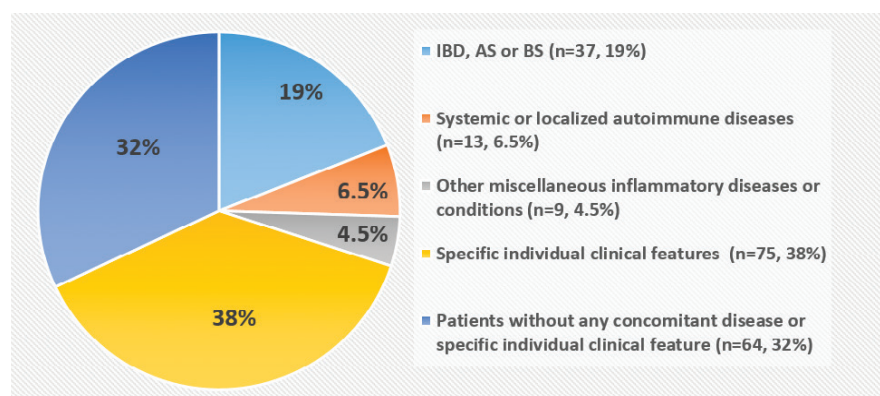
| Characteristics                           | n (%)           |
|---|-----------------|
| Gender, female/male                       | 175/23          |
| Mean $\pm$ SD age at symptom onset, years | 31.7 $\pm$ 11.2 |
| Mean $\pm$ SD age TAK diagnosis, years    | 35.3 $\pm$ 12.4 |
| Median (IQR) follow-up time, years        | 8 (4-13)        |
| Current age, years                        | 45.2 $\pm$ 12.2 |
| Involved vessels <sup>1</sup>             |                 |
| Subclavian artery                         | 159 (80)        |
| Carotid artery                            | 137 (69)        |
| Thoracic aorta                            | 45 (23)         |
| Abdominal aorta                           | 71 (36)         |
| Renal artery                              | 52 (26)         |
| Iliac artery                              | 16 (8)          |
| Visceral artery                           | 92 (46)         |
| Pulmonary artery                          | 14 (7)          |
| Coronary artery                           | 15 (8)          |
| Others                                    | 24 (12)         |
| Current therapies <sup>1</sup>            |                 |
| Off-treatment                             | 40 (20)         |
| Glucocorticoid                            | 113 (57)        |
| Conventional immunosuppressives           | 122 (62)        |
| Cyclophosphamide                          | 7 (3.5)         |
| Biologic therapies                        | 60 (30)         |

<sup>1</sup>Percentages of current therapies and included vessels may not sum to 100 because of rounding. TAK: Takayasu's arteritis.

tients (19%) who had IBD, AS or BS. Thirteen (6.5%) patients had systemic or localised autoimmune diseases. Miscellaneous diseases were present in 9 patients (4.5%). Apart from these, a total of 75 patients (38%) had one or more specific individual clinical features. Sixty-four patients (32%) did not have any concomitant disease/condition or specific individual clinical feature.

#### Inflammatory bowel disease, ankylosing spondylitis and Behçet's syndrome

We identified 12 (6%) patients with IBD, 15 (8%) with AS, and 10 (5%) with BS, all verified by chart review. Among these 37 (19%) patients with IBD, AS or BS, mean  $\pm$  SD age at symptom onset of TAK, mean  $\pm$  SD age at TAK diagnosis and mean  $\pm$  SD age at diagnosis of the concomitant disease were 31.7 $\pm$ 11.2, 35.3 $\pm$ 12.4, and 34 $\pm$ 11 years, respectively. Six patients were male, 1 with IBD, 2 with AS and 3 with BS. Seventeen patients (9 IBD, 3 AS and 5 BS) were diagnosed simultaneously. The onset of TAK preceded IBD



**Fig. 1.** Distribution of associated diseases or conditions of all studied 198 TAK patients. IBD: inflammatory bowel disease; AS: ankylosing spondylitis; BS: Behçet's syndrome.

in 1 patient and AS in 7 patients. The onset of concomitant disease preceded TAK in 2 patients with IBD, 5 with AS and 5 with BS. The demographic and clinical characteristics of these patients are detailed in Tables II-IV.

#### a) Systemic or localised autoimmune diseases

Thirteen (6.5%) TAK patients had autoimmune diseases, including autoimmune thyroid disease in 4, autoimmune hepatitis in 3, seronegative RA in 2 patients, SLE in 2, SSc and SS in 1 patient each. In 3 patients, autoimmune hepatitis developed after anti-tumour necrosis factor alpha (TNF) treatment.

#### b) Miscellaneous inflammatory diseases or conditions

Nine patients (4.5%) had miscellaneous conditions without being labeled as AS/IBD/BS or autoimmune condition. These were amyloidosis in 3 patients (in one along with eosinophilic fasciitis), sarcoidosis in 2 and IgA vasculitis in 2. Additionally, 2 patients had psoriasis, both having disease onset after anti-TNF treatment. Apart from these one patient with TAK and UC had also morphea.

#### c) Specific individual clinical features associated with IBD, AS/SpA or BS

The frequencies of specific individual clinical features in 198 TAK patients are given in Figure 2A. After excluding patients with associated IBD (n=12), AS (n=15), BS (n=10), systemic or localised autoimmune (n=13), or miscellaneous inflammatory diseases or conditions (n=9), the frequencies of these

features in 139 patients were rather similar among TAK patients without any concomitant disease as shown in Figure 2B. When patients with concomitant diseases were excluded, inflammatory back pain was the most common feature (n=49, 35%) followed by oral ulcer (n=20, 14%) erythema nodosum (n=17, 12%), arthritis (n=12, 9%), papulopustular lesions (n=8, 6%), uveitis/scleritis (n=6, 4%) and genital ulcers (n=1, 1%). Inflammatory back pain was reported mostly in the dorsal spine level alone (n=30), less commonly in both dorsal and lumbar spine (n=16) and least common in the lumbar spine alone (n=3). Six (4%) patients had inflammatory eye disease, including episcleritis in 2 patients, anterior uveitis in 2, posterior uveitis in 1 patient and both posterior uveitis and scleritis in 1 patient. Interestingly, one patient reported having recurrent genital ulcers similar to that seen in BS, however she did not fulfill the ISG criteria.

#### Echocardiographic findings

Echocardiographic evaluation was available in 177 TAK patients. Among them, higher than 25 mm/Hg of systolic pulmonary hypertension was present in 51 (29%) patients, dilatation of ascending aorta in 13 (7%) patients, aorta insufficiency in 44 (25%) patients and left ventricular hypertrophy in 27 (15%) patients. Additionally, one patient had mild pericarditis.

#### Discussion

In this survey, we assessed systematically how frequently the inflammatory

symptoms and the concomitant inflammatory diseases in a large cohort of TAK patients registered in a single tertiary centre occurred. We found that TAK can co-occur with IBD, AS or BS in 19% of the TAK patients. This seems to be without a clear temporal pattern. Additionally, clinical features that can be ascribed to extraintestinal IBD, AS/SpA or BS are found in 38% of the patients. On the other hand, association with an autoimmune disease was less frequent (13/198, 6.5%), and of these, 3 had developed after anti-TNF treatment. Only about one third (32%) of the cohort presented without having any concomitant inflammatory feature/disease or condition. Our study indicates that associated diseases in TAK have a clear trend towards MHC-I associated diseases.

IBD is the most reported associated disease with TAK (9). Previous reports indicated a frequency of IBD in TAK ranging from 6.3% to 9.3% (18), which is similar to what was found in our series (6%). IBD in TAK patients does not seem to differ in frequency between different populations, contrary to what have been observed in BS in which the association is more frequently reported among BS patients from Japan or Korea (19). On the other hand, the association is still apparent when reversely investigated. TAK was found the most frequent type of vasculitis among diverse types of vasculitides among patients with IBD (9). In a large multi-centre collaborative study, by Sy *et al.* among 32 patients with IBD and vasculitis, there were 12 with TAK, 1 with giant cell arteritis, 8 with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis, 5 with isolated cutaneous vasculitis and 6 with other vasculitides (9).

Given the rarity of the two conditions, the plausible causes of this frequent association (whether it is a true association or mere co-existence) have been discussed in several reports (20-22). Some authors suggested that there may be a common genetic background (23). Terao *et al.* studied demographic and clinical characteristics as well as genetic associations in 30 patients with UC among 470 patients with TAK coming



**Table II.** Demographic and clinical characteristics of 12 TAK patients with IBD.

| No., Sex | Age at TAK diagnosis | Age at IBD diagnosis | Symptoms at TAK diagnosis          | Symptoms at IBD diagnosis       | UC/CD involvement      | Involved vessels        | Other features  | All medications             | Complications Follow-up                    |
|----------|----------------------|----------------------|------------------------------------|---------------------------------|------------------------|-------------------------|---|-----------------------------|--|
| 1, F     | 36                   | 36                   | Claudication, haemoptysis          | Diarrhea, abdominal pain        | CD, Terminal ileum     | SBC, CCA, ThAo, SMA, PA | Inflammatory dorsal back pain                                     | GC, IFX, MTX, AZA, CYC, RTX | SVE, 8 years                               |
| 2, F     | 46                   | 46                   | Claudication                       | Diarrhea                        | UC, Pancolitis         | CCA, SBC, ThAo, ReA     | FSGS  | GC, AZA, 5-ASA              | ESRD, 5 years                              |
| 3, F     | 28                   | 31                   | Claudication                       | Acute abdominal pain, tenesmus  | CD, Colonic            | SBC, CCA                | OU, Inflammatory dorsal back pain                                 | GC, IFX, AZA                | Perianal fistula, 7 years                  |
| 4, F     | 27                   | 20                   | Carotidynia, tinnitus, weight loss | Bloody diarrhea, tenesmus       | UC, Left-sided colitis | CCA, vertebral          | OU, Inflammatory dorsal back pain                                 | GC, IFX, MTX, 5-ASA         | 14 years                                   |
| 5, F     | 43                   | 43                   | Carotid murmur                     | Diarrhea, abdominal pain        | CD, Ileocolonic        | SBC, CCA, ThAo, PA      | OU, GU Inflammatory dorsal back pain,                             | GC, IFX, AZA, MTX           | PAH, 7 years                               |
| 6, F     | 23                   | 23                   | Claudication                       | Abdominal pain                  | CD, Ileocolonic        | SBC                     | EN, arthritis   | GC, ADA, AZA                | 9 years                                    |
| 7, M     | 47                   | 47                   | High APR, recurrent AMI            | Perianal pain                   | CD, Colonic            | SBC, CCA, ThAo, RA, LAD | PP, anterior uveitis, Inflammatory dorsal back pain,              | GC, IFX, AZA, CYC           | Perianal fistula, recurrent AMI, 4 years   |
| 8, F     | 22                   | 22                   | Claudication, weight loss, fever   | Bloody diarrhea, abdominal pain | UC, Pancolitis         | SBC, CCA, SMA           | OU Inflammatory dorsal and lower back pain, arthritis             | GC, IFX, AZA                | 3 years                                    |
| 9, F     | 26                   | 26                   | Hypertension, fever                | Bloody diarrhea, fever          | UC, Pancolitis         | SBC, BST, AA, CT, IMA   | PP, panuveitis, arthritis, Inflammatory lower back pain           | GC, AZA                     | 17 years                                   |
| 10, F    | 30                   | 30                   | Arthritis                          | None                            | CD, Ileocecal          | AA, SMA, CT, RA         | OU, Inflammatory dorsal and lower back pain, arthritis, psoriasis | GC, AZA                     | 1 year                                     |
| 11, F    | 29                   | 29                   | Claudication                       | Abdominal pain                  | CD, Ileal              | SBC, AA                 | None  | GC, AZA, 5-ASA              | Right colectomy due to stricture, 14 years |
| 12, F    | 34                   | 21                   | Claudication                       | Bloody diarrhea,                | UC, Left-sides colitis | SBC, CCA                | Inflammatory dorsal back pain                                     | GC, AZA                     | 13 years                                   |

5-ASA: 5-aminosalicylic acid; AA: abdominal aorta; ADA: adalimumab; AMI: acute myocardial infarction; APR: acute phase reactants; AZA: azathioprine; BST: brachiocephalic trunk; CCA: common carotid artery; CD: Crohn's disease; CT: celiac trunk; CYC: cyclophosphamide; EN: erythema nodosum; ESRD: end stage renal disease; F: female; FSGS: focal segmental glomerulosclerosis; GC: glucocorticoid; GU: genital ulcers; IBD: inflammatory bowel disease; IFX: infliximab; IMA: inferior mesenteric artery; M: male; MTX: methotrexate; NA: not available; OU: oral ulcers; PA: pulmonary artery; PAH: pulmonary artery hypertension; PP: papulopustular lesions; ReA: renal artery; SBC: subclavian artery; SMA: superior mesenteric artery; SVE: cerebrovascular event, TAK: Takayasu's arteritis; ThAo: thoracic aorta; UC: ulcerative colitis.

from the 14 institutions in Japan (23). Authors indicated that multiple common genetic determinants including HLA\*B52, IL12B and non-HLA markers may contribute to the co-occurrence of TAK and UC.

It seems also that two conditions have similar granulomatous histopathology and hence inflammatory pathways, but we have no solid evidence for this, at least on the basis of serologic markers. Our group had previously studied the frequency of anti-saccharomyces cer-

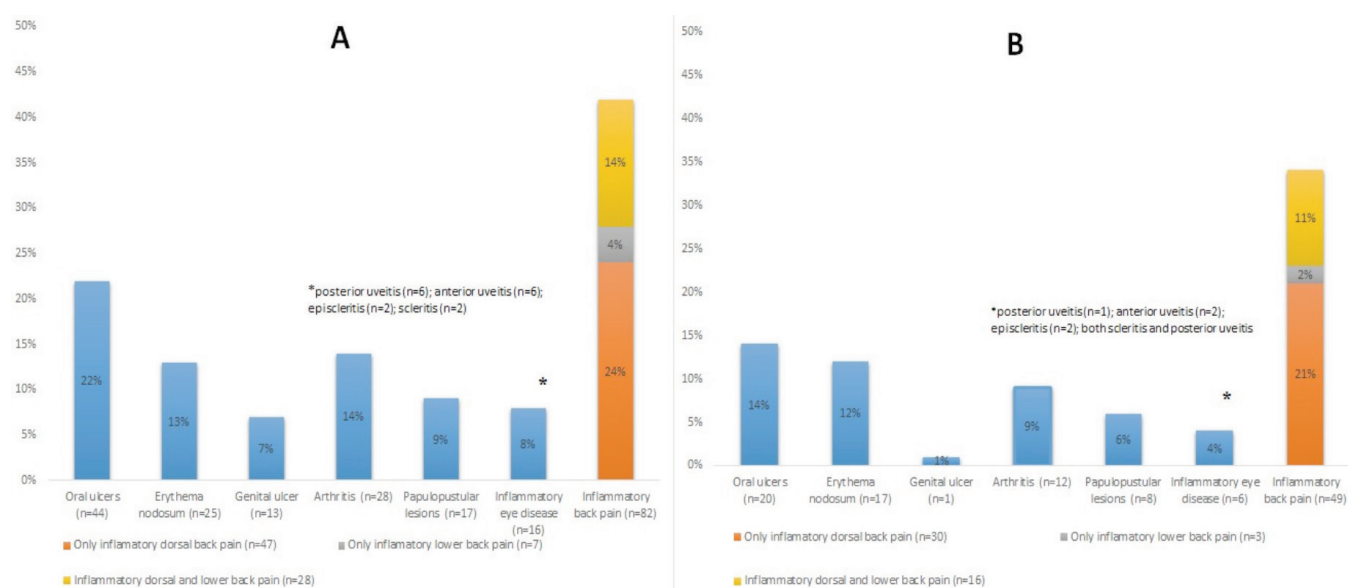
visiae (ASCA) antibodies and ANCA antibodies, serological markers for IBD, among 32 patients with TAK, 38 patients with IBD (21 with CD and 17 with UC) and 34 healthy controls (24). Only patients with CD were found to have significantly higher levels of both ASCA Ig A and Ig G (10/21). The frequency of ASCA positivity in TAK (5/32) was similar to that found in UC (6/17) and healthy controls (3/34), while ANCA antibodies were not found among patients with TAK.

In addition to a few case series and case reports (12, 25, 26), there were 3 formal studies reporting the prevalence of AS in TAK. In the first retrospective study from South Korea, using ICD code research, AS accompanied TAK in 13/268 (5%) of the patients (7). The second study was from Norway where the population frequency of HLA-B27 is high. This was a population-based survey using ICD-10 code search and reported a frequency of 7% among their 78 patients (8). In the last study

**Table III.** Demographic and clinical characteristics of 15 TAK patients with AS.

| No., Sex | Age at TAK diagnosis | Age at AS diagnosis | HLA B27  | Symptoms at TAK diagnosis | Involved vessels                  | Other features           | All medications   | Follow-up |
|----------|----------------------|---------------------|----------|---------------------------|-----------------------------------|--------------------------|-------------------|-----------|
| 1, F     | 21                   | 43                  | NA       | Claudication              | SBC, CCA                          | OU                       | GC, AZA           | 28 years  |
| 2, F     | 25                   | 17                  | NA       | None                      | SBC, CCA, CT, SMA                 | OU                       | GC, AZA           | 5 years   |
| 3, F     | 49                   | 47                  | NA       | Hypertension              | ReA                               | None                     | GC, MTX           | 14 years  |
| 4, F     | 45                   | 45                  | NA       | Claudication              | CCA, ThAo, AA                     | OU                       | GC, IFX, ETA, MTX | 9 years   |
| 5, F     | 27                   | 27                  | Negative | Blurred vision            | SBC, CCA, sinus valsalva aneurysm | None                     | GC, IFX, AZA      | 5 years   |
| 6, F     | 36                   | 36                  | Negative | Claudication              | SBC, CCA, ThAo, AA, CT, SMA, ReA  | EN, PP, anterior uveitis | GC, MTX           | 1 year    |
| 7, F     | 24                   | 29                  | Negative | Claudication              | SBC, CCA, ThAo                    | OU                       | GC, AZA           | 5 years   |
| 8, M     | 31                   | 26                  | NA       | Abdominal pain            | CT, SMA                           | None                     | Golimumab         | 1 year    |
| 9, F     | 37                   | 25                  | Negative | Claudication              | SBC, CCA, ThAo, AA, CT            | None                     | GC, ADA,          | 11 years  |
| 10, M    | 21                   | 18                  | Negative | Angina pectoris           | Coronary arteries, CT             | PP                       | GC, IFX, AZA      | 3 years   |
| 11, F    | 38                   | 39                  | NA       | Fatigue                   | CCA, ThAo, AA, CT, SMA, axillary  | None                     | GC, AZA           | 8 years   |
| 12, F    | 27                   | 44                  | NA       | Myalgia                   | SBC, CCA, internal iliac artery   | OU, anterior uveitis     | GC, CYC, IFX, MTX | 23 years  |
| 13, F    | 31                   | 56                  | NA       | Hypertension              | ThAo, AA, ReA                     | None                     | GC                | 25 years  |
| 14, F    | 20                   | 25                  | Positive | Claudication              | CCA                               | None                     | GC, IFX           | 6 years   |
| 15, F    | 47                   | 49                  | NA       | Claudication              | SBC, ReA, AA, coronary artery     | None                     | GC, MTX           | 2 years   |

ADA: adalimumab; AZA: azathioprine; AA: abdominal aorta; BCT: brachiocephalic trunk; CCA: common carotid artery; CT: celiac trunk; CYC: cyclophosphamide; EN: erythema nodosum; ETA: etanercept; F: female; GC: glucocorticoid; IFX: infliximab; M: male; MTX: methotrexate; NA: not available; OU: oral ulcers; PP: papulopustular lesions; ReA: renal artery; SBC: subclavian artery; SMA: superior mesenteric artery; TAK: Takayasu's arteritis; ThAo: thoracic aorta.



**Fig. 2.** The frequencies of specific individual clinical features among 198 TAK patients (2A) and among 139 patients without any associated disease/s (2B).

**Table IV.** Demographic and clinical characteristics of 10 TAK patients with BS.

| No., Sex | Age at TAK diagnosis | Age at BS diagnosis | Symptoms at TAK diagnosis | BS manifestations              | Involved vessels        | Other features                | All medications   | Follow-up |
|----------|----------------------|---------------------|---------------------------|--------------------------------|-------------------------|-------------------------------|-------------------|-----------|
| 1, M     | 27                   | 27                  | None                      | OU, GU, PAA, STM, Pathergy     | CCA, BCT                | None                          | GC, AZA           | 10 years  |
| 2, F     | 39                   | 27                  | Fatigue                   | OU, GU, EN, Uveitis            | CCA, SBC, ThAo, CT, SMA | None                          | GC, CYC, AZA      | 14 years  |
| 3, F     | 44                   | 44                  | None                      | OU, GU, PP Arthritis, HLA B51  | CCA, SBC, BCT, CT       | None                          | GC, IFX, MTX      | 3 years   |
| 4, F     | 22                   | 22                  | Claudication              | OU, EN, PP, Uveitis            | CCA, SBC, ReA, CT, SMA  | None                          | GC, MTX           | 20 years  |
| 5, M     | 39                   | 39                  | Fatigue, fever            | OU, GU, PP, Arthritis, Uveitis | CCA, ThAo               | None                          | GC, IFX, AZA      | 3 years   |
| 6, F     | 58                   | 51                  | Absent pulse              | OU, GU, PP, Uveitis, Arthritis | SBC                     | None                          | GC, AZA, MTX      | 14 years  |
| 7, F     | 35                   | 20                  | Fatigue, fever            | OU, GU, Arthritis, Uveitis     | CCA, ThAo               | Inflammatory dorsal back pain | GC, MTX, AZA      | 19 years  |
| 8, F     | 37                   | 32                  | Absent pulse              | OU, GU, EN, Pathergy           | SBC, SFA                | Inflammatory dorsal back pain | GC, MTX, CYC, IFX | 27 years  |
| 9, F     | 37                   | 37                  | Fatigue                   | OU, GU, EN, HLA B51            | CCA, ReA                | Inflammatory dorsal back pain | GC, AZA           | 8 years   |
| 10, M    | 69                   | 47                  | None                      | OU, GU, EN, Uveitis            | CCA, SBC                | None                          | AZA, INF          | 29 years  |

AZA: azathioprine; BS: Behçet's syndrome; BCT: brachiocephalic trunk; CCA: common carotid artery; CT: celiac trunk; CYC: cyclophosphamide; EN: erythema nodosum; F: female; GC: glucocorticoid; GU: genital ulcers; IFX: infliximab; INF: interferon alpha; M: male; MTX: methotrexate; OU: oral ulcers; PAA: pulmonary artery aneurysm; PP: papulopustular lesions; ReA: renal artery; SBC: subclavian artery; SFA: superficial femoral artery; SMA: superior mesenteric artery; STM: superficial thrombophlebitis; TAK: Takayasu's arteritis; ThAo: thoracic aorta.

from Turkey, 69 TAK patients were prospectively screened to investigate the incidence of spondyloarthropathy (SpA) in TAK (6). Fourteen patients (20%) were found to fulfill the ASAS criteria, the frequency of AS was 7% in this cohort. We observed a similar AS frequency (8%) in our TAK patients although a routine sacroiliac imaging was not performed in all patients having inflammatory back pain. The prevalence of AS did not differ among different ethnic populations similar to that in IBD, however differences in the study designs make comparisons difficult. Another finding was the low rate of HLA-B27 observed by us and others. This was interesting since aortitis is a well-known pathology in HLA-B27-associated spondyloarthropathies (27). The high prevalence of inflammatory dorsal back pain without lower back pain is a novel finding and deserves further scrutiny. It could be due to aortitis due to TAK, enthesopathy due to

SpA or simply due to fibromyalgia. We did not formally screen SpA in patients with inflammatory back pain which is one of the limitations of our study and we cannot exclude the possibility of concomitant SpA in these patients. There were statistically non-significant increased trends of ascending aortic involvement (40% vs. 20%) and both ascending aortic involvement and aorta insufficiency (20% vs. 9%) in TAK patients with AS compared to those without (data not given). The same was also true for those with IBD. In an animal model, Sherlock *et al.* demonstrated that IL-23, a member of the IL-12 signalling pathway, overexpression led to the development of inflammation in the entheses and in the aortic root also (28). These may be considered in the context of "aortitis of the ascending aorta associated with SpA or associated with Takayasu's arteritis" (29). BS associated with TAK is reported to be very rare (13). In our series, 10 (5%)

TAK patients were diagnosed as BS. One might ask whether these arterial lesions in these patients would be a part of arterial involvement of BS. However, arterial involvement of BS mostly occurs in males and in patients with a history of venous thrombosis (30, 31). On the contrary, 70% of our patients were female and only 1 of them had venous thrombosis. Moreover, BS tends to affect arterial vessels leading to the formation of aneurysms rather than occlusions (32) and none of our patients had an arterial aneurysm. Another confounding factor may be our study site. We run a dedicated multidisciplinary BS clinic in Turkey where BS is also prevalent. Interestingly an association of TAK and BS has, as far as we are aware, not been reported from the Far East where both TAK and BS are also considered to be prevalent. Another speculation might be around the concept of "MHC-opathy" that attempts to bring out an association be-

tween spondyloarthropathies and BS (33). In this scheme BS-associated TAK could be explained by a close association of both BS and TAK with MHC class-1 alleles. The low rate of concomitant autoimmune diseases would also support this contention. Similar assumptions have been made in other articles, as well (29, 31). Authors who had observed the striking increased frequency of associations with AS and IBD, suggested that TAK like arteritis could be one of the conditions included in seronegative spondyloarthropathy family (29).

The aetiology of TAK is yet unknown. Several hypotheses have been proposed. Tuberculosis has been the oldest and the most commonly reported association with TAK (34). The suggestive reasons for this possible association have been a complete remission of TAK after anti-tuberculosis therapy in one report (35), a more frequent purified protein derivative skin test positivity in TAK patients compared to healthy controls and a higher incidence of active tuberculosis in TAK patients (36). However, co-occurrence of TAK and tuberculosis has been mostly reported from areas where tuberculosis is also endemic. Considering the genetic studies, HLA-B52, a MHC class I molecule, was the only established genetic component associated with TAK that has been repeatedly shown in different populations, such as Mexican, Turkish and Japanese (37). As we had already mentioned earlier, HLA-B\*52:01 displayed an OR as high as 12.14 for the complication of UC among TAK patients, as well (23). Recently, 2 genome-wide association studies (GWAS) have provided valuable information on the genetic susceptibility loci in TAK patients. In the first GWAS, FCGR2A/FCGR3A and IL12B have been found to be susceptibility loci for TAK (38). Immediately after that, the second GWAS added three new susceptibility loci for TAK, including IL6 locus, RPS9/LILRB3 locus and an intergenic locus on chromosome 21q22 (39). Interestingly, IL12B is also associated with psoriasis and IBD and chromosome 21q22 is associated with UC and AS.

There are some similarities with the study by Kwon *et al.* (7). We did likewise a systematic evaluation of a large cohort of patients with TAK from a single centre. Different from what was done in their study, we included in the questionnaire, BS and its stigmata, diverse autoimmune conditions and other miscellaneous inflammatory diseases. Our study is also important in that it shows similar trends in disease associations in a totally different ethnicity. There are several limitations in the present study. First and the most important of all is that all patients were followed up in a tertiary rheumatology centre. The increased frequency of disease associations could be due to in fact because people are more likely to be hospitalised or registered in a clinic if they have more than one disease. Second, because of the absence of a diseased control group, it is unclear whether the prevalence of specific individual clinical features of other inflammatory diseases is actually higher in patients with TAK than in those without. Our finding of more or less similar frequency of specific individual clinical features other than aortitis, among our TAK patients with no associated inflammatory disease provides some evidence against this bias. Finally, it is difficult to determine the chronological assessment of the relationship between TAK and other inflammatory diseases since TAK symptoms are generally nonspecific and the presence of asymptomatic periods during vascular inflammation may further delay the diagnosis.

In conclusion, this survey provides new information on the association of TAK and other inflammatory diseases all followed in a single center by the same observers. IBD, AS and BS seem to be associated with TAK in about 1/5th of the cohort. Individual clinical features that can be ascribed to these diseases are found in another ~ 40%. On the other hand, association with an autoimmune condition or diseases seems to be rare. Our findings suggest a clear trend towards association with MHC-1 associated diseases. The high prevalence of inflammatory dorsal back pain without lower back pain is another issue that needs further scrutiny.

## References

1. NUMANO F, KOBAYASHI Y: Takayasu arteritis--beyond pulselessness. *Intern Med* 1999; 38: 226-32.
2. HOTCHI M: Pathological studies on Takayasu arteritis. *Heart Vessels Suppl* 1992; 7: 11-7.
3. MONT'ALVERNE AR, PAULA LE, SHINJO SK: Features of the onset of Takayasu's arteritis according to gender. *Arq Bras Cardiol* 2013; 101: 359-63.
4. WATTS R, AL-TAIAR A, MOONEY J, SCOTT D, MACGREGOR A: The epidemiology of Takayasu arteritis in the UK. *Rheumatology (Oxford)* 2009; 48: 1008-11.
5. SARITAS F, DONMEZ S, DIRESKENELI H, PAMUK ON: The epidemiology of Takayasu arteritis: a hospital-based study from north-western part of Turkey. *Rheumatol Int* 2016; 36: 911-6.
6. GUZEL ESEN S, ARMAGAN B, ATAS N *et al.*: Increased incidence of spondyloarthropathies in patients with Takayasu arteritis: a systematic clinical survey. *Joint Bone Spine* 2019; 86: 497-501.
7. KWON OC, LEE SW, PARK YB *et al.*: Extravascular manifestations of Takayasu arteritis: focusing on the features shared with spondyloarthritis. *Arthritis Res Ther* 2018; 20: 142.
8. GUDBRANDSSON B, MOLBERG O, GAREN T, PALM O: Prevalence, incidence, and disease characteristics of takayasu arteritis by ethnic background: data from a large, population-based cohort resident in Southern Norway. *Arthritis Care Res (Hoboken)* 2017; 69: 278-85.
9. SY A, KHALIDI N, DEHGHAN N *et al.*: Vasculitis in patients with inflammatory bowel diseases: A study of 32 patients and systematic review of the literature. *Semin Arthritis Rheum* 2016; 45: 475-82.
10. RIVIERE E, ARNAUD L, EBBO M *et al.*: Takayasu arteritis and spondyloarthritis: coincidence or association? A study of 14 cases. *J Rheumatol* 2017; 44: 1011-7.
11. CHAPELON-ABRIC C, SAADOUN D, MARIE I *et al.*: Sarcoidosis with Takayasu arteritis: a model of overlapping granulomatosis. A report of seven cases and literature review. *Int J Rheum Dis* 2018; 21: 740-5.
12. BEN ABDELGHANI K, FAZAA A, BEN ABDELGHANI K, LAATAR A, KHEDHER A, ZAKRAOUI L: Chronic inflammatory rheumatism associated with Takayasu disease. *Ann Vasc Surg* 2013; 27: 353 e1-6.
13. IINO K, TOMITA S, HIGASHIDANI K, UJIE T, ARAI S, WATANABE G: Successful coronary revascularization using the PAS-Port system in a patient with Takayasu's arteritis and Behçet's disease. *Ann Thorac Surg* 2006; 82: 1889-91.
14. FUKUI S, HIROTA S, IWAMOTO N, KARATA H, KAWAKAMI A: Takayasu arteritis with antiphosphatidylserine/prothrombin antibody-positive antiphospholipid syndrome: case report and literature review. *Medicine (Baltimore)* 2015; 94: e2345.
15. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
16. SIEPER J, VAN DER HEIJDE D, LANDEWÉ R *et*

- al.: New criteria for inflammatory back pain in patients with chronic back pain: a real patient exercise by experts from the Assessment of SpondyloArthritis international Society (ASAS). *Ann Rheum Dis* 2009; 68: 784-8.
17. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. *Lancet* 1990; 335: 1078-80.
  18. KILIC L, KALYONCU U, KARADAG O *et al.*: Inflammatory bowel diseases and Takayasu's arteritis: coincidence or association? *Int J Rheum Dis* 2016; 19: 814-8.
  19. HATEMI I, HATEMI G, CELIK AF: Gastrointestinal involvement in Behçet Disease. *Rheum Dis Clin North Am* 2018; 44: 45-64.
  20. WATANABE R, ISHII T, NAKAMURA K *et al.*: Ulcerative colitis is not a rare complication of Takayasu arteritis. *Mod Rheumatol* 2014; 24: 372-3.
  21. TAKAHASHI N, TANABE K, SUGAMORI T *et al.*: Association between Takayasu arteritis and ulcerative colitis - case report and review of serological HLA analysis. *Med Sci Monit* 2011; 17: CS81-4.
  22. GECSE K, RUZSA Z, NAGY F, WITTMANN T, MOLNAR T: Successful infliximab treatment in a patient with Takayasu arteritis associated with ulcerative colitis or migration does not override genetics. *Inflamm Bowel Dis* 2011; 17: E69-70.
  23. TERAO C, MATSUMURA T, YOSHIFUJI H *et al.*: Takayasu arteritis and ulcerative colitis: high rate of co-occurrence and genetic overlap. *Arthritis Rheumatol* 2015; 67: 2226-32.
  24. OZBAKIR F, UGURLU S, CELIK AF, SEYAHİ E: Anti-Saccharomyces cerevisiae (ASCA) and anti-neutrophil cytoplasmic (ANCA) antibodies are not increased in Takayasu arteritis. *Acta Reumatol Port* 2011; 36: 20-3.
  25. TAHARBOUCHT S, LANASRI N, LAROCHE JP: [Ankylosing spondylarthritis associated with Takayasu disease: a new case]. *J Mal Vasc* 2010; 35: 259-62.
  26. CHERIN P, BLETRY O, ZIZA JM *et al.*: [The association of ankylosing spondylitis and Takayasu's disease. 3 new cases]. *Rev Rhum Mal Osteoartic* 1990; 57: 33-7.
  27. PALAZZI C, SALVARANI C, D'ANGELO S, OLIVIERI I: Aortitis and periaortitis in ankylosing spondylitis. *Joint Bone Spine* 2011; 78: 451-5.
  28. SHERLOCK JP, JOYCE-SHAIKH B, TURNER SP *et al.*: IL-23 induces spondyloarthropathy by acting on ROR-gammat+ CD3+CD4-CD8- enthesal resident T cells. *Nat Med* 2012; 18: 1069-76.
  29. MIELNIK P, HJELLE AM, NORDEIDE JL: Coexistence of Takayasu's arteritis and ankylosing spondylitis may not be accidental - Is there a need for a new subgroup in the spondyloarthritis family? *Mod Rheumatol* 2018; 28: 313-8.
  30. CEYRAN H, AKCALI Y, KAHRAMAN C: Surgical treatment of vasculo-Behçet's disease. A review of patients with concomitant multiple aneurysms and venous lesions. *Vasa* 2003; 32: 149-53.
  31. HATEMI G, SEYAHİ E, FRESKO I, TALARICO R, HAMURYUDAN V: One year in review 2018: Behçet's syndrome. *Clin Exp Rheumatol* 2018; 36 (Suppl. 115): S13-27.
  32. OZEREN M, MAVIOGLU I, DOGAN OV, YUCEL E: Reoperation results of arterial involvement in Behçet's disease. *Eur J Vasc Endovasc Surg* 2000; 20: 512-9.
  33. MCGONAGLE D, AYDIN SZ, GUL A, MAHR A, DİRESKENELİ H: 'MHC-I-opathy'-unified concept for spondyloarthritis and Behçet disease. *Nat Rev Rheumatol* 2015; 11: 731-40.
  34. CICERO R, CELIS A: Ante-mortem and post-mortem angiography of the pulmonary arterial tree in advanced tuberculosis. *Am Rev Tuberc* 1955; 71: 810-21.
  35. PANTELL RH, GOODMAN BW JR: Takayasu's arteritis: the relationship with tuberculosis. *Pediatrics* 1981; 67: 84-8.
  36. KINARE SG: Nonspecific aortitis (Takayasu's disease). Autopsy study of 35 cases. *Pathol Microbiol (Basel)* 1975; 43: 134-9.
  37. TERAO C, YOSHIFUJI H, MIMORI T: Recent advances in Takayasu arteritis. *Int J Rheum Dis* 2014; 17: 238-47.
  38. SARUHAN-DİRESKENELİ G, HUGHES T, AKSU K *et al.*: Identification of multiple genetic susceptibility loci in Takayasu arteritis. *Am J Hum Genet* 2013; 93: 298-305.
  39. RENAUER PA, SARUHAN-DİRESKENELİ G, COIT P *et al.*: Identification of Susceptibility Loci in IL6, RPS9/LILRB3, and an Intergenic Locus on Chromosome 21q22 in Takayasu Arteritis in a Genome-Wide Association Study. *Arthritis Rheumatol* 2015; 67: 1361-8.