Tuberculosis in Takayasu arteritis: a retrospective study in 1105 Chinese patients

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Abstract

Background  Tuberculosis (TB) infection has been reported to have a possible relationship with the occurrence and clinical course of Takayasu arteritis (TA). We aimed to describe the characteristics of TB in a large population of TA patients. Methods We included a total of 1105 patients with TA, who were hospitalized between January 1992 and December 2017. Comparisons of clinical features were made according to the presence of TB. Results Among the 1105 patients, 109 (9.9%) had TB, including 53 patients (48.6%) diagnosed with TB before the onset of TA, 23 (21.1%) with a concurrent diagnosis of TB and TA, and 24 patients (22.0%) who developed TB after TA. Pulmonary TB was the most frequently identified (97 patients, 89.0%). Patients with TB had more frequent involvement of the pulmonary artery and experienced more chest discomfort and constitutional symptoms but had less interventional treatment. Demographic characteristics, comorbid diseases, and use of steroids were similar between patients with and without TB. Conclusions The proportion of Chinese TA patients with TB was not low, and about half of the patients had TB before TA. Pulmonary TB was the most common. Pulmonary artery involvement and pulmonary hypertension was more frequent in TA patients with TB.

Keywords: Immunosuppressive agents; Mycobacterium tuberculosis; Pulmonary artery; Takayasu arteritis

1 Introduction

Takayasu arteritis (TA) is a rare, chronic vasculitis, which mainly involves the aorta and its main branches. Coronary arteries and pulmonary arteries can also be involved. Initially, patients with TA present constitutional symptoms, including low-grade fever, fatigue, night sweats, and weight loss. As inflammation of the artery walls progresses, symptoms of organic ischemia appear, such as weak pulse, exertion fatigue of the limbs, renovascular hypertension, and even ischemic stroke.[1,2] Prednisone and immunosuppressive agents are essential anti-inflammatory medications and can achieve and maintain remission in most patients.[3] TA is more common in Asia area, Turkey, Mexico, and South Africa.[4-6] The exact etiology of TA remains to be elucidated. Genetic, environmental, and autoimmune factors have been suggested to have important roles.[7]

Infection with Mycobacterium tuberculosis (MtB) is very common, affecting one-third of the world’s population, although only a small proportion of people with MtB infection (nine million new cases annually) develop tuberculosis (TB).[8] The prevalence of TB is relatively high in China, although the prevalence of TB is continuously decreasing in the Chinese population.[9] Previous studies have shown that the proportion of the general Chinese population with a history of TB is between 1.36% and 1.69%.[10,11] China remains a country with one of the highest TB burdens and the rate of decline is slower than expected, according to the Global Tuberculosis Report of 2017 published by the World Health Organization.[12] TB is reportedly related to TA, based on observational data. Compared with healthy Brazilian children, the ratio of those with a positive tuberculin skin test (TST) was higher in children with TA.[13] A Korean study showed that the incidence of TB in patients with TA (17%) was higher than that of the general population (5.5%-5.8%).[14] Pathological characteristics of both TA and TB are granulomas and caseous necrosis.[15,16] Some studies
have reported the concurrence of TA and TB, and they have suggested that anti-inflammation therapy should be carefully initiated after the control of active TB.\(^{[17–19]}\) Despite these study findings, how TB manifests in patients with TA remains to be elucidated in a large population.

In this retrospective study, we aimed to describe the proportion of TB and clinical features of patients with TA who have TB, and to determine whether TB affects the clinical course of patients with TA in a large patient population.

2 Methods

2.1 Study population

This study protocol was approved by the Ethics Committee of Fuwai hospital, and was conducted in accordance with the 1964 Helsinki declaration and its later amendments. All patients were given their informed consent for access to their medical records during hospitalization. We retrospectively reviewed the electronic medical records of 1105 patients with TA admitted to Fuwai Hospital from January 1992 to December 2017. All patients fulfilled the TA diagnostic criteria established by the American College of Rheumatology in 1990.\(^{[20]}\) Angiographic classification was made according to the criteria set out by Hata and Numan.\(^{[21]}\)

Disease activity was assessed using the modified National Institutes of Health criteria.\(^{[22]}\) Patient was defined as having active disease if the patient met two or more of the followings: (1) systemic symptoms without another cause; (2) elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) without infection, anemia, or other cause; (3) new onset or deterioration of vascular ischemia or inflammation; and (4) typical angiographic features.

TB was defined according to past medical history and the first discharge diagnosis at our hospital. We calculated the age of the first TB infection and TA symptom onset, respectively. Active TB was diagnosed based on the combination of TB symptoms (cough, sputum, hemoptysis, fever, and chest pain for more than two weeks), chest radiography, and bacteriological examination (sputum smear microscopy or culture).\(^{[9]}\) The TST was defined as strongly positive if the diameter of induration was more than 20 mm or with the presence of blistering, hemorrhage, necrosis, or lymphangitis. TSTs and interferon-gamma release assays (IGRAs) are not done routinely in patients with TA. They were performed if a patient was suspected with TB by physicians. People with latent tuberculosis infection (LTBI) were infected with and had immune sensitization to Mtb and were asymptomatic. We did not describe LTBI in the present study.

2.2 Data collection

Artery lesions (including lesions in the pulmonary artery) were determined with catheter angiography, digital subtraction angiography, computed tomography angiography, and magnetic resonance angiography. For carotid and subclavian arteries, sonographic results were acceptable. We defined results of 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG PET/CT) as PET-active if the maximum standardized uptake value (SUV) of the region of interest was higher than the average SUV in liver.

Laboratory findings, such as hemoglobin, white blood cell count, serum creatinine, blood urea nitrogen, ESR, and CRP at the time of admission were noted and compared between patients with and without TB.

Concomitant diseases, such as hepatitis virus B infection, stroke, hypertension, hyperlipidemia, mellitus diabetes, aortic regurgitation, and pulmonary hypertension were also recorded. Pulmonary hypertension was diagnosed according to the results of right heart catheterization (RHC) or estimated pulmonary arterial systolic pressure (PASP). Pulmonary hypertension was defined as a mean pulmonary arterial pressure > 25 mmHg at rest by RHC or PASP > 40 mmHg by transthoracic echocardiography in patients without RHC.\(^{[23]}\)

2.3 Statistical analysis

Continuous variables were expressed as mean ± SD for normally distributed data and as median (interquartile rank) for data with a skewed distribution. Classification variables were described as percentages. Differences were examined using the independent t-test, chi-square test, Fisher’s exact test, or Mann–Whitney U test, as appropriate. Analysis was performed using IBM SPSS software, version 19.0 (IBM Corp., Armonk, NY, USA). We analyzed the proportion of TB in TA on a five-yearly basis, as follows: 1992.01–1996.12, 1997.01–2001.12, 2002.01–2006.12, 2007.01–2011.12, and 2012.01–2017.12. The time trend in the proportion of patients with TA and TB was analyzed using the Cochran–Armitage test (R version 3.5.1). Statistical differences were set at P-value < 0.05.

3 Results

3.1 Demographic data

Of the 1105 patients with TA, 109 patients (9.9%) had TB infection. The proportion of patients with TA and TB...
decreased from 13.7% to 8.3% over time. However, the decrease was not significant ($Z = 1.132, P = 0.190$). The sex ratio was 1 : 3.8 (23 men and 86 women). The mean age at TA onset was 26.7 ± 10.0 years, and the duration from symptom onset to first hospitalization was 56.3 (20.1–143.4) months. These data were similar between patients with and without TB (Table 1).

### 3.2 TB in patients with TA

Pulmonary TB was most common in 97 patients (89.0%), followed by TB lymphadenitis in eight patients (7.3%), cutaneous TB in two patients (1.8%), joint TB in one patient (0.9%), intestinal TB in one patient (0.9%), and pericardial TB in one patient (0.9%). Among the 97 patients with pulmonary TB, fourteen patients had TB pleurisy. Of the 109 patients with TA and TB, 53 patients (48.6%) were diagnosed with TB before symptom onset of TA, and the interval was 8.0 (3.0–14.5) years. Twenty-four patients (22.0%) developed TB during the follow-up period of TA, and the period between onset of TA and TB was 4.5 (2.0–8.8) years. Nine patients (8.3%) did not have a confirmed time of TB infection. Twenty-three patients (21.1%) were found to have TB concurrently with TA. Among them, ten patients were diagnosed in our hospital.

| Variables                        | Without TB | With TB | P-value |
|----------------------------------|------------|---------|---------|
| Total                            | 996 (90.1%)| 109 (9.9%)| 0.523   |
| Female                           | 809 (73.2%)| 86 (7.8%) |         |
| Male                             | 187 (16.9%)| 23 (2.1%) |         |
| Age at symptom onset, yrs       | 26.5 ± 10.2| 27.6 ± 10.0| 0.281   |
| Duration of clinical course, months | 57.3 (18.1–156.0)| 56.3 (20.1–143.4)| 0.848   |
| Symptoms and signs               |            |         |         |
| Fever or fatigue                 | 87 (8.7%)  | 17 (15.6%)| 0.020*  |
| Carotidynia                      | 14 (1.4%)  | 1 (0.9%)  | 1.000   |
| Dizziness                        | 262 (26.3%)| 30 (27.5%)| 0.784   |
| Headache                         | 109 (10.9%)| 13 (11.9%)| 0.756   |
| Syncope                          | 48 (4.8%)  | 9 (8.4%)  | 0.123   |
| Amaurosis                        | 39 (3.9%)  | 1 (0.9%)  | 0.171   |
| Visual disorders                 | 74 (7.4%)  | 6 (5.5%)  | 0.462   |
| Weak pulse                       | 164 (16.5%)| 17 (15.6%)| 0.815   |
| BP discrepancies between arms    | 39 (3.9%)  | 7 (6.4%)  | 0.207   |
| Easy fatigability                | 136 (13.7%)| 14 (12.8%)| 0.815   |
| Intermittent claudication        | 75 (7.5%)  | 6 (5.5%)  | 0.441   |
| Exertional dyspnea               | 173 (17.4%)| 36 (33.0%)| < 0.001*|
| Chest tightness                  | 218 (21.9%)| 27 (24.8%)| 0.491   |
| Chest pain                       | 81 (8.1%)  | 4 (3.7%)  | 0.097   |
| Hemoptysis                       | 14 (1.4%)  | 8 (7.3%)  | 0.001*  |
| Cough                            | 25 (2.5%)  | 4 (3.7%)  | 0.520   |
| Comorbid diseases                |            |         |         |
| Hypertension                     | 544 (54.6%)| 60 (55.0%)| 0.932   |
| Dyslipidemia                     | 110 (11.0%)| 8 (7.3%)  | 0.234   |
| Diabetes mellitus                | 21 (2.1%)  | 0 (0.0%)  | 0.255   |
| Stroke                           | 51 (5.1%)  | 4 (3.7%)  | 0.508   |
| Angina                           | 74 (7.4%)  | 5 (4.6%)  | 0.274   |
| Renal dysfunction                | 39 (3.9%)  | 3 (2.8%)  | 0.791   |
| Heart failure                    | 65 (6.3%)  | 11 (10.1%)| 0.135   |
| Hepatitis B infection            | 17 (1.7%)  | 4 (3.7%)  | 0.145   |
| Aortic regurgitation             | 240 (24.1%)| 21 (19.3%)| 0.788   |
| Pulmonary hypertension           | 107 (10.7%)| 21 (19.3%)| 0.008*  |
| NIH active                       | 482 (48.4%)| 67 (61.5%)| 0.010*  |

Data are presented as means ± SD, median (interquartile range) or n (%). *P < 0.05. BP: blood pressure; TA: Takayasu arteritis; TB: tuberculosis.
3.3 Clinical manifestations

The proportion of active TA in patients with TB was 61.5% versus 48.4% in patients without TB ($P = 0.010$). Pulmonary artery involvement was more common in patients with TB (31.2% vs. 17.3%, $P = 0.001$). There were no significant differences between patients with and without TB regarding involvement of the aorta and its major branches, except for involvement of the aortic arch ($P = 0.019$). The angiographic classification was similar between patients with and without TB. The ratio of occlusion (19.3% vs. 16.2%) of arteries was similar in patients with and without TB ($P > 0.05$) (Table 2).

| Variables                      | Without TB | With TB | $P$-value |
|--------------------------------|------------|---------|-----------|
| Angiographic type ($n = 1062$) | 0.606      |         |           |
| I                             | 269 (28.1%)| 28 (27.2%)|           |
| IIa                            | 45 (4.7%)  | 7 (6.8%) |           |
| IIb                            | 62 (6.5%)  | 4 (3.9%) |           |
| III                            | 131 (13.7%)| 10 (9.7%)|           |
| IV                             | 92 (9.6%)  | 10 (9.7%)|           |
| V                              | 360 (37.5%)| 44 (42.7%)|           |
| Lesions                        |            |         |           |
| Ascending aorta                | 109 (10.9%)| 12 (11.0%)| 0.899     |
| Thoracic aorta                 | 188 (18.9%)| 16 (14.7%)| 0.502     |
| Abdominal aorta                | 297 (29.8%)| 29 (26.6%)| 0.741     |
| Aortic arch                    | 37 (3.7%)  | 10 (9.2%) | 0.019*    |
| Left subclavian artery         | 497 (49.9%)| 50 (45.9%)| 0.529     |
| Right subclavian artery        | 284 (28.5%)| 29 (26.6%)| 0.734     |
| Left vertebral artery          | 81 (8.1%)  | 8 (7.3%)  | 0.947     |
| Right vertebral artery         | 60 (6.0%)  | 5 (4.6%)  | 0.707     |
| Left carotid artery            | 343 (34.4%)| 30 (27.6%)| 0.182     |
| Right carotid artery           | 232 (23.3%)| 26 (23.9%)| 0.814     |
| Branchiocephalic artery        | 83 (8.3%)  | 10 (9.2%) | 0.986     |
| Axillary artery                | 60 (6.0%)  | 11 (10.1%)| 0.090     |
| Left renal artery              | 329 (33.0%)| 28 (25.7%)| 0.142     |
| Right renal artery             | 312 (31.3%)| 33 (30.3%)| 0.475     |
| Superior mesenteric artery     | 107 (10.7%)| 8 (7.3%)  | 0.199     |
| Coeliac trunk                  | 68 (6.8%)  | 4 (3.7%)  | 0.126     |
| Iliacofemoral artery           | 103 (10.3%)| 9 (8.3%)  | 0.522     |
| Pulmonary artery               | 172 (17.3%)| 34 (31.2%)| 0.001*    |
| Coronary artery                | 51 (5.1%)  | 5 (4.6%)  | 0.810     |
| Occlusion                      | 238 (23.9%)| 21 (19.3%)| 0.279     |
| Dilatation                     | 161 (16.2%)| 20 (18.3%)| 0.559     |
| Stent implantation             | 235 (23.6%)| 16 (14.7%)| 0.035*    |
| PTA                            | 427 (42.9%)| 36 (33.0%)| 0.048*    |

Data are presented as $n$ (%). $P < 0.05$. PTA: percutaneous transluminal angiography; TA: Takayasu arteritis; TB: tuberculosis.

3.4 Laboratory findings

The level of ESR was significantly higher in patients with TB. Other relevant laboratory results did not show significant differences (Table 3).

3.5 18F-FDG PET/CT with elevated SUV in lymph nodes

Six patients had 18F-FDG PET/CT referred to the SUV of lymph nodes. Elevated SUV of the mediastinal and cervical lymph nodes was found in three patients and of the hilar and supraclavicular lymph nodes in two patients. The diameter of lymph nodes ranged from 1.2 to 2.0 cm, and their SUVs ranged from 3.9 to 8.7. TB infection was ruled out in three patients. One patient had pulmonary TB fourteen years earlier, and two patients had active pulmonary TB. No patients underwent lymph node aspiration.

3.6 Treatment

The initiation of prednisone at discharge was similar with respect to TB (56.0% vs. 57.0%). The most frequent dose at discharge was 20 mg per day, followed by 30 mg per day. Intervention treatment for revascularization, percutaneous transluminal angioplasty and stent implantation was performed more frequently in patients without TB than in those with TB (both $P < 0.05$) (Table 2).

Ten patients had active TB. Elevated ESR was found in eight patients and elevated CRP was found in three patients. They were treated with anti-TB drugs (isoniazid, rifampicin and pyrazinamide), none of them had TB diffusion during follow-up (Table 4).

4 Discussion

In this retrospective study, we found that TB was common in patients with TA, most patients had TB before the
Table 3. Laboratory findings in TA patients according to TB.

| Variables                      | Without TB | With TB | n   | With TB | n   | P-value |
|--------------------------------|------------|---------|-----|---------|-----|---------|
| C-reactive protein, mg/L       | 4.0 (2.1–12.0) | 646     | 4.37 (2.42–16.5) | 63 | 0.233 |
| Erythrocyte sedimentation rate, mm/h | 13.0 (6.0–30.0) | 729     | 17.0 (9.0–45.0) | 87 | 0.010 |
| White blood cells, ×10^9/L     | 7.12 (5.85–8.68) | 510     | 7.39 (6.40–8.40) | 54 | 0.328 |
| Hemoglobin, g/L                | 125.0 (113.0–140.0) | 591     | 124.0 (111.5–142.0) | 61 | 0.733 |
| Serum creatinine, umol/L       | 63.75 (53.71–74.89) | 483     | 65.21 (53.78–75.93) | 51 | 0.723 |
| Blood urea nitrogen, mmol/L    | 5.0 (4.0–6.26) | 494     | 5.0 (4.5–6.5) | 54 | 0.426 |

Data are presented as median (interquartile range). *P < 0.05. TA: Takayasu arteritis; TB: tuberculosis.

Table 4. Detailed information for TA patients with active TB.

| Number/Gender/Age | Clinical duration, months | Symptoms & Signs                     | ESR, mm/h | CRP, mg/L | Hb, g/L | WBC, ×10^9/L | Evidence for active TB                        | Dosage of prednisone per day, milligram |
|-------------------|----------------------------|--------------------------------------|-----------|-----------|---------|--------------|-----------------------------------------------|------------------------------------------|
| 1/Female/19       | III 84                     | Extertional chest tightness and dyspnea | 75        | 29.1      | -       | -            | Imaging: cavitary pulmonary tuberculosis       | 0                                        |
| 2/Female/21       | V 48                       | Weak pulse, cardiac murmurs          | 26        | -         | -       | -            | TST (++++)                                     | 0                                        |
| 3/Female/21       | VI 12                      | Fatigue, HTN                         | 40        | 4.3       | 109     | 11.3         | Triple anti-tuberculosis regimen on admission | 0                                        |
| 4/Female/54       | V 216                      | Dizziness, headache, CHF             | 75        | -         | 73      | -            | Imaging: military pulmonary tuberculosis      | 20                                       |
| 5/Female/23       | V 2                        | HTN                                  | 28        | 2.7       | 112     | 11.1         | Triple anti-tuberculosis regimen on admission | 20                                       |
| 6/Female/33       | III 246                    | Headache, CHF, CRF                   | 32        | 2.1       | 111     | 7.8          | Triple anti-tuberculosis regimen on admission | 0                                        |
| 7/Female/39       | VI 156                     | HTN, dizziness                       | 67        | 26.7      | 108     | 10.9         | Elevated SUV of carotid lymph nodes, T-SPOT.TB(+) | 0                                        |
| 8/Female/45       | I 188                      | Fever, stroke                        | 27        | 2.6       | 119     | 16.0         | TST (++++)                                     | 0                                        |
| 9/Female/13       | V 18                       | Fever, cough, carotidynia, discrepancy of blood pressure | 6         | 14.8      | 139     | 11.0         | Triple anti-tuberculosis regimen on admission | 15                                       |
| 10/Female/55      | VI 18                      | HTN, stroke, cough, hemoptysis       | 19        | 2.0       | 128     | 7.5          | T-SPOT.TB(+); PET/CT: Patchy shadow in right lower lobe | 0                                        |

All of the patients received triple anti-tuberculosis medication and prednisone was used in three patients (Number: 4, 5, 9). Type refers to angiographic classification according to Hata criteria. CHF: chronic heart failure; CRF: chronic renal failure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; HTN: hypertension; TA: Takayasu arteritis; TB: tuberculosis; TST: tuberculin skin test; WBC: white blood cells counts.

onset of TA, and pulmonary TB was predominant. These findings were consistent with results of studies conducted in other populations.[14,24] Interestingly, compared with patients who did not have TB infection, the ratio of pulmonary artery involvement was higher in patients with TB infection. Furthermore, symptoms related to pulmonary artery involvement, such as pulmonary hypertension, exertional dyspnea, and hemoptysis, were also more common in patients with TB. In addition, we found that more patients with a history of TB were in active disease stage, indicating that TB infection may affect the clinical course and treatment of TA.

Several explanations for how TB triggers TA have been proposed, but the exact mechanism and relationship between TA and TB remain to be elucidated. One possible hypothesis involves superantigens. Mt in widely activates T cells, dendritic cells, and macrophages, mainly via the lipoolarabinomannan on its wall structure. IL-12, IL-18, and resuscitation-promoting factor promote the differentiation of CD4+ T cells into Th1 and Th17 lymphocytes.[25–27] A variety of cytokines, including tumor necrosis factor alpha (TNF-α), IL-1, IL-6 and MMP-1, are upregulated in patients with TA and TB.[28,29] Autoimmune disorder is another possible explanation. The 65 kDa heat shock protein of Mt, hHSP65, is implicated in various rheumatic diseases, indicating a relationship between Mt infection and autoimmune disorders.[30] Cross-reactivity of hHSP65 and human HSP60 (hHSP60) has also been proved in patients with TA. Compared with healthy controls, levels of anti-hHSP60 antibodies were found to be substantially elevated in patients with TA.[31] No studies to date have detected Mt in
artery walls using acid-fast staining. Furthermore, polymerase chain reaction results for the specific gene sequence IS6110 of Mtb are controversial. A previous study reported detection of the IS6110 sequence of Mtb by polymerase chain reaction in 70% of 33 tissue samples from patients with TA. A recent study from Brazil reported that the IS6110 sequence could not be amplified in peripheral blood from 32 patients with TA or in artery tissue samples from 10 patients with TA. This indicates that persistent Mtb infection is not necessary for maintaining inflammation in TA.

Elevated ESR or CRP, fever, and night sweats are indications of active TA, according to the modified National Institutes of Health criteria; however, these could well be owing to active TB. These characteristics are strong indications for initiating anti-inflammatory regimens in patients with TA. Physicians should be attentive for active TB in patients with TA, as treatment with glucocorticoids could cause worsening of constitutional symptoms such as weight loss, night sweats, and low-grade fever, then chest radiography, IGRA, and sputum fast-acid staining should be performed to exclude TB infection. It is advisable to consult an infectious disease specialist for the diagnosis of active TB infection.

### 4.1 Limitations

Regarding study limitations, this was a retrospective study based on data from a single center for cardiovascular diseases; thus, there might be selection bias. Another shortcoming was that we had no results of lymph node or artery tissue biopsy. Nevertheless, considering the large sample size, comprehensive clinical and imaging evaluation of each patient, the clinical features of TA patients with TB could be well elucidated.

### 4.2 Conclusions

The proportion of Chinese patients with TA and TB was not low. About half of the patients had TB before TA symptom onset. Pulmonary TB was most common. Pulmonary artery involvement and pulmonary hypertension was more common in TA patients with TB. Active TB should be ruled out before and during anti-inflammatory therapy.

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