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ORIGINAL ARTICLE

High prevalence of latent tuberculosis using the QuantiFERON-TB Gold Plus test in Takayasu arteritis

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ABSTRACT

Objectives: This study aims to investigate latent tuberculosis using the QuantiFERON-TB Gold Plus (QFT-Plus) method in patients with Takayasu arteritis (TA).

Patients and methods: This case-control study included 22 patients with TA (3 males, 19 females; median age: 36.5 years; IQR, 32 to 50 years), 22 healthy individuals (3 males, 19 females; median age: 38.5 years; IQR, 32.5 to 50 years), and 66 patients with diffuse connective tissue diseases (DCTDs) (4 males, 62 females; median age: 41 years; IQR, 29.8 to 54 years). Two control groups were formed: *(i)* age- and sex-matched healthy individuals and *(ii)* patients with other DCTDs. Epidemiological data were collected, and the QFT-Plus test was performed. The QFT-plus positivity was compared among the groups.

Results: A higher prevalence of QFT-Plus positive cases was observed in the TA group (8/22) than in the healthy control group (1/22) (p=0.020) or in the group with other DCTDs (3/66) (p=0.001). There was a statistically significant difference in the past pulmonary tuberculosis prevalence between the TA and DCTD groups (p=0.013).

Conclusion: The prevalence of latent tuberculosis in TA patients (36.4%) was higher than that in both control groups and higher than the prevalence of latent tuberculosis among the general Brazilian population. Although a positive association was found, it is not possible to establish a direct cause-effect relationship. Given the increasing use of anti-cytokine therapies in TA, it is necessary to thoroughly screen patients with TA before initiating immunosuppressive therapy to avoid tuberculosis reactivation.

Keywords: Interferon gamma release test, latent tuberculosis, *Mycobacterium tuberculosis*, Takayasu arteritis, tuberculosis.

Takayasu arteritis (TA) is a rare form of large vessel primary vasculitis that affects the aorta and its main branches, predominantly in young women in the second or third decades of life.[1] The annual incidence ranges from 0.4 to 3 cases per million, and clinical manifestations vary with the extent of vascular involvement.[2,3] At the time of diagnosis, arterial murmurs, asymmetry of pulses, and inconsistent measurements of blood pressure are common. The pathogenesis is not fully understood, but cellular immunity plays a central role in chronic granulomatous inflammation.[4,5]

For several decades, an association between TA and tuberculosis (TB) has been suggested.[6] In a recent systematic review, two hypotheses have been proposed to explain this scenario: the first is that the loss of tolerance against self-stress proteins would be a primary pathogenic event in TA, as extensive sequence homology between mycobacterial and human stress-proteins would lead to cross-reactions and the second hypothesis is based on the possibility that arteritis results directly from a latent or active TB infection.[6-8]

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Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to *Mycobacterium tuberculosis* (MT) antigens with no evidence of clinically manifested active TB. There is no gold-standard test for LTBI, and according to the World Health Organization (WHO) guidelines on LTBI, either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) can be used.[9]

A meta-analysis comparing TST and IGRA showed that IGRA had a high specificity and that it was unaffected by Bacille Calmette-Guérin (BCG) vaccination. Since the late 1970s, BCG vaccination coverage has been universal in Brazil and is administered in the first month of life. In this scenario, IGRA appears to provide better information about LTBI.[10,11]

The prevalence of LTBI in TA patients as measured by TST is high in different studies.[12-15] However, in a previous study that compared IGRA among TA patients and healthy controls, there was no significant difference between the groups.[16]

The year 2017 witnessed the launch of a new IGRA test, the fourth-generation QuantiFERON-TB Gold Plus (QFT-Plus) (Cellestis Limited, Carnegie, Austrália), which adds CD8 T-cell stimulating antigens to existing CD4 antigens, providing a broader immune assessment. In the present study, we aimed to investigate LTBI in TA patients using the QFT-Plus method and to compare it with healthy controls and patients with other diffuse connective tissue diseases (DCTDs).

PATIENTS AND METHODS

This two-center, retrospective, case-control study was conducted in two rheumatology clinics of Salvador and Brazil between January 2018 and June 2018. Patients diagnosed with TA based on the 1990 American College of Rheumatology (ACR) criteria[17] were included in this study. Evaluation of all patients included their history and clinical examination results. Imaging findings (conventional angiography, angio-computed tomography or angio-magnetic resonance imaging), TST results, and treatments were obtained retrospectively from the medical records. The cut-off used to define TST positivity was ≥5 mm, based on our national recommendations.[18]

The TA patients were classified according to their angiographic pattern as follows: type I, branches from the aortic arch; type IIa, ascending aorta, aortic arch, and its branches; type IIb: ascending aorta, aortic arch and its branches, thoracic descending aorta; type III: thoracic descending aorta, abdominal aorta, and/or renal arteries; type IV: abdominal aorta and/or renal arteries; type V: combined features of types IIb and IV.[19]

Two age- and sex-matched control groups of healthy individuals and patients with other DCTDs were followed by the same rheumatology services. We also reviewed the patients' medical histories, glucocorticoids, and other immunosuppressive therapy doses. Those having a diagnosis of other chronic conditions, including neoplasia or those who were healthcare professionals were excluded from the study. Data including history of TB exposure and previous BCG vaccination were collected from the two groups. Finally, 22 patients with TA (3 males, 19 females; median age: 36.5 years; IQR, 32 to 50 years), 22 healthy individuals (3 males, 19 females; median age: 38.5 years; IQR, 32.5 to 50 years), and 66 patients with DCTDs (4 males, 62 females; median age: 41 years; IQR, 29.8 to 54 years) were included in the study.

The QuantiFERON-TB Gold Plus (QFT-Plus) test (Qiagen GmbH, Hilden, Germany) was performed according to the manufacturer's instructions. Briefly, 1 mL of whole blood was collected by venipuncture directly into each of the four tubes in the following order: Nil (negative control), TB antigen tube 1 (TB1), TB antigen tube 2 (TB2), and mitogen (positive control). The samples were incubated at 37°C for 16 to 24 h. The plasma was separated after centrifugation and stored at -20°C. On the same day, the interferon gamma (IFN-γ) enzyme-linked immunosorbent assay (ELISA) was performed on all samples, and the results were interpreted using the QFT Analysis Software version 2.71 (QIAGEN, Hilden, Germany).

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp.,

Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (interquartile range [IQR]), while categorical variables were expressed in number and frequency. The normality of the numerical variables was verified through descriptive statistics, graphical analysis, and the Kolmogorov-Smirnov test. The Fischer exact test was used to compare sex, QFT-plus, BCG, TB exposure, and active TB history between the groups. The Kruskal-Wallis test was used to compare age between the groups, and the kappa (κ) coefficient was used to analyze the concordance between QFT-plus and TST in TA patients. A p value of <0.05 was considered statistically significant.

RESULTS

The main clinical features of patients with TA and the TST results obtained from medical records are shown in Table 1. The most frequent manifestations were upper limb claudication (63.6%) and malaise (59.1%). Hypertension was the most common comorbidity, followed by valvular and ischemic heart disease (18.2% each). Of note, 64.7% of the patients with TA presented with positive TST results. The median TST was 12 mm (IQR, 0 to 20 mm).

Eighty-eight control subjects were divided into two groups: 22 healthy individuals and 66 patients with other DCTDs: systemic lupus erythematosus (SLE) (n=40), Sjögren syndrome (n=12), idiopathic inflammatory myopathies (n=9), rheumatoid arthritis (n=4), and psoriatic arthritis (n=1). Data on the TST results in the control group were not obtained.

Table 2 shows a comparison of TA patients and controls. There was no significant difference in the following variable between the groups: age, sex, and TB exposure. Eight patients (36.4%) with TA, presented a positive QFT-plus result compared to only one patient in the healthy control group (p=0.02) and three patients in the group with other DCTDs (p=0.001).

Table 1. Clinical and laboratory features of TA patients (n=22)

	n	%	Mean±SD	Median	IQR
Age (symptom onset)			27.7±10.9		
Age (diagnosis)			31.7±10.4		
Signs and symptoms					
Fever	2	9.1			
Malaise	13	59.1			
Arthralgia	10	45.5			
Upper limb claudication	14	63.6			
Carotidynia	6	27.3			
Dizziness	10	45.5			
Comorbidities					
Any hypertension	18	81.8			
Renovascular hypertension	7	31.8			
Valvular heart disease	4	18.2			
Ischemic heart disease	4	18.2			
Cardiac failure	3	13.6			
Stroke	3	13.6			
Classification					
Type I	5	22.7			
Type IIa	2	9.1			
Type IIb	2	9.1			
Type III	0	0.0			
Type IV	2	9.1			
Type V	11	50.0			
Laboratorial					
TST (mm)				12	0.20
TST positivity >5 mm	11	64.7			

TA: Takayasu arteritis; SD: Standard deviation; IQR: Interquartile range; TST: Tuberculin skin test.

Table 2. Comparison of the frequency of QFT-Plus between TA patients and controls

	TA patients (n=22)				Healthy controls (n=22)					DCTD patients (n=66)				
	n	%	Median	IQR	n		Median	IQR	*p*	n		Median	IQR	*p*
Age*			36.5	32-50			38.5	32.5-50	0.778			41	29.8-54	0.675
Sex**									1.000					0.360
Male	3				3					4				
Female	19				19					62				
QFT-plus†**									0.020					0.000
Negative	13	59.1			20	90.9				62	93.9			
Positive	8	36.4			1	4.5				03	4.5			
Indeterminate	1	4.5			1	4.5				1	1.5			
BCG**	11	50.0			19	86.4			0.022	48	72.7			0.067
TB exposure**	2	9.1			6	27.3			0.240	8	12.1			1.000
Active TB history**	4	18.2			0	0.0			0.108	1	1.5			0.013

QFT-Plus: QuantiFERON-TB Gold Plus; TA: Takayasu arteritis; DCTDs: Diffuse connective tissue diseases; IQR: Interquartile range; BCG: Calmette-Guérin Bacillus; TB: Tuberculosis; * Kruskal-Wallis test; ** Fisher exact test; † The indeterminate result was not considered.

Table 3. Characteristics of positive QFT-plus TA patients

No	Age/Sex	Clinical manifestations	Classification	Treatment	TB status
1	22/F	Renovascular hypertension, pulselessness, subclavian and carotid bruits	V	Previous use of prednisone 20 mg/day Two years without immunosuppressive drugs	TST: 0 mm BCG scar No TB exposure
2	29/F	Stroke, pulselessness, carotid bruit	V	MTX (15 mg/week)	TST: 30 mm BCG scar No TB exposure
3	47/F	Systemic hypertension, pulselessness, subclavian bruit	V	Prednisone (10 mg/day) MTX (15 mg/week)	TST: 19 mm BCG scar No TB exposure
4	26/F	Renovascular hypertension, pulselessness	V	Previous use of cyclophosphamide and azathioprine One year without immunosupressive drugs	TST: 0 mm No BCG scar No TB exposure
5	34/F	Systemic hypertension, pulselessness	I	Prednisone (5 mg/day) MTX (25 mg/week)	TST: 0 mm BCG scar No TB exposure
6	27/M	Renovascular hypertension Myocarditis and cardiac failure Ischemic heart disease	V	Previous use of cyclophosphamide Now with azathioprine 150 mg/day	TST: 12 mm No BCG scar No TB exposure
7	23/F	Asymmetry of pulses and multiple aneurysms	IIbP+	No immunosuppressive drugs at TA and TB diagnosis Now with MTX (20 mg/week)	TST: 23 mm BCG scar Active pulmonary TB concomitant with TA diagnosis
8	34/F	Pulselessness APS	I	Use of Infliximab at TB diagnosis	TST: 0 mm BCG scar Active pulmonary TB 4 years after TA diagnosis

QFT: Quantiferon-plus test; TA: Takayasu arteritis; MTX: Methotrexate; TST: Tuberculin skin test; BCG: Calmette-Guérin Bacillus; TB: Tuberculosis; APS: Antiphospholipid syndrome.

Among the TA patients, 10 (50%) were vaccinated with BCG compared to 19 (86.4%) in the healthy control group (p=0.022) and 48 (72.7%) in the DCTD control group (p=0.067). Four TA patients had a history of previous active pulmonary TB, confirmed by positive acid-fast bacilli in the sputum, compared to only one patient in the other DCTD group (p=0.013).

Of note, from the three QFT-Plus positive patients in the DCTDs group, two had SLE, one Sjögren disease, and the only patient in the control group with confirmed previous pulmonary TB had Sjögren syndrome.

Table 3 presents the characteristics of the QFT-Plus positive subgroup of patients with TA (n=8). No concordance was identified between QFT-Plus and TST in the TA group. The κ coefficient was 0.029 (p=0.856).

Among the four TA patients with a confirmed history of TB, concordance was found between QFT-Plus and TST in two (50%) cases. In one patient, the diagnosis of active TB occurred three years before the diagnosis of TA; in two patients, the diagnosis of both diseases was established concomitantly, and in the remaining one patient, TA developed after anti-TNF (infliximab) therapy for TB.

In the 30-day period prior to the IGRA test, the treatment for TA patients consisted of corticosteroids in 31.8%, methotrexate in 54.6%, azathioprine in 31.8%, and mycophenolate mofetil in 4.8% of patients.

DISCUSSION

Two relevant facts in the scenario of a possible association between TA and TB are that TA is more common in individuals from countries where the incidence of TB is high and that both diseases share the pathology of granulomatous lesions.[20,21]

Up to one-third of the world's population is estimated to be infected with MT.[9] The prevalence among the general Brazilian population is approximately 25% as estimated from previous studies.[22]

Among the TA population, the highest indices using the TST method were found in a Mexican study, where the prevalence of TST >10 mm was 82%.[14]

The prevalence of active TB in TA patients varies from 6.3% in Türkiye to 20% in South Africa. The study with the greatest number of TA patients (n=267) was performed in South Korea, and it showed the presence of active TB in 17.7% of these cases, similar to our study (18%), while a history of TB was found in 5.8% of the general population of that country.[16,21,23]

Pulmonary TB may also cause aortitis, leading to the formation of single or multiple saccular aneurysms or pseudoaneurysms. A vessel lesion located near the cavitation is described as a Rasmussen aneurysm. In a previously published case report of one of our patients, the finding of a bronchiolar mucoid impaction in the apicoposterior pulmonary segment extending to the aortic arch indicated the probable route of dissemination and illustrates the challenge in accurately distinguishing a diagnosis of TA from tuberculous aortitis.[24]

The prevalence of LTBI by QFT-plus in 36.4% of TA patients was higher than that in the other rheumatic diseases and in normal controls. The only previous study that used QFT to assess LTBI in patients with TA was conducted in Türkiye in 2010. While assessing 94 patients with TA and 107 controls, they found a 22.3% positivity in the TA group and 22.4% in the control group, with no statistically significant significance (p>0.05).[16] They used QuantiFERON-TB Gold In-Tube (QFT-IT; QuantiFERON-TB Gold Plus), an earlier version of the kit we used in this study. Hence, the response of CD8 + T lymphocytes to MT antigens might not have been satisfactorily evaluated. The QFT-Plus seemed to have greater sensitivity and specificity. In addition, differences in the genetic backgrounds of the study population may explain the discrepancies in the results.

Previous studies revealed a higher prevalence of IGRA in patients with non-TA rheumatic diseases: 12.1% in 142 patients with autoimmune diseases,[25] 24.8% in 631 patients with rheumatic diseases,[26] and 19.1% in 136 patients with SLE.[27]

There are no data on IGRA positivity among rheumatic patients in Brazil, but in a cross-sectional study of 110 patients with inflammatory bowel disease (IBD) and 64 healthy controls, conducted in Rio de Janeiro, the prevalence

of positive IGRA tests was 12.8% in IBD patients and 13.5% in controls.[28] In another study, 11 out of 57 healthy controls (19%) with negative TST tested positive for QFT-IT.[29] Methodological differences seem to be the only plausible explanation to justify the lower prevalence of IGRA positivity in the healthy and DCTD controls of our study compared to that of other studies.

We also observed a discrepancy between the QFT-Plus and TST results in TA patients. These findings are similar to those in another study on 757 patients with rheumatoid arthritis and ankylosing spondylitis, in which the agreement between the two tests was very low (κ:0.285). Notably, corticosteroid use was more frequent in QFT positive and TST negative patients, suggesting that IGRA is less influenced by immunosuppressive therapies and has high sensitivity and specificity for diagnosis of LTBI in patients with rheumatic diseases compared to TST.[25,30,31]

The main limitations of our study are relatively small sample size and the observation that data of QFT-Plus were not collected at the time of TA diagnosis before the use of glucocorticoids and/or immunosuppressive therapy. Therefore, we included patients with other DCTDs (mainly SLE), as a potential comparison for the use of glucocorticoids and/or immunosuppressive agents.

In conclusion, although a positive association between QFT-Plus positivity and TA compared to controls was found in our study, it is not possible to establish a direct cause-effect relationship between TB and TA. However, in line with other studies, this association cannot be discarded, and if an etiologic relationship cannot be defined, greater care should be taken with latent TB screening in patients who are TA candidates for immunosuppressive therapy. It is necessary to advance studies of infectious triggers in systemic vasculitis. The prospect of a TA phenotype associated with TB remains intriguing.

Ethics Committee Approval: The study protocol was approved by the Escola Bahiana de Medicina e Saúde Pública, Salvador, Brazil Ethics Committee (CAEE: 73383717.3.0000.544). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception, analysis, writing: A.L.S.P., M.B.S.; Corrected the data analysis, drafting: R.P.L.C., J.F.P.S.

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