

Prevalence of Auto-antibodies in Pulmonary Tuberculosis

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The relationship between pulmonary tuberculosis and auto-antibodies remains undefined. In a study of 75 patients with pulmonary tuberculosis and 75 controls, the prevalence of auto-antibodies was assessed in a reference laboratory using a comprehensive panel with standardized methodology. No significant relationship was found between auto-antibody prevalence and pulmonary tuberculosis.

Keywords. tuberculosis; auto-immunity; rheumatological conditions.

Autoimmune disorders represent a broad spectrum of diseases characterized by a pathological immune response directed at self-antigens and are hypothesized to arise from a constellation of genetic, hormonal, immunological, and environmental factors [1]. Certain chronic infections are thought to trigger the production of auto-antibodies through molecular mimicry or exuberant and persistent host responses that result in auto-immune or inflammatory pathologies [2].

Tuberculosis (TB) is the most common chronic bacterial infection worldwide, with an estimated 10.2 million incident cases and 10.1 million prevalent cases per year [3]. Like other infections, it has been associated with autoimmune manifestations, including nodular vasculitis [4]. TB has reportedly been linked with autoimmune disorders such as Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, and polymyositis [5]. However, the nature, directionality, and robustness of this association remain unknown.

Serological studies have suggested that patients with TB have increased auto-antibody titers. Rates as high as 44%, 11%, and 6% have been reported for antineutrophil cytoplasmic autoantibody (ANCA), anti-cardiolipin antibody (ACA), and anti-Scl-70, respectively [6, 7].

Although it is biologically plausible for patients with TB to develop auto-antibodies, the extent and magnitude to which this phenomenon occurs are unknown. The relationship between pulmonary TB and auto-antibodies remains undefined due to conflicting reports in the literature, inconsistent test selection, and nonstandardized testing methodology. The objective of this study was to determine if active TB is associated with an increased prevalence of auto-antibodies using a comprehensive panel with standardized methodology performed in a reference laboratory.

METHODS

We performed a cross-sectional study involving patients evaluated for active pulmonary tuberculosis from Bangladesh, South Africa, Peru, and Uganda. Patients 18 years of age or older who were treated at 1 of the study sites and provided written informed consent to participate were eligible. Patients were included in this study if they provided sputum samples for mycobacterial culture. Baseline characteristics were collected at the time of medical assessment. Covariates of interest included age, sex, and relevant medical comorbidities such as HIV co-infection status and chronic rheumatological diseases. Patients with a diagnosis of active pulmonary TB were compared with controls who were selected from a similar patient population and who sought medical attention due to a febrile respiratory illness. The subjects in the control group had multiple negative sputum cultures for *Mycobacterium tuberculosis*.

To test the hypothesis that patients with active TB have a higher prevalence of auto-antibodies, we performed comprehensive serological testing in our patient population. Patient samples were obtained at the time of presentation to medical care and before starting antimicrobial therapy. From a review of the literature, we identified several serological markers that could be produced in response to a chronic bacterial infection. Investigations were performed for ACA, ANCA (MPO-ANCA and PR-3 ANCA), antimitochondrial antibodies (AMAs), anti-nuclear antibodies (ANAs), B2GP1-Domain 1, dsDNA, and Rheumatoid Factor (RF). A comprehensive connective tissue panel was performed to assess for BIC-D2, Centromere, DFS70, Elastase, HCP1, HCP2, Jo-1, Ku, LAMP2, Nucleosome, p155, PCNA, Pm/Scl, Ribo-P, RNA Pol III, RNP, RNP A, RNP C, Ro52, Ro60, Rpp25, Rpp38, SS-B, Scl-70, Sm, Sm-Peptide, VCP1, and VCP2. Please see the Supplementary Data for a

Received 21 December 2018; editorial decision 26 February 2019; accepted 4 March 2019.

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complete list of all antibodies tested, their methods of assessment, and cutoffs for positivity. These assays were performed in a blinded fashion at the Mitogen Diagnostic Laboratory in Calgary, Alberta, Canada.

The relationship between different serological markers and tuberculosis was first analyzed using direct graphical visualization, followed by a classical hypothesis testing framework using the Fisher exact and Mann-Whitney *U* tests. Subsequently, sensitivity analysis was performed using multiple machine learning algorithms. First, Lasso logistic regression was used. The Lasso method allows for automatic variable selection and shrinkage, bypassing multiple comparison and effect inflation problems inherent with methods like stepwise regression. Second, 2 highly nonparametric tree-based methods were implemented: random forests and hierarchical cluster analysis (HCA). Finally, principal component analysis (PCA) was performed, and the first 3 principal components were plotted against each other to determine if they could discriminate between TB patients and controls. A detailed explanation of each procedure can be found in the references [8, 9]. All analyses were performed using the base R statistical package (3.2.0) and the glmnet library (2.0–10). The study was approved by the FIND Office for Human Research Studies.

RESULTS

One hundred fifty patients were selected to participate in the study and provided serum samples for this analysis. Patient characteristics are presented in Table 1. The median age of the cohort at the time of testing was 33 years; 17 patients (11.3%) had a previous history of active TB, and 65 (43.3%) had a history of Bacillus Calmette-Guérin vaccination. In total, 75 patients

were diagnosed with active pulmonary tuberculosis, and 75 presented with an acute febrile respiratory illness and were found to have an alternative diagnosis (other than TB). The most common alternate diagnoses in the control group were viral and bacterial respiratory tract infections. No patient had a reported history of HIV infection or of a primary rheumatological condition, including granulomatosis with polyangiitis.

A detailed summary of serum auto-antibody testing results is shown in Table 2. When comparing cases and controls, the prevalence of ANA was not statistically different regardless of staining pattern: 46.7% of cases and controls had a nuclear pattern, 14.7% of cases and 18.7% of controls had a cytoplasmic pattern, and 30.7% of cases and 24.0% of controls had a mitotic pattern.

Similar proportions were found among both groups for common rheumatological auto-antibodies, including ACA (1.3% in cases, 4.0% in controls), β 2GP1-Domain 1 (1.3% in cases, 1.4% in controls), centromere (8.0% in cases, 2.7% in controls), dsDNA (1.3% in cases, 0% in controls), Ro-52 (4.0% in cases, 5.3% in controls), Ro-60 (1.3% in cases, 0% in controls), Scl-70 (1.3% in cases, 0% in controls), Sm (1.3% in cases, 0% in controls), and SS-B (1.3% in cases, 1.4% in controls). The most commonly present auto-antibodies were RF (56.0% in cases, 53.3% in controls) and antimitochondrial antibodies (12.0% in cases, 8.0% in controls). The proportion of ANCA positivity was found to be 1.3% and 0% for MPO-ANCA and 1.3% and 1.3% for PR3-ANCA among cases and controls, respectively. No patient in either group tested positive for Jo-1.

Among less frequently tested auto-antibodies, both groups had a similar prevalence of positive results (see Table 2 for

Table 1. Patient Characteristics

Patient Characteristics	Tuberculosis (n = 75)		Controls (n = 75)	
	No.	% ^a	No.	% ^a
Median age (range), y	31 (18–70)		35 (18–76)	
Male sex	45	63.4	21	50.0
Country				
Peru	61	81.3	34	45.3
Bangladesh	4	5.3	33	44.0
South Africa	1	1.3	8	10.7
Uganda	9	12.0	0	0
Medical comorbidities				
Asthma	0	0	3	4.0
Bronchiectasis	0	0	1	1.3
HIV	0	0	0	0
Rheumatological conditions	0	0	0	0
BCG vaccination	51	92.7	14	43.8
History of tuberculosis	3	6.4	14	18.7

Abbreviation: BCG, Bacillus Calmette-Guérin.

^a% refers to available data; no imputations were made for missing data.

Table 2. Prevalence of Different Auto-antibodies Among Patients With Active Pulmonary TB and Controls^a

Test ^b	Tuberculosis	Controls	P Value
NovaView HEp-2 ANA kit with DAPI			
Nuclear pattern (proportion > 1:80)	35/75 (46.7)	35/75 (46.7)	1
Cytoplasmic pattern (proportion > 1:80)	11/75 (14.7)	14/75 (18.7)	.662
Mitotic pattern (proportion > 1:80)	23/75 (30.7)	18/75 (24.0)	.464
MagPiX CTD			
dsDNA (MFU; n = 150)	20.0 (18.0–24.0)	19.0 (16.5–24.0)	.0878
dsDNA (proportion positive)	1/75 (1.33)	0/75 (0)	1
RNP (MFU; n = 150)	32.0 (28.0–42.0)	36.0 (30.2–43.5)	.158
RNP (proportion positive)	1/75 (1.33)	0/75 (0)	1
Sm (MFU; n = 150)	25.0 (22.0–35.0)	30.0 (25.8–40.5)	.012
Sm (proportion positive)	1/75 (1.33)	0/75 (0)	1
Ro52/TRIM21 (MFU; n = 150)	130.0 (88.8–161.2)	116.0 (84.5–165.2)	.415
Ro52/TRIM21 (proportion positive)	3/75 (4.00)	4/75 (5.33)	.741
SS-A/Ro60 (MFU; n = 150)	83.0 (64.5–106.5)	70.0 (54.0–97.0)	.0189
SS-A/Ro60 (proportion positive)	1/75 (1.33)	0/75 (0)	1
SS-B/La (MFU; n = 149)	35.5 (26.5–51.5)	37.0 (28.2–48.0)	.964
SS-B/La (proportion positive)	1/75 (1.33)	1/74 (1.35)	1
Scl-70 (MFU; n = 150)	86.0 (66.0–123.5)	77.0 (57.2–96.0)	.00537
Scl-70 (proportion positive)	1/75 (1.27)	0/75 (0)	1
Jo-1 (MFU; n = 150)	45.0 (39.8–55.0)	45.0 (38.0–51.0)	.257
Jo-1 (proportion positive)	0/75 (0)	0/75 (0)	n/a
Centromere (MFU; n = 150)	95.0 (66.5–188.0)	78.0 (60.0–106.5)	.0126
Centromere (proportion positive)	6/75 (8.00)	2/75 (2.67)	.276
DFS70 (MFU; n = 150)	90.0 (60.0–187.5)	69.5 (52.0–133.8)	.0766
DFS70 (proportion positive)	16/75 (21.3)	15/75 (20.0)	1
Nucleosome (MFU; n = 150)	20.0 (19.0–24.0)	20.0 (18.0–22.5)	.12
Nucleosome (proportion positive)	0/75 (0)	0/75 (0)	n/a
Ribo-P (MFU; n = 150)	23.0 (17.0–35.5)	19.0 (14.5–26.5)	.0127
Ribo-P (proportion positive)	2/75 (2.53)	0/75 (0)	.497
Ku (MFU; n = 150)	42.0 (37.5–51.5)	40.5 (34.0–50.5)	.0791
Ku (proportion positive)	1/75 (1.33)	1/75 (1.33)	1
RNP A (MFU; n = 150)	78.5 (54.0–129.2)	93.0 (62.8–126.0)	.162
RNP A (proportion positive)	3/75 (4.00)	9/75 (12.0)	.130
PCNA (MFU; n = 150)	37.0 (29.2–46.5)	31.0 (24.2–45.0)	.0403
PCNA (proportion positive)	0/75 (0)	0/75 (0)	n/a
RNA Pol III (MFU; n = 150)	37.0 (31.0–46.5)	34.0 (24.8–44.5)	.0694
RNA Pol III (proportion positive)	0/75 (0)	1/75 (1.33)	1
Rpp25 (MFU; n = 150)	28.0 (24.0–36.8)	26.0 (22.0–33.0)	.127
Rpp25 (proportion positive)	1/75 (1.33)	0/75 (0)	1
RNP C (MFU; n = 150)	65.0 (53.2–86.5)	58.0 (48.5–77.2)	.0844
RNP C (proportion positive)	3/75 (4.00)	3/75 (4.00)	1
Rpp38 (MFU; n = 150)	29.0 (24.0–33.5)	28.0 (23.0–35.5)	.841
Rpp38 (proportion positive)	0/75 (0)	0/75 (0)	n/a
Rpp38-1 (MFU; n = 150)	46.0 (31.0–82.0)	42.0 (32.0–60.2)	.31
Rpp38-1 (proportion positive)	5/75 (6.67)	1/75 (1.33)	.209
BIC-D2 (MFU; n = 150)	54.0 (41.0–84.0)	49.0 (38.5–73.5)	.184
BIC-D2 (proportion positive)	1/75 (1.33)	0/75 (0)	1
Pm/Scl (MFU; n = 150)	63.0 (47.8–88.0)	57.0 (47.8–96.8)	.664
Pm/Scl (proportion positive)	3/75 (4.00)	4/75 (5.33)	1
Sm-Peptide (MFU; n = 150)	16.0 (15.0–18.5)	16.0 (14.0–18.0)	.176
Sm-Peptide (proportion positive)	0/75 (0)	0/75 (0)	n/a
Anti-IgG (MFU; n = 150)	2105.5 (1873.0–2364.0)	2097.0 (1841.0–2422.8)	.999
Anti-IgG (proportion positive)	75/75 (100)	75/75 (100)	n/a
Bio-Flash CIA			
dsDNA (CU; n = 150)	0.0 (0.0–10.2)	0.0 (0.0–9.85)	.716
dsDNA (proportion positive)	2/75 (2.67)	3/75 (4.00)	1
MPO-ANCA (CIU; n = 150)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	.00656

Table 2. Continued

Test ^b	Tuberculosis	Controls	PValue
MPO-ANCA (proportion positive)	1/75 (1.33)	0/75 (0)	1
PR3-ANCA (CIU; n = 150)	3.2 (0.0–4.55)	2.4 (0.0–3.35)	.0759
PR3-ANCA (proportion positive)	1/75 (1.33)	1/75 (1.33)	1
β2GP1-Domain 1 (CIU; n = 149)	4.0 (0.0–5.65)	3.8 (0.0–4.97)	.332
β2GP1-Domain 1 (proportion positive)	1/75 (1.33)	1/74 (1.35)	1
QUANTA Lie ELISA (AU)			
β2GP1-GP1 IgG (AU; n = 149)	0 (0.0–0.0)	0 (0.0–0.0)	.195
β2GP1-GP1 IgG (proportion positive)	2/75 (2.67)	5/75 (6.67)	.442
ACA IgG (AU; n = 150)	4.56 (2.62–8.0)	3.52 (1.72–5.85)	.0879
ACA IgG (proportion positive)	1/75 (1.33)	3/75 (4.00)	.620
ALBIA-FIDIS arthritis profile			
RF (MFU; n = 150)	39.1 (16.6–114.0)	43.6 (17.4–138.2)	.457
RF (proportion positive)	42/75 (56.0)	40/75 (53.3)	.870
HCP1 (MFU; n = 148)	10.5 (4.35–21.8)	6.78 (3.38–13.5)	.215
HCP1 (proportion positive)	0/74 (0)	1/74 (1.35)	1
HCP2 (MFU; n = 147)	4.37 (1.56–8.9)	4.37 (2.84–7.64)	.697
HCP2 (proportion positive)	0/74 (0)	0/73 (0)	n/a
VCP1 (MFU; n = 145)	2.76 (1.36–5.73)	3.78 (1.61–7.76)	.124
VCP1 (proportion positive)	1/73 (1.37)	2/72 (2.78)	.620
VCP2 (MFU; n = 142)	6.78 (2.6–14.2)	8.45 (3.51–13.7)	.269
VCP2 (proportion positive)	0/72 (0)	0/70 (0)	n/a
ALBIA atypical-ANCA			
LAMP2 (MFU; n = 148)	342.5 (173.0–902.0)	653.5 (279.0–1437.0)	.0211
LAMP2 (proportion positive)	18/75 (24.0)	29/73 (39.7)	.520
Elastase (MFU; n = 148)	28.0 (23.0–38.0)	29.0 (23.0–38.0)	.855
Elastase (proportion positive)	0/75 (0)	2/71 (2.74)	.242
p155 (MFU; n = 149)	44.0 (33.5–76.5)	41.0 (32.0–55.8)	.091
p155 (proportion positive)	2/75 (2.67)	1/74 (1.35)	1
QUANTA Lite M2 EP (MIT3)			
Mitochondria antibodies (AU; n = 150)	7.58 (4.57–12.7)	6.89 (4.86–12.7)	.952
Mitochondria antibodies (proportion positive)	9/75 (12.0)	6/75 (8.00)	.588

Data are presented as No. (%) or median (interquartile range).

Abbreviations: β2GP1, beta 2 glycoprotein 1; ACA, anticardiolipin antibody; ANCA, antineutrophil cytoplasmic antibodies; AU, absorbance unit; BICD2, bicaudal D2; CIU, chemi-luminescence unit; DFS, dense fine speckled; dsDNA, double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; HCP, human citrullinated protein; IU, international unit; LAMP, lysosome-associated membrane protein; MFU, mean fluorescence unit; MIT, mitochondrial; MPO, myeloperoxidase; PCNA, proliferating cell nuclear antigen; PR3, proteinase 3; Ribo-P, ribosomal P protein (C22 peptide); RNP, ribonucleoprotein; RF, rheumatoid factor; TRIM, tripartite motif; Scl-70, 70 kDa scleroderma antigen/topoisomerase I; SSA/SSB, Sjögren's syndrome antigen A/B; VCP, viral citrullinated protein.

^aSome patients provided insufficient plasma for all testing requirements. No assumptions or imputations were made in these cases.

^bPlease see the Supplementary Data for a complete list of all antibodies tested, their methods of assessment, and cutoffs for positivity.

details). The highest prevalence of auto-antibodies was found for LAMP2 (24.0% in cases, 39.7% in controls), followed by DFS70 (21.3% in cases, 20.0% in controls) and RNP-A (4.0% in cases, 12.0% in controls). No patient tested positive for the following antibodies: HCP2, nucleosome, PCNA, Rpp38, Sm-Peptide, and VCP2.

After Bonferroni correction, no single test was found to be statistically different between groups. Primary analysis using hypothesis testing and visual inspection did not reveal any statistically significant relationship between the diagnosis of tuberculosis and immune profiles. Variable selection using lasso regression also could not identify variables with significant discriminatory power. Random forests and HCA were used as nonparametric methods but failed to identify clusters

of patients based on immune profile and tuberculosis diagnosis. PCA found no relationship between the covariates and the outcome of interest. Please see the Supplementary Data for additional details.

DISCUSSION

Despite effective antimicrobial therapy, TB remains a significant cause of morbidity and mortality worldwide. Although TB has been associated with autoimmune manifestations and rheumatological conditions, our data reveal that it is not associated with conventional or novel serological markers of autoimmunity. Our results contradict previous reports [6, 7] and suggest that active TB is not associated with the presence of ANCA, ACA, and Scl-70 positivity.

Several studies have linked TB with the development of auto-antibodies. Several mechanisms have been proposed to explain this association, including molecular mimicry. In vitro data suggest homology between species in cell wall glycolipids and DNA [10], bystander activation of CD8+ lymphocytes [11], and TLR agonism [12]. However, conflicting data exist regarding the association between TB and clinical autoimmune disease; our patient population did not have any reported rheumatological conditions. It is of note that our population was tested before the onset of treatment, which could theoretically affect auto-antibody production. It is possible that antimycobacterial treatment increases auto-antibody production by exposing novel antigens, which could explain a higher prevalence of certain markers of auto-immunity in other studies [13].

Our results must be interpreted in the context of the study characteristics. We were unable to follow patients longitudinally to assess for the development of auto-antibodies or autoimmune manifestations. Furthermore, all samples in our study were obtained from passive case finding. As such, it was not possible to determine the duration of disease before seeking medical attention. From epidemiologic studies, those diagnosed passively tend to have more severe disease and a longer duration of symptoms than those detected through active case finding, such as immigrant screening [14]. We also evaluated auto-antibodies in a relatively small patient population with imbalances in baseline characteristics between groups. However, there is no reason a priori to suggest that these imbalances would explain the negative results of our study.

We selected patients with active TB from 4 geographically diverse areas and patients with febrile respiratory conditions as opposed to healthy volunteers. Due to the limited diagnostic capacity in many of the study centers, we were unable to diagnose a microbial pathogen in the control population. We performed the most thorough auto-immune workup in patients with active TB to date with a complete panel of novel serological assays and assessed them in a blinded fashion in a reference laboratory. In conclusion, we did not observe an association between serological markers of auto-immunity and active TB when compared with patients with acute febrile respiratory illnesses.

Acknowledgments

We would like to thank Fiona McIntosh and the Foundation for Innovative New Diagnostics (FIND) for their assistance and support regarding this project.

Financial support. This research project was funded by a foundation grant to M.A.B. from the Canadian Institute of Health Research. M.P.C. receives salary support from a postdoctoral training grant, provided by the Fonds de Recherche Santé Québec.

Potential conflicts of interest. This manuscript was prepared as part of routine work. M.P.C., G.B.L., L.O.P., D.T.B., M.J.F., and M.A.B. have no disclosures to report. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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