CONCISE REPORT

Positive anti-cyclic citrullinated proteins and rheumatoid factor during active lung tuberculosis

O Elkayam, R Segal, M Lidgi, D Caspi

....

Objectives: To determine the prevalence of anti-cyclic citrullinated proteins (anti-CCP) and IgM rheumatoid factor (RF) in sera of patients with TB compared with healthy controls.

Patients and methods: 47 consecutive patients with recently diagnosed active pulmonary TB and 39 healthy controls were studied. Data were collected by questionnaire on clinical features of the disease, duration of symptoms, fever, cough, arthralgia, myalgia, sicca symptoms. Serum samples were collected from patients before starting treatment for TB and frozen at −20°C. Anti-CCP and IgM RF were evaluated by ELISA.

Results: The mean (SD) duration of TB related symptoms was 4.4 (1.7) months, 73% had fever, 94% a cough. Rheumatic symptoms were relatively rare: arthralgia (4%), myalgias (4%), eye and mouth dryness (2% and 9%, respectively). Mean (SD) levels of anti-CCP were significantly increased in patients with TB compared with controls: 44.9 (51) IU v 20 (7.3) IU (p = 0.002). Serum levels >40 U were found in 15/47 (32%) patients compared with 1/39 (2.6%) controls (p = 0.002). Mean (SD) serum levels of IgM RF were significantly increased in patients with TB: 17.8 (19) v 4.3 (5) (p<0.0001). IgM RF was positive (>6 IU) in 29/47 (62%) patients v 1/39 (2.6%) controls (p<0.0001).

Conclusions: A significant proportion of patients with active TB have an increased titre of anti-CCP and IgM RF.

The past two decades have been marked by a worldwide resurgence of tuberculosis (TB). About two billion people have latent TB and about eight million will develop active TB.[1] It has been shown that both pulmonary TB and also cases of extrapulmonary disease are increasing.[2] About 10% of extrapulmonary TB affects the bones and joints.[2] Patients with TB, even those without evidence of a direct musculoskeletal/local involvement, may present with a variety of rheumatic symptoms and signs. Although TB arthritis most commonly manifests as a monarthritis of the weightbearing joints,[3] oligoarticular or polyarticular presentation is not rare, mimicking inflammatory diseases such as the spondyloarthropathies[4] or rheumatoid arthritis (RA), or both.[5] Poncet's disease is the classic example of TB-induced polyarthritis.[6] Furthermore, the serum of patients with TB may contain rheumatoid factors (RFs) in up to 40% of cases.[7]

Antibodies recognising cyclic citrullinated peptides are highly specific for RA.[8] The specificity for RA has been shown to be up to 98% in comparison with 0–1% of healthy controls and 2–5% of disease controls.[8] Anti-cyclic citrullinated proteins (anti-CCP) are present early in the disease process and may even pre-date the onset of RA by many years.[9]

This study aimed at determining the prevalence and associations of anti-CCP in patients with TB.

PATIENTS AND METHODS

Patients

Forty seven patients with recently diagnosed active pulmonary TB were included in the study. All were admitted to the hospital department of tuberculosis, with clinical symptoms and radiological signs of TB as well as positive cultures for *Mycobacterium tuberculosis*. A questionnaire was used to determine data on the clinical features of the disease, such as duration of symptoms, the presence of fever, cough, as well as rheumatological manifestations such as arthralgia/arthritis, myalgia, rash, mucocutaneous symptoms, sicca symptoms, spontaneous abortion, history of thrombosis, and familial history of autoimmune diseases. Serum samples were collected before starting treatment for TB and frozen at −20°C. Controls were 39 aged matched healthy personnel.

Anti-CCP

Serum IgG anti-CCP2 was studied by enzyme linked immunosorbent assay (ELISA) using a commercial kit (Quanta lite; Inova Diagnostics, San Diego CA, USA), according to the manufacturer's instructions. Samples were considered weakly positive if the antibody titre was 20–39 IU, moderately positive between 40 and 59, and strongly positive if >60 IU.

IgM RF

An ELISA commercial kit (Quanta lite; Inova Diagnostics) was used to determine serum IgM RF, according to the manufacturer's instructions. Samples were considered positive if the antibody titre was >6 IU.

Statistical analysis

Statistical analysis was performed by the SPSS software, using Student's t test and a χ^2 test to compare antibody titres or positivity rate, respectively, between patients with TB and controls. Pearson correlation coefficients were used to study the relationship between clinical measures and the levels of anti-CCP and IgM RF. A value of p<0.05 was considered significant.

RESULTS

Patients

Table 1 summarises the demographic and clinical characteristics of patients with TB and healthy controls. The patients had a mean (SD) duration of symptoms of 4.4 (1.7) months; 73% had fever, 94% presented with cough. Only a small minority had symptoms such as arthralgia (4%), myalgias (4%), or eye and mouth dryness (2% and 9%, respectively). None of the patients had signs typical of rheumatoid arthritis such as arthritis, morning stiffness or rheumatoid nodules. None had mucocutaneous aphthae or skin manifestations or

....

Abbreviations: CCP, cyclic citrullinated protein; HCV, hepatitis C virus; RA, rheumatoid arthritis; RF, rheumatoid factor; TB, tuberculosis

Table 1 Demographic and clinical characteristics of patients with TB and healthy controls

Characteristics	Patients with TB (n = 47)	Controls (n = 39)
Age (years), mean (SD)	52.3 (17)	47 (21)
Sex (M/F)	26/21	13/26
Duration of symptoms (months), mean (SD)	4.4 (1.7)	
No (%) of patients with:		
Fever	34 (72)	
Cough	42 (89)	None
Arthralgia	2 (4)	
Myalgia	2 (4)	
Eye dryness	1 (2)	
Mouth dryness	4 (9)	

a history of spontaneous abortion, thrombosis or known first degree familial autoimmune disease.

Serum levels of anti-CCP and IgM RF

The mean (SD) levels of anti-CCP were significantly increased in patients with TB in comparison with controls: 44.9 (51) IU v 20 (7.3) IU (p = 0.002). Serum levels above the upper normal limits (>40 IU) were found in 15/47 (32%) patients in comparison with 1/39 (2.6%) controls (p = 0.002) (fig 1).

The mean (SD) serum levels of IgM RF were significantly increased in patients with TB: 17.8 (19) v 4.3 (5) (p<0.0001). IgM RF was found positive (>6 IU) in 29/47 (62%) patients in comparison with 1/39 (2.6%) controls (p<0.0001) (fig 2).

In patients with increased levels of anti-CCP and IgM RF, the mean (SD) levels were of 126.3 (52) IU (range 49.7–205) and 32.8 (31.4) IU (range 6.1–105), respectively.

Associations between clinical manifestations and serological studies

The presence of anti-CCP significantly correlated with a history of prolonged fever (p = 0.005). No correlation was found between the presence of anti-CCP or IgM RF and any rheumatic symptom. A significant correlation was found between symptoms of fever and cough (p = 0.003), and between arthralgia and sicca (p<0.0001).

No association was found between anti-CCP and RF.

DISCUSSION

In this study we found that 15/47 (32%) patients with TB have positive levels of anti-CCP. Although the presence of anti-CCP correlated with fever, it was not associated with symptoms and signs of arthritis.

Anti-CCP are a family of antibodies with specificities directed against a variety of citrullinated peptides.[8] They are present in most patients with RA and have been found to have a specificity of >90%.[8] However, recent investigators have shown that anti-CCP are present in the serum of 8% of patients with psoriatic arthritis and have questioned its specificity.[10] It is not clear whether the false positive anti-CCP reactivity seen in patients with TB is directed against citrullinated or non-citrullinated epitopes in the substrate for the CCP test.

Except for hepatitis C virus (HCV), the presence of anti-CCP in infectious diseases has not been well studied. It seems that in contrast with RF, which is present in the great majority of patients with hepatitis C arthritis, as well as in a proportion of patients with other subacute infections, particularly bacterial endocarditis, anti-CCP is negative in patients with HCV and may help in discriminating between HCV related arthritis and RA.[11 12]
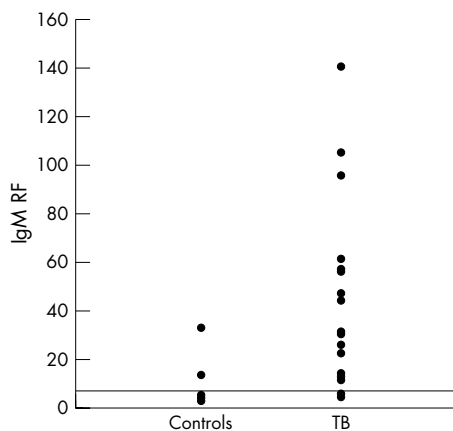
Figure 1 Serum IgM RF in patients with TB and controls.
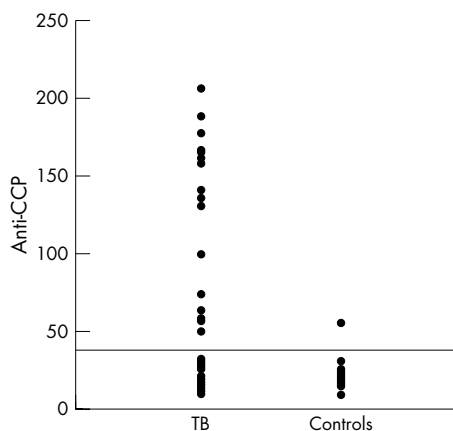
Figure 2 Serum anti-CCP in patients with TB and controls.

TB is a multifaceted disease, which may present with a variety of symptoms, sometimes mimicking autoimmune diseases. Involvement of the bones and joints is the most common extrapulmonary manifestation of TB.[2] There are many pitfalls in the diagnosis of tuberculous arthritis. Clinically, it may imitate other inflammatory rheumatic diseases, such as RA.[5] The triad of radiological abnormalities observed in tuberculous arthritis may simulate RA and includes periarticular osteoporosis, peripherally located osseous erosion, and gradual diminution of the joint space.[13] Furthermore, it has been reported that RF is present in up to 40% of patients with TB.[7] Djavad *et al* have analysed the RFs produced by Epstein-Barr virus transformed monoclonal B cells obtained from patients with RA and TB, and shown that they have a similar avidity and affinity to different antigens.[14] In addition to RF, patients with TB may present a variety of autoantibodies[15] such as antinuclear antibodies, anticardiolipin,[15] and antineutrophil cytoplasmic antibodies.[16] Thus patients with TB may present both clinical and laboratory parameters indicative of rheumatic conditions, in general, and RA, in particular.

In conclusion, a significant proportion of our present series of patients with active TB had higher titres of anti-CCP and IgM RF. These findings should be kept in mind in the interpretation of serological studies in the differential diagnosis of patients with systemic manifestations.

. . . .
Authors' affiliations
O Elkayam, D Caspi, Department of Rheumatology, Tel Aviv Medical Centre, Israel

R Segal, Department of Geriatrics, Shmuel-Harofeh Geriatric Medical Centre and the ''Sackler'' Faculty of Medicine, University of Tel Aviv, Israel

M Lidgi, Department of Tuberculosis, Shmuel-Harofeh Geriatric Medical Center and the ''Sackler'' Faculty of Medicine, University of Tel Aviv, Israel

Correspondence to: Dr O Elkayam, Department of Rheumatology, Tel Aviv Medical Centre, 6 Weizman Street, Tel Aviv 64239, Israel; oribe14@netvision.net.il

REFERENCES
1 **Mandalakas AM**, Starke JR. Current concepts of childhood tuberculosis. *Semin Pediatr Infect Dis* 2005;**16**:93–104.
2 **Malaviya AN**, Kotwal PP. Arthritis associated with tuberculosis. *Best Pract Res Clin Rheumatol* 2003;**17**:319–43.
3 **Watts HG**, Lifeso RM. Tuberculosis of bones and joints. *J Bone Joint Surg Am* 1996;**78**:288–98.
4 **Hammoudeh M**, Khanjar I. Skeletal tuberculosis mimicking seronegative spondyloarthropathy. *Rheumatol Int.* 2004;24: 50–2, Epub 2003 May 29..
5 **Bush DC**, Schneider LH. Tuberculosis of the hand and wrist. *J Hand Surg [Am]* 1984;**9**:391–8.
6 **Sood R**, Wali JP, Handa R. Poncet's disease in a north Indian hospital. *Trop Doct* 1999;**29**:33–6.
7 **Isenberg DA**, Maddison P, Swana G, Skinner RP, Swana M, Jones M, *et al.* Profile of autoantibodies in the serum of patients with tuberculosis, klebsiella and other gram-negative infections. *Clin Exp Immunol* 1987;**76**:516–23.
8 **Van Venrooj WJ**, Hazes JMW, Visser H. Anti-citrullinated protein/peptide antibody and its role in the diagnosis and prognosis of early rheumatoid arthritis. *Neth J Med* 2002;**60**:383–8.
9 **van Gaalen FA**, Linn-Rasker SP, van Venrooij WJ, de Jong BA, Breedveld FC, Verweij CL, *et al.* Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004;**50**:709–15.
10 **Vander Cruyssen B**, Hoffman IE, Zmierczak H, Van den Berghe M, Kruithof E, De Rycke L, *et al.* Anti-citrullinated peptide antibodies may occur in patients with psoriatic arthritis. *Ann Rheum Dis* 2005;**64**:1145–9.
11 **Wener MH**, Hutchinson K, Morishima C, Gretch DR. Absence of antibodies to cyclic citrullinated peptide in sera of patients with hepatitis C infection and cryoglobulinemia. *Arthritis Rheum* 2004;**50**:2305–8.
12 **Bombardieri M**, Alessandri C, Labbadia G, Iannuccelli C, Carlucci F, Riccieri V, *et al.* Role of anti-cyclic citrullinated peptide antibodies in discriminating patients with rheumatoid arthritis from patients with chronic hepatitis C infection-associated polyarticular involvement. *Arthritis Res Ther* 2004;**6**:R137–41.
13 **Hugosson C**, Nyman RS, Brismar J, Larsson SG, Lindahl S, Lundstedt C. Imaging of tuberculosis. Peripheral osteoarticular and soft tissue tuberculosis. *Acta Radiol* 1996;**37**:512–16.
14 **Djavad N**, Bas S, Shi X, Scwager J, Jeannet M, Vischer T, *et al.* Comparison of rheumatoid factors of rheumatoid arthritis patients, of individuals with mycobacterial infections and of normal controls: evidence for maturation in the absence of an autoimmune response. *Eur J Immunol* 1996;**26**:2480–6.
15 **Adebajo AO**, Charles P, Maini RN, Hazleman BL. Autoantibodies in malaria, tuberculosis and hepatitis B in a west African population. *Clin Exp Immunol* 1993;**92**:73–6.
16 **Flores-Suarez LF**, Cabiedes J, Villa AR, van der Woude FJ, Alcocer-Varela J. Prevalence of antineutrophilic cytoplasmic autoantibodies in patients with Tuberculosis. *Rheumatology (Oxford)* 2003;**42**:711.