

A low prevalence of purified protein derivative test positivity in Turkish patients with rheumatoid arthritis. Association with clinical features and HRCT findings

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Abstract

Objectives

In this study, we aimed to evaluate the frequency of purified protein derivative (PPD) skin test positivity and associated clinical features in RA patients.

Materials and methods

We included 94 (80 F, 14 M, mean age: 55.8) consecutive RA patients with a disease duration of 8.7 years. PPD test was performed in all RA patients; clinical features were recorded down; chest x-ray, pulmonary function tests and HRCT were available in all cases. As the control group, we included data of 21 SLE, 44 AS, 27 OA, 16 gouty arthritis and 18 vasculitis patients.

Results

The frequencies of PPD positivity in RA (29.8%) and SLE (19%) patients were lower than in patients with AS (65.9%), gouty arthritis (68.8%) and OA (63%) (all p values < 0.01). PPD-positive RA patients were more frequently smokers ($p = 0.005$) and had a higher rate of RF seropositivity ($p = 0.04$) than PPD-negatives. PPD was less frequently positive in erosive RA disease ($p = 0.033$). Chest x-rays and HRCT abnormalities were detected in 41.8% and 62.7% of RA patients, respectively. Frequencies of chest x-ray and HRCT abnormalities in PPD-positive and PPD-negative patients were not different from each other ($p > 0.05$).

Conclusion

In our country in which tuberculosis is relatively frequent -contrary to the situation in AS patients- we observed a lower frequency of PPD positivity in RA and SLE patients compared to patients with other rheumatic diseases. We did not find any relationship between PPD positivity and the frequency of chest x-ray, HRCT abnormalities.

Key words

Rheumatoid arthritis, tuberculosis, high-resolution computerized tomography, chest x-ray, purified protein derivative (PPD) test.

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Introduction

Pleuroparenchymal complications are one of the important factors leading to the increased morbidity and mortality in rheumatoid arthritis (RA) (1). These complications are mainly observed in patients with severe chronic articular disease who are seropositive, and who have other extraarticular findings (2).

The usage of TNF-blockers in the treatment of RA in recent years and the increased incidence of infections - especially tuberculosis (TB) - with these drugs make it obligatory to interpret the pulmonary findings and purified protein derivative (PPD) skin test (3, 4). PPD is currently the only method which detects latent TB (5). Nevertheless, there is a defect in cellular immunity in RA and patients' response to PPD test might not be sufficient (6).

Chest x-ray is an easy and cheap method; however, its sensitivity is relatively low, and the presence of sequela findings might pose problems. High-resolution CT (HRCT) is quite a sensitive method to detect pulmonary pathologies. After the usage of HRCT became more common, the association of many lesions that could not be detected on routine x-rays with RA have been defined.

In our study, we determined the frequency of pulmonary involvement in our RA patients and compared the results of various diagnostic methods. Chest x-rays were interpreted; pulmonary function tests (PFT), HRCT, and PPD were obtained and their relationship with the clinical features of RA was determined.

Materials and methods

Ninety-four (80 females, 14 males, mean age: 55.8 ± 12) consecutive RA patients followed up at the Division of Rheumatology, Trakya University Medical Faculty were included in the study. RA patients were diagnosed according to ACR 1987 criteria (7). Patients with nonspecific immunosuppression (chronic hepatic and renal diseases, diabetes, or malignant diseases) and known chronic obstructive pulmonary disease, cardiac failure, pneumoconiosis were excluded. The study was approved by the ethical committee of

our center. All patients were given detailed information and written consent was obtained from each patient.

Data about age, sex, disease duration, medical treatment and drug history, extraarticular manifestations and other diseases of RA patients were recorded down from the hospital files. All RA patients and controls were questioned about history of smoking and pulmonary symptoms. RA patients underwent detailed joint and respiratory system examination. In addition, blood samples were drawn from RA patients for ESR, CRP, rheumatoid factor (RF), and whole blood count. DAS28 was estimated and patients were grouped as active or inactive. Active disease was defined as DAS28 score more than 3.1 (8). Hand x-rays of all patients were available.

All RA patients had chest x-rays. HRCT was performed in 67 RA patients (Toshiba TCT 300S Scanner). The sections were 2 mm-thick and obtained at 20 mm-intervals starting from apices of the lungs till the bases of the costophrenic sinuses. The sections were recorded at "end-inspiratory volume" the scanning time of which is 1 second. The images were reconstructed with high spatial frequency algorithm for parenchymal evaluation and with standard algorithm for mediastinal evaluation. HRCT findings were divided into the following as; bronchiectasis, bronchial wall thickening, nodule, emphysema, pleural thickening/calcification, pleural effusion, septal thickening/parenchymal bands, ground-glass and honeycomb appearance. The classification of "typical" findings of reactivated pulmonary TB were according to a previous report (9). Typical findings for TB included centrilobular nodules, "tree in bud" appearance, a single cavitary nodule and acinar or lobular nodule. All chest x-rays were interpreted at two different time periods by one radiologist (NT) and one pneumologist (CK) who were blind to one another and also to the clinical features of the patients. The intraobserver agreement for chest x-rays was excellent ($\kappa = 0.81$ and 0.90); interobserver agreement was good ($\kappa = 0.62$). All

HRCT scans were interpreted at two different time periods by one radiologist (NT). The intraobserver concordance of chest x-ray evaluations was good ($\kappa = 0.63$).

The PFT of the patient and the control groups were determined by computerized spirometry (Sensor Medics, V-max 22, Yorbolinda, CA). PFT included forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), and the diffusing capacity for carbon monoxide (DLCO) using the single breath technique and corrected for lung volume and hemoglobin levels. The results were expressed as a percentage of the predicted value compared with individuals of similar sex, age, weight and height.

PPD was performed using the Mantoux method (5) and was measured 48 to 72 hours later. PPD was considered positive if the induration was 5 mm. The PPD test was performed simultaneously with the HRCT. We routinely apply PPD test to all patients who are admitted to our department because the frequency of TB in our country is high. In addition, as a control group, we retrospectively evaluated PPD results of 21 systemic lupus erythematosus (SLE), 44 ankylosing spondylitis (AS), 16 gouty arthritis, 27 osteoarthritis (OA), and 18 vasculitis patients who were admitted to our department within the last 4 years. All SLE patients fulfilled the revised ACR criteria (10), all AS patients fulfilled modified New York classification criteria (11), gouty arthritis patients met the American Rheumatology Association diagnostic criteria for acute gout (12), and OA patients fulfilled the ACR criteria (13).

Chi-square test was used to compare categorical variables, and to determine intraobserver and interobserver agreement; and concordance coefficient, kappa, was calculated. In the comparison of quantitative variables, Mann-Whitney U test was used.

Results

The mean disease duration in RA patients was 8.7 years (10.2), RF was positive in 55.3%, 66% had erosive disease. Fifty percent of RA patients were using

at least one DMARD, 36.2% methotrexate, 22.3% sulphasalazine, 14.9% antimalarial drugs, and 50% were using steroids. In 17.2% of RA patients, FEV1 and FVC; in 52.5%, FEF25-75; and in 45.8%, DLCO were low.

The clinical and demographic features, and results of PPD skin tests of RA patients and other groups are seen in Table I. Mean ages of AS and SLE patients were significantly lower than the other groups (all p values < 0.01). The mean age of gouty arthritis patients was significantly higher than RA and OA patients (p values 0.05). The frequency of PPD positivity in RA patients (29.8%) was significantly lower than in AS (65.9%), gouty arthritis (68.8%) and OA (63%) patients (all p values < 0.01). The frequency of PPD positivity in SLE patients (19%) was significantly lower than in AS, gouty arthritis and OA patients (all p values < 0.01). The frequency of PPD positivity in vasculitis group was lower than in gouty arthritis and AS groups ($p < 0.05$). Fifty-two RA patients (55.3%) had no reaction to PPD (0 mm) compared with 12 (27.3%) AS patients ($p = 0.002$). In addition, the mean size of the PPD induration in patients with RA and SLE were significantly less than those in AS and gouty arthritis patients (p values < 0.01).

When clinical features of PPD-positive RA patients were compared to PPD-negative patients, it was observed that PPD positivity was more frequent in smoking patients (39.3% vs. 13.6%, $p = 0.005$) and in seropositives (71.4% vs. 48.5%, $p = 0.04$). PPD was less fre-

quently positive in erosive RA disease (50% vs. 72.7%, $p = 0.033$). Mean hemoglobin level was higher in PPD-positive RA patients than in the PPD-negative group ($p = 0.026$). RA patients with a positive PPD were similar to others in ESR, CRP, disease duration, DMARD and steroid intake, and PFT. Clinical features of PPD-positive and negative patients are seen in Table II.

The frequency of pathologic chest x-rays in RA patients was 41.8%. Abnormalities on HRCT were recorded in 42 (62.7%) RA patients. Agreement between HRCT and chest x-ray results was 71.1% ($\kappa = 0.43$). The lesions detected on HRCT were septal thickening/parenchymal bands (25 cases, 37.3%), pleural thickening (18 cases, 26.9%), bronchiectasis (15 cases, 22.4%), pulmonary nodules (12 cases, 17.9%), pleural effusion (6 cases, 9%), bronchial wall thickness (5 cases, 7.5%), emphysema (4 cases, 6%). In addition, 5 subjects had ground-glass (7.5%), and 3 (4.5%) had honeycomb appearance. None of the patients had HRCT lesions typical for TB. The pulmonary nodules did not have typical features for TB.

When the clinical features of patients who had HRCT abnormalities were compared to others, it was observed that their mean age ($p = 0.002$) was higher, and duration of RA ($p = 0.03$) was longer. It was observed that the probability of detecting pulmonary lesions on HRCT was affected significantly by the pre-sence of pulmonary symptoms ($p = 0.023$), and the presence of chest x-ray abnormalities ($p < 0.001$).

Table I. The clinical features of patients with various rheumatic diseases and results of PPD test.

	n (F/M)	Age (mean SD)	Steroid usage n (%)	PPD positivity n (%)	PPD (mm)
RA	94 (80/14)	55.8 \pm 12.1	47 (50)	28 (29.8)	4.46 \pm 6.9
SLE	21 (19/2)	37.6 \pm 15.3	10 (47.6)	4 (19)	2.9 \pm 6.2
AS	44 (13/31)	36.3 \pm 13.4	2 (4.5)	29 (65.9)	9.8 \pm 8
Gouty arthritis	16 (5/11)	68.2 \pm 13.8	0	11 (68.8)	11 \pm 9.8
Vasculitis	18 (6/12)	54.6 \pm 16	14 (77.8)	6 (33.3)	4.1 \pm 5.4
Osteoarthritis	27 (13/14)	50.9 \pm 17.3	4 (14.8)	17 (63)	7.8 \pm 6.7

Table II. The clinical features of our RA patients who are PPD-positive and PPD-negative.

Clinical features	PPD (+) RA patients	PPD (-) RA patients	p
n (%)	28 (29.8)	66 (70.2)	NS
Female, n (%)	22 (78.6)	58 (87.9)	NS
Age (years)	52.8 ± 11.9	57.1 ± 12	NS
RA duration (years)	7.9 ± 8.6	91 ± 0.6	NS
Active disease, n (%)	16 (57.1)	44 (66.7)	NS
Erosive disease, n (%)	14 (50)	48 (72.7)	0.033
RF positivity, n (%)	20 (71.4)	32 (48.5)	0.04
ESR (mm/h)	60.3 ± 34.4	64.4 ± 36.9	NS
CRP (mg/dl)	4.03 ± 3.9	5.51 ± 2.2	NS
Hemoglobin (g/dl)	11.7 ± 1.3	10.9 ± 1.3	0.03
Smoking, n (%)	11 (39.3)	9 (13.6)	0.005
DMARD usage, n (%)	14 (50)	33 (50)	NS
MTX usage, n (%)	10 (35.7)	24 (36.4)	NS
Sulphasalazine usage, n (%)	6 (21.4)	15 (22.7)	NS
Antimalarial usage, n (%)	4 (14.3)	10 (15.2)	NS
Leflunomide usage, n (%)	2 (7.1)	1 (1.5)	NS
Steroid usage, n (%)	13 (46.4)	34 (51.5)	NS
Pulmonary symptoms, n (%)	3 (10.7)	12 (18.2)	NS
TB history, n (%)	4 (14.3)	3 (4.5)	NS
FEV1 (% predicted)	95 ± 22.4	97.6 ± 22.9	NS
FVC (% predicted)	97.1 ± 27.5	95.2 ± 19	NS
DLCO (% predicted)	86.9 ± 29.7	80.1 ± 2.9	NS

NS: not significant.

The frequencies of chest x-ray (46.7% vs. 33.3%) and HRCT abnormalities (66.7% vs. 58.5%) in PPD-positive and PPD-negative patients were not different from each other ($p > 0.05$). The frequencies of TB history were similar in patients with and without HRCT abnormalities (10% vs. 7.4%). PPD test was more frequently positive in patients with pleural thickening on HRCT (58.3 vs. 24.4%, $p = 0.038$).

One of the patients who was PPD positive had thickening of the bronchial wall and findings of segmental consolidation on HRCT. In this patient, bronchoscopy was undertaken; caseification necrosis was observed in histopathologic examination; and his pulmonary lesion disappeared after anti-TB therapy. In another PPD negative patient with mild renal insufficiency due to secondary amyloidosis, miliary TB and renal failure developed three months after adalimumab therapy. This

patient was not on TB prophylaxis and she died. There was ground glass appearance on her initial HRCT.

Discussion

TNF-blockers have recently come into use in RA and they are quite effective. The most important risks of these drugs are the development of infection and TB reactivation (3, 4, 14). Therefore, it is important to determine RA patients who will have increased risk of TB after the administration of TNF-blockers. The employment of TNF-blockers in PPD positive RA patients is of increasing relevance (15,16). Guidelines suggest that PPD test should be performed and a chest x-ray should be evaluated before therapy in RA patients, and they advise prophylactic INH usage in the presence of a positive test and/or a suspected chest x-ray (4). In Spain, the risk of TB in RA patients was found to be increased 4-fold when compared to

the general population (14). Although there is no definite data from Turkey, it is known that the prevalence of TB in Turkey is high (0.38%, unpublished data from the Ministry of Health, 1992).

We diagnosed abnormalities on chest x-ray in 41.8% of RA patients. Various studies reported a frequency of 2-18.7% for chest x-ray abnormalities in RA (17,18). One study from Turkey stated that the frequency of abnormalities on chest x-ray in RA patients was 22.5% (19). In addition, we detected pulmonary abnormalities on HRCT in 62.7% of our RA patients. The above-mentioned study from our country (19) found a prevalence of pulmonary lesions (57.5%) similar to ours. Some series reported HRCT abnormalities reaching up to 90% (17, 20). These percentages are quite high when compared to the percentages of chest x-ray abnormalities reported in previous studies. In our study, there were fewer patients with pulmonary symptoms than patients with HRCT abnormalities. This might be explained by most HRCT lesions not being serious enough to cause symptoms. We found that RA patients with HRCT abnormalities were older, had longer disease duration, more frequent pulmonary symptoms at initial presentation, erosive disease, and chest x-ray abnormalities were more frequent in these patients.

Although we found a high prevalence of chest x-ray and HRCT abnormalities in RA, PPD test was less frequently positive. This condition is important as one Spanish study reported that PPD was negative in patients who developed TB after TNF-blocker usage (14). Recently, one study from Peru (21), which is a country with a high prevalence of TB similar to ours, stated that RA patients had a lower frequency of PPD positivity than controls (29% vs. 71%). Nevertheless, contrary to this, one study from USA (22) which has a low prevalence of TB reported that the frequency of PPD positivity (9.2%) was not lower in RA. We might, therefore, say that PPD might be positive less frequently than expected in RA; however, when chest x-rays are evaluated

pulmonary pathologies are diagnosed in more patients.

In Turkey, BCG vaccination is applied to everyone shortly after birth. Therefore, one factor which affects PPD results might be the BCG. This might partly explain why AS patients who are younger have a higher frequency of PPD positivity than RA patients. It is suggested that BCG might affect PPD test for up to 15 years. Nevertheless, OA patients who are similar in age to RA patients and gouty arthritis patients who are older than RA patients have high frequencies of PPD positivity; this excludes the above-mentioned probability.

In addition to cellular immune dysfunction, another factor which might explain the increased frequency of PPD negativity in RA might be the usage of steroids and immunosuppressives. Nevertheless, the frequencies of steroid, methotrexate usage in PPD-positive and PPD-negative RA patients were similar. Besides, it was reported that steroid intake of less than 15 mg/day did not affect tuberculin reactivity (23). It was interesting that smoking and seropositive RA patients had higher frequencies of PPD positivity; however, positivity in the erosive group was significantly lower. HRCT and chest x-ray abnormalities were not different between PPD-positive and PPD-negative RA patients; nevertheless, patients with pleural thickening on HRCT had more frequent PPD positivity.

In our study, we did not search for specific antibodies anti-mycobacterium and we did not investigate the presence of *M. tuberculosis* in organic fluids. We diagnosed active TB in one PPD positive patient who had HRCT abnormalities. Although we do not have follow-up data of all patients; interestingly one PPD negative patient with ground glass appearance on HRCT developed miliary TB. When we consider data from the above-mentioned Spanish study (14), we might conclude that the PPD test might be unreliable to decide whether TB prophylaxis will be administered to RA patients who are planned to be put on TNF-blocker therapy.

One of our important results was that the frequency of PPD positivity was increased in AS which is a disease in which TNF-blockers are used commonly. SLE patients had quite a lower frequency of PPD positivity than others; and, probably steroid intake by most subjects have contributed to this result.

In Turkey, which is a country with a relatively high prevalence of TB, we found a low frequency of PPD positivity in RA (29.8%) and a high frequency (65.9%) in AS. Consequently when we consider data from Peru and Spain, when using TNF-blockers in areas where the frequency of disease is high - contrary to AS - the decision for prophylaxis in RA should not be based upon only PPD results. In addition, we observed that RA patients had a high frequency of abnormalities in chest x-ray and HRCT; nevertheless, these generally did not have any clinical significance and had no relationship with PPD results. Consequently, it might be wise to perform HRCT in patients with a negative PPD and a suspect chest x-ray lesion in order to decide on long-term prophylaxis. Our RA patients had no typical findings for TB on HRCT and these findings generally had no association with PPD results. Therefore, we cannot comment on the effective utility of performing an HRCT along with a PPD test.

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