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Latent tuberculosis infection in psoriasis patients

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ABSTRACT

Aims: Psoriasis is a chronic, inflammatory, and life-long skin disease. Patients may need to change the treatment regimen by time due to the course of the disease. According to the guidelines, patients should be screened for latent tuberculosis infection (LTBI) before starting treatment with biological agents. We aimed to evaluate the associations between positive interferon-gamma release assay (IGRA) tests, the chest CT findings and inflammatory blood markers of the psoriasis patients who have undergone screening for LTBI before starting systemic treatment with biological agents or conventional options.

Methods: The electronic medical records, Chest CT reports and blood tests of 123 consecutive patients with a diagnosis of psoriasis who were candidates for systemic treatment (methotrexate, cyclosporin and biological agents) and screened for LTBI were examined.

Results: The mean age of the patients was 49.24 and 64 (52%) of them were males. 37(30%) had a family history of tuberculosis 103(83%) of them had BCG vaccination scars. 59% had radiological features on their Chest CT scans. 28% of the patients had positive Quantiferon test results. When compared to the Quantiferon negative group, there was no difference between the two groups according to demographic characteristics, comorbidities, family history of tuberculosis, BCG vaccination status, smoking habits, occupation, and qualification details ($p>0.05$). The values of WBC, neutrophils, lymphocyte, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, systemic inflammation index and erythrocyte sedimentation rates were found statistically higher in the patients with positive Quantiferon test ($p<0.05$).

Conclusion: The patients with psoriasis requiring systemic treatment and having positive IGRA test results have increased levels of inflammation. Psoriasis and LTBI might have a synergistic action in the inflammatory response which necessitates further studies to find out the associations between these two entities.

Keywords: Latent TB, psoriasis, quantiferon, lung, chest CT

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with a complex pathogenesis, that may cause an impairment in a patient's quality of life.[1] The disease is most likely as old as mankind. Hippocrates used the word "psora" for the itchy lesions on the skin.[2] During the Roman Empire, Galen was the first physician who use the term "psoriasis".[2] D. Turner described the disease and tried to apply some treatment modalities containing mercury.[3]

Today, conventional systemic treatment with acitretin, methotrexate, cyclosporine, and biologics are the options for therapy in moderate to severe psoriasis.1 Biological agents are a new era in treating psoriasis patients, bringing a marked improvement in managing the disease. However, as the other systemic treatment agents do biologics also include the risk of *Mycobacterium tuberculosis (M. tuberculosis)* infection reactivation as a severe complication, which leads to problems in a high-burden country for tuberculosis.[3]

Mycobacterium tuberculosis is the infectious disease that causes tuberculosis (TB). The TB etiologic agent most likely existed before humans evolved on Earth.[4] It evolved into an uncommon endemic illness in humans around the time that they started to establish villages and advance agriculture. Robert Koch discovered the microscopic cause only in 1882.[4] According to the Global Tuberculosis Report, about a quarter of the world's population is infected with MTB.[5] In Turkiye, with the efforts of the National Tuberculosis Control Program, the number of TB patients decreased from 20,535 in 2005 to 10,600 in 2020.[6]

A considerable portion of the population, particularly in areas with high endemicity, has latent tubercle bacilli, which act as a reservoir for active tuberculosis depending on the host conditions.[7] *M. tuberculosis* exposure is a frequent cause of latent TB infection

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(LTBI), which has a 5-10% lifetime probability of evolving into active TB, with most TB cases occurring within the first two years of infection.[7,8] The diagnosis and treatment of *M. tuberculosis*-infected individuals who would otherwise be at a high risk of acquiring and transmitting active disease is crucial for the complete eradication of tuberculosis according to the End TB strategy that was adopted by the World Health Assembly.[7]

Therefore, it is a firm requirement for patients to be screened for LTBI who are candidates for either biological agents or conventional therapeutic options. According to WHO guidelines, LTBI is characterized as a condition of sustained immunological response to *M. tuberculosis* antigen stimulation without signs of clinically manifested active TB.[9] The diagnosis of LTBI is currently made using either a positive interferon-gamma release assay (IGRA) or a reactive tuberculin skin test (TST). The activity of the infectious focus or the likelihood of developing into active TB is not determined by any diagnostic test.[7] Quantiferon-TB Gold Plus (QFT-Plus) is a T-cell interferon-gamma release assay test, which is one of the diagnostic tools used for LTBI and provides some practical advantages in a population that has received bacilli Calmette-Guerin (BCG) vaccinations.[10] IGRAs are not utilized to diagnose active tuberculosis because they are unable to differentiate between LTBI and active TB.[7] The assessments are based on patient and household anamnesis of past history of TB infection, chest X-rays, and chest computed tomography (CT) findings in some cases where required, as it is crucial to assess the presence of previous exposure to TB infection prior to treatment with methotrexate, cyclosporin, and biological agents.

The objective of our study was to investigate the associations between IGRA tests, the chest CT findings and inflammatory blood markers of psoriasis patients who have undergone screening for LTBI before starting systemic treatment with either biological therapy or other conventional agents.

METHODS

The study was conducted in a single center after the Health Science University Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee approved it (Date: 21.02.2023, Decision No: 2248). The medical records of 123 consecutive patients with a diagnosis of psoriasis who were candidates for systemic treatment (methotrexate, cyclosporin and biological agents) and consulted for evaluating LTBI in the Chest Diseases Outpatient Department between 2019 and 2023 were retrospectively examined. Patients were referred from the department of dermatology and the diagnosis of plaque psoriasis was based on clinical symptoms and histopathological evaluations. The psoriasis area severity index (PASI) score was utilized for evaluating the severity of psoriasis.

The patients who had QFT-Plus tests resulting in negative or positive but not indeterminate, who had blood tests (complete blood count and blood biochemistry) during admission, and who have undergone Chest CT for some purpose in the last four weeks prior to the study period were enrolled. Exclusion criteria were as follows: patients <18 years old, having a history of tuberculosis, autoimmune diseases, malignancies, active infections in the last two weeks, and administration of systemic corticosteroids prior to the study were not included. Patients having confirmed diagnosis of active TB with sputum smear/culture were exempted from the study. All the patients were provided with written consent forms. The study was performed in line with the criteria of the Declaration of Helsinki.

Systemic inflammation index (SII) is developed for assessing chronic inflammation which reflects increased counts of blood neutrophils and platelets and decreased counts of blood lymphocytes. SII= platelet counts X neutrophil counts / lymphocyte counts. The inflammatory markers were calculated as follows: The neutrophil-to-lymphocyte ratio (NLR)=neutrophil counts/lymphocyte counts, the platelet to lymphocyte ratio (PLR)=platelet counts/lymphocyte counts.

The demographic characteristics, comorbidities, family history of tuberculosis, BCG vaccination status, smoking habits, occupation, and qualification details of the patients were all recorded. Psoriasis area and severity index (PASI), the scoring system defined for psoriasis patients has been noted for each of the patients. The findings on Chest CT were reported by an experienced thoracic radiologist and categorized as; fibrotic irregular lines, nodules uncalcified or calcified, fibrotic consolidation, mediastinal or hilar lymphadenopathy, pleural thickening, volume loss, and bronchiectasis. Also, the localization of the lesions on CT was examined.

The commercial name of the IGRA test used in the study was Quantiferon-TB Gold Plus (Qiagen, Germany).

Statistical Analysis

Statistical analysis of the data was performed in IBM SPSS Version 26 program. Pearson Chi-Square and Fisher's Exact tests were used to compare categorical variables between groups, and Mann Whitney U statistical analyzes were used to compare between two groups since continuous variables are not normally distributed (Kolmogorov Smirnov $p<0.05$). Variables affecting the positivity of Quantiferon test were evaluated with logistic regression analysis. $p<0.05$ was considered statistically significant.

RESULTS

As shown in Table 1, according to PASI scores 78% of the patients had mild to moderate psoriasis. The mean age of the participants was 49.24 and 52% were males. 40% had graduated from university, 53% had a normal income standard and 52% of the patients were married.

Current smokers presented 37% of the study group, whereas 18% had physician-diagnosed asthma and 0.6% had COPD. Twenty-six percent of the patients had cardiovascular disease, and seventeen percent had diabetes.

30% of the participants had a family history of TB and 83% of them had BCG vaccination scars.

When we examined the CT scans, radiological findings were reported in 58% of the patients. The most common CT findings were fibrotic irregular lines (48%), followed by calcified nodules (31%), fibrotic consolidation and pleural thickening (12%, 13%). Besides, right upper lobe localization was found to be dominant.

We divided the patients into two groups based on whether they had a positive or negative Quantiferon test, as 28% of the individuals had a positive result. Upon comparing the sociodemographic factors of the groups, the only variable that was determined to be statistically significantly different was income status ($p<0.05$). There were no differences noted between the groups according to disease severity, age, gender, BMI, educational or marital status, smoking habits, presence of comorbidity, family history of TB and chest CT findings ($p>0.05$). The patients whose Quantiferon test resulted positive, had significantly higher values of white blood cell count, neutrophils, lymphocytes, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, systemic inflammation index, and erythrocyte sedimentation rates (ESR) ($p<0.05$) (Table 2).

The effects of WBC, neutrophil, lymphocyte, NLR, and SII variables on Quantiferon test positivity were shown to be statistically significant ($p\sim<0.05$) in the logistic regression analysis. It was determined that the presence of radiological findings on the chest CT scan or comorbidities were not statistically significant on Quantiferon test positivity ($p>0.005$). (Table 3).

Table 1: Comparison of sociodemographic variables and Chest CT findings according to Quantiferon test

	Quantiferon negative		Quantiferon positive		X2	p
	n	%	n	%		
PASI scores						
Mild	23	26.1	8	22.9	0.701	0.704
Moderate	51	58	23	65.7		
Severe	14	15.9	4	11.4		
Gender						
Female	46	52.3	13	37.1	2.297	0.130
Male	42	47.7	22	62.9		
Marital status						
Married	46	52.3	19	54.3	0.041	0.840
Single	42	47.7	16	45.7		
Education						
University graduate	33	37.5	17	48.6	1.272	0.259
High school and lower	55	62.5	18	51.4		
Income status						
Normal standard	41	46.6	25	71.4	6.212	0.013
Lower income	47	53.4	10	28.6		
Smoking status						
Former smoker	30	34.1	10	28.6	2.716	0.257
Current smoker	29	33	17	48.6		
Never smoker	29	33	8	22.9		
Presence of comorbidity						
+	27	30.7	7	20	1.428	0.232
-	61	69.3	28	80		
Asthma	19	21.6	4	11.4	1.701	0.192
COPD	8	9.1	0	0	3.403	0.104
Allergic rhinitis	0	0	3	8.6	7.731	0.022
Diabetes	16	18	5	14	1.810	0.189
Cardiovascular disease	24	27	8	22	1.911	0,103
BCG scar						
>1	6	6,8	1	2,9	1.116	0.655
+	69	78.4	27	77.1		
-	13	14.8	7	20		
Family history of tuberculosis						
+	27	30.7	10	28.6	0.053	0.818
-	61	69.3	25	71.4		
Localization of chest CT findings						
Left lower lobe	3	6.3	0	0	2.978	0.569
Right lower lobe	3	6.3	0	0		
Bilateral	9	18.8	7	29.2		
Left upper lobe	6	12.5	3	12.5		
Right upper lobe	27	56.3	14	58.3		
Presence of chest CT findings						
+	48	54.5	24	68.6	2.03	0.154
-	40	45.5	11	31.4		
Fibrotic irregular lines	24	27.3	11	31.4	0.212	0.645
Uncalcified nodules	1	1.1	2	5.7	2.205	0.195
Calcified nodules	18	20.5	5	14.3	0.627	0.429
Fibrotic consolidation	5	5.7	4	11.4	1.219	0.272
Mediastinal lymphadenopathy	1	1.1	2	5.7	2.205	0.195
Pleural thickening	5	5.7	5	14.3	2.482	0.146
Volume loss + Bronchiectasis	2	2.3	2	5.7	0.943	0.320

Pearson Chi Square, Fisher's Exact test, CT: Computerized Tomography, BCG: Bacille Calmette-Guerin, COPD: Chronic Obstructive Pulmonary Disease

Table 2: Comparison of laboratory findings according to Quantiferon test

	Quantiferon negative Mean±SD	Quantiferon positive Mean±SD	Z / t	p
Age	49.48±9.61	48.63±10.65	-0.087	0.931
BMI	24.83±1.89	25.2±1.73	-1.492	0.136
PASI scores	8.03±3.55	7.93± 4.39	-0.526	0.599
WBC	7.38±1.63	8.72±1.97	-3.871	<0.001
Neutrophil	4.62±1.36	6.35±1.59	-6.046	<0.001
Lymphocyte	2.49±0.7	2.04±0.55	-3.574	<0.001
Platelet	286.49±62.02	262.97±63.15	1.888	0.061
NLR	1.97±0.69	3.22±0.82	-8.550	<0.001
PLR	124.99±47.58	138.64±50.25	-1.412	0.160
RDW	12.59±1.05	12.59±0.98	-0.180	0.857
SII	562.05±233.71	839.37±270.04	-5.333	<0.001
AST	20.61±11.48	18.49±6.98	-0.306	0.760
ALT	20.5±8.62	19.34±5.32	-0.096	0.924
CRP	5.39±7.5	6.12±9.03	-0.572	0.567
Hemoglobin	14.4±1.48	14.55±1.65	-0.575	0.565
ESR	24.35±8.77	27.89±10.03	-2.108	0.035

Independent sample t test, Mann Whitney U analysis, BMI: Body mass index, WBC: White blood cell count, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RDW: Red cell distribution width, SII: Systemic inflammation index, AST: Aspartate aminotransferase ALT: Alanine aminotransferase, CRP: C-reactive protein ESR: Erythrocyte sedimentation rate.

Table 3: Logistic regression analysis for the effect of laboratory values on Quantiferon positivity

	B	S.E.	Wald	p	Exp (B)	95% C.I.	
Presence of CT finding	0.598	0.422	2.003	0.157	1.818	0.795	4.161
Presence of comorbidities	0.799	0.501	3.012	0.611	1.455	0.887	7.223
WBC	0.425	0.122	12.037	0.001	1.529	1.203	1.943
Neutrophil	0.810	0.173	21.816	0.000	2.247	1.600	3.156
Lymphocyte	-1.181	0.372	10.075	0.002	0.307	0.148	0.636
Platelet	-0.006	0.003	3.430	0.064	0.994	0.987	1.000
NLR	2.257	0.424	28.333	0.000	9.550	4.161	21.921
PLR	0.006	0.004	1.932	0.165	1.006	0.998	1.014
RDW	0.003	0.195	0.000	0.989	1.003	0.685	1.468
SII	0.004	0.001	20.663	0.000	1.004	1.002	1.006
CRP	0.011	0.024	0.216	0.642	1.011	0.965	1.060
ESR	0.040	0.022	3.517	0.061	1.041	0.998	1.086

S.E: Standard error, C.I.: Confidence Interval, , WBC: White blood cell count, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, RDW: Red cell distribution width, SII: Systemic inflammation index, CRP: C-reactive protein ESR: Erythrocyte sedimentation rate CT: Computerized Tomography.

DISCUSSION

Patients with psoriasis who were evaluated for LTBI and had no evidence of infection or respiratory symptoms were included in this study. The Quantiferon test, a screening tool for LTBI, was positive in 28% of the study group. A family history of tuberculosis was present in 30% of the individuals, and 16% of them showed no scars from the BCG immunization. It's interesting to note that 59% of the patients exhibited radiological abnormalities on their CT scans, which could indicate a history of tuberculosis infection and need to be considered when these individuals are being monitored.

Psoriasis is a complex disease and given the rapid developments in this field, more frequent updates to psoriasis treatment recommendations are becoming more crucial.[1] The novel therapies allow for significant symptom reduction and quality of life improvement. The treatment recommendations might not be applicable in all cases because psoriasis is a complicated condition with numerous co-morbidities.[11] The basic treatment algorithms include patient preference, disease severity, comorbidities, and specific conditions that should be considered particularly.[11] Due to the risk of LTBI, screening before starting biological agents may be challenging in psoriasis patients who are living in a country with a high prevalence of TB.[9]

According to the guidelines, once biologic therapy has begun, all patients should undergo an annual TB screening.[12] Prophylactic treatment should be started two months before the commencement of biological agents in latent TB patients.[12] LTBI contributes to the continuation of the disease cycle at the population level as a reservoir for new diseases and continuous Mtb transmission within communities.[12]

The conventional description of LTBI is, measurably elevated immunological sensitivity to Mtb in the absence of symptoms of the disease, such as fever, chills, night sweats, weight loss, cough, hemoptysis, or a newly generating finding on a chest radiograph.[13] The duration and activity of the latent focus varies from person to person based on timing, and host- and pathogen-specific characteristics, which are not addressed by this confounding definition.14 The course of LTBI is influenced by host variables such age and immunological state.[14]

In our study, when compared to the Quantiferon negative group, patients with Quantiferon positive tests did not differ in demographic characteristics, family history of TB or chest CT findings. In contrast, their inflammatory blood parameters were found to be higher. The biology of LTBI has remained a poorly understood area in TB research. In a previous study the researchers observed a correlation between the cellular activity in the thoracic lymph nodes shown with the positron emission tomography and IGRA responses in the patients with LTBI which suggested the immune response to *M. tuberculosis* infection.[15] The tuberculosis antigen-stimulated interferon release assay detects sensitization to mycobacterial antigens, but it does not distinguish between latent infection that has resolved and infection that is still present.[16]

Inflammation plays an important role in LTBI and prior to any clinical symptoms, an increase in the host biomarkers may be valuable as the first sign of infection or inflammation in the body. In research conducted in

Nigeria, while the values of WBC in the LTBI group approximated the normal range, ESR and CRP levels were found to be higher in these patients than in the healthy group.[17] In our results, not the CRP levels, but white blood cell count, and ESR were found to be higher in the psoriasis patients with positive Quantiferon test than in the negative ones. In a Japanese study comparing blood markers in LTBI and active TB patients, WBC and lymphocyte counts were higher in LTBI patients whereas neutrophil, platelet counts, and CRP levels were higher in patients with sputum-positive active tuberculosis.[18]

In our study, 28.6% of the patients had a family history of TB and 68.6% of the subjects in the positive Quantiferon test group had radiological findings in Chest CT, but this displayed no effect on regression analysis. Besides, no participant had a prior history of TB or contact with a person with TB, so, the CT findings were incidental. Chest CT is an important imaging modality in detecting LTBI for candidates scheduled for systemic treatment, particularly with immunomodulatory biologic drugs in daily practice.[19] On the other hand, as commented on the previous reports, due to the risk of radiation exposure, CT should be performed only in specific subgroups when the diagnostic indications are present, or disagreement occurs in clinical examinations.[19] Therefore, when screening patients for LTBI, the radiological findings should be evaluated more cautiously since these might be suggestive of an old TB rather than a latent infection in a country with a high prevalence of TB.

Our data, which showed an elevated inflammatory status, were consistent with our hypothesis that psoriasis and LTBI would have a synergistic effect in the inflammatory response. This increased inflammatory process was accordingly reflected by an increase in other parameters such as neutrophil-to-lymphocyte ratio, and systemic inflammation index.[20] It has been shown that the systemic immune inflammation index (SII), a unique blood cell index that provides an opinion about ongoing inflammation, is a simple and useful prognostic factor for diseases with an inflammatory etiology.[21] Furthermore, WBC subtypes that are well-known as systemic, non-specific cellular indicators of general inflammation include neutrophils, lymphocytes, and monocytes. In recent years, clinical practice has increasingly used inflammation-based indices, such as the NLR and PLR, as assessment tools for disease activity of many forms of inflammatory illnesses.

It is currently widely acknowledged that psoriasis is an immune-mediated inflammatory disease, with the primary cause being an abnormal immune response in the skin.11 In a recent study, SII, NLR, and WBC were found to be higher in the patients' group which comprised the patients mostly with the mildly severe psoriasis.[22] Comparably, a different study that examined the SII in psoriasis patients found that it was higher than in the group of healthy controls.[23] Although several pathophysiological factors lead to psoriasis, immune-mediated processes involving T lymphocytes, dendritic cells, and other cytokines that result in a markedly inflammatory process are the primary culprits.1 Physicians need to measure inflammation for developing more effective treatment plans.

Limitationsww

Our limitations in the study were the retrospective design, small sample size and the lack of other clinically assayed biomarkers such as albumin, LDH, IL-2, and tumor necrosis factor-alpha for more accurate evaluation of inflammation and LTBI in psoriasis patients. Since there is still no gold standard for the diagnosis of LTBI and the number of cases with LTBI is on the rise due to the screening procedure of patients treated with biological agents by IGRAs, larger studies combining radiologic procedures and available biomarkers are needed to expand the knowledge in this field.

CONCLUSION

Psoriasis is a systemic inflammatory disease. Inflammation levels are higher in the psoriasis patients in this study who need systemic treatment, are being screened for LTBI, and have positive IGRA test results. Future studies may help to define new parameters to assess the inflammatory status of these patients in clinical judgment for new therapeutic options.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Health Science University Şişli Hamidiye Etfal Training and Research Hospital Clinical Researches Ethics Committee (Date: 21.02.2023, Decision No: 2248).

Informed Consent

All patients signed an informed consent form.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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