Frequency of pulmonary tuberculosis in patients with skin diseases requiring high dose long-term systemic steroid therapy

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Abstract

**Objective** To determine the frequency of pulmonary tuberculosis in patients with skin diseases requiring high dose long-term systemic steroid therapy.

**Patients and methods** This cross-sectional study was conducted in the Department of Dermatology Unit-II, Mayo Hospital, Lahore. Newly diagnosed patients of skin disease were screened for tuberculosis and then followed up after 6 weeks, 3 months and 6 months to evaluate pulmonary tuberculosis while patients were on high dose systemic steroids. At each visit, history, examination and screening tests for tuberculosis were performed which included sputum smear for acid-fast bacilli (AFB), chest radiograph and sputum culture for AFB.

**Results** Out of fifty patients, who were on high dose long-term systemic steroid therapy, four patients (8%) developed pulmonary tuberculosis after a period of three months ($P=0.0001$).

**Conclusion** Patients on high dose long-term systemic steroid therapy can develop pulmonary tuberculosis.

**Key words** Frequency, tuberculosis, steroids.

Introduction

Tuberculosis is a chronic and serious infection, if left untreated. It is caused by the acid-fast bacillus, *Mycobacterium tuberculosis*. The disease affects various systems of the body including lungs, gastrointestinal tract, genitourinary system, skin, bones, joints, lymphoreticular and central nervous systems.

A patient suffering from active tuberculosis infects 10 to 15 persons every year. People carrying tubercle bacilli in their body do not necessarily present with the signs and symptoms of tuberculosis because the immune system walls off the causative organism and keeps it dormant for years. When someone's immune system is compromised, the chances of tuberculosis to become active are greater. Every second a new person is infected with the tubercle bacilli. Currently, one third of the world population is infected with this bacillus. Five to ten percent of immunocompetent world population suffers from tuberculosis during their life span. In Pakistan, the prevalence of tuberculosis (including HIV) was 355 per 100,000 populations in the year 2009. There is a greater risk of acquiring tuberculosis in immunocompromised individuals e.g. AIDS.
patients and those on immunosuppressive therapy. Tuberculosis in an immunosuppressed person may arise from primary infection, by reactivation and/or reinfection.

In dermatology, systemic glucocorticoids are the mainstay of immunosuppressive therapy for immunobullous diseases and collagen vascular disorders. Prolonged and high dose administration of glucocorticoids is often needed to control certain diseases such as pemphigus, bullous pemphigoid, lupus erythematosus and dermatomyositis. Such patients are at risk for both the acquisition of primary tuberculosis and the reactivation of non-active tuberculosis. The immunosuppression due to glucocorticoids in such patients not only masks the symptoms and signs of tuberculosis leading to a delay in diagnosis but also predisposes the patients to more severe variants of the disease, e.g. disseminated tuberculosis.

Patients and methods

Patients presenting in dermatology department Mayo Hospital, Lahore and fulfilling the inclusion criteria (patient of either sex, belonging to adult (≥12 years) age group, requiring high dose long-term systemic steroid therapy for their skin problem, were enrolled. Patients currently on antituberculous therapy (ATT), systemic steroid therapy, any other immunosuppressive therapy and with uncontrolled diabetes were excluded from the study. After getting informed consent, demographic data were obtained. History was taken; clinical examination and screening tests were performed on first visit. Patients were followed after six weeks, three months and finally at six months to evaluate them for pulmonary tuberculosis.

At each visit (Figure 1), sputum smear for acid-fast bacilli (AFB) was done for three consecutive days. No further test was performed if two or more sputum smears were positive for AFB.

If only one sputum smear was positive for AFB, then X-ray chest was carried out to detect any abnormalities that were consistent with active pulmonary tuberculosis. If positive, no further test was performed. If one sputum smear was positive for AFB and X-ray chest findings were not supportive of pulmonary tuberculosis then sputum culture was carried out. If positive, the patient was diagnosed as a case of pulmonary tuberculosis.

If sputum smear for AFB was negative for three consecutive days then sputum culture was carried out. If one or more sputum cultures were positive, patient was diagnosed as a case of pulmonary tuberculosis.

If sputum smear for AFB was negative for three consecutive days and sputum culture was also negative, then patient was labelled as a case of pulmonary tuberculosis if at least two series of smears from samples taken at least two weeks apart were negative, and persistent radiographic abnormalities compatible with active tuberculosis which did not improve with treatment using broad spectrum antibiotics for at least one week.

A pro forma was used to record the history, physical examination and the results of screening tests. Collected information was transferred to SPSS (Statistical Package for the Social Sciences) version 19 computer software program and was analyzed accordingly. Mean, median and standard deviation were used to represent the quantitative variables. McNemar test was applied to calculate the P value.
Results

In this study, fifty patients suffering from skin diseases requiring long-term high dose systemic steroid therapy were enrolled. There were 24 male and 26 female patients. The age range of patients was 15-75 years with a mean age of 39 years.

Most of the patients were suffering from pemphigus vulgaris (n=37), while five patients were of systemic lupus erythematosus. Patients with other skin diseases are shown in Table 1.

Table 1  Frequency of different skin diseases requiring long-term high dose steroid therapy (n=50).

<table>
<thead>
<tr>
<th>Dermatoses</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Pemphigus vulgaris</td>
<td>37 (74)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Lupus erythematosus/lichen planus</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

This study concluded that 4 patients (8%) suffering from pemphigus vulgaris, who were on high dose long-term systemic steroid therapy, developed pulmonary tuberculosis after a period of three months. Out of these 4, 1 was female and 3 were male patients. At six week’s evaluation, 2 patients showed abnormal chest X-ray findings but sputum smear and culture for AFB were negative at that time. At 3 months follow-up, in addition to the above 2 patients, 2 more patients developed chest X-ray abnormalities and in these again sputum smear and culture for AFB were negative (Figure 2). All these patients were given broad spectrum antibiotics for two weeks in addition to high dose systemic steroid therapy, but their X-ray chest findings did not resolve. At that time sputum smear and culture were performed which turned out to be positive and patients were put.
on ATT. One patient at 6 months follow-up developed X-ray chest abnormalities and was given antibiotics for 2 weeks and his radiological chest findings resolved.

Out of 4 patients who developed pulmonary tuberculosis, 3 were male and one female. One male patient was labourer and 2 were unemployed. All patients were married. The female was a housewife. All these 4 patients belonged to poor socioeconomic class. Two male patients were smokers. Three patients were underweight and one was of normal BMI. Family history of pulmonary tuberculosis was present in two patients. History of BCG vaccination was present in all 4 patients. ESR was also high in all patients.

Discussion

Research on the role of steroid therapy in precipitating tuberculosis is limited.\(^7\) Aggravation of infections is a known side effect of steroids.\(^7\) Some maintain that steroid therapy might cause exacerbation of active or apparently inactive tuberculosis while others conclude that steroid treatment has negligible influence on the incidence of tuberculosis.\(^8\)

In this study, we found statistically significant (\(P<0.05\)) association between prednisolone dosage i.e. more than 1 mg/kg daily for six months and development of pulmonary tuberculosis. Studies from different parts of the world also support our findings. Kim \textit{et al.}\(^9\) reported an increase in the incidence of active tuberculosis among 269 patients of rheumatic disease on moderate to high doses of corticosteroids. The risk factors were, cumulative and mean daily steroid doses taken during the first year of therapy. Sasaki \textit{et al.}\(^10\) found that the mean length of time from start of corticosteroids, with the dose that ranged between 13.9 mg to 20 mg, to the occurrence of tuberculosis was 4.1 years in most of his patients suffering from collagen vascular disease. Kobashi \textit{et al.}\(^11\) found five patients among a total of 162 (3.1%) who developed pulmonary tuberculosis on long-term corticosteroid therapy. The total corticosteroids consumed, until the clinical diagnosis of pulmonary tuberculosis were 1.16 gms to 5.6gms, lasting two to nine and a half months. Dryga \textit{et al.}\(^12\) found 39 cases
of progressive tuberculosis among those on glucocorticoid treatment with different doses.

Jick et al.\textsuperscript{13} found that patients treated with glucocorticoids have an increased risk of developing tuberculosis independent of other risk factors. Chan and Yosipovitch\textsuperscript{6} carried out screening of tuberculosis in patients taking oral glucocorticoids and they found that lower or intermittent doses of glucocorticoids are not associated with tuberculosis. Sayarlioglu et al.\textsuperscript{7} determined that high doses of prednisolone were important determinant for increased risk of tuberculosis in patients with SLE. Pal et al.\textsuperscript{8} also concluded that systemic steroid therapy over long periods causes significant increase in the incidence of tuberculosis.

There are many mechanisms by which glucocorticoids can increase the risk of tuberculosis. Corticosteroids, through their immunosuppressive and antiinflammatory effects, impair antibody formation and cell-mediated immunity that tuberculosis requires for its control.\textsuperscript{13} Glucocorticoids inhibit the lymphokine effect and monocyte chemotaxis and also block Fc receptor binding and function.\textsuperscript{13} Glucocorticoids depress the number of peripheral blood monocytes as well as monocyte functions, including bactericidal activity and production of interleukin-1 and TNF-\(\alpha\). Glucocorticoids also inhibit T cell activation, leading to reduced proliferative responses and cytokine production, and they also induce a redistribution of lymphocytes (predominantly T-cells) out of the circulation, leading to peripheral lymphocytopenia.\textsuperscript{13} These various effects of glucocorticoids on the cellular immune system may play a significant role in predisposing to tuberculosis infection. These effects are most evident if steroid doses exceed 0.03mg/kg/day of prednisolone or equivalent. At doses higher than 1 mg/kg/day, a marked increase in susceptibility to a wide variety of infections is experienced after several weeks. Treatment for less than 5 days appears to have less effect on immune function and predisposition to infections. Continuous therapy has longer and more profound immunosuppressive effects as compared to intermittent therapy.\textsuperscript{5}

Smoking can be an important modifiable risk factor for tuberculosis in developing countries. We found that 2 of the patients who developed pulmonary tuberculosis were smokers. A substantially stronger association exists between smoking and tuberculosis. The impact of smoking on the potential conversion of latent infection into active disease is higher in the countries with high tuberculosis prevalence. An Indian study\textsuperscript{14} showed that individuals who had ever smoked were 3 times more likely to develop tuberculosis than individuals who had never smoked. Similarly, tuberculosis deaths among those who had ever smoked were 4 times higher than non-smokers. Iron loading in the bronchoalveolar macrophages, secondary to tobacco smoking, has been implicated in promoting the growth of \textit{M. tuberculosis}, thus potentially contributing to the disease manifestation and progress.\textsuperscript{13}

In our study, all the four patients belonged to poor socioeconomic class. There is a very strong correlation between poverty and tuberculosis. It is likely that poor housing in terms of crowding leads to increased transmission and poor nutrition leading to diminished immunity.\textsuperscript{15}

The association of tuberculosis with body build has been well reviewed. Lean underweight people have a significantly higher risk of developing tuberculosis than persons of or above ideal body weight.\textsuperscript{15} Three of our patients who
developed pulmonary tuberculosis were underweight and one was of normal BMI.

In our study, all the 4 patients gave the history of BCG vaccination. In terms of risk for tuberculosis, infants and teenagers who have had BCG vaccination are probably at reduced risk of developing tuberculosis by about 75% for no more than 15 years. Some trials have shown that BCG vaccine is 80% protective and in others it is 20%. Because of variation in trial results, most countries give BCG vaccine at birth to provide protection in the early years when infection can often lead to devastating widespread disease such as miliary tuberculosis or tuberculous meningitis. This is particularly important in high prevalence countries where the chance of being infected in very early life is high.

The importance of establishing an association between high dose, long-term systemic steroid therapy and development of pulmonary tuberculosis is that tuberculosis is a contagious and a common disease in Pakistan. High dose long-term systemic steroid therapy causes immunosuppression and masking of symptoms and signs of tuberculosis causing a delay in diagnosis and also primary infection, re-infection and reactivation of non-active tuberculosis. By screening for tuberculosis in patients with skin diseases, before or after commencement of high dose long-term systemic steroid therapy, we can prevent spread of infection, reactivation of dormant tuberculosis, complications, morbidity and mortality arising from undiagnosed tuberculosis. Furthermore, timely treatment for tuberculosis can be started, thus benefiting the patient.

Patients with skin diseases requiring high dose long-term systemic steroid therapy should be screened for pulmonary tuberculosis before and at intervals of three months after commencement of systemic steroids and provided with appropriate treatment if it is detected. Failure to do so may result in reactivation of tuberculosis and subsequent dissemination of the disease.

References


