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Review Article

Pulmonary tuberculosis in dermatological patients on high-dose, long-term steroid therapy

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Abstract Tuberculosis is a chronic and serious infection if left untreated. Currently one third of the world population is infected with this bacillus. The immunosuppression due to glucocorticoids in patients with skin diseases may cause acquisition of primary tuberculosis and the reactivation of nonactive tuberculosis. This review focuses on risk involved, diagnosis and treatment in such patients.

Key words
Pulmonary tuberculosis, steroids, high-dose, long-term.

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 system.[1]

Every patient suffering from active tuberculosis infects 10 to 15 persons every year.[2] People carrying tubercle bacilli in their body do not necessarily present with the signs and symptoms of tuberculosis because our 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.[2] In Pakistan, the prevalence of tuberculosis (including HIV) was 355 per 100,000 population in the year 2013.[3]

There is greater risk of acquiring tuberculosis in immunocompromised individuals e.g. AIDS patients and those on immunosuppressive therapy.[4] Tuberculosis in an immunosuppressed person may arise from primary infection, by reactivation and by reinfection.[5]

In dermatology, systemic glucocorticoids are the mainstay of immunosuppressive therapy for a number of diseases especially 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 nonactive 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.[6,7]

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It is a leading cause of death and statistics have shown that 1/7 of all humans die of tuberculosis.

Pulmonary Tuberculosis

Definition

Tuberculosis or TB (tubercle bacillus) is a common and an often deadly infectious disease in humans caused by *Mycobacterium tuberculosis.*[8] The disease usually attacks the lungs but can also affect other parts of the body. It spreads through the air, when people who have the disease cough, sneeze or spit.[9] Most infections in humans result in an asymptomatic, latent infection and about one in ten latent infections eventually progress to active disease, which if left untreated kills more than 50% of its victims.[9]

Incidence and prevalence

Tuberculosis is contagious and airborne. It is a disease of poverty affecting mostly young adults in their most productive years.[10] The vast majority of tuberculosis deaths are in the developing world. Globally, the latest estimates are 9.0 million new TB cases in 2013 and 1.5 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people). In 2013, there were an estimated 3.3 million cases and 510000 TB deaths among women, as well as an estimated 550000 cases and 80000 deaths among children.[10]

1.7 million people died from tuberculosis (including 380,000 women) in 2009, including 380 000 people with HIV, equal to 4700 deaths a day. The tuberculosis death rate has fallen by 35% since 1990. Tuberculosis is among the three greatest causes of death among women aged 15-44. There were 9.4 million new tuberculosis cases (including 3.3 million women) in 2009, including 1.1 million cases among people with HIV. The estimated global incidence rate fell to 137 cases per 100 000 population in 2009, after a peak in 2004 at 142 cases per 100,000.[10] There is an increasing incidence of tuberculosis in developing countries. More people are contracting the disease because their immune systems are compromised by immunosuppressive drugs, substance abuse, or AIDS.[9] Every patient suffering from active tuberculosis infects 10 to 15 persons each year.[2] Every second a new person is infected with this bacillus.[11] Currently one third of the world population is infected with this organism.[2]

Pakistan, among the top 22 high tuberculosis risk countries, stands at position 6 and it shares the 43% of the disease burden in Eastern-Mediterranean region, according to the World Health Organization (WHO). In Pakistan, incidence of tuberculosis (including HIV) is estimated as 181 per 100,000 populations in the year 2012. Case notification rate was 150 per 100,000 population and treatment success rate of 85%. The rate of mortality from tuberculosis (excluding HIV) was 38 per 100,000 population and prevalence was 373 per 100,000 population. Smear positive new cases in 2012 were 101887 and smear negative cases were 112948.[12]

Clinical manifestations

Symptoms of pulmonary tuberculosis include productive, prolonged cough of three or more weeks, chest pain and hemoptysis. There may be fever, chills, night sweats, appetite loss, weight loss and easy fatiguability. Other medical history includes prior tuberculosis exposure, infection or disease, past tuberculosis treatment, medical conditions that increase risk of tuberculosis like immunosuppressive conditions and immunosuppressive drugs.[9]

Transmission

When people suffering from active pulmonary tuberculosis cough, sneeze, speak, or spit, they expel infectious aerosol droplets 0.5 to 5 μm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease. The infectious dose of tuberculosis is very low and inhaling less than ten bacteria may cause an infection.[9]

People with prolonged, frequent or intense contact are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis can infect 10-15 other people per year. Others at risk include people living in TB endemic areas, people who inject drugs using unsanitary needles, residents and employees of high-risk congregate settings, medically under-served and low-income populations, high-risk racial or ethnic minority populations, children exposed to adults in high-risk categories, patients immunocompromised by conditions such as HIV/AIDS, people who take immunosuppressant drugs, and health care workers serving these high-risk clients.[9]

Transmission can only occur from people with active, not latent, TB. The probability of transmission from one person to another depends upon the number of infectious droplets expelled by a carrier, the effectiveness of ventilation, the duration of exposure, and the virulence of the *M. tuberculosis* strain. The chain of transmission can, therefore, be broken by isolating patients with active disease and starting effective anti-tuberculous therapy. After two weeks of such treatment, people with non-resistant active tuberculosis generally cease to be contagious. If someone does become infected, then it will take at least 21 days, or three to four weeks, before the newly infected person can transmit the disease to others.[9]

Pathogenesis

About 90% of those infected with *M. tuberculosis* have asymptomatic, latent TB infection (LTBI), with only a 10% lifetime chance that a latent infection will progress to TB disease. However, if untreated, the death rate for these active TB cases is more than 50%.[9]

TB infection begins when the mycobacteria reach the pulmonary alveoli, where they invade and replicate within the endosomes of alveolar macrophages. The primary site of infection in the lungs is called the Ghon focus, and is generally located in either the upper part of the lower lobe, or the lower part of the upper lobe. Bacteria are picked up by dendritic cells, which do not allow replication, although these cells can transport the bacilli to local (mediastinal) lymph nodes. Further spread is through the bloodstream to other tissues and organs where secondary TB lesions can develop as in other parts of the lung (particularly the apex of the upper lobes), peripheral lymph nodes, kidneys, brain and bone. All parts of the body can be affected by the disease.[9]

Tuberculosis is classified as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding the infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes secrete cytokines such as interferon gamma, which activate macrophages to destroy the bacteria with which they are infected. Cytotoxic T cells can also directly kill infected cells, by secreting perforin and granulysin.[9]

Importantly, bacteria are not always eliminated within the granuloma, but can become dormant, resulting in a latent infection. Another feature of the granulomas of human tuberculosis is the development of abnormal cell death, also called necrosis, in the center of tubercles. To the naked eye this has the texture of soft white cheese and is termed as caseous necrosis. If TB bacteria gain entry to the bloodstream from an area of damaged tissue, they spread through the body and set up many foci of infection, all appearing as tiny white tubercles in the tissues. This severe form of TB is most common in infants and the elderly and is called miliary tuberculosis. Patients with this disseminated TB have a fatality rate near 100% if untreated. However, if treated early, the fatality rate is reduced to near 10%.[9]

In many patients the infection waxes and wanes. Tissue destruction and necrosis are balanced by healing and fibrosis. Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease, some of these cavities are joined to the bronchi and this material can be coughed up. It contains living bacteria and can therefore pass on infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Upon cure, affected areas are eventually replaced by scar tissue.

If untreated, infection with *M. tuberculosis* can become lobar pneumonia.[9]

Diagnosis

A number of tests are available to confirm active tuberculosis or latent TB infection (**Table 1**).

Table 1 Laboratory tests recommended in the diagnosis and managements of pulmonary tuberculosis [5,6,9].

For active TB
1. Microscopy for acid-fast bacilli
2. Mycobacterial growth detection by culture
3. Nucleic acid amplification assay
4. Drug susceptibility tests
5. Chest radiography
For latent TB infection
1. Tuberculin skin testing
2. Interferon gamma release assay

Sputum smear positive pulmonary tuberculosis
The diagnosis of sputum smear positive pulmonary tuberculosis is made if there are at least two positive sputum smears OR one positive sputum smear and radiographic abnormalities compatible with pulmonary tuberculosis OR one positive sputum smear and one positive sputum culture.[13]

Sputum smear negative pulmonary tuberculosis
The diagnosis of sputum smear negative pulmonary tuberculosis is made if there are at least three negative sputum smears and one or more positive sputum culture OR at least two series of negative sputum smears from samples taken at least two weeks apart with persisting radiographic abnormalities compatible with active tuberculosis not improved with treatment using broad spectrum antibiotics for at least one week.[13]

Treatment

Active tuberculosis kills about 2 of every 3 people affected if left untreated. Treated tuberculosis has a mortality rate of less then 5%. The standard course of treatment for pulmonary tuberculosis caused by drug susceptible *M. tuberculosis* is shown in **Table 2**.

Contacts are also screened and treated if necessary. Prevention relies on screening programme and vaccination usually with Calmette-Guerin vaccine.[9]

Table 2 Treatment schedule of antituberculous therapy [24].

Initial phase		*Continuation phase*					Rating evidence	
Regimen	Drugs	*Interval and doses‡ (minimal duration)*	*Regimen*	*Drugs*	*Interval and doses† § (minimal duration)*	*Range of total doses (minimal duration)*	*HIV−*	*HIV+*
1	Isoniazid, Rifampin, Pyrazinamide, Ethambutol	Seven days per week for 56 doses (8 weeks) *or* 5 days per week for 40 doses (8 weeks)//	1a	Isoniazid/rifampin	Seven days per week for 126 doses (18 weeks) *or* 5 days per week for 90 doses (18 weeks)//	182 to 130 (26 weeks)	A (I)	A (II)
			1b	Isoniazid/rifampin	Twice weekly for 36 doses (18 weeks)	92 to 76 (26 weeks)	A (I)	A (II)¶
			1c#	Isoniazid/rifapentine	Once weekly for 18 doses (18 weeks)	74 to 58 (26 weeks)	B (I)	E (I)
2	Isoniazid, Rifampin, Pyrazinamide, Ethambutol	Seven days per week for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks) *or* 5 days per week for 10 doses (2 weeks),// then twice weekly for 12 doses (6 weeks)	2a	Isoniazid/rifampin	Twice weekly for 36 doses (18 weeks)	62 to 58 (26 weeks)	A (II)	B (II)¶
			2b#	Isoniazid/rifapentine	Once weekly for 18 doses (18 weeks)	44 to 40 (26 weeks)	B (I)	E (I)
3	Isoniazid, Rifampin, Pyrazinamide, Ethambutol	Three times weekly for 24 doses (8 weeks)	3a	Isoniazid/rifampin	Three times weekly for 54 doses (18 weeks)	78 (26 weeks)	B (I)	B (II)
4	Isoniazid, Rifampin, Ethambutol	Seven days per week for 56 doses (8 weeks) *or* 5 days per week for 40 doses (8 weeks)//	4a	Isoniazid/rifampin	Seven days per week for 217 doses (31 weeks) *or* 5 days per week for	273 to 195 (39	C (I)	C (II)

*HIV = human immunodeficiency virus. *—Definitions of evidence ratings: A = preferred; B = acceptable alternative; C = offer when A and B cannot be given; E = should never be given. †—Definition of evidence ratings: I = randomized clinical trial; II = data from clinical trials that were not randomized or were conducted in other populations; III = expert opinion. ‡—When direct observation therapy is used, drugs may be given five days per week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicates this would be an effective practice.*

§—*Patients with cavitation on initial chest radiograph and positive cultures at completion of two months of therapy should receive a seven-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.*

//—*Five-day-a-week administration is always given by direct observation therapy. Rating for five-day-a-week regimens is A (III).*

¶—*Not recommended for HIV-infected patients with CD4+ cell counts less than 100 per mm3 (100 ×106 per L).*

#—*Options 1c and 2b should be used only in HIV-negative patients who have negative sputum smears at the time of completion of two months of therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the two-month specimen, treatment should be extended an extra three months.*

Use of systemic steroids in dermatological practice

Glucocorticoids are a class of steroid hormones that bind to the glucocorticoid receptors. The name glucocorticoids (glucose+cortex+steroid) is derived from their role in the regulation of the metabolism of glucose, their synthesis in the adrenal cortex and their steroidal structure. Glucocorticoids are part of the feedback mechanism in the immune system that turns immune activity (and inflammation) down. They are, therefore, used in medicine to treat diseases that are caused by an overactive immune system such as allergies, asthma, autoimmune diseases and sepsis.[15]

Glucocorticoids through interaction with the glucocorticoid receptor upregulate the expression of antiinflammatory proteins and downregulate the expression of proinflammatory proteins.[15] Due to their strong antiinflammatory and immunosuppressive effects, systemic steroids are used in a variety of conditions listed in **Table 3**. Different systemic steroids, taken by mouth or given by injection, used in dermatology practice include hydrocortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone and betamethasone. These differ in their relative antiinflammatory and mineralocorticoid activity, plasma half-life and duration of ACTH suppression. Prednisolone, because of its intermediate half-life, minimal mineralocorticoid activity, relatively less adverse effects and sufficiently long duration of action, is oral steroid of choice. It can be given in doses ranging from 0.5-3mg/kg/day, depending on the severity of dermatosis under treatment. It can be given as single morning dose or split dose to gain control of disease activity during initial phases of treatment. Treatment regimen is called low-dose if <10mg/day prednisolone or equivalent is used and high-dose when >20mg prednisolone per day is prescribed. Similarly, steroid treatment is called short-term treatment when used for ≤3 weeks and long-term when given for >4 weeks.[16]

Table 3 Indications of high dose steroids in dermatology [16].

Bullous dermatoses
• Pemphigus vulgaris
• Bullous pemphigoid
• Cicatricial pemphigoid
• Linear immunoglobulin A bullous dermatosis
• Epidermolysis bullosa acquisita
• Herpes gestationis
• Erythema multiforme
• Toxic epidermal necrolysis and Stevens-Johnson syndrome
Autoimmune connective tissue diseases
• Systemic lupus erythematosus
• Dermatomyositis
• Mixed connective-tissue disease
• Eosinophilic fasciitis
• Relapsing polychondritis
Neutrophilic dermatoses
• Pyoderma gangrenosum
• Acute febrile neutrophilic dermatosis (Sweet syndrome)
• Behcet disease
Papulosquamous and eczematous dermatoses
• Contact dermatitis
• Atopic dermatitis
• Photodermatitis
• Exfoliative dermatitis
• Erythrodermas
• Lichen planus
Vasculitis
• Cutaneous and systemic
Others
• Sarcoidosis Urticaria/angioedema
• Androgen excess (acne, hirsutism)
• Type I reactive leprosy
• Problematic hemangiomas of infancy
• Kasabach-Merritt syndrome
• Panniculitis

Dermatoses, widespread or associated with systemic involvement, often necessitate high-dose and long-term steroid treatment to prevent

risk of end-organ damage. Once the disease is under control, slow dose tapering is required to avoid disease flare and prevent withdrawal symptoms of prolonged suppression of hypothalamus-pituitary-adrenal axis. It is done by decrements of 10% to 20%, every week or 2 weeks according to the disease response and patient's condition.

Mechanism of immunosuppression caused by steroids

Glucocorticoids suppress the cell-mediated immunity. They act by inhibiting genes that code for the cytokines, IL-1, IL-2, IL-3, IL-4, IL-5, IL-8 and IFN-γ. Glucocorticoids not only reduce T-cell proliferation but also cause glucocorticoid-induced apoptosis. The effect is more pronounced in immature T-cells that still reside in the thymus, but also affect peripheral T-cells. Glucocorticoids also suppress the humoral immunity, causing B-cells to express smaller amounts of IL-2 and of IL-2 receptors. This diminishes both B-cell clone expansion and antibody synthesis.[15]

Since glucocorticoid is a steroid, it regulates transcription factors. Another factor it downregulates is the expression of Fc receptors on macrophages, so there is decreased phagocytosis of opsonised cells.[15]

Pulmonary TB and systemic steroid therapy

Dermatological patients undergoing prolonged and high-dose glucocorticoids treatment are at increased risk for both the acquisition of primary tuberculosis and the reactivation of nonactive tuberculosis. Other co-morbid conditions can add to this risk (**Table 4**). 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 patients to more severe variants of the disease, e.g. disseminated tuberculosis.[6]

Table 4 Risk factors for pulmonary tuberculosis [9]

- Diabetes mellitus
- IV drug abuse
- Immunocompromised patients
- Patients with hematological and recticuloendothelial diseases e.g. leukemia, Hodgkin's disease
- Carcinoma (esp. head and neck region)
- HIV infection
- End stage kidney disease/hemodialysis
- Intestinal bypass surgery
- Chronic malabsorption syndrome
- Prolonged corticosteroids therapy (≥15 mg/day prednisolone, for >1 month)
- Other immunosuppressive therapy
    - ≥2 mg/kg/day of azathioprine
    - ≥ 25 mg/week of methotrexate
    - >1 mg/kg/day of 6-mercaptopurine
    - Any anti-TNF-α medication

A number of studies have addressed this issue and **Table 5** compares the incidence of pulmonary TB reported in different studies in patients using high-dose, long-term systemic steroids in dermatological patients.

Pal *et al*.[17] carried out a study in Chandigarh, India, in which 143 patients taking oral steroids for various respiratory disorders were followed up for one year to study the incidence of tuberculosis. Another group of patients (141) suffering from similar disorders and not requiring steroids were used as controls. Seven patients (4.9%) receiving steroids developed tuberculosis compared with none amongst the controls ($p<0.05$). Of these, 4 had pulmonary lesions, 2 had tuberculous pleural effusion and one had tuberculous meningitis. All these patients were treated with standard anti-tuberculosis drugs; 6 patients improved whereas one died due to complications of the disease. The study concluded that long-term systemic steroids therapy causes a significant increase in the incidence of tuberculosis. Another study was

Table 5 Incidence of pulmonary tuberculosis in different studies.

Country	*Year*	*No. of patients*	*Dose of steroids*	*Duration of treatment*	*Incidence of pulmonary TB*
India [17]	2002	143	>1g (cumulative)	1 year	4.9%
Korea [18]	2002	283	>1g (cumulative)	1 year	7.9%
Japan [22]	1999	162	1.16-5.60g (cumulative)	2-9 months	3.1%
Turkey [19]	2004	556	2.2g (cumulative)	1 year	3.6%
Japan [20]	2000	14	13mg/day	1 year	7%
U.K [23]	2006	497	15mg/day	2 years	29%
Pakistan [26]	2013	50	20mg/day	6 months	8%

carried out in United Kingdom by Jick *et al.*[17] in which risk factors for tuberculosis were determined. The study involved 497 new cases of tuberculosis and 1966 controls at risk. The risk factors were glucocorticoids, smoking, diabetes, emphysema, bronchitis and asthma. The study concluded that the patients treated with glucocorticoids have an increased risk of developing tuberculosis independent of other risk factors.

Chan and Yosipovitch[7] carried out a review on screening and management of tuberculosis in patients taking oral glucocorticoids. They found that steroids given at a dose of more than 15 milligrams daily for two to four weeks suppress tuberculin reactivity. Lower or intermittent doses of glucocorticoid are not associated with tuberculosis. Therefore, high dose long-term systemic steroid therapy can predispose patients to primary infection and reactivation of nonactive tuberculosis. Their study found several patients with immunobullous disorders and dermatomyositis having nonactive tuberculosis on screening before the commencement of oral corticosteroids. The authors concluded that the patients with dermatological conditions who are receiving prolonged glucocorticoid therapy should be screened for tuberculosis and provided with appropriate treatment if it is detected.

Sayarlioglu *et al.*[19] carried out a study in Turkey in which they investigated the frequency and characteristics of tuberculosis in patients with systemic lupus erythematosus (SLE). Of the 556 patients evaluated, 20 patients had tuberculosis. Nine of these cases had extrapulmonary tuberculosis. The mean daily dose and the cumulative dose of prednisolone before the diagnosis of tuberculosis were significantly higher in the patients of systemic lupus erythematosus with tuberculosis compared to systemic lupus erythematosus nontuberculosis group. Therefore, the doses of prednisolone were important determinants for increased risk of tuberculosis in the patients with systemic lupus erythematosus.

Sasaki *et al.*[20] carried out a study in Japan in which they enrolled patients with collagen vascular disease who developed pulmonary tuberculosis during corticosteroid administration. The group consisted of 14 pulmonary tuberculosis (PTB) patients with collagen disease. They were under corticosteroid treatment and the mean age was 56.4 years. The length of time from the development of collagen disease to the development of PTB averaged 4.1 years. The breakdown of collagen diseases included SLE (6 patients), mixed connective tissue disease (3 patients), polyarteritis nodosa (2 patients), and polymyositis, Sjogren syndrome (1 case each). Thirteen cases were bacilli positive by the sputum examination. Chest X-ray findings revealed cavitation in 3 cases and non-cavitation in 11 cases, of which 5 cases had miliary tuberculosis. Corticosteroid

preparation had been administered to all of the 14 cases for more than one year. The mean dose of corticosteroid preparation administered when PTB developed was 13.9 mg (prednisolone) and it was more than 20 mg in 8 cases. The median duration from the start of the respiratory symptoms to diagnosis was 39.2 days. The delay in the discovery exceeding 1 month was seen in 9 cases. In the cases of collagen disease,[20] when the disease course extends over a long period of time, and even when the dose of corticosteroid preparations are decreased, there is a need to note the risk of developing PTB. There are many non-cavity cases with sputum smear positive. The fact suggested that an appropriate diagnosis is needed so that the discovery of PTB should not be delayed.

Kobashi *et al.*[22] carried out a study in Japan regarding 'clinical analysis of pulmonary tuberculosis in association with corticosteroid therapy' which states that in the last five years, five patients (three males and two females) among a total of 162 patients (3.1%) ranging from 63 to 79 years old developed pulmonary tuberculosis during the long-term corticosteroid therapy. The underlying diseases of these cases were pulmonary fibrosis in two; polyarteritis nodosa, rapidly progressive glomerulonephritis with pulmonary bleeding and mycosis fungoides in one each. The total corticosteroid dose used until the clinical diagnosis of pulmonary tuberculosis was 1.16g to 5.60g and the duration of administration was two to nine and a half months. Other immunosuppressive drugs were administered to two patients. Though chemoprophylaxis with INH was done in two patients for three months, it was impossible to prevent the development of pulmonary tuberculosis. Since almost all patients except one complained no symptoms at the onset, the follow-up with chest radiographs seemed to be most important during corticosteroid therapy, and in fact, four patients were detected during follow-up. Anti-tuberculous chemotherapy was effective in four patients. Careful clinical observation, such as by chest radiographs, seems to be appropriate for the early diagnosis and treatment of pulmonary tuberculosis in patients on corticosteroid therapy.

Isabelle *et al.*[23] carried out a study in France to see opportunistic infections in polymyositis and dermatomyositis and they found that out of 156 patients, 18 developed opportunistic infections, one of which was *M. tuberculosis*. They found that higher mean daily doses of steroids, lymphopenia and lower serum total protein levels were more frequent in the group of polymyositis and dermatomyositis with opportunistic infections.

Screening for pulmonary TB during prolonged, high-dose steroid therapy

Pulmonary TB constitutes a relative contraindication for systemic steroid treatment. Before initiating system steroid therapy, a detailed history should be taken about exposure history of tuberculosis, history of previous treatments used for active TB or LTBI, BCG vaccination and current symptoms suggestive of TB. A PPD/Mantoux test should be done at baseline and in endemic areas like Pakistan, a screening X-ray chest (CXR) is also warranted. **Figure 1** illustrates the selection of patients requiring LTBI treatment.

a). If a patient, based on clinical features and CXR findings, is suspected of active TB, work up for active disease is recommended (**Figure 2**).

b). If the patient does not have evidence of active disease, and past history is positive for adequate treatment of TB, and there is no further exposure to new TB patient, there is no need for any additional TB infection tests and patient is

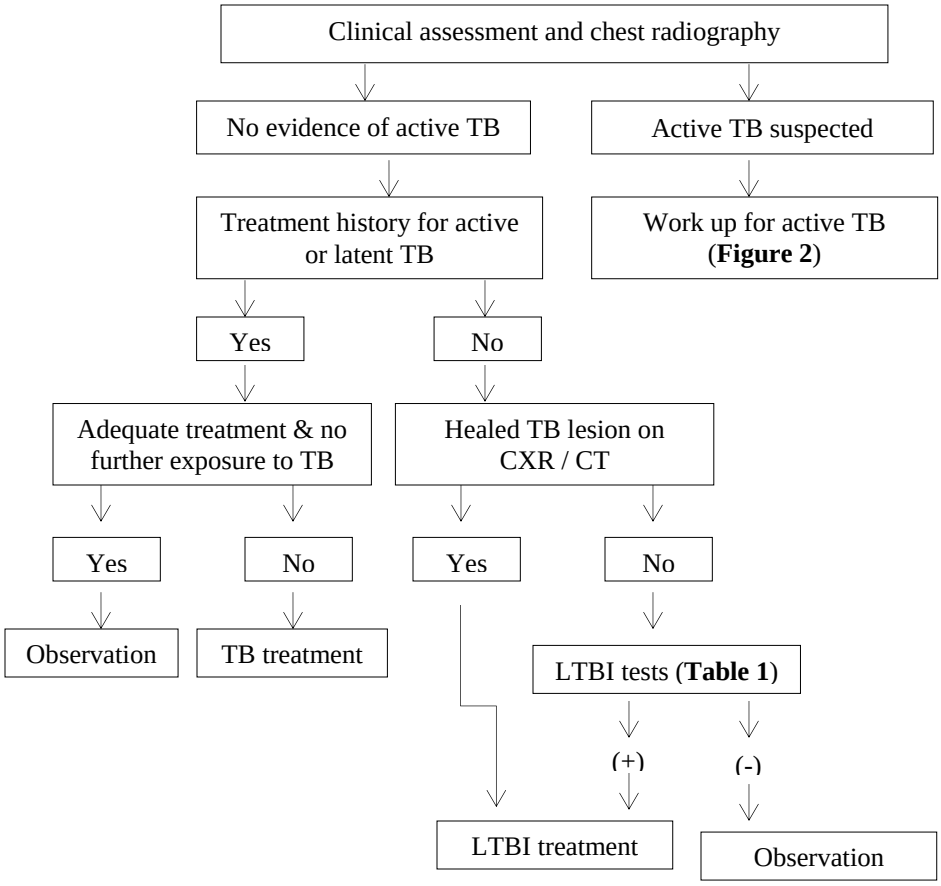

Figure 1 Algorithm for selection of candidates requiring LTBI treatment. TB: tuberculosis; CXR: chest X-ray; CT: computerized tomography; LTBI: latent tuberculosis infection [26].

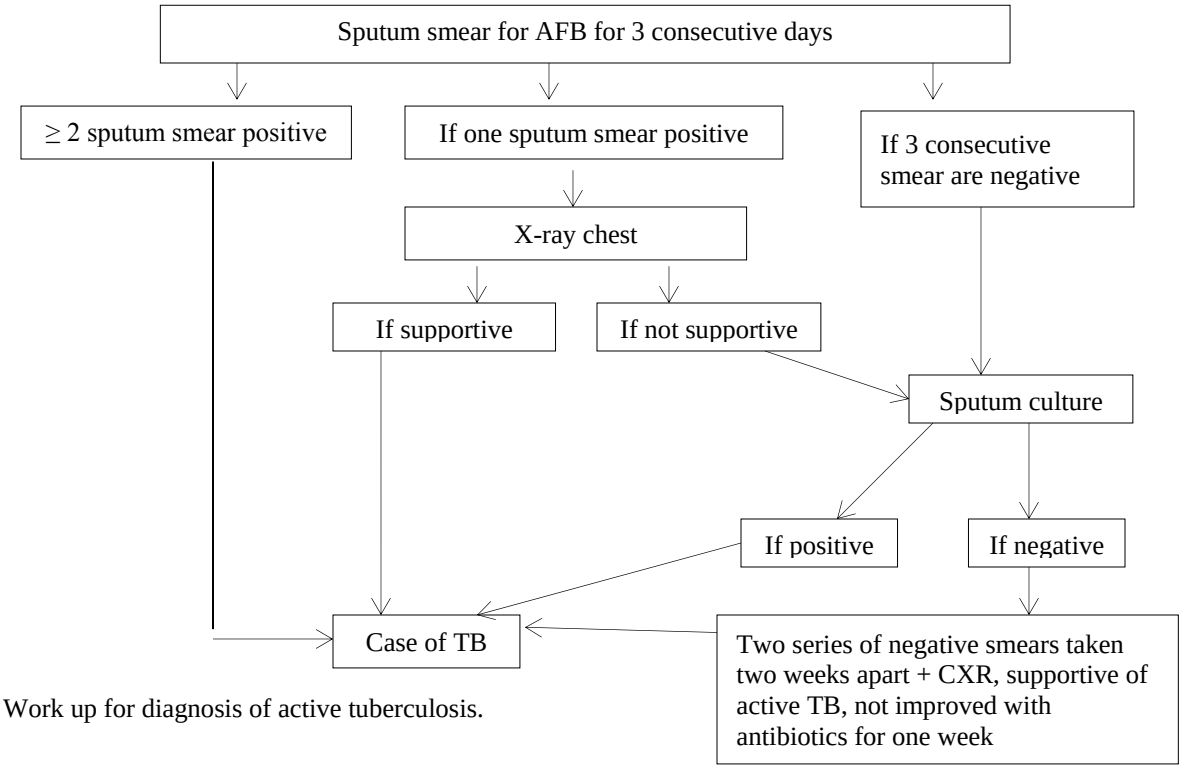

Figure 2 Work up for diagnosis of active tuberculosis.

kept under observation. In case there is exposure to TB patient, patient is treated for LTBI.

c). When history of treatment is not clear, the radiological findings should be reevaluated. LTBI treatment is performed if fibrostreaky lesions in upper lobes, suggestive of spontaneously healed TB, are seen. The presence of only small calcified pulmonary nodules does not merit treatment.

d). If there is neither history of previous treatment for TB nor abnormal TB-related findings, TB infection tests are done to determine LTBI. However, cannot differentiate between active TB and LTBI. Therefore, LTBI is diagnosed after excluding active TB in cases with a positive TB infection test. TB infection tests include tuberculin skin test (TST) and interferon gamma (IFN-γ) release assays (IGRA) including QuantiFERON-TB Gold In-Tube (QFT-GIT; Cellestis, Carnegie, VIC, Australia) and T-SPOT.TB (T-SPOT; Oxford Immunotec, Abingdon, UK), which detect cell-mediated IFN-γ responses to *M. tuberculosis*-specific antigens. Both these tests have high specificity.[21]

Treatment of latent TB infection

For LTBI, a 9-month course of isoniazid is considered the standard regimen; this has an efficacy of 90%. A 4-month regimen of RIF is also recommend in the United States,[12] while a 3-month regimen of the INH/RIF combination is recommended in the UK. A 3-month regimen of the INH/rifapentine (RPT) combination (once a week for a total of 12 intermittent treatment sessions) has been approved and recommended for treating LTBI in the United States since 2011. Before starting LTBI treatment, it is essential to rule out the possibility of active TB. If the possibility of active TB is not precluded, LTBI treatment should be withheld. As both INH and RIF are hepatotoxic drugs, liver function tests should be assessed before initiating LTBI treatment.[24]

Follow-up during steroid therapy

In endemic areas of TB, there is always a risk of contact with infectious TB patients. Patients should be educated about the suspected TB symptoms and signs and in case they develop such symptoms, they should immediately visit hospital for the diagnostic tests for TB e.g. TB infection tests or CXR.[25] However, the necessity of regular TB infection tests has not been universally recommended at present.

Development of TB during steroid therapy

When a patient on high-dose long-term treatment with systemic steroids is diagnosed with active TB, anti-TB treatment should be initiated without stopping the steroid treatment; however, the dose of steroid should be just sufficient enough to curtail the activity of underlying dermatosis and tapered to the minimum possible level. Rapid drug susceptibility tests should be performed to identify drug resistance.[17] The treatment period for active TB is identical to that of ordinary TB patients.

Recommendations

Table 6 summarizes the recommendations for patients undergoing prolonged, high-dose steroid treatment. They should be screened at baseline and evaluated periodically for any new pulmonary symptoms during follow-up period. If the clinical features are suggestive of pulmonary TB, patient should be rigorously investigated (**Figure 1**) and treated with multidrug antituberculous therapy. The treatment period for active TB is identical to that of ordinary TB patients.

Table 6 Summary of recommendations for patients undergoing long-term high-dose systemic steroid treatment.

1. Patients potential candidates for long-term high-dose steroid treatment should be assessed for TB infection.
2. Baseline data should include current symptoms, TB contacts, previous TB treatment and a chest X-ray. If active TB is suspected, further workup should be performed.
3. LTBI is diagnosed by using both TST and IGRA. If either test is positive patient is regarded as LTBI.
4. If there is evidence of TB scars on CXR without a history of adequate treatment, patient is diagnosed as LTBI and without testing for LTBI treatment is started after excluding active TB.
5. LTBI treatment regimens include 9 months of INH, 4 months of rifampicin, or 3 months of INH/rifampicin.
6. Development of TB during steroid treatment should be observed vigilantly.
7. If during treatment, there is history of contact with an infectious TB patient, patient should be investigated for LTBI and active TB.
8. If during steroid therapy, patient develops active TB, steroid, should be continued and anti-TB treatment is started.

IGRA: interferon-gamma releasing assay; LTBI latent tuberculosis infection; TB Tuberculosis; TNF: Tumour necrosis factor; TST: tuberculin skin test.

Conclusion

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.

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