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Update on tuberculous pleural effusion

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ABSTRACT

The possibility of tuberculous pleuritis should be considered in every patient with an undiagnosed pleural effusion, for if this diagnosis is not made the patient will recover only to have a high likelihood of subsequently developing pulmonary or extrapulmonary tuberculosis Between 3% and 25% of patients with tuberculosis will have tuberculous pleuritis. The incidence of pleural tuberculosis is higher in patients who are HIV positive. Tuberculous pleuritis usually presents as an acute illness with fever, cough and pleuritic chest pain. The pleural fluid is an exudate that usually has predominantly lymphocytes. Pleural fluid cultures are positive for *Mycobacterium tuberculosis* in less than 40% and smears are virtually always negative. The easiest way to establish the diagnosis of tuberculous pleuritis in a patient with a lymphocytic pleural effusion is to generally demonstrate a pleural fluid adenosine deaminase level above 40 U/L. Lymphocytic exudates not due to tuberculosis almost always have adenosine deaminase levels below 40 U/L. Elevated pleural fluid levels of γ-interferon also are virtually diagnostic of tuberculous pleuritis in patients with lymphocytic exudates. In questionable cases the diagnosis can be established by demonstrating granulomas or organisms on tissue specimens obtained via needle biopsy of the pleura or thoracoscopy. The chemotherapy for tuberculous pleuritis is the same as that for pulmonary tuberculosis.

Key words: adenosine deaminase, anti-tuberculous therapy, gamma interferon, pleural biopsy, pleural effusion.

INTRODUCTION

Tuberculosis (TB) is a major public health problem in developing countries. Although the majority of patients with TB have pulmonary TB, extrapulmonary TB affecting mainly the lymph nodes and pleura serves as the initial presentation in about 25% of adults.[1] TB is the leading cause of pleural effusions in some countries.[2]

It is important to consider the possibility of tuberculous pleuritis in all patients with an undiagnosed pleural effusion. A pleural effusion as an isolated manifestation of TB has been likened to a primary chancre as a manifestation of syphilis. Both are self-limited and of little immediate concern, but both may lead to serious disease many years later. Tuberculous pleuritis is thought to represent primarily a hypersensitivity reaction to tuberculous protein and the bacillary burden in the pleural space is low.

PATHOGENESIS

A tuberculous pleural effusion that occurs in the absence of radiologically apparent TB may be the sequel to a primary infection 6–12 weeks previously or it may represent reactivation TB.[3] In industrialized countries, it is thought that more pleural effusions are due to reactivation than follow a primary infection.[3] One epidemiologic study in San Francisco assessing the genotyping of mycobacterial organisms demonstrated that pleural TB patients were twice as likely to be clustered than pulmonary TB and three times more likely to be clustered than non-respiratory TB patients.[4] This observation suggested that the majority of patients of pleural effusion were post primary infection. However, a second study on clustering in Houston found that patients with pleural TB were less likely to be clustered than those with pulmonary TB.[5]

The pathogenesis of a tuberculous pleural effusion is thought to be related to the rupture of a subpleural

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caseous focus in the lung into the pleural space.[6] The basis for this is the observation by Stead *et al.*[7] that they could demonstrate a caseous tuberculous focus in the lung contiguous to the diseased pleura in 12 of 15 patients with tuberculous pleuritis. The three other patients in this study had parenchymal disease although they did not have caseous foci adjacent to the pleura.

It is believed that delayed hypersensitivity plays a large role in the pathogenesis of tuberculous pleural effusion. The hypersensitivity reaction is initiated when tuberculous protein gains access to the pleural space. Evidence for the role of hypersensitivity includes the following: (i) When tuberculous protein is injected into the pleural spaces of guinea pigs sensitized to purified protein derivative, an exudative pleural effusion rapidly develops.[8] (ii) When the sensitized guinea pigs are given antilymphocyte serum, the development of the pleural effusion is suppressed.[9] (iii) The mycobacterial cultures of the pleural fluid from most patients with tuberculous pleural effusions are negative.[1,10]

The tuberculous pleural effusion develops when the delayed hypersensitivity reaction increases the permeability of the pleural capillaries to protein and then the increased protein levels in the pleural fluid result in a much higher rate of pleural fluid formation. In addition, the lymphocytic pleuritis obstructs the lymphatics in the parietal pleura, which leads to decreased pleural fluid clearance from the pleural space. The pleural effusion results from the combination of the increased pleural fluid formation and the decreased pleural fluid removal.[2]

INCIDENCE

The percentage of patients with TB who have pleural effusions has varied markedly from county to country. In Burundi more than 25% of patient with TB have tuberculous pleural effusions[11] while in South Africa 20% of TB patients have tuberculous pleural effusions.[12] In contrast only 3–5% of patients in the USA are reported to have tuberculous pleural effusions.[13,14] The lower percentage in the USA is probably in part due to under reporting of the disease in the USA because the pleural fluid cultures are frequently negative.[2]

Patients who are immunocompromised are more likely to develop TB than non-immunocompromised individuals. Because tuberculous pleuritis is thought to be due to delayed hypersensitivity, one might hypothesize that the percentage of immunocompromised hosts with TB who would have pleural effusions would be lower than that in the immunocompetent host. However, this is not usually the case. In patients with AIDS and TB it appears that the incidence of pleural effusions is higher than in immunocompetent patients. The percentage of patients with thoracic TB who had a pleural effusion was higher in HIV-positive patients than immunocompetent patients in reports from South Africa (38% vs 20%),[12] Uganda (23% vs 11%),[15] and Zimbabwe (27% vs 13%).[16]

In other series of immunocompromised hosts without AIDS, the percentage of TB patients with pleural effusions has been less. Pleural effusions occurred in only 3/27 patients (11%) with kidney transplants who developed TB.[17] In another series pleural effusions occurred in only 5/48 patients (10.4 %) who were on renal dialysis and developed TB.[18]

CLINICAL MANIFESTATIONS

Tuberculous pleuritis usually presents as an acute illness. Upon presentation symptoms in one series had been present for less than 1 week in 25/71 patients (35%) and had been present for less than a month 50/71 patients (71%).[19] The most frequent symptoms are cough (~70%), which is usually nonproductive and chest pain (~70%), which is usually pleuritic in nature.[2,3,6] If both cough and pleuritic pain are present, the pain usually precedes the cough. Most patients are febrile but approximately 15% will be afebrile.[6] Patients with tuberculous pleural effusions may be dyspneic if the effusion is large. On occasions the onset of tuberculous pleuritis is less acute with mild chest pain, at most a low grade fever, a non-productive cough, weight loss and easy fatigability.

Patients with tuberculous pleuritis tend to be younger than patients with parenchymal TB. In one recent series from Qatar, the mean age of 100 patients with tuberculous pleuritis was 31.5 years.[20] However, in industrialized countries the mean age of patients with tuberculous pleuritis tends to be older because it is reactivation TB.[3] In a recent study from the USA, the mean age of 14 000 patients reported to the Communicable Disease Center between 1993 and 2003 was 49.9 years.[14]

The pleural effusions secondary to tuberculous pleuritis are usually unilateral and can be of any size. In one series of 254 patients the effusions occupied more than two-thirds of the hemithorax in 18%, between one-third and two-thirds of the hemithorax in 47%, and less than one-third of the hemithorax in 34%.[21] TB was the third leading cause of large or massive pleural effusion (12%) after malignancy (55%) and pneumonia (22%)[22] Approximately 20% of patients with tuberculous pleural effusions have coexisting parenchymal disease on chest radiograph.[21] However, if chest CT scans are performed, more than 80% may have parenchymal abnormalities.[23] The parenchymal disease is almost always on the side of the pleural effusion and is invariably active. On rare occasions, pleural TB can present with pleural-based nodules and thickening.

Pleural fluid characteristics

The pleural fluid with tuberculous pleuritis is invariably an exudate. Indeed, the pleural fluid protein level frequently exceeds 5 g/dL and this finding suggests tuberculous pleuritis.[2] Most patients with tuberculous pleuritis have more than 50% small lymphocytes in their pleural fluid and many have more than 90%.[6,21]

Only 6.7% of 254 patients in one study had fewer than 50% lymphocytes in their pleural fluid.[21] Patients with symptoms less than 2 weeks in duration are more likely to have predominantly polymorphonuclear leucocytes in their pleural fluid.[19] If the pleural fluid contains more than 10% eosinophils, the diagnosis of tuberculous pleuritis is unlikely unless the patient has a pneumothorax or has had a previous thoracentesis.[2]

The pleural fluid glucose level with tuberculous pleural effusions may be reduced but it usually is similar to the serum level. The pleural fluid pH is usually above 7.30, but it also may be reduced. The pleural fluid lactic acid dehydrogenase (LDH) level is usually higher than the serum LDH level.

One characteristic of pleural fluid from patients with tuberculous pleuritis is that it rarely has more than scattered mesothelial cells. Mesothelial cells are the cells that cover both the visceral and parietal pleura. Transudative pleural fluids contain many mesothelial cells. However, the intense lymphocytic infiltration with tuberculous pleuritis covers both pleural surfaces and prevents the mesothelial cells from entering the pleural space. Four separate series have confirmed that pleural fluid from patients with TB rarely contains more than 5% mesothelial cells.[24–27] The absence of mesothelial cells is not diagnostic of tuberculous pleuritis because any condition in which the pleural surfaces are extensively involved by an inflammatory process will be associated with a paucity of mesothelial cells in the pleural space. HIV-infected patients with tuberculous pleuritis may have mesothelial cells in their pleural fluid. Three such patients in one report had significant numbers of mesothelial cells in their pleural fluid.[28] Each of the three patients had CD4 counts below 100 mm^3 in their peripheral blood.[28]

Clinical manifestations in HIV-positive patients

The clinical manifestations of tuberculous pleuritis tend to be different in the HIV-positive patient. These patients have a longer duration of illness and a lower incidence of chest pain.[29] Moreover, systemic signs and symptoms such as night sweats, fatigue, diarrhoea, hepatomegaly, splenomegaly and lymphadenopathy are more common in HIV-infected patients.[30] The pleural fluid is much more likely to be smear and culture positive for mycobacteria.[29,31] If the peripheral CD4 count is less than 100 cells/mm^3, approximately 50% of patients will have a positive smear for AFB on their pleural fluid.[29] The viral load per millilitre is higher in the pleural fluid than in the simultaneously obtained serum.[32]

NATURAL HISTORY OF UNTREATED TUBERCULOUS PLEURITIS

Without treatment, tuberculous pleuritis usually resolves spontaneously, but the patient frequently develops active TB at a later date. In one study Patiala followed for at least 7 years all 2816 members of the Finnish Armed Forces who developed pleural effusion between 1939 and 1945.[33] He reported that 43% of this large group of young men developed TB during the follow-up period.[33] A second study followed 141 military personnel first seen in the USA between 1940 and 1944 with a pleural effusion and a positive tuberculin skin test.[34] Although the effusions resolved and all other symptoms disappeared within 2–4 months, 92 of the 141 individuals (65%) subsequently developed some form of active TB.[34] The subsequent incidence of TB was comparable in these whose pleural fluid cultures were initially positive for TB (60%) and those in whom the initial cultures were negative (65%).[34] Moreover, the size of the original effusions and the presence or the absence of small radiological residual pleural disease were not correlated with the subsequently development of active TB.[34] These two studies underline the importance of making the diagnosis of tuberculous pleuritis if that is what the patient has.

DIAGNOSIS

The diagnosis of tuberculous pleuritis depends upon the demonstration of tubercle bacilli in the sputum, pleural fluid, or pleural biopsy specimens, or the demonstration of granulomas in the pleura. The diagnosis can also be established with reasonable certainty by demonstrating elevated levels of adenosine deaminase (ADA) or γ-interferon in the pleural fluid.[35]

Mycobacterial stain and culture

One test that is frequently overlooked in the diagnostic work-up of patients with an undiagnosed pleural effusion is examination of the sputum for mycobacteria. Conde and associated prospectively evaluated the diagnostic yield of mycobacterial smears and cultures in 84 patients with tuberculous pleuritis.[36] They induced sputum in those unable to spontaneously expectorate. They reported that the sputum studies were positive in 44 of the 84 patients (52%).[36] In 10 of the 44 patients, sputum smears were positive, whereas cultures were positive in all.[36] The sputum was positive in 35 of 64 patients (55%) who had a normal chest radiograph except for the effusion and in whom the sputum was induced.[36] Probably sputum examination is underutilized in the diagnosis of tuberculous pleuritis.

Routine smears of the pleural fluid for mycobacteria in immunocompetent individuals are not indicated because they are almost always negative unless the patient has a tuberculous empyema.[10,21] Smears should be obtained in immunocompromised hosts. Smears are positive in approximately 20% of HIV-positive individuals.[29] However, pleural fluid cultures for mycobacteria should be obtained in any patient with an undiagnosed pleural effusion. In most series of immunocompetent patients with tuberculous pleuritis, the cultures are positive in less than 40%.[6,21] The use of a BACTEC system with bedside inoculation of the pleural fluid provides higher yields and faster results than do conventional methods. In one study

the BACTEC system provided positive cultures in 24% of HIV-negative patients and 75% of HIV-positive patients while the cultures were positive by the Lowenstein–Jensen medium in 12% of HIV-negative patients and 56% of HIV-positive patients.[31] In this series the mean time to a positive culture with the BACTEC system was 3.5 weeks compared with 4.7 weeks with the Lowenstein–Jensen medium.[31]

Skin tests

The tuberculin skin test is being utilized less and less in patients suspected of having tuberculous pleuritis. This is primarily because a negative test does not rule out the diagnosis of tuberculous pleuritis. In a series of 254 patients from Spain, only 66.5% of the patients had a positive skin test.[21] In another series from Hong Kong, more than half the patients tested had a negative skin test.[37] If a patient with a negative tuberculin skin test and tuberculous pleuritis is skin tested more than 8 weeks after the development of symptoms, the skin test will almost always be positive. However, if the patient is markedly immunosuppressed with HIV infection or is severely malnourished, the skin test may remain negative.

Adenosine deaminase

Testing for pleural fluid ADA levels is an easy and inexpensive method for establishing the diagnosis of TB pleuritis.[1] ADA, a predominant T-lymphocyte enzyme, catalyses the conversion of adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. A recent meta-analysis of 63 studies including 2796 patients with tuberculous pleuritis and 5297 with non-tuberculous effusion reported that the sensitivity and specificity of ADA in the diagnosis of pleural TB were 92% and 90%, respectively. The positive likelihood ratio was 9.03, the negative likelihood ratio was 0.10, and the diagnostic odds ratio was 110.08.[38] ADA levels in pleural fluid are also elevated in HIV patients even with very low CD4 cell counts.[39] The most widely accepted cut-off value for pleural fluid ADA is 40 U/L. The higher the level, the greater the chance of the patient having TB while the lower the level the lesser the chance of the patient having TB.[1]

The main disease other than TB that causes an elevated pleural fluid ADA is empyema. Roughly one-third of parapneumonic effusions and two-thirds of empyemas have ADA levels that exceed 40 U/L.[40] However, tuberculous pleuritis and parapneumonic effusions are easily distinguished by the clinical pictures and the fact that parapneumonic effusions have predominantly polymorphonuclear leucocytes instead of the lymphocytes typical of TB. Less commonly high pleural fluid ADA has been reported in malignancies (5%, particularly lymphomas), infectious diseases (e.g. brucellosis, Q fever) and connective tissue diseases such as rheumatoid arthritis.[1]

The pleural fluid ADA level can be used to exclude the diagnosis of tuberculous pleuritis in patients with undiagnosed pleural effusions. Ferrer and associates followed 40 patients with undiagnosed pleural effusions and a pleural fluid ADA level below 43 U/L for a mean of 5 years and reported that none developed TB.[41] Lymphocytic pleural effusions not due to tuberculous pleuritis usually have pleural fluid ADA levels below 40 U/L. Castro *et al.* measured the pleural fluid ADA levels in 410 lymphocytic non-tuberculous pleural fluids and found that the ADA was above 40 IU/L in on seven (1.7%).[42]

Adenosine deaminase has two molecular forms, ADA1 and ADA2. ADA1 is found in all cells and has it greatest activity in lymphocytes and monocytes while ADA2 is found only in monocytes.[43] Most of the ADA in tuberculous pleural fluid is ADA2 which seems paradoxical as ADA1 comes from lymphocytes and lymphocytes predominate in pleural fluid from patients with TB pleuritis. Although a ratio of the ADA1 to the total ADA of less than 0.42 will slightly increase the sensitivity and specificity of the ADA measurement in diagnosing tuberculous pleuritis, the separation of ADA into its isoenzymes is not necessary in the vast majority of cases.[43]

The pleural fluid ADA level will remain stable during transportation if preservatives are added to the pleural fluid. Miller *et al.* have shown that if 0.10 mL of a mixture of 50% glycerol and 50% ethylene glycol is added to a 1-mL test tube, the levels of ADA in the pleural fluid remain stable.[44] The levels of ADA remain the same whether the sample is sent by air on dry ice or if it is sent by regular mail.[44] If pleural fluid is maintained at ambient temperature without preservatives, the level of ADA will decrease linearly.[44] The ADA levels remain stable for long periods in pleural fluid frozen at −70°C.[45]

Gamma interferon

The level of pleural fluid γ-interferon is also very efficient at distinguishing tuberculous from non-tuberculous pleural effusions. Gamma interferon is a cytokine released by activated CD4 + T lymphocytes that increases the mycobactericidal activity of macrophages. A meta-analysis of 22 studies that included 782 patients with TB and 1319 patients with non-tuberculous pleural effusion showed that the mean sensitivity of the γ-interferon assay was 89%, the mean specificity was 97%, and the maximum joint sensitivity and specificity was 95%.[46] It is impossible to establish a cut-off value overall as the units and the methods of measurement differ from study to study.[1] A previous meta-analysis that reviewed 13 studies on γ-interferon and 31 on ADA, which included 1189 patients concluded that both ADA and γ-interferon are accurate in diagnosing TB pleuritis.[47] In this latter study the maximum joint sensitivity and specificity were 93% for ADA and 96% for γ-interferon.[47] Similarly to the ADA levels, levels of γ-interferon are sometimes elevated with haematologic malignancies and empyemas.[48] In summary, the long historical success of ADA and the fact that it is simpler and less expensive that the γ-interferon test makes it the preferred test.

Gamma interferon release assays

The γ-interferon release assays (IGRA) are T cell-based *in vitro* assays that measure γ-interferon release by sensitized T cells from peripheral blood or pleural fluid in response to highly *Mycobacterium tuberculosis*-specific antigens such as early secretory antigen (ESAT)-6 and culture filtrate protein (CFP)-10.[1] There are now two IGRA which are commercially available (QuantiFERON-TB Gold and T-SPOT.TB). These tests are good at identifying patients who have been infected with *M. tuberculosis*. However, they are much less useful in identifying patients with pleural TB. A recent study showed that pleural fluid γ-interferon levels themselves were much superior to the IGRA in regards to both sensitivity and specificity.[49] The IGRA are not recommended on either the blood or the pleural fluid to make a diagnosis of tuberculous pleuritis.[50]

Nucleic acid amplification tests

Nucleic acid amplification (NAA) assays amplify *M. tuberculosis*-specific nucleic acid sequences with a nucleic acid probe. This allows direct detection of *M. tuberculosis* in clinical specimens like pleural fluid within hours of their receipt. There are two widely available assays, the AMPLICOR MTB and the AMTD.[1] A pooled analysis of the data from 20 studies assessing the use of pleural fluid NAA tests concluded that these tests demonstrated reasonably high specificity (97% for commercial and 91% for in-house tests), but generally poor and variable sensitivity (62% for commercial and 76.5% for in-house tests).[51] An earlier meta-analysis of 40 studies came to very similar conclusions.[52] The disappointingly low sensitivities of NAA techniques might be due to the presence of inhibitors in the pleural fluid or to intracellular sequestration of the mycobacteria. At the present time, the use of the NAA assays in the diagnosis of tuberculous pleurisy should be limited to investigational settings.

Pleural biopsy

The most common way to make the diagnosis of tuberculous pleuritis over the past 50 years has been with a blind needle biopsy of the pleura. The demonstration of granuloma in the parietal pleura suggests tuberculous pleuritis; caseous necrosis and AFB need not be demonstrated. Although other disorders including fungal diseases, sarcoidosis, tularemia and rheumatoid pleuritis may produce granulomatous pleuritis, more than 95% of patient with granulomatous pleuritis have TB.[2] Even if no granulomas are present on the biopsy, the biopsy specimen should be stained for AFB and cultured for *M. tuberculosis*. In one study of 248 patients with tuberculous pleuritis who underwent needle biopsy of the pleura, the biopsy showed granulomas in 198 patients (80%), the AFB stain of the biopsy was positive in 64 (25.8%) and the culture of the biopsy tissue was positive in 140 (56%).[21] In this study at least one of the three tests was positive in 227 (91%).[21]

Pleural tissue can also be obtained at thoracoscopy, but thoracoscopy is usually not necessary to make the diagnosis of tuberculous pleuritis. Thoracoscopy is sometimes indicated when the clinical picture is confusing. If the patient does have tuberculous pleuritis, thoracoscopy will establish the diagnosis in nearly 100% of cases.[53]

RECOMMENDED DIAGNOSTIC APPROACH

When a patient with an undiagnosed pleural effusion is initially evaluated, the diagnosis of tuberculous pleuritis should always be considered because if the diagnosis is not made, the patient will subsequently develop TB. At the time of the initial thoracentesis, the pleural fluid should be analysed for the ADA level and differential cell count and the fluid should be cultured for mycobacteria. If the fluid ADA is above 70 U/L and the pleural fluid has a lymphocyte-to-neutrophil ratio greater than 0.75, the diagnosis of tuberculous pleuritis is virtually established. If the pleural fluid ADA is between 40 and 70 U/L and the patient has a lymphocyte-to-neutrophil ratio of more than 0.75, one can make a presumptive diagnosis of tuberculous pleuritis. In this situation, if the patient's clinical picture is not typical for tuberculous pleuritis, consideration can be given to performing a needle biopsy of the pleura or thoracoscopy. If the patient's pleural fluid ADA level is below 40 U/L, the diagnosis of TB is unlikely. Nevertheless, if the patient has a clinical picture typical of tuberculous pleuritis and particularly, if the pleural fluid has a high percentage of lymphocytes, the possibility of tuberculous pleuritis can be further evaluated with needle biopsy of the pleura or thoracoscopy.[2]

One criticism of relying primarily on the pleural fluid level of ADA to make the diagnosis of tuberculous pleuritis is that no culture results are obtained. Accordingly, the sensitivities of the organisms cannot be determined. It should be noted that cultures of the pleural fluid itself are positive in 35% while cultures of the pleural biopsy are positive in approximately 55%. Therefore, the addition of a culture of the biopsy only increases the overall percentage of positive cultures by 20%.[2] The yield of only 20% extra positive cultures is not worthwhile in my opinion.

TREATMENT

The treatment of tuberculous pleuritis has three goals: (i) to prevent the subsequent development of active TB, (ii) to relieve the symptoms of the patient, and (iii) to prevent the development of a fibrothorax.

Chemotherapy

The recommendations for the treatment of all pulmonary and extrapulmonary TB are as follows.[54,55] The

initial phase of a 6-month regimen should consist of a 2-month period of isoniazid (INH), rifampin and pyrazinamide. Ethambutol should be included in the initial regimen until the results of drug susceptibility studies are available, unless there is little possibility of drug resistance. The second phase of the treatment should be INH and rifampin given for 4 months. Directly observed therapy (DOT) is recommended. Nine-month regimens using INH and rifampin are also effective when the organisms are fully susceptible to the drug.

The recommendations mentioned above may be somewhat intensive for isolated tuberculous pleuritis because the mycobacterial burden is relative low as the main pathophysiologic abnormality is hypersensitivity. Canete and associates treated 130 patients with 5 mg/kg of INH and 10 mg/kg of rifampin daily for 6 months and reported no treatment failures.[56] Dutt and associates treated 198 patients with 300 mg INH and 600 mg of rifampin daily for 1 month followed by 900 mg INH plus 600 mg of rifampin twice a week for the next 5 months and reported only one failure.[57]

With treatment, the patient's symptoms and radiological abnormalities gradually abate. The typical patient becomes afebrile within 2 weeks, but temperature elevations may persist as long as 2 months.[58] If a therapeutical thoracentesis is performed at the same time that antituberculous therapy is initiated, most patients become afebrile within 5 days.[59,60] The mean time for the complete resorption of pleural fluid is approximately 6 weeks, but it can be as long as 12 weeks.[58] There is no reason to keep the patient at bed rest and the patient needs to be isolated only if their sputum is positive for mycobacteria.

Approximately 50% of patients will have some residual pleural thickening 6–12 months after the initiation of treatment.[61] The pleural thickening may result in a reduction in the VC. The FVC was less than 80% of predicted at the end of their TB treatment in 8 of 81 patients (10%).[62] However, in this study there was only a weak correlation ($r = -0.298$) between the degree of pleural thickening and the reduction in the FVC.[62] The incidence of residual pleural thickening is slightly more common in patients with a low pleural fluid glucose, a high pleural fluid LDH level and high pleural fluid cytokine levels.[61,63] The administration of 2.5 mL of a hyaluronate-based gel resulted in significantly faster fluid absorption and significantly less pleural thickening at 3 months (0.57 vs 1.14 cm) in one randomized controlled study of 52 patients.[64] The residual pleural thickening is more common if the pleural effusion is initially loculated.[65]

Complete removal of the pleural fluid does not appear to decrease the amount of residual pleural thickening. In one study 61 patients were randomized to receive pigtail drainage until the drainage was less than 50 mL/day or no drainage and the residual pleural thickening was basically identical in both groups.[66]

The administration of a fibrinolytic may decrease the degree of residual pleural thickening in patients with loculated tuberculous pleural effusions. Kwak *et al.* randomized 43 patients with loculated pleural effusions to receive 100 000 urokinase daily administered through a pigtail catheter starting when the pleural fluid drainage was less than 100 mL/day and finishing when the amount of pleural fluid was less than 50 mL/day or only antituberculous therapy.[67] They reported that the mean width of the pleural thickening was 0.46 cm in the urokinase group and 1.86 cm in the control group.[67]

Paradoxical worsening of the pleural effusion occurs in a few patients after the initiation of antituberculous therapy. In one study of 61 patients who were started on a standard regimen of rifampin, INH, pyrazinamide and ethambutol, 10 patients (17%) had an increase in the size of their effusion after therapy was started.[68] A second report suggested that such paradoxical responses might be due to INH-induced lupus pleuritis.[69] An occasional patient with tuberculous pleuritis will also develop a peripheral lung nodule while being treated for the pleuritis.[70] Such nodules almost always represent pulmonary TB and disappear when the antituberculous therapy is continued.[70]

Interestingly, some patients will develop a pleural effusion while being treated for pulmonary TB. Gupta *et al.* reported 29 patients who developed pleural effusions while receiving chemotherapy for pulmonary (16 patients) or extrapulmonary TB (13 patients).[71] The pleural effusion developed between the 5th and 8th week of starting chemotherapy in 13, between the 9th and 12th week in 9 and between the 13th and 25th week in 5.[71] The pleural fluid was exudative in all cases and cultures for *M. tuberculosis* were positive in four. Most patients had a good response to the same chemotherapeutical regimen without any interruption[71]

Corticosteroids

The role of corticosteroids in the treatment of tuberculous pleurisy is controversial. In two controlled studies in which therapeutical thoracentesis was performed there were no benefits.[59,60] In a third study in which no therapeutical thoracentesis was performed, the duration of fever and the time required for fluid resorption were decreased.[72] The administration of corticosteroids did not decrease the degree of residual pleural thickening and 6 or 12 months after therapy was initiated in any of the three studies. In one randomized study of 197 patients with HIV-associated pleural TB, the administration of prednisolone was associated with an increased risk of Kaposi sarcoma.[73] A recent Cochrane review concluded that there are insufficient data to support evidence-based recommendations regarding the use of adjunctive corticosteroids in people with tuberculous pleurisy.[74]

The recommended approach to the patient with tuberculous pleuritis is as follows. If the patient is more than mildly symptomatic, a therapeutical thoracentesis is recommended. If the patient continues to have severe systemic symptoms (fever, malaise, pleuritic chest pain) after the therapeutical

thoracentesis, the administration of 80 mg of prednisone every other day until the acute symptoms have subsided is recommended. Thereafter the corticosteroids are rapidly tapered.

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