Chapter 14

Tuberculous Pleural Effusion

Wolfgang Frank

Additional information is available at the end of the chapter

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1. Introduction

Tuberculosis (TB) has traditionally been one of the major causes of pleural disease and until the earlier decades of the past century held as a principal paradigm of "pleuritis". Indeed in the presence of a distinctly exudative effusion and a compatible clinical presentation the widely used term "pleuritis exudativa" insinuated a tuberculous aetiology and has therefore been understood to be synonymous with "pleuritis exudativa tuberculosa". Whilst in the era of TB decline in the Western hemisphere the term "pleuritis exudativa" (which actually is a tautology!) has largely survived but should now describe exudative effusions in general, the full and precise term "pleuritis exudativa tuberculosa" is therefore suggested whenever the possibility of a tuberculous background is addressed. Otherwise the term "tuberculous pleurisy" or "tuberculous pleuritis" is used to describe this entity, in some countries also the term "specific pleurisy" is common. Apart from acute pleuritis exudative tuberculosa, TB of the pleura may however rarely present as a rather chronic disease state in terms of caseous pleurisy or specific (i. e. tuberculous) empyema, respectively. The following chapter reviews the different features and mechanisms of tuberculous pleural involvement as well as their diagnostic and therapeutic implications.

2. Epidemiology

In many regions of the world tuberculous effusion maintains its role as the leading inflammatory pleural disease. With the worldwide unabated HIV epidemic and related immune deficiency syndrome this state of affairs is likely to continue or being even aggravated within least in certain high risk populations. On a global scale the current significance of human immunodeficiency virus (HIV)-co-infection may be illustrated by WHO data, indicating at a TB-prevalence of 1/3 of the world´s population – similar to the past decade – a HIV-association

of approximately 13 % by the year 2009 [1, 2]. Conversely it is assumed, that 33 % to 50 % of HIV infected individuals are co-infected with M. tuberculosis [2]. The MTB/HIV-association however shows a huge intercontinental and regional variance, with the highest rate of HIV-pleural tuberculosis-coincidence being reported in Zimbabwe where 95 % of Patients with tuberculosis pleurisy were HIV positive [3]. In Burundi and Tansania a HIV-coinfection was found in 60 % of all cases of tuberculous pleurisy [4]. One of the lowest rates is reported from Spain with 10 % [5]. Am example of the impact of a high HIV-endemic environment on the incidence of tuberculous pleurisy is also given in a series from Ruanda, where TB accounted for as much as 86 % of all diagnosed pleural effusions [4]. Pleurisy incidence obviously and essentially parallels variability of global TB prevalence with an overwhelming share of 95 % occurring in developing countries. In TB-patients as a whole, pleural involvement varies between ~ 3-5 % in Western Europe and the USA vs. ~ 30 % in developing, HIV-high-prevalence-countries [6, 7, 8]. The differences clearly underline the modifying role of immunological determinants, stage and severity of the disease, general health status and nutritional factors. The effect of HIV on the occurrence of pleural involvement in a given TB-patient is illustrated by a study reporting a 38 % pleurisy incidence in AIDS-associated TB as compared with 20 % in matched HIV-negative TB patients [5]. On the basis of the presented data according to even conservative WHO estimates the TB-pleurisy incidence throughout the current decade is expected to remain grossly unchanged compared to the past decade, i. e. 18.2 – 62/100.000 in the developing countries vs. 0.42-0.77/100.000 in Western countries [6, 7, 10]. When the epidemiology of pleurisy (or pleural effusion in general) is analysed in terms of the magnitude of TB-contribution, a probably still valid estimate in Western countries is as low as 0.1 – 0.2 % and remains distinctly < 1 % even when referring to pleurisy in a strict sense (i. e. exudates) [11]. By comparison the previously reported percentages of 30-86 % in developing countries are – and remain – indeed dramatically different.

3. Pathophysiology and natural history

3.1. Immunological and microbiological factors

MTB may affect the pleura at different stages of pulmonary or systemic disease and by a number of different mechanisms. Thus pleural involvement occurs in primary, postprimary and reactivated TB alike and is basically believed to arise directly from contiguous macroscopic or microscopic lung lesions or else lymphogenic or hematogenic spread, but probably also via immunogenic mechanisms. Pleuritis exudativa tuberculosa is by far the most common clinical variety and has been classically interpreted as an early delayed-hypersensitivity-type phenomenon rather than direct organ involvement [12, 13]. Many clinical observations and experimental findings are in favour of this hypothesis such as:

- its frequent association with known primary infection and a typical 6-12 weeks latency,
- an often striking absence of significant pulmonary or systemic TB-lesions,
- an often culturally negative or paucibacillary effusion [14],

- the sometimes abundant isolation of specifically purified protein derivative (PPD)- protein sensitized T-lymphocytes from pleural fluid [15] and
- more recently the inducible pleurisy in previously PPD-sensitized animals when exposed to intra-pleural mycobacterial protein.

Also the vigorous expression of inflammatory mediators interleukins (IL) like interferon (IFN) γ, IL-1 and IL-8 observed in this model (or conversely their suppression by antilymphocyte serum) support this view [16, 17].

On the other hand there is also strong evidence, that infectious invasion of the pleural space actually occurs at a substantial, albeit variable degree. At thoracoscopy, even with negative fluids studies, extensive inflammatory granuloma formation and fibrin deposits with unexpected abundant mycobacteria recovery are a common finding (see also section on invasive endoscopic-bioptic studies) [18]. The increasingly emerging evidence of a preferred association of TB-pleurisy with reactivated TB in Western populations clearly points to infectious as well as immunological mechanisms being interrelated and operative in a complex manner. Direct infectious invasion however clearly prevails in chronic tuberculous involvement of the pleura as in specific empyema.

According to present views and based on experimental evidence the sequence of immunological processes involved in TB-pleuritis appears to follow a three stage pattern of cellular reactions and granuloma formation as a topic variant of general interaction mechanisms between MTB and the human immune system. A schematic representation is given in figure 1 [19, 20].

Any trigger-mechanism that allows access of mycobacterial protein to the pleura will set off a rapid mesothelial cell initiated and IL-8 mediated polymorphonuclear neutrophil (PMN) influx within a few hours [21]. In addition macrophages and blood-borne monocytes determine this IL-1, IL-6 and tumor necrosis factor (TNF)-α-orchestrated *early stage* reaction.

Within roughly 3 days, in the following *intermediate stage* lymphocyte subpopulations, mainly of CD4+ helper cells but also a substantial CD8+ cytotoxic (natural killer cells) fraction dominate the scene resulting in a CD4+/CD8+-ratio of ~ 4.3 [22]. A minor contribution includes so-called T-cell receptor double negative (DN) αβ-T-cells and γδ-T-cells which appear to have regulatory functions. More recently in tuberculous pleural fluid another unique CD4+CD25+ T-cell-class could be demonstrated being specifically involved in the down-regulation of autoreactive IFN-γ-producing T-cells, thus preventing inflammatory overshoot [23]. IFN-γ a strong promoter of macrophage activation and granuloma formation (together with TNF-α) is the predominant interleukin in this stage. IFN-γ-producing cells have been phenotypically indentified as CDW29+ subpopulation and make up a substantial portion of the granuloma core structure [24].

The *late phase* is characterised by an equilibrated and sustained CD4+/CD8+ cell-based response with continued IFN-γ release and prolonged granuloma formation. Several modulating interleukins are involved in this process such as T-helper-cells (CD4+)-supporting IL-12 and counter-regulatory antiinflammarory cytokines like IL-10 and transforming growth factor (TGF-β).

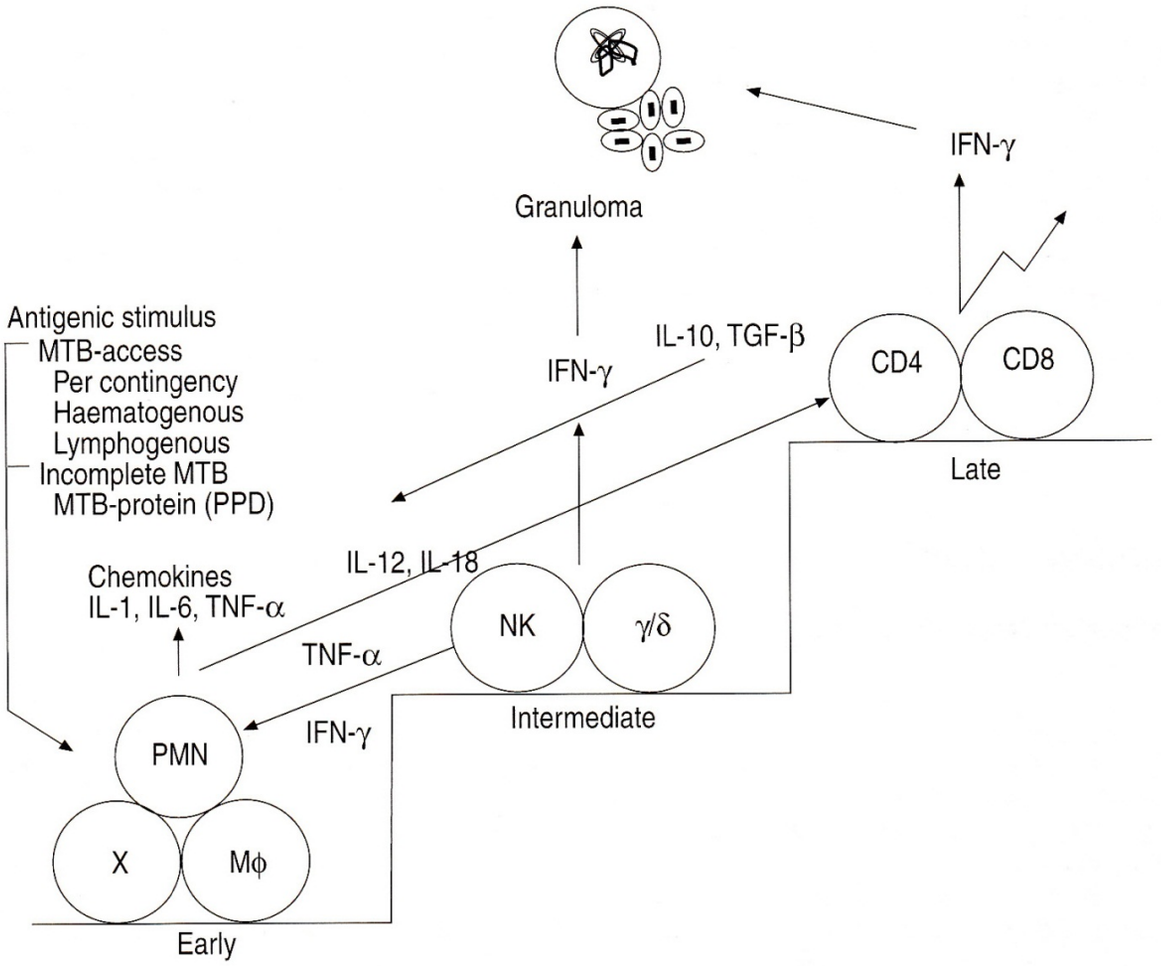


Figure 1. Mechanisms and immunogenesis of tuberculous pleurisy: the three stages of protective immune response. IFN: interferon; TNF: tumor necrosis factor; IL: interleukin; PMN: polymorphonuclear granulocyte; X: undefined cell; MΦ: macrophage, MTB: mycobacterium tuberculosis; PPD purified protein derivative

Results of HIV and AIDS research also emphasize the importance of T-cell response. Several working groups have shown, that the prevalence of tuberculous pleurisy in HIV-infected patients with TB is strikingly correlated with their CD4+ blood lymphocyte count. In one series pleurisy prevalence in individuals with a count of > 200 cells/ml was 27 % as compared to 10 % in those with a count of < 200 cells/ml [25]. The data support the view, that the clinical expression of exudative pleural effusion requires a largely intact cellular immune system and features pleurisy as a high activity response in a still immunocompetent individual. In epidemiologic terms one would conclude that pleural effusion should be more frequent in the still immunocompetent host than in patients with AIDS. In reality however in most HIV-high-prevalence countries like South Africa, Uganda and Zimbabwe the percentage of thoracic TB-patients with pleural effusion is reportedly higher in HIV+ patients [26]. As an explanation the situation is probably blurred by a variable and poorly defined immune status in HIV+ individuals.

3.2. Other factors

The mechanisms of fluid accumulation and of abundant protein leakage to the pleura with often extensive fibrin deposits in tuberculous pleurisy have so far not been fully elucidated. In actual fact pleuritis exudativa tuberculosa generally presents with the highest protein levels commonly seen in exudative conditions. The intensity of inflammation and a proportionately increased vascular permeability would provide a satisfying explanation [25, 27] although at least in animal models, no such significantly altered vascular permeability could be demonstrated [12]. Current opinion holds that grossly impeded lymphatic protein clearance from the pleura due to altered parietal lymphatic channels is probably of tantamount importance.

Again the *entry mechanism* of mycobacteria to the pleura has remained unclear. It is usually assumed that the release of infectious material from a ruptured subpleural TB-lesion is the most common mechanism. While this is likely to occur in more or less extensive pulmonary TB, it would not explain the frequent association of tuberculous pleuritis with an – at least radiographically – unaffected lung. There are also no convincing data yet to quantify the contribution of a purported hematogenous or lymphogenous contribution. One might reasonably speculate that different patterns of pleural tuberculous involvement are operative which might correspond to the different clinical settings of primary, post-primary and reactivated TB.

Caseous tuberculous pleuritis or specific empyema is nowadays a rare condition which is believed to be the result of longstanding or chronic infection of the pleura, when either caseous material gains access to the pleura or chronic pleuritis develops on the background of impaired local defence such as pre-existing fibrous damage of the pleura or as a sequel and complication of artificial pneumothorax, oleothorax or other TB-specific surgery dating back to the pre-chemotherapy era. Correspondingly there is usually an extremely long history often with a remarkable paucity or even absence of symptoms. Penetration to deeper chest wall structures (specific abscess) and ultimately transcutaneous discharge (empyema necessitans) or creation of a specific bronchopleural fistula, as not infrequently seen in the pre-chemotherapeutic era, may complicate this condition [27]. Putrid discharge from a thoracic mass or putrid expectoration with or without haemoptysis may ultimately advert to the condition.

4. Clinical manifestations and natural course

Tuberculous pleurisy may occur as an acute, subacute or rather chronic disease. At times the course is also surprisingly oligosymtomatic. Therefore duration of symptoms or major illness prior to hospital admission and diagnosis varies considerably from < 1 week (31 %) to < 1months (62 %) or even longer (7 %) [28]. These data refer to the pre-HIV era and would not apply for HIV-seropositive patients and elderly populations, which both tend to have a particularly long symptomatic or else oligosymtomatic period. An infectious, i. e. febrile illness is nevertheless by far the most common clinical presentation. As a general rule, an acute febrile illness is the more likely to occur the younger and the more immunocompetent a given patient is. In developing, high-prevalence and high primary-TB-affected countries the age peak of incidence is in the mid

thirties, whereas in industrialized countries with a major contribution of reactivated TB it has shifted to about 50 yrs [29]. But still the age-related incidence peak of tuberculous pleuritis is distinctly lower than of parenchymal pulmonary TB which used to peak around 55 yrs [30]. Implicitly by the same statement in Western populations TB-pleurisy was historically more symptomatic than is currently the case. In a representative series from the 1960-1970s ~ 60 % of patients developed an acute illness mimicking bacterial (pleuro)-pneumonia with cough (70 %), chest pain (75 %) and low- to high-grade fever (86 %) as the most frequent symptoms [31, 32]. Other symptoms include those commonly occurring in various TB disease states such as weight loss, malaise and night sweat. Severe or even live threatening disease, defined as persistent high-grade fever > 38,3°C over > 2 weeks or respiratory distress has been in reported in a more recent series in only 7 % [31], whereas an oligosymptomatic or a febrile course is described in 14-33 % [32]. Tuberculous pleurisy usually involves one hemithorax only (90-95 %) and is of limited size (roughly up to one-half of the hemithorax volume). In a major series (n=254) effusions occupying more than 2/3 of a hemithorax were noted in only 18 % [33]. Rarely effusion will occupy the entire hemithorax and will almost never reveal compressive or displacing features [31]. Basically there are no specific clinical clues to tuberculous etiology in pleurisy unless some TB-contact is revealed or suspected. An HIV-related background may be suspected in a compatible clinical and history setting or when there is a long preclinical period, unusual additional symptoms like diarrhea and more hepato(spleno)-megaly or lymphadenopathy as might be attributed to the tuberculous condition. Untreated, lone pleuritis exudativa tuberculosa in the short term seems to be a self-limited inflammatory process in most instances, terminating in complete or incomplete resolution within weeks or month. Frequently observed otherwise unexplained diaphragmatic adhesions may be a late sequel of clinical silent or oligosymtomatic TB pleurisy. Importantly however progression or reactivation to active pleuropulmonary or extrapulmonary TB occurs in an important fraction. In one follow-up study the recurrence rate within 1 year was 5 %, where TB did not relapse earlier than 8 month after the onset of pleurisy. Within a 4-5 yr period however the rate was dramatically higher and in initially culture positive and culture negative subjects with 65 % and 60 % respectively roughly alike [27]. One major outcome determinant clearly is the presence and the extent of pulmonary involvement. At a similar therapeutic intensity in a very recent major clinical study from Taiwan, 51 (24,9 %) out of 205 hospitalised patients having been identified to have isolated (lone) pleuritis had a significantly better outcome, shorter hospital stay and less comorbidity than the patients with pleuropulmonary disease [34].

5. Diagnosis

5.1. Clinical findings

5.1.1. Signs at physical examination

Physical examination clearly will provide only non-specific signs of pleural effusion in general including dullness to percussion and the occasional demonstration of a pleural rub at auscultation ("snow-ball-crunching sign") in particular in the presence of chest pain. Signs of a trapped or loculated rather than free flowing fluid collection may suggest a tuberculous

aetiology, but this observation holds also true for "plain" parapneumonic pleurisy. Usual signs of systemic infection, as mentioned above, that should be looked for, may alert to the possibility of a HIV-related background.

5.1.2. Imaging studies

Imaging techniques are engaged in the evaluation of tuberculous pleurisy following general diagnostic pathway recommendations for effusion. *Conventional chest radiography (CRX)* requires fluid amounts of at least 150 ml to become clearly detectable as blunting of the costodiaphragmatic angle in standard projections. Profuse effusion with opacification of an entire hemithorax would rather favour differential diagnoses like malignancy in the elderly and afebrile patient [35]. Free flowing effusion may be easily identified, but one should look specifically for signs of loculation, pleural thickening or adhesions and in profuse effusion for compressive signs interfering with the respiratory performance. Apart from pleural changes pulmonary infiltrates, nodules, lymphnodes and other suggestive signs of TB like encapsulated or cavitary lesions must be carefully looked for using routine *CT-imaging*. CT-based prevalence of lung perenchymal tuberculous lesions in mixed populations appears to be significantly higher than previously assessed based on conventional radiography. In one recent series from Korea comprising 106 patients with an age distribution from 16-89 yrs (mean 53) with 86% a remarkable high rate of parenchymal changes was found, presumed to represent active tuberculosis in 59 % [36]. Most of these lesions revealed features of reactivated rather than primary tuberculosis. *Sonography (Ultrasound, US)* using innovative technical achievements like high frequency (5-7.5 MHz) – US and convex or sector scanners allow extended exploration of the chest wall structures, the diaphragm and the anterior mediastinum up to a penetration depth of ~ 25 cm. Specific advantages of US are a more precise fluid volumetry than by CRX, precise localisation of septae, membranes and chambers as well as pleural thickening along with its particular versatility for bedside diagnosis. On demand guidance for interventions such as thoracentesis is a particular asset of US.. Examples are shown in figure 2, 3. *Magnetic-resonance imaging (MRI)* is a highly refined, not generally available technique, which will rarely be required but does have differential diagnostic merits in the analysis of critical borderline relationships i. e. distinguishing between inflammatory-infiltrative and malignant-destructive pleural processes via different T-weighted sequences [37]. Very recently a role of PET-CT has also been described. PET-imaging may indeed provide differently extensive focal and impressing laminar changes which however remain indistinguishable from malignant lesions [38].

5.2. Immunologic tests

5.2.1. Tuberculin skin reaction

The tuberculin skin reaction is traditionally considered an indispensable tool in the diagnosis of tuberculosis in general and likewise in tuberculous pleurisy although it is less reliable than in pulmonary TB. The rate of false negative reactions to PPD has been given as high 30 % of cases but even figures up to < 41 % have been reported [31, 32, 33], the variability possibly reflecting non-standardised test doses. Still however there remains an amazing false negative rate. There is no absolutely satisfying hypothesis to explain this paradoxon, let alone unequiv-

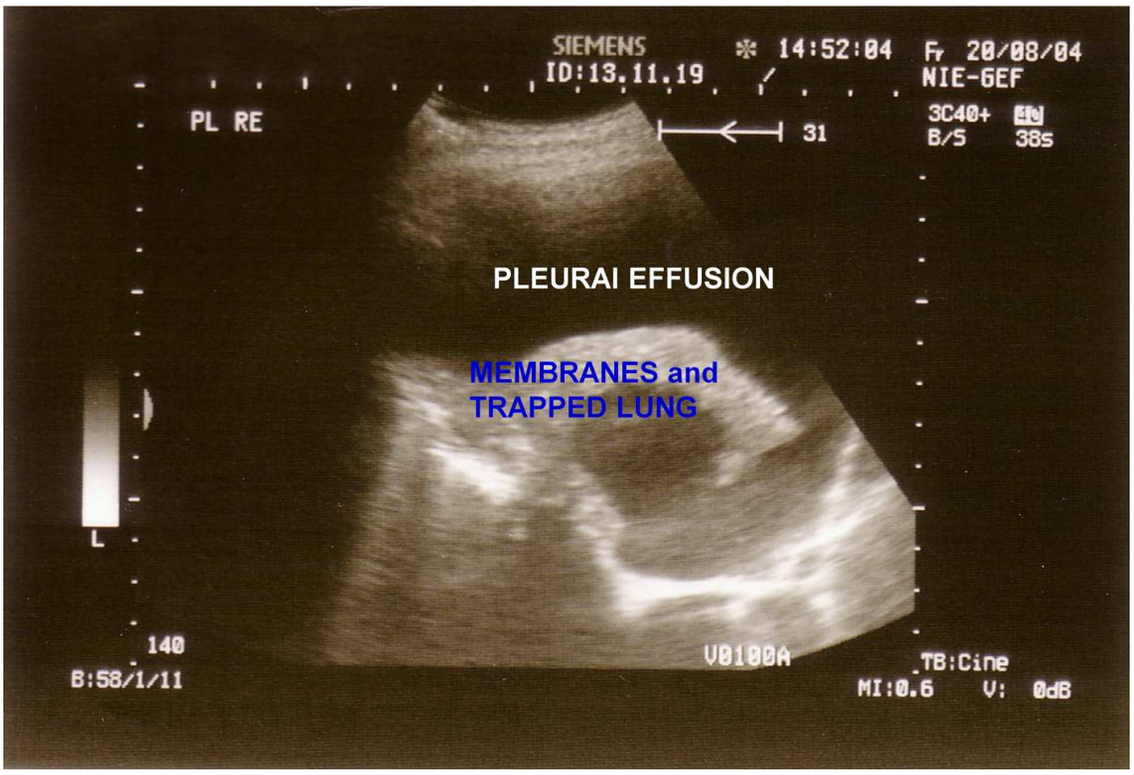


Figure 2. Ultrasound detection of inflammatory visceral membranes and consecutively trapped lung in pleuritis exudativa tuberculosa

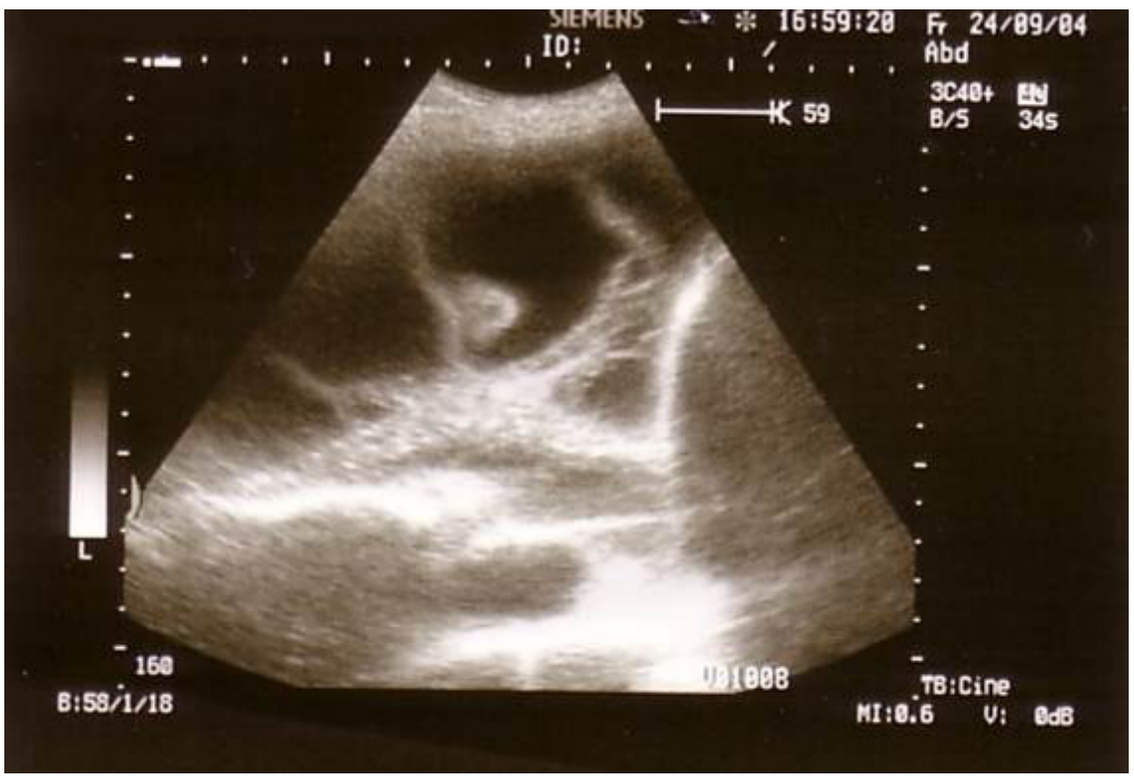


Figure 3. Ultrasound detection of multiple chambers in pleuritis exudativa tuberculosa

ocal experimental evidence. It appears a valid speculation to consider a local pooling of sensitised T-lymphocytes at the site of infection responsible. Animal experiments and clinical investigations have shown sequestration of PPD-sensitized lymphocytes to the pleural compartment actually to occur in the early phase of infection leading to their systemic depletion [39]. As a presumptive additional mechanism the presence of adhering suppressor cells to blood lymphocytes has been demonstrated in PPD-anergic patients [39]. While the explanatory evidence may remain scanty, it should be emphasised that in clinical practice the phenomenon appears to be transitory and restricted to the early phase of tuberculous infection. It might thus be associated with the pre-allergic phase of tuberculous infection, since conversion of skin reactivity has been subsequently observed within a 6-8 weeks delay [27]. As a reverse conclusion in the framework of discussed hypotheses the observation of a delayed PPD-conversion might be interpreted as a clue to primary infection to have occurred. Persisting anergy would then point to other immune-modulating factors like advanced age, certain drug interference or immune-compromising comorbidity.

5.2.2. Interferon-γ-release assays

In Europe commercially available Interferon-γ-release assays (IGRA) are the QuantiFERON-TB-Gold-Test and the T-Spot-TB-Test. Both use the MTB-RD1-region antigen sequences CFP10 and ESAT 6 and measure the specific lymphocyte-induced quantitative IFN-γ-response or the sensitized IFN-γ-producing lymphocyte response, respectively. There has been elaborated a body of clinical data in practical use highlighting both the assets and pitfalls of the investigation. In summary and in general there is distinct superiority to the PPD-skin-test with an overall sensitivity of ~ 85 % and a high specificity well > 90 % [40]. The concordance of the PPD-test and IFN-γ-release assays is in the order of 60-85 % [41]. However in the identification of active clinical tuberculosis blood-based IFN-γ-release assays also have revealed a considerable rate of false negative findings. In several studies including pulmonary a well as pleural tuberculosis, sensitivity was limited to 60-64 % [42, 43, 44]. There have also been a number of inconsistent and equivocal reports where the results obviously vary with different TB-prevalence settings (i. e. pretest probability). In a number of studies the variability of sensitivity ranges between 96 % in low prevalence settings down to 58 % in studies featuring high prevalence areas, also specificity setbacks are reported [45]. Blood-based IGRA´s therefore seem to share the limitations of PPD-testing. Since they cannot distinguish latent from active TB, in conclusion, the diagnostic value for identification of tuberculous pleurisy in high prevalence settings is very low and has even only limited value in industrialized countries.

5.3. Pleural fluid analysis

5.3.1. Biochemical parameters

When there is enough effusion to allow safe puncture and TB is suspected, *thoracentesis* is a mandatory diagnostic step. The effusion will be invariably and markedly exudative with a (unless in tuberculous empyema) clear, straw- to amber-coloured appearance and a mean protein content above 5.0 g/dl, in one series (n=83) it was 5.2 g/dl (range 3.5 – 7.0) [32]. Glucose and pH-values have traditionally believed to be characteristically low in TB. It appears however, that on the basis of more recent data, as also confirmed in the author´s own experi-

ence these values are not substantially different from exudates due to other aetiologies. SAHN [46] found pH-values < 7.29 and glucose values < 30 mg/dl in only 20% of patients and this has been confirmed by others [47]. Interestingly however, if low values actually occur, they appear to correlate with the pleural bacillary load and are to some extent predictive of cultural results. In one thoracoscopic study positive pleural fluid culture yield was 59 % when the glucose level was < 50 mg/dl but only 25 % when the glucose values were > 50 mg/dl ($p<0.005$) [18]. Lactic dehydrogenase (LDH) is a non-specific marker of pleural inflammation, which may be excessively elevated in tuberculous pleurisy, although with a mean value of 423 IU/ml (range 43 – 1.575) as reported in a representative series again does not discriminate TB from parapneumonic and not even from malignant effusion [32]. Adenosine deaminase (ADA) has been a promising and much hailed semispecific biochemical parameter. ADA is an inflammatory enzyme expressed predominantly by sensitized and activated T-lymphocytes. Isoenzymes (ADA2) in addition reflect to some extent monocyte/macrophage activation. Thus increased ADA-activity in general indicates various T cell/macrophage interactive inflammatory processes like granulomatous disease but also empyema and collagen vascular disease. It appears however particularly sensitive to TB. In a key study (n=129) in patients < 35 yrs a receiver operating characteristics (ROC) –derived cut-off level of 47 U/ml allowed distinction of tuberculous effusion from empyema, rheumatic and neoplastic disease with a 100 % sensitivity and 87.5 specificity. When empyema was eliminated, specificity and the positive predictive value even attained 100 % [48]. There are important limitations to the interpretation of these results and their clinical relevance:

- the data reflect the afore mentioned age group only, in more heterogenous groups both sensitivity and specificity have to be (down)-corrected to 95 % and 90 % respectively [22, 49, 50].
- the results strictly apply to high TB prevalence settings only and do not allow for different pre-test prohabilities [3].
- also immune suppression like in AIDS endemic areas may interfere with inflammatory ADA-release and invalidate diagnostic conclusions [3, 51].

Nevertheless, based on the most accepted cut-off level of 40 IU/l and provided its critical use in areas of at least intermediate TB-prevalence ADA determination must be regarded as a true diagnostic enrichment. An era of successful ADA-use has been recently summarized and confirmed by a large size metaanalysis (63 studies, 5297 tuberculous and non-tuberculous effusions) resulting in a sensitivity and specificity of 92 % and 90 % respectively [52].

5.3.2. Cytological analysis

Based on the immunological processes involved, a marked lymphocytosis is the predicted and characteristic feature of TB-pleurisy along with significantly increased total white cell counts as reflected in one representative study with a mean count of 2.309/mm^3 (range 30 – 24.009 mm^3) [32]. Usually 90 – 95 % of pleural fluid cells are T-lymphocytes, the remainder being B-lymphocytes and (mostly) activated mesothelial cells. Only exceptionally (in ~ 5 %) lymphocyte counts < 50 % may occur [27]. Thus when an 80 % lymphocyte reference line is chosen,

pleuritis tuberculosa exudativa is by far the most frequent cause of pleural lymphocytosis [46]. Rarely, in particular in the early phase of inflammation fluid cytology may reveal neutrophil leucocyte (PMN) predominance. Expansion of the eosinophil compartment would be an extremely unusual finding. In the presence of significant numbers of eosinophils (> 5 %) differential diagnoses should be considered.

5.3.3. Microbiological studies

The microbiological yield from diagnostic (low volume) thoracentesis as far the smear is concerned is very low unless the whole effusion or large amounts are being centrifuged or the patient has a tuberculous empyema [14, 29]. In HIV positive individuals, particularly in those with CD4 cell counts < 200 x 10^6/l significantly higher yields are being reported amounting in one study to 37 % vs. 0 % in non HIV-patients [53]. In a comprehensive study on microbiologic smear findings in pleural fluid specimens in non-selected HIV negative out-patients, the positive acid fast smear yield (n=232) again was actually zero [54]. Cultures should be obtained both from the sputum and pleural fluid. The positive cultural yield from pleural fluid has been given in collective reviews with 10 – 35 %, being ~ 25 % in the mean [14, 30]. In one of the largest series (n=100] the sensitivity of pleural fluid culture was 28 % [18, 55]. The use of radiometric or non-radiometric liquid culture systems (BACTEC, MB/BacT, MGIT) will markedly accelerate results and possibly lead to an enhanced yield (~ 50 %), when bedside instead of laboratory inoculation is used [56]. The yield of sputum cultures in tuberculous effusion is expectedly largely dependent on the extent and nature of pulmonary involvement and may mount up to ~ 50 %. In the non-expectorating patient the use of induced sputum is advised [57]. The positive yield is also believed to be higher in HIV-infected patients [53, 57]. In the complete absence of pulmonary lesions according to most sources the sensitivity will be no more than 4-7 % [30]. Only exceptionally a surprisingly high figure of 31 % for induced sputum has been reported [57].

5.3.4. Immunological and molecular studies

Immunological studies of pleural fluid in TB-pleurisy focus on the measurement and analysis of chemokins and interleukins that are characteristically associated with the tuberculous immune response. TNFα and IFNγ revealed at a cut-off 140 pg/ml a sensitivity of 94 % and a specificity of 85 % [58,60]. Similarly as for ADA the major confounders were bacterial empyema and parapneumonic effusion respectively. Interestingly TNFα did not attain enough discriminatory power to separate TB from various inflammatory conditions and is no more considered a valid option in the diagnosis of TB. More recent meta analysis-derived collective data from 22 studies resulted in an overall sensitivity of 89 % at a 97 % specificity [61]. Thus at present IFNγ-determination in pleural fluid – contrasting to systemic IGRA-application – would appear a useful diagnostic test with a sensitivity and discriminatory power comparable to that of ADA-determination if one was to accept the significantly higher costs and disregard more powerful diagnostic options as provided by subsequently discussed invasive biopsy techniques.

Molecular mycobacterial identification methods employing a variety of *nucleic acid amplification techniques (NAAT)* have been applied in TB pleurisy with considerable enthusiasm and expectations ever since their first application in TB in 1989 [62]. The techniques that have been used include target amplification (polymerase chain reaction, PCR), strand displacement amplification (SDA), transcription mediated amplification (TMA), probe/primer amplification (ligand chain reaction, LCR) and Q-Beta replicase amplification mostly with the IS 6110, 16S recombinant ribonucleic acid (rRNA) and 65 XD target sequence [63-66]. So far published data, both biopsy- and pleural fluid-based have shown considerable variance of diagnostic yield, which ranged from 20-81 % as to sensitivity with an expectedly high specificity in the order of 98-100 % (table 1). When analyzing the sources of this high variance, apart from technical factors like contamination-related "carry over" or amplification inhibitors, the most important determinant appeared to be the number of bacilli in the pleura fluid or specimen sample [31]. Although theoretically requiring the presence of merely one microorganism to trigger amplification, similar to sputum anlysis, failed to detect pleural MTB in particular when the pleurisy was paucibacillar, correlating with cultural negativity. In addition to fluid samples numerous studies have evaluated the value of various nucleic acid extraction and amplifications techniques in formalin-fixed and paraffin-embedded pleural tissue specimen [67-71]. With the use of commercial kits of both DNA amplicons (ligand chain MTB assay, LCxMTB or AMPLICOR MTB) or RNA amplicons (amplified MTB direct test, AMTDT) according to the latest currently available sources, the sensitivity of each single technique did not exceed 63.2 % albeit at an expected 100 % specificity [71]. The so far largest meta-analysis including 40 studies and featuring commercial as well as in-house ("home-brew") tests, confirms a low and heterogeneous sensitivity (in the mean 62 %) and high specificity of 98 % [72]. Thus there is no convincing evidence, that generally and especially in the critical issue of paucibacillar (cultural negative) pleurisy, NAATs perform substantially better in tissue than in effusion specimens (table 1). Although in-house assays have been reported to be slightly superior [73], there remain significant sensitivity set backs both in liquid- and tissue-derived specimen. In summary NAATs may offer certain advantages like quick results within hours or added specificity. They may also improve sensitivity in combined and parallel use with conventional methods and multiple amplicors (diagnostic confirmation), but can certainly not replace or obviate the need for conventional tools in the diagnosis of TB pleurisy.

5.3.5. Invasive bioptic and endoscopic studies

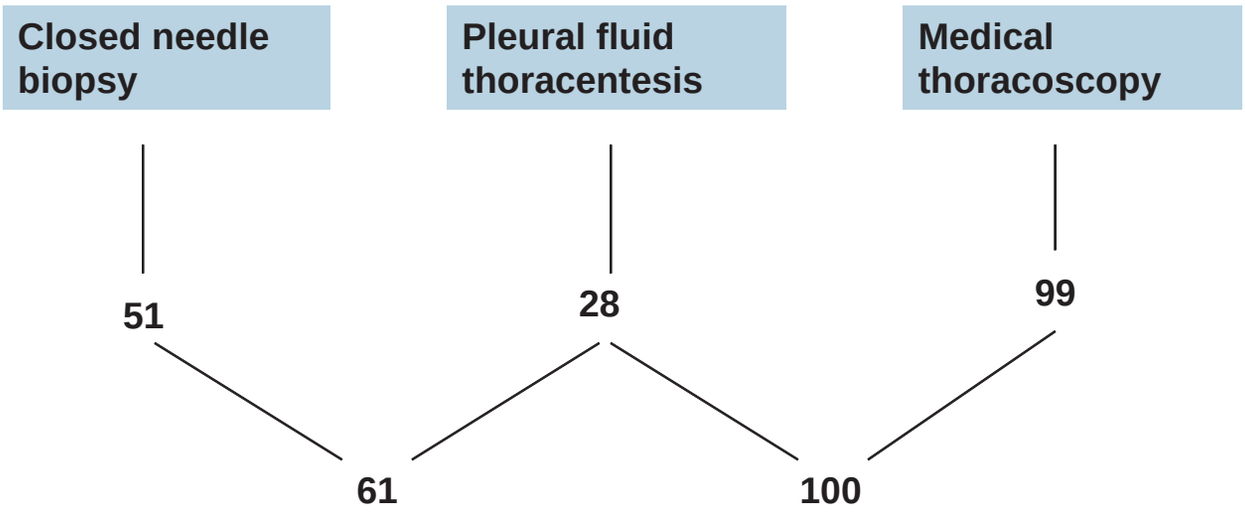
Bioptic techniques in the evaluation of tuberculous effusions incorporate closed blind or imaging guided needle biopsy and medical (video)-thoracoscopy. Only exceptionally, if ever, surgical diagnostic efforts including video-assisted surgical thoracoscopy (VATS) would appear appropriate. Invasive techniques are indicated when clinical investigation and pleural fluid analysis provide only ambiguous or conflicting results and this is particularly true if relevant differential diagnoses like malignancy need to be reliably excluded. *Needle biopsy* may be considered a first step. There are no clear preferences as to the type of needle to be used, although in the author´s opinion the Tru-Cut or Raja-system may be preferable to the older Abrams- or Ramel-needle by providing a larger specimen along with easier handling. It is recommended, that at least six biopsies are obtained, since they will not regular-

First Author	case-# TB / non-TB	Amplicor Kit	Sensitivity [%]			Specificity [%]
			overall	culture-positive	culture-negative	
effus.-based						
deWit	53/31	336 r.squ.	81	-	-	78
Lassence	14/10	IS 6110	60	100	50	100
		65 XD	20	66	8	100
Querol	21/86	IS 6110	81	100	60	98
tissue-based						
Salian	25/ 35	IS 6110	73	-	-	100
Marchetti	26/ 11	IS 6110	80-87	100	73-82	100
Gamboa	67/ 97	AMTDT	83	-	-	100
Palacios	18/168	LCxMTB	90.4	-	-	98.5
Ruiz-Manzano	57/ 17	AMTDT/ LCxMTB	80.7	- -	- -	100 100
Pai (eff + tiss)	metaan	various	63.2	-	-	100

Table 1. Role of Nucleic-Acid-Amplification-Techniques (NAAT) in the Diagnosis of Tuberculous Pleuritis

ly contain a representative parietal pleural sample [74]. With this premise and the expected yield of at least two valid samples closed needle biopsy should be diagnostic in tuberculous pleurisy in ~ 60 % of cases, when histology and tissue-, as well as fluid-culture are being combined. In a major series (n=100 %) a 61 % positive yield was composed of 51 % biopsy yield and 28 % positive fluid culture (figure 4) [18, 55]. Distinctly higher yields have also been reported in the literature, leading in a collective review to an average sensitivity of 69 % (range 28-88 %) [75]. The difference and wide range is likely to be due to technical disparities and inclusion of data originating from largely different prevalence areas. In one study from a high prevalence area (South Africa) comprising 51 patients with undiagnosed pleurisy the positive closed needle yield in tuberculous pleurisy (histology+AFB-stain+culture) was 79%, when combined with pleural fluid ADA-determination and a lymphocyte/neutrophil ratio > 0.75 sensitivity increased to 93% at a specificity of 100% [76]. Thus with the parallel use of less invasive parameters needle biopsy approaches the diagnostic potency of more invasive techniques and would appear the second best diagnostic option in areas with limited medical logistics and resources.

Medical thoracoscopy as a *"window to the pleural space"* [77] is the gold standard procedure in the evaluation of exudative pleural effusion, hence also pleural pleurisy. The current and future role of thoracoscopy needs to be redefined for its diagnostic and interventional efficacy in the light of its close historical affiliation with TB. In fact tuberculosis was already a major focus of medical thoracoscopy or *"pleuroscopy"* as referred to and initiated by JACOBAEUS back in



According to Loddenkemer et al. [55]

Figure 4. Single and cumulated yield (%) of various microbiological and bioptical investigations in tuberculous pleurisy

1910 [78]. Anticipating modern minimally invasive surgical techniques, now all included under the heading *video-assisted thoracic surgery (VATS),* his pioneering approach to thoracoscopy was basically interventional with the intention to optimize pneumolysis and to break strands for artificial pneumothorax induction in pulmonary TB *("Jacobaeus operation")*. However the ability to visualize major portions of the pleural surface, to intervene in the presence of membranes, adhesions and septae with the option of numerous dedicated biopsies also ensures optimum diagnostic results that are reflected in a yield of 94-99 % as confirmed in decades of clinical experience [18, 77-81]. At thoracoscopy tuberculous pleurisy usually appeals to the experienced investigator with characteristic and fairly diagnostic inflammatory patterns.

- One may present with abundant fibrinous membranes, septae, loculations and diffuse inflammatory thickening of the parietal and visceral pleura as the prevailing pattern. An example of this endoscopic pattern is shown in figure 5.

- A second characteristic feature is a more or less intensive seeding of the pleural surface with solid or caseous, sago-like nodules and only scanty fibrin deposits as shown in figure 6. Although usually fairly small, major nodules as also shown in figure 6 may easily be confused with malignant lesions.

- *Tuberculous empyema* as exemplified in figure 7 may be visually indistinguishable from non-specific bacterial empyema unless calcifications, irreversible lung trapping or suspect pulmonary lesions suggest a tuberculous origin.

Similarly to closed needle biopsy a sufficient number of biopsies – at least three- should be obtained to warrant optimum and representative results. This may often require mechanical debridement of membranes and septae to gain access to the inflamed pleura. When thoraco-

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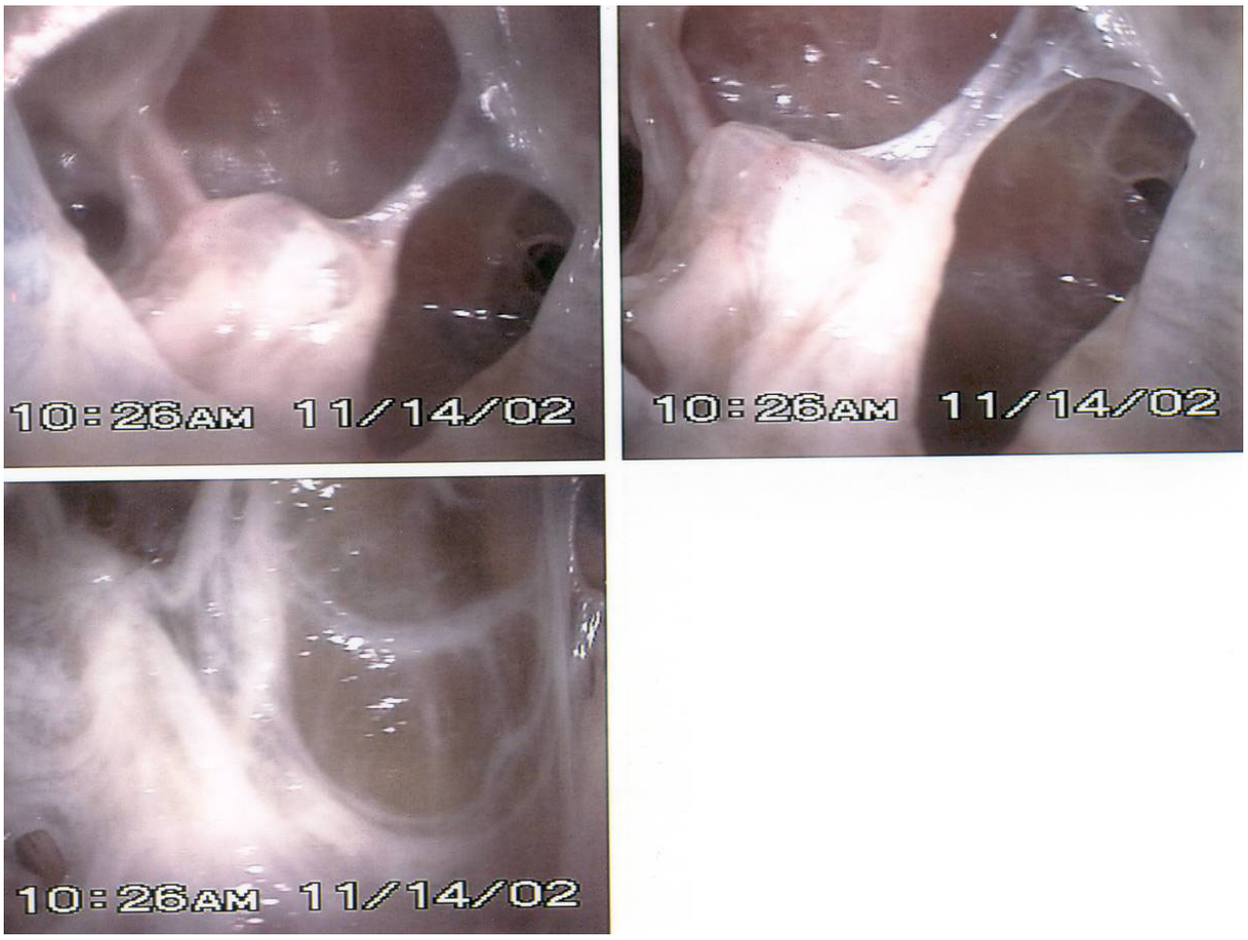


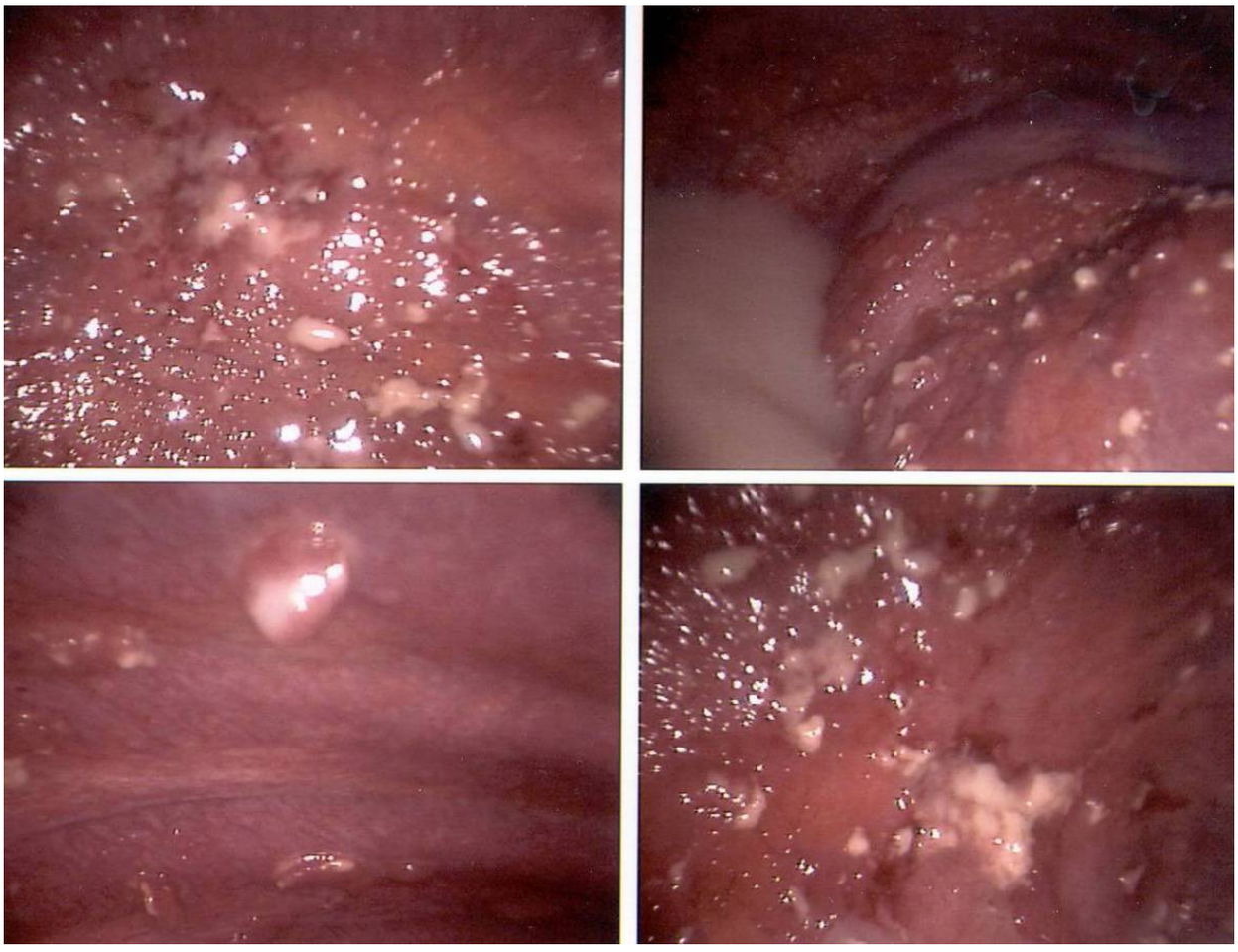
Male 48 years, pleuritis tuberculosa exsudativa

Figure 5. Typical thoracoscopic aspect of fibrin-type multi-loculated effusion including septae and chambers in tuberculous pleurisy

scopic results are combined with aforementioned techniques positive results may be augmented to virtually 100 % (fig. 2) [18].

Thoracoscopy also provides a number of additional advantages:

- With the reasonable diagnostic certainty of visual findings combined with an immediate histological yield of > 90 % it allows instant implementation of antituberculous chemotherapy
- The percentage of positive TB-cultures obtained from biopsies and fibrous membranes may be twice as high (78 %) as from needle biopsies and pleural fluid combined (39 %) [77]. This in turn provides superior opportunity for drug susceptibility testing.
- Complete removal and subsequent drainage of pleural fluid with pulmonary re-expansion provides instant relief to the patients and warrants better healing and outcome options (see section on therapy).



Male 24 years, pleuritis exsudativa tuberculosa

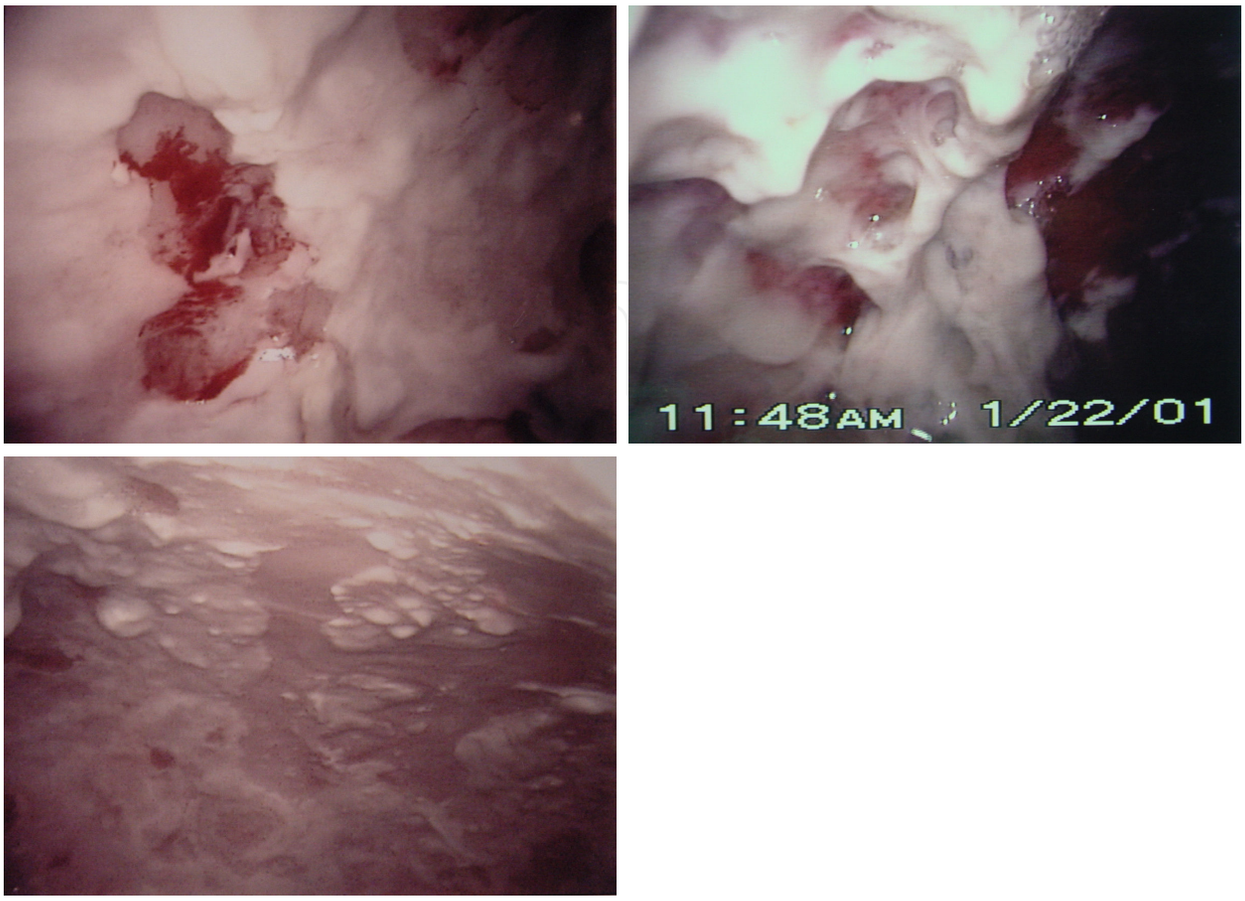
Figure 6. Typical thoracoscopic aspect of sago-type disseminated small and larger nodules both of the parietal and visceral pleura giving rise to confusion with malignancy

- In addition thoracoscopy may be easily expanded to an adjuvant therapeutic intervention by breaking adhesions and debridement of membranes as also discussed in the section on therapy.

In the overall assessment of biopsy techniques the experienced investigator will therefore bypass closed needle biopsy and prefer thoracoscopy. Closed needle biopsy however will remain the second best alternative if

- there is no logistic option for thoracoscopy or
- in the presence of clinical obstacles such as contraindications or mal-detachment of the lung due to adhesions or advanced obliteration of the pleural space.

In summary, for the diagnosis of tuberculous pleurisy it appears and remains a well-founded clinical policy to push for the recovery of biopsy specimens whenever possible and to combine these with less invasive test results to ensure optimum management of the condition.



Male patient, 48 yrs

Figure 7. Typical thoracoscopic aspect of tuberculous („specific") empyema showing putrid parietal coverings including bioptic lesion and circumscript coin-like pleural thickening

6. Therapy options

6.1. Systemic therapy

Basically systemic therapy of tuberculous pleurisy in the moderately ill patient neither differs in intensity nor duration from antituberculous chemotherapy of pulmonary and other organ tuberculosis in general. Current short term recommendations for non-complicated pulmonary and extrapulmonary organ tuberculosis call for a quadruple drug therapy in the 2-month acute phase in the combination of 5 mg/kg Isoniacid (INH), 10 mg/kg Rifampicin (RMP), 30-35 mg/kg Pyrazinamid (PZA) and 20-25 mg/kg Ethambutol (EMB) or 15 mg/kg Streptomycin (SM), where daily alternation of the SM and EMB component may be preferable [82]. In the second 4-month stabilizing phase a INH/RMP dual therapy is recommended. Until the 1990-years a triple therapy in the initial phase for Tb was considered safe enough in view of a low incidence of primary drug resistance. The quadruple therapy recommendation is therefore an amendment to a meanwhile globally changed drug susceptibility situation. Thus in an un-clarified clinical setting the extent of drug resistance expectation will modify treatment strategies. The

current policy in the case of tuberculous pleurisy therefore holds, that in lone and paucibacillar pleurisy (without lung parenchymal lesions) after immediate quadruple therapy a down-grading to a historical triple scheme is safe enough, provided full drug susceptibility is warranted. In the presence of lung parenchymal involvement the full standard scheme would however apply. The current average drug resistance probability is reflected in one major series (n=78) with a rate of 6.4 %, being probably representative for Middle Europe [55].

The addition of an oral or parenteral steroid regimen to antituberculous drug therapy has been discussed controversially. The rationale put forward for this approach focuses on

- the assumption of a shorter, attenuated clinical course in the severely ill patient,
- improved outcome by prevention of sequels in terms of pulmonary encasement and fibrothorax.

Three valid clinical studies employing a randomized, double-blind controlled design may be considered to have basically settled the issue [83, 84, 85]. These studies consistently showed, that a tapering steroid therapy for 4 and up to 12 weeks starting with 0.5, 0.75 and 1.0 mg/kg/day prednisone added to a standard antituberculous drug regimen, although mitigating and shortening the clinical course to a moderate extent in two studies, did not alter any of the outcome endpoints (clinical status, effusion resolution, pleural sequelae, lung volume and gas exchange). In conclusion from these data, steroids would generally not appear indicated in TB-pleurisy, a reasonable practice however would be a temporary use in the presence of a severe febrile and consumptive clinical course. Their long term use for the prevention of fibrotic sequels would appear obsolete.

6.2. Local therapy

Local therapy is an option, which is usually directly derived from a thoracoscopic approach to the management of the condition. First of all it needs to be emphasized that the (possibly complete) evacuation of pleural effusion is already an important topic treatment approach. While this can basically be achieved by non-endoscopic techniques like simple thoracentesis and small bore catheters as well, there is no doubt, that thoracoscopy will be disparately more effective due to the ability of visual guided optimum positioning and the use of large bore drains. In addition there is ample clinical evidence, that expert medical thoracoscopy can open intrapleural loculations and chambers, completely evacuate sequestrated effusion compartments and also to some extent produce effective debridement of membranes. Although no controlled study has so far proven the value of such efforts, from the view of the expert endoscopist it would appear a straightforward and convincing approach. Together with the early induction of antituberculous chemotherapy it might be responsible for the fact that in our institution over more than two decades of experience none of the patients needed decortication subsequently.

Another more recently discussed approach in topical therapy would be, by a rationale analogue to non-specific bacterial empyema, the use of fibrinolysis (streptokinase) which even need not necessarily be linked to an endoscopic protocol. There is so far only scanty experience [85]. However one fairly comprehensive study from Taiwan using a non-endoscopic pigtail

catheter technique and comparing a loculated streptokinase group (n=22) with a loculated normal saline irrigation group (n=22), reported significantly better outcome both in clinical terms of imaging and functional criteria [86]. Additional future evidence provided, this would seem an encouraging step towards further improvement in acute tuberculous pleurisy management.

Surgery in the era of antituberculous chemotherapy is only exceptionally required in the management of tuberculous involvement of the pleura. Remaining indications refer to rare instances of previously mentioned tuberculous empyema and in particular its complications. Specific issues in this context would be excessive membrane formation with trapped lung and significant long term pulmonary encasement due to fibrothorax. Due to the scarcity of pertinent cases and studies (at least in the western hemisphere) there are no generally accepted surgical guidelines for the management of these conditions. Surgical decisions must be created in an individual case-determined approach. A reasonable policy would appear to perform lone or combined empyemectomy/pleurectomy, also termed *early decortication* in clinically severe and functionally disabling conditions refractory to medical efforts. These indications may be amenable to video-assisted thoracic surgery (VATS)-based interventions. Formal thoracotomy would however be required if it comes to additional lung parenchymal resection or thoracoplasty in rare complicated cases e.g. with persisting pyopneumothorax with or without trapped lung due to a large, medically intractable broncho-pleural fistula.

A different issue is severe, chronically trapped lung due to fibrothorax. A reserved approach to surgical strategies is generally advised because unexpected long term remission of inflammatory peels is sometimes impressing. Although decortication has been performed as early as 6 weeks after the precipitating insult (empyema), the indication to *late decortication* is basically discussed in the context of definitely and irreversibly trapped lung (fibrothorax) i.e. when at least 6 months have elapsed. With a focus on repair of lung function and prevention of chest deformity most investigators agree that the indication requires a significant decrement of lung function (TLC<60% pred., reduction of perfusion>50%) and level of deformity in the absence of significant calcifications (*pleuritis calcarea*). Even then with extensive fibrotic fusion of both pleural sheaths not only will surgery be fraught with considerable technical problems but also the certainty and extent of functional improvement may not be predictable and warranted.

6.3. Sequels and prognosis

There are largely diverging data as to the prevalence of fibrothorax and permanent pleural thickening as the most important sequel of pleural TB. In one source based on standard radiographs in pleuritis exudative tuberculosa a percentage as high as 49 % has been given [32]. With the strict definition of fibrothorax as a pleural membrane of at least 5 mm thickness extending across major portions of the hemithorax and persisting > 8 weeks after initiation of therapy a figure of ~ 5 % is a more likely and widely accepted rate of this complication. The intensity of pleural inflammation expressed as interleukin levels and derangement of biochemical parameters is assumed to be to some extent predictive for this complication. In one study residual pleural thickening was indeed significantly correlated with the magnitude of the intitial change of inflammatory glucose-, pH- and TNF-α-levels [87].

Caseous tubercus pleurisy and specific empyema respectively is in its natural course and in prognostic terms an entirely different entity. These patients will invariably and typically develop an extensive calcified fibrothorax (pleuritis calcarea) with or without concomitant chest deformity. Also chronic non-specific lung disease (COPD) with or without bronchiectasis, late TB-exacerbations and internal or external fistulisation (specific empyema necessitans) may develop. Anecdotical occurrence of non-HODGKIN lymphomas arising from long term smouldering encasements has also been described.

Author details

Wolfgang Frank*

Address all correspondence to: wfrank@klinikamsee.de

Lungenklinik Amsee, Waren (Müritz), Germany

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