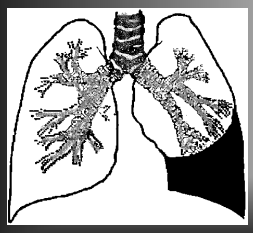
International Pleural Newsletter



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Are Interferon Gamma Release Assays Useful in Workup of Pleural TB?

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T cell interferon gamma release assays (IGRAs) have been developed as blood tests with excellent specificity for diagnosing latent TB. They are now recommended by American and European guidelines for contact screening. Extending the use of IGRAs to the diagnosis of active TB, especially TB pleuritis, has attracted considerable interests.

During active TB, sensitized T cells migrate to the site(s) of infection where they can be compartmentalized. Concentrations of T lymphocytes can be significantly higher in pleural fluid than blood in patients with TB pleuritis.

Recent studies that applied IGRAs to pleural fluid in the setting of TB pleuritis (table 1) have shown dichotomous results. In low TB prevalence settings[1,2] use of IGRAs on pleural fluid has shown good sensitivity and specificity: up to 96.4% and 97.8% respectively[2]. This differed from studies conducted in countries where TB and TB-HIV co-infection is common[3,4]. Baba et al reported a poor sensitivity when a whole blood ELISA based IGRA was applied to either blood (71%) or pleural fluid (44%) in a largely HIV-positive cohort[4].

IGRAs cannot distinguish latent and active TB. Hence, their positive predictive value in the diagnosis of pleural TB is limited. False positive results are common in patients with latent TB, due to the inevitable passage of pre-sensitized circulating T cells into the pleural fluids regardless of the cause of the effusion. This significantly limits their utility, particularly in endemic regions.

In developed countries, the place for pleural fluid surrogate markers is arguably in the exclusion of TB as a cause of undiagnosed lymphocytic pleural effusions where the pre-test probability for the infection is low. Such effusions commonly occur in frail and elderly patients for whom both avoidance of invasive diagnostic tests and inappropriate empirical anti–TB therapy, is desirable. A test with a good negative predictive value is required and non-specific markers of immune response: pleural fluid adenosine deaminase (ADA) and unstimulated interferon gamma (IFN-γ) levels have demonstrated the best diagnostic performances to date: sensitivity and specificity of 92% and 89% (ADA), and 89% and 97% (IFN-γ) respectively[5,6].

Studies conducted in settings of low TB and HIV prevalence have yielded a reasonable negative predictive value for active pleural TB using IGRAs applied to blood, and the pleural fluid test appears to produce even fewer false negative results. However, there is inadequate evidence to suggest that IGRAs offer additional contribution to ADA and IFN-γ, particularly as they are cheaper and technically simpler to perform. To fully assess the utility of IGRAs in this setting, optimization of the test for pleural fluid and validatation of the best cut-off value are necessary. This should then allow prospective, head-to-head comparisons with ADA and IFN-γ tests.

Table 1. *Recent studies comparing the accuracy of pleural fluid IGRAs for the diagnosis of TB pleuritis.* E=Whole Blood ELISA; E-S=ELISPOT.

Country	IGRA used	N= (Pleural TB:control)	Immuno-compromised hosts	Sensitivity/ Specificity
Japan (ref 2)	E	28 /47	None known	96% / 98%
Germany, Italy & the Netherlands (ref 1)	E-S	20 /21	None	95% / 76%
S Africa (ref 4)	E	28 /6	74% HIV +ve	44% / 60%
S Africa (ref 3)	E	30 /20	30% TB HIV +ve	57% / 87%

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IMAGES OF THE PLEURA

Pleural Lymphatic Drainage

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The anatomy and lymphatic draiange of the pleura is complex. The pleura extends more caudally than the accompanying lung, to the level of T12 vertebra (fig 1). The pleural lymphatics are subdivided into those draining the visceral or parietal pleura.

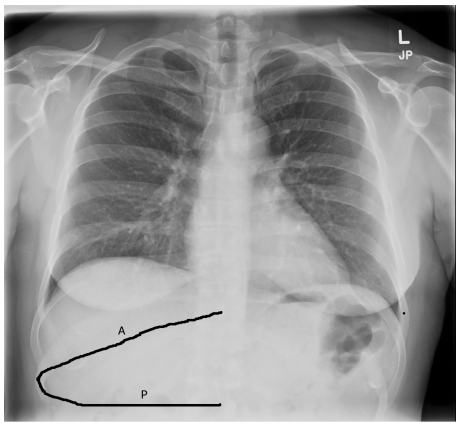


Figure 1. Chest radiograph showing pleural attchments anteriorly (A) and posteriorly (P). The pleura attaches to the xiphisternum, 8th anterior costal cartilage, 10th rib laterally and T12 vertebral body.

The visceral pleural lymphatics follow the same pattern of drainage as the lung, namely bronchopulmonary and hilar nodes, and then to mediastinal nodes (fig 2).

Fig 2. Axial CT image showing left sided pleural effusion and thickening in a patient with mesothelioma. There are enlarged right paratracheal (white asterisk) and aortopulmonary window (black asterisk) nodes, from tumor involvement of the visceral pleura.

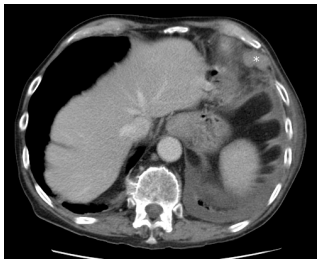
The lymphatic drainage of the parietal pleura is very different. The anterior costal pleura drains to the internal mammary nodes, while the posterior costal pleura drains to the extrapleural lymph nodes that lie adjacent to the heads of the ribs in the paraspinal fat (figs 3-4).

Fig 3. Axial CT image showing enlarged left internal mammary nodes (arrow) in a patient with a left sided mesothelioma. There is a part-calcified pleural plaque in the posterior aspect of the right hemithorax, indicating prior asbestos exposure.

Fig 4. Axial CT image showing an enlarged left sided extrapleural node in the same patient with mesothelioma.

The diaphragmatic pleural lymphatics drain to internal mammary, anterior diaphragmatic, para-aortic and posterior mediastinal nodes[1] (fig 5). There is also free communication with lymphatics on the abdominal surface of the diaphragm, and coeliac axis or gastrohepatic nodes. The diaphragm is commonly involved in malignant pleural processes, and therefore a careful inspection for nodal enlargement both above and below the diaphragm is required[2]. In practice, the parietal pleural lymphatic drainage can be thought of simplistically as a circle of nodes within the extrapleural space, and when staging patients for suspected cancer, any nodes seen in these locations should be viewed with suspicion.

Fig. 5 Axial CT image showing an enlarged left sided anterior diaphragmatic node (asterisk) in the same patient with a left sided mesothelioma



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Pain and Analgesia Following Small Bore Chest Drain Insertion

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Pain during, and following, chest drain insertion has long been acknowledged: as many as 46% of patients experienced significant pain. The use of the modified Seldinger technique to insert small bore chest drains has increased in popularity over recent years. It has been demonstrated that smaller bore chest drains cause less pain[1-3]. An audit of our practice (45 drain insertions, all guidewire-assisted) has revealed that 38.5% of patients still reported moderate or significant pain using a visual analog scale (VAS) assessed at least three times daily.

The use of pre-medication (i.v. benzodiazepine and/or opiate) is encouraged in international guidelines, although some reports fail to demonstrate benefits in reducing reported pain[4]. It would seem that there is a clear role for the education of the procedurist, with emphasis on premedication and adequate delivery of local anaesthesia, with at least one report[5] of such practice significantly reducing pain and anxiety at the time of insertion compared to a 'conventional' approach.

There is evidence that the use of premedication is low when placing smaller bore chest drains, with our series finding its use in only 11.1%, and another UK series 9.6%[4]. It is possible that doctors perceive that smaller bore chest drains are less painful, and are therefore not prescribing as much analgesia.

Several studies have demonstrated that even a correctly placed chest tube can be painful[2]; additionally, it has been shown that a smaller tube size[2] and type[3] can reduce reported pain. Guidelines recommend analgesia for chest drain insertion, but make no specific reference for its use afterwards. We have found that the use of regular simple analgesia (e.g. the use of paracetamol with codeine phosphate) significantly reduced risk of reported pain (RR 0.60, 95% CI 0.42-0.85; $p<0.01$). However, this was not routinely prescribed at the time of insertion in 60% of cases; this may be of particular importance as our data suggests that after insertion, reported pain levels

and analgesia use was highest the day after drain placement.

Our practice employs an approach based on the WHO pain ladder to achieving adequate analgesia, (http://whqlibdoc.who.int/publications/9241544821.pdf) using a sequential approach according to the individual pain intensity. Step I includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Caution is noted as conflicting evidence exists on whether NSAIDs reduce efficacy of pleurodesis[6,7]. In our series, a malignant diagnosis did not increase pain scores *per se*, however, pleurodesis by talc slurry via the chest tube significantly increased the likelihood of reported pain (RR 2.11 (95% CI 1.46-3.04); p<0.001), despite administration of intrapleural lidocaine and systemic opiate. A randomized controlled trial is underway in the UK to assess pleurodesis efficacy when NSAIDs or opiates are utilised at the time of pleurodesis.

Pain should not be regarded as an inevitable consequence of chest tube placement as in the vast majority of cases it can be overcome with due diligence and simple interventions. Routine prescription of regular simple analgesia, and the use of a VAS to assess patient comfort, should be encouraged following chest drain placement. Incorporation of such practices should be promoted on training programs for medical and nursing staff.

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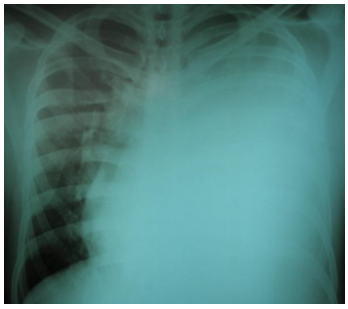
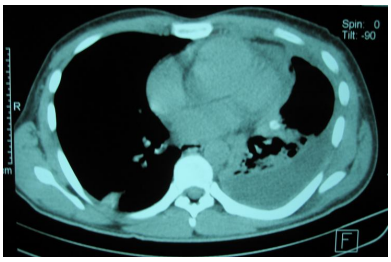
Pleural Case Reports…

Coccidioidal Pleural Effusion

A 24-year-old native of a rural desert area of north Mexico presented with a 3-week history of fever, sweating, progressive dyspnea, and chest pain. His

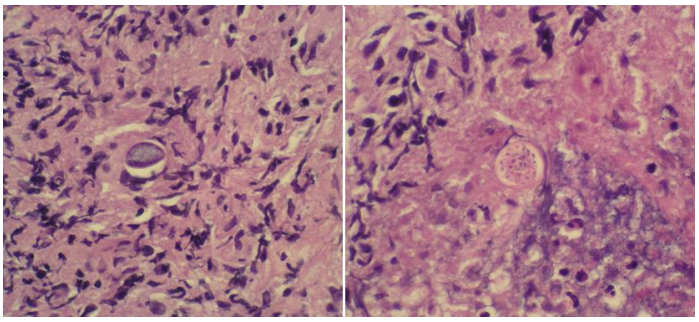


chest radiograph showed a large left pleural effusion (left). Lab tests showed a leukocyte count of 10300/mm³ without eosinophilia and HIV test was negative. Chest CT scan revealed right peripheral opacities and left pleural effusion and thickening and parenchyma infiltrates associated with an ipsilateral



calcified hilar node (left). Chest tube drainage yielded 1.8L of serous fluid: pH 7.4, glucose 70mg/dL, and LDH 336 U/L. Bacteriology cultures were negative.

Despite broad antimicrobial coverage, his constitutional symptoms persisted. Medical thoracoscopy showed parietal pleural inflammation with scattered nodules and fibrinous adhesions. A repeat analysis of pleural fluid yielded abundant polymorphs, pH 7.2, glucose 4mg/dL, and LDH of 3620 U/L. Histopathology of the pleural biopsies, stained with heamatoxylin-eosin, showed fibrous thickening and granulomatous inflammation containing *Coccidioides immitis* endospores (below, left) and spherules (right).



Antimicrobial therapy was changed to amphotericin B and the patient improved within several days and was discharged with a long course of itraconazole.

***Discussion*:** Pleural infection is a serious complication of pulmonary Coccidioidomycosis. Although intrathoracic complications are considered unusual, pleural effusions occur in 7–20% of all symptomatic patients[1]. Approximately 2% of effusions may be large in volume but the incidence can be as high as 40% in hospitalized patients[1,2]. Pleural effusion is typically ipsilateral to the lung infiltrate with predominance on left sided, but bilateral effusions have also been reported[3].

Most predominant cells in the pleural fluid usually are lymphocytes and eosinophils. Pleural fluid culture has a low yield of 20% but serologic data are typically helpful as they are nearly always positive[1]. In Mexico, where financial resources and diagnostic infrastructure are limited, pleural biopsy is the most effective method in establishing the diagnosis of Coccidioidal effusion. Guidelines recommend open decortication as the preferred management but acceptable alternatives may include antifungal drugs with chest tube drainage[4], as successfully demonstrated in this case.

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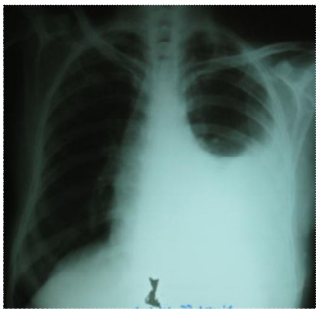
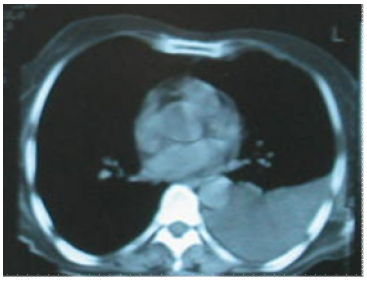
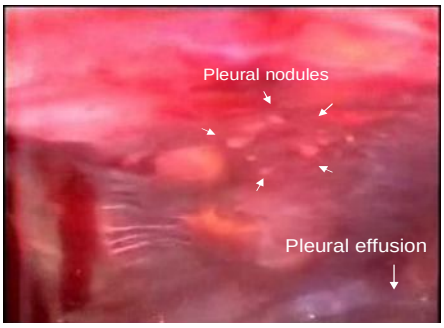
A Case of Nodular Pleural Involvement

A 78 year old female presented with chest pain and dyspnea. All routine blood and sputum examinations were normal. Chest radiograph showed left pleural effusion and CT scan revealed no additional radiologic evidence (next column).





Abdominal sonography and tomography, flexible bronchoscopy showed normal findings. Thoracentesis and closed pleural biopy failed to produce a diagnosis. VATS was performed, and a suspicious area of nodularity was noticed on the posterior thoracic wall (Figure 3). This part of parietal pleura was excised and a histopathological diagnosis was Non-Hodgkin's lymphoma (NHL) was made.



Intrathoracic Non-Hodgkin's Lymphoma usually presents with radiological findings of mediastinal lymphadenopathies, pleural effusion or pulmonary masses. Clinical findings such as dyspnea, chest pain or cough depend on dissemination of the lymphoma or its mediastinal involvement. Isolated pleural involvement of primary Non-Hodgkin's Lymphoma, as presented in this case, is rare.

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If you have any comment on the Newsletter or interesting cases of pleural disease, contact:
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