Review Article

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Ultrasound-guided pleural biopsy

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Abstract:

A pleural exudate that remains undiagnosed after a combined clinical assessment, thoracentesis, and imaging requires a pleural biopsy for a definitive diagnosis. Thoracoscopy is often the first method of choice to obtain tissue as it offers greater sensitivity and there is a perception of less risk. However, with imaging guidance, closed pleural biopsy is a safe, affordable, and effective alternative to diagnose all forms of pleural disease. Ultrasound (US) has several benefits when compared with computed tomography for image-guided biopsy, as it is widely available, can be performed bedside, and does not expose the patient to radiation. If performed in optimal conditions, a transthoracic US-guided closed pleural biopsy can yield results comparable to those of thoracoscopy and a marked reduction in the complication rate versus blind biopsy. Abrams and Tru-Cut needles are the most widely used for a closed pleural biopsy. Either may be used with real-time image guidance or with a free-hand image-assisted technique to harvest up to 6 separate tissue samples. The needle choice will depend on the morphology of the lesion observed on imaging. The Tru-Cut is generally preferred for mass lesions of the pleura or pleura that is >20 mm in thickness, and the Abrams for pleural thickening of <20 mm or radiologically normal pleura. A transthoracic US may be used to detect, rule out, and prevent complications, such as bleeding, solid organ injury, or pneumothorax. The ability to perform thoracic US is a necessary skill in current respiratory practice, and US-guided closed pleural biopsy has a critical role in diagnosis.

Keywords:

Pleural biopsy, pleural effusion, ultrasound

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Introduction

The annual global incidence of pleural disease is estimated to be 350 per 100,000 individuals.[1] Robust epidemiological data are lacking, and the relative incidence of different pleural diseases varies by geographic region. Most sources from high-income regions agree that non-malignant pleural effusion, including parapneumonic and cardiac effusion, remains the most common cause of pleural disease, followed by metastatic pleural malignancy.[1] Despite the high incidence, few tools are available for the investigation and treatment of these diseases: up to half of patients with an eventual diagnosis of malignant pleural effusion remain undiagnosed, despite repeated thoracocentesis.[2] Therefore,

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obtaining pleural tissue through some form of pleural biopsy is necessary for a definitive diagnosis of many pleural exudates. Thoracoscopy has long been considered the best tool for acquiring pleural tissue, but in many regions of the world this is not feasible. In addition, an alternative must be available for patients who are medically unsuitable for thoracoscopy.[3] Arguably, the most important development in pleural diagnostics has been the addition of image-guidance to closed pleural biopsy techniques, which have been out of favor with the respiratory medicine community.

The mid-20th century saw the arrival of the Abrams (guillotine, or "reverse bevel") needle, the Cope (hook) needle, and the Vim Silverman (puncture) needle.[4–6] The modified Vim-Silverman needle, initially used to biopsy tumors, quickly became less popular due to the small and under-representative samples retrieved.[7] Despite the similar performance of the Abrams and Cope needles, the Abrams needle [Fig. 1] became the preferred device due to quantitative (larger sample size) and qualitative (more preserved mesothelial and fibrin layers) superiority.[8] In 1989, McLeod et al.[9] published the first use of a "core-cutting" Tru-Cut needle (Travenol Laboratories, Inc., Deerfield, IL, USA) [Fig. 2] for pleural sampling in a comparative study and demonstrated that it was an equivalent and useful alternative to the Abrams needle. At that time, closed pleural biopsies were still performed without image guidance, and had a yield of some 60% for malignant effusion, and 70% to 90% for tuberculous pleural effusion.[10] These unguided procedures were also associated with a high rate of complications, such as pneumothorax (3–15%) and hemothorax, or other bleeding (~2%).[11]

In 1988, Mueller et al.[12] published the earliest series of ultrasound (US)-guided pleural biopsies, in which the authors reported a diagnostic yield of 87% across all diagnoses.[12] Despite the subsequent call for US before all procedures over 3 decades ago, the uptake of US-guided biopsies has remained slow until recently. The British Thoracic Society Guidelines on Pleural Disease, now over a decade old, recommend thoracoscopy as the investigative method of choice in patients with undiagnosed pleural exudates with a high suspicion of malignancy.[11] The resurgence of US use is, in part, due to a report published by the National Patient Safety Agency of the United Kingdom in 2009, in which the lack of US use was cited as one of the chief contributors to undue morbidity and mortality from intercostal drain insertion.[13]

Figure 1: An Abrams biopsy needle (assembled)

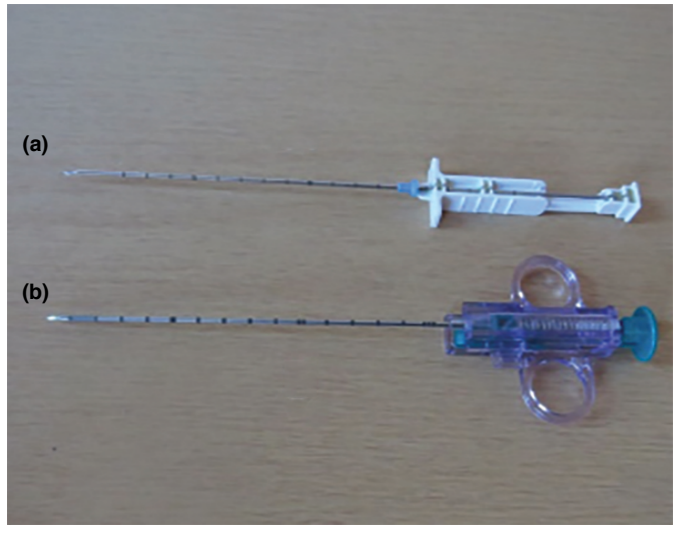

Figure 2: An original manual Tru-Cut biopsy needle (Travenol Laboratories, Inc., Deerfield, IL, USA) (a) and a more modern, spring-loaded, semiautomatic core biopsy needle (b)

For the majority of the world, routine thoracoscopy for undiagnosed pleural exudates is not feasible. It requires a sterile theater with staff, a sedation practitioner, advanced imaging equipment, an inpatient hospital admission, and technical expertise.[14] Similarly, computed tomography (CT), often used for real-time image guidance, is an expensive modality not universally available, and includes exposure to ionizing radiation. In contrast, an US-guided pleural biopsy can be performed by a single practitioner, under local anesthetic, with minimal consumables, using an US machine that

may be shared by many departments in a single facility. Moreover, it has been shown to improve both the safety and the yield of closed pleural biopsy. This review provides an overview of the literature related to US-guided closed pleural biopsy, highlighting the technique, comparing different needles and methodology, and providing practical guidance on incorporating this tool into everyday practice. The authors used their own literature repositories, updated with a comprehensive search of PubMed, Scopus, and Embase using accepted terminology. For example, (PubMed): "Ultrasonography" [MeSH Terms] OR "Ultrasound" [tiab] OR "Radiography, Interventional" [MeSH Terms]) AND ("Pleural diseases" [MeSH Terms] OR "Pleura" [MeSH Terms] OR "pleural" [tiab] OR "pleura" [tiab]) AND "Biopsy" [MeSH Terms] NOT "Case Reports" [Publication Type] NOT "Review" [Publication Type]. Articles were selected based on their relevance and quality.

Biopsy needles

The Abrams and Tru-Cut biopsy needles are the most commonly used devices for closed pleural biopsy.[15,16] The Abrams needle [Fig. 3] consists of 3 individual components: 2 concentric tubes and a stylet. The outer tube has a trocar point, sharp enough to penetrate the chest wall but not puncture the lung in the absence of pleural fluid. Behind the trocar point is a deep notch with a reverse cutting bevel. After penetration of the parietal pleura, the notch is opened, the needle is vertically angulated to 45° and then retracted until pleural tissue is gripped within the notch. The inner tube's sharp cutting cylinder is then rotationally advanced, cutting the tissue like a guillotine and retaining the sheared portion within the notch. The needle is then again advanced, straightened, and withdrawn, tearing any remaining adherent tissue. The inner stylet simply prevents air or fluid leak and can be withdrawn to confirm the position within the pleural space or to aspirate fluid for investigation. An indicator on the Abrams needle displays the orientation of the cutting edge. Care should be taken to avoid the neurovascular bundle on the inferior surface of the superior rib at a 12 o'clock position to the needle, preferably sampling sequentially at positions between 3 and 9 o'clock.[15]

There are 2 main types of cutting needles: the modified Tru-Cut needle and the modified Menghini needle. The Tru-Cut needle [Fig. 2] has an outer cutting cylinder and an inner trocar with a notch for specimen collection.

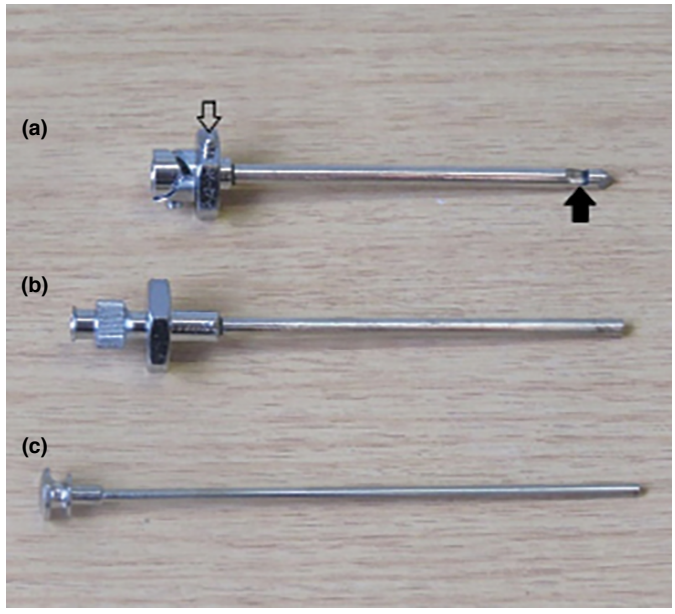

Figure 3: An Abrams needle disassembled. Note the outer tube (a) has a trocar point, sharp enough to penetrate the chest wall. Behind the trocar point is a deep notch (solid arrow) with a reverse cutting bevel, which corresponds in direction to the proximal indicator (arrow). The inner tube (b) acts as a sharp cutting cylinder. The inner stylet (c) simply prevents air or fluid leak and can be withdrawn to confirm adequate positioning

Most often, automated spring-loaded devices are used. After priming the system, the cutting needle is advanced through a small incision in the chest wall toward the pleural target. After the needle has penetrated the abnormal pleural layer (which can be felt by the operator as a distinct "give"), the needle is marginally withdrawn so the trocar abuts the pleural target. The device is then angulated horizontally toward the skin, aiming the trocar away from the lung and along the inner thoracic wall. On triggering the spring-loaded system, the inner trocar shoots forward, followed by the outer cutting cylinder, shearing off and trapping the specimen within the notch. The device hand should be braced against the chest wall to prevent ejection of the needle from the pleural space as a result of the spring-loaded action. The Menghini-type needle is only differentiated by the absence of a notched trocar; this model captures whole cores of tissue in the hollow inner cylinder.[17]

Very few studies have directly compared the diagnostic accuracy of the Abrams needle and cutting needle biopsies, and interpretation is often complicated by the use of different imaging modalities for guidance. Our group found that the Abrams needle was superior to the Tru-Cut needle for diagnosis of pleural tuberculosis, with

sensitivities of 81.8% and 65.2%, respectively. However, the yield of pleural tissue with a Tru-Cut biopsy was lower than expected in this study (78.7%).[18] Jayaram et al.[19] reported that for non-granulomatous pleural disease, there was no statistically significant difference between the 2 needle types, despite almost double the median tissue volume in the Abrams group (14 mm^3 versus 8 mm^3). In all-cause pleural disease, Sivakumar et al.[20] found that the sensitivity of a US-guided Abrams needle was non-inferior to a CT-guided cutting needle (71.43% versus 75%), while Metintas et al.[21] reported that a CT-guided Abrams needle biopsy was superior to a US-guided cutting needle biopsy (82.4% versus 66.7%).

In 2016, Wang et al.[22] reported on 172 patients with pleural disease who underwent both ultrasound-guided cutting needle biopsy and ultrasound-assisted Abrams needle biopsy during the same sitting at different sites on the hemithorax. The difference in sensitivity achieved with each needle (51.2% and 63.4%, respectively) is likely explained by the different biopsy sites. Importantly, the routine use of both needles in a single patient and sitting is not recommended, despite the findings of their study.

Ultrasound guidance

Much of the literature related to image-guided closed pleural biopsy recommends CT as the imaging modality of choice. It is still unclear whether CT or US is superior. One meta-analysis found that the diagnostic yield of US-guided and CT-guided pleural biopsy was 84% and 93%, respectively, a difference which was considered non-significant.[15] Nonetheless, CT is not always available, and is usually the purview of radiologists, whereas US is safer (being radiation-free), and allows the user to perform procedures entirely in real-time.[23]

Transthoracic US, at its most basic, requires a 2-dimensional (2D) US machine and a curvilinear probe in the 2-5 MHz range [Fig. 4a]. This allows for a wide field of scanning to identify abnormal pleural layers, pleural-based masses, and the location and size of pleural effusions. A linear probe in the 5–10 MHz range is a useful addition [Fig. 4b]. It sacrifices depth for a higher resolution image closer to the probe, allowing for better investigation of target areas of abnormal pleura.

Two principal US-based pleural biopsy techniques have been described. Direct US-guided pleural biopsy refers to

Figure 4: (a) A standard ultrasound unit with a low frequency abdominal probe, used for low resolution examination of deep structures, such as in a large pleural effusion. This specific unit is a FujiFilm SonoSite SII with a C60 curvilinear probe (2-5 MHz) (FujiFilm Corp., Tokyo, Japan). (b) A high-frequency linear probe, used for high resolution examination of the lung-pleura interface, ideal for ruling out pneumothorax and identifying intercostal vessels in the color Doppler mode. This specific transducer is a FujiFilm HFL38 linear probe (6-13 MHz) (FujiFilm Corp., Tokyo, Japan)

real-time visualization of a cutting needle into the pleural tissue. This is usually performed in-plane with the US probe held horizontally and the cutting needle introduced at a 45° angle, producing a long axis image on the screen [Fig. 5a]. The technique can also be performed "out-of-plane" with the needle orientated over the center of the probe, generating a short axis view [Fig. 5b]. Various guide devices are available for both techniques. Recently, a systematic review and metanalysis reported that direct US-guided closed pleural biopsy had a pooled sensitivity and specificity for undiagnosed exudates of 83% and 100%, respectively.[16] Alternatively, "ultrasound-assistance" describes a free-hand technique in which the pleural target is marked on the skin after noting the angle, depth, and location of the diaphragm and neurovascular bundle. The procedure is then performed during a breath hold without changing the patient's position.

Thoracoscopic studies have shown that pleural disease is not uniformly distributed across the pleura.[24] Therefore, the use of imaging significantly increases the yield of pleural biopsies.[25] Zhang et al.[26] showed that diagnostic yield increased when targeting a pleural thickness of >3 mm (61–85.2%) and pleural nodularity (71.4–95.2%). Certain characteristics are considered highly suggestive of malignant pleural disease. In a study of pleural thickening >10 mm, pleural nodularity and diaphragmatic thickening of >7mm had a sensitivity of 79% and specificity 100%.[27] Where no pleural abnormality is seen, biopsies should be taken as low/supradiaphragmatic as possible, once the safest interspace has been identified.

Optimizing patient safety

A US-guided closed pleural biopsy is most often performed as an outpatient or day procedure. It should be performed in a controlled environment, preferably a clean room or pleural theater, with a recovery area and adequate resuscitation equipment. The procedure should be performed or supervised by a physician with sufficient training and expertise, in a hospital with clear referral pathways to either a radiologist or emergency center with surgical services for assistance in a severe adverse event.[28] In our center, it is performed as a day procedure, with most patients discharged home after a short observation period.

Pre-procedure imaging with CT or positron emission tomography-CT (PET-CT) is not essential, but where

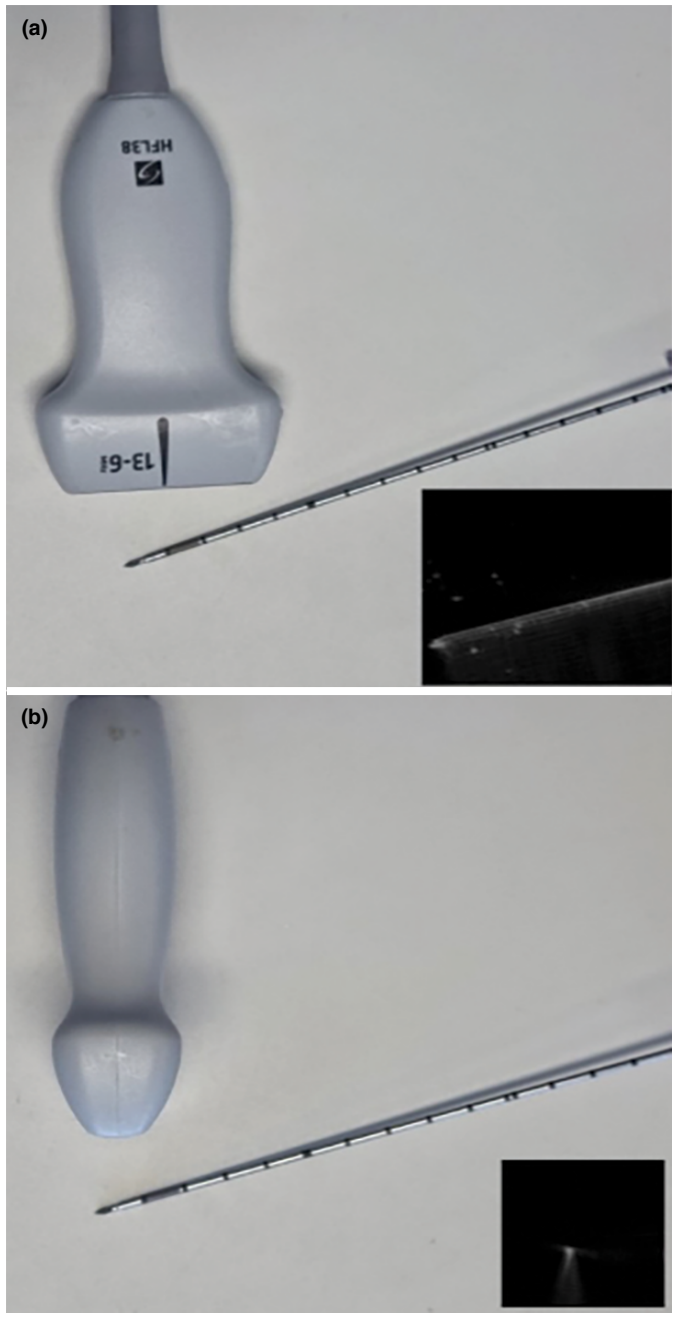

Figure 5: (a) In-plane ultrasound needle guidance. The whole length of the needle can be seen on the ultrasound image. (b) Out-of-plane ultrasound needle guidance. Only the tip of the needle is seen on the ultrasound image

available, the results will assist with localizing the disease and positioning the patient [Fig. 6a-c]. In cases where the largest quantity of abnormal pleura (and therefore the area of highest yield) is posterior/dorsal, the optimal position for the patient is to be seated on the bed, legs over the side, with the arms crossed to retract the scapulae and the head resting on an elevated surface with a pillow [Fig. 7]. This provides both stabil-

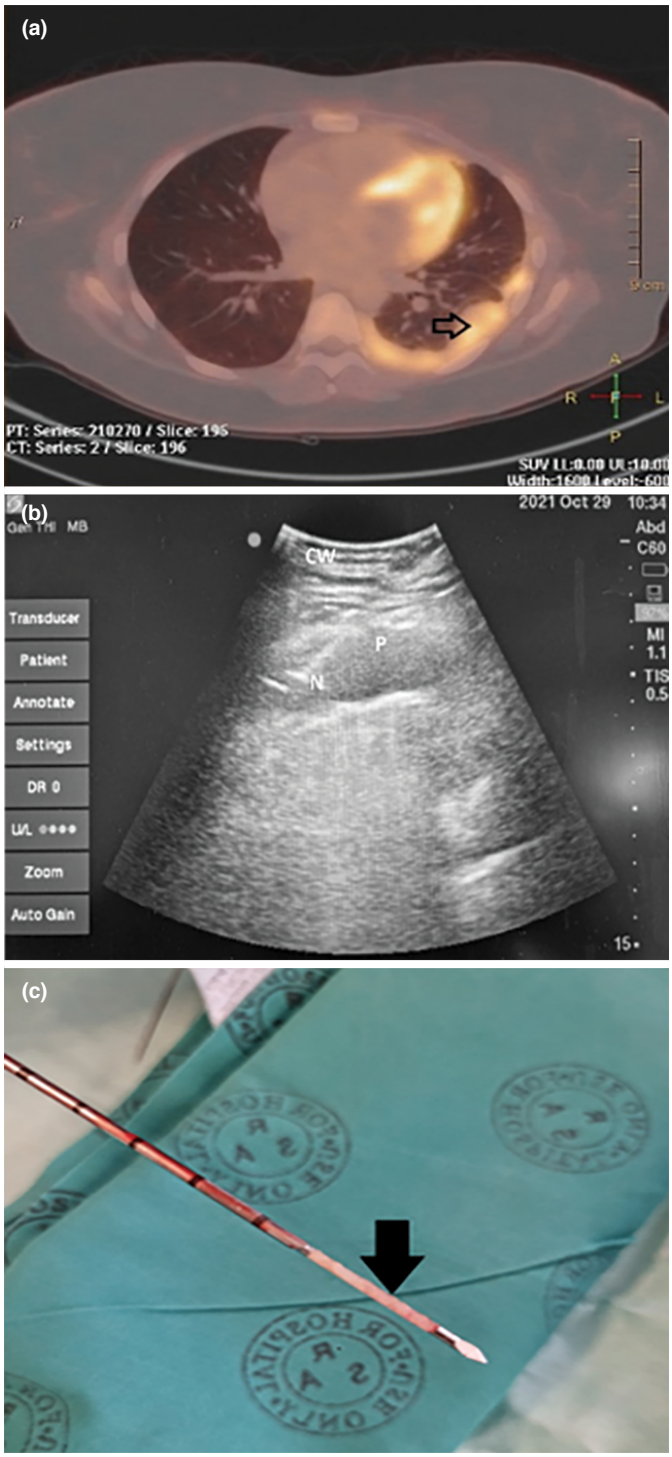

Figure 6: (a) Positron emission tomography image illustrating avid nodular pleural thickening (arrow) in a patient with suspected lymphoblastic lymphoma recurrence. Note the absence of pleural effusion. (b) An ultrasound-guided in-line pleural biopsy with a Tru-Cut biopsy needle. (Travenol Laboratories, Inc., Deerfield, IL, USA). Note the needle (N) entered through the chest wall (CW) and into the thickened pleura (P) under real-time ultrasound guidance. (c) Pleural tissue core (arrow) harvested with the Tru-Cut needle (Travenol Laboratories, Inc., Deerfield, IL, USA). The material was placed in a liquid fixative solution and sent for histological analysis, which confirmed recurrence of the disease

ity and comfort for the patient. However, the procedure can also be performed with the patient in a supine position when the pleural target is anterior, or in the lateral decubitus position.[28]

There are only 2 absolute contraindications for pleural biopsy. Patient cooperation is essential, and therefore, patients should not have an altered mental status. It is also essential that any underlying coagulopathy be addressed. An international normalized ratio of <1.4, an activated partial thromboplastin time of <1.5x the upper limit of normal and a platelet count of >100 per mcL of blood are the recommended safety limits.[3] There are currently no specific recommendations for perioperative discontinuation of antiplatelet or anticoagulant medications. Extrapolating from other pleural interventions, it is reasonable to continue administration of aspirin, while discontinuing other antiplatelet medications and anticoagulants, such as clopidogrel, vitamin K antagonists, and direct anti-factor Xa inhibitors for 3–5 days prior to the procedure, provided the patient's clinical condition allows.[29]

Patients may experience extreme discomfort during a closed pleural biopsy if there is inadequate analgesia. A local injection of a topical anesthetic, such as 1% lignocaine, must be applied to the skin, the periostea, and the pleura. Alternatives include an intercostal block, in which a local anesthetic is injected along the inferior border of the superior rib a few centimeters proximal to the planned biopsy site. Anxious patients may benefit from a mild oral sedative, such as lorazepam, or even intravenous sedation with midazolam or the like, or a short-acting opioid, such as fentanyl. These drugs are safe in medical thoracoscopy, but require continuous monitoring and a sedation practitioner.[30]

Using ultrasound to reduce complications

US-guided closed pleural biopsy is a safe procedure when performed by an experienced operator. In a meta-analysis of 30 original articles, the complication rate of US-guided closed pleural biopsy was 3% (1% major and 2% minor complications), which was significantly better than that of CT-guided biopsy at 7%.[15]

Pneumothorax is the most common complication, particularly when using the large caliber Abrams needle.[11] Care should be taken to keep the stylet in place, or if necessary, to close the bevel during removal of the

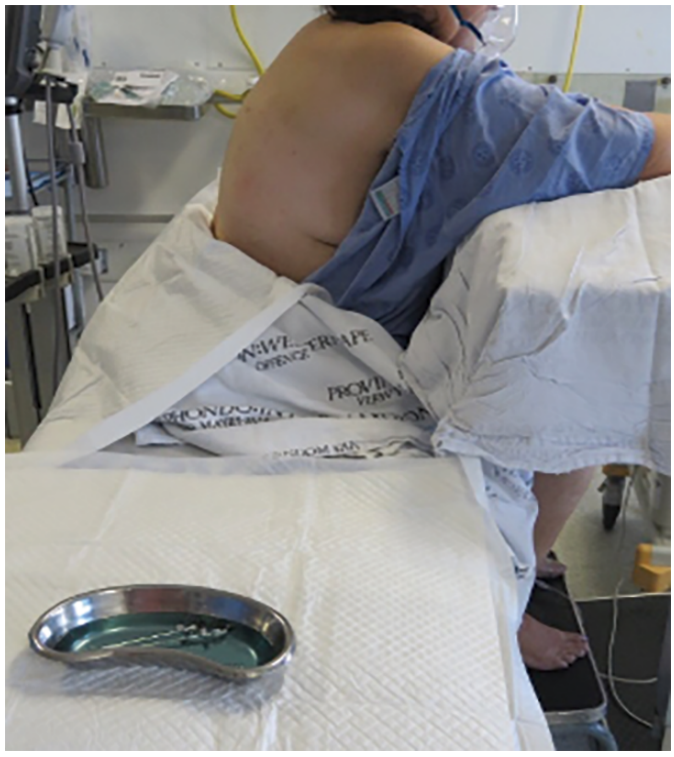

Figure 7: Positioning of a patient for a posterior approach pleural biopsy. The patient sits with feet and arms resting on supportive surfaces. The screen of the ultrasound machine and the site of biopsy should both be within the same field of view of the operator for real-time guidance

stylet. Postprocedural ultrasound has a sensitivity of 78% to 90% for the detection of pneumothoraces, which is significantly better than that of conventional radiography (39–52%).[31] Several sonographic signs have been described that assist in the ruling out a pneumothorax, of which the most commonly used are the presence of "lung sliding" and "B lines".

Other common complications are site pain (up to 15%), vasovagal syncope (up to 5%), local wound infection (up to 5%), hemothorax (<2%), site hematoma (<1%), fever (<1%), and empyema and minor bleeding.[11, 15, 16, 18]

Life threatening hemorrhage is the most feared complication, but it is exceedingly rare. Although it could arise from a puncture of the viscera, it usually originates from the intercostal arteries. Older patients are at greater risk due to the increased variability of their intercostal artery anatomy and longer exposed portion of the artery closer to the spine.[32] Wound compression and local injection of adrenaline should be attempted, but ultimately hemodynamic resuscitation, thoracotomy with ligation of the bleeding vessel, or endovascular embolization may be required.[33] Color Doppler US can reduce the risk of hemorrhage when used to identify vascular structures before the procedure, especially posteriorly, where intercostal vessels are more likely to be exposed.[32]

A recent advance in pleural US is contrast-enhanced US. This technique entails the injection of an intravenous contrast agent (SonoVue; Bracco S.p.A., Milan, Italy) which not only allows for the more accurate detection of vasculature structures, but also for the identification of necrotic areas.[34] Basic 2D scanning afterwards at the site of intervention can also exclude bleeding within the pleural space, which would present as a "swirling" or "gradient" effect, as heavier, more echogenic material (red blood cells) is rapidly deposited in the dependent part of the collection.[28]

Seeding of metastatic malignancy at sites of previous pleural intervention is a complication which occurs most frequently in malignant mesothelioma. Clive et al.[35] reported a 9% to 16% rate of metastatic nodules after pleural intervention. Some data suggest that the incidence of tract metastasis may be lower in US-guided Tru-Cut biopsy than in surgical biopsy.[36]

Integrating ultrasound-guided closed pleural biopsy into diagnostic pathways

Closed pleural biopsy should only be performed within the parameters of a defined diagnostic pathway for pleural disease [Fig. 8]. In countries with a high burden of tuberculosis, a repeat US-guided thoracocentesis is recommended before proceeding to pleural biopsy for an undiagnosed pleural exudate, especially in the absence of imaging features suggestive of malignant effusions. This is because a lymphocyte-predominant effusion with a high level of adenosine deaminase in this setting has a positive-predictive value of 98% for tuberculosis.[37] When used in conjunction with conventional microbiological tests, up to 80% of cases of tuberculous pleural effusion can be diagnosed by a second thoracocentesis.[2]

In regions with a low tuberculosis incidence, or when the effusion imaging features suggest malignancy, we recommend proceeding directly to closed pleural biopsy after a first non-diagnostic thoracocentesis. When combined with pleural biopsy during the same procedure,

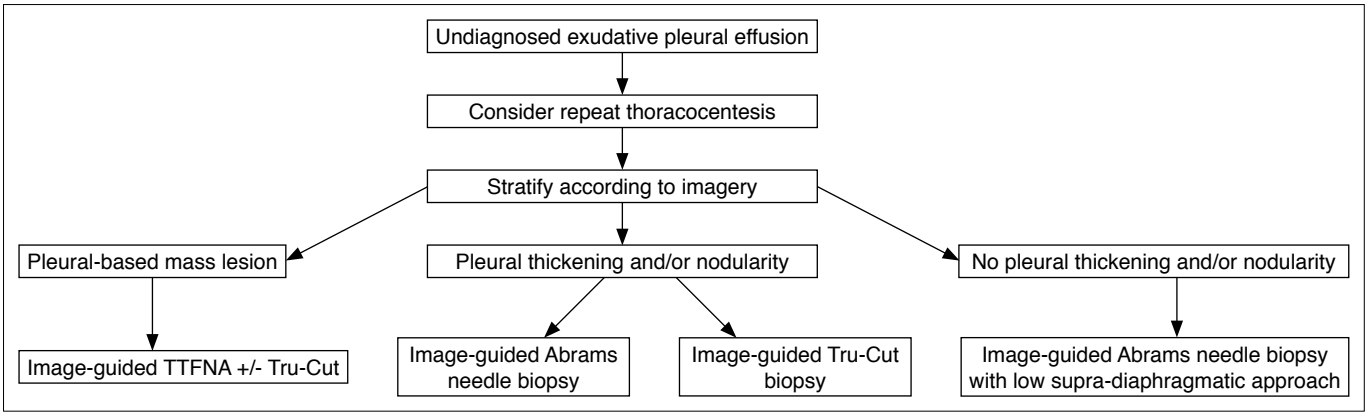

Figure 8: A suggested diagnostic algorithm for undiagnosed pleural exudates. Based on all imaging available, patients can be stratified into 3 groups, namely 'pleural effusion with an associated mass lesion', 'pleural thickening and/or nodularity and insignificant pleural thickening', and 'radiologically normal pleura'. In a pleural-based mass lesion, we recommend a transthoracic fine needle aspiration (TTFNA) with rapid onsite evaluation by an attending pathologist. Should there be diagnostic uncertainty or insufficient material we proceed to Tru-Cut needle (Travenol Laboratories, Inc., Deerfield, IL, USA) biopsy. The pleural thickening/nodularity group can be further subdivided based on thickness. Abrams needle biopsies are performed for lesions of 10-20 mm, while Tru-Cut is used for pleura thicker than 20 mm. The Abrams needle should be used where no significant pleural target is identified, and the supradiaphragmatic intercostal space should be sampled

the diagnostic yield of repeat thoracentesis increases from 15% to 30% to as much as 90%.[2]

The method of pleural biopsy should be guided by the underlying appearance of the pleura on all imaging available. Work done by our group previously has shown that stratifying patients into 3 groups, namely those with (1) pleural effusion with an associated mass lesion, (2) pleural thickening and/or nodularity and (3) insignificant pleural thickening and radiologically normal pleura, is an effective decision-making tool.[14] In the presence of a pleural-based mass lesion [Fig. 9a], we initially perform a transthoracic fine-needle aspiration with rapid onsite evaluation by an attending pathologist. Should there be diagnostic uncertainty or insufficient material, we proceed to a Tru-Cut needle biopsy. The pleural thickening/nodularity group is subdivided based on thickness. Abrams needle biopsies are performed for cases of diffuse pleural thickening of 10–20 mm [Fig. 9b], while Tru-Cut biopsies are utilized for diffuse pleural thickening of >20 mm [Fig. 9c]. Where no significant pleural thickening is identified, we use the Abrams needle in the safest basal supradiaphragmatic intercostal space to potentially increase the yield for malignancy.[14]

The absence of pleural effusion is not a contraindication for pleural biopsy. In an analysis of 56 patients with malignant mesothelioma, 14 patients with minimal or no pleural effusion underwent US-guided core-cutting needle biopsy with a diagnostic yield of 80%.[38] Only 1 patient experienced mild hemoptysis post procedure. In this setting, core-cutting needles are preferred to the Abrams needle, as they can be angulated along the length of the thickened pleura and away from the parenchyma. It has been proposed that when there is pleural thickening/nodularity in the absence of pleural thickening, thoracoscopy should be considered if lung sliding is still seen on US images (implying that pneumothorax induction would be successful), and that PET-CT is a useful tool for identifying a pleural target in this setting.[23]

In all, 4–6 separate pleural biopsy specimens are sufficient for histology and microbiologic testing, but a greater number of specimens may be needed for molecular profiling of malignancy.[39] Kirsch et al.[40] reported that the diagnostic sensitivity for tuberculous effusion approached 100% at 6 samples. Jiménez et al.[41] found diminishing returns with additional samples in tuberculous effusion due to the high diagnostic yield of the first specimen (81%). This likely reflects the diffuse involvement of the pleura in tuberculous disease. The same study found that 4 samples achieved a diagnostic sensitivity of 89% for pleural malignancy. In our center, we perform a minimum of 6 samples, 5 in formalin for histology and 1 in saline for microbiology.

Pleural biopsy may also be used to diagnose non-tuberculous pleural infection. In most cases, causative organisms are not identified from thoracocentesis, resulting in non-specific broad spectrum antibiotic use. The proof-of-

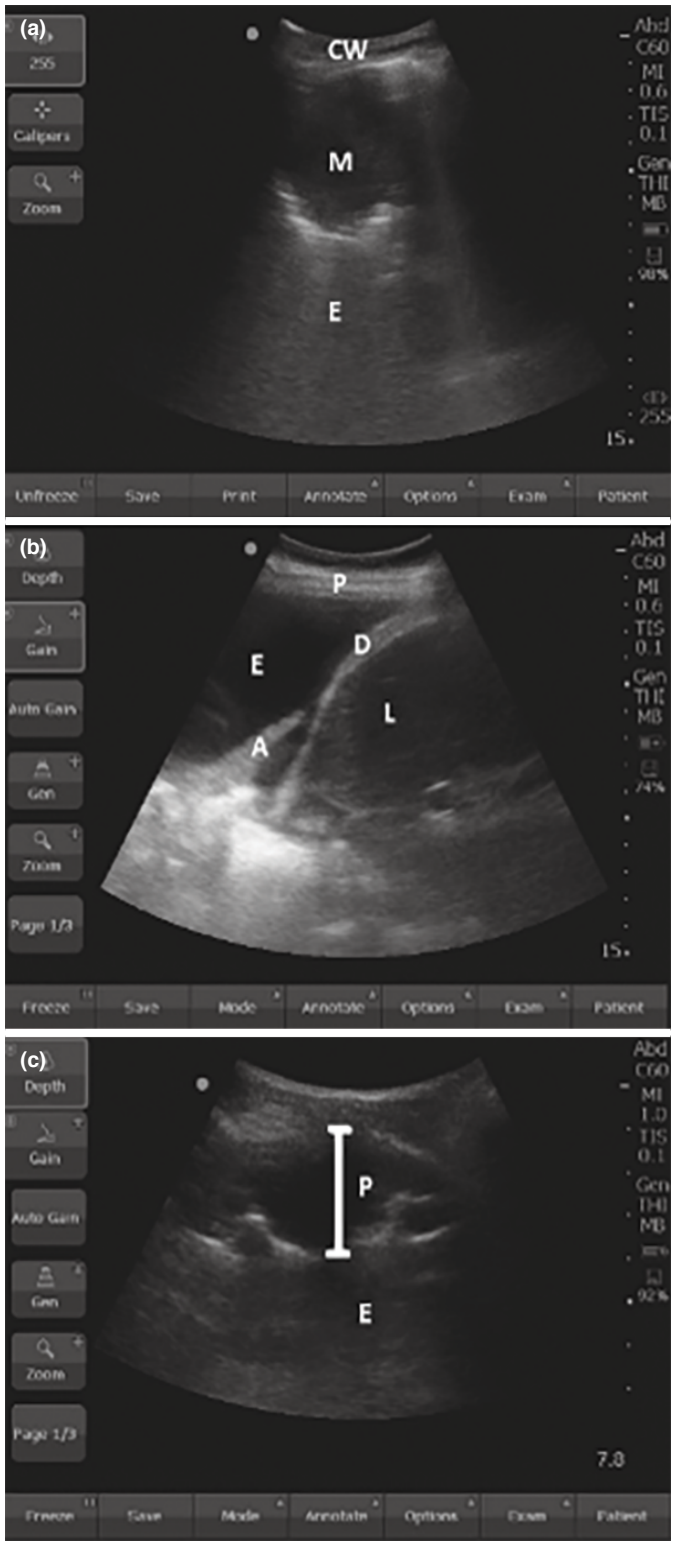

Figure 9: (a) A low frequency ultrasound image showing a pleural-based mass (M) infiltrating the chest wall (CW) and an associated pleural effusion (E). (b) A low-frequency ultrasound image showing <1 cm pleural thickening of the parietal pleura (P), including the diagrammatic (D) pleura. Note the large effusion (E), atelectatic lung (A) and liver (L). (c) A low-frequency ultrasound image showing >2 cm pleural thickening of the parietal pleura (P) with an associated effusion (E)

concept AUDIO study (A Pilot Feasibility Study in Establishing the Role of Ultrasound-Guided Pleural Biopsies in Pleural Infection) demonstrated that pleural biopsies had a diagnostic yield of 45%, compared to pleural fluid (25%) and blood (10%), despite most patients already being on antibiotics.[42] With rapidly increasing antibiotic resistance becoming a worldwide healthcare issue, further randomized controlled trials are eagerly awaited.

Conclusion

US-guided closed pleural biopsy is a cost-effective and readily available technique for the assessment of pleural disease, with a variable, but generally high, diagnostic yield for all forms of pleural disease. In the correct setting and trained hands, it is also safe and likely equivalent to CT-guided biopsy. When used as part of a structured approach, it is an essential tool in the respiratory physician's armamentarium, particularly where thoracoscopy is not readily available. Basic training in thoracic US, and more advanced training in US-guided procedures should form part of the respiratory physician curriculum in all regions of the world. This has the advantage of upskilling respiratory physicians for independent practice, reducing the burden on surgical services and tertiary referral, and facilitating a faster pathway for patients from presentation to treatment.

Conflicts of interest
There are no conflicts of interest.

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