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TITLE PAGE

Pleural biopsies in undiagnosed pleural effusions; Abrams vs image-guided vs thoracoscopic biopsies

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ABSTRACT

Purpose of review: Pleural biopsies are often necessary if a pleural effusion remains undiagnosed after radiological imaging and pleural fluid analysis. There are many methods of obtaining pleural biopsies, including blind or image-guided procedures, closed-bevel or cutting-edge needles, and percutaneous or thoracoscopic approaches. This article will review recent research relating to these methods, aiming to provide an overview of the strengths and limitations of each technique.

Recent findings: Historically pleural biopsies were undertaken using a blind, closed "Abrams" needle method. However low diagnostic yields and high complication rates are seen with this technique compared to newer methods. Recent research compares image-guided, cutting needle approaches to traditional Abrams biopsies, and evaluates the role of medical thoracoscopy in comparison to other techniques.

Summary: Thoracoscopic biopsies are the gold standard for investigating pleural disease. However this service is not universally available and may be unsuitable for some patients. Image-guided cutting-needle biopsies under computed tomography or ultrasound guidance have high diagnostic rates and are useful in a wide patient population. The main role of Abrams biopsies is in the diagnosis of tuberculous pleuritis in resource-poor settings.

Keywords: pleura, biopsy, thoracoscopy, image-guided

INTRODUCTION

Pleural effusions are common, with over 1.5 million people presenting with undiagnosed effusions in the US each year [1,2]. There are over 50 recognised causes for pleural effusions, and the most common causes vary depending on geographical location and population

demographics [3, 4]. In Europe and America the commonest aetiologies are heart failure, pneumonia and malignancy, whilst in India and Indonesia it is tuberculous pleuritis [5,6].

There are several national guidelines that outline the investigatory pathway for undiagnosed effusions [3,7]. Radiological imaging and biochemical analysis of pleural fluid provide initial diagnostic information, but histological confirmation is usually required, particularly if malignancy is suspected. Because cytological examination of pleural fluid has a low sensitivity for malignant cells (less than 60%), pleural biopsy is often required [3, 8, 9].

Pleural biopsies can be undertaken percutaneously, using "closed-bevel" needles or cutting-edge needles. The procedure can be performed blind, under image-guidance using ultrasound or computed tomography (CT), or under direct vision during thoracoscopy. Thoracoscopy can be performed using local anaesthetic and sedation (local anaesthetic thoracoscopy, LAT, also sometimes called medical thoracoscopy) or as a surgical procedure (video-assisted thoracoscopic surgery, VATS). The question of which method is optimal has been much debated, and over the past 18 months, a number of relevant articles have been published on this subject. These articles will be reviewed here, in the context of pre-existing evidence.

BLIND CLOSED-NEEDLE BIOPSIES

Percutaneous pleural biopsy was originally described in the 1950s by Abrams and Cope, after whom the two original reverse-bevel "closed" needles are named [10, 11]. Abrams needles are still used in some countries, as they can be employed at the bedside without imaging. Consequently the procedure is inexpensive and relatively straightforward.

However, there are disadvantages to Abrams biopsy. Complications are not uncommon, particularly in the hands of inexperienced practitioners [12]. The most frequent complications are pain at the site of biopsy (up to 15%) and pneumothorax (also 15%) [3]. Less common are

vasovagal symptoms (approximately 5%), haemothorax (less than 2%) or transient fever (less than 1%) [3, 12]. Death secondary to haemorrhage has been reported, but this is rare [12].

The sensitivity of Abrams biopsies for malignancy is between 27% and 60% [12, 13, 14, 15, 16]. In the largest review of 2893 Abrams samples, diagnostic yield was 57% for malignant disease [15]. In people who have had previous thoracentesis with negative cytology, closed pleural biopsy may provide additional diagnostic information in up to 12% [8]. This low sensitivity reflects the irregular distribution of malignant deposits across the pleura; tumours often cluster around the diaphragm and midline, areas that are technically difficult and dangerous to access with Abrams needles [3]. The low sensitivity rate, combined with the risk of complications, has led to a decrease in the use of Abrams biopsies in suspected malignant pleural effusions.

Abrams biopsies have a higher sensitivity in tuberculous pleural disease. This is because tuberculosis affects the pleura diffusely, thus increasing the probability that an area of disease will be sampled during blind biopsies. The sensitivity for diagnosing tuberculosis with Abrams biopsies ranges from 67% to 92% [16, 17, 18, 19, 20*]. Yield is higher if pleural fluid is analysed concurrently for lymphocyte count or adenosine deaminase (ADA) [18, 19, 20*]. Pleural fluid or tissue culture using liquid media further increases the sensitivity [16, 17].

For this reason, blind pleural biopsies are often used as a first line diagnostic tool in resource-poor settings, where prevalence of tuberculosis is high [19]. However, outside of this scenario, alternative methods are advocated [3].

IMAGE-GUIDED CLOSED-NEEDLE BIOPSIES

Image guidance can increase the yield of Abrams biopsies and reduce complication rates [21]. In one randomised trial, patients with exudative effusions who underwent CT-guided Abrams

biopsy achieved a diagnosis in 87.5% [21]. Complications were few, with one significant bleed requiring blood transfusion.

More recently a randomised trial compared medical thoracoscopy with Abrams biopsies taken under direct ultrasound vision at a pre-determined site chosen from CT, in patients with undiagnosed exudative effusions [22]. Image-guided Abrams biopsy had a diagnostic sensitivity of 75%, and this increased to 90% in patients with pleural thickening of greater than 1cm. This compared with an overall diagnostic sensitivity of 85% in the 20 participants who underwent medical thoracoscopy. In people whose pleural thickening was greater than 1cm, medical thoracoscopy had a similar diagnostic yield of 90%.

IMAGE-GUIDED CUTTING NEEDLE BIOPSIES

Cutting needles have been shown to be advantageous to Abrams biopsies with sensitivities of up to 88% in observational studies [23, 24, 25]. Cutting needles perform well in the presence of pleural thickening, which makes them a useful tool in the diagnosis of malignant pleural mesothelioma; a tumour for which pleural fluid cytology has a low yield [25, 26].

The only well-powered, prospective, randomised trial comparing CT-guided cutting needle biopsies with Abrams biopsy demonstrated that cutting needle biopsies were 40% more sensitive at diagnosing malignancy [27]. The yield from CT-guided biopsy was 87%, compared with 47% for Abrams biopsies ($p=0.02$), with the added benefit of fewer passes of the needle in the image-guided group. The authors conclude that CT-guided pleural biopsy using a cutting needle, as shown in Figure 1, should be the preferred method where malignancy is suspected.

This result was replicated in a recent, small randomised trial comparing Abrams biopsy with CT-guided biopsy [28*]. This study of 31 patients demonstrated a diagnostic yield of 87.5% (14/16) in the CT-guided group, compared with 40% (6/15) in the Abrams group.

The accuracy and diagnostic sensitivity of CT-guided biopsies can be increased by using "pleural-phase" imaging, in which images are captures at least 60 seconds after the delivery of contrast. This method produces greater pleural enhancement, and clearer visualisation of pleural deposits [29].

Ultrasound-guided pleural biopsies have a similar diagnostic yield to CT-guided biopsies [30]. The choice of modality is guided by availability and operator preference. However, ultrasound offers specific benefits, including real-time visualisation of needle movement and monitoring of movement of the target lesion with respiration. Ultrasound does not entail exposure to ionising radiation, and the equipment is substantially cheaper. In a retrospective review of 273 biopsies of pleural lesions and peripheral lung lesions abutting the pleura, technical success was high with both ultrasound and CT guidance (97.1% and 96.5% respectively) [31]. Procedures using ultrasound were substantially faster and resulted in fewer negative biopsy results. There were significantly fewer pneumothoraces in the ultrasound group (5.5% vs 14.7%), however the relevance of this result is difficult to interpret since participants were not randomised. Importantly, information on the incidence of COPD was not collected and this may represent a relevant confounding factor in the incidence of iatrogenic pneumothoraces.

Ultrasound-guided cutting needle biopsies can be performed by respiratory physicians, with no drop in diagnostic sensitivity [32]. A recent review article suggested that physician-led, ultrasound-guided pleural biopsy was effective, both as a planned procedure in patients not suitable for thoracoscopy, and as a secondary "on-the-table" option if thoracoscopy failed [33*]. Diagnoses were obtained in 47 out of 50 patients (94%) of which 46 were correct. Of 15 patients with a final diagnosis of malignancy, ultrasound-guided biopsy provided diagnostic material in 13 (87%).

As well as guiding the choice of biopsy site, ultrasound can also be used influence technique. In a prospective series of 100 patients, ultrasound was used to assess the extent of pleural disease and inform subsequent intervention [34*]. Pleural disease was classified as well-circumscribed mass lesions, diffuse pleural thickening/nodularity or insignificant/no pleural thickening, based on ultrasound appearance. In patients with a mass, fine needle aspiration with rapid on-site cytological evaluation (ROSE) was undertaken, followed by cutting-needle biopsy if the initial diagnosis was non-malignant. In the presence of pleural thickening biopsies were undertaken, using an Abrams needle if the pleura measured 10-24mm or a cutting needle if greater than 25mm. If there was no obvious pleural thickening, Abrams biopsy was employed. This method increased the diagnostic yield for malignancy from 31.0% to 89.7% ($p<0.001$), and for all diagnoses to 90%.

These results suggest that when undertaken by experienced operators, image-guided pleural biopsies have a high diagnostic sensitivity, and can reliably differentiate between benign and malignant disease.

COMPLICATIONS FROM IMAGE-GUIDED BIOPSIES

Complication rates from image-guided biopsies are low. In a retrospective analysis of over 500 acute care hospitals in the US, 79,518 patients were identified who underwent trans-thoracic image-guided needle biopsies for cancer. Of these, 13,091 (16.5%) developed a pneumothorax within a month of biopsy and 3,074 (3.9%) required chest tube drainage [35].

Pneumothorax risk may be reduced by injecting saline as the biopsy needle is withdrawn, or by rapidly turning the patient onto the side of the biopsy once the procedure is complete [36, 37]. The use of saline reduced the incidence of pneumothorax to 6.2% compared with 26.1% in the control group ($p<0.001$) [36], whilst the “rapid roll-over” method reduced the incidence of

pneumothoraces requiring drains, but not the overall incidence of pneumothorax [37]. More trials are necessary before these techniques become common practice.

LOCAL ANAESTHESTIC THORACOSCOPY

Local anaesthetic thoracoscopy (LAT) is a procedure in which a rigid or semi-rigid thoracoscope is passed into the pleural cavity via a port inserted by blunt dissection. The procedure is performed under conscious sedation and local anaesthesia, and can take place in a dedicated procedure room, bronchoscopy suite or operating theatre [38**]. It allows direct visualisation of the pleural surface and targeted sampling of areas of disease (see Figure 2).

A major advantage of LAT over percutaneous biopsies is that both diagnostic and therapeutic procedures can be undertaken. Fluid is drained at the start of the procedure, and a wide-bore drain left in place at the end, with associated symptomatic benefit for most patients. Talc poudrage can be performed for pleurodesis at the end of the procedure, provided the pleura looks malignant and the lung likely to re-expand.

The diagnostic yield of LAT for pleural malignancy is high. Pooled results from 22 case series, involving 1369 patients, showed an overall diagnostic sensitivity of 92% [39]. LAT is more successful at diagnosing malignancy than blind or image-guided Abrams biopsies [22, 40, 41, 42]. LAT also had a higher diagnostic yield than CT-guided cutting-needle biopsies in one small randomised trial [43].

For tuberculous pleuritis the yield with LAT is even higher. A recent prospective case series reported a positive LAT diagnosis of TB in 330 of 333 confirmed cases, giving an overall sensitivity of 99.1% [44]. However this study took place in a high prevalence area and may not be generalizable. Additionally the diagnostic criteria for 'confirmed' tuberculous pleuritis was

based on histological parameters alone, which may have increased the apparent sensitivity by reducing the denominator population.

However, even taking these interpretive issues into account, LAT biopsies are clearly a reliable diagnostic tool for both tuberculous pleuritis and pleural malignancy. Table 1 summarises the diagnostic sensitivity of LAT reported in recent studies.

COMPLICATIONS OF LOCAL ANAESTHETIC THORACOSCOPY

LAT is generally safe. In a combined analysis of 47 studies of 4756 patients who underwent LAT, mortality was reported in 0.34% of cases, major complications in 1.8% and minor complications in 7.8% [39]. Similar rates were reported in recent articles [45, 46, 47]. Table 1 shows the complication rates of LAT from recent publications.

Potential major complications from LAT include empyema, haemorrhage, pneumonia, tumour seeding along procedure tract and bronchopleural fistula causing postoperative pneumothorax or prolonged air leak [38**]. Minor complications include subcutaneous emphysema, minor bleeding, local wound infection, hypotension during procedure and transient fever.

Table 1 – A summary of the diagnostic yield and complication rates of local anaesthetic thoracoscopy reported in recent studies

DISADVANTAGES OF LOCAL ANAESTHETIC THORACOSCOPY

For LAT, a patient must be able to lie still, in the lateral decubitus position, for a minimum of 30 minutes. Joint problems, uncontrollable pain or intractable cough may make the procedure impossible due to the risk of movement. Patients with lung disease who desaturate when lying flat are not safe for LAT and patients must be able to maintain adequate oxygen saturations

during conscious sedation. Supplementary oxygen may be necessary. Unfortunately, some patients are too frail to tolerate LAT.

LAT requires a pleural effusion of sufficient size into which the introducer port can be safely inserted. In patients with small effusions, an iatrogenic pneumothorax can be induced to allow LAT to proceed, although this is associated with a higher risk of complications. Once the port is inserted the lung needs to be able to collapse freely away from the chest wall, therefore patients with a highly loculated effusion or tethered lung may not be suitable [38**].

Unfortunately, access to LAT is not universal, and thoracoscopy is not available in some areas. LAT usually requires an overnight in-patient stay (sometimes longer), which puts strain on healthcare providers, and may not be acceptable to patients. Day-case LAT is possible, and is becoming more popular, but this requires either the avoidance of talc poudrage or the use of an ambulatory pleural catheter on discharge [38**]

Overall, LAT is a safe and well-tolerated procedure with a high diagnostic sensitivity. Pleural biopsy taken at thoracoscopy (LAT or VATS) is considered the gold standard for diagnosing pleural malignancy [3]. Access to LAT services, although not universal, is increasing and the advent of day-case LAT may improve this further.

VIDEO-ASSISTED THORACOSCOPIC SURGERY (VATS)

Pleural biopsies taken at VATS carry a sensitivity of 95%, specificity of 100% and negative predictive value of 94% [45]. This is similar to LAT, although no randomised trial has directly compared the two procedures. VATS offers the additional benefit of allowing therapeutic interventions to be performed at the same time as the diagnostic procedure. Surgeons are able to perform lung resection, tumour de-bulking or talc poudrage during VATS.

However, VATS requires a general anaesthetic, and therefore require a higher degree of physical fitness than other biopsy techniques. Patients with poor performance status are precluded, and stronger patients may be unsuitable due to specific co-morbidities such as ischaemic heart disease. Major complications, including bleeding, infection and post-operative air leak have been reported in up to 15% of VATS cases [45]. However in a more recent, albeit smaller, audit from a UK hospital, a major complication rate of just 1.2% was noted, with minor complications occurring in 15.1% [46].

Due to the invasive nature of VATS, it is generally considered when less aggressive approaches (i.e. image-guided biopsy) have failed to provide a diagnosis.

NEW DIRECTIONS

There are a number of new diagnostic techniques under investigation. Positron-emission tomography (PET-CT) can differentiate benign pleural disease from malignant [47]. PET-CT may also be a useful tool for identifying potential biopsy sites. Baseline metabolic activity on PET-CT appears to correlate with survival in mesothelioma [48].

Similarly Magnetic Resonance Imaging (MRI) may have a role in the evaluation of pleural disease [48, 49**]. MRI avoids the use of ionising radiation, and can provide both morphological and functional information on pleural pathology, as shown in Figure 3. MRI may be useful for targeting pleural biopsies, and can provide information on prognostication and response to treatment [49**].

Cryobiopsy is a new sampling method that uses a cooling probe to 'freeze' samples as they are taken. In patients with undiagnosed pleural effusions, cryobiopsies taken during flexi-rigid thoracoscopy produced larger samples, with greater preservation of tissue architecture compared with standard flexible forceps [50*]. The procedure was safe, with no major

complications seen, and similar rates of mild, self-limiting bleeding seen following both biopsy methods. The procedure requires deep sedation or general anaesthesia, which be a limitation for some patients. Nonetheless, cryobiopsies are an exciting new diagnostic approach, which warrant further investigation in larger randomised trials.

CONCLUSION

There are different options for obtaining pleural biopsies in undiagnosed pleural effusions. Abrams biopsies are associated with low diagnostic yields and significant complications, and should be avoided where possible. However, Abrams biopsies may have a role in resource-poor settings with high incidence of tuberculous disease. Image-guided cutting-needle biopsies using ultrasound or CT are straightforward, quick, and associated with high diagnostic sensitivity and few complications. They are an excellent option for people in whom thoracoscopy is not possible, or has been attempted and failed. Thoracoscopy is the gold standard, with diagnostic yields over 92% in both medical (local anaesthetic) and surgical procedures. Thoracoscopy is generally safe, but some patients may not be suitable. Access to medical thoracoscopy is likely to increase over the next decade. New techniques, including day-case thoracoscopy, PET-CT and MRI-guided biopsy and cryobiopsies require further research, but may provide alternative diagnostic options in the future.

KEY POINTS

- "Closed" pleural biopsies using Abrams needles should not be performed unless resources are limited and likelihood of Tb is high.
- Image-guided pleural biopsies using cutting-needles have a high diagnostic yield with few associated complications.
- Medical thoracoscopy, if available, is the gold standard for obtaining pleural biopsies, with a high sensitivity rates and few complications.

- Surgical VATS has a high diagnostic yield, but is invasive and only suitable for patients with good performance status and few medical co-morbidities.
- New techniques are being investigated in the diagnosis of pleural disease, including day-case thoracoscopy, MRI- and PET-CT-guided biopsy, and cryobiopsy.

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Figure 1 – CT guided biopsy

The biopsy needle (A) can be seen passing through the chest wall, aiming for a right-sided apical lung mass (B).

Figure 2 – Pleural malignancy seen at local anaesthetic thoracoscopy

The parietal pleural is inflamed and diffusely infiltrated (A), with discrete, irregular nodular tumours clearly visible (B & C). The collapsed lung can be seen at the bottom of the picture (D), lying within a small pool of pleural fluid (E).

Figure 3 – Thoracic MRI

Thoracic MRI demonstrating right sided, circumferential pleural thickening with high intensity (A) extending over the mediastinum. This is causing significant restriction and volume loss on the right side. Appearances are consistent with mesothelioma.

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FIGURES

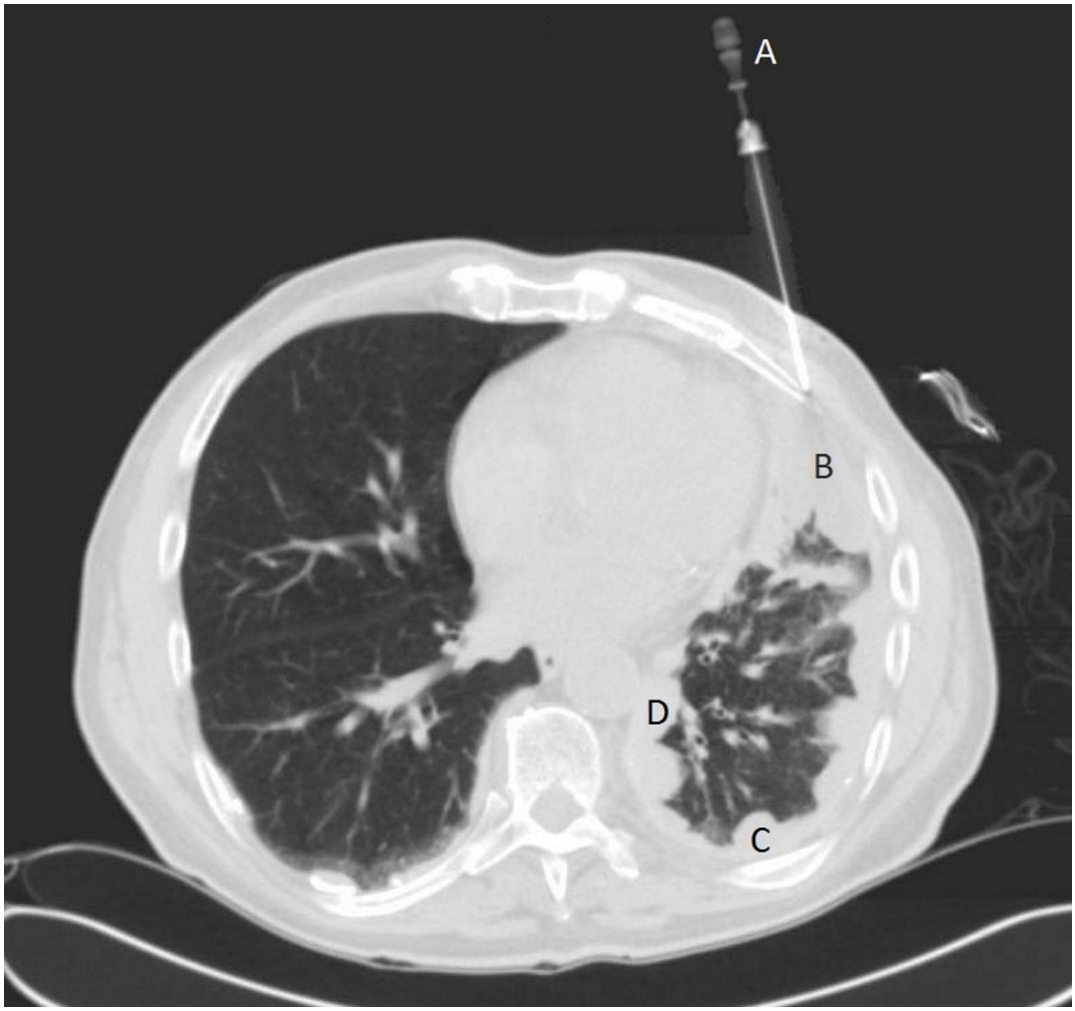

Fig. 1

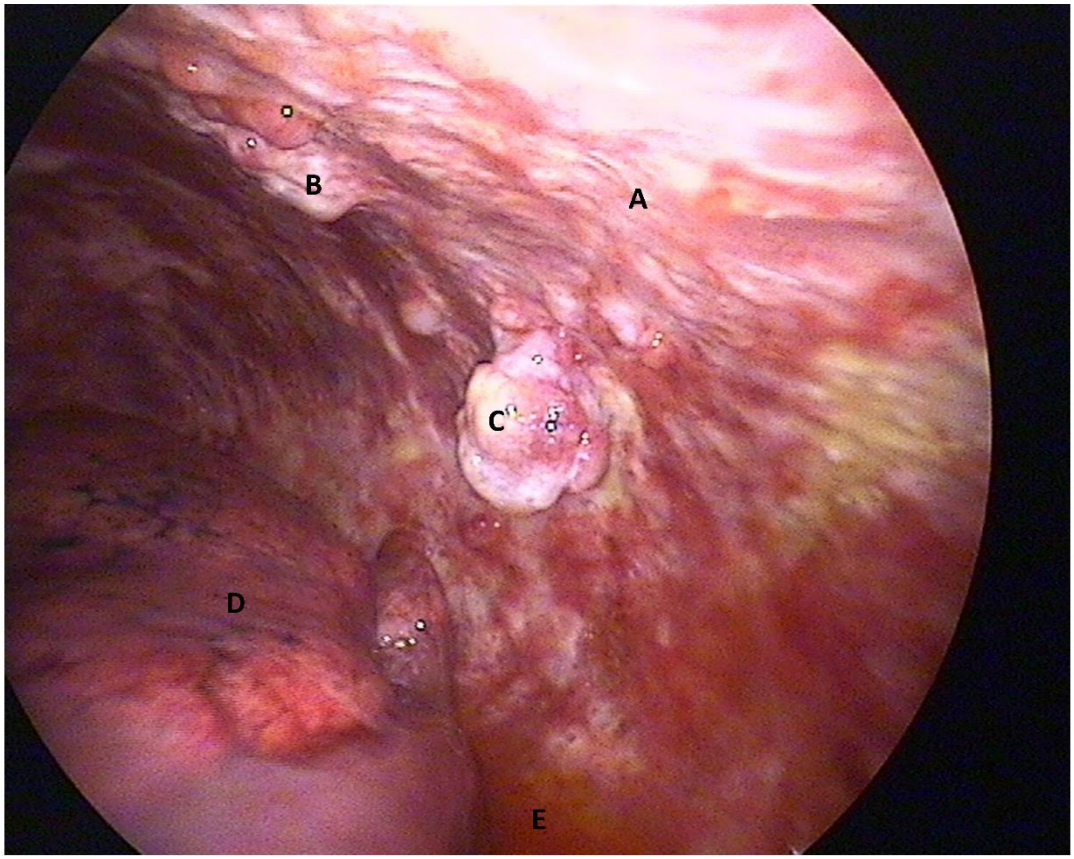

Fig. 2

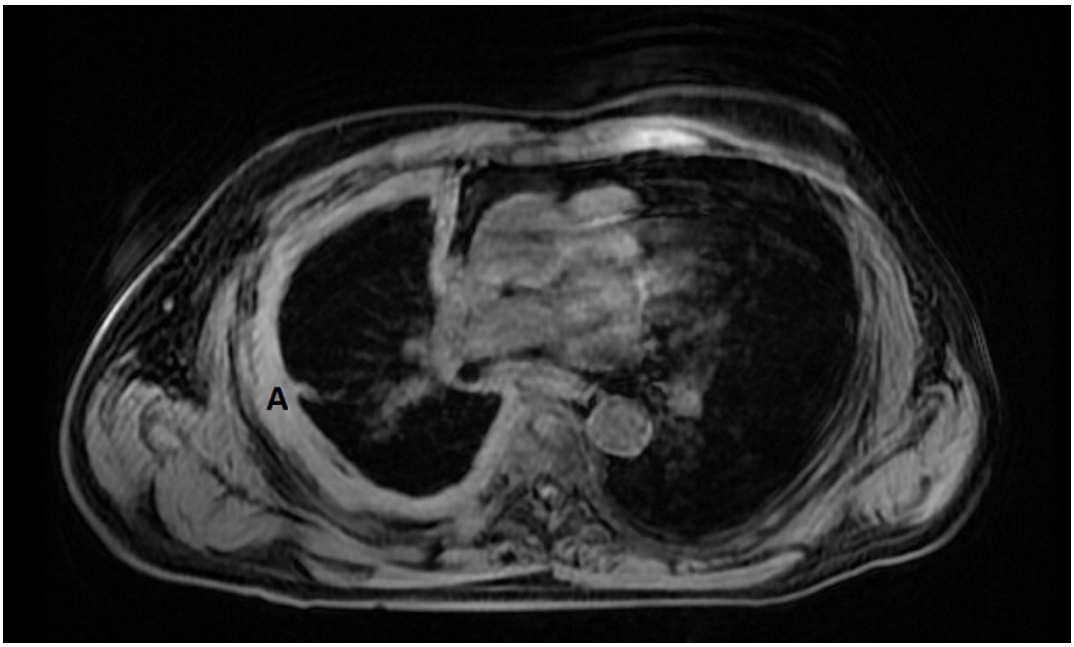

Fig. 3