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Re-expansion Pulmonary Edema following Medical Thoracoscopy in Patients with Tuberculous Pleural Effusion

Tüberküloz Plevral Efüzyonlu Hastalarda Medikal Torakoskopi Sonrası Re-ekspansiyon Akciğer Ödemi

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Abstract

Medical thoracoscopy (MT) procedures are witnessing increased use worldwide as a minimally-invasive modality offering simultaneous diagnostic and therapeutic benefits to patients with unexplained pleural effusions. Re-expansion pulmonary edema (REPE) is a rare but potentially life-threatening complication associated with pleural effusion drainage that can happen following MT. Little is known about the incidence, risk factors or management strategies of REPE post-MT. We report here on the largest case series to date involving three patients with tuberculous pleural effusion (TPE) who developed REPE after MT. All three patients responded well to supportive measures, including oxygen therapy, intravenous diuretics and hydrocortisone. We believe this case series and literature review serve to highlight an uncommon but dangerous complication of MT. Early recognition, followed by prompt treatment of REPE can ensure a better clinical outcome.

Keywords: *Tuberculosis, pleural effusion, re-expansion pulmonary oedema, thoracoscopy.*

Öz

Medikal torakoskopi (MT), açıklanamayan plevral efüzyonları olan hastalar için eş zamanlı tanısal ve terapötik çözümler sunan minimal invazif bir araç olarak dünya çapında giderek daha fazla kullanılmaktadır. Re-ekspansiyon pulmoner ödem (REPO), MT'yi takiben meydana gelebilecek, drene olan plevral efüzyonların nadir fakat potansiyel olarak yaşamı tehdit eden bir komplikasyonudur. MT sonrası REPO insidansı, risk faktörleri ve tedavi stratejileri hakkında az şey bilinmektedir. MT sonrası REPO gelişen tüberküloz plevral efüzyonlu (TPE) 3 hastayı içeren bugüne kadarki en büyük olgu serisini sunuyoruz. Hastaların her üçü de oksijen tedavisi, diüretik ve hidrokortizon içeren destek tedavisine iyi cevap vermiştir. Literatür taraması ile birlikte bu olgu serisinin MT'nin nadir fakat tehlikeli bir komplikasyonunu aydınlatmak için bir fırsat sağlayabileceğini umuyoruz. Erken tanı ve ardından REPO'nun hızlı tedavisi daha iyi bir klinik sonuç sağlayabilir.

Anahtar Sözcükler: *Tüberküloz, plevral efüzyon, re-ekspansiyon akciğer ödemi, torakoskopi.*

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Medical thoracoscopy (MT) is being increasingly used around the world as a minimally invasive tool that provides simultaneous diagnostic and therapeutic benefits to patients with unexplained pleural effusions. Re-expansion pulmonary edema (REPE) is a rare but potentially life-threatening complication associated with pleural effusion drainage that can occur when carrying out an MT. Little is known, however, about the exact incidence, risk factors and optimal management strategy for REPE after MT. Moreover, there is a significant gap in knowledge on whether certain pleural ultrasonography features and/or pleural pathologies (such as tuberculous or malignant pleural effusions) predispose patients to the development of REPE post-MT. We present here our evaluation of the largest case series to date, involving three patients with biopsy-proven tuberculous pleural effusions (TPE) who developed REPE following MT (Table 1, cases 1-3).

CASE

Case 1: A 34-year-old nurse presented with a 3-week history of cough, malaise and worsening shortness of breath. A chest X-ray upon arrival showed bilateral pleural effusions that were worse on the left side (Figure 1A). The baseline electrocardiogram (ECG) was normal. Diagnostic thoracocentesis confirmed an exudative effusion, while other studies, including pleural fluid cytology, acid-fast bacilli, gram stain and cultures, were unremarkable. An MT performed under sedation revealed diffuse sago-like micronodules over the parietal pleura (Figure 1B). A total of 1.4 liters of fluid was drained prior to the performance of pleural biopsies. The patient developed breathlessness within 30 minutes of the procedure requiring oxygen support via a high-flow mask (10 liters/minute) and subsequently via non-invasive ventilation (NIV). A rapid bedside echocardiogram revealed no significant cardiac abnormalities. The patient continued to deteriorate, despite mechanical ventilation. An urgent chest X-ray revealed rapid development of left lower zone alveolar opacities after the evacuation of pleural fluid, and the imaging appearance and clinical picture were suggestive of REPE (Figure 1C). The patient responded well to supportive measures, including intravenous hydrocortisone and diuretics, and was extubated 36 hours later. A repeat chest X-ray revealed the complete resolution of the alveolar opacities (Figure 1D), while biopsy results showed necrotizing granulomatous inflammation, consistent with TPE. The patient was started on quadruple anti-tuberculous agents, including rifampicin, isoniazid, pyrazinamide and ethambutol. She was discharged after 6 days of hospitalization and remained well with no recurrence of effusion upon a review two months later in the outpatient clinic.

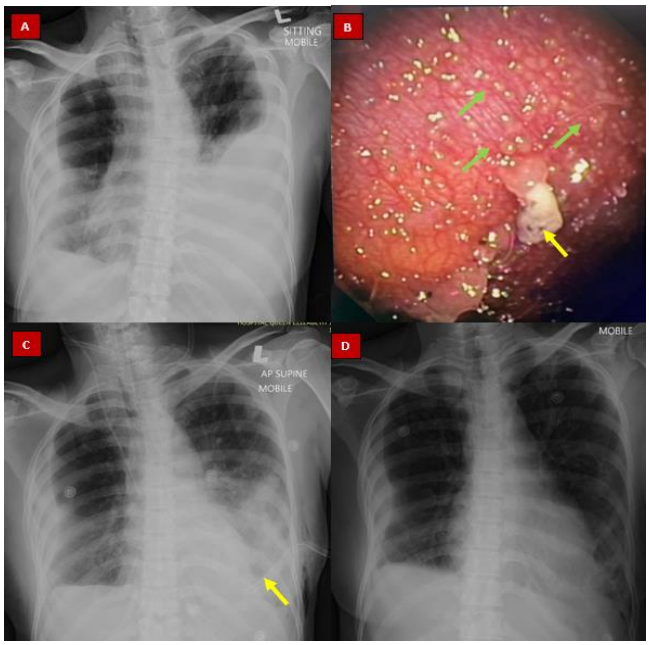

*Figure 1: Initial chest X-ray showing bilateral pleural effusion, worse on the left side **(a)**, diffuse sago-like micronodules (some pointed with green arrows) and whitish nodules (yellow arrow) seen over a parietal pleura on medical thoracoscopy **(b)**, chest X-ray post procedure showing left lower zone alveolar opacities following the evacuation of pleural fluid due to re-expansion pulmonary edema. Chest tube indicated with a yellow arrow **(c)**, repeat chest X-ray on day 5 of admission showing complete resolution of alveolar opacities **(d)***

Case 2: We report here on a 20-year-old male with a 1-week history of fever, non-productive cough and shortness of breath. Chest X-ray showed bilateral pleural effusions that were worse on the left side (Figure 2A). The patient's ECG was normal. A diagnostic thoracocentesis showed an exudative pleural effusion, while fluid cytology, gram stain, acid-fast bacilli and cultures were negative. MT revealed multiple whitish nodules scattered over the parietal pleura and diaphragm. A liter of pleural fluid was rapidly drained prior to the pleural biopsies, and a repeat chest X-ray immediately after the procedure showed the resolution of left pleural effusion while the left lung was not fully expanded (Figure 2B). The patient developed central chest pain, breathlessness and desaturation to 82% (from 95% pre-procedure) approximately 4 hours post-procedure. Oxygen support (high-flow mask oxygen 10 liters/minute) was commenced immediately to maintain his saturation at 95%. An urgent chest radiograph demonstrated the rapid formation of left mid and lower alveolar opacities with the re-expansion of the left lung, consistent with REPE (Figure 2C). Intravenous furosemide 40mg and intravenous hydrocortisone 100mg were given immediately, after which the patient was transferred to the intensive care unit for close monitoring. Similar to the previous case, the patient responded well to supportive measures and required no oxygen support 48 hours later. Pleural biopsy results showed evidence of necrotizing granulomatous inflammation, and the patient completed

a total of 6 months of anti-tuberculous therapy with no recurrence of pleural effusion, and was found to be well during follow-up clinic reviews (Figure 2D).

Case 3: A 57-year-old male with underlying hypertension presented with a 1-month history of intermittent fever, weight loss and shortness of breath. Pleural ultrasonography revealed complete displacement of the right lung due to pleural effusion but without septations (Figure 3A). Baseline ECG was unremarkable, while thoracentesis revealed an exudative pleural effusion that was predominantly lymphocytic in nature. MT revealed multiple small, whitish and sago-like micronodules in the parietal pleura (Figure 3B). Some 1.3 liters of fluid were removed during the procedure, after which the patient immediately began to cough profusely and was breathless with desaturations to 85%, despite oxygen support (nasal prong 3 liters/minute). Immediately after clamping his chest drain, the patient was provided with high-flow mask oxygen at a rate of 10 liters per minute to maintain his saturation at 95%. In addition, intravenous furosemide 40mg and hydrocortisone 100mg were administered. An urgent chest X-ray revealed a partially expanded right lung with new alveolar opacities over the right lower zone due to REPE (Figure 3C). The patient responded well to supportive measures, and was weaned from oxygen gradually over the next 24 hours. A repeat chest X-ray on day 3 of admission revealed the resolution of the right lung alveolar opacities (Figure 3D). The patient's overall clinical picture, namely the presenting symptoms, pleural fluid characteristics and MT findings, were consistent with TPE. Based on this diagnosis, the patient was started on anti-tuberculosis medications that led to an improvement in symptoms; there was no recurrence of pleural effusion.

DISCUSSION

TPE is responsible for up to 44% of cases of exudative pleural effusion in tuberculosis-endemic countries such as Malaysia (1). The prompt delineation of TPE from other causes of pleural effusion is vital for therapeutic and public health reasons. Routine empirical treatments of TPE subject patients to the potential adverse effects of anti-tuberculous chemotherapy, while misclassifying patients with true TPE can inadvertently cause delays in identifying competing differential diagnoses. Despite being a common condition, diagnosing TPE can be challenging. Pleural fluids sent for conventional smear microscopy and solid media cultures have low yields for tuberculosis at below 10% and 30%, respectively (2). MT offers simultaneous diagnostic and therapeutic benefits to patients with suspected TPE, and is able to identify up to 100% of patients with TPE (3). The presence of sago-like pleural micronodules (seen in cases 1 and 3) during MT confers a high specificity and positive predictive value for TPE (4).

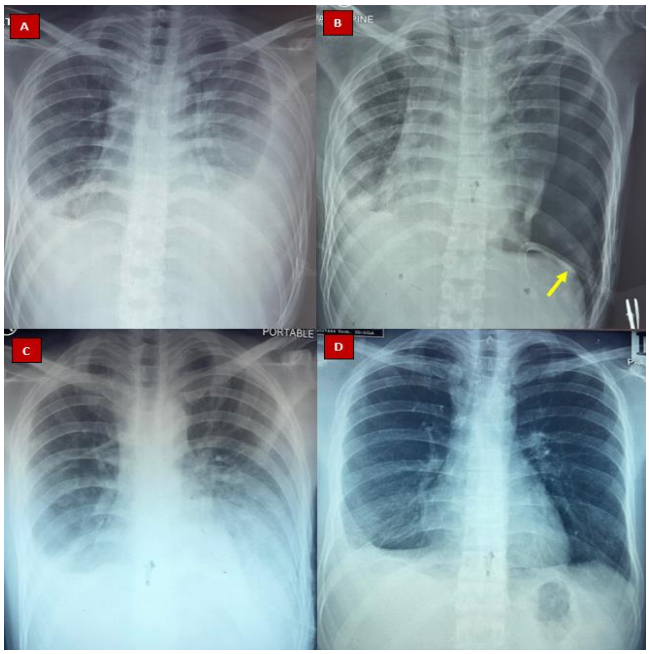

Figure 2: Chest X-ray on arrival showing bilateral pleural effusion, worse on the left side (a), chest X-ray immediately after procedure demonstrating resolution of pleural effusion. The left lung not yet fully expanded. Chest tube indicated with a yellow arrow (b). Chest X-ray taken during patient desaturation showing the rapid formation of left lung alveolar opacities, consistent with re-expansion pulmonary edema (c), total resolution of left pleural effusion with residual right pleural thickening 2 months after the initial event (d)

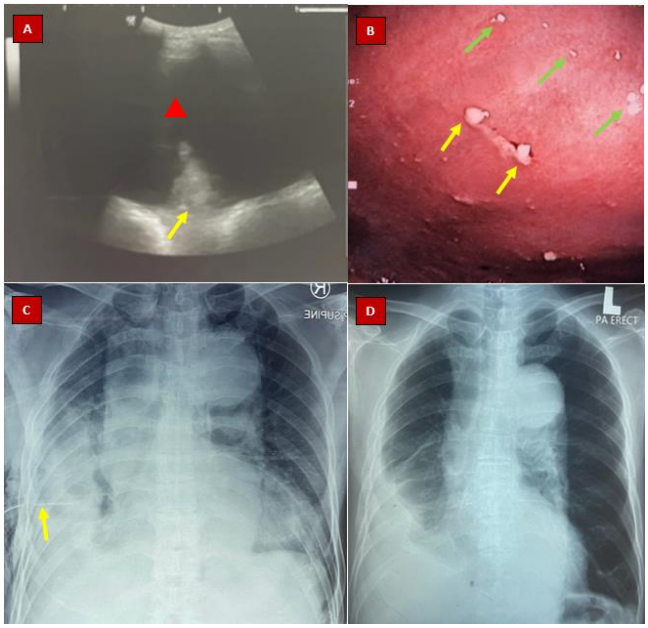

Figure 3: Pleural ultrasonography confirming a massive right pleural effusion (red triangle) with minimal septations. Collapsed right lung indicated by yellow arrow (a). Multiple whitish nodules (yellow arrows) and sago-like micronodules (green arrows) seen over the parietal pleura on medical thoracoscopy (b). Urgent chest radiograph taken during patient desaturation showing formation of new right lung alveolar opacities, consistent with re-expansion pulmonary edema. Chest tube indicated by yellow arrow (c). Repeat chest X-ray on day 3 of admission showing resolution of right lung alveolar opacities (d)

Table 1: Clinical characteristics and outcomes of patients with REPO post MT

Case number	Case 1	Case 2	Case 3	Case 4 (Rai et al.)	Case 5 (Corcoran et al.)
Age (years), Gender	34, female	20, male	57, male	29, male	52, male
Co-morbidities	Nil	Nil	Hypertension, dyslipidaemia	Nil	Familial cardiomyopathy, implantable cardioverter defibrillator in situ
Symptoms	Cough, malaise, worsening shortness of breath	Fever, cough, shortness of breath	Fever, weight loss and shortness of breath	Shortness of breath, cough, abdominal fullness, constipation	Not specified
Side of effusion	Bilateral, worse on the left	Bilateral, worse on the left	Right	Left	Right
Size of effusion	2/3 of left hemithorax, <1/3 of right hemithorax	2/3 of left hemithorax, <1/3 of right hemithorax	2/3 of right hemithorax	>2/3 of left hemithorax	>2/3 of right hemithorax
Estimated duration of symptoms prior to procedure	3 weeks	Approximately 2 weeks	4 weeks	6 weeks	Not specified
Pleural ultrasound findings	Flattened left hemidiaphragm. Complete displacement of lung within effusion. Minimal septations.	Flattened left hemidiaphragm. Complete displacement of lung within effusion. Minimal septations.	Flattened left hemidiaphragm. Complete displacement of lung within effusion. No septations.	Not specified	Not specified
Medical thoracoscopy (MT) findings	Diffuse dissemination of sago-like micronodules at the parietal pleura with minimal fibrin adhesions between parietal and visceral pleura	Multiple whitish nodules scattered over parietal pleura with minimal fibrin adhesions between parietal and visceral pleura	Diffuse dissemination of sago-like micronodules at the parietal pleura with minimal fibrin adhesions between parietal and visceral pleura	Nodular deposits at parietal pleura. Presence of fibrin adhesions not specified	No macroscopic features of malignancy. Right middle and lower lobes appeared hypoxic
Amount of fluid drained during MT	1.4 litres	1 litre	1.3 litres	1.5 litres	3.1 litres
Timing of symptom onset post procedure	30 minutes	4 hours	Immediately after procedure	1 hour post procedure	3 hours post procedure
Highest oxygen support given	Intubation with invasive mechanical ventilation	High-flow mask oxygen 10 litres/minute	High-flow mask oxygen 10 litres/minute	Non-invasive ventilation (BiPAP)	High-flow humidified oxygen (dosage not specified)
Other adjunct treatment given	Intravenous hydrocortisone 100mg and intravenous frusemide 40mg	Intravenous hydrocortisone 100mg and intravenous frusemide 40mg	Intravenous hydrocortisone 100mg and intravenous frusemide 40mg	Nil	Intravenous diuretics (dosage not specified)
Final diagnosis	Tuberculous pleural effusion	Tuberculous pleural effusion	Tuberculous pleural effusion	Non-Hodgkin's lymphoma	Inflammatory pleuritis (chronic inflammation with no evidence of malignancy / infection)
Progress	Extubated after 36 hours and was discharged after 6 days of hospitalization. Responded well to anti-tuberculous medications.	Weaned off oxygen after 48 hours and was discharged after 3 days of hospitalization. Responded well to anti-tuberculous medications.	Weaned off oxygen after 24 hours and was discharged after 3 days of hospitalization. Responded well to anti-tuberculous medications.	Weaned from BiPAP to nasal prong 1 litre/minute after 24hours. Weaned off oxygen completely by day 3 post procedure and was discharged after 5 days of hospitalization. Referred to medical oncology for further treatment	Weaned off oxygen and was discharged 3 days after procedure.

REPO: Re-expansion pulmonary oedema; MT: medical thoracoscopy

With an estimated incidence of less than 1% but a mortality rate of up to 20%, REPE is a rare but life-threatening complication in the treatment of pleural effusion, pneumothorax and/or lung atelectasis (5). Although first being described by Pinault in 1853 following the drainage of 3 liters of pleural fluid from a patient, the exact pathogenesis of REPO has yet to be fully elucidated (6). Possible mechanisms include reperfusion injury, excess negative pleural pressure during fluid or air drainage, and/or increased alveolar-capillary permeability and hypoxic damage to chronically atelectatic lungs (5). The suggested risk factors for REPE include long-duration lung collapse, rapid lung re-expansion, large volume fluid evacuation, female sex and/or the use of suction devices for fluid drainage (7). The symptoms of REPE typically develop within 3 hours of lung re-expansion, although delays of up to 48 hours have been reported (7). Rapid onset dyspnea and cough are cardinal features, and all three of the patients presented here developed cough and dyspnea within 4 hours of MT. The rapid drainage of large amounts of fluid (beyond 1 liter) to facilitate the better visualization of the pleural cavity were potential contributing factors to REPE in our cases. REPE management is supportive and should be guided by symptoms and physiologic parameters. Common interventions include oxygen support (with positive pressure and invasive ventilation, as necessary), diuretics, steroids and/or vasopressor support (8). We believe that the insertion of an intercostal drain with controlled fluid drainage prior to MT may help to reduce the risks associated with REPE.

REPE has been described following therapeutic thoracentesis (8), talc pleurodesis (9), chest tube drainage (8) and video-assisted thoracoscopic surgery (10), but in only two studies in the context of MT (7,11) (table 1, cases 4 and 5). A search of Online PubMed using the terms "re-expansion pulmonary edema" and "medical thoracoscopy" yielded only two relevant papers reporting on a total of two patients experiencing REPE following MT. The first patient developed pleural effusion secondary to non-Hodgkin's lymphoma, while the second patient's pleural biopsy results were suggestive of inflammatory pleuritis. Similar to our case series, more than 1 liter of pleural fluid was rapidly removed via suctioning in both of the described cases. To the best of our knowledge, our case series is the largest to date and the first to describe REPE occurring post-MT in patients with TPE. It remains unknown as to whether certain pleural ultrasound features, pleural pathologies or MT findings can predispose patients to REPE following MT. Previous studies have reported that the extent of displacement of a collapsed lung inside effusion seen on ultrasound can predict a non-expandable lung during drainage (12). The question remains, however, as to whether this feature, in addition to other ultrasound findings, such as the presence of septations/adhesions, can predict the risk of pulmonary edema following pleural drainage. Minimal pleural septations were observed in all of the patients in the present study during ultrasonography prior to MT. We hypothesize that the lack of septation, coupled with the rapid evacuation of pleural fluid during MT, may encourage more rapid lung re-expansion, thereby predisposing patients to REPE.

In conclusion, given the increasing use of MT for the provision of simultaneous diagnostic and therapeutic benefits to patients with unexplained pleural effusion, healthcare workers ought to be aware of REPE as a rare but potentially fatal complication of MT. Rapid recognition and prompt treatment are vital for a positive clinical outcome. We believe that future studies may aid in bridging the current gap in knowledge regarding the predictors and optimal management strategies of REPE following MT.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - N.C.H., K.L.N., H.Y.R., K.M.N., K.K.S.K.; Planning and Design - N.C.H., K.L.N., H.Y.R., K.M.N., K.K.S.K.; Supervision - N.C.H., K.L.N., H.Y.R., K.M.N., K.K.S.K.; Funding -; Materials -; Data Collection and/or Processing - N.C.H., K.L.N.; Analysis and/or Interpretation - N.C.H., K.L.N., H.Y.R.; Literature Review - N.C.H., K.L.N., H.Y.R., K.M.N., K.K.S.K.; Writing - N.C.H., K.L.N.; Critical Review - K.M.N., K.K.S.K.

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