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Editorial

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Allergic Rhinitis and Asthma: The United Airways Disease

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Interactions between the upper and lower airways have been well investigated in the past 30 years. The nasal and bronchial mucosa share similarities, in addition to their functional interaction. At least 80% of asthmatics have rhinitis and up to 40% of patients with rhinitis have asthma proposing the concept of 'one airway one disease' although there is still some differences between rhinitis and asthma.[1]

Recently, many clinical and as well as experimental studies suggested uniting the upper and lower airway diseases in a single term (allergic rhinobronchitis or united airways disease (UAD) as was proposed by Passalacqua et al.[2] This new link was founded by clinical epidemiological and immunological studies in addition to therapeutic outcomes. The recent understanding of the underlying pathogenetic mechanisms, including the cells, mediators and cytokines involved in the allergic inflammation in the respiratory tract has added more proof to the functional links between the nose and bronchi.[3]

According to the latest guidelines on the treatment and control of allergic rhinitis: The Allergic rhinitis and its impact on asthma (ARIA) workshop report; bronchial asthma and allergic rhinitis are distinct manifestations of a single airway and of the same disease.[4] Among the underlying evidence of the link between rhinitis and asthma is the common coexistence of rhinitis and asthma as patients can present with symptoms of allergic rhinitis then later develop asthma or the opposite can be the presenting scenario. Since, upper respiratory tract infections are among the very important causes of asthma exacerbation and also rhinitis has been found to be an important risk factor for developing asthma through postnasal drip into the lower airways or through mediators that directly alter airway reactivity or cause lower airway inflammation.[5]

Moreover, bronchial hyperreactivity (BHR) which is a characteristic of bronchial asthma, is also present in patients with allergic rhinitis who have no clinical evidence of asthma.[6] Many patients with rhinitis do not report the classical bronchial asthma symptoms and have no proof of airway obstruction on spirometry, but they present mainly with bronchial hyperreactivity which could be due to the presence of subclinical inflammation of the lower respiratory airway. Many studies were done on patients with seasonal allergic rhinitis, where bonchoalveolar lavage (BAL), bronchial biopsy and sputum samples have provided evidence of lower airway inflammation including eosinophils. This supports the presence of subclinical inflammation within the lower airways of patients with allergic rhinitis, which might be the underlying cause of the BHR in these patients.[7]

Therefore, there is a category of patients with persistent allergic rhinitis who present with symptoms of cough and/or chest tightness and show no evidence of airway obstruction on spirometry, their symptoms could be due to bronchial hyperreactivity. In addition to adequate rhinitis treatment, these patients usually benefit from asthma medications such as inhaled corticosteroids as well as leukotriene modifiers which can be of value in controlling upper as well as lower airway allergy. From practical experience it's believed that the early recognition and treatment of those patients might prevent their subsequent development of full blown asthma.

Moreover, in patients with asthma, rhinitis should be appropriately evaluated and

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treated to ensure good control of their asthma symptoms. Hence, a combined therapeutic approach should ideally be used to manage the upper and lower airway diseases, benefiting from the concept of united airways disease (UAD).

In conclusion, allergy is a systemic disorder and should not be considered as an organ disease, thus patients with respiratory allergy can present with rhinitis, bronchial hyperrreactivity and/or asthma.

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Editorial

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Misdiagnosis Murder: Disguised TB or Lung Cancer?

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Medical misdiagnosis dilemma of Tuberculosis (TB) *versus* Lung Cancer (LC) and their pre-judged unsuitable grueling treatment leading to numerous unnecessary deaths worldwide.[1] Globally, numerous patients with incurable LC are often misdiagnosed as sputum smear-negative pulmonary-TB (PTB) and *vice-versa* leading to delayed treatment and incorrect medication.[1-3] In most of the cases, LC stay undiagnosed for long periods of time as it shows no symptoms in early stages of disease. PTB and LC often show analogous symptoms including short painful breathing, persistent cough (sometimes bloody cough), tired-ness and inexplicable weight loss of patient.[4] Preliminary radiological features and symptoms of both ailments are so similar and imitate each-other; clinicians over and over again fail to distinguish it, resulting in many avoidable losses. In low-income countries like Africa, China and India, with high prevalence of PTB, misdiagnosis is more often which deceive clinicians to diagnose LC as PTB. Various factors are cited to be responsible for this situation in developing countries, includes insufficient infrastructure and socio-economic condition. Deferred prognosis and diagnosis promotes spread of the disease to other parts of the body, which can lead to more serious symptoms and eventual fatalities. Timely diagnosis of LC can increase the possibility of tumor ablation and chemo-radiotherapy to stave off the ailment. More often, clinicians begin anti-TB treatment for LC without confirmation of diagnosis that worsens the situation, to which I censure as "Misdiagnosis-murder". Similarly, wrong or delayed diagnosis of TB leads to poorer prognosis and higher likelihood of relapse of disease. In many instances, diagnosis of latent TB remains unnoticed as it does not display symptoms of TB in the most of the infected individuals.

Physicians primarily rely on chest X-rays as the initial step for detecting the LC or PTB. One of the major reasons of misdiagnosis may be the unremembered art of examination of chest X-rays and its mis-interpretation by clinicians in the era of advanced magnetic resonance imaging (MRI) and computed tomography (CT) scan. Lack of awareness, high cost of diagnosis and limited availability of high-end diagnosis machines in developing countries adds to wrong judgment.

Sceptical lung opacities in chest X-rays are repeatedly mis-interpreted as PTB in developing countries without further investigations and authentication. This pacification may be suggestive but not diagnostic as it only show concerned suspicious areas in the lungs but are not capable to confirm the disease. Opacities can be non-specific indication with a broad aetiology for any of these lung ailments including PTB, pneumonia, LC, bronchitis, sarcoidosis, upper respiratory infection etc.[5] Calcified nodular granulomas/lesions, fibrotic scars and enlarged lymph nodes in TB infected lungs may be recognized on X-ray film which could imitate lumps of LC.[5] Furthermore, enlarged lymph nodes and pleural effusion are common features for both the diseases. Here, physicians need to carefully review the diagnosis and relate it with existing symptoms and patients history of TB infection or LC. Once suspected mass or lump emerge in chest X-ray; further examination including bronchoscopy, CT, MRI, etc, is to be done to verify and confirm the disease. A CT and Positron Emission Tomography (PET) may be used for differential diagnosis of concerned ailments, which present cross-sectional 3D imaging with comprehensive details of the lung.[6] Investigational clinical and radiological attributes indicative of LC, such as opacification of air-spaces of lungs, pulmonary consolidations with irregular

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margins, thick-walled cavities and parenchyma infiltrate with elevated metabolic activity on the CT and PET scan are also similar for PTB4.[5]

The most suitable and inexpensive way to evade misdiagnosis is to examine each and every patient suspected with PTB and also having risk factor history for LC, is sputum analysis for mycobacterium (AFB staining) and tumor cells (Cytology). Biospsy or lymph node aspiration fluid can be used for cytology or microbiological studies (AFB Staining, microscopy, PCR and bacterial culture) further authenticate the diagnosis results. Once disease is identified, a therapeutic strategy can be designed.

Certainly, these diagnosis tests ought to be checked, re-checked, verified and confirmed to end the stigma. Careful history and examination can help clinician to suspect the right disease. Relying solely on the radiological finding for differentiation of both of these diseases cannot be judicious and the diagnosis should be confirmed by pathological and microbiological tests. From my perspective, differential-diagnosis should be conducted holistically encompassing (i) identification of probable ailment associated with particular symptoms (ii) carry out a set of specific diagnostic tests and (iii) exclude other medical conditions that do not correlate with diagnosis results, until a decisive diagnosis is found.

CONFLICT OF INTEREST

There are no potential conflicts of interest to disclose for this work.

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Review

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Diagnosis and Management of Spontaneous Pneumothorax in the Emergency Department: A Review of the Most Current Clinical Evidence for Diagnosis and Treatment

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ABSTRACT

Background: Spontaneous non-traumatic pneumothorax is a relatively common clinical presentation in the Emergency Department. The diagnosis of spontaneous non-traumatic pneumothorax has evolved from basic chest radiography to the reference standard of CT imaging. Point-of-care ultrasound is another highly sensitive diagnostic modality that has gained increasing acceptance. Finally, the treatment of this type of pneumothorax has also been rapidly changing.

Objective: We give an overview of the current literature regarding the definition and classification for pneumothorax. We discuss the current methods of diagnosis and management of spontaneous non-traumatic pneumothorax, which now include the promising treatment alternative of smaller pigtail thoracostomy catheters. We also discuss how a rapidly placed smaller pigtail catheter may be a viable single management option for a spontaneous tension pneumothorax.

Discussion: The management of spontaneous non-traumatic pneumothorax has been rapidly advancing. Viable treatment options now include observation alone, needle aspiration and placement of a small pigtail thoracostomy catheter, in addition to the use of a traditional thoracostomy tube.

Conclusion: Although the traditional treatment for a spontaneous non-traumatic pneumothorax was placement of a larger thoracostomy tube, this may no longer be the optimal management approach in these patients. The use of smaller pigtail thoracostomy catheters provides a viable treatment alternative to these larger catheters, and may also be used effectively as the only treatment step in a spontaneous tension pneumothorax. Placement of these smaller catheters sets the stage for potential outpatient management of pneumothorax, with increased comfort for the patient and possible cost savings.

KEYWORDS: Spontaneous pneumothorax; Primary pneumothorax; Tension pneumothorax; Pneumothorax; Pigtail catheter; Mini-catheter; Thoracostomy; Needle aspiration; Observation; Chest tube; Emergency department.

INTRODUCTION

Spontaneous non-traumatic pneumothorax (PTX) is a relatively common clinical problem in the Emergency Department (ED).[1] Interestingly, there is currently considerable variation in clinical practice with regard to the management of PTX.[2,3] In this article, we review the most

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current clinical evidence regarding the diagnosis and treatment of non-traumatic PTX in the ED.

Categories of Pneumothorax

A PTX is classified into a few categories based on the etiology: spontaneous, traumatic or iatrogenic. A spontaneous PTX can further be classified as primary or secondary (Table 1).

A primary spontaneous PTX occurs in patients without previously diagnosed pulmonary disease, when weakened architecture of the lung allows for sudden rupture of the visceral pleura. This leads to a loss of the negative pressure of -5 mm Hg normally found in the pleural space, with resulting accumulation of air between the normally tightly opposed layers of the parietal and visceral pleura.[4] Primary spontaneous PTX occurs in 7.4 to 18 cases per 100,000 population per year in men and in 1.2 to 6 cases per 100,000 population per year in women.[5] Smoking cigarettes or drugs, and a taller, thin physique are risk factors for developing primary spontaneous PTX in men.[6,7]

A secondary spontaneous PTX often results from an underlying disease process in the lungs, such as chronic obstructive pulmonary disease.[5] This accounts for one-third of cases of spontaneous PTX.[4] The incidence is 6.3 cases per 100,000 each year among men, and 2.0 cases per 100,000 each year among women.[5] The peak incidence of secondary spontaneous PTX occurs in patients between the ages of 60 to 65.[5]

A PTX can be further characterized as a 'tension PTX' when progressive accumulation of air leads to a corresponding increase in intrathoracic pressure. A tension PTX may occur in cases where there is a 'ball-valve effect' within the lung, allowing air to flow out into the chest cavity without allowing re-entry. The resultant increased intrathoracic pressure causes under-filling of the right side of the heart, due to limitation of venous blood return from the vena cavae.[8] Tension PTX is clinically recognized when evidence of hemodynamic instability is present, with findings that may include tachycardia, tachypnea, hypoxia and hypotension. Tracheal deviation away from the affected side may also be recognized.[4,9]

Diagnosis of Spontaneous Pneumothorax

ECG changes from a PTX are a common finding.[10] Lowered QRS voltage has been noted in lead I as a possible sign of a PTX.[11] In one study, 40% of the study group with a PTX on the right side had lowered QRS voltage and 70% of the study group with a PTX on the left side had lowered QRS voltage.[11]

CXR is often utilized for the initial diagnosis of PTX, due to its comparative low cost and easy obtainability at the patient's bedside. The traditional standard for PTX evaluation is with an expiratory, upright CXR.[12] Limiting the sensitivity of this test, a large PTX that layers anteriorly may potentially be missed in a supine patient who cannot sit upright.

Chest CT, which is considered the gold standard in the diagnosis of PTX, has a much higher sensitivity as compared to CXR.[13-15] The pooled sensitivity and specificity for CXR were shown in one study to be 31.8% and 100% (respectively) when compared with chest CT.[16] Chest CT scan has the ability to image the chest in 3-dimensions, thus easily detecting a PTX of any size within all locations of the thoracic cavity. A PTX that is missed on CXR, but seen on CT scan, has defined the term occult PTX in the modern literature. The incidence of occult PTX ranges from 3.7% to 64%.[17] The occult PTX that is relatively small in size is often clinically less important, as many sources urge no intervention for this finding.[13,17,18] However, especially when a supine CXR is used for diagnosis, a relatively large PTX that requires emergent treatment may not be adequately visualized. CT scan can be especially helpful in diagnosing these types of PTX.

Though CT scan has an excellent sensitivity in diagnosing PTX, point-of-care ultrasound (US) has emerged as a rapid and accurate bedside technique for the diagnosis of PTX because of its relative ease of use and lack of radiation. US has been shown in multiple studies to be far superior to a supine CXR for PTX. A recent meta-analysis of US for PTX demonstrated a sensitivity of 95.3%, a specificity of 91.1%, and a negative predictive value of 100%.[19,20] In 1986, the absence of "lung sliding" was noted in animals with PTX.[21] This was successfully applied to human patients in 1995.[20] Lung sliding refers to the back and forth respiratory movement of the normally tightly opposed visceral and parietal pleura of the lung that is seen on US. This pleural line can be visualized just beneath the level of the ribs and is best appreciated using a high frequency linear probe. Because the US probe is placed anteriorly at the more superior aspect of the supine patient's chest, a PTX that collects anteriorly and is difficult to see on CXR can be well visualized on US. The probe can then be moved more laterally and inferiorly to assess the size of the PTX. A large PTX will result in a lack of lung sliding at both positions, while a smaller one may result in

Pneumothorax Classifications
Spontaneous pneumothorax • Primary: secondary to rupture in the subpleural lining of the lung in a patient without any previously diagnosed lung disease • Secondary: secondary to pre-existing pulmonary disease
Traumatic pneumothorax: resulting from penetrating or blunt trauma to the chest
Iatrogenic: due to a medical intervention

Table 1: Classification of pneumothorax.[5,13]

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a lack of sliding anteriorly with sliding preserved laterally.

In addition to lung sliding, normal respiratory movement of the lung creates comet-tail artifacts, which are vertical hyperechoic (bright) lines that arise from the normal pleural line and extend a short distance towards the bottom of the image.[22] The accumulation of intrathoracic air in a PTX splits the normally tightly opposed pleural visceral and parietal layers. This leads to the disappearance of both normal lung sliding and comet-tail artifacts.

Of note, it should be known that there are several circumstances in which one may detect the absence of lung sliding on US when in fact there is no PTX, leading to a potentially false positive examination. This may occur in patients with large bullae in the setting of chronic obstructive pulmonary disease. Lung sliding will also not be appreciated in patients with adhesions, such as in patients who have undergone prior lung surgery or pleurodesis. Finally, patients with large pleural effusions, where fluid disrupts the interface between the normally opposed visceral and parietal pleura, will also not have appreciable lung sliding on US. Caution should be taken when using US to assess for the presence of PTX in these patients.[23]

Management Options for Spontaneous Pneumothorax

The treatment of spontaneous PTX is largely dependent on the patient's clinical presentation. If the patient is stable and has less than 15-20% involvement of the hemithorax, observation without intervention may be appropriate.[13,24] The British Thoracic Society additionally recommends that the patient must not exhibit any dyspnea to qualify for observation alone.[25] A PTX is reabsorbed at a rate of 1-2% per day, which may be accelerated by the administration of supplemental high flow oxygen.[26,27]

For a stable patient with a spontaneous PTX involving greater than 15-20% of the hemithorax, there is controversy with regard to the management options. These include observation alone (usually in the hospital for a period of time), needle aspiration, placement of a smaller thoracostomy catheter or insertion of a standard chest tube. More recent literature has focused on treatment with smaller pigtail thoracostomy tubes (typically 8-9 French size), a much more comfortable option for the patient. This also allows for increased mobility and sets the stage for potential outpatient management of PTX. A summary of treatment guidelines for subtypes of pneumothorax is listed in Table 2.

The literature supporting specific management of PTX has been evolving rapidly in the recent years. A systematic review of the literature by Brims and Maskell in 2013 identified 18 studies with a total of 1235 patients. Of these, 992 cases were identified as spontaneous PTX. The success of treatment with smaller catheters attached to Heimlich flutter valves was 1060/1235 (85.8%). Outpatient treatment was possible in 761/977 (77.9%). Complications were rare.[28] In a 2014 article by Voisin et al[2], 132 patients with spontaneous PTX were managed as outpatients with a pigtail thoracostomy tube attached to a Heimlich flutter valve. Of these 132 patients, 110 had primary PTX and 22 had secondary PTX. 103 of the 132 patients were exclusively managed as outpatients, with the ambulatory success rate of 78%. 7 patients were initially admitted but then quickly discharged, bringing the success rate to 83%. Of these 7 patients; 2 were observed as they were the first patients to be treated with pigtail catheters, 2 had severe dyspnea and COPD requiring hospital observation and 1 had chest pain requiring additional evaluation. Furthermore, in the author's opinion, 3 patients were unnecessarily admitted.[2] Of all patients, 26% had recurrence at 1 year. The authors describe a significant cost savings with outpatient management: $926 *versus* $4,276 with placement of a chest tube and admission to the hospital for a significant period of time (typically 4 days in this study).

Finally, a 2014 study by Massongo et al enrolled 60 patients with primary spontaneous PTX. Of these, 20% were characterized as small and all were successfully managed with observation alone.[29] In the remaining 80% that were characterized as large, all patients underwent placement of a smaller 8.5 French pigtail catheter.[29] 79.2% of these patients were successfully managed with the catheter alone.[29] 20.8% of the patients went on to require video-assisted thoracoscopy for definitive management of the PTX.[29] These studies make the strong argument for the management of hemodynamically stable patients with spontaneous PTX, even of a larger size, as outpatients with a smaller thoracostomy tube attached to a Heimlich valve.

Pneumothorax Size (% of hemithorax)	Interventions with Options
<15-20%	Observation and oxygen
≥20% (asymptomatic)	1) Pigtail catheter placement 2) Needle aspiration
≥20% (symptomatic)	1) Pigtail catheter placement 2) Chest tube placement
Tension pneumothorax	1) Immediate needle decompression then followed by placement of pigtail catheter or chest tube 2) Immediate pigtail catheter placement 3) Immediate chest tube placement
Pneumothorax with hemothorax	Chest tube placement

Table 2: Treatment guidelines for subtypes of pneumothorax.[13,25,33]

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An alternative management strategy is needle aspiration using an intravenous catheter.[4,13] Air aspiration has been shown to be a relatively effective treatment option as compared to chest tube drainage for the first episode of a primary spontaneous PTX.[1,13,30-32] 30-80% of these patients may be successfully treated (defined as requiring no additional invasive intervention) with the aspiration technique alone.[33] Patient treated with catheter aspiration require a period of hospital observation, with a repeat CXR at 6 hours. If the patient is clinically improving and the PTX has significantly decreased in size, they may be discharged. However, as compared to a first time spontaneous PTX, recurrent PTX is best managed with a thoracostomy tube. In these patients, repeated needle aspiration is less likely to be successful.[25]

The management of first time PTX measuring greater than 20% of the hemithorax is therefore controversial.[34] There have been several studies comparing these treatment modalities.[1,31,35,36] Based on a systematic review and meta-analysis of these articles by Aguinalde et al, a thoracostomy tube may be more effective in the immediate post-treatment period. However, after 1 week this advantage ceases to exist.[37] Currently, the British Thoracic Society currently recommends needle aspiration as the first line of action for a symptomatic and larger spontaneous PTX. Advantages of needle aspiration include less pain than chest tube insertion, less material and human resources, and potential reduction in hospitalization and hospital length of stay.[25,37] Unfortunately, needle aspiration is associated with a failure in one-third of patients, and repeat needle aspiration is unlikely to be successful unless associated with an initial technical difficulty.[25] Therefore, the current guidelines of the American College of Chest Physicians advocate for the use of a smaller thoracostomy catheter over aspiration.[37,38] Table 3 summarizes studies to date on management of PTX.

For management of a tension PTX, and especially if associated with hemodynamic instability, it has been recommended that the patient undergo immediate large bore needle chest decompression.[39] Because needle decompression is only a temporary measure which may have variable success, the patient will then typically require placement of a thoracostomy tube for definitive management of the PTX.[13] Immediate placement of a smaller thoracostomy catheter is a viable single step alternative to needle decompression, if this can be done expeditiously.

METHODOLOGY OF TREATMENT OF SPONTANEOUS PNEUMOTHORAX

Pigtail Thoracostomy Tube Placement

Use of smaller pigtail thoracostomy catheters is an increasingly important and effective treatment option for the management of spontaneous PTX, even with tension physiology.[2,38] To place a pigtail catheter, one can use a commercial catheter kit that is readily available in most hospitals. These kits employ the Seldinger technique to place a 8-9 French thoracostomy tube. The most common insertion site is at the second intercostal space along the mid-clavicular line. Alternatively, a second position is at the same location for traditional chest tubes (fourth or fifth intercostal space along the anterior axillary line). The technique for thoracostomy tube catheter placement will be familiar to most clinicians, as using the Seldinger technique will make this

Study	Population	#Patients	Outcome		Success rate		
				Intervention	Aspiration	Pigtail	Chest tube
Ayed 2006 RCT[30]	PSP symptomatic or >20% size	137	Re-expansion at 1 wk		89%		88%
Massongo 2013 POS[44]	PSP: small undergo observation alone, large/dyspnea	60	Re-expansion at 1 wk	100%		83%	
Parlak 2012 PRT[45]	PSP symptomatic or >20% size	56	Immediate re-expansion		68%		80%
Voisin 2014 RR[2]	Large PSP and SSP	132	Outpt management at day 4			78%	
Harvey 1994 PRT[34]	PSP	73	1 yr recurrence		86%		74%
Brown 2014 RC[43]	PSP and SSP	323	1 yr recurrence	95%			83%
Ho 2010 RCT[46]	PSP	48	Re-expansion at 1 wk		91%	88%	
Kelly 2008 RC[24]	PSP	154	Need for additional intervention	79%	50%		73%
Noppen 2002 RCT[1]	PSP	60	Re-expansion at 1 wk		93%		85%

RCT: Randomized Control Trial; POS: Prospective observational Study; PRT: Prospective Randomized Trial; RR: Retrospective Review; RC: Retrospective Cohort; PSP: Primary Spontaneous Pneumothorax; SSP: Secondary Spontaneous Pneumothorax.

Table 3: Comprehensive summary of studies to date on pneumothorax management.

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very similar to placement of a central line.

A Pleurovac chest tube drainage system is most commonly used for the initial removal of air from the thoracic cavity. Make sure to cut the tip of the long plastic tubing that comes off the Pleurovac, so that the adaptor can be easily inserted. Apply tape to both the Pleurovac tubing and the adaptor to prevent air leaks. The plastic adaptor is then connected to a 3-way stopcock. Last, the pigtail thoracostomy catheter is connected to the stopcock to complete the drainage system.

Gentle wall suction through the pleural drainage device is often used to initially inflate the lung. Once the lung has been adequately inflated, the tube can be placed to water seal. A Heimlich valve may alternatively be utilized in place of a water-seal device.[13] A less common, but potentially effective method for lung re-inflation, is to attach the thoracostomy catheter to a 3-way stopcock, and then to slowly aspirate the air from the chest. Confirm the tube placement and change in PTX size after treatment with a CXR.

Needle Aspiration

The British Thoracic Society advises needle aspiration for initial treatment of a spontaneous PTX and is an alternative approach to placement of a thoracostomy catheter.[25] For needle aspiration, a 16 French angiocatheter is used. Insertion sites are similar to those used for pigtail thoracostomy tube placement. After infiltration of local anesthetic, the angiocatheter is inserted while also aspirating with a syringe. Once air is withdrawn, the catheter is then advanced while the needle is simultaneously withdrawn. When the catheter is in adequate position, air can then be manually aspirated using a 3-way stopcock. Another strategy is to connect the catheter to a vacuum bottle with a water seal that generates a negative pressure. The vacuum bottle is connected until there is no further air bubbling in the bottle for 30 minutes.[31] Of note, aspiration should be stopped if more than 2.5 liters of air have been removed, as this suggests that further lung expansion is unlikely.[1,25] If there is complete re-expansion, or only a small rim of apical PTX on repeat CXR, the procedure is complete. If the lung is not significantly expanded and the procedure was technically successful, consider placement of a pigtail thoracostomy catheter.

Prophylactic Antibiotics

The use of prophylactic antibiotics is controversial.[40] There is no consensus on the use of prophylactic antibiotics after thoracostomy catheter placement in the ED. The rate of empyema from chest tube insertion is estimated to be 1%.[41] Some data suggests that antibiotics may reduce the incidence of pneumonia or empyema associated with thoracostomy tubes.[42] If the decision is made to utilize antibiotics, first generation cephalosporins administered for the first 24 hours are recommended (although it should be noted that this recommendation was created in the setting of a hemothorax).[43] However, there is also data suggesting that prophylactic antibiotics are unnecessary.[42] Regardless of the decision on prophylactic antibiotics, sterile technique should be the priority during placement of a thoracostomy catheter.[41]

CONCLUSION

In this article, we have reviewed the definition and classifications for PTX. We have also focused on the most current diagnosis and management of primary spontaneous PTX, so that clinicians will have the latest information to optimize patient care. As treatment of PTX evolves, there is currently no set standard for the treatment of primary PTX. American and British Thoracic Society recommendations differ from simple needle aspiration to placement of a small-bore thoracostomy tube. These smaller pigtail thoracostomy catheters present a promising treatment alternative to traditional larger chest tubes, even in a tension PTX. Outpatient management of hemodynamically stable patients with primary spontaneous non-traumatic PTX has now become a viable management option with potential treatment benefits and cost savings.

CONFLICTS OF INTEREST: No conflicts of interest.

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Review

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Pulmonary Endometriosis: A Review

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KEYWORDS: Pulmonary endometriosis; Benign; Catamenial pneumothorax; Catamenial haemothorax; Catamenial haemoptysis; Life-threatening; Thoracotomy.

INTRODUCTION

Endometriosis is a benign gynaecological condition whereby endometrial tissue exists outside the uterus in women of reproductive age group. It occurs mainly in the pelvis and rarely extra-pelvic areas such as the lungs. Pulmonary endometriosis is a rare but can be life-threatening. There is active endometrial tissue in the tracheobronchial tree, lung parenchyma and lung pleura.[1] Pulmonary endometriosis has four main clinical conditions namely catamenial pneumothorax, catamenial haemothorax, catamenial haemoptysis and endometrial nodules in the lung. Catamenial pneumothorax is the most common manifestation.[2] Pulmonary endometriosis is associated with pelvic endometriosis and subfertility. Because of its rare phenomenon, there may be delayed diagnosis leading to serious life-threatening complications. This article aims to raise awareness amongst clinicians particularly gynaecologists about this rare but life-threatening condition. It is a benign, treatable condition and no women should die from it.

AETIOLOGY

The aetiological mechanisms of pulmonary endometriosis are not well known.[3] There are no predisposing factors.[4] A possible explanation for the pathogenesis may involve peritoneal-pleural movement of endometrial tissue through diaphragmatic defects and microembolisation through pelvic veins.[5] Endometriotic deposits can be found in the diaphragm, pleura, lung parenchyma and tracheobronchial tree. The preferred sites are the diaphragm in keeping with the embryological suspected peritoneal-pleural migration route.

Clinical Presentation

Classically there are chest symptoms associated with menstruation. These include dyspnoea,[6] intermittent productive coughing with blood-tinged sputum, chronic anemia, loss of appetite, generalised weakness[7] and chest pains.[8] Patients can also present with catamenial haemoptysis.[9,10] All these symptoms can be found in patients with pulmonary tubercoloisis. Some patients may be asymptomatic.

Complications

The complications of pulmonary endometriosis can be repeated mild symptoms to massive pulmonary complications. Catamenial pneumothoraces can be recurrent needing repeated pleurodesis. If massive they can lead to lung collapse, respiratory compromise and death. Catamenial haemothoraces can lead to chronic pulmonary bleeding and chronic anemia. If they are massive, catastrophic pulmonary haemorrhage can occur leading to cardiovascular shock and death. Repeated pleurodeisis run the risks of infection, lung punch and fibrosis.

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Investigations

The cycle of pulmonary symptoms associated with menstruation can lead to a clinical[11] diagnosis of pulmonary endometriosis. Many diagnostic methods both clinical and laboratory have been used but none of them is the golden standard.[12] Investigations can be done during and after menses to compare appearances of lesions. Imaging techniques may be non-specific.[13] The diagnosis can be difficult to make.[4] A chest x-ray or computed tomography (CT) can reveal multiple lung nodules,[14] if these are present. A computed tomography during and after menstruation can be useful in precise location of paranchymal pulmonary endometriotic lesions.[15] Magnetic resonance imaging is now increasingly being used for assessment of lung conditions such as endometriosis.[16] It is good at characterization of pleural endometriotic nodules and haemorrhagic pleural effusions.[17] Broncial angiography can demonstrate prominent vasculature.[18]

Rigid broncoscopy can allow bronchial samples to be obtained from tracheobroncial lesions[6] and samples sent for histological examination. Through the broncoscope hyperaemic tissue in the tracheobronchial tree can be seen.[1] Fibre-optic broncoscopy can also reveal lesions such as diffuse erthyma and also allows bronchial washings to be obtained for histological testing.[8,19] Video-assisted thoracoscopic surgery can reveal endometrial tissue embedded in the diaphragmatic pleura.[9,20]

Tumour markers CA125[4] and CA19-9[7] can be elevated causing fears of the existence of malignancy. Pulmonary tuberculosis[21] is another differential diagnosis that may be considered during the investigations for pulmonary endometriosis. Lesions found during investigations can cause confusion with lung cancer.[6]

Management

The treatment of pulmonary endometriosis can be commenced based on the clinical history alone of cyclical chest symptoms associated with menses with complete resolution of symptoms.[11] The management of pulmonary endometriosis calls for a multi-disciplinary approach involving the anaesthetist, gynaecologist, pneumologist and thoracic surgeon.[22,23]

Medical therapy involves the use of oral contraceptives[11] or medroxyprogesterone acetate for 3 to 6 months and patients can be asymptomatic 12 months after treatment.[19] Danazol therapy was previously extensively used to treat endometriosis[24] but it has fallen off due to its side effects profile. Currently GnRH analogues[4,8,25] are the ones widely used. Courses of 3 to 6 months produce good outcomes. The GnRH analogues cause a reversible hpyo-estrogenic state that starves endometrial tissue of oestrogen hence growth and the tissue dies out. Urgent tube thoracostomy for patients in respiratory distress relieves pnuemothoraces and haemothoraces while awaiting definitive treatment. Thoracotomy[26] with lobectomy,[27] parietal pleurectomy and partial diaphragmatic excision[28] can be done in life-threatening endometriosis. This is life-saving surgery.

Immediately after surgical treatment, medical therapy must be started[4,13] as recurrence is common since the endometrial tissue will be responsive to ovarian hormones.

Prognosis

Following treatment complete cure is possible.[1,8,29] Fertility returns to normal after treatment.

CONCLUSION

This benign gynaecological disorder that is common in the pelvis but rare in the lungs can have life-threatening consequences. Clinicians must be made aware of this condition so that they have a high index of clinical suspicion[30] to prevent deaths in young women. Prompt treatment of pneumothoraces and haemathoraces by a multidisciplinary team will save lives.

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Research Letter

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Periostin Levels do not Distinguish Chronic Obstructive Pulmonary Disease Patients with Frequent and Infrequent Exacerbations

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ABSTRACT

Background: Periostin, an extracellular matrix protein, is involved in inflammatory processes of the lung. To date, most studies have focused on periostin in asthma patients, its role in chronic obstructive pulmonary disease (COPD) is less clear and no information has been reported on blood levels of periostin in COPD patients in the context of exacerbation rates. As such, this exploratory study aimed to investigate whether periostin is helpful to distinguish between COPD patients with frequent and infrequent exacerbations.
Methods: We performed an examination of patients with COPD participating in a COPD cohort study in Switzerland. Periostin levels were determined in serum samples by using a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Patients underwent evaluation of clinical symptoms including exacerbation rate (exacerbation defined by requiring oral corticosteroids and/or antibiotics) and lung function. In a subgroup of patients an annual follow-up was available that was considered in an additional analysis.
Results: Twenty six patients (global initiative of obstructive lung disease (GOLD) stage 1 none, 31% stage 2, 38% stage 3, 31% stage 4) were included in the analysis. The mean±standard deviation (SD) age of the patients was 63±5.9 years, 16 were males, 24 were smokers or ex-smokers. The median (quartiles) post-bronchodilator FEV_1% predicted was 36(27/57). There was no significant difference in periostin levels between patients with frequent and infrequent exacerbations. The follow-up data revealed no evidence that periostin is helpful in distinguishing frequent from infrequent exacerbators.
Conclusion: Our analysis performed in a small group of carefully matched COPD patients demonstrates that there is no significant relationship between exacerbation rate and periostin levels in blood.

KEYWORDS: COPD; Periostin; Eosinophilic inflamation; Exacerbations.

ABBREVIATIONS: BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; ELISA: Enzyme-Linked Immunosorbent Assay; FEV_1: Forced expiratory volume in one second; GOLD: Global Initiative of Obstructive Lung Disease; SD: Standard Deviation; WISDOM: Withdrawal of Inhaled Steroids during Optimised bronchodilator Management; QoL: Quality of Life; CGPS: Copenhagen General Population Study.

Trial Registration: https://clinicaltrials.gov/, NCT01527773. Registered 18.01.2012 (retrospectively registered).

To the Editor,

Periostin, a multifunctional matricelluar protein, has been reported to be an excellent predictor of airway eosinophilia.[1] Eosinophilic inflammation within the airways is usually considered as a hallmark of patients with asthma and it was found that the exacerbation rate was significantly reduced in patients with high levels of periostin.[2] While, to date, most studies have focused on

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periostin in asthma, its role in COPD is less clear and no information has been reported on blood levels of periostin in COPD patients in the context of exacerbation rates. However, recent publications focused on the important role of eosinophils and their association with exacerbation rate.[3,4] Moreover, COPD patients with elevated eosinophil counts also had an increased risk of exacerbations.[5] A recent publication implied that high blood eosinophils and high plasma periostin were associated with improved lung function three months after starting treatment with inhaled corticosteroids in combination with a long acting bronchodilator.[5]

These data suggest that periostin may serve as a biomarker in COPD patients. As such, this exploratory study aimed to gain insight whether periostin is helpful to distinguish between COPD patients with frequent and infrequent exacerbations.

We performed an examination of patients with COPD participating in a COPD cohort study from seven pulmonary clinics in Switzerland (NCT01527773). The cantonal ethics committee of Zurich approved the study and patients provided written informed consent (KEK-ZH-Nr. 2011-0106). Periostin levels were determined in serum samples by using a commercially available ELISA kit (Thermo Fisher Scientific, Zug, Switzerland). COPD severity was defined according to GOLD guidelines. Patients underwent evaluation of clinical symptoms including exacerbation rate (exacerbation defined by requiring oral corticosteroids and/or antibiotics) and lung function. All patients were examined in a stable phase of the disease and, in case of an acute exacerbation, the evaluation was postponed by at least 6 weeks.

Comparisons among groups were performed with paired *t*-test, Wilcoxon signed ranks test and chi-square test.

Since the number of patients with frequent exacerbations (≥2 per year) was considerably lower than the number of patients with infrequent exacerbations, we matched every patient from the frequent exacerbator group to a patient with infrequent exacerbations. Matching criteria included age, body mass index (BMI) and disease severity according to FEV_1. Smoking was considered as additional confounder in the analysis because it has been reported recently that periostin may be repressed by smoking.[6]

Twenty six patients (GOLD stage 1 none, 31% stage 2, 38% stage 3, 31% stage 4) were included in the analysis. The mean±SD age of the patients was 63±5.9 years, 16 were males, 24 were smokers or ex-smokers. The median (quartiles) post-bronchodilator FEV_1% predicted was 36(27/57). There was no significant difference among the two groups for demographic data. In a subgroup of patients an annual follow-up was available that was considered in an additional analysis.

When COPD patients with frequent exacerbations were compared to their matched peers with infrequent exacerbations, no signifcant difference in periostin blood levels was detected. Since in a subgroup of patients annual measurements were available, we also analyzed patients that changed their exacerbation frequency over time, e.g. from frequent to infrequent or *vice versa*. This additional analysis provided no evidence to support that periostin is helpful in segregating both groups. No correlation was found between the level of serum eosinophils and periostin in our cohort (Table 1).

Frequent exacerbations, predominantly found in patients with severe COPD, result in accelerated disease progression and mortality.[7] These patients usually have a more rapid decline in lung function, worse quality of life (QoL) and decreased exercise performance. In a stepwise regression performed in more than 2000 COPD patients the history of previous exacerbations was found to be the strongest predictor of subsequent COPD exacerbations.[8]

In addition, a number of previous studies were undertaken to identify biomarkers that may help to predict exacerbation frequency.[9] To date, however, no serum biomarkers reliably predict exacerbation frequency in COPD patients.

Blood eosinophils in COPD have been shown to predict corticosteroid responsiveness during acute exacerbation. Patients with a peripheral blood eosinophil count of ≥2% at the onset of an outpatient managed exacerbation responded promptly to prednisolone, whereas those with a count of <2% had a higher rate of treatment failure compared with placebo.[10] In a post-hoc analysis of the withdrawal of inhaled steroids during optimised bronchodilator management (WISDOM)-trial Watz and colleagues[4] demonstrated that withdrawal of inhaled corticosteroids in COPD patients with an elevated baseline serum eosinophil count led to a higher risk of moderate to severe exacerbations. The authors concluded that an eosinophil count of 4% or greater 300 cells per µl may predispose to a deleterious effect of inhaled corticosteroid withdrawal.[4] A recent analysis of the data from the Copenhagen General Population Study (CGPS) revealed that in COPD patients an increased blood eosinophil level above 0.34 (gram/liter) g/l was associated with a 1.76-fold increased risk of severe exacerbations.[3]

While these publications highlight the role of eosinophils in COPD, in particular in the context of acute exacerbations, to the best of our knowledge our study is the first report on the levels of periostin in COPD and exacerbation rate.

The current analysis focusing on the role of periostinin stable patients with COPD however did not help to stratify patients into frequent or infrequent exacerbators.

Smoking was recently postulated to repress periostin at the individual gene level.[6] However, in our study only 1 patient in the infrequent exacerbation group and two patients of the frequent exacerbators were active smokers and the association

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	All COPD patients (n=26)	Infrequent exacerbators (n=13)	Frequent exacerbators (n=13)	*p* value
Clinical characteristics				
Age, years	63(5.9)	64(6.2)	61(5.6)	0.059
Male/Female	16/10	8/5	8/5	1.000
Body mass index, kg/m^2	25.7(23.5/28.1)	26.6(24.7/28.1)	24.5(22.9/26.5)	0.422
Pack years of smoking	38(26.4)	46(29.6)	29(20.7)	0.148
Current smokers, N(%)	3(12)	1(8)	2(15)	
LAMA+LABA, N(%)	2(8)	2(15)	0(0)	0.157
LAMA+LABA+GC, N(%)	20(77)	10(77)	10(77)	1.000
Lung function				
FEV_1, % pred.	36(27/57)	41(23/57)	33(28/57)	0.779
FVC, % pred.	77(15.7)	78(15.8)	76(16.2)	0.672
TLC, % pred.	115(21.5)	117(21.6)	113(21.9)	0.497
RV/TLC-ratio	138(45.8)	133(55.9)	142(35.1)	0.394
DLCO, % pred.	36(32/47)	36(33/47)	37(32/60)	0.136
Blood gas analysis				
PaO_2, kpa	9.4(8.1/11.0)	8.8(8.1/9.9)	9.5(8.1/11.0)	0.753
$PaCO_2$, kpa	5.0(0.7)	5.2(0.8)	4.8(0.6)	0.113
Laboratory parameters				
Periostin, ng/ml	9.39(6.79/17.93)	7.85(6.40/9.04)	12.32(9.73/20.21)	0.133
Hemoglobin, g/dl	14.6(1.2)	14.6(1.4)	14.6(1.1)	0.865
Leukocytes, G/l	8.6(2.08)	8.1(2.13)	9.1(1.99)	0.215
Lymphocytes, G/l	1.56(1.27/2.12)	1.60(1.46/1.89)	1.42(1.20/2.42)	0.534
Neutrophils, G/l	6.15(1.93)	5.67(1.72)	6.72(2.08)	0.144
Eosinophils, G/l	0.08(0.05/0.16)	0.08(0.08/0.16)	0.08(0.03/0.16)	0.267
CRP, mg/l	2.5(1.1/4.0)	2.6(1.2/4.0)	1.5(1.0/4.0)	0.382

Values are mean(SD) or median(quartiles) unless otherwise stated; LAMA: long-acting muscarinergic antagonist; LABA: long-acting beta-agonist; GC: glucocorticoids;FEV1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; DLCO: Diffusing capacity of the lung for carbon monoxide. *p<0.05 for comparison of differences between the two groups.

Table 1: Characteristics of patients with frequent and infrequent exacerbations.

between smoking status and periostin level was not significant. Moreover, recent findings from a large cross-sectional study suggested that serum levels of periostin do not have to be adjusted for smoking history, age and gender.[11] As such, it is unlikely that the levels of periostin in our cohort have been under estimated.

In summary, our observation, although limited by the small size, suggests that serum periostin levels do not help distinguishing COPD patients with frequent from those with infrequent exacerbations. Future studies will have to determine whether periostin levels are useful in guiding therapeutic strategies in patients with COPD as it has been demonstrated in asthma patients.

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CONFLICTS OF INTEREST

None of the authors has competing interest relating to this article.

CONSENT

The Cantonal Ethics Committee of Zurich approved the study and patients provided written informed consent (KEK-ZH-Nr. 2011-0106). The study was performed in accordance with the Declaration of Helsinki.

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