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Ode to our best teachers

Evelyn Victoria E. Reside, MD, FPCCP
Editor-in-Chief

"You cannot open a book without learning something from it." – Confucious

And so here we are again, with another issue of the PJCD, another book with something for everyone to learn from.

Indeed, for this issue, we present here an interesting collection of case reports, a reminder to us that no two patients are alike, and that we should never stop discovering something new and different from them who are our best sources of learning.

Skimming through the patient cases presented here, it is evident that our featured patients initially present with more common dilemmas: central sleep apnea, a vehicular accident, hemoptysis, pleural effusion, a concomitant systemic comorbid disease, and an elevated hemidiaphragm. Easily, these are some of the more common reasons for either consultation to a pulmonary specialist, or admission to a hospital.

But as individual as our patients are, each of these cases featured in this issue offer something new, or something different, that makes them less common than at first look. The two cases of central sleep apnea reported by Rillera et al are both noted for two male patients with elevated body mass index. However, other than that, they seem to have no other commonalities in either age or medical circumstance. Abenojar-Concon et al, meanwhile, reminds us to consider conditions other than pneumonia for hospitalized patients who develop progressive dyspnea. In fact, the message here is that Venous Thromboembolism should be considered for all patients with trauma involving the chest or the trunk. The case of hemoptysis as described by Villalobos et al takes us on the ideal journey of a patient with bleeding who undergoes the necessary pertinent diagnostic workup and receives the appropriate therapy; indeed, it is not often that a patient presenting with massive hemoptysis is able to access not only the textbook diagnostic work-up, but also the ideal treatment plan in the local setting. Due to constraints in resources, both from the patient and the provider side, more often than not expensive interventions such as CT scans, bronchoscopy and embolization are not done.

Chua and Dy-Agra, on the other hand, provide a snapshot of how it is to manage out of the box; instead of the usual chest tube insertion with or without VATS or intrapleural catheterization to drain documented loculated pleural effusion, we are now presented with two cases who received intrapleural streptokinase and recombinant tissue plasminogen activator with acceptable results. Another of the less common conditions are the connective tissue diseases (CTD); despite the fact that awareness for CTDs is improving, they remain diagnoses of exclusion

for many patients and physicians. Moreover, clinching the diagnosis of CTD may be expensive and therefore inaccessible to many patients.

Our last featured case definitely presented as the diagnostic dilemma of paradoxical breathing not associated with flail chest. Since an elevated hemidiaphragm is not pathognomonic of only one particular diagnosis, this finding on chest x-ray, coupled with abnormal breathing patterns, is not necessarily diagnostic of phrenic nerve paralysis. A keen clinical eye and heightened suspicion for this uncommon diagnosis are key in identifying the condition at the start. But similar to our other featured cases, work-up and treatment remain expensive and therefore inaccessible to many patients. It is thus advantageous that an algorithm is presented here.

Aside from the medical challenge these cases present to clinicians, and the valuable lessons they impart such as the value of thinking outside the box, what glaringly pops out of these pages is that none of them were diagnosed using only the simple tried-and-tested means of history and physical examination. Every medical student has heard this before: "A good history and physical examination clinches the diagnosis almost always"; and yet we have here patient stories who might not have found their ending without a barrage of diagnostic testing and thus significant cost. Such misfortune for these patients indeed: the physical burden of their "mystery illness" is further compounded by the additional financial burden of having to spend more just because their conditions are uncommon and less easily recognized.

In these difficult times when the out-of-pocket expenditure of patients is magnified by the increasing cost of living, it definitely brings a sigh of relief to hear of the promise of universal health coverage. Of course, it cannot implemented any time soon, and surely there will be birthing pains, but for now, it brings much hope for the less fortunate patient even as it still remains a promise. For sure, our featured cases document the medical journey of our patients, but just like any scientific manuscript, they are silent on the socioeconomic contexts of their illnesses. The extraordinary efforts oftentimes taken by patients and physicians to support diagnostic tests and ensuing medical treatment are never chronicled in these pages, and yet without these efforts perhaps none of these patients would have been managed without difficulty.

Here's to hoping that none of our patients will ever have to worry about support for quality health.

CASE REPORT

Central sleep apnea: Report of two cases and review of literature

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ABSTRACT

Central sleep apnea (CSA) syndromes, characterized by the absence of both airflow and ventilatory effort during sleep, are rare. In the general population, the prevalence of central sleep apnea is less than 1%. And for patients who underwent polysomnography, only less than 10% of patients have central sleep apnea. Nonetheless, it is important for clinicians to understand the different types of sleep disordered breathing to be able to catch the signs and symptoms, to appreciate the significance of doing a polysomnogram and to understand the value of using positive airway pressure in the management of these cases. Here, we present two cases of CSA and discuss their management in our setting.

INTRODUCTION

Central sleep apnea (CSA) syndromes are characterized by the absence of both airflow and ventilatory effort during sleep. In the general population, the prevalence of central sleep apnea is less than 1%. And for patients who underwent polysomnography, only less than 10% of patients have central sleep apnea.[1]

It is important for clinicians to understand the different types of sleep disordered breathing to be able to catch the signs and symptoms, to appreciate the significance of doing a polysomnogram and to understand the value of using positive airway pressure in the management of these cases.

THE CASES

Case 1

AC is a 55-year-old Filipino male from Bacoor, Cavite who came in due to left sided body weakness. The patient was apparently well until 3 hours prior to admission, when was noted to have sudden onset of left sided body weakness associated with slurring of speech. This prompted emergency room consult and subsequent admission.

Review of systems was unremarkable. The patient is a known hypertensive, maintained on amlodipine. His family history included diabetes on the maternal side. He works as an accountant, is a non-smoker, an occasional alcoholic beverage drinker and denies use of prohibited drugs.

On physical examination, his BMI was high at 28 kg/m^2, blood pressure was elevated at 150/100, tachycardic at 110, with an irregularly irregular rhythm. Chest findings were unremarkable. On neurologic exam there was preferential gaze to the left, and a weak shoulder shrug on the same side. There was also a 2/5 motor deficit and a 70% sensory deficit on the left upper and lower extremities. Admitting impression was cerebrovascular disease infarct, right middle cerebral artery territory probably cardioembolic in origin; hypertensive atherosclerotic cardiovascular disease; congestive heart failure New York heart class II.

Cranial CT scan revealed ill-defined hypodensities in both centrum semiovale suggestive of acute infarct. Chest x-ray showed cardiomegaly and atheromatous aorta. 12 lead ECG revealed atrial fibrillation in rapid ventricular response, and left ventricular hypertrophy. Echocardiogram showed diffusely hypokinetic

walls with decreased ejection fraction of 40%. Concentric left ventricular hypertrophy was also noted. Pro-BNP was elevated at 14,754.

On the 4th hospital day, the patient complained of severe dizziness and was noted to have episodes of drowsiness and confusion. On physical examination, the patient was noted with waxing and waning sensorium with a decrease in Glasgow coma scale from 15 to 14. The patient had horizontal nystagmus, a positive Babinski reflex on the left and episodes of witnessed apneas. Cheyne-Stokes breathing, interrupted sleep and desaturation as low as 89% were noted. Repeat cranial study showed progression of isodense to slightly hypodense foci, now seen in the right frontal lobe, bilateral posterior parietal lobe, right medial temporo-parietal lobes, and cerebellar hemisphere with noted compression in the pontomedullary angle.

Epworth sleepiness scale was 6. Arterial blood gas was compensated respiratory alkalosis with mild hypoxemia. On diagnostic polysomnogram, the respiratory disturbance index (RDI) was 71.1 events/hour, predominantly central, with a breakdown of 43% central apneas, 6% obstructive apneas, 11% mixed apneas, and 40% hypopneas. The lowest oxygen saturation was 74%. On therapeutic polysomnogram with bi-level positive airway pressure, at titration of inspiratory pressure of 10 and expiratory pressure of 6, no obstructive events and no desaturation was noted (Figure 1). However, there was persistence of central apnea. Also seen in the diagnostic and therapeutic polysomnogram were the Cheyne-Stokes breathing pattern (Figure 2). Final impression was severe obstructive sleep apnea and central sleep apnea with Cheyne Stokes respiration.

Case 2

JM, a 32-year-old male, single, from Las Piñas City, Philippines, sought consult for snoring. Ten years prior to consult, he had witnessed apnea, daytime sleepiness, and easy fatigability. Two months prior to consult, the patient noted on-and-Epworth sleepiness scale was 19.

On physical exam BMI was elevated at 38 kg/m^2 and neck circumference was 18 inches. Chest findings and neurologic examination were unremarkable. STOP BANG score was 6/8. Echocardiogram and arterial blood gas were normal. On diagnostic polysomnogram, (Figure 3), RDI was 101.3 events/hour, with 77% obstructive apneas, 13% central apneas and 10% hypopneas. Central apnea index was 13.1. Lowest oxygen saturation was 89%. During the titration study, central apnea index increased to 57.2. The patient underwent a repeat therapeutic polysomnogram since the ending pressures of the first titration study failed to normalize the respiratory disturbance index. On repeat titration study, there was resolution of the central apnea events at bi-level positive airway pressure (PAP) with pressures of inspiratory PAP (IPAP) of 13, expiratory PAP (EPAP) of 5 and a back-up rate of 12 (Figure 4). These settings were later recommended for the patient, with the final diagnosis was severe obstructive sleep apnea, and treatment-emergent central sleep apnea.

DISCUSSION

Central Sleep Apnea (CSA) is defined as complete or partial reduction in central neural outflow to the respiratory muscles during sleep that lead to complete or partial cessation of airflow for at least 10 seconds, coupled with the presence of symptoms including excessive daytime sleepiness, difficulty initiating or maintaining sleep or insomnia, frequent awakenings or non-restorative sleep, awakenings with short of breath, snoring in central sleep apnea cases wherein there are obstructive events, witnessed apneas, and nocturnal dyspnea.[2,3]

International Classification of Sleep Disorders diagnostic criteria polysomnographic findings of central sleep apnea include one or more of the following: (1) at least 5 central apneas or hypopneas are present per hour of sleep; (2) central apneas comprise more than 50% of the

Figure 1. Hypnogram of patient AC, showing decrease in the obstructive apnea events on the titration study

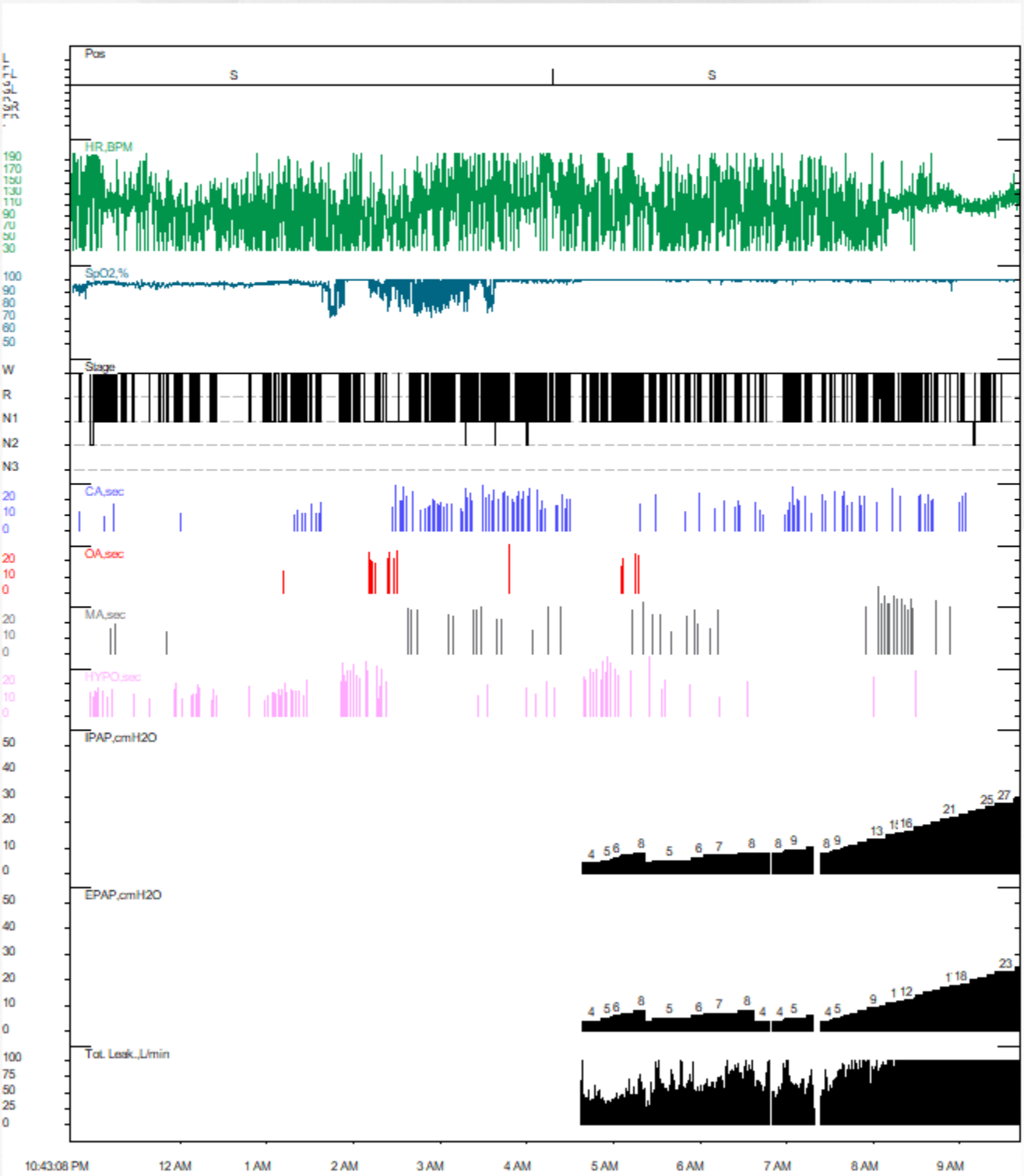
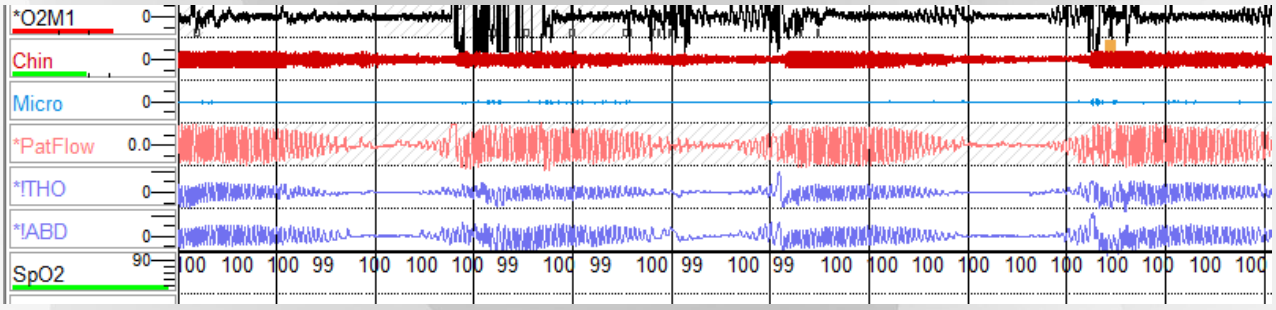


Figure 2. Hypnogram of patient AC showing Cheyne-Stokes breathing pattern



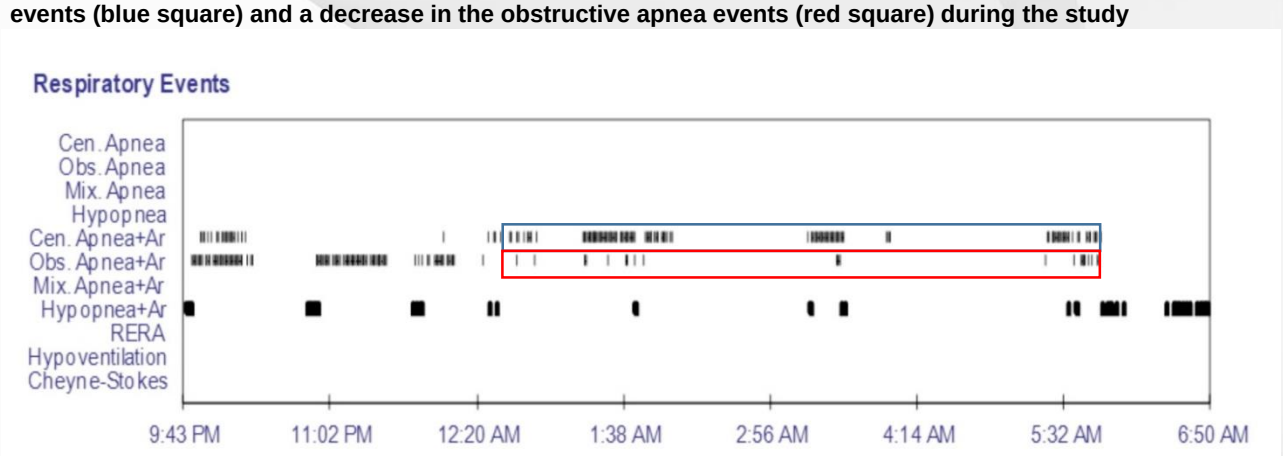
total respiratory events; and (3) may be observed during a diagnostic or therapeutic poly-somnogram.[4]

Central sleep apnea with Cheyne-Stokes breathing is a form of periodic breathing, in which central apneas alternate with hyperpneas that have a waxing-waning pattern of tidal volume. It is commonly observed in patients with heart failure (CHF). These patients are generally hypocapnic, with arterial carbon dioxide closer than normal to the apneic threshold such that even slight augmentation in ventilation drives arterial carbon dioxide below threshold and triggers apnea. Cheyne-Stokes respiration is characterized by a periodic waxing-hyperpnoea, typically 40 seconds in length and can include gasping breaths that tend to arouse the patient, while the waning periods-hypopneas or apneas, typically 20 seconds in length and cause desaturations.[3]

A study done in 2009 evaluated patients with CHF and identified risk factors for central sleep apnea which includes age older than 60 years, male sex, high body mass index, hypercapnia during wakefulness, and atrial fibrillation. The presence of central sleep apnea with Cheyne-Stokes breathing is associated with a worse prognosis.[5]

Prevalence of this breathing disorder in the setting of congestive heart failure has been reported to be 25% to 40%. There is a striking male predominance in the occurrence of central sleep apnea with Cheyne-Stokes breathing. Some form of central sleep apnea with Cheyne-Stokes

Figure 3. Hypnogram of the first titration study of patient JM, showing an increase in the central apnea events (blue square) and a decrease in the obstructive apnea events (red square) during the study



breathing is reported in 50-70% of patients following stroke. Although renal failure is often listed as a possible cause of central sleep apnea with Cheyne-Stokes breathing, there is scant literature documenting this association.[5]

Central sleep apnea with Cheyne-Stokes breathing patients with heart failure arises because of respiratory control system instability. Central sleep apnea patients with Cheyne-Stokes respiration have a longer circulatory time up to 60 seconds.[6] Heart failure leads to decreased cardiac output resulting in to prolonged circulatory time from the lung to central and peripheral chemoreceptors. This circulatory delay leads to gradual arterial carbon dioxide build-up and activation of the central and peripheral chemoreceptors. This will trigger a gradual increase in ventilation, causing a gradual decrease in carbon dioxide falling below the apneic threshold which in turn is detected by the central and peripheral chemoreceptors to signal a gradual decrease in ventilation until apnea occurs. This produces a "Crescendo-Decrescendo" pattern typically seen in Cheyne-Stokes breathing.[6]

In idiopathic central sleep apnea, there is typically a short ventilatory phase at 35 seconds and arousals tend to occur at apnea termination. In contrast, patients with Cheyne-Stokes breathing have a longer ventilatory phase between consecutive apneas and arousals occur at the zenith of ventilation.[7]

In central sleep apnea with Cheyne-Stokes breathing, the diagnostic criteria require that symptoms of excessive daytime sleepiness, insomnia, nocturnal dyspnea same as in other central sleep apnea, or a comorbid condition like atrial fibrillation, congestive heart failure, neurologic disorder must be present. Polysomnogram is same with other central sleep apnea but meets the criteria for Cheyne-Stokes breathing, and it is simply considered a polysomnographic finding if neither symptoms nor comorbid conditions are present.[5]

Treatment options for patients with central sleep apnea secondary to Cheyne-Stokes breathing includes oxygen supplementation which prevents desaturation and reduce central apnea. Continuous Positive Airway Pressure (CPAP) is the most commonly used therapy to treat sleep apnea. It delivers a single continuous stream of pressurized air to help keep the upper airway from collapsing. CPAP may be used together with oxygen therapy. It is effective in about 50% of patients with central sleep apnea with Cheyne-Stokes breathing. Bi-level PAP (Bi-level PAP) is set up to provide dual pressures: one for inhalation and another pressure for exhalation which is set to the lowest level maintaining upper airway patency, thus suppressing obstructive disturbances.[3] Bi-level PAP may be used in patients with heart failure with reduced ejection fraction. It may be applied without a back-up rate or spontaneous mode and with a back-up rate or spontaneous-timed mode. Both of these treatment modalities reduce apnea-hypopnea index (AHI) but bi-level PAP with BUR is superior in improving left ventricular ejection fraction compared to CPAP. Bi-level PAP is used if CPAP, Adaptive Servo Ventilation (ASV), and oxygen are not effective.[7]

ASV is the most sophisticated form of non-invasive ventilation and its use is reserved for specific kinds of patients. It utilizes positive airway pressure ventilatory support that is adjusted based on the detection of apneas, or pauses in breathing, during sleep. Variable IPAP or pressure support adapts by providing higher support when flow and tidal volume are decreased and lower support when flow and tidal volume are increased, with back-up rate delivering inspiratory time automatically. Variable EPAP prevents upper airway obstruction or narrowing by preventing excessive ventilation and hypocapnia, and eliminates central apnea. ASV is effective in most central sleep apnea patients. AHI decreases to less than 10/hour using ASV.[2,7-10]

A study done by SERVE-Heart Failure[11] on ASV had no significant effect on the primary end points in patients who had heart failure and predominantly central sleep apnea. Surprisingly, all-cause and cardiovascular mortality were both increased by 34% with this therapy.

We should optimize treatment of CHF because studies have shown that patients effectively treated for congestive heart failure had markedly decreased Apnea-Hypopnea Index with decreased wedge pressure. Aminophylline is considered if PAP therapy is not successful but it can worsen ventricular arrhythmias. Aceta-zolamide is considered if PAP therapy is not successful.[12]

Optimal cardiac treatment should be given in patients with central sleep apnea in heart failure. If there is less than 45% ejection fraction, as seen in our patient, with predominant central sleep apnea, determine the severity of symptoms. If there are only minor symptoms, heart failure therapy should be continued. If patients had concomitant stroke, like in our first patient, optimal therapy should be given. If there is persistent central sleep apnea with AHI more than 15 events per hour, PAP therapy is recommended.[13] However, ASV is not appropriate in our case because of the previously mentioned SERVE-Heart Failure study. Cheyne-Stokes breathing is regarded as a characteristic sequel of an extensive cerebrovascular accident and regularly found immediately after the stroke. The prevalence varies widely from 3-72% and it declines markedly in 3 to 6 months into recovery.[13]

The terms complex sleep apnea and treatment-emergent central sleep apnea (T-E CSA) are often used to designate the same condition. Treatment-emergent central sleep apnea is a form of central apnea wherein a patient was initially observed with obstructive events, undergoes PAP therapy which results in the disappearance of obstructive events, however, there is emergence of central apneas.

There is limited information available regarding prevalence; researchers found that in 2006 study, 15% of patients of Sleep Related Breathing Disorder (SRBD) have T-E CSA.[6] In a study by Cassel et al,[18] 1.5% to 20% had T-E CSA on the 1st titration, which decreased to 1.5% to 3% after chronic treatment with CPAP.

Untreated T-E central sleep apnea patients frequently experience central events while on CPAP or bi-level therapy. The patients often get frustrated because they continue to have symptoms such as fatigue, sleepiness, headaches and irritability. In our second case, the patient had symptoms of easy fatigability, daytime sleepiness, and morning headaches. OSA patients who are currently having residual symptoms and respiratory events should be evaluated for T-E CSA through polysomnography.[14]

Treatment-emergent central sleep apnea diagnostic criteria are as follows: (1) any circumstance in which a patient has symptoms of sleep apnea; (2) predominantly obstructive events during a diagnostic study but during the therapeutic study there is emergence or persistence of central sleep apnea; (3) central AHI of more than or equal to 5 per hour; and more than 50% of the residual events being central. The following risk factors were observed in patients who underwent polysomnography eventually diagnosed to have T-E CSA: (1) predominantly seen in men; (2) occurs mostly at a supine position; (3) apneas seen are predominantly at non-REM (stages N1, N2); (4) high apnea hypopnea index or RDI; (5) central apnea may appear at split night study; (6) central apnea appears frequently on bi-level PAP without back-up rate; and (7) central apneas occur during the diagnostic study.[15]

The pathogenesis is not completely understood but there seems to be interplay of several factors. In the setting of a patient with obstructive sleep apnea wherein CPAP is applied,

obstructive events will resolve. In the event of pressure over titration, it may lead to an increased ventilatory response that results to activation of lung stretch receptors. If the ventilatory response is exaggerated, the arterial carbon dioxide can easily drop below the apneic threshold resulting in central apneas.[10]

In treatment-emergent sleep apnea, a large proportion of patients will respond to CPAP.[16] Most obstructive events will disappear with a certain CPAP pressure. However, central sleep apnea may occur during high pressures thus a lower CPAP pressure is chosen, enough to resolve obstructive events likewise to eliminate central apneas. Hence, close follow-up is needed. If they do not respond to CPAP treatment, adaptive servo-ventilation titration should be ordered. An alternative treatment for T-E CSA is a combination of oxygen and ASV.[12]

A retrospective review of patients with T-E CSA and treated with ASV, reported improvement in sleep quality and/or daytime sleepiness.[17] One short-term randomized trial showed equivalence using bi-level PAP or ASV for correcting obstructive and central events in treatment emergent patients, most of whom had very large numbers of residual central events on CPAP.[16] The ASV device was superior in eliminating respiratory related arousals and all residual disordered breathing events, and it normalized the AHI.[10,15] Two brands of ASV are available in the market: bi-level PAP auto servo-ventilation advanced device and VPAP adapt servo-ventilation with the same indication but using different algorithms. Other advanced mode positive airway pressure devices are volume-assured pressure support such as Average Volume Assured Pressure Support (AVAPS) developed to automatically adjust the pressure support to deliver adequate tidal volume or ventilatory target.[12,18]

RECOMMENDATION FOR PRACTICE AND RESEARCH

Our first patient had witnessed apnea, Cheyne-Stokes breathing, atrial fibrillation, congestive heart failure, and a cerebrovascular infarct. Diagnostic polysomnogram revealed central apnea with "crescendo-decrescendo" pattern and resolution of central apneas were seen after the therapeutic polysomnogram. Bi-level PAP without back-up rate was used. ASV was not given due to low ejection fraction. In our second case, he had witnessed apnea, daytime sleepiness and easy fatigability. Both patients were obese with high BMI. Diagnostic polysomnogram of the second case revealed obstructive sleep apnea. On therapeutic polysomnogram, there was resolution of the obstructive events and emergence of central apneas. Hence, bi-level PAP with BUR was given.

It is important to note that optimizing therapy for heart failure is central in treating CSA and Cheyne-Stokes breathing with CHF. Several treatment modalities, including CPAP, bi-level PAP, ASV, and pharmacological therapies, have been studied to address in such patients.[9] The most crucial concern for those with T-E CSA is whether there is a preferential treatment approach. Patients who have a poor initial experience with CPAP have a worse adherence to therapy and those that fail with CPAP compliance over longer periods have limited recovery even with alternative devices. With the potential of increasing early adherence to therapy such as CPAP and ASV, it may resolve the disorder and relieve the symptoms of this disease.

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CASE REPORT

A double-edged sword: A case report of venous thromboembolism associated with vehicular accident

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ABSTRACT
The association between injury and venous thromboembolic events (VTEs) is well recognized. The reported incidence of VTE after trauma varies from seven to 58%, depending on the demographics of the patients, the nature of the injuries and the method of detection, either via surveillance imaging or through clinical detection. We discuss a patient with pulmonary sequelae of blunt trauma to the chest, secondary to motor vehicular accident; the pathophysiology, diagnosis, management, and prognosis of pulmonary embolism (PE); and the risk-benefit ratio of anticoagulation in PE in a patient with a pulmonary contusion and possible hemothorax.

THE CASE

A 60-year-old female, married, Roman Catholic, from Bulacan, was admitted into our institution due to dyspnea. Symptoms started two days prior to admission. The patient had been riding a cab about to make a U-turn when a fast-approaching vehicle hit the cab. The patient was sitting at the back, opposite the driver's seat, where the lateral collision happened. The patient experienced no headache, vomiting, or loss of consciousness but noted right-sided chest pain, dyspnea and pain upon movement of right upper and lower extremities. She was immediately brought to and admitted at a nearby hospital, where she was given hydration, oxygen supplementation, and analgesics. Antibiotics were started.

Chest radiography (Figure 1) revealed haziness at the right hemithorax, with partial obliteration of the distal half of the right hemidiaphragm and costophrenic angle. Alveolar densities were seen in both lung fields, probably secondary to pulmonary contusions. Rib fractures were noted at the second, third, and fifth posterior ribs at the right, as well as in the second anterior rib at the left. A comminuted fracture was at the middle third of the right clavicle. X-ray of the right upper extremity was unremarkable, while x-ray of the right leg revealed tibiofibular facture (Figure 2). Patient underwent casting of the right leg.

A day prior to admission, her dyspnea progressed with increasing oxygen requirement and increasing intensity of right-sided chest pain. No further work-ups were done. A few hours prior to admission, the patient was noted to be orthopneic, speaking in phrases, and had further

Figure 1. Chest radiograph on admission

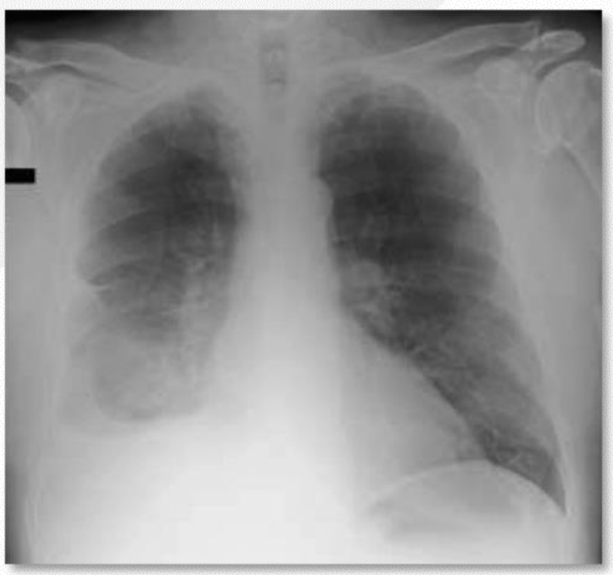
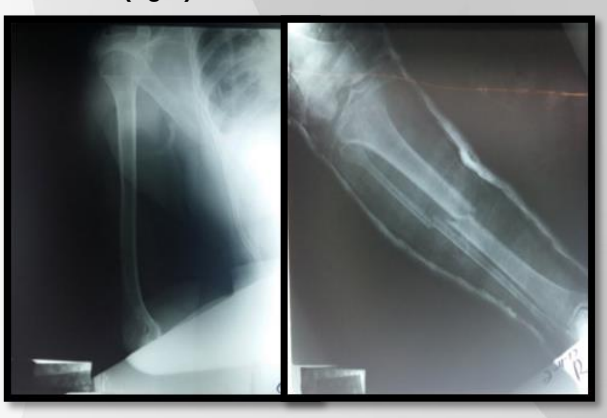


Figure 2. X-ray of Right Upper Extremity (left) and Right Lower Extremity showing Tibiofibular Fracture (right)



progression of dyspnea; hence, she was transferred to our institution for further evaluation and management.

The only pertinent family history was paternal hypertension. The patient was a housewife and a non-smoker with no exposure to secondhand smoke or biomass fuel, did not drink alcoholic beverages, denied illicit drug use, had no known food or drug allergies and had no history of oral contraceptive use. R

Upon arrival at the emergency room, the patient was seen awake, conscious, coherent, stretcher borne, and in respiratory distress, with BP 180/100 mmHg, HR 124 bpm, RR 32cpm, temperature 36. 8 ºC, O_2 saturation 95% with supplemental oxygen at four liters per minute via nasal cannula, and BMI 20. 34 kg/m^2. There was a 10/10 shooting pain over the right upper and lower extremities; a hematoma on the lateral aspect of the proximal third of the right arm measuring approximately five by six centimeters; a two-by-two centimeter abrasion on the medial aspect of the proximal third of the right thigh and in the medial aspect of the distal third of the left thigh; a two-by-three centimeter abrasion on the lower-right quadrant of the abdomen; and an 8. 5-by-5 cm soft-tissue contusion on the distal two-third antero-medial aspect of the right thigh.

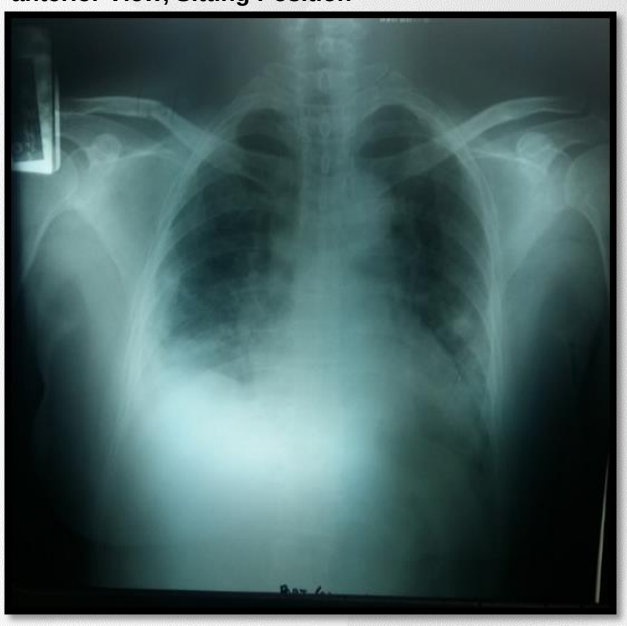
Patient had asymmetrical chest expansion with noted lagging on the right; trachea was midline, with noted supraclavicular retractions and tenderness on the right anterior chest wall; and there was dullness on the right at level T6 down. There was also decreased vocal fremitus and decreased breath sound at level T6 down on the right lung field, and crackles on left base. Cardiac examination revealed an adynamic precordium with apex beat at the fifth left intercostal space, midclavicular line. There were no heaves, PA lifts and thrills, or distinct heart sounds. S1 was loud at the apex, S2 at the base, with no murmurs appreciated. Examination of the abdomen revealed no tenderness over the liver and spleen. The right leg was in a cast and attached to a Balkan frame. Movement of the right extremities was limited. Neurologic examination results were unremarkable.

Patient was admitted under surgical service with the admitting diagnosis of multiple physical injuries, blunt chest trauma (pulmonary contusion), right clavicular fracture, tibiofibular fracture and multiple ribs fracture secondary to motor vehicular accident, with the right leg treated with casting.

Repeat chest radiography (Figure 3) showed previous findings of pulmonary contusions, clavicular fracture and multiple rib fractures. The 12-lead electrocardiogram showed sinus tachy-cardia with heart rate in the 150s. Complete blood count showed leukocytosis at 12. 90x10^9 per liter, anemia at 92, with predominance of neutrophils at 0. 87. The prothrombin time (PT) and activated partial thromboplastin time (aPTT) were unremarkable. Serum sodium and potassium were at normal levels. Arterial blood gas test revealed uncompensated respiratory alkalosis with hypoxemia (pH, 7. 47; pCO_2, 32; pO_2, 92; HCO_3, 24; O_2 saturation, 97%; FiO_2, 0. 60; $aADO_2$, 296; a/A, 0. 24; PF, 153). Patient was then referred to cardiology, orthopedics, thoracovascular surgery and pulmonology services.

Upon referral to pulmonology, our assess-ment was (1) pulmonary contusion secondary to

Figure 3. Repeat Chest Radiography, Postero-anterior View, Sitting Position



motor vehicular accident, (2) hospital acquired pneumonia, or (3) venous thromboembolism risk. On the same day, patient was noted to have progression of dyspnea and increasing right-sided pleuritic chest pain. Our assessment was acute respiratory failure secondary to (1) restrictive lung disease due to pleuritic chest pain, due to multiple rib fractures; (2) pulmonary contusion. Patient was then hooked to non-invasive mechanical ventilation (NMV), mode ACMV, BUR 20, FiO_2 60%, PEEP 5, PF 50.

Serial arterial blood gas (Table 1) showed worsening of hypoxemia within the first 24 hours of admission. The chest computed tomography (CT) scan (Figure 4) revealed an elongated central intraluminal filling defect in the left interlobar pulmonary artery, representing acute PE. A non-enhancing focal consolidation at the lateral basal segment of the left lower lobe was suspicious for pulmonary infarction. Confluent linear and ground glass opacities in both lungs may relate to pulmonary contusion changes. There was bilateral pleural effusion, more at the right side, with associated relaxation/passive atelectasis. Hemothorax was not entirely ruled out, in the light of the of the patient's history of trauma. Subcutaneous emphysema, right upper lateral hemithorax; multiple fractures, with compression deformity of T11 vertebral body; atherosclerotic changes of the thoracic aorta; and hypertrophic degenerative changes of the thoracic spine were observed.

A whole abdomen CT scan (Figure 5) showed a grossly unremarkable spleen, pancreas, and the rest of the imaged solid organs. No focal

Table 1. Serial Arterial Blood Gas for the First 24 Hours of Hospital Stay

ABG	Normal Value	Upon admission	Prior to NIMV	On NIMV
pH	7. 35-7. 45	7. 47	7. 47	7. 47
pCO_2 (mmHg)	35-45	32	23	29
pO_2 (mmHg)	80-100	92	75	59
HCO_3 (mEq/L)	22-26	24	17	21
O_2 saturation (%)	90-100%	97%	96%	92%
FiO_2 (%)	20-100%	60%	32%	32%
a/A	0. 75-0. 8	0. 24	0. 38	0. 31
$AaDO_2$ (mmHg)	25-65	296	124	133
P/Fratio	250-350	153	234	185

intra-abdominal fluid collection, stranding densities, or pneumoperitoneum were seen. Bilateral non-obstructing nephrolithiasis, atherosclerotic vessel disease, probable venous thrombosis at the partially visualized right femoral vein and osteodegenerative changes at the lumbar spine were also observed.

A hemothorax was considered, and the patient underwent chest tube thoracostomy insertion on the right. Fifty cc of bloody fluid was drained. Despite the findings of probable hemothorax, patient was started on low molecular weight heparin(LMWH) enoxaparin for the treatment of PE. Serial arterial blood gas monitoring (Table 2) showed improving parameters, and the patient began to be weaned off from NMV on the fifth hospital day. On the seventh hospital day, NMV was discontinued, and the patient was shifted to oxygen inhalation via nasal cannula. Trial of oral feeding was initiated. On the 14th hospital day, patient showed further clinical improvement, with no episodes of desaturation. Pain was likewise controlled. Serial monitoring of the draining chest tube thoracostomy fluid revealed no persistence of bloody effusion and no increase in amount, which was already less than 100 cc. There were no noted hematuria, melena, or epistaxis by the patient. She was also able to tolerate oral feeding. Oxygen supplementation was eventually discontinued; nasogastric tube and chest tube thoracostomy were removed.

Figure 4. Chest Computed Tomography, Contrast Enhanced, showing elongated central intraluminal filling defect in the left interlobar pulmonary artery; a non-enhancing focal consolidation at the lateral basal segment of the left lower lobe suspicious for pulmonary infarction; a confluent linear and ground glass opacities in both lungs; and bilateral pleural effusion, more at the right side, with associated relaxation/passive atelectasis.

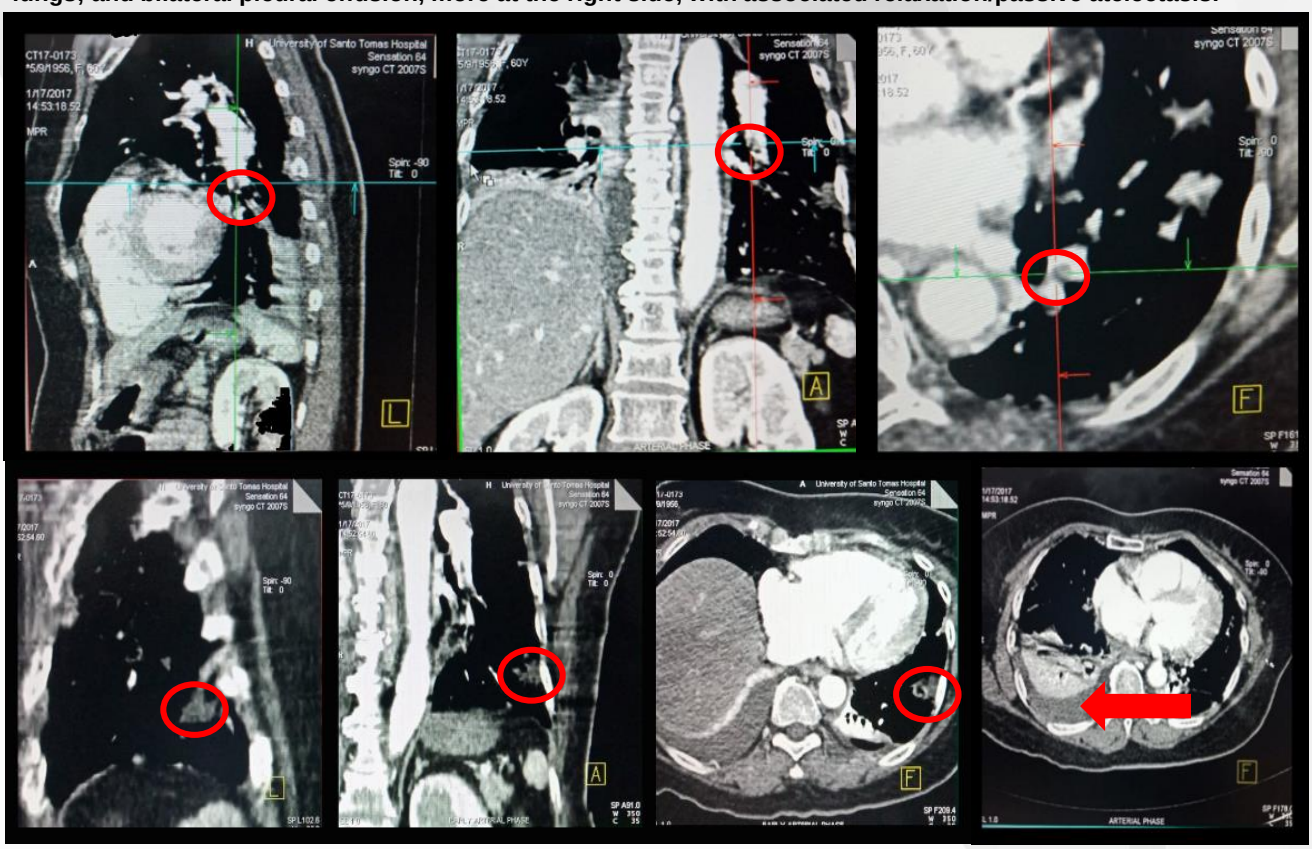
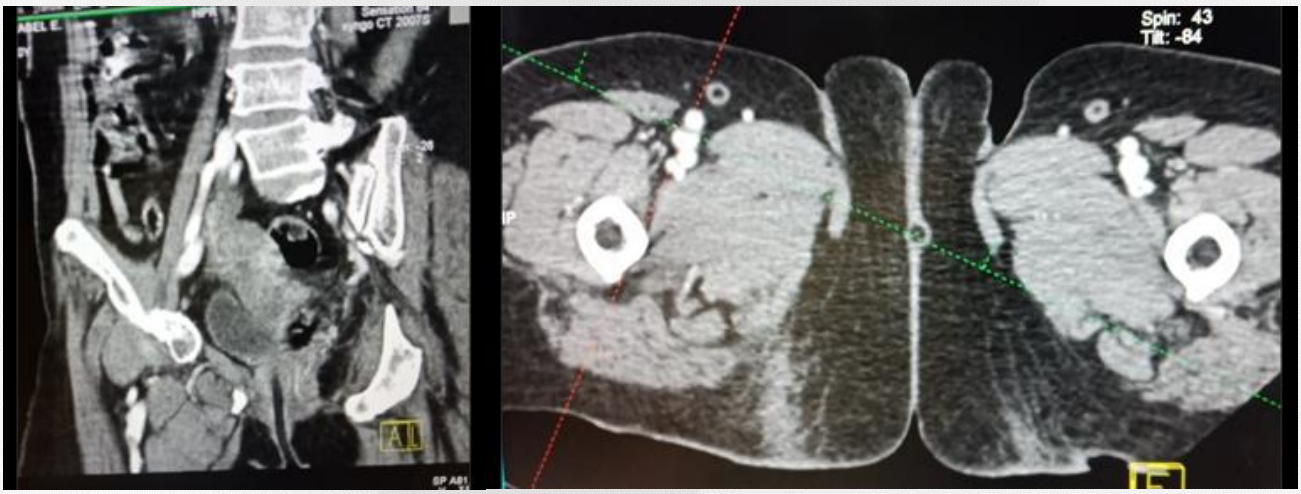


Figure 5. Whole-Abdomen Computed Tomography, Contrast Enhanced, showing probable venous thrombosis at the partially visualized right femoral vein.



Enoxaparin was eventually shifted to rivaroxaban. On the 24th hospital day, patient was cleared to undergo intramedullary nailing of the right tibia. Patient underwent rehabilitation and was subsequently discharged improved on the 42nd hospital day, with the plan to continue rivaroxaban for three months then reassess.

DISCUSSION

According to the Philippine Statistics Authority, the total number of deaths due to road crashes have been increasing worldwide. Road accident is the top cause of death among 15- to 19-year-olds, and motorcycle-related injuries comprise 69% of the total identified transport incidents nationwide, with males as the most common victims.[1]

Pulmonary contusion is the most common lung injury identified in the setting of blunt chest trauma, occurring in 17% of multiple-trauma patients. Pulmonary contusion is often not initially suspected because of delay in clinical and radiographic findings, and also because it can occur without any visible chest wall injury or radiographic evidence of rib fractures, especially among children. Treatment is supportive. Hemorrhage within the lung parenchyma occurs at the time of trauma, followed by interstitial edema, which usually begins within one to two hours and peaks at 24 hours following injury. Such hemorrhage may cause significant difficulties with oxygenation and ventilation.[2]

On the day of admission, patient was hooked to NMV due to worsening dyspnea. Hernandez et al conducted a randomized controlled trial to determine whether NMV reduces intubation in severe trauma-related hypoxemia. Patients were randomized to remain on high-flow oxygen mask or receive NMV. The trial ended prematurely because the intubation rate was much higher in controls than in NMV patients. Analysis revealed NMV as the only variable independently related to intubation. Length of hospital stay was shorter in NMV patients, but no differences were observed in survival or other secondary end points. The authors concluded that NMV reduced intubation more than oxygen therapy in severe thoracic trauma-related hypoxemia.[3]

One study evaluated the use of non-invasive positive pressure ventilation (NPPV), all others evaluated the use of NPPV and continuous positive airway pressure. Overall, up to 18%of the NIV group needed intubation. The authors concluded that early use of NIV in appropriately identified patients with chest trauma and without respiratory distress may

prevent intubation and decrease complications and ICU length of stay. Use of NIV to prevent intubation in patients with chest trauma who have acute lung injury that is associated with respiratory distress remains controversial because of the lack of good-quality data.[4]

Our patient was also started on a broad-spectrum antibiotic for the pneumonia. Antonelli et al identified risk factors for early-onset pneumonia (EOP) in trauma patients. The strongest risk factor for EOP was a combined severe abdominal and thoracic trauma, which increased the risk of EOP by 11 times. An age greater than 40 years and MV of less than 24 hours during the first four days of hospitalization were also independent risk factors. MV administered during the first days after trauma seemed to reduce the risk of EOP, and mechanical ventilatory support lasting more than five days is associated with an increased risk of late-onset pneumonia.[5]

In the prospective study by Artigas et al on the risk factors for hospital-acquired pneumonia in critically ill trauma patients, it seemed that the factors that would exert an influence on the development of nosocomial pneumonia in critically ill trauma patients were those that were related to the patient's clinical course rather than variables registered on the first days of ICU admission. These included nasogastric tube; continuous enteral feeding; prolonged MV (more than one day); use of H_2-receptor antagonist, sucralfate, muscle relaxants, corticosteroids, barbiturates, and inotropic agents; positive end-expiratory pressure; intense sedation; reintubation; tracheotomy; urgent brain CT scan; craniotomy; iatrogenic event; and hyperventilation. Pneumonia is the most common infection following multiple trauma, with a wide range of reported incidences, from four to 87%. Previous studies by Walker et al and Antonelli et al have both pegged the incidence at 33%.[5] Most patients develop pneumonia within the first four days after trauma. The maximum duration of pneumonia onset was on day three after trauma.[6]

Due to the blunt trauma on her chest and her risk of deep vein thrombosis (DVT), the patient underwent chest CT scan and whole abdomen CT scan. The chest scan revealed elongated central intraluminal filling defect in the left interlobar pulmonary artery, which represents acute PE. The whole abdomen scan revealed incidental findings of probable venous thrombosis at the partially

Table 2. Serial Arterial Blood Gas for Hospital Days (HD) 0 to 6

ABG	Normal Value	HD 0	HD 1	HD 2	HD 3	HD 4	HD 5	HD 6
pH	7. 35-7.45	7. 467	7. 418	7. 459	7. 403	7. 397	7. 418	7. 474
pCO_2	35-45	29	32. 0	41. 4	28. 4	46. 3	42. 5	33. 8
pO_2	80-100	59. 3	233. 1	237. 7	49. 6	210. 4	225. 7	88. 2
hCO_3	22-26	20. 9	20. 6	29. 4	17. 7	28. 4	27. 4	24. 8
O_2 saturation, %	90-100%	92. 4%	99. 5%	99. 6%	84. 9%	99. 4%	99. 5%	97. 2%
FiO_2, %	20-100%	32%	60%	40%	40%	40%	40%	28%
a/A	0. 75-0. 8	0. 30	0. 56	0. 99	0. 19	0. 90	0. 42	0. 54
PF ratio	250-350	185. 3	371. 8	594. 25	124	526	564. 2	315

visualized right femoral vein. The reported incidence of DVT in trauma patients ranges from 20 to 90%, while the reported incidence of PE in trauma patients varies between 2.3 and 22%. Based on the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, our patient was classified as having the highest risk for DVT and PE, which warranted the use of LMWH.[7]

The traditional clinical Gestalt or clinical suspicion that a physician makes about a patient's likelihood of having PE was first quantified by Wells et al in 1998. They were able to develop a numerical scoring system using logistic regression analysis of 40 clinical variables to assign points that correlate with increasing risk of PE. This system was used to create a pretest probability and has been validated by multiple centers. Our patient's Wells score for DVT was 1, which corresponds to a low probability of DVT. The Wells score of 6 for PE corresponds to a moderate probability. In the simplified version of this pretest probability, any score above 4 corresponds to a high likelihood of PE.[7]

According to Knudson et al, the association between injury and VTEs is well recognized. The reported incidence of VTE after trauma varies from seven to 58%, depending upon the demographics of the patients, the nature of the injuries and the method of detection, either surveillance imaging or clinical detection.[8] Prior to the era of routine prophylactic anticoagulation, PE after blunt trauma remained the third leading cause of death in patients surviving for at least 24 hours. Traditional teaching has it that PE is uncommon soon after injury, leading to a low index of suspicion and withholding of venous thromboembolism prophylaxis. More recent reports have shown that immediate PE can occur within six hours of the trauma, early PE within seven to 96 hours, and late PE beyond 96 hours.[9]

Trauma patients are at risk for DVT and PE. Thrombus formation was observed within 24 hours of injury and involved both the injured and the uninjured extremities. Majority of these patients were asymptomatic.[9] There is an extensive collection of predisposing genetic and environmental factors, which is a result of the interaction between the patient and setting-related risk factors.[10] In our patient, the risk factors include advanced age and immobilization due to history of major trauma.

PE causes a number of consequences to gas exchange and other pulmonary functions. Regional obstruction of pulmonary blood flow and diversion of flow to unobstructed portions may alter the ventilation-perfusion balance, leading to mismatch. Likewise, in regions with pulmonary vascular obstruction, alveolar dead space is created. After approximately 24 hours of total occlusion and lack of blood flow, the surfactant becomes depleted, leading to atelectasis and edema, ultimately contributing to the hypoxemia. With less than 20% obstruction of the pulmonary vessels, pulmonary vessels are recruited and become distended, resulting in normal or near-normal pulmonary vascular pressures.[11] When the degree of pulmonary artery obstruction exceeds 50%, compensatory mechanisms are overwhelmed with increases in the right atrial pressure, ultimately decreasing the cardiac output. An increase in RV pressure and volume leads to an increase in wall tension and myocyte stretch. RV contraction time is prolonged, while neurohumoral activation leads to inotropic and chronotropic stimulation. The prolongation of RV contraction time into early diastole in the left ventricle leads to leftward bowing of the interventricular septum. As a result, left ventricular filling is impeded in early diastole.[12]

PE can be classified by the temporal pattern of presentation. Patients with acute PE, like our patient, typically develop symptoms and signs immediately after obstruction of pulmonary vessels. Some patients with PE may also present subacutely within days or weeks following the initial event. Patients with chronic PE slowly develop symptoms of pulmonary hypertension

over many years (i.e., chronic thromboembolic pulmonary hypertension).[13]

The most common presenting symptom of acute embolism is the sudden onset of dyspnea. However, in the PIOPED study, dyspnea was not present in 27% of patients ultimately proven to have embolism. Pleuritic chest pain was present in 66% of patients, whereas hemoptysis (15%) was uncommon. Less than 50% of patients had cough (37%), leg swelling (28%), and leg pain (26%). Our patient presented with dyspnea and pleuritic chest pain. The most common physical finding is tachypnea (respiratory rate >20/min). In the PIOPED study, however, tachypnea was not present in approximately 30% of patients with embolism. Clinical findings noted less frequently include crackles (55%), tachycardia (30%) and an increased pulmonic component of the second heart sound (23%).[14]

The diagnosis of PE relies on the combination of the use of several validated clinical prediction rules, laboratory, and non-invasive or sometimes invasive imaging modalities. These rules have comparable efficiency, with sensitivity ranging from 88 to 96% and specificity from 48 to 53%. However, the Wells rules gave the best performance in terms of lower failure rates (1.2%).[7]

The chest radiograph, although not specific, may give clues as to the diagnosis. This includes focal areas of vascularity, or Westermark sign; a dilated right descending pulmonary artery, or Palla's sign; a pleural-based, wedge-shaped density, or Hampton's hump; or a prominent central pulmonary artery, or Fleischner's sign.[10] As with the chest radiograph, the 12-leadechocardiogram (ECG) findings may also be non-specific, showing only sinus tachycardia or signs of right ventricular dysfunction such as T-wave inversion in leads V1 to V3 and complete right bundle branch block. The S wave in lead I, Q wave and T wave inversion in lead III and the S1Q3T3 pattern have good specificity but moderate accuracy, according to one study.[15] The arterial blood gas will not help in the diagnosis but may identify the severity of hypoxemia and hypocapnia due to hyperventilation.[16]

The clinical dilemma is deciding whether to give anticoagulation in a patient with PE, knowing that the concomitant hemothorax may be aggravated. A study done by Karmy-Jones et al, which involved 157 patients with traumatic chest injuries, concluded that mortality increased as total chest blood loss increased, with the risk of death being three times greater at a blood loss of 1500 ml than at 500 mL.[17] In comparison, in the study by Goldhaber et al in 1999, PE accounted for 45.1% of deaths.[18] Carson et al determined that the mortality rate of acute PE approaches 30% in patients who received no treatment and 2.8% in patients who received anti-coagulant therapy.Weighing the risk-benefit ratio, the mortality in PE is higher if left untreated as compared to hemothorax.[19] Thus, the team decided to initiate anticoagulation for this patient, and she was started on subcutaneous enoxaparin 0. 6 twice a day.

Due to the probable venous thrombosis at the right femoral vein, anticoagulation vs inferior vena cava filter (IVCF) insertion was also contemplated and offered. Patient however opted to maximize medical management. Currently there is consensus among guidelines that IVCF is indicated for patients who have suffered an acute venous thromboembolic event and cannot receive anticoagulation. The latest ACCP guidelines see no added benefit of IVCF insertion for patients who are already receiving anticoagulation.[20]

A randomized, trial also concluded that a fixed-dose regimen of rivaroxaban alone was non-inferior to standard therapy for the initial and long-term treatment of PE and had a potentially improved benefit-risk profile.[21] The latest ACCP guidelines recommend the use of novel oral anticoagulants (NOAC) over warfarin therapy. The suggested length of treatment for VTE provoked by a non-surgical transient risk factor—in this case, trauma—is three months[20].

PE needs immediate treatment because the highest risk for events is within the first seven days. Shock can be the initial presentation or an early complication of PE; it is the most common cause of early death and, when present, is associated with a 30 to 50% risk of death. Even with treatment, PE tends to recur within the first two weeks but tends to decline thereafter.[22]

The incidence of late events—at three months or later following a diagnosis of PE—ranges from nine to 32%. Late mortality is mostly due to predisposing comorbidities and less commonly due to recurrent thromboembolism or chronic thromboembolic pulmonary hypertension. The cumulative rate of late recurrence has been reported to be eight% at six months, 13% at one year, 23% at five years, and 30% at 10 years. In general, the rate is lowered with therapeutic anticoagulation and increased by the presence of select risk factors such as unprovoked PE or malignancy. Patients with PE should be monitored for early and late complications of PE and the treatment-related complications it may entail. We also need to reassess the risk of recurrence.[22] Since our patient was on rivaroxaban, we did not require routine coagulation monitoring or dose titration, with unlike vitamin K antagonists and unfractionated heparin.

This case report shows the usefulness of a high index of suspicion to make an early diagnosis so that timely treatment options may be offered. We need to be vigilant in monitoring, anticipate complications that may arise and treat all complications immediately upon recognition.

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CASE REPORT

"Invictus": A case report of a patient with massive hemoptysis due to a bleeding right bronchial artery, with pseudo-aneurysm formation due to malignancy

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ABSTRACT

Introduction: Hemoptysis is one of the most important pulmonary complaints that warrants immediate medical attention. It is commonly self-limiting, but in some cases, it may be severe or massive.

The case: This is a case of a 71-year old female with papillary thyroid cancer with presumed lung metastasis who was admitted due to massive hemoptysis. Despite conservative management, bleeding was persistent hence an endobronchial tamponade was inserted. Definite source of bleeding was identified to be the right bronchial artery with pseudoaneurysm formation through bronchial angiogram. Bronchial artery embolization was done which provided cessation of bleeding.

Conclusion: In patients with massive hemoptysis, bleeding bronchial artery is an important consideration in the differential diagnosis. Bronchial angiogram is the definitive intervention to detect the exact source of bleeding. However, recurrence rate is high with no definite treatment for the primary condition.

THE CASE

The patient was a 71-year-old female diagnosed with papillary thyroid cancer with presumed lung metastasis, and had undergone total thyroidectomy, modified radical neck dissection, and tracheostomy tube insertion in April 2017. She was admitted due to a two-week history of productive cough with thick yellowish sputum, with intermittent undocumented fever and decreased appetite. She denied difficulty of breathing. No prior consult was done and no medications taken. There was persistence of symptoms until two days prior to admission, she had hemoptysis described as bright red fresh blood with some clots coming out of the tracheostomy tube amounting to approximately 500 ml in 24 hours. It was associated with dyspnea even at rest. Persistence of symptoms prompted consult and subsequent admission.

She is a known hypertensive and diabetic, with unremarkable pulmonary history. She has post-surgical hypothyroidism and hypoparathyroidism. She has no history of intake of anti-platelets or anticoagulants. She is a non-smoker and non-alcoholic beverage drinker. She denied use of illicit drugs and herbal medications. She has no history of recent travels. She has family history of colon cancer, diabetes mellitus and stroke.

On physical examination, she was seen conscious, coherent, weak-looking, wheelchair borne, not in cardiorespiratory distress. Vital signs were stable, with a blood pressure of 122/80 mmHg, heart rate of 81 beats per minute,

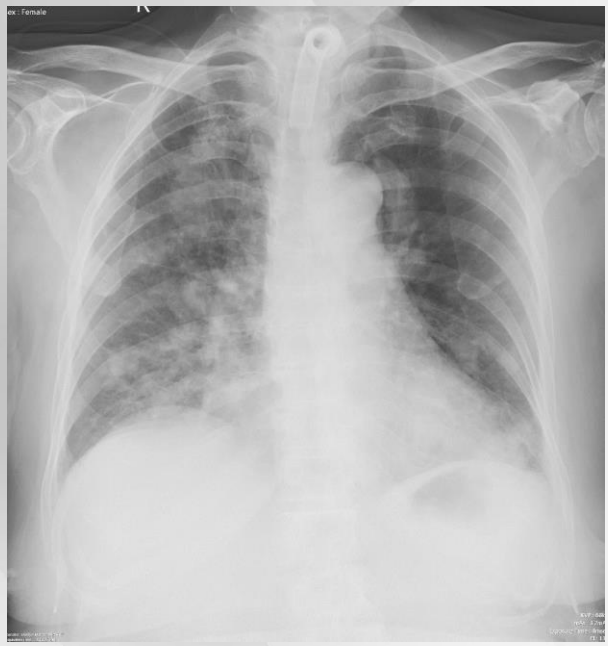
respiratory rate of 21 cycles per minute, afebrile at 37.5C, and oxygen saturation of 98% at room air. She had normosthenic habitus with BMI of 20.4kg/m^2. Her tracheostomy tube was in place with note of clotted blood. She had symmetrical chest expansion, no retractions, equal tactile vocal fremitus, resonant on percussion, with crackles on both bases and no wheeze. The rest of the physical examination were unremarkable.

Diagnostics showed low hemoglobin of 9.1g/dl, elevated WBC of 15,350, platelet count of 467,000. Coagulation parameters were within normal with an INR of 1.07. Creatinine was elevated at 1.56 mg/dl with a low estimated creatinine clearance of 33.1. Serum sodium was 142 and serum potassium was low at 2.9.

Chest x-ray on admission showed confluent opacities in the right mid and both lower lungs which may be related to a pneumonic process, and stable varisized bilateral nodular opacities previously ascribed to metastasis (Figure 1). High-resolution CT scan showed varisized pulmonary nodules scattered in both lungs, predominantly in the lung bases, with the largest seen at the anterior segments of both upper lobes, measuring 2.9 x 3 cm on the right and 2.6 x 1.9 cm on the left (Figure 2), indicative of a metastatic process. There were reticulonodular densities in the right upper lobe and ground-glass densities in the lingual and both lower lobes which may represent an infectious or inflammatory process, and bilateral hilar fullness with foci of calcifications, which may represent calcified hilar and segmental lymph nodes or bronchial wall calcifications.

During admission, she developed dyspnea and had a febrile episode with accompanying tachypnea and desaturation as low as 85% at room air which improved after suctioning of blood clots. She was initially stabilized by starting IV fluids and transfusion of 1 unit of packed red blood cells. Oxygen supplementation with tracheal mask at 2 lpm was also started. Antitussive, empiric antibiotics, and tranexamic acid were started. She underwent flexible bronchoscopy via tracheal approach under IV sedation. The carina was sharp and midline. Inspection of the left mainstem

Figure 1. Chest x-ray on admission showed confluent opacities in the right mid and both lower lungs, and stable varisized bilateral nodular opacities.



bronchus was done and showed no active bleeding. Inspection of the right upper lobe showed blood clots which were removed using biopsy forceps. Active bleeding on the posterior segment of the right upper lobe was noted.

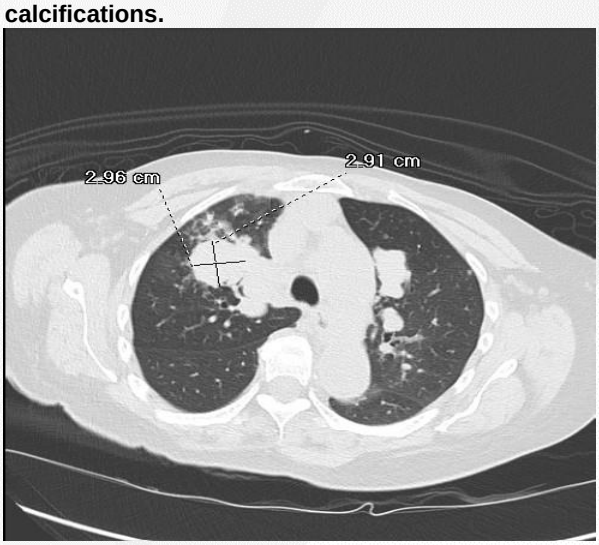
Despite administration of cold saline and epinephrine, there was persistence of active bleeding. Hence an endobronchial balloon tamponade was inserted at the level of RB3. Inspection of the right upper lobe post insertion of the endobronchial tamponade showed no active bleeding.

She underwent bronchial angiogram and selective embolization using the right transfemoral route. An enlarged, tortuous bronchial branch of the intercostobronchial artery was identified showing abnormal contrast staining and pseudoaneurysm formation indicative of active bleeding (Figure 3). The intercostobronchial trunk was selectively cauterized enabling embolization using 250-500 micron polyvinyl alcohol (PVA) particles allowing complete devascularization of

the upper lobe branches of the right bronchial artery. Angiogram post embolization showed non-visualization of the source of bleeding.

Given the patient's history, physical examination, and diagnostics done, the final diagnosis was massive hemoptysis secondary to bleeding right bronchial artery with pseudo-aneurysm formation secondary to malignancy. Two months post bronchial artery embolization, the patient has had no recurrence of hemoptysis.. Total body scan (I-131) showed functioning thyroid tissue remnants in the anterior neck. Non-iodine avid anterior neck mass may represent dedifferentiation of the known thyroid carcinoma. Non-visualization of iodine avidity in the pulmonary nodules may also represent dedifferentiation or may be due to the low diagnostic yield of this study. In our patient, we cannot totally rule out the consideration that the pulmonary metastases is from an unknown primary due to the non-visualization of iodine avidity in the pulmonary nodules. Hence further work-up is still warranted. Future plans for the patient is to undergo repeat biopsy of the remaining anterior neck mass for targeted treatment possibly with biological therapy. PET scan was also offered to out other primary malignancies.

Figure 2. High-resolution CT scan showed varisized pulmonary nodules scattered in both lungs and bilateral hilar fullness with foci of calcifications.



DISCUSSION

This is the case of a patient who experienced massive hemoptysis that presented as a pseudoaneurysm. While a true aneurysm is a segmental dilatation of blood vessels, including all wall layers, a pseudoaneurysm represents a collection of blood outside the vessel wall, contained by the surrounding tissues. Pseudoaneurysms appear as an enhanced round lung mass that is isodense to the central pulmonary arteries. In the setting of chronic inflammation, the liberation of numerous angiogenic growth factors promotes neovascularity from the bronchial arteries with abnormally thin vascular walls that could rupture, forming the pseudoaneurysm.

Massive hemoptysis has been defined in literature by several different criteria, ranging from 100 ml to more than 600ml of blood over a 24-hour period.[1-4] Variations in definition are compounded by the difficulty in quantifying the amount of blood expectorated, which is usually overestimated by patients. However, under-estimation is also an issue, as part of the blood may be retained in the tracheobronchial tree. Risk factors to be taken into account include the volume of hemoptysis which is greater than 100 ml in 24 hours, presence of airway obstruction, respiratory failure, or hemodynamic instability.

Suspected hemoptysis in a patient must be confirmed, its severity established, the origin of bleeding located and the cause determined. Confirmation of hemoptysis is based on direct observation of bleeding or bleeding reported by the patient. Airway bleeding must be differentiated from hematemesis on the basis of accompanying symptoms, the appearance of the blood, and the patient's concomitant diseases. Our patient was not in cardiorespiratory distress but had a history of pulmonary nodules secondary to possible metastasis. She did not have a history of gastrointestinal diseases. She presented with cough and dyspnea, and expect-

orated bright red foamy secretions from the tracheostomy tube. From this, we can conclude that she was having true hemoptysis.

Pulmonary tuberculosis sequelae, bronchiectasis, and lung cancer are the main etiology of hemoptysis in adults. Hemoptysis has multiple causes usually categorized into airway diseases, parenchymal diseases, or vascular diseases. The most common overall cause of hemoptysis is airway diseases, which include bronchiectasis, lung cancer, injury, foreign bodies, and fistulas between the tracheobronchial tree and blood vessel.[3]

The first step in an algorithm for the diagnosis and management of hemoptysis by Cordovilla[5] in 2016 involves resuscitation and protecting the airway. The goal of initial management is maintenance of gas exchange. Attempts should be made to determine the side of bleeding. The patient should be positioned with the bleeding side on the dependent portion to prevent aspiration into the unaffected lung. This is done since spillage of blood into the nonbleeding lung may prevent gas exchange due to clots and alveolar filling with blood. If large volume bleeding continues or the airway is compromised, the patient should be intubated with large endotracheal tube, size 8 or greater, if possible. The purpose of the large lumen size is to facilitate interventional and diagnostic bronchoscopy. Apart from airway protection, volume resuscitation is also essential in managing hemoptysis. Blood loss should be treated with volume replacement with crystalloid intravenous fluids, blood products, and correction of underlying coagulopathy.

Tranexamic acid is a widely used medication to control bleeding. It is an antifibrinolytic agent used to promote hemostasis. Oral tranexamic acid is not effective in decreasing bleeding time in hemoptysis, but IV tranexamic acid significantly reduces volume and time for cessation of hemoptysis in tuberculosis patients. Overall, tranexamic acid is an under-recognized treatment that may have temporizing value in managing patients with non-massive hemoptysis. In the context that the available literature is sparse, large, well-designed clinical trials are needed to advance understanding of the role of tranexamic acid in hemoptysis especially in cases of massive hemoptysis.

Following patient stabilization, initial laboratory examinations and imaging were requested. Initial investigations should include complete blood count, coagulation parameters, arterial blood gas, and chest x-ray. Chest X-rays are the initial imaging tests performed in patients with hemoptysis. It has a sensitivity of 50% and a specificity of 35% in identifying the site and cause of hemoptysis. Based on the algorithm, all patients with massive hemoptysis should be monitored in an intensive care unit (ICU) or high dependency unit (HDU) and the patient's fitness for surgery established.

For patients with massive hemoptysis, multidetector CT scan with contrast is recommended.[5] However, it was not done in our patient because of an ongoing acute kidney injury. Hence plain high-resolution CT scan (HRCT) was done instead. HRCT provides more detail than either chest radiography or conventional CT scan, with an overall sensitivity of 95 percent and a specificity approaching 100 percent. In a stable patient whose definite source of bleeding is not yet identified, the next intervention of choice is bronchoscopy.

In our patient, there was inadequate control of bleeding as reflected by persistently declining hemoglobin levels despite blood transfusion and antifibrinolytics. Thus, bronchoscopy was warranted, which locates the origin of bleeding in 73 to 93% of cases.[6] The source of active bleeding is more likely to be located when bronchoscopy is performed during active hemoptysis or within 24 to 48 hours after cessation of bleeding. Furthermore, bronchoscopy also allow therapeutic interventions to be performed. It can be performed with a flexible or a rigid device. Visible sources of bleeding in the central airways can be reliably detected and

Figure 3. Bronchial angiogram showing an enlarged, tortuous bronchial branch of the intercostobronchial artery with abnormal contrast staining and a pseudoaneurysm formation.

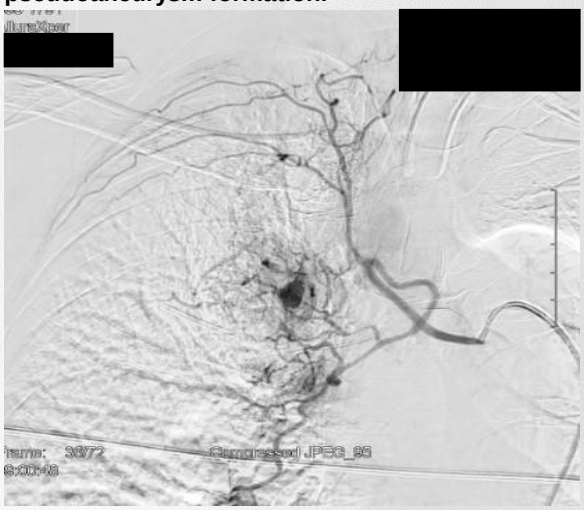
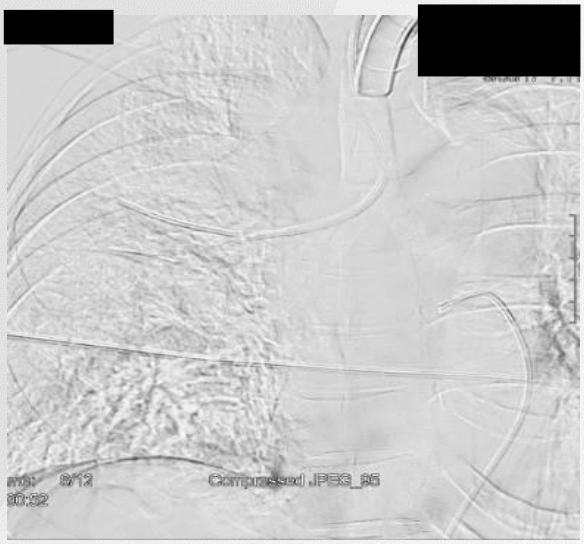


Figure 4. Angiogram post-embolization showing non-visualization of the source of bleeding.



treated locally. However, when the bleeding is in the periphery of the lungs, the role of bronchoscopy is to estimate the location of the bleeding as an aid to the planning of subsequent treatment including bronchial artery embolization or surgery. Bronchoscopy is also used for tissue sampling for microbiologic, cytological, or histological examination.

In practice, there is no consensus yet in the order of bronchoscopy and CT scans. Some prefer to perform a CT scan first before bronchoscopy since it is a non- invasive technique which is useful in planning for bronchoscopy. Overall the combination of bronchoscopy and CT scan yields the best results in the diagnosis.

Flexible bronchoscopy is the initial diagnostic procedure of choice, as it can be performed at bedside, is readily available and is highly successful at localizing the bleeding site. However, rigid bronchoscopy has merits with regard to airway assessment and management in patients with massive life-threatening hemoptysis. It is very efficient at securing airway patency and safeguarding ventilation, thereby preventing asphyxia. It allows better suction of blood clots and secretions through larger working channels, and improves visualization of the airways. It also provides effective tamponade of accessible bleeding sites and allows isolation of the non-affected lung. It allows further management like laser therapy. Rigid bronchoscopy is safer and much more efficient than its flexible counterpart at controlling hemoptysis in patients with compromised airways.

Various bronchoscopic treatment strategies can be used to control bleeding, including therapeutic rinsing with vasoconstrictive substances such as cold physiological saline solution, which cause local vasoconstriction. In a study described by Conlan et al[4] lavage with normal saline at 4°C stopped the bleeding in patients with massive hemoptysis. To perform iced saline lavage, approximately 1 liter of saline should be cooled in ice while the bronchoscopy equipment is being set up. Once the saline has cooled, bronchoscopy is performed to localize the source of bleeding.

Temporary control of hemoptysis can also be achieved with topical instillations of epinephrine.[6] However, it is used more often only in mild to moderate hemoptysis as studies on its efficacy on massive hemoptysis are lacking. Complications of its use include hypertension and tachyarrythmia.

Endoscopic instillation of fibrinogen-thrombin combination is another option for massive hemoptysis.[6] The mixture can be instilled through a catheter using a fiberoptic bronchoscope. In addition, factor XIII and aprotinin can be added to the mixture for better stabilization of the fibrin clot.

A Fogarty balloon catheter can be used for endobronchial tamponade in life-threatening hemoptysis. The catheter can be inserted through a flexible fiberoptic bronchoscope in the right main bronchus, inflated and kept in place as an emergency measure in a hemodynamically unstable patient following bouts of severe hemoptysis. This enables airway protection and resuscitation maneuvers before surgical resection of lung tissue.

EZ blocker has a Y-shaped distal end, and both distal ends are fitted with an inflatable cuff so a balloon can be placed on the right or left mainstem bronchus.[6] Advantages of balloon tamponade are protection of the airway; allows gas exchange; and supports patients before embolization or surgery. Disadvantages include ischemic mucosal injury and post-obstructive pneumonia.

Endobronchial airway blockade may also be done through silicone spigot which is a silicone bronchial filler or plug. Endobronchial placement of a silicone spigot has proved adequate for temporary control of bleeding, allowing subsequent endovascular embolization.[2] A flexible biopsy forceps is introduced through a flexible fiberoptic bronchoscope, with its distal end out of the bronchoscope, grasping a 6-mm silicone spigot. There were no severe complications related to these procedures. In their study, bronchial occlusion with silicone provided a more definite and longer lasting bronchial blockade than conventional methods. In a study by Brandes et al,[2] successful tamponade and isolation of the bleeding site in patients with massive hemoptysis was achieved by placement of two covered self-expanding airway stents.

Laser coagulation can be an effective treatment option for hemoptysis when the source of bleeding is visible.[7] It allows photocoagulation of the bleeding mucosa with resulting hemostasis, and can help achieve photoresection and vaporization of the underlying lesion. Argon plasma coagulation (APC), a non-contact electrocoagulation method employed through a flexible probe, is another option, but, as with laser coagulation, should be used only when the source of bleeding is within the reach of the bronchoscopy.

The lung is supplied by the pulmonary arteries and the bronchial arteries. Even though the bronchial circulation contributes less to the pulmonary blood flow, they are responsible for 90% of cases of hemoptysis requiring intervention with arterial embolization or surgery.[8] The right intercostobronchial trunk is the most common culprit artery as the source of bleeding. Nonbronchial systemic arteries have been reported to be important contributing sources in 41%–88% of cases of massive hemoptysis. Bronchial artery embolization can be done to address hemoptysis arising from these bronchial arteries.

Since its initial descriptions, bronchial artery embolization has evolved in terms of indications, technique, and efficacy.[9-12] It has been used for treatment of both benign and malignant causes of hemoptysis and for all grades of hemoptysis. Bronchial artery embolization is most commonly done by using the transfemoral route to access the bronchial circulation. A variety of 4F or 5F catheters can be used for selection of the bronchial arteries. Following stable catheter placement, embolization proceeds under continuous fluoroscopic visualization until flow in the vessel is significantly slower. At that point, the remaining embolic material is flushed with saline with the goal of achieving distal stasis in the vessel while avoiding reflux back into the normal circulation.

Contraindications for bronchial artery embolization are uncorrectable coagulopathy, renal failure, and severe contrast allergy.[8] Abnormal findings on angiography necessitating embolization are the following: enlarged or

tortuous arteries, hypervascularity, parenchymal blush, active contrast extravasation, broncho-pulmonary shunting, artery-artery and artery-vein shunting.

The choice of embolizing agents also evolved over the years. Spherical embolizing agents include trisacyl gelatin microspheres, PVA microspheres, or contour SE particles.[8] Gelfoam or gelatin sponge is water-insoluble and prepared from purified pig skin. Its effect is temporary within 4 weeks to 4 months.

The most commonly preferred embolizing agent is PVA, which can be either used alone or in combination with other embolizing agents.[8] Unlike gelatin sponge, PVA is non-resorbable and thus acts as a permanent occluding agent. Its disadvantages include clumping within the microcatheter leading to more proximal occlusion and catheter blockage.

Liquid agents like ethanol absolute alcohol are not radioopaque and highly diffusible. Severe complications such as cardiac arrest and pulmonary embolism have been reported. N-Butyl-2-cyanoacrylate (NCBA) is less preferred as the primary embolizing agent due to the need for greater expertise and increased chances of necrosis and other complications. However, Woo et al[12] compared the safety and efficacy of NBCA versus PVA and found that there were no significant differences in the technical and clinical success rates as well as complication rates between PVA and NBCA. The latter was also associated with better hemoptysis control rates in patients with bronchiectasis. Patients who underwent embolization with NBCA also experienced a higher long-term hemoptysis-free survival rate.

Coils provide more proximal occlusion compared with PVA, gelatin sponge, and liquid embolizing agents, and thus are used for embolization of pseudoaneurysms, arteriovenous malformations and nonbronchial systemic collaterals in combination with other embolizing agents.[8]

Super-selective catheterization enables bypassing anterior spinal arteries and cauterization of smaller, more distal, and torturous arteries; thereby providing better overall hemoptysis control and lesser risk of complications.[8]

The most common complications after bronchial artery embolization include transient chest or back pain and dysphagia.[8] Neurologic complications due to spinal cord ischemia leading to transient or permanent paraparesis or paraplegia are the most feared complications. This risk exists because the anterior spinal artery or artery of Adamkiewicz can originate from a bronchial artery in up to 5% of patients, more often on the right side. Other complications include postembolization characterized by fever, leukocytosis, and pain. vascular injuries include vasospasm, dissection and perforation with wire or catheter.

Immediate clinical success rates of bronchial artery embolization ranges from 70% to 99%, but hemoptysis recurrence rates range from 9.8% to 57.5%. The median time for recurrent hemoptysis varies between 6 months to 1 year, and the recurrence rate increases with time. Early recurrences could be attributed to technically inadequate or incomplete embolization due to lack of complete search for all offending vessels or inability to embolize all arteries including non-bronchial systemic vessels in the first session due to extensive collateralization. Late recurrences can be attributed to recanalization of previously embolized arteries or recruitment of new arteries, especially non-bronchial systemic arteries, due to underlying disease progression

Surgery remains the definitive form of therapy for patients with hemoptysis because it removes the source of bleeding. However, it is associated with mortality of 37 to 42%.[3] Surgical intervention should be considered in operable candidates with unilateral bleeding when embolization is not available or feasible; when bleeding comes from necrotizing tumors; in cavernous tuberculosis; in refractory aspergilloma; when bleeding continues despite embolization; or when bleeding is associated with persistent hemodynamic or respiratory compromise. Surgical resection reaches its limits in the presence of

extensive carcinoma with invasion of trachea, mediastinum, heart or great vessels and in patients with severe comorbidity, in patients with advance pulmonary disease with poor pulmonary reserve, and in patients with terminal malignancy.

Emergency surgery should be reserved only for patients with continuing hemoptysis despite the adequate measures taken, the exact site of bleeding definitely defined, and have adequate lung function. In our patient, surgery was not an option as was already in the advanced stage of malignancy.

SUMMARY

We presented a case of a 71-year-old female with papillary thyroid cancer stage 4 with presumed lung metastasis but cannot rule out metastasis from another primary, admitted due to massive hemoptysis. Bleeding was identified in the posterior segment of right upper lobe. Conservative treatment with cold saline and epinephrine were instilled however bleeding was persistent hence an endobronchial tamponade was inserted. Definite source of bleeding was identified to be the right bronchial artery with pseudoaneurysm formation through bronchial angiogram. Bronchial artery embolization was done which provided cessation of bleeding. Other strategies in management including surgery was also presented, however, surgical intervention was not warranted since patient is in the advanced stage of malignancy. Despite our success in controlling the bleeding, the chances of recurrence of the same problem is high with no definite treatment for the primary condition. Prognosis remains guarded.

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CASE REPORT

True lyse: Intrapleural Streptokinase and Recombinant Tissue Plasminogen Activator in the Management of Patients with Loculated Pleural Effusion

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ABSTRACT

Loculated pleural effusion is characterized by pleural fluid that is difficult to drain due to the presence of fibrous septations and high fluid viscosity. Fibrinolytic agents such as streptokinase and alteplase could lyse pleural adhesions by activation of plasmin, which hydrolyzes fibrin into soluble fragments and thereby facilitate fluid drainage. We present two cases of loculated pleural effusion managed with streptokinase and recombinant Tissue Plasminogen Activator (rTPA). This shows that the use of fibrinolytic agents, streptokinase and alteplase, may be a safe, easy, and cost-effective option for patients with loculated pleural effusion.

INTRODUCTION

Loculated pleural effusion is characterized by pleural fluid that is difficult to drain due to presence of fibrous septations and high fluid viscosity.[1] Loculated effusions are most commonly due to complicated parapneumonic effusions, followed by tuberculosis, hemothorax, and malignant effusions.[2]

Pleural injury results in local inflammation and increased microvascular permeability, favoring formation of an exudative pleural effusion.[1] This is associated with release of pro-inflammatory mediators, and the local procoagulant activity exceeds coagulation inhibition which leads to fibrin deposition and loculations within the pleural space.[2] In the United States, parapneumonic effusion is responsible for 90,000 hospital admissions a year and up to 50% are referred for surgical intervention due to development of loculations and empyema, often causing increased length of hospital stay and costs.[3] Parapneumonic effusions usually develop as a consequence of delayed antibiotic and pleural fluid drainage and are associated with considerable morbidity.[4]

Standard nonsurgical therapy for loculated pleural effusion consists of drainage through a chest tube and administration of antibiotics (for parapneumonic effusions). When the chest tube is correctly positioned with drainage of less than 50 mL per day and a significant amount of pleural fluid on imaging, the major reasons for failed drainage are multiple loculations or tube obstruction by thick and viscous fluid. At this point, options are to flush the tube with saline; insert more chest tubes or pleural catheters into the loculations; or more invasive surgical procedures.[1] Surgery, such as video assisted thoracic surgery (VATS) or invasive thoracotomy, is often needed to physically break down the septations in order to facilitate drainage. These measures are effective, but are expensive and not easily accessible in smaller hospitals and rural areas.

The use of intrapleural fibrinolytics has been shown in some small studies to be a safer and cheaper option in the management of complicated loculated parapneumonic effusion (secondary to bacterial pneumonia), tuberculosis, and malignant pleural effusion.[5] Intrapleural fibrinolytics lyse pleural adhesions by activation of plasmin, aiding drainage of the effusion by

breaking down fibrinous septations.[6]

The objectives of this paper include the following: To present two representative cases of loculated pleural effusion managed with streptokinase and Recombinant Tissue Plasminogen Activator (rTPA); to briefly discuss the pathophysiology, classification, and treatment options for loculated effusion; to discuss fibrinolytic therapy and its benefits in the management of loculated pleural effusion; and to present our institution's data on intrapleural fibrinolytic therapy on loculated effusion.

CASE 1

M.P., a 43 y/o female, Filipino, single mother from Marikina, consulted with a chief complaint of difficulty of breathing. History started 2 weeks prior to admission, when patient experienced non-productive cough that was not associated fever or dyspnea. She self-medicated with Amoxicillin 500 mg taken three times a day, for 5 days but this did not resolve her coughing. Two days prior to admission, still with non-productive cough, the patient developed shortness of breath, left sided chest pain and shoulder pain which was aggravated by cough & deep inspiration. She consulted a surgeon through a phone call, and was assessed to have costochondritis. She was told to take Mefenamic Acid 500 mg twice a day. The following day, due to persistence of symptoms, she went to a nearby hospital, where she was assessed to have costochondritis and prescribed Etoricoxib 90mg. The following day, the patient still had non-productive cough and increased severity of shortness of breath. She went back to the same hospital, and a complete blood count (CBC) with platelet count and chest radiograph were done. CBC showed anemia with Hgb 8.8, leukocytosis of 18.8 with segmenter predominance, and normal platelet count. Chest radiograph showed a pneumothorax. There was homogenous opacification of the left mid to lower hemithorax with pleural fluid. She was advised admission to our institution by the attending surgeon.

Review of systems was unremarkable. She had no history of weight changes, weakness, night sweats, and trauma. The patient is non-hypertensive, non-diabetic. She has no asthma, COPD, or previous treatment for tuberculosis. She has no allergies and is not taking any maintenance medications or supplements. Personal, social, and family history were unremarkable.

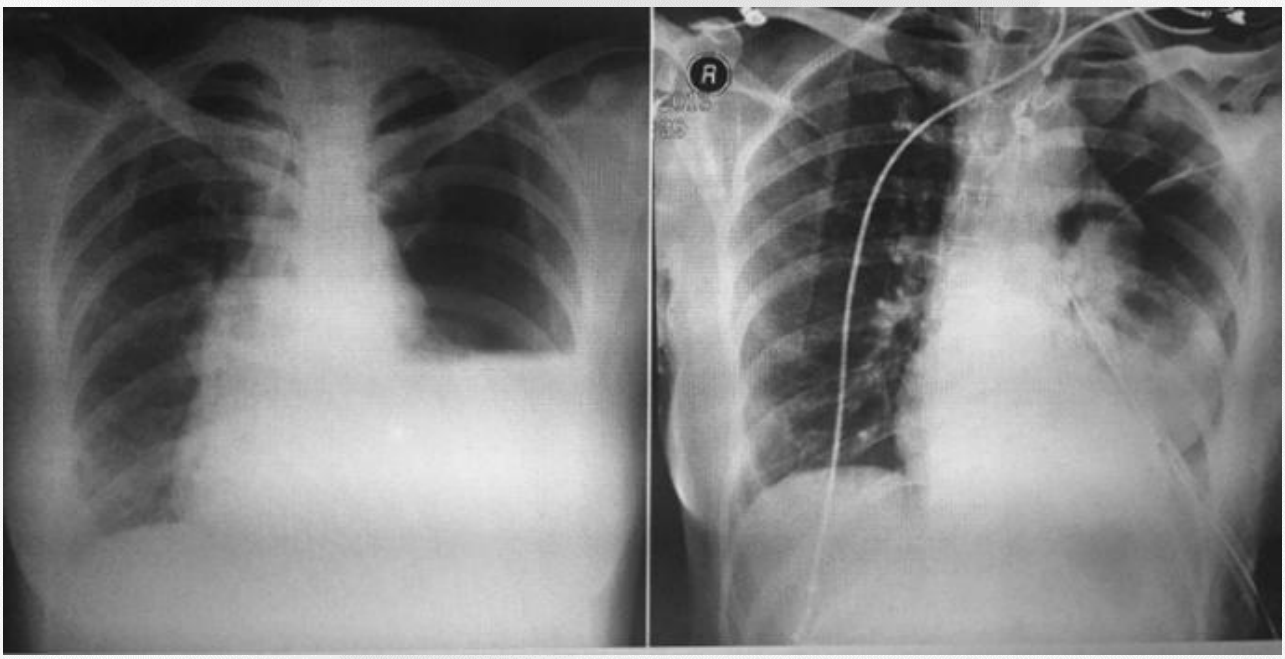
On admission, patient's blood pressure was 110/70, tachycardic at 110 bpm, tachypneic at 24 cpm, and afebrile. She was awake, weak looking, with symmetrical chest expansion, and decreased breath sounds at the mid to base of the left lung. There was no cyanosis or edema. Neurologic examination was unremarkable. Admitting impression was Hydropneumothorax, left probably secondary to community acquired Pneumonia moderate risk vs Pulmonary Tuberculosis (PTB).

The patient underwent immediate chest tube thoracostomy (CTT) with the tip at the 7th posterior inter-costal space (ICS) with a sentinel hole at the 9th posterior ICS. A total of 1,300 mL of serosanguinous, non-clotting pleural fluid was drained. She was also started on oral Cefuroxime 500mg. Post thoracostomy, chest radiograph showed (Figure 1) partial re-expansion of the left lung but still with 40% pneumothorax; hazy opacities in the left lung probably secondary to re-expansion edema; decrease in the pleural effusion of the left lung with no active infiltrates in the right lung. Pleural fluid analysis was exudative by Light's criteria. Pleural fluid culture, AFB smear, TB PCR, and MTB culture were all negative. Antibiotics were shifted to Piperacillin-Tazobactam and the patient was started on Salbutamol nebulization TID via intrapulmonary percussive ventilator (IPV).

During the course of the admission, CTT output was decreasing from 1300 mL/day to 20 mL/day over 1 week. Serial chest radiographs showed no significant change in the left sided effusion (Figure 2). A chest CT scan showed minimal pneumothorax on the left lung with a significant amount of loculated effusion.

Patients with loculated effusion that persist

Figure 1. Patient 1: Chest x-ray on admission (left), and immediately post chest tube insertion (right)



chest tube placement and antibiotic therapy traditionally require surgical intervention to avoid the complication of fibrothorax resulting in pulmonary compromise. Non-surgical candidates or those who refused surgery often have multiple image-guided catheters placed by interventional radiologists or surgeons at different locations.

Due to the chest CT scan findings, VATS was offered but due to financial constraints and the invasive nature of the procedure, the patient did not give consent. The decision to do intrapleural fibrinolysis using streptokinase was made. This would facilitate drainage of fluid before pulling out the chest tube.

In our hospital, streptokinase is available as 1.5 million units powder for injection, and costs approximately P10,000 per vial. This is good for 6 doses. We dissolved the streptokinase in normal saline solution (NSS) then aspirated 250,000 IU and diluted this in 50 mL NSS. This is then infused through the pigtail catheter or chest tube and clamped for 2 hours before being released. In our patient, we gave 250,000 IU streptokinase every 12 hours for a total of 6 doses. After streptokinase was started, a significant increase in CTT output was noted. This was correlated with serial chest radiographs done during that time (Fig. 3), which showed significant decrease in pleural effusion on the left lung. CTT was pulled out on the 5th day post infusion, and the patient was discharged stable and improved.

Follow up chest radiographs done 1 week and 3 months (Figure 4) after discharge showed minimal residual pleural thickening on the left lung but with no active infiltrates. The final diagnosis for this patient was complicated parapneumonic effusion secondary to CAP-MR, resolved, status post- chest tube thoracostomy, status post- intrapleural streptokinase infusion.

CASE 2

JG, a 35 y/o female, Filipino from Las Piñas, came in with a chief complaint of difficulty of breathing. The patient has Renal Cell Carcinoma (RCC) stage 4 with peritoneal, bone,

Figure 2. Patient 1: CTT output (in mL/day) and trend of serial chest radiographs done, showing no improvement despite minimal pleural fluid drainage

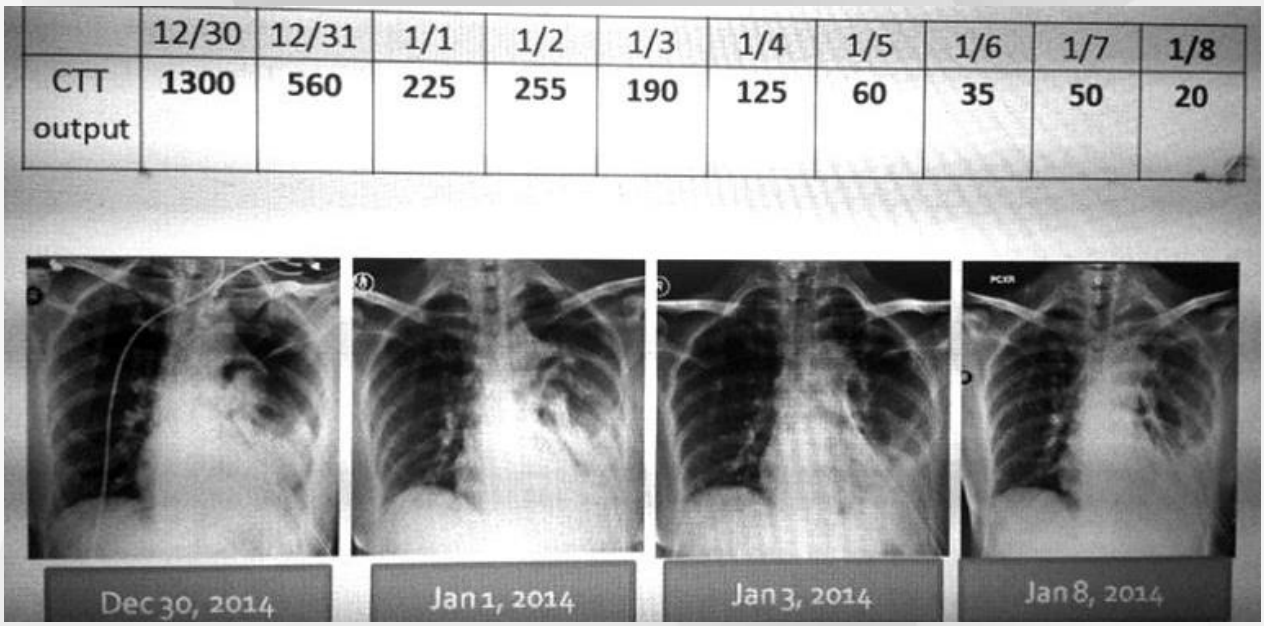


Figure 3. Patient 1: CTT output (in mL/day) and trend of serial chest radiographs done after streptokinase was started, showing improvement in pleural fluid drainage

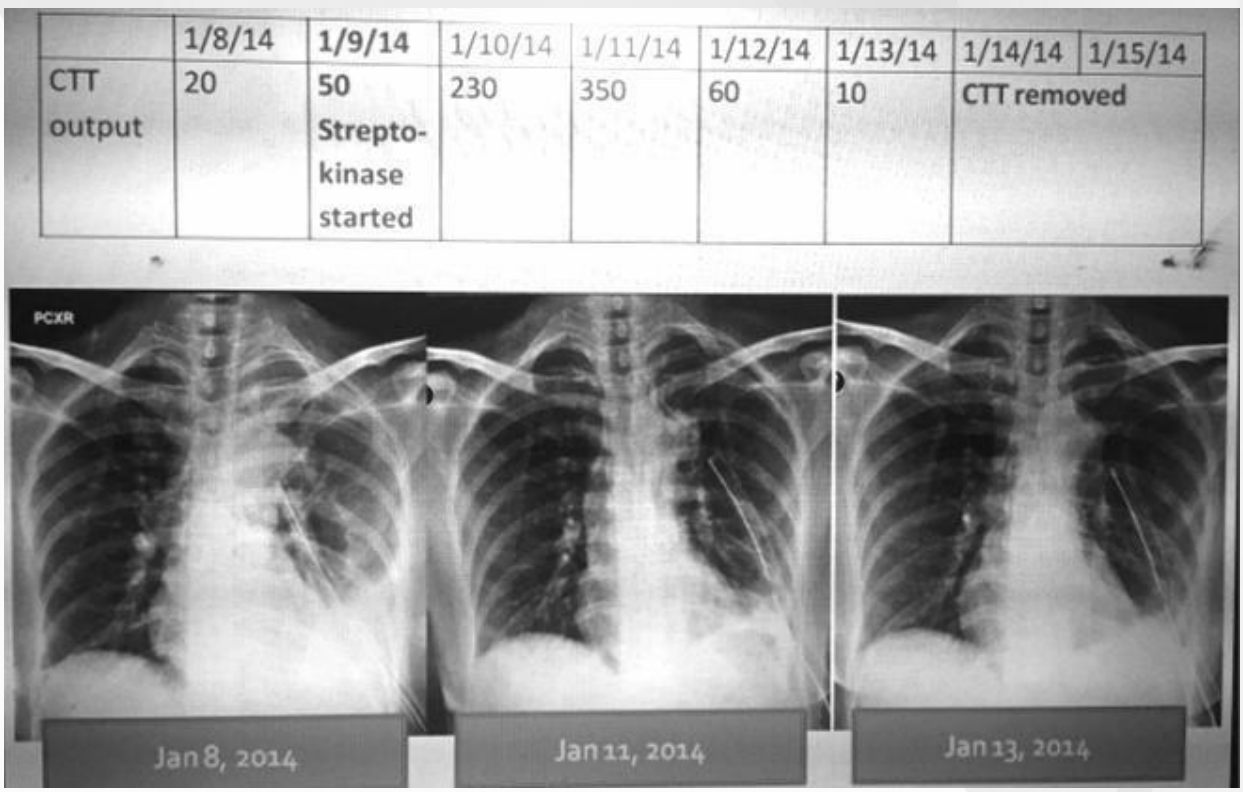
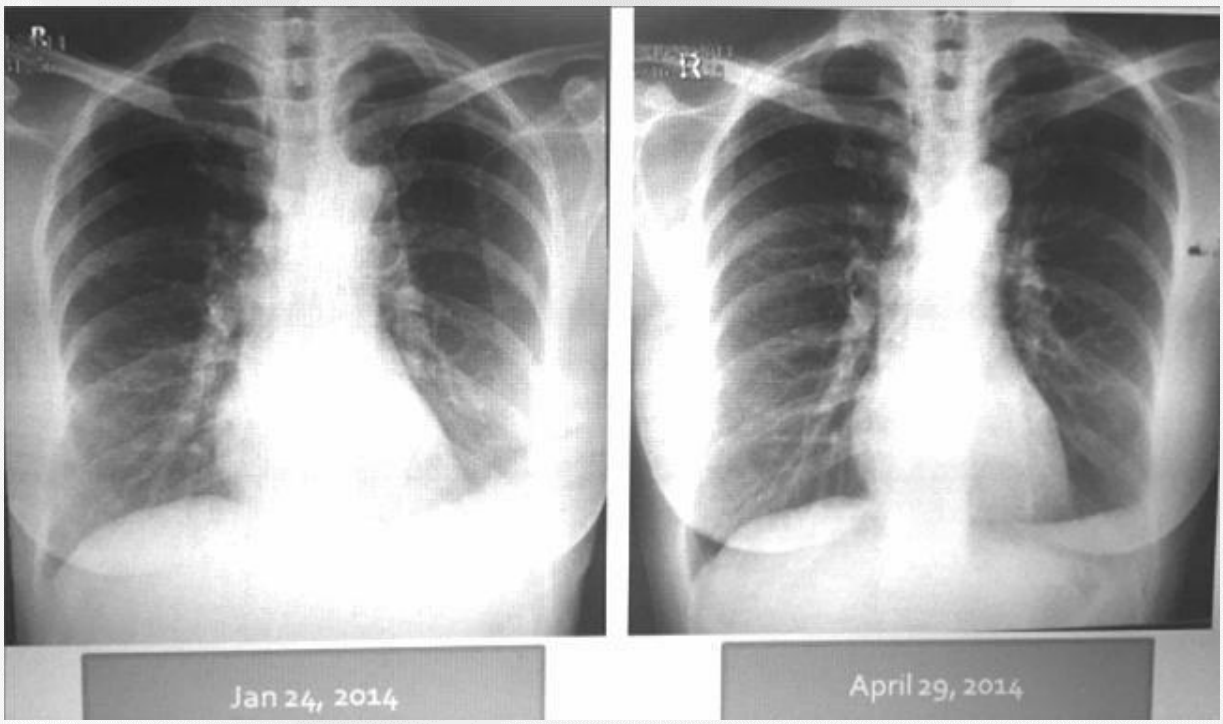


Figure 4. Patient 1: Follow up chest radiographs done 1 week (left) and 3 months (right) after discharge



pleural, and lung metastasis; has had nephrectomy and 5 cycles of immunotherapy. Two days prior to admission, she experienced shortness of breath associated with fever and pleuritic chest pain but had no cough or colds at that time. No consult was done and no medications were taken. Progression of symptoms prompted emergency consult and subsequent admission. The patient is hypertensive with a usual BP of 110/80 and maintained on Amlodipine 5mg daily. She also has Chordoma and underwent Gamma knife surgery in 2011. She is maintained on anti-seizure medications. She does not have diabetes or asthma, and has no previous pulmonary tuberculosis (PTB) treatment. She has no known allergies. Personal, social, and family history were unremarkable. Review of systems was likewise unremarkable.

On admission, her blood pressure was 100/70, and heart rate was regular at 65 beats per minute. She was tachypneic at 26 cpm, febrile at 38.9 ^{o}C, and had an O_2 saturation of 97% at room air. Patient was awake and conversant but weak looking. She had decreased breath sounds in the left lung mid to base. She had no cyanosis or edema, and had an unremarkable neuro examination. Complete Blood Count showed anemia with Hgb at 9.9 and leukocytosis at 11.5. Chest radiograph showed homogenous opacification of the left lung mid to lower hemithorax with plueral effusion. Underlying pneumonia could not be ruled out.

Our admitting impression was malignant pleural effusion left, secondary to RCC with peritoneal, pleural, lung, and bone metastasis; pneumonia in the immunocompromised host; controlled hypertension.

On admission, patient was started on Piperacillin-Tazobactam. Chest ultrasound showed 1,289 mL of free pleural fluid on the left with a nodular structure measuring 5x3 cm. She was referred to Interventional Radiology for pigtail insertion in the left hemithorax. Initial drainage

was 600mL of serous fluid. Post-pigtail insertion, the patient was referred to the Pulmonology service for co-management. Levofloxacin was added to the antibiotic regimen and the patient was also started on Salbutamol nebulization via IPV.

Daily pigtail output showed decreasing trend. On the 3rd hospital day, a chest CT scan showed a significant amount of loculated effusion in the left, with nodular pleural thickening, bilateral non-calcified pulmonary nodules, and blastic changes at T12 and L1. Chest ultrasound on the 5th hospital day showed loculated effusion on the left with an approximate volume of 849 mL. Intrapleural administration of rTPA or chest tube thoracostomy was offered to the patient. The patient chose rTPA.

The rTPA available in our institution is Actilyse 50mg powder, and costs around P50,000 per vial. Each vial is good for 5-10 doses. This vial is dissolved in 50mL NSS. Once this is diluted, the concentration of the solution is 1mg per 1mL volume. To get 5 mg, we used a syringe to aspirate 5mL of the diluted solution, and diluted this further in a pre-filled syringe with 40-50mL NSS. We then infused this diluted solution through the pigtail catheter.

We gave the patient a total of 2 doses of rTPA, 5 mg per dose. The pigtail output correlated with decreasing trend of effusion on chest radiograph and chest ultrasound (Figure 6). Two days after the 2nd dose of rTPA, the patient underwent pleurodesis with tetracycline, and the pigtail catheter was pulled out 2 days after. She was discharged stable on the 15th hospital day., Her chest ultrasound on discharge detected 2 pockets of loculations on the left, measuring 57 mL and 12 mL.

Our final diagnosis was malignant loculated pleural effusion secondary to RCC stage 4 with peritoneal, pleural, lung, and bone metastatis, status post 2 cycles of intrapleural rPTA; pneumonia in the immunocompromised host – resolved; hypertension controlled.

DISCUSSION

Intrapleural fibrinolysis was first done in 1949 by Tillet and Sherry[7], who instilled a partially purified concentrate of streptokinase and streptococcal DNAse in 23 patients with empyema and hemothorax. The investigators noted significant improvement in drainage of pleural fluid, but the major adverse effects of fever, leukocytosis, and generalized body weakness attributed to an immunologic reaction to the impurities in the agents made the procedure unpopular until the advent of purified streptokinase.

In the last 30 years, there have been at least 25 case series reports using streptokinase and urokinase in complicated parapneumonic effusion & empyema with encouraging results. The number of patients in these case series reports varied from 3-30, and the indication for initiating fibrinolytic therapy was failed chest tube drainage in the presence of patent & adequately positioned tube or catheter. Success rates ranged from 67-100% in these studies. The largest study done on strepto-

Figure 5. Patient 2: Chest radiograph on admission

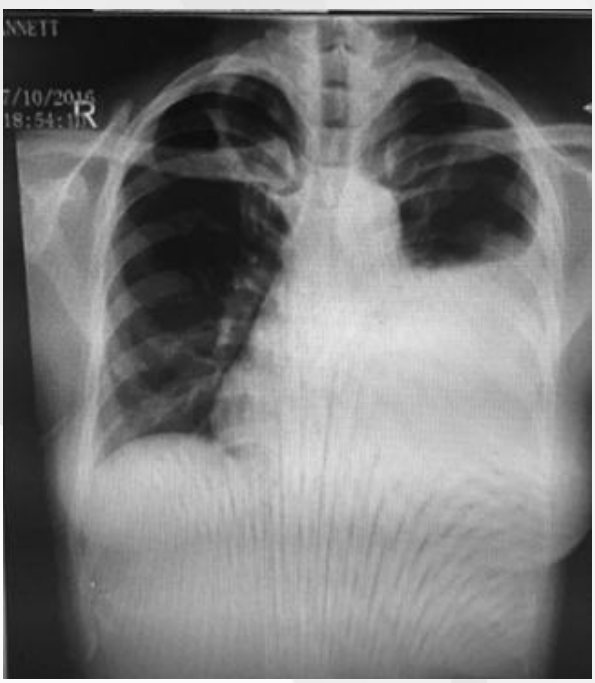
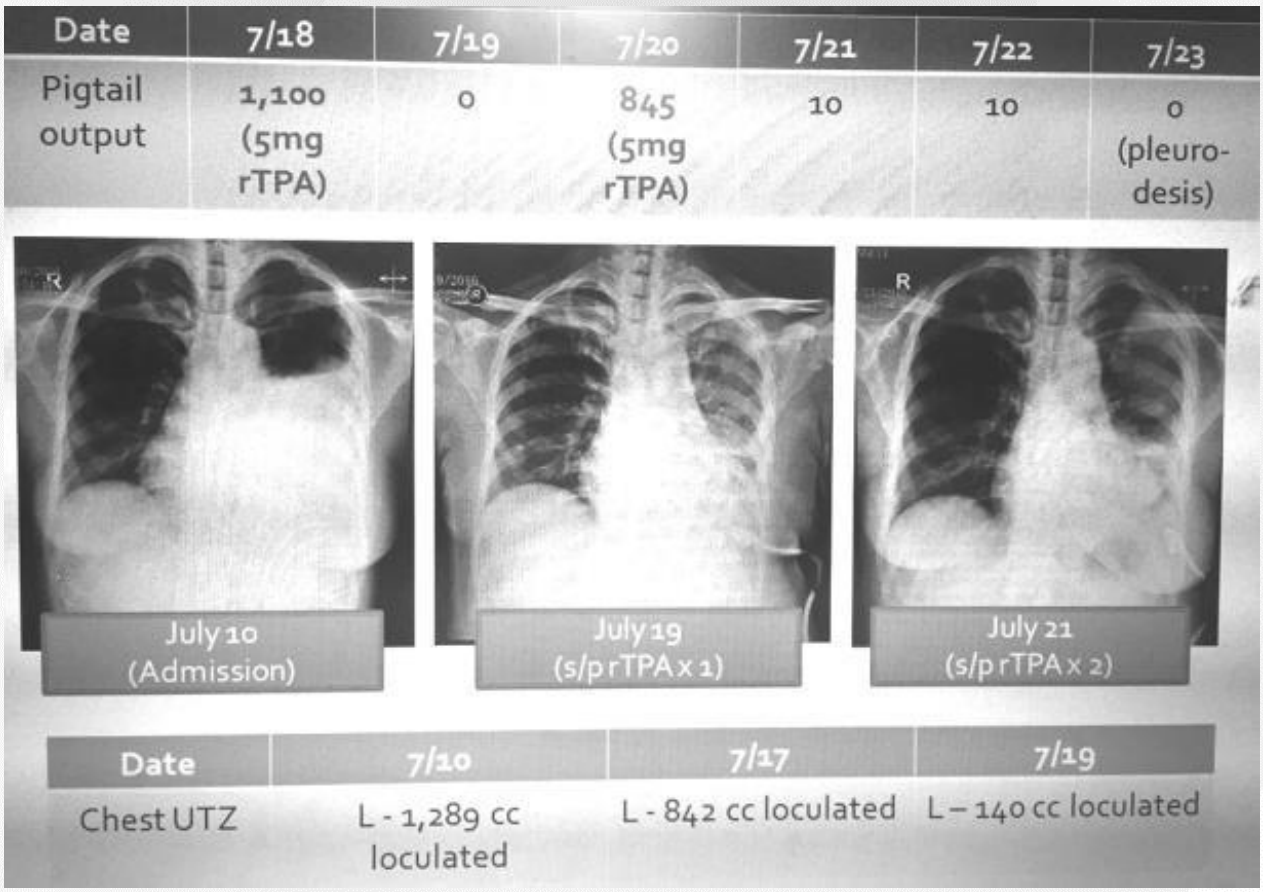


Figure 6. Patient 2: Pigtail output, correlated with chest xray and chest ultrasound after rTPA was given



kinase is the Multicenter Intrapleural Sepsis Trial or MIST 1 published in 2005.[5] It was a double blind RCT involving 454 patients from 52 UK centers, and compared the use intrapleural streptokinase versus saline placebo for complicated effusion and empyema. They found no difference in any primary or secondary outcomes between streptokinase and placebo, including mortality, surgery, length of hospital stay, or lung function at 3 months. This study was criticized for not recruiting patients early in the disease process, and not assessing for presence of loculations and septations since the inclusion criteria were macroscopically purulent effusions, (+) gram stain, and pH < 7.2). A possible explanations for the results include streptokinase may be the incorrect fibrinolytic since acts indirectly and may not be sufficient to resolve the systemic sepsis associated with infection.

Majority of patients who undergo intrapleural fibrinolysis with streptokinase have no complications, but 5-10% have transient fever, pleuritic chest pain, and chest wall erythema. Other studies done on streptokinase showed that it induced antibody formation and some patients developed a delayed hypersensitivity reaction. Urokinase was introduced to alleviate those issues seen with streptokinase, but was discontinued by the US Food and Drug Administration because of the risk of viral transmission.

Streptokinase is usually given at a dose of 250,000 IU once daily or q12, diluted in 5-50 cc Plain NSS, with the chest tube clamped for 2-4 hours. The maximum treatment duration is 5 days.

Streptokinase is renally excreted and does not cause systemic activation of the fibrinolytic system. Contraindications include the following: bleeding diathesis, stroke, peptic ulcer disease, significant hemorrhage in the past 6 months, and use of fibrinolytic agents by any route in the previous 2 years.

Alteplase is a second generation fibrinolytic with high specificity for fibrin and a short half-life. It is a recognized systemic treatment for myocardial infarction, pulmonary embolism and thromboembolic stroke. It is fibrin-selective and preferentially activates plasminogen at the surface of a clot, It then converts plasminogen to the active protease plasmin, which degrades fibrin into soluble products. Alteplase also potentially addresses the decreased level of endogenous tPA in pleural fluid. It is less antigenic compared to streptokinase and undergoes hepatic elimination.

In a study published in CHEST last 2015 on patients with malignant pleural effusion who are already on pigtail catheters, intrapleural fibrinolysis with streptokinase, urokinase, and rTPA was done in 66 patients in 4 centers in Australia.[8] Pleural fluid drainage increased in 93% of patients, and dyspnea improved in 83% following therapy. The median cumulative pleural fluid volume drained 24 h post treatment was 500 mL. They concluded that intrapleural fibrinolytic therapy can improve pleural fluid drainage and symptoms in selected patients with IPC and symptomatic loculation, but it carries a small risk of pleural bleeding. There is currently no consensus on the dosage of intrapleural alteplase, with studies ranging from 5mg to 100mg per day. In our institution, we usually give 5 to 10 mg dissolved in 50 mL NSS per dose once a day.

Intrapleural fibrinolysis is included in the recommendations of the American College of Chest Physicians (ACCP)[9] and British Thoracic Society (BTS)[10] for the management of loculated parapneumonic effusion, albeit not for routine use based on Level C evidence. Intrapleural instillation of fibrinolytic drugs is also recommended by the BTS for the relief of dyspnea due to malignant effusion.[11]

CONCLUSION

Loculated pleural effusions are most commonly due to complicated parapneumonic effusions, PTB, hemothorax, and malignancy; and usually develop due to either delayed initiation of antibiotics and/or delayed pleural spaces drainage. Although this is effectively and traditionally managed with VATS or open thoracostomy, these measures are expensive and not easily accessible in smaller hospitals and rural areas in the Philippines. International and our local hospital data show that the use of fibrinolytic agents streptokinase and alteplase may be a safe, easy, and cost-effective option for patients with loculated pleural effusion.

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CASE REPORT

Pulmonary Manifestations in Rheumatologic Diseases: A Case Series

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ABSTRACT

The lungs are commonly involved in rheumatologic disease and this involvement may carry significant morbidity and mortality. Patients may experience respiratory symptoms during the course of their illness or may initially present with such complaints. Whatever the case may be, the importance of recognizing pulmonary involvement cannot be overemphasized as early detection allows the physician to intervene quickly and limit adverse outcomes. This case series reports various pulmonary complications of different rheumatologic diseases with emphasis on the signs and symptoms to recognize such conditions, examinations for diagnosis and subsequent management.

INTRODUCTION

Connective tissue disease often has multisystem involvement and the lungs are vulnerable to involvement in these diseases. Respiratory manifestations are a significant cause of morbidity and mortality in patients with rheumatologic disease. The severity of manifestations is variable with complaints ranging from cough, pleuritic pain to severe respiratory distress and frank respiratory failure. The frequency of pulmonary involvement varies in each disorder which makes the diagnosis particularly difficult. This case series describes various pulmonary complications of a number rheumatologic diseases as well as the approach to diagnosis and general management.

CASE 1. ILD IN MIXED CONNECTIVE TISSUE DISEASE

A 31-year old woman was referred to the pulmonary service due to 2 month history of pleuritic chest pain, intermittent non-productive cough, easy fatigability and exertional dyspnea which limits her daily activity. She denied any orthopnea, paroxysmal nocturnal dyspnea, bipedal edema, fever, chills, night sweats, and hemoptysis.

She has been diagnosed with mixed connective tissue disease (MCTD) following an initial presentation 4 years ago of bluish discoloration, numbness and pain of fingers when exposed to cold temperature that was associated with joint stiffness and swelling of the proximal interphalangeal joints of both hands, bilateral wrist, elbow, knee and ankle joints, low grade fever, loss of appetite and weight loss. Later, she reported having myalgia and falling hair. Laboratory results at the time demonstrated elevated anti-U1 ribonucleoprotein (anti-U1 RNP >240U/mL), anti-double-stranded DNA (anti-dsDNA (93.5IU/mL) and rheumatoid factor (>20IU/mL). She was subsequently given Prednisone 20 mg/day, Hydroxychloroquine 20 mg/day, Nifedipine 10 mg/day, Calcium + Vitamin D tab, Methotrexate 7.5 mg/week, Folic Acid 10 mg/week, and Celecoxib 200 mg PO q12 prn for pain, with relief of symptoms. Glucocorticoids were gradually tapered off.

On examination, she had thin sparse hair, stable vital signs, cold extremities, no rashes and unremarkable chest and cardiac findings.

Laboratory examinations showed normal complete blood count and serum chemistry. Chest radiography (Figure 1) showed reticulonodular densities on the apicoposterior segment of the left upper lobe and posterior basal segments of both lower lobes with a primary consideration of pneumonia by the radiologist. Subsequent high-resolution chest computed tomography (HRCT, Figure 2) demonstrated honeycombing changes in the peripheral and subpleural aspects of both lungs predominantly in the lower lobes and scattered subpleural reticulations suggestive of a usual interstitial pneumonia pattern. Two-dimensional echocardiography showed normal mean pulmonary artery pressure (28mmHg by RV acceleration time). Pulmonary function test showed mild restrictive ventilatory defect. Total Lung Capacity (TLC) was 75% with moderately reduced Carbon Monoxide Diffusing Capacity (DLCO) at 48%. A diagnosis of connective tissue disease-associated interstitial lung disease (CTD-ILD) was made.

CASE 2. SHRINKING LUNG SYNDROME IN MCTD

A 30-year-old Filipino female, diagnosed with MCTD, was referred by the rheumatology service to the pulmonary service for evaluation of dyspnea.

At age 20 years, she presented with malar rash, joint pains, and alopecia, Raynaud's phenomenon, Morphea on the chest, sclerodactyly, myositis and synovitis. Positive anti-nuclear antibody (ANA), anti-dsDNA, and anti-u1-RNP confirmed the diagnosis of MCTD (systemic lupus erythematosus-scleroderma-polymyositis). She was maintained on Prednisone 5 tablet once a day, Hydroxychloroquine 200mg tablet once a day and Calcium carbonate tablet once a day. She was previously well until she experienced a 6-month history of progressive

Figure 1. Chest radiography (posteroanterior and lateral views) showed reticulonodular densities in the apicoposterior segment of the left upper lobe and posterior basal segments of the bilateral lower lobes, more on the right.

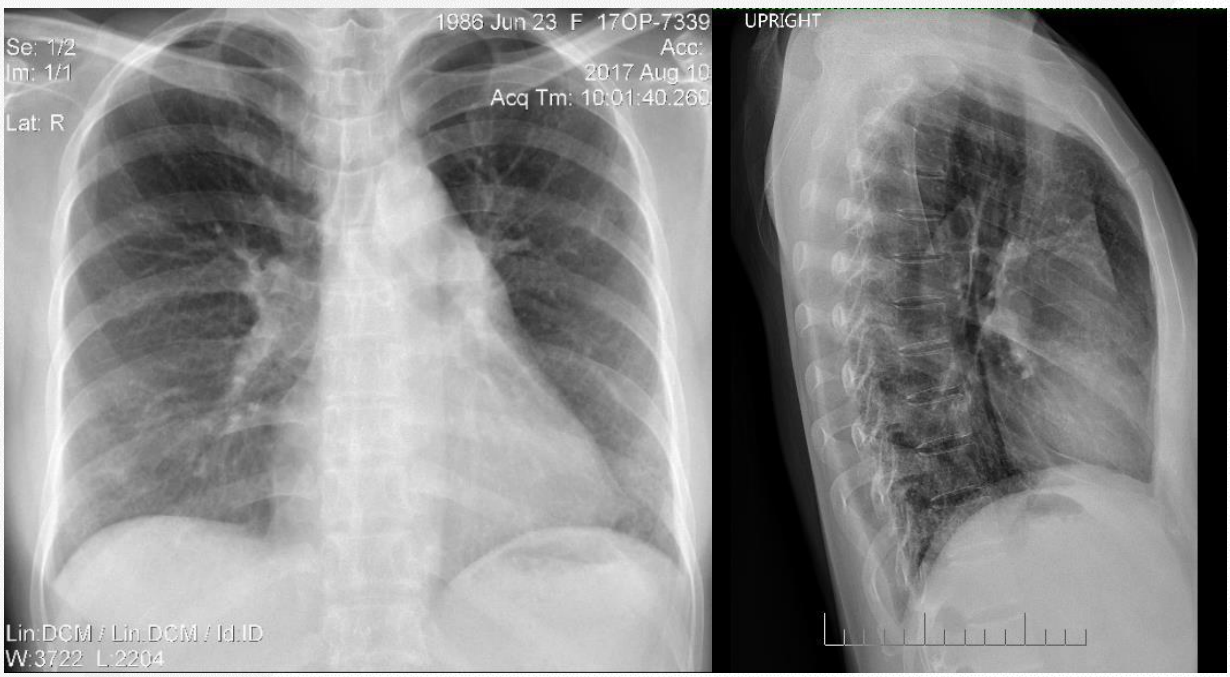
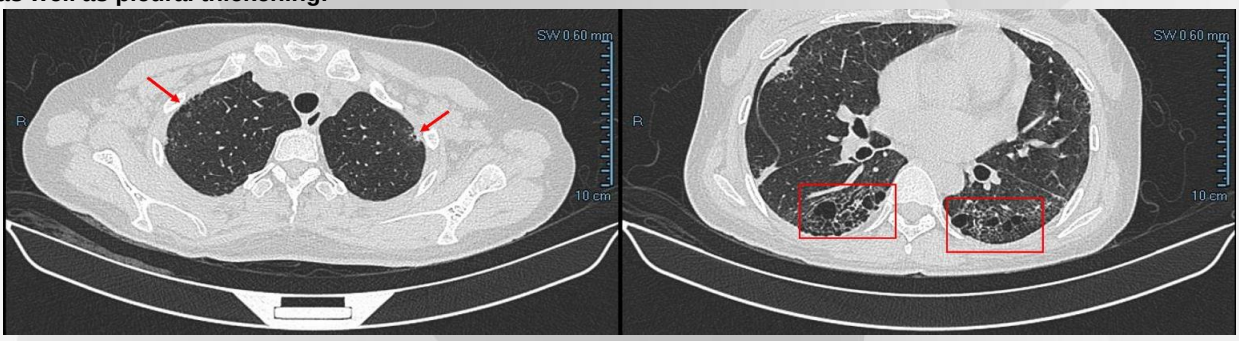


Figure 2. High resolution chest CT scan showed subpleural reticulations (red arrow) and honeycombing changes (red box) in the peripheral and subpleural aspects of both lungs predominantly in the lower lobes as well as pleural thickening.



shortness of breath associated with sudden onset of chest pain even on respiration and becomes more severe on supine position. She had no fever or cough. Due to her worsening dyspnea and orthopnea, she was admitted at the emergency room.

On physical examination, she was awake, conscious, afebrile, tachypneic with normal oxygen saturation at room air. She had moon facies from chronic steroid use, bilateral lower lung fields had decreased breath sounds, and she had hyperkeratotic hyperpigmented plaques on her elbows.

Initial laboratory workup showed mild lymphopenia on complete blood count and normal serum chemistry. Her arterial blood gas showed respiratory alkalosis with adequate oxygenation at room air. Her chest radiograph showed small lung volumes with bilateral elevated hemidiaphragm and minimal pleural effusion (Figure 3). Chest ultrasound also showed the same findings. Hence a preliminary diagnosis of shrinking lung syndrome was suspected. This was further supported by chest computed tomo-

Figure 3. Chest radiograph (PA view) of showing small lung volumes with bilateral elevated hemidiaphragm and minimal pleural effusion (right) compared to chest radiograph 6 months prior (left).

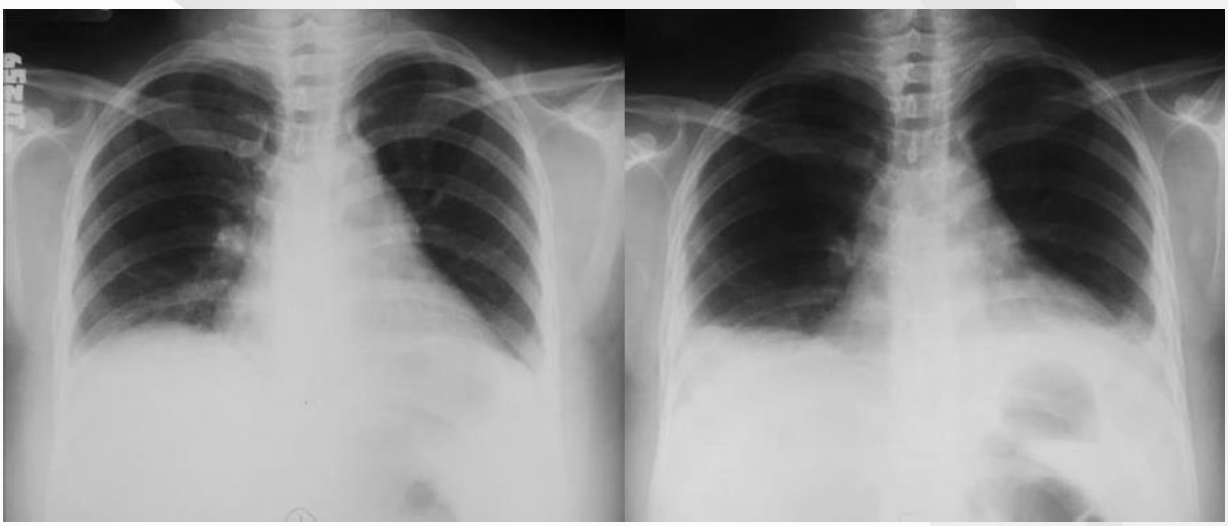
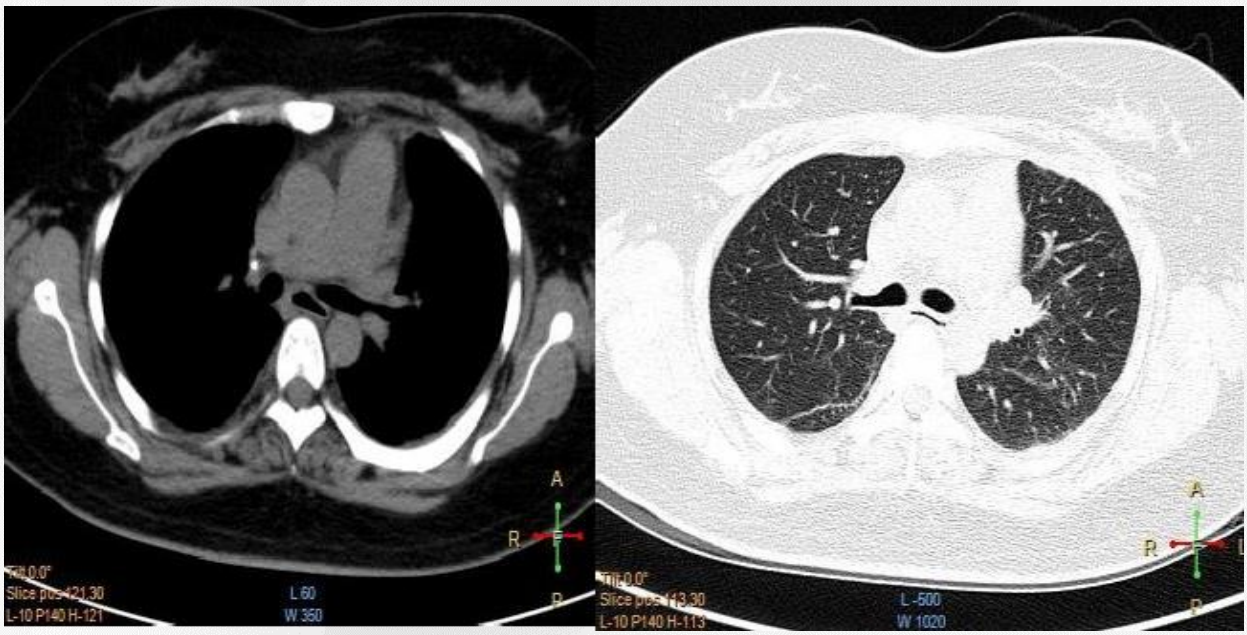


Figure 4. Chest computed tomography demonstrated no active parenchymal infiltrates.



graphy (CT) finding of elevated bilateral hemidiaphragm with low lung volumes, no active parenchymal infiltrates seen, and a minimal pleural effusion on the left (Figure 4). She was treated for community acquired pneumonia – low risk and was eventually discharged with a prescription of Prednisone 20 mg once a day and Hydroxychloroquine 200 mg once a day.

After discharge, she still experienced shortness of breath while doing normal activities and right sided pleuritic chest pain. Further outpatient workup showed very severe restrictive ventilatory defect (predicted FEV1 31%/ 0.89L) on spirometry. A phrenic nerve conduction velocity and diaphragm electromyography revealed findings consistent with axonal dysfunction of bilateral phrenic nerves. A sniff fluoroscopy showed minimal bilateral diaphragmatic excursion. These findings supported the diagnosis of shrinking lung syndrome. The patient was referred for pulmonary rehabilitation.

MCTD DISCUSSION

MCTD is a connective tissue disorder typified by an overlap of clinical features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and polymyositis with high titers of anti-U1 RNP antibodies. It was first described by Sharp et al[1] in 1972. The occurrence of overlapping features is usually sequential and would rarely happen simultaneously. This overlap of clinical features coupled with the absence a universally accepted diagnostic criteria, makes the diagnosis of MCTD challenging.

High titers of anti-U1 RNP is associated with distinct clinical characteristics and is the primary reason for considering MCTD as a separate clinical entity. For instance, glomerulonephritis, psychosis and seizure are infrequent among patients with high U1 RNP antibodies.[2,3] They also nearly always have early onset of Raynaud phenomenon; are more likely to develop PH; and are more likely to test positive to rheumatoid factor.[1,4-9]

The early clinical features of MCTD are usually nonspecific like malaise, fatigue, myalgia,

arthralgia and fever.[1,4,10] Almost any organ can be affected but prominent clinical features include Raynaud's phenomenon, absence of severe kidney or central nervous system involvement, severe arthritis and high titers of anti-U1 RNP antibodies.

The lungs are affected in 75% of MCTD patients and may exhibit a variety of complications.[11,12] Pleural effusions, thromboembolic disease, pulmonary infections, alveolar hemorrhage, diaphragmatic dysfunction, obstructive airway disease, interstitial lung disease (ILD) and pulmonary hypertension (PH) have all been reported by Farhey, with PH being a major cause of death in these patients.[5,13]

The first case illustrates the usual early symptoms of pulmonary involvement in MCTD: dry cough, pleuritic chest pain and dyspnea. Since interstitial lung disease occurs in more than half of MCTD patients, it must always be included in the differential diagnosis of these patients presenting with a respiratory complaint. An HRCT is a sensitive test to detect ILD. Common findings include ground glass attenuation, subpleural micronodules, linear opacities with lower lobe and peripheral predominance.[14] The HRCT of the patient in the first case showed subpleural reticulations and lower lobe, peripheral/subpleural predominant honeycombing consistent with a usual interstitial pneumonia (UIP) pattern.

A 2002 review by Kim et al focused on the parenchymal changes of CTD-associated interstitial lung disease (CTD-ILD) and found that the most common radiologic pattern of CTD-ILD is non-specific interstitial pneumonia (NSIP), a morphologic pattern with findings of predominant ground-glass opacities, reticular opacities and subpleural sparing.[15] Like UIP, however, there is also symmetric, bibasal involvement. Although NSIP is more commonly seen, UIP has also been reported among MCTD patients.

The pattern revealed by HRCT scans of the chest may sometimes predict the underlying histologic pattern. One example is that of a definite UIP pattern, which consists of subpleural, basal predominance, reticular abnormality, honeycombing with or without traction bronchiectasis in the absence of peribronchovascular predominance, extensive ground glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation or air-trapping (bilateral in ≥3 lobes and consolidation in bronchopulmonary segments or lobes). When a UIP pattern is seen on HRCT, it is specific but not sensitive for UIP on histopathology after surgical lung biopsy and precludes the need for invasive procedures.[11]

Most patients with MCTD are responsive to steroids. The usual therapy for MCTD-ILD includes corticosteroids with steroid sparing agents such as cyclophosphamide, methotrexate and hydroxychloroquine.[1,16]

Untreated ILD is usually progressive with development of severe pulmonary fibrosis in one-fourth of patients after 4 years. Mortality is about 8% with higher rates (~21%) among those with severe lung fibrosis.[17]

Another potential pulmonary complication of MCTD is diaphragmatic dysfunction which may remain unrecognized during the early phase. It is important to recognize it promptly as it may be a pathogenic mechanism underlying a rare complication, shrinking lung syndrome (SLS). SLS is widely studied in patients with SLE but data on its occurrence in MCTD is limited. Shrinking lung syndrome may occur as early as 3 months and as late as 38 years after diagnosis of rheumatic disease. The second case satisfies the criteria for the diagnosis of SLS, which includes progressive dyspnea, decreased lung volumes on chest radiograph and/or elevated bilateral hemidiaphragm, pulmonary function test demonstrating a restrictive ventilatory defect and absence of parenchymal pathology on chest CT scan.[18]

The precise pathogenic mechanism underlying SLS remains controversial. In the past, it has been attributed to a surfactant deficit,

phrenic nerve dysfunction, chest wall dysfunction and pleural adhesions.[19] It is proposed that SLS begins with pleural inflammation as a result of the underlying rheumatic disease. Pleural inflammation causes an inhibition of deep inspiration either by neural reflexes or pain, and inhibits diaphragmatic activation leading to diaphragmatic dysfunction.[20] Eventually, chronic lung hypoinflation ensues which, in predisposed patients, may cause parenchymal remodeling and decreased lung compliance. Impaired compliance worsens hypoinflation, initiating a positive feedback loop. This helps explain the gradual progression of SLS. Since this defect is primarily functional, the patient's ventilatory drive is expected to limit further respiratory deterioration, accounting for the low mortality of SLS despite its alarming clinical presentation.

In one report, a neurogenic origin of SLS though phrenic nerve involvement was proposed.[21] They described a patient with SLE who presented with bilateral phrenic nerve paralysis documented by surface electromyogram in response to cervical magnetic stimulation and transcutaneous electrical stimulation at the time of diagnosis of rheumatic disease.

In our second case, the patient's phrenic nerve stimulation test was positive for diaphragmatic dysfunction which was supported by the minimal diaphragm excursion on sniff fluoroscopy. There are no standardized guidelines for the treatment of SLS. Majority of patients should be initially treated with medium or high doses of glucocorticoids.[22] Those who respond to this treatment usually improve after several weeks or months, but possibly earlier with symptomatic improvement seen within 48 hours in some cases. Theophylline has been shown to increase diaphragmatic muscle strength in healthy volunteers while inhaled β2 agonist decrease diaphragmatic fatigue through their positive inotropic effect. The use of β2-agonist therapy has only been described in case reports. For patients who are at risk for chronic respiratory failure, non-invasive positive pressure ventilation plays a role in supporting the paretic diaphragms, as in other neuromuscular disorders, in addition to immunosuppressive therapies to prevent nocturnal hypoventilation and support quality of sleep.[23] Pulmonary rehabilitation in patients with restrictive lung disease lead to clinically relevant improvements of the maximal and submaximal exercise capacity, muscle force, and quality of life after 12 weeks and with further improvements after 24 weeks.[24]

In conclusion, ILD and SLS are restrictive lung diseases which represent two potential pulmonary complications of MCTD. It is important to recognize such complications as they have significant implications to the overall management of these patients.

CASE 3. ACUTE LUPUS PNEUMONITIS

This is a case of a 28-year-old female from Manila who was admitted due to dyspnea. She is a known case of SLE since 2008 and is presently being treated for pulmonary tuberculosis, clinically diagnosed on intensive phase. She is maintained on prednisone 0.5mg/kg/day, Hydroxychloroquine and anti-Kochs medications. Two weeks prior to admission, she developed productive cough with yellowish sputum associated with dyspnea, pleuritic chest pain and undocumented fever. There was no consult done. During her outpatient follow up with her rheumatologist, she reported she had joint pains, loss of appetite, persistent cough and progressive dyspnea. She was brought to the emergency room (ER) and was advised admission.

At the ER, patient was awake, in mild cardiorespiratory distress, febrile with desaturation at room air. Physical examination showed prominent alopecia, discoid rash and malar rash. There were bibasal crackles noted on auscultation. Vasculitic lesions were seen on bilateral fingertips and there was tenderness of bilateral knee joints on movement and palpation.

She was managed as a case of sepsis from pneumonia in the immunocompromised; SLE in activity with SLEDAI score 23 (vasculitis, alopecia, arthritis, myositis, rash, pleuritis, fever); pulmonary tuberculosis (PTB) on CAT 1 intensive phase. Arterial blood gas showed partially compensated respiratory alkalosis with moderate hypoxemia at room air. CBC showed neutrophilic predominance. Serum chemistry was normal except for elevated levels of LDH and CK total. Sputum Gram stain showed initial presence of gram negative bacilli. Sputum AFB was negative. Baseline chest radiographs revealed reticular bibasal infiltrates consistent with interstitial pneumonia (Figure 5A). Patient was referred to an infectious disease specialist and to the rheumatology service. She was started on broad spectrum antibiotics including meropenem and colistin for gram negative bacilli, cotrimoxazole for possible *Pneumocystis carinii* pneumonia coverage, and antifungals. Anti-Kochs medications were continued. However, chest radiograph showed progression of bilateral reticulonodular infiltrates (Figure 5B). After a course of piperacillin-tazobactam, infiltrates still progressed, with areas of consolidation (Figure 6).

The patient had episodes of desaturation on 60% FiO2 via face mask. Repeat blood and sputum cultures were negative after 2 weeks on colistin. 2D echo showed normal sized left ventricle with good wall motion and contractility. The left and right atria, right ventricle and pulmonary artery pressures were normal with small posterior pericardial effusion. Pulmonary edema was ruled out since the patient had adequate fluid balance, neck vein engorgement and peripheral edema was not seen. High resolution chest CT scan showed ground glass opacities in the left lung with prominent septal thickening, more prominent in the left lung, thin walled lucency in the apicoposterior segment of left upper lung with calcific densities and few reticulonodular densities in the periphery of the right upper lung. Consolidation with air bronchogram was seen in the posterior basal area of both lower lobes. There was also an incidental finding of extensive air pockets in the mediastinum. Bronchoalveolar lavage was contemplated but was postponed due to worsening hypoxemia. She was advised non-

Figure 5. Chest radiographs during admission (left) and worsening of the reticular infiltrates involving the upper lobes and showing areas of consolidation (right).

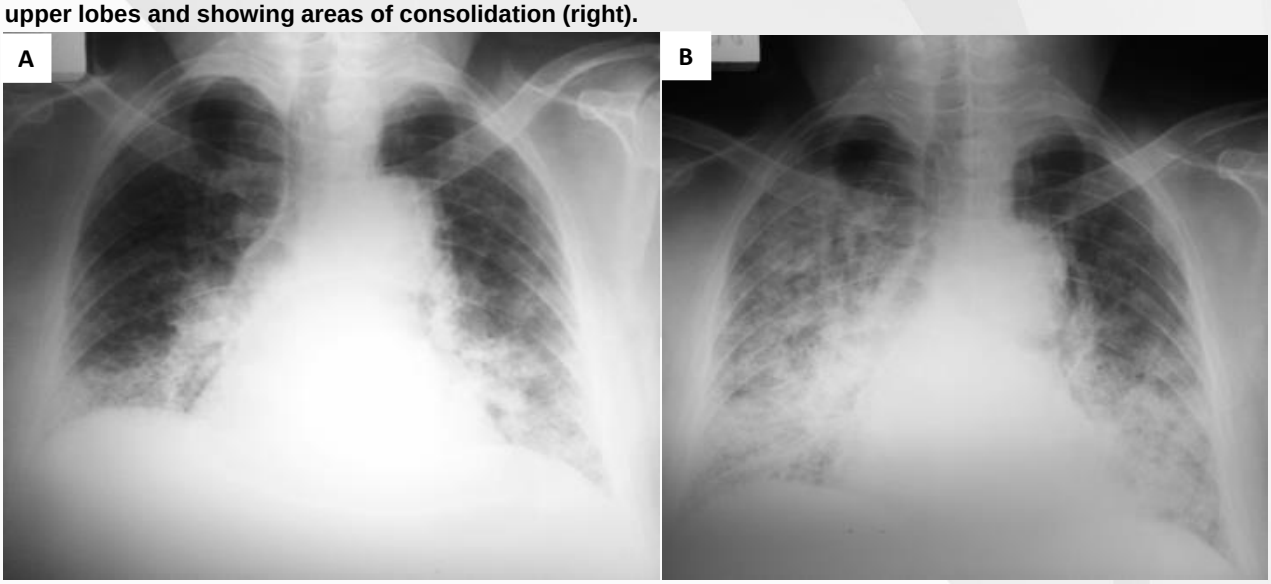
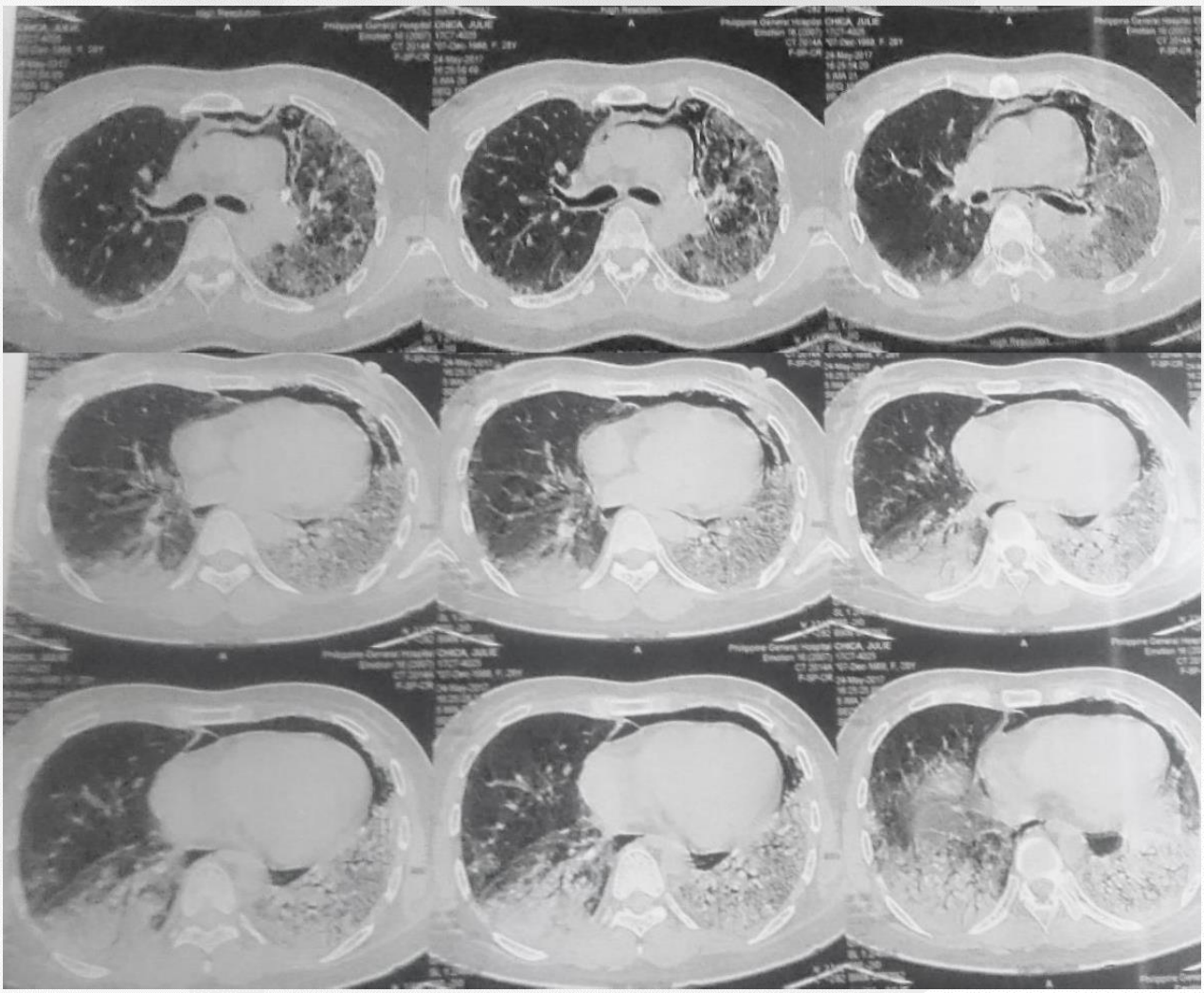


Figure 6. Chest CT scans after a course of intravenous piperacillin-tazobactam, showing large areas of reticular infiltrates involving the upper lobes and now showing areas of consolidation.



invasive ventilation and subsequent intubation. Assessment at this time was acute respiratory distress syndrome secondary to acute lupus pneumonitis. Methyprednisolone pulse therapy was advised.

LUPUS PNEUMONITIS DISCUSSION

According to the Systemic Lupus International Collaborating Clinics (SLICC) criteria, the diagnosis of SLE requires that patients to satisfy at least 4 of 17 criteria, including at least one clinical and one immunologic criteria, or that the patient has biopsy-proven nephritis compatible with SLE in the presence of ANA or anti-double-stranded DNA (dsDNA) antibodies. This patient satisfied the presence of acute cutaneous lupus, oral ulcers, synovitis and serositis with (+) ANA and anti dsDNA. 4/11 + 2/6 immunologic criteria in the SLICC. SLE can include a wide spectrum of diseases. The most common is lupus pleuritis while less common is parenchymal involvement presenting either as

acute lupus pneumonitis or chronic interstitial lung disease.[25]

Acute pneumonitis is an uncommon (1% to 12%) manifestation of SLE. There is a mortality rate of more than 50% despite treatment especially once ventilator failure sets in.[27] Patients with SLE have a complex array of abnormalities involving the immune system leading to an inflammatory process and autoantibody production. Many biochemical studies have revealed abnormalities in T cell and B cell function, apoptosis, immune complex clearance and nucleosome processing. Acute lupus pneumonitis is a clinical syndrome with an underlying histology of diffuse alveolar damage, organizing pneumonia or non-specific interstitial pneumonia.[26,27] Diffuse alveolar damage reveals presence of alveolar edema, inflammatory cell infiltration, and fibrin and hyaline membrane formation. Alveolar hemorrhage may also be present. However, there are no histopathologic features which are considered pathognomonic of lupus pneumonitis.[28] The majority of the pathology in lupus is related to immune complex depositions as seen on immunofluorescence studies demonstrating granular deposits of immunoglobulin G (IgG) and C3 along the alveolar walls, the interstitium and endothelial cells.[29]

The diagnosis of acute lupus pneumonitis should be suspected in a patient with SLE who presents with acute onset of fever and cough. Physical examination reveals tachypnea, tachycardia, basilar crackles and hypoxemia.[25,26] As diagnosis is one of exclusion, the evaluation focuses on excluding heart failure, infection, pulmonary embolism, drug toxicity, and malignancy. A high index of suspicion is made when the patient does not respond to empiric treatment for pneumonia and when extrapulmonary features of SLE are noted such as malar rash, oral ulcers, alopecia, arthritis and vasculitis to this patient.[36]

Since most conditions are indistinguishable on clinical bases, chest radiograph is taken. If normal, dyspnea is likely due to either acute reversible hypoxia or pulmonary embolism which can be differentiated by V/Q scan. On the other hand, if the chest radiograph shows pleural effusion or wedge-shaped opacities, CT pulmonary angiogram is requested to look for evidence of pulmonary embolism. High resolution chest CT scan is requested if chest radiograph shows mainly alveolar infiltrates.[30] Since lupus pneumonitis may be difficult to distinguish from infective pneumonia, it is usually prudent to treat for infection initially with broad spectrum antibiotics, and once infection has been ruled out, to think about giving immunosuppressive therapy. In this patient, HRCT was requested after chest radiograph showed progression of bilateral reticulonodular infiltrates.

Bronchoscopy with BAL, with or without transbronchial biopsy is recommended in the diagnosis of acute lupus pneumonitis to exclude infection, alveolar hemorrhage, eosinophilia and diffuse infiltration by cancer. In the cellular analysis of BAL in the evaluation of acute onset ILD, greater than or equal to 50% neutrophil count strongly supports acute lung injury, aspiration pneumonia, or suppurative infection.[31] The BAL cellular profile in lupus pneumonitis may show a marked increase in neutrophils but this is nonspecific.

Little is known about the distribution and state of activation of lymphocyte phenotypes and their relationship with SLE disease activity.[32] A lung biopsy is rarely necessary to confirm the diagnosis of acute lupus pneumonitis or exclude infection but may performed prior to adding immunosuppressive therapy when a patient has not responded to systemic glucocorticoids. It is also use to rule out malignancy.[1]

There have been no controlled trials addressing treatment of acute lupus pneumonitis. Recommendations are based on the authors' experience and case reports. The mainstay of acute lupus pneumonitis treatment is systemic

corticosteroids usually prednisone 1–1.5 mg/kg/day.[25] If there is no response to oral corticosteroids within 72 hours and the patient worsens, treatment should include intravenous corticosteroid pulse therapy (1g methylprednisolone per day for 3 days). Immunosuppressive agents such as cyclophosphamide may be initiated if there would still be no prompt recuperation.[33]

Another treatment option is intravenous immunoglobulin (IVIg) therapy which has been used if patients is unresponsive to corticosteroid and immunosuppressive therapy. Continuous treatment with IVIg every 4 weeks for up to 20 months induced a prolonged clinical and laboratory remission.[34] Noninvasive or invasive mechanical ventilation is usually required in the treatment of lupus pneumonitis since most patients develop respiratory failure.[35]

In lupus pneumonitis, survival rates depend on early aggressive diagnostic approach, lung-protective mechanical ventilation, and the early institution of immunosuppressive therapy. Early diagnosis and treatment elucidated from a multidisciplinary approach among experienced pulmonologists, rheumatologists, radiologists, and pathologists would be the unsurpassed recommendation.

CASE 4. DISCERNING PH IN SSC

A 65-year-old female came in for a ten-year history of progressive dyspnea, nonproductive cough as well as salt and pepper skin changes on her anterior chest and upper back. In the last three years, she had multiple consults and admissions for productive cough and difficulty of breathing which were treated as pneumonia.

One week prior to consult, the patient developed bipedal edema and severe breathlessness even at rest. 2d echocardiogram and doppler studies revealed signs of PH with dilatation of the right ventricle, flattening of the intraventricular septum in systole and diastole as well as a systolic pulmonary artery pressure of 104 mmHg by Tricuspid Regurgitant Jet.

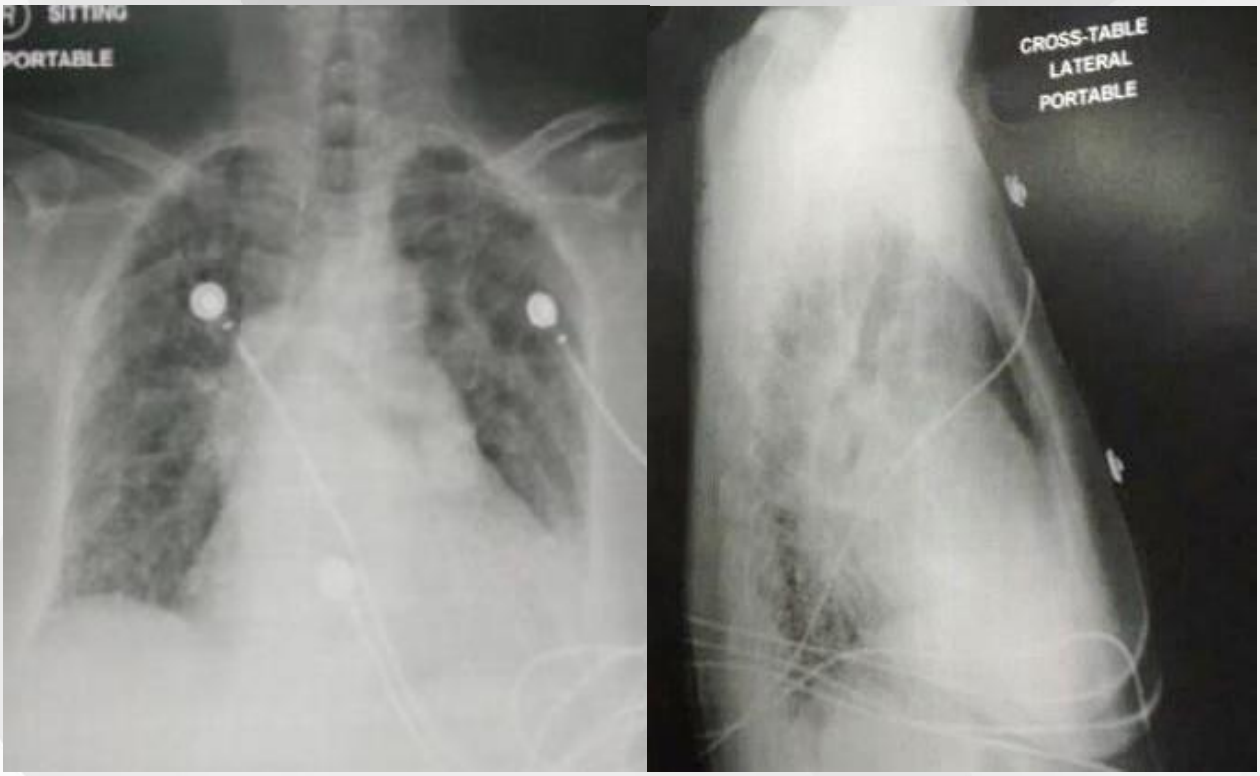
On physical examination, signs of SSc was evident as the patient presented with puckering of mouth, depigmentation of skin in a salt and pepper fashion on her trunk as well as sclerodactyly and tightening of her skin over her elbows and forearms. She also had signs of right-sided heart failure with the presence of a right ventricular heave, an accentuated and palpable p2 as well as bipedal edema. Chest findings showed prominent bibasilar crackles.

Chest radiographs and chest CT scan images showed prominence and dilatation of the main pulmonary trunk as well as its proximal branches (Figures 7 and 8). Lung window of these CT images showed honeycombing and subpleural fibrosis in the bases and ground glass opacities in the upper lobes. There was also an incidental finding of an acute pulmonary embolism (not shown) in both distal segmental branches of the lower lobe pulmonary arteries. Arterial blood gas analysis showed paO2 of 66 at room air with an A-a gradient of 31/16mmHg. Anti-Scl 70 was strongly positive while ANA IF, lupus anticoagulant and an initial APAS panel were all negative.

The patient was managed as a case of Pulmonary Arterial Hypertension (PAH) Type 1 from SSc (SSc-PAH); New York Heart Association Functional Class III, in sinus rhythm; Interstitial Lung Disease (probable UIP pattern). The patient underwent cyclophosphamide infusion and was maintained on azathioprine and mycophenolate mofetil for the patient's ILD. Sildenafil was started for PAH and Raynaud's syndrome pending right heart catheterization. She was also on Digoxin, low dose Furosemide and Enalapril.

The patient is undergoing cardiopulmonary rehab and is expected to be discharged from the hospital on continuous oxygen support at home.

Figure 7. Chest radiographs in PA (left) and lateral view (right) showing reticular infiltrates in both lung fields illustrating retrosternal fullness.



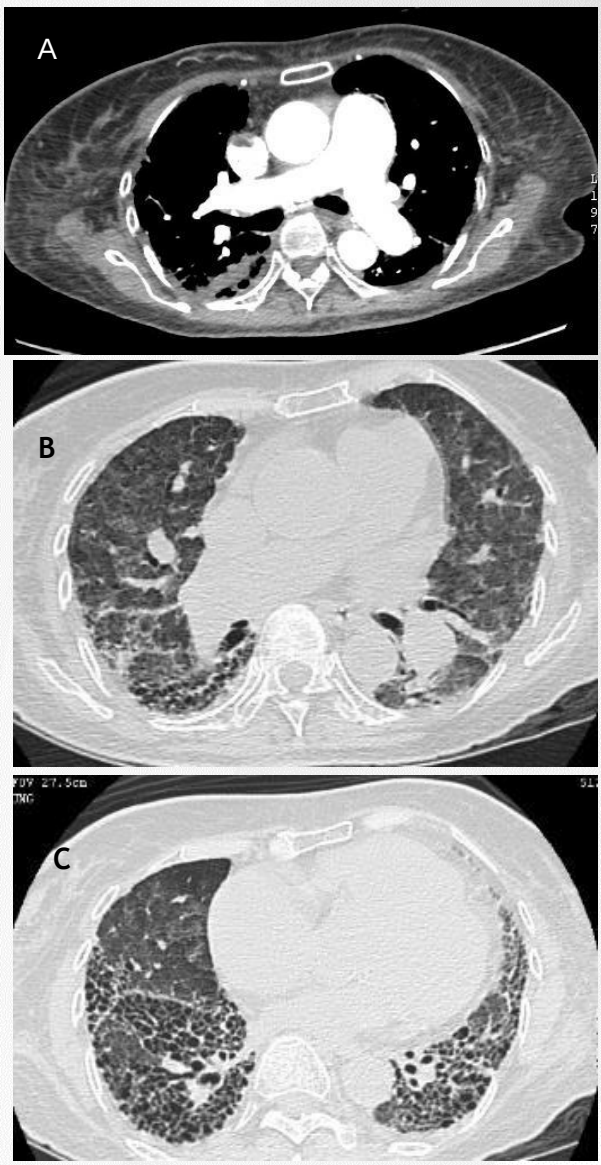
PH IN SSC DISCUSSION

Connective Tissue Disease related Pulmonary Arterial Hypertension (CTD-PAH) accounts for the 2nd most common cause of Type 1 PH following Idiopathic Pulmonary Arterial Hypertension.[36] SSc-PAH accounts for 75% of CTD-related PAH, followed by those associated with SLE and MCTD. Among the risks for SSc-PAH are older age of diagnosis, presence of Raynaud's phenomenon and limited SSc. Moreover, presence of autoantibodies such as anti-U3RNP, anti- topoisomerase IIa and anti-centromere increases the risk of SSc-PAH.[37]

It is not uncommon for an SSc patient to present with PH with a concurrent ILD. Chang et al illustrated that there is not much difference in the right ventricular systolic pressure of SSc patients with isolated PH and those with restrictive ventilatory defect from an ILD combined with PH.[38] Launay et al further showed that among patients with SSc-ILD both with and without significant restrictive lung disease, only a decreased paO_2 in ABG predicts the presence of PH.[39] These findings stressed that among SSc patients with PH, type 1 Pulmonary Arterial Hypertension is the predominant cause of hypertension rather than type 3; and only when there is hypoxemia did type 3 PH become clinically relevant.

Not only did the patient present with ILD but she also had an incidental finding of an acute pulmonary embolism. This probably increased her pulmonary pressures even more and pushed her into decompensation on her initial admission. SSc is not a traditional risk factor for developing a pulmonary embolism or deep vein thrombo-

Figure 8. Chest CT showing prominence of the main pulmonary trunk with dilatation of the left and right pulmonary arteries in the contrast enhanced film (A). Ground glass opacities are prominent in the upper lobes (B) while subpleural fibrosis and honeycombing are prominent in the lung bases (C).



sis.[40] However a nationwide cohort study by Chung et al showed that SSc confers a 7.8- to 8.11-fold risk of pulmonary embolism and is seen highest during the first year of diagnosis and is associated with the presence of lupus anticoagulant.[41] Pulmonary embolism in SSc is treated with anticoagulants and the concomitant presence of anti-phospholipid antibody syndrome confers lifetime anticoagulation.

There are four distinct pathophysiologies that contribute to the PH seen in SSc.[42] These are the activation of autoimmune cells; hyperplasia of fibroblasts; diminished collagen breakdown; and promulgation of autoantibodies. Almost always, the target tissue of this inflammatory bath is the vascular endothelium and the interstitium leading to unregulated fibrosis coursed through the keystone cell of SSc – the fibroblast. Treatment options for SSc-PAH involve the use of endothelin receptor antagonists, phosphodiesterase 5-inhibitors, guanylate cyclase stimulators and prostacyclins. Unlike idiopathic PAH, acute vasoreactivity testing using nitric oxide during right heart catheterization has little role in this setting. This is because SSc-PAH does not respond to nitric oxide and does not predict response to current therapies.[42] Due to the inherent unresponsiveness to nitric oxide, calcium channel blockers are of limited use in SSc-PAH. In fact, calcium channel blockers are only used in SSc as low dose therapy for symptomatic Raynaud's phenomenon and not for SSc-PAH. Among the endothelin receptor antagonists, only macitentan decreased the hospitalization rate but did not increase exercise capacity in 6-minute walk test. In contrast, phosphodiesterase-5 inhibitors like sildenafil and taladafil, and the guanylate cyclase stimulator riociguat, are all known to improve 6-minute walk test. Recently, the GRIPHON study showed that selaxipag had mortality and morbidity benefits over placebo.[43] It is important to note that studies in pharmacologic interventions in SSc-PAH are often pooled with other type 1 PH etiologies.

SUMMARY

These cases presented a spectrum of pulmonary manifestations in select rheumatologic diseases. All the patients presented with dyspnea

accompanied by often subtle signs of their underlying rheumatologic disease. Rheumatologic diseases are uncommon, more so are the pulmonary complications they entail. These pulmonary complications should be distinguished from the more common infectious causes which afflicts connective tissue disease patients. A good history and physical examination as well as familiarity and knowledge of potential involvement of the lung can never be overemphasized in these cases. With the advent of different lung imaging studies and the therapeutic interventions becoming more accessible to the public, it is the responsibility of clinicians to diagnose well, utilize appropriate diagnostics efficiently and institute proper and cost-effective treatment to save a patient.

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CASE REPORT

Bilateral diaphragmatic dysfunction due to bilateral phrenic nerve neuropathy in a patient with dyspnea on supine position

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ABSTRACT

Diaphragmatic dysfunction is a rare cause of unexplained respiratory failure with a median delay for diagnosis of 2 years. This paper reports a 65-year-old male who came in due to dyspnea in supine position associated with sleep disturbance and daytime sleepiness. Work-up revealed an elevated and dome-shaped right hemidiaphragm on chest radiograph; a right parathyroid adenoma inferoposterior to the thyroid gland without noted nerve infiltration or compression along the tract of the brachial plexus and phrenic nerve on plain neck and chest CT scan, and plain neck MRI; a moderate restrictive ventilatory defect with decrease in forced vital capacity by 30% when supine on spirometry; possible left hemidiaphragm paralysis and right paradoxical movement on diaphragm ultrasound (M-mode); and severe bilateral phrenic neuropathy on electromyography-nerve conduction velocity study. Polysomnography documented obstructive sleep apnea and possible sleep hypoventilation syndrome that improved with Average Volume Assured Pressure Support Mode (AVAPS) S/T mode. The patient was able to tolerate AVAPS S/T mode, and was liberated from nocturnal mechanical ventilator support. He later underwent decannulation of tracheostomy tube.

Key words: bilateral diaphragmatic dysfunction, paradoxical breathing, sleep hypoventilation, non-invasive ventilator support.

INTRODUCTION

Diaphragmatic dysfunction is a term used to describe a condition that results from weakness to complete paralysis of the diaphragm. Diaphragmatic weakness implies a decrease in strength of the diaphragm while diaphragmatic paralysis is an extreme form of diaphragmatic weakness wherein there is termination of the impulse of respiratory stimuli from the brain.

When patients have diaphragmatic dysfunction, the caudal displacement of the diaphragm during its contraction is abolished resulting in limited chest expansion. Furthermore, during inspiration because of the more negative pleural pressure, the diaphragm is displaced cephalad further compromising lung inflation. In the supine position, the weight of the abdominal viscera and the pressure generated in the abdomen enhances the cephalad displacement of the diaphragm further limiting lung expansion causing dyspnea and aggravating hypoxemia. This presents as paradoxical breathing in supine position.

Diaphragmatic dysfunction is a rare cause of unexplained respiratory failure. There is median delay for diagnosis of 2 years with a range of 6 weeks to 10 years. Incidence is unknown but 2/3 of cases are found to be idiopathic. However, there are a number of identified etiologies that need to be ruled out in order to manage patients appropriately. Among these etiologies include spinal cord diseases

(spinal cord tumors, spinal cord injury secondary to trauma), motor neuron diseases (amyotrophic lateral sclerosis, multiple sclerosis), neuromuscular junction disease (myasthenia gravis, botulism), muscle disease (dermatomyostis, polymyositis, acid maltase deficiency, malnutrition), and neuropathy (radiation or trauma-induced, toxic/endocrine-induced, autoimmune, idiopathic). For this reason, an algorithmic approach to diagnosis and management of diaphragmatic dysfunction is needed.

CASE REPORT

This is the case of a 65-year-old male, married, Filipino, Catholic from Pampanga who came in due to dyspnea on supine position.

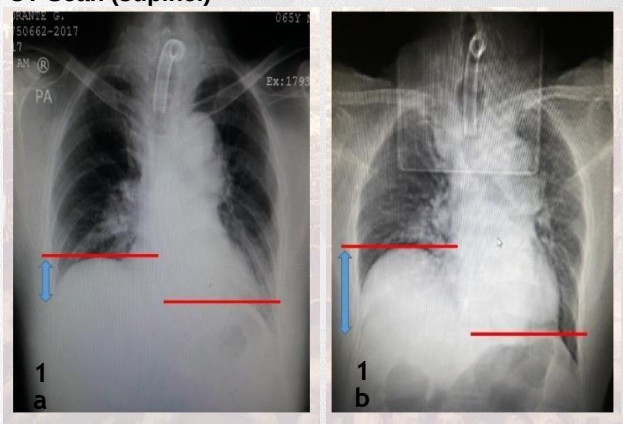
In 2000, he experienced sudden progressive dyspnea on supine position associated with sleep disturbance described as difficulty finding a sleeping position and episodes of waking up at night due to dyspnea, and daytime sleepiness. There was no associated cough, colds, fever or chest pain. Persistence of these symptoms prompted consult with different physicians but work-up was unremarkable, and patient was advised physical therapy and rehabilitation. There was no noted improvement hence another consult in 2005 during which work-up revealed an elevated left hemidiaphragm on chest radiograph, a negative Sniff test and chronic respiratory acidosis with mild hypoxemia on Arterial Blood Gas (ABG). The official results of these work-ups were not currently available for reviewing. The patient was diagnosed with diaphragmatic eventration left and underwent plication of the left hemidiaphragm. He was sent home, but continued to notice dyspnea on supine position with progressive daytime sleepiness.

In 2010, the patient was suddenly difficult to rouse from sleep and was admitted in a hospital where he was intubated. Working impression was central hypoventilation. There was prolonged intubation due to difficulty weaning hence patient underwent tracheostomy and was sent home with mechanical ventilator (MV) support on AC mode tidal volume 500 and FiO_2 zero. At home, physical therapy and body reconditioning was continued. The patient eventually discovered and did not need MV support when in an upright position. He was able to walk and go back to work. However, he is hooked back to MV support AC mode when supine (usually during sleep), because of difficulty in breathing within 10 seconds of lying down. This routine of MV support at night persisted until 2017. At this time, the patient wanted to be liberated from mechanical ventilator support at night and wanted to have the tracheostomy tube removed. Hence consult at our institution.

The patient is also known to have hypertension, chronic kidney disease secondary to hypertensive nephrosclerosis and is maintained on tamsulosin, finasteride and ketoanalogues, and primary hyperparathyroidism with a history of elevated serum calcium, intact parathyroid hormone (iPTH) and a right parathyroid adenoma on ultrasound and is maintained on Cinacalcet, a calcimimetic. He has 20-pack year smoking history but stopped 15 years ago, and previously worked in an office setting as a municipal assessor. Family history only revealed hypertension and type 2 Diabetes Mellitus, without history of asthma, pulmonary tuberculosis, malignancy, congenital or neurologic disorders.

Upon consult at our institution patient was awake and conversant with normal Body Mass Index (BMI) and stable vital signs. Oxygen saturation at room air on sitting position was at 98%. Head and neck examination was normal. In sitting position patient had a normal heart rate at 75bpm, regular rhythm, symmetric chest expansion, no crackles or wheezing, with decreased breath sounds on the right base. However, upon assuming supine position there was noted paradoxical breathing described as downward movement of the abdomen during inspiration. He brought a chest radiograph show-

Figure 1. a. Chest x-ray (upright). b. Survey chest CT Scan (supine.)



ing an elevated right hemidiaphragm. He is right handed and with normal neurologic examination.

Baseline laboratory tests were within normal limits except for an elevated creatinine level at 235 mmol/L. ABG taken at RA in upright position revealed uncompensated metabolic acidosis with adequate oxygenation. Chest radiograph revealed an elevated, dome-shaped right hemidiaphragm, and considered eventration as shown in Figure 1a. There were mild compressive changes seen at the adjacent right lower lung parenchyma. When compared to a survey chest CT scan image, the elevation of the right hemidiaphragm became more apparent on supine position (Figure 1b).

Plain chest and neck CT scan and plain neck magnetic resonance imaging (MRI) were also done to check for any mass lesions that may be causing the patient's symptoms. There were no pulmonary nodules or masses and there were no mediastinal lymphadenopathies. Plain neck CT scan revealed a nodular soft tissue fullness, measuring 1 x 2 x 2 cm, in the retrotracheal space at the level of C7. This may be a lymph node or parathyroid adenoma or lesion. This finding was confirmed on plain neck MRI revealing a right parathyroid mass measuring 2.1 cm x 2.1 cm x 1.2 cm inferoposterior to the right thyroid gland. It was not affecting the phrenic nerve tract (Figure 2).

There was also cervical spondylosis noted on plain neck CT scan described as uneven contour of the cervical vertebra. However plain neck MRI revealed that despite narrowing of the spinal canal due to spondylosis, the spinal cord was not affected. Plain neck MRI also confirmed that there was no compression or infiltration of the brachial plexus (Figure 3).

Spirometry was also done in upright posit-

Figure 2. a. Plain neck CT scan revealing a nodular soft tissue fullness (outlined) on the right retrotracheal space. b. Plain neck MRI showing a parathyroid mass inferoposterior to the right thyroid gland (encircled) that is not affecting the phrenic nerve (arrow).

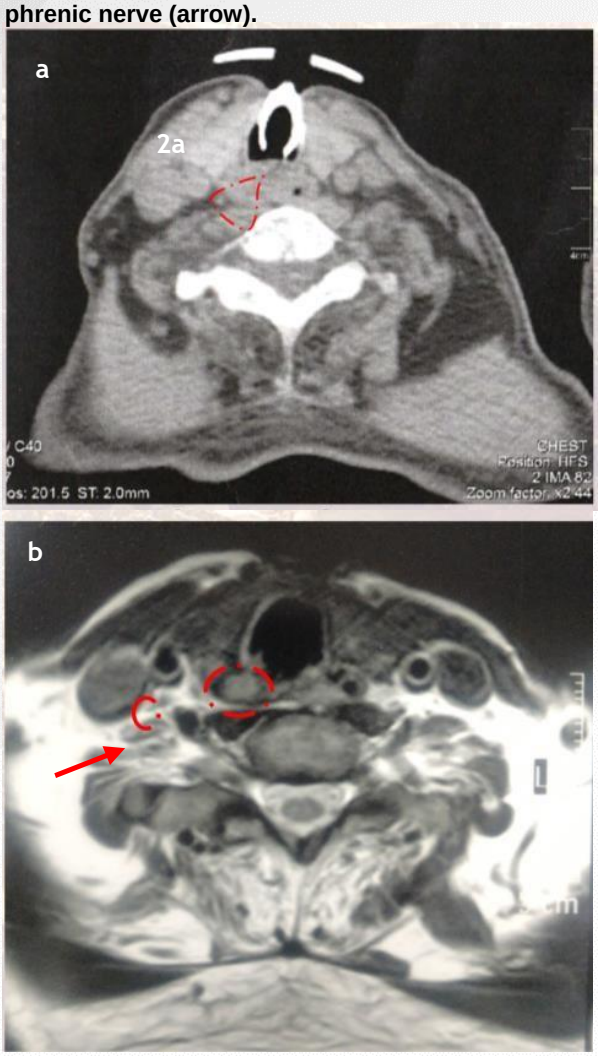
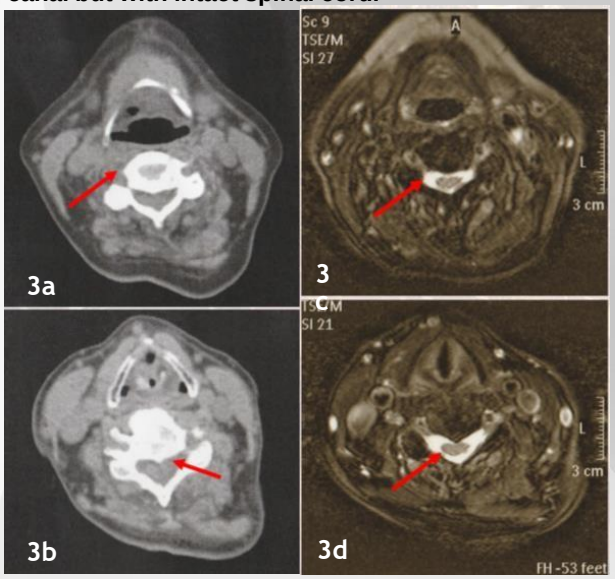


Figure 3. a and b. Plain neck CT scan spondylosis of the cervical vertebra. c and d. Plain neck MRI confirming spondylosis and narrowing of spinal canal but with intact spinal cord.



ion revealing a low Forced Vital Capacity (FVC) and low Total Lung Capacity (TLC) consistent with moderate restrictive ventilatory defect (Table 1). Spirometry done in supine position revealed a 30% decrease in FVC (Table 2). The expected decrease in FVC during supine position is only 10%.

Figure 4 shows the patient's flow volume loop revealing a normal-shaped but smaller sized volume loop compatible with restrictive lung disease. This was further accentuated in the volume loop taken in supine position.

Maximum Inspiratory Pressure (MIP) was also determined for the patient and it was low at -7 cm H_2O. Expected value for age is at -75.05 cm H_2O.

Fluoroscopy or Sniff Test showed elevation of the right hemidiaphragm compared to its counterpart. There was normal bilateral diaphragmatic motion, described as downward movement of the diaphragm, during inspiration and sniffling. Assessment was an elevated right hemidiaphragm, consider eventration.

Diaphragm ultrasound was also performed to assess diaphragmatic movement. On B-mode, diaphragm thickening is assessed during maximal inspiration to assess degree of muscle contraction. For our patient both diaphragm thickness ratio and diaphragm thickening fraction were within normal limits (Table 3).[1]

The patient was then asked to sniff while ultrasound was done on M-mode. A normal diaphragm will show sharp upstroke during sniffing reflective of a downward movement of the diaphragm.[2] However, for our patient there was noted minimal movement of the left diaphragm and paradoxical movement of the right diaphragm as shown by the downward sloping of the waveform on sniffing (Figure 5).

Table 1. Spirometry done in upright position

	Reference	Pre-bronch	Pre % Ref	Post-bronch	Post % Ref
FEV1/ FVC	71 %	76%	-	73	-
FEV1	2.57 L	1.31	51	1.26	49
FVC	2.64 L	1.73	48	1.73	48
VC	3.64 L	1.72	47	-	-
RV	2.06 L	0.65	41	-	-
TLC	5.20 L	3.27	63	-	-

Table 2. Comparison of spirometry done in upright and supine position

		Upright		Supine	
	Ref	Pre- bronch	Pre % Ref	Pre- bronch	Pre % Ref
FEV1/ FVC	71 %	76%		67%	
FEV1	2.57 L	1.31	51	0.43	17
FVC	2.64 L	1.73	48	0.65	18

To confirm the presence of a diaphragmatic pathology, electrophysiologic studies using Electromyogram-Nerve Conduction Velocity (EMG- NCV) was done. EMG did not show any myopathic changes, ruling out possible myopathies. Meanwhile, Repetitive Nerve Stimulation (RNS) did not show any significant and classic decremental and incremental response which ruled out neuromuscular junction pathology. NCV findings were compatible with multifocal compressive or entrapment syndromes involving the distal right median nerve (sensorimotor neuropathy consistent with carpal tunnel syndrome) and bilateral deep peroneal nerve (primarily axonal). NCV also showed severe focal neuropathy involving bilateral phrenic nerves.

Two-dimensional echocardiography was done to check for any cardiac cause of dyspnea on supine position. Findings were normal.

Figure 4. Flow volume loop of spirometry done in upright (A) and supine (B) positions. These are compatible with restrictive physiology accentuated in the supine position.

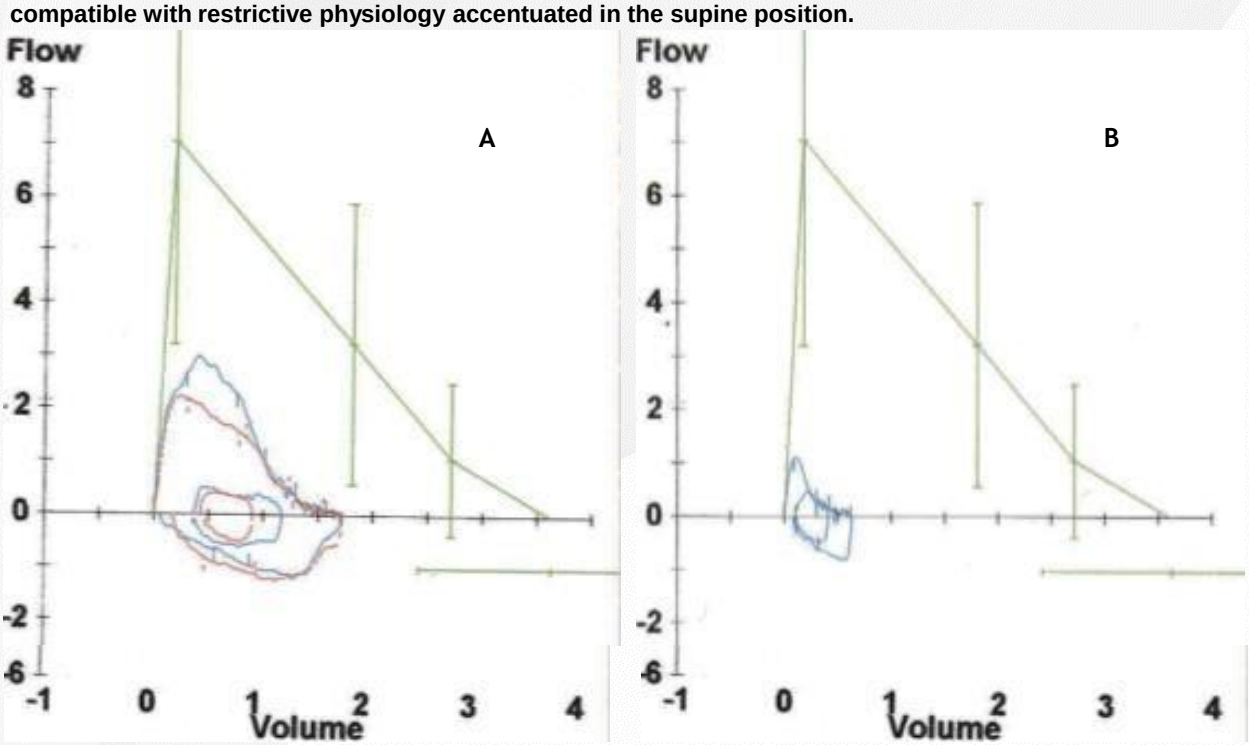


Table 3. Measurement of the Diaphragm thickness on ultrasound, B-mode

	Diaphragm Thickness		Thickening ratio	Diaphragm Thickness Fraction (DTF)
	End Inspiration	End Expiration		
Right	0.5cm	0.41cm	1.21	21.1 %
Left	0.32cm	0.22cm	1.45	45.4%

Since the patient also had history of sleep disturbance and daytime sleepiness, polysomynography was also done. A diagnostic sleep study could not be performed since the patient cannot tolerate the supine position without positive pressure ventilation. Hence, a complete nocturnal polysomnogram was performed with AVAPS titration. The Respiratory Disturbance Index (RDI) was mildly increased at 7.5 events /hour. The minimum oxygen saturation during the study was 83%. After using AVAPS S/T mode at maximum IPAP of 25 cmH_2O, minimum IPAP 15 cmH_2O and EPAP of 5 cmH_2O, tidal volume of 500 ml, and BUR 20, the RDI decreased to 1.1 event/hour, and minimum oxygen saturation improved to 87 %. Based on the patient's recording, he has mild obstructive sleep apnea and possible sleep hypoventilation syndrome that improved with AVAPS S/T mode titration.

Since patient was able to tolerate AVAPS S/T mode, patient was a candidate for possible decannulation. Fiberoptic bronchoscopy was then performed to assess airway patency. Tracheostomy tube was removed and granulation tissue was noted at tracheostomy site. There was no luminal stenosis or obstruction along the trachea, main stem bronchus and its tributaries.

The patient was appraised regarding the results of the diagnostic tests and he was sent home on AVAP S/T mode at night. He was liberated from mechanical ventilator support at night and underwent decannulation of tracheostomy tube.

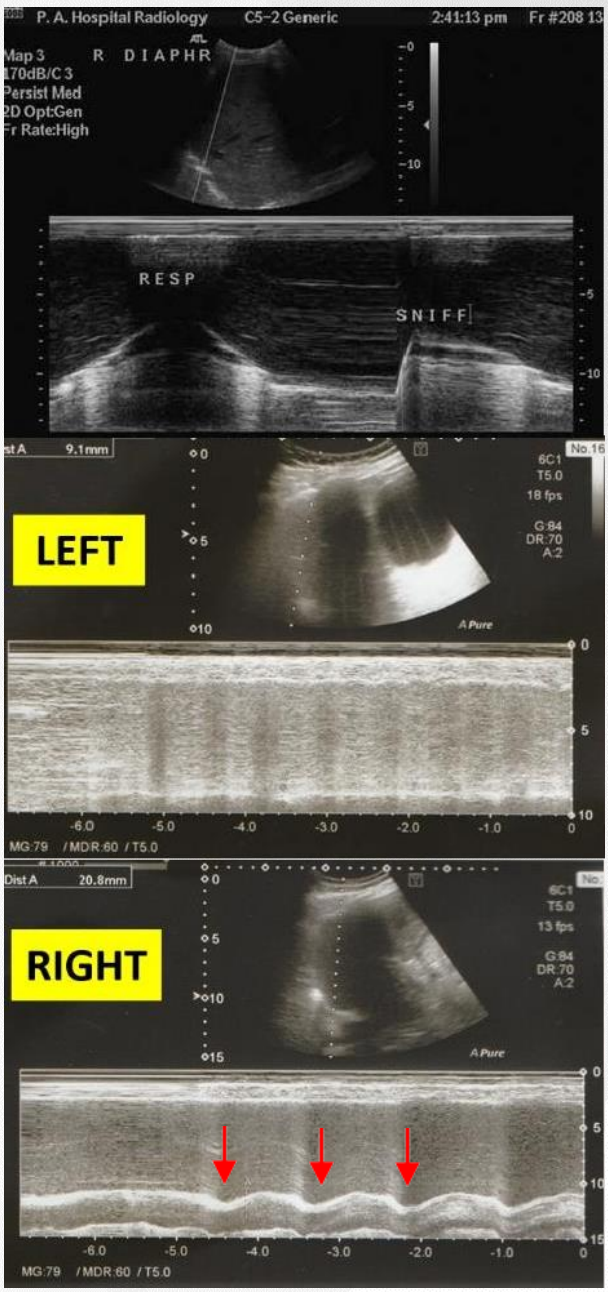
DISCUSSION

Bilateral Diaphragmatic dysfunction is a rare but important cause of unexplained respiratory failure.[3,4,5] This seems to result to a delay in diagnosis for about 2 years with a range of 6 weeks to 10 years.[5] The current incidence is still unknown but studies have noted that there was a preponderance of male subjects being more affected than females which was being attributed to increased incidences of trauma, surgeries and chiropractic manipulations.[3,6] There are many etiologies that have been identified to cause bilateral diaphragmatic dysfunction, however around two thirds of the time the etiology remains to be unknown.[3,4,7]

In patients diagnosed to have bilateral diaphragmatic dysfunction, they typically present with dyspnea that can occur at rest, during increased activity and in supine position.[3,8] The dyspnea is also noted to be out of proportion from their cardiac and pulmonary findings. Orthopnea is very common and is distinctly differentiated from orthopnea of cardiac origin. Orthopnea due diaphragmatic dysfunction is immediately relieved by assuming an upright position. In most cases, paradoxical breathing is a characteristic finding among patients with bilateral diaphragmatic dysfunction.[3,4,5,9]

Sleep seems to aggravate the symptoms of patients suspected to have bilateral diaphragmatic dysfunction.[8,10] During sleep, there is a ventilatory shift of burden to the diaphragm accom-

Figure 5. M-mode ultrasound of the diaphragm. a. Normal diaphragm contraction when sniffing (sharp upstroke of the waveforms). b. The patient's left hemidiaphragm showing minimal contraction. 5c. The patient's right hemidiaphragm showing paradoxical movement (downward deflection) (arrow).



panied by hypotonia of the accessory muscles of respiration.[10] This results to decreased REM percentage of sleep, increased night time arousals and presence of sleep disordered breathing like hypoventilation.[8,10]

Our patient presented with paradoxical abdominal breathing. The abnormal pattern of breathing occurs due to the inward motion of the abdomen as the rib cage expands during inspiration.[3,7] During inspiration and when the respiratory muscles contract, the weakened or flaccid diaphragm moves inward leading to limited lung expansion which contributes to dyspnea and aggravating hypoxemia.[3,7] This sign is rarely seen among those with unilateral diaphragmatic dysfunction due to the compensatory mechanism of the unaffected hemidiaphragm, thus strengthening our impression of the presence of bilateral diaphragmatic dysfunction.[3,4,7]

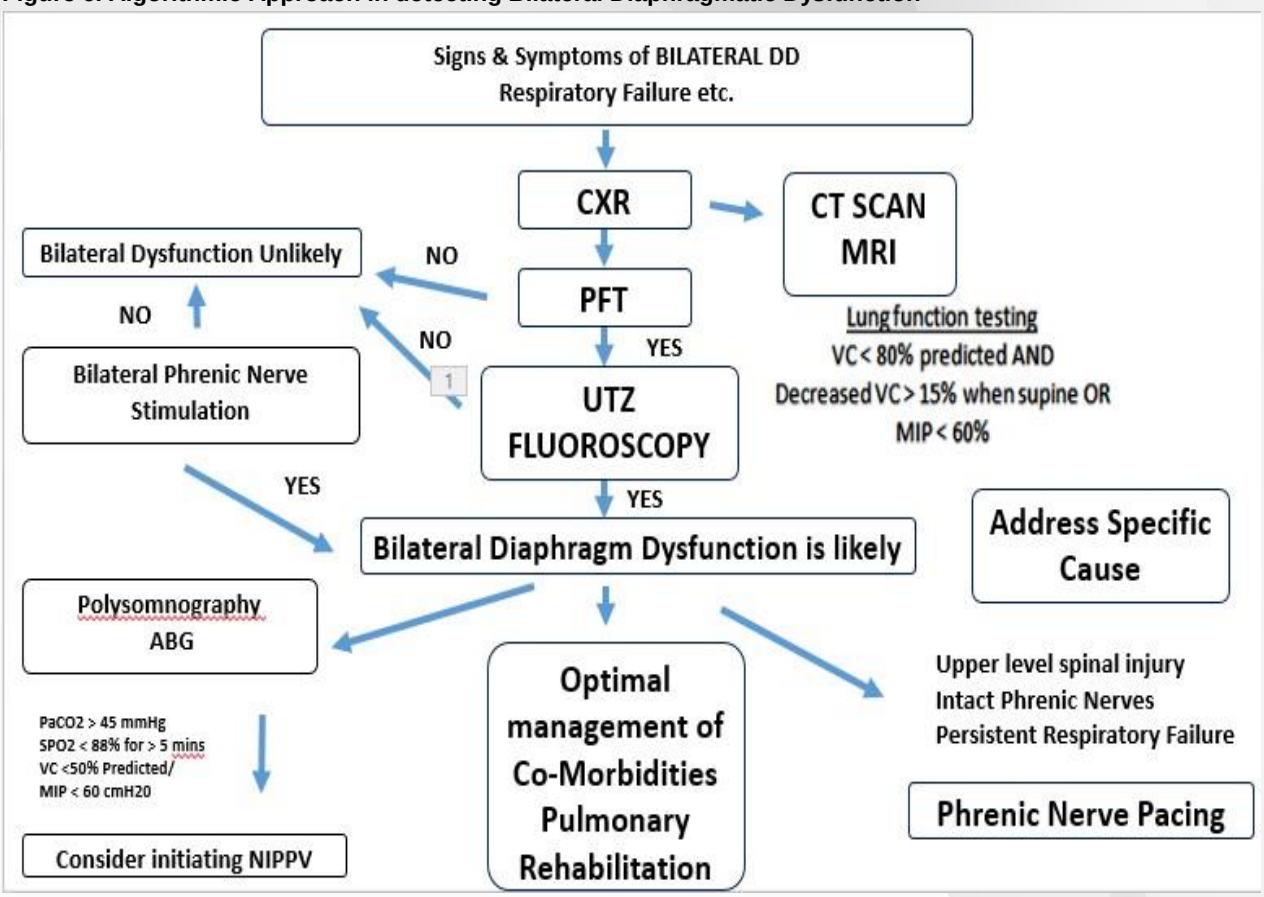
Bilateral diaphragmatic dysfunction is usually associated with severe generalized muscle weakness, although the diaphragm could be the initial or the only muscle involved in some cases.[4,7] The etiologies can be generalized into myopathic and neurologic causes.[7] Neurologic conditions such as spinal cord diseases, motor neuron diseases, neuromuscular disease, and neuropathic causes need to be taken into consideration and ruled out.[7] Myopathic diseases such as polymyositis, dermatomyositis, myopathies, thyroid diseases and malnutrition can cause generalized muscle weakness. However, the weakness of the diaphragm is generally in proportion to the degree of skeletal weakness.

The gold standard for diagnosis of bilateral diaphragmatic dysfunction is by measuring trans-diaphragmatic pressure.[3,4,7,9] However, this was not performed for this patient due to unavailability of this procedure in our institution. Instead, in order to identify and confirm the presence of bilateral diaphragmatic dysfunction, we adapted an algorithm proposed by Dube et al[11] to guide us in our diagnosis (Figure 6).

Our patient presented with signs and symptoms pointing to the presence of bilateral diaphragmatic dysfunction. Chest radiograph was done to identify diaphragmatic elevation and exclude other possible cardiac and pulmonary causes of dyspnea. Typical findings of bilateral elevation of hemidiaphragm with small lung volumes, narrowed costophrenic and costovertebral sulci and presence of plate-like atelectasis[7] were not observed in our patient probably due to the history of left hemidiaphragm plication in 2010.

The presence of cervical or thoracic malignancy which can cause compression on the phrenic nerve tract, was ruled out by performing neck and chest CT scan and MRI.[11] The imaging results excluded the presence of parathyroid adenoma, mass or lymph nodes that could have compressed the right phrenic nerve tract. Further evaluation by MRI showed that the cervical and brachial plexus were intact and there was no significant narrowing of the spinal cord. Pulmonary function test was performed to assess the physiologic impact of diaphragmatic dysfunction in our patient.[11] The test confirmed the presence of a moderate restrictive ventilatory defect and confirmed weakness of the diaphragm. Results showed upright FVC of 48% and supine FVC of 18%, decreased TLC at 63, and MIP of –17 cmH20, which coincided with the expected findings among patients with bilateral diaphragmatic dysfunction; FVC < 50%

Figure 6. Algorithmic Approach in detecting Bilateral Diaphragmatic Dysfunction



and 30-50% decrease in supine and/or MIP of less than - 60 cmH_20.[7,11]

Fluoroscopy and ultrasound of the diaphragm are imaging modalities that can visualize the dynamic movement of the diaphragm.[11] Fluoroscopy (Sniff Test) is used to assess the excursion of the diaphragm during forced sniffing maneuvers. This test has a 90% sensitivity for patients with unilateral diaphragmatic dysfunction.[11,13] However, in cases of bilateral diaphragmatic dysfunction, the cephalad movement of the contraction of the ribs and accessory muscles of inspiration gives the false appearance of caudal displacement of the diaphragm mimicking movement, hence this test is frequently misinterpreted and not recommended for evaluation of bilateral diaphragmatic dysfunction.[4,7,11,13]

Ultrasound of the diaphragm is a safe and non-invasive method of evaluating diaphragmatic movement.[12] In a study done by Boon et al[19] they found out that ultrasound of the diaphragm in patients with diaphragmatic dysfunction has a sensitivity of 93% and specificity of 100%. Imaging suggests presence of diaphragmatic weakness when the thin diaphragm fails to thicken with inspiration and does not reach the normal value of the Inspiratory Diaphragm Thickening Fraction (Tfdi).[7,12] The Tfdi is correlated with the pressure generating capacity of the diaphragm, work of breathing and respiratory effort. However, in our patient we found out that the Tfdi is within normal ranges. This finding may be attributed to intra-operator variability and the patient's history of diaphragm plication.

Dynamic imaging in this patient yielded inconclusive results to confirm the presence of diaphragmatic weakness.

Nerve conduction studies including myography and repetitive nerve stimulation with particular focus on bilateral phrenic nerve stimulation was done. These tests were used to detect presence of delay in the phrenic nerve conduction, myopathic changes and neuromuscular junction diseases.[7,11] Compound Motor Action Potential (CMAP), which is the summation of a group of almost simultaneous action potentials from several muscle fibers in the same area was noted to be absent during both phrenic nerve stimulation in our patient. This reflected the presence of a complete phrenic nerve lesion.[7,11] Nerve conduction studies of other nerves tested negative. Thus an impression of focal neuropathy of the bilateral phrenic nerves was made. Further testing did not reveal any focal myopathic changes as well as incremental or decremental decrease in repetitive nerve stimulation, ruling out the presence of a myopathic and a neuromuscular disease.

Since the presence of bilateral diaphragmatic dysfunction was already confirmed. We were able to narrow down the possible etiology of this case given the patient's presenting signs and symptoms, physical and neurological examination results, disease chronicity and EMG–NCV findings of focal bilateral phrenic neuropathy. Results pointed to a neuropathic problem as the cause of the diaphragmatic dysfunction. However, further testing to rule out the possibility for an autoimmune etiology of the neuropathy (antiganglioside antibodies, lumbar tap and nerve biopsy) were not performed due to patient's refusal.

To ameliorate the patient's dyspnea, multichannel sleep polysomnography which is the gold standard in detecting sleep and respiratory problems was performed.[7,8,11] It is a diagnostic and therapeutic exam performed to identify the optimal pressure to address patient's sleep disordered breathing specifically obstructive sleep apnea and hypoventilation.[8] In our patient, optimal pressure was obtained using AVAPS (IPAP 15 cmH2O, EPAP of 5 cmH_2O and tidal volume of 500 mL). This setting resolved patient's hypoventilation, increased REM sleep and provided comfort.

The mainstay of treatment in bilateral diaphragmatic dysfunction is the institution of

non-invasive positive pressure ventilation.[6,7,8] It can significantly improve rate of lung function deterioration, quality of life and survival.[8] In our patient we used AVAPS because it automatically adapts pressure support, guarantees an average tidal volume and was more comfortable.[14,15]

Phrenic nerve pacing is another treatment option for patients presenting with bilateral diaphragmatic dysfunction. It makes use of implanted electrodes that send signal down the phrenic nerve to stimulate the diaphragm to contract. However, it is contraindicated in our patient who has phrenic neuropathy.[7]

Surgical nerve transfer is a novel treatment modality for diaphragmatic dysfunction brought about by phrenic nerve damage. This is done by grafting a spinal accessory nerve into a single phrenic nerve which can result to regeneration and re-innervation. This procedure can restore function to the diaphragm.[7,16] However, there are still limited studies for bilateral phrenic nerve neuropathy and this procedure is not available in our country.

Finally, patients with idiopathic phrenic neuropathy generally have minimal recovery of normal diaphragmatic function and require long term treatment of non-invasive ventilation.[6,17,18] The lack of an identifiable cause of bilateral diaphragmatic dysfunction predicts poor prognosis.

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