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Academy of Pulmonary & Critical Care Medicine

Pulmon

The Journal of Respiratory Sciences

Editorial

Pulmonary Rehabilitation for Chronic Obstructive Pulmonary Disease (COPD)

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Chronic obstructive pulmonary disease is one of the major causes of chronic morbidity and mortality on a global basis. It is the third leading cause of global Disability Adjusted Life Year (DALY) among non communicable diseases.[1] Intense research and subsequent advances in the molecular pathogenesis of COPD has lead to a dramatic refinement in the pharmacologic management of the disease.

In spite of the various treatment modalities , COPD continues to be a relentlessly progressive disease , associated with significant reduction in the physical activity and psychological profile, all of them contribute to the patient's disability and poor health related quality of life (HRQoL).[2] Skeletal muscle impairment is a cardinal feature of COPD. It is associated with reduced exercise capacity, decreased quality of life and survival. In addition, concomitant chronic diseases occur frequently in COPD patients.[3]Physical inactivity is a well-recognized disadvantageous lifestyle factor, leading to a downward spiral which predisposes patients to an impaired health status, increased rates of hospitalization and mortality.[4,5] Over the last two decades, growing evidence of systemic nature of COPD and its negative impact on the performance status of these patients has accelerated the development and use of non-pharmacological interventions like pulmonary rehabilitation.

As per the updated statement of the American Thoracic Society and the European Respiratory Society (ATS/ERS) Task Force on PR, Pulmonary Rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies, which include , but are not limited to exercise training , education and behavior changes , designed to improve the physical and emotional condition of people with chronic respiratory disease and to promote the long term adherence of health enhancing behaviors.[6]

Since the first controlled trials on PR in the mid 1970's [7,8]and the initial skepticism in the early 1980's[9], pulmonary rehabilitation has proven to result in clinically significant improvements in more than 20 methodologically well designed randomized controlled trials.[10] According to the WHO's Global Initiative for Chronic Obstructive Pulmonary Disease Consensus document on the management of COPD, Pulmonary Rehabilitation should be considered in all patients with an FEV1below80% of the predicted value.[11] Besides, most national and international guidelines consider PR as an important treatment option.[12] PR and Pharmacological therapy are not competitive but rather, must work closely together for a successful outcome.[13]One particular study has shown that a better outcome (exercise tolerance) of PR can be obtained when it is combined with a long acting anticholinergic bronchodilator.[14]

Given the finite health care resources, it is of paramount importance to ensure that they are put to the best use. Value in health represents the relationship between health outcomes accomplished and resources utilized. In a highly prevalent condition like COPD it is prudent to ensure that the highest value interventions are employed effectively. In COPD, they involve smoking cessation, regular influenza vaccination and pulmonary rehabilitation.Considering the disease complexity and disease severity, PR must integrate the translation of knowledge and evidence of identified features in to

a multifaceted, complex intervention in order to deliver optimal PR. Thus PR will reinforce the individual autonomy of the patient and facilitate enhanced performance in the community.[15]

Although exercise training is the cornerstone of PR, different flavors of training must be considered based on a profound pathophysiological understanding of the mechanisms underlying exercise tolerance of COPD patients. A standard PR programme is an 8 weeks of twice weekly sessions, with encouragement of home based exercises. A mixture of aerobic and strength training is used, supervised by health professionals. The venue can be hospital based or community based locations. It should be integrated into clinical management and include education about self management.There is compelling evidence base for definite benefit for PR in COPD, reversing the effects of deconditioning, improving exercise capacity and quality of life. The cost per QALY of PR is significantly higher than for pharmacotherapy for COPD.

Assessment of the patient, prior to initiation of PR, but also during and at the end of PR is an essential element in the practice of PR. This allows the patient to have an individually tailored treatment protocol based on their needs and problems and for adaptation of the PR programme as per the progress.[16] The usual assessments include past medical history, (polymorbidities) , physical examination , cycling cardiopulmonary exercises (incremental work load) , the 6 minute walk test , the shuttle walking test, pulmonary function test, maximal expiratory and inspiratory pressure evaluations, measurement of peripheral muscle forces, disease specific questionnaires, nutritional and psychological evaluations.

Exercise training, an integral component of PR involves both continuous and interval training as well as strength training as the major components of exercise.[17] This may include lower extremity exercise training, upper limb training and strength training. As an adjunct to the main stream exercise module, other modalities like Neuro Muscular Electrical Stimulation (NMES) , Respiratory muscle training are found to be particularly beneficial in selected subgroups of COPD patients.

NMES may be conducted at home and is safe and relatively inexpensive.[18] It is shown to enhance walking performance in patients with severe COPD. Inspiratory Muscle Training (IMT) should be considered in COPD patients with ventilatory muscle weakness.[16]

Normocapnic hyperpnoea resistive training and threshold loading have been described as training modalities.[16] A meta-analysis of 25 studies assessing the efficacy of IMT in patients with stable COPD found significant increase in inspiratory muscle strength, exercise capacity and one measure of QoL and significant decrease in dyspnea.[19]

Apart from the conventional modes of training, there have been a few recently published results using alternative modes like water based rehabilitation for patients with polymorbidities and Taichi that seem to be well tolerated and enjoyed by patients.[20,21] Education of the patient on the various aspects of the disease, physiotherapy skills, nutritional intervention, energy conservation and psychosocial interventions are of paramount importance which may pay rich dividends in the long term.

Among the various phenotype of COPD, one that has attracted recent attention is the COPD frailty type. Frailty is found to affect one in every four patients with COPD. Many studies have demonstrated the beneficial effects of PR in this frailty COPD phenotype. Frail patients are found to respond favourably to PR, but it is an independent predictor of poor compliance.[22]

A recent meta-analysis and systematic review of 13 RCTs involving 801 participants on supervised PR has shown that apart from the overall improvement in HRQoL parameters, there is a moderate quality of evidence towards mortality reductions. It also revealed that there is a significant reduction in the number of hospital days, number of re-admission after early PR in patients with a COPD flare. Improvements in HRQoL and exercise capacity remained improved for at least 12 months though the mortality benefit was not statistically significant.[23]

The results of the review support the substantial and clinically significant benefits of supervised early PR indicating that this is an effective intervention with the purpose of reducing mortality following hospitalization for AECOPD. It further shows that supervised PR during the recovery period after a COPD flare is superior to usual care in terms of improving prognosis, HRQoL and walking distance.[24–26] These favorable data strongly recommend supervised PR for patients with COPD exacerbations and initiation during hospital stay or within 4 weeks of discharge.[23]

A retrospective study in JAMA also shows that PR significantly lowers the risk of mortality. It examined a large data set of patients enrolled in free service in Medicare in 4446 hospitals across US in 2014. It was found that initiation of PR within 90 days was associated with a lower risk of death over 1 year, with 7.3% deaths among patients who started PR within 90 days while patients who started PR after the 90 days or didn't begin at all had higher mortality with 19.6% death.[27]

Ameer KA, Arjun P and colleagues in the current edition of the journal report the result of a prospective cohort study on the outcome of a supervised structured PR of COPD patients conducted in one of the tertiary care centers in South India. It was a 6 week study with a follow up of 6 months. The results are comparable to the results of several other similar studies. The beneficial outcome of supervised PR for COPD patients is now well acknowledged. Nevertheless it needs to be seen that the benefits of PR tend to diminish over months following its discontinuation. This fact is also reflected in the current study as well. PR programs are usually not associated with sustained benefits beyond 12 months.[28,29]

Rehabilitation programs vary from as short as few weeks to as long as 1 year. Despite the lack of a clear dose response relation in the immediate outcomes there is consensus that programs shorter than 6-8 weeks are less effective.[12,30] In this context more studies are clearly needed to investigate how long the programs should be run and how frequently the sessions to be held to obtain maximal effects. In addition, the somewhat disappointing results of 'remote' (i.e., home programs, with telephonic support) maintenance programs should prompt further studies to devise the most appropriate strategies to sustain the beneficial effects as long as possible. The potential of supervised telemedicine program is worth considering; this may probably be fuelled by the ongoing Covid-19 pandemic.

Selection of the optimal candidate for exercise training and other interventions that are part of PR is a focal point for further research. The decision to enroll all patients for PR other than exercise training currently lacks solid evidence. But it has to be seen that certain interventions may be particularly beneficial in certain carefully selected subgroups. Supplemental O2 along with anabolic steroids may be useful adjunct for some groups. The role of erythropoietin to improve the anemia in COPD patients is being studied with encouraging results. Some recent data shows that erythropoietin could act as a protective cytokine to hypoxia induced damage and exert anti inflammatory properties.18Similarly, pre-treatment of some subset of patients with N. Acetyl cysteine is found to increase endurance time. The effects of combining bronchodilators with PR programs have been found to increase ventilatory capacity and exercise capacity. One study has revealed that the benefits of rehabilitative exercise were amplified when participants received the long acting anticholinergic agent tiotropium.[14]

Attempt by Ameer K.A, Arjun P. and colleagues in this journal needs to be appreciated for their initiative at a time of under utilization of a well proven , documented, highly beneficial intervention for millions of COPD patients disabled by the disease. We can be optimistic that the study and its communication would trigger a renewed enthusiasm among the professionals caring COPD patients to promote this intervention more aggressively.

Successful PR therefore needs behavioral changes. To accomplish this, patient's skill and

adherence may be facilitated if they are enrolled in long or comprehensive programs consisting of interactions with a multidisciplinary team offering support, counseling encouragement and coaching. These changes may centre on the following: exercise training, psychosocial support, nutritional support, self management, education, pacing and energy conservation. Hence PR embodies a very important and safe intervention with the objective of reversing the systemic effects of COPD with optimal drug therapy. This may help the COPD patients accomplish maximum performance in the community.[13] As COPD is moving to the 3rd most common cause of mortality and morbidity in the world, there is an urgent need for advocacy with concerned authorities for a more widespread utilization of this highly proven beneficial intervention if possible making wide spread reimbursement of PR programs worldwide.

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Post COVID Pulmonary Fibrosis – Lessons from the past

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"The more you know about the past,
The better prepared you are for the future"
- Theodore Roosevelt

It is now almost one year since the first case of COVID 19 was reported in our country. And now we, as pulmonologists face a new challenge – the management of the most dreaded aftermath of the disease –pulmonary fibrosis. Fibrosis can occur following any severe respiratory infections or insults. It has been reported following Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), etc too. But the gravity of the situation is much more with COVID-19 because of the huge burden of the pandemic. We may be left with an enormous number of patients with fibrotic lung diseases. Moreover, we are yet to understand fully the pathogenesis of this pulmonary fibrosis, risk factors for developing it, possible drugs that can reverse or at least arrest the pathology, etc.

However, much is now known about the immune reactions to viral antigens that set in fibrogenesis. The innate immune system with its armamentarium consisting of macrophages and their Toll-like receptors-7, transcription factors like nuclear factor–kB (NF-KB) and interferon regulatory factors, which regulate pro inflammatory factors and interferons, all these resulting in inhibition of viral proliferation. At the same time, overstimulation of the immune system results in the so called "cytokine storm" and the excess release of various factors like IL1-â, IL-7, IL-8, IL-9, IL-10, granulocyte-macrophage colony-stimulating factor (GMCSF), IFN-ã, monocyte chemoattractant protein (MCP1), and tumor necrosis factor- á (TNF-á) bring about inflammation and damage of lungs along with various other organs.[1] Meanwhile, the adaptive immunity, via CD4 cells and activated macrophages play their role too.

Mechanisms of pathogenesis of post COVID pulmonary fibrosis are not fully unveiled, but seem to be similar that of Idiopathic Pulmonary Fibrosis (IPF) and drug induced fibrosis. Pulmonary fibrosis may result as sequelae of wound healing or may be related to an exaggerated immune response to the viral insult to the lungs. So the amount of fibrosis would depend on the severity of infection as well as individual host response. This explains why some patients do not develop fibrosis even after an extensive pneumonia.

We all know that wound healing has three phases – injury, inflammation and repair. Dysregulation of any of the three phases can result in fibrosis. Attempts to repair instantly follows lung injury and inflammation, which involves regeneration of native stem cells and collagen deposition at the defective areas.[2] T Venkataraman et al has emphasized the pivotal role played by alveolar macrophages, which not only phagocytose the debris, but also synthesize cytokines and growth factors.[3] This is followed by activation of fibroblasts which deposit extracellular matrix which get organized and later fibrosed.[4] There is sequestration of lymphocytes in various tissues including lungs, which also results in peripheral lymphopenia.

Barrientos et all in their article in "Wound Repair and Regeneration" highlights the role of epidermal growth factor (EGF), transforming growth factor-alpha (TGF-á), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) in fibrogenesis of post COVID lungs.[5] These mediators result in pulmonary capillary angiogenesis. Whether the repair results in fibrosis or just organizing depends on whether or not there is damage to the basement membranes. Excessive deposition of extracellular matrix results in interlobular septal thickening. Two other molecules also have been recognized in the pathogenesis of infection associated lung injury – the damage associated molecular patterns (DAMPs) released by the injured cells and the pathogen associated molecular patterns (PAMPs) from the micro organisms, both of which play a vital role in the cytokine cascade.[6]

Fibroblasts are the key cells which result in fibrosis. Alveolar fibroblasts accumulate at the site of injury under the effect of fibroblast growth factor and various chemokines. They differentiate into myofibroblasts which are more potent in synthesizing and deposition of extracellular matrix, collagen and fibronectin.[7,8] Moreover, bone marrow derived fibrocytes also play an important role in post viral fibrogenesis.[9]

Huang et al have studied the radiological and functional impact by COVID 19 on 103 patients in early convalescence period. They have noticed impairment in DLCO and respiratory muscle strength in approximately 75 percent of patients with moderate to severe patients They also noticed that more than 50 % patients had residual HRCT changes at the time of discharge. Zhou et al also have noticed fibrosis in HRCT of 34% of 62 patients with COVID -19 infection[10]. These findings are also supported by autopsy and histopathological examination of lung explants from patients who have undergone lung transplants.

In our country too, we are facing an inflow of patients with radiological as well as pulmonary function changes suggestive of post COVID fibrosis. There is a growing concern among the medical community whether these changes suggest permanent lung damage and whether to treat it aggressively or not. So it is imperative at this juncture to analyze past experiences.

Lessons from SARS & MERS

Long term outcomes of SARS-COVID 19 are still unknown. However, experiences from past SARS and MERS may be extrapolated to COVID, especially because post infective radiological findings are similar among the diseases.

In a 15 year follow up of 71 patients, who suffered SARS in 2003, the largest prospective cohort study ever made in this respect, Peixun Zhang, et al have made significant observations, which may be of benefit in the COVID-19 management. The salient points from their conclusions are[11]:

- Persistent diffusion defects and small airway dysfunction were seen in one third of patients, which persisted for more than one year.
- Fibrosis seen in one fifth of SARS patients after 9 months of discharge.
- Ground glass opacities were common in the initial 6 months, while interlobular and intralobular septal thickening dominated after 5 years.
- Persistent ground glassing is more likely to be due to fibrosis rather than alveolitis.
- SARS induced fibrosis radiologically resolved in the majority within one year.
- Radiological changes and functional changes had fair correlation.
- Those patients who received intensive treatment of viral pneumonia in the initial phase and had radiological clearance in the immediate post infective phase had better long term outcome than those who had persistent lesions and incomplete recovery. 5-10% patients had developed femoral head subchondral necrosis secondary to pulse therapy with methyl prednisolone.

- However, femoral head necrosis in majority remained stable or even reversed, unlike the same that occurred with long term steroid therapy as in leukemia or rheumatoid arthritis.

In 2003 Antonio et al also had demonstrated that there was CT evidence of fibrosis in 62 % of SARS patients at 1 month of discharge[12]. But the same authors in another study have reported in the next year, the evolution of radiological changes among 99 SARS patients[13]. They found that most common radiological changes in HRCT were a mixture of ground glassing and reticulations, both of them resolving significantly over a period of 6 months. This suggests that such changes do not necessarily mean irreversible fibrosis. They postulated that the changes could also be due to post inflammatory atelectasis, changes in vascularity of the lung, pulmonary thromboembolism, airway diseases, etc. This view was supported by few open lung biopsy specimens too. This is of considerable relief to both patients and treating physicians alike in present scenario. However persistent changes even after 6 months may suggest "real" fibrosis.

Who all are at risk?

Studies have identified various risk factors for development of pulmonary fibrosis following COVID -19 infections. These include: advance age, male sex, severity of infection, prolonged ICU stay, comorbidities like diabetes and hypertension, smoking and consumption of alcohol[14, 15]. Chronic ethanol abuse can result in deficiency of glutathione, chronic oxidative stress and increased levels of TGF-â in the lungs, hence increasing risk of ARDS and lung fibrosis. Mechanical ventilation induces lung injury and prolonged high flow oxygen induced oxidative lung injury are also identified as potential risk factors.

When to suspect?

When there is persistent hypoxia and when the need for ventilation or high flow oxygen persists beyond a period of 3-6 weeks, one should be prudent enough to suspect onset of post COVID fibrosis. A reduced DLCO, desaturation on 6-minute walk test and X-ray showing persistent abnormalities are other supporting evidences. However, HRCT is the most important tool to confirm, since most of such patients are not fit to be subjected to histopathological confirmation. HRCT may show persistent GGO, band like opacities(especially in subpleural regions), reticulations, inter and intralobular thickening in the early stages, while traction bronchiectasis and honey combing are late signs.

Antifibrotics – to be given or not?

Since post COVID pulmonary fibrosis and IPF share much regarding the pathogenesis, there is a therapeutic logic in considering anti fibrotic therapy for post COVID fibrosis.

Rationale

Currently 2 drugs have been approved globally as anti fibrotics - Pirfenidone and nintedanib. Nintedanib is an intracellular inhibitor of tyrosine kinase. Even though they act by different mechanisms, they have been proved to attenuate lung function decline in nearly half the patients treated and increase the life expectancy approximately by 2.5 years in IPF [16, 17]. Both of them have broad spectrum anti fibrotic activity, irrespective of the causes of fibrosis. But their injudicious use may be detrimental. Before starting antifibrotics, there should be multidisciplinary discussions by the pathologist, radiologist and pulmonologist. Neither of them are immunosuppressants, so not contraindicated in the settings of viral or superadded bacterial infections. Role of interleukins in lung damage and fibrosis in COVID-19 is proved beyond doubt. So the experimental findings that nintedanib attenuates BAL concentrations of IL-1â and pirfenidone causes reduction in IL-6 levels in murine models of pulmonary fibrosis also provides biological rationale for their use in COVID-19[18,19, 20, 21, 22].

Caveats

First of all, there are no clinical trials for these drugs in post COVID lung fibrosis and rationale for use is based on our experience in IPF and interstitial fibrosis associated with connective tissue diseases, which are being extrapolated to post COVID scenario. Only time will prove whether we are on the right track or not. Both pirfenidone and nintedanib are hepatotoxic, the former being more so. Elevation of transaminases is seen in upto 40 percent of severe COVID-19 pneumonia patients. Also the anti virals used against COVID- both remdesivir and favipiravir and many of the broad spectrum antibiotics are hepatotoxic. So a fairly good hepatic function should be ensured before starting such drugs. However, antifibrotics are to be considered only in a late stage, where infections and use of antivirals and antibiotics would have settled. Moreover, pirfenidone should be given only if the patient's estimated glomerular filtration rate is more than 30ml/min per 1.73 m^2. Further, nintedanib can cause increased bleeding risk in those patients who are on extended anticoagulants. In short, these drugs should be considered only in the late phase, where patient has completely recovered from sepsis, ARDS, viremia, and multi organ dysfunction. Also an inadequate response to an optimal trial of corticosteroids should be documented before embarking upon these drugs. Yet another concern is that HRCT may not always be able to differentiate early fibrosis from organizing pneumonia, changes due to thromboembolism or regional differences in vascularity, and so starting anti fibrotics purely on radiology would be too empirical.

When to start?

When to start antifibrotics is still unknown and though generally believed to be started late as discussed above, a new school of thought advocating earlier start do exist . As Peter M George, et al points out in his article in Lancet, starting antifibrotics too late in the course of the disease may be futile, especially since some patients do develop fibrosis too rapidly.[23] Since the above drugs don't act rapidly, and their role is rather preventing than resolving fibrosis that has already occurred, it is probably wise to start them as early as possible[18]. But identifying such patients early, who may develop and have progression in fibrosis, with the help of radiological features or appropriate biomarkers is not easy at the moment.

Since several other mechanisms have been identified that result in IPF and post viral fibrosis, there are many other novel antifibrotic molecules in the pipeline. These include mTOR inhibitor rapamycin, avâ6 integrin blockers, Gal-3 inhibitor, autotoxin inhibitors, lysophosphatidic acid inhibitors, JNK inhibitors, SAP (also known as PTX2) etc are some of them.

To conclude, post COVID pulmonary fibrosis is going to daunt us in coming days. At present there is no evidence to support use of antifibrotics, but it may be imprudent to wait till evidence builds up and it may be too late. Since their overuse and misuse may do more harm than good, they should be taken up only with caution. Systematic research in this field is undoubtedly need of the hour.

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Acute Respiratory Distress Syndrome

Rohith.S

Introduction

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by poor oxygenation, lung infiltrates, and acuity of onset. ARDS was first reported in 1967 by Ashbaugh and colleagues.[1] Initial terminology was adult respiratory distress syndrome, but subsequent recognition that individuals of any age could be afflicted led to the current term, acute respiratory distress syndrome (ARDS). Onset of ARDS is within 7 days of the inciting event and is characterized by bilateral lung infiltrates and severe progressive hypoxemia in the absence of cardiogenic pulmonary oedema.

The definition of ARDS was updated in 2012 and is known as the Berlin definition. ARDS is defined by the patient's oxygen in arterial blood (PaO2) to the fraction of the oxygen in the inspired air (FiO2). This is also known as the PF ratio. ARDS patients have a PaO2/FiO2 ratio of less than 300. It differs from previous American European Consensus definition (published in 1994) by excluding the term Acute Lung Injury, removing the requirement for wedge pressure <18 mmHg and inclusion of positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) of greater than or equal to 5 cm H_2O.[2]
Abbreviations – CPAP - continuous positive airway pressure; P/F ratio -partial pressure of arterial oxygen/fraction of inspired oxygen ratio; PEEP - positive end expiratory pressure

Etiology

ARDS can be caused by a variety of insults, which can be broadly classified as pulmonary and extrapulmonary (Table 1).[3,4]

Berlin definition

Acute Respiratory Distress Syndrome	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of oedema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg-echocardiography) to exclude hydrostatic edema if no risk factor present.

Oxygenation

Mild -P/F ratio 201- 300 with PEEP/CPAP > 5 cm H2O

Moderate-P/F ratio 101-200 with PEEP > 5cm H2O

Severe-P/F ratio < 100 with PEEP >5 cm H2O

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Table 1- Etiology

Pulmonary causes	Extrapulmonary causes
Pulmonary infection	Trauma
Aspiration	Sepsis
	Massive transfusion
	Drowning
	Drug overdose
	Fat embolism
	Inhalation of toxic fumes
	Pancreatitis

These insults trigger an inflammatory cascade resulting in pulmonary injury.[4] In one study of 107 patients in a medical intensive care unit, the most common aetiologies were pneumonia (40 percent), sepsis (32 percent), and aspiration (9 percent).[5] Lung Injury Prevention Score (LIPS) is useful to identify low-risk patients.[6] Some risk factors for ARDS are shown in table 2.

Table 2-Risk factors**Epidemiology**

Advanced age
Female gender
Smoking
Alcohol use
Aortic vascular surgery
Cardiovascular surgery
Traumatic brain injury

Incidence of ARDS in the United States of America range from 64.2 to 78.9 cases/100,000 person-years. 25% of ARDS cases are initially classified as mild and 75% as moderate or severe. However, a third of the mild cases progress to moderate or severe disease.[7] A literature review showed a decrease in mortality of 1.1% every year for the period from 1994 to 2006. The overall pooled mortality rate for all the studies evaluated was 43%.The mortality of ARDS corresponds well to the severity of the disease - it is 27%, 32%, and 45% for mild, moderate, and severe disease, respectively.[8,9]

Pathophysiology

ARDS represents a conventional response to various etiologies. It progresses through four phases, starting with an early exudative stage, a proliferative phase characterized by improved lung function and healing, and a final fibrotic phase which signals the end of the acute disease process. The pulmonary epithelial and endothelial cellular damage is characterized by inflammation, apoptosis, necrosis, and increased alveolar-capillary permeability, leading to the development of alveolar oedema and proteinosis. Alveolar oedema, in turn, impairs gas exchange, leading to hypoxemia. The key histologic changes in ARDS are the presence of alveolar oedema in areas of the affected lung. The type I pneumocytes and vascular endothelium are injured, which leads to the leakage of proteinaceous fluid and blood into the alveoli. Other findings seen are alveolar haemorrhage, pulmonary capillary congestion, interstitial oedema, and hyaline membrane formation.[10]

A characteristic pattern of injury seen in ARDS is the nonuniform involvement. Some segments of the lung can be more severely affected, resulting in decreased regional lung compliance, which classically involves the lung bases more than the apices. This intrapulmonary differential in lung involvement results in a variant response to oxygenation strategies. Increased positive end-expiratory pressure (PEEP) may improve oxygen diffusion in affected alveoli, but it can result in deleterious volutrauma and atelectrauma of adjacent unaffected alveoli.[11]

History and physical examination

ARDS patients will present with features of ARDS itself and also features of the inciting event[3]. ARDS should be suspected in patients with progressive symptoms of dyspnoea, an increasing requirement for oxygen, and alveolar infiltrates on chest imaging within 6 to 72 hours of an inciting event. The history is to be directed to identify the underlying cause which has precipitated the disease. Symptoms often start as mild dyspnoea initially, but within 12-24 hours, the respiratory distress worsens, requiring mechanical ventilation to prevent hypoxia. The aetiology may be obvious in the case of pneumonia or sepsis. In other cases history of recent exposures is very important in identifying the causative agent.

The physical examination includes findings associated with the respiratory system, such as tachypnoea and laboured breathing. Systemic signs may also be evident depending on the severity of illness such as altered mental status, central or peripheral cyanosis as a result of hypoxemia and tachycardia. Despite 100% oxygen, patients have low oxygen saturation. Chest auscultation mostly reveals bibasilar crackles.

Evaluation

ARDS is diagnosed based on the following criteria: acute onset of symptoms, bilateral alveolar infiltrates on chest radiography (non-cardiac origin), and a PaO2/FiO ratio of less than 300 mmHg. It is further classified into mild (PaO2/FiO2 200 to 300mmHg), moderate

(PaO2/FiO2 100 to 200mmHg), and severe (PaO2/FiO2 less than 100mmHg).[2]

The initial chest radiograph typically has bilateral diffuse alveolar opacities with basal atelectasis (image 1).[12] Computed tomography (CT) of the chest may show diffuse patchy and/or coalescent alveolar opacities that are more apparent in the dependent lung zones (image 1).[13,14] The opacities can vary as the disease progresses, from patchy ground glass in early ARDS to consolidative pattern.[12]

Assessment of left ventricular function is to be done to rule out heart failure. Estimation of BNP or N-terminal proBNP (NT-proBNP), with transthoracic echocardiography is used to exclude pulmonary edema. Assessment can be made via invasive methods such as pulmonary artery catheter measurements or non-invasively with cardiac echocardiography or thoracic bioimpedance or pulse contour analysis. However, the use of pulmonary artery catheterization (PAC) is controversial and should be avoided if clinically possible.

Bronchoscopy can be used to exclude pulmonary infections and obtain material for culture. Other investigative tests will be guided by the suspected or underlying disease process, which has triggered the inflammatory process that has led to the development of ARDS. Detailed laboratory tests will be needed as patients with ARDS are highly likely to develop or have associated multi-organ failure including renal, hepatic, and hematopoietic. Complete blood count with differential counts, comprehensive metabolic panel, serum electrolytes, blood lactate level, coagulation panel, cardiac enzymes, and CKMB can be repeated if clinically indicated.[15]

Management

Currently management of ARDS is supportive.Treatment is mainly focused on the management of the underlying precipitating event and the supportive treatment is aimed at maintaining adequate oxygenation and tissue perfusion through mechanical ventilation and appropriate fluid therapy.

Treatment strategy focuses on:

1) Reducing shunt fraction
2) Increasing oxygen delivery
3) Decreasing oxygen consumption
4) Avoiding further injury

Patients are mechanically ventilated, initiated on diuretics to prevent fluid overload, and given nutritional support until clinical improvement is noted. The ventilatory mode has an effect on lung recovery. There is evidence that some ventilatory strategies can aggravate the alveolar damage and exacerbate the lung injury inARDS. Care should be taken in preventing volutrauma (exposure to large tidal volumes), barotrauma (exposure to high plateau pressures), and atelectrauma (exposure to atelectasis). [16,17,18,19,20,21]

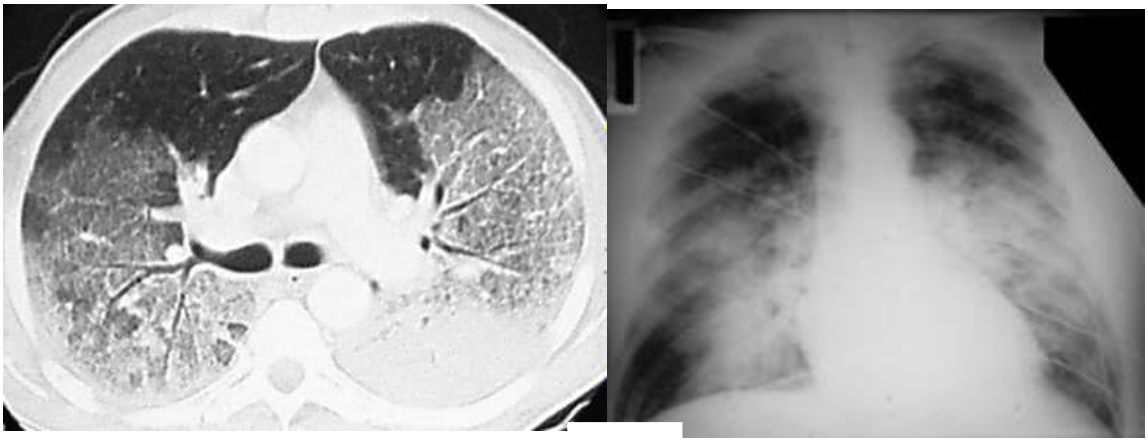
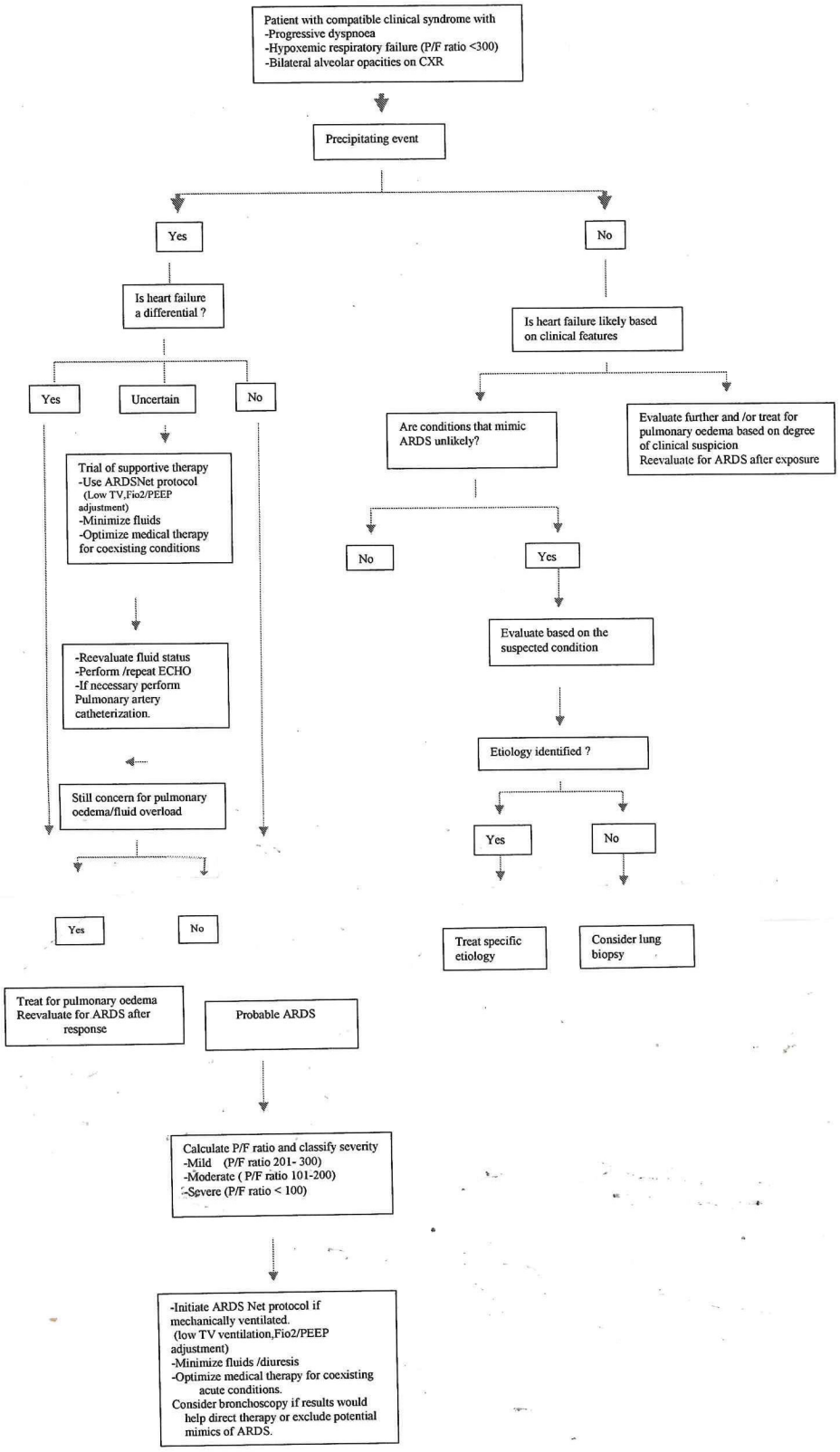


Figure- 1

A lung-protective ventilatory strategy is recommended to reduce the lung injury. The NIH-NHLBI ARDS Clinical Network Mechanical Ventilation Protocol (ARDSnet) advocates the following goals: Tidal volume (V) from 4 to 8 mL/kg of ideal body weight (IBW), respiratory rate (RR) up to 35 bpm, SpO2 88% to 95%, plateau pressure (P) less than 30 cm H2O, pH goal 7.30 to 7.45, and inspiratory-to-expiratory(I:E) time ratio less than 1. To maintain oxygenation, ARDS net recognizes the benefit of PEEP. The protocol allows for a low or a high PEEP strategy relative to FiO2. Both the strategies tolerates a PEEP of up to 24 cm H_2O in patients requiring 100% FiO2.

Diagnostic evaluation of suspected ARDS



The inspiratory-to-expiratory time ratio is modified and an inverse inspiratory-to-expiratory time ratio strategy instituted to improve oxygenation.[22,23]

Novel invasive ventilation strategies have been developed to improve oxygenation. These include airway pressure release ventilation (APRV) and high-frequency oscillation ventilation. Recruitment manoeuvre used along with APRV, has shown to improve oxygenation. Patients with mild and some with moderate ARDS may benefit from non-invasive ventilation to avoid endotracheal intubation and invasive mechanical ventilation. These modalities include continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP), proportional-assist ventilation, and high flow nasal cannula (HFNC). Such patients should be continuously monitored and if they deteriorate, should be intubated and initiated on mechanical ventilation.

A plateau pressure of less than 30 cm H_2O should be maintained to reduce the risk of barotrauma. One strategy is to maintain a low tidal volume and PEEP. Also, increasing the rise and/or inspiration time can help maintain the PEEP goal. The flow rate can be decreased as an adjunct to decreasing the PEEP. High PEEP is also a product of decreased lung compliance from non-cardiogenic pulmonary edema, a salient feature of ARDS pathophysiology.Improving lung compliance will improve PEEP and help to attain the oxygenation goal. Neuromuscular blockade has been used in this endeavour. Neuromuscular blockers instituted during the initial 48 hours of ARDS onset was found to improve 90-day survival and increase time off the ventilator.[24,25,26] However, the most recent trial published in 2019 showed that there is no significant difference in mortality with continuous infusion of paralytics as compared to lighter sedation goals. Other causes of decreased lung compliance should be sought for and managed. Prone position has been shown to be beneficial in 50% to 70% of ARDS patients. The improvement in oxygenation occurs rapidly and allows reduction in FiO2 and PEEP. Though the prone position is safe, there is always a risk of dislodgement of lines and tubes. During proning, recruitment of dependent lung zones occurs; there is improved diaphragmatic excursion, and also an increase in functional residual capacity. The patient needs to be maintained in the prone position for at least 8 hours a day, to attain the optimum effects.

Non-ventilatory strategies include prone positioning and conservative fluid management after resuscitation.[27] Extracorporeal membrane oxygenation (ECMO) has been advocated as salvage therapy in refractory hypoxemic ARDS.[28] However, two major trials that compared venovenous (VV) ECMO to standard care showed no difference in mortality between the two groups.[29] Nutritional support is recommended via enteral feeding. A high-fat, low-carbohydrate diet containing gamma-linolenic acid and eicosapentaenoic acid has been shown to improve oxygenation. Proper care must also be taken to prevent pressure sores.So, frequent patient repositioning is recommended whenever feasible. Physical rehabilitation should be started when the patientis extubated from mechanical ventilation and is stable to participate in therapy. Glucocorticoids can be administered in the following patients- acute eosinophilic pneumonia precipitated ARDS, ARDS with refractory sepsis or community-acquired pneumonia, persistent or refractory moderate to severe ARDS early in the disease course (within 14 days of onset). Regimens of glucocorticoid therapy in ARDS include: Methylprednisolone 1 mg/kg per day for 21 to 28 days followed by a tapering course,[30,31] Dexamethasone 20 mg IV once daily for five days, then 10 mg once daily for the next five days [32].

Patients who require prolonged mechanical ventilation are at increased risk for gastrointestinal bleeding. Prophylaxis against stress ulcers is to be considered in such patients. Patients with ARDS often have multiple risk factors for venous thrombosis, including prolonged immobility, trauma, activation of the coagulation pathway, and predisposing illnesses, such as sepsis, obesity, and malignancy. So, all patients admitted to intensive care units require some form of thromboprophylaxis.

Differential diagnosis

Cardiogenic edema, exacerbation of interstitial lung disease, acute interstitial pneumonia, alveolar haemorrhage, acute eosinophilic lung disease, organizing pneumonia.

Prognosis

The prognosis for ARDS was abysmal until very recently. There are reports of a 30% to 40% mortality up until the 1990s, but over the past 20 years, there has been a significant decrease in the mortality rate, even for severe ARDS. These accomplishments are secondary to a better understanding of and advancements in mechanical ventilation, and earlier antibiotic administration and selection. The major cause of death in patients with ARDS was from sepsis or multiorgan failure. While mortality rates are now around 9% to 20%, it is much higher in older patients. ARDS has significant morbidity as these patients

remain in the hospital for extended periods and have significant weight loss, poor muscle function, and functional impairment. Hypoxia from the inciting illness also leads to a variety of cognitive changes that may persist for a long period after discharge. Fortunately, for many survivors, there is an almost near-complete return of pulmonary capacity, as measured by functional testing. Nonetheless, many patients report sense of dyspnoea on exertion and decreased exercise tolerance. For these patients, this ARDS sequelae makes returning to a normal life challenging as they have to adjust to a new baseline.[33]

Complications

Patients with ARDS are at high risk for complications related to mechanical ventilation or critical illness (Table 3).

Table 3- Complications of ARDS.

- Barotrauma from high PEEP
- Post extubation laryngeal edema and subglottic stenosis
- Nosocomial infections
- Pneumonia
- Line sepsis
- Urinary tract infection
- Deep venous thrombosis
- Antibiotic resistance
- Muscle weakness
- Renal failure
- Post-traumatic stress disorder
- Multiorgan failure
- Critical care neuromyopathies
- Sleep disturbance

Outcome

ARDS still has high morbidity and mortality, in spite of the advances in critical care. Even those who survive can have functional impairment and a poor quality of life. While many risk factors are known for ARDS, there is no way to prevent the condition. Close monitoring for hypoxia is vital. The earlier the hypoxia is identified, the better is the outcome. Those who survive have a long recovery period to regain functional status.[34] Many continue to have dyspnoea even with mild exertion and thus are dependent on care from others.

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Orginal article

Evaluation of the clinical outcomes in patients with chronic obstructive pulmonary disease who undergo structured and supervised pulmonary rehabilitation in a tertiary care centre in South India

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Abstract:

Background & Objectives: Chronic Obstructive Pulmonary Disease [COPD] is one of the world's most common non communicable health problems. COPD is a leading cause of morbidity and mortality in both developing and developed world resulting in substantial economic and social burden. To date, none of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function in various studies. Pulmonary Rehabilitation is a multidisciplinary intervention that integrates patient education, physical exercise training, nutritional therapy and psychosocial support. This study is proposed to evaluate the clinical outcomes in COPD patients who undergo structured and supervised Pulmonary Rehabilitation in our population in south India where such structured programs are either rarely practiced or not easily accessible.

Methods: We conducted a prospective cohort study in which the clinical outcomes were analyzed in 32 adult COPD patients who underwent a structured and supervised Pulmonary Rehabilitation programme with 48 comparable COPD patients kept as control. COPD was diagnosed as per GOLD guidelines using post bronchodilator spirometry. The outcome was evaluated using Post bronchodilator FEV1, MMRC dyspnea scale, Modified Borg score for perceived dyspnea, CAT score, Six minute walk distance (6MWD) and exacerbation rate at 6 months which were measured before initiation of the program, after 6 weeks of rehabilitation program and at 6 months after completion of the rehabilitation in the study group and at the time of recruitment, at 6 weeks and at 6 months in control group. The outcome was analyzed for statistical significance within the study group pre and post PR and between the study and control groups.

Results: There was significant improvement in CAT score (22.8Vs 12.1), mean Six-minute walk distance (255.8 Vs 377.2), Dyspnea grading (Modified Borg score 6.2 Vs 3.6) and number of exacerbations in the study group after 6 weeks of supervised pulmonary rehabilitation. The beneficial effects of pulmonary rehabilitation were sustained only in those who were reasonably compliant with the same even after the 6 weeks supervised programme.

Conclusions: Pulmonary rehabilitation significantly improves the severity of symptoms, exercise tolerance and quality of life as evidenced by improved MMRC grades, BORG scores, 6 MWD and CAT scores of patients in the study group after the programme. Pulmonary rehabilitation is also beneficial in terms of reducing the exacerbation rate.

Key words: COPD, Pulmonary rehabilitation

Introduction:

Chronic Obstructive Pulmonary Disease [COPD] is one of the world's most common non communicable health problems. COPD is a leading cause of morbidity and mortality in both developing and developed world resulting in substantial economic and social burden. By 2030, COPD is predicted to become the third leading cause of death worldwide[1]. COPD is the result of cumulative exposure over decades and is directly related to tobacco smoking. Outdoor, occupational and indoor air pollution are also risk factors for COPD. Although COPD is consid-

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ered to be a disease of later years, estimates suggest that 50% of those with COPD are less than 65 years old[2,3].

Therapeutic options for COPD include both pharmacologic and non-pharmacologic therapies. The mainstay of drug therapy of stable COPD is bronchodilators, primarily beta agonists and anticholinergics, and inhaled glucocorticoids, given alone or in combination depending upon the severity of disease and response to therapy. These are generally administered via metered dose or dry powder inhalers. The bronchodilator, Theophylline, which is only modestly effective and has more side effects than other bronchodilators, is occasionally used for patients with refractory COPD.

To date, none of the existing medications for COPD has been conclusively shown to modify the long-term decline in lung function in various studies[4,5,6,7]

Pulmonary Rehabilitation is a multidisciplinary intervention that integrates patient education, physical exercise training, nutritional therapy and psychosocial support. Evidence indicates that Pulmonary rehabilitation offers benefits such as improved health related quality of life, increased tolerance to physical exercise, reduced anxiety and depression and a reduction in the number of hospitalizations for chronic respiratory diseases[8,9,10,11]. GOLD guidelines for COPD recommend pulmonary rehabilitation as a non-pharmacological treatment option. Despite strong recommendation for routine use in the management of COPD, Pulmonary rehabilitation is generally underutilized as per the statistics from different countries[12,13,14.] This study is proposed to evaluate the clinical outcomes in COPD patients who undergo structured and supervised Pulmonary Rehabilitation in our population in south India where such structured programs are either rarely practiced or not easily accessible.

Materials & methods:

Our study was a prospective cohort study conducted between December 2013 and November 2014 in the department of Respiratory Medicine, Kerala Institute of Medical Sciences, Thiruvananthapuram, Kerala, India. *Study participants*: We recruited all patients who were diagnosed as COPD as per GOLD guidelines and willing to undergo structured and supervised Pulmonary Rehabilitation program at KIMS, Trivandrum. Patients with overlap syndromes, those with history of recent acute coronary syndromes and those who were unwilling to participate in the study were excluded from the study. Informed written consent was taken from patient and his close relative and documented in patient's record in accordance with the institution policy.

Sample Size: 32 in the study group. An equal number of comparable COPD patients who were not willing for the rehabilitation programme were kept under follow up as control.

Calculated using Epi-Info software version 7.0.9.7, putting power as 80 %, percentage outcome in exposed – 64 % and percentage outcome in the non exposed – 13 % based on a previous study[22].

Tools:

1. Spirometry: FEV 1 value
2. Six-minute walk test (6MWT) – 6 MW distance
3. CAT (COPD Assessment Test) score
4. Modified Borg scale for perceived dyspnea
5. Exacerbation rate

For those who were enrolled in the study, optimization of pharmacotherapy and adequate immunization according to guidelines were ensured before initiating the rehabilitation programme. Prior to starting of the program, basic epidemiologic data of the patients were recorded. The lung function, exercise capacity and quality of life of each patient were assessed using spirometry, Six Minute Walk Test, CAT score and Modified Borg scale. The assessment and documentation were done by the investigator with the help of a trained respiratory therapist / technician. The control group were also assessed using the same tools.

Then the patients in the study group were briefed about the rehabilitation program. Then they were subjected to an individually tailored stepwise rehabilitation program under the supervision of an experienced physiotherapist, three days per week for 6 weeks.

Proceedings of the rehabilitation program:

The daily schedule consisted of education regarding the program followed by warm up in the form of relaxed breathing and range of motion exercise of all joints. Then they were subjected to graded exercise daily which included walking, cycling, squatting, shoulder bracing, elbow and knee flexion and extension exercises. Each of these endurance exercises were practiced in sets of 5 or 10 repetitions depending on patient's exercise tolerance. Vital signs – Pulse rate, Blood pressure, Arterial oxygen saturation, and Borg's dyspnea scale were documented before and after each session. After 3- 4 weeks, they were subjected to muscle strengthening exercises with small weights of 1 – 2 kg. All patients were demonstrated techniques of breathing retraining exercises like pursed lip breathing, diaphragmatic breathing and assisted coughing.

The rehabilitation regimen was framed according to patient's age, current occupation if any, performance status, expected quality of life and need of the patient. Regimen was modified according to patient tolerance.

At the end of 6 weeks, the lung function, exercise tolerance and quality of life were reassessed using the same tools as before. Those in the control group were also reassessed after 6 weeks using the same.All efforts were taken to maintain compliance with the program and those who were not turning up after repeated efforts were considered as dropouts.

Both the group were followed up for 6 months after completing 6 weeks rehabilitation in the case of the study group and following optimization of treatment in the case of controls. Follow up was in the form of telephonic interviews once in two weeks and outpatient follow up every month. Reassessment using same tools was done at the end of 6 months of follow up.

Statistical analysis:

Data was analyzed using SPSS version 17.0. Quantitative variables were described by Mean, Standard deviation, Minimum, Maximum and Quartiles. Qualitative variables were described by percentage distribution.

Between group comparisons of quantitative variables were analyzed by independent sample t test or Mann Whitney U test according to the nature of the data. Between group comparisons of qualitative variables were analyzed by Chi square test. Paired comparison of quantitative variables was analyzed by paired t test or Wilcoxon signed rank test according to the nature of the data.

A 'p' value of 0.05 was taken as the level of significance.

In our study, more numbers were recruited in the control arm as all those COPD patients who refused to undergo supervised rehabilitation programme were taken as controls and were followed up.

Results:

Distribution of the patients according to the severity of airway obstruction. Majority of patients in both cases and controls were having moderate to severe airflow obstruction according to GOLD guidelines.

BMI of cases and controls:

The mean BMI was 21.9 among cases and 22 among controls.

Severity of symptoms according to different tools:

- Majority of patients in both case and control groups were having dyspnea of grade 2-3 MMRC.
- Mean initial CAT score was 22.8 among cases and 16 among controls.
- The Borg dyspnea scale ranged from 4 to 8 with a mean of 6.2 among cases and from 3 to 8 with a mean of 4.8 among controls.
- The mean six-minute walk distance was 257.8 m among cases and 278.1 m among controls.

Comparison of parameters before and after pulmonary rehabilitation and after 6 months of follow up in the study group and comparison of the same with that of the control group:

1. Spirometry – FEV 1

There was a slight improvement in FEV1 among cases after 6 weeks of pulmonary rehabilitation. We could not follow up all the patients in the study group. But the data from 17 patients whom we were able to follow up showed no significant change in FEV1 6 months after completion of their rehabilitation program. A decline in FEV1 values among controls were observed after 6 weeks. The 28 patients that we could follow up among control group showed reduced values after 6 months.

There was slight improvement in FEV1 values of cases after 6 weeks of pulmonary rehabilitation but it was statistically insignificant. There was slight decrease in their FEV1 values after 6 months of follow up.

There was statistically significant reduction in FEV1 values after 6 weeks when compared to initial assessment and the values again declined after 6 months which was also statistically significant.

Between group comparison after 6 weeks and 6 months showed a significant difference in change in FEV 1 among cases after 6 weeks compared to controls. The same after 6 months was not statistically significant.

2. CAT score:`

In cases the mean CAT score showed reduction after 6 weeks of pulmonary rehabilitation. In the 17 patients who were followed up, the CAT score had decreased after 6 months. The patients of control group showed no significant change in CAT score after 6 weeks. But the patients whom we were able to follow up showed an increase in CAT score after 6 months.

The reduction in CAT score of patients from initial assessment to that after 6 weeks was statistically significant whereas that from 6 weeks to 6 months was not significant.

There was statistically significant increase in CAT scores of controls from initial assessment to that after 6 weeks and also from 6 weeks to 6 months.

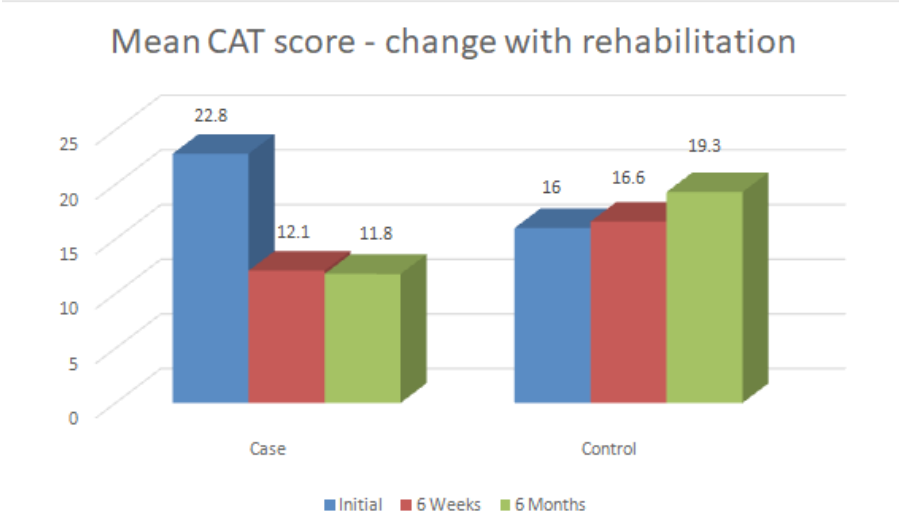

Figure 1: Bar diagram of Mean CAT score – change with rehabilitation

Table 1: Between group comparison of Change in CAT score after 6 weeks of cases and controls

	N	**Change in CAT score after 6 weeks**		**t**	**P**
		mean	sd		<0.001
Case	32	10.8	6.5	12.0014	
Control	48	-.7	.9		

Table 2: Between group comparison of Change in CAT score after 6 months of cases and controls

	N	Change in CAT score after 6 months		t	P
		mean	sd		
Case	17	.52	2.69	.801	<0.001
Control	28	-2.04	1.84		

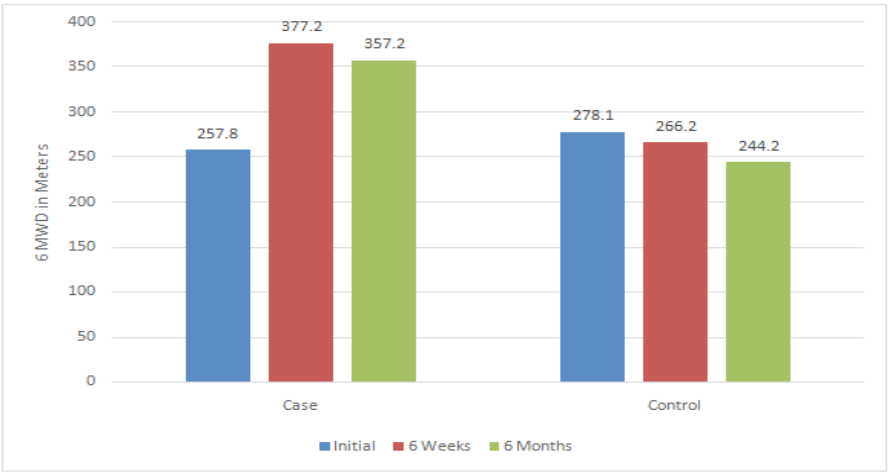

Figure 2 : Change in 6MWD with rehabilitation – graphical representation

Between group comparison after 6 weeks and 6 months showed that there was a significant difference in change in CAT score among cases and controls – a reduction in CAT score in cases and increase in controls.

3. **Six Minute Walk Distance (6MWD):**There was considerable increase in the exercise capacity of patients after 6 weeks of pulmonary rehabilitation.

Paired Differences in 6MWD of cases and controls.
The increase in 6MWD was significant after 6 weeks. But the difference in 6 weeks to 6 months interval was statistically insignificant.

The reduction in 6MWD among control group after 6 weeks and after 6 months was significant.
Between group comparison of change in 6 MWD of case and control groups after 6 weeks and after 6 months: Between group comparison of change in 6 MWD showed significant differences -increase among cases and reduction among controls – after 6 weeks and 6 months follow up periods.

4. **Severity of Dyspnea.**

There was a significant decrease in the severity of dyspnea as assessed by MMRC grading among cases. In control group the severity of dyspnea showed no significant change.

Paired comparison of MMRC among Cases

The mean MMRC grades among cases showed significant reduction after 6 weeks of rehabilitation. There was no significant change in the MMRC grades in the 6 weeks to 6months period.

Paired comparison of MMRC among control:

No significant change was noted in the MMRC grades among controls.

Table 3: Between group comparison of change in MMRC score in 6 weeks of Rehabilitation

	Mann-Whitney U	
	Z	P
Between group comparison of change in MMRC score in 6 weeks of PR	7.426	<0.001

BORG score in cases and control – changes with Pulmonary rehabilitation

There was statistically significant improvement in BORG score after 6 weeks of pulmonary rehabilitation. After 6 months there was no significant change compared to the score at 6 weeks. The improvement in dyspnea score was seen to be maintained throughout the follow up period of 6 months in those for whom follow up evaluation could be performed (N = 17).There was significant deterioration in BORG score after 6 months in patients of control group.

Statistical analysis showed that the improvement following 6 weeks of rehabilitation was significant. There was no statistically significant improvement in dyspnea scores in the six months follow up period after completion of the program even though there was no deterioration in most of them. In case of patients of control group, the dyspnea score deteriorated both after 6 weeks and 6 months.

Paired comparison of BORG score among Cases and Controls

The improvement in BORG score after 6 weeks of pulmonary rehabilitation was statistically significant. After 6 months there was no significant change when compared to the score after 6 weeks.

There is significant deterioration in BORG score after 6 months in patients of control group.

Between group comparison of change in BORG score showed that there was a significant difference between cases and controls over a period of 6 weeks and 6 months of follow up – a reduction among cases and increase among controls.

5. **Exacerbations:**

The rate of exacerbation was reduced in the study group compared to that in the past six months prior to starting of rehabilitation program. In control group there was no significant change in number of exacerbations after the end of 6 months.

A subgroup among the case group showed increased rate of exacerbations in the 6 months follow up period which was possibly secondary to noncompliance with the components of rehabilitation programme after the supervised session.
There was significant reduction in the number of exacerbations after 6 weeks and 6 months of pulmonary rehabilitation among cases.
There was no significant change in number of exacerbations in control group after 6 months.

Between group comparison of change in number of exacerbations in 6 months

There was a significant difference in the number of exacerbations between cases and controls after 6 months

Table 4: Number of exacerbations in case and control groups:

Number of exacerbations	Case			Control		
	Initial	After 6 weeks of PR	After 6 months of PR	Initial	After 6 weeks	After 6 months
N	32	32	17	48	37	28
Mean	2.4	0.3	0.8	1.3	0.9	1.5
Sd	0.8	0.5	0.9	0.7	0.8	.8
Minimum	1	0	0	0	0	.0
Q1	2	0	0	1	0	1
Median	2	0	0	1	1	1
Q3	3	1	2	2	2	2
Maximum	4	1	2	3	2	3

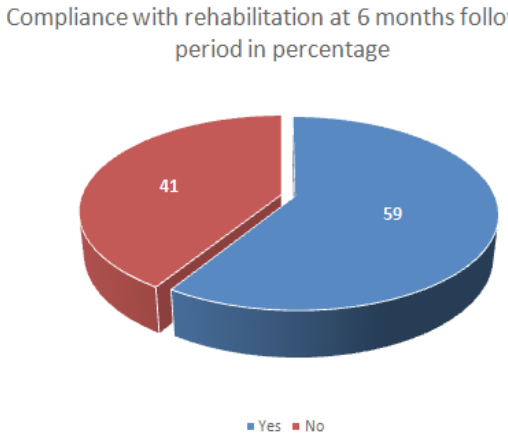

Figure 3: Compliance with rehabilitation at 6 months follow

Table 5: Relation between compliance to rehabilitation after completion of 6 weeks supervised program and FEV1, CAT score, 6MWD and MMRC after 6 months of follow up.

	COMPLIANCE	N	Mean	sd	t	p
Change in FEV1 post PR to 6 months	Yes	10	2.30	2.54	1.882	.079
	No	7	5.14	3.72		
Change in CAT post PR to 6 months	Yes	10	2.40	1.65	6.386	**<0.001**
	No	7	-2.14	1.07		
Change in 6MWD post PR to 6 months	Yes	10	-6.50	18.20	4.533	**<0.001**
	No	7	39.29	23.53		
Change in MMRC post PR to 6 months	Yes	10	.10	.32	.828	.420
	No	7	.00	.00		

follow up from the initial period of enrolling in to the study.

6. BMI

There was no significant difference in the body mass index among cases and controls pre and post rehabilitation and after 6 months of follow up.

Complaince with the Pulmonary rehabilitation after supervised programme:

Of the seventeen patients we were able to follow up completely, ten patients were fully complaint with the pulmionary rehabilitation whereas the rest were either non complaint or partially complaint with the same

Table 6: Compliance with rehabilitation and exacerbation rate

COMPLIANCE	N	Change in Exacerbation After 6 Months		t	P
		Mean	Sd		
Yes	10	2.70	.48	5.491	<0.001
No	7	.86	.90		

There was a positive relation between compliance with rehabilitation after completion of the program and improvement of CAT score, 6MWD and exacerbation rate among cases.

Discussion:

Our study was a prospective cohort study with 32 patients with COPD enrolled in the study group and 48 comparable patients with COPD as a control group. Both groups were periodically evaluated using the same tools for assessing the impact of structured and supervised pulmonary rehabilitation on COPD through parameters like severity of dyspnea, CAT score, Lung function, Exercise capacity, Exacerbation rate etc.

All of our patients in both the groups were males. The prevalence of comorbidities was comparable among cases and controls. Most prevalent comorbid condition in both the groups was Hypertension.

In initial assessment, majority of patients in both cases and controls were having moderate to severe airflow obstruction according to GOLD guidelines. Very severe airflow obstruction was present in 18.8 % of cases and 13.8 % of controls.

After six weeks of pulmonary rehabilitation all the cases were reassessed using the same tools. The patients of control group were also reassessed. After completion of six months also the patients whom we were able to follow up (17 of study group and 28 of control group) were evaluated using the same tools. The results obtained were analyzed for statistical significance.

1.Spirometry

There was no statistically significant change in lung function as measured by the FEV1 value of cases and controls before and after rehabilitation period. This observation correlates with the results of previous studies[15,16.]

2. CAT score

The mean CAT score of study group reduced from 22.8 at the initial assessment to 12.1 at the end of 6 weeks of pulmonary rehabilitation. This reduction was statistically significant. Whereas the mean CAT score of control group increased from 16 at the initial assessment to 16.6 at the end of 6 weeks of pulmonary rehabilitation. This increase was statistically significant. In the 17 patients of study group the mean CAT score reduced from 12.1at the end of 6 weeks to 11.8 at the end of 6 months of pulmonary rehabilitation. This reduction was not statistically significant. The mean CAT score of control group increased from 16.6 at the end of 6 weeks to 19.36 at the end of 6 months of pulmonary rehabilitation. This increase was statistically significant.

The improvement in CAT score after six weeks of rehabilitation in our study was higher compared to the values in some of the similar studies in the literature[17,18,19].

Table 7: Improvement in CAT score comparison with other studies

Study	Mean CAT Score Improvement
Dodd J W. 2011[17]	2.9 +/- 5.6
Paul W Jones. 2012[19]	2.2 +/- 5.3
Kon S S 2013[18]	3 +/- 0.8
Present study	10.7 +/- 6.5

3. MMRC grading

Majority of patients in both case and control groups were having dyspnea of grade 2-3 MMRC at initial assessment. There was a significant reduction in mean MMRC grade after 6 weeks in patients of study group. There was no significant change in the control group after 6 weeks. After six months of pulmonary rehabilitation, there was no significant reduction in mean MMRC grade in study group when compared to the grades at the end of 6 weeks. In the control group also, there was no significant

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change after 6 months In a study by Evans et al[20], there was a mean improvement in MRC grade of 0.7 with 54 % of patients improving by at least one MRC grade. Our study got a similar result with mean MMRC grade improvement of 1.0 in the rehabilitation group which was statistically significant.

4. BORG score

The mean and range of BORG score among cases were 6.2 and 4-8 and among patients of control group were 4.8 and 3-8 respectively before pulmonary rehabilitation. The mean value of study group at the end of 6 weeks was 3.6 which was significantly less compared to the value in the initial assessment. But in control group the mean value after six weeks showed no significant change compared to the value in the initial assessment. After six months of pulmonary rehabilitation, no significant change was noted in BORG score of study group when compared to the values at the end of 6 weeks. But there was significant deterioration in BORG score after 6 months in patients of control group.

5. Six-minute walk distance

Initially the mean six-minute walk distance was 257.8 m among cases and 278.1 m among controls. In the study group there was a significant increase in 6-minute walk distance from 257.8 to 377.2 after the end of 6 weeks. There was a significant decrease in 6-minute walk distance from 278.1 to 266.2 after the end of 6 weeks in case of control group. There was no significant change in 6-minute walk distance for study group from the end of 6 weeks to the end of 6 months. But for control group there was a significant decrease in 6-minute walk distance from the end of 6 weeks to the end of 6 months.

Most of the similar studies on pulmonary rehabilitation in COPD have shown significant improvement in six-minute walk distance after rehabilitation as shown in table

Table 8: Mean difference in 6MWD Comparison with similar studies

Study	Mean Difference
(Meters)	
Kirsten 1998	158
Nava 1998	68
Behnke 2000	215
Troosters 2000	64
Virendra Singh 2001	54.2
Eaton 2009	-2
Carr 2009	-25
Present Study	119.4

6. BMI

At the end of six weeks of pulmonary rehabilitation there was no significant change in BMI of both case and control groups. The BMI remained more or less same after the end of six months for the study group. But there was significant reduction in BMI for control group after 6 months when compared to that at the end of 6 weeks.

7. Number of exacerbations

There was significant reduction in number of exacerbations after the end of 6 weeks in study group which was not seen in control group. After the end of six months there was no significant change when compared to the situation at the end of 6 weeks in both case and control groups. Studies by Murphy N et al[21] and BehnkeM et al[22] have also come up with similar improvements in exacerbation rate and hospital readmissions after rehabilitation. A meta-analysis of six trials on pulmonary rehabilitation after acute exacerbation of COPD including 230 patients by Puhan et al[11] showed a reduced risk for hospital readmissions (Pooled relative risk 0.26) and mortality (Pooled relative risk 0.45) in the rehabilitation group.

Comparison of change between case and control groups

A group comparison was done to assess the change in these parameters between the rehabilitation group and the control group. This showed a statistically significant change in severity of dyspnea in terms of MMRC grading and BORG score, exercise capacity in terms of 6MWD, CAT score and number of exacerbations in the rehabilitation group compared to control group.

Compliance with the components of rehabilitation and sustained benefits:

Of the 32 patients who underwent supervised rehabilitation program we could follow up seventeen patients. It was found that out of them only 10 were fully compliant with all the components of the program and the rest seven patients were either not compliant or partially compliant.

Those who were compliant had sustained beneficial effects in terms of severity of dyspnea, exercise tolerance, exacerbation rate etc. compared to the other group. A few studies in literature have attempted for following up patients for compliance after supervised rehabilitation and have got similar results[23].

Conclusion:

This study emphasizes on the importance of Pulmonary Rehabilitation in the treatment of chronic lung diseases like COPD.Pulmonary rehabilitation significantly improves the severity of symptoms, exercise toler-

ance and quality of life as evidenced by improved MMRC grades, BORG scores, 6 MWD and CAT scores of patients in the study group after the program. Pulmonary rehabilitation is also beneficial in terms of reducing the exacerbation rate. The effect of rehabilitation on lung function in terms of FEV1 is unremarkable. The beneficial effects from pulmonary rehabilitation are ill-sustained unless the individuals continue to practice the components at home.

Hence a good level of motivation and support are essential for achieving the goals of pulmonary rehabilitation in COPD.

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Original article

Clinical course and outcome of dengue fever patients admitted with respiratory manifestations

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Abstract: Respiratory system involvement in dengue fever is relatively rare. In the monsoon season of June 2017, we had a change in the pattern of dengue with several patients getting admitted with respiratory symptoms. Hence the study was undertaken.

Objectives: To compare the multi organ involvement, ICU admissions, respiratory failure, platelet count and mortality in patients with and without respiratory manifestations.

Methods: All patients admitted in our institute in the monsoon (June 2017 to September 2017) with proven dengue fever by card test were included in the study. They were categorized into those with respiratory manifestations (RM) and those without (NRM). The outcomes measured were analyzed.

Statistical tools: Chi square test, Fisher's exact test, Independent sample test.

Study Design: Case Control Study

Results: Fever was the most common presenting symptoms in both groups. Cough was the most predominant symptom in the respiratory group. More patients in the NRM group had persistent vomiting. More patients in the RM group had bleeding manifestations. Respiratory rate was found to be elevated in the RM group. The platelet counts had a lower baseline value in the RM group. The hematocrit had a higher baseline in the RM group. Predominant lung manifestations seen in the RM group were pleural effusion, perihilar interstitial infiltrates and pneumonitis. Multisystem involvement observed was more in the RM group. RM group had more patients requiring ICU admissions. Comparing mortality in the two groups, 3 patients expired in the RM group, none in the NRM group.

Conclusion: Dengue fever patients with respiratory manifestations had poorer outcome as compared to those without respiratory manifestations. Hence dengue fever patients with respiratory manifestations may require special attention and monitoring using chest x-ray, especially in the first week. The onset of respiratory symptoms may be an early indicator of multisystem involvement.

Key words: Dengue fever, ARDS, Pulmonary hemorrhage

Introduction:

Dengue fever is a common mosquito borne arboviral infection in humans. It has been especially prevalent in tropical south East Asian countries since around a century. Most dengue fever cases are self-limiting, but complications like dengue hemorrhagic fever and shock are life threatening. Mortality from these complications can be as high as 20%.It is known that the endothelium is the target of the immunopathological mechanisms in dengue. The hall-mark is vascular permeability and coagulation disorders.[1]This mechanism can explain the respiratory manifestations of pleural effusion, pulmonary hemorrhage and ARDS commonly seen in patients. During the monsoon season of June 2017- September 2017, we came across a large number of dengue positive patients with respiratory complaints. This was seldom seen in our practice, and it seemed that this caused a worse outcome. However in our state, studies investigating the outcome of such respiratory manifestations as defined by multiorgan involvement, ICU admission, respiratory failure, platelet

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counts, mortality were lacking and hence this study was undertaken.

Subjects and Methods:

A large number of dengue patients are usually seen in the monsoon season of Kerala. We included patients with serologically confirmed dengue in our institution between the months of June and September of 2017. Many patients were excluded as they were referred to our hospital after testing from outside laboratory, the validity of which was uncertain. A detailed history and physical examination according to WHO (clinical suspicion of dengue fever on the basis of the presence of acute febrile illness, myalgia, headache, retro-orbital pain, bleeding manifestations, shock, low platelet count, cough, dyspnea and chest pain) were registered in the study, informed consent was obtained from the patients or their relatives. Baseline investigations, including CBC, hematocrit, liver profile, renal profile, bleeding parameters were done for most patients. Dengue virus IgM or NS 1 antigen serological tests were done in all patients. Chest X-ray PA view and USG abdomen were done in many cases. Our aim was to classify into cases with respiratory manifestations (RM) and a control group with no respiratory manifestations (NRM). The RM group was characterized by symptoms of cough, dyspnea, respiratory failure (SpO2 less than 90), Chest Xray findings and relevant USG findings and the rest were assigned to NRM group. Bleeding manifestations include epistaxis, gum bleeding, hematemesis and hemoptysis. Multisystem involvement was defined as involvement of any two organ systems as witnessed in abnormalities of Liver function tests, Renal function tests, abnormalities in chest X ray or USG abdomen. We then proceeded to compare the symptomatology, examination findings, radiological findings, laboratory values, multi organ involvement, ICU admissions, respiratory failure and mortality wherever possible.

Statistical tools:

Chi square test and fishers exact test were used for the analysis of p values for symptomatology. Chi square test alone was used for p values of bleeding manifestations, tourniquet test, multisystem involvement, ICU admissions and respiratory failure in both groups. Fisher's exact test alone was used for analysis of p values of lung manifestation across both groups. Independent sample test was used for the analysis of p values of vital signs, respiratory rate, platelet count and hematocrit.

Results:

There were 215 patients in the study sample. 126 patients (58.6%) were included in the NRM group while 89 patients (41.4%) were included in the RM group. Results are charted below: P value=0.0001

Table 1: Distribution of patients with or without respiratory manifestations

Group	Frequency	Percent
NRM	126	58.6
RM (cough/ dyspnea / USG finding/ CXR finding)	89	41.4
Total	215	100.0

Table 2: Comparison of Symptomatology Persistent Vomit-

Symptoms	Group		Total	Chi-Square test/ Fishers exact test p value
	NRM	RM		
Fever	125	88	213	0.805[$]
Cough	1	29	30	0.0001[$]
Myalgia	97	69	166	0.925
Syncope	4	5	9	0.383[$]
Dyspnea	1	14	15	0.0001[$]
Abdominal Pain	42	27	69	0.643
Retro orbital Pain	5	5	10	0.574[$]
Rash	6	13	19	0.012

Table 3: Comparison of Persistent vomiting in both groups

Persistent Vomiting	Group		Total
	NRM	RM	
Present	95	81	176
Absent	31	8	39
Total	126	89	215

Chi-Square test p value =0.003

Table 4: Bleeding manifestations in both groups

	Group		Total	Chi-Square test p value
	NRM	RM		
Bleeding	13	19	32	0.025

Table 5: Comparison of Vital Signs in both groups

	Group		Independent Samples Test
	NRM	RM	**P value**
SBP	109.238±14.8202	108.427±14.2939	0.689
DBP	70.238±8.8962	70.562±9.5774	0.799
Pulse Pressure	39.635±10.4656	37.978±9.4364	0.235
Pulse Rate	82.833±14.3012	86.494±19.0669	0.109
SpO2	97.246±1.7649	96.551±3.3643	0.050

Table 6: Comparison of Respiratory rate in both groups

	Group		Independent Samples Test(p value)
	NRM	RM	
Respiratory Rate	20.500±4.0115	22.652±5.8116	0.002

Table 7: The tourniquet or HESS test revealed no difference in both groups.

	Group		Total	Chi-Square test p value
	NRM	RM		
HESS Test	25	25	50	0.159

Table 8: Comparison between platelet counts and PCV or hematocrit in the two groups.

	Group		Independent Samples Test(p value)
	NRM	RM	
Platelet($10^3/mm^3$)	71.50±6.01	49.65±5.58	0.007
PCV (%)	40.96±5.58m	43.77±6.22	0.001

Table 9: The comparison between SGOT or AST levels are shown in both groups

SGOT(IU/ml)	Normal	45-224	225-999	>1000
NRM	16	85	22	3
RM	15	43	26	5

Table 10: Lung manifestations seen in the RM group as per Chest Xray PA view

CXR Finding	NRM	RM	Total
Normal	102	55	157
Bilateral pleural effusion	1	4	5
Right sided effusion	0	6	6
Perihilar interstitial infiltrates	1	14	15
Pneumonitis	0	4	4
Not taken	22	6	28

Table 11: Comparison of Multisystem involvement, ICU admissions, respiratory failures in both groups.

	Group		Total	Chi-Square test p value
	NRM	RM		
Multi system involvement	27	73	100	0.0001
ICU admission	11	21	32	0.003
Respiratory failure	1	10	11	0.0001[$]

Table 12: Odds ratio calculated for Multisystem involvement

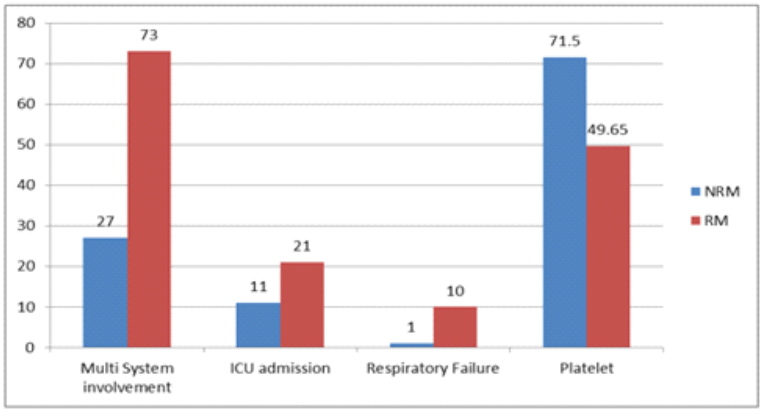
Multi System involvement	Group		Total
	RM	NRM	
Present	73	27	100
Absent	16	99	115
Total	89	126	215

Table 13: Comparison of mortality among the two groups.

Death	Group		Total
	NRM	RM	
Expired	0	3	3
Survived	126	86	212
Total	126	89	215

Fisher's Exact Test p value =.069

Figure 1: Comparing platelet counts and above parameters as a Bar graph.



Discussion:

Dengue is an arthropod vector borne infection caused by Flavivirus. It is a mosquito born disease and is spread by Aedes aegypti commonly, though aedes albopictus also has been implicated.It is estimated that 50 million dengue infections occur each year with 5,000,000 cases of DHF and at least 12,000 deaths annually[1,2,3]. Dengue has been classically described in three forms, Dengue fever (DF), dengue hemorrhagic syndrome (DHS) and dengue shock syndrome (DSS). These terms are commonly used even nowadays, even though WHO has updated definitions into mild and severe dengue and associated warning signs. Warning signs include pain in the abdomen, persistent vomiting, clinical evidence of fluid accumulation like effusion and ascites, bleeding, lassitude or restiveness, liver enlargement, or rise in hematocrit (e" 20%) with rapid reduction in thrombocyte count (< 50000/ mm^3). Signs of severe dengue include evidence of severe plasma leakage, bleeding, and organ impairment. Organ impairment includes hepatic involvement in the form of transaminases elevated beyond 1000 IU/L and central nervous system manifestations like alteration in sensorium or cardiac or other organ involvement.[2] The common respiratory manifestations are ARDS, pulmonary hemorrhage, pneumonitis, pleural effusion and non cardiogenic pulmonary edema.[3,4]

There were 215 patients in the study sample. 126 patients (58.6%) were included in the NRM group while 89 patients (41.4%) were included in the RM group.
The ages of both groups were roughly similar, NRM: 38.56±17.57 years and RM: 37.55±16.72 years as seen in Table 1. The number of males in NRM was 76(60%) and in RM group was 57(64%). Hence young males were the predominantly affected group with respect to respiratory manifestations. More respiratory manifestations were seen in females in the article published by Simmons et al.[4]

Table 2 showed that fever was the most common presenting symptom (99%) in both groups. Cough was the most predominant symptom in the respiratory group (32%). Statistical significance was observed with p value of 0.0001. However, dyspnea was seen as the most common symptom in respiratory group according to the study by Mohammed et al.[1]

As per Table 3, it was seen that more patients in the NRM group [95] had persistent vomiting with a p value of 0.003. This pattern was also seen in the study by Mohammed et al.[1]Persistent vomiting was highlighted as this is a warning sign, as per WHO, of severe Dengue.[5]

In Table 4, more patients in the RM group had bleeding manifestations [19] compared to NRM group [13]. This was found to be statistically significant with a p value of 0.025. Some of the established bleeding manifestations include petechiae, hemoptysis, hematemesis, epistaxis, gum bleeding, pulmonary hemorrhage. These cases maybe underreported due to lack of knowledge of Dengue virus effect on lungs and decreased use of radiologic investigations in these patients. The bleeding manifestations seen in our study were petechial rash, epistaxis and hemoptysis.

Regarding vital signs as seen in Table 5, oxygen saturation and respiratory rate was found to have a statistically significant difference between the two groups. Since respiratory failure was a criterion for categorization into two groups, the result was expected. Respiratory rate was found to be elevated in the RM group with a p-value of 0.002. This is also expected as the patients in the RM group would be expected to have direct or indirect lung pathology causing some form of tachypnea.

In Table 8, there is a statistically significant difference in Respiratory group and Non respiratory group with respect to platelet counts, NRM: 71.50±6.01; RM: 49.65±5.58 with p value of 0.007. This correlated with the data of Hu et al[6]. A statistically significant difference in Respiratory group and Non respiratory group with respect to PCV or hematocrit was observed, NRM: 40.96±5.58, RM: 43.77±6.22 with p value of 0.001. This shows that patients in the respiratory group had lower platelet counts and a higher hematocrit. WHO warning signs include thrombocytopenia and a rising hematocrit[3,7]. A rise in hematocrit could not be compared in the two groups. Similar studies with such a comparison with respect to hematocrit seem to be lacking.

In Table 9, the AST levels on day 3 or highest value were taken for both groups. The values were classified into three ranges of values. The results showed that marked elevations in enzymes were seen in patients in the RM group. The p value as calculated for the above findings were 0.037 as per Fishers Exact test. The AST levels were chosen as this is the highest elevated enzyme in Dengue patients due to its presence in multiple locations in the body including muscles as seen in the study by Samanta et al[2]. The same study also showed higher AST levels in complicated and severe cases of Dengue.

Table 10 shows Lung manifestations seen in the RM group were pleural effusion, pneumonitis and perihilar interstitial infiltrates. These were diagnosed by

either CXR or USG abdomen with chest screening. Chest Xray was taken within the first week of presentation and was normal in 102 patients in the NRM group, and in 55 patients in the RM group. In the NRM group, one patient had bilateral pleural effusion and one patient had perihilar interstitial infiltrates. In the RM group, 55 patients had normal Chest Xray and most common finding was perihilar interstitial infiltrates in 14 patients. Right sided [6] and bilateral [4] pleural effusion were seen. Isolated left sided effusion was not seen. Four patients had pneumonitis. These findings tallied with the study by Hu et al[6] and Basilio-de-oliveira et al[7] in terms of findings but not their frequency in the patients. We hypothesize that the CXR could be a useful modality to assess for degree of plasma leakage if taken in the first week. Hu et al also went on to suggest a correlation between CXR in the first week of illness and disease severity or progression.

Table 11 shows us that NRM group had a patient with respiratory failure. This was attributed to severe hypotension and hence the patient was put in NRM group. In this patient,pulmonary embolism was not ruled out. More multisystem involvement was seen in RM [73] group than in NRM group [27] {p value of 0.0001}. RM group also had more patients requiring ICU admissions [21], NRM group [11] {p value of 0.003}. Table 12: Odds ratio=16.729 (95% Confidence Interval=8.405-33.297). This tallied with the previous study conducted by Hu et al.[6]

Table 13 compares mortality in the two groups, three patients expired in the RM group while there were no deaths in the control group. Statistical significance was observed with p value of 0.069. No such correlation was obtained in study by wang et al[7]. Other similar studies were lacking.

Limitations of the study:

Interobserver variations were there in the interpretation of data like Chest Xray. Moreover, manifestations like pulmonary hemorrhage may have been missed as CT scans for these patients were not done. Hospital stay was not taken into consideration in the study especially because of wide variation in the same. Most patients were discharged after fever subsided or liver enzymes started a downward trend. Comorbid illnesses of the patients were not considered. Differences in the treatment among the two groups were not assessed, for example treatment with antibiotics, steroids, bronchodilators, platelet or FFP transfusion. The treatments had wide variation due to admission in different hospitals and subsequent referral.A single center study can also have a certain amount of bias attached to it.An effort to minimize Type 2 error was taken by considering a larger sample size.

Conclusion:

In our study, it was seen that young males were predominantly affected. The incidence of bleeding manifestations was more among the patients in the respiratory group. Lower levels of platelet counts were seen in the respiratory group. Multisystem involvement and ICU admissions were more in the respiratory group. Mortality was also more in the respiratory group. Hence Dengue fever patients with respiratory manifestations may require special attention and monitoring using chest x-ray, especially in the first week. The onset of respiratory symptoms may be an early indicator of multisystem involvement. The addition of cough, dyspnea as early warning signs of poor outcome needs to be considered.

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A study on anatomical variations in the tracheobronchial division by CT scan

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Abstract

Introduction

Anatomical variations in the division of the trachea and bronchial tree may predispose to recurrent infections, problems during intubation and general anaesthesia. Failure to identify the anatomical variations may lead to complications during a lung resection surgery. Hence it is important to identify these anatomical variations.There is a paucity of studies in this aspect based on chest CT images in the Indian population. Hence we undertook this study.

Aims and objectives

· To find variations if any, in tracheobronchial divisions up to segmental bronchus in patients undergoing CT scan of the thorax.

· To compare the prevalence of variations in tracheobronchial divisions in both genders.

· To compare the prevalence of variations in tracheobronchial divisions in both lungs.

Material and methods

This was an observational study conducted from December 2013 to December 2015. Data were collected from the patients who underwent CT scan thorax as a part of diagnostic imaging. Total of 560 cases was included in the study.

All CT scans were performed using a 64 Slice Volume CT Scanner (VCT). The tracheobronchial division were studied up to segmental divisions. Any deviation from the Boyden classification of the tracheobronchial division was taken as ananatomical variation. The trachea was carefully inspected for any tracheal bronchus. Division of trachea into right and left main bronchus, lobar and segmental division and any accessory division or absence of any division was carefully looked into and recorded. Data was compiled and analyzed.

Results

Among 560 study population, 4.46% (n=25) cases ofthe tracheobronchial division variations (TBV) were detected. 4.56% (n=18) variations were detected in males and 4.21% (n=7) in females.

The most common TBV detected was 2 divisions in right upper lobe which accounted for 40% (n=10) of all TBV. Right upper lobe bronchus having 4 divisions was seen in 28% (n=7) cases. Accessory right lower lobe bronchus was identified in 12% (n=3) of cases.1 case of tracheal bronchus was identified. There was no statistically significant difference in the prevalence of variations in tracheobronchial divisions in both genders or in both lungs.

Conclusions

The most common TBV detected was 2 divisions in the right upper lobe. The difference in anatomical variations observed in right and left lung when compared was not found to be statistically significant. There was no gender-wise preponderance for the anatomical variations.

Key words. Anatomical variations, Tracheobronchial divisions, Chest CT scan.

Introduction

Variations in the tracheobronchial divisions are not uncommon. Knowledge of these anatomical variations is important to clinicians, radiologists, and cardiothoracic surgeons. During the interpretation of chest CT images, anatomical variations should be kept in mind to differentiate these from other pathological conditions.

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Anatomical variations may predispose to recurrent infections, may alter the progression and extent of lung diseases. Prior identification of anatomical abnormalities is essential for cardiothoracic surgeons to properly plan lung resection surgery. Recognition of tracheobronchial variations will help in bronchoscopic procedures, pulmonary resection surgeries, endotracheal intubation, and endobronchial therapy[1].

Various modern techniques in the thoracic CT scan can now delineate the anatomy of the airways up to the subsegmental level in the lungs. Hence anatomical variations in the tracheobronchial divisions can now be diagnosed with CT scan of the thorax.

The majority ofthe studies conducted regarding these anatomical variations are cadaveric[1]. There is a paucity of studies based on chest CT images in the Indian population. Hence we undertook this study.

Aims and objectives

· To find variations if any, in tracheobronchial divisions up to segmental bronchus in patients undergoing CT scan of the thorax.

· To compare the prevalence of variations in tracheobronchial divisions in both genders.

· To compare the prevalence of variations in tracheobronchial divisions in both lungs.

Material and methods

This was an observational study conducted from December 2013 to December 2015. Data were collected from the patients who underwent CT scan thorax in the department of Radio-diagnosis in AJ Institute of Medical Sciences and Reasearch Centre, Mangalore for any diagnostic purpose. Patients in whom normal anatomy of the lung was distorted by disease or any other pathology and cases where both lungs were not visualized completely due to disease or previous surgery were excluded from the study. Total of 560 cases were included in the study.

All the CT scans were performed using a 64 Slice Volume CT Scanner (VCT). The subject was asked to hold the breath at the end of deep inspiration and scan was performed from lung base to the apex. Multiplanar reformatted images (MPR) and axial images were obtained. All the CT images were reviewed by a single radiologist with ten years of experience in the interpretation of thoracic CT scan. Tracheobronchial divisions were studied up to segmental divisions. Any deviation from Boyden classification[2] of the tracheobronchial divisions was taken as an anatomical variation. The trachea was carefully inspected for any tracheal bronchus. Division of trachea into right and left main bronchus, lobar and segmental division and any accessory division or absence of any division was carefully looked into and recorded.

Statistical Package for Social Science (SPSS v 13) package was used for the analysis of the data. Potential differences in gender and side of the lung were assessed using the chi-square test of significance. For grouped data, Fisher's exact test was used. In all the above tests the "p" value of less than 0.01 was accepted as indicating statistical significance.

Results

Among the 560 study population, 394 were males and 116 were females (Table -1). 4.46% (n=25) of anatomical variations in the tracheobronchial division were detected. 4.56% (n=18) variations were detected in males and 4.21% (n=7) in females (Table-2). In this study,TBV were more commonly found on the right side.4.1% of cases (n=23) had variations in the right tracheobronchial tree (Table-3).

The most common TBV detected was the right upper lobe 2 divisions which accounted for 40% (n=10) of all TBV. Right upper lobe bronchus having 4 divisions was seen in 28 % (n=7) cases, Accessory right upper lobe bronchus was detected in 12% (n=3) of cases. An accessory right lower lobe bronchus in 12% (n=3) of cases.1 (0.2%) case of left upper lobe tracheobronchial variation was detected.1 (0.2%) case of tracheal bronchus was seen in this study population (Table -3).

Table 1: Gender wise distribution of the total study population

Total number of cases	Males	Females
560	394 (70.4%)	166 (29.6%)

Table 2: Gender wise distribution of those with tracheobronchial variations

Total number of tracheobronchial variations	Males	Females
25 (4.46%)	18 (4.56%)	7 (4.21%)

Table 3: Types of tracheobronchial variations

Localisation	Type of variation	Male	Female	n (%)
Trachea	Tracheal bronchus	1 (4%)	Nil	1 (4%)
Right upper lobe bronchus	2 divisions	8 (32%)	2 (8%)	10 (40%)
Right upper lobe bronchus	4 divisions	6 (24%)	1 (4%)	7 (28%)
Right upper lobe	Accessory bronchus	1 (4%)	2 (8%)	3 (12%)
Right lower lobe	Accessory bronchus	2 (8%)	1 (4%)	3 (12%)
Left upper lobe	3 divisions	Nil	1 (4%)	1 (4%)

Table 4: Gender based comparison of prevalence of tracheobronchial anatomical variations (n=560)

Abnormality	Males (%)	Females (%)	Prevalence (%)	p- value
Right sided bronchial variationUpper lobe 2 divisions	18(3.21)	6(1.1)	23(4.1)	
Upper lobe 4 divisions	8(1.4)	2(0.4)	10(1.8)	
Upper lobe accessory bronchus	6(1.1)	6(1.1)	1(0.4)	>0.05
Lower lobe accessory bronchus	1(0.2)	2(0.4)	3(0.5)	
Left sided bronchial variation (upper lobe 2 divisions)	0(0)	1(0.2)	1(0.2)	>0.05
Tracheal bronchus	1(0.2)	0(0)	1(0.2)	>0.05

The prevalence of tracheobronchial variations observed on the right side was (4.1%), but the difference in prevalence observed in right and left lung when compared was not found to be statistically significant. Tracheobronchial variations were more common on the right side in males but this was also not statistically significant.

In this study, TBV were detected in 17 males and 6 females on the right side. The most common TBV detected was 2 divisions in the right upper lobe, which accounted for 40%(n=10) of all TBVdetected on the right side. Out of 10 cases, 8 (80%) were in males and 2(20%) in females (Table -4).

Discussion

During the interpretation of chest CT images, anatomical variations should be kept in mind to differentiate these from other pathological conditions. Anatomical variations may alter the progression and extent of lung diseases. Prior identification of anatomical variations is essential for cardiothoracic surgeons to plan properly for lung resection surgery. Recognition of tracheobronchial variations will help in bronchoscopic procedures, pulmonary resection surgeries, endotracheal intubation and,endobronchial therapy.

Existing literature indicates a prevalence[3] of TBV from 1 to 4%. In our study, 4.46 % of cases (n=25) had variations in the division of the tracheobronchial tree. Most of the variations were in the right lung.The TBV noted in frequency order were in right upper lobe (n=20), right

lower lobe (n=3), left upper lobe (n=1), and tracheal bronchus (n=1) case. The most common type of TBV noted was the right upper lobe bifurcate pattern (2 divisions), 40% cases among the total variations (n=10).

In a bronchoscopy based study of 4882 patients by Abakay A et al (2011), 198 patients were found to have TBV. 68 TBV (33.1%) were in the right upper lobe bronchus[4]. The most common type of TBV in this region was the right upper lobe with two segments. This is comparable to our study.

A study was done by VanRodrigues et al, in Portugal to assess the TBV through bronchoscopy[5]. Out of 181 individuals, anatomical variations were found in 79 individuals (43%) in his study, which is very high as compared to our study. Variations were more common in the right upper lobe (16.6%), with no variations in the middle and the lingular lobe. The most frequent was right upper lobe bronchus with two segmental divisions (13.8%) which is similar to the findings in our study.A study conducted by Sharma Vishnu et al from India revealed right upper lobe 2 divisions as the most common prevailing pattern of TBV[6].

In our study tracheal bronchus was noted in 1 case (frequency 0.2%).A review of 17,500 patients to study the congenital bronchial abnormalities was done by Ghaye B et al[7] and detected a total of 35 tracheal bronchi were detected with a frequency of 0.2%. A retrospective analysis of 12,648 adult patients by Findik revealed 8 (0.06%). cases of tracheal bronchus[8]. A study was done by Beder.s etal in theTurkish population also showed an incidence of the tracheal bronchus is low[9]. These studies support our finding that the incidence of the tracheal bronchus is very low.Tracheal bronchus can lead to persistent or recurrent pneumonia and bronchiectasis which may be difficult to treat and may need surgical resection[10]. In patients with tracheal bronchus, unexplained hypoxemia, difficult intubation, intubation into a tracheal bronchus, and isolation of lung, during intubation and mechanical ventilation or general anaesthesia can occur[11].

A study of tracheobronchial variations evaluated by thoracic CT scan combined with CT virtual bronchoscopy by Vassiou K et al showed findings similar to our study. This may indicatethe incidence of TBV in various populations may be the same[12].

A bronchoscopic study by Amitha S et al in 2018 from a tertiary care institute in wynad, Kerala found that the most common site of variation was the right upper lobe which is comparable to our study[13].

Bronchoscopy is the ideal investigation to detect tracheobronchial branching anomalies. But in recent years,MDCT has been shown to be sensitive to detect tracheobronchial branching anomalies[14].Knowledge and awareness about anatomical variations in tracheobronchial branching pattern are essential for Bronchoscopists, when preparing endobronchial therapies or during surgical procedures. Hence while reporting CT scans, particular attention should be paid to find any major airway anatomical abnormalities and this should be a part of thoracic CT reporting.

Most of the studies indicate variations are most common in the right upper lobe. Incidence of the tracheal bronchus is rare. Our study did not reveal any statistically significant difference between males and females.

Conclusions

Anatomical variations in the tracheobronchial division are more common on the right side. Right upper lobe having 2 divisions is the most common TBV detected. The incidence of the tracheal bronchus is rare (0.2%).The difference in anatomical variations observed in right and left lung when compared was not found to be statistically significant. There was no gender-wise preponderance for the anatomical variations.

Limitations of the study

Small sample size which may not represent the general population.

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A "Radiologic Negative" of Pulmonary Thromboembolism

Rajesh V[1], Anand V[2], Vinayak Jayaram[3], Ajith Toms[4], Koruth George[5], Jolsana Augustine[6], Divya R[7], MelcyCleetus[8]

Case Summary

A 75-year-old lady, known case of type 2 diabetes mellitus for 18 years, presented with cough, belching and difficulty in swallowing for 1 month. She denied any history of fever, shortness of breath, chest pain or loss of appetite. She had history of an osteoporotic compression fracture of L1 vertebra 1 year back which was treated by pedicular screw fixation at D12 to L2 levels supplemented by cement augmented vertebroplasty. She had no allergic or atopic background. Chest Xray- posteroanterior projection (Fig 1) as well as representative images of CT chest – mediastinal window plain study (Fig 2 – a, b, and c) are shown below.

What is the diagnosis?

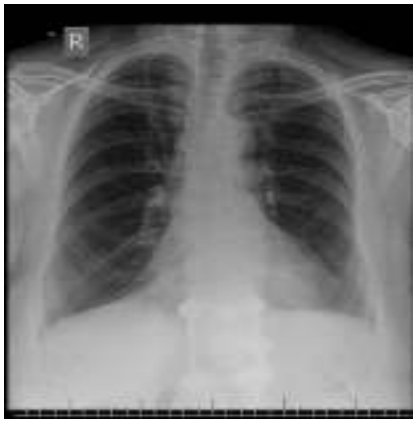

Fig 1

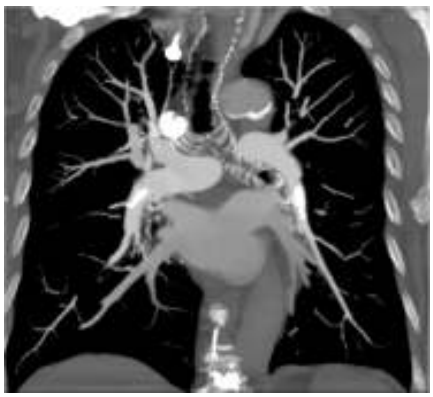

Fig 2a

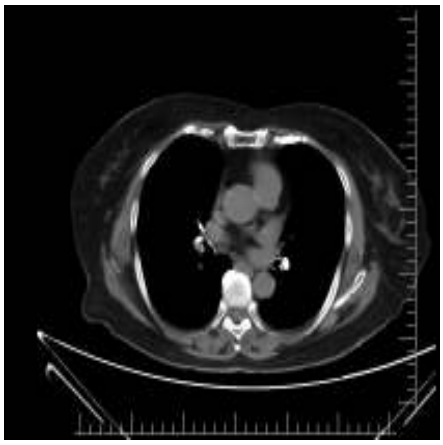

Fig 2b

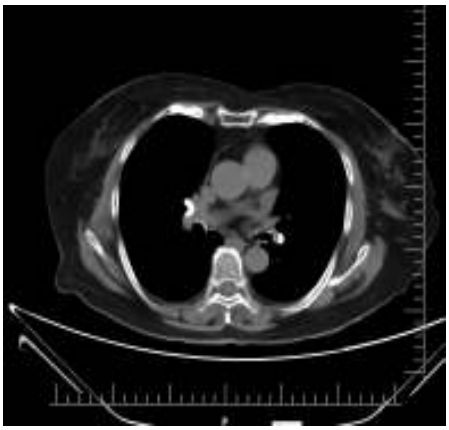

Fig 2c

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Diagnosis

Bilateral pulmonary artery bone cement embolism

Discussion

Chest radiograph reveals normal lung fields. Calcific densities are seen in both hilar regions and lumbar vertebral fixation with pedicle screws is appreciated. Representative images of plain CT chest (mediastinal window) reveal branching hyper densities in bilateral proximal descending pulmonary arteries and proximal right middle lobe pulmonary artery. Hyper densities are also visualised in right paravertebral veins at D12 and L2 levels adjacent to the post-operative site of vertebral fixation with some extension into the azygos vein at D11 level. The opacities have density equivalent to bone / bone cement. The overall appearance is highly suggestive of bilateral pulmonary embolism with bone cement.

Percutaneous vertebroplasty is emerging as a standard of care procedure to treat vertebral compression fractures[1]. This involves injection of polymethyl methacrylate (PMMA) cement under radiologic (fluoroscopic or computerized tomography) guidance. The cement retains its fluidity for an average of 20 minutes after instillation and can extravasate out of the vertebral body into the venous system or spinal canal. Although extra-vertebral leakage occurs in up to 65% of cases, pulmonary cement embolism (PCE) occurs much less commonly[2]. The reported occurrence of PCE is about 4.6% to 23% of Vertebroplasty cases. The mechanism is of development of pulmonary embolism is by cement extravasation into the basivertebral veins, which drain into the inferior vena cava (IVC) and ultimately lodge in the pulmonary capillaries. The vascular anatomy, the fracture pattern, the force with which the cement is applied, and the viscosity of the cement are likely play a crucial role in the development of PCE. Optimisation of technique for avoidance of complications have been reviewed previously[3,4].

The vast majority of PCEs are asymptomatic; they go undetected or are revealed in chest imaging done for alternate reasons. In the symptomatic subset, clinical presentation can vary and dyspnea is the most common presenting symptom[5]. Presenting features can be chest pain, cough, hemoptysis and sweating. ARDS can ensue and presentation as sudden death post vertebroplasty has also been reported[6]. If symptomatic the onset of symptoms is usually within 48 hours of vertebroplasty, but occasional delayed presentation after days to weeks may occur.

The radiological appearance of PCE has been extensively reviewed[2,7]. Chest X-ray finding is that of high-density opacities in the pulmonary artery distribution in a post vertebroplasty patient. However, since these characteristic findings may not be readily appreciable, CT scan of the chest is resorted to in most cases. The cement emboli are best appreciated in plain CT scan images and appear as radiodensities of more than 1,000 HU within the pulmonary arteries. We suggest the term "**radiologic negative of pulmonary thromboembolism**" because of the following features

1.Pulmonary thromboembolism is visualised in contrast enhanced CT pulmonary angiogram images whereas cement emboli are best appreciated in plain CT chest images.

2.Thromboembolisms appear as radiolucent filling defect within contrast opacified pulmonary arteries whereas cement emboli appear as high-density radiopaque material within the non-contrast enhanced vessels.

While the diagnosis of symptomatic PCE is easily made by imaging, an individual case-based approach is often resorted to in management[8]. Treatment options include supportive care in the mildest of cases to anticoagulation and embolectomy in more severe cases. Resuscitation may be needed in cases presenting with cardiopulmonary collapse. Anticoagulation is the preferred treatment in most symptomatic cases. Our patient had a delayed presentation after one year and her symptoms were attributed to gastro-oesophageal reflux. She responded well to proton pump inhibitors and no specific treatment was needed for PCE.

Acknowledgements

We sincerely acknowledge the efforts of Dr Ameer S Theruvath, consultant spinal surgeon and Dr Koruth George P, senior consultant physician for helping out in the clinical care of the patient.

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Radiology Spotter

Vishnu Sharma. M.

See the CT picture below.

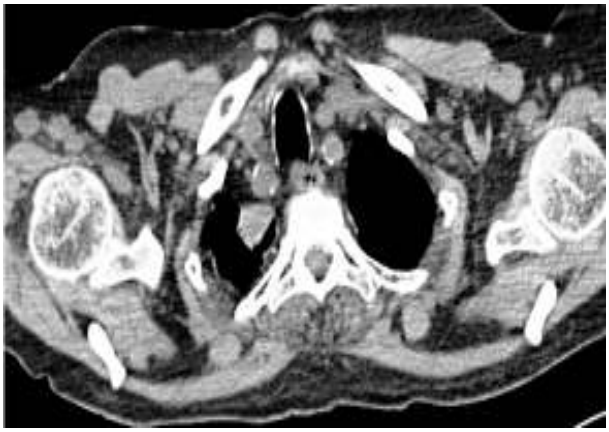

Fig 1 CT image mediastinal window

What is the tracheal abnormality?

Answer

Saber sheath trachea

The word "Saber," means a heavy cavalry sword with a slightly curved blade which is sharp on one edge and blunt on the other edge. "Sheath" is "a close-fitting covering or a case for the sword". The name is derived because of the shape of trachea.

Normal trachea is round or oval in shape. The "saber-sheath" trachea is defined as intrathoracic narrowing of the trachea where the internal coronal diameter is two thirds or less than the sagittal diameter at the same level without any mediastinal pathology causing extrinsic compression.[1]

Tracheal index is the ratio of coronal to the sagittal length of the trachea in the axial plane measured 1cm above the upper margin of the aortic arch[2]. Saber sheath trachea is considered to be present when the tracheal index is less than 0.67.

Saber sheath deformity usually involves the entire length of the intrathoracic part of the trachea with an abrupt widening at the thoracic outlet[3]. Extrathoracic part of the trachea usually has a normal shape in these patients. Ring-like ossification of the tracheal cartilages may be seen on computed tomography[3].

Hyperinflation of lung leads to an increase of the anteroposterior diameter of the chest and increase in sagittal dimension of the trachea. Because of their "U" shape, tracheal cartilaginous rings resist such elongation. This leads to excessive strain on both lateral walls of trachea. This strain causes the tracheal cartilages to weaken, degenerate and calcify, especially in the anterior part[4]. This effect is accentuated by recurrent coughing seen with patients with COPD[5].

The most common cause for "Saber-sheath" deformity of the trachea is pulmonary hyperinflation which occurs in COPD patients with emphysema phenotype[6]. It is more common in males[6]. Rarely it can occur in bronchiolitis obliterans syndrome after lung transplantation[7].

The saber-sheath trachea has a rigid shape due to calcification of cartilages. Hence saber sheath trachea does not tend to collapse during coughing and expiration, unlike in Tracheobronchomalacia where the tracheal wall will collapse during coughing[2]. Decrease of the cross-sectional area of the tracheal lumen by at least 50% at end-expiration is considered to be diagnostic of Tracheobronchomalacia. In saber sheath trachea the inner wall of the trachea is smooth without any nodularity and thickening. In other diseases with tracheal involvement (eg-tracheopathia osteochondroplastica, relapsing polychondritis, amyloidosis, sarcoidosis, and granulomatosis with polyangiitis) inner wall the trachea may show nodularity, thickening, calcification of these nodules, and involvement of posterior membrane or localized narrowing[2]. This may vary from one disease to the other. Involvement of the inner wall of the trachea excludes saber sheath trachea.

Mediastinal pathology should be ruled out in patients with saber-sheath trachea[2]. Superior mediastinal lesions like thymoma, substernal goiter can lead to external compression of the trachea leading to tracheal deformity which may mimic saber sheath trachea. Contrast-enhanced CT scan of the thorax will demonstrate the mediastinal lesion.

Air leak around the endotracheal cuff can be a problem for maintaining adequate ventilation in patients who are on invasive mechanical ventilation. This is because the circular-shaped endotracheal cuff may not approxi-

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mate the sagittal elongation of the stiff tracheal wall. In such cases, Laryngeal mask airway is the option to maintain adequate mechanical ventilation[8].

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ABPA Mimicking Malignancy

Akhilesh Kunoor[1], Aswathy Thazhakottuvalappil[2], Asmitha A Mehta[3], Subin Ahmed[4] , Rajesh Venkitakrishnan[5]

Abstract

Endobronchial obstruction can be due to variety of causes and it may not necessarily be due to tumour occlusion. Complete history taking and diagnostic work up is needed in such cases which include CT Chest and Fibreoptic Bronchoscopy (FOB).Here we describe a case of asthma with allergic bronchopulmonary aspergillosis (ABPA) who presented with an endobronchial mass. Resolution of the lesion with oral steroid probably represents broncho centric granuloma along with ABPA which is a rare entity.

Key Words: Allergic Bronchopulmonary Aspergillosis, Bronchocentric Granuloma, Endobronchial Mass

Introduction

Allergic Bronchopulmonary Aspergillosis (ABPA) is a hypersensitivity reaction to fungal sensitisation for Aspergillus species especially in patients with Asthma. It has variable presentation. It can present with central bronchiectasis, mucous impaction and /or with recurrent exacerbation. Here we describe a case which mimics malignancy in its clinical presentation

Case report

A 30 year old gentleman, reformed smoker, a known case of bronchial asthma intermittent type, on short acting bronchodilator inhaler use whenever needed (sos), presented to our OPD with complaints of intermittent cough with mucoid expectoration, dyspnoea on exertion Grade 2 mMRC of 2 years duration and pleuritic type of chest pain of 2 weeks duration. There was no history of hemoptysis, loss of weight, loss of appetite, nocturnal fever, and skin allergies. He was a hotel employee, residing in the Middle East for 10 years. His living surroundings had pigeons and other birds in abundance. He had childhood history of asthma and had history of allergic rhinitis. He had no other comorbidities and had history of contact with pulmonary Tuberculosis. He had no family history of asthma.

He was evaluated with routine blood investigations and chest X-ray. His blood leukocyte count was 13300 cells/cmm. Peripheral Blood eosinophils were 12.6%. His absolute eosinophil count was 1676×10^3 /µ L. On chest X-ray, there was a well defined opacity close to the left hilum and bilateral infiltrates (Figure 1). CT chest showed a hyper dense area suggestive of alveolar consolidation at posterior segment of right upper lobe & anterior segment of left upper lobe radiating from the hilum towards chest wall with bronchiectasis changes and bullae at the right upper lobe. Smear AFB was negative. Sputum cytology was suggestive of suppurative inflammation.

His total serum IgE was 2317 Ul/ml. His Aspergillus specific IgE was 25.6 k U/L. Aspergillus skin prick test was positive for Aspergillus Niger, Aspergillus Mixed, Aspergillus Flavus, Aspergillus Terrus, Aspergillus Tamari, Aspergillus Versicolor, and Candida Albicans. PFT was showing small airway obstruction only.[Pre bronchodilator FeV1-83.8% FVC-84% FEV1/FVC -102.6 FEF 25-75%-61.9%].

The patient was started on oral steroids with a provisional diagnosis of ABPA. He returned to OPD after one week, due to worsening cough with expectoration, left sided pleuritic chest pain and fever. On examination, he was febrile and tachypneic. On auscultation there was bronchial breathing, egophony and whispering pectoriloquy in the left infrascapular area and mammary area. Chest X-ray was showing left mid and lower zone homog-

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enous opacity with airbronchogram and blunting of the left costophrenic angle.

His WBC Count was 16700 cells/cmm with 77.8% polymorphonuclear leucocytes 12.5% lymphocytes, 9.45% monocytes and CRP was 261.2 mg /L. He was admitted and started on antibiotics [Piperacillin - Tazobactum and Levofloxacin]. By next day morning he desaturated to 87% warranting supplemental oxygen. A chest X-ray was repeated and there was worsening opacity in the left lower zone(Figure 2)

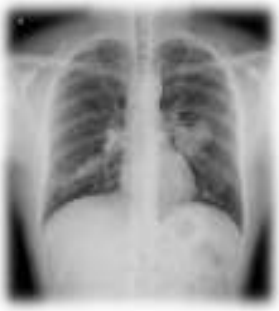

Figure 1
[Chest Xray at Presentation 23/09/2013]

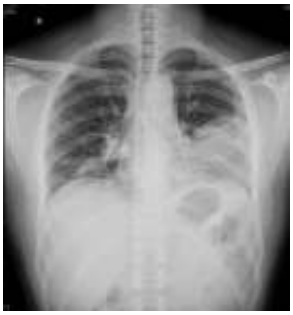

Figure 2
[Chest Xray during worsening 15/10/2013]

CECT chest with HRCT was done which showed cystic and cylindrical bronchiectasis in bilateral lung with impacted mucus within and break down consolidation in left lingular segment with mild to moderate left pleural effusion, causing a partial collapse of left lower lobe.(Figure 3). We proceeded with bronchoscopy. On FOB, Left upper lobe anterior segment had soft tissue mass, partially occluding the lumen.(Figure 4)

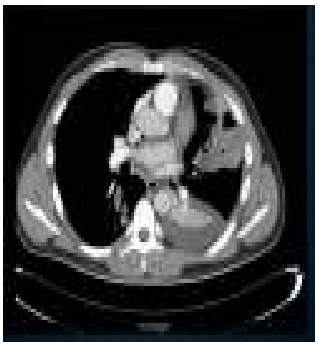

Figure 3 [CT Image 21/10/2013]

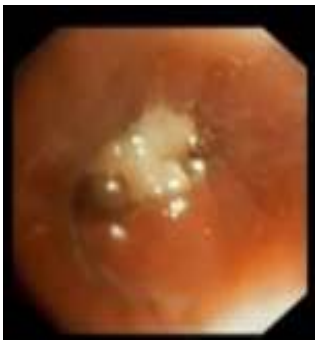

Figure 4(FOB image)

BAL smear AFB and AFB Culture at 6 weeks was negative .Smear Fungal was normal.

Fungal culture was showing filamentous fungi. Cytology was showing no malignant cell or granuloma but occasional fungal organisms.BAL culture was showing Klebsiella Pneumonia with colony count 100000 cfu/ml.

Biopsy from left upper lobe lung lesion described tissue lined by respiratory epithelium with subepithelial area showing large mucus glands and smooth muscle. There was subepithelial hyalinised zone and inflammatory infiltrate with conspicuous eosinophils and lymphocytes. Fragments of mucus with entrapped eosinophils, Charcot Leyden crystals and eosinophilic necrotic material with ghost outlines were seen. PAS highlighted the inflammation and Charcot Leyden crystals. Culture grew Aspergillus fumigatus.

Clinicoradiologically it mimicked ABPA with probable associated bronchocentric granuloma though the definite diagnosis is by a biopsy followed by resection. From the available bronchoscopic biopsy sample, the histopathology was not definitive of bronchocentric granuloma. As the patient denied for surgical lung biopsy he was treated with oral steroids for 3 years in tapering doses and antifungal agents (Itraconazole). Clinicoradiologically he improved with above treatment.

(Figure - 5,6.7)

Discussion

Pulmonary Aspergillosis has diverse presentations. The most common clinical forms include Simple colonisation, Aspergilloma, Chronic necrotising aspergillosis, Allergic Bronchopulmonary Aspergillosis (ABPA) and Invasive Aspergillosis.[1] Classical diagnostic criteria of ABPA and its association with Asthma and bronchocentric granuloma is well described in several literatures[2]

Bronchocentric granuloma (BCG) is a necrotising granulomatous destruction of the bronchial wall, bronchioles and adjacent lung parenchyma[3]. Laboratory features of bronchocentric granuloma are similar with ABPA. It usually consists of peripheral eosinophilia, elevated total IgE and Aspergillus specific IgE, sputum gram stain or culture which reveals fungal elements.

Usually bronchocentric granuloma presents as solitary or multiple pulmonary nodules, mass like lesion or consolidation in chest imaging. Usually it is unilateral

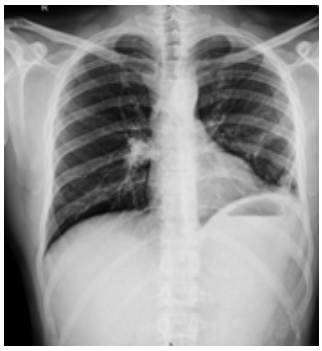

Figure 5(Chest Xray)
[Dated 23/11/2013]

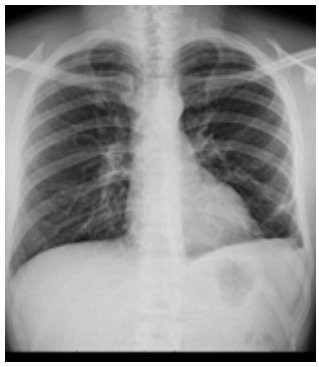

Figure 6(Chest Xray)
[Dated 11/6/2016]

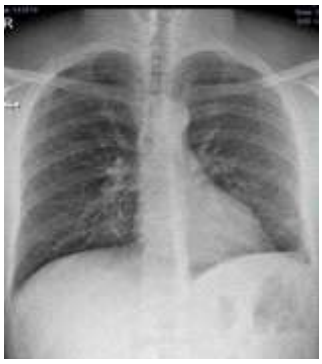

Figure 7(Chest Xray)
[Dated 16/8/2019]

and common in upper lobes[4,5] Though usually presents in association with asthma it can present in non asthmatics also. Such cases usually presents in older individuals.

A definitive diagnosis of BCG can be made by histopathology. In most of the cases surgical lung biopsy is needed[6]. BCG usually responds well with treatment with oral corticosteroids[7]. Similar cases have been reported previously also.[8,9]

In our case all the clinicoradiological and bronchoscopic manifestations were suggestive of ABPA with probable BCG though the gold standard surgical lung biopsy was not done as the patient deferred and patient improved with medical treatment. We want to highlight the point that ABPA and Bronchocentric granuloma should be kept in differential diagnosis of mass lesion in chest imaging in the back ground of asthma and diagnostic evaluation is warranted for ABPA and above described entity.

Conclusion

In all cases of asthma, there should be a thorough evaluation for ABPA if there is any abnormal chest radiology present. Bronchocentric granuloma which can be associated with asthma and ABPA may mimic malignancy and there should be a high index of suspicion for the same should be there especially in cases of atopic individuals.

Acknowledgement

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A case of extramedullary haematopoiesis presenting as pleural effusion

Sonia Santhakumar [1], Abdul Latheef A[2], Jyolsna Santhosh [3], Sreechithra Kartha [4]

Abstract:
Megakaryocytes and haematopoietic precursor cells have been reported very rarely in pleural fluid. Significance of megakaryocytes in pleural fluid is not often discussed in available literature[1]. The incidence is reported to be less than 0.83% of all pleural fluids analysed. Extramedullary haematopoiesis (EMH) is the formation of haematopoietic cells outside the bone marrow. Intrathoracic extramedullary haematopoiesis is a rare condition as the usual sites of extramedullary haematopoiesis are liver and spleen in the postnatal period. We hereby report a case with bilateral pleural effusion, anaemia and thrombocytopenia where diagnostic thoracocentesis gave the first clue to underlying haematological malignancy and extramedullary haematopoiesis (EMH). Our patient did not have hepatomegaly or splenomegaly. Patient was subsequently found to have a lymphoplasmacytoid infiltrate of bone marrow with grade 3 marrow fibrosis.

Introduction

Extramedullary haematopoietic effusions are rare and very few cases are reported[1]. It is commonly associated with benign haematological disorders like chronic haemolytic anaemia as well as other neoplastic causes of bone marrow failure like myelofibrosis and myelodysplasia and certain storage disorders. Though the common sites of EMH are liver and spleen, it can affect lungs, pleura, pericardium, mediastinum and intra spinal epidural spaces in thoracic cavity. Presence of trilineage cells in pleural fluid is diagnostic of extramedullary haematopoiesis in appropriate settings[2]. Though haemorrhagic pleural effusions are described in literature secondary to extramedullary haematopoiesis, presence of bone marrow elements in serous fluid has been reported very rarely[3]

Case Report

53 yr old male patient came to medical department with history of breathlessness on exertion, melena and generalized oedema .He was a non smoker and non alcoholic and did not have any comorbid conditions previously.

On examination patient was ill looking, pale with no cyanosis, icterus, and clubbing or lymphadenopathy .He had bilateral pedal oedema. He was afebrile. Blood pressure-150/90, pulse rate-90/min, respiratory rate of 24/min and spo2 was 96% on room air. Examination of chest revealed features left sided pleural effusion. Examination of other systems was within normal limits at the time of admission.

Investigations- Haemoglobin-8.2gm, Total WBC count-11200/cmm, Neutrophils-69% ,Lymphocytes-26%, Eosnophil-5%, Platelet count - 57,000/cmm .Liver and renal function tests were normal .Uric-acid-5.8, ANA–Nonreactive (0.199).Peripheral smear showed leucoerythroblastic blood picture with thrombocytopenia. Chest x-ray and Ultrasound examination of chest showed bilateral pleural effusion left more than right. Echo done was normal. Ultra sound of the abdomen was normal. There was no hepatosplenomegaly. Serum protein electrophoresis showed a suspicious band in gamma globulin region. Immuno fixation was advised.

Patient was started on diuretics, proton pump inhibitors and broad spectrum antibiotics. A decision was made to aspirate left sided effusion as pleural effusion was asymmetrical and the left sided effusion was much larger than the right.

About 1000ml of blood-stained fluid was aspirated under ultrasound guidance. Pleural surface appeared irregular. Repeat chest x-ray showed marked clearing of fluid.

Pleural fluid was exudative according to Lights criteria with pleural fluid protein of 4.42g/dl and LDH of

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1000 U/l. Pleural fluid was found cellular on cytological examination with presence of haematopoietic elements of all series and precursors of myeloid series and megakaryocytes which was suggestive of Extramedullary haematopoiesis.

A CT scan was done after drainage of pleural fluid which showed bilateral pleural effusion and collapse of left lower lobe basal segments. Multiple small pleural soft tissue density lesions anterosuperiorly on both sides and extrapleural lesions anterior to the posterior aspects of bilateral 2nd, 3rd, 4th, 5th ribs .

Bone marrow biopsy showed monomorphic infiltrates of lymphoid and plasmacytoid cells completely replacing bone marrow.

Meanwhile patient developed para paresis and acute kidney injury.

MRI dorsal spine showed bilateral paravertebral soft tissue signal intensity mass lesions from D1toD12 vertebral levels with no obvious vertebral destruction. Posterior epidural soft tissue signal intensity lesions was seen from C7 to D3 levels displacing and compressing spinal cord to left.

Patient was referred to government medical college due to financial constraints but he expired 2 weeks later at home while awaiting IHC report of bone marrow specimen. Final diagnosis was Multiple myeloma with extra medullary haematopoiesis.

Figure1: 1(a) Monomorphic and lymphoplasmacytoid infiltrate 1(b) grade3 marrow fibrosis

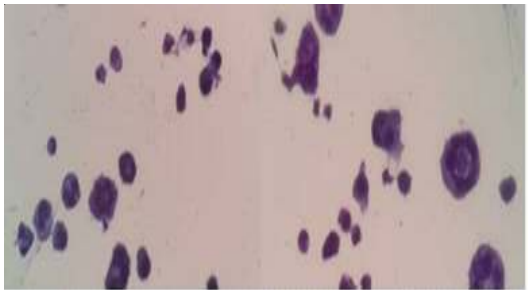

Figure-2 : Megakaryocytes, myeloid cells and erythroid cells

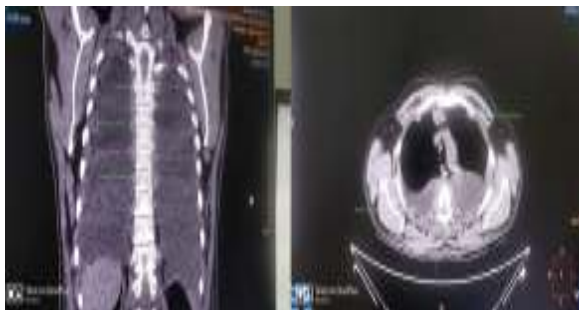

Fig 3(a) AXIAL CT-extra pleural lesions posteriorly 3(b) CORONAL CT-paravertebral soft tissue density lesions, bilateral pleural effusion and pleural lesions posteriorly

Discussion

Extramedullary haematopoiesis is the formation of haematopoietic elements outside the bone marrow. During foetal development it occurs as a normal physiological mechanism but it can occur pathologically as a compensatory mechanism to hypoxia as well as in other myelodysplastic or proliferative states in which bone marrow becomes non functional.

It can involve any organ or tissue like liver, spleen, abdominal viscera, pleura, lymph nodes, adrenal glands, breast, thymus, kidneys, intracranial structures and para spinal regions. It may be asymptomatic but at times lead to grave complications especially when it causes spinal cord compression or fatal haemorrhagic pleural effusion[4].

Intrathoracic EMH usually presents as paravertebral soft tissue masses. Pulmonary extramedullary haematopoiesis is a known but rare condition that may occur in lung parenchyma, pleura, pulmonary airways and blood vessels[5]. Pleural extramedullary haematopoiesis is also rare with only 3 biopsy proven cases reported so far[6]

Effusions in various body cavities containing haematopoietic elements can occur from extramedullary haematopoiesis arising from cranium, intra spinal epidural spaces, pericardium, pleura and peritoneum.[1,7]

Cause of pleural effusions in intrathoracic extramedullary haematopoiesis is believed to be due to mechanical interaction between the para spinal masses and pleura resulting in rupture of these vascular masses resulting in haemorrhagic effusion. Another theory is that the effusion is caused by primary pleural foci as opposed to the secondary mechanism of rupture of juxta- pleural paraspinal masses[6].Excessive extra medullary haematopoiesis may cause chronic inflammation and resultant effusion.

Diagnosis of intra thoracic EMH is suggested by presence

of immature blood cells and megakaryocytes[8] in pleural fluid. These cells can rarely be seen in patients with trauma, cancer and conditions causing bone marrow contamination[1]

A Bone marrow biopsy consistent with myelodysplastic disorder along with pleural fluid with trilineage precursor cells especially megakaryocytes[8] and presence of paravertebral[9] and pleural masses confirms the diagnosis of intrathoracic extramedullary haematopoiesis and possibly pleural extramedullary haematopoiesis in this patient. Other methods of diagnosis are biopsy of paravertebral soft tissues masses or pleural masses and technetium-99m Sulphur bone marrow scan .^{99m}Tc-SC BM scintigraphy is the non-invasive imaging modality of choice in the diagnosis of EMH as it targets the macrophages in reticuloendothelial system seen in liver spleen or bonemarrow[10]. Our patient could not afford the investigation and a biopsy from the masses described which would have been the gold standard in diagnosis could not be done due to deteriorating general condition and falling platelet count and risk for fatal haemothorax due to vascular nature of lesions.

Importance of diagnosing EMH is illustrated in this case as it is rare and should be kept in the differentials of non traumatic haemorrhagic pleural effusion associated with haemolytic anaemia or myelodysplastic syndrome as it may be cause of fatal haemorrhagic effusion and paralysis or death.

An uncomplicated EMH does not always merit treatment. Since these are radio sensitive low-dose external beam radiation therapy may be used as a palliation for respiratory symptoms and control pulmonary extramedullary haematopoiesis associated pleural effusions [11].Tube thoracostomy and occasional use of sclerosing agents[3] has also been used with success for recurrent haemothorax.

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Dengue fever presenting as influenza like illness: an unusual presentation of Dengue or coinfection with Influenza? - A case report

Preethi V[1], Manaf M A[2], Hari T A[3], Deepak V[4], Arjun P[5]

Abstract

The classical presentation of dengue fever is with fever, myalgia, headache, nausea and vomiting. Upper respiratory symptoms are uncommon and usually lead to an alternate diagnosis of influenza like illness (ILI). Herein we present the case of a 49 year old asthmatic, who presented with classical symptoms of asthma flare up following influenza like illness, responded very promptly to medical management, and was on the verge of getting discharged from the hospital, when she was detected to have thrombocytopenia, and on evaluation was diagnosed to have dengue fever. It is possible that she had Dengue with atypical symptoms of ILI, or perhaps the patient could have been simultaneously infected with both Dengue and Influenza.

Key words: dengue, respiratory, influenza like illness

Introduction

The onset of monsoon in the first week of June 2017 saw the outbreak of fever in Kerala, particularly the southern districts. Dengue fever and H1N1 pandemic influenza A virus accounted for a majority of these cases. The classical presenting symptoms of both these illnesses are different, thus enabling a quick clinical differentiation of these cases and cohort them for further management. Dengue fever to present with upper respiratory symptoms is extremely rare. Our case was a lady with bronchial asthma, whose initial presentation with fever, rhinitis and sore throat, satisfied the clinical criteria to be classified as Influenza like illness. Subsequent evaluation showed that she really had dengue fever and not a viral respiratory illness. This case is being presented to highlight this unique presentation of dengue fever as Influenza like illness.

Case report:

A 49 year old female who is a known asthmatic on regular inhaler medication was admitted to our hospital with complaints of high grade fever, sore throat, rhinitis, cough and breathing difficulty of two days duration. She did not have nausea, vomiting, abdominal pain, loose stools, headache, rashes, myalgia or dysuria at the time of admission.

On examination she was febrile with a temperature of 101 degree Fahrenheit, vitals were stable, upper respiratory examination revealed a congested throat and respiratory system examination showed bilateral wheezes. She was hypoxic with 92% saturation on room air. Other system examination was unremarkable. Laboratory tests showed a total count of 8700/cumm, platelet count of 2.02 lakhs/cumm and CRP of 15.9mg/l, chest X ray was also normal. ABG in room air showed pH-7.4, PO2-59mmHg, PCO2-27mmHg,HCO3-22mmol/l.

A diagnosis of viral exacerbation of asthma with influenza like illness was made and she was started on treatment with oxygen inhalation, non invasive ventilation (NIV), antiviral agent - Oseltamivir, Azithromycin, intravenous steroids, nebulised bronchodilators and other supportive measures. As per the protocol followed in the hospital, since she was a case that could be labelled as Influenza like illness (ILI) Category B, she was empirically started on Oseltamivir, without testing for influenza virus. This protocol has been adopted from the guidelines issued by the Government of India. The patient had a quick clinical recovery with our treatment. Fever, respiratory symptoms and chest signs subsided. On Day 3, she was totally asymptomatic, vitals were stable, saturation

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was 97% in room air, chest was clear on auscultation and she was planned to be discharged the next day.

On day 4 of admission she developed lower abdominal pain, vomiting and tiredness. Systemic examination at that time was normal. It was decided to repeat the basic blood counts and electrolytes. Laboratory tests on day 4 showed a total count of 7500/cu mm and a platelet count of 18000/cumm. PCV was 43%, Prothrombin time was normal but partial thromboplastin time was prolonged (44.7 sec). To rule out a possible cause for thrombocytopenia, Dengue NS1 antigen was tested, which was positive. Viral PCR (Filmarray, Bioemeurix, France) for influenza was negative. She was managed with adequate intravenous hydration and monitoring of platelet counts which showed serial improvement. Three days later, the platelet counts rose to 85,000/cumm , other blood parameters were also normal and she was discharged from the hospital. At one week of follow up the counts had become 3 lakhs/cumm and she was totally asymptomatic.

Discussion

The Centres for Disease Control and Prevention (CDC) defines Influenza like illness (ILI) as temperature greater than 100^F plus either cough or sore throat in the absence of a known cause other than influenza. In many studies, the influenza virus is identified in 25% or fewer patients with ILI only. Rhino virus, corona virus, respiratory syncitial virus, parainfluenza virus, adeno virus and oraganisms like mycoplasma, Chlamydia, legionella and even streptococcal infection can present with an ILI like picture.

According to WHO, dengue characteristics, dengue should be suspected when a high fever (104^0F or 40^0C) is accompanied by two of the following symptoms: severe headache, pain behind the eyes, muscle and joint pain, nausea, vomiting, swollen glands or rash.[1]

Though ILI could be due to any infection other than influenza, ILI like presentation of dengue is extremely rare. Few cases have been reported in literature. Cunha BA, et al reported a case of a woman who had dengue, presenting as ILI after a recent trip to Haiti.[2] Two cases of dengue presenting as upper respiratory tract infection have been reported from JIPMER, in India. [3]

Our patient solely had influenza like symptoms at the time of admission and she improved greatly with our initial treatment. Only the thrombocytopenia in blood tests done on day 4 of hospital admission for her vomiting and abdominal pain raised the suspicion of dengue. This lead to testing of dengue NS 1 antigen which came as positive and subsequently she improved with standard treatment protocol for dengue fever.

With large number of influenza like illnesses presenting to the hospital, the treating physician should be alert to other infections presenting as ILI, particularly dengue fever, especially when there is an epidemic of both influenza and dengue simultaneously as is being experienced in Kerala at present. The consequence of not suspecting dengue could be serious, since the routine clinical and laboratory monitoring as well as medical management with adequate hydration, which are followed in all cases of dengue are overlooked and the patient could end up with severe thrombocytopenia and bleeding manifestations.

In a case series published from Malaysia, the authors have reported respiratory symptoms (sore throat with or without rhinorrhea) in 50% of children and 44% of adults who were ambulatory and 34% of children and 24% of adults who were hospitalised with dengue fever.[4] There are also reports of co-infection with dengue virus and H1 N1 pandemic influenza A [swine flu] virus. [5]

This case report is aimed to highlight the need for screening for dengue, particularly during epidemics, even in patients who have upper respiratory symptoms, and monitor them with at least a follow up complete blood count after a couple of days, even though they seem to have clinical improvement, to prevent a development of a precipitously low platelet count as was seen in our patient.

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Ankylosing Spondylitis with lung manifestations - A case report and short review of literature

VenuGopal Panicker[1], Arjun Suresh[2], Suma Job[3]

Abstract: A 60 year male patient presented to us with bilateral upper lobe fibrosis with no past history of tuberculosis and lumbosacral and cervical pain of long standing duration. His skeletal survey showed typical changes of ankylosing spondylitis. The case is being published because of its rarity and the typical bone as well as lung radiological features.
Key words: Ankylosing spondylitis, upper lobe fibrosis

A 60 year old male, presented with progressive cough with mucoid expectoration and dyspnea on exertion for the last 6 years. He was a non smoker with no other addictions. He gave no history of tuberculosis in the past. He also complained of chronic joint pains involving mainly the lumbosacral and cervical regions with morning stiffness of the neck and back.

Respiratory examination revealed bilateral medium pitched crepitations. His pulmonary function test showed moderate restriction with decrease in DLCO. He had exercise desaturation too. His ESR was raised (60 mm at 1 hour).

His chest radiograph showed bilateral upper lobe fibrosis with emphysematous changes (Figure 1). A High Resolution CT was done which revealed fibrosis with traction bronchiectasis predominantly in both the upper and right middle lobes. Mosaic attenuation also was noted. (Figure 2a & 2b).

Skeletal survey shows typical changes of ankylosing spondylitis (AS). (fig 3,4 & 5)

His echocardiography revealed mild aortic regurgitation, mild tricuspid regurgitation and moderate pulmonary hypertension. Bronchoscopy was normal except for distortion of upper lobe segments. Both the sputum and bronchial washings didn't reveal any acid fast bacilli, fungus or any other pathogens. Polysomnography was done and sleep apnea ruled out.

The case is published because of its rarity and the typical bone as well as lung radiological features.

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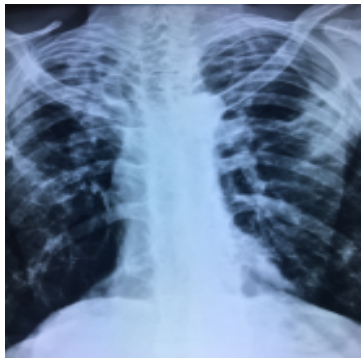
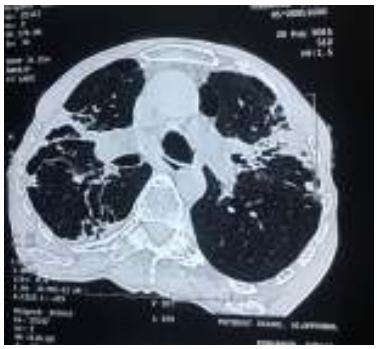


Figure 1 X ray chest shows bilateral upper lobe fibrosis with emphysematous changes



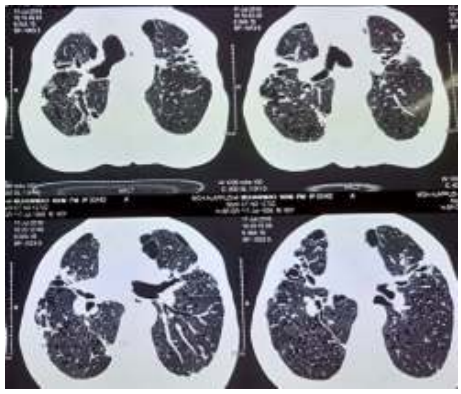


Figure 2a & 2b HRCT thorax reveals fibrosis with traction bronchiectasis and mosaic attenuation, predominantly in both the upper and right middle lobes.

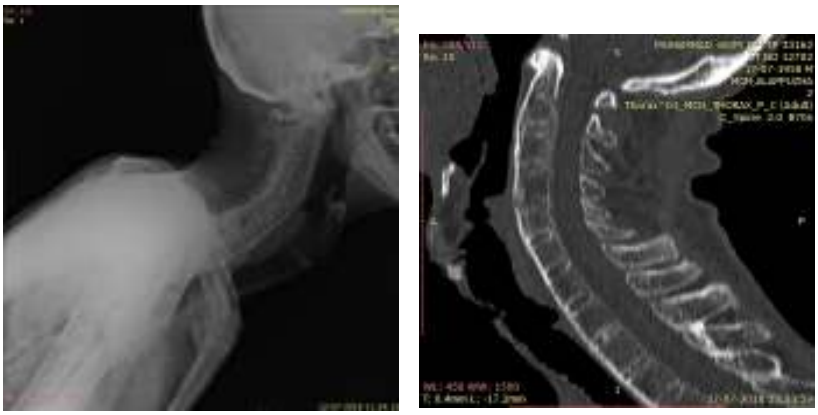


Fig 3a 3b Lateral X-ray and CT of cervical spine show anterior carriage of head with fusion of the apophyseal joints and bodies

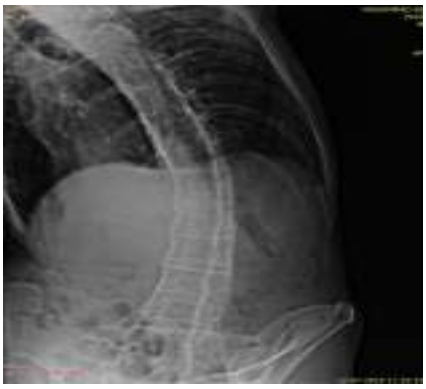


Fig 4 X-ray AP view of Thoracolumbar region shows levoscoliosis with extensive calcification of anterior ligament

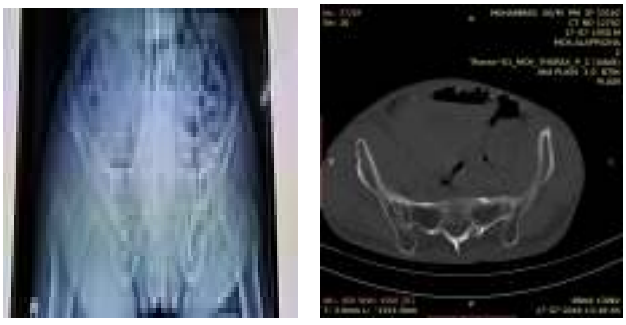


Fig 5 a & 5b Xray AP view of Sacroiliac joint shows bony ankylosis of the SI joint

Discussion

Introduction

Ankylosing Spondylitis (AS) is a chronic inflammatory arthritis which predominantly affects the axial skeleton[1]. The term originates from Greek terms ankylos and spondylos meaning stiffening of joint and vertebrae respectively. AS is recognized as part of the spondyloarthropathy group of rheumatic diseases, which also include psoriatic arthritis, reactive arthritis, and arthritis associated with inflammatory bowel seronegative spondyloarthropathy". Males are more affected than females with ratio of 2:1. Over 80 % of patients have symptom onset before 30 years of age and mean age of presentation in often in third decade of life. Only 5% patients have age more than 45 at presentation[4]. Radiological changes often occur late and hence diagnosis is delayed by around 8 years in HLAB27 positive patients and 11 years in negative patients. Patients without radiological findings are described as having non radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis usually affects spine and sacroiliac joints manifested as stiffening of joints and kyphosis[5]. Untreated or undiagnosed patients may develop complete spinal fusion described as bamboo spine.

Genetics and Pathophysiology

AS is considered inherited with risk of heritance >95%[6]. AS have been strongly associated with HLA-B27 in up to 20%, however only 2% patients with HLA-B7 have ankylosing spondylitis. HLA-B60 has also been linked. Genome Wide Association Study (GWAS) have revealed multiple association including ERAP 1&2,IL 12 R beta 2, IL 23R and CARD9. GWAS also have shown multiple loci common for IBD and AS .ERAP1 interact with HLAB27 increasing risk for AS[7].

Skeletal Manifestations

Spine and sacroiliac joints are primarily involved. AS can also involve other peripheral joints, enthesis (insertion sites of tendons) and digits. Low back pain, often insidious in onset is the commonest symptom[8]. Buttock pain which may be alternating is also seen in as many as

much as 25% of patients. Dactylitis and enthesitis is also seen[9]. Radiological changes appear late in disease and hence diagnosis is often delayed. Inflammatory pain is usually dull and insidious, which is often nocturnal and disturbs sleep. Inflammatory pain usually worsens with rest, however improve with activity. Early morning stiffness is also seen.[8] Any patient with inflammatory back pain for more than three months needs further evaluation with MRI which is more sensitive than CT scan and CXR [9] Patients can have tender sacroiliac joints. In advanced disease patients can have reduced spinal mobility demonstrable by Schober's test showing lumbar flexion less than 5 cm.[2,8] Straightening of spine is seen in advanced disease. Thoracic and cervical spine involvement is uncommon.[9]Sacroilitis on x ray can be graded radiologically[10]

Grade 0	Normal sacroiliac joints
Grade 1	Blurring of joint margin
Grade 2	Solitary erosion and juxta articular sclerosis in small sacral or iliac areas
Grade 3	Manifested juxta articular sclerosis, numerous erosions with widening of joint spaces and possible partial ankylosis
Grade 4	Complete ankylosis

Modified New York Criteria for Ankylosing Spondylitis[3]
Radiologic criterion Sacroiliitis , grade >II bilaterally or grade III to IV unilaterally
Clinical criteria Low back pain and stiffness for more than 3 months that improves with exercise but is not relieved by restLimitation of motion of the lumbar spine in both the sagittal and frontal planes Limitation of chest expansion relative to normal values correlated for age and sex
Note: The condition is definitely AS if the radiological criterion is associated with at least 1 clinical criterion.

MRI shows bone marrow edema, capsulitis, synovitis and enthesitis which are indicative of active inflammatory lesions. Chronic inflammatory lesions seen on MRI are sclerosis, fat deposition, erosion and bony bridge or ankylosis.[11]Peripheral joint involvement is usually asymmetric and is mono articular or oligoarticular and is predominantly seen in lower limbs. Hip and shoulder joint involvement can also be seen. Enthesitis can be seen especially in Achilles tendon and plantar fascia on MRI evaluation. Osteoporosis and vertebral fractures are more common in patients with Ankylosing spondylitis.[9,11]Thoracic manifestations of AS include those affecting chest wall, airways, lung parenchyma, pleura, heart and great vessels.

Anterior chest wall pain (ACW pain)

ACW pain is a classic symptom of AS, seen in more than 30 percent patients. It arises due to enthesitis of the rib cage and inflammation of sternoclavicular and manubriosternal joints. The pain is often sharp and restrict respiratory movements.

Pulmonary Involvement

Incidence of pulmonary manifestation in AS has been variably reported. However, a large study by Rosenow et al including 2080 patients showed lung involvement in 1.3% using chest x ray.[12]

Restrictive lung disease

Berdal et al in a study enrolling 147 AS patients found 18 % to have restrictive lung disease in contrast to literature which shows a prevalence of 20 % to 57%. However this study used actual height of the patient than recalled height or arm span which was done in other trials to compensate for loss of height due to kyphosis. They also noted that patients with restrictive disease had reduced spinal mobility, chest expansion, lumbar flexion, lateral lumbar flexion as well as dorsal kyphosis. Pain can occur on chest wall expansion secondary to straightening of lumbar spine. Limited chest expansion occur secondary to inflammation or ankylosis of sternocostal and costovertebral joints and adjacent synchondroses.[13]

Zaki et al found that 12.5 % patients showed normal pulmonary function tests, 78 % showed restrictive pattern, 53 % had obstructive pattern and 81 % had reduced DLCO.[14]

Radiological Findings

Frequency of lung involvement depends on the diagnostic modality used.

	Prevalence
Spirometry	20 - 52 %
CXR	1 - 15 %
HRCT	40 - 80 %

Rosenow et al in a study of 2080 patients found lung involvement in 1.3%. Apical fibrosis was seen in 26

patients aspergilloma in 5, pleural effusion and pneumothorax in 3 each and cor pulmonale in one patient.[12] Zaki et al found apical lung fibrosis in 6%, interstitial lung disease in 19%, minor interstitial abnormalities in 25%, bronchiectasis in 12.5%, lung nodules in 6 % and pleural thickening in 6 %. 28% patients who had HRCT changes had normal CXR. 15% showed positive findings on both HRCT and plain chest X-ray.[14]

Hasiloglu et al found parenchymal involvement in around 60 % patients which were in form of parenchymal bands in 27% , lobular septal thickening and emphysema in 12%, apical fibrosis 10% , GGO 9%, micronodules (6%), bronchial dilation (4%), mosaic pattern in 3%.[15] Casserly et al found features suggestive of interstitial lung disease (fibrosing alveolitis) in 16% of patients. HRCT features was suggestive of fibrosing alveolitis characterized by sub pleural bands, nondependent areas of attenuation, thickening of interlobular septae, parenchymal bands and honeycombing[16]. Similar findings were obtained by Zaki et al who noted ILD in 18%. ILD may co-exist with apicobullous disease or may even be independent entity.[14] Apical fibrosis is seen in up to 30%, may be unilateral or bilateral but is seen more on right side. Apical fibrobullous disease is seen more in males than females (50:1). Though mechanisms are unknown it's believed to be due to repeated aspiration due to altered mechanical stress from rigid spine and impaired cough reflex secondary to altered respiratory mechanics though hypoventilation secondary to stiff and spondylitic thorax is another proposed mechanism.[4,13] Apical bullous lesions are asymptomatic are seen in patients who have had Ankylosing Spondylitis for 15 years or more. Apical fibrobullous disease increases the risk of spontaneous pneumothorax which is seen in 0.29%. Recurrences have also been reported.[17]

Pulmonary Super infection

Pulmonary infection by tuberculosis or fungi are seen in upper lobe cavities and cyst in up to one third of patients. Mycobacterium avium, M.fortuitum, M.Kansasii, M.Scrofulaceum have been isolated from patients with Ankylosing spondylitis. Aspergillus fumigatus and Aspergillus niger have also been isolated.[12, 17]

Obstructive Sleep Apnoea (OSA)

Obstructive sleep apnea syndrome is seen in 12%-26% patients of Ankylosing spondylitis. Prevalence of OSA increasing with age with only 6% in patients less than 35 having OSA while it is seen in more than 40% of patients above 35 yrs. Daytime fatigue and snoring was seen among 48% patients.[18]

Ankylosing spondylitis can also alter sleep efficiency which could also be due to pain. OSA in Ankylosing spondylitis is believed to be secondary to restriction of the oropharyngeal airway by compression from cervical spine involvement or temporomandibular involvement, restrictive pulmonary disease, or cervical spine disease causing compression of the respiratory centers found in the medulla.[19, 20]

Cardiovascular manifestation

Sclerosis inflammation of aortic roots (aortitis), aortic valve and interventricular septum may be seen causing aortic regurgitation, conduction abnormalities (AV block, QRS prolongation, and even complete heart block). AS patients have 3-4 times higher risk for MI. Other findings include cardiomyopathy and increased risk of thromboembolism.[3,4,21]

Renal involvement is uncommon and is seen in form of non-specific glomerulonephritis, IgA nephropathy and renal amyloidosis. [22]

Eye involvement is often seen in form of recurrent anterior uveitis seen in around 25% cases. Acute anterior uveitis though recurrent rarely cause permanent damage. It has been associated with longer duration of disease as well as HLAB 27 positivity. Other manifestations include posterior synechae, raised intra ocular tension, cystoid macular oedema and cataract.

Psoriasis may be seen in as much as 10 % and have more peripheral involvement. [23]

Treatment

NSAID are main stay of treatment to control pain and stiffness. Continuous therapy modified to severity of disease is considered acceptable.[1] Continuous use of NSAID appears to reduce progression of radiological changes.[24] Disease not controlled by NSAID or when side effects are unacceptable TNF inhibitors can be used. Agents currently recommended are adalimumab, certolizumab, pegol, etanercept, golimumab, and infliximab, and their biosimilars. Anti TNF agents have shown to reduce inflammation in MRI with good clinical results in up to 60% patients. Infections like tuberculosis, HIV and hepatitis needs to be ruled out before starting these agents.[11] Though no specific agent is preferred as start of therapy etanercept has been shown be ineffective in patients with uveitis or inflammatory bowel disease.[9] Secukinumab, IL17 inhibitors may be used in patients who do not respond to Anti TNF agents.[2] Surgical options may be explored in selected groups.[11]

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