# Pulmon

The Journal of Respiratory Sciences





**Vol 17, Number 3, (Sep - Dec) 2015**
**ISSN 0973 - 3809**

OFFICIAL PUBLICATION OF ACADEMY OF PULMONARY AND CRITICAL CARE MEDICINE

Contents

Vol 17, Number 3, (Sep - Dec) 2015 ISSN 0973 - 3809

Pulmon
The Journal of Respiratory Sciences

## General Information

Pulmon 2015; 17:3 95 - 136

# Pulmon

The Journal of Respiratory Sciences

**Proprietor**

Academy of Pulmonary and Critical Care Medicine

Head office (Ernakulam)

**Publication data**

3 issues published in a year

**Web site :** www.apccm.in

**Journal office & Correspondence**

Editor-in-chief PULMON
Dr. Suraj K.P.
Professor,
Dept. of Pulmonary Medicine
Govt. Medical College,
Kozhikode, Kerala, India - 673008
E mail: drsurajkp@yahoo.com

**Advertising and tariff requests**

**Head Office of Academy of Pulmonary and Critical Care Medicine**

Dr. Kurian Oommen

Thottathil

Kavumbhagom PO

Thiruvalla -689102

Ph: 0469 2604796, 9847248015

drkurianoommen@gmail.com

**Subscription rates**

Personal
Single : Rs. 250
Annual : Rs. 600

Institutional
Single : Rs. 250
Annual : Rs. 600

Contact e-mail ID : drsurajkp@yahoo.com

**Instructions for Authors**

Instructions for submission of manuscripts are published in the journal. Also available in editorial office

**Registration**

Registrar of Newspapers of India
RK Puram, New Delhi
Regn. No. M6/6468/2001
ISSN 0973 – 3809

**Type setting and Printing**

Kamala Offset, Calicut
Ph: 2721020

# Pulmon The Journal of Respiratory Sciences

*"Committed to the Care of Lungs"*

The Official Publication of the
Academy of Pulmonary and Critical Care Medicine





**Editor**
Dr. SuraJ K.P.
Professor,
Dept. of Pulmonary Medicine
Govt. Medical College,
Kozhikode, Kerala, India - 673008
E mail: drsurajkp@yahoo.com

Academy of Pulmonary & Critical Care Medicine

# Pulmon

The Journal of Respiratory Sciences

## Editorial

# How far does the platelets and fibrin contribute to allergic asthma??

**Mohankumar T.**
Senior Consultant Pulmonologist & HOD
Institute of Pulmonary Medicine & Research
Sri Ramakrishna Hospital, Coimbatore - 641044
E-mail : tmkdr@yahoo.co.in

We know that the symptoms of asthma are due to infiltration of eosinophils, mast cells and T helper 2 cells to the airway walls. This produce airflow obstruction, airway hyper responsiveness, wheezing chest tightness and coughing. Structural remodelling due to this will later progress to decline in lung function. Steroid resistance and frequent exacerbations as an aftermath can present as a clinical problem.

There is evidence suggesting contribution of coagulation factors and fibrinolysis to the pathophysiological changes in asthma[1,2]. Airway coagulation and anticoagulant mechanisms is regulated locally. The main mediator of coagulation including tissue factor (TF) initiate the coagulation and changes fibrinogen to fibrin which usually occurs locally in the lung. The leakage of plasma proteins into the broncho alveolar space produces the inflammation in the lung. Acute exacerbation of moderate asthma appears to be associated with a shift to a profibrinogenic, possibly antifibrinolytic, environment in the airways[3]

The haemostatic imbalance in the airways contribute to the allergic inflammation where cytokines and protease activated receptors play a role. Aside from their role in haemostasis, coagulant and fibrinolytic proteases are important mediators of inflammation in diseases such as asthma[4]

In asthmatic patients increased platelets are seen during asthma exacerbations. Coagulation is activated in different types of airway cells like alveolar epithelium, macrophages and eosinophils by leakage of clotting factors and tissue factor. Decreased activity of the anticoagulant Protein C and fibrinolysis by Plasminogen Activator Inhibitor (PAI-1) produces fibrin deposition. Untreated moderate asthma is associated with increased fibrinolysis that is corrected by inhaled corticosteroid (ICS). Severe asthma and high dose corticosteroid therapy is associated with a profibrinogenic, antifibrinolytic environment in the airways. This suggests that inhibition of fibrin deposition in severe asthma may be used as a therapeutic approach[5].

Local coagulation activation in lung is seen as an elevated thrombin and antithrombin complexes in the sputum and BAL fluid of the asthmatic patients after allergen challenge. By releasing tryptase which cleaves $\alpha$ and $\beta$ chain of fibrinogen, mast cells play an important role as the regulator of fibrin metabolism in asthma. It is known that elevated fibrin concentration in the airway can produce a decline in lung function.

Exposure of plasma to cell-bound tissue factor (TF), the principal activator of the extrinsic coagulation cascade, initiates fibrin clot formation within minutes, although the rate of fibrin formation is determined by components of the intrinsic coagulation cascade[6]

Neutrophils, mast cells, macrophages, fibroblasts and the bronchial epithelium are potential local sources of of Plasminogen Activator Inhibitor- 1 ( PAI-1). A 4G/5G polymorphism in the PAI-1 promoter region has been reported, and preferential transmission of the 4G allele correlates with increased PAI-1 expression in asthma. PAI-1 andThrombin Activatable Fibrinolysis Inhibitor( TAFI)have been implicated in normal wound healing, and increased expression of both PAI-1 and TAFI has also been implicated in fibrin formation leading to the development of lung fibrosis[7,8,9,10,11]

Thrombin is seen in asthma pathophysiology in vitro and vivo[12]. Thrombomodulin expressed by dendritic cells, activated protein C and fibrin are involved in allergic asthma through various pathways. Thrombomodulin positive dendritic cells are seen in the peripheral blood of allergic asthmatics[13]. So platelets may also contribute to the pathophysiology of asthma. Plasma (containing clotting factors, such as FVII and FX) leaks from lung capillaries as a consequence of the inflammatory response. TF expression on epithelial cells, eosinophils, and macrophages initiates intra-alveolar coagulation by activation of FVII (which can also be produced by epithelial cells). Interventions with the anticoagulants fondaparinux (FXa inhibitor) and hirudin (thrombin inhibitor) and the plasminogen activators tPA and uPA improve the disturbed pulmonary hemostatic balance and concurrently diminish allergic inflammation and asthma parameters in experimental settings[14,15]

In summary, the coagulation is activated in the airways of patients with asthma by leak of clotting factors and TF expressed on various cell types, including alveolar epithelium, macrophages, and eosinophils. Fibrin deposition is further facilitated by decreased activity of the anticoagulant protein C system and inhibition of fibrinolysis by enhanced production of PAI-1. Allergens are responsible for an inflammatory response in the lungs, which is aggravated by proinflammatory effects of platelets and decreased cytoprotective effects of the Protein C system.

Do we need to pursue these data for treating allergic asthma in a new way? A point to ponder!

## References

1. Pretorius E, Oberholzer HM. Ultrastructural changes of platelets and fibrin networks in human asthma: a qualitative case study..Blood Coagul Fibrinolysis 2009 Mar;20(2):146-9.

2. Pretorius E, Ekpo OE, Smit E.Comparative ultrastructural analyses of platelets and fibrin networks using the murine model of asthma. Exp Toxicol Pathol 2007 Oct;59(2):105-14. Epub 2007 Jun 27.

3. Brims FJ, Chauhan AJ, Higgins B, Shute JK. Up-regulation of the extrinsic coagulation pathway in acute asthma—a case study. J Asthma 2010 Aug;47(6):695-8.

4. Schuliga M. The inflammatory actions of coagulant and fibrinolytic proteases in disease. Mediators Inflamm 2015; 2015:437695. doi: 10.1155/2015/437695. Epub 2015 Mar 24.

5. Brims F J H, Chauhan A J, Higgins B, Shute J K. Coagulation factors in the airways in moderate and severe asthma and the effect of inhaled steroids Thorax 2009; 64:1037-1043 doi:10.1136/thx.2009.114439

6. Ovanesov MV, Ananyeva NM, Panteleev MA, et al. Initiation and propagation of coagulation from tissue factor-bearing cell monolayers to plasma: initiator cells do not regulate spatial growth rate. J Thromb Haemost 2005; 3:321–31.

7. Cho SH, Ryu CH, Oh CK. Plasminogen activator inhibitor-1 in the pathogenesis of asthma. Exp Biol Med (Maywood) 2004; 229:138–46.

8. Boffa MB, Koschinsky ML. Curiouser and curiouser: recent advances in measurement of thrombin-activatable fibrinolysis inhibitor (TAFI) and in understanding its molecular genetics, gene regulation, and biological roles. Clin Biochem 2007; 40:431–42. 31.μ! Xiao W,

9. Hsu YP, Ishizaka A, et al. Sputum cathelicidin, urokinase plasminogen activation system components, and cytokines discriminate cystic fibrosis, COPD, and asthma inflammation. Chest 2005; 128:2316–26

10. Kowal K, Zukowski S, Moniuszko M, et al. Plasminogen activator inhibitor-1 (PAI-1) and urokinase plasminogen activator (uPA) in sputum of allergic asthma patients. Folia Histochem Cytobiol 2008; 46:193–8.

11. Fujimoto H, Gabazza EC, Taguchi O, et al. Thrombin-activatable fibrinolysis inhibitor deficiency attenuates bleomycin-induced lung fibrosis. Am J Pathol 2006; 168:1086–96.

12. Shimizu S, Gabazza EC, Hayashi T, et al. Thrombin stimulates the expression of PDGF in lung epithelial cells. Am J Physiol Lung Cell Mol Physiol 2000;279(3): 503-510.

13. Terada M, Kelly EAB, Jarjour NN. Increased thrombin activity after allergen challenge: a potential link to airway remodelling? Am J Respir Crit Care Med 2004;169(3):373-377.

14. Hauck RW, Schulz C, Schomig A, et al. á-Thrombin stimulates contraction of human bronchial rings by activation of protease-activated receptors. Am J Physiol Lung Cell Mol Physiol 1999;277: 22-29.

15. Danese S, Vetrano S, Zhang L, et al. The protein C pathway in tissue inflammation and injury: pathogenic role and therapeutic implications. Blood 2010;115(6):1121-1130.

## Review Article

# Venous Thromboembolism : Current Management Strategies

**Anand M.**
Associate Professor, Dept. of Pulmonary Medicine
Govt. Medical College, Kozhikode.

***Key words :*** Venous Thromboembolism, Anticoagulation, Thrombolytic Therapy.

## Introduction

Venous thromboembolism is the third most common cardiovascular disease following myocardial infarction and stroke and has primary brunt on pulmonary circulation. These patients present with a wide spectrum of clinical severity and early mortality rates range from < 1 % to > 50%[1-2]. The patients with sustained hypotension or cardiogenic shock due to acute corpulmonale (ACP), which carry a mortality rate of 35% to 58%, are considered as high-risk patients[3]. However, nearly half of the patients actually die before their admission in hospital within the first hour following onset of symptoms.

## Risk factors and outcome

Deficiencies of natural human anticoagulants like antithrombin, protein C and protein S are the strongest inherited risk factors for pulmonary embolism (PE), but they account for only 1% of all cases of PE. Factor V Leiden and prothrombin (factor II) G20210A are the two most common mutations that cause more than half of inherited forms of venous thromboembolism[4].

Acquired risk factors predispose to majority of the cases of PE. The highest risk factors for PE are surgery (particularly orthopaedic surgery, oncosurgery and neurosurgery), history of previous venous thromboembolism, immobility for more than 48 h, hospitalization, infection and cancer[5-6]. In the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED), atleast one of these risk factors was present in more than 80% of patients with established PE and in about 70% of those without PE[5].Other medical conditions associated with increased risk for PE include congestive cardiac failure, ischemic stroke, acute respiratoryfailure or intubation, sepsis, acute rheumatic disease and inflammatory bowel disease.

Advanced age, major underlying conditions (cancer and cardiac or respiratory disease), clinical evidence of right ventricular dysfunction (tachycardia and hypotension) and hypoxemia are the main factors that define the outcome of patients with PE. This has been amply illustrated by the pulmonary embolism severity index (PESI) and its simplified version (sPESI)[7, 8]. PESI and sPESI reliably exclude an elevated risk for 30-day mortality in confirmed cases of PE (indicatedby PESI classes I and II or by a sPESI< 1). On the other hand, these clinical rules have a low positive predictive value in the absence of hypotension.

**Table 1**

**Simplified pulmonary embolism severity index**

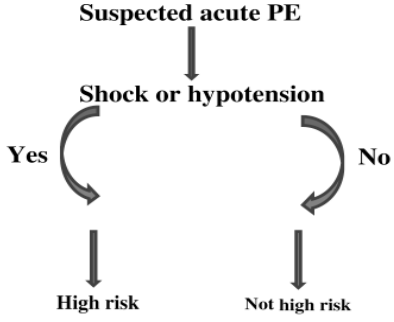
| Variable | Points |
|---|---|
| Age >80 years | 1 |
| History of cancer | 1 |
| History of heart failure or chronic lung disease | 1 |
| Pulse rate ≥110 bpm | 1 |
| Systolic blood pressure <100 mmHg | 1 |
| Oxygen saturation <90 % on room air | 1 |

Patients with none of the clinical variable (i.e., total score of 0) are considered as low risk and have mortality and pulmonary embolism-related complication rates significantly lower than those with a score of ≥1.

According to the recent guidelines of the European Society of Cardiology, patients with hypotension are defined as high-risk patients; among normotensive patients, those with a sPESI< 1 or PESI I-II are considered as low-risk patients without further risk stratification, those with a sPESI = 1 or those with either right ventricular dysfunction (RVD) or elevated cardiac biomarkers are considered as intermediate-low-risk patients and those with sPESI = 1 and both RVD and elevated cardiac biomarkers are considered as intermediate-high-risk patients[9]. Echocardiographic findings used to risk stratify patients with PE include RV dilation, an increased RV–LV diameter ratio, hypokinesia of the free RV wall, increased velocity of tricuspid regurgitation jet, decreased tricuspid annulus plane systolic excursion or combinations of the above.

## Diagnosis

In most patients, PE is suspected on the basis of dyspnoea, chest pain, pre-syncope or syncope and/or haemoptysis[10].Arterial hypotension and shock are rare and indicate central PE and/or a severely reduced haemodynamic reserve. Syncope may occur even without haemodynamic instability. Symptoms and signs evaluated by clinical judgement or by the use of prediction rules allow to classify patients with suspected PE into distinct categories of clinical or pre-test probability. The most frequently used prediction rule is the Wells score which use both a three-category (low, moderate, or highclinical probability of PE) and a two category scheme (PE likely or unlikely). The revised Geneva rule is also simple and standardized.




Systolic blood pressure < 90 mm Hg or a drop of ≥ 40 mm Hg for > 15 minutes in the absence of new onset arrhythmias, hypovolaemia or sepsis

## Electrocardiogram and Cardiac Biomarkers

Findings in acute PE are generally nonspecific and include T-wave changes, ST-segment abnormalities and left- or right-axis deviation.The presence of an S1Q3T3 pattern, right bundle branch block or T-wave inversion in leads V1 toV3 in a patient with PE should suggest the presence of right ventriculardys function[11]. 51% of patients with acute PE had elevated BNP or NT-proBNP levels on admission. These patients had a 10% risk of early death and a 23% risk of an adverse clinical outcome. Troponins and heart-type fatty acid-binding protein (H-FABP) possess prognostic value in acute PE.Elevated neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C also define outcome in PE.

## D-dimer Testing

The negative predictive value of D-dimer testing is high and a normal D-dimer level virtually rules out acute PE or DVT. The quantitative enzyme-linked immunosorbent assay (ELISA) have a diagnostic sensitivity of 95% or better and hence used to exclude PE in patients with either a low or a moderate pre-test probability[12]. The performance of D-dimer testing in the elderly can be improved further by using age-adjusted cut-off values(age×10 μg/ml above 50 years).

## Computed Tomographic Pulmonary Angiography

In patients with a low or intermediate clinical probability of PE asassessed by the Wells rule, a negative CTPA had a high negative predictive value for PE (96% and 89%, respectively). A negative CTPA is an adequate criterion for excluding PE in patients with a non-high clinical probability of PE. CTPAshowing PE at the segmental or more proximal level is adequate proof of PE in patients with a non-low clinical probability; however, the positive predictive value of CTPA is lower in patients with a low clinical probability of PE, and further testing may be considered, especially if the clots are limited to segmental or sub-segmental arteries[13].

## Ventilation Perfusion Scintigraphy

The V/Q scan may be considered in outpatients with low clinical probability and a normal chest X-ray, in young (particularly female) patients, in pregnancy, in pa-

tients with history of contrast medium-induced anaphylaxis and strong allergic history, in severe renal failure, and in patients with myeloma and paraproteinaemia[14]. Lung scan can be classified as normal scan (excluding PE), high probability scan (considered diagnostic of PE in most patients), and non-diagnostic scan. Performing only a perfusion scan is acceptable in patients with a normal chest X-ray.

## Pulmonary Angiography

Pulmonary angiography is more often used to guide percutaneous catheter-directed treatment of acute PE.

## Magnetic Resonance Angiography

This technique, although promising, is not yet ready for clinical practice.

## Echocardiography

RV dilation is found in at least 25% of patients with PE and its detection either by echocardiography or CTPA is useful for risk stratification of the disease[15]. Echocardiographic examination is not recommended as part of the diagnostic work-up in haemodynamically stable, normotensive patients with suspected (not high-risk) PE. Likewise absence of echocardiographic signs of RV overload or dysfunction practically excludes PE as the cause of haemodynamic instability. Mobile right heart thrombi confirms the diagnosis of PE and their presence is associated with RV dysfunction and high early mortality is associated in the above line

## Compression Venous Ultrasonography

In the majority of cases, PE originates from DVT in a lower limb. In a study using venography, DVT was found in 70% of patients with proven PE. CUS shows a DVT in 30–50% of patients with PE, and finding a proximal DVT in patients suspected of having PE is considered sufficient to start anticoagulant treatment without further testing[16].

## Diagnostic strategies:

**Suspected pulmonary embolism with shock or hypotension**

In this case, a rapid diagnosis by CTPA is recommended if immediately available. If not, critical care echocardiography (CCE) is mandatory to look for signs of RV overload. It may rule out the diagnosis or confirm the high suspicion of PE if it demonstrates right ventricular dilatation whereas many other causes in the ICU may induce RV dilatation, especially in ventilated patients. In intubated patients under mechanical ventilation, a transesophageal echocardiography may be performed to directly visualise thrombi in the main or right pulmonary arteries, avoiding transferring unstable patients for CTPA.

**Suspected pulmonary embolism without shock or hypotension**

In patients admitted to the emergency department, plasma D-dimer measurement combined with clinical probability assessment rules out PE in around 30% of patients. D-dimer should not be measured in patients with a high clinical probability. It is also less useful in hospitalized patients. CTPA is the second-line test in patients with an elevated D-dimer level and the first-line test in patients with a high clinical probability. Performing CUS before CTPA may be an option in patients with relative contra indications for CT such as in renal failure, allergy to contrast dye or pregnancy.

## Prevention of Venous Thromboembolism

Four categories of drugs have been used successfully: unfractionated heparin, LMWH (enoxaparin, dalteparin), factor Xa inhibitors (fondaparinux, rivaroxaban) and the vitamin K antagonist warfarin.When administered correctly in appropriate patients, prophylactic anticoagulation is safe and effective with an absolute reduction in the incidence of venous thromboembolism in the range of 40%to 60%. Major bleeding complications occur in less than 1% of patients.

## Low Dose Heparin

Heparin given subcutaneously in a dose of 5000 units every 8 or 12 hours is effective in reducing the incidence of DVT, PE and fatal PE inpatients at low to moderate risk such as those under going surgey requiring general anesthesia for $\geq$ 30 minutes and with medical conditions requiring bed rest for many days[17]. However, it is not optimal in high risk patients such as those with hip fracture or hip replacement, those undergoing prostate surgery and patients suffering major traumatic injuries.

Patients placed on prophylactic heparin should be screened with an initial platelet count, partial thromboplastin time, and prothrombin time. Monitoring of platelet counts on a weekly basis can also be done. LMWH preparations are more effective than unfractionated heparin as prophylactic agents in high-risk groups: patients undergoing hip or knee replacement, patients with spinal cord injury, patients with ischemic strokes and patients with multiple trauma.

## Pneumatic Compression Devices

A variety of devices are available: thigh-length systems that provide both thigh and calf compression, calf-compressive devices, single-pulse systems and sequential compression systems[18]. Their use is indicated in patients in whom pharmacologic methods of prophylaxis are contraindicated.

Other agents like warfarin sodium and fondaparinux, a synthetic pentasaccharide that selectively inhibits activated factor X, are also effective in the prevention of VTE in patients undergoing lower extremity orthopedic surgery[19]. In those with pelvic or lower extremity fractures and internal or intracranial bleeding, prophylactic placement of an inferior vena cava filter provides protection against emboli in selected patients[20].

## Treatment of Venous Thromboembolism

### Haemodynamic and Respiratory Support

Acute RV failure with resulting low cardiac index (CI) is the leading cause of death in patients with high-risk PE. Aggressive volume expansion is of no benefit but modest (500 mL) fluid challenge may increase CI. Norepinephrine should be limited to hypotensive patients[21]. The use of dobutamine and / or dopamine is considered for patients with low CI and normal blood pressure (BP). Inhalation of nitric oxide may improve the haemodynamic status and gas exchange of patients with PE[22]. Levosimendan may restore right ventricular–pulmonary arterial coupling by combining pulmonary vasodilation with an increase in RV contractility. Sometimes mechanical ventilation is required after cardiac arrest or for refractory shock.Low tidal volumes (appro. 6 mL/kg lean body weight) should be used in an attempt to keep the end inspiratory plateau pressure <30 cm and PEEP should be minimal as far as possible. Extra corporeal cardiopulmonary support can be an effective procedure in massive PE[23].

## Heparin

Heparin, both unfractionated and low molecular weight, remains the mainstay of therapy for venous thrombosis and for PE not associated with hemodynamic compromise.The most widely utilized of these is a weight-based system that includes an 80unit/kg intravenous bolus of heparin followed by an 18unit/kg/hr infusion[24]. An activated partial thromboplastin time (aPTT) is obtained 6 hours after the bolus dose, 6 hours after each dose adjustment and then on a daily basis for the duration of therapy.The therapeutic range of aPTTcorresponds to heparin levels of 0.2 to 0.4 unit/mL by protamine sulfate titration or 0.3 to 0.7 unit/mL by anti–factor Xa assay[25].For patients with heparin resistance (defined as the need for >40,000 units/day), monitoring heparin with anti–factor Xa assay is preferred. More recently, a fixed dose of subcutaneous unfractionated heparin without aPTT monitoring, administered as an initial dose of 333 U/kg followed by a dose of 250 U/kg every12 hours, has been demonstrated to be as safe and effective as LMWH in patients presenting with DVT and PE[26]. Eventhough LMWH administration doesn't require aPTTmonitoring, monitoring with anti-Xa levels is indicated in patients with antiphospholipid antibodies or other circulating anticoagulants who have elevated baseline aPTT, extremes of body weight (less than 40 kg and greater than 150 kg), significant renal disease (creatinine clearance less than 30 mL/min), pregnancy and unexplained bleeding or recurrent thrombosis during therapy[27]. A therapeutic target range for peak anti-Xa levels ranges from 0.6 to 1.0 IU/mL, 4 hours after administration.

## Factor Xa Inhibitors and Direct Thrombin Inhibitors

Parenteral fondaparinux has been approved for prophylaxis in patients undergoing hip, knee and abdominal surgery as well as for treatment of DVTand PE in conjunction with warfarin[28]. Rivaroxaban, apixaban and edoxaban are the oral factor Xa inhibitors available for the treatment venous thromboembolism[29]. Intravenous direct thrombin inhibitors (lepirudin, argatroban) andthe oral direct thrombin inhibitors (dabigatran) represent another class of anticoagulant agents approved for the management of patients with venousthromboembolism in the setting of heparin-induced thrombocytopenia (HIT)[30]. Advantages of these new agents include the uses of fixed-dosing with no need for monitoring, few interactions and

a wider therapeutic window. The lack of an effective antidote, their cost and limited utility in patients with kidney disease are the main disadvantages.

Dabigatran etexilate is a highly specific and competitive direct thrombin inhibitor,which has a rapid onset of action(1–2 h), a short half-life (12–17 h) and has an 80% renal excretion. Concurrent administrationwith P-glycoprotein inhibitors or P- glycoprotein inducers is contraindicated. Approximately two-thirds of an administered dose of rivaroxaban and apixiban are metabolized by the liver via cytochrome P450 enzymes (CYP3A4 and CYP2J2). Therefore,concomitant treatment with cytochrome P450 isoenzymes and P-glycoprotein inhibitors such as itraconazole and voriconazole,is contraindicated due to an increased risk of bleeding. Since one-third of the drug is eliminated by the kidneys, rivaroxaban is contraindicated in patients with severe renal insufficiency.

## Anticoagulation

The objective is to prevent both early death and recurrent symptomatic or fatal PE. The standard duration of anticoagulation is 3 months. During acutephase, parenteral anticoagulation [UFH, LMWH or fondaparinux] is given for thefirst 5–10 days. An oral vitamin K antagonist (VKA) is usually started along with it; alternatively, it can befollowed by administration of dabigatran or edoxaban. The treatment with rivaroxaban or apixaban should be started directly or after a 1–2 day administration of UFH,LMWH or fondaparinux. In patients with high or intermediate clinical probability for PE subcutaneous LMWH or fondaparinux are preferred, as they carry a lower risk of major bleeding and heparin-induced thrombocytopenia(HIT). On the other hand, UFH is recommended for patients in whom primary reperfusion is considered, as well as for those with creatinine clearance <30 mL/min or severe obesity.Warfarin can be started at a dose of 10 mg in younger (<60 years of age), otherwise healthy outpatients and at a dose of 5 mg in older and hospitalized patients.

Active cancer is a major risk factor for recurrence of VTE. At least 3–6 months of treatment with LMWH is recommended for patients with VTE and cancer and after first 6 months, treatment with LMWH or VKA is recommended as long as the disease is considered active. Indefinite anticoagulation therapy should be considered for patients with a first unprovoked proximal DVT or PE and for patients with lupus anticoagulant, deficiency of protein C and S, with homozygousfactor V Leiden and homozygous prothrombin G20210A. Lifelong treatment is recommended for patients with second unprovoked DVT or PE. Therapy with aspirin after termination of oral anticoagulation may reduce the risk of recurrence. Rivaroxaban (20 mg once daily), dabigatran (150 mg twice daily or 110 mg twice daily for patients $\geq$ 80 years) or apixaban (2.5 mg twice daily) should be considered as an alternative to VKA (except for patients with severe renal impairment) if extended anticoagulation treatment is necessary[31].

## Thrombolytic Therapy

If no contraindication, thrombolytic therapy may be considered in patients with PE who present with hemodynamic compromise (in whom the mortality rate is 30%), patients who develop hemodynamic compromise during conventional therapy with heparin and patients with PE associated with intracavitary right heart thrombi. UFH infusion should be stopped during administration of streptokinase or urokinase; it can be continued during rtPA infusion. Anticoagulation with UFH should be continued for several hours after the end of thrombolytic treatment before switching to LMWH or fondaparinux[32]. Pulmonary Embolism Thrombolysis (PEITHO) trial compared tenecteplase plus heparin vs. placebo plus heparin in acute PE patients with RV dysfunction and positive troponin. The primary efficacy outcome, a composite of all-cause death orhaemo dynamic decompensation/collapse within 7 days of randomization, was significantly reduced with tenecteplase (2.6% vs. 5.6% in the placebo group; P < 0.015; OR 0.44; 95% CI0.23–0.88)[33].

**Table 2 : Approved Thrombolytic Regimens for Pulmonary Embolism**

| | |
|---|---|
| Streptokinase | 250000 IU as a loading dose over 30 min, followed by 100000 IU/h over 12–24 h Accelerated regimen: 1.5 million IU over 2 h |
| Urokinase | 4400 IU/kg as a loading dose over 10 min, followed by 4400 IU/kg per hour over 12–24 h<br>Accelerated regimen : 3 million IU over 2 h |
| rtPA | 100 mg over 2 h; or<br>0.6 mg/kg over 15 min (maximum dose 50 mg) |
| IU = international units; rtPA = recombinant tissue plasminogen activator | |

**Table 3**
**Contraindications to Thrombolytic Therapy**

| **Absolute Contraindications** |
|---|
| Haemorrhagic stroke or stroke of unknown origin at any time |
| Ischaemic stroke in the preceding 6 months |
| Central nervous system damage or neoplasms |
| Recent major trauma/surgery/head injury in the preceding 3 weeks |
| Gastrointestinal bleeding within the last month Known bleeding risk |
| **Relative Contraindications** |
| Transient ischaemic attack in the preceding 6 months |
| Oral anticoagulant therapy |
| Pregnancy, or within one week postpartum |
| Non-compressible puncture site |
| Traumatic resuscitation |
| Refractory hypertension (systolic blood pressure >180 mm Hg) |
| Advanced liver disease |
| Infective endocarditis |
| Active peptic ulcer |

## Surgical Embolectomy

Surgical embolectomy can be considered for high-risk PE and for selected patients with intermediate-high-risk PE if thrombolysis is contraindicated or has failed.Surgical embolectomy is also performed in patients with right heart thrombi straddling the interatrial septum through a patent foramen ovale.

## Percutaneous Catheter-directed Treatment

For patients with absolute contraindications to thrombolysis, interventional treatment options include (i) thrombus fragmentation with pigtail or balloon catheter, (ii) rheolytic thrombectomy with hydrodynamic catheter devices, (iii)suction thrombectomy with aspiration catheters and (iv)rotational thrombectomy[34].They are usually performed in patients with acute high-risk (massive) PE, in whom thrombolysisis is contraindicated or has failed and in whom surgical intervention is not available or contraindicated[35].

## Vena Cava Interruption and Vena Cava Filter

IVC filters should be considered in patients with acute PE and absolute contraindications to anticoagulation, major bleeding complication during anticoagulation, recurrent embolism while receiving therapeutic anticoagulation and usually in patients who have required ECMO after PE. The filters are usually placed in the infrarenal IVC and can be permanent or retrievable. Early complications include device malposition, pneumothorax, hematoma, air embolism, inadvertent carotidartery puncture and arteriovenous fistula[36].

## Conclusions

Pulmonary embolism is a potentially life-threatening condition,difficult to diagnose in majority of the patients. Clinical sings of PEare neither sensitive nor specific enough to conclusively arrive at the diagnosis. The diagnostic strategy depends on the pretest clinical probability of PE, the conditionof the patient, the availability of the necessary test, the risk of an inaccurate positive or negative diagnosis and the cost. Exclusion of PE by clinical probability assessment and D-dimer spares the cost and radiation of an imaging evaluation. CTPA has become the method of choice for imaging the pulmonary vasculature when pulmonary embolism is suspected in routineclinical practice. A standard 3 months anticoagulation is recommended for confirmed cases of PE. Extended or lifelong anticoagulation may be required for those with unprovoked embolism or non modifiable risk factors. Role thrombolytic therapy and interventional procedures still need to be defined in those patients with moderate- high risk PE.Long-term follow-up of patients after acute PE is required to monitor for the development of chronic thromboembolic pulmonaryhypertension[37].

## References

1. Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, GrosserKD, et al. Management strategies and determinants of outcome in acutemajor pulmonary embolism: results of a multicenter registry. J Am CollCardiol. 1997;30:1165–71.

2. Laporte S, Mismetti P, Decousus H, Uresandi F, Otero R, Lobo JL, et al.Clinical predictors for fatal pulmonary embolism in 15,520 patients withvenous throm-

boembolism: findings from the Registro Informatizadode la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation.2008;117:1711–6.

3. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinicaloutcomes in the International Cooperative Pulmonary Embolism Registry(ICOPER). Lancet. 1999;353:1386–9.

4. Jacobsen AF, Dahm A, Bergrem A, Jacobsen EM, Sandset PM. Risk of venous thrombosis in pregnancy among carriers of the factor V Leiden and the prothrombin gene G20210 A polymorphisms. J Thromb Haemost.2010;8:2443–49.

5. Miniati M, Prediletto R, Formichi B, Marini C, Di Ricco G, Tonelli L, Allescia G,Pistolesi M: Accuracy of clinical assessment in the diagnosis ofpulmonary embolism. Am J Respir Crit Care Med 1999, 159:864–871.

6. Blom JW, Doggen CJ, Osanto S, Rosendaal FR: Malignancies,prothrombotic mutations, and the risk of venous thrombosis. JAMA 2005,293:715–722.

7. Aujesky D, Roy PM, Le Manach CP, Verschuren F, Meyer G, Obrosky DS, et al. Validation of a model to predict adverse outcomes in patients withpulmonary embolism. Eur Heart J. 2006;27:476–81.

8. Jimenez D, Aujesky D, Moores L, Gomez V, Lobo JL, Uresandi F, et al. Simplificationof the pulmonary embolism severity index for prognostictionin patients with acute symptomatic pulmonary embolism. Arch InternMed. 2010;170:1383–9.

9. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, GaliéN, et al. 2014 ESC Guidelines on the diagnosis and management of acutepulmonary embolism: The Task Force for the Diagnosis and Managementof Acute Pulmonary Embolism of the European Society of Cardiology(ESC) Endorsed by the European Respiratory Society (ERS). Eur Heart J.2014;35:3033–6946.

10. Stein PD, Beemath A, Matta F, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. Am J Med. 2007;120:871–879.

11. Daniel KR, Courtney DM, Kline JA. Assessment of cardiac stress from massive pulmonaryembolism with 12-lead ECG. Chest. 2001;120:474–481.

12. Rathbun SW, Whitsett TL, Vesely SK, Raskob GE. Clinical utility of D-dimer in patients with suspected pulmonary embolism and nondiagnostic lung scans or negative CT findings. Chest.2004;125:851–855.

13. Crichlow A, Cuker A, Mill AM. Overuse of computed tomography pulmonary angiography in the evaluation of patients with suspected pulmonary embolism in the emergency department. AcadEmerg Med. 2012;19:1220–1226.14.Revel MP, Cohen S, Sanchez O, et al. Pulmonary embolism during pregnancy: diagnosis with lung scintigraphy or CT angiography. Radiology. 2011;258:590–598.

15. Vieillard-Baron A, Qanadli SD, Antakly Y, Fourme T, Loubières Y, Jardin F, et al. Transesophageal echocardiography for the diagnosis of pulmonaryembolism with acute cor pulmonale: a comparison with radiologicalprocedures. Intensive Care Med. 1998;24:429–33.

16. Pomero F, Brignone C, Serraino C, et al. Venous lowerlimb evaluation in patients with acutepulmonary embolism. South Med J. 2011;104:405–411.

17. Geerts WH, Bergqvist D, PineoGF, et al: Prevention of venous thromboembolism: American College of Chest Physicians Evidence Based Clinical Practice Guidelines (8th ed). Chest 133(6Suppl):381S–453S, 2008.

18. Proctor MC, Greenfield LJ, Wakefield TW, Zajkowski PJ: A clinical comparison of pneumatic compression devices: The basis forselection. J VascSurg 34:459–463 2001 [discussion appears 463–454].

19. Turpie AG, Bauer KA, Eriksson BI, Lassen MR: Postoperative fondaparinux versus postoperative enoxaparin for prevention ofvenous thromboembolism after elective hip-replacement surgery:A randomised double-blind trial. Lancet 359:1721–1726, 2002.

20. Girard TD, Philbrick JT, Fritz Angle J, Becker DM: Prophylacticvena cava filters for trauma patients: A systematic review of theliterature. Thromb Res 112:261–267, 2003.

21. Angle MR, Molloy DW, Penner B, Jones D, Prewitt RM. The cardiopulmonary and renal hemodynamic effects of norepinephrine in caninepulmonary embolism. Chest. 1989;95:1333–7.

22. Szold O, Khoury W, Biderman P, Klausner JM, Halpern P, Weinbroum AA. Inhaled nitric oxide improves pulmonary functions following massive pulmonary embolism: a report of four patients and review of the literature.Lung. 2006;184:1–5.

23. Swol J, Buchwald D, Strauch J, SchildhauerTA. Extracorporeal life support (ECLS) for cardiopulmonary resuscitation (CPR) with pulmonary embolismin surgical patients—a case series. Perfusion. 2016;31:54–9.

24. Raschke RA, Reilly BM, Guidry JR, et al: The weight-based heparindosing nomogram compared with a "standard care" nomogram.A randomized controlled trial. Ann Intern Med 119:874–881,1993.

25. Bates SM, Weitz JI, Johnston M, et al: Use of a fixed activatedpartial thromboplastin time ratio to establish a therapeutic rangefor unfractionated heparin. Arch Intern Med 161:385–391, 2001.

26. Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venousthromboembolism. JAMA. 2006;296(8):935–942.

27. Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev.2010;9:CD001100.

28. The Matisse Investigators. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. N Engl J Med. 2003;349:1695–702.

29. EINSTEIN-PE investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287–1297.

30. Linkins L-A, Dans AL, Moores LK, et al. Treatment and prevention of heparin-inducedthrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: AmericanCollege of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest.2012;141:e495S–e530S.

31. vanEs N, Coppens M, Schulman S, Middeldorp S, Buller HR. Direct oral anticoagulants compared with vitamin K antagonists for acutevenous thromboembolism: evidence from phase 3 trials. Blood. 2014; 124:1968–75.

32. Marti C, John G, Konstantinides S, Combescure C, Sanchez O, Lankeit M, et al. Systemic thrombolytic therapy for acute pulmonary embolism: asystematic review and meta-analysis. Eur Heart J. 2014;36:605–14.

33. Meyer GVE, Danays T, Agnelli G, Becattini C, Beyer-WestendorfJ, Bluhmki E, for the PEITHO Investigators, et al. Fibrinolysis forpatients with intermediate-risk pulmonary embolism. N Engl J Med. 2014; 370:1402–11.

34. Kucher N, Boekstegers P, Muller OJ, Kupatt C, Beyer-Westendorf J, HeitzerT, et al. Randomized, controlled trial of ultrasound-assisted catheter directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation. 2014;129:479–86.

35. R. Sebik, B. Cortese, D. Buccheri, P. Silva-Orrego, A. Rubboli, Effective treatment of intermediate-risk pulmonary embolism by manual thrombus aspiration. A report oftwo cases, Heart Lung Circ. 24 (2015) 130–132.

36. Sarosiek S, Crowther M, Sloan JM. Indications, complications, and management of inferior venacava filters: the experience in 952 patients at anacademic hospital with a level I trauma centre.JAMA Intern Med 2013;173(7):513–7.

37. Pepke-Zaba J, Delcroix M, Lang I, et al. Chronic thromboembolic pulmonary hypertension (CTEPH):results from an international prospective registry.Circulation 2011;124(18):1973–81.

## Original Article

# Relapse of Tuberculosis among TB Patients on RNTCP Treatment - A Comparison of HIV Co-Infected Vs HIV Non-Infected

**Dinesa Prabhu V.[1], Ajith Kumar K.[2], Sanjeev Nair[3], Sunil Kumar M.[4], Shibu Balakrishnan[5], Jayasankar S.[4]**

1) Department of Pulmonary Medicine, Medical College, Kottayam,
2) Kerala University of Health Sciences, Thrissur
3) Department of Pulmonary Medicine, Medical College, Trivandrum
4) State TB Cell, Directorate of Health Services, Kerala
5) World Health Organisation, New Delhi

***Corresponding Author :*** Dr. Sanjeev Nair

*Complete address for correspondence*

***Official Address :*** Dr. Sanjeev Nair, Department of Pulmonary Medicine, Medical College, Trivandrum.
***Personal Address :*** Dr. Sanjeev Nair, Sreebhavan, TC 14 / 1030, Voltas Lane, Vazhuthacaud, Trivandrum - 695014.
Phone : +91 9446327204, 91 471 2327204, Email : drsanjeevnair@gmail.com

## Abstract

HIV co-infection is the strongest risk factor for progression of Tuberculosis (TB) infection to disease. It is generally believed that the relapse of TB in patients cured of previous TB disease is higher in TB-HIV co-infected subjects; however there is scarce data regarding relapse in TB patients treated under the Revised National Tuberculosis Control program (RNTCP).

**Objective :** To determine the proportion of relapse in Human Immunodeficiency Virus (HIV) co-infected TB patients as compared to HIV negative TB patients who received RNTCP treatment for TB.

**Methods :** A retrospective study was done among patients attending the Anti-retroviral therapy (ART) center in Thrissur Medical College and those patients under Revised National Tuberculosis (TB) Control program (RNTCP) from Thrissur district. HIV patients diagnosed with TB during a period of 6 years were compared with age-sex matched TB cases without HIV co-infection and both groups of patients were evaluated at the study period for relapse of TB or other adverse outcomes including death.

**Results :** 236 HIV co-infected TB patients and 151 HIV negative TB patients were included in the study. Among the HIV positive TB patients the proportion of patients who relapsed was 7.6% as compared to 4.6% relapse among the non-HIV TB patients and the difference was not statistically significant (p=0.243). (Relative risk of 1.65, 95% confidence intervals of 0.69, 4.17).

**Conclusion :** The proportion of relapse in HIV-infected TB patients is only 7.6% and not significantly different from that in HIV-negative TB patients.

**Key Words :** Tuberculosis, HIV, RNTCP, Relapse, Kerala

## Introduction

Tuberculosis (TB) is an ancient killer disease of mankind, which still remains a leading cause of suffering and death. In 2013, there were an estimated 9 million new TB cases in the world and 1.5 million TB deaths.[1]The TB scenario is further worsened by the global HIV epidemic. An estimated 1.1 million (13% of incident cases) TB cases worldwide are co-infected with HIV and an estimated 360,000 HIV-TB co-infected persons died in 2012.[1] HIV co-infected TB patients are known to have a worse treatment outcome for TB as compared to TB patients who are not co-infected. There are higher rates of relapse, failure and death due to TB reported in TB-HIV co-infected subjects.[2]HIV-Co-infection remains one of the major challenges in global TB control efforts.

India is the highest TB burden country in the world, with an estimated fifth of the global TB incidence. In 2013, an estimated 2.1 million new TB cases occurred in India, as per WHO reports, including 140,000 TB cases co-infected with HIV (5.7%).[1] In 2013, in India, a total of 14, 16,014 TB cases were initiated on treatment. [3]Case detection rate of New Smear Positive TB cases was 63% with a treatment success rate of 88%. HIV status of TB was known for 63% of patients and 5% were found to be HIV positive. About 91% HIV infected TB patients were initiated on Co-trimoxazole Preventive Therapy (CPT) and 84% were initiated on Anti-Retroviral Therapy (ART).[3] Mortality among TB patients co-infected with HIV, who are offered RNTCP treatment, remains high. There may be several reasons for the high mortality among HIV-infected TB patients: these include undiagnosed or late diagnosis of HIV, delayed or missed TB diagnosis among person living with HIV/AIDS (PLHIV), provision of inadequate chemotherapy to drug-resistant TB cases in the context of unavailability of decentralized culture and DST facilities, late presentation by HIV/TB patients (indicated by low CD4 counts at the time of diagnosis), and operational issues like long distances to travel for patients and lack of finances resulting in suboptimal linkages to centralized ART services.[3]

WHO TB treatment guidelines recommend daily anti-TB regimes for HIV co-infected TB patients.[4] However as per current National policy and RNTCP guidelines patients with HIV-co-infected TB are offered the same treatment as other TB patients, which is a standardized thrice weekly, supervised treatment with four drugs in the intensive phase and two drugs in the continuation phase.[5] Current RNTCP guidelines recommend the testing of all TB patients for HIV and provision of ART to all HIV infected TB patients. Current national guidelines also recommend that all HIV- TB patients have to be tested for drug susceptibility testing to Rifampicin and / or INH.

The state of Kerala in the south of India has a population of 34.6 million. The state treated 24204 tuberculosis patients under the RNCTP in 2013, including all types of tuberculosis.[3] The state has a lower prevalence of HIV as compared to the national average as of 2007 (0.26% in Kerala and 0.34% in India).[6] Care for TB is provided through district TB centers and Tuberculosis units (TUs, which are sub-district level units catering to 500,000 population, there are 72 such TUs in Kerala). Care and support for PLHIV including anti-retroviral therapy (ART), are provided through seven ART centers in the state, one of which is located at the Government. Medical College, Thrissur. As on 31st March, 2011, 9923 PLHIV were initiated on ART in Kerala under the AIDS control program.[7] All patients receiving HIV care, including ART, are screened for TB and if diagnosed as TB, are treated with RNTCP regimens, i.e. standardized intermittent, supervised treatment for TB.

In view of significant differences between existing international guidelines and the current treatment offered to TB patients under the National TB Control program, there have been concerns raised about the possibility of high relapses and other adverse outcomes among TB patients with HIV co-infection. However, there have been no studies looking at the relapse rates among TB patients or TB HIV co-infected persons, among the patients routinely treated in the RNTCP Units and the ART centers. This study was designed to determine whether the TB relapse, for HIV co-infected patients are different from that of the TB patients who are not HIV infected.

## Methods

A retrospective cohort study was designed to compare the proportion or relapses of TB among cured HIV-TB patients as compared to relapse in TB patients not co-infected with HIV. The study group included patients who were ever treated for TB among those registered for HIV care, including ART, at the ART center at the Medical College, Thrissur. The comparator group included age-sex

matched TB patients, who took treatment from RNTCP during the same period

Based on an expected relapse of TB for HIV-Infected TB cases of 15% as opposed to an expected relapse of 5% in non-HIV TB patients, the sample size was calculated as 161 in each group (with confidence level of 95% and power of 80%) using the formula.

$$n = \frac{\left[Z_\alpha \sqrt{(1+1/m)\bar{p}(1-\bar{p})} + Z_\beta \sqrt{p_0(1-p_0)/m + p_1(1-p_1)}\right]^2}{(p_0 - p_1)^2}$$

All patients registered at the ART Centre, with a history of treatment for tuberculosis any time in the past, were included as study subjects for the exposure group, taking HIV infection as exposure. They were evaluated from the period of past treatment for tuberculosis to the current period, both from the records as well as by direct interview. TB patients who took treatment during the same period as the study subjects in the tuberculosis units under District TB center, Thrissur were included as the comparison group. For patients belonging to Thrissur district, the patients in the comparison group were also selected from the TB registers of the same tuberculosis units (TU). TB patients, registered at the same time (± one week), of the same sex and age (± 5 years) were taken from the Tuberculosis register of the same TU. For patients under care at the ART center at Thrissur, but belonging to other districts, an age-sex matched control was selected at random from one of the TUs of Thrissur district itself. All the patients were interviewed by the field research assistant using a structured questionnaire. Patients who had cough more than two weeks were tested by sputum direct smear for Acid Fast Bacilli (AFB) as per RNTCP guidelines, if the patient had not already approached a health care provider and done the sputum examination. The process of evaluation of all symptomatic patients for TB was facilitated by the field investigator.

Data entry was done on MS Excel and data analysis done on EPI-Info 3.5.3 and student t-test / Kruskal-Wallis test, as appropriate, were done to compare numerical variables and Chi-square to determine difference in discrete variables. Relative risk was calculated for relapse in HIV infected TB patients as opposed to relapse in TB patients who are not HIV infected. A case-control analysis was done including both groups of patients to determine the factors associated with relapse in all the patients taken together.

Institutional Ethics Committee clearance was obtained for the study. Written informed consent was obtained from patients. Study was funded by the RNTCP Operational research mechanism and administrative clearance was granted from the RNTCP for the study. Strict confidentiality was maintained for all patients included in the study. Patients were linked to treatment and care if they were diagnosed to have TB or any other opportunistic infection.

## Results

There were 387 patients included in the study, of which 236 (61%) were HIV positive TB patients and 151 (39%) were HIV negative TB patients. The mean age of patients included in the study was 38.7 yrs (with a standard deviation of 10.1 yrs). 277 of the patients were males (75.9%) and 88 (23.1%) were females. 130 (55%) of HIV patients were on ART. Patients were followed up for a mean period of 3.16 yrs (standard deviation of 2.21 yrs). Maximum period a patient has (retrospective) follow-up, since the period of first treatment of TB was 10 years. The basic socio-demographic characteristics of the study population are described in Table 1.

**Table 1 : Socio-Demographic and Clinical Characteristics of the Study Population**

| Variable | Mean / proportion | Standard deviation / 95% CI |
|---|---|---|
| Age (yrs) | 38.6 | ±10.1 |
| Sex (Males) | 75.90% | (71.2%, 80.2%) |
| Socioeconomic status (BPL) | 59% | (53.8%, 64.3%) |
| Diabetes | 13% | (9.8%, 17%) |
| Smokers | 32.50% | (30%, 40.6%) |
| Alcoholics | 33.10% | (28.1%, 38.6%) |
| Side effects to drugs | 20.40% | (16.2%, 25.3%) |

*Values expressed in means ± standard deviation or as proportions % (95 % confidence limits)*

The basic demographic factors were compared between HIV positive TB patients and HIV negative TB patients (Table 2). There was statistically significant difference between HIV and non-HIV TB patients in age (the exposure and comparator groups were age matched to a level of +/- 5 years, however there is a difference in 2 yrs in median age between the groups which is statistically significant).

**Table 2.Differences between HIV-Positive TB patients and HIV-negative TB patients in Socio-Demographic Factors and Factors Associated with Treatment Outcome of TB Treatment**

| Variable | HIV Positive (Median (IQR) / proportion) | HIV Negative (Median (IQR) / proportion) | Significance of difference between groups (p value) (Kruskal-Wallis test / Chi-square) |
|---|---|---|---|
| Age (yrs) | 38 (32.5 – 43.5) | 40 (31 – 49) | 0.027 |
| Sex (Males) | 78.8% | 70.5% | 0.139 |
| Socioeconomic status (BPL) | 57.3% | 62.6% | 0.336 |

Among the HIV positive TB patients the proportion of patients who relapsed was 7.3% and among the non-HIV TB patients it was 4.6%, the difference being not statistically significant (p=0.28). (Relative risk of 1.59, 95% confidence intervals of 0.67, 3.74). (Table 3)

**Table 3. Proportion of relapse in HIV positive and HIV negative TB patients**

| | Relapsed | | Did not relapse | | Total |
|---|---|---|---|---|---|
| | Number | % | Number | % | |
| HIV Positive | 17 | 7.30% | 217 | 92.70% | 234 |
| HIV Negative | 7 | 4.60% | 146 | 95.40% | 153 |

***Relative risk – 1.59 (95% CI – 0.67, 3.74); p value – 0.28***

The factors affecting TB relapse, as observed in other studies, like diabetes, smoking, provision of DOT, etc were compared between HIV positive TB patients and HIV negative TB patients (Table 4).There was statistically significant difference between HIV and non-HIV TB patients in proportion of diabetic, smokers and alcoholics, convenience of treatment and in the satisfaction with the confidentiality of treatment.

**Table 4 : Difference in known risk factors of Relapse between the HIV positive and HIV negative groups of the Study Population**

| | HIV Positive | HIV Negative | Significance of difference between groups (p value) |
|---|---|---|---|
| Diabetes | 6.5% | 23.7% | <0.001 |
| Smokers | 25.2% | 63.4% | <0.001 |
| Alcoholics | 21.8% | 62.6% | <0.001 |
| Occurrence side effects | 23.9% | 13.2% | 0.026 |
| Concern about loss of confidentiality of treatment | 27.8% | 5.6% | <0.001 |
| IP as DOT | 97.7% | 98.4% | 0.629 |
| CP as DOT | 91.5% | 92% | 0.177 |
| DOT time convenient | 99.1% | 97.1% | 0.186 |
| DOT place convenient | 98.2% | 87.6% | <0.001 |
| Acceptance of further decentralization of DOT to neighbor | 16.3% | 15% | 0.754 |

Factors like age, sex, smoking, alcohol and diabetes were not significantly associated with relapse when relapse of TB in all cases (HIV Positive and negative, put together) were analysed by a case control analysis. (Table 4)

**Table 5**

**Factors associated with relapse in TB patients**

| | Patients who had relapse | | Patients who didn't have relapse | | p Value |
|---|---|---|---|---|---|
| | n = 24 | | n = 363 | | |
| Age | 40.33 | ± 11.23 | 38.56 | ± 9.9 | 0.4 |
| Male sex | 21 | 87.50% | 275 | 75.80% | 0.19 |
| Diabetes | 1 | 4.30% | 47 | 13.60% | 0.2 |
| Smoking | 10 | 41.70% | 127 | 39.40% | 0.83 |
| Alcohol use | 8 | 38.10% | 115 | 35.80% | 0.83 |

*"Values expressed in means ± standard deviation or as proportions %"*

## Discussion

This study compared the relapse of TB among HIV positive and HIV negative TB patients. The relapse rates in both groups were low (overall 6.2%) and even though the proportion of relapse in HIV-TB patients was higher than that in HIV negative TB patients, the difference was not statistically significant. The relapse rates reported in this study are much lower than what is reported in literature. A pooled relapse rate in a meta-analysis on relapses in TB in HIV-TB co-infected patients was 12%.[2]

This study determined relapse by sputum direct smear examination only and not by culture. Also the patients were under care for HIV and those with a low CD4 count were treated with ART, 55% of the HIV-TB patients were also on ART, which might have reduced the relapse rates in HIV patients.

The study also highlights the fact that DOT can be done properly in patients with HIV co-infection. A very high proportion of TB-HIV patients got treatment under supervision in the periphery and found the DOT convenient in terms of place and timing. Very small proportion of these patients was interested in an alternate DOT provider in their neighborhood. However a significantly higher proportion of TB-HIV patients reported a loss of confidentiality as compared to HIV negative TB patients, so arranging DOT for TB patients with protection of confidentiality remains a challenge. Also, as expected a significantly higher proportion of TB-HIV patients had side effects to drugs as compared to HIV negative TB patients.

While higher relapse rates are expected in TB-HIV patients, particularly due to re-infection and reactivation, this study doesn't show significantly higher rates of relapse. The probable reasons for this could be a high proportion of HIV patients getting ART and the fact that other risk factors associated with relapse, particularly diabetes, smoking and alcoholism are significantly lower in this cohort of HIV-TB patients as compared to the controls, i.e. the HIV negative TB patients. This highlights the success of the counseling at the ART centre which has resulted in reduced proportion of smoking and alcohol intake among the patients registered at the ART center. Also the fact that the patients find the DOT convenient and took treatment under strict supervision might have resulted in higher relapse free cure. It is known that one of the major factors associated with higher relapse is that the patient is taking treatment without supervision.[8]

In the background of current international guidelines suggesting that all HIV-TB patients should be treated with daily regime anti-TB treatment, this study highlights the fact that with good HIV care, counseling and high proportion of patients receiving ART, intermittent regimes also work well in HIV-TB patients under programmatic conditions. However, this study also highlights the fact that a high proportion of TB patients continue to smoke and consume alcohol, which may affect their treatment outcomes. The TB control program needs to address this issue for better treatment outcomes. The fact that proper counseling at the ART centre has reduced the proportion of smoking and alcohol intake among the HIV patients highlights the fact that this can be achieved under programmatic conditions. Also shown in the study is the high proportion of diabetes in TB patients in Kerala, which has been already reported elsewhere.[9, 10]

The RNTCP needs to do further studies , to determine the relapse rates among patients with HIV-TB Co-infection so as to determine the efficacy of the programmatic regime for HIV-TB under field conditions and also ensure that all HIV-TB patients receive early ART for better treatment outcomes.

The strength of this study is that a large retrospective cohort of HIV co-infected TB patients has been evaluated and compared to non-HIV TB patients. A high rate of follow-up has been ensured at the ART centre. Other co-morbidities which could modify the treatment outcome have also been studied.

The major limitations in this study are that it is a retrospective study and as such can result in recall bias and inaccuracy in past data. The study protocol required 161 controls to be included but due to inability to track patients at field level the number of controls was limited to 151, however the number of HIV-TB cases was much higher than the required number of 161. Also the study diagnoses relapse by sputum direct smear examination, as defined in the RNTCP definitions. Evaluation of symptomatic patients by culture might have resulted in higher relapse rates in both groups. The cases with relapse have not been evaluated by culture and drug susceptibility testing to determine what proportion of relapsed TB patients develop drug resistance which is one of the areas

of concern. In view of the retrospective nature of the study, mortality might not be captured completely.

## Conclusions

Under routine programmatic conditions, thrice weekly intermittent standardized regimes offer high proportion of relapse free cure rates. There is no significant difference in relapse rates between HIV positive TB patients as compared to HIV- negative TB patients. Overall relapse rates in this study are lower than those reported elsewhere.

## Acknowledgements

The authors sincerely acknowledge the help and support provided by the District TB Officers of Thrissur district, and the RNTCP field staff of Thrissur district. We also acknowledge the financial, administrative and technical support and encouragement provided for the study by the RNTCP Medical College Task force OR committee and the State TB cell.

## Reference

1. Global TB Report 2014, WHO Publication.

2. Faiz A. Khan, Jessica Minion, MadhukarPai, Sarah Royce, William Burman,Anthony D. Harries,et al. Treatment of Active Tuberculosis in HIV-Coinfected Patients: A Systematic Review and Meta-Analysis; Clin Infect Dis. (2010) 50 (9):1288-1299.

3. TB India 2014. RNTCP Status report. Central TB Division Publication

4. Treatment of tuberculosis: guidelines – 4th edition. WHO/HTM/TB/2009.420. Accessed from http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf

5. Technical and operational guidelines for TB Control. October 2005. Central TB Division, Government of India publication. http://tbcindia.nic.in

6. Accessed from the Kerala State AIDS Control Society website on 16/09/2013 http://www.ksacs.in/hivprevalence.php

7. ART center and ART data accessed from the Kerala State AIDS Control Society website on 16/09/2013. http://www.ksacs.in/ushus-art-ksacs.php

8. Balasubramanian, V. N.; Oommen, K.; Samuel, R.DOT or not? Direct observation of anti-tuberculosis treatment and patient outcomes, Kerala State, India.The International Journal of Tuberculosis and Lung Disease, Volume 4, Number 5, May 2000 , pp. 409-413(5)

9. Balakrishnan S, Vijayan S, Nair S, Jayasankar Subramoniapillai, Sunilkumar Mrithyunjayan, Nevin Wilson, et al. High diabetes prevalence among tuberculosis cases in Kerala, India. PLoS ONE 2012;7, e46502

10. Nair, S., Kumari, A. K., Subramonianpillai, J., Shabna, D. S., Kumar, et al (2013). High prevalence of undiagnosed diabetes among tuberculosis patients in peripheral health facilities in Kerala. Public Health Action, 3(Suppl 1), S38–S42. http://doi.org/10.5588/pha.13.0037

# Radiology Pearl

**Rajesh V.*, Jolsana Augustine***
* Consultant Pulmonologist, Rajagiri hospital, Ernakulam

A 58 year old gentleman with history of intermittent wheezing for last 2 years presented with acute onset of fever, expectoration and shortness of breath for 3 days. He was febrile and tachypneic at presentation. Chest radiograph and representative CT images are shown.

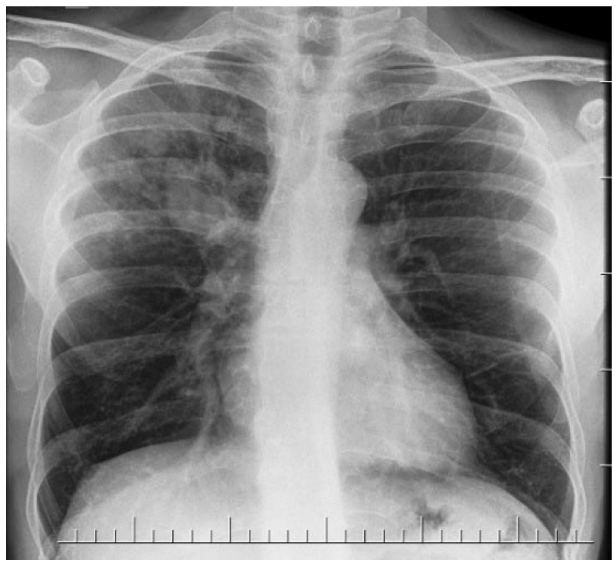


*Fig 1 : Chest radiograph PA view at presentation showing upper zone nodular ovoid lesion with surrounding infiltrates*

## Answer

Allergic bronchopulmonary aspergillosis with right upper lobe mucoid impaction.

## Discussion

Mucoid impaction is defined as filling of the airway by mucoid secretions. The affected airway is often, but not invariably, dilated resulting in bronchiectasis. Common causes of mucoid impaction include congenital segmental bronchial atresia, allergic bronchopulmonary aspergillosis (in asthmatic or cystic fibrosis subject), bronchiectasis of any aetiology, cystic fibrosis, aspirated foreign body, neoplasms (both benign and malignant) etc. The classical radiological sign is tubular or branching opacities that resemble fingers – the so called finger-in-glove sign. Atypical appearances do occur such as ovoid and mass like opacities[1]. The clue to aetiology in CT chest comes from the fact that there is usually a clear connection bronchus (which is often dilated), the opacity has a branching nature and is filled with low attenuation mucus.

Although the airway mucus plugging in allergic bronchopulmonary aspergillosis (ABPA) is usually hypodense, a minority of subjects can have high attenuation mucus (HAM) defined as a mucus plug density visually higher than the normal paraspinal skeletal muscle[2]. The presence of HAM in CT chest image is virtually pathognomonic of ABPA in the appropriate clinical setting.

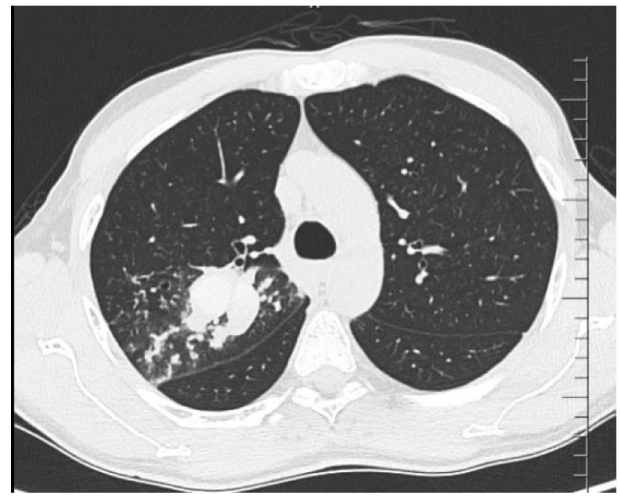


*Fig. 2 CT thorax representative cut – high resolution lung window at presentation showing adjacent infiltrates and bronchiectasis*

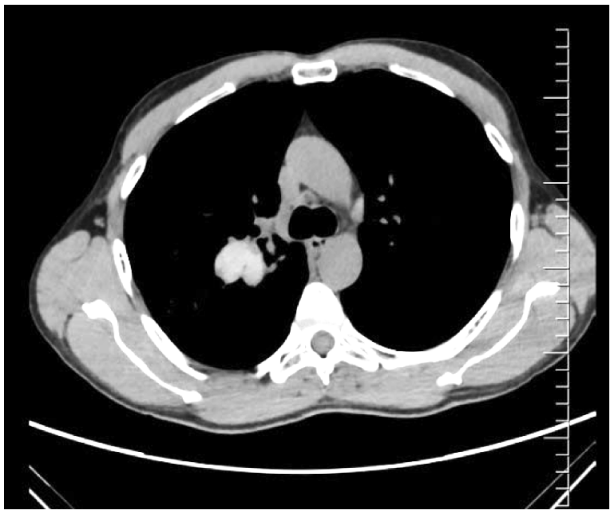


*Fig 3 : CT thorax representative cut – mediastinal window at presentation showing hyperdense branching opacity with connection to underlying bronchus*

The diagnosis of ABPA can be made in cases of mucoid impaction based on the criteria laid down by ISHAM group[3]. Key features include the presence of asthma or cystic fibrosis, elevated serum IgE level > 1000 IU / ml, peripheral blood eosinophilia > 500 / $MM^3$ in steroid naïve subjects, consistent radiographic abnormalities, positive type 1 skin test against aspergillus and presence of precipitating antibodies. A handful of patients have been described where ABPA occurs in the absence of clinical asthma[4]. Our patient had asthma, elevated IgE levels and positive skin prick test for aspergillus fumigatus along with radiographic abnormalities consistent with ABPA. Bronchoscopy revealed this mucus plug in right upper lobe bronchus which was lavaged out. He responded remarkably to oral steroids and itraconazole with good clinical remission and radiological improvement in 4 weeks.

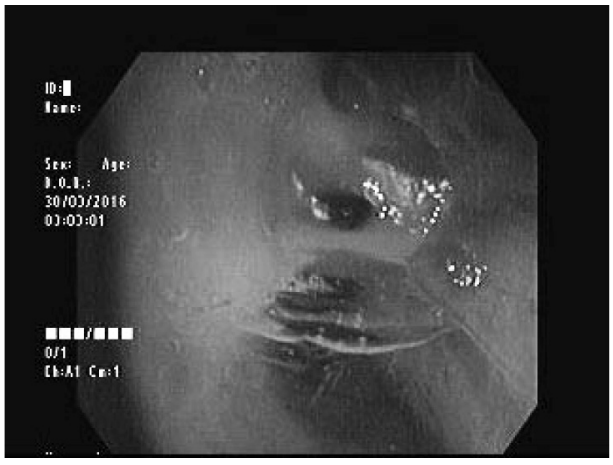



*Fig.4 Fibreoptic bronchoscopy image showing mucoid impaction in right upper lobe posterior segment orifice*

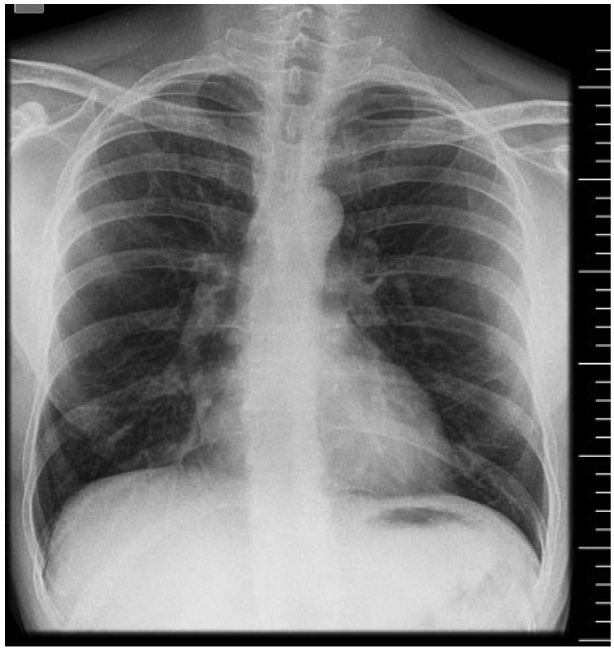


*Fig. 5 Chest radiograph PA view after 1 month of appropriate therapy showing resolution of lesion*

## References

1. Santiago M, Heyneman LE, McAdams P et al. Mucoid Impactions: Finger-in-Glove Sign and Other CT and Radiographic Features. RadioGraphics 2008; 28: 1369-82.

2. Agarwal R. High attenuation mucoid impaction in allergicbronchopulmonary aspergillosis. World J Radiol2010 January 28; 2(1): 41-43.

3. Agarwal R, Chakrabarti A, Shah A, et al. Allergic bronchopulmonary aspergillosis: review of literature and proposalof new diagnostic and classification criteria. ClinExp Allergy 2013; 43: 850–873.

4. Shah A, Maurya V, Panjabi C, et al. Allergic bronchopulmonary aspergillosis without clinical asthma caused byAspergillus niger. Allergy 2004; 59: 236–237.

## Case Report

# Lung Malignancy and Thrombocytopenia : A Rare Association

**Gayathri Mohan*, Shone James**, Safreena Mohamed***, Mohamed Musthafa***, Rajagopal TP******

*Junior Resident, **Senior Resident, ***Assistant Professor, ****Professor
Department of Pulmonary Medicine, Government Medical College, Kozhikode

***Key Words :*** Small cell lung cancer, Thrombocytopenia, Bone marrow metastasis

A fifty-year-old housewife presented with complaints of low grade fever of two months duration. She also complained of right-sided pleuritic chest pain, exertional breathlessness and two episodes of streaky hemoptysis. There was no history of any co morbidities. She was a smoker with a smoking score of 450. On physical examination, there was no pallor, lymphadenopathy or clubbing. Breast and thyroid examinations were normal. Respiratory system examination revealed a dull note in the right infrascapular, axillary and infra axillary areas with decreased breath sounds in the same areas. There was no tracheomediastinal shift. There was no hepatosplenomegaly, abdominal distension or focal neurological deficits.

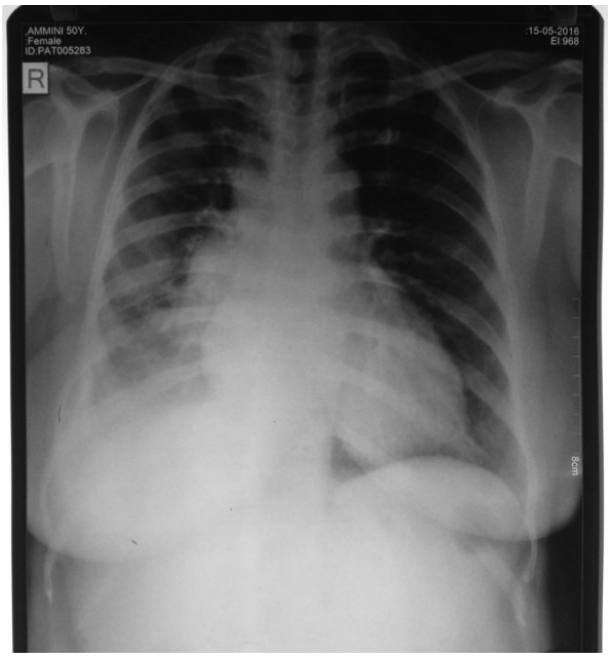



*Fig. 1: CXR PA view showing a right hilar mass with non-homogenous opacity in right mid and lower zones.*

Initial blood investigations showed a hemoglobin value of 10.5 g/dL, total leucocyte count of 5900 cells/$mm^3$and platelet count of 1.5 lakh/$mm^3$. Liver and renal function tests were within normal limits.

The Chest Xray of the patent showed a right hilar mass with non-homogenous opacity involving right mid and lower zones with blunting of the right costophrenic angle (Figure 1). CECT thorax (Figures 2 and 3) showed a right hilar mass with right-sided pleural effusion. There were areas of consolidation involving right lower lobe, possibly a post obstructive consolidation. Pleural fluid was exudative with low ADA. Transthoracic needle aspiration from was attempted from the lung lesion, which resulted in a small pneumothorax. Both transthoracic needle aspiration cytology and pleural fluid cytology were negative for malignant cells. Bronchoscopy showed extraluminal compression and irregular mucosa in right intermediate bronchus and lower lobe bronchus. Biopsy and bronchial imprint yielded benign bronchial epithelial cells only.

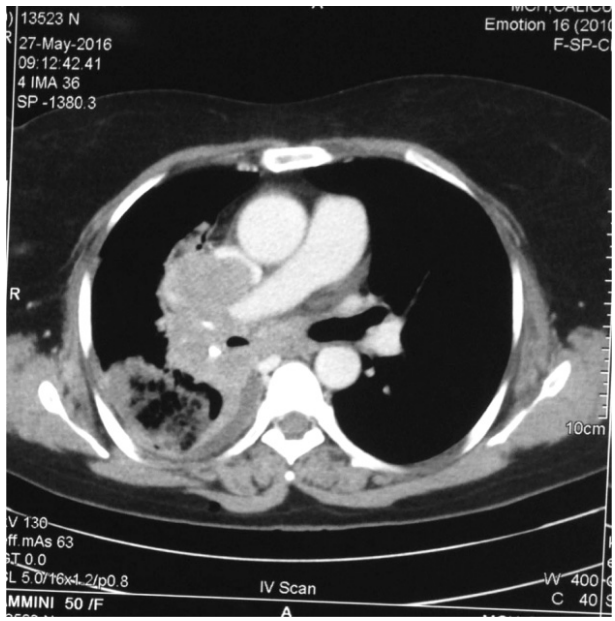



*Fig. 2: CECT Thorax Mediastinal window showing right hilar mass with consolidation and pleural effusion*

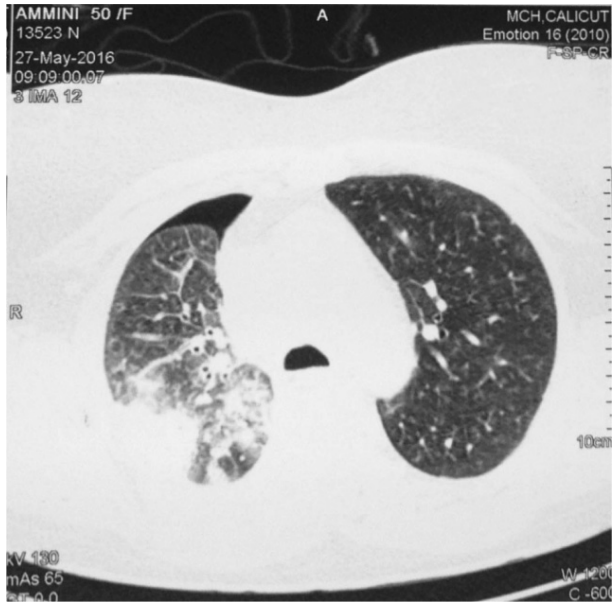



*Fig. 3: CECT Thorax lung window showing areas of consolidation in right lower lobe with a small right-sided pneumothorax*

Meanwhile, patient had persistent fever and generalized bone pain. A repeat blood count showed a fall in platelet count to 75000/mm$^3$ without a fall in other cell counts. She was supplemented with multiple platelet transfusions but there was a rapid decline in platelet counts to 7000/mm$^3$. The differential diagnosis considered for thrombocytopenia were sepsis, drug induced thrombocytopenia, paraneoplastic syndrome and bone marrow metastasis.

A bone marrow biopsy was done after platelet transfusion. The bone marrow imprint (Figure 4) and biopsy came as metastatic involvement of bone marrow with small cell carcinoma lung. At this late stage, she also developed anemia and neutropenia. Oncology consultation was done and she was started on single agent chemotherapy with Etoposide along with multiple blood transfusions. After initial improvement with treatment initiation, the patient succumbed to the illness.

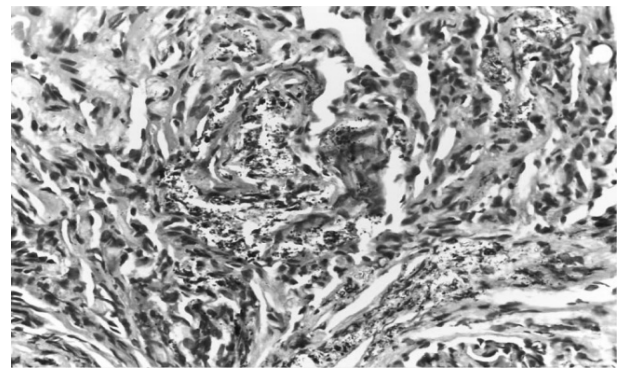


*Fig. 4: Bone marrow trephine biopsy showing small blue cells of SCLC*

## DISCUSSION

Small cell lung cancer (SCLC) is a neuro endocrine carcinoma that exhibits aggressive growth, rapid spread, exquisite sensitivity to chemotherapy and radiation. Small cell carcinoma lung accounts for approximately 15% of all lung cancers. This cell type has the strongest association with cigarette smoking and is rarely observed in a never smoker. It is the cell type most commonly associated with paraneoplastic syndromes such as Syndrome of Inappropriate Anti Diuretic Hormone Secretion (SIADH), Ectopic Adrenocorticotropic Hormone Secretion, Lambert Eaton Myasthenic Syndrome (LEMS) and Sensory Neuropathy[1].

SCLC usually presents as a centrally located mass in the hilum in chest radiograph and may be associated with obstructive pneumonia. SCLC is generally staged according to the Veterans Administration Lung Study Group Staging System, and classified as Limited Disease (LD) or Extensive Disease (ED). LD is confined to one hemithorax, the mediastinum, and the ipsilateral supraclavicular lymph nodes and the disease can be encompassed adequately in a safe radiation portal. ED is any disease spread beyond these limits. Malignant pleural effusion or disease extending to the contralateral supraclavicular or hilar lymph nodes is generally

considered to be ED[2].

After establishing histological diagnosis of SCLC, patients are usually staged with MRI of brain, CT Chest and bone scan or PET. In the unusual case when SCLC presents as a peripheral nodule, the treatment of choice is surgical resection followed by adjuvant chemotherapy and possibly sequential thoracic radiotherapy. Careful pre operative staging should be performed in these individuals to rule out metastatic disease. Pre resection mediastinoscopy should also be performed in all patients being considered for resection with curative intent. If there is a mediastinal node metastasis, surgery should be abandoned and patient treated with concurrent chemoradiotherapy.

The 5-year survival for peripheral SCLC that is treated with surgery and adjuvant therapy is approximately 40% to 50%. Approximately one third of patients have LD at diagnosis. Chemotherapy usually consists of platinum based regimen. The two most commonly used regimens are etoposide and cisplatin or etoposide and carboplatin. The National Comprehensive Cancer Network and the ACCP guidelines recommend treatment with four to six cycles of a platinum-based chemotherapy with either cisplatin or carboplatin plus either etoposide or irinotecan[3].

SCLC may be associated with many paraneoplastic manifestations, SIADH being the most common one. Thrombocytopenia can be caused by multiple causes. In the background of malignancy the most common causes are paraneoplastic manifestation and bone marrow metastasis. Other hematological paraneoplastic associations include anemia and thrombocytopenia in the form of Idiopathic Thrombocytopenic Purpura, Thrombotic Thrombocytopenic Purpura and Amegakaryocytic thrombocytopenia.

Incidence of bone marrow metastasis in small cell carcinoma lung is 30- 40%. Bone marrow metastasis signifies an extensive disease with possible brain metastasis and poorer prognosis. In literature, bone marrow infiltration in small cell lung cancer results in anemia and neutropenia with leucoerythroblastic blood picture. Isolated thrombocytopenia due to bone marrow metastasis in SCLC is unusual[4]. Interestingly, our patient had isolated thrombocytopenia initially due to bone marrow metastasis.

## REFERENCES

1. Tritz DB, Doll DC, Ringenberg QS, Anderson S, et al. Bone marrow involvement in small cell lung cancer-Clinical significance and correlation with routine laboratory variables. Cancer 1989; 63(4):763-6.

2. Jett JR, Schild SE, Kesler KA, Kalemkerian GP: Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013; 143:e400S–419S.

3. Shepherd FA, Crowley J, Van Houtte P, et al: The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol 2007; 2:1067–1077.

4. Madaliya R, Hughes L, Auerbach H, and LePar F. Small cell lung cancer presenting as severe thrombocytopenia and refractory hypokalemia. Case reports in Oncological medicine 2014. Article ID 874831. doi:10.1155/2014/874831

## Case Report

# Primary Pulmonary Amoebiasis

**Ajoy Samuel Mammen*, Binoy U.*, Ashique Ali*, Neethu Mohan**, Madhu K.***, Ravindran Nair****, Ravindran P.*******

*DNB Resident, **Junior Consultant, ***Senior Consultant,
****Head of the Department, *****Chairman, Pulmonology and Critical Care, Cosmopolitan Hospital, Trivandrum

**Abstract**

Presenting a case of primary pulmonary amoebiasis. Importance of radiological imaging, clinical history and diagnostic modalities are highlighted.

62 year old male, with a 50 pack year smoking history, chronic alcoholic, diabetic presented with one week history of fever, cough with expectoration , breathlessness and right side chest pain. There was no history of hemoptysis, weight loss or aspiration. On examination, temperature was 39.2°C, respiratory rate 26 per minute and there was no clubbing. Chest examination revealed stony dullness, tenderness on percussion and decreased breath sounds in the right infrascapular, infraaxillary and mammary areas. On abdominal examination, liver was not enlarged or tender. Rest of the examination was normal. Investigation revealed WBC count of 11,500/cmm (N 80% L 15%) and normal liver function tests. Chest Xray showed right lower zone non homogenous opacity with right sided moderate pleural effusion. CT abdomen was within normal limits ( liver - normal in size and echo texture). Sputum was negative for AFB, fungi and malignant cells. Sputum culture showed normal bacterial flora. Pleural fluid aspiration showed "anchovy sauce like" pleural fluid. Microscopic examination revealed Entamoeba Histolytica cysts and trophozoites. ELISA assay for anti-entamoeba antibodies was positive. Stool examination for E.Histolytica cyst was positive. He was given intravenous metronidazole, then oral metronidazole and had fully recovered. His underlying chronic immune deficient status(chronic alcoholism, diabetic status) are possible contributing factors to this rare presentation. Pleurisy secondary to amoebiasis is extremely rare, rarer still when present without liver involvement. In 1962, Chest journal had a case report [5] and a short letter to Editor communication on this disease in 1992 [6].

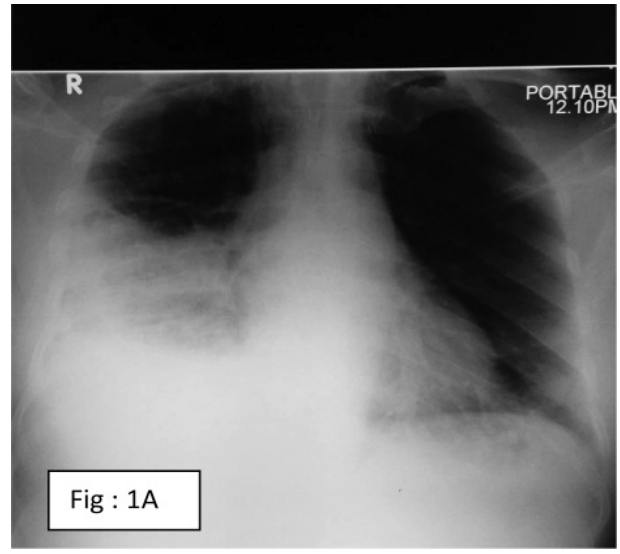



*Fig : 1A Chest Xray showing Right Lower Zone Non-homogenous opacity with moderate pleural effusion*

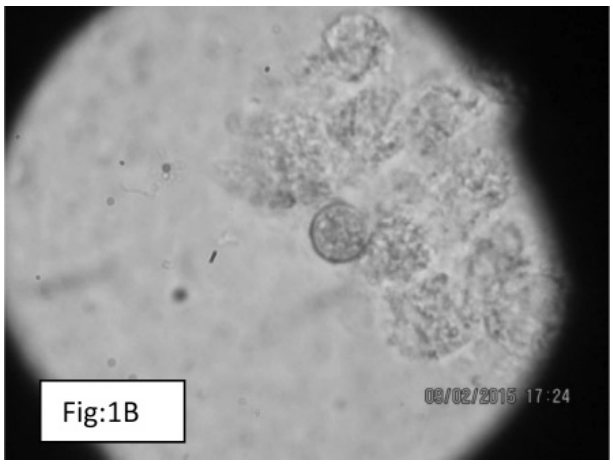



*Fig : 1B Microscopic examination of pleural fluid (simple saline mount and iodine mount) showing E.Histolytica trophozoites.*

## CT Abdomen

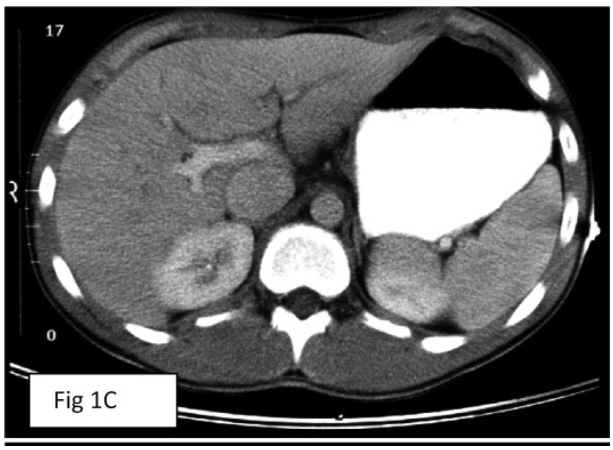



*Fig 1C : CT abdomen showing liver, normal in size and echo texture.*

## Discussion

The lung is involved often by the extension of liver abscesses (6–40% of patients with amoebic liver abscess).[3] The lower and middle lobes of the right lung are affected in the form of hepatobronchial fistula and empyema, with or without bilioptysis. It is generally confounded with bacterial pneumonia resulting in prolonged illness of the patient and eventually death.[7] The mortality rate in one case series of 501 patients was 11.4%.[8]

While colonic and hepatic amoebiasis occur commonly in tropical countries, primary pulmonary amoebiasis remains a rare condition ·It is estimated that amoebic lung disease without liver involvement occurs in 14.3% of all cases with lung involvement by amoeba, and there are sporadic case reports showing this type of appearance.[9]

In tropical countries pulmonary amoebiasis presents as basal pneumonia or abscess secondary to direct extension from liver. Various routes of spread, without involving the liver, have been suggested. The most accepted view is that the trophozoites enter through branches of middle and inferior haemorrhoidal or vertebral system of veins into the inferior vena cava and then reach the pulmonary circulation.

The presence of amoeba in the stool does not signify that the disease is due to E. histolytica as other two nonpathogenic species found in humans (E. dispar and E. moshkovskii) are indistinguishable morphologically which can be distinguished by a single-round polymerase chain reaction (PCR) assay . Other tests include culture of E. histolytica and serological tests [indirect hemagglutination test, enzyme-linked immunosorbent assay (ELISA) and indirect fluorescent antibody test]. A combination of serological tests with detection of the parasite by antigen detection or PCR is the best approach to diagnosis. Metronidazole is the treatment of choice.

We recommend that E histolytica should be included as a possible cause in the differential diagnosis of lung lesions in patients, especially in countries where amoebiasis is endemic.

## Acknowledgement

We thank Dr. Narendra S Patil, Consultant Microbiologist, DDRC SRL Diagnostics Pvt Ltd. for his prompt services and also the management of Cosmopolitan Hospital for giving us permission to publish this report.

## References

1. Shamsuzzaman SM, Hashiguchi Y. Thoracic amebiasis. Clin Chest Med 2002; 23: 479–92.

2. Anon. WHO/ PAHO/ UNESCO report of a consultation of experts on amebiasis. Weekly Epidemiological Report of the World Health Organization1997; 72:97–9.

3. Petri AW Jr, Singh U. Diagnosis and management of amebiasis. Clin Infect Dis1999; 29:1117–25.

4. Braga LL, Lima AA, Sears CL, et al. Seroepidemiology of Entamoeba histolytica in a slum in northeastern Brazil. Am J Trop Med Hyg1996;55:693–7.

5. Thiruvengengagam KV, Madanagopalan N, Solomon V and Anguli VC. Chest 1962; 42: 111-13.

6. First SR, Weinger MB. Pleropulmonary amebiasis. Chest 1991; 1: 293

7. Stanley SL Jr. Amoebiasis. Lancet2003;361:1025–34.

8. Ibarra-Perez C . Thoracic complications of amebic abscess of the liver.Chest1981;79:672

9. Afsar S, Choudhri AN, Ali J, et al. Primary pulmonary amoebiasis: an unusual cause of pulmonary consolidation. J Pak Med Assoc1992;42:245

10. Rachid H, Alaoui Yazidi A, Loudadssi F, El Biaze M, Bakhatar A, Yassine N, El Meziane A, Bahlaoui A (2005) Amoebic infections of the lung and pleura. Rev Mal Respir 22:1035-7.

11. WHO/PAHO/UNESCO report. (1997). A consultation with experts on amoebiasis: Mexico City, Mexico 28 - 29 January.Epidemiology Bulletin , 18 (1), 13–14.

12. Lichtenstein A, Kondo AT, Visvesvara GS, Fernandez A, Paiva EF, Mauad T, Dolhnikoff M, Martins MA. (2005). Pulmonary amoebiasis presenting as superior vena cava syndrome.Thorax, 60,350-2.

13. Sethi S, Sehgal R, Malla N, Dubey ML, Mahajan RC. (2000). Changing trends of intestinal parasitic infections in Chandigarh (Northern India): A hospital based study. Ind J Med Microbiol,18,106-19.

14. Singh U, Petri Jr WA (2001) Amebas. In: Gillespie SH, Pearson RD., editors. Principles and Practice of Clinical Parasitology. Chichester: John Wiley & Sons, Ltd. 197-212.

## Case Report

# Tracheobronchopathia Osteochondroplastica - A Rare Cause for Dyspnea

**Rakhi R.*, Jyothi E.**, Suraj K. P.*****
*Junior resident, **Associate Professor, ***Professor;
Dept. of Pulmonary Medicine, Govt. Medical College, Kozhikode.

## Introduction

Tracheobronchopathia osteochondroplastica (TO) is a rare, slow-growing, benign disorder involving the lumen of the tracheo-bronchial tree and characterized by multiple submucosal osseous and cartilaginous nodules in the trachea and bronchus, sparing the posterior wall. It was first described in1857 as ossific deposits in the larynx, trachea and bronchi by Wilks and colleagues in a 38 year old man with tuberculosis. Accumulation of calcium phosphate in the submucosa of the large airways, and benign proliferation of bone and cartilage lead to the narrowing of the airways .It is more frequent than it has been reported, as it can be asymptomatic or present with non-specific respiratory symptoms.

## Case Report

44 year old male, auto driver by profession presented with complaints of dyspnoea, cough and recurrent hemoptysis . There is history of recurrent respiratory infections since 15 years of age, cough with copious amount of expectoration, with multiple episodes of recurrent hemoptysis – minimal to moderate amount over last 4 years for which he was taking symptomatic treatment from peripheral hospital .He was neither a smoker nor has any other co morbidities.

On examination , vitals were stable and there was clubbing. Lower respiratory tract examination revealed bilateral coarse mid inspiratory crackles. Rest of system examination was within normal limits. With these findings he was clinically diagnosed to have bilateral Bronchiectasis

Routine hematological investigations were within normal limits. Chest radiograph - PA view showed bilateral cystic shadows in lower zone extending into midzone, presence of increased vascularity and acinar shadows. (Fig. 1)

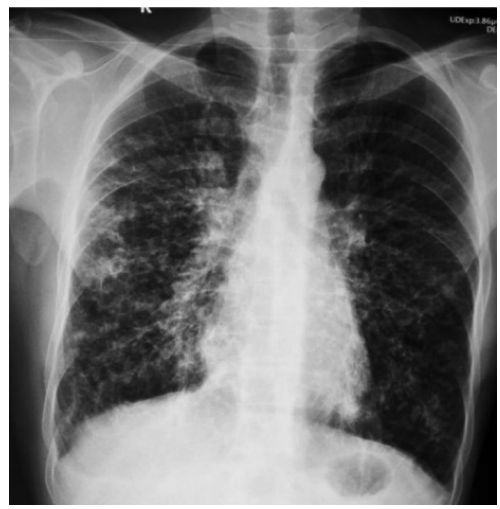


**Fig. 1 Chest radiograph - PA view showing bilateral cystic shadows lower zone extending into midzone and acinar shadow**

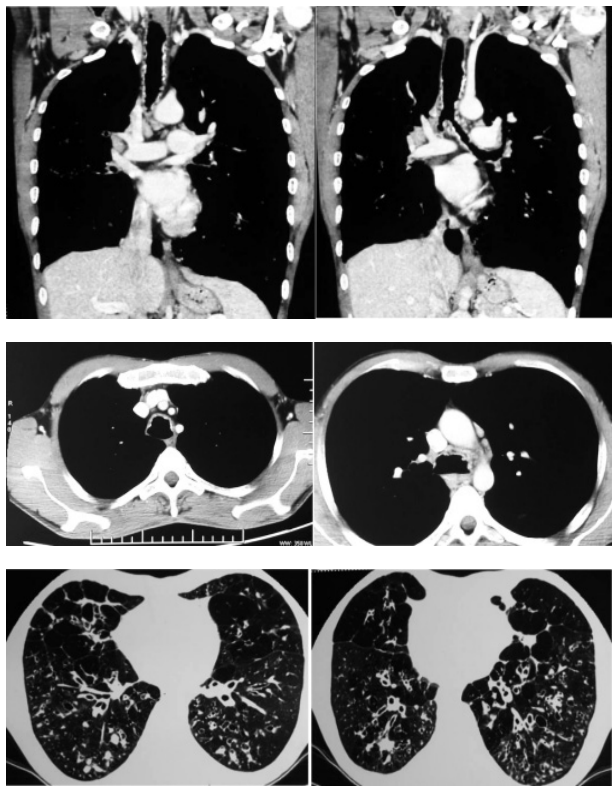


**Fig. 2 : C T Thorax representative cuts**

Ct torax (Fig. 2) revealed tracheal wall thickening and calcification involving anterior 2/3rd with sparing of posterior 1/3rd . Wall thickening with calcification was also seen in bilateral main bronchus . There was bronchiectatic changes bilateral lung fields, panacinar emphysema in bilateral lower lobes (alpha 1 antitrypsin - normal).

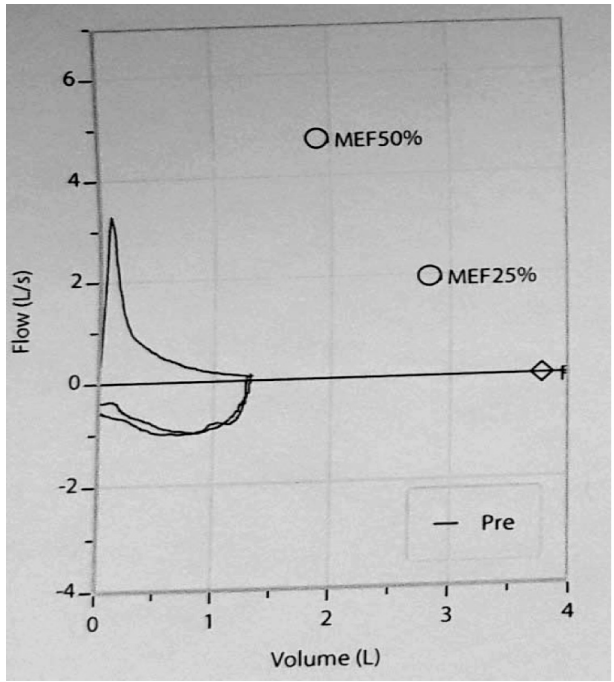



**Fig.3 : Spirometry showed severe obstruction - ( FEV1 - 23, FVC - 35 , FEV1/FVC - 54.2 )**

Fibre optic bronchoscopy revealed the presence of mucosal irregularities with multiple projections into the lumen spread throughout the trachea involving the anterior and lateral walls of the tracheo bronchial tree, sparing pars membranosa (Fig. 4). Plenty of secretions was present. Multiple biopsies were taken and these nodules were firm to hard in consistency when grasped with the biopsy forceps. Bronchial washings and BAL were obtained.

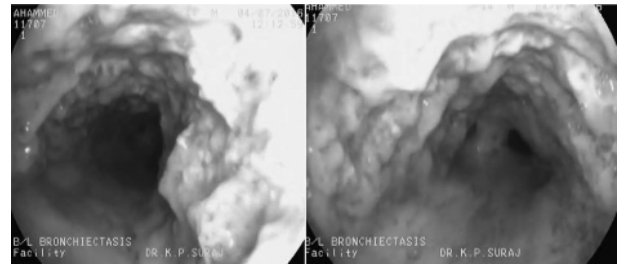



**Fig. 4 : Bronchoscopic picture**

Histopathological examination revealed cartilage and multiple fragments of bone consistent with tracheo bronchopathia osteochondroplastica. Bronchial washings yielded normal flora on routine cultures; fungal and tuberculous stains and cultures were negative. No malignant cells were identified

Hence final diagnosis of tracheobronchopathia osteochondroplastica with bilateral Bronchiectasis was made.

## Discussion

Tracheobronchopathia Osteochondroplastica is an idiopathic and benign disease of the large airways characterized by submucosal osteocartilagenous nodules, which project into tracheobronchial lumen. The nodules orginate in the airway cartilages and thus typically spare the posterior membraneous wall.

The prevalence of this disease, often asymptomatic or associated with nonspecific symptoms, is underestimated. An incidence of 0.01 to 4.2 per 100,000 has been estimated, with no difference in gender distribution. The mean age at diagnosis is 50 years.

The theories regarding the formation of these nodules include chronic airway inflammation, ecchondrosis and exostosis arising from the cartilaginous tracheal rings and metaplasia of submucosal elastic and connective tissue. The etiology remains unknown. In 1997 Tajima et al. hypothesized the possible involvement of a bone morphogenetic protein (Bone Morphogenetic Protein-

2, BMP-2) and of TGF-beta1(transforming growth factor-beta 1) in inducing the formation of submucosal osseous and cartilaginous nodules in the tracheobronchial system.

Most of the patients are asymptomatic, symptoms usually correlate with the site and degree of airway obstruction. Cough, sputum production, dyspnea, recurrent respiratory tract infections and hemoptysis due to an acute infection, bronchiectasis or ulceration of a nodule are common. Physical examination may be unremarkable. Stridor and rhonchi may be present if there is severe airway obstruction.

Chest X-ray is not useful for detecting the nodules and is usually normal. Computed tomography (CT) of the chest reveals the protrusion of calcified cartilaginous nodules through the lumen of trachea. Multiple sessile submucosal nodules with or without calcifications with sparing membranous posterior wall and deformed tracheal cartilage rings without external compression or submucosal calcification are the pathognomonic CT findings .

Pulmonary Function Test is affected by site of lesion and degree of obstruction. Normal spirometry can be present in mild cases while obstructive pattern or fixed upper airway obstruction may be observed in symptomatic patients with extensive disease. If the tracheal involvement is prominent,flow volume loops can be helpful in suspecting the condition and for the follow up.

Bronchoscopic visualization of the lesion is diagnostic. The characteristic bronchoscopic finding is described as beaded, spiculated, rockgarden, cobble stoned or stalactite grotto appearance. In 2004 Dutau et al. proposed a disease severity classification based on the extent of endoscopic lesions:

Stage A: Scattered Nodules (few nodules with large areas of normal mucosa in between)

Stage B: Diffuse Nodules (many nodules affecting the entire mucosa,without areas of normal mucosa)

Stage C: Lesions Confluent (fusion of adjacent lesions) - severe breathing impairment due to mechanical obstruction.

Epithelial squamous metaplasia, submucosal cartilage (continuous with or distinctive from the large airway cartilage rings), submucosal ossification (bone formation), calcification and hematopoietic bone marrow within the ossified areas are the histopathologic findings.

Differential diagnosis to be considered include tracheobronchial amylodosis, but it usually involves entire tracheal wall including posterior membranous wall. Posterior wall involvement of trachea increases the suspicion for polychondritis, Sarcoidosis and papillomatosis. Diffuse calcification of trachea can also be seen in elderly patients or patients with tuberculosis, chondrosarcoma, Wegener's granulomatosis and fibroma. Asthma is the most common misdiagnosis.

There is no specific treatment. Use of antibiotics in cases of respiratory infections, endoscopic and surgery treatment is reserved for cases of major bronchial obstruction and include the resection of tracheal segment, partial laryngectomy, LASER removal of nodules, rigid bronchoscope dilation, and stent placement (T-Y tube).Prognosis is favorable but usually depends upon the extension and location of the nodular lesions.

## References

1. Alessandro G. Fois, Antonella Arcadu, Luigi Santoru, Rocco Trisolini, Vincenzo Marras, Giorgio C.Ginesu, et al. Tracheobronchopathia Osteochondroplastica: Multidisciplinary Respiratory Medicine (2016) 11:16

2. Xiao-Bin Zhang, Hui-Qing Zeng, Xue-Ying Cai, Yong-Jun Zhang: Tracheobronchopathia osteochondroplastica: a case report and literature review J Thorac Dis 2013;5(5):E182-E184. doi: 10.3978/j.issn.2072-1439.2013.08.64

3. SevincSarincUlasli and ElifKupeli: Tracheo bronchopathia osteochondroplasticaa review of the literature. Clin Respir J 2014; DOI:10.1111/crj.12166.

4. M.S. Barthwal, R.S. Chatterji and A. Mehta: Tracheobronchopathiaosteochondroplastica[Indian J Chest Dis Allied Sci 2004; 46 : 43-46]

5. Shilin Luo, Longfei W, Jiang Zhou, Shicheng Xu, Qingsong Yang, Yao Li, et al. Tracheobronchopathiaosteochondroplastica: two cases and a review of the literature-Int J ClinExpPathol 2015;8(8):9681-9686www.ijcep.com

## Case Report

# Lung Aplasia Associated with Klippel - Feil Syndrome

**Shibini P.*, Davis P.**, Sajitha VM***, Harsha P.V.******
*Junior Resident, **Professor, *** Assiistant Professor,**** Senior Resident
Govt. Medical College, Thrissur

## Abstract

Twenty five year old lady presented with recurrent cough, wheezing and breathlessness since early childhood. She was previously diagnosed and treated as a case of pulmonary tuberculosis, later underwent surgery for suspected sequelae of tuberculosis. It was finally diagnosed as a case of left lung aplasia associated with Klippel -Feil syndrome and multiple congenital anomalies.

**Key words :** Congenital anomalies of lung, Agenesis, Aplasia, Klippel-Feil syndrome

## Introduction

Agenesis and aplasia of lung are rare congenital anomalies. It can be unilateral or bilateral, as bilateral absence is incompatible with life, in clinical presentation they are unilateral[1]. Pulmonary agenesis is the complete absence of lung and bronchus[2].Pulmonary aplasia, its most common variant will have bronchial stump with absent distal lung[1]. Functionally there is little difference between agenesis and aplasia. The prevalence of aplasia and agenesis is reported to be between 0.0034% to 0.0097%[3]. The first description of agenesis of lung was by De Pozze in 1673[4].Both agenesis and aplasia of lung can be associated with anomalies involving cardiovascular, central nervous, gastrointestinal, and genitourinary system and VACTERAL sequence[3,5,6].It can be associated with anomalies involving musculoskeletal system, the most common is congenital scoliosis of cervical spine[7].The association with Klippel-Feil syndrome (KFS) is rarely reported[7,8,14,15].KFS is a triad of short neck, limitation of neck movements and low posterior hairline with fused cervical vertebra. We are reporting a case of aplasia of left lung with KFS.

## Case report

25 year old female presented with recurrent episodes of cough, wheezing and breathlessness since early childhood. She was diagnosed to have tuberculosis at the age of 3 years and treated with anti tuberculosis drugs. At the age of 16 years because of persistent respiratory symptoms she was referred to thoracic surgeon and underwent surgery. After surgery she was relatively free of symptoms for about 9 years. Present admission was because of the recurrence of symptoms. She was born out of non-consanguineous marriage. Her developmental milestones were delayed and had history of late menarche, but her menstrual cycles were normal.

On general examination she was short statured

with a BMI of 13.8kg/m$^2$.There was facial asymmetry. Neck was short and webbed with painless restriction of movement (Fig 1). There was bilateral flat foot. Palate was high arched, but there were no other features of a Marfans syndrome.

On respiratory system examination, chest was asymmetrical with drooping and flattening of chest on left side. There was a scar of posterolateral thoracotomy in left hemithorax. The mediastinum was shifted to left with reduction in movement and expansion. The percussion was dull in most part with a tympanic note in mammary and infra axillary areas. Breath sounds, vocal fremitus and vocal resonance were reduced in most of the areas on left except in the infra clavicular area. These clinical features were consistent with fibrosis of left lung. The scar mark of the thoracic surgery and the physical findings were also suggestive of a possible pneumonectomy.

An X-ray of chest showed opacity in left hemithorax with crowding of ribs, shift of heart and trachea to same side and an elevation of diaphragm. The right lung was hyperinflated (Fig 2).

**Fig - 1 : Short neck with webbing**

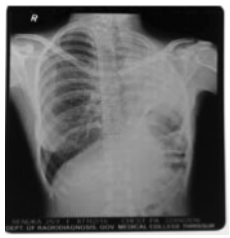


**Fig - 2 : X-ray chest Contracted left hemithorax resembling fibrosis of left lung**

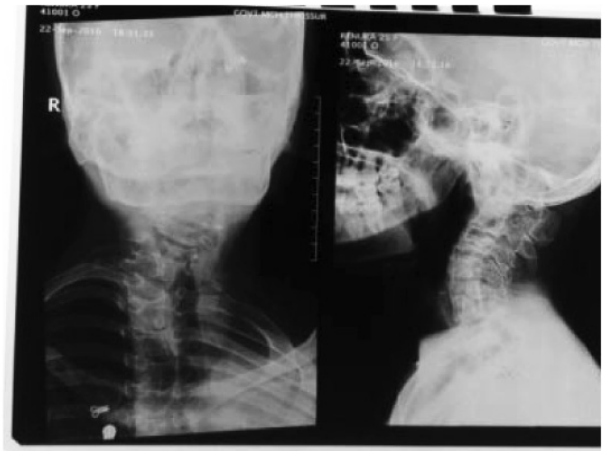


**Fig - 3 : X-ray cervical spine Fused cervical vertebrae**

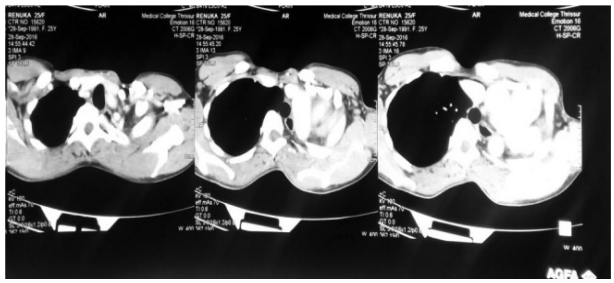


**Fig - 4 : CT Thorax with contrast- absent lungs in left side, heart occupying left hemithorax**

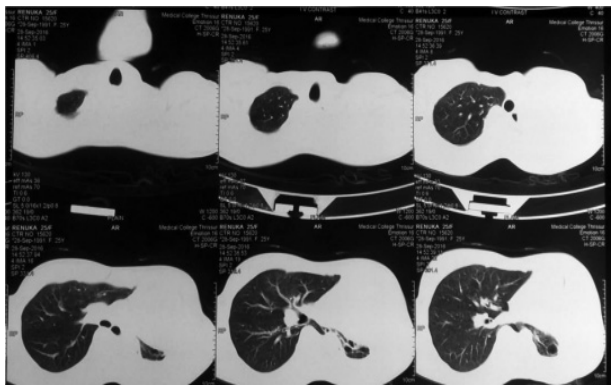


**Fig - 5 : CT thorax lung window- posterior herniation of Rt. Lung**

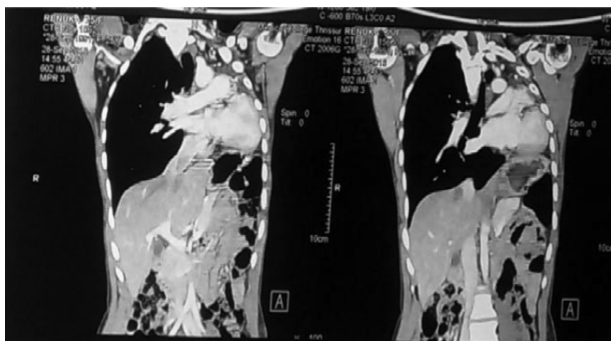


**Fig - 6 : CT thorax absent left pulmonary artery and lung, Herniation of right lung through posterior part, Elevated diaphragm**

In x-ray of cervical spine there was fusion of cervical vertebrae (Fig 3). Contrast Enhanced Computed Tomogram (CECT) of thorax revealed absence of lung tissue on left side with a rudimentary bronchus. The left main pulmonary artery was absent. Left hemi thorax was occupied by heart. The right lung was hyper inflated and crossed the junctional line occupying the left hemithorax. A diagnosis of aplasia of left lung was made because of rudimentary bronchus, absent lung tissue and main pulmonary artery (Fig 4). Ultra sound abdomen showed left kidney in pelvis and non visualization of left ovary. ECHO was normal. Final diagnosis was left lung aplasia with klippel-Feil syndrome, facial asymmetry, ectopic kidney and probably with an absent left ovary.

## Discussion

Development of the bronchial tree takes place at about 26th to 31st day of intrauterine life. Monaldi divided the mal-development of lung in four groups. Group I: No bifurcation of trachea; Group II: Only rudimentary main bronchus; Group III: Incomplete development after division of main bronchus; and Group IV: Incomplete development of subsegmental bronchi and small segment of the corresponding lobe.

Schneiderin[10] 1912 classified agenesis into three groups, which have been modified by Boyden[13]. Depending upon the stage of development of the primitive lung bud, pulmonary agenesis is classified into three categories:

**(a) Agenesis**—Complete absence of lung and bronchus and no vascular supply to the affected side.

**(b) Aplasia**—Rudimentary bronchus with complete absence of pulmonary parenchyma.

**(c) Hypoplasia**—Presence of variable amounts of bronchial tree, pulmonary parenchyma and supporting vasculature.

Aetiology of lung aplasia is not well established but believed to be due to certain genetic factors, vitamin A, folic acid deficiency and viral infection during early pregnancy[12]. Frequency of anomalies is equal in both genders and involve both lungs equally[1,3]. Agenesis and aplasia have been reported at different age groups ranging from new born to old age[1,3,13]. In clinical practice left sided agenesis is encountered more frequently as the subjects have a longer life expectancy than those with right sided agenesis[13].

There is a high incidence (>50%) of associated congenital defects which usually involve cardiovascular, skeletal, gastrointestinal and genitourinary system[2,3,12].Agenesis involving right side are more commonly associated with serious anomalies involving cardiovascular system[15]. Aplasia associated with skeletal anomalies is rare. In our case left lung aplasia associated with klippel-Fiel syndrome with left ectopic kidney with non-visualization of left ovary. Bhagat R et al reported that a patient with Klippel-Feil syndrome and associated agenesis of right upper and middle lobes, hypoplasia of the right lower lobe of the lung, and Lown-Ganong-Levine syndrome[15].There can be multiple anomalies like absence of gall bladder[14]. There are reports of ectopic kidneys, unilateral ovaries and facial malformation of which facial malformation is the most common association[16].

The onset of symptoms in pulmonary agenesis is remarkably variable. In our case symptoms started at the age of 2yrs. In many cases, presence of this anomaly reported during infancy because of recurrent chest infections, cardiopulmonary insufficiency or due to associated congenital anomalies. Our patient had wheezing without allergic symptoms. She was on metered dose inhaler with long acting beta agonist and inhaled steroids and had good symptom relief. There are case reports of allergic asthma in patients with agenesis and KFS[14].

The various differential diagnosis that has to be considered are collapse, thickened pleura, destroyed lung, diaphragmatic hernia and pneumonectomy. The final diagnosis can only be established by CECT thorax and, in some cases, angiography. Brochoscopy helps in visualizing the blind ending of the bronchial stump. In CECT we can demonstrate rudimentary bronchus, absence of pulmonary vessels and pulmonary parenchyma by which we can differentiate from lung hypoplasia where hypoplasia of pulmonary vessels can be seen[17,18].We have not done bronchoscopy as the diagnosis was obvious from the CECT thorax and from the surgical report. She had multiple congenital malformations like facial asymmetry, ectopic kidney, absent left ovary, flat foot and KFS

Surgery is seldom required for agenesis or aplasia and can be managed conservatively. In our patient surgery

was done because it was misdiagnosed as sequelae of tuberculosis. When thoracic cavity was opened there was no lung tissue and it was closed without doing any procedure. The improvement of symptoms following surgery is probably due to postoperative antibiotics and care. Her main problems were recurrent respiratory infections, airway obstruction and deformities. Our patient was relatively healthy as there was good compensation by right lung without pulmonary hypertension and the associated anomalies were not of a serious nature.

The prognosis of lung aplasia generally depends upon the functional integrity of the remaining lung as well as upon the seriousness of associated anomalies [19].

## References


1) Lee P, Westra S, Baba T, MaCauley R. Pedia Radiol 2006;36: 449-52

2) Krummel TM. Chapter 14-Congenital Malformations of the Lower Respiratory Tract. In: Chernick V, Boat TF (eds). Kendig's Disorders of the Respiratory Tract in Children, sixth edition. 1998, Philadelphia: W.B. Saunders Co, pp. 311-317.

3) Mardini M K, Nyhan WL. Agenesis of lung report of 4 patients with unusual anomalies Chest 1983;87:522-527

4) De Pozze, S. cited by Brescia M.A., Amermon E.E., Sharma K.K. Agenesis of the Left Lung. Arch. Paediatric 1960; 77:485-490.

5) Finda JD, Micheison PH. Congenital disorders of lung Nelson Text Book of Pediatrics 18th Editon 2008 p 1783

6) Fitoz S, Ucar T, Erden A, Gunlemez A. DiGeorge syndrome associated with left lung aplasia Br J Radiology 2001;74:764-766

7) Hensinger RN, Lang JE, MacEven GD. Klippel-Fiel syndrome A constellation of associated anomalies J Bone Joint Surgeries 1974;56:1246-1253

8) Menon MP, Singla R, Chhabra SK. A case of agenesis of right lung with other rare congenital malformations Indian J Chest Dis Allied Sci 1987;29:98-102

9) Klippel M ,Feil A Nour Icon Salpetriere 1912;25:223-250

10) Schneider, P. and Schwatbe, E. Die Morphologie der Missbildungen Des Menschen Under Thiere, Jena:Gustav Fischar.1912 Vol. 3, Part 2. PP817-822

11) Boyden EA. Developmental anomalies of the lungs. Am J Surg 1955; 89: 79-89.

12) Sbokos C.B. and McMillan I.R.K. Agenesis of the lung. Brit J Dis Chest 1977; 3 :183-197.

13) Yuetian YU,Cheng Zhu, Qian X, Ding Y, Zhongheng Z Adult patient with pulmonary agenesis:focusing on one lung ventilation during general anaestheisia J Thoracic Med 2016;8(1):124-129

14) Khanna P, Punjabi C, Shah A, Saudi Med J 2005;26(5):862-865

15) Bhagat R, Pant K, Singh VK, Pant C, Gupta A, Jaggi OP. Pulmonary developmental anomaly associated with Klippel-Feil Syndrome and anomalous atrioventricular conduction. Chest. 1992, 101(4):115758

16) Booth J B,Berry CL Arch Dis Childhood 1967;42:361-374

17) Mata JM, Caceres j, Lucaya J. et al.: CT of congenital malformations of lung. Radiographics. 1990; 10: 651

18) Bhagat R, Panchal N, Shah A. Pulmonary aplasia: A CT appearance. Indian Paediatr. 1992; 29:1410-1412.

19) Chopra K, Sethi GR, Kumar A, Kapoor R, Saha MM, Mital M, Saluja S. Pulmonary agenesis. Indian Pediatr 1988;25:678-82.

# GUIDELINES FOR AUTHORS

The merit of the publication lies in its quality and content. Contributions are invited on any aspect of Pulmonary and critical care medicine. Articles are accepted on the basis of significance, scientific perfection and practical applicability. Authors are requested to base their papers on the basis of original work carried out by themselves or their groups. Manuscripts should not be submitted to more than one journal at a time.

All articles are subjected to a peer review process. Each article is assessed blindly by one or more referees depending on the manuscript type and comments sent back to the authors for revision as required. The Editor's decision is final on accepting or rejecting an article.

The types of articles published in the journal are as follows

1. Editorials
2. Reports of original research
3. Critical reviews
4. Meta analysis
5. Case reports (series) with discussions
6. Radiology pearls
7. Educational forum
8. Letters to editor

Manuslcripts should be submitted by e-mail or CD in MS Word addressed to,

**Dr. Suraj K.P.**
**The Editor-in-Chief, Pulmon,**
***Professor, Dept. of Pulmonary Medicine,***
***Govt. Medical College, Kozhikode, Kerala, 673008.***
***Ph. 9447445135***
***E mail: drsurajkp@yahoo.com***

## Requirements for submission of manuscript

Presentation of manuscripts should conform with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (see Ann Intern Med 1997;126:36-47).

The manuscript should be accompanied by

1. Covering letter
2. Undertaking by authors
3. Copyright transfer agreement form.

## Covering Letter

The covering letter should explain why the paper should be published in the Pulmon. One of the authors could be identified as the corresponding author of the paper, who will bear the responsibility of the contents of the paper. The name, address, and telephone number of the corresponding author should be provided for all future communication related with the publication of the article. The letter should give any additional information that may be helpful to the editor, such as the type of article and whether the author(s) would be willing to meet the cost of reproducing color illustrations.

## Undertaking by Author(s)

It is necessary that all the authors give an undertaking (in the format specified by the journal) indicating their consent to be co-authors in the sequence indicated on the title page. Each author should give his or her names as well as the address and designation current at the time the work was done, plus a current address for correspondence including telephone and fax numbers and email address. A senior author may sign the Undertaking by Authors for a junior author who has left the institution and whose whereabouts are not known and take the responsibility. (Format for submission of undertaking is provided at the end of the session.)

## Copyright Transfer Agreemnet

Author(s) will be asked to sign a transfer of copyright agreement, which recognizes the common interest that both journal and author(s) have in the protection of copyright. It will also allow us to tackle copyright infringements ourselves without having to go back to authors each time. (Format for submission of copyright is provided at the end of the session.)

## Manuscript

Manuscripts should be presented in as concise a form as possible, typewritten in double space and numbered consecutively. The contents should be arranged in the following order:

**Title page, Abstract, Key words, Introduction, Material & Methods, Results, Discussion, Summary, Acknowledgement and References. Abstract, Tables and legends for Figures** should be typed on separate sheets and not in continuation of the main text. *Figures and Photographs should be presented in JPEG or GIF format.*

## Title Page

The title page should carry 1) the title of the article, 2) the name by which each author is known, with his or her highest academic degree and institutional affiliation, 3) the name of the department(s) and institution(s) to which the work should be attributed; 4) disclaimers, if any; 5) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; 6) source(s) of support in the form of grants, equipment, drugs, or all of these.

Title of the article should be short, continuous (broken or hyphenated titles are *not* acceptable) and yet sufficiently descriptive and informative so as to be useful in indexing and information retrieval. A short running title not

exceeding 6-7 words to be provided at the foot of the title page.

## Abstract

All manuscripts should have a structured abstract (not more than 250 words) with subheadings of Background

& objectives, Methods, Results ,Interpretation and Conclusions.Abstract should be brief and indicate the scope and significant results of the paper. It should only highlight the principal findings and conclusions so that it can be used by abstracting services without modification. Conclusions and recommendations not found in the text of the articles should not be inserted in the abstract. A set of suitable key words arranged alphabetically may be provided.

## Introduction

Introduction should be brief and state precisely the scope of the paper. Review of the literature should be restricted to reasons for undertaking the present study and provide only the most essential background.

## Material & Methods

The procedures adopted should be explicitly stated to enable other workers to reproduce the results, if necessary. New methods may be described in sufficient detail and indicating their limitations. While reporting experiments on human subjects and animals, it should be clearly mentioned that procedures followed are in accordance with the ethical standards laid down by the national bodies or organizations of the particular country. Scanned certificate of ethical clearance should be provided along with manuscript manuscripts in relevant context. The drugs and chemicals used should be precisely identified, including generic name(s), dosage(s) and route(s) of administration.

The statistical analysis done and statistical significance of the findings when appropriate should be mentioned. Unless absolutely necessary for a clear understanding of the article, detailed description of statistical treatment may be avoided.

## Results

Only such data as are essential for understanding the discussion and main conclusions emerging from the study should be included. The data should be arranged in unified and coherent sequence so that the report develops clearly and logically. Data presented in tables and figures should *not* be repeated in the text. Only important observations need to be emphasized or summarised. The same data should not be presented both in tabular and graphic forms. Interpretation of the data should be taken up only under the Discussion and *not* under Results.

## Discussion

The discussion should deal with the interpretation of results without repeating information already presented under Results. It should relate new findings to the known ones and include logical deductions. It should also mention any weaknesses of the study.

## Summary and conclusions

The summary should provide a brief account of most the relevant observations and conclusions based on the observed data only. This should be linked with the objectives of the study. Statements and conclusions not supported by the data should be avoided. Claims of ongoing studies should also be avoided.

## Acknowledgment

Acknowledgment should be brief and made for specific scientific/technical assistance and financial support only and *not* for providing routine departmental facilities and encouragement or for help in the preparation of the manuscripts (including typing or secretarial assistance).

## References

References should be typed on separate page after the text. The total number of References should normally be restricted to a maximum of 30. They should be numbered consecutively in the order in which they are first mentioned in the text. In the text they should be indicated above the line (superior). As far as possible avoid mentioning names of author(s) in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses. References cited only in tables or figure or legends should be numbered in accordance with the sequence in which they appear in the manuscript.

## Style of citing references

Use the style of the examples below. The titles of journals should be abbreviated according to the style used in Index Medicus. Avoid using abstracts as references. References of papers accepted but not yet published should be designated as ? in press or ? forthcoming. Authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as ? unpublished observations with written permission from the source.

Avoid citing a personal communication, unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, authors should obtain written permission and confirmation of accuracy from the source of a personal communication. Please refer http://wwwicmje.org for further details.

All references must be verified by the author(s) against the original documents.

*1. Standard Journal article*

List the first six authors followed by et al. The usual style is surname followed by initials as shown below

Vega KJ, Pina I, Krevsky B. Heart transplanation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996; 124:980-3.

*2. Organization as author*

The Cardiac Society of Australia and NewZealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 124:282-4.

*3.Books and other Monographs*

Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.

*4. Editor(s), compiler(s) as author*

Norman IJ, Redfern SJ. editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

*5. Chapter in a book*

Philips SJ, Whisnant JP Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press;1995.p.465-78.

*6. Unpublished Material In press*

LeshnerAl. Molecular mechanisms of cocaine addiction. N Engl J Med. In Press 1996.

*7. Journal article in electronic format*

Morse SS. Factors in the emergence of infectious diseases.Emerge Infect Dis [serial online] 1995 Jan-Mar (cited 1996 Jun 5); 1 (1): [24 screens]. Available from: URL: http://wwwcdc.gov/ncidod/EID/eid.htm.

## Tables

Type each table with double spacing *on a separate sheet of paper.* Do not submit tables as photographs. Number the tables consecutively (in Arabic numerals) in the order of their first citation in the text and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter as footnotes, and not in the heading. For footnotes use the following symbols, in this sequence: *, t, ~, §, I I, ~[, **, tt, ~~. Explain in footnotes all abbreviations that are used in each table.

### *Illustrations (Figures)*

Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 x 173 mm (5 x 7 inches).

Letters, numbers, and symbols on figures should be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Photomicrographs should have internal scale markers.

Symbols, arrows, or letters used in photomicrographs should contrast with the background.

Figures should be numbered consecutively according to the order in which they have been cited in the text. Titles and explanations should be provided in the legendsnot on the illustrations themselves. **Each figure should have a label pasted on its back indicating the number of the figure and the running title.** Do not write on **the back** of figures, scratch, or mark them by using paper clips.

### *Legends for Illustrations (Figures)*

Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When **symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.**

If a **figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce the figure.** Photographs of potentially identifiable people must be accompanied by written permission to use the photograph.

Color printing requires additional cost that will be communicated to the author.

An electronic version of the figures in JPEG or GIF should be provided for web version. The authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards.

## Units of Measurements

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be given in degrees Celsius. Blood pressures should be given in millimeters of mercury. All hematologic and clinical chemistry measurements should be reported in the metric system in terms of the International System of Unts (SI). Editors may request that alternative or non-SI units be added by the authors before publication.

## Abbreviations and Symbols

Use only standard abbreviations. Avoid abbreviations in the title and abstract. The full term for which an abbreviation stands should **precede its first use in the text unless it is a standard unit of measurements.**

## Proofs and reprints

Authors of accepted articles are supplied printer's proofs either by post or through e-mail. Corrections on the proof should be restricted to printer's errors only and no substantial additions/deletions should be made. **No change in the names of the authors** is permissible at the proof stage. Reprints up to 10 would be supplied as per request of the corresponding author.

## UNDERTAKING BY AUTHORS

We, the undersigned, give an undertaking to the following effect with regard to our article entitled "..... ....." submitted for publication in Pulmon, the journal of Respiratory Sciences.

1. The article mentioned above has not been published or submitted to or accepted for publication in any form, in any other journal.

2. We also vouchsafe that the authorship of this article will *not* be contested by anyone whose name(s) is/are not listed by us here.

3. I/We declare that I/We contributed significantly towards the research study *i.e.*, (a) conception, design and/or analysis and interpretation of data and to (b) drafting the article or revising it critically for important intellectual content and on (c) final approval of the version to be published.

4. I/We hereby acknowledge the journal's **conflict of interest** policy requirement to scrupulously avoid direct and indirect conflicts of interest and, accordingly, hereby agree to promptly inform the editor or editor's designee of any business, commercial, or other proprietary support, relationships, or interests that I/We may have which relate directly or indirectly to the subject of the work.

5. I/We also agree to the authorship of the article in the following sequence:-

| Authors' Names (in sequence) | Signature of Authors |
|---|---|
| 1. ..... | ..... |
| 2. ..... | ..... |
| 3. ..... | ..... |
| 4. ..... | ..... |
| 5. ..... | ..... |
| 6. ..... | ..... |
| 7. ..... | ..... |
| 8. ..... | ..... |

Copyright Transfer Agreement Form

This document must be signed by all authors and submitted with the manuscript.

## COPYRIGHT TRANSFER AGREEMENT

Pulmon, the Journal of Respiratory Sciences is published in 3 issues a year by the Academy of Pulmonary and CriticalC are Medicine.

The Pulmon and Authors hereby agree as follows: In consideration of Pulmon reviewing and editing the following described work for first publication on an exclusive basis:

Title of manuscript: ……..……..

The undersigned author(s) hereby assigns, conveys, and otherwise transfers all rights, title, interest, and copyright ownership of said work for publication. Work includes the material submitted for publication and any other related material submitted to Pulmon. In the event that Pulmon does not publish said work, the author(s) will be so notified and all rights assigned hereunder will revert to the author(s).

The assignment of rights to Pulmon includes but is not expressly limited to rights to edit, publish, reproduce, distribute copies, include in indexes or search databases in print, electronic, or other media, whether or not in use at the time of execution of this agreement, and claim copyright in said work throughout the world for the full duration of the copyright and any renewals or extensions thereof.

All accepted works become the property of Pulmon and may not be published elsewhere without prior written permission from Pulmon. The author(s) hereby represents and warrants that they are sole author(s) of the work, that all authors have participated in and agree with the content and conclusions of the work, that the work is original, and does not infringe upon any copyright, propriety, or personal right of any third party, and that no part of it nor any work based on substantially similar data has been submitted to another publication.

| Authors' Names (in sequence) | Signature of Authors |
|---|---|
| 1. ..... | ..... |
| 2. ..... | ..... |
| 3. ..... | ..... |
| 4. ..... | ..... |
| 5. ..... | ..... |
| 6. ..... | ..... |
| 7. ..... | ..... |
| 8. ..... | ..... |