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Editorial

Emerging Respiratory Viral Infections

Infectious diseases are the second leading cause of death and the leading cause of disability-adjusted life years[1]. Despite earlier predictions to the contrary, infectious diseases remain a dominant feature of domestic and international public health considerations for the 21st century. In fact, the continual evolution of emerging and reemerging diseases will heighten the global impact of infectious diseases. At the dawn of the 21st century, the future of infectious diseases and its impact on societies throughout the world is strikingly apparent. The successful diagnosis, prevention, and treatment of a wide array of infectious diseases have altered the very fabric of society, providing important social, economic and political benefits. Like pandemic influenza, which has had an extraordinary impact on global health, there is a continual evolution of a wide range of emerging and reemerging infectious diseases with varying potentials for global spread.

Respiratory infections are among the most common causes of morbidity and mortality worldwide. These infections present a special challenge to physicians for several reasons, including the recent disasters caused by severe acute respiratory syndrome (SARS) and bird and swine influenza. In the developing world, respiratory infections are also a major cause of childhood death, although the contribution of viruses to such deaths is unclear[2]. Recently, a newly identified human respiratory virus, human metapneumovirus (hMPV), was reported by investigators in Netherlands. Human metapneumovirus is a respiratory virus belonging to the family paramyxoviridae [3,4] and its clinical significance is yet to be defined. After its initial discovery in the Netherlands, hMPV has been detected in respiratory specimens from patients of all ages in a number of countries.

Human Meta pneumo virus (hMPV) may be the cause of a significant proportion of both upper and lower respiratory tract infection in infants, children, and adults. The results of several studies suggest that hMPV may account for about 10% of respiratory tract infections in which a common respiratory virus, such as respiratory syncytial virus, or influenza or parainfluenza viruses, could not be detected. hMPV has been detected in patients with either upper or lower respiratory tract disease, or both. Symptoms associated with hMPV include cough, dyspnea, wheeze, and hypoxia. Epidemiological findings suggest that it may circulate worldwide and may have a seasonal distribution. So far this infection is not reported in tropical and subtropical countries.

hMPV infection was associated with clinical diagnoses of pneumonia (36%), asthma exacerbation (23%), or acute bronchiolitis (10%). When compared to those with respiratory syncytial virus infection, children with hMPV infection were older, and wheezing was more likely to represent asthma exacerbation rather than acute bronchiolitis. hMPV viral activity peaked during the spring-summer period. hMPV contributed to 441.6 hospital admissions

per 100,000 population <6 years of age., Approximately one third of patients with hMPV infection were clinically diagnosed to have pneumonia. Over half of the patients with hMPV had influenza like illness reported in one or more of their family contacts (all ages), while 26% reported an adult family member with influenza like illness. Seroepidemiologic data in Netherlands showed that all children are seropositive for hMPV antibody by 10 years of age[3]. Recurrent infection has been documented in a few children, and the virus has also been detected in adults [3,5,6,7,8]. hMPV is only found in a very small number of patients with AE-COPD. However it should be considered as a further possible viral trigger of AE-COPD because asymptomatic carriage is unlikely.

Human bocavirus (HBoV) is another worldwide-distributed respiratory pathogen which is highly diverse, dispersed, recombination prone, and prevalent in enteric infections. Human bocavirus 1 (HBoV1), a member of the parvovirus family, was first identified as a potential human pathogen in the year 2005. HBoV1 is found associated with lower respiratory infections in young children. Recently human bocavirus 2-4 has also been discovered associated mainly with gastroenteritis. HBoV infection is associated with a variety of signs and symptoms which include rhinitis, pharyngitis, cough, dyspnea, wheezing, pneumonia, acute otitis media, fever, nausea, vomiting, and diarrhea. HBoV1 is fairly prevalent in children presenting with acute wheezing. In a particular study, serologic specimen obtained from the patients with acute wheezing were found to be positive for human bocavirus DNA, representing systemic infection.

A new strain of Corona virus has emerged this year in Saudi Arabia. This virus aggressively attacks the lower respiratory system, leading to fever, pneumonia and even death. So far, 17 cases of Corona virus infection have been confirmed by the World Health Organization. Though the number of people affected is less, it has killed 65% of its known hosts and raises concern among health workers.

Viral cause of pediatric respiratory illness is identifiable in up to 95% of cases, but the detection rates decrease steadily by age, to 30-40% in the elderly[9]. The new viruses cause respiratory illnesses such as common cold, bronchitis, bronchiolitis, exacerbations of asthma and chronic obstructive pulmonary disease and pneumonia. Rarely acute respiratory failure may occur. The clinical role of other new viruses, KI and WU polyoma viruses and the torque teno virus, as respiratory pathogens is not clear.

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Review Article

Immunohistochemistry in Respiratory diseases

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Introduction:

Immunohistochemistry (IHC) or Immunocyto chemistry is a method for localizing specific antigens in tissues or cells based on antigen-antibody reaction. It seeks to exploit the specificity provided by the binding of an antibody with its antigen at the light microscopic level[1]. Over the last several decades, an impressive array of antibodies has become commercially available and many of the antibodies have become integrated in to the routine practice of pathology. Pathologic classification of lung cancer remains a critical cornerstone of decision-making in managing patients with lung cancer. Newer targeted therapies further underscore the need for correct classification, both to select patients likely to benefit from these therapies and to avoid potential adverse effects of individual agents when used in patients with specific histologic types of cancers. The increasingly common use of bronchoscopic samples, core-needle biopsies and fine-needle aspiration samples have posed challenges to the pathologist in achieving accurate and definitive diagnosis[2]. IHC is widely used by the pathologist in modern pathology practice. The awareness of IHC and its specific use will be very useful for the pulmonologist for making a correct and more specific diagnosis. IHC is a commonly used effective adjuvant technique in diagnosing primary and metastatic neoplasms of the lung and pleura. Because of its relative ease of use and specificity, IHC has largely replaced histochemistry and electron microscopy in diagnosing pulmonary and pleural neoplasms. Even though most primary lung cancers can be diagnosed by histologic criteria alone, it becomes difficult when they are poorly differentiated or clinical situations become complicated. IHC techniques are often used to confirm or eliminate a pathological diagnosis. In addition, many metastatic tumors are morphologically similar to primary lung and pleural tumors and IHC is an effective way to distinguish them. Even though IHC has come in to wide use in diagnostic pathology since 1990s, the knowledge about different immunostains and its specific role for the accurate diagnosis is poor among practicing pulmonologists. Unless the physician who is evaluating a patient with pulmonary disease gives the detailed clinical history and diagnostic possibilities the pathologist may not be able to do the specific immunomarker. IHC can be performed on a recut section of a paraffin embedded or frozen tissue block or on a cytologic preparation such as a smear or cytospin.

Role of Inmmunohistochemistry in Respiratory diseases

1. Small cell carcinoma Vs Non small cell lung cancer
2. Squamous cell carcinoma Vs Adeno carcinoma
3. Primary pulmonary or Metastatic adenocarcinoma
4. Epitheloid Mesothelioma or Adenocarcinoma
5. Mesothelioma or Squamous cell carcinoma
6. Spindle cell neoplasms
7. Diagnosis of Lymphoma
8. Detection of primary in metastatic carcinoma
9. Pulmonary neuroendocrine tumors
10. Non neoplastic pulmonary diseases

Common Immunohistochemical Markers for lung neoplasms

Thyroid Transcription Factor-1 (TTF-1)

Adenocarcinoma is the most common epithelial malignancy in lung. Adenocarcinoma account for 38%of all lung cancers in the United States[9,10]. Sub classification of adenocarcinomas according to primary site can be a challenging task. Thyroid transcription factor-1 (TTF-1) has been the most widely used antibody to identify pulmonary origin. Greater than 80% of adenocarcinoma express this protein.TTF 1 is a nuclear transcription factor that is expressed in normal lung, in thyroid and in their neoplasms. In normal lung tissues, TTF-1 is expressed in the nuclei of epithelial cells in the distal lung parenchyma, type 2 pneumocytes, and nonciliated bronchiolar cells (Claracells)[6]. Expression of TTF-1 by a tumor in the lung usually indicates a pulmonary or thyroid carcinoma. These two alternatives can usually be differentiated based on additional staining for the surfactant protein B (positive in many lung adenocarcinomas) and thyroglobulin (positive in many thyroid cancers). TTF-1 is a highly specific immunomarker for adenocarcinoma of the lung and malignant effusion[3]. Su YC etal found that 73% of primary lung adenocarcinomas expressed TTF-1, whereas all nonpulmonary adenocarcinomas except thyroid lacked TTF-1 staining.

Metastatic tumors are more common than primary tumors in the lung, and the most frequent histological type is adenocarcinoma[4]. Microscopic comparison of the pulmonary tumor with slides of the previous tumor can frequently help to differentiate primary from metastatic tumor[5].In other cases judicious use of other immunostains will help to identify the primary site.

Cytokeratin(CK)

Carcinoma demonstrate epithelial characteristics including production of cytokeratins and epithelial differentiation is therefore usually reflected by staining for one or more CKs. Cytokeratin7 (CK7) and Cytokeratin 20 (CK20) are the most commonly used cytokeratin markers. CK7 is expressed by almost all primary lung adenocarcinomas and CK 20 is usually negative, even though it is co expressed in less than 10%primary mucinous adenocarcinomas[11]. Metastatic adenocarcinoma from an unknown primary site is a common clinical problem. The use of CK20 and CK7 was proposed to identify the primary sites in this situation[8]. If the primary site of malignancy is lung, breast, ovary or thyroid CK 7 will be positive and CK20 negative. Colorectal cancers will be negative for CK7 and positive for CK20. Mesotheliomas are also CK positive, but they stain positive for other mesothelial markers such as Calretinin, WT-1 and Vimentin also. Melanoma and lymphoma are negative for CK. Some sarcomas especially synovial sarcoma and rarely angiosarcoma and leiomyosarcoma can also be positive for CK. Small cell carcinomas show paranuclear dot positivity for cytokeratin.

Other immunomarkers

Surfactant protein B - adenocarcinoma

p63,CK 5/6 - squamous cell carcinoma

WT-1,Calretinin, Vimentin, Mesothelin - Mesothelioma

S 100 - Nerve sheath tumors, Melanoma

CDX2 - Colorectal carcinoma

PE 10 - Bronchoalveolar carcinoma

CD34- Solitary fibrous tumor

Synaptophysin, CD56, Neuron specific Enolase (NSE) and Chromogranin A - Neuroendocrine tumors including small cell carcinoma

CD45 (LCA) - lymphoma

Application of IHC in diagnosis of lung cancer

1. Small cell lung cancer (SCLC) Vs Non small cell lung cancer (NSCLC)

In most cases, SCLC can be differentiated from NSCLC by morphologic criteria. However, biopsy crush artifact, tumor necrosis, poor fixation, and limited tumor representation can occasionally result in suboptimal morphology, making definitive diagnosis more difficult[2]. Cytokeratin (CK) immunostaining show paranuclear dot positivity in most of the cases of SCLC[12]. Commonly used immunostains for detecting neuroendocrine differentiation are chromogranin, synaptophysin and CD56[13]. Recognizing the fact that an individual tumor may stain with one, several, or none of these markers, many pathologists order two or three of the neuroendocrine markers to increase the probability of detecting neuroendocrine differentiation.

Distinguishing SCLC from large cell neuroendocrine carcinoma (LCNEC) on occasion can be difficult, since SCLC and LCNEC overlap in their histologic and immunophenotypic characteristics. Hiroshima K etal reported more frequent CD56 expression in SCLC (96%) than LCNEC (53%), whereas synaptophysin was expressed in 77% of LCNECs and 57% of SCLCs, and chromogranin A in 59% of LCNECs and 36% of SCLCs[14]

2. Squamous cell carcinoma Vs Adeno carcinoma

The differentiation in to Squamous cell carcinoma or Adeno carcinoma is important for targeted therapies and further genetic evaluation. TTF-1 and napsin-A will be positive in 90% of pulmonary adenocarcinoma. Squamous cell carcinoma is almost always negative for TTF-1. P63 and CK5/6 are valuable in confirming squamous cell carcinoma.[15]

3. Primary Pulmonary Vs Metastatic Adenocarcinoma

Metastatic neoplasms are more common than primary tumors of lung. Detailed history with image findings must be provided to the pathologist along with the specimen and any past history of malignancy and its reports must be communicated. In difficult situation IHC is of immense value in differentiating primary pulmonary or metastatic tumors. Thyroid transcription factor-1 (TTF-1) has been the most widely used antibody to identify pulmonary origin. More than 80% of pulmonary adenocarcinoma express this protein. Extra pulmonary adenocarcinomas except thyroid are usually negative for TTF-1. Although TTF-1 immunohistochemistry has clearly advanced the diagnosis of primary and metastatic adenocarcinomas in the lung, antibodies to napsin-A and surfactant protein B have also demonstrated its usefulness for this purpose. 80% of primary adenocarcinoma stain positive for napsin-A. The combined use of napsin A or surfactant protein B and TTF-1 may improve the likelihood of confirming pulmonary origin of an adenocarcinoma[16].

4. Mesothelioma Vs Adenocarcinoma

The important differential diagnosis of pleural malignant epithelial tumors are malignant mesothelioma and metastasis. IHC is now an integral part of the diagnosis of malignant mesothelioma. Unfortunately, despite extensive investigation, there is no immunostain that can reliably differentiate mesothelial hyperplasia from malignant mesothelioma, and this remains a topic of continued interest[17]. Currently, the most commonly used mesothelial markers include antibodies to CK5/6, Calretinin and Vimentin. Anti-podoplanin (D240) is also gaining popularity and is an emerging marker that is highly sensitive and specific for epitheliod mesothelioma[18]. Epithelioid mesotheliomas are more likely to stain for these markers than sarcomatoid mesotheliomas[19]. Adenocarcinomas, on the other hand, are usually positive for one or more of the following antibodies: Carcino embryonic antigen (CEA), Leu-M1, B72.3 20.

5. Mesothelioma vs Squamous cell carcinoma

Squamous cell carcinoma can also present as pleural or subpleural mass and may mimic a mesothelioma both clinically and radiologically. True keratinisation and p63 staining is highly suggestive of squamous cell carcinoma. Negative p63 and positive calretinin are diagnostic of mesothelioma

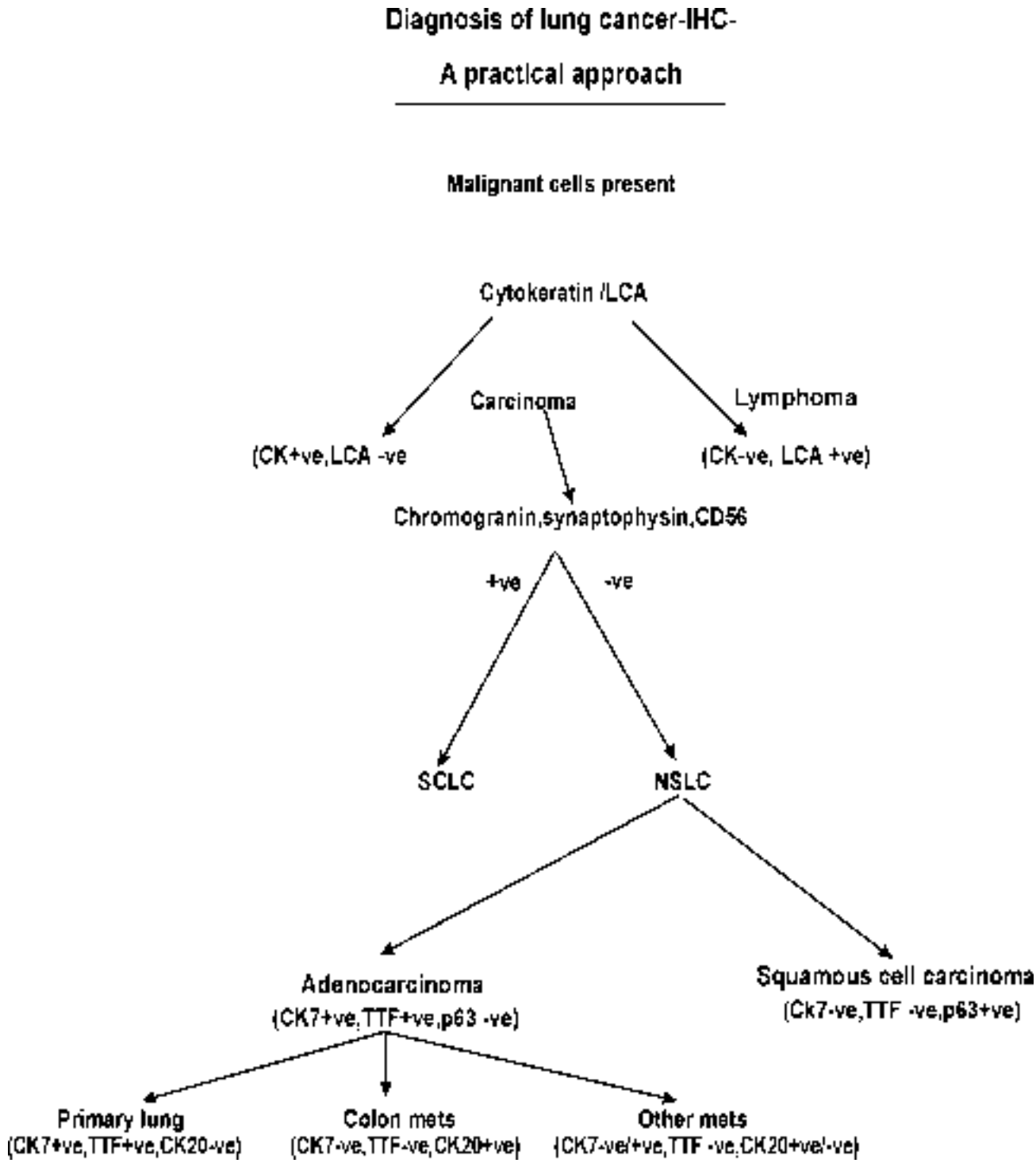
6. Solitary fibrous tumor of pleura(SFT)

Pleuropulmonary fibrous tumor of pleura is a rare mesenchymal cell tumor which has gained importance during the last two decades. SFT originate from the submesothelial tissue of pleura. Fibrous tumor of pleura is positive for CD34 in most of the cases and some of the tumors are also positive for Bcl-2, smooth muscle actin, Desmin, Leu 7 and Vimentin[21].

7. Spindle Cell Neoplasms

The lung and pleural neoplasm with spindle cell morphology include sarcomatoid and pleomorphic carcinomas, sarcomatoid and biphasic mesotheliomas, true sarcomas and melanoma. A neoplasm arising in lung and consisting of spindled cells is most often a sarcomatoid carcinoma. But sarcomatoid carcinoma of the lung is rare, and its incidence is estimated as 0.3-1.3% of all lung malignancies [22, 23,.]

IHC by itself may not always be definitive in resolving

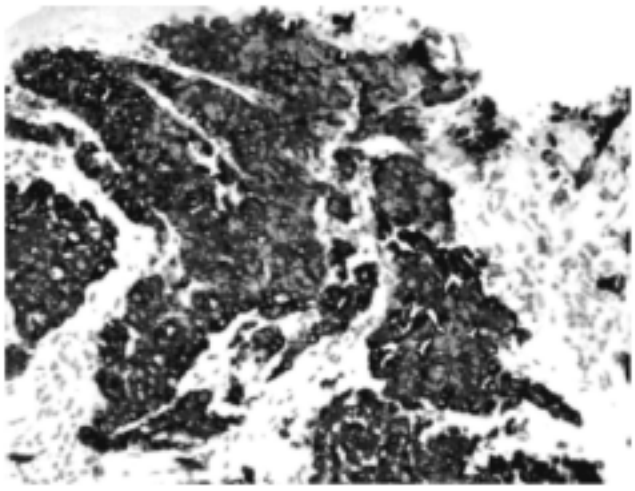

Diagnosis of lung cancer-IHC-
A practical approach
Malignant cells present
Cytokeratin /LCA
Carcinoma
Lymphoma
(CK+ve,LCA -ve
(CK-ve, LCA +ve)
Chromogranin,synaptophysin,CD56
+ve
-ve
SCLC
NSLC
Adenocarcinoma
(CK7+ve,TTF+ve,p63 -ve)
Squamous cell carcinoma
(Ck7-ve,TTF -ve,p63+ve)
Primary lung
(CK7+ve,TTF+ve,CK20-ve)
Colon mets
(CK7-ve,TTF-ve,CK20+ve)
Other mets
(CK7-ve/+ve,TTF -ve,CK20+ve/-ve)

the exact differential diagnosis in case of spindle cell neoplasm. In pleura, mesothelioma, metastases from other carcinomas, synovial sarcoma, angiosarcoma and leiomyosarcoma are other possibilities. Cytokeratin is positive for 90% of sarcomatoid carcinoma. Cytokeratin (65%) and Bcl2 are used for synovial sarcoma. Desmin, Smooth muscle actin (SMA) and Muscle specific actin (MSA) are the markers for leiomyosarcoma. CD34 and CD31 are useful for angiosarcoma. If melanoma is suspected S100, HMB 45 and melan-A is advisable.

EGFR (Epidermal Growth Factor Receptor Gene)

Among the targeted therapies the most widely used for the treatment of lung cancers are currently the EGFR tyrosine kinase inhibitors. Epidermal growth factor pathway has been found to be activated in a significant percentage of lung cancers, particularly adenocarcinomas. Mutations that lead to EGFR over expression or over activity have been associated with a number of cancers, including lung cancer[24].

High EGFR expression by IHC can identify patients who may benefit from tyrosine kinase inhibitors[25]. Identification of those patients with lung cancer who have EGFR mutations in advance can not only determine which patients will benefit from EGFR TKIs but also identify those patients who will not benefit from standard cytotoxic chemotherapy and also spare them from the potential complications of these drugs.



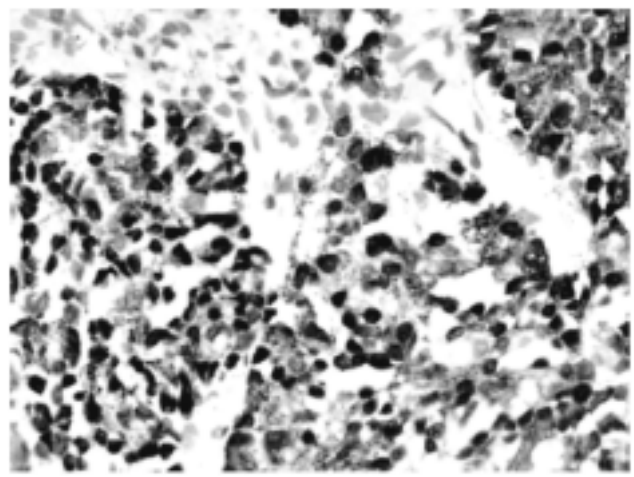
CK 7

8. IHC for non neoplastic Pulmonary diseases

The role of immunohistochemistry in the diagnosis of non neoplastic respiratory diseases is limited. A number of studies are available in the literature looking to the utility of IHC in non neoplastic respiratory diseases. Musthafa et al reported that Immuno histochemistry with anti-MPT64 antiserum is a rapid, sensitive, and specific method for establishing an etiological diagnosis of tuberculosis in histologic specimens[26]. Ki67 monoclonal antibody for sarcoidosis[27], Cathepsin-K for detection of micro-granulomas in hypersensitivity pneumonitis [28], Langerin and CD1a markers in distinguishing LCH from other interstitial and inflammatory processes[29]. N-cadherin, Ki-67, PI3K and p110 marker expression in IPF[30]. are few immunomarkers identified.

Conclusion.

Immunohistochemistry represents an important complementary tool for the routine diagnosis of lung cancer and for the identification of the different histological types and prognostic factors. Targeted therapy for lung cancer has emerged as an important component for the treatment of defined groups of patients and immunohistochemistry is among the techniques that have been investigated for their usefulness in identifying patients whose tumors are likely to respond to individual agents. IHC is an invaluable tool for the pathologist in resolving the diagnostic issues in lung tumors. The awareness among the practising pulmonologists is vital because proper clinical details and discussion will direct the pathologist to choose the correct IHC.



TTF1

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Review Article

Idiopathic Pulmonary Fibrosis

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Interstitial lung diseases are a clinically challenging and diverse group of over 150 disorders characterized by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium. Idiopathic interstitial pneumonias (IIP) are a subset of diffuse interstitial lung diseases of unknown etiology. Idiopathic pulmonary fibrosis (IPF) is the most common disorder of idiopathic interstitial pneumonias. IPF is defined by the Official ATS/ERS/JRS/ ALAT Statement 2011 as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs and associated with the histopathologic and/or radiologic pattern of Usual Interstitial Pneumonia (UIP). [1]

Epidemiology

World wide, the incidence of idiopathic pulmonary fibrosis is estimated to be 10.7 cases per 100,000 person-years for males and 7.4 cases per 100,000 person years for females. The prevalence of idiopathic pulmonary fibrosis is estimated to be 20 cases per 100,000 persons for males and 13 cases per 100,000 persons for females [2]. In India, this was earlier considered to be a rare disease. In 1979, Jindal *et al* published their data on 61 cases of Diffuse Parenchymal Lung Disease (DPLD) seen over a period of five years. However, the scenario is different now and the disease is no longer rare or uncommon. Recently the same center published data on 76 patients with IPF diagnosed over a 16-month period showing a definite increase in the frequency of diagnosis.[3,4,5]

Risk factors

Cigarette smoking increases the risk of developing IPF several-fold, as do other exposures such as metal-fume and wood-dust exposure. Occupations that increase the risk of IPF are agricultural work, hairdressing, and stone polishing, supporting the role of environmental exposure in disease pathogenesis.[1] Viruses like Human Herpes Virus, Epstein Barr Virus and Hepatitis C Virus have been linked to the aetiology of IPF [6]

Various comorbid conditions including gastro-esophageal reflux disease(GERD), venous thromboembolism, coronary artery disease, sleep-disordered breathing, depression, emphysema, pulmonary hypertension, lung cancer, diabetes mellitus and hypothyroidism contribute to the morbidity and mortality of fibrotic lung disease[7]. There is mounting evidence that abnormal reflux (GERD) and aspiration of gastric contents may play a role in the pathogenesis of this disease [8].

Genetic Factors

Mutations in surfactant protein C (SP-C) gene lead to abnormal cleaving and accumulation of surfactant in endoplasmic reticulum leading to endoplasmic reticulum stress. Various other pathways leading to endoplasmic reticulum stress like viral infections have also been identified. The endoplasmic reticulum stress can contribute to the epithelial mesenchymal transition which is supposed to be the basis of fibrosis in IPF [10].

It has been described that mutant telomerase is associated with familial idiopathic pulmonary fibrosis [11]. Telomerase is a specialized polymerase that adds telomere repeats to the ends of chromosomes. This helps to prevent shortening that occurs during DNA replication. TGF-β negatively regulates telomerase activity. This telomere shortening may lead to the loss of alveolar epithelial cells,

resulting in aberrant epithelial cell repair.

A common variant in the putative promoter of the gene that encodes mucin 5B *(MUC5B)* has been associated with the development of both familial interstitial pneumonia and sporadic pulmonary fibrosis. *MUC5B* expression in the lung was reported to be 14.1 times as high in subjects who had idiopathic pulmonary fibrosis as in those who did not[12].

Pathogenesis

It was previously thought that the fibrosis in IPFwas the result of persistent or recurrent inflammation. However, anti-inflammatory agents and immune modulators have proved to be minimally effective in modifying the natural course of the disease. It is currently believed that IPF is an epithelial-fibroblastic disease, in which unknown endogenous or environmental stimuli disrupt the homeostasis of alveolar epithelial cells, resulting in diffuse epithelial cell activation and aberrant epithelial cell repair.

The major cell types involved in the pathogenesis are

Type II alveolar epithelial cells (AECs): These cells residing in the 'corners' of alveoli produce surfactant proteins. They also serve as progenitors of type I AECs, which make up the respiratory gas exchange surface.

Fibroblasts: Mesenchymal cells that reside in the pulmonary interstitium and produce collagen and extracellular matrix (ECM).

Myofibroblasts: These are contractile mesenchymal cells expressing alpha-smooth muscle actin. It is thought that these cells have an activated phenotype, and contribute to exuberant collagen and ECM production inIPF[9].

It seems likely that progression to lung fibrosis involves both genetic background and environmental exposures (analogous to carcinogenesis), and that 'multiple hits' might be required to induce overt fibrotic lung disease. Based on the current evidence, it has been proposed that genetic

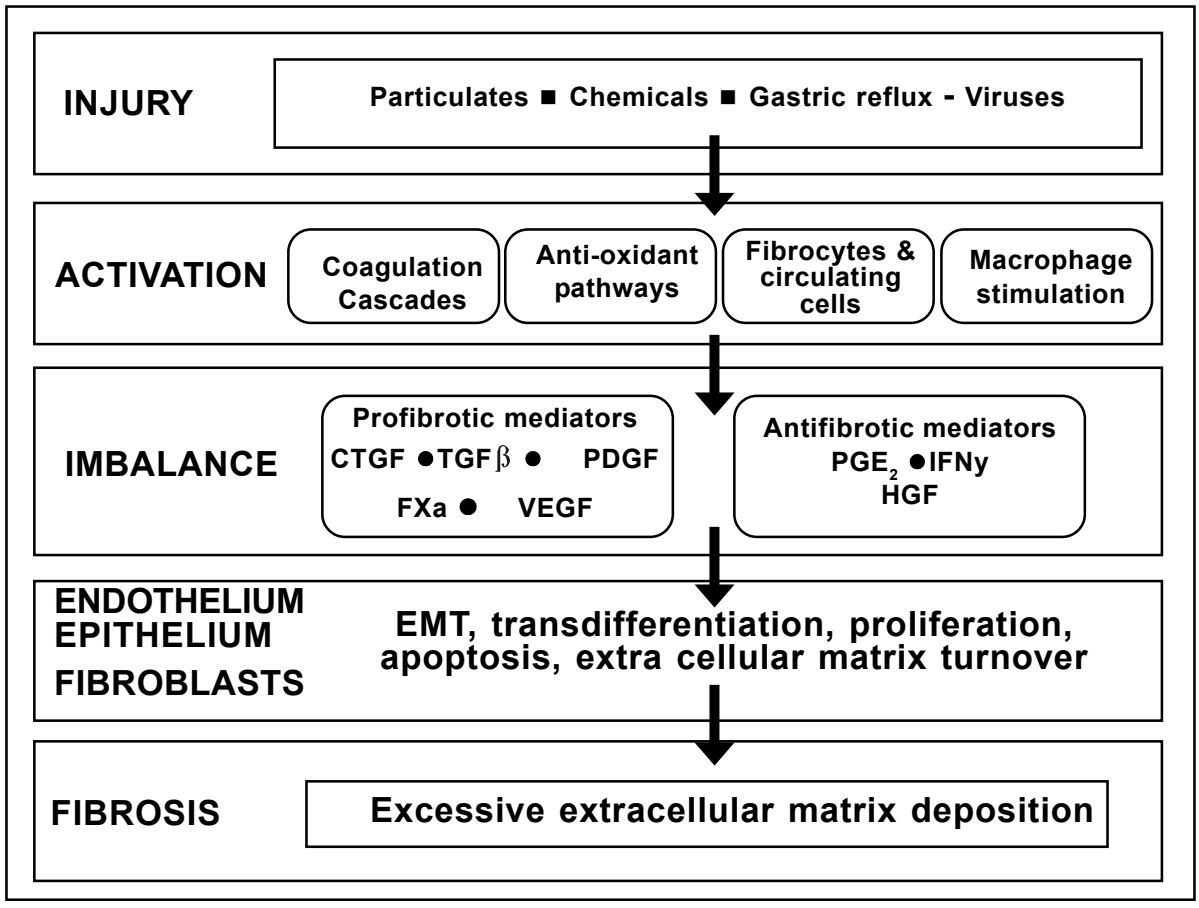

Figure 1. Proposed pathogenetic events in development of IPF
EMT-Epithelialmesenchymal transition

Courtesy :Clinics in Chest Medicine, Interstitial lung Disease, March 2012, Volume 33, Number 1

and acquired or environmental insults converge to render AECs vulnerable to subsequent injury. When subjected to repeat or persistent injurious stimuli (such as aspiration, inhaled particulates, tobacco smoke and respiratory viruses), normal alveolar repair mechanisms fail and culminate instead in persistent collagen deposition, scar formation and progressive distortion of lung architecture. Over time, clinically evident pulmonary fibrosis develops[9].

Clinical features and diagnosis

IPF is a disease of elderly. Median age of presentation is 66 years with a male predominance. IPF should be considered as a diagnostic possibility in all patients above 50years presenting with unexplained chronic exertional dyspnea, dry cough, bibasilar inspiratory crackles, and finger clubbing. It is usually progressive with a 5 year survival rate of 20% , though variant forms with a much faster decline in lung function and some stable chronic forms of the disease have been recognized recently[1].

Clinical phenotypes of IPF

It has been proposed that the disease has a long (months to years) asymptomatic period. Patients consult physician when the severity of the lung lesions reaches a threshold that is enough to provoke symptoms. Most patients follow a relatively slow clinical and functional decline (slowly progressive) after diagnosis. About 10% of these patients present with episodes of acute clinical deterioration (acute exacerbations) that precede and possibly initiate the terminal phase of their disease. A few patients have a short duration of illness with a rapidly progressive clinical course. Heavy smokers might develop pulmonary fibrosis combined with emphysema, with shorter survival compared with patients with IPF alone.[13] So 3 distinct phenotypes have been proposed.

1. Combined pulmonary fibrosis and emphysema (CPFE)
2. Disproportionate pulmonary hypertension in IPF
3. Rapidly progressive IPF [14]

The major and minor criteria for diagnosis of IPF in the absence of a lung biopsy which was proposed in 2000 by ATS/ERS has been done away with. The diagnosis requires a joint effort between clinician, pathologist and radiologist. Lung biopsy may be excluded in cases with conclusive radiology and clinical features. Since a similar radiological pattern may be seen in other ILDs also, exclusion of connective tissue disorders, drugs and toxin exposures are a prerequisite for the diagnosis of IPF.

Diagnostic Criteria

The diagnosis of IPF requires the following:

1. Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).

2. The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy.

3. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy[1].

HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN[1]

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
o Subpleural, basal predominance o Reticular abnormality o Honeycombing with or without traction bronchiectasis o Absence of features listed as inconsistent with UIP pattern (see third column)	o Subpleural, basal predominance o Reticular abnormality o Absence of features listed as inconsistent with UIP pattern (see third column)	o Upper or mid-lung predominance o Peribronchovascular predominance o Extensive ground glass abnormality (extent > reticular abnormality) o Profuse micronodules (bilateral, predominantly upper lobes) o Discrete cysts (multiple, bilateral, away from areas of honeycombing) o Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) o Consolidation in bronchopulmonary segment(s)/lobe(s)

The major differential diagnostic considerations include UIP in other clinical settings such as connective tissue diseases, chronic hypersensitivity pneumonitis (extrinsic allergic alveolitis), and pneumoconiosis (especially asbestosis).

HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN[1]

UIP Pattern (All Four Criteria)	Probable UIP Pattern (First three or four Criteria)	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution Presence of patchy involvement of lung parenchyma by fibrosis Presence of fibroblast foci Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	Evidence of marked fibrosis / architectural distortion, ± honeycombing Absence of either patchy involvement or fibroblastic foci, but not both Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR Honeycomb changes only	Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation Absence of other criteria for UIP (*see*UIP Pattern column) Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	Hyaline membranes* Organizing pneumonia*† Granulomas† Marked interstitial inflammatory cell infiltrate away from honeycombing Predominant airway centered changes Other features suggestive of an alternate diagnosis

Scoring system and predictors of prognosis

6 minute walk Test (6MWT): Distance covered in 6MWT of less than 200 - 250 mtrs predict a 2 to 4 fold increase in mortality risk. But due to difficulty in performing and lack of reproducibility of 6MWT, it is not widely recommended as a prognostic tool[15]. Hypoxemia with rest or exertion has also predicted a worse prognosis. Comorbidities like associated emphysema, cardiovascular disease, lung cancer may affect the morbidity and mortality. Red Cell Distribution Width has also been described as a prognostic marker in IPF.

GAP Index[1]

Predictor	Points
Gender	
Female	0
Male	1
Age	
<60	0
61 - 65	1
>65	2
FVC % predicted	
>75	0
50 - 75	1
<50	2
DLCO % Predicted	
>55	0
36 - 55	1
</= 35	2
Cannot perform	3

% Mortality	Stage I 0-3	Stage II 4- 5	Stage III 6 - 8
1 year	6	16	39
2 years	11	30	62
3 years	16	42	77

Composite Physiologic Index [17]

Wells et al devised Composite Physiologic Index (CPI) which correlated better with extent of diseases on CT than the pulmonary function test alone. The formula for the CPI was as follows: extent of disease on CT = 91.0 – (0.65 × percent predicted diffusing capacity for carbon monoxide [DL_{CO}])–(0.53 × percent predicted FVC) + (0.34 × percent predicted FEV_1).

A Clinical Radiological and Physiological (CRP) prediction model by King et al [18] correlated with pathological derangement in IPF

Treatment options

The various completed trials in IPF have yielded the following results

Trial	Drugs	End points	Outcome	
IFIGENIA [19]	NAC vs Prednisone Azathioprine	Change in vital capacity (VC) and diffusing capacity of the lung	Significant reduction in the decline of both VC and D_{LCO} was shown, whereas there was no effect on the survival between the two groups	
PANTHER-IPF [20]	1)prednisone, azathioprine and NAC; 2) NAC alone; and 3) placebo.	The primary outcome was the change in forced vital capacity (FVC) at 60 weeks.	Triple therapy arm had been discontinued due to an excess number of deaths (11% *versus* 1%), hospitalisations (29% versus 8%) and higher prevalence of adverse effects (31% *versus* 9%)	The other two arms are ongoing
CAPACITY 1 and 2 TANIGUCHI[21,22,]	Pirfenidone		A recent Cochrane review, including the four studies mentioned above, has shown that treatment with pirfenidone reduced the risk for disease progression by 30% (HR 0.70, 95% CI 0.56-0.88) [39].	Based on the results of these studies, pirfenidone was licensed in Europe in 2011, for patients with mild-to-moderate disease.

Trial	Drugs	End points	Outcome	
ACE - IPF[23]	Warfarin vsplacebo		The study was prematurely terminated, due to an increase in mortality and low evidence of benefit in the warfarin group compared with placebo.	
TOMORROW[24]	BIBF 1120 is a triple inhibitor of tyrosine kinases receptors, such as platelet derived growth factor (PDGF), vascular endothelial growth factor and fibroblast growth factor receptors,	Annual rate of decline in FVC, and the secondary end-points included acute exacerbations, quality of life measures and total lung capacity (TLC).	Lesser rate of decline of FVC, fewer acute exacerbations, a preserved quality of life, moderate gastrointestinal symptoms and liver toxicity were also observed in the high dose arm compared with placebo.	
DANIELS [25]	Imatinib mesylate		Not effective	
STEP - IPF[26]	Sildenafil	Improvement in 6MWT	Primary outcome not met , but many secondary objectives were achieved	
BUILD-1 [27] BUILD-3 [28] ARTEMIS-IPF MUSIC-IPF [30]	Bosentan Ambrisentan Macitentan Vs placebo		Not effective	
INSPIRE [31]	IFN-γ		Not effective	
R RAGHU [32]	Subcutaneous IFN- for 58 weeks in 330 patients with IPF compared with placebo,		Not effective	

TABLE 2. ONGOING CLINICAL TRIALS IN IDIOPATHIC PULMONARY FIBROSIS [33]

Trial#	Drug	Mechanism of action
ASCEND (NCT01366209)	Pirfenidone	Antifibrotic
RECAP	Pirfenidone	
NCT01335477	BIBF 1120	Tyrosine-kinase inhibitor
NCT01335464	BIBF 1120	Tyrosine-kinase inhibitor
NCT01266135	QAX576	Anti-IL-13 monoclonal antibody
NCT00786201	CNTO 888	Anti-CCL-2 monoclonal antibody
NCT01262001	FG-3019	Anti-CTGF antibody
NCT01362231	AB0024	Anti-LOXL2 monoclonal antibody
NCT01385644	MSCs	Epithelial tissue repair

Pirfenidone

Of all medications studied for the treatment of IPF so far, Pirfenidone currently has the highest grade of evidence to support its efficacy and is the only medication approved for the treatment of IPF. Pirfenidone has been evaluated in four randomised, double-blind, placebo-controlled clinical trials conducted in Japan, North America and Europe. The totality of the data from these trials indicate that Pirfenidone is able to reduce the rate of decline in lung function, measured as change in per cent predicted forced vital capacity (FVC) or vital capacity. In vitro studies have demonstrated that pirfenidone inhibits transforming growth factor (TGF)-β-stimulated collagen synthesis, decreases extracellular matrix deposition and blocks the mitogenic effects of platelet-derived growth factor in lung fibroblasts derived from patients with IPF[34,35,36]

Pirfenedone Trials

Following an open-label phase II pilot study[37] and an open-label 1-yr study,[38] a double-blind, placebo-controlled clinical trial of Pirfenidone was conducted in 107 Japanese patients with IPF [39]. This study was terminated early due to a higher number of acute exacerbations in the placebo group than in the Pirfenidone group.

Based on the positive results from this trial, which demonstrated a reduced decline in VC at 9 months in patients receiving Pirfenidone, a phase III trial was conducted in Japanese patients with well-defined IPF and mild-to-moderate impairment in lung function. This three-armed phase III, multicentre, double-blind, placebo-controlled study randomised patients to either high-dose pirfenidone (600 mg three times per day; n = 108), low-dose pirfenidone (400 mg three times per day; n = 55) or placebo (n = 104) in the ratio 2:1:2. The pirfenidone dose was increased in a stepwise manner up to the full dose over 4 weeks [22]. A 44% reduction in VC decline in the high dose Pirfenidone group compared to placebo was observed as the primary end point. A significant difference was also seen between the low-dose pirfenidone and placebo groups (p = 0.0394).

Two concurrent, multinational, randomised, double-blind placebo controlled trials with Pirfenidone in IPF patients have been conducted in Europe and North America. In the study 004 (CAPACITY 1) patients were randomized 2:2:1 to receive Pirfenidone in the dose of 2403mg, placebo or 1197mg Pirfenidone. It was found that pirfenidone was statistically significantly superior compared to placebo in the primary end-point (FVC % pred) at week 72 (p = 0.001). Secondary end-points (defined as death or decline 10% of FVC or ≥15% in $D_{L,CO}$; p = 0.023) were also statistically significant.[15]

In the second study patients were randomized to receive 2403mg of Pirfenidone or placebo in 1:1 ratio. However, in this study Pirfenidone was not found to be statistically significantly superior compared to placebo for the primary end-point (p = 0.501), although the results were generally consistent with and supportive of the results from CAPACITY 1 trial. In CAPACITY 2, Pirfenidone treatment was associated with a significant beneficial effect on the secondary end-point of the 6MWT distance when compared to placebo[21].

The Cochrane Collaboration recently published the results of a meta-analysis to assess the efficacy of nonsteroid agents in adults with IPF, including Pirfenidone. Four trials involving 1,155 patients were reviewed comparing Pirfenidone with placebo, including the three phase III Pirfenidone trials that reported progression free survival (PFS) as an outcome. The result of the meta-analysis suggested that Pirfenidone significantly reduced the risk of disease progression by 30%. In this Cochrane review the effect of Pirfenidone on pulmonary function in IPF patients revealed a significantly reduced decline in VC from baseline [21, 40, 41].

Adverse reactions

The summary of product characteristics lists the following adverse reactions for Pirfenidone as the most commonly reported (10% or higher): nausea, rash, fatigue, diarrhoea, dyspepsia and photosensitivity reaction. The adverse effects were generally transient and usually resolved if the dose of Pirfenidone was reduced or temporarily discontinued.

NAcetyl Cysteine (NAC), Prednisone and Azathioprine

Data from the IFIGENIA Study[19] provided support for the use of NAC plus prednisone and azathioprine to treat IPF patients. Patients were treated with high-dose NAC (600 mg TID) plus prednisone and azathioprine. The primary endpoint of the study was change in vital capacity. The NAC-based triple-therapy was found to significantly reduce decline in VC after one year of treatment. However, this study had several limitations. There was no direct comparison with placebo group. In view of the drop-out rate from this study of approximately 30% (including deaths), questions were raised regarding the clinical relevance and robustness of the treatment effect. Subgroup analyses from the study confirmed the favourable effects of NAC on lung function, and patients with less advanced disease at baseline appeared to be more responsive to NAC treatment. [42]

The PANTHER-IPF[20] Study was designed to determine whether NAC-based triple-therapy could slow disease progression and improve lung function in patients with moderate IPF. In addition, this study compared the triple-therapy regimen with NAC monotherapy and placebo alone. In 2011, the NIH announced that the triple-therapy arm of the trial had been stopped due to increased mortality observed in this treatment group [43]. Increased risks of death and hospitalization were observed in patients with idiopathic pulmonary fibrosis who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo. These findings provide evidence against the use of this combination in patients with IPF.[44]

Currently major international guidelines give the following recommendations for treatment of IPF[1,15]

Strong NO

- Ambrisentan
- Azathioprine
- Bosentan
- Co-Trimoxazole
- MycophenolateMofetil
- Corticosteroid Monotherapy
- Colchicines
- Cyclosporine A
- Combine Steroid Plus Immunomodulator
- Interferon Gamma 1b
- Etanercept

Weak NO- the well informed patient may make a choice of treatment from this group

- Pirfenidone
- Combined acetyl cysteine plus azathioprine and prednisolone
- Acetylcysteine monotherapy
- Anticoagulation
- Mechanical ventilation in advanced cases

Strong YES

- Lung transplantation
- Supplemental oxygen

Weak YES

- Treatment of pulmonary hypertension
- Corticosteroids in exacerbation
- Pulmonary rehabilitation
- Treatment of asymptomatic GERD

Idiopathic pulmonary fibrosis is a disease, having a prognosis similar to, or even worse than, many cancers. So far lung transplantation is the only therapeutic intervention that has offered definite prospect of improved survival for individuals with IPF. The past decade has, however, witnessed an explosion of interest in IPF and Pirfenidone appears to be a promising drug.

Regarding the relation between the IPF patient and the doctor, an interesting observation was made by Craig Conoscenti, et al [34] that pulmonologists with a 'sustained optimism' typology spent longer explaining the prognosis and treatment options to the patient and actively considered clinical trials and lung transplants. Pulmonologists with a 'pragmatic acceptance' typology lacked faith in trials and transplants and focused on managing symptoms. Pulmonologists with this typology may fail to build an appropriate relationship with the patient, leaving them unprepared for the end of life journey.

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Original Article

Lung Function Abnormality in Cashew - Nut Factory Workers in Kollam District

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Abstract:

Background of the study: Cashew processing is a labour -intensive industry with limited use of technology. Workers in cashew industry are exposed to smoke, fumes and dust, which are well known risk factors for various respiratory diseases like Asthma, COPD and ILD. Little information is available on the magnitude of lung function abnormalities in cashew factory workers. Objectives of the study: 1. To study the spirometric abnormality among symptomatic cashew factory workers. 2. To study the relationship between the severity of spirometric abnormality and the duration of job and various job sections respectively.

Materials and methods: Descriptive study was conducted among workers from 10 cashew factories of Kollam district from June 2012 to December 2012. Workers from different job sections with respiratory symptoms were interviewed with a structured questionnaire and all the workers were subjected to spirometry with reversibility. Data was analysed to find out the relationship between the severity of spirometric abnormality and the duration of job and various job sections respectively after adjusting for age, sex and smoking status.

Results: 250 patients were included in the study. Mean age was 47.4 years. 32% males and 68% females. 56.25% of males were smokers.41.6% workers were from shelling section, 20% from roasting section and 17.2% from peeling section. Mean duration of job was 19 yrs. Dyspnea (80.4%) was the most common symptom followed by cough(53.2%), allergic rhinitis (26.4%) and chest pain(4.8 %). Spirometry showed obstructive pattern in 52.4%, restriction in 8.8% and normal pattern in 38.8%. Analysis of data showed that severity of spirometric abnormality had no statistically significant association with duration of job or various job sections.

Conclusion: 61.2% of the study population had abnormal spirometry and obstructive pattern was most common abnormality .There was no statistically significant association between severity of spirometric abnormality and the duration of job or various job sections.

Suggestions: Steps like use of personal protection devices, improvement in ventilation at job sections with high smoke and dust exposure will help to reduce the respiratory morbidity in cashew factory workers.

Key words: COPD, Asthma, ILD,spirometry

Introduction

The cashew tree (Anacardium occidentale) was brought to India by Portuguese in 1500's. Today India is the largest producer and exporter of cashew kernels in the world. Cashew nut shell liquid (CSNL) is used for the preparation of resins, varnishes,paints, insecticides, wood preservatives etc.

Cashew processing is a labour intensive industry with limited use of technology. The steps in cashew processing include roasting, shelling, peeling, grading and packing. During roasting workers are exposed to noxious fumes and smoke. Workers in shelling and peeling section are exposed to soot particles, cashew peel dust etc. Exposure to smoke,fumes and dust are well known risk factors for various lung diseases including asthma[1], COPD[2] and hypersensitivity pneumonitis. Very little information is available on the magnitude of lung function abnormalities in cashew factory workers.

Objectives of the study

Primary Objective

To study the spirometric abnormality in symptomatic cashew factory workers.

Secondary Objectives

1. To study the relationship between the severity of spirometric abnormality and the duration of job.
2. To study the relationship between the severity of spirometric abnormality and various job sections

Materials and Methods

Descriptive study was conducted in 10 cashew factories of Kollam district from June 2012 to December 2012. Workers from different job sections with respiratory symptoms were included in the study. This study was conducted as a survey among cashew factory workers during medical camps organized in 10 factories. A total of 5420 people were working in these 10 cashew factories. Out of this 434 workers got registered for the section of medical camp dealing with Pulmonary Medicine. Symptomatic workers were selected based on a questionnaire. Workers with diagnosed respiratory diseases like asthma, pulmonary tuberculosis, bronchiectasis, COPD, ILD before joining the cashew factories and persons with systemic diseases like cardiac disease, chronic liver diseases, chronic renal disease, and thyroid diseases were excluded from the study. So from the registered group of workers 184 were excluded, and finally 250 persons were selected for the study. All the workers were interviewed with a structured questionnaire containing socio-demographic variables, detailed occupational history, hazards involved, smoking history, respiratory symptoms and other systemic diseases. All the selected workers were subjected to spirometry with reversibility using Vitalograph as part of camp itself. Spirometry results were interpreted using ATS/ERS guideline[3].Data was analysed using SPSS.11 to find out the relationship between the severity of spirometric abnormality and the duration of job and various job sections respectively after adjusting for age, gender and smoking status.

Results

250 patients were included in the study. Mean age of the study population was 47.4 years and 32%were males and 68% were females. 45 (56.25%) males were smokers. None of the females were smokers (table 1).

Table 1: Baseline characteristics of the study population

Age (mean)	47.4 yrs
Males	80(32%)
Females	170(68%)
Smoking status(males)	45 (56.25%)

Percentage distribution of the sample according to the job section is given in Table 2. 41.6% workers were from shelling section,20% from roasting and 17.2% from peeling.

Table 2 : Distribution of the sample according to the job section

Job section	Number	Percentage
Shelling	104	41.6
Roasting	50	20.0
Peeling	43	17.2
Grading	25	10.0
Cleaning	10	4.0
Watchmen	6	2.4
Supervisor	8	3.2
Clerk	4	1.6

Mean duration of job was 19 yrs (table 3). Dust, smoke and soot were the main hazards to which workers were exposed.

Table 3:Duration of job

Duration of job (yrs)	Number	Percentage
<10	72	28.8
10-19	59	23.6
20-29	60	24.0
30-39	37	14.8
>40	22	8.8

Dyspnea (80.4%) was the most common symptom followed by cough(53.2%), allergic rhinitis (26.4%) and chest pain (4.8%). (table 4)

Table4: Sympt]oms

Symptom	Number	Percentage
Dyspnoea	201	80.4
Cough	133	53.2
Allergic rhinitis	66	26.4
Chest pain	12	4.80

Spirometry showed obstructive pattern in 52.4%, restriction in 8.8% and normal pattern in 38.8% (table 5).15.2% patients had mild obstruction, 22% patients had moderate obstruction, 12.8% patients had severe obstruction and 2.4% patients had very severe obstruction. 54 (39%) patients with obstructive pattern showed reversibility to bronchodilator.

Table 5 : PFT Pattern

PFT pattern	Number	Percentage
Normal	97	38.8
Mild obstruction	38	15.2
Moderate Obstruction	55	22.0
Severe Obstruction	32	12.8
Very Severe obstruction	6	2.4
Restriction	22	8.8

Analysis of data showed that severity of spirometric abnormality had no statistically significant association with duration of job or various job sections while adjusting for age, sex and smoking status. There was no significant difference in spirometric abnormality among smokers and non smokers.

Discussion

Present study demonstrates that cashew factory workers are suffering from various respiratory symptoms like dyspnoea, cough, allergic rhinitis and chest pain. Dyspnea (80.4%) was the most common symptom in our study. Study on occupational diseases among cashew factory workers in coastal Karnataka by Ramachandra kamath showed that 11.3% of the workers were suffering from respiratory diseases[4]. In our study 61.2% of the study population had abnormal spirometry. Most common spirometric abnormality was obstructive pattern, of which 39% had reversible obstruction suggesting the possibility of asthma and 61% had non reversible obstruction suggesting the possibility of COPD. 15.2% patients had mild obstruction, 22% patients had moderate obstruction, 12.8% patients had severe obstruction and 2.4% patients had very severe obstruction. In this study there was no significant difference in airway obstruction among smokers and non smokers. This may be due to the fact that only a small portion of study population were smokers (45/250). 8.8% had restrictive pattern and 38.8% patients had normal pattern. This study identified dust, smoke and soot as main hazards in cashew processing which can cause respiratory diseases. Limited use of technology to contain processes like roasting, poor ventilation and lack of use of personal protection devices increases the chance for inhalation of dust and smoke. Smoking among male workers may have an additive effect on lung damage caused by occupational exposure. Analysis of data showed that severity of spirometric abnormality had no statistically significant association with duration of job or various job sections while adjusting for age, sex and smoking status.

Conclusion

Cashew factory workers are suffering from various respiratory symptoms like dyspnoea, cough, allergic rhinitis and chest pain. 61.2% of the study population had abnormal spirometry and obstructive pattern was the most common abnormality. Severity of spirometric abnormality had no statistically significant association with the duration of job or different job sections.

Suggesions

Steps like use of personal protection devices, improvement in ventilation at job sections with high smoke and dust exposure and use of technology to contain processes like roasting will help to reduce the respiratory morbidity in cashew factory workers.

Limitation

Only symptomatic individuals who volunteered to get registered for the camp were included in the study and the sample size was small. A large study including asymptomatic workers may be useful to find out the deleterious effect. Further evaluation of those individuals with abnormal spirometry, especially those with restrictive pattern, is needed.

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Radiology Quiz

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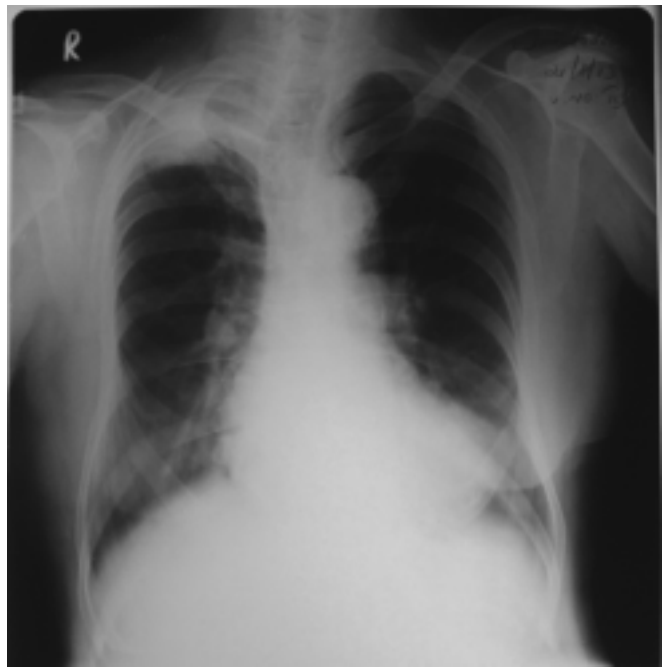
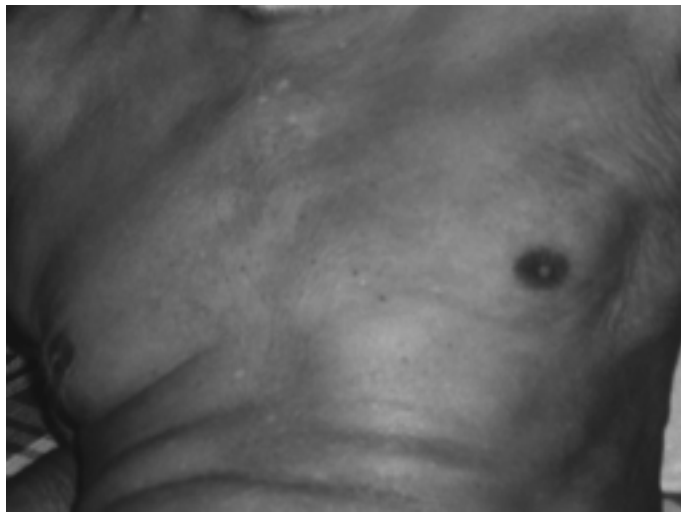


Chest X-ray PA view



This elderly male was diagnosed to have right upper lobe mass lesion which was proved to be carcinoma lung. His left lower zone showed an abnormal shadow not silhouetting with the cardiac border. He did not have gynaecomastia. Possible Diagnosis?

Answer in Page : 36

Case Report

An uncommon presentation of lung cancer - a case report

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Abstract:

Although bronchogenic carcinoma is one of the commonest malignancies affecting both men and women alike, it is more commonly seen in smokers and has a predilection to affect older people. One subtype of Non small cell lung cancer - adenocarcinoma has been described to occur more frequently in non smokers. It is known to affect women more than men and is very commonly seen in Asians and has a reasonably better prognosis compared to other subtypes of adenocarcinoma. Bronchogenic carcinoma is extremely uncommon in younger age group and herein we present the case of a 25 year old non smoking male who presented with cough of 1 month duration and on evaluation was found to have Non small cell lung cancer.

Keywords: Bronchogenic carcinoma, Non small cell lung cancer, young male

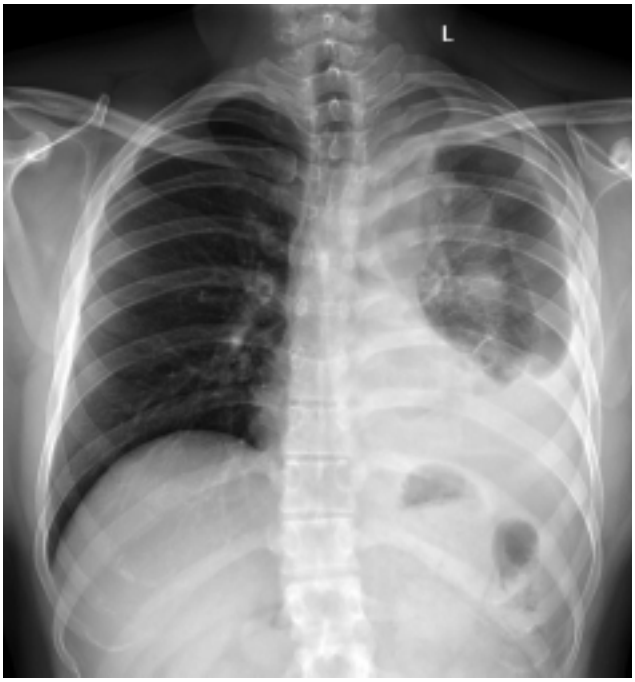
Introduction

Malignant neoplasms of lung are typically seen in smokers, past middle age. Recent studies have shown that one subtype of non small cell cancer namely adenocarcinoma is increasingly being detected and in some case series has been documented to be the commonest type of lung cancer. One subtype of adenocarcinoma is seen to occur more commonly in non smoking Asians and has a gender predilection, affecting women more commonly. This subtype on immunohistochemistry is usually positive for either EGFR or ALK mutations, which makes it more responsive for "targeted therapy" with drugs like tyrosine kinase inhibitors and ALK inhibitors. Bronchogenic carcinoma is uncommon in age less than 40 years and especially so, in non smokers. Herein we report the case of 25 year old non smoking male who presented with cough of 1 month duration and on investigation was found to have non small cell lung cancer. The case is being presented because of its rarity and also to highlight the fact that malignancy can never be overlooked in any age group

Case report

A 25 year old non smoking male, software engineer by profession, presented to our hospital for evaluation of cough of 1 month duration. Cough was non productive in nature. He denied having fever, weight loss, breathlessness, wheeze or chest pain. He did not have any relevant respiratory illness in the past. Clinical examination revealed a healthy man, not in any kind of distress. General examination did not reveal any abnormality. His vital signs were normal. Clinical examination of the respiratory system revealed a reduced intensity of breath sounds in the left infraxillary and infrascapular area. Other systems were within normal limits. Laboratory investigation revealed normal blood counts, an erythrocyte sedimentation rate of 32 mm/hour, and

normal hepatic and renal functions. Chest radiograph postero-anterior view revealed the presence of left hilar mass with minimal left sided pleural effusion (Fig 1).



Chest X-ray PA view showing a left paratracheal opacity extending to left hilum and minimal left sided pleural effusion

Sputum gram stain, cultures and acid fast staining were negative. He underwent a pleural aspiration which revealed the presence of exudative pleural effusion (protein-5.3mg%, glucose-75mg%, LDH-478 U/l, Serum LDH-263 u/l). There were 864 cell/mm3 of which 70% were lymphocytes and 30% were polymorphs. Pleural fluid ADA was 6.4. A CT scan of the thorax was taken which showed a large multilobulated mass lesion of size 14 x 8.1 x 6.3 cm involving the mediastinal pleural surface of left hemithorax including the left hilum. Multiple pleural and fissural based nodules were also seen. Moderate left sided pleural effusion was also seen (Figure 2). Since the radiological picture was suggestive of possible malignant process he was subjected to a CT guided biopsy.

Histopathological examination of biopsy specimen revealed patchy areas showing glandular spaces lined by columnar epithelium having vesicular nuclei with mild to moderate pleomorphism. These features were consistent with mucin secreting adenocarcinoma (Figure 3). Endothelial growth factor receptor (EGFR) and Echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase (EML-ALK) mutations were negative. Bronchoscopy was not done because tissue

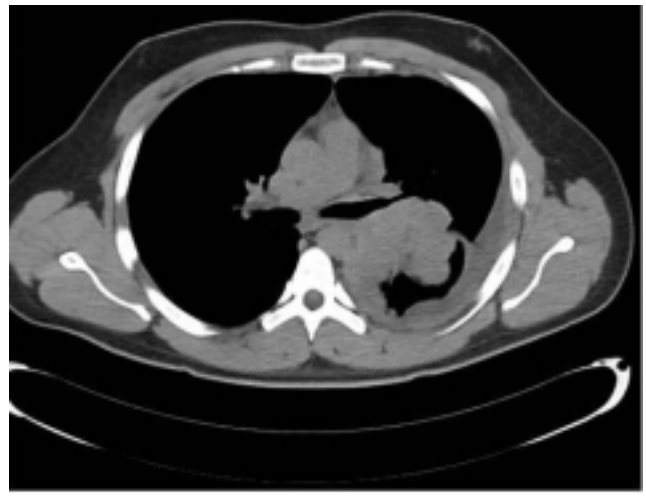


Fig. 2: CT thorax showing a multilobulated mass with left pleural effusion

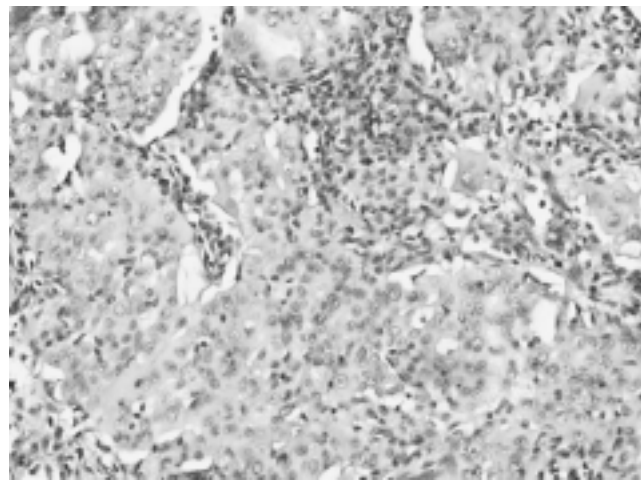


Fig. 3: Histopathology section (H and E, 400 X) showing tumor cells stained with PAS-D.

diagnosis was reached with CT guided biopsy itself. He was worked up for distant metastases with MRI brain, CT abdomen, Bone scan and PET CT scan, none of which showed any evidence of metastases elsewhere. He was started on chemotherapy with cisplatin and pemetrexed and after 4 cycles of chemotherapy has shown significant reduction in size of the tumor.

Discussion

Lung cancer is the leading cause of death worldwide[1] and it is among most common causes of cancer in india particularly in men with around 63000 new cases reported each year[2]. In patients under 25 years of age NSCLC is exceedingly rare, having an incidence rate for 2002-2006 of 0.3 per 100,000. Over the past four decades, there has been a shift in the pathologic distribution of NSCLC. Prior to the 1970s, squamous-cell carcinoma was

the most common histological type of NSCLC, however, after 1975, there has been a dramatic increase in the incidence of adenocarcinoma, making it the predominant histological subtype of NSCLC[3]. Presently, there is not much data on the distribution of the histological subtypes in India. A review article from 2004 stated that squamous-cell carcinoma was still the predominant histological subtype of NSCLC in India[4]. A more recent study found that adenocarcinoma accounts for 44% of NSCLC, while only 26% are squamous-cell carcinoma.[5]

Traditionally the strongest risk factors for lung cancer are tobacco use and age. The increase in the incidence of adenocarcinoma was thought to be mainly attributable to a change in smoking pattern and an increased preference for filter cigarettes that have low tar, but high nitrate content.[6] Earlier studies reported that the increased incidence of adenocarcinoma was confined to smokers. In contrast, recent studies found a statistically higher occurrence of adenocarcinoma in non-smokers as compared to smokers. This is supported by other studies in the literature. Thus, our case and other recent studies suggest that the increase in adenocarcinoma is not solely due to a change in pattern of cigarette smoking, but must be due to non-smoking-related factors, since the increase is demonstrated in non-smokers as well.[7,8] NSCLC occurring in young people have a higher incidence of adenocarcinoma especially in female patients, and most cases show no history of tobacco use. Genetic factors are known to play a role in the development of lung adenocarcinoma, and familial genetic clustering of lung cancer has been found. Common gene mutations in KRAS, EGFR, and p53 have been associated with a higher risk for development of lung adenocarcinoma. Survival in this group of patients remains highly variable with some studies showing a promising response to targeted therapy using novel drugs like Geftinib and Crizotinib. One study found no difference in survival between lung adenocarcinoma patients more than and less than 30 years of age [9]. Similarly, a retrospective study of patients younger than 50 years of age compared with those older than 50 found no difference in survival or in time to disease progression[10]. Survival in these young patients is associated primarily with stage, but it is not dependent on sex, age younger or older than 30 years, smoking history, histological type, or degree of differentiation. Overall the survival and prognosis of NSCLC in young patients remains dismal.

The aim of presenting this case report is to underline the fact that bronchogenic carcinoma can occur in any age group, and in non smokers and that it should be always considered as a differential diagnosis in any patient who presents with symptoms and radiological findings similar to what our patient had.

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Case Report

Unusual metastasis in a case of Carcinoma Lung

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Abstract:

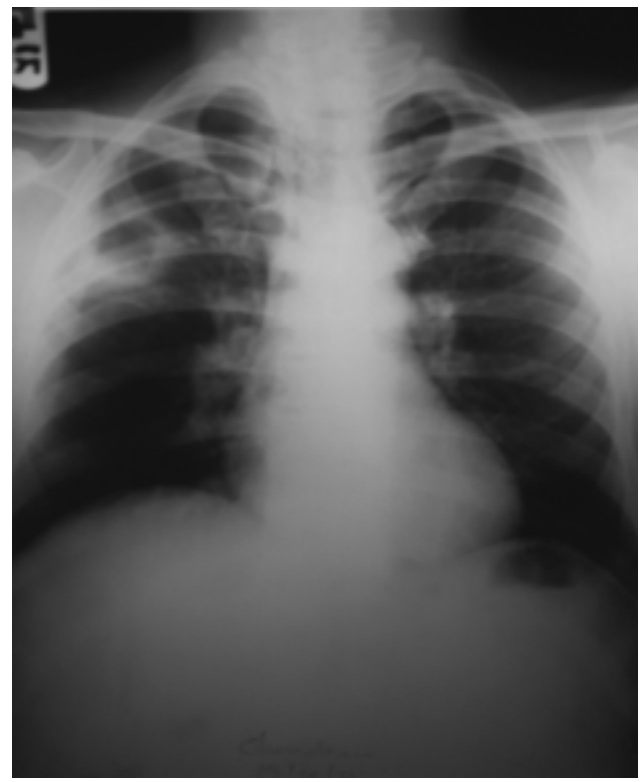
Metastasis from carcinoma lung occurs commonly to the brain, bone, adrenal glands, opposite lung, liver, pericardium, and kidneys. Adenocarcinoma of the lung metastasing to small bowel presenting as intussuception has been reported in literature. We here report the case of an elderly male who presented to us with a cavitating lung mass and colonic metastasis which turned out to be a very rare case of squamous cell carcinoma lung metastasing to the large bowel presenting as ileocaecal mass and intestinal obstruction.

Key words: Squamous cell carcinoma, Bowel metastasis

Case report

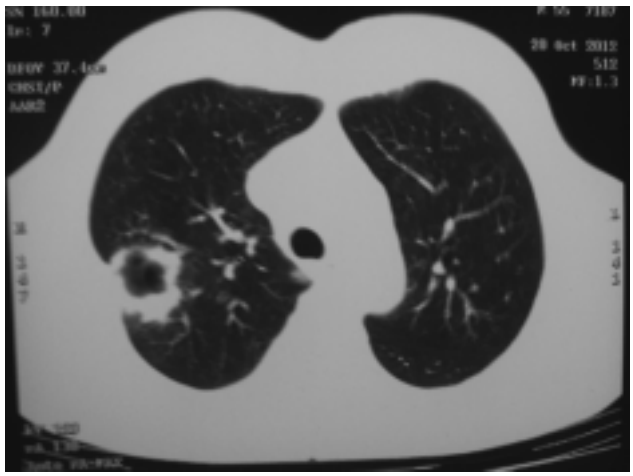
A Fifty five year old male smoker presented to us with fever and cough of one month duration. He gave history of loss of appetite and loss of weight of about five kilograms during this period. He did not have chest pain, expectoration or haemoptysis. There was no history of any major co-morbidities nor did he give any history suggestive of chronic obstructive pulmonary disease despite being a heavy smoker with smoking score of 1200. General examination revealed clubbing and pallor. There was no lymphadenopathy.Respiratory system examination showed tracheal deviation to right and a cavernous bronchial breath sounds in the infraclavicular and axillary area on the right side. Hence a provisional diagnosis of right upper lobe fibrocavitory disease was made and he was investigated for ruling out active tuberculosis.

His investigations were as follows; Hb: 8gm%, TC-12500 DC N34 L 66 ESR -55 mm/1st hr, RBS-125mg%, Sputum AFB X 2 samples -negative. His Chest X-ray PA view revealed a well defined cavity with irregular thick wall involving predominantly the right upper zone extending to the mid zone fig (1). His sputum cytology was negative and sputum culture and sensitivity revealed normal flora. Mantoux



Chest X-ray PA view Fig (1)

reaction was 15 mm. A CT-Chest taken showed thick walled cavity in the right upper lobe posterior segment and the radiologist gave the possibility of an infectious cause in the form of cavitating pneumonia, possibly tuberculosis as there was no evidence of any luminal mass, mediastinal nodes or bony lesions to suggest a malignancy fig (2)



CT chest showing peripheral cavity Fig (2)

Hence he was started on empirical CAT-I anti tuberculous chemotherapy(ATT) and was advised strict follow up to ensure clearance of the radiological lesion as he was smear negative and the possibility of a cavitating malignancy could not be fully ruled out at this point of time. A repeat chest X-ray at 3 months of CAT-I showed some clearance of the upper zone shadow fig (3). After

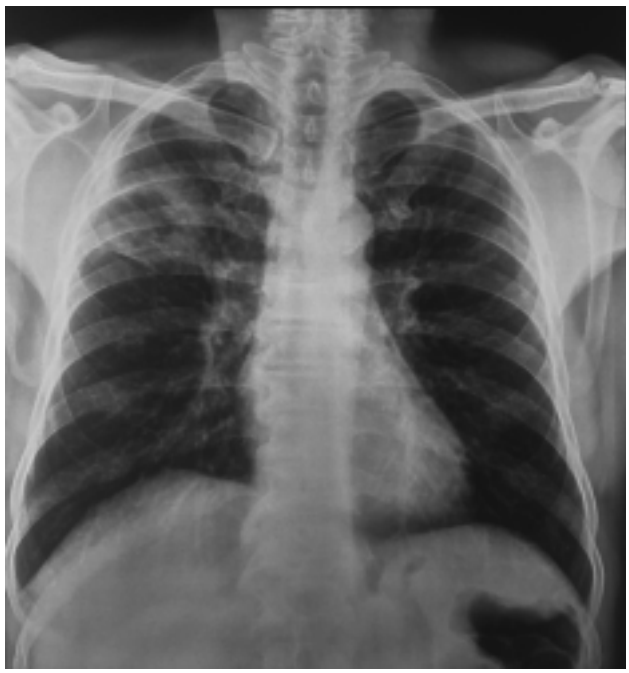


Fig (3) Chest X-ray PA after 3 months of CAT-I

about a month later patient developed severe abdominal pain and vomiting. He did not have any hepatic derangement following ATT intake. Hence a surgery consultation was sought to rule out alternate cause for his gastrointestinal problem. On evaluation he had features of sub acute intestinal obstruction and an erect abdomen AP view showed multiple air fluid levels and distended bowel loops and a clinical impression of ileocaecal mass possibly tuberculous aetiology with intestinal obstruction was made, Fig (4).

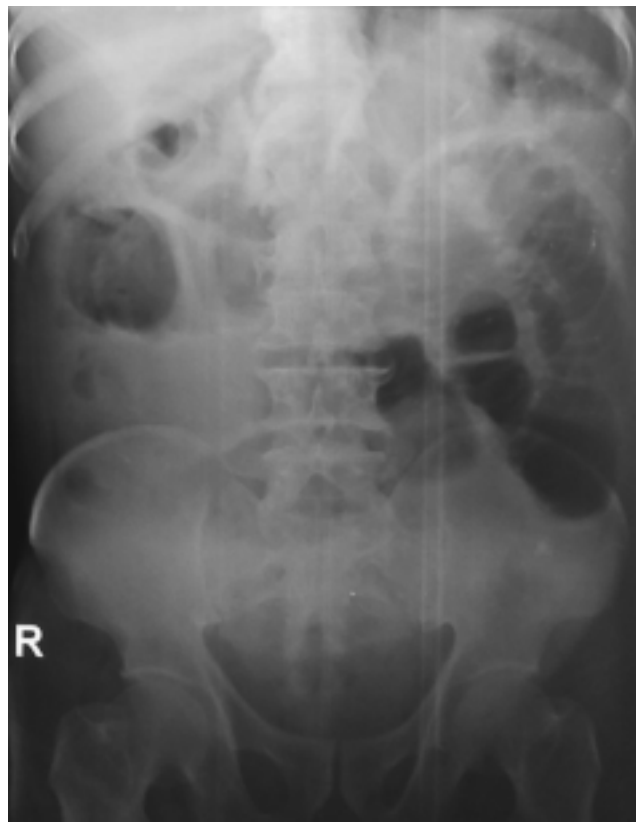


Fig (4) Digital X-ray abdomen AP erect view

An ultrasound abdomen confirmed mass in the right iliac fossa and it also revealed evidence of intestinal obstruction. The patient was immediately subjected to a laparotomy and the mass was resected along with distal ileum and right hemicolectomy was performed followed by end to end anastomosis. The post operative period was uneventful and he was restarted on ATT on the third post operative day. However there was a turn of events when the histopathology report of the resected specimen came as poorly differentiated squamous cell carcinoma which can only be a possibility from a metastasis from a primary elsewhere. This warranted a fibreoptic bronchoscopy and

there was evidence of a predominantly extra luminal compression of the right upper lobe apical segment with intra luminal extension. The biopsy and imprint smear report came as squamous cell carcinoma. A repeat Chest X-ray PA view at 5 months showed evidence of increasing opacity which earlier showed partial resolution which was the reason for the mistaken impression of response to empirical ATT. Finally this case turned out to be one of the most unusual presentation of a primary bronchogenic carcinoma presenting as a cavitating peripheral lung mass leading to intestinal metastasis and ileocaecal mass formation with intestinal obstruction. This was an eye opener to us and prompted us to pursue fibreoptic bronchoscopy in smear negative cases of peripheral cavitating lung lesions without adequate response to antibiotics.

Discussion

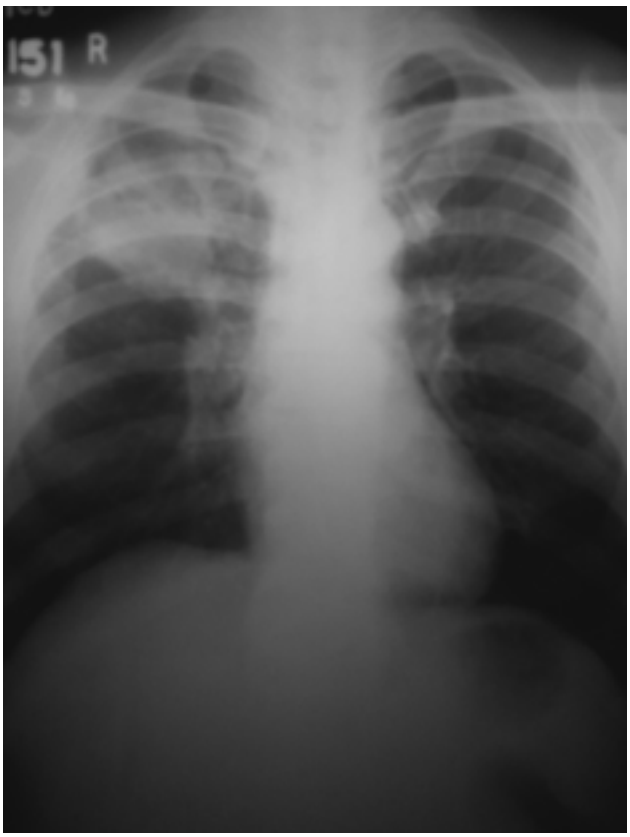


Fig (6) Repeat Chest X-ray showing increasing opacity

Primary carcinoma lung metastasing to the bowel, though very rare, has been reported in the literature[1,2,3.]Unusual histology from a resected specimen of bowel should raise this suspicion and alert the treating physician to search for a feasible primary elsewhere.Our case developed intestinal obstruction secondary to a metastatic lesion with a totally incompatible histology for a primary gastrointestinal malignancy which aided in the confirmation of primary malignancy in the lung with consistent histology of squamous cell carcinoma. The malignancies known to cause secondaries in the large bowel are stomach, breast, ovary, cervix, kidney, lung, bladder, prostate, head and neck tumors and melanoma [4,5]. The usual presentation is with multiple metastatic deposits, but can present as solitary lesion also. Clinically they present with symptoms of colonic obstruction, lower gastrointestinal bleed, weight loss, anemia, bowel perforation, or gastrointestinal fistula [6, 7, 8,9,10]. The usual presentation is after the diagnosis of the primary lesion, but can occur synchronously or before the diagnosis of the primary. Richie et al. suggested intra-luminal seedling of the tumor cells from ingestion of expectorated tumor cells from carcinoma lung [11].

Extrinsic tumours may involve small intestine by direct invasion, intra-peritoneal seeding or via the haematogenous route. The tumour emboli usually lodge into the submucosal layer, and their growth typically results in intramural masses with a bulky polypoid extension into the lumen. These polypoid lesions may obstruct the lumen or may ulcerate and present as perforation peritonitis. Sometimes they may ulcerate or erode into a vessel and present as gastrointestinal bleeding.

The lung cancer with intestinal metastasis has been reported to have poor prognosis with mean survival of only 4-8 weeks. The resection of the colonic and lung lesions, in selected patients, is reported to have survival advantage[12].

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Case Report

CPFE : The widening spectrum of Smoking related diseases

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Abstract:

Several recent studies have described a syndrome in which idiopathic pulmonary fibrosis (IPF) coexists with pulmonary emphysema. This comes as no surprise since both diseases are associated with a history of exposure to cigarette smoke. We report a case of combined pulmonary fibrosis and emphysema (CPFE) with severe pulmonary hypertension and corpulmonale in a 53-year-old farmer associated with tobacco smoking. Environmental exposure in the form of agrochemical compounds may be an additional risk factor in this case and confirms the clinical features of CPFE described elsewhere.

Key words Combined pulmonary fibrosis and emphysema (CPFE), idiopathic pulmonary fibrosis (IPF), pulmonary hypertension (PH).

Introduction

The findings of co-existing IPF and emphysema were first described in 1990 by Wiggins et al and the term combined pulmonary fibrosis and emphysema (CPFE) was coined by Cottin et al.[1] CPFE has been proposed as a new clinical entity in smokers or a different clinical phenotype in smokers developing idiopathic pulmonary fibrosis (IPF). These patients have severe dyspnoea, nearly stable lung functions, exercise desaturation, reduced diffusion capacity, severe pulmonary hypertension (PH) and associated shortened survival. High-resolution computed tomography (HRCT) usually shows upper lobe centrilobular emphysema and lower lobe fibrosis. The prevalence of CPFE may be close to 30% among cases of IPF and they have a significantly lower survival than those with only IPF.[2]

Case Report

A 53 year old farmer from Wayanad district of Kerala presented with progressive dyspnoea on exertion from grade 1 to grade 3, cough with scanty mucoid expectoration of 4 years and tiredness/fatigue on exertion of 1year duration which worsened since last one month with symptoms at rest. He, along with his father, were involved in agricultural activities from the age of fifteen, cultivating coffee, pepper and rice; not associated with rearing of cattle or birds. On examination, he was tachypnoeic, with a respiratory rate of 36/min, showed clubbing, had pedal oedema with elevated jugular venous pressure and bilateral fine crackles and minimal wheeze. His blood and sputum tests were within normal limits. Though he had a raised RA factor of 153, there were no joint symptoms or stigmata suggestive of a connective tissue disease. Arterial blood gas analysis showed pH 7.39/ PaO2 36.7/ PaCO2 49.3/ HCO3 29.8, with an alveolar arterial gradient of 67.13. X-ray chest [Figure 1] showed reticulonodular pattern mainly on left. HRCT [Figure 2] showed extensive fibrosis and ground glass pattern with mid-zone predominance with areas of honeycombing and upper lobe bullae. Spirometry showed mild restrictive abnormality with forced vital capacity (FVC) 1.86 L (65%predicted), forced expiratory volume in one second (FEV1) 1.48 L (65% predicted) and FEV1/FVC 80%. Diffusion capacity for carbon monoxide (DLCO) was 36% of the predicted value. On performing a six minute walk test, he could cover 56 metres only in two minutes with 11% Spo2 fall and increase in dyspnoea to 9 in BORG scale along with a pulse rate of 140/min and BP of 140/88 following which the test was terminated. Two-dimensional echocardiography (2D-ECHO) showed PH with tricuspid

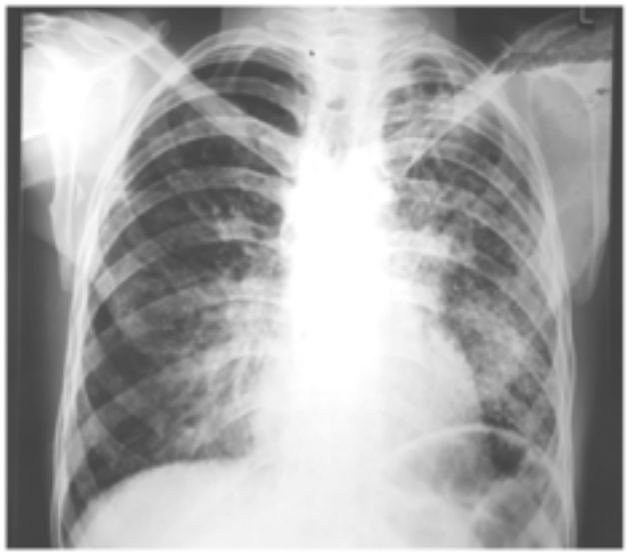

Fig. 1: Chest X-ray P/A view

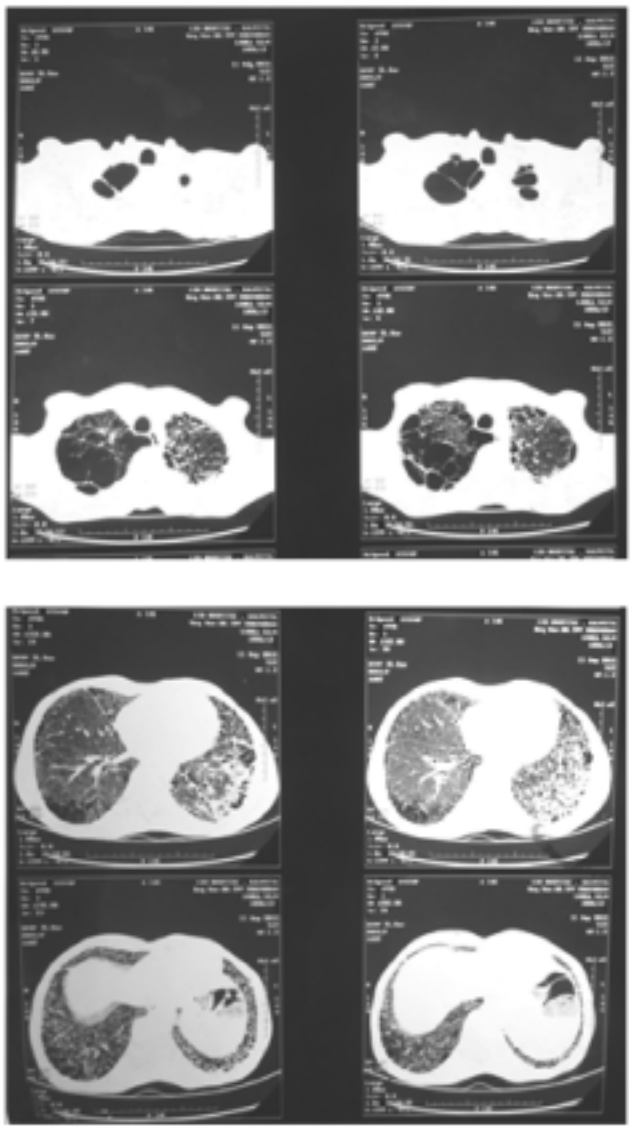

Figure2: HRCT Thorax

regurgitation (TR) jet- estimated pulmonary artery systolic pressure (PASP) of 68 mmHg with dilatation of right atrium and right ventricle. The clinical features, Pulmonary function tests and radiological picture was suggestive of CPFE. Thus a diagnosis of CPFE with corpulmonale was made and patient was treated with bronchodilators, LTOT, N Acetyl Cysteine, anticoagulants and other supportive measures. His condition gradually worsened over next two months period and finally succumbed to his illness.

Discussion

CPFE is most often observed in males (mean age of 65 years) who are tobacco smokers or ex-smokers of >40 pack-years [3]. CPFE has a poor prognosis, with a 5-year survival of 55%. CPFE may be found in patients presenting with lung cancer and cancer may develop in patients followed for CPFE, probably reflecting similarities in the susceptibility to chronic smoking-induced inflammation and carcinogenesis [4].Its association with connective tissue diseases like rheumatoid arthritis and systemic sclerosis and exposure to agrochemical compounds has also been described [5]. The risk of development of PH is higher (about 50%) in patients with CPFE than either IPF or emphysema alone, and its onset heralds a poor prognosis and increased mortality.

In most cases, CPFE occurs as a result of development of fibrosis in a known case of emphysema that may modify its progression. Conversely, the presence of pulmonary emphysema modifies the outcome of patients with IPF. A variety of pathologic patterns of pulmonary fibrosis have been reported in conjunction with emphysema in the CPFE syndrome including usual interstitial pneumonia, airspace enlargement with fibrosis, nonspecifc interstitial pneumonia, respiratory bronchiolitis associated interstitial lung disease with alveolar septal fbrosis, desquamative interstitial pneumonia with extensive fbrosis and unclassifiable smoking-related interstitial fbrosis.

Smoking results in the over expression of tumor necrosis factor-alfa (TNF-α), IL-1ß and neutrophil elastase which may be important in producing emphysema and pulmonary fibrosis. In a study by Wei et al, [6] pulmonary fibrosis in CPFE showed intrinsic characteristics, with smoking not being the major or direct pulmonary fibrosis-

driven factor. He suggested the role of serum pro-collagen III N-terminal peptide (PIIINP) as a marker of early detection and efficacy assessment parameter of treatment and the possible utility of anti-lymphocytes and immune regulation strategy for disease intervention. A heterozygous mutation in SFTPC (the gene encoding surfactant protein C) has been reported in a non-smoking young female with CPFE. In addition, both fibrosis and emphysema are associated with shorter telomeres and smokers also have shorter telomeres as compared with non-smokers.

The physiologic consequences of the CPFE syndrome include preservation of spirometric values and lung volumes despite extensive radiographic evidence of lung disease as well as marked impairment of gas exchange manifested as a reduction in DLco. Resting and exertional hypoxemia is common in CPFE syndrome. In the series by Cottin et al, mean PaO2 at rest on room air was 63± 14 mm Hg, with an elevated average A-a gradient of 41± 16 mm Hg and average exertional desaturation of 8.9% during 6-min walk testing.

Although emphysema may modify the HRCT appearance of fibrosis, the characteristic imaging features of CPFE include radiological evidence of emphysema in the upper zones (i.e. centrilobular and/or paraseptal emphysema) in 90% of cases, and diffuse infiltrating fibrosing lung disease at the bases (subpleural reticular opacities, honeycomb images and traction bronchiectasis), with more frequent ground-glass opacities than in IPF. The composite physiologic index (CPI) was developed to improve on previous prognostic measures in IPF by adjusting for emphysema and incorporating multiple measures of pulmonary function, namely forced expiratory volume in 1 s (FEV1), FVC and DLCo . The CPI score at diagnosis more accurately predicted mortality than the individual pulmonary function tests (PFTs) alone in patients with concomitant emphysema.

Therapeutic options for patients with CPFE are limited and may require treatment for both IPF and emphysema. Smoking cessation is an obvious objective. Oxygen therapy is appropriate for the management of hypoxaemia. Inhaled bronchodilators are often prescribed. Treatment with immunomodulator therapy, similar to that used for treating IPF e.g. N-acetylcysteine or novel agents such as pirfenidone, has been considered although no studies have been published to date on this issue. Lung transplantation should be considered for patients with CPFE, given the signifcant mortality associated with this disorder. The relatively preserved spirometry associated with CPFE may disfavour such patients for lung allocation.

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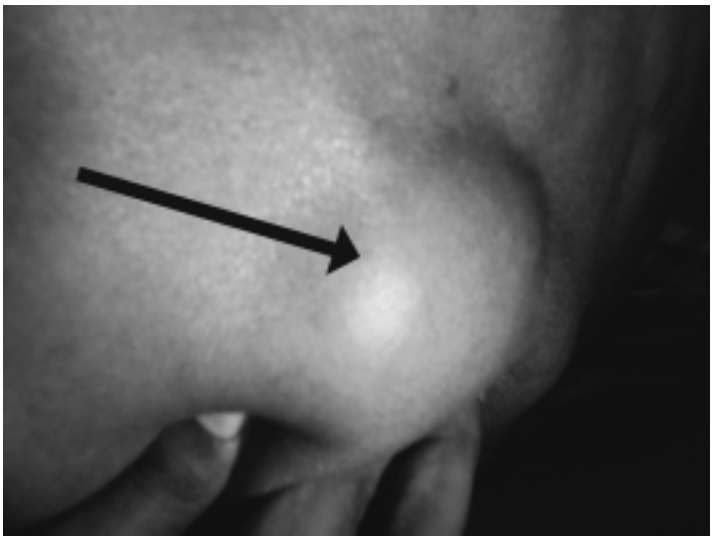
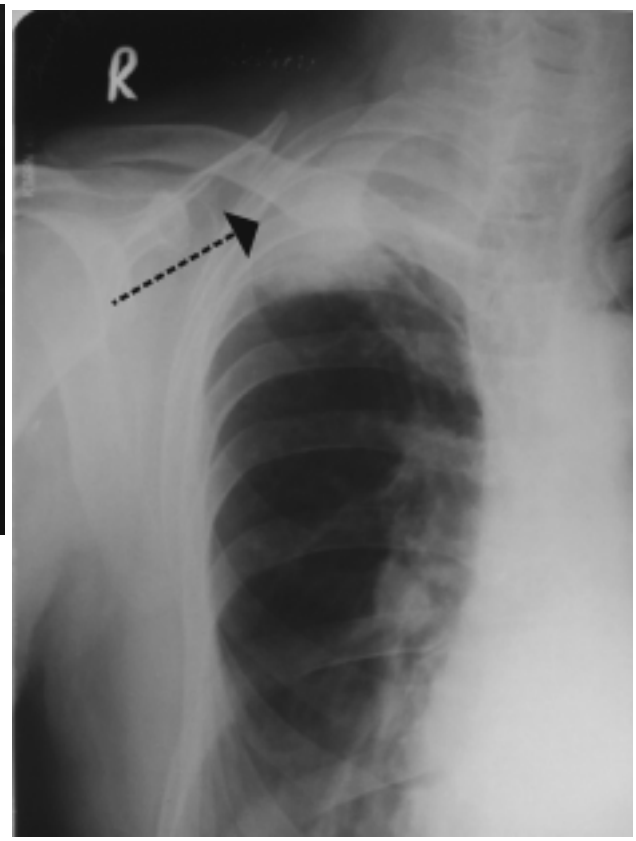
Answer

Posterior Chest wall lipoma (bold arrow).

The Left lower zone opacity turned out to be a posterior chest wall lipoma which was embedded deep beneath the chest wall musculature and could only be made prominent by deep palpation. A non silhouetting opacity adjacent to cardiac shadow need not always necessarily be an intra thoracic posterior lesion, as chest wall swellings cast similar shadows in a PA projection. He also had a fracture malunion of the right clavicle (interrupted arrow). Though the patient had carcinoma lung to account for his right upper lobe opacity he also had two co existent radiological abnormalities which were incidental findings emphasising the need for systematic reading of chest radiographs.



Posterior chest wall lipoma



Incidental finding of malunion fracture right clavicle

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