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Out of the Fire and into the Fire Again- Advanced Interstitial Lung Disease due to Disseminated Adenocarcinoma Lung A Case Report & Review of the Subject

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SUMMARY

This case describes an elderly lady who developed an advanced fibrotic lung disease without any accompanying systemic illness or occupational exposures. She presented with gradually progressive exertional dyspnea and was found to have bilateral wheezes and inspiratory crackles on respiratory system examination. She was put on empirical steroids due to her high resolution computerized tomography (HRCT) chest findings which were consistent with bilateral areas of ground glass opacification (GGO) and fibrotic lesions suggestive of interstitial lung diseases (ILD) like sarcoidosis, chronic hypersensitivity pneumonitis or an idiopathic interstitial pneumonia e.g NSIP. Furthermore, she underwent bronchoscopy with transbronchial lung biopsy (TBLB) showing chronic inflammation while the bronchoalveolar lavage (BAL) was neutrophilic with positive malignant cytology for disseminated lung adenocarcinoma. This case is reported to highlight the importance of BAL in patients with undiagnosed ILD as well as atypical presentations of malignancies masquerading as ILD.

Key words: Adenocarcinoma, bronchoalveolar lavage, BAL, interstitial lung disease.

INTRODUCTION

Diffuse interstitial lung disease/diffuse parenchymal lung disease (DPLD) is a generic term encompassing a broad range of largely unrelated conditions that share the propensity to cause breathlessness and/or cough associated with bilateral abnormal opacities of various types on conventional chest radiographs or HRCT scans.[1] The initial evaluation of patients with ILD is aimed at identifying its etiology and severity.[2] The results of laboratory, radiographic, and pulmonary function tests guide the decisions about whether to pursue for BAL and/or transbronchial, thoracoscopic, or open lung biopsy.[2] Besides primary ILDs (unknown etiology), the differential diagnosis of DPLDs include ILDs associated with a broad range of systemic diseases like sarcoidosis and connective tissue disorders, organic and inorganic dust exposures, and drugs like nitrofurantoin, amiodarone or ethambutol exposure.[1,2] Malignant processes which can cause diffuse parenchymal shadowing include pulmonary lymphoma, multiple pulmonary nodules, miliary metastasis and/or lymphangitis carcinomatosis. Adenocarcinoma (formerly bronchioloalveolar carcinoma/BAC) can rarely have a confusing radiological presentation characterized by diffuse parenchymal or interstitial infiltrates resembling pneumonic infiltrates or an ILD.[3]

CASE REPORT

A 65-year-old lady from Sargodha was evaluated in pulmonary clinic due to gradually progressive exertional dyspnea and dry cough of 2-3 years duration. There was no history of wheezes, chest pain or hemoptysis. There was accompanying

anorexia and considerable weight loss during this illness. As prescribed by her family physician, she was using oral prednisolone and inhaled bronchodilators and steroids without any relief in symptoms. Her past, family and drug histories were not contributory. On examination, she had tachycardia (regular pulse 100/m), BP 110/76 mmHg, tachypnea (respiratory rate 36/min) and was afebrile with SpO_2 of 88%. She was pale, had mild epigastric tenderness and there were bilateral coarse crackles and occasional wheezes on chest examination. Remaining systemic examination was unremarkable.

Investigations included CBC (haemoglobin 9.7 g/dL, WCC 6 x 10^9, platelets 243 x 10^9 and ESR was 24 mm at 1st hour. Biochemical profile revealed slight elevation of liver enzymes (bilirubin 0.4 mg/dL, ALT 64 IU/L, AST 55 IU/L, alkaline phosphatase 103 IU/L). Renal functions were normal. Spirometry illustrated severe restriction (FEV_1 43 % and FVC 46 % predicted) and blood gas analysis showed a respiratory alkalosis with arterial hypoxemia (pO_2 70 mmHg).

Chest radiograph (seen on top right image of Fig. 1) showed bilateral loss of lung volumes and prominent broncho-vascular markings. HRCT chest findings (Fig. 2 & 3) were suggestive of ILD including bilateral diffuse areas of GGO interspersed with fibrotic foci characterized by interlobar and intralobular septal thickening and honey combing. Right upper and left lower lobes had more fibrotic lesions compared to left upper and right lower lobes which had more GGOs. Small volume mediastinal lymphadenomegaly was also appreciated on CT imaging. The radiological differentials included sarcoidosis, chronic hypersensitivity pneumonitis, non specific interstitial pneumonitis (NSIP) or idiopathic pulmonary fibrosis (IPF).

Patient was counseled for bronchoscopy to make an accurate etiological diagnosis of ILD to find steroid responsive versus non responsive disease. On bronchoscopic evaluation, all airways on both sides of bronchial tree were clear having normal mucosal color, texture, architecture, orifices and sub-carinae up to sub-segmental level. Bronchoalveolar lavage (hazy non hemorrhagic fluid return) and transbronchial lung biopsies were taken from the basal segments of right lower lobe. BAL total white cell count was 70/cmm and differential cells were neutrophils 90 % and lymphocytes 10 %. BAL malignant cytology was diagnostic for non small cell lung cancer of adenocarcinoma sub type and TBLB showed non-specific inflammation. She was advised to taper her steroids and was discharged on domiciliary oxygen and was further instructed to seek consultation from oncologist.

DISCUSSION

Precise diagnosis in ILD is of prime importance because the treatment choices and prognosis vary among the different causes and types of ILDs.[1] A detailed history especially of the hobbies, environmental exposures, use of drugs and occupational details in a chronological fashion are important to dig into the current and sometimes forgotten past local and foreign exposures.[1,2] In patients without any relevant exposures history, serologic studies should be considered to ensure that subclinical connective tissue disorders are not overlooked. [1, 3] Radiological patterns of ILDs can provide important diagnostic clues and map for planning further diagnostic procedures including bronchoscopy or lung biopsy. The most common radiographic abnormality on conventional chest radiograph is a reticular pattern; however, nodular or mixed patterns (alveolar filling and increased interstitial markings) are not unusual in clinical practice.[1] HRCT chest (supine and prone images to avoid confusing dependent atelectasis with interstitial opacities) should be considered in all patients having suspicion of ILD because of its high diagnostic accuracy.[5] Certain HRCT findings help to narrow the differential diagnosis of ILD like bilateral hilar lymphadenopathy and upper zone reticular opacities (sarcoidosis), pleural plaques with linear calcification (asbestosis), centrilobular nodules that spare the subpleural region (hypersensitivity pneumonitis, sarcoidosis, Langerhans cell histiocytosis and respiratory/ follicular/cellular bronchiolitis), irregular cysts associated with nodules in the upper and middle lung zones (pulmonary Langerhans cell histiocytosis), subpleural and bibasilar reticular

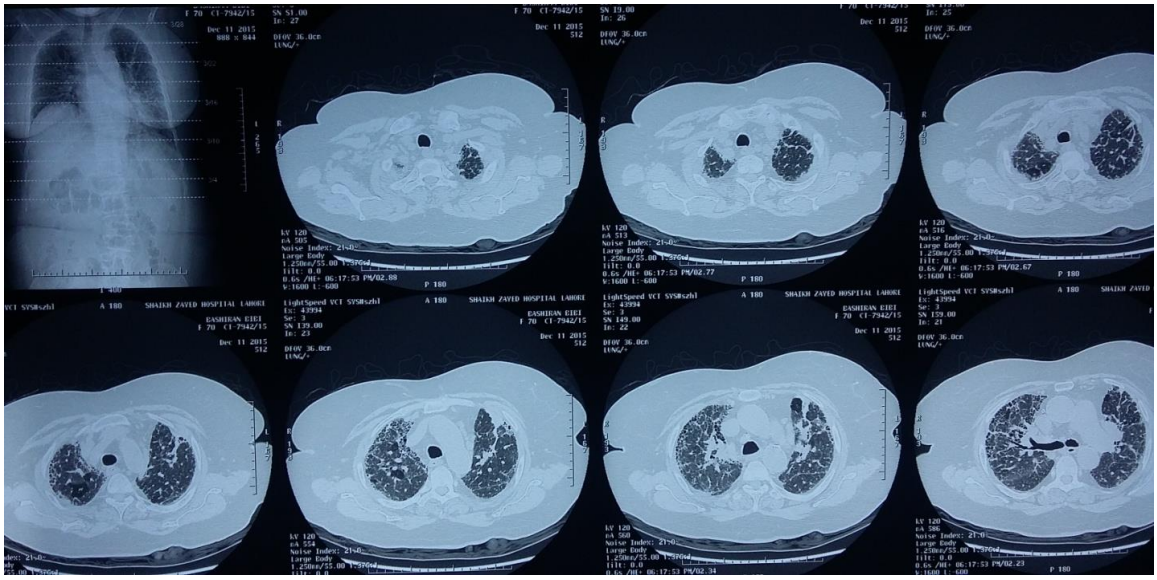

Fig. 1: HRCT chest mages from the level of trachea to carina showing bilateral diffuse areas of GGOs, interspersed with fibrotic foci characterized by interlobar and intralobular septal thickening and honey combing. There is bilateral loss of volume predominantly on left side.

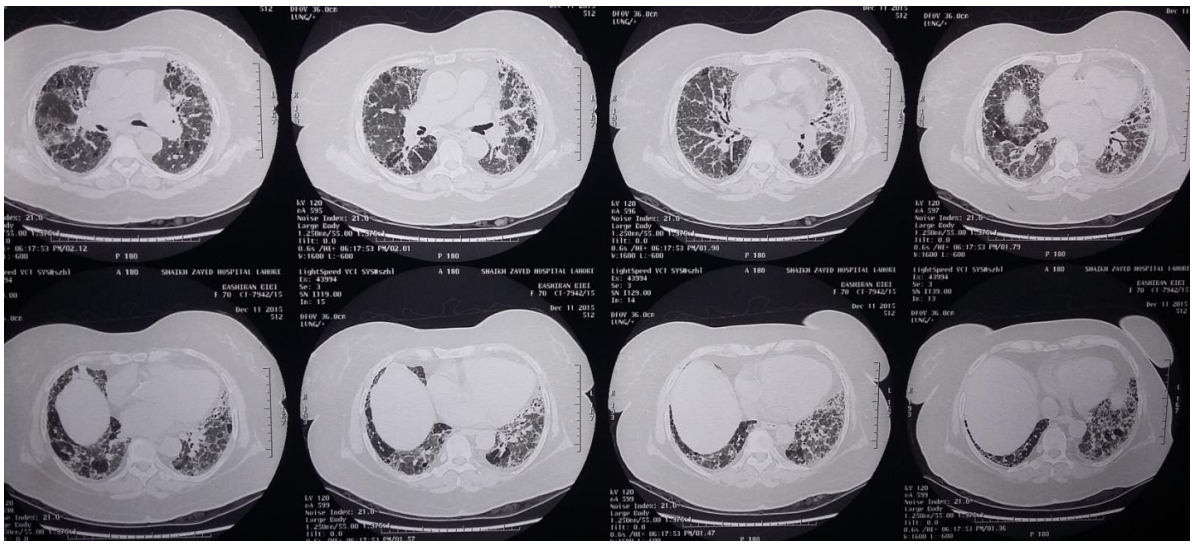

Fig. 2: HRCT chest imaging from the level below the carina to lung bases showing bilateral diffuse GGOs, interspersed with fibrotic foci characterized by interlobar and intralobular septal thickening and honey combing. Right upper and left lower lobes show more fibrotic lesions compared to left upper and right lower lobes containing more GGOs.

opacities associated with honeycombing and traction bronchiectasis (IPF, drug induced pulmonary fibrosis, chronic hypersensitivity pneumonitis, or rheumatoid arthritis associated ILD).[1, 5]

Bronchoalveolar lavage, also termed as liquid lung biopsy is performed using flexible fiberoptic bronchoscopy to obtain samples of cells and fluid from the distal airways and alveoli. [1, 4] It can be utilized to further evaluate lung abnormalities that

suggest infectious, immunologic, or malignant etiology.[4] If disease is diffuse, BAL is obtained from the right middle lobe otherwise it should be taken from the involved lobe or segment. BAL can be sent for cell counts, microbiology, cytology, flow cytometry, polymerase chain reaction, DNA probes, and tissue markers. [1, 4] It can be literally diagnostic in a variety of pulmonary conditions including but not limited to opportunistic infections, pulmonary alveolar proteinosis (milky or opaque appearance; alveolar macrophages filled with periodic acid-Schiff–positive material and lamellar bodies), alveolar hemorrhage, eosinophilic pneumonias (acute > 25% eosinophils; chronic > 40%), chronic beryllium disease (beryllium lymphocyte proliferative test), Langerhans cell histocytosis (> 4% CD1+ Langerhans cells) and ventilator-associated pneumonia (quantitative cultures showing ≥ 104 CFU/mL).[1, 2, 4] Besides these benign processes, BAL can be diagnostic when obtained from a localized or diffuse malignant infiltrate.[4] When the results of the above evaluation do not allow the clinician to make a confident diagnosis of a given type or stage of ILD, lung biopsy (transbronchial/thoracoscopic/open) with careful examination of lung tissue may be necessary.[1] Gallium-67 lung scanning and FDG-PET scanning are not routinely recommended for the diagnostic work up of ILD.[6]

Adenocarcinoma can have a highly variable clinical presentation, ranging from a small solitary pulmonary nodule or limited number of pulmonary nodules, to more extensive miliary disease, or diffuse interstitial or parenchymal infiltrates resembling pneumonia.[3, 7] Different areas of disease may progress at different rates within the same patient, and foci of disease that are initially indolent may become more rapidly progressive over time.[7] As described above, BAL and/or lung biopsy (TBLB, imaging guided trucut biopsy, thoracoscopic or open surgical techniques) can help diagnosing a diffuse malignant process if this is the clinical presentation of lung adenocarcinoma.[4] Rarely patients with disseminated adenocarcinoma presenting as ILD may be diagnosed on postmortem examination.[8]

In this patient there was diffuse pulmonary parenchymal shadowing on HRCT that carried high clinical suspicion for an ILD like IPF that typically occurs in this age group albeit NSIP and sarcoidosis or extrinsic allergic alveolitis and other primary interstitial pneumonias could also be found in elderly population. Use of prednisolone is recommended only in steroid responsive ILDs like organizing pneumonia (OP), eosinophilic pneumonia and NSIP or sarcoidosis etc, so it is wiser to consider an invasive procedure like BAL and TBLB/open lung biopsy to make an accurate diagnosis. Invasive diagnostic procedure besides providing an accurate diagnosis is also useful to rule out an infectious or a malignant disease process where use of empirical steroids can lead to fatal outcomes. Weather the cause of adenocarcinoma in this patient was scarring (scar carcinoma) due to ILD (chronic non specific inflammation on TBLB) or the malignancy itself (BAL cytology positive for adenocarcinoma) was responsible for pulmonary fibrosis remains inconclusive. Neutrophilic BAL is against the diagnosis of a chronic ILD like OP, NSIP and drug induced pulmonary fibrosis or sarcoidosis where lymphocytic predominance is typically seen or even eosinophilic pneumonias which are characterized predominantly by BAL eosinophilia. The argument against an ILD also arises from the fact that if this chronic non specific inflammation was due to NSIP or a steroid responsive ILD, it should have at least partially responded to steroids which it did not. IPF as a radiological diagnosis is also questionable because of predominance of ground glass opacities, involvement of central lung regions, relative sparing of right lower lobe and absent typical honey combing in lung bases bilaterally. Right upper and left lower lobes had more fibrotic lesions (favors IPF) compared to left upper and right lower lobes which had more GGOs (against IPF). Lastly, the diffuse interstitial shadowing could be partly attributed to lymphangitis carcinomatosis in this case and GGOs could be representative of tumor cells filling the air spaces.

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