CLINICAL VIGNETTE

A Second Opinion

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A 37-year-old woman was evaluated for a three-year history of ongoing shortness of breath and productive cough at interstitial lung disease (ILD) clinic. The patient's medical history included allergic rhinitis and a hospitalization four years ago for pneumonia. Following her admission for pneumonia, she required daily moderate dose oral steroid treatment to maintain her daily activities. She was followed by a pulmonologist at an outside hospital and was diagnosed with ILD. Upon transfer to UCLA, a repeat computed tomography (CT) (Figure 1) showed bilateral diffuse upper lobe dominant ground glass opacities and pulmonary fibrosis, consistent with ILD and she was referred to the ILD clinic for a second opinion.

Evaluation for ILD

There are more than 300 causes of ILD and evaluation typically requires a multidisciplinary approach. The general elements of clinical evaluation are: detailed medical, social, family, and exposure histories, routine laboratory evaluation and specialized testing for auto antibodies, IgG precipitin testing against environmental toxins, detailed cardiac and pulmonary physical examination, high resolution (HR) CT imaging, lung function testing and exercise tolerance analysis (e.g., six-minute walk test). Symptoms permitting, echocardiogram and modified barium swallow testing can be performed. In many cases, bronchofiberoscopic exam or surgical lung biopsy (SLB) are also necessary to further narrow the diagnosis. SLB, most commonly performed as video-assisted thoracoscopic surgery (VATS) from multiple lung lobes, is the "gold standard" for the evaluation of ILD.[1] It provides sufficient material to evaluate histology even in diseases which may spare parts of the lung.

Our Patient

Our patient's distant medical history was only positive for allergic rhinitis. She was a never smoker and had no drug or alcohol abuse history. She had no family members with pulmonary problems. She works as a laboratory technician but did not report exposure to environmental irritants or medications known to cause lung disease. On physical exam, we noted trachycardia on minimal exertion and diffuse expiratory crackles throughout the lungs. She is moderately obese with BMI of 35. Complete blood count and complete metabolic panel results were within normal limits. Auto antibodies including rheumatoid factor, cyclic citrullinated peptide, antiRo/SSA- antiLa/SSB, double stranded DNA, opoisomerase I (SCL-70), antinuclear antibody, antinuclear cytoplasmic antibody and Smith/ribonucleic protein were negative. Urine analysis, C-reactive protein and red blood cell sedimentation rate were within normal limits. IgG precipitin testing was performed for common bird and fungal elements, but only showed mild sensitization against Aspergillus flavus. Moderately severe restrictive lung disease with moderate diffusion defect was seen on lung function testing, which was consistent with ILD observed on HRCT imaging. At the visit the patient was able to ambulate 489 meters on six-minute walk test but her oxygen saturation dropped to 89%. Based on the available data a differential diagnosis was generated, which is listed with its typical characteristics in Table 1. SLB biopsy done one year previously was requested.

Lung Pathology

Initial pathological review the described SLB diffuse bronchiolocentric fibrosis. No granulomas or honeycombing were present, but the pathological picture was suggestive of chronic hypersensitivity pneumonitis (Figure 2).

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (HP) is also called extrinsic allergic alveolitis reflecting alveolar inflammation mediated by IgG antibodies formed against organic or inorganic environmental pollutants. HP is a rare disease with an estimated prevalence of 1.6 to 2.7 cases per 100,000 persons.[2] HP has been commonly associated with specific agricultural exposures including paprika peelers disease, farmers' lung and bird breeders' disease, but there is a large list of fungal and bacterial elements, industrial and agricultural dusts that can cause the disease. HP is usually categorized based on chronicity as either acute, subacute, or chronic. The acute and subacute forms represent changes in the lung that are primarily inflammatory and potentially reversible with less than 6 month exposure history, while chronic HP (CHP) usually presents with irreversible reticulation, fibrosis and honeycombing with greater than 6 months exposure history. CT imaging typically includes upper lobe predominant lung opacities with diffuse air trapping best appreciated on expiratory sequences. Lung pathology is best evaluated in lung tissue obtained with SLB. Histological changes consist of loosely formed granulomas with lymphocytic bronchiolitis and no evidence of lung infection. Bronchoscopic evaluation with bronchoalveolar lavage (BAL) is also recommended by some

experts.[3] Lymphocyte predominance in the BAL with a low CD4/CD8 lymphocyte ratio makes HP the likely diagnosis, but this test has a relatively low sensitivity and specificity.[4] Blood based IgG antigen testing for mold and organic dust such as bird dropping or feathers, commonly referred to as HP panel, can also be suggestive of the diagnosis. However, HP panels have a low negative predictive value, because they test only for a few environmental factors. As there is no specific testing for HP, pulmonologists heavily rely on a multidisciplinary consensus opinion to make the diagnosis.

The treatment for HP usually consist of prolonged oral steroid therapy in combination with a steroid sparing agent such as mycophenolate mofetil (MMF) or azathioprine. Despite the availability of these medications, average survival of CHP is approximately 7 years and many patients, if eligible, require lung transplantation due to continued clinical deterioration.[5]

Interstitial Lung Disease Multidisciplinary Conference

The lack of response to usual corticosteroid therapy puzzled us and the case was presented at the intestinal lung disease (ILD) multidisciplinary conference. Current international guidelines recommend multidisciplinary evaluation of ILD cases.[1] Our team consists of rheumatology, pathology, radiology and pulmonology. Thoracic surgery, oncology, physical therapy and respiratory therapy consultations are available as needed. Cases are reviewed weekly by the conference committee members after a brief live presentation. The team review has multiple advantages: A) It allows input from different subspecialties in these often challenging cases. B) A consensus opinion can be formed, which helps with therapeutic decision-making. C) Patients and their families can obtain a second opinion of care management from the ILD team. D) Conference cases are a teaching tool for physicians in training. E) Reviewed cases are categorized based on disease and can be contacted for ongoing basic and clinical research studies.

Re-review of the lung pathology was recommended by the conference for this case.

Invasive Mucinous Adenocarcinoma

Pathology re-review identified invasive mucinous adenocarcinoma in combination with fibrosis. Invasive mucinous adenocarcinoma is an independent subtype of non- small cell lung cancers and represent only 5% of all adenocarcinomas.[6] Initially described as mucinous bronchioloalveolar carcinoma, these rare cancers clinically present as non-resolving pneumonias or ILD.[7] Clinical suspicion is often raised when younger and never smoker patients present with large quantities of sputum production. These tumors tend to spread via airspaces and the lymphatic system and less commonly have extrapulmonary metastases. The cancer cells also have an atypical immunophenotype for lung adenocarcinoma and express antigens to cytokeratin 20 (CK20) and caudal type homeobox 2 (CDX2). The tumors often lack thyroid transcription factor 1 (TTF-1) which is common in other adenocarcinomas.[8] Most cases do not demonstrate epidermal growth factor receptor (EGFR)-1 mutations, anaplastic lymphoma kinase (ALK) translocations or programmed cell death (PD)-1 ligand expression. Therefore, they are usually not susceptible to newer systemic therapies. Patients are usually treated with conventional platinum-based chemotherapy, but re-occurrence rates are high and the prognosis remains poor.[9] A survival timeline is difficult to provide due to the rarity of the disease.

Our Case

The consensus of the tumor and ILD conference members was that the patient has both CHP and invasive adenocarcinoma. She was initially advised against immunosuppressive drugs for CHP treatment given their potential to fuel malignancy. Given the relative stability of chest imaging over one year, lack of systemic symptoms, extremely high risk of ILD flare with chemotherapy and general poor response to platinum-based treatment she was not recommended to start chemotherapy. However, a more prominent but not enlarging nodule in the right lower lobe, suspicious for malignancy, was re-identified on 6-month follow-up chest CT and was cryo-ablated by interventional radiology (Figure 3). Her oral corticosteroid regimen was re-assessed due to unchanged respiratory symptoms over the past year, worsening obesity, glaucoma, prediabetes and mood lability. The decision was recently made to stop steroids and start immunosuppression with MMF for her CHP. This case highlights the complexity of ILD cases and the added benefit of ILD conference to the care of our patients.

Figures

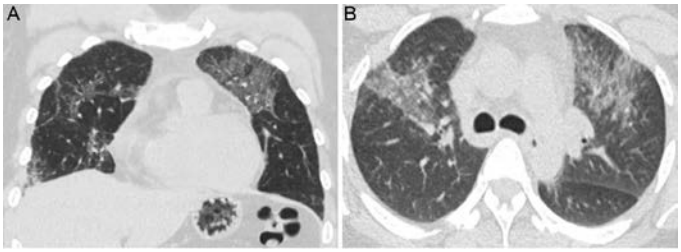

Figure 1. High resolution lung CT imaging of the patient on initial presentation to clinic. A. Sagittal reconstruction imaging showed upper lobe dominant ground glass opacities with diffuse fibrosis. Mediastina lymphadenopathy was not observed. B. Expiratory axial imaging did not reveal diffuse air trapping.

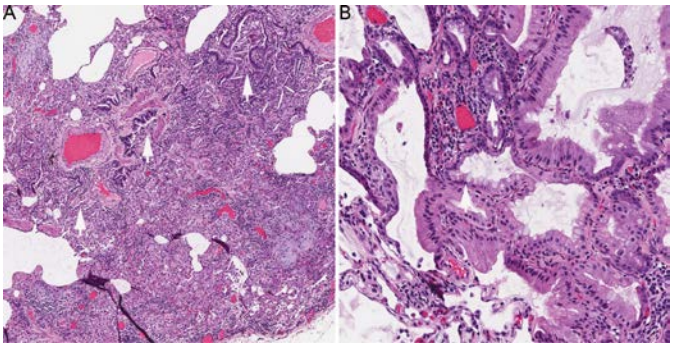

Figure 2. Histopathology analysis of surgical lung biopsy with hematoxylin-eosin staining. A. Light microscopic analysis identified peribronchiolar inflammation with mild fibrotic changes. Arrows are pointing at mononuclear cell infiltration in the peribronchiolar tissue. 40x magnification. B. Incidentally discovered invasive mucinous adenocarcinoma of the right lower lung lobe. Arrows are pointing at atypical mucus producing cells lining the alveolai. 110x magnification.

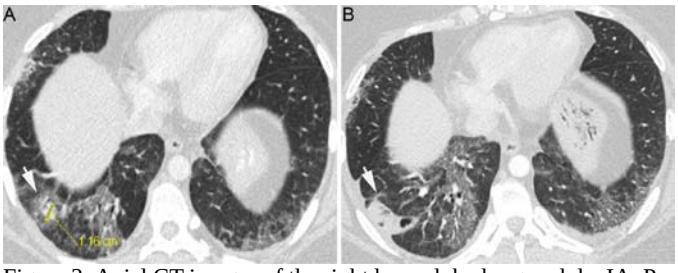

Figure 3. Axial CT images of the right lower lobe lung nodule. IA. Pre ablation image. B. Post ablation image. Interstitial lung changes remain constant.

Table 1. Common differential diagnostic considerations in diffuse pulmonary fibrosis among non-smokers

Diagnosis	Radiological Presentation	Lung Pathology	Specific Factors
chronic hypersensitivity pneumonitis (CHP)	upper lobe predominance diffuse air trapping centrilobular nodules	lymphocytic bronchiolitis loosely formed granulomas low BAL[1] CD4/CD8 lymphocyte ratio	divers organic and inorganic dust inhalation
pulmonary sarcoidosis	upper lobe predominance peribronchovascular nodules	non caseating granulomas increased BAL CD4/CD8 lymphocyte ratio	unknown
usual interstitial pneumonia (UIP)	lower lobe predominance traction bronchiectasis honeycombing	well-formed fibroblastic foci	family inheritance (e.g., TERT[2] gene mutations)
nonspecific interstitial pneumonia (NSIP)	no organizing pattern	monocytic inflammation with or without fibrosis	can be associated with collagen vascular disease
mucinous adenocarcinoma	interstitial or lobar involvement	malignant cells	unknown
collagen vascular disease (CVD)- related pulmonary fibrosis	usually presents as NSIP, but can present as UIP	bronchial and alveolar inflammation	underlying collagen vascular disease
drug/irradiation-induced fibrosis	commonly presents as UIP	same as UIP	drug exposure[3] chest/head irradiation
pneumoconiosis (e.g., silica and beryllium)	coarse fibrosis predominantly in upper lobes	silicosis-silica crystals berylliosis- loosely formed granuloma	coal and cement mining (silica) airplane manufacturing (beryllium)
asbestos-induced pulmonary fibrosis	UIP pattern pleural plaques	asbestos fibers fibroblastic foci are rare	car break repair asbestos removal boat manufacturing
pleuropulmonary fibroelastosis	upper lobe predominance	pleural and subpleural fibrosis	unknown
chronic aspiration	asymmetric fibrosis usually in the right lower lung	neutrophilic inflammation fibroblastic foci can be seen	dysphagia scleroderma
chronic pulmonary edema	diffuse distribution pleural effusion maybe present	non-specific inflammation or absence of inflammation	significant heart disease

1. BAL, bronchoalveolar lavage
2. TERT, telomerase reverse transcriptase
3. Common drug associations with pulmonary fibrosis: amiodarone, methotrexate, bleomycin, cyclophosphamide, nitrofurantoin and bleomycin

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Submitted June 6, 2019