When Malignancies Mimic Interstitial Lung Disease: A Case Series and Review of the Literature

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Abstract

Interstitial lung diseases (ILD) are difficult to diagnose and to classify. Despite symptoms and clinical findings typical for ILD, a broad differential diagnosis must be kept in mind. Multidisciplinary discussion (MDD) contributes to correct diagnosis and is therefore considered the diagnostic gold standard in ILD. Here we report on three patients that were referred to our ILD clinic with suspected ILD. They all presented with chronic dyspnea on exertion, cough and abnormal lung function tests showing reduced diffusing capacity as well as hypoxemia. Chest CT scans were compatible with ILD. Further diagnostic workup was performed, revealing two adenocarcinomas of the lung and one malignant B cell lymphoma. In summary, despite clinical, physiological and radiological presentation typical for ILD, further workup is needed early in the course of the disease to rule out possible differential diagnoses including malignancies.

Keywords: Interstitial lung disease; Multidisciplinary discussion; Lung cancer; Adenocarcinoma; B cell lymphoma

Introduction

Interstitial lung diseases (ILD) represent a variety of disorders that affect the lung parenchyma and cause unspecific respiratory symptoms such as increasing dyspnea and cough. Correct diagnosis and classification of ILD is crucial in order to avoid exposures that may be responsible for ILD, to decide about specific treatment with novel antifibrotic drugs [1,2] and to inform the patient about prognosis of the disease. Classification of ILD may be challenging with a spectrum from ILD with known etiologies (occupational and environmental exposures, drugs or connective tissue diseases) to idiopathic forms (idiopathic interstitial pneumonias, e.g. idiopathic pulmonary fibrosis [IPF]). Based on the current guidelines [3,4], a histological diagnosis for IPF is not always mandatory and depends on the clinical and radiological presentation. Bronchoscopy and bronchoalveolar lavage (BAL) are not routinely recommended.

We present three cases that were referred to our ILD clinic with respiratory symptoms, physiological and radiological findings typical for ILD. Further workup was performed, resulting in a different diagnosis than initially suspected.

Case Reports

Case 1

A 65 year old Caucasian male and current smoker (40 pack years) was referred to the ILD clinic with increasing dyspnea at minimal physical efforts. The retired locksmith stated an exposure to hard metal dust by tool grinding over decades. Arterial hypertension was treated with candesartan and depression with citalopram. Physical examination showed an overweight (BMI 29 kg/m²), non-febrile patient, with bilateral, basal, inspiratory crackles, without clinical signs of heart failure. Laboratory blood tests (CRP, hematology, liver and renal functions) were normal, but mild respiratory insufficiency was detected in arterial blood gas analysis (pO₂ 66 mmHg, pCO₂ 49 mmHg). Pulmonary function tests (PFT) showed severe obstructive airflow limitation (FVC 2.14l/49% predicted, FEV₁ 0.72l/21% predicted) and moderately decreased adjusted diffusing capacity for carbon monoxide (DLCO) of 42% predicted. Chest CT scan showed an interstitial disease pattern with subpleural reticulations, disseminated, multiple small parenchymal nodules and slightly enlarged mediastinal and hilar lymph nodes (Figure 1a). Initial differential diagnosis included sarcoidosis and hard metal lung. Further diagnostic workup included bronchoscopy including BAL and transbronchial biopsy (TBB), revealed adenocarcinoma of the lung with lymphangitis carcinomatosa, positivity for thyroid transcription factor (TTF)-1 (Figure 1b), without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. Contralateral pulmonary and spinal metastases were detected on CT scan. A palliative chemotherapy with carboplatin and permetrexed was started, to which the patient responded well.

Case 2

A 76 year old Caucasian female, never-smoker and housewife, was referred for the evaluation of recurrent cough with whitish sputum and progressive dyspnea on exertion. Except for esomprazole (treatment of gastroesophageal reflux) the patient was on no regular medication. She presented with velcro rales (discontinuous, inspiratory, non-musical crackles). Laboratory tests showed anemia (hemoglobin 116 g/l), but no signs of inflammation, metabolic disturbances, rheumatologic or autoimmune diseases. The patient was hypoxic (pO₂ 58 mmHg) and PFT revealed mild restrictive limitation (FVC 1.87l/90% predicted) and a mild decrease in adjusted DLCO (70% predicted). A chest CT scan showed mainly right sided ground-glass opacities and dense interstitial disease pattern with subpleural reticulations, disseminated, multiple small parenchymal nodules and slightly enlarged mediastinal and hilar lymph nodes. Positivity for thyroid transcription factor (TTF)-1 (Figure 1b) and cytokeratin (CK)5/6 (Figure 1c) together with positivity for thyroid transcription factor (TTF)-1 (Figure 1b) and positive for epithelial membrane antigen (EMA) (Figure 1d). A histological diagnosis of adenocarcinoma of the lung with lymphangitis carcinomatosa, positivity for thyroid transcription factor (TTF)-1 (Figure 1b), revealed adenocarcinoma of the lung with lymphangitis carcinomatosa, positivity for thyroid transcription factor (TTF)-1 (Figure 1b), and minimal respiratory insufficiency was detected in arterial blood gas analysis (pO₂ 66 mmHg, pCO₂ 49 mmHg). Pulmonary function tests (PFT) showed severe obstructive airflow limitation (FVC 2.14l/49% predicted, FEV₁ 0.72l/21% predicted) and moderately decreased adjusted diffusing capacity for carbon monoxide (DLCO) of 42% predicted. Chest CT scan showed an interstitial disease pattern with subpleural reticulations, disseminated, multiple small parenchymal nodules and slightly enlarged mediastinal and hilar lymph nodes (Figure 1a). Initial differential diagnosis included sarcoidosis and hard metal lung. Further diagnostic workup included bronchoscopy including BAL and transbronchial biopsy (TBB), revealed adenocarcinoma of the lung with lymphangitis carcinomatosa, positivity for thyroid transcription factor (TTF)-1 (Figure 1b), without epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements. Contralateral pulmonary and spinal metastases were detected on CT scan. A palliative chemotherapy with carboplatin and permetrexed was started, to which the patient responded well.

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consolidations with air bronchogram and cystic changes (Figure 2a).
Small caverns and tree-in-bud pattern were also present on the left side,
and all changes showed a basal predominance. In face of the radiological
presentation, the suspected diagnosis was cryptogenic organizing
pneumonia. Bronchoscopy, BAL and TBB were not diagnostic. Finally,
surgical lung biopsies revealed multifocal adenocarcinoma, cytokeratin
(CK)7 positive, TTF-1 negative, with a predominantly lepidic growth pattern
without EGFR mutation or ALK rearrangement (Figure 2b). No
evidence of distant metastases or primary tumors as possible origins
of the pulmonary malignancy were found by further staging. The
patient equally received palliative chemotherapy with carboplatin and
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evidence of distant metastases or primary tumors as possible origins
of the pulmonary malignancy were found by further staging. The
patient equally received palliative chemotherapy with carboplatin and
empiric treatment with oral steroids for her suspected ILD during the
last 2 months prior to referral, which ameliorated her symptoms to some
degree. She was on metformin due to diabetes [5]. BAL revealed 47% lymphocytes with 35% atypical B cells on flow cytometry. Biopsy of a left, supraclavicular lymph node finally showed a low-grade malignant follicular B cell lymphoma WHO grade II (Figure 3b), with bone marrow involvement in the staging biopsy. A modified COP chemotherapy (cyclophosphamide, vincristine, prednisone) including rituximab was administered.

Case 3

A 59 year old asian female, never smoker, was referred for suspected
ILD of unknown origin. She reported dry cough, wheezing and dyspnea
on physical effort during the last 4 months. The patient had received
empiric treatment with oral steroids for her suspected ILD during the
last 2 months prior to referral, which ameliorated her symptoms to some
treatment with oral steroids for her suspected ILD during the
last 2 months prior to referral, which ameliorated her symptoms to some
extent. She presented with bilateral, inspiratory crackles, hypoxemia
(pO2 65 mmHg), severe anemia (hemoglobin 73 g/l), and a severe
restrictive limitation (FVC 0.79/37% predicted) on PFT. CT scan of the
lungs showed multiple, bilateral noduli, consolidations and ground-
glass opacities with bilar and mediastinal lymphadenopathy (Figure
3a). Drug-induced ILD was suspected since she was on metformin due
to diabetes [5]. BAL revealed 47% lymphocytes with 35% atypical B cells
on flow cytometry. Biopsy of a left, supraclavicular lymph node finally
showed a low-grade malignant follicular B cell lymphoma WHO grade
II (Figure 3b), with bone marrow involvement in the staging biopsy. A
modified COP chemotherapy (cyclophosphamide, vincristine, prednisone) including rituximab was administered.

Discussion

We present three cases referred to our ILD clinic with suspected
ILD based on clinical and radiological presentation. Further workup,
however, revealed malignant disease. Since the clinical presentations
of ILD patients are often unspecific, high-resolution CT scans of the
chest are performed. Despite correlation with the clinical picture
during MDD this does not always result in a clear diagnosis. As the
reported three cases illustrate, a broad differential diagnosis needs to be
considered, including malignant disease.

Our cases speak in favour of acquiring histological diagnosis, in
particular if the clinical and radiological presentations are unclear or
not conclusive. On the other hand especially in elderly patients with
comorbidities, the necessity of invasive procedures should be carefully
accessed and the diagnostic intervention carefully planned, keeping in
mind possible complications of invasive procedures, such as surgical
lung biopsy, with bronchoscopy being less invasive.

Adenocarcinoma of the lung has been reported in the literature
mimicking "benign" processes such as pneumonia [6], desquamative
interstitial pneumonia (DIP) [7] or lung fibrosis with honeycombng
[8]. Lymphangiosis carcinomatosa can also present as ILD due to
thickening of the bronchovascular bundles prominent in the axial
compartment and/or thickened peripheral interlobular septa shaping
a polygonal pattern [9]. The typical fibrotic changes in reaction to the
proliferation of malignant cells (desmoplastic reaction) can further
contribute to misdiagnosis. Lymphoma, another differential diagnosis
of ILD with malignant etiology, may show lymphangitic spread with the
radio-pathological changes mentioned above [10].

Although BAL is not recommended in the current ATS/ERS
recommendations for ILD on a regular basis [3], we routinely perform
BAL in patients with suspected ILD, primarily to rule out infections
of 77% for adenocarcinoma, 93% for bronchioloalveolar carcinoma
(adenocarcinoma in situ and adenocarcinoma with predominant
lepidic growth pattern) and 67% for Non-Hodgkin lymphoma.

In the three reported cases, malignancies presented as ILD. But
ILD may also co-exist with malignant disease. In these cases, the
diagnosis of a neoplasm is particularly important and challenging due
to several overlaps. Chronic inflammation leads to impaired epithelial
cell repARATION, with proliferation and metaplasia [14] and cytologically
atypical epithelial proliferations can be demonstrated in areas of
honeycombing. On the other hand, a recent review [15,16] recorded
an explicitly higher prevalence of lung cancer in the IPF population
of 4.8%-48% versus 2%-6.4% in the non-IPF affected cohort. The
prognosis of IPF is worse in those patients, making lung cancer an
important adverse factor concerning morbidity and mortality [17]. Lung cancer treatment and the development of ILD are also associated: the development of fibrotic lung parenchymal changes after radio- and chemotherapy has been repeatedly demonstrated [18]. In addition, cancer treatment is postulated to cause acute exacerbation of ILD and may trigger a “latent” ILD [19]. The question if malignant tumors themselves can trigger the development of extensive lung fibrosis has not yet been resolved.

In summary, these case series and findings support our standard practice to perform bronchoscopy and BAL and, if rendered necessary after MDD, surgical lung biopsies, in patients with suspected ILD. Only in cases of matching clinical findings and UIP pattern on CT scans IPF can be diagnosed without tissue diagnosis by experienced ILD specialists [3,20]. Similarly as in cancer care, decision-making about diagnostic steps, final diagnosis and treatment in ILD benefits from the opinion of several experts, especially pulmonologists, radiologists and pathologists. Therefore MDD should be integrated in clinical ILD routine like multidisciplinary tumor boards are part of the oncologic routine.

References