Editorial

Multidisciplinary team approach on a case of bilateral interstitial pneumonia

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Summary

It is an honor to comment on the report entitled, "Multidisciplinary team approach on a case of bilateral interstitial pneumonia," by He *et al.* The authors present a case of interstitial lung disease (ILD) with a pathological pattern suggesting hypersensitive pneumonia (HP). The report includes a discussion by experts regarding the diagnosis and treatment of this case.

The patient was 44-year-old man who presented to our hospital because of acute-on-chronic respiratory symptoms (i.e., coughing, shortness of breath). He had a 5-year history of ulcerative colitis, for which he had been taking salazosulfapyridine for more than 4 years. He had no history of environmental exposure that would have caused HP or pneumoconiosis. He had no symptoms or serological findings indicating a connective tissue disease (CTD). Laboratory tests showed that serum markers indicating an infectious disease were negative. Pulmonary function tests—forced vital capacity (FVC) 41.5%, lung diffusion capacity for carbon monoxide (D_{LCO}) 31.7%—indicated severe restrictive ventilatory impairment and decreased diffuse function. High-resolution CT (HRCT) images showed diffuse ground-glass opacities, traction bronchiectasis, honeycombing, and uneven and decreased attenuation predominantly around the bronchial vascular bundle in both lungs.

Thoracoscopic lung biopsy was performed on the lower right lung. The main pathological findings in the specimen included alveolar adenomatous hyperplasia, macrophage accumulation in the alveolar space, interstitial fibrosis, patchy distribution, lymphocytic infiltration, non-necrotic granuloma, and bronchiolitis. The radiological and pathological findings, along with the imaging features, were consistent with a diagnosis of chronic HP (CHP). The clinical diagnoses of the patient were chronic interstitial pneumonia (related to the use of sulfasalazine), pulmonary infection, and ulcerative colitis. The author discontinued the patient's use of sulfasalazine and prescribed oral glucocorticoids.

Questions arising from this case

Question 1: can a diagnosis of CHP be made in this case? Question 2: was the disease caused by sulfasalazine use?

The radiological and pathological findings were consistent with CHP, and the patient had a history of taking salazosulfapyridine (drug toxicity due to salazosulfapyridine is a possible cause of CHP). Nevertheless, it is difficult to distinguish inflammatory bowel disease (IBD)-related lung parenchymal disease. Thus, it was necessary to assess the patient's clinical and radiological responses after discontinuing salazosulfapyridine to confirm the diagnosis.

Question 3: was the patient at high risk for acute exacerbation (AE) during the surgical lung biopsy (SLB)?

Although there are no well-designed studies identifying risk factors for AE of ILD, some retrospective studies have suggested that patients with male gender, low pulmonary function, a history of steroid use, and a radiological pattern indicating usual interstitial pneumonia (UIP) are at an increased risk of AE (1,2). In the present case, it was thought that the patient was not at high risk for AE after SLB because only two risk factors were present (i.e., male gender, low FVC).

Question 4: if drug treatment is still considered, which drug is preferred?

The drug of choice in such cases should be a corticosteroid because it is standard treatment for CHP. A randomized, controlled trial (INBUILD) suggested the efficacy of nintedanib (an anti-fibrosis agent) for treating progressive, fibrotic ILD, including CHP (3). Anti-fibrotic agents such as nintedanib would likely have been effective in the present case, but we needed more data from ongoing clinical trials to support its benefit for treating CHP.

Question 5: what is the patient's prognosis?

The prognosis for the described patient is likely poor because the radiological and histological findings indicating fibrosis suggests a worse prognosis in CHP. The patient's responsiveness to corticosteroid therapy and avoiding the use of sulfasalazine are the prognostic predictors in the present case.

Discussion

ILD is a broad term that includes diseases with various etiologies and subtypes. The causes of ILD are CTD, drugs, and environmental exposure, etc. ILD of unknown cause is clinically classified as idiopathic interstitial pneumonia (IIP). Idiopathic pulmonary fibrosis (IPF), the most common IIP subtype, is associated with significant mortality. Current guidelines emphasize that multidisciplinary discussion (MDD) of the case is the gold standard for diagnosing IIP (4-6). Fujisawa et al suggested that the MDD diagnosis yielded better prognostic distinction among the IIPs than did the institutional diagnosis by nationwide cloud-based integrated database study (7). Diagnosing ILD of known cause includes perusal of the patient's histories of medication intake and environmental exposure s, as well as the physical and laboratory findings that suggest a CTD. As Takei suggested, analysis of bronchoalveolar lavage fluid was important for the differential diagnosis of CHP in the present case. The median proportion of lymphocytes in the bronchoalveolar lavage fluid has been reported as 52–69% in acute HP patients and 17–84% in CHP patients (8,9). Pathological ILD patterns, such as that for UIP, are diagnosed via SLB. Pathological findings from SLB often reveal signs of a secondary ILD, such as bronchiolocentric distribution and a non-necrotizing granuloma, suggesting HP, or the presence of lymphoid follicles, small airway involvement, and pleuritis, suggesting CTD (10,11). It should be noted that AE of ILD after SLB has been reported (2,12). Thus, when debating whether SLB is needed to diagnose ILD, the risk factors for AE reported in some retrospective studies should be considered (1,2). In a prospective study, Iwata et al suggested the prophylactic effect of perioperative pirfenidone treatment for postoperative AE of IPF (13,14). The Japanese prospective PEOPLE study showed that the incidence of AE in 1 in 36 (2.7%) IPF patients with lung cancer was lower than that reported in a previous study (14). As in this study, therapeutic efforts to prevent postoperative AE in ILD patients with lung cancer has recently attracted attention. Transbronchial cryobiopsy (TBLC) is a relatively new method for diagnosing ILD (15) and its use has been increasing in Europe since 2014 (16). The concordance of ILD diagnoses between TBLC and SLB was widely reported in two multi-center, prospective studies. Kappa-concordance coefficients were reported as 0.22 by Romagnoli *et al.* (17) and 0.70 by Troy *et al.* (18). Zaizen *et al.* suggested that the histological findings of UIP (e.g., dense fibrosis) showed high concordance between the TBLC and SLB techniques, whereas the histological findings of non-UIP (e.g., cellular infiltration, airway disease) did not (19). These two diagnostic methods (TBLC and SLB) may have to be used differently depending on whether the purpose is the diagnosis of a UIP pattern or the etiology of ILD.

Recently, "progressive, fibrosing ILD (PF-ILD)", a new term for the phenotype showing progressive fibrosis in ILD—has been proposed for the purpose of clinical research or treatment (20). Establishing the efficacy of anti-fibrotic agent for progressive fibrosis in ILD may reduce the significance of the pathological diagnosis by invasive SLB and/or TBLC. The presence of a UIP pattern (e.g.,

fibroblastic foci), however, is a poor prognostic predictor of ILD. Hence, the significance of SLB and TBLC should be reviewed. Moreover, the treatment for secondary ILD should be used in accordance with the etiology. Corticosteroid therapy is the first choice for patients with some CTDs (e.g., dermatomyositis-associated ILD), drug-induced ILD (which is not alleviated by discontinuing the drug), and CHP. Having a working diagnosis achieved by evaluating the clinical, radiological, and pathological findings, as well as the clinical course, is important for selecting the appropriate treatment.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2020.03.04). The authors have no conflicts of interest to declare.

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