The significance of multidisciplinary classifications based on transbronchial pathology in possible idiopathic interstitial pneumonias

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Research article

Keywords: interstitial lung diseases, idiopathic interstitial pneumonias, transbronchial lung cryobiopsy, bronchoscopy and interventional techniques, transbronchial pathology

Posted Date: October 10th, 2019

DOI: https://doi.org/10.21203/rs.2.15939/v1

Abstract

Background the multidisciplinary diagnosis based on clinic–radiologic–pathologic information had been widely used as the diagnostic gold standard for idiopathic interstitial pneumonias (IIPs). Surgical lung biopsy (SLB) had been recommended as the standard method to sample lung parenchymal lesions for suspected IIPs. Here, we attempted to show the diagnostic confidence of multidisciplinary classifications based on transbronchial pathology including transbronchial lung cryobiopsy (TBLC), bronchoalveolar lavage fluid (BALF) and endobronchial ultrasound-guided transbronchial needle aspiration biopsy (EBUS-TBNA) in IIPs.

Methods all new suspected interstitial lung diseases (ILD) were in-patient at the respiratory department of Dalian Municipal Central Hospital from June 2016 to December 2018. The multidisciplinary discussion (MDD) were made to exclude known causes of ILD and typical IPF depending on clinical, radiological information. The cases of atypical IPF, and possible IIPs were included and suggested to transbronchial pathological evaluation. Initial MDD classifications were made depending on clinical, radiological and transbronchial pathological information. The final MDD classifications was confirmed by following therapeutic effect.

Results 70 subjects were eligible including 24 males and 46 females. The sampled lung parenchyma from TBLC were enough for confirmation of pathological diagnosis in 68.6% (48/70) cases. If the confirmed pathological evaluations through EBUS-TBNA and BALF were involved, 77.1% (54/70) cases had gotten the defined diagnosis. All cases were following up. Meanwhile, 60% was improved, 11.43% was relapsed when glucocorticoid was reduced to small dose or withdrawal, 14.29% was steady and 8.57% was progressed in which the diagnosis were modified in 4 cases. 94.3% initial MDD classifications based on transbronchial pathology were agreed with the final MDD, the difference of diagnostic yield wasn't significant between initial and final MDD (Z=-1.414, p=0.157).

Conclusion classifications of IIPs based on transbronchial pathology were useful and quite agreed with final MDD.

Background

The idiopathic interstitial pneumonias (IIPs) comprise a number of clinicopathological entities, which are quite different as separate diseases. As a group, they can be distinguished from other forms of diffuse parenchymal lung diseases (DPLD) by clinical methods including history, physical examination, chest radiology laboratory studies, and pathology. Idiopathic indicates unknown causes and interstitial pneumonia refers to involvement of the lung parenchyma by varying combinations of fibrosis and inflammation. As ATS/ERS new classifications [1], IIPs are now divided into major, rare and unclassifiable. The major IIPs are further divded into idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), desquamative interstitial pneumonia (DIP), cryptogenic organizing pneumonia (COP), and acute

interstitial pneumonia (AIP). Those associated with occupational or environmental exposures and/or collagen vascular disease (CTD-ILD), granulomatous lung disorders are excluded [2]. According to current guidelines [1,2,3], the diagnosis of IIPs requires a multidisciplinary discussion (MDD) with the reconciliation of clinical, radiological and histopathological information. MDD based on clinic–radiologic–pathologic information has been widely used as the diagnostic gold standard. Except typical IPF as the only IIPs for clinic-radiologic diagnosis [4,5], pathological evaluation is recommended for all others [6]. Surgical lung biopsy (SLB) is recommended for suspected IIPs involved that the HRCT scan pattern is not typical IPF [6]. Enough lung tissue can identify pathologists to define a characteristic pattern and the histopathological criteria. However, SLB which represents a small sample of the whole lung and the minimal quantity of lung is necessary to guarantee the maximum morphological information [7]. Recently, flexible cryoprobes have been used for peripheral lung parenchymal biopsy. Studies on the use of flexible cryoprobes for transbronchial lung cryobiopsy (TBLC) have shown improvements in diagnostic yield, sample size, and architectural preservation of the biopsy specimens [8, 9]. Its adverse events is significantly lower than SLB [10]. Along with the progress of transbronchial intervention techniques, the more invasive diagnostic techniques including bronchoalveolar lavage fluid (BALF), transbronchial forceps lung biopsy (TBLB), TBLC and endobronchial ultrasound-guided transbronchial needle aspiration biopsy (EBUS-TBNA) can be used for pathological and cytological evaluation [11]. In this study, we attempt to show the diagnostic confidence of MDD classifications based on transbronchial pathology including TBLC, BALF and EBUS-TBNA in IIPs.

Methods

We collected all new inpatients who suspected interstitial lung diseases (ILD) by chest CT or HRCT scan at the respiratory department of Dalian Municipal Central Hospital affiliated of Dalian Medical University from June 2016 to December 2018. All included patients completed medical history, physical examination, serological examination, pulmonary function test and chest HRCT. Multidisciplinary team which contained rheumatologists, respiratory physicians, radiologists and pathologists made a multidisciplinary discussion to exclude known causes ILD such as occupational or environmental exposures and CTD-ILD. The diagnosis of typical IPF, atypical IPF, or possible IIPs were also made. The eligible cases including atypical IPF, and possible IIPs were suggested to transbronchial pathological evaluation. Informed consents were signed before transbronchial examination from all eligible patients. Approval for this study had obtained from the Dalian Municipal Central Hospital Human Ethics Committee.

TBLC and BALF were performed in all cases by bronchoscopy (Olympus, BF-IT260) using a cryoprobe (ERBE ErbokryoCA, 1.9 mm diameter) under radical endobronchial ultrasond (Olympus UM-S20–17S, 1.4 mm diameter) guidance, meanwhile patients were intravenous deep sedation and breathed through mechanical ventilation by a size 4 laryngeal mask airway. The target bronchus were most affected pulmonary parenchymal areas matched chest HRCT images. TBLC was performed at 1–3 pulmonary subsegments in every case and 1–3 specimens were taken at each subsegment. EBUS-TBNA were simultaneously done in cases accompanying with the enlarged mediastinal lymph nodes. Pathological

diagnosis was made by two pathologists discussing together. Initial MDD classifications were reconciled by multidisciplinary team based on clinical, radiological and thransbronchial pathological information according to ATS/ERS classification [1]. Appropriate treatments were carried out according to initial MDD classifications and the prognosis were following. The initial MDD classifications were confirmed as the final classifications if diseases were improved. The further clinical, radiological, pathological evaluation should be performed again while diseases progressed.

Statistical Analysis

Statistical analyses were carried out using SPSS 22.0. Data was reported as the median and standard deviation for continuous variables, and numbers and percentages for discrete variables. The diagnostic yield between the initial and final MDD classifications was compared using standard statistical approaches of Wilcoxon and McNemar nonparametric tests for categorical variables, and p value of <0.05 was defined as a statistically significant difference.

Results

Finally, 70 subjects were eligible. Their clinical information were listed in table 1. All cases were performed TBLC and BALF, and EBUS-TBNA were simultaneously done in 6 cases. TBLC was completed in three different subsegments in 10 cases, two in 56 cases and only one in 4 cases owing to severe bleeding. Pneumothorax was complicated after TBLC in 3 cases which all treated with drainage. The complication of severe bleeding was 5.7% (4/70 cases) and pneumothorax was 4.29% (3/70 cases). A case died of progressing NSIP after 2 week owing to severe condition before TBLC.

Whether or not the sampled lung parenchyma from TBLC being enough for pathological diagnosis was also discussed by MDD, and the confirmed pathological diagnosis was made in 68.6% (48/70) cases. 31.4% (22/70) cases didn't get definitive pathological confirmation, including 2 cases involved only bronchus. If the confirmed pathological evaluations through EBUS-TBNA and BALF were involved, 77.1% (54/70) cases had been gotten the defined diagnosis by transbronchial pathology.

Initial MDD classifications were made depending on the reconciliation of clinical, radiological and pathological information by MDD, they were listed in table 2. Appropriate therapies were made depending on initial MDD classifications and the prognosis were following up. The following time was more than 6 months for all cases except one died in 2 weeks. During the following time, 60% (42/70) cases were improved, 11.43% (8/70) cases were cured and relapsed when glucocorticoid was reduced to small dose or withdrawal which had been diagnosed as COP by initial and final MDD, 14.29% (10/70) cases were steady, 8.57% (6/70) cases were progressed in which one had gotten the improvement about a year by taking prednison (figure 1) and gradually progressed after that (figure 2). In the progressive cases, 6 were evaluated again though clinical, radiological and serological examination and 3 were repeated transbronchial pathological evaluation. The diagnosis of 4 cases was modified, including that a case was diagnosed as systemic lupus erythematosus, a case was diagnosed as ANCA associated systemtc vasculitis depended on serological examination and 2 cases were diagnosed as pulmonary

adenocarcinoma by TBLC once again (table 2). The diagnosis of 2 cases were as before because one case was died in 2 weeks and another was confirmed same diagnosis by a repeated TBLC. 5.7% (4/70) cases were died of the progressive IIPs including acute exacerbation in 1 case after 8 months of improvement. 5.7% (4/70) cases were died of other diseases. The final MDD classification were also listed in table 1. 94.3% (66/70) initial MDD classifications based on transbronchial pathology was agreed with the final. The difference wasn't significant between initial and final MDD classifications ($Z = -1.414$, $p = 0.157$), the probability was 0.500 by McNemar Test.

Discussion

A broad range of non-neoplastic and non-infectious DPLD existed under the less specific umbrella term of ILD. This large group of diseases included those with histopathological findings identical to IIPs but with known etiology, commonly connective tissue diseases and respiratory exposures, and those with defined clinical, radiological, and pathological definitions including lymphangioleiomyomatosis, sarcoidosis, pulmonary Langerhans cell histiocytosis, and eosinophilic pneumonia. Some neoplastic or infectious processes masquerading as suspected ILD by diffuse abnormalities were also commonly encountered. So, the pathological diagnosis only from pulmonary parenchyma wasn't enough in some conditions. Microbiological and cytological information might also be needed in these cases. The progress of transbronchial techniques ensured all these procedure to be performed at the same examination. BALF was not always required in the assessment of the IIPs but to exclude infection or tumor [2,3]. TBLB was used to excluding infection and tumors and not for diagnosis of IIPs because traditional forceps yielded small biopsy samples with significant crush artifacts which were only sufficient for 20–30% and occasionally misrepresented the overall diseases [6]. Many studies indicated that the mean length and area of the specimens from lung parenchymal tissues by TBLC were substantially larger than TBLB, and the specimens didn't have crush artifacts [6,10,12,13,14]. Samples obtained through TBLC contained peripheral structures of the secondary pulmonary lobules [8]. There was a significant difference between TBLC and TBLB in terms of the percentage of sampled tissue containing open alveoli [10]. The mean maximal diameter of the samples were around 9 mm [15,16]. It was sufficient for histological diagnosis that the samples were larger than 5 mm in diameter as the experts suggestion [17]. Although SLB had been recommended as golden standard for pathological biopsies, the morbidity and mortality limited its clinic performance. A large dataset study showed the rate of in-hospital mortality following SLB for DPLD was 1.7%, the rate of complication was 30% including postoperative pneumothorax, pneumonia, and respiratory failure [18]. Bleeding complications occurred in 22% of patients and pneumothorax was 1.4%. The adverse events during TBLC were significantly lower than during SLB [6,11]. Mortality due to adverse events was observed for 2.7% (SLB) and 0.3% (TBLC) of the patients [18]. In our study, the severe bleeding which prohibited examination was 5.7% and pneumothorax was 2.9%. The advantage of TBLC was more suitable for following and supervising the progressive diseases than SLB owing to less adverse events.

As the gold standard approach for the diagnosis of IIPs, MDD classifications needed to be reached by a multidisciplinary team comprised of expert pulmonologists, pathologists and radiologists after reviewing

the available clinical, radiological and pathological data. Clinic and radiological information (from HRCT) alone might lead to typical IPF, cytological or histological information were warranted in others [6, 19]. Tomassetti [20] indicated that the diagnostic confidence was significantly increased depending on the histopathological information from both TBLC and SLB in IPF compared with only clinical-radiological diagnosis. As for DPLD, Ravaglia [21] compared diagnostic yield and showed that the diagnostic pattern was 82.8% in TBLC vs 98.7% in SLB. Kropski [16] and Poletti [18] reported that pathological diagnostic pattern from TBLC was 80%. Ussavarungsi [15] indicated that the definite MDD was yielded in 51% of subjects, and nonspecific histopathologic finding was in 49%. Hetzel indicated that the nondiagnostic rate were about 20% of cryobiopsies [17], the reasons included inadequate lung tissue (the specimen is predominantly airway wall), normal lung tissue (sampling error), or lung tissue with very minor and nonspecific pathology. In this study, the confident diagnostic yield based on transbronchial pathology in IIPs was 77.1%. 94.3% (66/70) initial MDD classifications based on transbronchial pathology was agreed with the final. To follow the therapy was essential for MDD classifications based on transbronchial pathology because 5.7% initial MDD classification was modified.

Conclusion

MDD classifications of IIPs based on transbronchial pathology was useful and quite agreed with the final. The following up was essential for MDD classifications based on transbronchial pathology.

Declarations

Ethics approval and consent to participate Approval for this study had obtained from the Dalian Municipal Central Hospital Human Ethics Committee. Informed consents were signed before transbronchial examination from all eligible patients.

Consent to publish All our authors had read and approved the manuscript to submit. And, this paper hadn't been submitted elsewhere.

Availability of data and materials all were presented within the manuscript.

Competing Interests The authors declared no competing interests.

Funding there wasn't funding in our study.

Author contributions Prof. JX and CL conceptualized the study and wrote the paper. Prof. RF and JZ gave their academic advice and paper check. WW, XH, NG, LJ, XZ, LR, XZ and YL collected cases, performing tests and preparing the figures.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

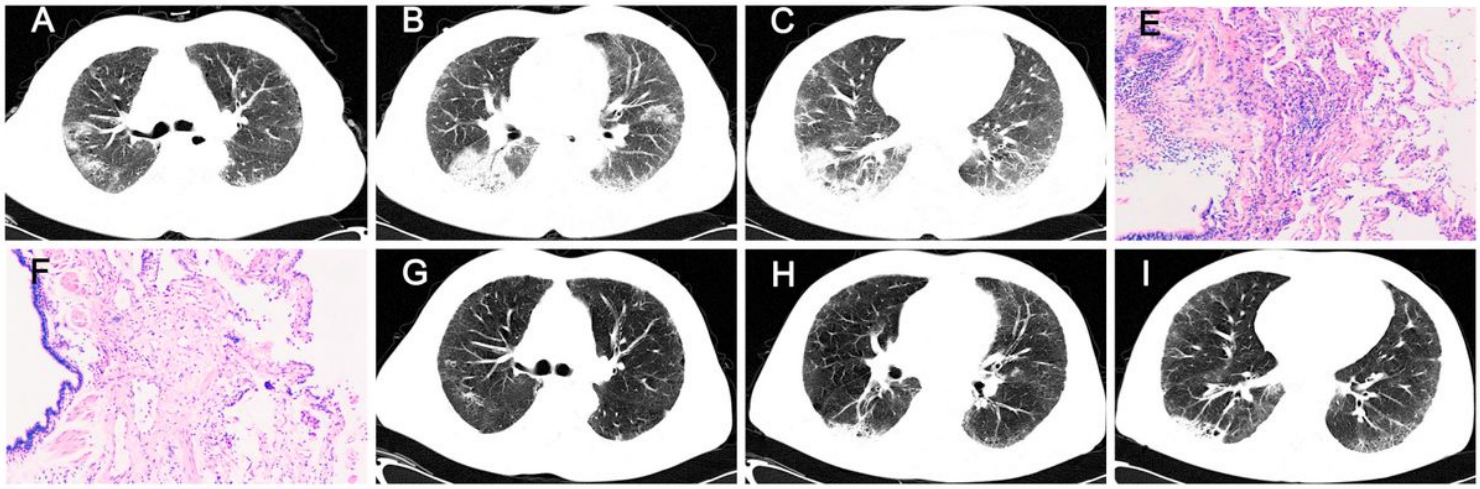

Figure 1

a case of NSIP was evaluated by initial MDD classifications. Bilateral ground glass opacity (GGO) was shown at the chest CT on May 5 in 2017 (A, B, C). The fibrous proliferation in pulmonary interstitial and lymphocytes infiltration in alveolar septum were shown in the histopathological slices (HE stained×100) based on TBLC at right upper lobe (E) and lower lobe (F). GGO was partially resolved at following chest CT on Jun 22 in 2017 (G, H, I) while prednison (1mg/kg per day) had been taken for more than a month.

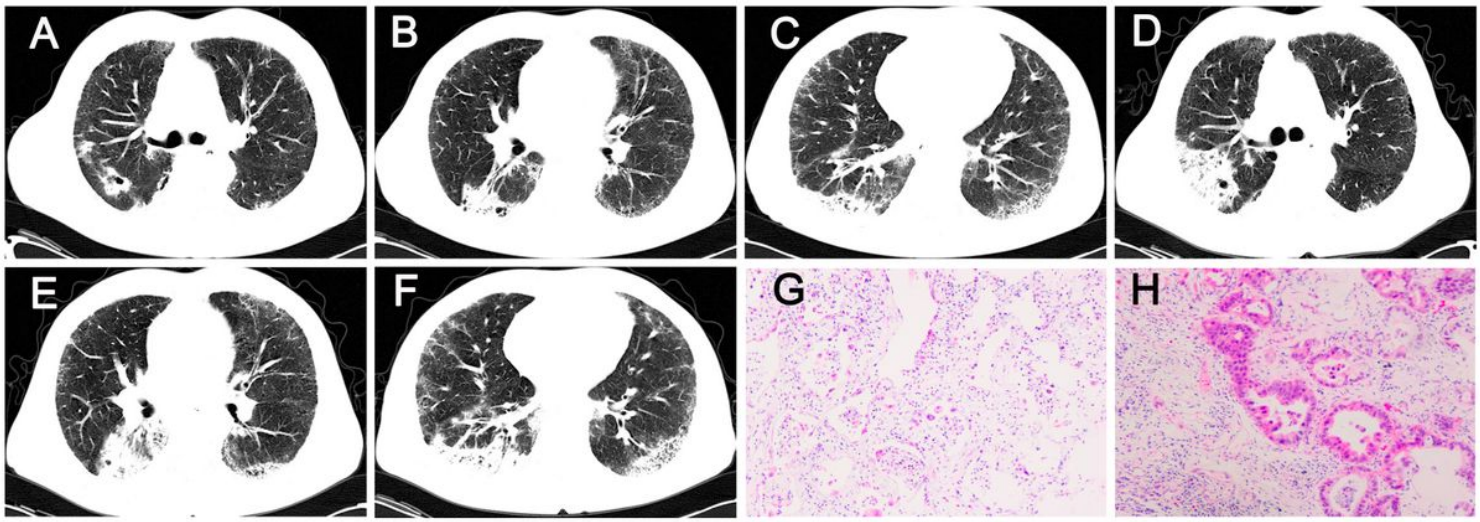

Figure 2

the same case with that in figure 1. Some lesions progressed and consolidated at chest CT on Jun 7 in 2018 (A, B, C) when prednison was reduced to 15mg per day, and the progression was much obvious on Dec 27 in 2018 (D, E, F). TBLC was performed once again and the diagnosis of NSIP was modified as pulmonary adenocarcinoma in the histopathological slices (HE stained×100) of right upper lobe (G) and lower lobe (H).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TABLE1.jpg
- TABLE2.jpg