Review Article

Idiopathic Interstitial Pneumonias: Discussion Issues

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Abstract

Idiopathic interstitial pneumonia (IIP) can be referred to as idiopathic fibrosing lung disease. This disease has typical clinical manifestations and morphological changes that depend on their course (acute, subacute, and chronic) and are not the same in the onset and the outcome of the disease. Uniting all IIPs (besides unclassifiable interstitial pneumonia and cryptogenic organizing pneumonia) under the term idiopathic fibrosing lung disease enables us to stop speculating about the so-called early diagnostics of idiopathic lung fibrosis, define the disease activity criteria and establish precise indications to prescribe systemic corticosteroids and anti-fibrotic drugs to treat IIP.

Keywords: *Idiopathic Interstitial Pneumonia, Idiopathic Lung Fibrosis, Early Diagnostics, Treatment Strategy.*

Abbreviations

IIPs - idiopathic interstitial pneumonias;

IPF - idiopathic pulmonary fibrosis;

UIP - usual interstitial pneumonia;

DIP - desquamative interstitial pneumonia;

AIP - acute interstitial pneumonia;

NSIP - nonspecific interstitial pneumonia;

RB-ILD - respiratory bronchiolitis, associated with interstitial lung disease;

COP - cryptogenic organizing pneumonia;

LIP - lymphoid interstitial pneumonia;

SCS – systemic corticosteroids;

HRCT - High-resolution computed tomography.

Introduction

Intensive research of idiopathic interstitial pneumonia (IIPs) represents a significant amount of findings accumulated during recent years. Unfortunately, the conclusions of the numerous publications, including ATS and ERS international regulation concerning the term “idiopathic interstitial pneumonia” seem to be not perfect.

Studying any complex issue, such as IIP, the most important task is to work out the classification that has a unified underlying criterion. Thus, in 2013 on the ATS/ERS Congress the final description of IIP has been given. All IIPs have been divided into three groups: major IIP, rare IIP and unclassifiable IIP. The major IIP group includes idiopathic lung fibrosis (ILF), corresponding to the morphologic pattern of ordinary lung fibrosis (OLF). It is the most common disease of all IIPs (about 40-60%). The group of other IIPs comprises desquamation interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), non-specific interstitial pneumonia (NSIP), and respiratory bronchiolitis, associated with interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP). The rare IIPs group includes lymphocytic interstitial pneumonia (LIP) and idiopathic pleura and lung fibroelastosis **(**1,2**)**. We believe that the classification of common diseases and rare diseases is not productive. On the first hand, this criterion is useless for diagnostics, and, on the second hand, it can’t be long-lasting for rare diseases can become common. Not analyzing his classification in detail, only one but the most principle disadvantage is to be noted: IIPs are divided into three groups according to three different criteria such as chronic and fibrosing, smoking-related or not smoking-related, acute and subacute.

Analysis of the clinical signs, course and X-ray morphologic and functional manifestations and outcomes of IIPs shows that most of their characteristics appear to be common. In all cases, the patients experience a different level of shortness of breath in physical exertion, the mostly non-productive cough, and auscultation detects crepitation. Considering the dynamics of the basic patterns that are important for IIP diagnostics, for instance, a high-resolution CT image with morphologic changes suggests that there are not only different specific diseases we deal with but there are various stages of one disease. Thus, let us try to prove our doubts about certain IPP being alone-standing diseases.

It is reasonable to suggest that the lung tissue response to different external and/or internal triggers is stereotypic and the range of the response reaction is rather wide and depends on the peculiarities of both etiologic factors and the body itself. In each case, there are individual aspects of the disease course that depend on both the stage of the disease and pathological process activity which appears to be natural.

It seems that we rather deal with individual aspects but not with principal differences that would allow us to consider them to be specific diseases. If it was true how could we explain the possible transformation of AIP, DIP, NSIP and other interstitial pneumonia to OIP? This fact has been proved not only by us **(**3-5**)** but also by numerous publications of other authors **(**6-9**)**.

Thus, ILF is defined to be a chronic progressing disease of the lungs of an unknown nature, being mostly found in elderly people, with X-ray and morphological signs complying with OIP pattern **(**2, 10**)**. The authors mention signs of chronic inflammation present in the lungs of patients with ILF, and case of aggravation – the signs of AIP such as diffuse alveolar damage. And it is hard to disagree with it. At the same time, it is proved that in the cellular type of NSIP the signs of inflammation are prevailing and subside as transforming into mixed and to the fibrotic type of the disease.

The differences in the lymphocyte percentage ratio in the lavage liquid of patients with NSIP and OIP show only the stage of the processing activity, but not different specific diseases. Indirectly, this idea is also supported by the fact that the cytological profile of the lavage liquid in fibrotic NSIP is similar to that in OIP. Common fibrotic changes in NSIP outcomes do not have pathognomonic morphological and CT signs that would cardinally differ from the OIP picture. Of course, in the case of OIP as a rule a honeycomb lung is observed while in NSIP it is observed more rarely. However, such characteristics as “more often – more rare”, “more – less” cannot be considered as criteria, differentiating one specific disease from the other.

Publications of several authors testify that NSIP, as it is progressing, can turn into OIP. For instance, C. Vancheri et al. in 2010 **(**11**)** have suggested that OIP and NSIP are different stages of one disease and there is no proof to exclude this suggestion. R. M. Strieter (2005) also considers NSI and OIP to be the stages of one disease **(**12**)**.

It is noted that DIP in certain conditions can turn into OIP associated with honeycomb lung formation and other CT signs of this disease **(**9**)**. Thus, observing DIP in dynamics enables to suggest that this disease is not an isolated form but an acute onset mode of ILF.

The transition of other types of IIP into OIP also appears not to be exotic. For instance, AIP in case of wrong diagnostics, incorrect or inadequate treatment can become chronic and lead to the development of the fibrosing process in the lungs and formation of honeycombs if they manage to prevent a lethal outcome. Only cryptogenic organizing pneumonia (COP) can be an exception, which is very difficult to refer to interstitial pneumonia according to its clinical, X-ray and morphological signs. Moreover, there is every reason to exclude COP from this group.

Non-classified IPs are to be further studied concerning their essence and disease classification. That is why COP and non-classified IPs are excluded from further discussions in this article. Let us try to assess the diagnostic information value of one of the most important CT signs (from image-diagnosticians) – a so-called frosted glass. Patients with DIP are diagnosed with this frosted glass in 100% of cases, and patients with NSIP – 80%. For patients with ILF having a frosted glass sign is not typical; however, as it is noted in the international guidelines, in the acute stage of ILF a CT shows bilateral frosted glass type changes. Can this kind of sign be used as a specific one (as CT specialists often practice upon) to differentiate NSIP from OIP? We believe that it can't, especially because the value of this sign has not been fully cleared up.

Lymphocytic interstitial pneumonia (LIP) is a rare disease. LIP is known to be characterized by lymphocytosis of the lavage liquid and prevalence of lymphocytes, plasma cells and serous liquid in the biopsy. Based on the found lymphocyte infiltration of the interstitial tissue, to distinguish a separate specific form of LIP seems to be unjustified.

Similar findings can be observed in several other diseases that are not directly connected with LIP such as immunodeficiency syndrome in viral diseases, in exogenous allergic alveolitis, primary biliary cirrhosis, B-cellular lymphoma, etc. For example, in two of our 15 patients who were suspected to have an LIP immunohistochemical study showed marked CD20 expression on the lymphocytic cells membrane and B-cell lymphoma was diagnosed.

It is also to be noted that as LIP progresses and becomes chronic the cells pattern of both lavage liquid and the lung tissue changes: neutrophils begin to prevail and interstitial fibrosis develops. The experience shows that morphological diagnosis of LIP may show not only exogenous fibrotic diseases, B-cell lymphoma, but also an acute or subacute course of ILF. The same idea is also supported in the international agreement of the American Thoracic Society and European Respiratory Society: LIP during observation can transform into NSIP **(**2**)** and NSIP, as we already know, may develop the properties of OIP.

Considering AIP a separate specific form appears to be unjustified because progressing AIP can obtain NSIP pattern leading to honeycomb lung (OIP) **(**2**)**. Finally, there is a similar picture of OIP and AIP aggravation noted.

OIP pattern showed by high-resolution CT image and histomorphology studies certainly depends on the stage of the disease, process activity (aggravation, remission). But what is also important is that it may match several other diseases, not relating to IIP, in the most advanced stages such as exogenous allergic alveolitis, lung syndrome in the connective tissue diffuse diseases, drug-

and professional lungs lesion. It also supports the suggestion that changes in the lungs are not pathognomonic for separate specific forms but are a stereotypic reaction of the lung tissue in response to the external and internal damaging factors.

That is why we believe that diagnosing IIP a physician, first of all, should solve practical issues, which influence the life prognosis of the patient. They should define the acuteness and activity of the pathological process, speed of the disease progression, stage of the disease based on the HRCT findings and, if needed, considering the histomorphological study of the biopsied material, as well as complex study of pulmonary function test and pulmonary circulation hemodynamics.

And, finally, it is high time to name one more conventional argument that is also mentioned in the agreement of the American Thoracic Society and European Respiratory Society (2013) **(**2**)** and no one doubts it. A significant number of patients with IIP can hardly be classified according to the specific forms of the disease due to the mixed pattern of lung damage. Different morphological patterns can be observed in one biopsy material, for instance, OIP in one lobe, NSIP in another lobe in 25-27% of cases **(**6**)**. We studied the biopsied material from 96 patients with IIP and found that in 23 of them in different segments (lobes) of one lung there were morphological signs of 2-3 IIPs. Other authors also report about the presence of different IIPs morphological patterns in one lung lobe **(**2, 10, 13**)**. We believe that the assumption about the presence of 2-3 rare diseases in one lung lobe sounds fantastic.

Considering the IIP group as one specific form enables us to be more precise in solving such important prognostic issues as defining the role of systemic corticosteroids (SCS) and antifibrotic drugs in the treatment of IIP. We emphasize: not of ILF but IIP.

During a lot of years, SCS has been administered in IIP as a basic drug. In the last 7-10 years, the situation has changed. It is generally accepted that epithelial damage, stimulation of TGF-β, FGF, and PDGF growth factors synthesis, proliferation, or differentiation of fibroblasts into myofibroblasts, i.e. so-called aberrant wound healing finally result in the lung tissue fibrosis with OIP morphological characteristics. It was this understanding of ILF pathogenesis that became the basis for categorical refusal from SCS by some specialists.

Although pathomorphologists don't deny that in the lung tissue of patients with ILF there are inflammation signs that manifest in varying degrees, which depends on the pathological process activity. We are deeply convinced that both extreme opinions are wrong. We consider inflammation to underlie the disease aggravation.

The problem is of another kind: it is in the stage of the inflammation activity. It is the inflammation activity that should be the principle criterion when deciding whether SCS is to be administered in the case of ILF. In our opinion, the administration of SCS to each patient having ILF or refusal to administer it to patients with acute ILF is destructive as well.

Let us consider one more recently widely discussed aspect of early ILF diagnostics. We believe that given the modern understanding of ILF this discussion is aimless. In all guidelines (international and national) ILF diagnosis can be made only in case of honeycomb lung and advanced reticular changes. Optional signs are traction bronchiectasis (often) and frozen glass (rare). The localization of the mentioned changes is in subpleural and basal compartments of the lung. As the represented findings show a honeycomb lung is the main CT sign of ILF (OIP). After such a statement of the fact, it seems awkward to ask the following question: what early diagnostics can we speak about if there is a honeycomb lung, traction bronchiectasis, and other CT-signs present, without which ILF diagnosis is just impossible?

Given the modern paradigm of ILF understanding, we have to diagnose late. Perspectives of early ILF diagnostic can become clear enough only if a unified IIP understanding is reached, i.e. uniting all IIPs under one term – idiopathic fibrotic lung disease.

Here are some perspectives on the treatment. Can the ILF patient treatment be effective if the diagnostics criteria are advanced lung fibrosis, honeycomb lung, and traction bronchiectases? Even antifibrotic drugs treatment is palliative only that can just prolong life for a limited time.

The stable course of the disease excludes SCS intake on the background of antifibrotic drugs. The signs of the disease activity and diagnosing its aggravation, presence of autoimmune and allergic components prove to be indications for SCS administration.

And finally, ILF understanding, as we have already mentioned above, can hardly be considered clinical. The term “fibrosis” doesn’t usually mean a disease. Strictly speaking, it is a scar, hyperplasia of the fibrous connective tissue, occurring in termination of the inflammation.

Though, according to the International agreement (2013, 2015), ILF is a clinical term. But morphologists use a term of OIP (ordinary interstitial pneumonia), which tends to be more clinical. But wouldn’t it be more logical to consider ILF to be a morphological term while OIP – a clinical one?

We believe that a significant part of the above-mentioned contraindications could be solved using a unifying term such as idiopathic fibrotic lung disease. That would help decide the early diagnostics issues, evaluate the pathological process activity, and establish indications and contraindications to administering several anti-inflammatories and/or antifibrotic drugs.

Without claiming a monopoly of absolute truth, we have formulated some conclusions, useful criticism of which will help clear up different aspects of this complex issue.

Conclusion

1. There are no grounds to distinguish multiple separate specific forms of idiopathic interstitial pneumonia (IIPs).

2. IIPs (except COP and non-classified Ips) can be united under the term of "idiopathic fibrotic lung disease".

3. Idiopathic fibrotic lung disease has its onset and outcome, own characteristic clinical manifestations, and morphological changes that depend on the course, such as acute, subacute and chronic one, and cannot be similar during its onset and outcome.

4. Unifying all IIPs (besides COP and non-classified interstitial pneumonia and cryptogenic organizing pneumonia that are to be further studied) under the term "idiopathic fibrotic lung disease" will enable to refuse from vague and still pointless speculations about so-called early diagnostics of idiopathic lung fibrosis, to define the criteria for the disease activity and to formulate distinct indications for administration of systemic corticosteroids and antifibrotic drugs to treat this disease.

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