

## Subacute Interstitial Pneumonia

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### Abstract

Idiopathic interstitial pneumonias (IIPs) is a broad category which usually involve interstitium and alveolar space. American thoracic society (ATS)/European respiratory society (ERS)/ published international official statement about IIPs. And this guideline divided into three subgroups of major IIPs such as chronic fibrosing, smoking-related and acute/subacute. This classification is understandable and practical. However, we sometimes see who present subacute progressive dyspnea with imaging pattern of organizing pneumonia (OP) associated with bronchial dilatation and volume loss. Previously, these patients were diagnosed as cellular and fibrosing non-specific interstitial pneumonia (NSIP). However, NSIP is categorized as chronic interstitial pneumonia in latest international guideline. Clinical problem is whether NSIP with subacute presentation match current classification. And differential diagnosis and management strategy of subacute interstitial pneumonia (IP) are different from acute and chronic interstitial pneumonia. In this mini-review, I focus on the clinical meaning and treatment of subacute IP.

### Introduction

Subacute IP present more progressive dyspnea with diffuse ground glass attenuation, consolidation, reticulation and volume loss. Patient usually report severe dyspnea. Therefore, pulmonary function test (PFT) or bronchoalveolar lavage (BAL) is sometimes not performed. However, complementary tool such as High-flow nasal cannula oxygen (HFNC) therapy can help for invasive procedure. In addition, this group show more aggressive clinical course compared to chronic IP. So, rapid management decision is required. I review major clinical symptoms, chest imaging, important differential diagnosis and real management.

### Clinical Symptom

In diffuse lung disease, subacute clinical course comprise of 1 month to 3 months [1,2]. Major symptoms are non-productive cough and progressive exertional dyspnea [3]. Sometimes, these patients notice constitutional symptoms such as low grade fever, body weight loss, myalgia, joint pain and rash [4]. If we see these symptoms in subacute IP patients, connective tissue disease (CTD) associated IP, especially anti-aminoacyl-tRNA synthetases (ARS) syndrome or rheumatoid arthritis (RA) are possible [5]. We sometimes see subacute IP which does not meet criteria of CTD such as polymyositis (PM)/dermatomyositis(DM) or RA. If pathological findings of these patients revealed non-specific interstitial pneumonia (NSIP), tentative diagnosis is idiopathic NSIP [6]. Majority of these patients show fine crackles. However, they rarely show finger clubbing.

### Laboratory Data

Serum white blood cell (WBC), C-reactive protein(CRP)are moderately elevated [3]. When we see eosinophilia with subacute IP, drug associated IP is leading diagnosis [7]. If patients have subclinical vasculitis or ARS syndrome, CRP is markedly elevated. When serum erythrocyte sedimentation rate (ESR) is over 50mm/hour, we should check autoimmune panel including vasculitis marker such as myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) [8]. In terms of fibrosis marker, lactate dehydrogenase (LDH), Krebs von den Lungen-6(KL-6), surfactant protein D(SP-D) are useful. LDH is a classic interstitial lung disease (ILD) marker and very sensitive during acute phase [9]. Both KL-6 and SP-D are recent sensitive marker. KL-6 is a high molecular weight protein [10-12]. Therefore, there is a gap between clinical situation and elevation. KL-6 is associated with extent of fibrosis and predictive marker of

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acute exacerbation (AE) [13,14]. On the other hand, SP-D is associated with inflammation, reversible fibrosis. SP-D is a low molecular weight and reflects rather real time change of clinical behavior [15,16]. Therefore, SP-D is useful for subacute IP such as organizing pneumonia (OP) or NSIP. In ARS syndrome, serum ferritin is helpful for prediction of disease activity. In addition, over 500 is associated with progressive clinical course.

### Radiological Findings

Based on subacute process, they usually do not show definite honeycombing which is a classic important findings of chronic IIPs such as idiopathic pulmonary fibrosis (IPF) or fibrotic NSIP(3). Typical crucial chest high-resolution computed tomography (HRCT) findings are diffuse ground-glass attenuation (GGA), peribronchial consolidation, subpleural reticulation, interlobular septal thickening and symmetric lower lung volume loss [5,17]. These findings are often seen, especially in ARS syndrome. Therefore, when we see subacute IP with typical HRCT findings, we should evaluate autoimmune panel including ARS antibody [3].

2013 international guideline described variant organizing pneumonia with supervening fibrosis which is almost identical to ARS syndrome [1].

### Differential Diagnosis

Connective-tissue disease (CTD), especially anti-aminoacyl-tRNA synthetases (ARS) syndrome, Drug associated, and hypersensitivity pneumonitis (HP), are representative category of subacute IP. We sometimes see OP with subacute dyspnea or NSIP with progressive dyspnea. I summarize clinical information of major three categories.

### ARS Syndrome

ARS syndrome is most common cause of subacute IP in daily practice. Middle aged patient, muscle weakness, symmetric proximal muscle pain and mechanic hand are key symptoms and findings. In radiological findings, lower lung field dominant GGA, axial consolidation, reticulation with lower lobe volume loss are crucial findings. Serum creatine phosphokinase (CPK) and ARS antibody including Jo-1 antibody should be checked [18].

### Drug Associated Lung Injury

Many causative agents have been reported. For clinicians, important issue is to predict prognosis. HRCT findings of diffuse alveolar damage (DAD) pattern such as diffuse GGA with bronchial

dilatation or subpleural linear consolidation are warning findings [19-21]. Fleishner society says we should use traction bronchiectasis exclusively for chronic IP. In drug associated lung injury with HRCT DAD pattern, we can raise tyrosine kinase inhibitor (TKI), biological agent as possible drugs [22]. Both amiodarone and methotrexate (MTX) show similar findings as DAD pattern. However, they usually have good clinical course [23]. So, clarification of causative agent is important for prediction of prognosis.

### Subacute HP

Leading cause of subacute HP are home dust and bird. And serum KL-6 show marked elevation over 1000. Chest HRCT show upper lung field dominant numerous centri-lobular granular shadow or GGA. In addition, BALF cell population provides quite useful information for definite diagnosis and usually show lymphocytosis over 30% [24] (Table 1).

### Diagnosis

According to the current guideline, NSIP is chronic fibrosing category [1]. However, we have subacute IIP with NSIP pattern radiologically or pathologically [25-27]. In clinical point of view, subacute NSIP or fibrosing OP requires urgent evaluation and treatment. Therefore, I propose both subacute NSIP and fibrosing OP should be categorized as subacute IIPs.

### RPIP

Kondoh, et al. reported that most valuable prognostic factor of rapidly progressive interstitial pneumonia (RPIP) is pathological DAD or OP/NSIP [28]. They defined as these patients who developed clinical symptoms within three months. Therefore, RPIP with DAD behave like acute interstitial pneumonia (AIP). But, AIP is more acute process such as within one month [29,30]. On the other hand, RPIP with OP/NSIP mimic subacute IIP including fibrosing OP. Distinction of these two groups is quite important. The former usually show poor treatment response, the latter show good response to steroid. If these subacute IIP patients could not undertake surgical lung biopsy because of severe respiratory failure, detailed clinical information, chest HRCT and BAL provide useful information for management. Ni, et al. reported that systematic review of HFNC (High Flow Nasal Cannula) oxygen therapy decrease the rate of endotracheal intubation of acute respiratory failure (ARF) [31]. In addition, subacute IP patients often show moderate to severe respiratory failure, BAL can be performed safely with HFNC. Therefore, HFNC contribute to both diagnosis and management of subacute IP.

Table 1. Clinical characteristics of four representative subacute IIPs.

	History	Physical Examination	Laboratory	Imaging
ARS syndrome	1 to 3 months	Fine crackles Muscle weakness Mechanic hand	CRP↑ CPK↑↑ Ferritin↑ LDH↑ ARS antibody↑ SP-D↑	GGA Axial Consolidation Volume loss in lower lobe Reticulation
Drug associated	1 to 3 months	Fine crackles	CRP↑ SP-D↑	GGA Consolidation
Subacute HP	Approximately 1 month	Subtle crackles	WBC↑ KL-6↑↑ LDH↑	Upper lung field dominant Numerous nodules
Unclassifiable	1 to 3 months	Fine crackles Sometimes Joint pain, fever	LDH↑ KL-6↑ SP-D↑	GGA Consolidation Reticulation

Definitions of abbreviations: ARS=anti-aminoacyl-tRNA synthetases; CPK=creatin phosphokinase; CRP=C-reactive protein; GGA=ground-glass attenuation; HP=hypersensitivity pneumonitis; KL-6= Krebs von den Lungen-6; LDH=lactate dehydrogenase; SP-D=surfactant protein D; WBC= white blood cell.

## Management

Clinical behavior is proposed for management of IIPs in latest international guideline [1]. Subacute IP patients have variable clinical course from reversible disease with risk of progression, stable with residual disease and progressive irreversible disease with potential for stabilization. Therefore, detailed clinical information and serial monitoring of crucial symptoms, surrogate markers such as percent predicted forced vital capacity (%FVC), KL-6, SP-D and extent of fibrosis in chest HRCT or pathological specimen provide useful information for real management of subacute IP patients. ARS syndrome often have good response to steroid or combination therapy including immunosuppressants. This syndrome show volume loss both radiologically and physiologically [5,17]. So, serial chest imaging and %FVC is associated clinical response. Checking minor fissure position and hilum deviation of chest imaging is important issue of management [9]. Mild symptom group can be controlled prednisolone (PSL) alone. However, ARS syndrome often show relapse same anatomical location of chest imaging, especially under 15 mg [32,33]. After relapse, immunosuppressants such as azathioprine (AZP) will be added [34,35]. When patient develop severe respiratory failure, I recommend both PSL and calcineurin inhibitor such as tacrolimus or cyclosporine [36-42]. When we see RA associated subacute IP, methotrexate (MTX) is usually avoided because of fear of MTX associated lung injury. Therefore, we usually use AZP for RA-IP.

Subacute HP is usually reversible with avoidance of antigen or systemic steroid. Patient education and cooperation is also central point of care. This group usually fit reversible disease with risk of progression. In drug associated lung injury, patient usually respond to withdrawal of causative drug or systemic steroid except for DAD such as gefitinib. In this group, diagnosis of DAD is quite important for physician. Careful monitoring of clinical symptoms and radiological findings are required. Remaining are idiopathic subacute progressive IP or unclassifiable IP. Hyldgaard, et al. reported both disease behavior classification and ILD-gender age physiology (GAP) model were complementary predictors of outcome in unclassifiable ILD [41,42]. Therefore, idiopathic subacute is manageable based on disease behavior and physiological state (Table 2).

In conclusion, subacute IP exist in real world and management strategy is different from acute and chronic IP. In addition, symptom progress rapidly and relapse is often seen. Early

detection and chronic meticulous monitoring is required for this category.

## Conflict of Interest

I declare no conflict of interest.

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Table 2. Management of subacute IP.

	Disease behavior	Treatment	Prognosis
ARS syndrome	Reversible disease with risk of progression	PSL alone or PSL+Tacrolimus or cyclosporine	Good Frequent relapse
Drug associated	Reversible or progressive	Stop agent PSL alone or PSL+AZP	Good except for TKI associated
Subacute HP	Reversible	Antigen avoidance PSL alone	Quite good
Unclassifiable	Stable to progressive despite therapy	PSL alone or PSL+AZP or PSL+CPA or PSL+MMF	Unpredictable

Definitions of abbreviations: ARS=anti-aminoacyl-tRNA synthetases; AZP=azathioprine; CPA=cyclophosphamide; HP=hypersensitivity pneumonitis; MMF= mycophenolate mofetil; PSL=prednisolone; TKI=tyrosine kinase inhibitor.

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