Pulmonary manifestations of anti-synthetase syndrome: a pictorial review to aid diagnosis and monitoring.

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Authors: M. Kudari, L. Wing, H. Elhassan, R. Hoyles, R. Benamore; Oxford/UK
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Learning objectives

• Describe the clinical features of 'antisynthetase syndrome'

• Review the imaging appearances of its pulmonary manifestations, focusing on interstitial lung disease

• Review several cases of antisynthetase syndrome from diagnosis to post-treatment follow-up

• Suggest a guide to radiological management of the pulmonary manifestations

Background

• Antisynthetase syndrome describes the triad of inflammatory myositis, interstitial lung disease and the presence of anti-aminoacyl-tRNA synthetase antibodies (ASA). It is often accompanied by a constellation of associated clinical findings including "mechanic's hands", Raynaud's phenomenon and polyarthritis.

• The clinical presentation varies greatly, but anti-histidyl-tRNA synthetase (anti-Jo-1) antibody was the first ASA to be discovered and is the most commonly reported (Table 1).

• The overall prognosis for antisynthetase syndrome seems to be worse than for other myositides. This is at least partly due to a higher prevalence of lung involvement, which in some studies is as high as 72% of patients \(^1\).

• Survival data for antisynthetase syndrome is limited but survival with ILD from polymyositis/dermatomyositis is reported as 94% at 1 year; 90.4% at 3 years and 86.5% at 5 years \(^5\). The presence of ILD increases mortality in antisynthetase syndrome by 40% \(^1\). Survival with antisynthetase syndrome and pulmonary hypertension at 3 years has been reported at 58% \(^6\).

• Radiological investigation for interstitial lung disease (ILD) is usually initiated by clinical presentation of breathlessness, sometimes with persistent cough, basal crepitations and a restrictive pattern on pulmonary function tests.

• Given that pulmonary involvement is the most common cause of morbidity in antisynthetase syndrome, HRCT plays a pivotal role in diagnosis and monitoring treatment response.
Table 1: Prevalence of anti-tRNA synthetase antibodies in inflammatory myopathies (adapted from Hervier & Benveniste 2013) (Ref 1)

<table>
<thead>
<tr>
<th>Anti-tRNA-synthetase antibody subtype</th>
<th>Prevalence in inflammatory myositis</th>
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<tbody>
<tr>
<td>Jo-1</td>
<td>20–25 %</td>
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<tr>
<td>PL12</td>
<td>5 %</td>
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<tr>
<td>PL7</td>
<td>5 %</td>
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<td>OJ</td>
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<td>KS</td>
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<tr>
<td>Zq</td>
<td>&lt;&lt;1 %</td>
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<tr>
<td>YRS/Tyr</td>
<td>&lt;&lt;1 %</td>
</tr>
</tbody>
</table>
Findings and procedure details

SUGGESTED INVESTIGATION

- Following preliminary assessment, non-contrast high resolution CT is recommended *(Fig. 1)*. Technique: High resolution axial images, 1.25mm thickness; inspiratory and expiratory phases.

- In our institution, for patients over 45 years, a volumetric acquisition is performed allowing us to obtain MinIPs (minimal intensity projections), which some find helpful in emphasizing subtle traction bronchiectasis and honeycombing disease. In patients under 45 years we perform HRCT in order to limit the dose.

- Auxillary techniques such as imaging the patient in the prone position may help to clarify areas of diagnostic uncertainty.

- If a high degree of confidence in the diagnosis is reached following HRCT, the patient may proceed to treatment, often with steroids or steroid sparing immunosuppression (see later).

- If no firm diagnosis is reached, open lung biopsy may be considered with caution.

FOLLOW UP INVESTIGATIONS

In addition to clinical parameters (pulmonary function tests, 6-minute walking time, systolic pulmonary artery pressure and arterial blood gas measurements) \(^8,9\) radiology forms a key component of disease monitoring.

*Figure 2* depicts our institution's practice in monitoring treatment response and investigating clinical deterioration.

In the event of clinical deterioration which may be characterized by worsening symptomatology or declining pulmonary function tests, prompt assessment of the patient is vital.

If preliminary investigations do not reveal an underlying cause (e.g. infection), CT is warranted to assess for disease progression or other complications such as opportunistic infection and drug reaction. In our experience, thromboembolic disease is rare (zero
cases in our case series) and therefore non-contrast HRCT is recommended unless there are specific indications for CTPA.

In the absence of radiographic progression or other complications, echocardiogram is recommended to assess for pulmonary arterial hypertension, which may arise secondary to chronic lung disease or as an independent manifestation of antisynthetase syndrome.

**PATTERNS OF DISEASE**

Studies have shown that the extent of interstitial lung disease correlates with its severity\(^2\).

An International Consensus Statement\(^3\) describes three main patterns for progressive ILD, as occurs in antisynthetase syndrome:

1) Nonspecific Interstitial Pneumonia (NSIP)
2) Organising pneumonia (OP)
3) Usual Interstitial pneumonia (UIP)

UIP tends to be associated with the worst prognosis.

**Non-Specific Interstitial Pneumonia (NSIP)**

- NSIP is associated with many collagen vascular diseases or drug reactions. Histologically, it is characterised by spatial and temporal homogeneity and two types are recognised - cellular and fibrotic.

- Cellular NSIP shows areas of ground glass opacity in a peripheral and lower zone distribution (**Fig. 3**).

- Fibrotic NSIP typically shows traction bronchial dilatation and linear opacities (**Fig. 4**). However, honeycombing is rare, helping to distinguish it from UIP.

Features of NSIP are variable\(^10\):

- Ground glass is found in 75-100% of cases: usually bilateral, symmetrical and subpleural in two-thirds of patients, with lower zone predominance in over 50%.
• Reticulation and irregular linear opacities in 50-85%
• Traction bronchiectasis in 35-95%.
• Honeycombing is not a major feature, but can occur in 25-30%.

Organising Pneumonia (OP)

OP in antisynthetase syndrome can reveal
• patchy consolidation or ground-glass opacity with either subpleural or peribronchial distribution, with basal predominance (*Fig. 5A*).
• multiple nodules or masses
• perilobular distribution of disease (*Fig. 6*)

Lung biopsy can be useful in differentiation from UIP - OP has an absence of parenchymal distortion of fibrosis.

OP is usually more treatment responsive than NSIP, particularly when it presents with airspace disease.

There can be overlap of NSIP and OP features (*Fig. 7 and Fig. 9*).

Usual Interstitial Pneumonia (UIP)

• UIP is the commonest of interstitial lung diseases and progresses along a course that involves inflammation initially, followed by repair and fibrosis.
• UIP is often at different stages within different areas of the lungs (i.e. temporally heterogeneous).
• Typical findings are of peripheral, basal and subpleural reticulation, traction bronchial dilatation and honeycombing, with minimal ground glass component (*Fig. 10*).

RESPONSE TO DRUG THERAPY
A range of drugs are used to combat the interstitial pulmonary disease of antisynthetase syndrome. The aim is to stabilise or reverse disease.

Corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil, tacrolimus, ciclosporin or rituximab may be used.

The disease response can vary amongst individuals with follow up studies showing:

- stable disease *(Fig. 8)*
- complete *(Fig. 9 and Fig. 11)* or partial response *(Fig. 5)*
- relapse *(Fig. 12)*

**COMPLICATIONS**

**Infection**

HRCT can be helpful in patients who become increasingly symptomatic on treatment.

- Patients on immunosuppressants are at increased risk of infection from typical and atypical organisms.
- HRCT may demonstrate features to suggest a specific aetiology, such as mycobacterial disease (tree-in-bud nodularity, lymphadenopathy, cavities)
- HRCT may sometimes demonstrate an increase in ground glass opacity which could either be due to disease progression, viral infection, PCP or drug reaction.
- The location of ground glass opacity on HRCT however, may help to guide bronchoscopic lavage.

**Drug related**

In addition to the gamut of clinical sequelae of steroids and steroid-sparing agents, some are of particular importance in the interpretation of HRCT during follow-up.

- OP can occur as a result of drug reactions
- Drug induced pneumonitis can resolve after withdrawal of treatment *(Fig. 13)*
Pulmonary Hypertension

- Pulmonary hypertension in ILD is well-established and also occurs in antisynthetase syndrome.

- Dissociation between severity of pulmonary hypertension and degree of fibrosing ILD may suggest a distinct pathological process. 4

- Other reported cardiac manifestations include cardiomyopathy, carditis and pleurisy (pericardial and pleural effusions).

- Progressive shortness of breath despite treatment of ILD should prompt investigation of cardiac complications.

Acute Interstitial Pneumonia / ARDS

Most cases have gradual onset, but ILD in antisynthetase syndrome may rarely present explosively as Acute Interstitial Pneumonia / ARDS with associated complications (Fig. 14 & Fig. 15)

Images for this section:

Fig. 1: Adapted from British Thoracic Society's Diagnostic Algorithm for Interstitial Lung Disease (2008) (Reference 7)
**Fig. 2:** Local algorithm for follow up after starting cyclophosphamide treatment in antisynthetase syndrome. (HRCT = High Resolution CT; PFTs = Pulmonary Function Tests; TLCO = Carbon Monoxide Transfer Factor; BAL = Bronchoalveolar Lavage)

**Fig. 3:** Basal ground glass change with septal thickening consistent with a cellular NSIP pattern. A and B are images from the same study.
Fig. 4: A - Basal and subpleural reticulation consistent with fibrosing NSIP; B - 23 months later, extensive subpleural intralobular septal thickening and traction bronchial dilatation, consistent with progressive fibrosing NSIP.

Fig. 5: A - Peribronchial consolidation with basal predominance and subpleural ground glass opacity and consolidation, in keeping with OP; B - 7 months later, minor residual peribronchial ground glass after treatment with cyclophosphamide
Fig. 6: Ill-defined linear opacities in perilobular distribution in keeping with perilobular OP
**Fig. 7:** A - Peribronchial consolidation and ground glass opacity, consistent with OP; B - In the same patient, basal peripheral, subpleural ground glass opacity, fine reticulation and bronchial dilation more consistent with fibrosing NSIP.

**Fig. 8:** A - Baseline scan, patient presented with polymyositis and dyspnoea; B - 5 years later with progressive symptoms, mild bilateral subpleural reticulation that has progressed since baseline; C - 7 months later, further mild progression; D - 5 months later, stable disease after treatment with methotrexate.
**Fig. 9:** A - Bilateral subpleural ground glass, peribronchial consolidation and traction bronchiectasis, in keeping with OP + NSIP overlap; B - 4 months later, complete resolution after cyclophosphamide

**Fig. 10:** Peripheral and subpleural reticulation with honeycombing, consistent with UIP
Fig. 11: A - Peribronchial consolidation in keeping with OP; B - 10 months later, complete resolution after cyclophosphamide
**Fig. 12:** A - Minor ground glass opacification in peripheral distribution with minor traction bronchiectasis (fibrosing NSIP); B - 8 months later, progression of disease after 6 cycles of cyclophosphamide; C - 11 months later, improvement after 2 cycles of rituximab; D - 5 months later, relapse with progressive fibrosing NSIP pattern.

![Images of thoracic CT scans showing lung conditions](image12)

**Fig. 13:** A - Baseline study, pre-treatment; B - 15 months later, widespread ground glass in keeping with hypersensitivity pneumonitis following methotrexate treatment; C - 2 months later, improvement in the mid zone ground glass after withdrawal of methotrexate.

![Image of thoracic CT scan showing lung conditions](image13)
**Fig. 14:** Extensive diffuse ground glass change with interlobular septal thickening and patchy lobular sparing. More dense consolidation was shown in the dependent areas. Findings in keeping with AIP and superadded ARDS.

**Fig. 15:** Same patient as Fig 14; 6 weeks later, small left pneumothorax from left lower lobe bronchopleural fistula, with intercostal drain shown in subcutaneous tissues. Both images from same study.
Conclusion

- Pulmonary manifestations of antisynthetase syndrome include diffuse interstitial lung disease, pulmonary hypertension and infectious or drug-related pulmonary sequelae of immunosuppression.

- We highlight early and appropriate radiological investigation as paramount in maximising diagnostic accuracy and monitoring response to treatment.

Personal information

References