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EDITORIAL

Antisynthetase syndrome with predominant lung involvement. An easy to miss diagnosis

Interstitial Lung Diseases can be extremely challenging in terms of diagnosis. Antisynthetase syndrome (ASYS) represents a major area of concern as it can present with isolated pulmonary involvement and can even mimic other diseases, notably hypersensitivity pneumonitis.[1] ASYS is a clinically distinct subset among the immune inflammatory myopathies, characterized by the presence of autoantibodies against aminoacyl-tRNA synthetases (anti-ARS) that are myositis-specific antibodies. The classic clinical triad of myositis, ILD and arthritis is referred to as complete ASYS. However, all triad findings are rarely found at presentation. Even after extended surveillance extending over one year, a complete ASYS is seen in no more than 50% of patients with anti-Jo1 and even less for patients with non-anti-Jo-1 autoantibodies. Organ involvement and thus clinical presentation depends on the type of anti-ARS antibody meaning that different medical specialties encounter different phenotypes. Rheumatologists are more likely to see patients in whom muscle and joint involvement predominates, while patients with predominant lung involvement are more likely to be referred to pulmonologists.[2] We analyze the diagnostic difficulties of ASYS from the pulmonologists perspective, focusing on four domains, clinical, laboratory, imaging and pathology.

Patients with ASYS, usually presenting to respiratory services are more likely to have isolated lung involvement. Myositis if present can be subclinical without muscle weakness. History is unhelpful and sometimes can be misleading as some patients report exposure to organic antigens, erroneously pointing towards hypersensitivity pneumonitis. Helpful physical findings as mechanic hands, Gottron papules, periorbital edema, and skin erythema, can easily go unnoticed by non experienced pulmonologists.

In cases of ASYS where lung is the first involved organ or in cases with subclinical myositis, muscle enzymes (creatine kinase and aldolase) can be normal. Aminoacyl-tRNA synthetases antibodies (anti-ARS) are located in the cytoplasm and result in a negative ANA test which does not indicate autoantibody negativity in the context of ASYS.[3] Furthermore, the extractable nuclear antigen (ENA) panel includes only anti-Jo-1 out of the eight known anti-ARS antibodies.[4] A negative ENA panel cannot exclude the diagnosis of ASYS and can miss patients that are at high risk for developing isolated or predominant lung involvement (e.g. anti-PL-7, anti-PL-12 and anti-EJ) [4]. A prominent bronchoalveolar lavage lymphocytosis (≥30%), usually pointing towards hypersensitivity pneumonitis has been reported in ASYS.[1]

Imaging findings of ASYS based on high resolution computed tomography (HRCT) are not specific. They include bilateral areas of ground glass, consolidation, and reticulation. Traction bronchiectasis points to the presence of underlying fibrosis. The corresponding patterns are Non Specific Interstitial Pneumonia (NSIP), Organizing Pneumonia (OP), mixed NSIP/OP, while a Usual Interstitial Pneumonia pattern (typical or probable) has only rarely been described.[5] In some patients there are diffuse areas of ground glass, alternating with normal parenchyma, resulting in a mosaic pattern. Also, consolidative areas tend to have a peribronchial distribution. The presence of mosaic attenuation and peribronchial distribution, especially when there is a history of exposure to an inciting antigen, can be strongly deceptive in favor of hypersensitivity pneumonitis. Coronal reformations can be helpful as they can highlight the predominant location of findings to the lung bases with sharp demarcation in the craniocaudal plane. This is known as the “straight edge” sign and is considered to be indicative of an underlying connective tissue-interstitial lung disease.

Lung biopsy findings in ASYS are also not specific. The presence of dense lymphocytic inflammation with peribronchial distribution, predominance of plasma cells, lymphoid aggregates with or without germinal centers, follicular bronchiolitis and pleuritis raise suspicion of an underlying collagen tissue disease. However, these findings are by no means pathognomonic of ASYS or connective tissue-interstitial lung disease in general. Furthermore, there can be significant overlap with other diseases with HP being a characteristic example.[1] In a patient with ASYS and avian exposure, prominent bronchoalveolar lavage lymphocytosis, mosaic pattern on HRCT, pathology could be considered compatible with HP, leading to a false diagnosis.

Timely diagnosis of ASYS has significant impact on patients’ outcome. Lung involvement in the context of ASYS is not only one of the most common manifestations but also a major factor of increased morbidity and mortality. Delayed diagnosis has

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Table 1 Diagnostic challenges in amyopathic lung predominant idiopathic inflammatory myositis.

Clinical	Laboratory
• Idiopathic inflammatory myositis with predominant lung involvement is rare.	• Muscle enzymes are within normal range.
• Musclesymptomsareabsent.	• ANA can be negative/lowtiterpositive.
• Exposure toan inciting antigen can be misleading.	• ENA panel tests only for anti-Jo-1.
• Skin findings or arthritis can be overlooked.	• BAL lymphocytosis is not pathognomonic
Imaging	Pathology
• Imaging patterns (NSIP, OP, mixed NSIP/OP) are not specific.	• Pathology findings (dense lymphocytic inflammation with peribronchial distribution, lymphoid aggregates with or without germi nal centers) are not specific.
• Mosaicattenuation orpredommant peribronchial distribution can be present pointing to more common diagnoses.	

been associated with worst prognosis and not surprisingly is most commonly observed in non-anti-Jo-1 patients.[6] The significance of this observation is twofold. First, ENA panel does not test for non-anti-Jo-1 autoantibodies. Second, patients with non-anti-Jo-1 autoantibodies, mainly anti-PL-7, anti-PL-12 and anti-EJ are most often associated with clinically isolated pulmonary involvement and thus more easily to be misdiagnosed. ASYS has the perfect camouflage recipe (Table 1). It can present with isolated pulmonary involvement, skin manifestations can be absent or go unnoticed by the non-experienced pulmonologist, and muscle involvement can be present, but subclinical, resulting in normal muscle enzymes. ANA can be negative and ENA panel does not test for anti-ARS except for anti-Jo-1. Furthermore, ASYS can notoriously masquerade as hypersensitivity pneumonitis in the presence of an inciting antigen, prominent bronchoalveolar lavage lymphocytosis, mosaic attenuation of the lung parenchyma and/or bronchocentric distribution on HRCT, and pathology findings exhibiting bronchiolocentric lymphocytic inflammation with lymphoid aggregates and peribronchiolar metaplasia.

In the above-mentioned clinical scenario imaging holds a key role. The presence of radiological NSIP and/or OP pattern should always raise suspicion of underlying ASYS even in the presence of a working diagnosis, as HP. It is impossible to exclude ASYS unless testing for anti-ARSs. Biomarkers are the basis of personalized medicine. Thankfully, in ASYS we have myositis specific antibodies as diagnostic biomarkers. It is important to actively involve rheumatologists in the context of multidisciplinary discussion to bridge the gap between the two medical specialties and increase awareness and expertise for both sides. Collaborative studies to determine the exact incidence of ASYS in ILD patients presenting to respiratory departments with radiological NSIP and/or OP pattern are needed. In the meantime, there should be a low threshold in ordering a myositis panel for these patients. A joint statement can serve as a valuable first step towards this goal.

Conflicts of interest

None related to the present work.

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