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# HIDDEN IN PLAIN SIGHT: PITFALLS OF A CASE OF AMYOPATHIC ANTI-SYNTHETASE SYNDROME ASSOCIATED WITH GRAWITZ TUMOR

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***Abstract***
*Anti-synthetase syndrome (ASS) is a rare autoimmune disease whose hallmark consists of the presence of autoantibodies directed against aminoacyl transfer RNA (tRNA) synthetases thus making it a distinctive pathology of the broad spectrum of idiopathic inflammatory myopathies (IIM). Clinically, lung involvement in the form of interstitial lung disease (ILD) and myositis are typical findings. Inflammatory myopathies should always raise the suspicion of an adjancent tumoral process and therefore prompt the clinician to perform a thorough screening. We present the case of a 55 year old caucasian male who was diagnosed with amyopathic ASS and a clear cell renal carcinoma (Grawitz tumor), along with the consequent therapeutic challenges.*
***Keywords****: amyopathic anti-synthetase syndrome, interstitial lung disease, Grawitz tumor.*

***Rezumat***
*Sindromul anti-sintetază este o boală autoimună care are ca particularitate prezența anticorpilor direcționați împotriva tRNA sintetazelor, fiind astfel o patologie distinctivă în cadrul miopatiilor inflamatorii idiopatice ale adultului. Prezența pneumopatiei interstițiale și a miozitei întregește tabloul clinic al bolii. Atunci când sunt diagnosticate, miopatiile inflamatorii ar trebui să ridice clinicianului suspiciunea unui proces tumoral subiacent. Vom prezenta în cele ce urmează cazul unui pacient caucazian în vârstă de 55 de ani care a fost diagnosticat cu sindrom anti-sintetază amiopatic și tumoră renală cu celule clare (tumoră Grawitz), alături de provocările terapeutice consecutive.*
***Cuvinte cheie:*** *sindromul anti-sintetază amiopatic, pneumopatie interstițială difuză, tumoră Grawitz.*



**Introduction**

ASS is an IIM included in the broad spectrum of autoimmune diseases which is characterized by the production of autoantibodies directed against tRNA synthetases[1]. Antisynthetase antibodies include: anti-histidyl- (anti-Jo-1), anti-threonyl- (anti-PL-7), anti-alanyl (anti-PL-12), anti-isoleucyl- (anti-OJ), anti-glycyl- (anti-EJ), anti-asparaginyl- (anti-KS), anti-tyrosil- (anti-YRS); each antibody or the combinations between them can predict a particular clinical pattern, disease activity, or outcome[2, 3, 4]. Anti-Jo-1 is the most common antisynthetase antibody and is found in 20-30% of patients diagnosed with ASS; considering the high variability between imunological findings, the ASS diagnostic is particularly difficult to assess[5]. ASS is a relatively new-found nosological entity derived from studying subjects presented with PM and DM. In 1990s, researchers acknowledged that patients who had antibodies against tRNA synthetase would form a distinct group with different clinical features and evolution, leading to theformal recognition of ASS[6]. Later on, Solomon et. al. and Connors et.al. developed the criteria for the diagnostic of ASS, which focused mainly on the presence of tRNA synthetase autoantibodies and findings consistent with ILD[7, 8]. Additionally, patients with ASS have more proeminent connective tissue disease hallmarks, such as Raynaud's phenomenon and gastro-intestinal involvement (i.e., esophageal reflux)[1]. Clinical findings traditionally consistent with DM or PM are also present, such as Gottron's papules, fever or arthritis[7, 8]. The treatment can be challenging as the management is solely based on data extrapolated from studies of patients with IIM that also included cases of ASS, but the target should be primarily focused on respiratory alleviation, with steroids being the cornerstone of therapeutic options[1]. The management of ASS implies an interdisciplinary approach, and the treatment is often times guided by the clinician's experience and judgement.

Allthough cases of DM and PM without muscular involvement have been broadly discussed, data involving amyopathic ASS is scarce, with only a few case reports publishedto date[9, 10]. Additionally, the association between DM and cancer is well documented, while PM is arguably linked to neoplasia, there is little evidence regarding the correlation between ASS and malignancy as the data is mostly derived from case series and case reports[11, 12, 13, 14, 15, 16, 17]. Interestingly, the presence of extramuscular features (Raynaud's phenomenon, arthritis) and especially the presence of ILD in patients with inflammatory myopathies was found to be protective against malignancy, while older age, male sex, and elevated levels of

creatinkinase (CK) pose a greater risk of malignant disease[18,19].

We present the case of a 55 year old white male who was first admitted to „Sfanta Maria" Clinical Hospital in 2022, along with the diagnostic and therapeutic pitfalls.

**Case presentation**

A 55 year old white male first presented to the rheumatology department of „Sfanta Maria" Clinical Hospital in 2022 for progressive dyspnea, fatigue, dry cough, and dry eye symptoms.

He was previously consulted in a pulmonology department, where he was diagnosed with nonspecific interstitial pneumonia (NSIP), CT scan presenting several „ground glass" opacities, spirometry showing a restrictive pattern with decreased forced vital capacity (FVC= 47,6%) and a severe decrease in the diffusing capacity of the lung for carbon monoxide (DLCO- no value available), thus prompting the suspicion of an adjacent rheumatological condition (Figure 1).

At admission, a high ESR (60 mm/h) with minimally elevated CRP (6,92 mg/dL) was observed, while creatin phosphokinase (CK) and *lactate dehydrogenase* (LDH) were normal; anti-La/SS-B, anti-dsDNA, anti-Sm, and anti-CCP antibodies were negative; ANA and anti-Ro/SS-A antibodies were positive (ANA=5,5, anti-Ro/SS-A=171,9 U/mL); additionally, an extended panel of myositic antibodies was requested, with results still pending by the time the patient was discharged. Schirmer's test was moderately positive (left eye=5 mm, right eye =6 mm). Chest x-ray revealed an enlarged cardiac silhouette, and ecocardiography showed increased left atrial volume (greater than 45 ml). An abdominal CT scan showed a left kidney tumoral mass suspicious of a clear cell renal carcinoma or Grawitz tumor (dimensions= 41 mm/46 mm) was performed.

A diagnosis of Sjogren's syndrome (SS) was raised by that time based on symptoms of dry eye, a borderline positive Schirmer's test, and laboratory findings showing positive anti-Ro/SS-A antibodies along with elevated ESR and slightly elevated CRP. At that moment, we considered that the ILD was due to the association with SS. The patient was started on a course of oral glucocorticosteroids (Medrol 32 mg/day) with a progressive decrease in doses, Hidroxicloroquin (400 mg/day), Mycophenolate Mofetil (MM) (1500 mg/day with a gradual increase to 2000 mg/day); moreover, considering the enlarged atrial measurements, the patient was administered Apixaban (5 mgx2/day). He was reffered for a small salivary gland biopsy and was advised to consult an urologist regarding the tumoral mass; we suggested a follow-up in 3 months.

In August 2023, the patient was reevaluated in the pulmonology department, where he underwent another CT scan and functional respiratory tests. The imaging showed improvement of the fibrosis with diminished areas of „ground glass" opacities; spirometry showed a minimal increase in FVC (FVC=52%), while DLCO remained severely decreased (DLCO=31,8% of the predicted value) (Figure 1).

The patient returned to our clinic in November 2023, complaining about left knee pain and Raynaud's phenomenon; he denied shortness of breath, cough, or fatigue (Figure 2). He partially complied with the medical treatment (maintained the initial dose of Medrol and did not increase the dose for MM), but did not undergo the minor salivary gland biopsy and did not go to the urology



department as advised previously. At admission, he complained of non-inflammatory knee arthralgia. Obvious signs of iatrogenic Cushing syndrome could be observed upon physical examination, along with a minimal increase in the left knee volume and a skin lesion on the anterior part of the right leg (Figure 3, Figure 4). Lung auscultation revealed globally diminished breath sounds and bilateral basal crackles. Muscular force, aprehension, and mobility were all within the normal range.

Laboratory findings showed elevated ESR (38 mm/h) and CRP (10,10 mg/dl), along with leukocytosis and neutrophilia. CK, LDH, and liver enzymes were normal. We performed a swab test on the skin lesion that came back positive for Staphylococcus aureus. Considering the lab findings and the positive bacterial swab test, we started the patient on a course of amoxicilin and clavulanic acid 2g/day for 7 days.

We revisited the results from the extended myositic panel that showed positivity for PL-7 antibodies and strong positivity for PL-12 and Ro-52 antibodies, findings that would be consistent with a diagnostic of ASS. However, we requested a salivary gland ultrasound that showed disorganized architecture with hyperechoic areas within the left parotid gland (Figure 5). A small salivary gland biopsy was not available, and a muscle biopsy was not feasible as the patient did not describe pain or a decrease in force, but we ordered an electromyography (EMG) that showed discrete myopathic aspects in the right deltoid muscle with otherwise normal miographic patterns. Knee ultrasound was also performed, revealing left knee bursitis and a Baker cyst (Figure 6). A knee x-ray revealed diminished femorotibial space visible on the left knee, an early sign of knee osteoarthritis (Figure 7).

Additionally, after a renal ultrasound, we performed an extensive CT scan evaluation that reconfirmed the presence of the left kidney tumoral mass with a minimal increase in dimensions (53,4mm/53,7mm) without metastatic dissemination (Figure 8, Figure 9).

We referred the patient to the cardiology department; pulmonary hypertension was ruled out, and atrial dimensions were deemed normal (right ventricle-right atrium gradient = 20 mmHg, left atrium = 17 $cm^2$, right atrium = 14 $cm^2$).

We concluded that the association between ILD, Raynaud's phenomenon, and the positivity for anti-PL7 and anti-PL12 antibodies would meet the criteria for ASS according to Connor's et al. criteria, even in the absence of myopathy (muscular force maintained, absence of myalgias, normal values of muscle enzymes, EMG uncharacteristic of IIM)[1,7,8] (table 1).

Considering the lab findings and the positive bacterial swab test, we started the patient on

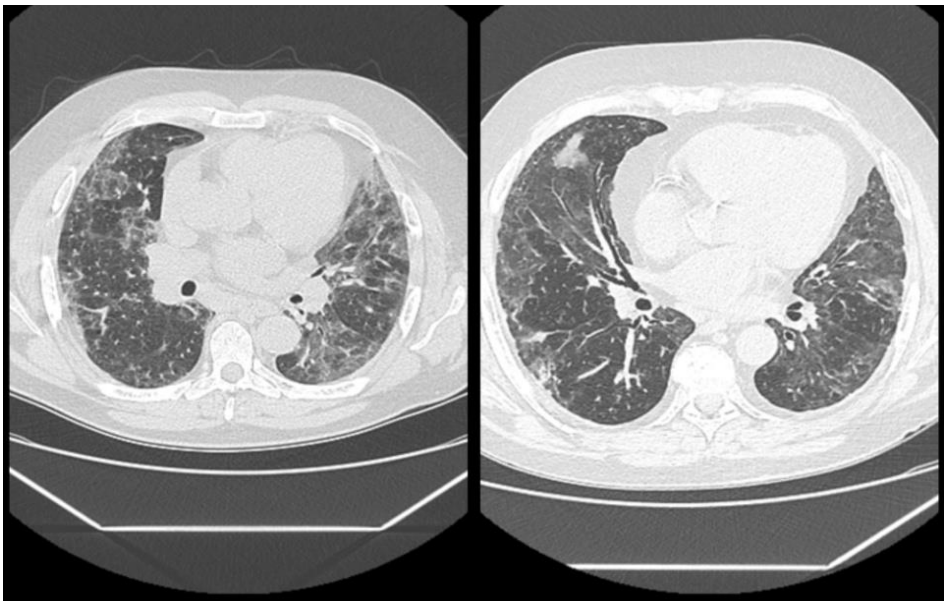
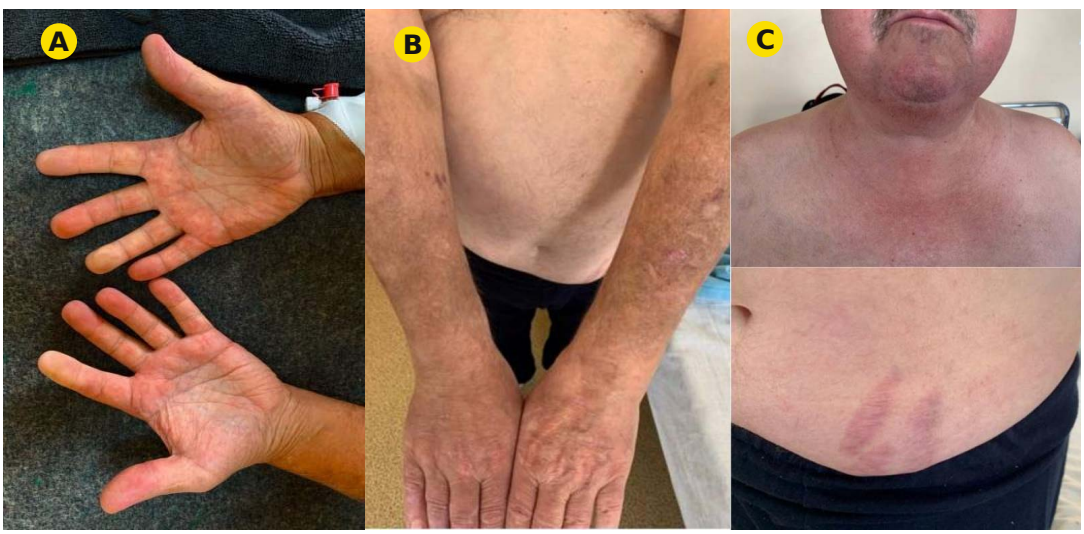


***Figure 1.*** *Progression towards malignancy*



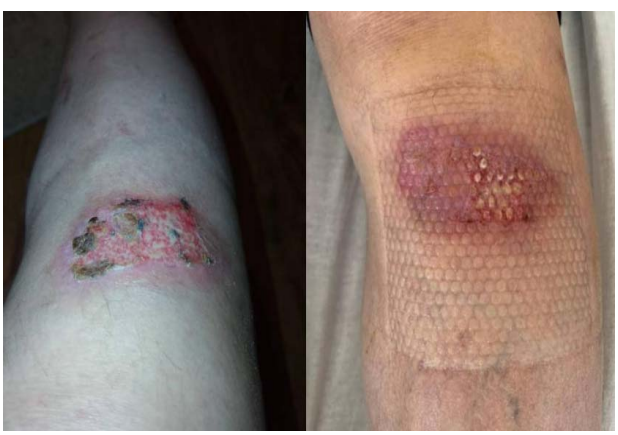



***Figure 2. A.*** *Raynaud's phenomenon*

***Figure 3. B.C.*** *Cushing-like syndrome with vascular frailty, „moon face" and stretch marks*

***Figure 4.*** *Skin lesion on the right leg caused by minor trauma in the context of skin frailty*

a course of amocixilin and clavulanic acid 2 g/day for 7 days with a remission of inflammatory and infectious markers. We decreased the dose of Medrol gradually to 8 mg/day and increased the dose of MM to 2000mg/day. We stopped Apixaban administration and performed a knee punction with successful synovial liquid extraction (non-rheumatoid exudate) and inoculated Betamethasone 7mg/ml in the joint; the knee pain resolved within a day (Figure 10).

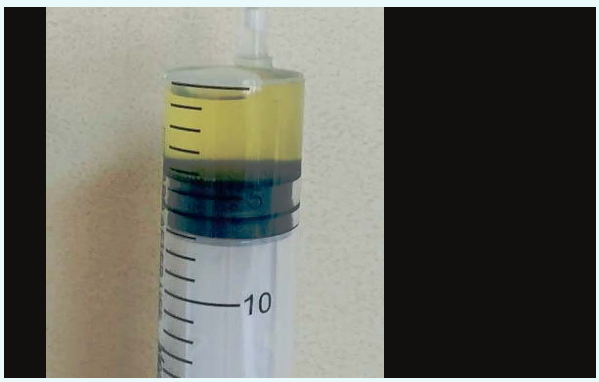



***Figure 5.*** *Serous synovial liquid*

Taking into consideration all the clinical elements corroborated with the paraclinical findings a positive diagnostic of amyopathic ASS in a patient with left kidney tumor, possibly Grawitz tumor was made. The associated osteo-arthritis of left knee and the infected leg wound had a favourable outcome.

The case was presented to a board of oncologists, urologists, pulmonologists, and anesthesiologists in order to decide the most suitable therapeutic option regarding the Grawitz tumour. The patient underwent a successful total left nephrectomy. Grossing examination revealed a small tumour, with a pushing, expansile appearance and a golden-yellow surface with frequent haemorrhage and fibrosis. Cystic change was frequent. Microscopic examination showed a tumour with an alveolar and nested architectural pattern (Figure 11); tumour cells have an optically clear cytoplasm and central nuclei with visible nucleoli (Figure 12). This type of renal tumour also shows a characteristic complex vascular network with capillaries surrounding every nest of tumour cells. Tumour necrosis is an unfavourable prognostic factor and was observed during examination. Final histopathological diagnosis was clear cell renal carcinoma (Grawitz tumor).

## Discussion

The diagnosis was particularly difficult to assess in regard to this case of a patient with ILD in the context of amyopathic ASS. Initially, we thought about primary SS, and the patient certainly met at least one criteria (positivity for anti-Ro/SSA antibodies) with borderline values for Schirmer's test, while the ecography was suggestive of arhitectural changes within the right parotid gland[20]. Unfortunately, the small salivary gland biopsy was not possible to

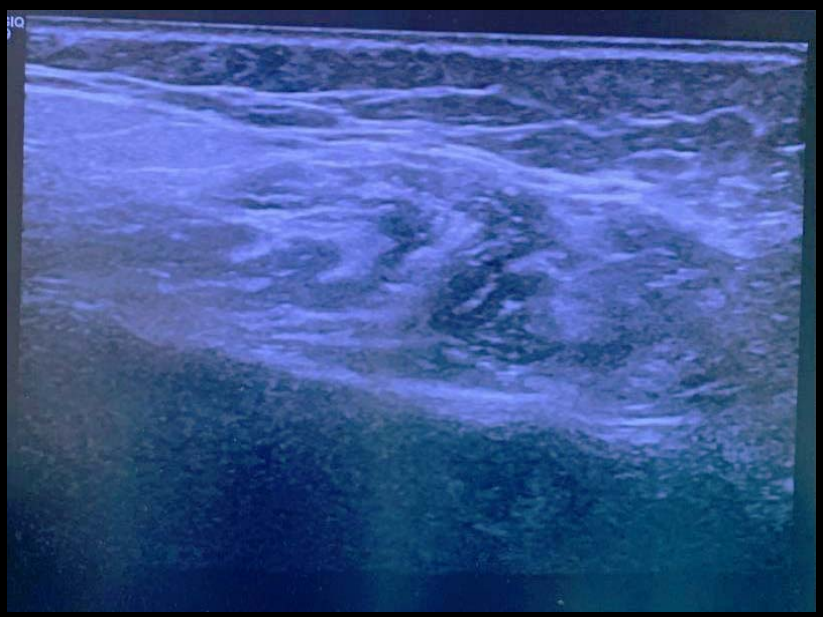


***Figure 6.*** *Left parotid gland with heterogeneous echotexture*

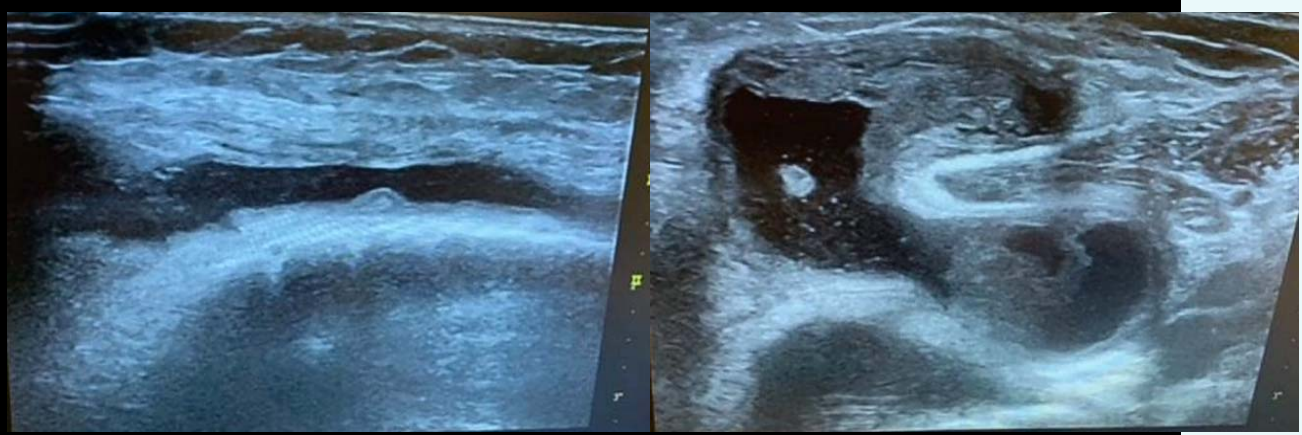


***Figure 7.*** *Left knee ultrasoundwith para-patellar fluid and Baker's cyst*

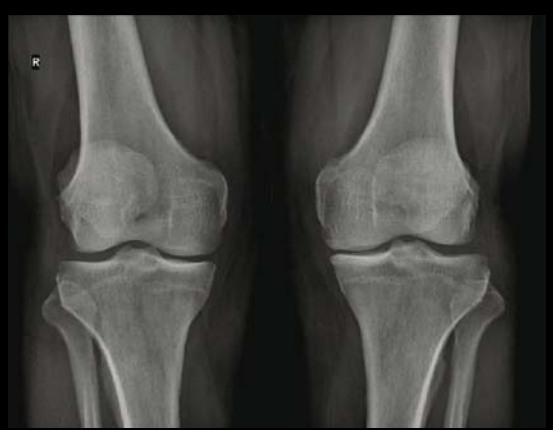


***Figure 8.*** *Knee x-ray showing narrowing of the femorotibial space*

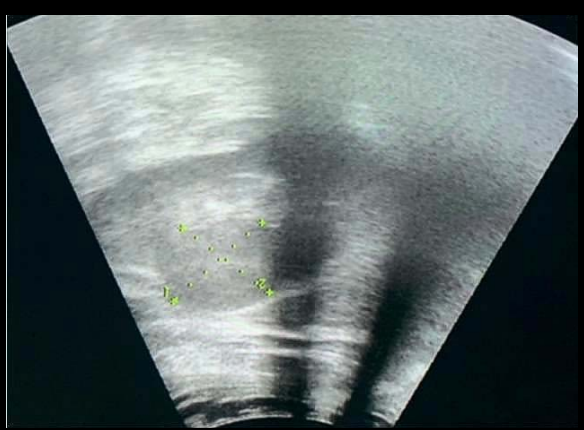


***Figure 9.*** *Renal ultrasound- left kidney showing heterogeneous irregular hypo- and hyperechoic formation at the inferior pole with a diameter of 46/39 mm suggestive of a tumoral formation*



obtain. Though rare, ILD is known to be associated with SS and has a prevalence of about 20%, resulting in a significant increase in morbidityand mortality[21].

Once confronted with the results from the extended myositic panel in this patient with ILD, namely the positivity for PL-7, PL-12, and Ro-52 antibodies, a suspicion of ASS was raised; the lack of myopathic involvement delayed the diagnostic; moreover, the biopsy was not feasible in this situation. Studies suggest that a definitive diagnostic can be made solely on the presence of tRNA synthetase antibodies without a muscle biopsy, as the antibodies are the mainstay of ASS andhistopathological findings may oftentimes be heterogenous and nonspecific[16]. Amyopathic ASS has been reported infrequently, and the literature lacks larger studies[9, 22, 23]. Given the fact that ASS has only recently been recognized, with proposed criteria for diagnosis emerging in 2010 and 2011, it is probable that amyopathic ASS may be a new subtype of ASS with a challenging diagnostic route that requires in-depth research.

It is also important to underline that we conducted a thorough assessment regarding malignancy, and surprisingly, a clear-cell renal carcinoma was revealed. We observed that the tumor had a slow growth pattern, and we cannot conclude if the autoimmune disease is related to the malignancy. Tumoral screening is well established for patients with DM, and opinions vary widely concerning patients with PM, but it is not clear whether patients with ASS need the same high-grade clinical suspicion for ongoing malignancies; moreover, we did not find any data regarding amyopathic ASS and the risk of neoplasia. Several manifestations that are present in ASS are considered protective of malignancy, namely ILD and Raynaud's phenomenon, though partial vasospasm may indicate neoplasia in selected cases[18,19,24].

The mainstay of therapeutic choices is represented by glucocorticosteroids coupled with additional immunosupressive therapies that target the ILD. Recognition of amyopathic ASS is not trivial because it has therapeutic implications. Unlike idiopathic pulmonary fibrosis, which has partial response to current medication, ASS-associated pulmonary fibrosis has favourable response to immunomodulatory treatments[16].

**Conclusions**

Amyopathic ASS is a challenging diagnostic that requires seroimmunological identification of targeted tRNA synthetase antibodies. The diagnostic criteria are based on immunological findings associated with ILD and several minor criteria, such as Raynaud's phenomenon, non-erosive arthritis, Gottron's papules, or fever. Data

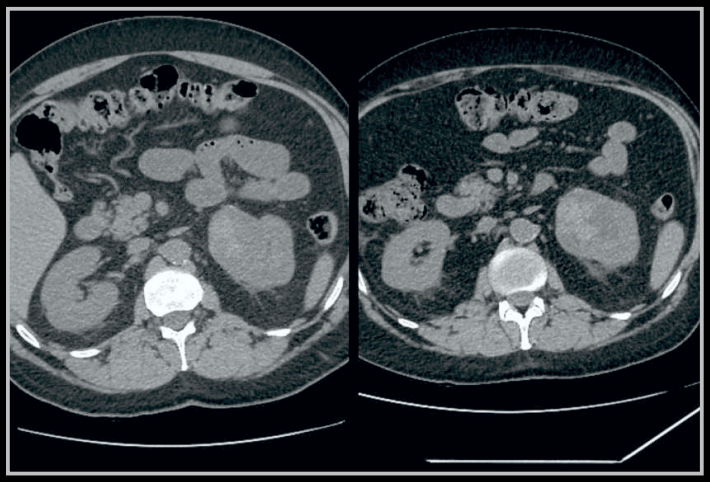


***Figure 10.*** *Abdominal CT scan - comparison of the Grawitz tumor between 2022 (left) and 2023 (right) showing minimal increase in dimensions- stable oncological aspect*

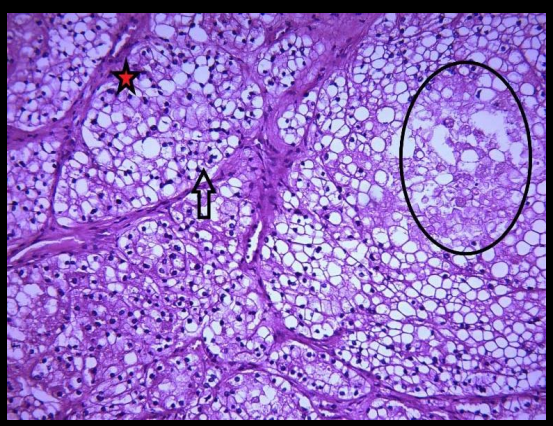


***Figure 11.*** *HE 10x Clear cell renal carcinoma with an alveolar and nested architectural pattern (arrow), tumour cells with optically clear cytoplasm (red star) and tumour necrosis (circle)*

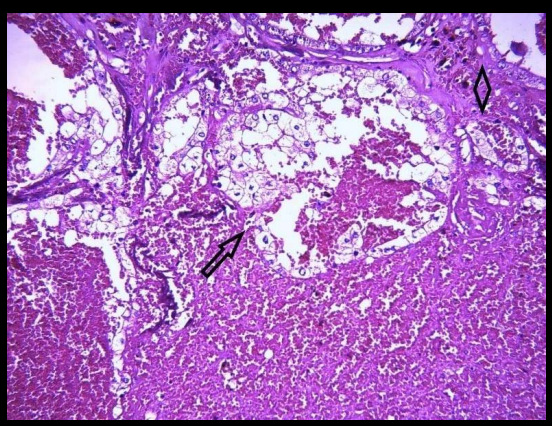


***Figure 12.*** *HE 10xClear cell renal carcinoma with an alveolar and nested architectural pattern and tumour cells with optically clear cytoplasm (arrow) and haemorrhage with deposits of hemosiderin (diamond)*

| **Connors et al (2010)[7]** | **Solomon et all (2011)[8]** |
|---|---|
| **Required:** Presence of an anti-aminoacyl tRNA synthetase antibody<br>**PLUS** *one or more* of the following clinical features: | **Required:** Presence of an anti-aminoacyl tRNA synthetase antibody<br>**PLUS** *two major* or *one major and two minor criteria*: |
| • Raynaud's phenomenon<br>• Arthritis<br>• Interstitial lung disease<br>• Fever (not attributable to another cause)<br>• Mechanic's hands (thickened and cracked skin on hands, particularly at fingertips) | Major:<br>1. Interstitial Lung Disease (not attributable to another cause)<br>2. Polymyositis or dermatomyositis by Bohan and Peter critieria |
| | Minor:<br>1. Arthritis<br>2. Raynaud's phenomenon<br>3. Mechanic's hands |

***Table 1.*** *Criteria for ASS*

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about the association between ASS and malignancy is scarce, but doctors should probably remain alert in regard to this possibility. The treatment is guided by the clinician's expertise with the help of data extrapolated from studies on DM and PM patients and should aggressively target the progression of ILD. Last but not least, interdisciplinary approach (rheumatologists, pulmonologists, urologists, oncologists) is mandatory for the best possible outcomes.

### *Conflict of interest disclosure*

*The authors declare that there are not conflicts of interest.*

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