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Single Case

Overlap Syndrome of Diffuse Systemic Sclerosis, Sjögren Syndrome, and ANCA-Associated Renal-Limited Vasculitis: Three Entities in One Patient – Case Report

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Keywords
Overlap syndrome · Diffuse systemic sclerosis · Sjögren syndrome · ANCA vasculitis · Glomerulopathies · Case report

Abstract
Introduction: The presence of three different entities in a single patient is usually of clinical interest and mostly anecdotal. The overlap of systemic sclerosis (SSc), Sjögren syndrome (SS), and ANCA-associated renal-limited vasculitis has been reported only once previously. ***Case Presentation:*** A 61-year-old female was evaluated at consultation with 2 years of symptomatology, presenting cardboard-like skin, sclerodactyly, limited oral opening, and dry skin and eyes. She was admitted for progressive renal failure (serum creatinine, 5.5 mg/dL). Her serology work-up showed positive anti-SCL-70, anti-Ro, anti-La, anti-MPO, and antinuclear antibodies. Renal biopsy was performed and confirmed histological findings for SSc, SS, and ANCA-associated vasculitis with active extracapillary glomerulonephritis with fibrous predominance (EUVAS-Berden sclerotic class), active tubulointerstitial nephritis, focal tubular injury, and moderate chronic arteriolopathy. Treatment with 6 monthly doses of methylprednisolone and cyclophosphamide was established. At the last follow-up, the patient maintained a stable serum creatinine level of 2.6 mg/dL and had decreased proteinuria, no erythrocyturia, and no requirement for renal replacement therapy. ***Conclusion:*** Systemic sclerosis is a rare autoimmune disease; nevertheless, overlap with

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Sjögren syndrome is relatively common, although its association with ANCA vasculitis is anecdotal. Diagnostic integration presents a challenge for nephrologists to define the prognosis and a specific treatment.

Introduction

Systemic sclerosis is an idiopathic connective tissue disease that is classified according to the extension of the cutaneous compromise in limited or diffuse systemic sclerosis. Systemic sclerosis is characterized by skin thickening and fibrosis of multiple organs, mainly the kidneys, lungs, heart, and gastrointestinal tract [1]. Renal complications have a prevalence of 50%, and the renal manifestations depend on the disease spectrum, with the most important being sclerodermic renal crisis, which affects between 5 and 10% of patients with systemic sclerosis [2].

The prevalence of overlap syndrome with other connective tissue diseases is variable, with reports of up to 17% incidence, with systemic lupus erythematous and Sjögren syndrome being the most frequently reported. While the presence of ANCA antibodies as an immunological epiphenomenon has been demonstrated in 7–13% of patients with systemic sclerosis [3, 4], clinically evident ANCA-associated vasculitis in patients with systemic sclerosis is relatively rare [4, 5].

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a group of diseases distinguished by inflammation, destruction of small-to medium-sized vessels, and the presence of circulating ANCAs; it is characterized by a systemic effect and has a predilection for renal vessels in over 75% of cases, with the most frequent presentation being rapidly progressive glomerulonephritis, with an increased incidence in patients over 60–70 years old. The prognosis of patients with vasculitis depends on ANCA specificity, with an increase in relapse among patients with anti-PR3 and an increase in mortality among patients with anti-MPO [6]. In patients with SSc, a second insult to the vasculature in the form of ANCA-associated vasculitis is rare; in the presence of overlap with SS, the disease constitutes a diagnostic challenge for the nephropathologist, and it is important for the nephrologist to establish proper treatment and determine the prognosis [7].

In the literature, there are a few case reports worldwide of a patient presenting with the coexistence of these three diseases with a renal effect [8]. We present the case of a 61-year-old patient evaluated during a nephrology consult who presented with necrotizing crescentic glomerulonephritis. The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for online suppl. material, see https://doi.org/10.1159/000537873).

Case Report

A 61-year-old female with a 10-year history of hypertension was being treated with enalapril 10 mg po qd. She received a consultation from a general practitioner for a 2-year clinical presentation characterized by asthenia, adynamia, thick cardboard-like skin, sclerodactyly (Fig. 1), limited ability to open her mouth, and a 10-kg weight loss associated with dry eye and mouth with no other manifestations. There was no evidence of elevated basal creatinine values, and the patient denied the presence of kidney disease. The first laboratory results sent by the general practitioner showed serum creatinine of 1.53 mg/dL, urea of 40 mg/dL, urinalysis with uncountable erythrocytes, and proteinuria +++ (qualitative evaluation).

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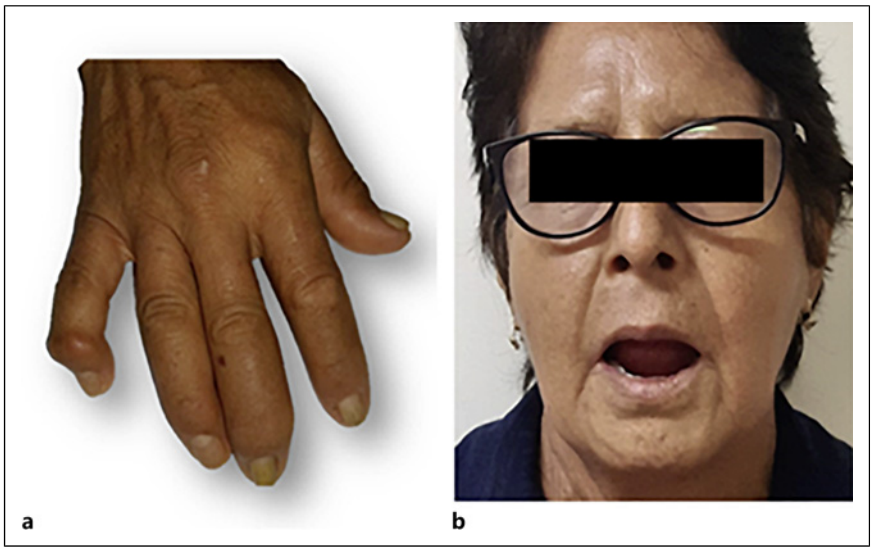

Fig. 1. a Sclerodactyly. **b** Sclerodermic facies.

The 3-month serology work-up presented elevated levels of serum creatinine (5.5 mg/dL) and urea (122 mg/dL) and a urinary protein-to-creatinine ratio (PrU/CrU) of 4.9 g/g (Fig. 2). The patient was referred to our tertiary care hospital for further evaluation and laboratory testing. In the nephrology consultation, the presence of countless erythrocytes with more than 50% dysmorphic RBC was reported. A diagnosis of rapidly progressive glomerulonephritis (RPGN) was established. Due to the increase in levels of nitrogen compound up to creatinine 5.7 mg/dL and urea 182 mg/dL, a hemodialysis catheter was inserted, and hemodialysis was initiated. Further immunological work-up revealed anti-Ro of 96 U/mL (positive), anti-La of 141 U/mL (positive), anti-SCL-70 of 702.92 U/mL (positive), anti-MPO (positive), and anti-PR3 (negative). A salivary gland biopsy was consistent with Sjögren syndrome. In a rheumatology consultation, overlap syndrome of diffuse systemic sclerosis and Sjögren syndrome were diagnosed, with a modified Rodnan score of 15/51 points.

After the initiation of hemodialysis, a kidney biopsy was performed, in which extracapillary glomerulonephritis with fibrous predominance (EUVAS-Berden sclerotic class), active tubulointerstitial nephritis rich in plasma cells, focal tubular injury, and narrowing of the arterial diameter with marked fibrotic changes in the intima were identified (Fig. 3 a–j). An overlap syndrome of systemic sclerosis, Sjögren syndrome, and anti-MPO ANCA-associated vasculitis (microscopic polyangiitis) were diagnosed according to the ACR-EULAR Criteria. Extrarenal involvement of vasculitis was excluded with sinus cavity tomography and high-resolution lung tomography. The abnormal finding on the tomography was esophageal dilatation and data suggestive of early pulmonary hypertension, both attributed to scleroderma. Screening for systemic sclerosis was performed with transthoracic echocardiography and right heart catheterization with normal values, ruling out pulmonary hypertension. Upper gastrointestinal endoscopy was performed with normal findings. Esophageal manometry could not be performed to rule out esophageal dysmotility, but it was suspected based on the tomographic findings. Induction treatment was started based on the results of the renal biopsy with methylprednisolone 1 g/day for 3 days followed by prednisone with a reduction phase as proposed by the PEXIVAS study [9]. Additionally, a CYCLOPS scheme with intravenous cyclophosphamide at a dose of 12.5 mg/kg was used in weeks 0, 2, 4, 7, 10, and 13 [10]. As maintenance treatment, a low-dose steroid regimen was established with prednisone 5 mg/day and mycophenolate mofetil 500 mg po bid. This treatment regimen was established by a

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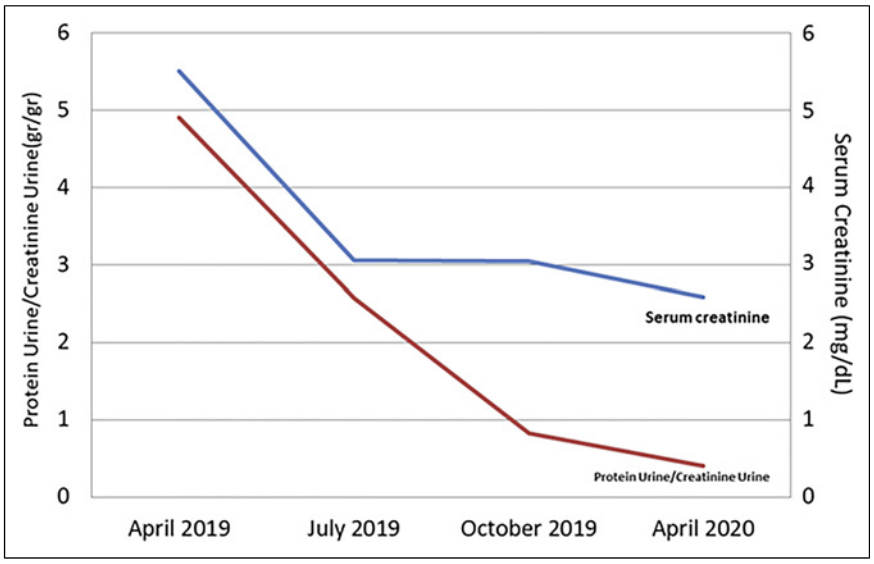

Fig. 2. Serum creatinine and proteinuria/creatinine ratio (PrU(/CrU) evaluation.

rheumatologist based on the multisystem involvement of systemic sclerosis and the absence of recurrence risk factors for ANCA-associated vasculitis, with progressive improvement. During hospitalization, the patient required temporary withholding of the ACE inhibitor due to blood pressure at the lower limit. Which was reintroduced as soon as the pressure improved. A year later, at the clinical level, there was improvement in asthenia, thick cardboard-like skin, and sclerodactyly, and the modified RODNAN score was reduced to 5/51 points, as reported by Rheumatology. The Birmingham Vasculitis Activity Score (BVAS) score improved with no signs of reactivation except for the chronic involvement mentioned above. Her serum creatinine was reported to be 2.6 mg/dL; urea, 132 mg/dL with no erythrocyturia; and the PrU/CrU, 0.41 gr/gr, with no requirement for kidney replacement therapy. Given the interstitial involvement with interstitial fibrosis and tubular atrophy of over 50%, the patient was not expected to recover renal function as initially reported and was diagnosed with chronic kidney disease (KDIGO G4A2).

Discussion

Systemic sclerosis is a connective tissue disease that is considered to be complex. Renal complications have a prevalence of 50%, although they have been reported in up to 80% of autopsies of affected patients [11]. Renal biopsy findings are common and are characterized by obliterans vasculopathy of the cortical arteries, thickening of the vascular wall, renal hypoperfusion, and juxtaglomerular hyperplasia [3]. Those cases that present a rapid deterioration of renal function are a challenge for nephrologists. A differential diagnosis must be made between the general causes of acute kidney injury and diseases associated with systemic sclerosis, such as sclerodermic renal crisis, ANCA-associated vasculitis, as in the case of our patient, and idiopathic thrombocytopenic purpura [3].

In this case, the presence of positive serology for anti-neutrophil cytoplasmic antibodies (ANCAs) should be taken with caution, since positivity for ANCAs coexisting with systemic sclerosis is between 9 and 12 [4, 5]. This finding has controversial clinical significance [4, 12]. In 2019, the Australian Scleroderma Cohort Study (ASCS) conducted a study to document the significance of these antibodies. They concluded that the coexistence of these conditions

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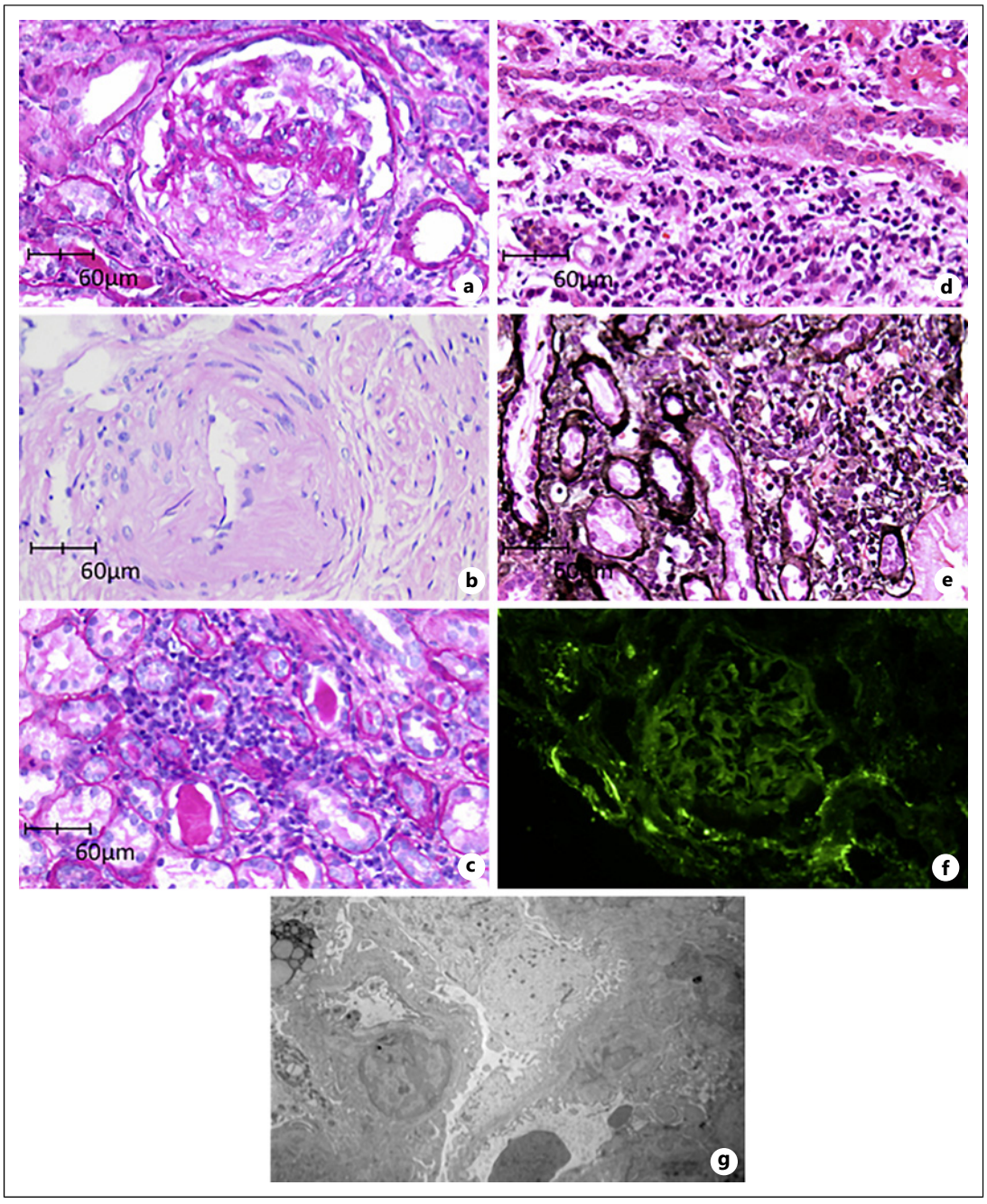

Fig. 3. Renal histopathology. **a** Extracapillary glomerulonephritis with active fibrocellular crescent stained with periodic acid Schiff, PAS at ×40. **b** Narrowing of the arterial diameter with marked fibrotic changes in the intima, PAS at ×40. **c** Foci of interstitial inflammatory infiltrate of mononuclear cells (plasma cells) extending to some walls. PAS at ×40. **d** Foci of interstitial inflammatory infiltrate of mononuclear cells (plasma cells) and tubular atrophy evaluated with H&E at ×40. **e** Focal acute tubular injury with intratubular blood debris evaluated with methenamine silver stain at ×40. **f** C3-negative, immunofluorescence, and the rest of the immunoreagents. **g** Electron microscopy, photomicrograph at ×5,000 magnification, the capillary loops with folded and healed segments are observed, there is preservation of podocyte processes, there is no evidence of electron-dense material that suggests immune complexes, in the urinary space there are also few cells of the parietal epithelium.

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presents atypical behavior associated with an increased risk of diffuse interstitial lung disease, pulmonary embolism, synovitis, overlap syndromes, and decreased survival compared with systemic sclerosis with negative serology for ANCAs and is considered to be a red flag in the disease course [4, 5].

Even if the prevalence of ANCA-positive patients with scleroderma is reported to be as high as 12%, only a minority of the patients develop an overlap syndrome with ANCA-associated vasculitis, similar to our patient, with 0.4% reported in an English population study [5]. Until 2016, in the English literature, there were only 60 reported cases of ANCA-associated vasculitis overlapping with scleroderma [3, 13]. Of these patients, up to 77% present anti-SCL70 antibodies, similar to our patient [1, 4, 5].

Compared with sclerodermic renal crisis, whose presentation is usually more sudden, in ANCA-associated vasculitis overlap syndrome, disease presentation tends to occur in patients with limited systemic sclerosis, subacute progression without hypertension or mild hypertension, and worsening renal function with active urinary sediment with erythrocytic cylinders and proteinuria, as in our patient [1, 3]. The presence of ANCA-associated vasculitis overlap syndrome urgently requires a kidney biopsy to distinguish the entity from the more common causes of acute kidney injury. The characteristic histopathological finding is the presence of crescents [14]. A treatment focused on the etiopathogenic cause will potentially diminish the possibility of chronic kidney disease and possible irreversible sequelae. There is no specific recommendation for the treatment of an overlap syndrome. Nevertheless, the actual tendency is to focus the treatment toward ANCA-associated vasculitis with high doses of steroids and immunosuppressants (rituximab, cyclophosphamide). In the patient's case, the only treatment available was steroids and cyclophosphamide, and the team decided to offer this treatment as induction, which is highly effective and a good option according to the KDIGO glomerulonephritis guidelines, especially in anti-MPO patients, in whom it is equally effective as steroid and rituximab. If we could access other treatments, we think that rituximab could be a good option in induction, but especially in maintenance, it becomes more relevant since it is the best option due to its superiority over azathioprine in the risk of relapses. Unfortunately, in our center, we do not have access to rituximab [6].

Patients with systemic sclerosis and ANCA-associated vasculitis have an up to 1.6-fold increase in the risk for mortality in comparison with patients without ANCA positivity, adjusted for age and sex. While the specific cause of mortality has not been evaluated, it is usually associated with thromboembolic complications and multiorgan compromise [4], with a reported 36% chance of death and up to a 64% chance of developing chronic kidney disease, as in our patient, even with adequate treatment [15].

Our patient also had a history of dry eye and mouth, with positivity for anti-Ro and anti-La and a salivary gland biopsy compatible with Sjögren syndrome. The finding of active tubulointerstitial nephritis rich in plasma cells in the renal biopsy could be explained by active tubulointestitial nephritis related to Sjögren syndrome, but also by ANCA vasculitis; although epidemiologically, it is more frequent to find this presentation associated with Sjögren syndrome compared to the infiltration seen in associated ANCA vasculitis since in this entity this finding is more frequently associated with active glomerular lesions compared to chronic ones, in our case there is glomerular evidence of chronic injury suggesting that this finding is more likely due to Sjögren syndrome.

The prevalence of overlap syndrome of systemic sclerosis and other connective tissue diseases has been evaluated in multiple cohorts. Recently, Moxey et al. [4] described the characteristics of 1,303 patients with this disease based on the Australian Scleroderma Cohort Study and found an increased prevalence of overlap of up to 5.8% with connective tissue diseases, with rheumatoid arthritis being the most common (2.1%), followed by polymyositis (1%) and Sjögren syndrome (1.8%) independent of positivity for ANCA antibodies [4]. There

are reports with prevalence rates of over 18.5% of systemic sclerosis overlapping with Sjögren syndrome, with anti-Ro and anti-La positivity of up to 38.8% and 22.3%, respectively [6]. Pakodzsi et al. [16], in a 1,700-patient English scleroderma study, reported the prevalence of antibodies with overlapping Sjögren syndrome, finding rates of 21% for anti-centromere antibodies in limited variety, 7.3% for anti-Scl70 in limited variety, 55.6% in diffuse variety, and 11% for anti-RNA polymerase.

Sicca syndrome presents in up to 68–83% of all cases of scleroderma, but only 14% of these patients meet the classification criteria for Sjögren syndrome with histopathological confirmation of lymphocytic infiltration of the salivary glands [17]. Sjögren syndrome has prevalence rates of a renal effect ranging from 1% to 14% in the European registry and 33.5% in a cohort in China and is considered underdiagnosed. Patients with renal compromise have been reported to have a reduced survival rate compared with patients without renal compromise. Reports show ANCA positivity (6–17%) in patients with Sjögren syndrome and, in isolated cases, the development of ANCA-associated vasculitis with Sjögren syndrome [7, 8].

In conclusion, the presentation of diffuse systemic sclerosis and ANCA-associated vasculitis is a rare finding that is usually associated with poor prognosis, and the overlap of these conditions and Sjögren syndrome is even rarer. We present the case of a female diagnosed with overlap syndrome, diffuse systemic sclerosis, Sjögren syndrome, and ANCA-associated vasculitis. The diagnosis and treatment of such patients is a great challenge and requires extreme caution, given the introduction of high-dose steroids in the context of an increased risk for a renal sclerodermic crisis.

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Statement of Ethics

The patient has given his written informed consent to publish his medical case, including images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have no founding sources to declare.

Author Contributions

Angela Cordoba-Hurtado M.D., Laura Fuentes-Mendez M.D., Monserrat Perez-Navarro Ph.D., and Rafael Valdez-Ortiz M.D. (corresponding author): substantial contributions to the conception and design of the work; acquisition, analysis, and drafting the work for important intellectual content; final approval of the version; and

agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Virgilia Soto-Abraham M.D.: substantial contributions to the conception and design of the work; acquisition and analysis of the histopathology; drafting the work for important intellectual content; final approval of the version; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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