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ANCA-negative idiopathic pulmonary fibrosis developed into ANCA-positive rapidly progressive glomerulonephritis after 12 years follow up

Fibrosis pulmonar idiopática ANCA negativa desarrollada en la glomerulonefritis de evolución rápida en ANCA positiva después de 12 años de seguimiento

Dear Editor,

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrotic disorder of the lung parenchyma. Rapidly progressive glomerulonephritis (RPGN) is a disease characterized by acute loss of renal function with glomerulonephritis, which is diagnosed by a pathologic pattern of crescent formation. A subgroup of RPGN is associated with anti-neutrophil cytoplasmic antibodies (ANCA). ANCA are abnormal auto-antibodies which are particularly related to small-vessel vasculitis in the kidneys. The perinuclear (p-ANCA) and cytoplasmic (c-ANCA) immunofluorescent patterns mainly correspond to antibodies directed against myeloperoxidase (MPO) and proteinase-3 (PR3), respectively. Herein, we report a case of a 37-year-old man with a history of ANCA (−) IPF who abruptly developed ANCA (+) RPGN with pulmonary renal syndrome after 12.5 years.

A 37-year-old man had a history of ANCA (−) IPF and gouty arthritis under control with prednisolone 5 mg QOD and colchicines 0.5 mg QD for over 12.5 years. A month prior to presentation, he began to experience intermittent muscle aches, arthralgias over bilateral hands and foamy urine. He finally presented to the emergency department with complaints of progressive shortness of breath, hemoptysis, poor urine output, and bilateral lower leg edema for one week. The physical examination was notable for respiratory discomfort, bilateral rales and grade 1 pitting edema of bilateral lower limbs. No petechiae, ecchymosis or costovertebral angle tenderness were noted. Blood tests showed leukocytosis, azotemia (BUN: 159 mg/dL, creatinine: 21.1 mg/dL), hyperkalemia, and anion gap metabolic acidosis. Urinalysis revealed proteinuria and hematuria. Immunologic studies showed mildly decreased C3 (76.5 mg/dL, reference range: 90–180 mg/dL) and positive MPO-ANCA (28 IU/ml, reference range: negative <3.5, positive >5 IU/mL). Chest X-ray showed infiltrates in both lungs. Non-contrast computed tomography of the chest showed interstitial reticular fibrotic infiltration with honeycomb appearance of bilateral lungs and consolidation in the left lung zone. Renal ultrasonography demonstrated normal-sized kidneys with increased cortical echogenicity. Ultrasound-guided renal biopsy was performed and revealed a proliferative glomerulonephritis with sclerosis and crescentic formation (Fig. 1). Immunofluorescent microscopy of the glomeruli was negative for staining of IgA, IgG, IgM, C1 and C3. Based on the above-mentioned examination results and clinical manifestations, severe MPO-ANCA (+) RPGN with pulmonary-renal syndrome was diagnosed. During the initial admission, emergent hemodialysis and plasmapheresis (5 sessions) were performed. Immunosuppressant therapy including pulse steroids (methylprednisolone 500 mg daily for 6 days) followed by oral prednisolone (5 mg BID) and azathioprine (50 mg daily) and targeted therapy with rituximab (total 3 g over 3 divided fractions) were also added. Nonetheless, high ANCA titers and poor renal function persisted so immunosuppression therapy and hemodialysis were

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Table 1 – Clinical characteristics of patients with idiopathic pulmonary fibrosis who developed into rapidly progressive glomerulonephritis.

Case(ref.)	Age (y)/Sex	Duration[a] (y)	Initial symptoms	SCr[b] (mg/dL)	MPO-ANCA levels (pre/post treatment)[c]	Seroconversion of ANCA	Renal histology	Treatment[d]	Renal outcome
Hiromura et al.[2]	48/F	1	Dyspnea, cough, fever	2.5	225, 15 (EU/ml)	N/A	Yes	S, C	Recovery
Hiromura et al.[2]	77/M	5	Shortness of breath	4.4	998,109 (EU/ml)	N/A	–	S, C	Recovery
Hiromura et al.[2]	72/F	6	Fatigue, appetite loss	3.4	1379, decreased (EU/ml)	N/A	Yes	S, C	Improved[e]
Hiromura et al.[2]	70/M	4	Fatigue, fever	11.1	581, decreased (EU/ml)	N/A	–	S, C	Hemodialysis
Chikaraishi et al.[3]	52/M	9	Claudication, paresthesia, hematuria	0.7	80, 33 (EU/ml)	Yes	Yes	S, C	Recovery
Matsuyama et al.[4]	72/M	10	Fatigue, abdominal pain, fever	1.3	869, N/A (EU/ml)	N/A	Yes	S	Recovery
Eschun et al.[5]	67/F	4	Shortness of breath	2.2	High titer, N/A	N/A	Yes	S, C	Recovery
Amir et al.[6]	69/F	0.8	Dyspnea	7.1	403, N/A (U/L)	Yes	Yes	S, C, P	Recovery
Pineton et al.[4]	71/F	3	Dyspnea	6.1	High titer, undetectable	Yes	Yes	S, C, P, R	Recovery
Presented case	37/M	12.5	Shortness of breath, edema	21.1	28, 29 (IU/ml)	Yes	Yes	S, A, P, R	Hemodialysis

ref.: reference, y: year, M: male, F: female, N/A: not applicable.

[a] Duration between the onset of IPF and RPGN.

[b] Serum creatinine level at RPGN diagnosed.

[c] MPO-ANCA levels before and after treatment during admission.

[d] S: steroids, C: cyclophosphamide, A: azathioprine, P: plasmapheresis, R: rituximab.

[e] The patient died during the treatment course due to respiratory failure.

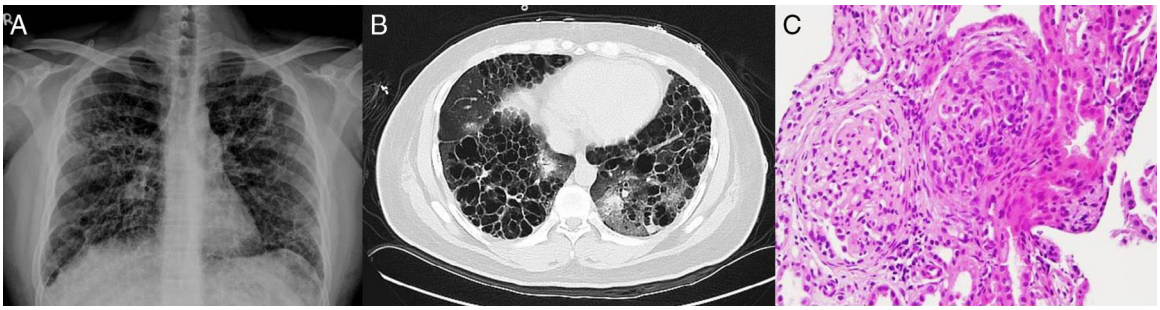

Fig. 1 – Imaging studies of the lungs and microscopic slides of renal tissue. (A) Chest X ray – Interstitial reticular fibrotic infiltration with honey comb appearance over both lungs. (B) Non-contrast computed tomography of the chest shows pulmonary fibrosis with cystic change in bilateral lung fields, with lower lung zones predominance. Infiltrates and ground-glass opacity in bilateral peri-hilar regions were also noted. (C) Renal biopsy (400×) – Glomeruli showed mesoangiocapillary proliferation and segmental sclerosis. Fibro-cellular crescents are also seen.

maintained. Unfortunately, the patient died 1.5 years later from septic shock due to community-acquired pneumonia.

IPF may be an insidious lesion of vasculitis or a separate entity. It is now known that a subset of IPF patients are ANCA positive.[1] A recent study examined the differences between ANCA positive and ANCA negative IPF. The levels of serum creatinine and C-reactive protein in patients with positive ANCA are significantly higher than those with negative ANCA. The survival rate of patients with higher titers of ANCA was less than patients with lower levels, implying the concentration of ANCA not only reflects the degree of systemic inflammation, but also indicates a more unfavorable prognosis. Most ANCA (+) IPF is MPO-ANCA, which is related to the development of crescentic glomerulonephritis in animal models[7] and could develop into RPGN clinically. In our literature search, we found 10 patients with acute ANCA (+) RPGN in IPF patients, all of whom had MPO-ANCA[2–4,8–10] (Table 1). Seven out of the 10 reported cases were Asians; however, the initial symptoms, time duration between IPF diagnosis and onset of RPGN, serum levels of MPO-ANCA varied widely, indicating the clinical manifestations of such cases are highly unpredictable. Recent studies have revealed two major pathways to tissue damage from ANCA associated vasculitis: the neutrophil pathway and the T-cell pathway. In the neutrophil pathway, an infection leads to the priming of neutrophils with an increase of adhesion molecules and ANCA-binding antigens on their surface. The binding of ANCA on neutrophils activates the degranulation process and cause damage to the endothelial layer. Under the T-cell pathway, regulatory T cells take over the function of tertiary lymphoid organs and promote further immune response. These two mechanisms interact with each other and magnify the cascade of inflammation and consequently causing vasculitis.[5]

To the best of our knowledge, the present case was the youngest and the longest interval between IPF and RPGN diagnoses in the reported literature. Despite ANCA-negativity at IPF diagnosis 12.5 years ago, he subsequently developed ANCA-positive RPGN; the trigger of this seroconversion is unknown. The long duration might have been affected by the patient's regular use of prednisolone and colchicine, as colchicine may down-regulate multiple inflammatory responses and slow down the cascade of vasculitis.[6] In conclusion, this case highlights the importance of regular monitoring levels of ANCA and alertness for renal involvement in patients with IPF.

Conflict of interests

The authors declare that they have no conflict of interests.

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Peritonitis caused by *Pantoea agglomerans* in peritoneal dialysis☆

Peritonitis causada por *Pantoea agglomerans* en diálisis peritoneal

Dear Editor,

Pantoea agglomerans is a germ that infrequently causes peritonitis in peritoneal dialysis patients. Let us look at the case of a peritoneal dialysis patient who presented with peritonitis due to this germ.

The patient was an 83-year-old man living in an urban environment, who carried out basic daily activities independently and who had been on outpatient peritoneal dialysis with 4 daily exchanges for 4 years. The cause of the chronic kidney disease was nephroangiosclerosis, with no other comorbidity. The patient was well adapted to the dialysis and had no adequacy, ultrafiltration or fluid overload problems. However, he had suffered 6 episodes of peritonitis. Peritonitis is defined as peritoneal inflammation caused by microorganisms, with the presence of cloudy peritoneal fluid, a count of more than 100 leukocytes/μl with more than 50% polymorphonuclear cells. It remains the most significant complication deriving from the dialysis technique itself. It is generally caused by Gram-positive skin bacteria such as *Staphylococcus epidermidis* and *Staphylococcus aureus*, or by enterobacteria and fungi. Prevention is the fundamental weapon, acting on the routes by which microorganisms enter the peritoneal cavity: peritoneal access, connection systems, dialysis solutions and examinations that enable infection. The germs identified in the previous peritonitis episodes were gram-positive. The patient had been retrained in the performance of the dialysis technique on multiple occasions to try to prevent new episodes and it had been proven that he was not a nasal carrier of *Staphylococcus aureus*.

The patient came to the dialysis unit complaining of abdominal pain and with a cloudy peritoneal effluent, detected in the last exchange. He had not had fever, nausea, or intestinal transit alterations. His count was 560 leukocytes/μl with 80% polymorphonuclear cells. Examination revealed signs of peritoneal irritation. Gram stain and cultures were taken. Treatment was started with intraperitoneal cefazolin and tobramycin. Since the patient's condition was unchanged, he was monitored as an outpatient. At the 48-h follow-up, he showed a clinical improvement with clear peritoneal fluid, a peritoneal count below 100 leukocytes/μl, and the culture received tested positive for *Pantoea agglomerans*.

Pantoea agglomerans (formerly known as *Enterobacter agglomerans* and previously as *Erwinia agglomerans*) is a gram-negative bacillus from the *Enterobacteriaceae* family which basically causes nosocomial infections in immunocompromised patients,[1] our elderly patient and in dialysis.

Species of the *Pantoea* genus are generally isolated from soil, plants, fruits and vegetables, but they have also been found in human and animal faeces. In our case, there is no evidence of contact with plants or animals, but it is possible that there were deficiencies in washing hands and making connections after touching fruit.

As a pathogen, it has traditionally been described as a causative factor of localised infections such as synovitis, post-traumatic arthritis[2] due to plant thorns or splinters, as well as

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