José R. Rodriguez-Palomares[a,b,*], Maria Carmen Japaz Cancino[c], Luis Blazquez Collado[a], Ruth Fiallos Criollo[a], Paola Milena Villabon Ochoa[a], Marta Sanchez Heras[a,b], Maria Angeles Basterrechea[a] y Gabriel de Arriba de la Fuente[a,b]

[a] *Sección de Nefrología, Hospital Universitario Guadalajara, Guadalajara, España*
[b] *Departamento de Medicina, Universidad de Alcalá de Henares, Alcalá de Henares, Madrid, España*
[c] *Unidad de Nefrología y Hemodiálisis, Clínica Fuensanta, Madrid, España*

* Autor para correspondencia.
Correo electrónico: athelas36@gmail.com
(J.R. Rodriguez-Palomares).

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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 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

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.

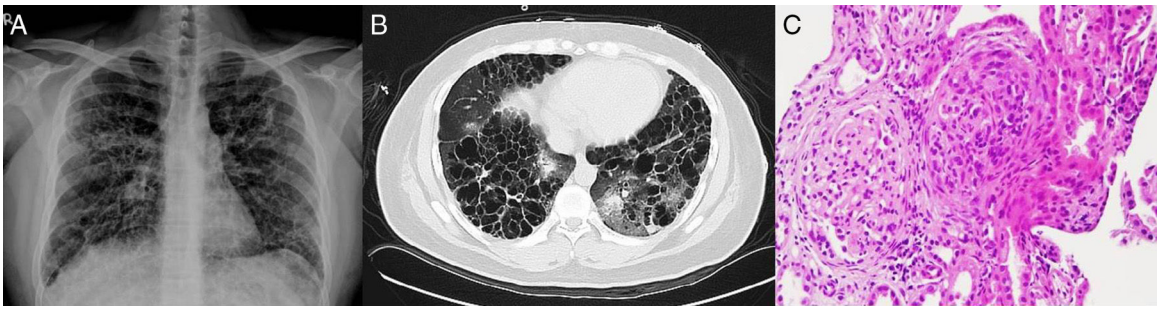

Fig. 1 – Imaging studies of the lungs and microscopic slides of renal tissue. (A) Chest X ray – Interstitial reticular fibrotic infiltration with honey comb appearance over both lungs. (B) Non-contrast computed tomography of the chest shows pulmonary fibrosis with cystic change in bilateral lung fields, 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.

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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Chi-Yung Yeung[a], Yi-Jen Peng[b], Tom Chau[c], Sung-Sen Yang[a,*]

[a] *Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*

[b] *Department of Pathology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*
[c] *Department of Medicine, Providence St. Vincent Medical Center, Portland, OR, United States*

[*] *Corresponding author*.
E-mail address: sungsenyang@hotmail.com (S.-S. Yang).

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Peritonitis causada por *Pantoea agglomerans* en diálisis peritoneal

Peritonitis caused by *Pantoea agglomerans* in peritoneal dialysis

Sr. Director:

Pantoea agglomerans es un germen que causa infrecuentemente peritonitis en pacientes de diálisis peritoneal. Remitimos el caso de un paciente en diálisis peritoneal que presentó una peritonitis por este germen.

Se trata de un paciente de 83 años que reside en medio urbano y es independiente para la realización de las actividades básicas de la vida diaria, y que realizaba diálisis peritoneal ambulatoria, con 4 intercambios diarios, desde hacía 4 años. La causa de la enfermedad renal crónica era nefroangioesclerosis y no presentaba otra comorbilidad. Se encontraba bien adaptado a la diálisis y no tenía problemas de adecuación ni de ultrafiltración o de sobrecarga de volumen. Sin embargo, había presentado 6 episodios de peritonitis. La peritonitis se define como la inflamación peritoneal causada por microorganismos con presencia de un líquido peritoneal turbio, un recuento de más de 100 leu/μl con más del 50% de polimorfonucleares. Continúa siendo la complicación más importante derivada de la propia técnica dialítica. Generalmente está causada por bacterias gram positivas de la piel como *Staphylococcus epidermidis* y *Staphylococcus aureus*, o por enterobacterias y hongos. La prevención es el arma fundamental y se debe actuar sobre las vías de entrada de los microorganismos a la cavidad peritoneal: acceso peritoneal, sistemas de conexión, soluciones de diálisis y exploraciones facilitadoras de la infección. Los gérmenes identificados en las anteriores peritonitis fueron gram positivos y en relación con la realización de la técnica dialítica, ya se le había reentrenado en múltiples ocasiones, para intentar prevenir nuevos episodios y se había comprobado que no era portador nasal de *Staphylococcus aureus*.

Acudió a la unidad de diálisis por dolor abdominal, y con efluente peritoneal turbio, detectado en el último intercambio. No había tenido fiebre, náuseas, ni alteraciones del tránsito intestinal. Se realizó recuento, obteniéndose 560 leu/μl con 80% polimorfonucleados. En la exploración presentaba signos de irritación peritoneal. Se extrajeron muestras para gram y cultivos. Iniciándose tratamiento con cefazolina y tobramicina intraperitoneal. Dado que el estado general del paciente estaba conservado, se mantuvo en régimen ambulatorio. A las 48 h volvió a revisión en la que mostraba mejoría clínica, líquido peritoneal claro, el recuento peritoneal ya estaba por debajo de 100 leu/μl, se recibió el cultivo que fue positivo para *Pantoea agglomerans*.

Pantoea agglomerans (antes conocida como *Enterobacter agglomerans* y previamente como *Erwinia agglomerans*) es un bacilo gram negativo de la familia *Enterobacteriaceae* que causa fundamentalmente infecciones nosocomiales en pacientes inmunocomprometidos[1], nuestro paciente anciano y en diálisis.

Las especies del género *Pantoea* se aíslan generalmente del suelo, de las plantas, frutas y vegetales, pero que también se ha encontrado en heces humanas y de animales. No nos consta que, en nuestro caso, haya había contacto con plantas ni con animales, pero sí es posible que hubiera deficiencias en el lavado de manos y en la realización de las conexiones después de haber tocado fruta.

Como patógeno, se ha descrito clásicamente como causante de infecciones localizadas sinovitis, artritis[2] postraumatismo con espinas o astillas de plantas, así como casos de peritonitis en pacientes en diálisis, ya que puede crecer en medios ricos en glucosa (¿peritonitis del jardinero?)[3–5] y en portadores de dispositivos invasivos, en población pediátrica puede causar sepsis [6], y también se ha cultivado en muestras de bilis de pacientes con colangitis y coledocolitiasis[7].

Se mantuvo el tratamiento con tobramicina durante 14 días, ya que existía una excelente sensibilidad a cefalosporinas, aminoglucósidos y ciprofloxacino.

Tras este nuevo episodio de peritonitis, y tras detectar fallos en la realización del intercambio en los reentrenamientos y debido a su avanzada edad decidimos transferir al paciente a diálisis peritoneal automática asistida por cuidador.

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