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Case report

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Pauci-immune glomerulonephritis with extracapillary proliferation; An unusual paraneoplastic manifestation associated with Mantle Cell Lymphoma (B)

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Summary

The relationship between neoplasia and secondary renal involvement is increasing. Membranous glomerulonephritis is the main cause of nephrotic syndrome, associated with solid tumors, and less frequently hematologic neoplasia. Hodgkin's lymphoma is the hematologic neoplasia most closely associated with minimal change disease. However, there are case reports that describe a relationship with non-Hodgkin's lymphomas and leukemias. The usual clinical manifestation is the nephrotic syndrome,which may precede for several months or coexist with the diagnosis of lymphoma. Its pathophysiology is not very clear. It is suggested that it is related to T lymphocyte dysfunction. In addition, there are reports of thrombotic microangiopathy, related to the use of biological therapy and antineoplastic agents.

Rapidly progressive glomerulonephritis is a clinical syndrome associated with glomerular extracapillary proliferation, usually related to vasculitis associated with ANCA and vasculitis mediated by immunocomplexes. Neoplasias are also related to a large number of vasculopathies. Glomerulonephritis with extracapillary proliferation are much more common in malignant solid tumors. In addition, associations with myelodysplastic syndrome, chronic lymphocytic leukemia and Hodgking lymphoma have been reported. The association between Mantle Cell B lymphomas and glomerulonephritis with extracapillary proliferation is unusual.

The following is a case of a patient diagnosed with Mantle Cell B lymphoma who has a rapidly progressive glomerulonephritis secondary to extracapillary, necrotizing and pauci-immune proliferative lesions.

Keywords: Rapidly progressive glomerulonephritis; extracapillary proliferation; lymphoma; neoplasia

Glomerulonefritis proliferativa extracapilar pauciinmune, una manifestación paraneoplásica inusual asociada a linfoma B del manto

Resumen

La relación entre neoplasia y compromiso renal secundario es creciente. La glomerulonefritis membranosa es la principal causa de síndrome nefrótico asociado a tumores sólidos y con menos frecuencia a neoplasia

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hematológica. El linfoma Hodgkin es la neoplasia hematológica que más se relaciona con enfermedad de cambios mínimos. Sin embargo, hay reportes de casos que describen una relación con linfomas no Hodgkin y leucemias. La manifestación clínica usual es el síndrome nefrótico; el cual puede preceder por varios meses o coexistir con el diagnóstico de linfoma. La fisiopatogénesis no está muy clara. Se sugiere que está relacionada con una disfunción del linfocito T. Adicionalmente, hay reportes de microangiopatía trombótica relacionada con el uso de terapia biológica y antineoplásicos.

La glomerulonefritis rápidamente progresiva, es un síndrome clínico asociado a proliferación extracapilar glomerular; usualmente relacionado con vasculitis asociadas a ANCAS y vasculitis mediadas por inmunocomplejos. Las neoplasias también están relacionadas con un amplio número de vasculopatías. Las glomerulonefritis con proliferación extracapilar son mucho más frecuentes en tumores sólidos malignos. Además, se han descrito asociaciones con síndrome mielodisplásico, leucemia linfocítica crónica y linfoma Hodgkin. La asociación entre linfomas B del manto y glomerulonefritis con proliferación extracapilar, es inusual.

A continuación, se describe un caso de un paciente con diagnóstico de linfoma B del manto que cursa con una glomerulonefritis rápidamente progresiva secundaria a lesiones proliferativas extracapilares, necrosantes y pauciinmunitaria.

Palabras clave: Glomerulonefritis rápidamente progresiva; proliferación extracapilar; linfoma; neoplasia

Clinical case

Male patient, 69 years old,Natural, Resident and Coming from Quibdó. He is admitted because of clinical picture of 1 year of evolution, consisting of evening edema of lower limbs,associated with inguinal adenomegalies. Progressive edema5 months before consultation, until compromising its functional class.

Regarding his personal history of relevance, he is hypertensive, heavy ex-smoker 20 years ago, and currently smokes occasionally.

On admission BP: 138/70 HR: 88 beats per minute Rf: 28 bpm Oxygen saturation: 91%, signs of water overload, no signs of ventilatory failure. At palpation, generalized ganglion clusters are identified, with no visceromegaly. In lower extremities with ulcerous lesions without signs of infection, grade III edema and signs of bilateral chronic venous insufficiency.

Chest x-ray is performed on admission, which shows signs of pulmonary congestion associated with increased cardiothoracic index and bilateral pleural effusion.

Transthoracic echocardiography is performed, and this documents a dilated left atrium, left ventricle with eccentric hypertrophy, ejection fraction of 45%, lower and inferolaterallyhypokinesia with diastolic dysfunction type I.

Deep Venous Thrombosis was discarded in Venous Doppler echocardiography.

Laboratory studies of admission are normal, including renal function and hematologic status.

Extension studies are performed with Computerized Axial Tomography, finding multiple ganglion clusters in the Neck, Thorax and Abdomen.

Ganglion biopsy is performed, which reports diffuse infiltration of small lymphoid cells, with variable-Ki67 up to 40%, CD10 negative, CD20 positive and Cyclin D1 positive. With CD3 positive in T lymphocytes,concluding as a diagnosis a Mantle Cell B Lymphoma.

CEOP-Rituximab Chemotherapy Management and Prophylaxis for tumor lysis is started. Along his evolution, he presents macroscopic hematuria, associated with progressive increase of creatinine and decrease in diuretic rhythm; without data suggesting tumor lysis and without alteration in coagulation times or thrombocytopenia. (Calcium: 7.8 mg / dl, uric acid: 6.1 mg / dl, Potassium: 4.3, LDH: 244 mg / dl, PT: 16.9 sec PTT: 26.5 sec).

CT Urography: Kidneys of normal size, shape and position RK: 128.4mm LK: 127.5 mm

Right kidney with simple cortical cyst. Normal Pyelocaliceal System.

Distended bladder with thin walls, no pathological content. Mass effect is visualized on the left by large lymph nodes in the right hemipelvis.

The patient is undergoing arterial hypertension, active sediment and Acute kidney injuryAKI 3, behaving like a rapidly progressive glomerulonephritis; Not clear in its etiology. A renal biopsy is performed, compatible with extracapillary proliferative necrotizing glomerulonephritis with crescents. Given the persistence of elevated azole with rate of filtration estimated by CKD-EPI 8.4 ml / min and anuria, renal replacement therapy (hemodialysis), steroid pulses, plasmapheresis for 5 sessions are started, associated with intravenous cyclophosphamide.

After the plasma exchange, steroids and Cyclophosphamide, marked improvement of renal function is observed. The patient is discharged with creatinine in 1.3 mg / dl, BUN: 39, without associated electrolytic disorders and hemogram with moderate anemia.

Results: Renal biopsy with 17 glomeruli per section, of which there is one 1 globally sclerotic glomeruli, 12 of them with epithelial crescents and 4 necrotizing segments. Interstitial tissue edema with moderate inflammatory mononuclear infiltrate, eosinophils in small numbers, dilated tubules with epithelial desquamation. Arteries and arterioles without lesions. Immunofluorescence with IgA: negative IgG: Negative, IgM: Negative C3 and C1q Negative.

Conclusion:Pauci-immune glomerulonephritis with extracapillary proliferation.

Figure 1.

Enlarged glomeruli by proliferation of epithelial-like cells that fill Bowman's space and compress the glomerulus. H & E, X400.

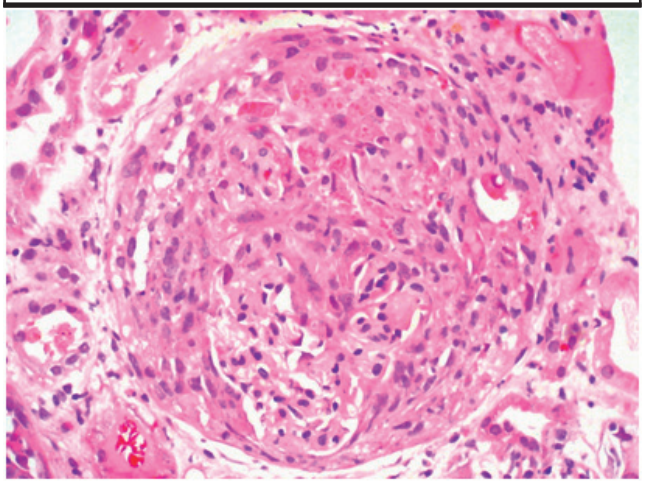
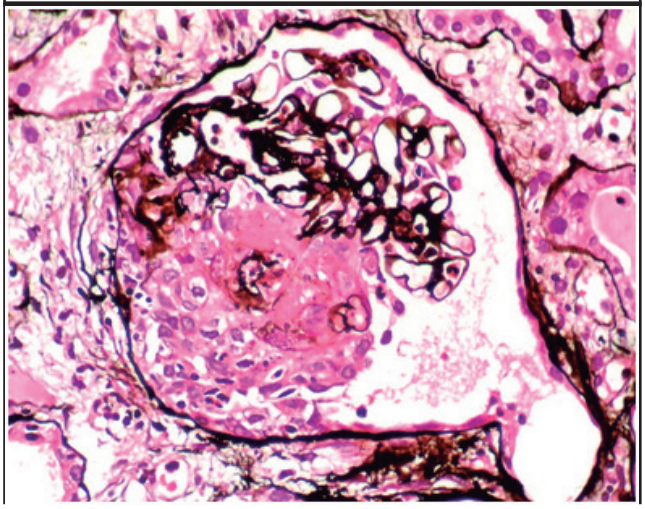


Figure 2.

The lower segment of this glomerulus shows rupture of capillary walls, which are surrounded by proliferation of epithelial cells. The upper portion of the capillary plume is normal in appearance. Silver-methenamine, X400.



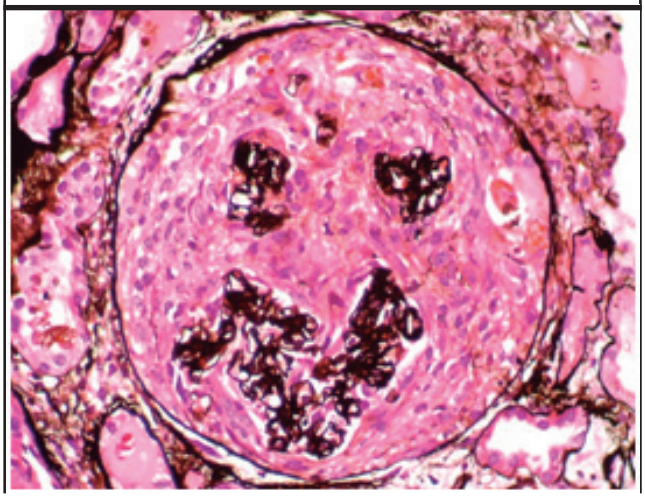
DISCUSSION

In recent decades, case reports have been increasing, showing a relationship between malignant neoplastic activity and the appearance of different types of glomerular lesions as a secondary complication.

In 1922, a patient with nephrotic syndrome apparently associated with neoplasia was first described. Membranous glomerulonephritis is the main cause of nephrotic syndrome associated with solid tumors,

Figure 3.

With this staining the glomerulus compressed by circumferential proliferation of epithelial cellsis more evident. Silver-methenamine, X400.

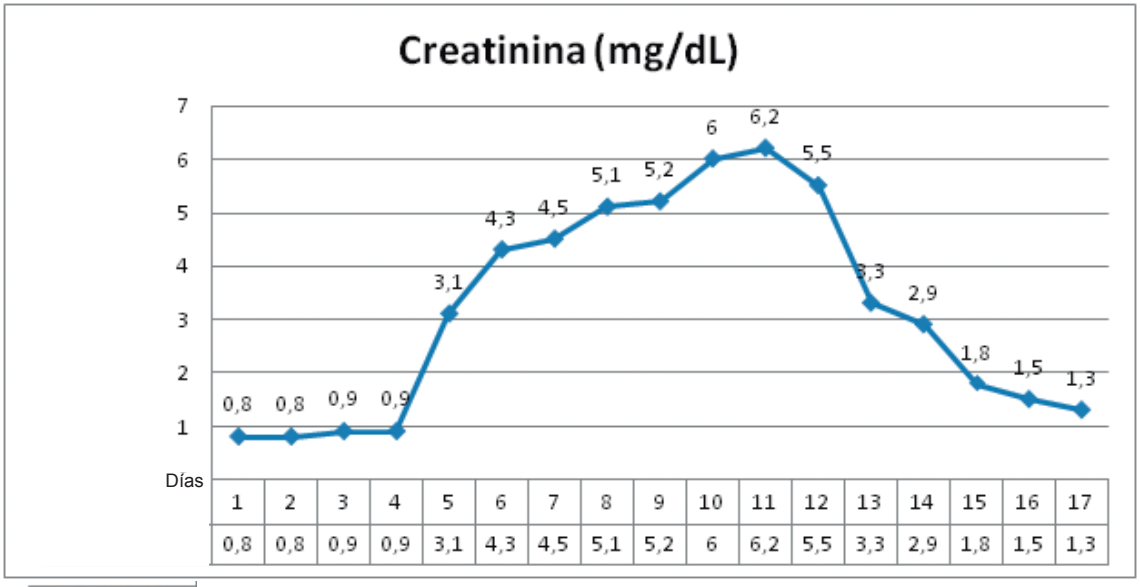


and in rare cases hematologic neoplasia [1].

On the other hand, the disease of minimal changes is the glomerulopathy that is more frequently associated with Hodgking lymphoma; some cases with non-Hodgkin's lymphoma and Leukemias. Nephrotic syndrome is the most common clinical manifestation. It is able to coexist with or precede for several months the diagnosis of lymphoma. Additionally, cases of patients with minimal change disease, with poor response to steroids or calcineurin inhibitors-presenting a lymphoproliferative disease at the time [2] have been described.

The pathophysiological mechanism of glomerulonephritis as a paraneoplastic manifestation is still unclear. However, it appears to be related to T lymphocyte dysfunction [3].

Da'as et al. perform a retrospective study of 700 patients with non-Hodgking lymphoma or chronic



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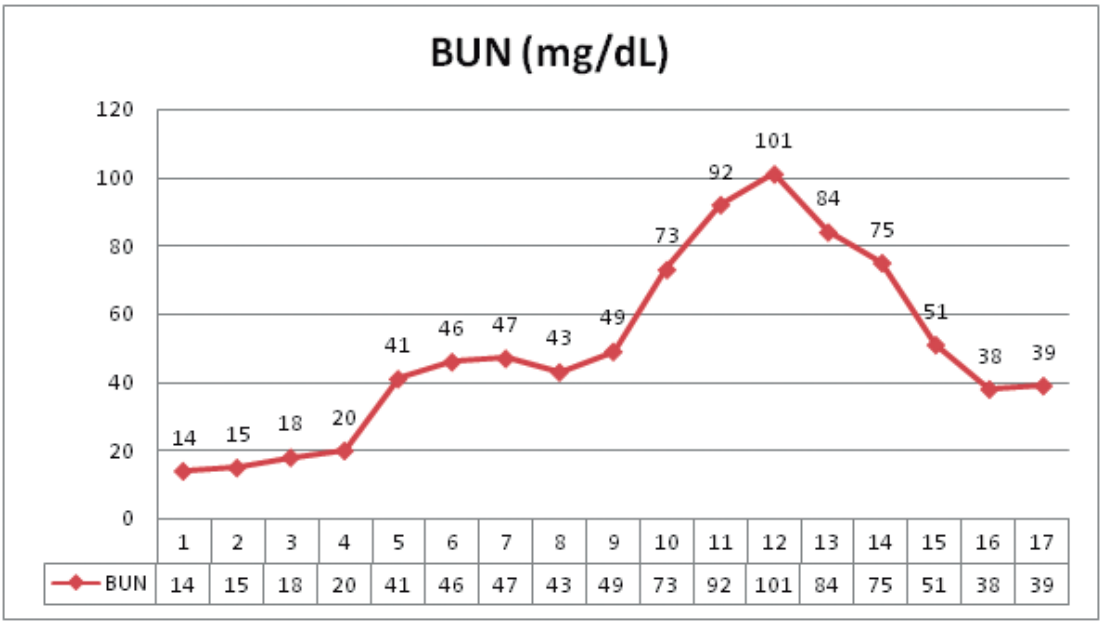
lymphocytic leukemia,evaluated between 1986 and 1995. They demonstrate that the renal compromise in patients with non-Hodgking lymphoma is very varied and infrequent. Of the 66 patients, 19 patients were directly affectedbecauseof lymphoma (5 due to renal infiltration and 14 due to obstruction), and 7 because of indirect or paraneoplastic manifestations (4 with glomerulonephritis, 1 with paraproteinemia and 2 with cryoglobulinemia). In addition, 15 were related to antitumor therapy (4 by tumor lysis syndrome, 4 by cyclophosphamide-induced cystitis, 7 by infection or nephrotoxic drugs). The remaining



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25 were from non-lymphoma-related causes, or unknown. Within the glomerulonephritis group, nephrotic syndrome is a frequent manifestation [4]. On the other hand, cases of glomerular diseases have been reported with the use of biological therapy in malignant neoplasia. Thrombotic microangiopathy is the most commonly associated glomerular entity, with the use of vascular endothelial growth anti-factor, tyrosine kinase inhibitors [5] mitomycin and gemcitabine [6,7].

Rapidly progressive glomerulonephritis is a clinical syndrome that may be associated with glomerular extracapillary proliferation, in the presence or absence of immune complexes. The most frequent injuries are the ones compromising small vessels. According to the Chapel Hill consensus of 2012, they can be classified into vasculitis mediated by ANCA (granulomatosis with polyangiitis, microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis) and vasculitis mediated by immune complexes [8].

Neoplasias are related to a large number of vasculopathies. There is a particularly significant association between cutaneous vasculitis and malignant lymphoproliferative and myeloproliferative diseases. However, there may also be compromise of internal organs, such as the kidney. Additionally, vasculitic phenomena may precede or concur with the diagnosis of neoplasia [9,10]. In contrast, crescentic glomerulonephritis is much more common in malignant solid tumors [11].

A variety of hematologic diseases with necrotizing glomerular lesions, extracapillary proliferation, and no deposits of immunocomplexes have been described. Among these, we found reported cases of myelodysplastic syndromes [12], chronic lymphocytic leukemia [13] and in 1% of the cases Hodgking lymphoma [14].

Glomerulonephritis with extracapillary proliferation is more commonly associated with non-Hodgkin's lymphoma, line B or T. The association between Mantle Cell B lymphomas and glomerulonephritis with crescents has been reported infrequently [15]. About 95% of extracapillary proliferation glomerulonephritis associated with lymphoma have positive ANCA. However, its absence does not discard it [14].

We illustrate a case where there is a diagnosis of Mantle Cell B lymphoma; and in its evolution, there is a rapidly progressive acute renal compromise with dialysis requirement. Other causes of acute deterioration of renal function, such as tumor lysis

EXLABORATORY EXAMS		
VDRL	Non-reactive	
Antibodies to HIV 1 and 2	Non- reactive	
Antibodies to Hep C Virus	Negative	
HBV Ags	Negative	
Urine Test:	A- Physical-Chemical	Reddish color- hematic appearance Negative glucose Proteins: 500 mg / dl Urobilinogen: negative Billirubina: negativo Bilirubin: negative pH: 6.5 Density: 1,010 Hemo group: 250 erit / ul Ketone bodies: Negative Nitrite: negative Leukocyte esterase test: 100 leu / ul
	B-UrinarySediment	Epithelial cells: 0-2 XC, Leukocytes 15-20 AP, erythrocytes: 60 AP bacteria: few
ANA	Negative	
ANCA	Negative	
Proteins Electrophoresis	Normal	
Anti DNA ss	Negative	
C3	105 (VN= 55-120 mg/dl)	
C4	15 (VN=12-72mg/dl)	
24-hour urine proteins	2,239 grs/24 hours	
Cryoglobulins	Negative	

syndrome, vasculitis due to other systemic diseases and nephrotoxicity due to chemotherapy, are discarded. A renal biopsy is performed, which shows Pauci-immune glomerulonephritis with extracapillary proliferation.

There was improvement in renal function, following the established immunosuppressive therapy. Therefore, we conclude that probably the documented glomerular lesion is an unusual Paraneoplastic manifestation of Mantle Cell B lymphoma.

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