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Pauci-Immune Vasculitis cANCA Positive with Renal-Lung Syndrome in Pediatrics: A Case Report

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ABSTRACT

Introduction: Small vessel vasculitis associated with neutrophil cytoplasm antibody (ANCA) presents with mild to severe clinical presentations, including renal failure and eye involvement. It is a rare disease with an incidence of 13-20 cases per million people globally, with an annual prevalence of 46-184 cases per million. In children, the incidence is 10-20 cases per million inhabitants per year, predominantly female.

Clinical case: A 5-year-old female patient presented with fever, cough, and hemoptysis. Laboratory tests revealed severe anemia, and acute renal injury. During admission, she suffered from nephritic syndrome with hypertension, hematuria, and non-nephrotic proteinuria. A renal biopsy revealed diffuse extracapilar proliferative glomerulonephritis, both active and chronic, pauci-immune type. Steroid and immunomodulator administration were effective, achieving clinical improvement and hematological recovery. Outpatient management was continued with prednisone and cyclophosphamide for 3 months, followed up every 6-12 months by pediatrics.

Discussion: A case is presented of a female patient with lung-kidney syndrome secondary to cANCA-positive vasculitis. This vasculitis, associated with anti-neutrophil cytoplasmic antibodies, is a rare disease characterized by necrotizing inflammation of small blood vessels. The lung-kidney syndrome manifests with alveolar hemorrhage and glomerulonephritis, with vasculitis being one of its most common causes. Its etiology is unknown and appears to result from a complex interaction between genetic, environmental, and immune dysregulation.

In the literature, a predominance of the female sex has been observed in ANCA-associated vasculitis in children, although the patient in this case began to show symptoms at an earlier age than usual. Pulmonary symptoms include dyspnea, chronic cough, and hemoptysis, while renal involvement is manifested by abnormal urinalysis and glomerulonephritis confirmed by biopsy. Diagnosis relies on the determination of ANCA antibodies and histopathological studies, which in this case showed scar lesions in the glomeruli. For treatment, the EULAR recommendations were followed, using cyclophosphamide and glucocorticoids, resulting in a favorable evolution of the patient.

Conclusion: Systemic vasculitis, a rare childhood disease, requires high suspicion rate and timely treatment, especially in children with lung-kidney syndrome, to improve survival rates.

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INTRODUCTION

Vasculitis is defined as inflammation of the walls of blood vessels and develops either primarily or secondarily from other conditions such as infections, malignant diseases, or rheumatic disorders. Classified according to the affected blood vessels into small, medium and large calibers. (1)

Small vessel vasculitis associated with neutrophil cytoplasm antibody (ANCA) are entities that have in common the

infiltration of leukocytes and the presence of ANCA, with a wide variety of clinical presentation, from mild manifestations in skin, joints or peripheral nervous system to severe compromise of vital organs. (2)

The characteristic presentation includes renal failure of rapid progression with hematuria and non-nephrotic proteinuria. Eye involvement is frequent and include manifestations such as conjunctivitis, episcleritis or retinal involvement. (3, 5)

It is a rare disease. Globally, an incidence of 13 to 20 cases per million people has been reported, with an annual prevalence of 46 to 184 cases per million. It is most common in adults aged 60 to 70, and in males. In the pediatric population, epidemiological data on vasculitis associated with ANCA are scarce, but the incidence of these diseases in children is estimated at 10-20 cases per million inhabitants per year, predominantly female and the average age of diagnosis is 12-14 years. (4, 5)

CLINICAL CASE

A 5-year-old female patient, Mexican, from rural environment, with a size of 108 cm, weight of 15.8 kg, previously healthy, without known allergies, who five months before his hospital admission, presented fever, cough and hemoptysis, receiving medical management with azithromycin (15 mg/kg/day, orally) and paracetamol (13 mg/kg, orally), with clinical improvement; two months prior to hospital admission she had a relapse, with fever, cough, hemoptysis and hematuria, on that occasion she was treated with ceftriaxone (75 mg/kg/day, IM) for 3 days, azithromycin (15 mg/kg/day, orally) for 5 days and antipyretic management with paracetamol 10-15 mg/kg orally every 8 h; without clinical improvement, therefore laboratory studies were performed in which severe anemia, grade IV (4.9 mg/dl) was detected.

Physical examination showed tegumentary pallor, tachycardia, hyperdynamic precordium, plurifocal systolic murmur.

In the blood biometrics was evidenced a hypochromic normocytic, regenerating severe anemia with reticulocyte production index of 0.7; in the blood chemistry no increase in serum bilirubines was evident, lactic dehydrogenase was in ranges of normal, and the Coombs test was negative, so hemolysis was ruled out.

It was reported with positive inflammatory markers (CRP of 40 mg/dl and platelets of 646,000/mcL), evidence of moderate risk acute renal injury (Cr 0.79 mg/dl), with a glomerular filtration rate of 73 ml/min/m^2. Moderate proteinuria and gross hematuria were found in the general urine examination. Clinically with cor anemic, therefore an erythrocyte concentrate was transfused. During admission she suffered from nephritic syndrome with hypertension, hematuria and non-nephrotic proteinuria. Before hemoptysis, a simple chest CT was performed, which reported findings suggestive of alveolar hemorrhage (Image 1). The approach was also complemented with an abdominal and renal ultrasound, which reported bilateral nephritis.

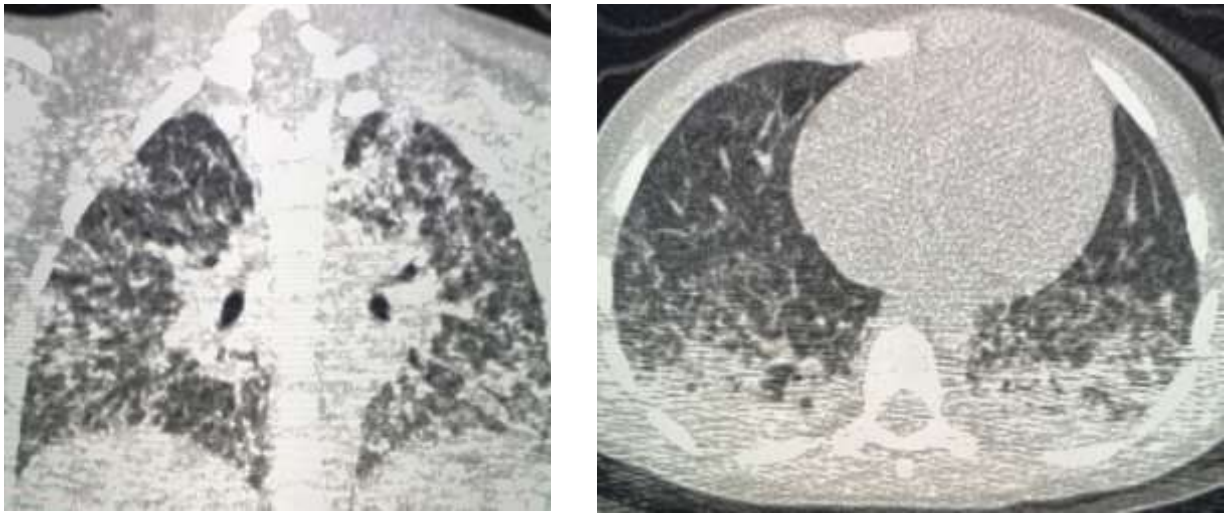

Image 1. CT scan of the chest with images consistent with a pulmonary hemorrhagic syndrome.

The infectious causes of the clinical picture were initially ruled out, and a TORCH profile, serology for Epstein barr virus, parvovirus B19 and dengue were performed; all with negative results. In addition, a blood culture and an urocultive were performed, which were reported as negative. The clinical approach was continued to look for immunological or rheumatological causes; with normal complement levels, normal IgE, lupus anticoagulant, double-stranded DNA antibodies and antinuclear antibodies, all normal. However, antibodies to neutrophil cytoplasm (cANCA) were reported positive.

The diagnosis of vasculitis was integrated, and it was decided to perform an aspiration renal biopsy with direct immunofluorescence, in which diffuse extracapilar proliferative glomerulonephritis was reported, both active and chronic, pauci-immune type and with segmental necrotizing lesions; Grade 1 fibrosis and focal acute tubular injury. The glomerular morphology and the direct

immunofluorescence study suggested small caliber, pauci-immune and renal vasculitis (Image 2).

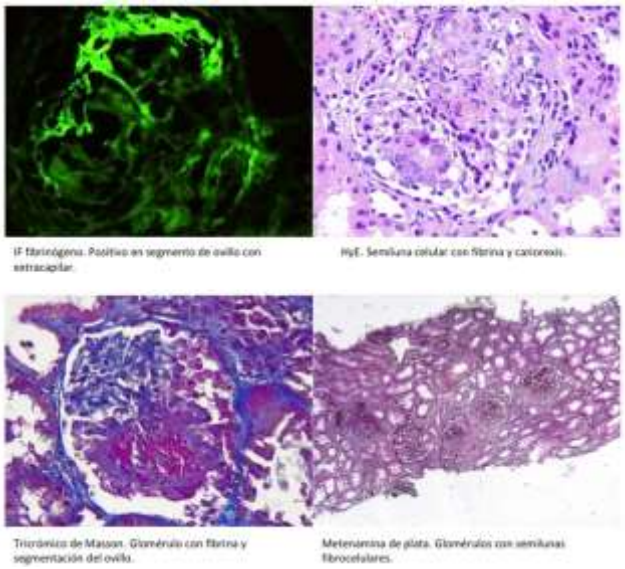

Image 2. Renal biopsy. Immunofluorescence for fibrinogen, positive in tangle segment with extracapillary. Hematoxylin and eosin stain, cellular crescent with fibrin and karyorexis. Masson trichrome stain, glomerulus with fibrin and tangle segmentation. Gomori methanamine silver stain, glomerulus with fibrocellular crescents

The diagnosis of cANCA positive acute vasculitis with acute nephritis was integrated. Steroid (Prednisone, 20 mg/kg/day OD for 7 days; continued at 10 mg/kg/day for 3 weeks) and immunomodulator (Cyclophosphamide, 150 mg/m2 IV for 10 days) were administered with adequate response. Subsequently, an ophthalmology evaluation was requested to rule out microvascular alterations of the retina, which were found without alterations.

The response to treatment was good, achieving clinical improvement and hematological recovery. A new renal ultrasound was performed one week after the start of medical treatment, still finding non-specific inflammatory changes.

The evolution during hospitalization (14 days) was good, achieving an increase of Hb to 7.9 g/dl, with improvement in clinical status; as well as improvement of renal function and with decrease of creatinine to 0.54 mg/dl.

The hospital discharge was followed up by pediatrics, where the remission of hematuria and hemoptysis were confirmed, in addition to improvement of renal function, with improvement in glomerular filtration rate (86 ml/min/m^2) and improvement in serum hemoglobin (9.4 g/dl), therefore it was decided to continue the outpatient management with prednisone (10 mg/kg/day, orally) and cyclophosphamide (5 mg/kg/dose, IV, twice weekly), both for 3 months. At the end of 3 months of treatment, it was decided to follow up every 6-12 months by pediatrics.

DISCUSSION

We present the case of a female patient with secondary kidney lung syndrome to cANCA positive vasculitis. Neutrophil anticitoplasmic antibody-associated vasculitis (ANCA) is a rare and heterogeneous disease characterized by necrotizing inflammation of small blood vessels. Lung-kidney syndrome is characterized by alveolar hemorrhage and glomerulonephritis and has a variety of etiologies, most often vasculitis. Its etiopathogenesis is unknown and appears to be the result of a complex interaction between genetic, environmental and immune deregulation, innate and adaptive. Due to the low incidence of the disease in children, most available data come from studies in adults. (5, 6)

In international series of pediatric ANCA-associated vasculitis a predominance of the female sex has been reported, consistent with our case. However, the age at the beginning was younger than described, usually 11 to 14 years. (7)

Ocular involvement is common in granulomatosis with polyangiitis and includes various manifestations such as conjunctivitis, episcleritis or involvement.

As for the pulmonary condition, it can be expressed as dyspnea (52.5%), chronic cough (52.3%), hemoptysis, alveolar hemorrhage (44.6%) and pulmonary nodules (42.5%); our patient presented alveolar hemorrhage and hemoptysis. Renal involvement is manifested as abnormal urinalysis (75.4%), glomerulonephritis confirmed by biopsy (52.3%) and elevated serum creatinine (41.5%); all of these are compatible with our clinical case. (6)

Although initially some series suggested more localized forms of the disease in childhood, in most cohorts it has been observed that, in children, as happened in our patient, it begins with multiple organ involvement. (8)

The determination of ANCA antibodies is useful for diagnosis. Histopathological study is the choice, particularly in cases of diagnostic difficulty and for investigation and grading of kidney damage. Glomerulonephritis associated

with ANCA is usually presented with pauci-immune, crementic and necrotizing glomerulonephritis. The most frequent morphological findings of this manifestation are glomeruli with disruption of the basal membrane, necrosis and increasing with varying degrees of organization, from cellular to fibrous. Electron microscopy may show, in some cases, deposits of immune complexes, basal membrane rupture, fibrin or glomerular growths. (5)

In our case, the histopathological findings were scar lesions at the glomerular level, with active cell with segmental fibrinoid necrosis. The interstice with mild inflammation; with immunofluorescence positive for IgG, IgM, IgA and fibrinogen in some segments. Meeting the criteria reported in previous case series.

Regarding management, the European Alliance of Associations for Rheumatology (EULAR) recommendations for the treatment of vasculitis in small and medium vessels were published in 2009 recommending as a first line management with cyclophosphamide and glucocorticoids, which was the one used in our case with favorable evolution. (6)

CONCLUSION

A high suspicion rate is required to identify cases of systemic vasculitis, particularly in the pediatric population. Although it is not a common disease in childhood, it should always be considered in the presence of lung-kidney syndrome. Proper and timely treatment improves the survival of patients with this type of vasculitis.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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