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CASE REPORTS

Concomitant pulmonary and renal diseases

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ABSTRACT

Pulmonary-renal syndrome may present in different ways and may be life threatening. The main conditions in which it is seen are Goodpasture syndrome, Wegener granulomatosis, microscopic polyangiitis, and connective tissue disorders. The various clinical presentation and etiology is challenging for the clinician. For pulmonologist the clinical presentation, chest imaging and bronchoalveolar lavage orient diagnosis, but definitive proof of the disease is given by biopsy. From the nephrological point of view current functional tests of the kidneys should always be accompanied by a renal biopsy. Corticosteroids and immunosuppressive agents that represent the gold standard for treatment significantly improved prognosis of the patients with pulmonary-renal syndrome.

Key words: pulmonary-renal syndrome, vasculitis, glomerulonephritis, alveolar hemorrhage

Diseases with concomitant pulmonary and renal involvement (pulmonary-renal syndrome) are a challenge, for both pulmonologist, and nephrologist. Pulmonary-renal syndrome is defined as the combination between diffuse alveolar hemorrhage and glomerulonephritis. Due to the severity and diversity of the patients' health condition during the medical consultation, often in emergency room, the quick and correct diagnosis of the patients with pulmonary-renal syndrome is difficult.

We present the case of a 65-year-old female patient, non-smoker, without professional exposure, admitted to our hospital with low-grade fever, progressive dyspnea and recurrent small hemoptysis started two month previously. Her medical history included recently diagnosed systemic hypertension. Clinical examination revealed skin pallor, and basal bilateral crackles on lung auscultation. The rest of the physical examination findings were within normal limits. The oxygen saturation was 84% at rest, while the patient was breathing room air. Biological findings: iron deficiency anemia with hemoglobin 6.69 g/dl, hematocrit 19.6%, the mean corpuscular volume was 86 fentoliter, serum iron level decreased at 31μg/dl. Patient also had leukocytosis (14,600/μl), and thrombocytosis (472,000/μl).

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Elevated blood urea nitrogen (76 mg/dl), and serum creatinine (2.0 mg/dl) indicated renal involvement. Urinary sediment revealed hematuria (250 red blood cells/μl), leucocyturia (25 white cells/μl) and proteinuria (0.1g/dl). A chest radiograph showed alveolar consolidation involving the entire right lung and the left lower lobe. Chest CT scan revealed bilateral diffuse alveolar infiltrates, with right predominance.

Therefore, we are in front of a patient with recurrent hemoptysis, iron deficiency anemia, bilateral airspaces infiltrates, and glomerulonephritis that are the main features of the pulmonary-renal syndrome.

Bronchoscopy showed no bronchial involvement. Broncho-alveolar lavage highlights a severe alveolar hemorrhagic syndrome (100% siderophages). These elements strongly suggest an antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculities (eg, Wegener granulomatosis or microscopic poliangiitis). Due to the severity of the disease, we started treatment before the immunological test results. The treatment consisted of corticosteroid pulse therapy (metylprednisolone 1g/day, 3 consecutive days), cyclophosphamide pulse therapy (1g/month), and oxygen therapy, with a favorable outcome (improving of clinical condition, renal state and decreasing of lung infiltrates) (FIGURE 1). Subsequently, pANCA proved positive, sustaining the diagnosis of ANCA – associated systemic vasculities (Wegener granulomatosis or microscopic polyangiitis). Patient continued treatment with oral cyclophosphamide (100mg/day) and metylprednisolone (48mg/day), with good outcome. Although diagnostic confirmation by biopsy is necessary, the severe cases of systemic vasculitis need a rapid diagnosis presumption and a rapid treatment, because delaying treatment is associated with fatal outcome.

The pulmonary-renal syndrome mainly comprises of: Goodpasture syndrome and vasculitis of small vessels. If we take into account all patients having glomerulonephritis and hemorrhagic alveolar syndrome, almost 20% have a Goodpasture syndrome (1,2), 50% have a certain form of systemic vasculitis (2); most of the remaining cases have connective tissue disease (eg, systemic lupus erythematosus and rheumatoid arthritis) or a diffuse hemorrhage in association with another form of glomerulonephritis (2).

Goodpasture Syndrome (anti-glomerular basement membrane disease) is the prototype of the pulmonary-renal syndrome. Classically, it is characterized by alveolar hemorrhagic syndrome and by rapidly progressive glomerulonephritis in patients with seric anti-glomerular basement membrane antibodies or linear bright deposits of immunoglobulin and complement along renal or alveolar epithelium in immunofluorescence stains.

The usual presentation is a young man (20-30 years old), complaining of hemoptysis (80-94%), cough and progressive dyspnea. Asthenia due to iron deficiency anemia and acute renal failure may be also patterns of presentation for patients without alveolar hemorrhage. Biological: retention of the nitrogenous products (55-71% at admission). The urinalysis frequently shows microscopic hematuria, red blood cell casts and proteinuria. More rarely

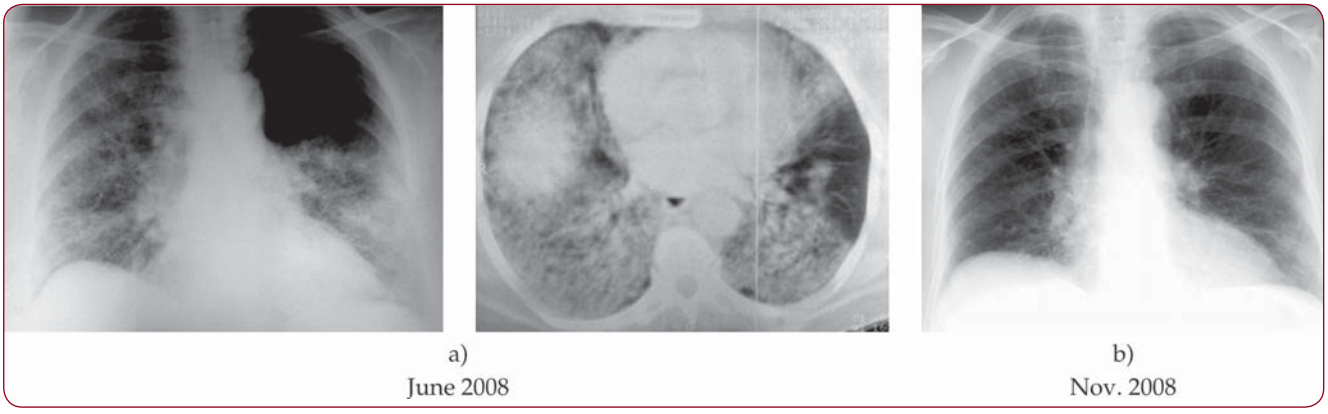

FIGURE 1. Case with ANCA associated vasculities. a) Initial chest radiograph and CT scan showing extensive right and less extensive left alveolar infiltrates and b) 5 month later images demonstrating remarkable clearing of intrapulmonary hemorrhagic infiltrates

macroscopic hematuria and/or systemic high blood pressure could appear. At ultrasounds kidneys are of normal or increased size (pattern of acute renal failure). Lung function tests show increased transfer factor though the alveolar-capillary membrane by the increase of carbon monoxide picked up by the extravasated blood in alveoli. Patients who develop diffuse alveolar hemorrhage are, usually, smokers, or they had in their recent history a viral disease or an exposure to volatile hydrocarbons. Among non-smokers, only 20% of the patients with this disease develop alveolar hemorrhage (3).

Anti-glomerular basement membrane antibodies are useful for positive diagnosis of the disease and for monitoring treatment. Unfortunately, there are few lab centers in Romania capable to measure these antibodies, and results need several days, a time than cannot be wasted therapeutically for these patients. The most accessible method for diagnosis is renal biopsy. Pathology frequently shows extra capillary proliferative glomerulonephritis with crescent formation. Since these modifications are non-specific, the certitude diagnosis is given by immunofluorescence. This highlights linear deposits of immunoglobulin G and complement C3 along the glomerular basement membrane. Sometimes we may see Ig A or Ig M. The electronic microscopy shows segmental fusion of podocytes, the thickening of the glomerular basement membrane and its fragmentation (4). Lung biopsy is seldom necessary, this being a more invasive and risky procedure.

In Goodpasture syndrome, up to 90% of patients have anti-glomerular basement membrane antibodies in serum, and the level of antibodies correlates only with the level of renal involvement not with the pulmonary one (5).

Goodpasture syndrome has different clinical phenotypes, thus the positive diagnosis may be challenging. The simultaneous renal and lung involvement appears in 60-80% of patients (6). Isolated glomerulonephritis appears in 10-30% of cases. For these patients general symptoms are not obvious, progression is silent especially in patients without hematuria, and the patients come too late to the doctor, when the renal failure is already installed. In rare cases, less than 10%, patients have only lung involvement. In this case, lung biopsy identifies typical lesion at immunofluorescence. Though renal involvement may be clinically silent, renal biopsy indicates the presence of tissular antibodies.

In absence of the adequate treatment, renal lesions evolve during days or weeks into severe renal failure. Treatment depends on the extension of lesions. For patients suffering only from lung involvement (diffuse alveolar hemorrhage), without renal lesions, the disease responds to corticosteroid treatment (7). Renal involvement needs a combination of corticosteroids, cytostatic-immunosuppressive medication (cyclophosphamide) and plasmapheresis (8). The treatment starts with intravenous therapy with methylprednisolone 15 mg/kg (1 g per day up to 3 consecutive days) followed by oral prednisolone 1mg/kg/day, up to a maximum of 60-80 mg, associated to oral cyclophosphamide (2-3 mg/kg/day), and plasmapheresis (50 ml/kg up to a limit of maximum 4 liters daily, for at least 14 days, or until antibodies are no longer detected). The dose of prednisone could be tapered after few months in patients with favorable response to treatment, associated with negativation of anti-glomerular basement membrane antibodies. Treatment with cyclophosphamide may continue up to a year.

The prognosis is severe. Mortality was up to 90% before the introduction of the therapeutic treatment with corticotherapy / cyclophosphamide / plasmapheresis. (9)

For treated patients, the survival rate after 2 years is about 50%. The best prognosis is in cases with undetectable renal involvement. The disease evolution may sometimes culminate with severe renal failure or massive hemoptysis. In cases without renal involvement spontaneous remissions could be possible. Renal biopsy, besides its diagnosis value, has also a prognosis value. For patients who, at the renal biopsy, have less than 30% of the examined glomeruli with crescents and have a relatively preserved renal function, the prognosis is good. In exchange, for cases which have at biopsy more than 70% of glomeruli with crescents, the renal disease is usually progressive even under correctly conducted treatment arriving up to dialysis and renal transplant. This makes Goodpasture syndrome having the worst prognosis among all the pulmonary-renal diseases.

The diagnosis of Goodpasture syndrome is easy when patients concomitantly have lung and renal involvement. The delay is frequent in those who come with sub-acute disease affecting either their kidney or their lung.

Another group of pulmonary and renal diseases is the group of necrotizing vasculitis of

small vessels, comprising Wegener granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome. These diseases appear more frequently between the fifth and the seventh decades of life having extremely diverse clinical manifestations.

Wegener granulomatosis is a necrotizing systemic vasculitis of small and medium vessels that typically involves superior respiratory airways, lungs and kidneys (the classical triad). There may also appear the involvement of other organs (skin, nervous system, eyes, and digestive tract). Patients come to doctor for hemoptysis, epistaxis, cough, progressive dyspnea and sometimes skin lesions (ulcerations, purpura). These patients subsequently present impairment of the renal function. Sometimes there may be abdominal pains, and then hematuria, proteinuria, nitrogenous products retention, and they are addressed to nephrologist. Systemic manifestations are prolonged fever, anorexia, weight loss, myalgias, arthralgias, and asthenia. Radiological aspects include bilateral lung nodular lesions with a necrosis tendency and formation of cavities or diffuse alveolar condensations (alveolar hemorrhage). Sinusal X-ray frequently shows granulomatous sinusitis and/or bone lytic lesions (FIGURE 2).

Laboratory findings are: anemia, leukocytosis, inflammatory syndrome, renal failure; urinalysis with hematuria, proteinuria (almost never of nephrotic level), and red blood cell casts (4). Most patients have positive c-ANCA (anti proteinase 3) in serum, 90% of those with generalized active disease and 40-70% with regional involvement. Five to 10% of patients may have positive p-ANCA. Lung biopsy characteristically shows necrotizing granulomatous vasculitis and renal biopsy shows a focal and segmental necrotizing glomerulonephritis (10, FIGURE 3).

For patients with classical clinical involvement, the diagnosis is usually confirmed by determining the neutrophils anti-cytoplasm antibodies (c-ANCA) in serum, but the pathologic confirmation is necessary. ANCA measurement should not be used alone in the initial diagnosis of ANCA-associated vasculitis but should be used in combination with tissue diagnosis. (11)

The strategy of the therapy implies induction of remission, followed by maintenance. Treatment options depend on determination of disease severity and extend, such that proposed by the European Vasculitis Study Group (EUVAS). Initial treatment for the patient with generalized disease comprise of cyclophosphamide orally or intravenously (daily oral 2 mg/kg or IV pulses 15mg/kg/pulse at 2-3 week intervals) and prednisolone (1mg/kg/day, with tapering dose), for 3-6 months. Intravenous steroids (methylprednisolone 500-3000 mg), can be given initially, for rapidly progressive glomerulonephritis.

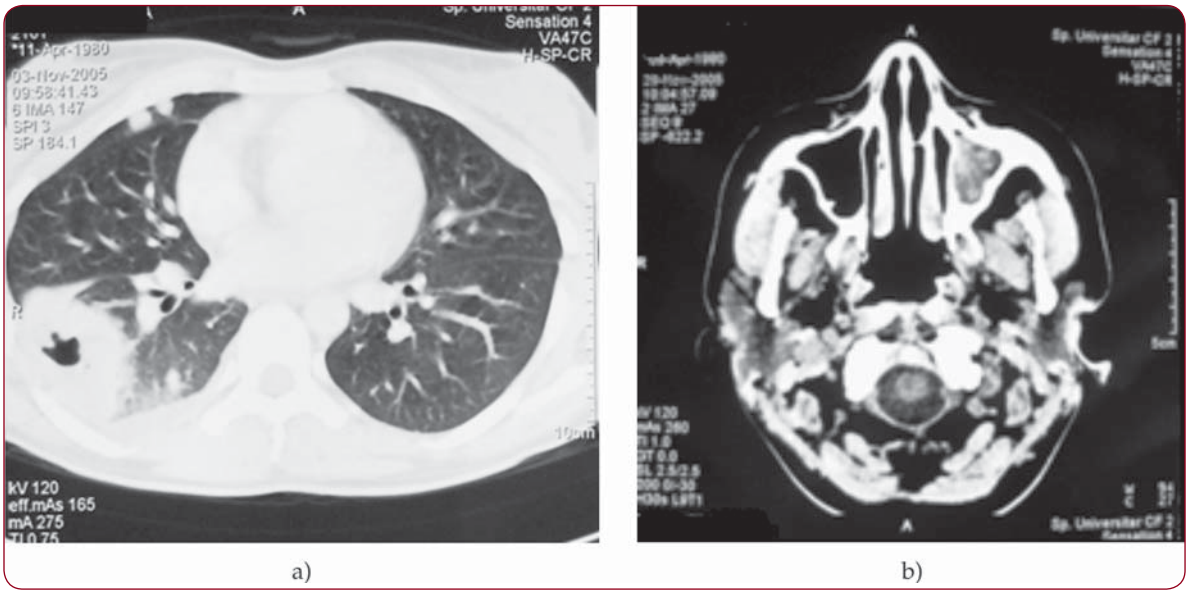

FIGURE 2. CT scans of the lung and sinuses at a patient with Wegener granulomatosis diagnosed in our clinic showing a) nodular lung lesion with necrosis; b) left maxillary sinusitis

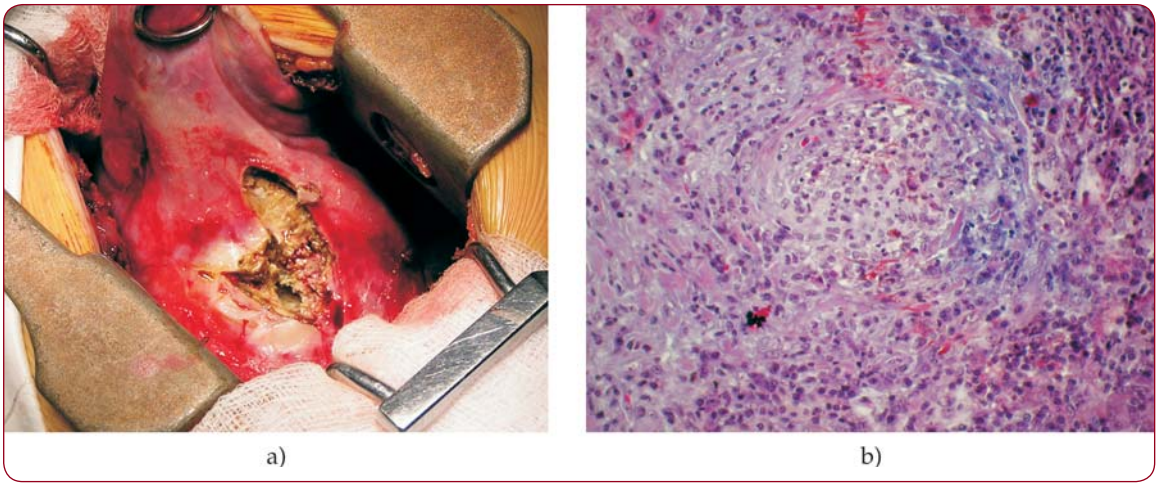

FIGURE 3. a) Macroscopic image of the necrotic lesion in the lung of the same patient with Wegener granulomatosis as in FIGURE 2. b) histological pattern with granulomatous vasculitis

Patient with severe life threatening disease should be treated with cyclophophamide and steroids with adjuvant plasma exchange (7×4 exchanges over 2 weeks). Plasmapheresis is useful for those with severe renal involvement. Patients with localized/early systemic disease may be treated with methotrexate (15 mg/week escalating to a maximum of 20-25 mg/week by week 12) instead of cyclophosphamide, associated with oral steroids.

After remission, in the maintenance phase, cyclophosphamide could be replaced with azatioprine (2mg/kg/day) or methotrexate in combination with oral, low-dose, steroids. In the maintenance phase, cyclophosphamide has been shown to be as effective as azatioprine. Azatioprine is preferred due to little side effects. Treatment continues up to 12-18 months. (12,13)

Relapse can occur in 50 percent of patients in a study with 5 years of follow-up. (14)

Microscopic polyangiitis is a rare paucimmune necrotizing vasculitis. Its manifestations almost always include a focal and segmental necrotizing glomerulonephritis (80-90%) and pulmonary capillarity with alveolar hemorrhage (30% of cases). From clinical and serologic viewpoint, it has common manifestations with Wegener granulomatosis and Churg Strauss syndrome. Unlike them, in microscopic polyangiitis there is no granulomatous or eosinophilic lesion, which is why diagnosis needs a bioptic procedure (eg. thoracoscopic lung biopsy or thoracotomy with lung biopsy). Cytoplasmatic anti-neutrophylic antibodies are positive in 75% of cases, and they are of the p-ANCA (anti-myeloperoxidase) type, and less of the c-ANCA type (10-15%). The treatment is similar to Wegener granulomatosis, with cyclophosphamide and prednisone. Additionally, intravenous immunoglobulin showed a slight benefit in persistent disease (15). Prognosis is favorable with corticosteroids, cyclophosphamide and sometimes immunoglobulines. Survival at 10 years exceeds 70%.

Churg-Strauss syndrome is a granulomatous vasculitis of small vessels associated to a strong involvement of eosinophils (asthma and eosinophilia in blood or affected organs). It is a rare disease with an annual incidence of 2-3 cases in a million. Clinically all patients have asthma. The asthma within Churg-Strauss syndrome appears later in life than usual asthma; it is usually severe and needs more frequent oral corticosteroids. Frequently, patients have allergic rhinitis and sinusitis but unlike Wegener granulomatosis, it does not show severe necrotizing forms. Radiological aspect includes transitory lung infiltrates (30-70% of cases). Alveolar hemorrhage is a rare complication. In classical form, vasculitis appears after several years of atopic manifestations (asthma and/or rhinosinusitis). The appearance of vasculitis is usually announced by fever, weight loss and increase of asthma severity. Precipitating factors for vasculitis are: vaccination, desensitization, some drugs, and infections. After introducing antileukotrienes in asthma treatment, more cases of Churg-Strauss syndrome were reported. This aspect may have appeared in the context of decreasing the doses of oral corticosteroids which otherwise masked the disease. Cardiac

Specific cause	Labs	Chest X-ray	Kidney involvement
Goodpasture syndrome	Anti GBM Linear antibody deposition on biopsy (immunofluorescence)	Diffuse alveolar infiltrates	41-71%
Wegener Granulomatosis	c-ANCA Anemia	Nodules Cavitation	70-85%
Microscopic Polyangiitis	p-ANCA	Diffuse alveolar infiltrates	80-90%
Churg Strauss syndrome	p-ANCA Peripheral eosinophilia	Diffuse alveolar infiltrates migratory, transient	25%

TABLE 1. Profiles of selected conditions that causes pulmonary-renal syndrome (17)
anti-GBM = antiglomerular basement membrane antibody; ANCA = antineutrophil cytoplasmic antibody; c-ANCA = ANCA type C; p-ANCA = ANCA type P

lesions are more frequent in patients with Churg-Strauss syndrome (pericarditis, myocarditis, endocarditis, myocardial infarction) unlike other vasculitis. Other systemic involvement comprise of: neurological lesions (mononeuritis multiplex), involvement of the gastro-intestinal tract or skin lesions (necrotizing vasculitis). Skin biopsy showing eosinophilic vasculitis may be a very valuable element in diagnosis. At the same time, renal involvement is much rarer and rarely leads to acute renal failure. (16) That is why the inclusion of the Churg – Strauss disease in the category of pulmonary-renal syndrome is rather an exception, putting it next to other nosological entities by the common vasculitic mechanism. Biological patients have hypereosinophilia and circulating ANCA (usually p-ANCA, rarer c-ANCA) in 30-70% of cases. Treatment consists of systemic corticosteroids. The role of the cytotoxic agents is not well defined like in Wegener granulomatosis, but it must be taken into account for patients with cardiac, neurological lesions or with acute renal failure where prognosis is much more serious.

Because the introduction of cyclophosphamide has dramatically improved the outcome of many patients with pulmonary-renal syndrome, early diagnostic confirmation is very important. This evidence reinforces the necessity of the active collaboration between the pulmonologist and the nephrologist. When a patient with suspected pulmonary-renal syndrome is seen (TABLE 1), each of these specialists should consider the possibility of a bipolar involvement (lung/kidney) and resort to a consultation in a specialized centre. These correlations are required to manage these serious, yet potentially reversible, syndromes.

CONCLUSION

Pulmonary-renal syndrome may be a severe condition since first presentation. In face of a pulmonary-renal syndrome, patients should be directed to specialized centers because in these rare diseases the diagnosis often requires invasive procedures (biopsies), which are procedures beyond the possibilities of an unspecialized centre. The clinical and therapeutic follow-up have to be done in collaboration by the pulmonology and nephrology specialists, due to the severity of underlying diseases. ❑

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