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Microscopic polyangiitis and systemic lupus erythematosus overlap syndrome; an unusual presentation

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ABSTRACT

Background: Lupus nephritis (LN) is characterized by glomerular immune-complex deposits usually in a full house (FH) pattern. In contrast, ANCA-associated glomerulonephritis (GN) is typically pauci-immune GN. Patients fulfilling both systemic lupus erythematosus (SLE) and ANCA-associated vasculitis (AAV) classification criteria defining "SLE/AAV overlap syndrome" have been rarely reported. However, FH nephropathy (FHN) without overt SLE at presentation is described and considering an overlap syndrome in this situation is challenging.

Case Presentation: A 40-year-old man presented to the emergency because of hemoptysis and macroscopic haematuria. We found acute kidney injury (plasma creatinine 5.16 mg/dL, N: 0.72- 1.17) with an active urinary sediment (proteinuria 3+, haematuria 3+). Chest computerized tomography showed intra-alveolar diffuse haemorrhage confirming pulmonary-renal syndrome. High titers of anti-MPO ANCA in the absence of ANA strongly correlated with microscopic polyangiitis. Kidney biopsy confirmed crescentic GN, however FH immunofluorescence (IF) pattern suggested a LN (class IV). Despite plasma exchanges associated to steroids and rituximab, kidney function declined and haemodialysis was initiated. During 12 months of follow-up on azathioprine-low dose steroids treatment, he remains still asymptomatic. However, considering the appearance of antinuclear antibodies (ANA), presence of antiphospholipid antibodies and low complement level, we considered the diagnosis of SLE/AAV overlap syndrome.

Conclusions: SLE/AAV overlap syndrome is a very rare condition and has a very poor kidney function outcome. We underline that the patients with AAV and FHN require a regular screening for clinical and biological SLE criteria, even in their absence at initial presentation as it could develop later.

Case Report

Implication for health policy/practice/research/medical education:
Lupus-like nephropathy associated to AAV has a very poor kidney outcome. The delayed appearance of ANA in association to other immunological SLE parameters correlated with SLE/AAV overlap syndrome diagnosis, we propose a regular screening for clinical and biological SLE criteria even in their absence at initial presentation.

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1. Background

According to the Systemic Lupus International Collaborating Clinics (SLICC), diagnosis of systemic lupus erythematosus (SLE) can be considered if at least four criteria are fulfilled, with at least one clinical criterion and one immunologic criterion or in presence of lupus nephritis (LN) together with the presence of antinuclear antibodies (ANA) or anti-dsDNA antibodies (1). LN is characterized by glomerular immune-complexes deposits that stain principally for IgG with co-deposition of IgA, IgM, C3 and C1q, defining a "full-house" pattern on immunofluorescence (IF), with coexistence of sub-endothelial, sub-epithelial and mesangial electron-dense deposits on electron microscopy and endothelial tubuloreticular inclusions (2-4). In contrast, glomerulonephritis (GN) in anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) is typically characterized by crescent formation with no

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or few immune deposits (5,6). Patients fulfilling both SLE and AAV classification criteria are rarely reported and are defined as having SLE/AAV overlap syndrome (7). Full house nephropathy (FHN), also called lupus-like nephropathy, without overt evidence of SLE is reported (8,9) and can also have a non-lupus origin (10). Considering an overlap syndrome in this situation is challenging. We present an atypical presentation of SLE/AAV overlap syndrome.

2. Case Presentation

A 40-year-old Caucasian man presented to the emergency department because of haemoptysis with macroscopic haematuria starting two days before his admission. He complained about dyspnoea with cough and chest pain but no fever or chills. He reported a weight loss of 10 kilograms in three months attributed to his stressful work. Two months earlier he reported a facial oedema without any trauma, for which ibuprofen have been successfully prescribed, but since this he was presenting a fluctuating oedema of the lower and upper limbs with asthenia. There was no neurological or musculoskeletal complaint. Two weeks before, he received antibiotic course with amoxicillin and metronidazole after tooth extraction. He had no personal or family history of kidney disease. He did not travel, had no allergies, and had no known contact with ill patients. On physical examination, he was found to be hypertensive (160/90 mm Hg), his baseline arterial O^2 saturation was 95%. We found bilateral pulmonary rales on auscultation, more pronounced on the left side and diffuse lower extremities oedema. There was no pericardial rub or palpable purpura. The laboratory findings are given in (Table 1). Urine dipstick analysis showed 3+ of proteins and 3+ of occult blood. Urine sediment revealed hematuria (1639 red blood cells/µL; N <25), spot high protein-to-creatinine ratio (6.24 g/g; N <0.2) and urine culture was negative. Diagnostic evaluation was suggestive of rapidly progressive glomerulonephritis (RPGN). Chest X-ray showed bilateral diffuse alveolar condensation and chest computed tomography confirmed diffuse intra-alveolar haemorrhage (Figures 1 and 2). There was no urinary obstruction on ultrasound imaging. These findings correlated with a diagnosis of pulmonary-renal syndrome. Patient was transferred to the intensive care unit for supportive care (blood transfusions and intravenous methylprednisolone pulses). Bronchoalveolar lavage confirmed the haemorrhage. Bacterial and fungal cultures were negative. Infectious serology and immunological workup are detailed in (Table 1). ANCA by indirect IF revealed a perinuclear ANCA (p-ANCA) with high titer of 1/320 accompanied by myeloperoxidase (MPO) ANCA. ANA were negative. Diagnostic work-up was therefore suggestive of ANCA-associated microscopic polyangiitis.

Kidney biopsy performed 10 days after admission showed crescentic GN with mesangial proliferation and accentuated lobulations without thrombi and interstitium

Table 1. Laboratory blood tests findings

Variables	Values	Normal range
Haemoglobin, g/dL	5.1	13- 18
CRP, mg/L	12.8	< 10
Albumin, g/L	30	34- 48
Potassium, mmol/L	5.4	3.5- 4.8
Bicarbonate, mmol/L	18	22- 29
Urea, mg/dL	130	13- 47
Creatinine, mg/dL	5.16	0.72- 1.17
eGFR (CKD-EPI), mL/min/1.73m^2	13	>90
HIV, syphilis, anti-HCV, HbsAg	Negative	NA
Anti-GBM	Negative	<1 AI
C3, g/L	0.79	0.90-1.80
C4, g/L	0.30	0.16-0.40

NA; not applicable, AI; activity index, CKD-EPI; chronic kidney disease - epidemiology collaboration, CRP; C-reactive protein, eGFR; estimated glomerular filtration rate, GBM; glomerular basement membrane, HCV; hepatitis C, HbsAg; hepatitis B surface antigen, HIV; human immunodeficiency virus.

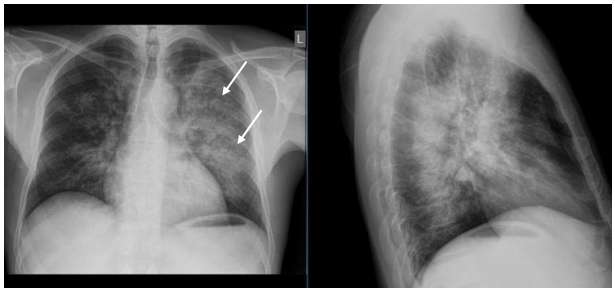

Figure 1. Representative chest radiography demonstrating diffuse bilateral alveolar shadowing (↓), predominantly on the left (L) lung at the day of admission in emergency room.

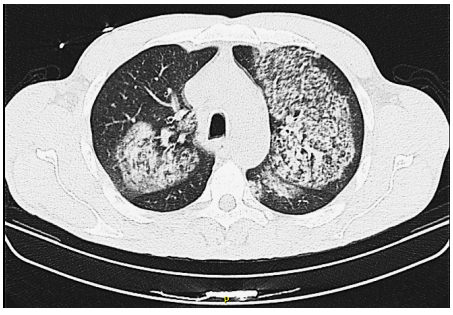

Figure 2. Representative chest CT showing diffuse intra-alveolar haemorrhage at the day of admission in emergency room.

showed only mild fibrosis and mild tubular atrophy (Figure 3A, B). A full-house pattern with equal granular staining pattern of IgG, IgM, IgA, C1q, C3, kappa and lambda chains was found within peripheral capillary loops and mesangium on IF study (Figure 4A - G). The electron microscopy was not performed. Proposed histological diagnosis, in line with characteristics in IF was LN stage IV following ISN/RPS classification, with an activity index of 7 and chronicity of 1 following NIH classification. However, patient has no other signs of SLE. We retained microscopic polyangiitis associated pulmonary-renal syndrome diagnosis.

Plasma exchanges were initiated three days after admission and he benefited from five courses in one week until haemoptysis disappeared. Immunosuppressive therapy was also continued; three boluses of methylprednisolone 500 mg followed by daily oral methylprednisolone (1.0 mg/kg) together with anti-CD20 monoclonal therapy with rituximab (375 mg/m^2 of body surface area) once a week during four consecutive weeks. The patient refused cyclophosphamide because of it gonadal toxicity. Despite intensive treatment, kidney function declined with an increase in blood creatinine level at 7.69 mg/dL, persistence of an active urinary sediment with nephrotic range proteinuria. Haemodialysis has been started one month following his admission. During 12 months of follow-up on azathioprine- low dose steroids maintenance treatment, he remains still asymptomatic. Azathioprine dose has been reduced because of a genetic susceptibility due to the presence of a heterozygote mutation in the *TPMT-3A* gene. His ANCA titers were high at 1/320 with an anti-MPO pattern. However, ANA became positive only after nine months of follow up, antiphospholipid antibodies testing has been performed three times and was positive and complement level was fluctuating between low and normal range. We concluded therefore to the diagnosis of SLE/AAV overlap syndrome.

3. Discussion

Pulmonary-renal syndrome is a life-threatening condition characterized by an auto-immune mediated rapidly progressive GN together with diffuse intra-alveolar haemorrhage (11). Histologically, there is a similar pattern with crescent formation (12). The most common causes of this syndrome are AAV most often microscopic polyangiitis- and anti-GBM disease (13,14). In a study by Niles et al (13) around 54% of patients had ANCA, 7% had ANCA and anti-GBM, and 6% had anti-GBM alone. In contrast, only about 5% of patients with SLE present pulmonary capillaritis (15,16). Our patient had

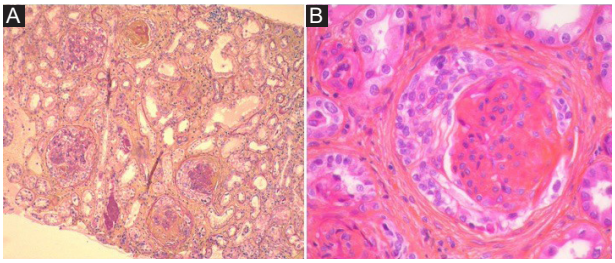

Figure 3. Representative images from kidney biopsy performed 10 days after patient admission. (A) Light microscopy showing glomeruli with accentuated lobulations, cellular crescent, mild interstitial fibrosis and tubular atrophy (HES, original magnification x100). (B) Cellular crescent with lobulated glomerulus and mesangial proliferation (HES, original magnification ×400).

clinical, serological and histological features (crescent GN) suggestive of a necrotizing vasculitis, namely microscopic polyangiitis, according to an algorithm proposed by Watts et al (17) but findings of FHN on IF is in contrast to the pauci-immune nature of the disease

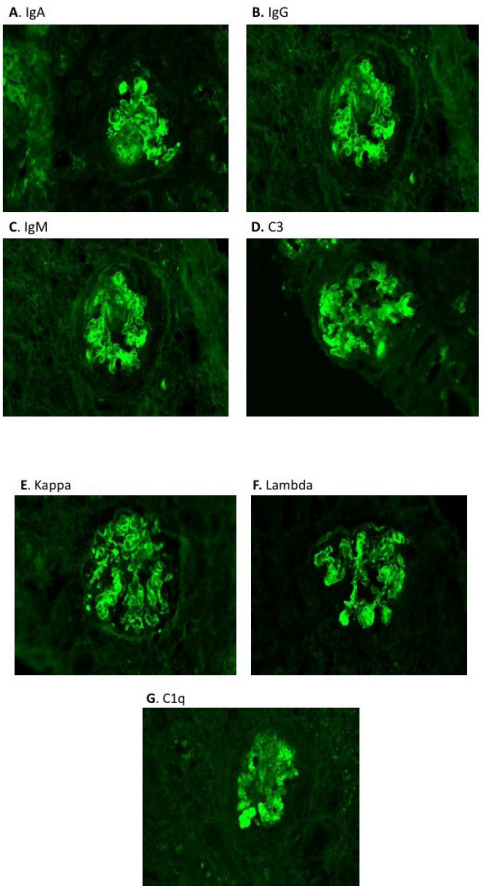

Figure 4. Representative images from kidney biopsy performed 10 days after patient admission. A to G- Full-house immunofluorescence pattern staining demonstrating respectively equal IgA, IgG, IgM, C3, kappa, lambda chains and C1q granular staining within peripheral capillary loops and mesangium (original magnification ×400).

(5). Nevertheless, some authors have reported glomerular immune deposits in patients with AAV, but without a full house (FH) pattern (18,19). In contrast, FHN with immune complex deposits is a common finding in LN (3). However, diagnosis of SLE cannot be established in presence of this single criterion (1), and FHN have been described in other non-lupus glomerular diseases, such as membranoproliferative nephritis, IgA nephropathy or post-infectious nephropathy (20,21). Wen et al. (8) identified 94 patients with FHN. Among them, 70 fulfilled SLE criteria and the remaining 24 patients were considered as having non-lupus FHN. Membranous nephropathy was the final diagnosis in 46% of them, IgA nephropathy in 21%, membranoproliferative nephritis and post-infectious GN in 12.5% and C1q nephropathy in one patient. No one had AAV. During follow up, two patients with originally non-LN have developed symptoms and signs of SLE. There have been other some reports of patients whose initial presentation of SLE was LN with absent clinical features or serology (9,22,23) who developed positive ANA with dsDNA-antibodies during follow-up (9). When both SLE and AAV classification criteria are fulfilled, patients are defined as having SLE/AAV overlap syndrome (24). A multicentric study by Jarrot et al (7) identified 8 patients with an overlap syndrome between 1995 and 2014. Around 75% had aggressive renal presentation with RPGN. Histologically, there have been pauci-immune GN in 5 patients and LN in 3 patients. Seven of 8 patients had pANCA directed against MPO. Pericarditis, arthritis and cytopenia have been reported as a common clinical presentation (24,25). Our patient did not fulfil SLE criteria initially but appearance of ANA during follow up allowed us to retrospectively make the diagnosis of SLE/AAV overlap syndrome as he also presented with hypocomplementemia and had positive antiphospholipid antibody testing, features usually found in SLE but not in AAV. Indeed, longer follow up is necessary as SLE may develop up to 10 years after renal-limited presentation (9). In some cases, FHN remains idiopathic and is then associated with poor renal outcome, with more end-stage renal disease risk compared to lupus FHN (10). Presence of tubuloreticular inclusions would have increase the likelihood of a superimposed LN, as these tubule-like structures are usually associated with viral infections or SLE (26). Unfortunately, in our patient electron microscopy has not been available.

4. Conclusions

In summary, pulmonary-renal syndrome is diagnostic and therapeutic emergency of immune mediated origin. Kidney biopsy is critical when rapidly progressive GN is suspected and IF allows defining pathogenic mechanisms. As in our case the delayed appearance of ANA in association to other immunological SLE parameters correlated with SLE/AAV overlap syndrome diagnosis. SLE/ AAV overlap syndrome is a very rare condition and has a very poor kidney function outcome. We underline that the patients with AAV and FHN require a regular screening for clinical and biological SLE criteria, even in their absence at initial presentation as it could develop later.

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Authors' contribution

Primary draft was done by FT and AP. CC participated in the case discussion and assisted the patient. The manuscript was edited by FT and AP. All authors read and signed the final version.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. The patient has given his informed consent regarding publication of this case report.

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