CASE REPORT

Nephrotic syndrome without kidney injury revealing intravascular large B cell lymphoma

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SUMMARY

We describe the case of a 64-year-old woman admitted for fever of unknown origin, who developed nephrotic syndrome during hospitalisation and pulmonary infiltrates. Renal biopsy disclosed intracapillary glomerular invasion by intravascular large B cell lymphoma. Clinical and biological evolution was favourable after rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone (R-CHOP) treatment and autologous stem cell transplant. Two years after diagnosis the patient was considered in remission.

BACKGROUND

Intravascular large B cell lymphoma (IVLBCL) is a very rare subtype of aggressive lymphoma that can affect various organs, which earned it the name of oncologist's 'great imitator'. However kidney involvement is rarely reported. Because of its behaviour and physician's lack of information, it remains a diagnostic challenge in a context of fever of unknown origin.

CASE PRESENTATION

A 64-year-old woman was admitted for a 3-week history of grade III dyspnea, fatigue, night sweats and fever up to 38.5°C. Medical history was notable for hypertension, hypothyroidism and hypercholesterolaemia. The patient medication's list included propranolol, omeprazole, L-thyroxin and folic acid. Physical examination on admission was unremarkable. Blood analysis revealed increased serum C-reactive Protein (CRP) levels at 137 mg/L, normocytic anaemia at 74 g/L of haemoglobin, lactate dehydrogenase (LDH) level at 405 U/L (normal value (NV) <250 U/L) and hypoalbuminaemia at 24.15 g/L (NV 34–52). Serum creatinine, liver-enzyme level, platelets and white blood cell counts were within the normal range. Serum protein electrophoresis showed hypogammaglobinaemia without monoclonal component. Coombs test was negative, haptoglobin level was normal and schizocytes were absent on blood smear. Antinuclear antibody was negative, as well as anti-neutrophil cytoplasmic antibody (ANCA) and cryoglobulin screening. Serologic tests including hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, cytomegalovirus (CMV), Epstein-Barr virus (EBV) and parvovirus B19 did not show recent infection. Repeat blood and urine cultures remained sterile. Proteinuria (4+) was present on urinary dipstick, estimated in urinary spot at 5.43 g/L with a protein/creatinine ratio of 29, without significant leucocyturia or haematuria. Urine protein electrophoresis revealed only massive albuminuria without monoclonal component. Thoraco-abdominal enhanced CT scan did not identify any deep abscess, tumour or lymphadenopathy. 18-F-fluoro-2-deoxyglucose (FDG) positron emission tomography/computed tomography (PET-CT) revealed a slight diffuse uptake of pulmonary parenchyma, and discrete splenomegaly. Evolution during hospitalisation was marked by persistent massive proteinuria, pitting oedema and hypoxaemia. Kidney function however remained stable. Control thorax CT scan performed 10 days after admission revealed worsening lung infiltration consistent with alveolar haemorrhage or undifferentiated parenchyma infiltration. Anti-glomerular basal membrane antibodies were absent.

Kidney biopsy revealed intracapillary glomerular invasion with CD20+ and focally CD5+ atypical lymphoid cells, corresponding to IVLBCL (figure 1). Rituximab, cyclophosphamide, doxorubicine, vincristine and prednisone (R-CHOP) regimen was started (rituximab, cyclophosphamide, adriamycin, oncovin and prednisone) with improvement of fever, inflammatory markers and proteinuria.

OUTCOME AND FOLLOW-UP

Unfortunately, after initial treatment, the patient's clinical situation rapidly deteriorated, with worsening pancytopenia and haemophagocytic syndrome identified on bone marrow biopsy. Treatment was intensified and the patient successfully underwent autologous stem cell transplantation. Two years after diagnosis, follow-up remains favourable, the patient is considered in remission and heavy proteinuria did not recur.

DISCUSSION

IVLBCL is a very rare aggressive subtype of diffuse B cell lymphoma, estimated incidence of less than one case per one million persons.[1] The median age at diagnosis is 67 years and both sexes are equally affected. Historically two clinical variants have been described: European phenotype with central nervous system, pulmonary and cutaneous involvement but without haematological involvement; and Asian phenotype, frequently including pancytopenia, haemophagocytosis and hepatosplenomegaly.[2–4] Pathologically, vascular lumens are invaded by CD20+, CD45+, CD5+, BCL2+ atypical lymphocytes and a lack of expression for

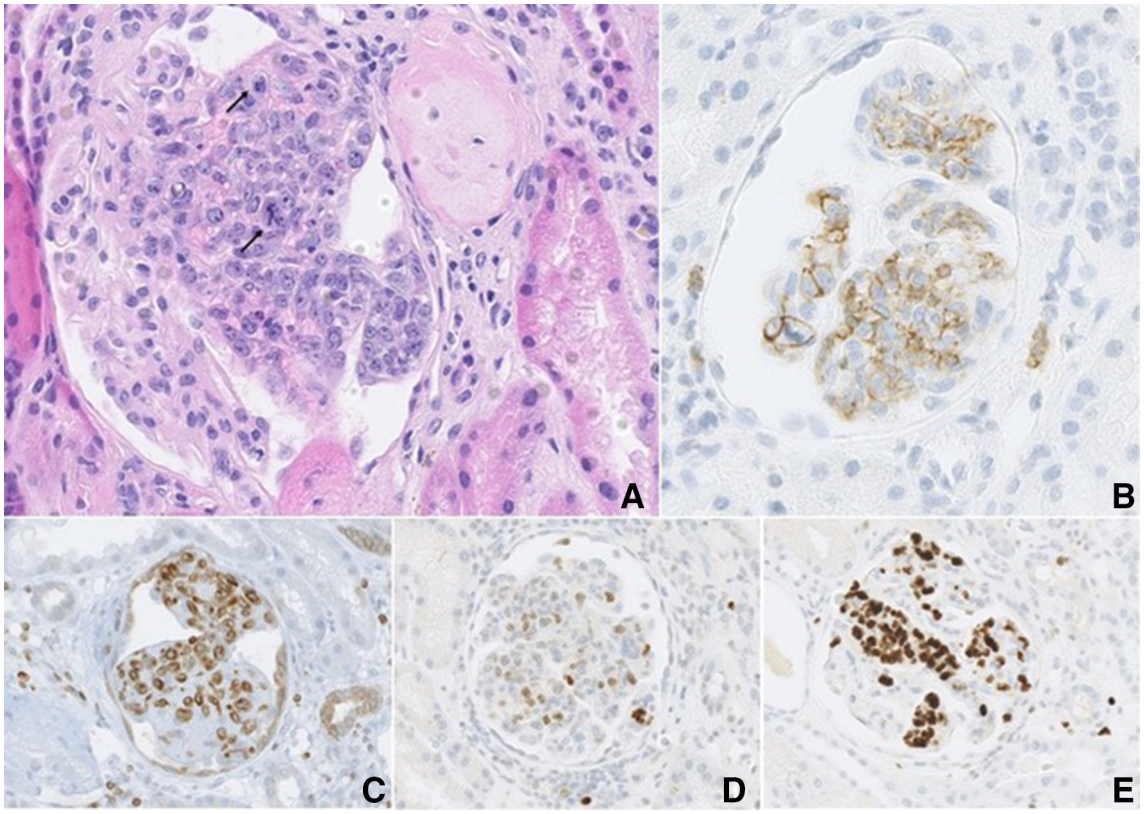

Figure 1 Renal biopsy shows large atypical lymphomatous cells filling the glomerular capillary lumina. Note the presence of mitosis (arrows) (A), (haematoxylin eosin staining; magnification: ×40). Intracapillary large lymphomatous cells are CD20+ (B), BCL2+ (C), MUM1+ (D); lymphomatous cells show a high Ki67 proliferation index (E) (immunoperoxydase haematoxylin counterstain; magnification: a ×40 and C–E, ×20).

surface adhesion proteins (eg, Intercellular Adhesion Molecule (ICAM)-1) may prohibit translocation, a potential explanation for endothelial containment.[5] This disease is, therefore, extremely heterogeneous, presenting locally or diffusely, perturbing vascularity in virtually any organ system, leading to protean, 'vasculitis-like' manifestations.[6] However, it is treatable. The poorly specific inaugural symptoms and the lack of lymphadenopathy or radiographic organ abnormalities further complicate the diagnosis, and require strong consideration for tissue biopsy of a suspected involved organ. In addition, random skin biopsy is a tool for diagnosis of IVLBCL with a sensitivity of 77.8% and specificity of 98.7%.[7] In our case, the presentation with fever of unknown origin, nephrotic syndrome and pulmonary infiltrates first orientated the diagnosis towards a systemic vasculitis; a negative autoimmune serology warranted further investigations including kidney biopsy. Surprisingly pathological examination revealed glomerular intravascular lymphoma without tubulointerstitial invasion.

In IVLBCL, kidney is involved in approximatively 2%–13% of cases.[4 8 9] A wide range of clinical presentation may be observed: from mild proteinuria to nephrotic syndrome with or without acute kidney injury, kidney enlargement or kidney mass. Renal involvement is usually classified as tubulointerstitial or glomerular. In cases of tubulointerstitial invasion, presentation consists of bilateral kidney enlargement or renal mass. Invasion of glomerular capillary by lymphomatous cells leads to obstruction and in some instance to acute kidney injury. Pathogenesis of the nephrotic syndrome is not clear: minimal change disease induced by cytokines that increased glomerular membrane permeability, or invasion of glomeruli by lymphomatous cells leading to effacement of foot processes.[8 10] Interestingly only a few cases of pure nephrotic syndrome without acute kidney injury or kidney enlargement caused by IVLBCL have been described in the literature, as now described in this case report.[10–14]

Overall prognosis of the disease is poor because of its usual aggressive behaviour and delayed diagnosis, but rituximab-based chemotherapy regimen improved clinical outcome

Learning points

- Fever of unknown origin (FUO) remains a diagnosis challenge for physicians. In this clinical situation, the presence of nephrotic syndrome associated to pulmonary infiltrates first orientates to autoimmune vasculitis, but alternative diagnosis as intravascular large B cell lymphoma (IVLBCL) should be considered, particularly in the setting of anaemia, elevated LDH and negative autoimmune serology.This case highlights that the Sutton's law ('Go where the money is') remains a corner stone in FUO's diagnosis process, with the clinician directing biopsies to any area of noted dysfunction.
- Because of its rarity, its usual aggressive behaviour and its variety of presentation as a 'great imitator', leading to delay in diagnosis, IVLBCL has poor prognosis. Heightening awareness for this severe disorder could improve time to diagnosis and potentially patient outcomes.
- Interestingly only a few cases of pure nephrotic syndrome without acute kidney injury or kidney enlargement caused by IVLBCL have been described in the literature, as now described in this case report.

with 24-month survival rate of 66% in the largest retrospective study.[15]

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