Methotrexate-associated B-cell lymphoma presenting with acute renal failure and bilateral nephromegaly

SH Nasr[1], B Alobeid[1], JM Jacobs[2], TE Peacock[3], VD D'Agati[1] and GS Markowitz[1]

[1]Department of Pathology, Columbia University, College of Physicians & Surgeons, New York, New York, USA; [2]Department of Medicine, St Lukes Medical Center, Bethlehem, Pennsylvania, USA and [3]Department of Medicine, Easton Hospital, Easton, Pennsylvania, USA

CASE PRESENTATION

A 73-year-old female patient with a history of systemic lupus erythematosus for 10 years presented with acute renal failure and a creatinine of 2.9 mg/dl (256 μmol/l). The patient had a baseline creatinine of 1.0 mg/dl (88 μmol/l) 3 months prior. Past medical history included *sicca* syndrome, Raynaud's phenomenon, longstanding low-grade proteinuria (<1 g/day) with minimal microhematuria, and persistently positive anti-nuclear and anti-double-stranded DNA antibodies. There was no history of diabetes or hypertension and the patient had not previously undergone renal biopsy. Physical examination revealed a blood pressure of 139/72 mm Hg and no edema or cutaneous manifestations. Her medications included methotrexate (MTX) 7.5 mg once per week (for 3 years) and plaquenil 200 mg twice per day. Urinalysis revealed 2+ protein and 1+ blood. Urine microscopic examination showed 6–10 red blood cells/high power field but no red blood cell casts. Laboratory evaluation revealed normal C3 and C4 complement levels, negative anti-nuclear cytoplasmic antibody, negative anti-cardiolipin antibody, normal erythrocyte sedimentation rate, serum albumin 3.4 g/dl (34 g/l) (normal range 3.5–5 g/dl (35–50 g/l)), and no evidence of a monoclonal serum spike. The kidneys measured 13.9 and 14.8 cm in length by ultrasound, without evidence of obstruction. This contrasted with a renal ultrasound from 7 years prior in which the kidneys measured 10.2 and 11.3 cm in length. Computed tomography (CT) scan revealed bilateral diffuse enlargement and hyperdensity of the kidneys (without mass lesions), a 1.5 cm mass in the left lower lobe of the lung, and multiple hypodense areas within the liver. Liver biopsy showed fibrosis, without evidence of neoplasia. The patient's creatinine rose further over 1 week to 3.9 mg/dl (345 μmol/l). Renal biopsy was performed.

KIDNEY BIOPSY FINDINGS

Sampling for light microscopy included three cores of renal cortex, one of which also contained medulla. There were 12 glomeruli present, three of which were globally sclerotic. Glomeruli appeared histologically unremarkable, without evidence of endocapillary proliferation, fibrinoid necrosis, or crescent formation. All three cores of renal cortex exhibited marked, diffuse interstitial expansion by a monotonous population of large atypical lymphoid cells with a high nuclear/cytoplasmic ratio and prominent nucleoli (Figure 1a). Immunohistochemical stains of the atypical large lymphoid cells were strongly positive for CD20 (a marker of B cells) and negative for CD3 (a marker of T cells), consistent with a B-cell lymphoma (Figure 1c and d). The lymphoma cells also stained negative for CD10 (common acute lymphoblastic leukemia antigen) and focally positive for BCL-2 (B-cell lymphoma/leukemia-2). CD3 stain highlighted interspersed small, non-neoplastic T cells. *In situ* hybridization performed on a paraffin-embedded renal biopsy section with an oligonucleotide probe specific for Epstein–Barr virus (EBV)-encoded RNA was negative. The malignant infiltrate spared glomeruli, tubules, and vessels, and was also prominently seen throughout the renal medulla. Despite the prominent interstitial expansion, no significant tubulitis was identified (Figure 1b). Vessels exhibited moderate arteriosclerosis.

The seven glomeruli sampled for immunofluorescence were negative for IgG, IgM, IgA, C3, C1, and kappa and lambda light chains. No tubulointerstitial or vascular deposits were identified. On ultrastructural evaluation, glomeruli were devoid of electron-dense deposits, endothelial tubuloreticular inclusions, or significant foot process effacement. The interstitium was diffusely permeated by large atypical lymphocytes showing oval vesicular nuclei with fine chromatin and prominent nucleoli.

FINAL DIAGNOSIS

Renal infiltration by diffuse large B-cell lymphoma, MTX associated.

Correspondence: *SH Nasr, Department of Pathology, Columbia University, College of Physicians & Surgeons, 630 West 168th Street, VC14-224, New York, New York 10032, USA. E-mail: sn386@columbia.edu*

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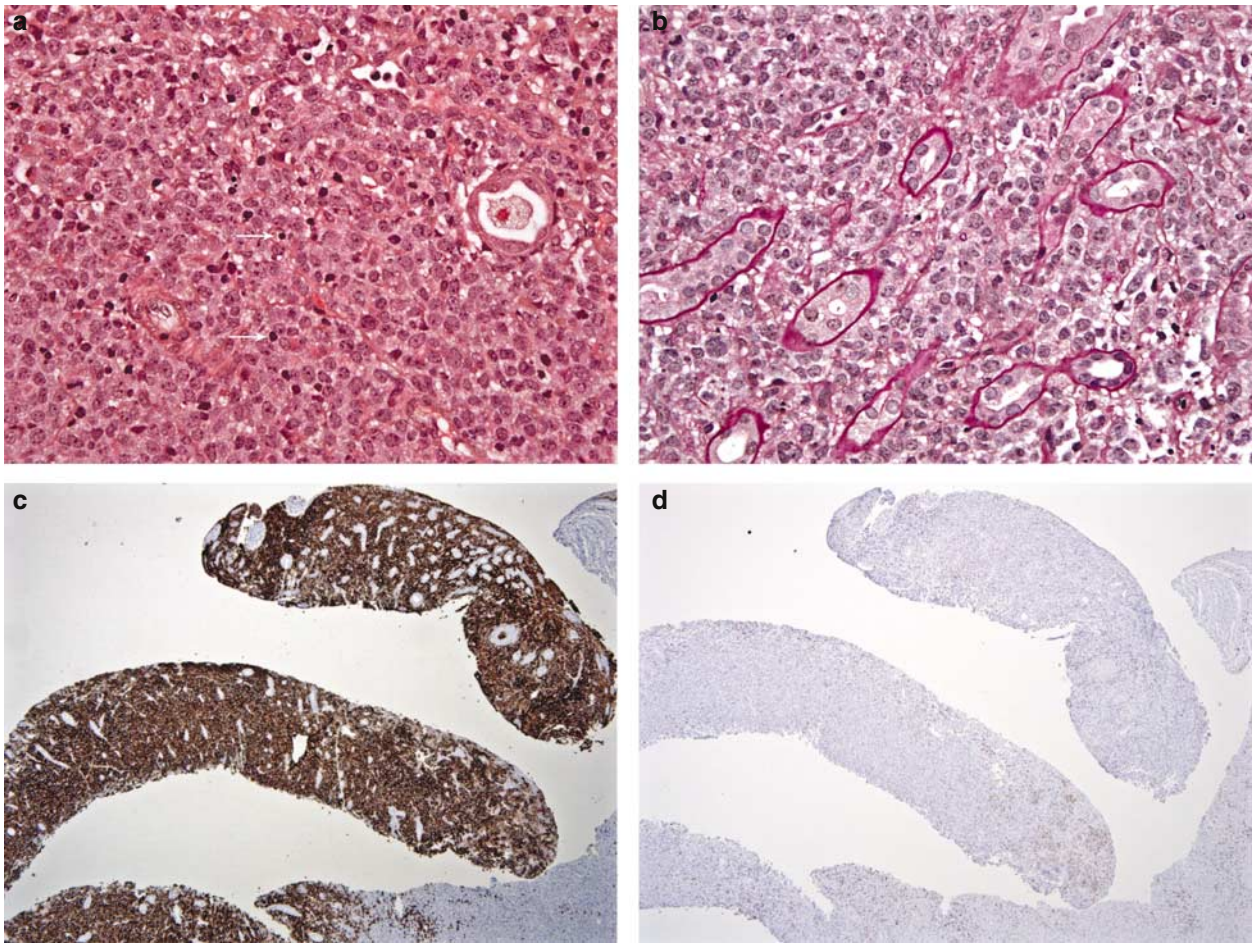

Figure 1 | Renal biopsy findings. (**a**) The renal interstitium is markedly expanded by atypical, large lymphoid cells which exhibit an increased nuclear:cytoplasmic ratio, vesicular chromatin, and prominent nucleoli. Interspersed, small non-neoplastic lymphocytes also are seen (arrows) (hematoxylin and eosin, original magnification $\times 400$). (**b**) The lymphomatous infiltrate expands the interstitium but spares tubules. In contrast to acute interstitial nephritis, there is no significant tubulitis (periodic acid Schiff, original magnification $\times 400$). (**c**) The lymphomatous infiltrate stains strongly for CD20 (a marker of B cells). The low power view highlights the diffuse involvement of the renal parenchyma (original magnification $\times 20$). (**d**) The lymphomatous infiltrate does not stain for CD3 (a marker of T cells). In contrast, there is scant, mild positivity in the distribution of small, mature T cells (original magnification $\times 20$).

CLINICAL FOLLOW-UP

Following receipt of the biopsy results, the patient was immediately started on high-dose dexamethasone and Rituximab, followed by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Bone marrow biopsy was unrevealing. The patient became pancytopenic and 2 weeks later was admitted and treated for *Escherichia coli* septicemia, at which time her creatinine was 3.0 mg/dl (265 μmol/l). At 3 months following renal biopsy, after completing six cycles of Rituximab/CHOP, the patient's creatinine had declined to 1.0 mg/dl (88 μmol/l). A CT scan performed 2 months following initiation of chemotherapy showed the kidneys to be smaller in size with improvement of the hypodense areas within the liver.

DISCUSSION

There are multiple mechanisms by which acute renal failure (ARF) can occur in patients with lymphoma. Lymphoma may precipitate ARF by direct effect, such as ureteral obstruction, compromise of the renal arteries or veins, or bilateral renal parenchymal infiltration, as seen in the case reported herein. Lymphoma may indirectly lead to ARF by causing sepsis, hypercalcemia, or hemolysis. ARF may also result from antitumor therapy, including nephrotoxicity of chemotherapeutic agents, tumor lysis syndrome, or radiation nephritis. Nephrotic-range proteinuria is less commonly seen in patients with lymphoma and is mainly associated with minimal change disease, type 1 cryoglobulinemic glomerulonephritis, amyloidosis, and rarely intraglomerular lymphoma.

Direct parenchymal infiltration of the kidney in advanced systemic lymphoma has been reported in up to one-third of patients at autopsy.[1] Renal lymphoma is diagnosed much less frequently in living patients, with a prevalence of 5% on CT scan.[2] Renal involvement is more frequent in non-Hodgkin's lymphoma than Hodgkin's lymphoma and is most common in diffuse large B-cell lymphoma.[3] The lymphomatous involvement of the kidneys is usually silent. Clinical

Table 1 | Comparison of interstitial and intraglomerular types of renal lymphoma diagnosed by percutaneous renal biopsy

	Interstitial type	Intraglomerular type
Number of cases	48 (77%)	14 (23%)
Most common clinical presentation	Acute renal failure	Proteinuria (nephrotic range in about 50% of cases) with or without renal failure
Findings by US/CT	Bilaterally enlarged kidneys	Normal-sized kidneys
Renal biopsy findings	Lymphomatous interstitial infiltration with sparing of tubules and glomeruli	Glomerular capillary occlusion by lymphoma cells with sparing of tubules and interstitium
Pathological differential diagnosis	Acute interstitial nephritis	Proliferative glomerulonephritis

CT, computed tomography; US, ultrasound.

manifestations, when present, are nonspecific and may include flank pain, abdominal distension, hypertension, or hematuria. The diagnosis is typically established by imaging studies or, less commonly, by histological examination. CT is the most sensitive and comprehensive imaging modality for diagnosing renal lymphoma and may reveal multiple bilateral masses, solitary masses, diffuse bilateral infiltration, or invasion from contiguous retroperitoneal disease.

Renal lymphoma, in the absence of a known history of lymphoma and clinically mimicking medical renal disease, is a rare finding on percutaneous renal biopsy with only 62 cases reported in the English literature.[4–9] Of these, 48 cases (77%) were of the interstitial type characterized by interstitial lymphomatous infiltration with sparing of glomeruli and tubules, as in the case reported herein. Most of these cases are of the diffuse large B-cell type. In contrast, the remaining 14 cases (23%) were of the intraglomerular type, also known as angiotropic large cell lymphoma or intravascular large B-cell lymphoma, manifesting exclusive localization of lymphoma cells within glomerular capillaries. ARF is the most common indication for renal biopsy in patients with interstitial lymphoma. In contrast, proteinuria, often in the nephrotic range, is the presenting feature in most reported cases of intraglomerular lymphoma (Table 1). Among the two patterns of disease, bilateral renal enlargement is limited to interstitial lymphoma. Although possible signs of extrarenal lymphoma such as lymphadenopathy or hepatosplenomegaly were reported in approximately 45% of cases of interstitial lymphoma, these findings did not typically lead to suspicion of the diagnosis. Overall, renal lymphoma was suspected in only a quarter of cases before renal biopsy, based mainly on the ultrasound/CT findings of bilaterally enlarged kidneys.[4] Chemotherapy with or without radiotherapy resulted in rapid improvement of renal function, size, and histology in most patients with interstitial lymphoma. Similarly, combined chemotherapy was effective in leading to a decline in proteinuria and remission of nephrotic syndrome in patients with intraglomerular renal lymphoma.[4,5]

The term 'primary renal lymphoma' has been applied to cases of renal lymphoma in which there is no extrarenal evidence of lymphoma at the time of diagnosis. This diagnosis can almost never be established with certainty and is therefore controversial. In the current case, this term would be inappropriate owing to the history of multiple hypodense areas within the liver and a 1.5 cm mass in the lung.

The pathomechanism of ARF in patients with interstitial lymphoma is not clear. It has been postulated that the dense lymphomatous interstitial infiltrate may compress tubules and interstitial capillaries, leading to intratubular obstruction and increased post-glomerular vascular resistance.[4] In intraglomerular lymphoma, the proteinuria and nephrotic syndrome may result from altered glomerular permeability mediated by local production of lymphokines by lymphoma cells, similar to that proposed for lymphoma-associated minimal change disease, or from mechanical effects on glomerular hemodynamics.[10] Obstruction of the glomerular capillaries by malignant cells may underlie the ARF seen in some patients with intraglomerular lymphoma.

MTX-associated lymphoproliferative disorder is defined by the World Health Organization as a lymphoid proliferation or lymphoma in a patient on MTX, most commonly for treatment of connective tissue disease.[11] The majority of reported cases have occurred in patients with rheumatoid arthritis, with fewer cases affecting patients with psoriasis, dermatomyositis, Sjogren's syndrome, and systemic lupus erythematosus.[12–15] The underlying immune deficiency in patients with connective tissue disease may contribute to the development of lymphoma, and there are several reports of malignant lymphoma developing in rheumatoid arthritis patients not on immunosuppressive therapy or receiving immunosuppressive drugs other than MTX (including prednisone, gold, hydroxychloroquine, and penicillamine).[16,17] In one study on MTX-associated lymphomas, the median cumulative dose of MTX was 0.8 g (range, 0.01–2.9 g) and the median interval from the start of MTX therapy to the diagnosis of lymphoma was 3.2 years (range, 0.67–10.9 years).[16] Approximately 50% of reported cases of MTX-associated lymphoma have been extranodal, involving a variety of sites including skin, lung, small bowel, and kidney.[12] The most common histological pattern of MTX-associated lymphoproliferative disorder is diffuse large B-cell lymphoma. Less common patterns include Hodgkin's disease, lymphoproliferations resembling Hodgkin's disease, follicular lymphoma, Burkitt lymphoma, and polymorphous lymphoplasmacytic infiltrates. A complete or partial response to MTX withdrawal alone is seen in approximately two-thirds of patients, and is more common in patients with EBV infection.[12] In patients treated with chemotherapy with or without radiotherapy, either initially or after failure to

respond to MTX withdrawal, a greater than 50% response rate was achieved.[13]

The mechanisms by which MTX increases the risk of lymphoma in patients with connective tissue disease are not well understood. Approximately 45% of cases of MTX-related lymphoproliferative disorders are associated with latent EBV infection.[12] Immunosuppression with MTX may lead to uninhibited expansion of EBV-infected B cells and may promote the reactivation of latent infection.[18] Both the latent and lytic forms of EBV infection are thought to be important in cellular transformation and the development of lymphomas in patients treated with MTX, similar to the mechanism thought to underlie post-transplant lymphoproliferative disorder following solid organ or bone marrow transplantation.[18]

The standard evaluation of a patient with ARF includes ultrasound to exclude the possibility of obstruction. When ARF is accompanied by nephromegaly and obstruction can be excluded, the differential diagnosis is limited and includes diabetic glomerulosclerosis, infiltrative disease (especially lymphoma and leukemia), and, less commonly, human immunodeficiency virus-associated nephropathy and bilateral renal vein thrombosis.

In summary, we report a case of diffuse large B-cell lymphoma presenting with ARF and bilateral nephromegaly in a patient with a history of systemic lupus erythematosus and long-term treatment with MTX. Renal biopsy was diagnostic of renal lymphoma, interstitial type. In patients with ARF and bilateral renal enlargement, renal lymphoma is an important differential diagnostic consideration. Furthermore, the nephrologist should be aware of the rare but important association between long-term treatment with MTX and the development of lymphoma. Early histological confirmation by renal biopsy and institution of chemotherapy are critical for both renal and patient survival.

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