รายงานผู้ป่วย

Intravascular Lymphomatosis: A case of bilateral renal enlargement and renal failure

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We report a case of intravascular lymphomatosis (IVL) presented with bilateral renal enlargement and renal failure. The patient had prolonged fever and encephalopathy. Radiological study showed both kidneys to be huge. No malignant cells were found in either a peripheral blood smear or a bone marrow examination. Kidney biopsy samples showed large lymphoid cells in small arteries, venules and the glomerular capillary lumen. There have been a few reported cases of IVL presenting with renal manifestations. We compare the renal manifestations of IVL and malignant lymphoma.

Key words: *Intravascular Lymphoma and renal enlargement.*

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ยิ่งยศ อวิหิงสานนท์, โศภณ นภาธร, ธานินทร์ อินทรกำธรชัย, พงษ์ศักดิ์ วรรณไกรโรจน์, เสาวณีย์ เย็นฤดี, กัมมันต์ พันธุมจินดา. Intravascular lymphomatosis: **รายงานผู้ป่วย 1 รายที่มีภาวะไตวายเฉียบพลันร่วมกับไตมีขนาดโตขึ้น. จุฬาลงกรณ์เวชสาร 2542 มิ.ย; 43(6): 399-407**

รายงานผู้ป่วย Intravascular lymphoma ซึ่งมีปัญหาไตทั้ง 2 ข้างมีขนาดโตขึ้นร่วมกับไตวาย ผู้ป่วยมีอาการไข้เรื้อรังมา 2 เดือน ต่อมาซึมลง การตรวจร่างกายและการตรวจทางรังสีวิทยาพบไตทั้ง 2 ข้างมีขนาดโตมาก การตรวจสเมียร์เลือดและไขกระดูกไม่พบเซลล์มะเร็ง ผู้ป่วยได้รับการวินิจฉัยโรคนี้จากการทำ kidney biopsy อย่างไรก็ตามผู้ป่วยอาการไม่ดีขึ้นหลังจากได้รับการรักษาด้วยเคมีบำบัด และเสียชีวิตจากการติดเชื้อในกระแสโลหิต มีรายงาน Intravascular lymphoma ที่ไตมีขนาดโตขึ้นร่วมกับไตวายเพียง 1 ราย ได้รวบรวมรายงานของผู้ป่วย Intravascular lymphoma รายอื่น ๆ ที่มีอาการทางไตเป็นอาการสำคัญ

Angioendotheliomatosis proliferans systemisata, first reported in 1959 by Pfleger and Tappeiner,[1] is characterized by a proliferation of neoplastic cells of small and medium sized subcutaneous vessels within the lumen. Early reports of this disease designated it as "malignant angioendotheliomatosis". In 1986, Sheibani et al described this process as of hematolymphatic origin based on immunohistochemical positivity of cells for leukocyte common antigen and the demonstration of monoclonal lymphoid populations of either B- or T-cell lineage.[2] Since then, the term "intravascular lymphomatosis" has become widely accepted.

The clinical manifestations of this syndrome usually comprise fever, encephalopathy, skin lesions and diffuse interstitial lung infiltrations.[3] Although multiple cases of renal involvement have been documented at autopsy,[2, 4-14] clinical renal disease rarely occurs. We report here a case of intravascular lymphomatosis presenting with bilateral renal enlargement and renal insufficiency.

Case report

A 50 year old male was admitted to King Chulalongkorn Memorial Hospital because of prolonged fever, bilateral renal enlargement and hepatosplenomegaly. Two months prior to admission, he had fever, a dry cough and was admitted to a provincial hospital. Physical examination revealed hepatosplenomegaly. Chest X-rays revealed minimal infiltration of the right upper lung. Liver function tests showed increased transaminase enzymes. Blood culture was negative. Various regimens of antibiotics were administered without improvement. Liver biopsy showed nonspecific inflammation without granuloma or malignant cells. Eventually dexamethasone was given and the patient improved dramatically. During steroid tapering, he experienced confusion and dyspnea. Thereupon he was transferred to King Chulalongkorn Memorial Hospital.

On admission the patient was stuporous. There were neither localized nor meningeal signs. Physical examination did not reveal either pallor or icterus. The liver was firm and smooth to the touch and palpable at 3-4 centimeters below the right costal margin. The spleen was palpable 2 centimeters below the left costal margin. Bilateral renal enlargement was detected by bimanual palpation. No lymphadenopathy was noted.

A complete blood count revealed hemoglobin at 11.3 g/dl, leukocyte count at 6.72 x 10^9/liter with 94% neutrophils, 3% band form, 2% lymphocytes, 1% monocytes and platelet count at 95.3 x10^9/liter. The peripheral blood smear showed hypochromic, microcytic red blood cells, anisopoikilocytosis 2+, target cells 3+. The urinalysis showed numerous red blood cells and proteinuria 1+. The blood urea nitrogen was 59 mg/dl, creatinine 4.6 mg/dl. Serum electrolytes showed sodium at 128 mEq/L, potassium at 3.9 mEq/L, chloride at 98 mEq/L and CO_2 at 10 mEq/L. Liver function tests and serum creatine phosphokinase were normal. Serum albumin and globulin were 2.6 and 2.2 g/dl respectively. Serum uric acid was 29.8 mg/dl, calcium 11.5 mg/dl, phosphate 6.8 mg/dl, and lactate dehydrogenase was 1544 units/liter. (normal level < 200 units/liter) Serum prothrombin time was prolonged for 5 seconds, and activated partial thromboplastin time was normal. Hemoglobin electrophoresis revealed homozygous hemoglobin E.

The chest X-rays demonstrated a faint nodule in the right upper lung. Magnetic resonance imaging of the whole abdomen showed moderate liver enlargement, moderate to marked splenomegaly, and bilaterally enlarged smooth kidneys without space occupying lesions (Figure 1). There was no lymphadenopathy. Otherwise, the abdomen was unremarkable.

The results of twice performed bone marrow examinations were unremarkable. Explorative laparotomy biopsy revealed the left kidney enlarged to a size of 16x8x7 centimeters, of dark red coloration and friable consistency. Histological examination of the excised renal tissues showed prominent infiltration of abnormal cells in small arteries and venules and also in the glomerular capillary lumen (Figure 2). The abnormal cells were positive for CD45 and CD20 (Figure 3). Immunofluorescent staining was negative for IgG, IgM and IgA. The pathological diagnosis was intravascular malignant lymphoma, B-cell lineage.

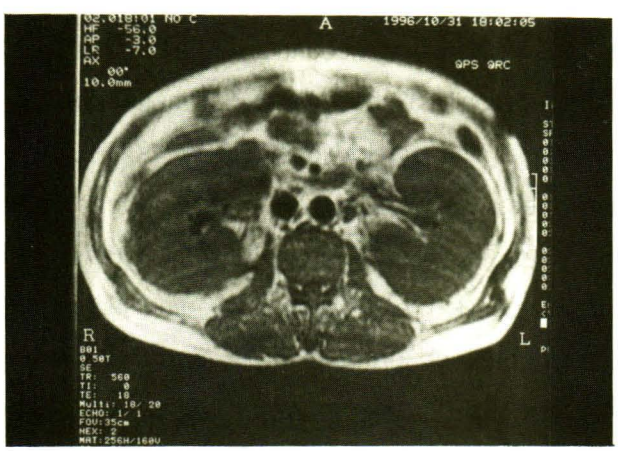

Figure 1. Renal Magnetic Resonance Imaging studies, performed on admission, showed bilaterally enlarged kidneys; the right kidney measured 17 cm. and the left kidney 19cm.

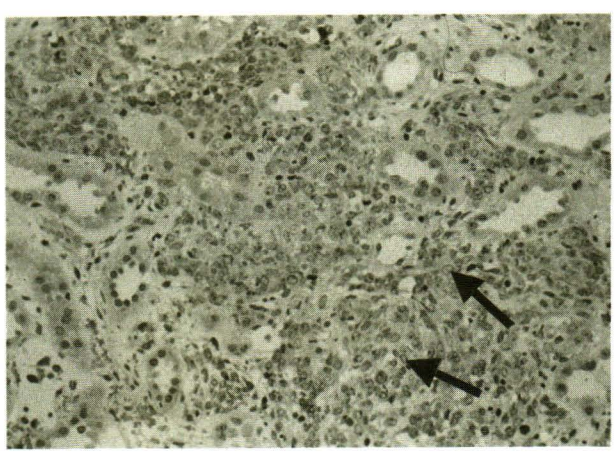

Figure 2. Histological features of the intravascular lymphoma in the kidney. Note the large lymphoid cells diffusely filling the dilated blood vessels in the interstitium. (Arrow)

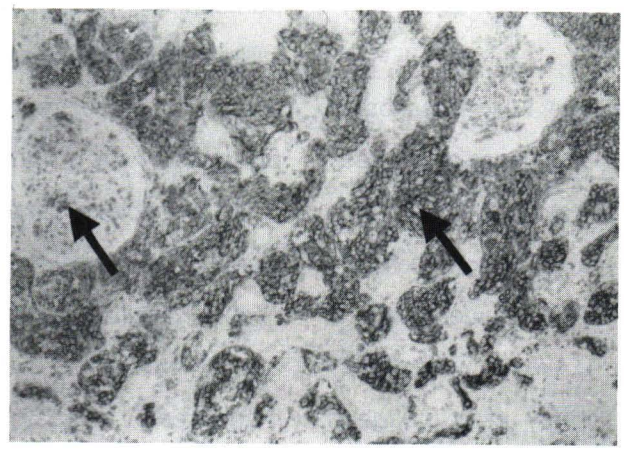

Figure 3. Renal intravascular lymphoma immunostained with anti-CD20. Note the positive lymphoma cells in most blood vessels and in some glomerular capillaries (Arrow). The tubules are not stained.

The patient was treated with a combination of cyclophosphamide, adriamycin, vincristine, prednisolone (CHOP regimen). His state of consciousness improved. However, he still had fever and finally passed away due to septic shock one month after admission.

Discussion

Intravascular lymphomatosis (IVL) is a rare form of lymphoma characterized by a high incidence of central nervous system and cutaneous abnormalities, an aggressive clinical course, and proliferation of mononuclear neoplastic cells in the blood vessels of entire organs resulting in thrombosis of capillaries, venules and the arteriole lumen. The malignant cells are predominantly found within the vascular lumen, although extravascular extension may occur.[15] Despite the large number of intravascular neoplastic cells, such cells are rarely found in peripheral blood smears.[6,16] Bone marrow and lymph nodes are typically uninvolved. The clinical presentations, as the prolonged fever and encephalopathy in our patient, are similar to the aforementioned reports. Lymph nodes and bone marrow were unaffected and there were no abnormal cells in the peripheral blood smears. The interesting manifestation in our patient was the renal involvement, not commonly described.

Renal involvement of malignant lymphoma is usually subclinical. However, the patient may have flank pain, hematuria, abdominal distention, or a palpable abdominal mass. Acute renal failure, as an initial presentation, is rarely reported. Nevertheless, the kidneys are common sites of involvement in postmortem studies. Martinez-Maldonado M. et al [17] reported 49 cases of malignant lymphoma , with renal involvement found in 42.3% of the postmortem examinations. Renal insufficiency, however, occurred in only 14 % and uremia in only 1 case. Microscopically, the renal interstitium was usually infiltrated with lymphomatous cells whereas glomeruli and intrarenal vessels were spared. Interstitial infiltrating cells may compress the renal tubules and cause renal

failure. Early recognition and prompt treatment usually improve renal function.

Postmortem examination of IVL cases mostly showed renal involvement, although those cases had no renal manifestations. In contrast to the malignant lymphoma, the IVL usually had neoplastic cells of intrarenal vessels and glomeruli in the lumen, but not in the interstitial tissues (Table 1). We reviewed cases of IVL that involved the KUB (kidney-ureter-bladder) system (Table 2). There have been two cases of nephrotic syndrome. Both cases had bilateral renal enlargement and histopathology showed lymphoma cells in the glomerular capillary beds.[18,19] Rarely, IVL presents with renal insufficiency. Only 3 cases with renal insufficiency have been described in the literature. The first reported case of renal insufficiency had a mass in the right groin, enlarged prostate gland and a non - functioning right kidney. Finally the patient died from renal and heart failure. Histopathology of the kidney showed neoplastic cells in glomerular and peritubular capillaries. The prostate gland was also infiltrated by lymphoma cells.[14] Demirer et al reported another case of renal insufficiency. The patient presented with progressive dementia, low grade fever, palpable purpura and had serum creatinine of 3 mg/dl. The postmortem study showed intravascular neoplastic cells in many organs. Glomerular tufts were also involved.[3] Interestingly, most cases of IVL were diagnosed by autopsy. This may be due to variations in clinical presentations. The diagnosis can only be made by tissue biopsy. In our case, a definite diagnosis of IVL was made by surgical renal biopsy. Renal histopathology demonstrated a dissemination of lymphoma cells throughout the small and medium sized intrarenal vessels, with the interstitial tissues mostly spared. Some lymphoma cells were also observed in the glomerular capillary bed. Renal failure could be explained by intrarenal vessel occlusion. Hyperuricemia and hypercalcemia partly contributed to renal failure.

Table 1. Difference between renal involvement of malignant lymphoma and intravascular lymphoma.

	Malignant lymphoma	**Intravascular lymphoma**
Renal manifestation	Usually subclinical flank pain, palpable mass hematuria, acute renal failure	Usually subclinical nephrotic syndrome, hematuria, acute renal failure, prostate gland enlargement
Renal pathology		
Gross	Bilateral renal enlargement single or multiple mass	Bilateral renal enlargement
Microscopy	Mostly interstitial infiltration glomerulus and renal blood vessels are often spared	Intraluminal neoplastic cells in glomerular capillaries and intrarenal vessels are often seen
Treatment	Most cases respond to chemotherapy	Respond poorly to chemotherapy

Table 2. Reported cases of IVL that involved KUB system.

Author	Clinical features	Renal failure	Prostate gland Involvement	Renal pathology glom.	vasc.	T-I	Renal imaging	Other organ affected
Sheibani K.[2] 1986	Stroke	NA	NA	⊕	⊕	⊖	NA	Brain, heart lung, pancreas
Ben-Ezra J.[22] 1986	Urinary retention due to enlarged prostate gland	⊖	⊕	NA	NA	NA	NA	NA
Banerjee SS.[14] 1987	rt. groin mass, enlarged prostate gland, non-functioning rt. kidney	⊕	⊕	⊕	⊕	NA	NA	Brain, lung, adrenal Retroperitoneum, para-aortic LN
D' Agati V.[19] 1989	Nephrotic syndrome	⊖	NA	⊕	⊕	⊖	Bilateral renal enlargement	NA
Walker UA[1] 1994	Nephrotic syndrome and clinical features mimicking vasculitis	⊕	NA	⊕	⊕	⊕	Bilateral renal enlargement with renal artery involvement	Brain, lung, spleen, kidney, bone marrow
Demirer T[3] 1994	Dementia	⊕	⊕	NA	NA	NA	NA	Brain, heart, lung GI tract
Avihingsanon Y. 1998	Bilat. renal enlargement renal failure	⊕	NA	⊕	⊕	⊕	Bilateral renal enlargement	NA

NA= not available, glom.=glomeruli, vasc.=renal vessels, T-I=tubulointerstitium, + = present, - =absent

There have been different reports regarding the origin of the neoplastic cells. On the basis of histological, ultrastructural and immunologic data, some investigators have considered this neoplasm to be of endothelial origin.[6, 20-21] This conclusion is based on the intravascular distribution of the neoplastic cells and on ultrastructural evidence. The immunohistologic reactivity of the neoplastic cells with antibody to factor VIII-related antigen also supports the endothelial origin. Recently, many investigators described the neoplastic cells to be of lymphoid origin[2,9,11] based on findings of the intravascular neoplastic cells showing strong immunoreactivity with leukocyte common antigen (LCA) and the cells being negative for Ulex europaeus-I lectin, an endothelial antigen.[11] Furthermore, the neoplastic cells are negative for factor VIII-related antigen, whereas the normal endothelial cells of the vessel wall tested positive. The cells entrapped within platelet-fibrin thrombi also tested positive for factor VIII-related antigen. This is probably related to nonspecific adsorption of the antigen from serum or platelets. Sheibani et al[2] reported 3 cases of malignant angioendotheliomatosis in which immunophenotypic studies performed on snap-frozen tissue, showed B- and T-cell lymphoid origin. They suggested the term "angiotropic (intravascular) large-cell lymphoma" as a name suitable for this disease.

Summary

A case of IVL, presented with bilateral renal enlargement and renal failure was reported. Renal histopathology showed the proliferation of neoplastic cells of small and medium size blood vessels within the lumen. Immunohistochemical markers were positive for B-cell lineage. The patient did not respond to chemotherapy and expired after three months of illness. Renal enlargement and renal failure are rare manifestations of IVL. Definite diagnosis should be made by renal biopsy.

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