Case Report

Renal manifestations of angiotrophic lymphoma: clinicopathological features

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Key words: angiotrophic lymphoma; renal biopsy

Introduction

Angiotrophic lymphoma is a rare malignancy typically characterized by extensive proliferation of large, atypical mononuclear cells within small and medium-sized blood vessels. The first description dates back to 1959 by Pfleger and Tappeiner [1] who designated this disease as ‘angioendotheliomatosis proliferans systemicata’. Since then, several other terms such as neoplastic angioendotheliomatosis [2], proliferating angioendotheliomatosis [3] and intravascular endothe
tlioma [4] have been used to describe the condition.

Although the disease predominantly affects vessels in the skin and central nervous system, blood vessels in many other organs may be involved, leading to a wide array of clinical symptoms [5]. Without treatment, this condition is universally fatal and most cases are identified on postmortem examination. Some controversy existed about the origin of these neoplastic cells; however, more recent immunophenotyping and southern blot analysis have demonstrated these cells to be derived from lymphoid cells and monoclonal populations of both B or T cell lineage have been described [5–10].

In many case reports, renal involvement has been described [6,11] and in one recent publication [11], renal biopsy was suggested as a means of diagnosis as well as monitoring chemotherapy efficacy. We report a case of a patient who had combined neurological, systemic, and renal abnormalities, where diagnosis was made and therapy followed using renal biopsy. We then reviewed our hospital’s Pathology records over the previous 10 years for case identification and assessment of the presence or absence of renal manifestations as well as the presence of disease on histological evaluation of the kidneys.

Case report

A 38-year-old woman was admitted to a peripheral hospital in April 1995 for investigation of low-grade fever, malaise, lethargy, night sweats, abdominal pain, diarrhea, and a 25-pound weight loss. These symp
toms had been present intermittently in different combi
nations in the preceding 6 months. Basic laboratory/ radiological examinations during this period had included CBC, biochemical screen, upper GI series, small bowel follow-through, ultrasound of the abdo
men, and evaluation for autoantibodies, all of which were unremarkable aside from an abnormal CBC with normocytic, normochromic anaemia and persistent monocytosis on peripheral smear. During her admission at the peripheral hospital, she had further investigations including chest X-ray, upper and lower GI endoscopy with biopsy, head CT, and a bone-marrow aspirate and biopsy, all of which were unremarkable. Abdominal ultrasound repeated showed mild splenomegaly with approximate spleen size of 14.5 cm. While on a weekend pass, the patient suffered a generalized seizure and was subsequently transferred to our hospital for further evaluation. MRI performed at this time showed signal-enhancing foci within the deep white matter in a periventricular distribution adjacent to the frontal and occipital horns bilaterally. Cerebral angiogram was completely normal. Repeat bone
marrow examination revealed erythroid hyperplasia and monocytosis with no evidence of malignancy. CT of the abdomen showed hepatosplenomegaly, border
line enlargement of both kidneys, and small pericardial effusion without any lymphadenopathy. No cause could be identified for the patient’s symptoms and she was discharged from the hospital after a seizure-free period of 1 week.

Her difficulties continued soon after discharge and she had further neurological symptoms over the follow
ning 3 months, including pain and paraesthesia in her limbs, speech disturbance, headaches, confusion, and alteration of level of consciousness requiring further hospital admissions. In October of 1995, about 12 months into her illness, she was once again admitted to hospital because of systemic symptoms and confu-
sion. Repeat MRI showed similar lesions as described previously. Gallium scan revealed faint diffuse increased uptake in both lung fields as well as increased uptake in both kidneys. At this time, her renal function had become abnormal with creatinine rising to 367 μmol/l, prompting a nephrological consultation. Urinalysis revealed 1+ haematuria and 0.3 g/l proteinuria on dipstick, and microscopic examination, aside from rare granular casts and few hyaline casts, was otherwise unremarkable. In view of the presence of a systemic illness with enlarged kidneys, abnormal urinalysis, and renal insufficiency, consideration had to be given to an infiltrative/malignant process and therefore a renal biopsy was performed.

Following the renal biopsy, which established the diagnosis, the patient received a combination of CHOP chemotherapy and radiation, to which she responded quite well with resolution of all neurological and systemic symptoms and normalization of renal function. Repeat gallium scan no longer demonstrated areas of increased uptake in her lungs or kidneys, and repeat kidney biopsy confirmed the disease to be in remission. The patient is now alive and well and remains free of symptoms.

**Renal biopsy**

On light-microscopy three glomeruli were noted and appeared unremarkable. Some tubules showed cytoplasmic vacuolization and few were associated with lymphomonomocytic infiltrate. The most prominent feature was the presence of marked mononuclear cell infiltrate in the interstitium of the cortex and medulla. Infiltrates were primarily large cells with vesicular nuclei and 1–2 nucleoli. They showed irregular nuclear borders. Cytoplasm was variable and poorly demarcated. Most cells appeared to be in the peritubular vessels; however, some were noted outside the vessel wall (Figure 1, 2). Occasional mitotic activity was noted. Immunohistochemical stains were strongly positive for leukocyte common antigen and for Pan-B cells. Some T cell population was also noted. Kappa and lambda stains were inconclusive.

On electron-microscopy, glomerular capillary basement membrane as well as endothelial and epithelial cells were unremarkable. A few large atypical mononuclear lymphoid cells were noted in the glomerular capillaries and in the peritubular vessels (Figure 3). They show irregular convoluted nuclei with nucleoli. Cytoplasm was abundant and showed rough and smooth endoplasmic reticulum with few mitochondria. Similar cells were also noted outside the vessel wall. Overall, the morphological features were consistent with angiotrophic lymphoma, large B cell type.

On repeat biopsy, no evidence of intravascular or interstitial mononuclear cell infiltrate was seen and histology was reported as normal (Figure 4).

**Discussion**

Angiotrophic lymphoma is a rare neoplasm of the B or T cell lineage, and diagnosis is usually made on post-mortem examination [6]. This condition is very difficult to diagnose since the peripheral blood film does not show circulating lymphoma cells nor does this form of lymphoma tend to affect the patient’s bone marrow or lymph nodes. Despite usual CNS involvement, examination of cerebrospinal fluid has been generally disappointing and fails to demonstrate malignant cells, and therefore tissue diagnosis can presumably only be made on histological evaluation of the neural tissue involved. The latter approach has
Fig. 2. Kidney biopsy. Atypical mononuclear cells with vesicular nuclei and nucleoli in the interstitium and inside small capillaries (arrows) (H&E × 400).

Fig. 3. Kidney biopsy. Peritubular vessel with two large atypical lymphoid cells (EM × 2500).

proven to be usually impractical and not pursued. There have been four previous reports of an antemortem diagnosis by renal biopsy [11–14]; in three the presenting renal manifestation had been nephrotic-range proteinuria and in the fourth acute renal failure was the predominant presenting feature similar to that in our feature case. It has been suggested in a recent publication [11] that renal biopsy would be the most appropriate means of establishing the diagnosis and following response to chemotherapy; however, this study was based on a single case. We reviewed our hospital Pathology records over a 10-year period (January 1986 to January 1996) for case identification and assessment of clinical and pathological renal manifestations of angiotrophic lymphoma. The results are summarized in Table 1. There were overall five cases identified, including the one described. In all but one, diagnosis was made on post-mortem examination; however, in one of the four autopsy cases a hint to the diagnosis was suggested on antemortem spinal cord
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Fig. 4. Kidney biopsy. Post-chemotherapy; note disappearance of atypical interstitial mononuclear-cell infiltrate (H&E × 160).

Table 1. Patient demographics, renal and non-renal manifestations, mode of diagnosis, evidence of renal involvement, and lymphoma cell type

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Presenting SX.</th>
<th>Renal abnormalities</th>
<th>Diagnosis</th>
<th>Renal involvement</th>
<th>Cell type</th>
</tr>
</thead>
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<tr>
<td>38</td>
<td>F</td>
<td>Neurological/systemic/renal</td>
<td>Renal insufficiency, haematuria, proteinuria</td>
<td>Renal biopsy</td>
<td>Yes</td>
<td>B cell</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>Neurological</td>
<td>Not available</td>
<td>Spinal cord lesion biopsy</td>
<td>Yes</td>
<td>T cell</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>Neurological/systemic</td>
<td>Renal insufficiency, haematuria, proteinuria</td>
<td>Autopsy</td>
<td>Yes</td>
<td>B cell</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>Neurological/systemic</td>
<td>Renal insufficiency, haematuria, proteinuria</td>
<td>Autopsy</td>
<td>Yes</td>
<td>B cell</td>
</tr>
<tr>
<td>77</td>
<td>F</td>
<td>Neurological</td>
<td>Haematuria, proteinuria</td>
<td>Autopsy</td>
<td>Yes</td>
<td>Not available</td>
</tr>
</tbody>
</table>

As is well demonstrated by our case, establishing diagnosis could be extremely difficult, and diagnosis considerably delayed in most cases until autopsy. We therefore propose that renal biopsy should be the modality of choice in establishing this diagnosis (excluding patients with skin involvement) whereby histological assessment can be obtained with minimal risk of complications, since the kidneys tend to be involved in the majority of cases if not all. Also, renal biopsy provides a convenient means of monitoring chemotherapeutic response in conjunction with clinical and biochemical evaluation of the patient. With expediting the establishment of appropriate diagnosis, renal biopsy could also potentially result in improvement of patient outcome by allowing initiation of chemotherapy at earlier stages of the disease and with a smaller burden of malignant cells.

In conclusion, a kidney biopsy provides the most appropriate and readily accessible organ for histological evaluation when the diagnosis of angiotrophic lymphoma is suspected, and additionally it can provide a means of assessment of efficacy of chemotherapy.
References


Received for publication: 29.5.96
Accepted in revised form: 16.9.96