Nephrotic Syndrome in a Patient with Intravascular Lymphomatosis

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Abstract

The association of malignancy with nephrotic syndrome and renal histopathologic abnormalities is well documented. We report a case of intravascular lymphomatosis (IVL) presenting as nephrotic syndrome which was diagnosed by renal biopsy. Histological examination of the renal biopsy specimens showed dissemination of neoplastic lymphoid cells throughout the glomerular capillary bed. These tumor cells were positive for CD20. Since the nephrotic syndrome improved with treatment of the lymphoma, intravascular lymphomatosis may well have played an important role in the pathogenesis of minimal change nephrotic syndrome in this patient. (Internal Medicine 42: 98-101, 2003)

Key words: fever, edema, hemophagocytosis, nephrotic syndrome, intravascular lymphomatosis

Introduction

The association of nephrotic syndrome and malignancies is a well-recognized phenomenon (1–4). However, glomerulopathies associated with lymphoid malignancies are relatively uncommon compared to carcinoma. The most common lymphoid malignancy related to glomerular lesions is Hodgkin's disease (5, 6), with the pathology being minimal change disease. Although there have been several case reports of nephrotic syndrome in patients with chronic lymphocytic leukemia (7), no other specific relationship between hematological neoplasms and glomerular diseases has been reported.

Intravascular lymphomatosis (IVL) is a rare disorder characterized by the proliferation of lymphoma cells within the lumens of small arteries, arterioles and capillaries throughout the body (8). The lymphoma cells most commonly spread within the central nervous system and the skin, whereas lymphoreticular organs such as the lymph node, bone marrow, spleen and liver are not typically involved. This peculiar location of lymphoma cells, inside small vessels without involvement of the lymphoreticular organs, makes it a difficult disease to diagnose ante mortem. The majority of cases have been diagnosed at autopsy.

Here, we report a case of intravascular lymphomatosis presenting as nephrotic syndrome. The diagnosis was made by renal biopsy. D'Agati et al and Nishikawa et al also reported a case of nephrotic syndrome in a patient with IVL which was also diagnosed by renal biopsy (9, 10). There are some similarities between these two cases and the current case both clinically and pathologically.

Case Report

A 58-year-old man was admitted to our hospital because of fever and edema of his lower extremities. Nine months before admission he was referred to our hospital for evaluation of fever. Because the test for antibodies against human T-cell lymphotropic virus type I (HTLV-1) was positive and the level of lactate dehydrogenase was elevated, the patient was examined for occult adult T-cell lymphoma (ATL). Bone marrow examination, total body computed tomography (CT) and gallium scan failed to demonstrate any abnormalities. Since the diagnosis of ATL was not confirmed, chemotherapy was not done. A low dose of prednisolone was administered as palliative therapy. His fever soon disappeared after commencing oral administration of 20 mg of prednisolone daily. Two weeks prior to admission, he noticed edema of his lower extremities in addition to the reappearance of fever.

On physical examination, his body temperature was 38.5°C. No lymphadenopathy or organomegaly was noted. On auscultation, neither fine nor coarse crackles were audible in the lung field. There was edema of the lower extremities. No significant skin lesions were found. Neurological findings

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were normal. Laboratory tests revealed a typical nephrotic state: urinary protein, 3.85 g/day; serum total protein, 4.6 g/day; and total cholesterol, 276 mg/dl. Other results included: white blood cell count 3,300/μl; hemoglobin, 7.5 g/dl; platelets, 12.1×10⁴/μl; alanine aminotransferase, 11 IU/l; asparate aminotransferase, 45 IU/l; lactate dehydrogenase, 4,321 IU/l; blood urea nitrogen, 13 mg/dl; creatinine, 0.7 mg/dl; triglyceride, 109 mg/dl; ferritin, 380 ng/ml; C-reactive protein, 6.8 mg/dl; and soluble IL-2 receptor, 3,550 U/ml. The bone marrow was normocellular and there were findings of hemophagocytosis. Resting arterial blood gases on room air showed a PaO₂ level of 60 mmHg, and a PaCO₂ level of 23.5 mmHg, although the patient did not complain of any symptoms. A chest radiograph and CT scan revealed interstitial shadows throughout both lung fields (Fig. 1). Mild splenomegaly was detected by abdominal ultrasonography but no para-aortic lymphadenopathy was found.

Transbronchial lung biopsy was performed first. The specimens documented the presence of atypical mononuclear cells within the alveolar capillary lumens. This finding was suspicious of intravascular lymphomatosis. However, since further studies, including immunohistochemical stain, failed to identify these atypical cells, the possibility of lung invasion arising from other malignancies could not be ignored.

To elucidate the cause of nephrotic syndrome, renal biopsy was then performed. On microscopic examination, the glomerular capillary lumens were filled with large atypical mononuclear cells. These neoplastic cells were characterized by large hyperchromatic nuclei with rich nucleoli, scanty cytoplasm, and mitotic activity (Fig. 2). Similar neoplastic cells were seen surrounding the interstitial capillaries and they focally extravasated into the interstitium. Immunohistochemistry showed that these cells were strongly positive for the B cell marker CD20 (Fig. 3). In contrast, they were nonreactive with the T cell markers CD3 and UCHL-1. Under electron microscopy, large intracapillary cells with features identical to those of neoplastic lymphoid cells were visible (Fig. 4). The glomerular basement membrane was

Figure 1. Computed tomography of the chest showing interstitial change.

Figure 2. Glomerular capillary lumens contain numerous neoplastic cells with large hyperchromatic nuclei and indistinct cytoplasm (periodic acid-Schiff stain, ×100).

Figure 3. Lymphoma cells are positive for CD20 (arrows) (CD20, ×150).

Figure 4. Electron micrography shows intracapillary lymphoma cells with folded nuclei and numerous nucleoli (×1,900).
normal in thickness. Diffuse effacement of the foot processes was seen over the glomerular capillaries in which neoplastic cells were evident. A diagnosis of intravascular lymphomatosis was made. Combination chemotherapy (comprising cyclophosphamide, vincristine, adriamycin, etoposide, mitoxantrone, ranimustine, vindesine, and prednisolone) was started. The levels of PaO₂ increased gradually and proteinuria disappeared 6 weeks after chemotherapy had been initiated. A chest CT scan was then obtained again, and it showed the complete disappearance of the interstitial shadows in the lung field.

Discussion

We report a unique case of intravascular lymphomatosis (IVL) presenting as nephrotic syndrome. The first case of IVL associated with nephrotic syndrome was reported by D'Agati et al, and they were also the first to make a diagnosis of IVL by renal biopsy (9). Nishikawa et al also reported a case of IVL manifesting as nephrotic syndrome which was diagnosed by renal biopsy (10). The histologies of both cases were minimal change disease, quite similar to the findings in the current case.

In the present case, remission of the nephrotic syndrome was observed after successful therapy for the lymphoma. This fact could be regarded as strong supporting evidence of the relationship between intravascular lymphomatosis and nephrotic syndrome. It has been suggested that lymphoma cells may release a cytokine which is involved in the pathogenesis of minimal change and which increases the glomerular membrane permeability (11, 12). This lymphokine is referred to as a vascular permeability factor (VPF) (13), however it has not yet been identified. We cannot refute the possibility that the IVL and minimal change disease occurred simultaneously in the current patient simply by chance. However, on electron microscopic examination, there was diffuse effacement of the foot processes overlying capillaries which were occupied with neoplastic cells. In contrast, foot processes which lay above uninvolved capillaries remained intact. These findings support the idea that the lymphocyte product released locally at the level of the glomerular capillaries had a role to play in the pathogenesis of minimal change disease in this patient.

Unfortunately, we failed to identify the atypical mononuclear cells seen within the alveolar capillary lumens on the lung biopsy specimen, but considering that the disappearance of proteinuria and the improvement of hypoxemia were observed concurrently, both abnormalities of the kidney and the lung are possible to regard as the involvement of IVL. In addition, chest CT scan showed no interstitial change in the lung field following chemotherapy for lymphoma. These findings may confirm the lung invasion of IVL in this case.

Another distinct feature of this case is the findings of hemophagocytosis in the bone marrow. Murase et al noted that diffuse large B-cell lymphoma with hemophagocytic syndrome, which has been mainly reported in Asia, should be regarded as a distinct variant of intravascular lymphomatosis. They proposed to refer to this variant as the Asian variant of intravascular lymphomatosis (AIVL) (14). Recently, they established diagnostic criteria for AIVL (15, 16). From their point of view, our case completely satisfies these criteria, and can be considered as AIVL.

IVL is a rare form of malignant lymphoma with an interesting but very confusing clinical presentation. It is a very aggressive disease, with death occurring rapidly in most cases. The diagnosis is often not made until autopsy (17, 18). Such a poor prognosis could be due to the delay in diagnosis and failure to receive early appropriate treatment (19). In fact, the present patient was not diagnosed as IVL after nine months when he referred for evaluation of fever. Complete remission can be achieved by the early initiation of combination chemotherapy (10, 20, 21). Cheng et al reported a case of IVL diagnosed by renal biopsy, but their patient showed no abnormal findings on urinalysis (22).

In summary, the possibility of intravascular lymphomatosis should be taken into consideration in patients with nephrotic syndrome, and renal biopsy seems to be a good tool with which to make an early diagnosis.

References

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