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Case study

# Minimal-change nephrotic syndrome preceding Hodgkin lymphoma by 5 years with expression of tumor necrosis factor α in Hodgkin-Reed-Sternberg cells☆

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**Summary** A 76-year-old man developed minimal-change nephrotic syndrome (NS). After treatment with prednisolone failed to induce sustained remission, cyclosporin was added. The NS improved, and prednisolone and cyclosporin doses were gradually decreased. However, he had repeated relapses of the syndrome, and at each relapse, the drug doses were increased. After 5 years, the patient developed left inguinal lymphadenopathy. The histological diagnosis was mixed cellularity classical Hodgkin lymphoma. He received 6 courses of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), and mixed cellularity classical Hodgkin lymphoma and NS both showed complete response. Although the association between Hodgkin lymphoma and minimal-change NS is well known, the pathogenesis is unknown. To the best of our knowledge, this is the first case report of minimal-change NS associated with Hodgkin lymphoma in which Hodgkin-Reed-Sternberg cells were immunostained for tumor necrosis factor-α (TNF-α) clearly demonstrating that Hodgkin–Reed–Sternberg produced TNF-α and in which the plasma level of TNF-α normalized after improvement of Hodgkin lymphoma by chemotherapy. The production of TNF-α by Hodgkin–Reed–Sternberg cells might play a key role as a potential mediator of minimal-change NS.


## 1. Introduction

Although it is well recognized that many types of glomerulonephritis are associated with classical Hodgkin lymphoma (CHL), the incidence of nephrotic syndrome (NS) is low and is estimated to be about 0.5 to 1% [1]. In two largest studies of 1700 Hodgkin lymphoma (HL) patients, 2 glomerulopathies were significantly associated with CHL:

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amyloidosis (0.1% of cases) and minimal-change NS (MCNS) (0.4% of cases) [2,3].

## 2. Case report

In November 2003, a 76-year-old man suffering from bilateral leg edema was admitted to our hospital. On admission, weight gain was 5 kg, blood pressure was 120/64 mm Hg, and physical examination did not show any enlargement of the liver, spleen, or lymph nodes. Urinalysis showed massive proteinuria (7.14 g/day). Total serum protein was 4.2 g/dL (reference range, 6.3–8.0 g/dL), serum albumin 1.5 g/dL (reference range, 3.5–5.0 g/dL), serum total cholesterol 640 mg/dL (reference range, 140–220 mg/dL), serum blood urea nitrogen 5 mg/dL (reference range 8–20 mg/dL), and serum creatinine 0.6 mg/dL (Cre) (reference range, 0.5–1.2 mg/dL). Total complement and C3 and C4 components were in the reference range. Serological studies including antinuclear and anti-DNA antibodies, rheumatic factor, and anti-streptolysin O titer were normal. A kidney biopsy was performed. Light microscopy showed normal glomeruli (Fig. 1A). Extensive loss of epithelial foot processes was indicated by electron microscopy (Fig. 1B), and negative immunofluorescence studies for immunoglobulin and complement led to the diagnosis of MCNS. Prednisolone therapy was started with 50 mg/d and the NS improved. Subsequently, the patient was placed on a long-term corticosteroid treatment, which was slowly tapered. In August 2004, a relapse occurred with proteinurea 2410 mg/dL. Methylprednisolone pulse therapy (1 g/day for 4 days) was given. However, there was an incomplete response to this therapy, and therefore cyclosporin 175 mg/day was included. The condition of proteinuria then resolved and the cyclosporin and prednisolone doses were gradually reduced. However, there were repeated relapses of the NS, and at each relapse the drug doses were increased.

Five years later, in July 2008, another relapse occurred and an enlarged left inguinal lymph node of 3 cm was noted. Laboratory data were as follows: white blood cell count $7.5\times10^9$/L (76.5% neutrophils and 17.0% lymphocytes), hemoglobin 108 g/L, platelet count, $429\times10^9$/L, total serum protein 4.9 g/dL, serum albumin 1.4 g/dL, total cholesterol 351 mg/dL, blood urea nitrogen 9 mg/dL, Cre 1.0 mg/dL, lactate dehydrogenase 161 IU/L (reference range 130-250 IU/L), and C-reactive protein 11.61 mg/dL (reference range <0.25 mg/dL). The plasma level of tumor necrosis factor-α (TNF-α) was elevated to 5.8 pg/mL (reference range <0.6–2.8 pg/mL) [4]. Computed tomography scans showed lymphadenopathy of the left inguinal region and external iliac region. A biopsy specimen obtained from the left inguinal lesion showed numerous mononuclear Hodgkin and multinuclear Reed-Sternberg (HRS) cells mixed with lymphocytes, plasma cells, and eosinophils (Fig. 2). Immunohistochemical analysis showed that the HRS cells were positive for CD15 and CD30. They were also positive for TNF-α (detected with antibody 52B83; Santa Cruz Biotechnology, Santa Cruz, CA, USA) (Fig. 3). Southern blot analysis showed clonal rearrangement of neither the immunoglobulin heavy chain gene nor the T-cell receptor gene. Clinical staging, comprising bone marrow biopsy and

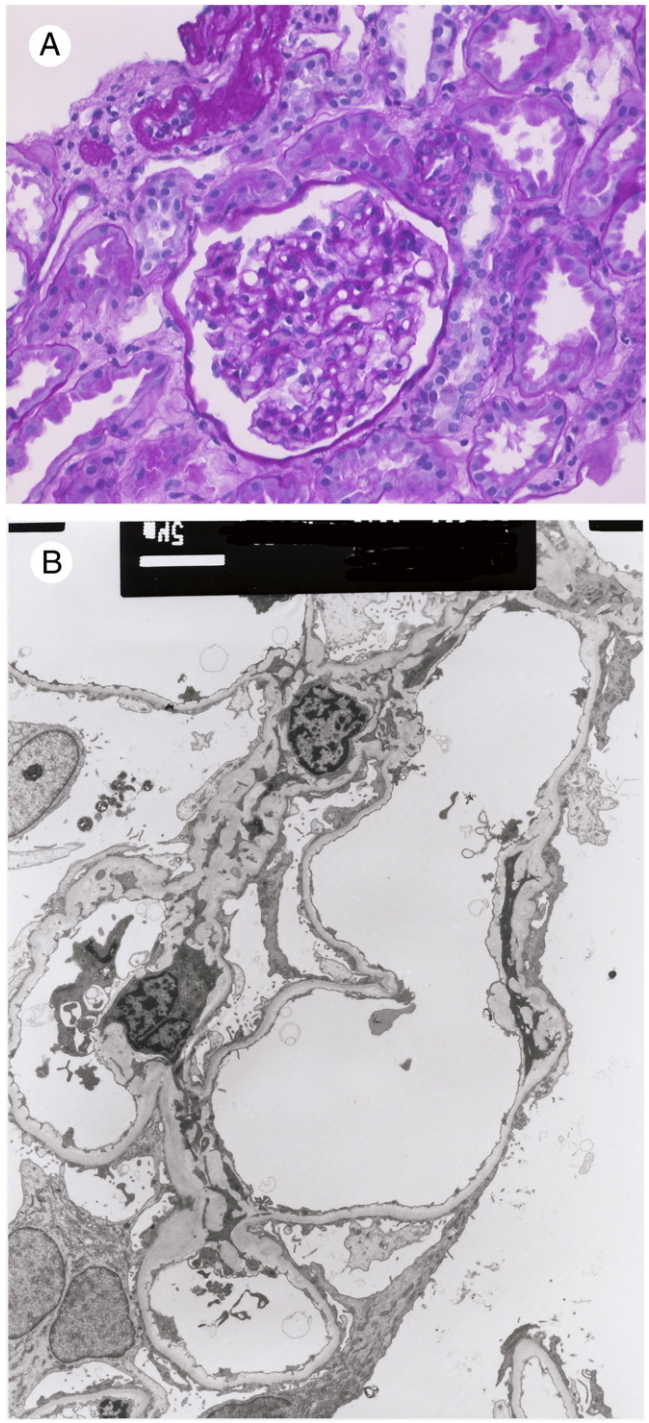


**Fig. 1** (A) Light micrograph of the patient showing a normal glomerulus. Hematoxylin-eosin stain (original magnification ×240). (B) Electron micrograph of a glomerulus showing extensive fusion of the foot processes of the visceral epithelial cells.