Membranoproliferative Glomerulonephritis Following Gemcitabine and Vinorelbine Chemotherapy for Peritoneal Mesothelioma

The most common types of malignancy-associated glomerular disease are membranous glomerulonephritis, minimal change glomerulopathy, and, rarely, membranoproliferative glomerulonephritis (MPGN) (1,2). We report a case of MPGN in a patient with peritoneal mesothelioma who responded to treatment with gemcitabine and vinorelbine.

A 29 year old Caucasian male, diagnosed in November 1996 with inoperable peritoneal mesothelioma (CA 125-positive), was treated without response for 2 months with doxorubicin and the multidrug resistance modulator, GG918 (Glaxo Wellcome, Inc., Research Triangle Park, NC) in a Phase I trial. In April 1997, he was enrolled in another Phase I trial and received gemcitabine at 1500 mg/m² and vinorelbine at 15 mg/m² on days 1 and 15 of a 28-day cycle. At this time, all his laboratory studies, including renal function, were normal.

After nine cycles of treatment, he improved symptomatically and had a minor response. In January 1998, the gemcitabine and vinorelbine dosages were increased to 2250 mg/m² and 20 mg/m², respectively. In February 1998, a progressive decline in serum albumin level was noted, which was followed in March 1998 by 2+ hematuria. In April 1998, a partial response was achieved. However, within weeks of receiving cumulative doses of gemcitabine 45 000 mg/m² and vinorelbine 430 mg/m², increasing abdominal girth, bipedal edema and a blood pressure of 186/112 were noted.

Laboratory analyses revealed the following abnormal values: hemoglobin 10.4 g/dL; albumin 1.3 g/dL; LDH 335 IU/L, and serum CA 125 80 U/mL. Urinalysis revealed 3+ occult blood, 2+ protein with fine and coarse granular casts on microscopy. The blood smear and creatinine were normal. A 24-hour creatinine clearance was 88 mL/min with 4.3 g/L of protein. A renal ultrasound was normal.

Renal biopsy showed no invasion by tumor and immunohistochemical staining for CA 125 was negative. Diffuse endocapillary mesangial cell proliferation and accentuation of the glomerular tuft were present (see Fig. 1, A). Type I MPGN was confirmed by silver stain. Electron microscopy demonstrated partial mesangial interposition within electron dense subendothelial and intramembranous deposits (see Fig. 1, B).

After chemotherapy was discontinued and antihypertensives (fosinopril, amlodipine, and clonidine), furosemide, and prednisone instituted, the 24-hour urine protein decreased to 1.4 g, but serum albumin remained low at 1.8 g/dL. Later, the patient developed fatal bronchopneumonia.

There is no previous report of the association of MPGN with peritoneal mesothelioma and his response to chemotherapy was documented prior to the development of MPGN. Gemcitabine is associated with renal dysfunction (3–5), unlike vinorelbine (6). Of 979 patients, enrolled in 22 studies, receiving single-agent gemcitabine (800–1250 mg/m²), on a days 1, 8, and 15 schedule every 28 days, 35.6% had proteinuria and 30.7% had hematuria (3). Among these cases, the majority experienced grade I proteinuria (32.9%) and microscopic hematuria (27.6%). Hemolytic-uremic syndrome was documented or suspected in six (0.6%) (3).

High doses and prolonged administration of gemcitabine and vinorelbine were given in this Phase I study (7). Our patient’s MPGN was thought to be due to gemcitabine and recent studies support that prolonged administration of gemcitabine may adversely affect renal function (4,5). Although clinically significant renal dysfunction is unusual in patients treated with gemcitabine, we recommend monitoring of renal function, particularly in patients who receive long-term treatment.

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Fig. 1. Renal histopathology demonstrating membranoproliferative glomerulonephropathy (MPGN). A) The glomeruli show cellularity, lobular accentuation, segmented increase in mesangial matrix, and thickening of the capillary wall characteristic of MPGN, type I (hematoxylin–eosin; magnification ×200). B) Electron micrograph demonstrating splitting of the basement membrane and mesangial cell cytoplasmic interposition with formation of new basement membrane-like material (large arrow). Small electron dense subendothelial deposits are also present as indicated by small arrows (US = urinary space; CL = capillary lumen; M = mesangial cell; magnification ×4400).
REFERENCES


NOTES

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