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Nephrotic syndrome associated with gemcitabine use in a patient with ovarian cancer

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Summary

Background:

Here we present a patient who developed nephrotic syndrome associated with gemcitabine use.

Case Report:

Gemcitabine therapy was initiated following tumor recurrence in a patient with ovarian cancer, who was previously treated twice with carboplatin and paclitaxel. Radiological findings waned and tumor marker concentrations decreased after gemcitabine treatment. However, edema and ascites development was observed on the fifth treatment cycle. Laboratory results revealed increased blood urea nitrogen and creatinine levels, decreased serum albumin concentrations, and increased 24-hour urinary protein excretion. Renal biopsy findings were compatible with membranous glomerulonephritis. Gemcitabine administration was stopped and the cyclophosphamide and steroid therapy were initiated. The symptoms and findings disappeared after the cessation of gemcitabine and immunosuppressive treatment.

Conclusions:

Gemcitabine treatment may be associated with proteinuria to the extent of nephrotic syndrome.

key words:

gemcitabine • nephrotic syndrome • ovarian cancer

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BACKGROUND

Gemcitabine (2',2'-difluorodeoxycytidine) is a novel deoxycytidine nucleotide analogue with a broad spectrum of antineoplastic effects [1,2]. It is most commonly used in the treatment of non-small-cell lung cancer, pancreatic and bladder cancers [3]. It is also used in the treatment of recurrent platinum-resistant ovarian and metastatic breast cancer, either as a single agent or in combination with other agents [4]. When used as a single agent, the usual dose is 1250 mg/m² on days 1, 8 and 15 in a 28-day cycle.

The common adverse effects associated with gemcitabine are bone marrow suppression, nausea, vomiting, allergic rash, bronchospasm, flu-like symptoms, alopecia, somnolence, oral toxicity, constipation and hypotension. Elevations of hepatic transaminases are usually transient and do not require dose restriction. Mild and transient proteinuria and hematuria are reported in approximately half of the patients and very few patients develop hemolytic uremia. Thus, it is advised that gemcitabine should be used with caution in patients with impaired renal function [1]. However, nephrotic syndrome associated with the use of gemcitabine is rarely reported in the literature. Here, we report the case of a patient with nephrotic syndrome associated with gemcitabine treatment.

CASE REPORT

A 65-year-old female patient initially admitted to hospital due to abdominal pain underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH+BSO) due to a cystic mass with solid components detected in her left ovary in November 2004. Histopathological examination revealed clear cell carcinoma. The patient was staged as Stage IIIC and adjuvant chemotherapy with paclitaxel (175 mg/m²) and carboplatin (400 mg/m²) was started and repeated every 21 days. The initial level of the biological tumor marker CA-125 decreased from 322.7 U/ml to 23.12 U/ml following 6 cycles of chemotherapy, which terminated in February 2005. No recurrent pelvic mass was detected in the ultrasonographic follow-ups. During the treatment period, peripheral edema or ascites accumulation were not observed. Serum albumin, creatinine and lipid parameters were within normal limits.

After nearly 2 years of follow-up in remission, the patient was admitted to hospital in January 2007 with complaints of dyspnea and abdominal pain. Her physical examination revealed pulmonary rales and abdominal tenderness. Malignant ¹⁸F-fluorodeoxyglucose (FDG) uptake was detected in the intraabdominal lymph nodes, pericardial, pleural and peritoneal regions in the positron emission tomography/computed tomography (PET/CT) scan. Serum CA-125 level was 83.98 U/ml. The patient had minimal peripheral edema, and serum albumin, creatinine and lipid parameters were within normal limits. The patient was evaluated as having recurrent metastatic disease, and paclitaxel and carboplatin were re-administered at the same doses. However, since interval evaluation following the second cycle revealed a serum CA-125 level of 191.20 U/ml and enlargement of lymph nodes on ultrasonographic examination, paclitaxel and carboplatin treatment was considered unsuccessful and on April 2007 gemcitabine monotherapy

(1000 mg/m², on days 1, 8 and 15 in a 28-day cycle) was initiated. The patient's CA-125 concentration decreased to 69.60 U/ml, lymph node sizes apparently diminished and thus treatment with gemcitabine was continued. However, lower-extremity edema and abdominal distension developed after the fifth cycle of gemcitabine. Physical examination findings were pitting peripheral edema and abdominal dullness. Laboratory studies showed serum albumin level of 2.3 g/dL, serum creatinine level of 1.96 mg/dL, total cholesterol level of 293 mg/dL and serum triglycerides of 95.88 mg/dL. Computerized tomography and ultrasonography revealed normal kidney size and configurations. Urinalysis showed granulated casts and a urinary protein excretion over 300 mg/dL. Urine collection revealed 5600 mg of protein excreted in 24 hours. Renal biopsy was performed and the reported pathological diagnosis was membranous glomerulonephritis (Figures 1A, B). Gemcitabine therapy was terminated and steroid and immunosuppressive (cyclophosphamide) therapy was started.

On follow-up evaluations, the amount of protein excreted in 24 hours decreased to 30 mg/dL, serum albumin concentration increased to 3.34 g/dL, serum creatinine decreased to 1.26 mg/dL, and serum total cholesterol and triglyceride levels decreased to normal levels. The patient is currently followed-up in the medical oncology unit, her renal functions are within normal limits and she does not receive any chemotherapeutic agents.

DISCUSSION

The renal glomeruli are vulnerable to injury by a number of drugs and other toxic agents. Drug toxicity may occur by 1 of 2 basic mechanisms: direct, dose-related toxic injury; or indirectly with immunologically-mediated injury, which is largely dose-independent. Clinically, most drug-mediated glomerulopathies present as membranous nephropathy, usually with a frank nephrotic syndrome [5]. Gemcitabine is an antineoplastic agent widely used in the treatment of pancreatic, lung, breast, ovarian and some other types of cancers. The most common renal adverse effect is mild and transient proteinuria [1,6,7]. However, nearly all cases present with WHO classification grade I-II proteinuria, and proteinuria to the extent of nephrotic syndrome is rarely reported in the literature [6,7]. Although the cause of proteinuria is not clearly identified, mechanisms like immune dysregulation, autoimmunity or inadequate response to a foreign antigen may be involved. Specifically, platinum group chemotherapeutic agents may cause proteinuria [8]. Gemcitabine is a pyrimidine antimetabolite and has no structural or pharmacological similarity with the platinum group agents. Cytarabine is the agent most structurally related to gemcitabine and it is known to cause proteinuria and nephrotic syndrome. However, nearly all of the cases reported in the literature are patients who underwent autologous bone marrow transplantation and received cytarabine as consolidation therapy [9]. Cytarabine may not be solely responsible for the development of the nephrotic syndrome in these patients, as some of the drugs among the several other administered agents and the renal load increasing effect of the primary disease may also be pathogenetically involved. Thus, it is not possible to generalize that cytarabine's effect of causing nephrotic syndrome is a common group effect for these agents.

Figure 1AB. Findings of light microscopic view of renal biopsy in our patient; Nine of 30 glomeruli were totally sclerotic, cellular crescents in two glomeruli, two glomeruli adherent to Bowman capsule, thickening in basal membrane, minimal mesengial expansion and congestion in all glomeruli, eosinophilic protein vacuoles in proximal tubules, multifocal fibrosis in interstitial space, tubuler atrophiah, eosinophilic chronic inflammation and granular IgG, C3 and IgM deposits all along the glomerular capillary wall. These findigs were eligible with membranous glomerulonephritis.

Hemolytic uremic syndrome is the most perilous adverse effect of gemcitabine; its incidence in patients receiving gemcitabine is approximately 0.15% based on the reported cases in the literature [10]. In our patient, we could not detect any of the findings of hemolytic anemia (fragmented erythrocytes, increased lactate dehydrogenase enzyme activity, increased levels of bilirubin, increased numbers of reticulocytes and decreased levels of haptoglobin) that might suggest the presence of hemolytic uremic syndrome.

Underlying malignancies are also known to cause nephrotic syndrome. Nephrotic syndrome may develop as a paraneoplastic syndrome in ovarian malignancies. However, nephrotic syndrome usually presents before the diagnosis of ovarian disease [11,12]. Unlike these cases, in our patient nephrotic syndrome findings became apparent in the second year of the disease and after the initiation of gemcitabine therapy. Moreover, these findings waned after the cessation of gemcitabine administration and did not reoccur.

The differential diagnosis of nephrotic syndrome developing during gemcitabine treatment maybe delayed because the presence of edema and ascites accumulation is often attributed to the primary involvement of the disease, to diminished oral intake, to advanced age or to comorbidities such as hypertension, diabetes and vascular disease. When severe proteinuria develops due to a chemotherapeutic agent, cessation of antineoplastic agents is essential for the recovery of renal functions. Immunosuppressive therapy may also be indicated in patients who are deteriorating despite drug cessation.

CONCLUSIONS

Our findings indicate that gemcitabine treatment may be associated with proteinuria to the extent of nephrotic

syndrome. In cancer patients who develop severe proteinuria, gemcitabine use should also be considered among the possible causative factors in addition to other causes of proteinuria such as development of paraneoplastic nephrotic syndrome due to the primary malignancy.

REFERENCES:

1. Heinemann V, Hertel LW, Grindey GB, Plunkett W: Comparison of the cellular pharmacokinetics and toxicity of 2',2'-difluorodeoxycytidine and 1-β-D-arabinofuranosylcytosine. *Cancer Res*, 1988; 48: 4024–31
2. Huang P, Chubb S, Hertel LW et al: Action of 2',2'-difluorodeoxycytidine on DNA synthesis. *Cancer Res*, 1991; 51: 6110–17
3. Kaye SB: Gemcitabine: current status of Phase I and II trials. *J Clin Oncol*, 1994; 12: 1527–31
4. Lund B, Neijt JP: Gemcitabine in cisplatin resistant ovarian cancer. *Sem Oncol*, 1996; 23(Suppl.10): 72–76
5. Hill GS: Drug-associated glomerulopathies. *Toxicol Pathol*, 1986; 14: 37–44
6. Elsaid A, Khaled H, Gaafar R, Abdelazim H: Cytotoxic profile of gemcitabine in elderly patients. *Proc Am Soc Clin Oncol*, 2000; Abstract Book: 19
7. Rydzewski A: The nephrologist role in the oncology and haematology ward. *Rocz Akad Med Białymst*, 2004; 49: 135–38
8. Steward DJ, Mikhael NZ, Nanji AA et al: Renal and hepatic concentrations of platinum: relationship to cisplatin time, dose, and nephrotoxicity. *J Clin Oncol*, 1985; 3: 1251–56
9. Thomson M, de Arriba G, Ordi J et al: Acute myelogenous leukemia treated with daunomycin associated with nephritic syndrome. *Nephron*, 1989; 51(2): 261–64
10. Saif MW, McGee PJ: Hemolytic-Uremic Syndrome associated with gemcitabine: A case report and review of literature. *J Pancreas*, 2005; 6: 369–74
11. Forgy AP, Ewing TL, Flaningam J: Two paraneoplastic syndromes in a patient with ovarian cancer: Nephrotic syndrome and paraneoplastic cerebellar degeneration. *Gynecol Oncol*, 2001; 80: 96–98
12. Kim YT, Rha SY, Shim CY: A case of paraneoplastic nephrotic syndrome in a patient with ovarian carcinoma. *Yonsei Medical Journal*, 2003; 44: 539–43