Nephrotoxicity in a Patient Treated with Pemetrexed

Sir,

Pemetrexed is an antifolate agent approved for the treatment of non-small cell lung cancer. A 62 year old male was admitted to our hospital in December 2014. He was diagnosed with metastatic non-small cell lung cancer. He was treated with first-line chemotherapy, including paclitaxel infusions and carboplatin, every 3 weeks for four cycles; the disease had partially responded with good tolerance. That is why a maintenance monotherapy by pemetrexed was administered at a dose of 500 mg/m^2 (900 mg) every 3 weeks, together with folic acid supplements for a total of 3 cycles. Serum creatinine before pemetrexed administration was 0.8 mg/dl. It progressively increased to 2.4 mg/dl, and he developed anemia (hemoglobin was 9.7 g/dl) after third cycle infusion of pemetrexed. Pemetrexed was stopped, and the patient was referred to a nephrologist. On presentation, blood pressure was 140/80 mmHg, and physical examination was unremarkable. He appeared euvolemic clinically. Serum creatinine level was 2.2 mg/dl. A 24 h urine collection revealed a 0.7 g proteinuria without hematuria, glycosuria, leukocyturia, or proximal tubular dysfunction. Serum electrolyte levels and renal ultrasound were both normal. The patient underwent kidney biopsy. Light microscopy examination revealed ten glomeruli, three of those showed global sclerosis, and the remaining were normal. The interstitial tissue had focal edema with moderate infiltration with mononuclear inflammatory cells and fibrosis in approximately 40% of the cortex with moderate tubular atrophy and acute tubular injury. Artery walls are thickened by intimal fibrosis. The immunofluorescent examination showed negative expression of immunoglobulins IgG, IgA, IgM, complement fragments C3, C1q, and k, l light chains in glomeruli, tubules, and vessels. Electron microscopy examination was not performed [Figure 1]. The patient's serum creatinine level remained elevated, but stable, 5 months after discontinuation of pemetrexed treatment. Cases of renal impairment have been reported after pemetrexed treatment, usually accompanied by significant myelosuppression that reversed after discontinuation of the drug. Our patient developed irreversible kidney injury related to interstitial fibrosis and acute tubular necrosis following treatment with pemetrexed for metastatic non-small cell lung cancer. Acute tubular necrosis seemed to be of nephrotoxic origin as there were no signs of prolonged significant renal hypoperfusion. Interstitial fibrosis was attributed to pemetrexed. Although our patient had previously received paclitaxel and carboplatin, acute renal failure appeared only after pemetrexed treatment.

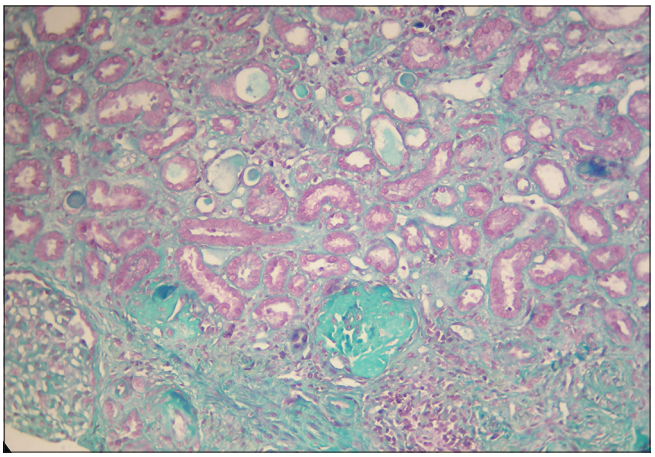

Figure 1: Renal biopsy (light microscopy): The interstitial tissue had focal edema with moderate infiltration from mononuclear inflammatory cells and fibrosis in approximately 40% of the cortex with moderate tubular atrophy (Masson's trichrome, ×200)

Showing a causal relationship between a drug treatment and kidney injury may be challenging. However, temporal association between administration of the agent and the development of kidney disease and improvement or stabilization of kidney function after the offending agent has been discontinued, may help establish an association between the drug and the pathologic process.

Several cases of acute kidney injury following pemetrexed administration had been previously reported. However, in the literature, renal biopsy was performed in only seven cases [Table 1].[1-4]

To conclude, pemetrexed toxicity should be considered as a cause for acute kidney injury. Physicians should be aware of early signs of pemetrexed renal toxicity, as cessation of the drug and early treatment if needed, may preserve renal function.

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Conflicts of interest

There are no conflicts of interest.

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Table 1: Clinical, biological and renal biopsy characteristics of patients with pemetrexed-induced acute kidney injury

Age (years) sex	Cancer type	Chemotherapy	Kidney biopsy	Serum creatinine (mg/dl)		Reversible acute kidney injury	References
				Before treatment	At diagnosis		
59 female	NSCLC	Pemetrexed 500 mg/m^2, 6 cycles	ATN interstitial fibrosis 60%	0.95	4.49	Partial	Chauvet *et al*.[1]
60 female	NSCLC	Cisplatin 80 mg/m^2 and Pemetrexed 500 mg/m^2, 4 cycles; Pemetrexed alone 500 mg/m^2, 3 cycles	ATN interstitial fibrosis 30%	1.01	4.07	Partial	Chauvet *et al*.[1]
65 male	Undifferentiated carcinoma	Pemetrexed 500 mg/m^2, 5 cycles	ATN interstitial fibrosis	1.13	4.52	Partial	Michels *et al*.[2]
67 male	Adenocarcinoma of the lung	Pemetrexed 500 mg/m^2, 11 cycles	ATN diffuse interstitial fibrosis arteriosclerosis	0.9	2.6	No	Glezerman *et al*.[3]
77 male	Adenocarcinoma of the lung	Pemetrexed 500 mg/m^2, 6 cycles	ATN diffuse interstitial fibrosis arteriosclerosis	1.1	1.8	Partial	Glezerman *et al*.[3]
57 female	NSCLC	Pemetrexed 500 mg/m^2, 4 cycles	ATN focal interstitial fibrosis arteriosclerosis	0.6	1.6	No	Glezerman *et al*.[3]
57 male	NSCLC	Pemetrexed 500 mg/m^2, 4 cycles	ATN interstitial fibrosis (25%) Interstitial inflammatory infiltrate of mononuclear cells	0.9	3.4	No	Stavroulopoulos *et al*.[4]
62 male	NSCLC	Pemetrexed 500 mg/m^2, 4 cycles	ATN interstitial fibrosis (40%) arteriosclerosis	0.8	2.4	No	Present report

ATN: Acute tubular necrosis, NSCLS: Nonsmall cell lung cancer

References

1. Chauvet S, Courbebaisse M, Ronco P, Plaisier E. Pemetrexed-induced acute kidney injury leading to chronic kidney disease. Clin Nephrol 2014;82:402-6.
2. Michels J, Spano JP, Brocheriou I, Deray G, Khayat D, Izzedine H. Acute tubular necrosis and interstitial nephritis during pemetrexed therapy. Case Rep Oncol 2009;2:53-56.
3. Glezerman IG, Pietanza MC, Miller V, Seshan SV. Kidney tubular toxicity of maintenance pemetrexed therapy. Am J Kidney Dis 2011;58:817-20.
4. Stavroulopoulos A, Nakopoulou L, Xydakis AM, Aresti V, Nikolakopoulou A, Klouvas G. Interstitial nephritis and nephrogenic diabetes insipidus in a patient treated with pemetrexed. Ren Fail 2010;32:1000-4.

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