Exceptional Case

Biopsy-proven acute interstitial nephritis associated with the tyrosine kinase inhibitor sunitinib: a class effect?

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Abstract
Since their introduction in 2006, the tyrosine kinase inhibitors (TKI) Sunitinib and Sorafenib have become the standard of care for many patients with renal cancer. They are generally well tolerated and have not been significantly implicated in renal toxicity. We report the first biopsy confirmed occurrence of acute interstitial nephritis in a patient receiving treatment with Sunitinib for metastatic renal cell cancer. However, two previous descriptions of interstitial nephritis related to treatment with TKIs, combined with this current report suggest that TKI therapy could be associated with this rare but life-threatening complication.

Keywords: acute interstitial nephritis; renal cell carcinoma; sunitinib; tyrosine kinase inhibitors

Background
Acute (tubulo) interstitial nephritis (AIN) is a common cause of acute renal failure (ARF), found in as many as 15% of renal biopsies performed in this setting. Drug-induced disease has been recognized in more than 90% of cases of AIN, and its incidence is increasing [1]. Tyrosine kinase inhibitors (TKI) are a relatively new class of drug that act by blocking different intracellular signal transduction pathways, thereby finding therapeutic application in a growing variety of clinical scenarios—notably as anticancer agents. Indeed, impressive results have been seen with these drugs in the face of treatment failure with established protocols [2,3].

Sunitinib (Stutent, Pfizer, La Jolla, California) is a multi-TKI approved by the Food and Drug Administration in January 2006 for the treatment of gastrointestinal stromal tumours and advanced renal cell carcinoma (RCC) [4]. It shares a side-effect profile that is similar to that of other TKI. A limited number of reports of ARF in the context of this novel class of medications have been described [5–9]. We report the first case of AIN seen in a patient receiving Sunitinib for the treatment of advanced RCC.

Case report
A 54-year-old hypertensive gentleman with inactive rheumatoid arthritis was diagnosed with metastatic RCC with lung, adrenal and peritoneal involvement in 2006. Initial therapy with IFN-alpha brought no significant benefit and was discontinued after 6 months. After a treatment break of ~4 months, Sunitinib was introduced. At initiation, renal function was as follows: urea 7.5 mmol/l, creatinine 119 µmol/l, eGFR 59 ml/min. Concomitant medication included amlodipine 5 mg once daily (od) and enalapril 4 mg od, with no non-steroidal anti-inflammatory drug (NSAID) nor antibiotic use and no known drug allergy. His antihypertensive medication had not changed for many months. On Day 21 of his first cycle of Sunitinib, the patient presented to his local hospital with a week-long history of diarrhoea, vomiting, rash and oliguria. Investigations revealed anaemia (Hb 8.5 g/dl), leucopaenia (0.8 10×9/l) and renal failure (urea 29 mmol/l, creatinine 725 µmol/l, vasculitic screen negative). Blood and protein were found on urine dipstick, and an ultrasound of the renal tract demonstrated the previously documented large right renal mass but a normal left kidney and renal outflow tract. A biopsy of the left kidney demonstrated interstitial nephritis with patchy infiltration of lymphocytes, plasma cells and eosinophils as well as evidence of acute tubular necrosis (Figure 1). There was no evidence of glomerulopathy, vessel disease or immune deposition. A tapering course of steroids was prescribed and the patient remained dialysis dependent for 2 weeks. Creatinine at 1 and 3 months was 200 µmol/l (eGFR 29 ml/min) and 134 µmol/l (eGFR 52 ml/min), respectively.

Discussion
TKIs are a relatively new class of anti-cancer drug. They rely on blocking signal transduction via various growth factor receptors, thereby interfering with biological outcomes...
as fundamental as cell division, growth and apoptosis. Such anti-proliferative actions have allowed TKIs to act as highly effective anti-cancer agents against a number of malignancies. Indeed Sunitinib, as a multi-tyrosine kinase receptor inhibitor, has found application in the treatment of gastrointestinal stromal tumours and advanced RCC. Interestingly, it is recognized that growth factors and their receptors play a fundamental role in the regeneration and repair of injured renal tubule cells [10] and it might be postulated that TKIs therefore interfere with this process.

Sunitinib shares a side-effect profile that is similar to that of other TKIs with gastrointestinal disturbance, skin toxicity and hypertension being the most frequent observations. Despite the lack of any apparent renal toxicity among the 375 patients receiving Sunitinib during the licensing trial [4], a small number of reports of ARF in the context of this novel class of medications have since been described [5–9]. A review of the literature revealed one case of AIN following administration of Sunitinib [9]. This was in a 69-year-old female with metastatic RCC who developed renal failure, proteinuria, eosinophiluria, and eosinophilia during her first cycle of Sunitinib, which worsened on continuation to a second cycle. Sorafenib was then trialled with a similar outcome. This patient did not have a renal biopsy. A second case is also recorded with the use of Sorafenib in a patient who had recently commenced treatment, after a previous prolonged course of Sunitinib. In this instance, AIN was demonstrated at renal biopsy [8]. Here, we report the first biopsy-proven case of AIN in a patient commencing TKI therapy with Sunitinib for advanced RCC.

AIN is a common cause of renal failure, seen in as many as 15% of renal biopsies performed as part of the work up for ARF. As in this case, there is often a non-specific prodromal phase that can progress to a more severe, generalized hypersensitivity reaction. Aetiological agents include drug-induced phenomena, infection-related processes and immune or neoplastic disease. Drug-induced AIN is by far the most common, accounting for more than 90% of cases with an increasing incidence recognized [1].

In summary, this is the first reported biopsy-proven case of interstitial nephritis shortly after starting Sunitinib. TKIs are proving to be powerful tools in the treatment of various cancers and their application to wider clinical scenarios is already under intense study. This report highlights a possible class adverse reaction profile with TKIs precipitating renal injury, in particular AIN. Supporting this hypothesis is the fact that certain growth factors targeted by these inhibitory drugs are seen to play a role in renal recovery following injury. Whether the acute renal injury described in patients taking TKI such as Sunitinib is precipitated or exacerbatated by their inhibitory action on these growth factors remains to be seen. Nonetheless, we advocate appropriate renal surveillance in patients being considered for treatment with such drugs.

Fig. 1. Renal biopsy (PAS × 400) demonstrating tubular lymphocytic infiltration with occasional plasma cells and eosinophils as well as evidence of acute tubular necrosis.
Conflict of interest statement. None declared.

References


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