CASE REPORT

Rare allergic reaction of the kidney: sitagliptin-induced acute tubulointerstitial nephritis

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SUMMARY

A 56-year-old man with a history of diabetes mellitus type-2 and stage-2 chronic kidney disease secondary to diabetic nephropathy presented with an acute deterioration of kidney function. Non-invasive work-up failed to reveal the underlying aetiology for the acute kidney failure. Kidney biopsy revealed acute tubulointerstitial nephritis (ATIN) which was attributed to sitagliptin use. Only few case reports have shown this correlation. Our aim is to alert physicians and other providers of the potential effect of sitagliptin to cause ATIN with this biopsy-proven case.

BACKGROUND

Acute tubulointerstitial (or interstitial) nephritis is a renal lesion that causes acute to subacute deterioration in creatinine clearance from the kidney.¹ The pathophysiology of the disease is induced by a hypersensitive (type 1) allergic reaction to an offending agent with the activation of the local and systemic eosinophils causing inflammatory infiltrates in the kidney's interstitium, while sparing the glomeruli and blood vessels.^{1 2} This trigger can be a medication, bacterial or viral infection or even reflux or obstruction leading to an intrinsic categorisation of renal injury. Three quarters of acute interstitial nephritis (AIN) aetiology is due to medication hypersensitivity, commonly to non-steroidal anti-inflammatory drugs, penicillin and xanthine oxidase inhibitors. The other quarter is attributed to autoimmune diseases such as Sjögren's syndrome and infectious culprits.¹ AIN is a dose-independent allergic reaction. The time from exposure to appearance of symptoms is widely variable and can be from a few days to years.^{2 3} We are reporting a case of biopsy-proven acute tubulointerstitial nephritis (ATIN) in a patient who was treated with sitagliptin.

CASE PRESENTATION

A 56-year-old man with type 2 diabetes and chronic kidney disease presented to the outpatient clinic with a history of fatigue, nausea and vomiting. There was no reported history of haematuria, foamy urine, discharge, dysuria, dyspnoea, chest pain or diarrhoea. Notably, he had been started on sitagliptin phosphate 2 weeks earlier for glycaemic control. The sitagliptin dose was calculated by his primary care physician according to the patient's kidney function to be 50 mg daily. His other relevant medications included insulin (with which he had poor compliance), simvastatin, diltiazem and doxazosin.

His physical examination including vital signs was within normal limits and without fever, rash, dry mucous membranes or oedema. His blood pressure at the time of evaluation was 133/72 mm Hg and he appeared euvolemic. Routine laboratory work was notable for serum creatinine of 2.2 mg/dL with a baseline of 1.5 mg/dL (normal reference range is 0.8–1.2 mg/dL). Autoimmune workup and viral studies were normal as were ACE inhibitors and IgG4 levels. Urinalysis demonstrated grade II proteinuria, red blood cells 2/high-power field (hpf) and hyaline casts. Calculated fractional excretion of sodium was 1.7%, referring to a likely intrinsic renal pathology. An ultrasound scan revealed that his kidneys were normal in size.

INVESTIGATIONS

Renal biopsy was performed. Light microscopy showed inflammatory changes in the interstitium with increased eosinophils, tubule eosinophil infiltration, interstitial oedema and tubular injury (figure 1). Glomeruli exhibited moderate-to-severe diabetic nephropathy, global glomerulosclerosis with vascular hyalinosis and advanced arteriosclerosis (figures 2 and 3). There was diffuse glomerular basement membrane (GBM) thickening and no evidence of an immune complex process on immunofluorescent or electron microscopy (figure 4). IgG4 immunostain showed no increase in IgG4 plasma cells. The findings are diagnostic of ATIN superimposing an advanced diabetic nephropathy.

The patient's medications list was reviewed for potential causes of ATIN. He had no recent use of non-steroidal anti-inflammatory medication, penicillin or other medications known to cause ATIN. Workup for common autoimmune diseases like systemic lupus and Sjögren's syndrome, complement factors 3 and 4 level and IgG subtype 4 in the serum sample were negative. Infectious workup including *Streptococcus pneumoniae*, *Legionella pneumophila*, cytomegalovirus and Epstein-Barr virus were negative as well. His creatinine phosphokinase level was within the normal range.

TREATMENT

Sitagliptin was immediately discontinued and replaced with an insulin regimen with a total exposure period to sitagliptin of 4 weeks. The patient was treated with a daily dose of 20 mg prednisone for 6 weeks to hasten recovery.^{4 5} Weekly follow-up of creatinine levels showed a downward trend from 2.2 to 1.6 mg/dL (baseline was 1.5 mg/dL) after 3–6 weeks from treatment

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Figure 1 Acute interstitial nephritis with interstitial oedema, tubulitis, lymphocytic inflammation and frequent eosinophils with tubule eosinophil infiltration suggesting medication-related aetiology (arrows) (H&E; original magnification $\times 400$).

initiation. Then, prednisone was tapered over a period of 6 weeks.

OUTCOME AND FOLLOW-UP

The patient was seen 1 and 3 months after the discontinuation of the steroids which he received for a total of 12 weeks including the taper. He was enjoying good health, and his kidney function was stable and his baseline creatinine level was 1.5 mg/dL.

DISCUSSION

Searching the literature (PubMed and Medline) using the words 'sitagliptin', 'AIN' and 'acute kidney injury' revealed only two case reports that show this kind of association between dipeptidyl peptidase-4 (DPP-4) inhibitors and AIN. The patient reported in one of the cases had erythematous skin rash and developed presumed AIN secondary to sitagliptin use.⁶ The other case was proven by biopsy.⁷ It has been reported by the drug manufacturer that several cases of acute kidney injury and abnormal kidney function were induced by sitagliptin.⁸ There is also evidence correlating sitagliptin with rhabdomyolysis and acute kidney injury induced by concomitant use of sitagliptin and statins.³ None of those cases was confirmed as ATIN because no biopsies were performed.

Figure 2 Advanced diabetic nephropathy with glomerular mesangial expansion and Kimmelstiel-Wilson nodule and prominent arteriolar hyalinosis (Periodic acid-Schiff (PAS); original magnification $\times 400$).

Figure 3 Hypertensive-associated injury with glomerulosclerosis, interstitial fibrosis, tubular atrophy and moderate-to-severe eccentric arteriosclerosis (PAS; original magnification $\times 200$).

A renal biopsy is required to confirm the diagnosis of AIN. Supportive findings in the presentation and the laboratory testing can initiate the diagnosis, including eosinophils in urine or blood, proteinuria and elevated blood urea nitrogen and creatinine levels. None of the preceding clinical findings is sensitive or specific to the diagnosis of ATIN.⁹ Our patient did not have a presentation suggestive of rhabdomyolysis, but the continuous deterioration in kidney function mandated an intervention with kidney biopsy.

Sitagliptin-induced acute kidney injury can be attributed to ATIN. Renal biopsy is preferred but not required to make the diagnosis, especially when the possible offending agent can be eliminated. In addition to discontinuing sitagliptin, glucocorticoid therapy, despite the lack of randomised controlled trials, can be used to hasten the recovery of the kidney function and

Figure 4 Diabetic nephropathy with expanded mesangium (Mes), diffusely thickened capillary loop basement membranes 2 to 2 times normal (GBM), and moderate podocyte foot process fusion (arrow) (electron micrograph, original magnification $\times 4800$).

should be considered when there is no improvement in renal function over the course of days despite discontinuation of the potential offending agents.^{4 5} In our experience with this patient and from a limited data in the literature, we suggest to

start steroid tapering once serum creatinine has returned to or near baseline values, with a taper over weeks to months.^{4 5}

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Patient's perspective

My doctor prescribed (sitagliptin) to better control my sugar. When I started to have nausea and vomiting and went to see my doctor, my doctor and I never realised that I was experiencing a side effect of the medicine I was taking. I am glad that my problem was identified and treated appropriately.

Learning points

- ▶ Drug-induced acute tubulointerstitial nephritis (ATIN) should be suspected in acute to subacute renal failure in the setting of a recently initiated medication.
- ▶ Sitagliptin has the potential to cause kidney injury in the form of ATIN.

REFERENCES

- 1 Michel DM, Kelly CJ. Acute interstitial nephritis. *J Am Soc Nephrol* 1998;9:506–15.
- 2 Schwarz A, Krause PH, Kunzendorf U, et al. The outcome of acute interstitial nephritis: risk factors for the transition from acute to chronic interstitial nephritis. *Clin Nephrol* 2000;54:179–90.
- 3 Kao DP, Kohrt HE, Kugler J. Renal failure and rhabdomyolysis associated with sitagliptin and simvastatin use. *Diabet Med* 2008;25:1229–30.
- 4 Muriithi AK, Leung N, Valeri AM, et al. Biopsy-proven acute interstitial nephritis, 1993–2001: a case series. *Am J Kidney Dis* 2014;64:558–66.
- 5 González E, Gutiérrez E, Galeano C, et al. Grupo Madrileño De Nefritis Intersticiales. Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis. *Kidney Int* 2008;73:940–6.
- 6 Quasem M, Liu Y. 257 Acute interstitial nephritis associated with sitagliptin use. *Am J Kidney Dis* 2011;57:B81.
- 7 Lin DY, Hoffman D, Pulivarti VV, et al. Sitagliptin caused acute drug induced interstitial nephritis. *Consultant* 2014;53:444–6.
- 8 Merck Sharp and Dohme Corp. *Product Information: JANUVIA (sitagliptin) oral tablets*. Whitehouse, NJ: Merck & Co, 2011.
- 9 Perazella MA, Bombardieri AS. Urinary eosinophils in AIN: farewell to an old biomarker? *Clin J Am Soc Nephrol* 2013;8:1841–3.

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