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Alogliptin and tubulointerstitial nephritis: A potential complication

Alogliptina y nefritis tubulointersticial: una complicación potencial

Dear Editor,

Alogliptin is one of the dipeptidyl-peptidase 4 (DPP4) inhibitors used in the treatment of type 2 diabetes mellitus. Acute pancreatitis, as well as hypersensitivity reactions and allergic reactions such as rash or pruritus have been reported as side effects. However, there are very few reported cases of renal adverse effects. Renal adverse reactions include isolated cases of acute interstitial nephritis associated with DPP4 inhibitors.[1,2]

We present the case of a 57-year-old female patient with a history of type 2 diabetes mellitus, being evaluated in the outpatient internal medicine department for constitutional syndrome of one and a half month duration. She was urgently admitted to the nephrology department after detecting creatinine levels of 5.1 mg/dl in a blood test carried out prior to the consultation. The patient exhibited no cardiovascular symptoms and was haemodynamically stable with a tendency to hypertension, 160/80 mmHg, heart rate 96 bpm and normal blood volume. In the Emergency room, impairement of renal function was confirmed, with potassium 4.6 mmol/l, sodium 138.6 mmol/l, pH 7.27, bicarbonate 18.4 mmol/l, pCO_2 40 mmHg and lactate 0.9 mmol/l. The patient's urinalysis and urinary sediment were normal, with proteinuria of less than 0.3 g/24 h, suggestive of tubulointerstitial damage.

Investigation of impaired renal function (autoimmunity, serology, complement and immunoglobulins) was extended

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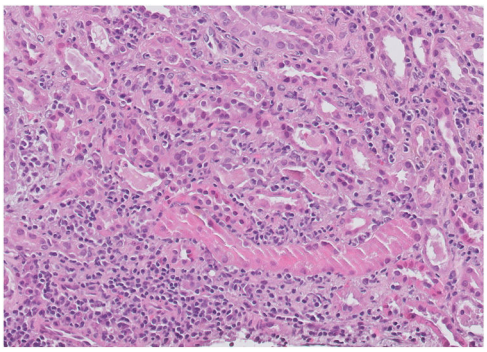

Fig. 1 – The interstitium shows a prominent polymorphous inflammatory infiltrate consisting of abundant polymorphonuclear leucocytes, lymphocytes, plasma cells and occasional eosinophils with images of tubulitis. Renal parenchyma with morphological data consistent with acute interstitial nephropathy and acute tubular necrosis with regenerative changes. PAS (periodic acid-schiff) stain, ×400.

Table 1 – Changes in renal function.

Month	Creatinine (mg/dl)	Treatment
December 2022	0.60	
February 2023	1.2	Alogliptin
March 2023	1.8	
May 2023	5.1	Alogliptin discontinued Methylprednisolone 250 mg IV
June 2023	1.9	Prednisone 1 mg/kg PO
July 2023	1.5	
October 2023	1.2	

The table shows changes in the patient's renal function and treatment received in chronological order.

and all were negative. Renal biopsy confirmed morphological data consistent with acute tubulointerstitial nephropathy and acute tubular necrosis (Fig. 1). With these findings, pulses of 250 mg methylprednisolone were started for three days followed by oral prednisone at a tapering dose of 1 mg/kg. After ruling out other possible causes of tubulointerstitial nephritis and conducting a thorough review of the patient's usual medication, we were able to relate the onset of symptoms and impaired renal function to the start of treatment with alogliptin. After starting corticosteroid therapy and discontinuing alogliptin, the patient's renal function progressively improved, with Cr 2.5 mg/dl upon hospital discharge. She is currently on outpatient follow-up at our clinic; renal function has been restored to previous values, recording 1.2 mg/dl at the last creatinine check (Table 1). We classified this adverse drug reaction as probable, according to the WHO causality criteria, as it had a reasonable time relationship between the clinical manifestations and drug intake, could not be attributed to other causes or medications, and responded favourably to drug withdrawal.

In our patient's case, the clinical presentation of tubulointerstitial nephritis was not classic, as she did not have skin rash, eosinophilia or joint pain.[3–5] Our patient's condition began with rapidly progressive renal failure accompanied by weight loss and asthenia. Other diseases and recent medication that could have triggered the condition were ruled out, with the most likely cause of tubulointerstitial nephritis being the initiation of alogliptin as an oral antidiabetic agent.[5,6]

Reviewing the literature, there are very few reported cases of adverse reactions to alogliptin compared to other DPP4 inhibitors, such as sitagliptin. Evidence supports starting corticosteroid therapy when renal function does not improve despite drug withdrawal and while awaiting renal biopsy results.[5–7] In our case, given the severity of the patient's renal failure, it was decided to start corticosteroid therapy early[8,9] after withdrawal of alogliptin and until the result was confirmed by the renal biopsy report. As a result, the patient experienced a marked clinical improvement and her renal function returned to its previous values.

Given that this is a rarely described adverse reaction and that these are commonly-used drugs, we believe it is important to consider the involvement of these drugs in patients presenting with acute renal failure in relation to tubulointerstitial nephritis.[10]

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Arteriovenous fistula in persistent left superior vena cava scenario

Fístula arteriovenosa en escenario de persistencia de vena cava superior izquierda

Dear Editor,

Persistent left superior vena cava (PLSVC), although rare, is the most common thoracic venous anomaly.[1] It results from persistence of the embryonic left anterior cardinal vein and is considered a normal variant.[2] The clinical significance depends mostly on the drainage site, and in 80%–90% of cases the drainage occurs to the coronary sinus (CS).[3] We present a case of PLSVE incidentally detected after dysfunctional maturation of an arteriovenous fistula (AVF).

A 68-year-old man with stage 4 chronic kidney disease of undetermined etiology with a left radiocephalic AVF created 11 years back but never used for dialysis access. He also has atrial fibrillation (AF) that was been diagnosed three years after AFV creation. Aneurysmal and serpiginous dilatation was found throughout the fistulous tract, with evidence of collateral circulation and edema of the left upper limb. Transthoracic echocardiography (TTE) showed normal left ventricular function, enlargement of left and right atrium, and a markedly dilated CS (33–35 mm of transverse diameter) (Fig. 1A). The presence of a PLSVC draining into the right atrium through a volume-overloaded CS was confirmed by use of saline contrast ("bubble study") echocardiography and by magnetic resonance imaging (Fig. 1B). Since the CS dilatation caused by volume overload due to draining of the PLSVC was presumably aggravated by the left sided AVF and the unknown risk of rupture in these cases, the arteriovenous access was ligated.

PLSVC occurs in approximately 0.3%–0.5% of the population.[2] Left superior vena cava (SVC) commonly coexists with right SVC, and it drains into the right atrium through the CS with no major hemodynamic effect.[1,3] The clinical significance of PLSVC also depends on the accompanying anomalies. The most common associated congenital heart defects are single ventricle, atrioventricular septal defect, and tetralogy of Fallot.[2,3] This anomaly should be suspected whenever a dilated CS is found on TTE and diagnosis can be confirmed by use of saline contrast echocardiography.[1]

Although PLSVC is mostly asymptomatic, the creation of an AVF in the left upper limb not only increases the amount of blood drained into the CS – which under normal conditions corresponds to only 20% of the total venous drainage[3] – but also increases the pressure at the level of this vascular bed. The enlargement of the CS, which can reach the aneurysmatic level, may cause compression of the sinus/atrioventricular node and His bundle, leading to cardiac arrhythmias such atrial and ventricular fibrillation.[2–6] In fact, PLSVC plays a considerable role in induction and maintenance of AF.[7] This fact could explain the development of AF after AVF construction in our patient. An atrioventricular flow obstruction, with consequent decreased cardiac output, may also occur secondary to the compression of the left atrium by the dilated CS.[6] In this scenario, the patient can develop symptoms of cardiac failure, particularly when there is a high-flow AVF draining into

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