C) BRIEF CASE REPORT

Relapse of minimal change disease nephrotic syndrome after administering intravitreal bevacizumab

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Dear Editor,

Minimal change disease (MCD) causes between 10 and 25% of nephrotic syndrome cases in adults. We describe a nephrotic syndrome relapse, in a patient previously diagnosed with MCD, after intravitreal bevacizumab[1,2] injections due to a branch retinal vein occlusion.

We report–the case of a 54 year-old male patient with a history of nephrotic syndrome due to MCD diagnosed in 1995. He received prednisone with a daily dose of 1mg/kg for four weeks resulting in a complete remission. Four subsequent relapses (the last one in 2000) were all resolved with steroid treatment.

In November 2012 he received a 1.25mg monthly dose of intravitreal bevacizumab[3] due to cystic macular edema secondary to inferotemporal branch retinal vein occlusion. Two weeks after the second administration of bevacizumab the patient developed marked lower extremities edema, nephrotic range proteinuria (11,000mg/24hours), hypoalbuminemia (serum albumin, 2.1g/dL) with an estimated glomerular filtration rate of 115mL/min/m^2 (2009 CKD-EPI). Bevacizumab was discontinued and prednisone started with a 1mg/kg/day dose resulting in a complete response in the fourth week.

Bevacizumab is a monoclonal antibody that neutralizes vascular endothelial growth factor (VEGF) and has shown efficacy in patients with advanced colorrectal cancer, non-small-cell lung cancer, breast cancer, renal cell carcinoma and multiforme gliobastoma. It is also used in intravitreal injections in macular pathologies such as age-related macular degeneration or macular edema due to central retinal vein occlusion as in our case. Its use in these macular pathologies is justified because of an overexpression of VEGF inducing an increase in retinal vascular permeability.

Proteinuria induced by VEGF may involve multiple pathways. VEGF produced by the podocytes plays a role in maintaining glomerular filtration barrier through receptors present in the adjacent endothelial cells; its inhibition could cause a loss in normal glomerular permeability which could induce proteinuria.[4]

The development of proteinuria, including nephrotic syndrome, is an adverse effect reported in several clinical trials with bevacizumab.[5] Concretely, 2.2% of patients developed a proteinuria of >3.5g/24hours and 0.8% a nephrotic syndrome. Clinical handling of this complication recommends discontinuing bevacizumab temporarily if proteinuria is above 2g/24hours and discontinue the treatment if nephrotic syndrome appears.

CONCLUSIONS

There is a very strong regulation of VEGF signaling within the glomerulus; the up or downregulation contributes to different phenotypes of renal diseases including the appearance of proteinuria or nephrotic syndrome. The appearance of proteinuria following intravenous bevacizumab has been described previously but the relapse of a nephrotic syndrome due to intravitreal bevacizumab is exceptional. To our knowledge only one case[1] concerning a 16 year old female patient suffering steroid-dependent nephrotic syndrome has been described. The patient had been diagnosed with myopic choroidal neovascularization and 9 days after receiving treatment with intravitreal bevacizumab she developed proteinuria and the nephrotic syndrome re-appeared. The problem was resolved after bevacizumab was suspended and administration of corticoids was restarted. It is reported that serum concentrations of bevacizumab reach a peak at day 8 after intravitreal use, which coincided with the onset of proteinuria in this patient. The onset of proteinuria after intravitreal injection in this case may be due to the passage of the drug into the blood stream directly inhibiting VEGF signaling in the glomerulus.

We believe it is important for the nephrologists to be aware of the risk of proteinuria and nephrotic syndrome associated with bevacizumab by any route in its presentations, whether intravenous or intravitreal as its appearance could decide the discontinuing of the treatment and a proposal for an alternative therapy for the patient.

Conflict of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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Iodide Mumps

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To the Editor,

Iodide Mumps, so-called in medical literature, is a rare, scarcely described adverse effect, consisting of an inflammation of the parotid, submandibular and/or sublingual glands, secondary to exposure to iodine contrasts.[1]

CASE REPORT

We present a 65-year-old male with a history of long-term arterial hypertension, surgical intervention of thoracic aortic aneurysm and abdominal aortic aneurysm being monitored for vascular surgery, benign prostatic hyperplasia (BPH), right parotid swelling, stage 5 chronic kidney disease (CKD) due to likely nephroangiosclerosis in kidney replacement therapy, on peritoneal dialysis since May 2012. He was admitted to our department due to intense abdominal pain, finding an inguinal hernia on the left side. An abdominal CT with contrast was performed which showed the hernia to be incarcerated, with decrease in pain following manual reduction. 48 hours after the radiology test the patient presented painless swelling of the right parotid and right submandibular gland (Figure 1). An ecography of the salivary glands was carried out which showed generalised swelling in all glands (Figures 2 and 3). The symptoms were self-limited, with full recovery after 6 days.

PATHOPHYSIOLOGY

Iodide mumps are characterised by a rapid and painless growth of the salivary glands following iodine contrast administration. It can present itself several minutes after exposure and up to 5 days later. Its incidence is unknown, with few reported cases: 40 until 2012.[2] It was described for the first time in 1956 by Sussman and Miller.[3] It is believed to be caused by iodine contrast, as an idiosyncratic reaction or due to its toxic accumulation which causes inflammation, oedema of mucous membranes and duct obstruction due to the concentration through the sodium iodide symporter of salivary gland tissue. 98% of iodine is excreted by the kidney and the remaining 2% by the salivary, sweat and lacrimal glands. As a result, CKD could be a risk factor for its development.[4] It can recur with successive exposures to iodine contrast.

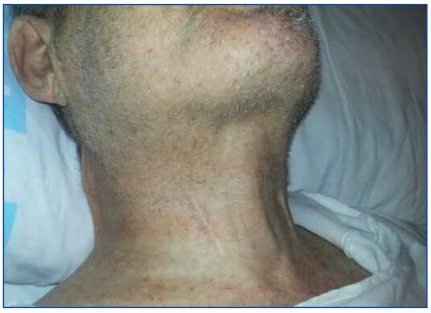

Figure 1. Swelling of the right parotid and right submandibular gland.

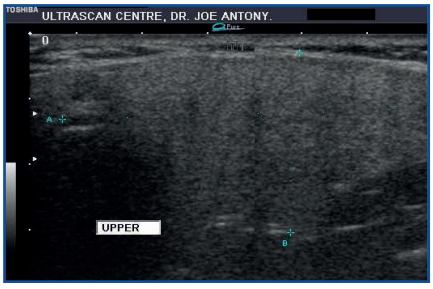

Figure 2. Ecography of normal parotid gland.

DIAGNOSIS AND TREATMENT

Clinical symptoms serve as a guideline and the ecography showed diffuse glandular swelling, dilated hyperechoic ducts and increase in central vascularisation. A differential diagnosis is made using entities that may put the patient's life at risk (angioedema, haemorrhage).[4] Treatment is conservative, supported with analgesic on demand. Corticosteroids and antihistamines have not proven effective.

CONCLUSIONS

Iodide mumps is a rare adverse effect of iodine contrast use, although its true incidence is unknown, due to under-recording, with unpublished incidental cases in our nephrology department.[5] We consider that this condition deserves more attention and a suitable register for recurrence, since there are no prophylactic measures and its long term significance is uncertain.

Conflicts of interest

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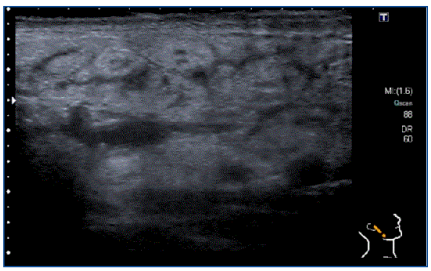

Figura 3. Swelling of right parotid.