Drug-induced liver injury attributable to terbinafine was identified with a cholestatic pattern: (GPT/40)/(alkaline phosphatase/105) = R 1.7, calculated on day +27. The causality was assessed using the CIOMS/RUCAM scale and it was considered to be probable (8 points): onset of symptoms five to 90 days after the start of treatment (+2); favourable course with >50% fall in alkaline phosphatase levels in the 180 days following treatment withdrawal (+2); complete exclusion of other causes or toxins (+2) and prior known terbinafine hepatotoxicity, reported on the label (+2). The abatement of cholestasis meant a liver biopsy was not required. Re-exposure was also discounted as it was considered disproportionate.

Although progression was favourable, complete resolution was not achieved by month nine, which is why ursodeoxycholic acid 300 mg every 12 h was then prescribed, with partial response (Fig. 1).

The exact mechanisms by which terbinafine can induce liver injury have still not been fully understood. The association between HLA-A*33:01 and susceptibility to terbinafine-induced cholestatic hepatotoxicity has recently been reported.[2] Terbinafine undergoes complex hepatic biotransformation and some of the resulting metabolites are able to bind to hepatobiliary proteins and promote an immune reaction,[3] while, in other cases, idiosyncratic hepatotoxicity manifests. Cholestatic toxicity is more typical and tends to be prolonged (2–12 months), which may even progress to ductopenia.[4] The latency period (exposure-jaundice) ranges from two to six weeks, while peak bilirubin levels tend to be seen three to five weeks after treatment withdrawal. The condition usually resolves itself after withdrawal. Although there is no specific treatment, ursodeoxycholic acid has been successfully trialled.[5]

In our case, it is well documented that cholestasis was attributable to terbinafine, prescribed for its standard indication. A high level of clinical suspicion is required to facilitate the early diagnosis of drug-induced liver injury. The aim of publishing cases such as this one is to promote knowledge and clinical awareness of drug-induced hepatotoxicity.

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2444-3824/

Upper gastrointestinal bleeding as a complication of Brunner's gland adenoma. An unusual presentation☆

Hemorragia digestiva alta como complicación de un adenoma de glándulas de Brunner. Una presentación inusual

Brunner's glands are found in the submucosa of the duodenal bulb and in the second portion of the duodenum. Their primary function is to secrete a mucin-rich alkaline fluid that protects the duodenal epithelium from the contents of the stomach. Brunner's gland adenoma is an extremely rare tumour, with an incidence of less than 0.4% in endoscopic studies.[1] It is usually identified by chance following a gastroscopy performed for other reasons and in extremely rare circumstances it can present as an acute complication.[2]

We present the case of a Brunner's gland adenoma that manifested as upper gastrointestinal bleeding.

The case concerns a 57-year-old woman with a prior history of hypertension and a former smoker who attended A&E due to a 48-h history of passing melaenic stool. The patient had no changes in her bowel habit nor a history of non-steroidal anti-inflammatory drug intake. She reported mild gastrointestinal symptoms such as pyrosis and occasional postprandial dyspepsia, with no warning signs.

Upon arrival at A&E, the patient was in good general condition and haemodynamically stable. The digital rectal examination was positive for melaena. The blood panel was completely normal (haemoglobin: 14.1 g/dl; haematocrit: 43.1%; platelets: 192×10^9/l; prothrombin time: 12.5 s; urea: 18 mg/dl).

☆ Please cite this article as: Herreras J, Giner F, Cordon G, Roca MJ, Bustamante-Balén M. Hemorragia digestiva alta como complicación de un adenoma de glándulas de Brunner. Una presentación inusual. Gastroenterol Hepatol. 2019;42:395–397.

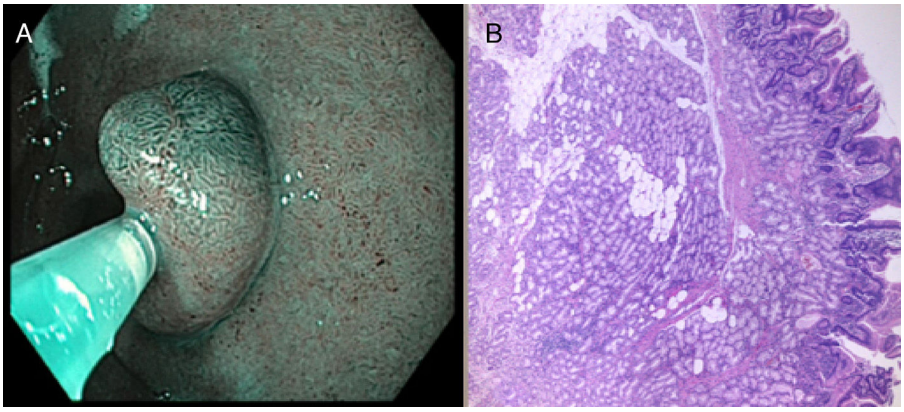

Figure 1 (A) Image of the adenoma using narrow-band imaging. Homogeneous surface pattern with preserved vascular pattern. (B) Proliferation of Brunner's glands and ducts without atypia, surrounded by islets of mature adipose stroma in duodenal submucosa (4× H&E).

The gastroscopy revealed a polypoid formation measuring approx. 8 mm in diameter on the anterior aspect of the apex of the duodenal bulb, with an erosion on the apex and haematin on the surface indicative of recent bleeding. Given the lack of active bleeding at that time, therapeutic endoscopy was not performed and the site was not biopsied. The patient was discharged with antisecretory therapy (omeprazole 40 mg/day) and an endoscopy was scheduled to assess the lesion.

At the second endoscopy, the lesion was characterised with narrow-band imaging: a homogeneous and preserved surface pattern was observed with a villus size similar to that of the surrounding mucosa and a preserved and regular vascular pattern (Fig. 1A), suggestive of a benign, probably subepithelial lesion. A mucosectomy was performed to excise the lesion en bloc, with no immediate complications. The pathology findings confirmed Brunner's gland adenoma with no associated dysplasia (Fig. 1B).

The gastroscopy performed four months after the excision revealed normal mucosa and, to date, the patient has experienced no further episodes of gastrointestinal bleeding.

Brunner's gland adenoma is a rare tumour found in the duodenal bulb and in the second portion of the duodenum. Although it tends to be asymptomatic, on rare occasions it can give rise to gastrointestinal bleeding, bowel obstruction, chronic anaemia and, anecdotally, recurrent pancreatitis. Fewer than 20 cases involving gastrointestinal bleeding have been published, the majority manifesting as melaena.[3] In most cases, the tumours measured in excess of 20 mm, approximately twice the size of the adenoma of our patient. However, the absence of other causes that could explain the bleeding, the finding of ulceration on the surface and the lack of recurrent bleeding once the adenoma had been excised confirmed the cause of the bleeding to be a tumour.

With regard to treatment, resection is not recommended in asymptomatic patients with lesions measuring less than 2 cm.[4] For symptomatic tumours, surgical resection was the treatment of choice in most of the published cases, due to the size of the lesion. However, endoscopic resection was performed in those cases, such as ours, where the tumour measured $\leq$2 cm. It may be feasible to confirm the diagnosis of subepithelial lesion by endoscopic ultrasound prior to resection. However, its diagnostic performance in duodenal lesions measuring less than 1 cm is not well documented and it may be complicated to obtain suitable samples for diagnosis by puncture.[5] Taking all of the above into consideration, together with its non-malignant appearance in the optical diagnosis and its manifestation as gastrointestinal bleeding, we opted for mucosal resection without prior endoscopic ultrasound.

Upper gastrointestinal bleeding secondary to Brunner's gland adenoma is a rare complication.Larger lesions have been associated with more significant bleeding with a greater impact on clinical status and blood test results. Resection of the lesion is indicated when any adenoma-associated complications manifest. Endoscopy is the approach of choice for lesions measuring less than 2 cm, while surgery is reserved for larger lesions.

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2444-3824/
Published by Elsevier España, S.L.U.

Syndrome of inappropriate antidiuretic hormone secretion following transarterial chemoembolisation of hepatocellular carcinoma☆

Síndrome de secreción inadecuada de hormona antidiurética postquimioembolización transarterial de un carcinoma hepatocelular

We present the case report of an 86-year-old woman with a prior history of hypertension and compensated chronic liver disease (in Child-Pugh grade A6) secondary to hepatitis c virus, treated with direct-acting antivirals with sustained virologic response, with large oesophageal varices treated with carvedilol in primary prophylaxis, oedema/ascites controlled with low-dose spironolactone and insomnia treated with lormetazepam, these being the only chronic treatments. Asymptomatic clinical course with preserved renal function (glomerular filtration rate 75 ml/min/1.73 m^2) and normal blood sodium levels. The patient was diagnosed with a 3-cm hepatocellular carcinoma in segment VIII in her six-monthly ultrasound scan. Following deliberation by a multidisciplinary committee, the patient was scheduled for transarterial chemoembolisation with doxorubicin (Adriamicina®). The blood tests performed as per routine clinical practice 24 h after the procedure revealed moderate hyponatraemia (serum Na: 124 mEq/l), which the patient did not have before (Na in plasma: 139 mEq/l previously). In light of this finding, plasma and urine osmolarity was measured, which identified hypoosmolar hyponatraemia (plasma osmolarity: 252 mOsm/kg), high urine osmolarity (463 mOsm/kg), increased urinary sodium excretion (118 mmol/l) and normal extracellular volume. Predominantly asymptomatic, the patient only reported paraesthesia in the distal phalanges of both hands.

Having ruled out other causes of hypoosmolar hyponatraemia (including central nervous system disorders and kidney disease), syndrome of inappropriate antidiuretic hormone secretion (SIADH) following transarterial chemoembolisation was diagnosed following a thyroid function test, coupled with normal baseline cortisol levels. The patient's progression was favourable, with gradual correction of serum sodium levels (serum Na: 134 mEq/l) and clinical improvement after fluid restriction and replacement with 0.9% physiological saline solution at 72 h.

Three months later, the patient remained asymptomatic and with no decompensations of her underlying disease, so a new chemoembolisation session was scheduled. Hypoosmolar hyponatraemia (plasma Na: 127 mEq/l) recurred 24 h following the procedure, having once again had normal baseline sodium levels (plasma Na: 135 mEq/l), which resolved within a similar timescale as before, with no other complications arising.

Discussion

Hepatocellular carcinoma is the most common primary hepatic malignancy. It tends not to respond to curative therapy, although other alternatives are available, like chemoembolisation.[1] This consists of the intra-arterial infusion of a cytotoxic drug and the embolisation of the tumour blood vessels. The most common complication is post-chemoembolisation syndrome, characterised by nonspecific symptoms such as nausea, fever and abdominal pain, which are usually mild in nature and transient.[2] SIADH is characterised by excess antidiuretic hormone in the absence of a physiological stimulus, which inhibits the secretion of free water and gives rise to hyponatraemia. It may be secondary to many different causes, such as medication (including chemotherapy), malignancies, bronchial diseases, hypopituitarism and hypothyroidism, to name a few. Complications arising from moderate to severe hyponatraemia, particularly when onset is acute (less than 24–48 h), range from mild (weakness, muscle cramps, etc.) to potentially fatal (seizures, coma with respiratory arrest). Appropriate treatment for asymptomatic patients consists of fluid restriction, whilst symptomatic patients require urgent but gradual correction of sodium levels to prevent complications, such as central pontine myelinolysis.[3]

In the differential diagnosis, we recommend considering the chronic liver disease itself, as well as chronic treatment with diuretics, beta-blockers and psychoactive drugs as potential causes of hyponatraemia. In addition, the possibility of paraneoplastic SIADH secondary to hepatocellular carcinoma should be ruled out[4] by a complete plasma and urine analysis that includes osmolarity and hormone profiles.

The onset of SIADH after chemoembolisation of hepatocellular carcinoma is a rare complication. In fact, only one other similar case has been reported, which describes

☆ Please cite this article as: Yebra Carmona J, Jaquotot Herranz M, Tavecchia M, Castillo Grau P. Síndrome de secreción inadecuada de hormona antidiurética postquimioembolización transarterial de un carcinoma hepatocelular. Gastroenterol Hepatol. 2019;42:397–398.