

Severe intra-abdominal bleeding after lenvatinib use in patient with follicular Hürthle cell carcinoma



Hemorragia grave intraabdominal tras el uso de lenvatinib en un paciente con carcinoma folicular de células de Hürthle

We present the case of a 46-year-old man with no relevant medical history who was referred to the endocrinology clinic due to a recent swelling on the left side of the anterior aspect of his neck. On examination, a goitre was found in the left lobe of his thyroid gland. A neck ultrasound scan revealed a mass in the upper and middle segments of the left lobe of the patient's thyroid gland measuring 46 × 33 × 50 mm (L × AP × CC), hypochoic, with lobulated borders and markedly vascularised, as well as lymphadenopathy on the left at levels II, III, V and VI. Taken the same time, fine needle aspiration biopsy showed a highly atypical cells, classified as Bethesda V, for which he was referred to endocrine surgery.

Two months later, he underwent total thyroidectomy and dissection of the central and left lateral cervical compartments. Pathology analysis of the surgical specimen revealed Hürthle cell follicular carcinoma with areas of carcinoma poorly differentiated in the left thyroid lobe and several areas of metastatic lymphadenopathy. The cancer had invaded the thyroid capsule and adjacent muscle tissue. There were also signs of extensive vascular invasion and the surgical margins were affected.

One month after surgery, an analysis was performed showing thyroglobulin (Tg) 244.9 ng/mL and thyroglobulin antibodies (TgAb) 37 IU/mL (the reference value at our hospital is less than 80 IU/mL). A whole body scan was carried out, revealing isotope retention at the left paratracheal, upper mediastinal and bilateral lung regions, consistent with tumour spread (pT3bN1M1). It was therefore decided to complete treatment with an ablative dose of 150 mCi of I-131. Subsequently, he was confirmed to be refractory to I-131, with a marked rise in Tg (592.4 ng/mL at three months and 1,071 ng/mL at six months).

The patient was referred to medical oncology, but before the first consultation, he was admitted due to superior vena cava syndrome related to disease progression, and it was decided to start lenvatinib. Two weeks later, new elevation of transaminases was found (AST 44 U/l [normal: 13–40] and ALT 172 U/l [normal: 7–40]), the figure prior to starting lenvatinib being 36 U/l). As such, treatment was discontinued.

Two weeks after that, the patient was readmitted with a 24-h history of epigastric pain, which he described as stabbing; radiating around the waist, with amylase 96 U/l and lipase 472 U/l. Lenvatinib-induced acute pancreatitis was suspected. The CT performed that day revealed an acute haematoma in the tail of pancreas, which was classified as acute pancreatitis secondary to pancreatic haemorrhage. Any history of abdominal trauma was ruled out.

The following day he became haemodynamically unstable and repeat CT scan showed atraumatic splenic rupture with haemoperitoneum (Fig. 1A and B). In view of the patient's hypovolaemic shock, it was decided to operate, performing splenectomy and resection of the tail of pancreas, with histopathology ruling out tumour invasion in these organs. He subsequently went into hypovolaemic shock again, this time due to bleeding from the short gastric arteries, which required urgent embolisation (Fig. 1C–G). He also developed a pulmonary embolism, but in view of his recent bleeding, he was not anticoagulated. At a later stage, the patient started having melaena, with worsening anaemia, requiring several transfusions and emergency sleeve gastrectomy after becoming haemodynamically unstable. Finally, the patient's pro-haemorrhagic state was brought under control and six weeks after admission we were able to discharge him home.

Lenvatinib is an oral tyrosine kinase inhibitor which inhibits vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, platelet-derived growth factor receptor- α (PDGFR α), RET and KIT.^{1–3} It is indicated for treatment in adult patients with progressive, locally advanced or metastatic differentiated thyroid carcinoma refractory to radioactive iodine therapy.¹

Lenvatinib demonstrated its clinical efficacy in the SELECT study, a multicentre, randomised, double-blind, placebo-controlled study conducted in 392 patients with radioactive iodine-refractory differentiated thyroid cancer. This study found a statistically significant increase in progression-free survival (PFS) in patients treated with lenvatinib compared to placebo (median PFS of 18.3 months with lenvatinib versus 3.6 months with placebo). A statistically significant increase was also seen in the response rate (64.8% in the lenvatinib group vs 1.5% in the placebo group).^{1,2}

Lenvatinib is not without its side effects. One of the adverse reactions attributable to this treatment is liver failure, classified as rare (affects 1/100 to 1/1,000 cases).¹ With the elevation of ALT, four times above the upper limit of normal, in our patient's blood tests two weeks after starting treatment, discontinuing the lenvatinib seemed prudent.

Bleeding as a side effect of lenvatinib is classified as very common, including epistaxis, gingival bleeding, haemoptysis, petechiae, haematuria, rectal bleeding and vaginal bleeding.¹ We have found no reported cases of non-cancer-related lenvatinib-induced haemorrhagic pancreatitis.

Among the causes of atraumatic rupture of the spleen, we mainly found infectious diseases (such as mononucleosis or malaria) and haematological cancers in up to half of the cases, with cancer of the spleen being rare.⁴ We also found no reports in the literature of non-cancer-related spontaneous rupture of the spleen associated with this drug.

Some authors propose personalising the lenvatinib dose in cases of severe bleeding, in order to avoid stopping treatment, and there have even been reports of a significant clinical and radiological response with a dose of 14 mg

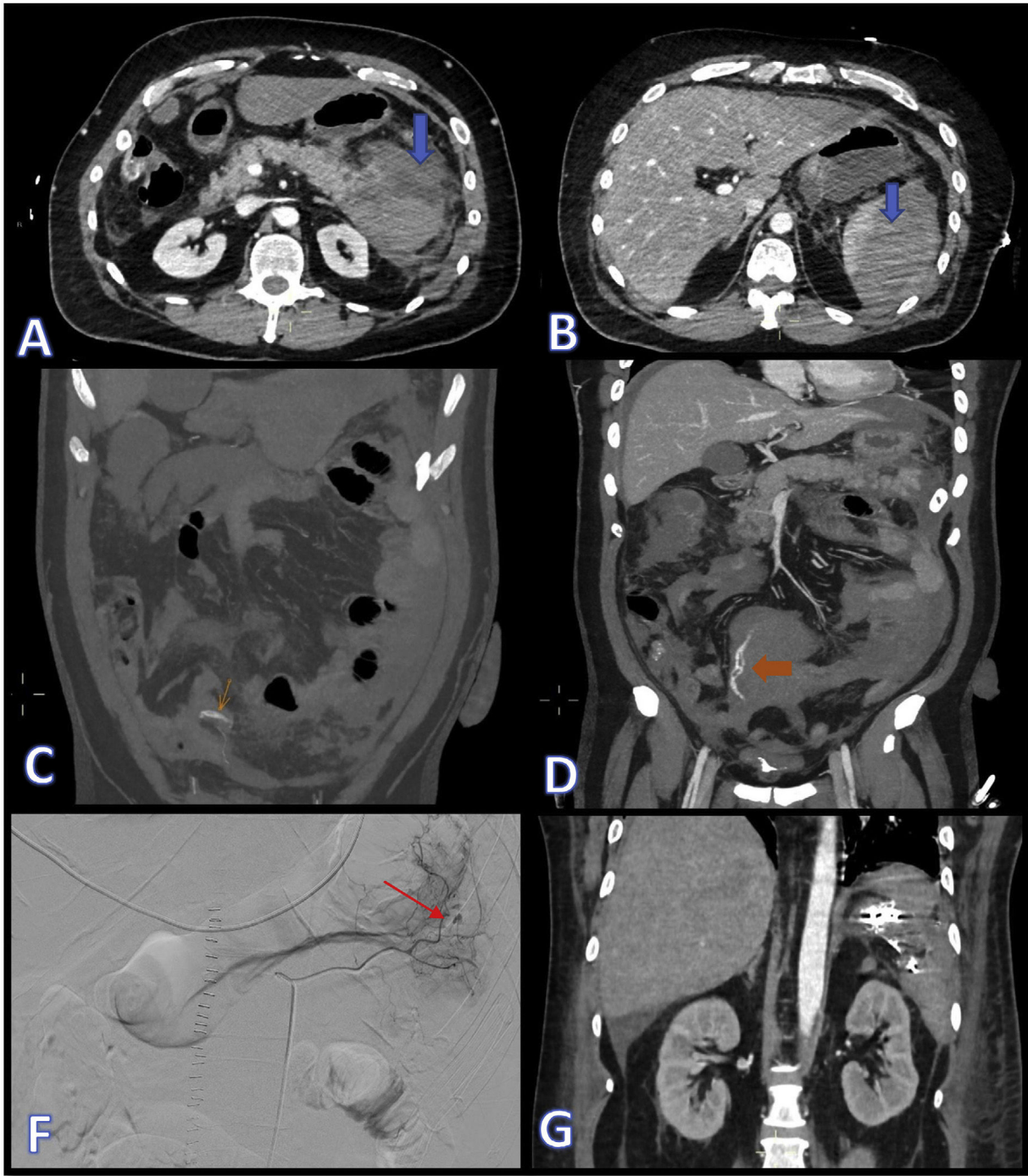


Figure 1 Images A and B show CT slices in the axial plane where dense fluid collections can be seen in relation to the pancreatic and splenic parenchyma, compatible with acute parenchymal haematomas (blue arrows). In images C and D, marked with orange arrows, signs of active bleeding can be seen, consistent with extravascular linear dense images, compatible with contrast extravasation. Images F and G show, respectively, the therapeutic arteriogram for control of the active bleeding (the red arrow indicates points of active bleeding) and the outcome by CT in the coronal plane with metallic embolisation material in the left hypochondrium.

every three days.⁵ Despite the serious adverse reactions our patient developed, we are considering reintroducing lenvatinib in an attempt to find an effective dose with no adverse effects.

Funding

No subsidies were received for the work.

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2530-0180/

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TSH elevation in neonatal screening as the first manifestation of other associated diseases



Elevación de TSH en el cribado neonatal como primera manifestación de otras enfermedades asociadas

The early detection programme for congenital endocrine and metabolic disease and other diseases screens all newborns. It enables early diagnosis and treatment of different diseases. One of these is congenital hypothyroidism, particularly important due to the involvement of thyroid hormones in brain development, and because it is an avoidable cause of cognitive deterioration.^{1,2} Although elevated TSH is usually a marker of primary congenital hypothyroidism,^{2,3} it is important to carry out a broad differential diagnosis, as it can be linked to other conditions, as occurred in the two case reports we present here.

Case 1

This was an 18-day-old baby girl who was admitted for jaundice, transient hyperinsulinaemic hypoglycaemia and dehydration, and was found to have elevated TSH on neonatal screening. She was the daughter of young, non-consanguineous parents, who had suffered interruption of the previous pregnancy due to myelomeningocele. Previous medical history: normal pregnancy, emergency Caesarean at 41+3 weeks due to abnormal cardiocography tracing (skullcap pH: 7.18). Anthropometric measurements at birth: weight 3,710 g (SD 0.78), length 50 cm (SD -0.2), head circumference 35.5 cm (SD 0.43). Physical examination normal except for mild macroglossia. While in hospital, the baby had episodes of hypoglycaemia due to transient hyperinsulinism (insulin 8.14 mIU/l in hypoglycaemia, rest of the examinations normal) which required enteral feeding and fluid therapy with a maximum glucose infusion

rate of 9 mg/kg/min, resolving at 12 days old. Neonatal screening showed TSH from dried blood spot 9 μ U/mL (cut-off point 7 μ U/mL); blood analysis: TSH 48.7 mIU/l (normal: 0.72–11); free T4 0.82 ng/dl (normal: 0.93–1.71); free T3 2.82 pg/mL (normal: 2.04–4.4); thyroid-binding globulin (TBG) and thyroid peroxidase (TPO) antibodies negative; thyroglobulin 49.85 ng/mL (normal: 1.4–78). Thyroid scintigraphy showed absence of uptake, and thyroid ultrasound was normal. In view of congenital hypothyroidism, treatment with levothyroxine was started at 13 μ g/kg/day. At the age of three months, she developed an irregular left axillary lesion measuring 3 × 1 cm adhered to the overlying skin, initially diagnosed as pilomatrixoma. From the age of six months, she had excessive weight gain, with a weight of 11.3 kg (SD +3.2), height 68.5 cm (SD +0.28), which was resolved with dietary measures. At 10 months, a new subcutaneous lesion was found in the left knee and there was a slight drop on the growth chart so, suspecting pseudohypoparathyroidism, blood tests were requested: calcium 9.1 mg/dl (normal: 9–11); phosphorus 5.9 mg/dl (normal: 3.1–6); PTH 614 pg/mL (normal: 15–65); alkaline phosphatase 201 U/l (normal: 0–300); magnesium 2.1 mg/dl (normal: 1.7–2.3); 25(OH) vitamin D 24.8 ng/mL. Urinalysis: normal, calcium/creatinine ratio 0.02, tubular reabsorption of phosphate 87.5%. Genetic study of the *GNAS* gene revealed the heterozygous presence of the pathogenic variant c.293delA, causing a truncated protein (p.Asn93Thrfs*3), confirming the clinical diagnosis of type 1A pseudohypoparathyroidism. The genetic study of both parents was normal, meaning this was a *de novo* variant. Allele-specific RT-PCR studies confirmed that the variant was in the maternal allele.

Case 2

Baby girl referred to the neonatal screening centre at the age of 23 days due to elevated TSH (first sample 10.8 μ U/mL, second sample 17.1 μ U/mL). Family history: father unknown, mother with unspecified intellectual disability and valvular pulmonary stenosis in childhood. Personal history: