Unusual presentation of more common disease/injury

Focal nodular hyperplasia with major sinusoidal dilatation: a misleading entity

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Summary

Focal nodular hyperplasia (FNH) is a benign liver lesion thought to be a non-specific response to locally increased blood flow. Although the diagnosis of FNH and hepatocellular adenoma (HCA) has made great progress over the last few years using modern imaging techniques, there are still in daily practice some difficulties concerning some atypical nodules. Here, the authors report the case of a 47-year-old woman with a single liver lesion thought to be, by imaging, an inflammatory HCA with major sinusoidal congestion. This nodule was revealed to be, at the microscopical level and after specific immunostaining and molecular analysis, an FNH with sinusoidal dilatation (so-called telangiectatic focal nodular hyperplasia).

BACKGROUND

Focal nodular hyperplasia (FNH) is thought to be a non-specific response to locally increased blood flow. In 1989, Wanless *et al* described an entity they called telangiectatic focal nodular hyperplasia (TFNH) occurring in the multiple FNH syndrome as well as in a minority of patients with solitary FNH.¹ Ten years later Nguyen *et al* described lesions classified as FNH of telangiectatic form.² In 2004, Paradis *et al* showed that the molecular profile of the TFNH at the DNA, gene and protein expression level was more similar to that of hepatocellular adenomas (HCA) than of typical FNH.³ In 2005, Bioulac-Sage *et al* reached the same conclusion using different molecular approaches⁴ and included in 2007 the so-called 'TFNH' in the subgroup of inflammatory HCA.⁵ Finally, in 2009, basis of the inflammatory phenotype was elucidated by the identification of gp130 activating mutations in 60% of the inflammatory HCA exhibiting sinusoidal dilatation or not.⁶

Here, we report the case of a patient with a single nodule thought to be by imaging an inflammatory HCA with major sinusoidal dilatation, which was revealed to be at the microscopical level a FNH.

CASE PRESENTATION

A routine blood test was performed in a 47-year-old mother of three children working as a house keeper and revealed a mild elevation of γ glutamyltransferase (46 IU N<39). On ultrasound (March 2009) a liver nodule of 55 mm diameter was discovered in segment VII. Liver stiffness was measured by the acoustic radiation force impulse imaging method. The median (M) speed of 10 measurements was 2.55 m/s (19.57 kPa) with interquartile range (IQR)/M=0.40 in the tumoural liver and 1.05 m/s (3.3 kPa) with IQR/M=0.19 in the non-tumoural liver.

MRI features were more indicative of an HCA than of a FNH (figure 1). Indeed, this large hypervascular lesion of the segment VII did not in particular exhibit any central scar and was heterogenous in all sequences. Furthermore, part of the lesion had high signal intensity on T2W sequences with persistent enhancement in the gadolinium-enhanced delayed phase. This feature was suggestive of sinusoidal congestion and, therefore, the diagnosis of inflammatory HCA was raised.

The patient had been on oral contraceptive (Diane 35, Adepal) for more than 20 years until the last 11 months (tube ligation). Aside a lombar scoliosis and a discal hernia, her past history was unremarkable. Preoperative blood tests, including transaminases, alkaline phosphatase, bilirubin, glycaemia, cholesterol, triglycerides, ferritin, fibrinogen, C reactive protein (CRP), were normal.

Pathological results

The surgical specimen weighed 66 g. A needle biopsy (tru-cut) was performed into the nodule before cutting the fresh specimen. The tumour was tan, with an irregular surface and congestive darker areas. The non-tumoural liver was limited to a small rim. Several samples of the tumour and non-tumour tissue were immediately frozen in liquid nitrogen and stored at -80°C and others were routinely processed for light microscopy and diagnosis purposes. The following stains were performed: H&E, Masson's trichrome, Perls, Gordon Sweet, as well as immunostains: cytokeratins 7 (CK7) and 19, liver fatty acid binding protein (LFABP), serum amyloid A (SAA), CRP, glutamine synthetase (GS) and β catenin.

Macroscopically, the tumour exhibited a vague nodularity (figure 1F), better seen after formol fixation, but without any fibrous scar. At the microscopic level (needle

Figure 1 MRI. (A) Axial fat suppressed T1W sequence shows a 55 mm diameter heterogenous nodule in the segment VII. (B) Axial fat suppressed T2W image shows heterogeneity of the lesion with a large hyperintense central area not suggestive of focal nodular hyperplasia (FNH). (C,D,E) Gadolinium enhanced fat suppressed T1W images in the arterial (C), portal venous (D) and delayed (E) phases: strong arterial enhancement of the nodule and heterogenous sustained enhancement in the portal and venous phases. The areas with delayed enhancement are corresponding with the highly hyperintense areas in T2W images (asterisks) suggesting areas of sinusoidal congestion in an inflammatory adenoma. (F) Cut fresh section of the FNH. The gross aspect looks more like a FNH than a hepatocellular adenoma, although there is no stellate scar.

biopsy and surgical specimen), the lesion corresponded to a benign hepatocellular proliferation with two parts: a dilated and a compact area (figure 2A,B, figure 3A,B,C and figure 4).

The dilated area was composed of atrophic hepatocytes bordered by dilated sinusoids and centred by arteries (figures 2B, 3 and 4). In some areas, sinusoids were massively dilated with almost no hepatocytes lining. In the

centre of these areas, abnormal arteries were surrounded by a lymphocytic reaction containing ductules (CK7 and 19 positive) themselves surrounded by collagen bundles (figure 4).

In the compact area (figures 5–7) there were major vascular abnormalities made of (1) numerous isolated dystrophic arteries with a thick wall, surrounded by a thin rim of collagen with no portal veins, and rare ductules; (2) hepatic

Figure 2 (A) Biopsy specimen performed on the resected nodule at low magnification. (B) H&E staining at high magnification: dilated sinusoids are visible (right) associated with thick walled arteries. This aspect could suggest the diagnosis of hepatocellular adenoma; however, the glutamine synthetase (GS) immunostaining (C) is characteristic of a focal nodular hyperplasia.

Figure 3 In this area, (A) trichrome (TRI) staining and (B) α smooth muscle (SMA) immunostaining, two zones are easily identified: one with dilated sinusoids and one compact. (C,D) Illustrate zones in the vicinity of A and B. Overall, there is little fibrotic bands visible on the trichrome staining.

Figure 4 (A,B,C) are identical zones with different stainings. (A) Heavy glutamine synthetase (GS) staining focalised in the compact zone (right) is faintly present in the dilated zone (left); in this zone, dilated sinusoids surround areas containing many arteries (B) and cytokeratin 7 (CK7) positive cells (C,D) mixed with inflammatory cells. SMA, α smooth muscle.

Figure 5 Compact zone. (A) Illustrates the typical aspect of glutamine synthetase (GS) in focal nodular hyperplasia (compact zone). This staining is sharply different in the non-tumoural liver (NTL) where the staining is limited around the hepatic veins. (C) Numerous arteries are visible in the vicinity of veins surrounded by areas that highly express GS (D). SMA, α smooth muscle.

Figure 6 Compact zone. (A,B,C,D) Illustrate the contact between arteries and veins. SMA, α smooth muscle.

Figure 7 Compact zone. The veins in (A) and (B) are occluded and in part recanalised. (C,D) The lumen of this artery surrounded by connective tissue is not visible. SMA, α smooth muscle. TRI, trichrome.

veins with different aspects: normal, surrounded by congestive areas, partially or completely occluded among oedematous fibrous tissue, or haemorrhagic areas, or in contact with arteries, linked to other hepatic veins by very thin bundles of collagen (figures 6 and 7).

The delimitation of the normal tissue was not clear.

LFABP, SAA, CRP and β catenin immunostaining was normal (not shown). In the compact area, GS pattern (figures 2C, 4A and 5A,B) was highly suggestive of FNH diagnosis as previously reported;⁷ this immunostaining was

fainter in the dilated area. The non-tumoural liver was normal (figure 5B).

The final report was FNH with major sinusoidal dilatation. Additional comments indicate that the FNH was lacking the key usual features such as central scar and fibrotic bands.

Molecular studies

Gene expression was examined by quantitative reverse transcriptase-PCR. Results were normalised to the mean expression level of normal liver samples. ANGPT1/ANGPT2, NTS/HAL, GLUL and GPR49 were 73, 980, 7 and 9, respectively. CRP, SAA, LFABP and UGT2B7 were in the normal limit.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis between so-called TFNH and inflammatory HCA is particularly difficult with both MRI and microscopic examination because the two entities share some pathological features (sinusoidal dilatation in particular).

TREATMENT

The nodule was thought to be a 55 mm diameter inflammatory HCA on MRI data and was subsequently surgically removed because of the high risk of bleeding.

OUTCOME AND FOLLOW-UP

In August 2010, the patient was in good health.

DISCUSSION

The diagnosis of FNH and HCA has made great progress over the last few years using modern imaging techniques.^{8 9} Despite these progresses, there is still in daily practice some difficulties concerning some atypical nodules. Today the firm diagnosis of HCA^{5 10–13} and FNH^{14–16} is mostly based on recent molecular data. Using appropriate immunohistochemical staining it is possible, at least on a whole specimen, to identify each entity.^{5 7 16}

Over the last few years, confusion has emerged in the literature between two entities—namely FNH with sinusoidal dilatation (so-called TFNH)¹ and inflammatory HCA with sinusoidal abnormalities (sinusoidal dilatation, congestion and peliosis). If a great number of so-called TFNH¹ are in fact inflammatory HCA with sinusoidal dilatation^{3 4} it does not imply that FNH with major sinusoidal dilatation does not exist.

Wanless *et al*¹ coined the term telangiectasia in FNH because, at the microscopic level, lesions were similar to those observed in hereditary haemorrhagic telangiectasia. The latter is characterised by widespread liver arteriovenous malformations, both microscopic and macroscopic, ranging from tiny telangiectases to discrete arteriovenous malformations. This term may not be appropriate in FNH and HCA.

Therefore, to avoid confusion between the two diagnoses, it is mandatory to perform immunostainings in order to confirm the diagnosis of either inflammatory hepatocellular adenoma by using SAA and CRP, or FNH by using GS (in addition to other markers such as CK7 and 19). Furthermore, the word telangiectasia should be avoided.¹⁵

In this case report, the diagnosis of FNH using GS was evident at least in some part of the nodule. The final proof was provided by the molecular analysis.

It is possible that the presence in the same nodule of two different parts (an area with major sinusoidal dilatation and a more compact one) has led to the conclusion that mixed form (adenoma/FNH) does exist.¹⁷ In the absence of convincing evidence, including inflammatory hepatocellular adenoma or even better molecular studies, it is presently preferable to conclude that this type of nodule does not exist.

A major clinical issue still remains. Indeed, can imaging and, if necessary, liver biopsy identify such a type of hepatocellular nodule with major sinusoidal dilatation/congestion/peliosis and differentiate FNH from HCA. The present case report showed that immunostaining, as well as molecular data are able to lead to the right diagnosis.

The main clinical question remains the bleeding eventuality of such a FNH with major sinusoidal dilatation. There are a few reports in the literature describing FNH bleeding.^{18 19} More than ever, the detection and characterisation of hepatocellular nodules requires appropriate tools, including immunohistochemistry^{5 7} and, if necessary, molecular approaches.^{6 10–13 16} The wide use of immunohistochemistry staining should help us to better classify patients and get rid off unnecessary terminology confusion.¹⁵

Competing interests None.

Patient consent Obtained.

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