Lymphopenia is associated with hypersplenism observed in cirrhotic patients is associated with impaired monocyte function, a bactericidal and opsonic activity deficit, depressed phagocytic activity in the reticuloendothelial system, defective chemotaxis and cytokine dysfunction. Furthermore, alcohol even without cirrhosis reduces the functional marrow granulocyte reserve, suggesting that there is a depressed granulopoietic activity.

The presentation of progressive multifocal leukoencephalopathy is usually multifocal with sub-acute neurological deficits including weakness (hemiparesis or monoparesis), confusion, appendicular or gait ataxia, and visual symptoms (hemianopsia or diplopia). However clinical manifestations vary depending on the distribution of the demyelinating lesions. Another particularity of this case is the monofocal presentation. Cases with a single lesion could be mistaken for a stroke or a tumour. Repeating cranial MRI and performing spectroscopy can help exclude these other diagnoses. The characteristics of MRI results in our patient’s lesion are quite typical, although progressive multifocal leukoencephalopathy lesions are usually multiple and asymmetric. Progressive multifocal leukoencephalopathy lesions are hypointense on T1 sequences and hyperintense on T2 sequences. There is no mass effect and no contrast enhancement. The demyelinating process affects the subcortical white matter and U fibers. In the past, the gold standard for the diagnosis of progressive multifocal leukoencephalopathy was brain biopsy. Due to the risk of fatal complications (2.9%) and morbidity (8.4%) with the procedure, detection of JC virus DNA in the cerebrospinal fluid by PCR has now replaced brain biopsy for the diagnosis of progressive multifocal leukoencephalopathy. PCR analysis has a sensitivity of 72 to 93% and specificity of 92 to 100% for the diagnosis of progressive multifocal leukoencephalopathy [5].

Although several drugs have been tested for progressive multifocal leukoencephalopathy there is no approved treatment for this disease. The cytosine arabinoside (cytarabine: two doses at 5 mg/kg) may be effective in decreasing JC virus replication in vitro and resulted in stabilization of seven out of 19 HIV negative patients with progressive multifocal leukoencephalopathy [6]. Nevertheless, whenever possible cell immunity should be restored. Thus, highly active antiretroviral therapy improved survival in HIV patients with progressive multifocal leukoencephalopathy. Therapy should be stopped or reduced in patients being treated by immunosuppressive therapy. Cytosine arabinoside was not administered to our patient with severe pancytopenia since this drug is toxic to bone marrow.

In conclusion, the diagnosis of progressive multifocal leukoencephalopathy should be considered in patients with cirrhosis who experience sub-acute, focal neurologic deficits and with MRI results showing demyelinating lesions. Funding: There are no financial disclosure.

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Positive PET-CT scan in hepatocellular adenoma with concomitant benign liver tumors

Fixation d’un adénome hépatocellulaire au TEP-scanner associée à d’autres tumeurs bénignes du foie

Introduction

Positive positron emission tomography (PET)-computed tomography (CT) in the diagnosis of hepatocellular adenoma without neoplastic transformation has never been described. Moreover, there is only one report of the association of hemangioma, focal nodular hyperplasia and hepatocellular adenoma in the literature [1].

We present a new case of three hemangiomas concomitant with two hepatocellular adenomas and focal nodular
hyperplasia, identified with 18-fluorodeoxyglucose (FDG) uptake on PET-CT in one of the hepatocellular adenoma.

**Observation**

A 65 year-old woman was referred for exploration of multiple liver tumors. The patient had a history of melanoma of the right foot treated by resection six years before (Breslow index 0.7 mm, Clark index 3), hormone replacement therapy for 10 years (estradiol, medrogestone) and haemangiomas of the liver discovered incidentally during pre-treatment of the melanoma, that did not receive treatment or follow-up.

A PET-CT performed for oncological follow-up of the melanoma showed focal 18-FDG uptake in the liver in segment VI (Fig. 1). CT-Scan revealed two types of liver tumors (Fig. 2): three 40, 100 and 40 millimeter lesions in segments I, VI and VIII, respectively, with hypoattenuation in the pre-
contrast phase and nodular enhancement that progressed centripetally, diagnosed as hemangioma; and three other 30, 40 and 30 millimeter lesions in segments IV–V, V and VI respectively, with heterogeneous and non specific enhancement, diagnosed as hepatocellular adenoma, focal nodular hyperplasia or hepatocellular carcinoma. The latter lesion in segment VI showed 18-FDG uptake on PET-CT.

Alpha-fetoprotein was normal, liver function tests only showed slightly elevated gamma-glutamyl-transpeptidase (1.5 N). Percutaneous CT-guided biopsy of the atypical lesion in segment VI identified a highly vascularized, fatty adenoma without neoplastic transformation.

Surgical exploration was performed two weeks after percutaneous biopsy. Magnetic resonance imaging was not performed preoperatively because of the absolute indication for surgical exploration, for at least three reasons:

- the patient had history of melanoma with undetermined but potentially malignant lesions in the liver;
- percutaneous biopsy only explored part of the tumor and could not rule out malignant transformation;
- there is a risk of rupture and bleeding in a massive subcapsular hepatocellular adenoma.

Anatomical resection was performed in segments V and VI, with atypical resection of the lesion in segments IV–V. The postoperative course was uneventful. The patient was discharged on postoperative day 7.

Final anatomopathology showed complete necrosis of the fatty hepatocellular adenoma in segment VI, without neoplastic transformation. The lesion in segments IV–V was a highly vascularized steatotic hepatocellular adenoma. Immunohistochemistry analysis of genetic alterations β-catenin and HNF-1α was negative. The other two resected lesions in segments V and VI were focal nodular hyperplasia and hemangioma respectively without any particularity (Table 1 for final findings).

After a six months follow-up, there was no recurrence or progression of the lesions.

Discussion

Various types of benign lesions of the liver may be present in the same patient. Focal nodular hyperplasia and hemangioma are associated in about 20 to 25% of cases, suggesting a common vascular origin [2]. However, hepatocellular adenoma is generally an isolated tumor, sometimes multiple but rarely associated with other benign lesions. In the first published case of this entity, tumors were discovered incidentally during the exploration of a hydatid cyst in a young woman with no history of oral contraceptive use [1]. Each tumor was unique and independent. We report the second association of these three types of tumors.

Our patient had six benign lesions: three hemangiomas, two hepatocellular adenomas and one focal nodular hyperplasia. Vascular anomalies may be the common step in the development of these tumors. Hemangiomas are hamartomas with a vascular origin. Focal nodular hyperplasias are reactional lesions from a vascular abnormality. Hepatocellular adenomas are a monoclonal proliferation but can be favored by vascular abnormalities. Thus angioarchitectural anomalies of the liver may promote the development of these "vascular related lesions", as previously hypothesized [1]. Furthermore, estrogenic receptors are present on the surface of the endothelium of the vessels and liaison with estrogens can stimulate the vasculature and favor tumor growth, whatever the type of lesion. Finally, anomalies of the liver vasculature may be both morphologic and functional, leading to excessive sensitivity of liver blood vessels, increasing angiogenic precursors and/or neoplastic growth factors.

Hepatocellular adenomas generally occur in young women and are related to oral contraceptive use. Oestrogen receptors are located on the membrane of hepatocytes, stimulating the growth and subsequent development of hepatocellular adenoma. On the other hand, oestrogens act on vascular structures and promote angiogenesis by endothelial cell proliferation, migration and organisation into capillary-like structures. Indeed, oestrogens may induce growth of vascular tumors — i.e. focal nodular hyperplasia and hemangioma — in this way [3]. Pharmacologically, hormone replacement therapy can be considered to be similar to oral contraceptive exposure. The influence of this treatment on the development of benign liver tumors has been previously suggested [3]. Thus, in our case, HRT may have enhanced the development and/or the growth of the tumors, especially in this case of suspected pathological angioarchitecture of the liver, as seen above.

In the present case, hepatocellular adenoma was positive on PET-CT. To our knowledge, this is the first description of positive PET-CT in the identification of hepatocellular adenoma. PET-CT can detect the activity of the glucose analogue, FDG. In the normal cell, FDG is taken up as 2-deoxy-D-glucose using glucose transporter proteins. After 6-phosphorylation by hexokinase, FDG-6-phosphate can’t be released from the cell once it has been absorbed. It also can’t be metabolized because the 2’ hydroxyl group...
(−OH), which is present in normal glucose and allows further glycolysis, is missing. Thus FDG-6-phosphate is trapped in the cell and is a good indication of both the distribution of glucose uptake and phosphorylation. After an intravenous injection of a radioactive metabolite of FDG (18-FDG), cells with increased metabolic activity — i.e. cancer cells, inflammatory cells — can be detected using PET. Usually, hepatocellular adenoma is a benign primary hepatic neoplasm with normal hepatocytes without a normal acinar structure. Close similarities between well-differentiated hepatocellular carcinoma and hepatocellular adenoma suggest similar uptake by both hepatocellular adenoma and the normal liver. Thus, hepatocellular adenoma and other benign liver tumors generally have poor or no 18-FDG uptake [4]. In our case, various hypotheses can explain the strong radiotracer uptake. Hepatocellular adenoma can degenerate into hepatocellular carcinoma. Some studies have reported that undifferentiated hepatocellular carcinoma may have a poor FDG metabolism resulting in hepatocyte accumulation and thus positive PET-CT. Moreover, radiotracer activity can increase at an early stage of malignant transformation before changes occur in the anatomical structure. In our report, percutaneous biopsy did not show any malignant transformation. However biopsies can underestimate the depth of invasion because it only analyzes a small part of the entire tumor. In addition, CT-Scan revealed a heterogeneous lesion that could suggest malignant transformation. However, this is rare in hepatocellular adenoma and usually involves lesions with genetic mutations (β-catenin and HNF-1α). Furthermore, 18-FDG uptake generally occurs in undifferentiated hepatocellular carcinoma while hepatocellular adenoma usually degrades into well-differentiated hepatocellular carcinoma.

Hepatocellular adenoma can have inflammatory features such as those in type III tumors of the histogenotypic classification by Zuchmann-Rossi [5]. This subgroup of hepatocellular adenoma includes unmutated lesions with inflammatory infiltrates and vessels with severe dystrophy that were previously classified as telangiectatic focal nodular hyperplasia. Hyper glucose consumption in these inflammatory cells could explain 18-FDG uptake. Nevertheless, 18-FDG uptake in inflammatory hepatocellular adenoma and telangiectatic focal nodular hyperplasia have never been reported in the literature. Moreover, in our report, the biopsy did not show any inflammatory reactions near or in the tumor.

The metabolism of hepatocellular adenoma is usually normal or even decreased, like other benign liver tumors [4]. However, these benign lesions may have hypermetabolic features, like those described in focal nodular hyperplasia [6]. In this case, FDG-PET imaging can show increased uptake compared to that of the normal liver. This phenomenon could be potentiated by hypervascularization of the hepatocellular adenoma inducing accumulation of glucose by excessive blood supply with insufficient “wash out”, due to normal or even decreased outflow which has been described for other molecules. This is the most credible hypothesis in relation to the final histology (lack of neoplastic or inflammatory components). However neither conventional imaging nor biopsy can detect this increase in activity. Thus, necrosis of the lesion after biopsy suggests intratumoral bleeding of a highly vascularized lesion and supports our metabolic hypothesis.

In conclusion, the occurrence of multiple hemangioma, hepatocellular adenoma and focal nodular hyperplasia of the liver confirms the hypothesis of a common origin of these solid benign tumors, probably due to anomalies of the angioarchitecture of the liver. It suggests that hormone replacement therapy, like oral contraceptives, can promote the development of these lesions. Moreover, this case shows that hepatocellular adenoma can exhibit 18-FDG uptake on PET-CT without malignant transformation. Because of the lack of sensitivity of percutaneous biopsy, we suggest that tumor resection be considered in this situation to confirm the diagnosis and avoid the risk of malignant transformation.

Conflict of interest statement

None declared.

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