Lymphopenia is associated with hypersplenism observed in cirrhotic patients is associated with impaired mono-
cyte 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 leukoen-
cephalopathy is usually multifocal with sub-acute neu-
rological 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 asym-
metric. Progressive multifocal leukoencephalopathy lesions
are hypointense on T1 sequences and hyperintense on T2
sequences. There is no mass effect and no contrast enhance-
ment. The demyelinating process affects the subcortical
white matter and U fibers. In the past, the gold standard for
the diagnosis of progressive multifocal leukoencephalopa-
thy 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 progres-
sive multifocal leukoencephalopathy there is no approved
treatment for this disease. The cytosine arabinoside (cytara-
bine: 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, when-
ever possible cell immunity should be restored. Thus,
highly active antiretroviral therapy improved survival in
HIV patients with progressive multifocal leukoencephalopa-
athy. 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 mar-
row.

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.

Conflict of interest statement

No conflict of interest.
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-
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

### 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

### Table 1: Specifications of each tumor after final anatomopathology.

<table>
<thead>
<tr>
<th>Liver segment</th>
<th>Preoperative diagnosis</th>
<th>Postoperative histology</th>
<th>Final diameter (millimeters)</th>
<th>18-FDG uptake</th>
<th>Resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>HA</td>
<td>HA</td>
<td>40</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>VI</td>
<td>HA</td>
<td>HA</td>
<td>100</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>VIII</td>
<td>HA</td>
<td>HA</td>
<td>40</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>IV–V</td>
<td>Not typed</td>
<td>HCA</td>
<td>20</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>V</td>
<td>Not typed</td>
<td>FNH</td>
<td>30</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>VI</td>
<td>HCA</td>
<td>Necrotic HCA</td>
<td>30</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

FDG: fluorodeoxyglucose; HA: hemangioma; HCA: hepatocellular adenoma; FNH: focal nodular hyperplasia.
(−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 degenerates 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.

References


*Service de chirurgie digestive et hépatobiliaire, Hôtel-Dieu, CHU de Clermont-Ferrand, boulevard Léon-Malfreyt, 63058 Clermont-Ferrand cedex 1, France
b Service de radiologie, hôpital Gabriel-Montpied, CHU de Clermont-Ferrand, Clermont-Ferrand, France

*Corresponding author.
E-mail address: ebuc@chu-clermontferrand.fr (E. Buc)
Available online 12 March 2010
doi:10.1016/j.gcb.2010.01.018