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Case study 2

Hepatocellular adenomas associated with hepatic granulomas:
Experiences in five cases

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The presence of multiple atypical hepatic lesions in combination with hepatocellular adenoma (HCA) confuses diagnosis when found on imaging or at laparotomy. HCA is a benign hepatic lesion occurring predominantly in young and middle-aged women [1]. Large HCA holds a risk of bleeding (5%) and malignant transformation (4.9%). Because of these risks, lesions >5 cm are generally resected. Molecular histopathological analysis categorizes HCA according to mutations within the lesions, each with a corresponding immunohistochemical phenotype [2].

Hepatic granulomas hold a wide variety of possible causes, although often a precise cause cannot be obtained [3]. Granulomas form in response to chronic exogenous or endogenous antigen presentation and may also form as a local response to specific agents or neoplasm [4]. Common causes of hepatic granulomas include sarcoidosis, tuberculosis, primary biliary cirrhosis, viral or bacterial hepatitis, parasites, and drugs.

In this paper we present five cases of HCA in whom granulomas in the tumor and/or surrounding liver parenchyma were found, and in 1 case even diffuse granulomatous hepatitis (GH). Three papers in the English literature and one in the French literature have reported the coexistence of HCA and liver granulomas in the past 30 years [5–7]. Patient characteristics are summarized in table 1 (upper part). Case 3 has been previously published [5]. An overview of previously published cases is shown in the lower part of table 1.

### Summary of patient and lesion characteristics

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, years</th>
<th>Sex</th>
<th>DM</th>
<th>BMI</th>
<th>OC, years</th>
<th>HCA, n</th>
<th>HCA location</th>
<th>HCA subtype</th>
<th>Location of hepatic granulomas</th>
<th>Characteristics of hepatic granulomas</th>
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<tbody>
<tr>
<td>This report (case 1)</td>
<td>36</td>
<td>f</td>
<td>II</td>
<td>27</td>
<td>15</td>
<td>7</td>
<td>diffuse</td>
<td>unclassified</td>
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<td>epithelioid, necrotizing; multinucleated giant cells; diffuse hilar lymphadenopathy</td>
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<td>f</td>
<td>I</td>
<td>31</td>
<td>10</td>
<td>&gt;10</td>
<td>diffuse</td>
<td>IHCA</td>
<td>border T and NT</td>
<td>epithelioid; non-necrotizing</td>
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<tr>
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<td>f</td>
<td>II</td>
<td>27</td>
<td>18</td>
<td>6</td>
<td>diffuse</td>
<td>IHCA</td>
<td>T</td>
<td>epithelioid; non-casing; multinucleated giant cells</td>
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<tr>
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<td>f</td>
<td>II</td>
<td>28</td>
<td>23</td>
<td>4</td>
<td>right</td>
<td>IHCA</td>
<td>T</td>
<td></td>
</tr>
<tr>
<td>This report (case 5)</td>
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<td>m</td>
<td>I</td>
<td>NA</td>
<td>1</td>
<td>left</td>
<td>IHCA</td>
<td>border T and NT</td>
<td>epithelioid</td>
<td></td>
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<td>diffuse</td>
<td></td>
<td></td>
<td>epithelioid; non-necrotizing</td>
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<td>Neuberger et al., 1980 [15]</td>
<td>28</td>
<td>f</td>
<td></td>
<td>5/9</td>
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<td>T</td>
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<td>f</td>
<td></td>
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<td>border T and NT</td>
<td>epithelioid; non-casing; multinucleated giant cells</td>
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<td>Le Bail et al., 1992 [5]</td>
<td>39</td>
<td>f</td>
<td></td>
<td>12</td>
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<td>Grazil et al., 2007 [6]</td>
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<td>f</td>
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<td>10</td>
<td>2</td>
<td>III &amp; IV-V</td>
<td>diffuse</td>
<td>multinucleated giant cells; diffuse hilar lymphadenopathy</td>
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</table>

### 1st Patient

A 29-year-old woman was referred to the surgical department. Patient history included 10 years of OC use, DM type I with diabetic nephropathy (creatinine 147 μmol/l; normal 90 μmol/l), and severe hypertension (up to 220/100 mm Hg) which caused encephalopathy (table 1). A contrast-enhanced MRI to evaluate her renal status incidentally showed multiple hepatic lesions <2 cm, one lesion of 5 cm in the left liver, and one lesion in segment 6 of 4.2 cm (fig. 2). Preoperative liver biopsy confirmed the diagnosis of HCA and showed hepatic granulomas in the biopsy specimen. The left-lateral segments of the liver were resected and local excision of the lesion in segment 6 was performed. The lesions were consistent with inflammatory HCA, with hemorrhagic changes, sinusoidal dilatation, infiltrate of inflammatory cells and irregular, thick blood vessels. Immunohistochemical staining showed overexpression of CRP and SAA. Beta-catenin, GS and LFABP expression were not aberrant. Within the HCA lesions and liver, tissue was disrupted by epithelioid granulomas with a necrotic center containing multinucleated giant cells (fig. 1f). Ziehl-Neelsen, PAS and Grocott staining were negative. At the outpatient clinic no evidence of sarcoidosis, bacterial or fungal infection was found. Three months after surgery, the patient had fully recovered and resumed work.

### 2nd Patient

A 36-year-old woman with a history of diabetes mellitus (DM) and 15 years of oral contraceptive (OC) use was referred to the surgical department. She presented with acute upper abdominal pain caused by bleeding of a hepatic lesion (12.5 cm) during the 19th week of pregnancy, which was treated by selective arterial embolization of the branches of the feeding hepatic arteries in segment 2 and 3 (fig. 1a). One year later, the patient presented with abdominal pain similar to the pain during the previous episode of bleeding, and imaging showed signs of recurrent bleeding (fig. 1b). At laparotomy the liver surface appeared macroscopically inhomogeneous with disseminated pale lesions of approximately 0.5-1.0 cm with a tendency to confluence (fig. 1c, d). A diffusely metastasized malignancy was suspected, however intraoperative frozen sections of these lesions revealed granulomas. Histopathological examination showed multiple HCAs: hepatocellular proliferation without cytonuclear atypia, but with the presence of thick-walled vessels, areas of necrosis, hemorrhage, and in some vessels embolization material (fig. 1e). These HCAs remained unclassified as liver fatty acid binding protein (LFABP), glutamine synthetase (GS), C-reactive protein (CRP) and serum amyloid A (SAA) did not show any aberrant expression patterns [8]. Throughout the HCA lesions and liver, tissue was disrupted by epithelioid granulomas with a necrotic center containing multinucleated giant cells (fig. 1f). Ziehl-Neelsen, PAS and Grocott staining were negative. At the outpatient clinic no evidence of sarcoidosis, bacterial or fungal infection was found. Three months after surgery, the patient had fully recovered and resumed work.
at the border of tumorous and non-tumorous tissue, an influx of epithelioid granulomas was found. There were no signs of sarcoidosis or opportunistic infections, and Ziehl-Neelsen and PAS staining were negative. No peri- or postoperative complications occurred and the patient could be discharged on day 7. Six months after surgery the patient was in good condition.

A 52-year-old woman with a history of type II diabetes was referred to the liver surgical department for resection of multiple hepatic lesions, as previously reported [5]. The patient had had three normal pregnancies after which she had taken OC for 18 years. In a period of 6 years, the tumor in segments 6/7 enlarged from 2 cm to 7 cm. Ultrasound showed 5 additional smaller nodules measuring 2–3 cm: 4 in the right liver and 1 in segment 2. A right hepatectomy and enucleation of the lesion in segment 2 was performed. All 6 lesions had the same histopathological characteristics consistent with inflammatory HCA. Immunohistochemical staining revealed an overexpression of SAA and CRP, without abnormalities for LFABP, GS and beta-catenin staining. In addition, there were numerous non-necrotizing granulomas inside all tumors which were not present in the non-tumoral liver. The granulomas were composed of lymphocytes, epithelioid cells and multinucleated giant cells, occasionally containing asteroid bodies. There was no argument for opportunistic infections and the following stainings were negative: Ziehl-Neelsen, PAS, Grocott and Warthin-Starry. The non-tumoral liver parenchyma was normal.

This 39-year-old woman was referred for resection of a 7 cm hepatic lesion in the right liver lobe discovered by hepatic ultrasound that was carried out for evaluation of elevated serum γGT (360 U/l; normal <40 U/l). Patient history revealed three normal pregnancies, one miscarriage and one abortion, OC use during 23 years, and DM type II. MRI showed a large subcapsular tumor with central necrosis in the right liver, and 2 hemangiomata in the left lobe. A right hemihepatectomy was performed. On histopathological examination a benign hepatocellular proliferation with necrotic and hemorrhagic changes was found, consistent with HCA. Three small nodules were discovered at some distance from the larger tumor, measuring between 1 and 2 cm. All lesions showed typical features of inflammatory HCA by standard microscopy, confirmed by additional immunohistochemistry with overexpression of SAA and CRP, whereas LFABP, GS and beta-catenin were normally expressed. In addition, small epithelioid granulomas were observed within the tumor mixed with inflammatory infiltrates. The non-tumoral liver was mildly steatotic without granulomas.

A 32-year-old man with DM type I was admitted to the liver surgical department after discovery by ultrasound of a 10 cm lesion in the left liver lobe. Serum alpha-fetoprotein was normal (<7 U/l) and there were no indications for primary or secondary malignant disease on additional imaging. A left hemihepatectomy was performed. The tumor, bulging from the posterior side of segment 3 of the liver, was well circumscribed and presented with congestive and hemorrhagic areas. In addition to a typical aspect of inflammatory HCA, there were numerous large epithelioid granulomas dispersed inside the tumor and in the immediate peritumoral parenchyma. The non-tumoral liver at distance was normal, except for many glycogenated nuclei. Immunohistochemical staining showed an overexpression of SAA and CRP inside the tumor, confirming inflammatory HCA. Follow-up after resection was uneventful.
Chapter 10

Case study 2

Conclusions

Finally, chronic OC use might also be an underlying etiological factor in both HCA and hepatic granulomas. OCs are listed as one of many drugs known to cause GH [5, 13]. This drug is also associated with growth and development of HCA [13, 14]. Therefore chronic OC use may be a common etiological factor in the formation of HCA and hepatic granulomas in our female patients. The first case presented with multiple HCAs and diffuse granulomatous infiltration in both the existing HCA and the entire liver. This case was not an inflammatory HCA, but remained unclassified. The extensive GH likely reflects a systemic cause. All previously reported cases in literature (table 1) presented with a history of chronic OC use. Interestingly, in the patient described by Neuberger et al. [15] in whom a GH was diagnosed in association with OC use, the liver biopsy performed 6 months after discontinuation of OC revealed no granulomas, which supports this hypothesis.

In conclusion, little has been reported on hepatic granulomas in association with HCA. We found, along with HCA, granulomas in (peri)tumorous tissue, but also diffusely infiltrated in the entire liver. We propose that the hepatic granulomas in these cases are a response to persistent inflammation caused by (inflammatory) HCA, a local reaction to a neoplasm, chronic use of OCs, or a combination of these factors.