Diffuse liver hamartomatosis (diffuse von Meyenburg complexes) mimicking hepatic metastases on a background of previous cancer

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ABSTRACT

Bile duct hamartomas are typically small benign liver lesions that can radiologically mimic metastases on ultrasound and computed tomography, as well as macroscopically. We present a rare and interesting case and review the relevant literature. A 49-year-old woman underwent ultrasound investigation for right upper quadrant pain, which revealed diffuse liver lesions. In the setting of her previous vulval cancer, it was suspected that she had hepatic metastases. This was strongly reinforced with computed tomography and elevated CA 19-9 levels. A liver biopsy revealed diffuse and multifocal bile duct hamartomas and positron emission tomography was negative for metastases or features of cancer recurrence. A diagnosis of diffuse liver hamartomatosis was made. In view of the continuing clinical and laboratory picture, she required regular follow-up. The collective features of this case are unique, as the isolated characteristics of particular interest have not been previously described in the context of a single case. Bile duct hamartomas should be included in the differential diagnosis of multiple liver lesions. CA 19-9 is not a reliable marker for differential diagnosis of this entity.

KEYWORDS

Bile duct hamartoma – Hamartomatosis – Liver metastases – von Meyenburg complexes – CA 19-9

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Background

Bile duct hamartomas are also called von Meyenburg complexes since their first recording in 1918 by the Swiss Pathologist Professor Hanns von Meyenburg.¹ They are small benign liver lesions consisting of dilated, cystic bile ducts embedded in a fibrous stroma.² They represent a type of ductal plate malformation resulting from a remodelling deficiency of the primitive ductal plate.⁵ Bile duct hamartomas are typically encountered incidentally as they tend to be entirely asymptomatic. There is an association with polycystic kidney and liver disease, and Caroli's disease.⁴ In an autopsy study of 70 cases of polycystic liver disease, 29 had multiple bile duct hamartomas.⁵ While this is a benign condition, there are sporadic reports of malignant transformation into intrahepatic cholangiocarcinoma.⁶

Bile duct hamartomas are either typically found at biopsy, during radiological investigations or on gross examination of the liver intraoperatively. The overriding clinical significance is that their appearance on ultrasound or computed tomography (CT) can be confused as liver metastases. Furthermore, their macroscopic appearance, typically white-grey 10–15mm nodules on the liver surface,

may also mimic metastases.⁷ This may cause significant concerns when it is an unexpected intraoperative finding. As bile duct hamartomas can be misdiagnosed, it is important to be able to accurately and promptly distinguish them from true metastases.

We report a unique case of diffuse liver hamartomatosis with particularly interesting collective features, and review the relevant literature.

Case history

A 49-year-old white woman presented with a one-day history of moderately severe, intermittent pain in the right hypochondrium and decreased appetite over the previous few weeks. Fevers or symptoms suggestive of biliary obstruction were absent. Her history included tonsillectomy and vulval cancer, for which she had undergone wide local excision twice, seven and eight years earlier. However, there was no indication at this stage that her right upper quadrant pain should be attributed to this pathology. After surgical treatment for vulval cancer, she had remained under gynaecological surveillance, including annual clinical review, and had remained well and asymptomatic. She was

a smoker of 15 cigarettes/day for over 30 years. There was no history of alcohol abuse and she was not on any regular medication.

On physical examination, her abdomen was soft but tender in the right upper quadrant. There were no masses or organomegaly. Her observations were normal. Blood tests showed a slightly raised C-reactive protein at 20mg/L and unremarkable liver function tests: bilirubin 8 μ mol/L (normal level < 21 μ mol/L), alkaline phosphatase (ALP) 130IU/L (normal range 30–130IU/L), alanine aminotransferase 21IU/L (normal level <40IU/L). Her haemoglobin was 130g/L and white blood cell count 8.2×10^9 /L. Possible biliary colic was suspected, but an ultrasound scan revealed a normal gallbladder with no gallstones, intra- or extrahepatic bile duct dilatation or other possible gallstone-related complications. Instead, a diffusely abnormal liver parenchyma with heterogeneous nodular areas of increased echogenicity was depicted, suggestive of metastatic disease (Fig 1).

In light of her past medical history and suspected metastases, an expedited CT of the thorax, abdomen and pelvis with contrast was performed, which showed a diffusely heterogeneous liver, with multiple low-attenuation lesions. There was no significant portal, para-aortic or pelvic sidewall lymphadenopathy, or other features suggestive of vulval cancer recurrence or another primary site of cancer (Figures 2 and 3). Tumour markers were carbohydrate antigen 19-9 (CA 19-9) 108kIU/L (range 0–35kIU/L), carcinoembryonic antigen 6.5ug/L (range 0–3.5ug/L), alpha-fetoprotein 6kIU/L (range 1–10kIU/L) and CA 125 12kU/L (range 1–35kU/L). CA 19-9 elevation further enhanced the concerns for the possible presence of a cancer (interpreted in isolation, this would be suspicious for a biliopancreatic cancer or another cancer of the

digestive tract or the lung). The case was discussed at the hepatopancreatobiliary multidisciplinary team meeting and, based upon the radiological appearances, a provisional diagnosis of disseminated malignancy in the liver of unknown primary was made.

As there was no evidence of vulval cancer recurrence or suspicion of a specific non-gynaecological primary from her history and examination, an urgent outpatient ultrasound-guided liver biopsy was scheduled. This revealed exclusively benign changes representing abnormal biliary ductules consistent with hamartomas (Fig 4). The surrounding liver parenchyma was normal with no suspicious features of liver pathology. Subsequently, positron emission tomography (PET) was arranged to rule out occult metastatic disease hiding among the hamartomas, especially in light of continuing symptoms and elevated tumour markers. This showed homogenous tracer uptake, without focal abnormalities. There was no significant 18F-fluorodeoxyglucose-avid lymphadenopathy or uptake in the inguinal regions. The diffuse and multifocal nature of these hamartomas implied the diagnosis of diffuse liver hamartomatosis.

On clinic review one month after the initial presentation, the patient was still experiencing pain and lack of appetite. Her liver function tests and tumour markers were at the same levels as previously noticed, while her gamma-glutamyl transpeptidase (γ GT) was raised at 125IU/L (5–35IU/L). She was subsequently referred to hepatology for further evaluation and management. Over six months following the diagnosis of diffuse liver hamartomatosis, the patient continued to have right upper quadrant pain and deranged liver function tests with raised ALP of 136IU/L and γ GT of 100IU/L. Despite histology showing an otherwise normal liver parenchyma with no features of liver disease other than the diffuse hamartomas, a full liver screen was undertaken to exclude possible underlying conditions, with

Figure 1 Liver ultrasound showing multiple heterogeneous nodular areas compatible with metastases

Figure 2 Computed tomography of the abdomen; axial section showing multiple low-attenuation liver lesions

negative results. Hence, the patient continued to be followed up with the diagnosis of diffuse liver hamartomatosis.

Her initial treatment with conventional analgesics was not particularly successful. A change to amitriptyline achieved symptom control. One year after the initial presentation, the patient continues to be under hepatological surveillance, her symptoms are well controlled and liver function tests are stable.

Discussion

Bile duct hamartomas are a rare clinical entity. However, in a study of 2,843 autopsies, a prevalence of 5.6% was reported.⁸ The rate is 0.6% for incidental findings in liver biopsies.⁹ The incidence of multiple bile duct hamartomas is less common at 0.35%.¹⁰ A small proportion of bile duct hamartomas may become symptomatic, causing pain because of the mass effect. This is more common in bile duct hamartomas that have developed into giant cysts rather than diffuse hamartomas.¹¹ A case series reported diffuse abdominal pain in two of four patients with multiple bile duct hamartomas, but this is a rare phenomenon.⁴ Equally, presentation with right upper quadrant pain, as in our case, is a rare manifestation.

The incidental finding of bile duct hamartomas from biopsies does not pose a clinical problem. The uncertainty lies in their macroscopic appearance, as well as their appearances on ultrasound and CT, which can be misinterpreted as metastases.^{12,13} This is especially understandable in patients with a history of current or previous malignancy, as in our case. However, unlike with metastases, a patient with multiple bile duct hamartomas is not expected to be clinically unwell or to have any features of malignancy on laboratory tests, and there will be no progression of the lesions on repeat scanning, as they do not tend to grow.¹²

In our case, the persistent symptoms of anorexia and right upper quadrant pain, together with the history of vulval cancer and relevant CT findings, suggested the diagnosis of metastatic disease.

In patients with known cancer, the misinterpretation of bile duct hamartomas as metastases may occur at the time of the staging CT.^{14,15} The modality of choice to clarify the nature of these lesions is magnetic resonance imaging (MRI), as demonstrated in previous cases.^{2,4,10,11,14} However, even multiple bile duct hamartomas have sporadically been missed.¹⁶ The typical appearance of bile duct hamartomas on MRI is of hyperintense cystic nodules on T2-weighted, low signal intensity on T1-weighted, and the lesions not communicating with the biliary tree.^{14,17} PET is used infrequently, and it is reserved for cases where MRI is inconclusive and there is a known primary cancer.^{18,19} We requested PET despite a biopsy showing bile duct hamartomas because of the continuing clinical and laboratory picture, to rule out that any hamartoma had undergone malignant change or an occult malignancy was present among the diffuse liver lesions.

A more acutely troubling presentation is when bile duct hamartomas have not been detected preoperatively during radiological investigations but are found on gross inspection of the liver intraoperatively.^{7,16,17} These metastasis-mimicking lesions can be widespread and affect both liver lobes. Patients with malignant deposits with a similar distribution will typically also have peritoneal carcinomatosis and deranged liver function tests preoperatively.²⁰ However, the absence of these findings does not provide complete reassurance. Understandably, the

Figure 3 Computed tomography of the abdomen; coronal section showing the multifocal nature of the lesions

Figure 4 Multiple dilated bile ductules consistent with bile duct hamartomas

potential implications of these lesions being misdiagnosed at any stage may be clinically very severe. In light of these facts, as regards intraoperative management, the importance of frozen sections in pursuit of clarification of the nature of these unexpected liver lesions is undoubted.⁷

As the presence of metastases is critical in determining the appropriate treatment, with many conditions being deemed palliative, it is imperative that suspected metastases are promptly investigated. Methodologically, only histological examination can guarantee correct identification.²¹ Of note, CA 19-9 cannot reliably be used in the differential diagnosis between bile duct hamartomas and metastases or malignant transformation of bile duct hamartomas, since its persistent elevation has occasionally been observed in bile duct hamartomas in the absence of malignancy, as in our case.²² It appears that our case is the third where this observation has been encountered, following two reports from 2017.^{23,24} In the first case, a patient with multicystic biliary hamartoma presented with extremely elevated CA 19-9, which decreased dramatically after surgical removal,²⁵ while in the second case, a patient with multiple bile duct hamartomas, steatosis, chronic cholecystitis and elevated CA 19-9, underwent exploratory laparotomy, biopsies and cholecystectomy (histology confirmed the diagnoses) and continued to have raised CA 19-9 after two years of follow-up.²⁴ These observations have recently prompted the authors of a case of multiple bile duct hamartomas, to suggest that the use of CA 19-9 should be discouraged in the differential diagnosis with malignancy,²² and our experience with the present case supports this approach.

Most patients are asymptomatic.^{21,22} However, rare cases such as ours with persistent symptoms, as well as deranged biochemical and tumour markers may occur. Even more rarely, as in our patient, specific treatment and follow-up may be required.

Conclusions

Bile duct hamartomas are of interest to clinicians and radiologists as they can mimic metastases on ultrasound and CT, as well as on gross inspection of the liver. As the presence of metastases is a crucial determinant of further treatment, it is imperative that they are definitively diagnosed. This can be achieved by MRI and/or imaging-guided biopsy or frozen section where applicable.

Although bile duct hamartomas are not uncommon, they rarely are numerous, diffuse and symptomatic, as in our case. Even so, they should be considered in the differential diagnosis of multifocal liver lesions. Regardless of their number and presentation, bile duct hamartomas should be part of the differential diagnosis particularly for anyone presenting with possible metastases. CA 19-9 cannot be considered a reliable marker in the differential diagnosis between bile duct hamartomas and liver metastases.

Symptom control may be achieved with amitriptyline in case of failure of conventional analgesics.

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