Thirty-six-year-old woman with a liver mass: diagnosis hidden in history

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CLINICAL QUESTION

A 36-year-old woman presented with postprandial abdominal pain. Radiological assessment showed an irregular endoluminal mass in intrahepatic bile ducts and a separate mass in liver segment 8. A liver biopsy was performed. In addition, medical history revealed two skin excisions of lesions on the left thigh (at 24 years of age), and in the left popliteal space (at 30 years of age). Family history revealed several grandparents who died of cancer at older age (specific types not fully clear). Review the high quality, interactive digital Aperio slide of the liver biopsy and the skin excision (popliteal space) at http://virtualacp.com/JCPCases/jclinpath-2019-206271.R2_1/ and http://virtualacp.com/JCPCases/jclinpath-2019-206271.R2/ and consider your diagnosis.

WHAT IS YOUR DIAGNOSIS?

A. Intrahepatic cholangiocarcinoma and *BAP1*-inactivated melanocytic nevus/tumour in the context of *BAP1* tumour predisposition syndrome.
B. Intrahepatic cholangiocarcinoma and melanoma in the context of *PALB2* tumour predisposition syndrome.
C. Intrahepatic cholangiocarcinoma and Spitz nevus with a ROS1 fusion.
D. Intrahepatic cholangiocarcinoma and Spitzoid melanoma in the context of Li Fraumeni syndrome.
E. Metastastic pancreatic carcinoma and Spitzoid melanoma in the context of familial atypical multiple mole/melanoma syndrome.

The correct answer is after the discussion.

DISCUSSION

The liver biopsy showed an adenocarcinoma of which the immunoprofile could fit the clinicoradiological picture of intrahepatic cholangiocarcinoma with a liver metastasis (CK7 positive, CK20 negative, DPC4 retained) (figure 1). The prior skin excisions showed an atypical melanocytic lesion (figure 2). A hereditary form of cholangiocarcinoma was

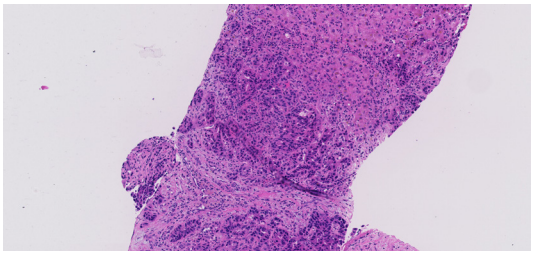

Figure 1 Liver biopsy. At the top of the figure, pre-existent liver parenchyma is present. In the middle and at the bottom of the biopsy, atypical, irregular ductular structures are seen.

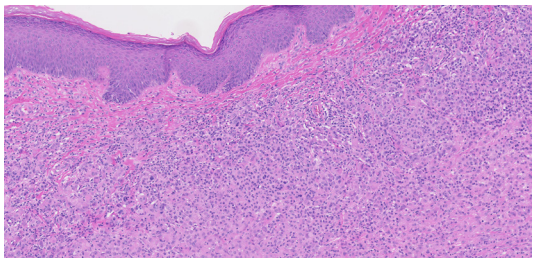

Figure 2 Skin excision. This figure shows a skin excision with pre-existent epidermis at the top. In the underlying dermis, a proliferation of epithelioid cells is seen with prominent nucleoli and variable amounts of cytoplasm, accompanied by a lymphocytic infiltrate.

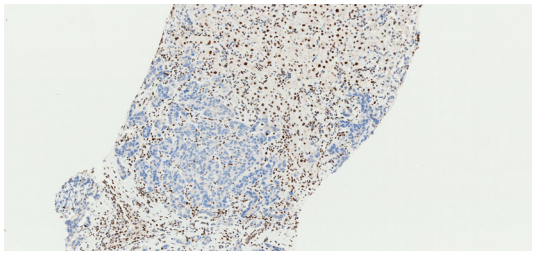

Figure 3 BAP1 immunostain on liver biopsy. BAP1 immunostain on the liver biopsy shows loss of BAP1 nuclear expression in the atypical cells forming irregular ductular structures. The hepatocytes and some inflammatory cells show normal BAP1 expression and serve as internal positive control. BAP1, BRCA1-associated protein-1.

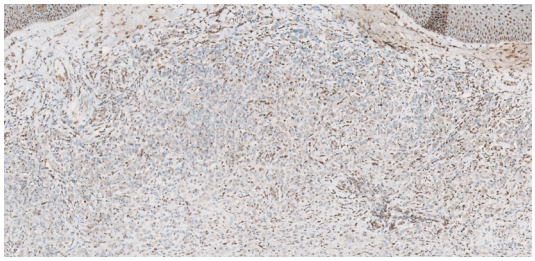

Figure 4 BAP1 immunostain on skin excision. The BAP1 immunostain on the skin excision shows loss of BAP1 nuclear expression in the atypical epithelioid cells. The cells of the epidermis as well as inflammatory and stromal cells in the dermis show normal BAP1 expression and serve as internal positive control. BAP1, BRCA1-associated protein-1.

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considered because of the patient's young age, absence of known risk factors (eg, primary sclerosing cholangitis or bile duct anomalies) and previous peculiar melanocytic lesions. This triggered us to reassess the slides and to perform a BRCA1-associated protein-1 (BAP1) immunostain on both the cholangiocarcinoma (figure 3) and the atypical melanocytic lesion (figure 4). Both lesions showed loss of nuclear BAP1 expression. The final diagnosis was *BAP1* tumour predisposition syndrome with associated cholangiocarcinoma, a *BAP1*-inactivated melanocytic nevus/tumour (BIMN/T) and a later confirmed *BAP1* germline mutation. This syndrome is associated with BIMN/Ts and an increased risk of several malignancies, in particular melanomas, mesotheliomas and clear cell renal cell carcinomas.[1] *BAP1* is a tumour suppressor gene with a role in transcription regulation and DNA damage response.[2] Somatic *BAP1* loss occurs in about 20% of intrahepatic cholangiocarcinomas.[2 3] However, germline *BAP1* mutations in cholangiocarcinomas have also been reported.[1] Identification of *BAP1* germline mutations has important clinical implications for the patient and (affected) family members with respect to screening. This case illustrates the importance to consider hereditary cholangiocarcinoma in certain circumstances, particularly in case of a young age of onset, certain tumours in the medical/family history and absence of acquired risk factors for cholangiocarcinoma.

Take home messages

- Think about the possibility of a hereditary cancer syndrome when there are no acquired risk factors, when there is a positive family history for cancers and when it concerns a young patient.
- Have a low threshold to check the medical history of the patient to be able to interpret the lesion you see in a broader context.
- *BAP1* germline mutations predispose to several tumours, including BRCA1-associated protein-1(*BAP1*)-inactivated melanocytic nevus/tumour, uveal melanoma, cutaneous melanoma, basal cell carcinoma, mesothelioma, clear cell renal cell carcinoma as well as cholangiocarcinoma. The diagnosis of *BAP1* tumour predisposition syndrome has important consequences in terms of regular screening for malignancies.
- *BAP1*-inactivated melanocytic nevi/tumours are characterised by polypoid lesions consisting of large epithelioid melanocytes with an intermixed lymphocytic infiltrate.
- BAP1 loss can be easily identified by immunohistochemistry.

ANSWER

A. Intrahepatic cholangiocarcinoma and *BAP1*-inactivated melanocytic nevus/tumour in the context of *BAP1* tumour predisposition syndrome.

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