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Letter to the editor

Adenosquamous intrahepatic cholangiocarcinoma in a patient with primary sclerosing cholangitis and ulcerative colitis

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A 35-year-old man presented to the emergency department in September 2023 with abdominal pain, anorexia and asthenia. He had been diagnosed with ulcerative colitis (UC) in 2010 and maintained endoscopic remission on 5-aminosalicylates. In 2015 he was also diagnosed with primary sclerosing cholangitis (PSC) and started ursodeoxycholic acid. There was no history of smoking. Laboratory tests revealed hypercalcemia (3.78 mmol/L). Computed tomography showed two hepatic hypodense lesions (65 × 56 mm in segment VII and 45 × 36 mm in segment II), with enlarged lymph nodes in the hepatic hilum and retroperitoneum (Fig. 1a–c). The initial biopsy of the right liver lesion revealed a carcinoma with squamous cell differentiation (Fig. 1d–f). PDL1 score was 5 % and TPS PDL-1 score was 0 %. DNA and RNA next-generation sequencing detected no targetable mutation or gene alteration. A biopsy of the non-tumoral liver confirmed absence of fibrosis. 2-[18F]fluoro-2-deoxy-d-glucose positron emission tomography was performed to exclude other primary lesion. The patient received systemic chemotherapy with gemcitabine and cisplatin combined with durvalumab. Tumor assessment after 6 cycles showed a dissociated response between the two liver lesions, with a right-sided response but progression on the left. A biopsy of the progressive liver lesion revealed a moderately differentiated adenocarcinoma (Fig. 1g, h). The final diagnosis was therefore an adenosquamous type cholangiocarcinoma of which the two contingents, squamous and adenocarcinomatous, were revealed on biopsies from two liver lesions. The patient then started second-line Folfox® chemotherapy with progressive disease after 4 cycles and died in July 2024 due to hepatic and peritoneal progression. Overall survival from histological diagnosis was 9.3 months.

There is an established association between PSC and cholangiocarcinoma (CC), patients with UC-PSC having an 8–15 % lifetime risk of developing this disease. CC with a histological subtype other than adenocarcinoma are considered rare. Some reports of adenosquamous intrahepatic CC have been published, mostly in patients treated by surgery. To our knowledge, only a few cases of adenosquamous CC associated with PSC have been published [1,2]. Few cases of CC with pure squamous cell carcinoma subtype have also been reported, but none of them associated with PSC [3,4]. Interestingly, one of these cases was associated with a paraneoplastic syndrome of hypercalcaemia-leucocytosis, similar to our case, which is also a rare feature in CC [4]. The combination of cisplatin-gemcitabine chemotherapy with an anti-PD1 antibody (durvalumab or pembrolizumab) is the standard first-line treatment for advanced biliary tract adenocarcinoma. Molecular alterations such as FGFR-2 fusions, IDH-1 mutations, BRAF V600E mutations, NTRK fusions, HER-2 amplifications and/or microsatellite instability can be detected and targeted [5]. Due to the rarity of biliary tract cancers of the adenosquamous and SCC subtypes, there are no guidelines for their management, and the efficacy and safety in these tumours are unknown, particularly in the context of PSC and UC. In our patient, no such molecular alteration could be identified, but we encourage this research in the context of this rare disease.

Ethics

Written informed consent was obtained from the patient for publication of this report.

CRediT authorship contribution statement

Inês Coelho Rodrigues: Writing – review & editing, Writing – original draft, Data curation. **Laure Dibombe:** Writing – review & editing, Writing – original draft, Validation, Data curation. **Pauline Guillouche:** Writing – review & editing, Writing – original draft, Validation, Data curation. **Tamara Matysiak-Budnik:** Writing – review & editing, Writing – original draft, Validation, Data curation. **Damien Bouda:** Writing – review & editing, Writing – original draft, Validation, Data curation. **Yann Touchefeu:** Writing – review & editing, Writing – original draft, Validation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Yann Touchefeu reports a relationship with AstraZeneca that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal

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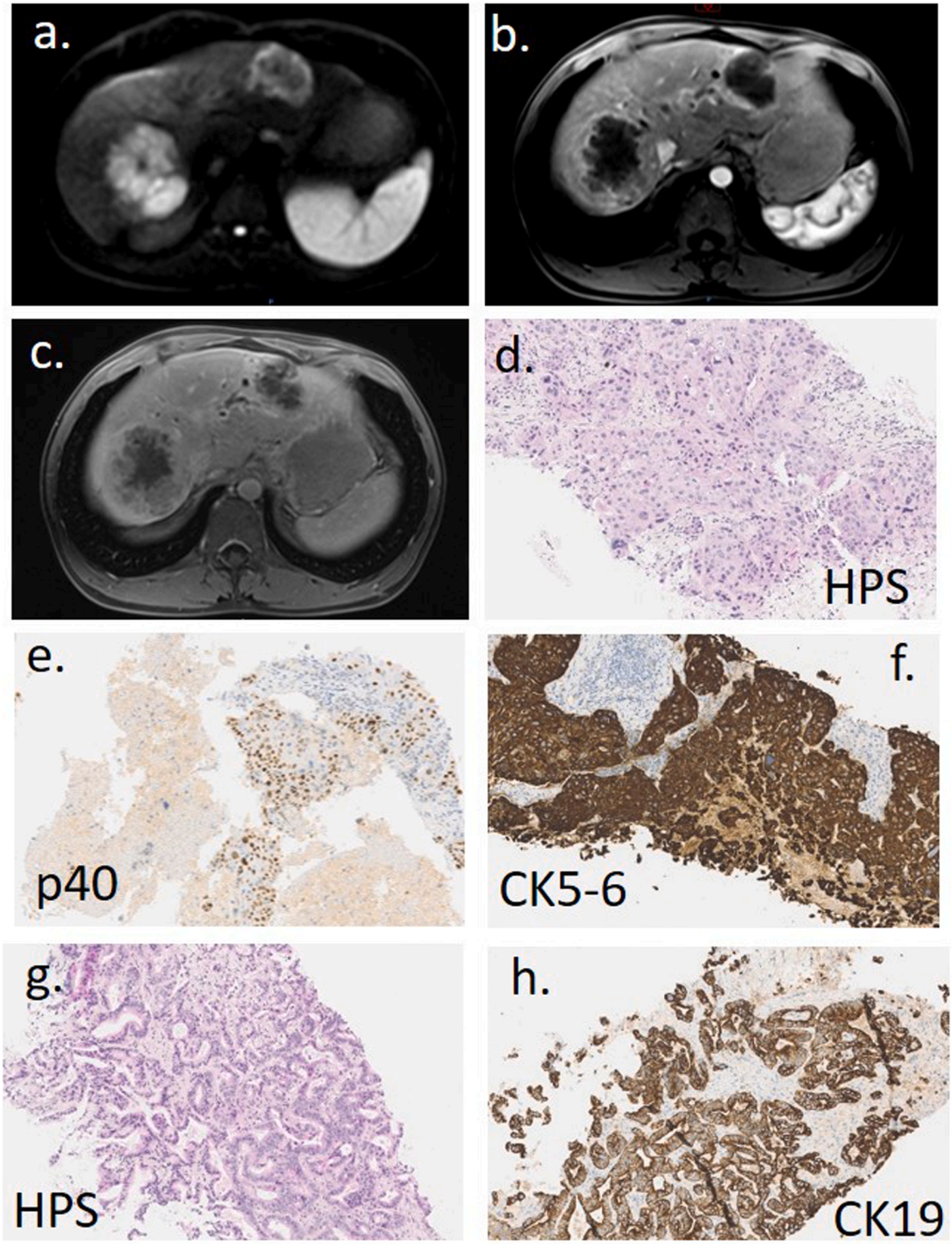

Fig. 1. Hepatic MRI imaging (b) Diffusion-weighted imaging (DWI) sequence with b-value 800 showed peripheral hyperintense rim suggesting malignant lesions (a). Post-contrast T1-weighted fat-saturated sequence during (c) arterial phase and (d) 3-minute delayed phase highlights hypervascular rimlike lesions with progressive internal fibrous enhancement suggestive of intrahepatic cholangiocarcinoma in this clinical context. Initial biopsy from the right liver lesion, revealing a carcinoma with squamous cell differentiation. Using hematoxylin phloxine saffron (HPS) X10 staining, the tumor cells were epithelioid with voluminous nucleolus nuclei (d). They expressed p40 (e) and CK5-6 (f) and did not express other markers of origin. Second biopsy of the left liver lesion revealing a moderately differentiated adenocarcinoma (g). These were glands of atypical cells (HPS X10) with a nonspecific phenotype (CK7+ CK19+ CK20−) (h).

relationships that could have appeared to influence the work reported in this paper.

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Inês Coelho Rodrigues[a,b], Laure Dibombe[c], Pauline Guillouche[d], Tamara Matysiak-Budnik[a], Damien Bouda[e], Yann Touchefeu[a,*]

[a] *Nantes Université, CHU Nantes, Institut des Maladies de l'Appareil Digestif (IMAD), Hépato-Gastroentérologie, Inserm CIC 1413, F-44000, Nantes, France*

[b] *Department of Gastroenterology and Hepatology, Hospital Santa Maria, Lisbon, Portugal*

[c] *Institut of Histopathology (IHP), 44104, Nantes, France*

[d] *Department of Gastroenterology, Clinique Jules Verne, Nantes, France*

[e] *IRIS GRIM – Site de la clinique Jules Verne, Nantes, France*

[*] Corresponding author at: Hépato-Gastroentérologie & Oncologie Digestive, Hôtel Dieu, CHU de Nantes, 1, Place Alexis Ricordeau, 44000, Nantes, France.

E-mail address: yann.touchefeu@chu-nantes.fr (Y. Touchefeu).