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Case Report

RARE LIVER TUMOUR — EPITHELIOID HAEMANGIOENDOTHELIOMA: A CASE REPORT

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Epithelioid haemangioendothelioma (EHE) is a rare vascular soft tissue malignant tumour with unknown etiology; the estimated prevalence of EHE is less than one in 1 million. A 56-year-old man was admitted in our department due to pain in the right side of the abdomen lasting for two years and weight loss up to 10 kg. Since 2012, the patient underwent lung and abdominal CT scanning as well as biopsy, however the diagnosis was challenging. In 2015, repeated abdominal CT scanning and a liver core biopsy was performed. The epithelioid haemangioendothelioma was diagnosed based by histopathological examination with subsequent radiological and clinical correlation. Therefore, accurate histopathological examination with radiological and clinical correlation is essential in the diagnosis of epithelioid haemangioendothelioma.

Keywords: *EHE, vascular tumour, epithelioid hemangioma.*

INTRODUCTION

Epithelioid haemangioendothelioma (EHE) is a rare vascular soft tissue sarcoma and at present its aetiology is unknown (Sangro *et al.,* 2012). The estimated prevalence of EHE is less than one in 1 million (Sardaro *et al.,* 2014). For hepatic EHE, a comprehensive review of literature from 1984 to 2005 included 402 published cases (Sangro *et al.,* 2012). In a survey of EHE, overall five-year survival demonstrated for 64–73% of patients (Antonescu *et al.,* 2014; Wang *et al.,* 2018).

EHE represents less than 1% of vascular tumours and was described for the first time in 1975 as pulmonary epithelioid haemangioendothelioma (Lerut *et al.,* 2018). Initially it was believed to be an aggressive tumour invading blood vessels and small airways (Sardaro *et al.,* 2014). Liver is the most commonly affected organ; however, it can be found at any site of soft tissue (Sangro *et al.,* 2012). For example, the Hemangioendothelioma, Epithelioid hemangioendothelioma And Related vascular Disorders (HEARD) Support Group observed that the most common EHE presentations are liver alone (21%), liver and lung (18%), lung alone (12%), and bone alone (14%) (Lerut *et al.,* 2018). At present, the World Health Organization classification (WHO, 2002) describes EHE as lesions that may be locally aggressive tumours with metastatic potential (Sardaro *et al.,* 2014).

CLINICAL CASE

In November 2015, a 56-year-old man was admitted in the Department of Gastroenterology, Rīga East University Hospital, due to pain in the right side of the abdomen that had lasted for two years. In addition, during this time the patient lost approximately 10 kg weight.

The data showed that the patient since 2012 had liver lesions described on ultrasound (US) as polymorphic with calcinations in the periphery — a CT scan was recommended. The patient subsequently underwent lung and abdominal CT scans, which found lesions in lungs and liver, with probably metastatic origin (Fig. 1).

In May 2013, a laparoscopic biopsy of liver lesions was performed. There were no signs of malignancy described, and in 2014 scintigraphy was performed, which did not find any lesions. In the beginning of 2015, a repeated CT for the lungs was performed and well marginated round lesions in the lungs were found. The diagnosis of sarcoidosis was favoured; however, the biopsy findings were unspecific and did not confirm the diagnosis. In February 2015, pulmonologists recommended repeated consultation of a hepatologist and abdominal surgeon. Additional laboratory tests were performed for markers of viral hepatitis, antibody tests for echinococcosis, CA 19-9, and beta-2-microglobulin, but all of those tests were negative.

Laboratory tests were within normal limits, except for slightly elevated liver transaminases ALAT (71 U/l) and ASAT (42 U/l) and impaired coagulation parameters (prothrombin index 57%, INR 1,32).

Upper and lower endoscopy revealed no pathological changes. As soon as possible, CT of the lungs and abdomen were performed, which showed multiple lesions in both lungs, more in the upper segment of the right lung, but without significant changes when compared to the CT in January 2015. Further, lesions in the liver were described as subcapsular hypodense regions approximately 3.5 cm in size in the right lobe of the liver, also some solitary hypodense lesions and some confluent ones in other parts of the liver. Also, larger *lobus caudatus* and S2 and S3, and narrower hepatic veins were described. In the mentioned hypodense parts of the liver, it was possible to differentiate blood vessels. In arterial and venous phases of contrasting, the mentioned hypodense parts of the liver did not collected contrast substance and in the late phase these parts looked same as other parts of the liver. Radiologists made the conclusion that the changes described might be typical to liver sinus thrombosis, Zahn infarction or type 3 Budd Chiari syndrome, but as a possible differential diagnosis, vasculitis and potential epithelioid haemangioendothelioma was mentioned (Figs. 1–3).

Thus, on March 2016, a percutaneous liver biopsy was performed. The lesion was composed of epithelioid cells arranged in strands, cords, and nests with abundant hyaline cytoplasm. The epithelioid cells had round or oval, hyperchromatic nuclei with smooth nuclear contours, delicate cytoplasm, and indistinct cytoplasmic borders. There was also often a histiocytoid cellular appearance. Some additional fusiform cells were observed. The nuclei were commonly irregular with small, often distinct nucleoli. Striking nuclear atypia was observed. Mitoses ranged from 5 to 15/High power field. In addition, nuclear pseudoinclusions were seen. A myxohyaline stroma was at least focally present at

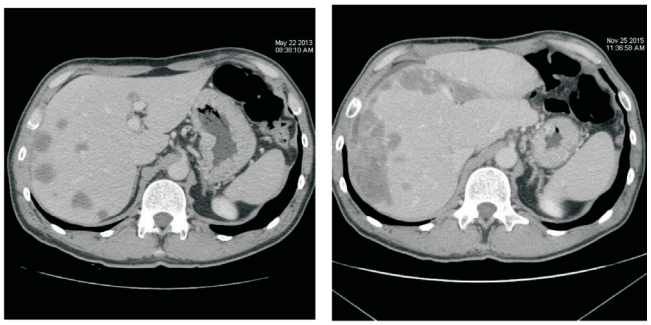

Fig. 1. On the left, the axial CT scan of the abdomen from May 2013 shows peripheral foci of homogeneous decreased attenuation compared to normal liver parenchyma in late portal phase. On the right, the axial CT scan of the abdomen from November 2015 shows that previously described liver lesions became a peripheral confluent mass with homogeneous decreased attenuation compared to normal liver parenchyma in the late portal phase. Compensatory hypertrophy of left liver lobe is also seen.

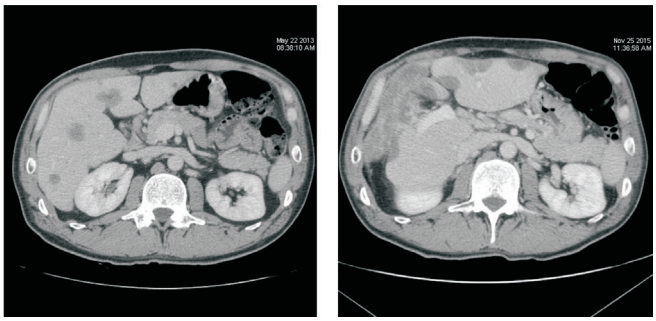

Fig. 2. Left – axial CT scan of the abdomen from May 2013 shows peripheral foci of homogeneous decreased attenuation compared to normal liver parenchyma in late portal phase. Right – axial CT scan of the abdomen from November 2015 shows that the previously described liver lesions became a peripheral confluent mass with homogeneous decreased attenuation compared to normal liver parenchyma in the late portal phase. Compensatory hypertrophy of the left liver lobe is also seen.

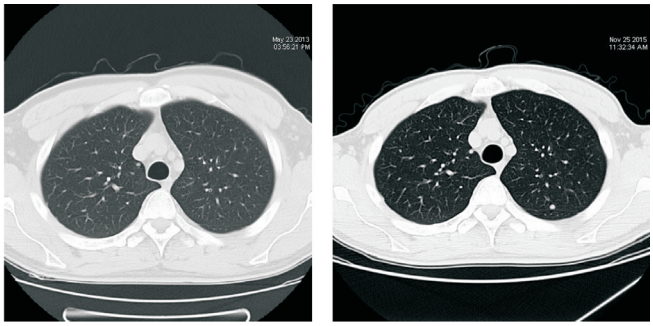

Fig. 3. Left – axial CT scan of the lungs from May 2013 shows some round metastatic lesions in both lungs. Right – axial CT scan of the lungs from November 2015 shows that previously described metastatic lesions became a little larger in size and also some new round lesions are seen in both lungs.

the periphery of lesion with moderate desmoplastic reaction (Fig. 4). The tumour cells were positive for CD31, CD34, and vimentin, and focal positivity for CKAE1/AE 3 was observed. The Ki-67 index was up to 12%, p53 was positive in up to 5% of cells (Fig. 5). The CD30 and Melan A was negative.

The authors also would like to mentation that even though the patient had not received any specific treatment, he is

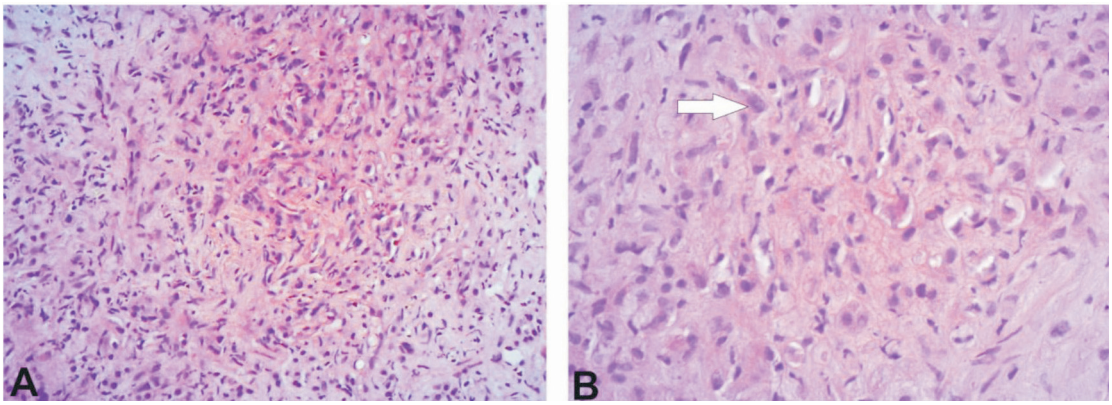

Fig. 4. Representative photomicrograph demonstrating striking nuclear atypia and desmoplastic stroma, haematoxylin eosin.

Magnification ×200 (A). Some tumour cells presented intracellular vascular lumina with cytoplasmatic vacuoles and haematoxylin eosin. Magnification ×400 (B).

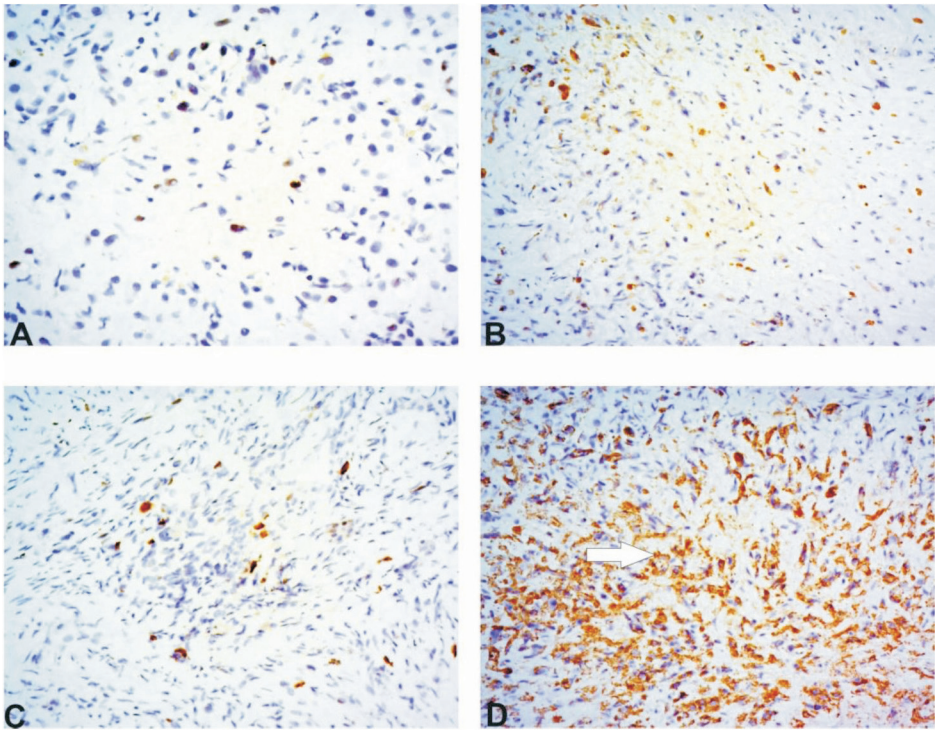

Fig. 5. Representative photomicrograph demonstrating Ki-67 (A), p53 (B), CKAE1/AE3 (C) and CD34 (D) expression. Immunohistochemical staining method. Magnification ×200.

still alive and well and was last by his attending doctor in autumn 2021.

DISCUSSION

Hepatic epithelioid haemangioendothelioma is a rare vascular neoplasm with an unpredictable malignant potential. In the recent WHO classification it was described as a low grade malignant vascular tumour (Neofytou *et al.,* 2013; Fletcher *et al.,* 2013). Different therapeutic options are available, depending on the basis of disease extension and the patient's overall condition (Sardaro *et al.,* 2014).

Previous studies showed a slight female predominance (male-to-female ratio, 2 : 3), and EHE usually occurs in middle-aged women (mean age, 41.7 years), although there are reports for younger patients as well (Llueca *et al.,* 2018). The causative factors are unknown (Neofytou *et al.,* 2013; Antonescu, 2014). Some cases were associated with the use of oral contraceptive pills and these findings may explain the female predominance of EHE; however, this relationship has not been validated (Neofytou *et al.,* 2013; Antonescu, 2014).

Vinyl chloride, asbestos, alcohol, liver trauma, hepatitis viruses, alcohol and chronic liver disease have been proposed as risk factors for the EHE (Makhouf *et al.,* 1999; Mehrabi *et al.,* 2006; Verma *et al.,* 2008; Neofytou *et al.,* 2013). Upon interviewing our patient the potential risk factors were not identified.

Clinically, 25% of the reported EHE cases were asymptomatic — the most frequent symptoms were right upper quadrant abdominal pain, hepatomegaly, and weight loss (Makhouf *et al.,* 1999; Verma *et al.,* 2008; Wu *et al.,* 2019).

Our case involved typical symptoms of hepatic EHE — abdominal pain, the site of metastases (lung) and bilobar liver involvement, which are all characteristic of the presentation

of this tumour as described by Sangro et al (2012). The most common clinical manifestations are right upper quadrant pain in 48.6%, hepatomegaly in 20.4% and weight loss in 15.6% (Mehrabi *et al.,* 2006), which also agrees with our data. However, in up to 25% of cases the patients were asymptomatic and EHE was an accidental finding (Neofytou *et al.,* 2013). It is important to mention that quite nonspecific symptoms and the lack of experience of different specialists like hepatologists, surgeons, radiologists, and histopathologists, due to the rarity of hepatic EHE, makes diagnosis challenging. For these reasons approximately 60–80% of patients with hepatic EHE initially have been misdiagnosed (Makhouf *et al.,* 1999; Gupta *et al.,* 2009; Neofytou *et al.,* 2013).

Laboratory testing is not helpful for diagnosis of liver EHE, although non-specific elevations of ALAT and ASAT may occur in combination or independent of AP and gGT elevations (Verma *et al.,* 2008; Neofytou *et al.,* 2013; Kubo *et al.,* 2018). Patients with hepatic EHE usually have normal serum alpha-fetoprotein, carcinoembryonic antigen (CEA), and cancer antigen (CA) 19–9 levels (Mehrabi *et al.,* 2006; Neofytou *et al.,* 2013;).

Hepatic EHE may be very heterogenous in imaging studies. These liver lesions are typically hypoechoic on US, but occasionally they can also be hyperechoic or isoechoic relative to the liver. Sometimes these hyperechoic or isoechoic lesions may have a peripheral hypoechoic rim. On CT, EHE may be seen as multiple nodules (more common) or as diffuse or extensive form (very rare). Usually, these lesions are located at the periphery with extension to the capsule, causing typical capsular retraction (due to tumour fibrosis and ischaemia) or flattening. Compensatory hypertrophy of uninvolved liver (predominantly left lobe), metastatic lesions and ascites are also seen. In a non-contrast CT scan, tumour nodules are seen as foci of homogeneous decreased attenuation compared to normal liver parenchyma. However, in contrast enhanced CT scans, these lesions may have a non-enhancing central part of tumour, enhancing peripheral inner rim (increased vascularity) and non-enhancing peripheral outer rim or halo (avascular rim), which that all together makes a "target" like enhancement pattern of the tumour. In MR studies, the most common findings in T1-weighted images are a hypointense central signal and a thin hypointense peripheral rim, but in T2-weighted images — a hyperintense central signal and hypointense peripheral rim. If intravenous contrast is used, then lesions may have a "target pattern" in T1-weighted images, with a central hypointense signal, thick peripheral enhancing inner rim and thin non-enhancing outer rim. As a helpful sign to improve the diagnostic accuracy, a "capsular retraction sign" is used in correlation with the "halo" sign after intravenous administration of contrast (Lyburn *et al.,* 2003; Jiang *et al.,* 2010; Neofytou *et al.,* 2013).

Histopathological examination is important in the diagnosis of EHE. Vimentin, CD10, CD31, CD34 and factor VIII antigen are the most important immunohistochemical markers. The important histopathologic findings like intracytoplasmic lumina with red blood cells with polygonal and spindle tumour cells in fibromyxoid are very specific in this disease (Neofytou *et al.,* 2013; Jurczyk *et al.,* 2014; Campione *et al.,* 2015; Shiba *et al.,* 2018).

Also, it has been estimated that approximately 80% of EHE might be initially misdiagnosed (Zhang *et al.,* 2018).

There is no standard therapeutic strategy for the treatment and follow-up of EHE because of its rarity and variable clinical course. Currently, the treatment for EHE includes liver transplantation (44.8%), chemotherapy or radiotherapy (21%), liver resection (9.4%) and no treatment (24.8%). Among them, the five-year survival rate of liver resection (75%) or transplantation (54.8–75%) is significantly higher than the survival rate associated with other treatments (30%) (Choi *et al.,* 2013; Konstantinidis *et al.,* 2018; Omerhodžic *et al.,* 2018).

CONCLUSIONS

In conclusion, the imaging and histopathological findings with clinical presentation of the presence of numerous intrahepatic tumours in patients with a good clinical condition, slow course of the disease, absence of chronic liver disease, normal tumour markers and normal or mildly changed laboratory parameters provide the diagnosis of hepatic EHE. Also, it is crucial to have an experienced histopathologist not to misdiagnose this condition, because this may result in non-appropriate treatment with impact to the survival of the patient.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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RETI SASTOPAMS AKNU AUDZĒJS — EPITELIOĪDĀ HEMANGIOENDOTELIOMA: KLĪNISKAIS GADĪJUMS

Epitēlioīdā hemangioendotelioma (EHE) ir rets mīksto audu vaskulārs potenciāli ļaundabīgs audzējs ar nezināmu etioloģiju; ir dati par to, ka EHE sastopamība ir mazāka par vienu gadījumu uz 1 miljonu cilvēku. Klīniskais gadījums ir par 56 gadus vecu vīrieti, kurš tika izmeklēts sakarā ar sāpēm vēdera labajā pusē, kas ilga divus gadus, kā arī svara zudumu līdz 10 kg. Kopš 2012. gada pacientam tika veikta plaušu un vēdera dobuma datortomogrāfija, kā arī biopsija, tomēr diagnoze netika precizēta. 2015. gadā tika veikta atkārtota vēdera dobuma datortomogrāfija un aknu biopsija. Epitēlioīdās hemangioendoteliomas diagnoze tika noteikta, pamatojoties uz histopatoloģisko izmeklēšanu ar sekojošiem radioloģiskiem izmeklējumiem un klīnisko ainu. Tāpēc epitēlioīdo hemangioendoteliomu diagnostikā būtiska loma ir multidisciplinārai pieejai pacientam.