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Primary Hepatic Epithelioid Hemangioendothelioma: A Case Report and Literature Review

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***Abstract*— Hepatic epithelioid haemangioendothelioma (HEHE) is a very rare malignant tumor of vascular origin and uncertain biological behaviour. New case of epithelioid hemangioendothelioma is reported to have occurred to a 65-year-old patient who consulted for right-sided abdominal and chest pain. The work-up showed a generalised form of disease, with involvement of the liver, lungs, peritoneum and lymph nodes. The definitive histological diagnosis was made by the pathologist on the basis of immunohistochemical analysis. The patient received a primary mono-chemotherapy with Adriamycin without response and general status impairment. The patient died after 12 months of follow-up.**

***Index Terms*— hepatic epithelioid hemangioendothelioma, vascular origin, immunohistochemical analysis, chemotherapy.**

I. INTRODUCTION

Epitheloid haemangioendothelioma (EHE) is a known—although rare—malignant vascular tumor, which represents less than 1% of all vascular tumours [1]. The aetiology of EHE is not completely understood; however, it is understood that the tumour originates from vascular endothelial, or preendothelial cells [2].

This tumor can involve soft tissues, as well as visceral organs, including the liver, lung, spleen, stomach, and heart. However, the most commonly involved organ is the liver [3].

Hepatic epithelioid hemangioendothelioma (HEHE) was first described by Weiss and Enzinger in 1982 [4].The incidence rate for hepatic EHE is approximately 1–2 per million individuals, while the mortality rate is between 40 and 65% [5,6].

HEHE is recognized as a low-grade tumor with a clinical course that lies intermediate to that of haemangioma and that of angiosarcoma [7].

Basic diagnosis using all available methods is very difficult and this entity is often mistaken for other primary or secondary liver tumors. The definitive diagnosis is frequently obtained based on histopathology and immunohistochemistry.

Due to its low incidence and variable clinical course, the standard treatment has not been established [8].

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Most of the HEHEs are published as case studies and/or histopathological original entities because of their non-specific clinical and/or radiological characteristics [9].

Here, we report a case of a 65-year-old woman with a generalized form of HEHE.

II. CASE REPORT

A 65-year-old woman presented with a two-month history of right upper quadrant abdominal pain and right-sided parietal chest pain associated with fatigability.

The patient had a past medical history of hypertension for 5 years and dyslipidemia. She had no hepatitis.

The physical examination showed right-sided abdominal tenderness. The systemic examination was unremarkable.

The routine blood cell count and biochemical investigations (serum bilirubin, transaminases, alkaline phosphatase, and proteins) were within reference ranges. The serological tests for hepatitis B and C were negative. Levels of CEA, CA 125, and CA 19-9 were normal.

The chest X-ray showed multiple right-sided opacities. The thoraco-abdominal computed tomography (CT) scan showed multiple right pulmonary lesions associated with right-sided minimal pleural effusion. Furthermore, many hypodense nodules in both lobes of the liver, with the largest lesion being 65 mm × 42 mm in size, enhanced by contrast material injection were revealed. Localized peritoneal carcinomatosis and enlarged lymph nodes in the retroperitoneum were also observed.

A liver biopsy under CT guidance was performed.

Pathological examination of the biopsy specimen revealed uneven pleomorphic epithelioid tumor cells, which spread into the sinusoids. Epithelioid tumor cells were filled with vacuoles. Immunohistochemically, the tumor cells were positive for endothelial marker CD34, CD31 and factor VIII-related antigen, and negative for cytokeratins confirming the vascular nature of the tumor and contributing to the final diagnosis of HEHE.

Given that the process was generalized, the multidisciplinary team decided oncological treatment with Adriamycin (75 mg/m² per three weeks).

A CT scan was performed after 6 cycles and demonstrated progressive disease. Supportive care was opted because of general status impairment. The patient died after 12 months of follow-up.

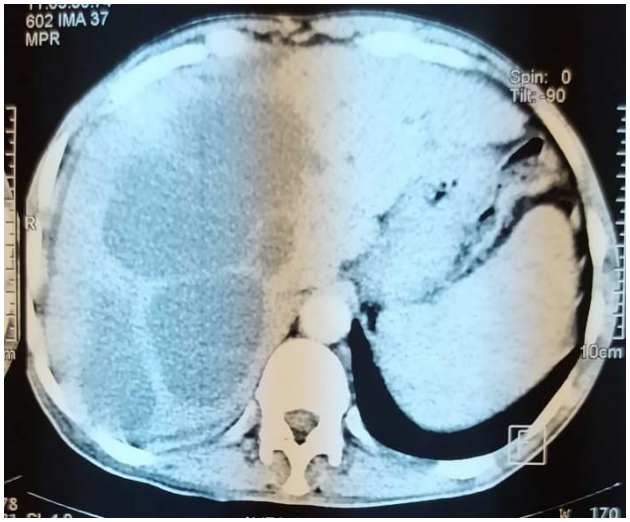

Figure 1: Multiple liver nodules in CT scan.

III. DISCUSSION

HEHE is a rare hepatic tumor originating from the endothelial cells of uncertain malignant potential. The incidence of HEHE is estimated to be 1/1 million inhabitants. It most frequently affects patients between the ages of 30 to 40 years [10, 11] and shows a predilection for females (male to female ratio, 1:1.5) [5, 12].
The exact cause of HEH is not known [13]. Risk factors are thought to include contraceptives, trauma to the liver, prior hepatitis, long-term contact with asbestos, vinyl chloride or thorotrast. However, no clear causal connection between the development of HEHE and the cited risk factors has been demonstrated to date [10,11].

HEHE presents with nonspecific and variable clinical manifestations. Approximately one-quarter of patients are asymptomatic at the time of diagnosis. Symptomatic patients usually have non specific complaints, the most common of which is right upper-quadrant pain [14]. Other reported symptoms include abdominal discomfort, anorexia, fever, vomiting, weight loss, ascites, and easy fatigability, as seen in the present case [13].
Rarely, hepatic EHE may present as Budd-Chiari syndrome, veno-occlusive disease, and/or portal hypertension because of a mass effect or invasive growth of the neoplasm into the surrounding vasculature [15-17].
In around 50% of patients, the haemangioendothelioma may occur in other locations, especially other visceral organs, lymph nodes, bones and lungs [9].

The most frequently reported laboratory abnormality associated with hepatic EHE is an elevation in alkaline phosphatase, but other liver enzymes (c-glutamyl transpeptidase, aspartate aminotransferase, and alanine aminotransferase) may be elevated as well [14].
On the basis of imaging features, HEHE can be divided into two forms: single nodular and diffuse nodular [18,11]. Most patients diagnosed with HEHE have a diffuse nodular type involving both lobes of the liver, which is usually unresectable. The single nodular type is found in only a minor proportion (13%) of patients, and most single tumors are reported to be situated in the right lobe of the liver [19]. Without timely treatment, the single nodular type of HEHE can easily progress to the diffuse nodular type [20], which is considered an advanced tumor stage.
Imaging findings should include the exact number, dimensions, location, vascular or ductal involvement, locoregional lymphadenopathy and extrahepatic extension, as they are important factors for surgical decision on resectability [3].
Hepatic EHE commonly demonstrates multifocal nodular presentation, with CT demonstrating clear margins, centripetal enhancement in arterial phase, and homogenous enhancement in the portal venous and delayed phases. On MRI, a characteristic peripheral ring enhancement with low central signal intensity (black target-like sign) and central enhancement with low signal intensity peripherally (white target-like sign) are some of the radiographic findings [21].
PET-CT has been recently shown to be useful for differentiating HEHE from metastatic carcinoma, with the metastatic carcinoma showing hepatic lesions with high glycometabolism. However, PET-CT is very expensive and sometimes only provides a reference, without revealing a definite diagnosis [22].

Diagnosis of HEHE primarily depends on immunohistochemical evidence of endothelial differentiation and the findings of histopathological examination, because the clinical and biological characteristics of this lesion are similar to those of hemangioma and angiosarcoma [23]. HEHE displays an infiltrative growth pattern, with epithelioid, dendritic, and intermediate cells interspersed in a matrix rich in hyaluronic acid [5,24].
Immunohistochemically, positive reactivity to endothelial markers such as vimentin, factor VIII-related antigen, CD31 and CD34 supports the endothelial nature of the tumor cells. The angiogenic vascular endothelial growth factor (VEGF) has also been found positive in HEHE [25].
Further molecular characterization has identified a gene fusion of WWTR1 (WW domain-containing transcription regulator 1) on 3q25.1 with CAMTA1 (calmodulin-binding transcription activator 1) on 1p36.23, leading to WWTR1-CAMTA1 fusion protein which was found to differentiate EHE from other morphologic mimics such as epithelioid hemangioma and epithelioid angiosarcoma [26]. This has been found in approximately 90% of cases of EHE [27]. A small subset of EHE demonstrate a YAP1 (Yes associated protein 1)-TFE3 (transcription factor E3) fusion gene leading to overexpression of TFE3 [28].
Fluorescence in situ hybridization or reverse transcription polymerase chain reaction has a high sensitivity and specificity to detect the WW domain-containing transcription regulator (WWTRI)-CAMTA1 fusion gene. However, this method is not routinely available [29].

Pathologically, EH can be misdiagnosed in up to 80% of cases. Most commonly, EH is misdiagnosed with angiosarcoma, cholangiocarcinomas (CC), metastatic carcinoma, and hepatocellular carcinoma (HCC) (sclerosing variant) [4,5,6,10]. Therefore, awareness of pathological differences is necessary to accurately diagnose these tumors.
Tumor cells containing the characteristic vascular vacuole may be mistaken for steatotic or mucin vacuoles of an

adenocarcinoma, but mucin staining is negative. Angiosarcoma is much more aggressive and destructive, eliminating acinar landmarks and leading to the appearance of cavities. For cholangiocarcinoma, tumor cells are often placed in a tubular or linear pattern with mucin production, positive staining for cytokeratin and negative staining for endothelial markers [30].

No consensus exists for a strategy of standardized treatment owing to limited data and the rarity of the disease. The disease is classically described as having behavior intermediate between hemangioma and angiosarcoma, but the clinical course can vary [4].

In a meta-analysis of treatment outcomes performed by Mehrabi et al, [5] the 1-, 3-, and 5- year survival rates for all 253 diagnosed individuals with survival information available, regardless of treatment, were 211 (83.4%), 141 (55.7%), and 104 (41.1%), respectively. The most common treatment modalities used were liver transplantation, liver resection, chemotherapy and/or radiation therapy, and surveillance, which had 5-year survival rates of 54.5%, 75%, 30%, and 4.5%, respectively.

The therapeutic method of choice involves radical resection or, in bilobar forms, liver transplantation. Both methods demonstrate good 70% five-year overall survival [31,32].

In cases where surgical treatment cannot be performed, oncological treatment is indicated [33]. Various chemotherapeutic drugs (including doxorubicin, 5-fluorouracil, vincristine, thalidomide, interferon-a, and monoclonal antibodies against vascular endothelial growth factor) have been used for the treatment of HEH [34]. Soape et al [35] reported a case of HEH with good response to sorafenib monotherapy.

In selected cases, radiotherapy may be used for patients unfit for surgery or chemotherapy [36].

Given the biological behavior of the disease, a conservative, watchful-waiting approach is possible also in long-term stable forms of HEHE [37].

The clinical course of HEHE is variable, ranging from spontaneous regression and long-term survival without any treatment to a rapidly progressive and deadly course. In total, the prognosis of HEHE is considered more favorable than that of other hepatic malignant tumors [38]; the 5-year survival rate of HEHE is 64% after treatment [39].

The prognostic factors of HEHE are unclear, even if some authors have reported that the presence of symptoms, older age, and elevated serum CA19-9 negatively affect the outcome [40]. Furthermore, Cardinal et al. [41] found that the presence of extrahepatic disease beyond regional portal nodes was a negative predictor of outcome.

IV. CONCLUSION

HEHE is a rare vascular malignancy with nonspecific clinical and laboratory findings. The imaging features can easily lead to misdiagnosis. Definitive Diagnosis of HEHE is difficult and primarily depends on the findings of histopathology and immunohistochemistry. Currently used treatment options for HEHE include LT, LR, chemotherapy, radiotherapy and observation without treatment.

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