Undifferentiated Embryonal Sarcoma of the Liver with Epithelioid Features: A Case Report of an Exceptional Histological Heterogeneity among Rare Diseases

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Introduction: Undifferentiated embryonal sarcoma of the liver (UESL) is a rare and aggressive malignant tumor, with nonspecific clinical symptoms and radiological features. Less than 150 cases have been reported in adults across the world.
Presentation of Case: We report a case of an extremely rare subtype of UESL with epithelioid features in a 29-year-old woman, presenting as a cystic lesion of 27 × 17 cm, completely subverting the right hepatic lobe. She underwent a right hepatectomy with anterior approach, complete hilum lymphadenectomy and partial diaphragmatic resection for local infiltration, followed by systemic chemotherapy. She remains with no evidence of disease and liver mass has been restored after 6 months.
Discussion: The present case report represents the second case of UESL with epithelioid features described across the world. The immunohistochemical expression pattern, cytokeratin (CK)19 + and CK7 –, strongly suggests an origin of this epithelioid component from native biliary cells and not from a reshaped ductal plate. Due to the rarity of this form, to date it is impossible to define the prognostic impact of this subtype of UESL, and treatment remains challenging.
Conclusion: UESL is associated with a poor prognosis, especially in adults, but a comprehensive and multidisciplinary treatment based on radical resection and adjuvant therapy may provide a survival benefit. Surgical excision with negative margins remains mandatory to diagnose and treat UESL.

Keywords: case report; liver cancer; undifferentiated embryonal sarcoma of the liver; epithelioid differentiation; multidisciplinary treatment; immunohistochemistry; hepatectomy with anterior approach

Introduction

Undifferentiated embryonal sarcoma of the liver (UESL) is a rare, undifferentiated, and aggressive malignant tumor originating from primary mesenchymal tissue [1]. It was formally distinguished from other embryonal tumors and introduced as an independent form in 1978 by Stocker and Ishak [2]. UESL represents the third most common primary liver malignancy.

UESL affects mainly infants, among whom it has no sex predilection. It is rather uncommon in adults, with a slightly female preference. Since UESL was first described, less than 150 cases have been reported in adults across the world [3, 4].

Because of its rarity and its nonspecific clinical symptoms and radiological features, UESL can represent a significant diagnostic challenge that can lead to a delay in appropriate management.

UESL usually occurs as a single and well-circumscribed lesion, often larger than 10 cm, and it consists of both solid and cystic components, with additional areas of hemorrhage and necrosis. Diagnosis relies on pathological and immunohistochemical examinations; a key feature is the presence of a population of spindle, ovoid, and large anaplastic multinucleated cells. This tumor is typically composed of undifferentiated mesenchymal cells and a mucus matrix, with frequent giant cells and eosinophilic bodies [5].

Herein, we present an extremely rare subtype of UESL with epithelioid features in a 29-year-old woman. To date, we have found just one other similar case reported in the scientific literature, in a 50-year-old man [6]. This report describes the second known case of UESL with epithelioid features, representing a true singularity among rare diseases.

Case Presentation

A 29-year-old woman was referred to the emergency department (ED) for the persistence of low back pain, abdominal tenderness, and dyspnea. Her family history was unremarkable with no pre-existing systemic disease. She had been working in a riding stable.

At physical examination, a marked epigastric tenderness

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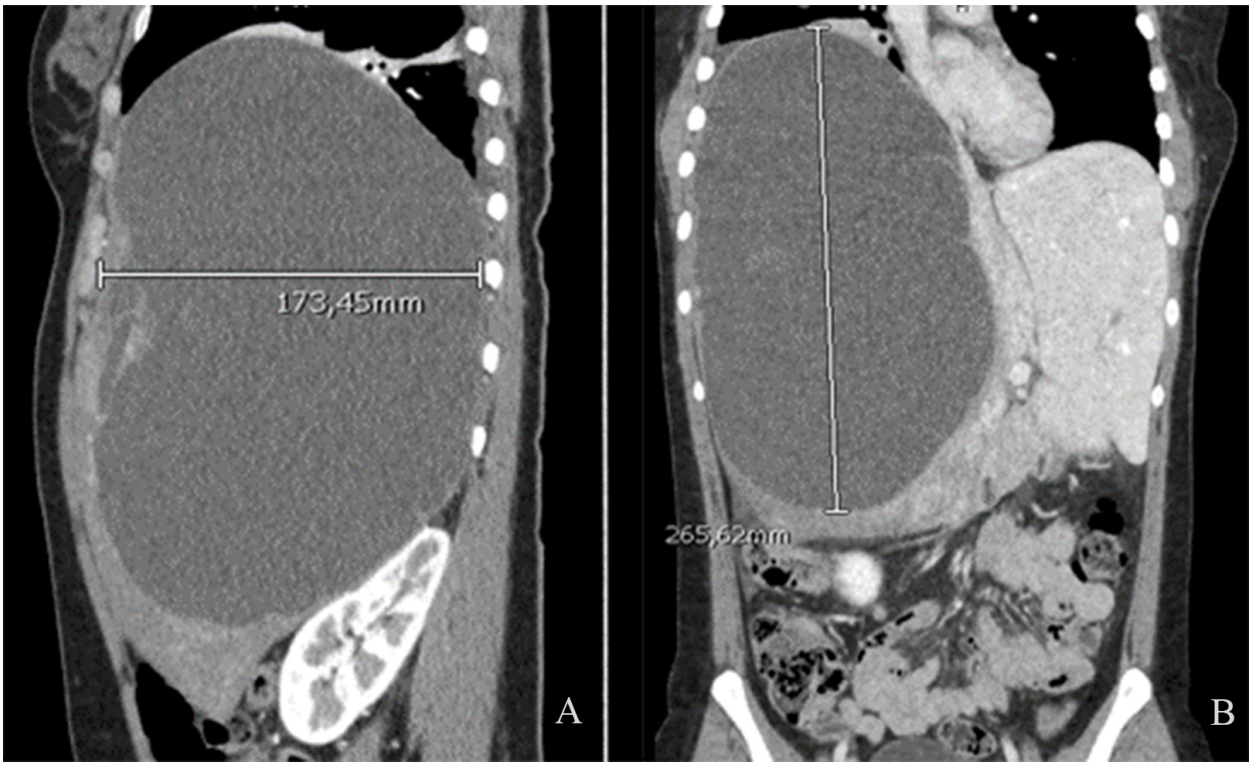

Fig. 1. Preoperative Sagittal and Coronal ce-CT scan. (A) Sagittal contrast-enhanced (ce)-computed tomography (CT) scan frame showing the antero-posterior diameter of the lesion. (B) Coronal ce-CT scan frame showing the cranio-caudal extension of the mass, the elevation of the right hemidiaphragm, and the left shift of the left hemiliver and hepatic hilum.

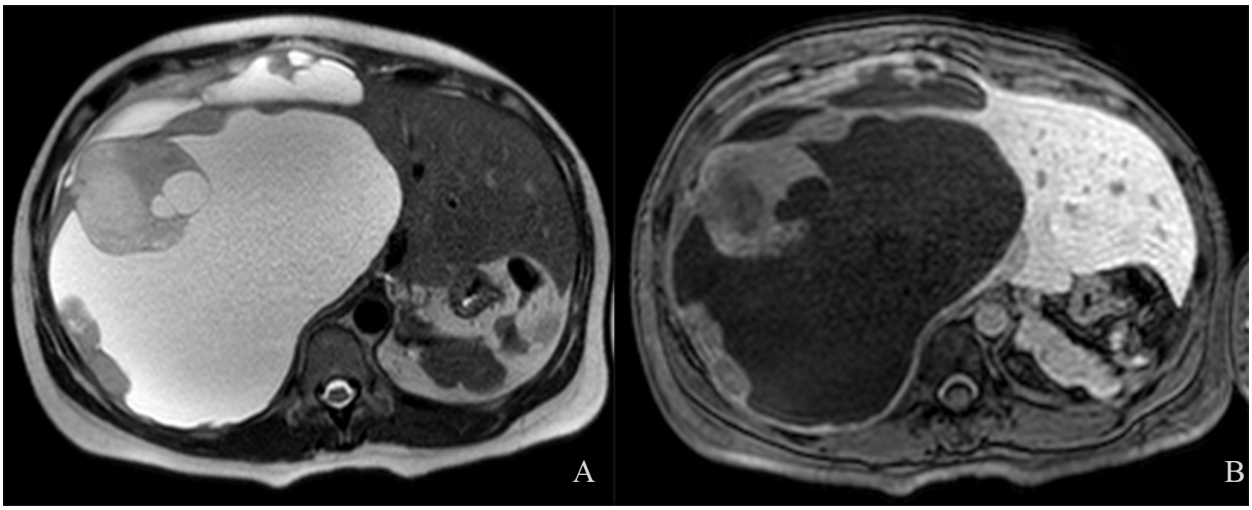

Fig. 2. Preoperative Magnetic Resonance scan. (A) T2-weighted Magnetic Resonance imaging (MRI) scan showing a well-defined polylobed lesion of high signal intensity. (B) T1-weighted MRI scan showing low signal intensity with the invasion of the Glisson's capsule.

was noticed. Upon arrival to the ED, an abdominal ultrasound was obtained, showing a giant anechoic lesion with an internal hyperechoic and heterogeneous mass.

The abdominal contrast-enhanced (ce)-computed tomography (CT) scan (Fig. 1) revealed an enormous, hypodense, and heterogeneous cystic lesion of 27 × 17 cm, completely subverting the right hepatic lobe and containing two solid components of 3.5 cm and 6 cm, with mild and marked enhancement in arterial and delayed phases, respectively. Once transferred to the ward, Magnetic Resonance imaging (MRI) confirmed a well-defined polylobed lesion of high signal intensity on T2-weighted images and low signal intensity on T1-weighted images (Fig. 2).

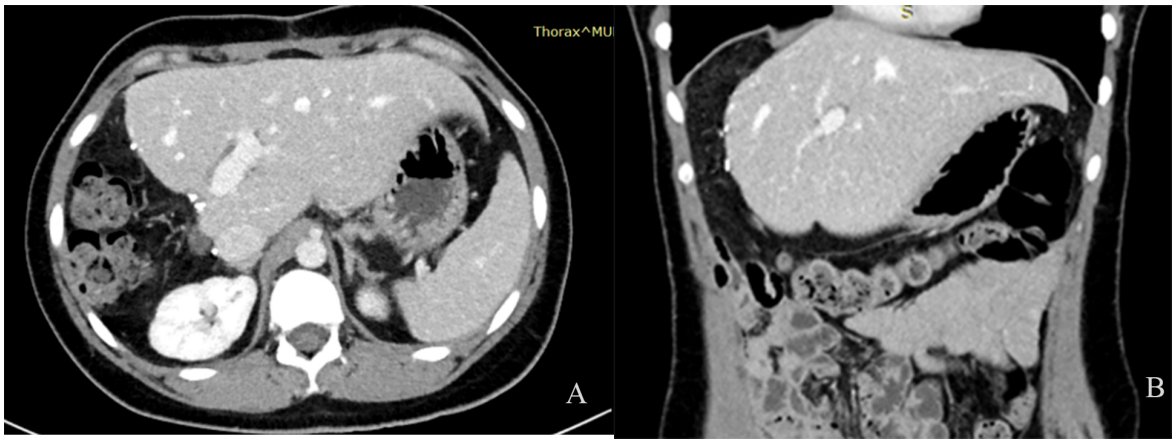

Fig. 3. Postoperative CT scan. (A,B) Coronal and sagittal CT scan frames showing the complete restoration of liver mass, now free to fill the right hypochondrium; no sign of tumour recurrence.

Laboratory tests showed alpha-fetoprotein 41.8 UI/mL (n.v. <6.7 UI/mL), CA 19–9 5.9 UI/mL (n.v. <37 UI/mL), carcinoembryonic antigen (CEA) <0.3 Ng/mL (n.v. <5 Ng/mL), and a normal liver test. An indocyanine green clearance test indicated that the retention rate at 15 minute (R_{15}) was 1.2%, and the plasma disappearance rate (PDR) was 29.5%.

Serological screening for Echinococcus was negative. However, due to the high suspicion of hydatid cyst based on her job-related risk and ultrasound, and knowing that serological test sensitivity is inversely related to the degree of sequestration of the echinococcal antigens inside cysts [7], prophylactic albendazole was administered.

After discussing the case at the multi-disciplinary team (MDT) meeting, we decided to perform intraoperative analysis of cystic fluid in order to rule out Echinococcus infection with the lowest risk of anaphylactic reactions, and, in case of negative result, to excise en bloc the lesion.

Intraoperatively we found a voluminous cystic lesion occupying the entire right hemiabdomen and causing a shift of the falciform ligament and hepatic hilum. Fluid content was sent for pathological examination, with no evidence of parasites. However, extemporaneous histological examination of the solid smaller mass contained in the cystic lesion demonstrated hepatocellular carcinoma cell lines. As planned preoperatively, right hepatectomy with anterior approach, complete hilum lymphadenectomy, and partial diaphragmatic resection for local infiltration were performed. Transhepatic anterior approach to the inferior vena cava (IVC) was chosen to improve vascular control, and limit hepatic mobilization and tumor spread, removing en bloc the lesion with the infiltrated diaphragm [8]. This technique required the hanging maneuver for liver transection, originally introduced to resect large hepatic tumors [9].

The postoperative course was uneventful, and the patient was discharged on post-operative day 7. After 3 months, she began chemotherapy with six cycles of vincristine, doxorubicin ifosfamide, and sodium-2-mercaptoethanesulphonate (MESNA). CT scan follow-up at six months was negative for oncological disease, and it showed a complete restoration of her liver mass (Fig. 3).

Final Diagnosis

The right hepatic lobe (24 × 12 × 2 cm) was almost entirely replaced by a giant cyst with a diameter of 19 cm, containing hemorrhagic fluid and a solid yellowish component of 16 cm, supple and partially exophytic, with an "iceberg" pattern of growth infiltrating the right diaphragm for 4 cm (Fig. 4).

Histology of the tumor showed a population of small "blue" cells with a rounded or ovoid nucleus characterized by intense chromatin and scarce cytoplasm; these cells were grouped compactly in a perivascular position, separated by intercellular edema with a myxoid appearance, and no specific pattern (Fig. 5). Many giant cells with large cytoplasm and a large, single, atypical nucleus or numerous nuclei were interposed; between them we found some cells of "monstrous" appearance and size (diameter between 60 and 110 microns). We found additional scattered cells with large cytoplasmic adipocyte-like vacuoles, signs of haemophagocytosis, large pinkish amorphous extracellular globular accumulations, and areas of necrosis.

In other areas we found a population of cells with a distinct epithelioid appearance of eosinophilic cytoplasm and polygonal edges, aggregated in trusses and cords, and inserted in the context previously described with a mitotic index of 25 × 10 high-power field (HPF) (Fig. 6).

Cyst walls were composed by atypical cells that were partially round, partially fusiform, and stellate, with marked vascular dilatation. In this context we found intense and widespread immunohistochemistry positivity for CD56 in both medium-small and large cells; these were negative for synaptophysin and Neuron-specific enolase (NSE).

Immunohistochemistry showed widespread positivity in all cells for Vimentin; moderate positivity for Smooth Muscle Actin; weak but widespread positivity for Sarcomeric

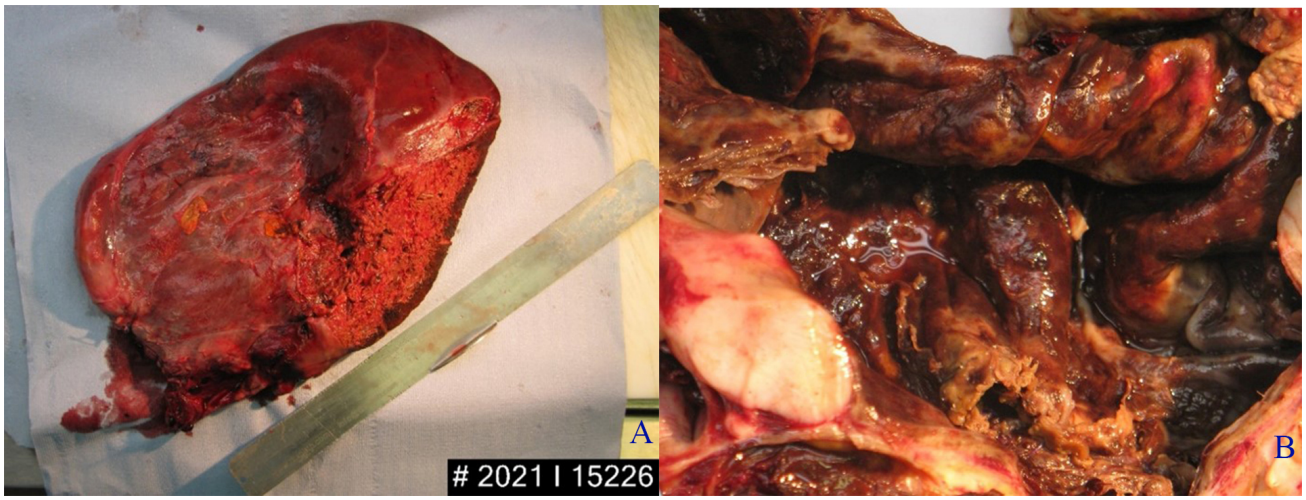

Fig. 4. Macroscopic appearance. (A) The right hepatic lobe (24 × 12 × 2 cm) containing the giant cyst, now emptied. (B) The hemorrhagic and necrotic content of the giant cyst.

Actin; moderate positivity for Desmin; widespread positivity for CD34; focal positivity in small cell groups for pooled anticytokeratin monoclonal antibodies AE1/AE3 and cytokeratin (CK)19; negativity for Alphafeto Protein, p40, Perforin, and CK7; and positivity in inflammatory cells for CD68.

Epithelioid cell section showed intense and widespread positivity for Vimentin; widespread positivity for Smooth Muscle Actin in interposed spindle cells; widespread positivity for CK pool AE1/AE3 and CK19 in epithelioid cells; areas of positivity for S100 in epithelioid cells; and negativity for Hep-Par1, Sarcomeric Actin, CK7, CK20, chromogranin, and synaptophysin (Fig. 7).

Based on pathological and immunohistochemical examinations we made a final diagnosis of UESL (according to WHO 2019) with epithelioid areas, G3 (G3; N1; M3); TNM staging system: pT1 (sec. AJCC VIII Ed.).

Discussion

Undifferentiated liver embryonal sarcoma, also known as malignant mesenchymoma, mesenchymal sarcoma, undifferentiated rhabdomyosarcoma, fibromyxosarcoma, and lipo-fibrosarcoma of the liver, is a rare tumor, most often occurring in late childhood (at the age of 6–10 years), and is extremely uncommon in adults [10].

Diagnosis is mostly incidental; UESL can be asymptomatic or have non-specific clinical manifestations, such as nausea, vomiting, weight loss, fever, abdominal pain, and bloating [5]. In most cases laboratory liver tests and tumor markers are normal. Our patient presented with an increased level of alpha-fetoprotein (41.8 UI/mL), whereas other oncological markers were negative. UESL diagnosis cannot rely on radiological features; no specific imaging and no typical signs are described in the literature [11].

The CT scan revealed an enormous, hypodense, and heterogeneous cystic lesion of the liver containing two solid components. These characteristics are shared among different benign cystic entities, such as biliary cystadenomas, hydatid cyst disease, abscess, mesenchymal hamartoma, or venolymphatic malformations [1, 12, 13]. The MRI showed a high heterogeneous signal on T2-WI and low signal on T1-WI, as already described in literature for UESL [14].

In our case, there was no discrepancy between US and CT/MRI appearance. In the literature, in contrast, it is often described as having a predominantly solid appearance at US, and a cyst-like appearance on CT/MRI [14].

UESL is characterized by a high-grade proliferation of undifferentiated cells with no specifically oriented differentiation. This tumor has a very heterogeneous histology, with a morphology that can vary considerably depending on the area of examination [11]. Some areas may appear to be composed of a relatively uniform sheet of undifferentiated cells, whereas other areas demonstrate wildly pleomorphic anaplastic cells, some with multinucleation and a myxosarcomatous background. The immunohistochemistry characteristics of embryonal sarcoma of the liver have no specific or diagnostic immunophenotype, variably staining with Cytokeratin, Vimentina, Alpha-1-antitrypsin, and Alpha-1-antichymotrypsin [15].

In the medical literature, less than 150 pure sarcomatous forms in adults across the world have been described [3, 4, 16], but the epithelioid feature has been reported in only one other adult case [6], and it has never been described in childhood.

To the best of our knowledge, the present case report represents the second case described across the world, and the first with an accurate description of histology. We found different cords of polygonal epithelioid cells with eosinophilic cytoplasm and mitotic index: 25 × 10 HPF. The associated expression pattern, CK19 + and CK7 –, strongly suggests an origin of this epithelioid component

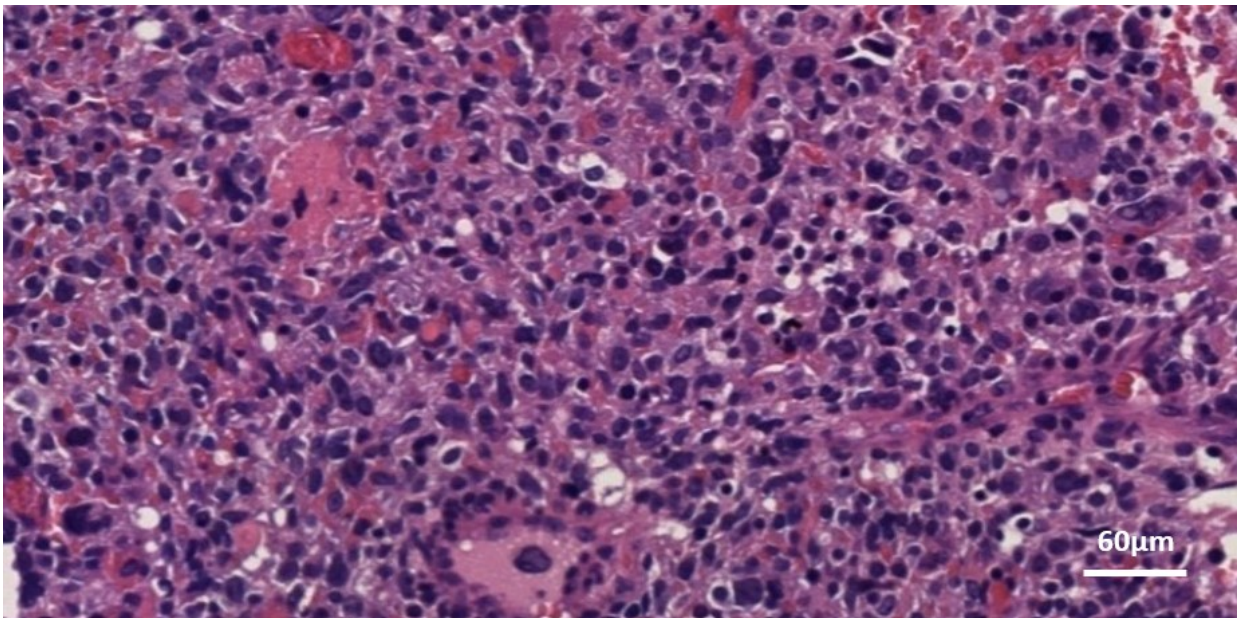

Fig. 5. Small "blue" cells population. Small "blue" cells with multiple nuclei characterized by intense chromatin and scarce cytoplasm, an index of high mitosis. These cells were grouped in a perivascular position, separated by intercellular edema with a myxoid appearance.

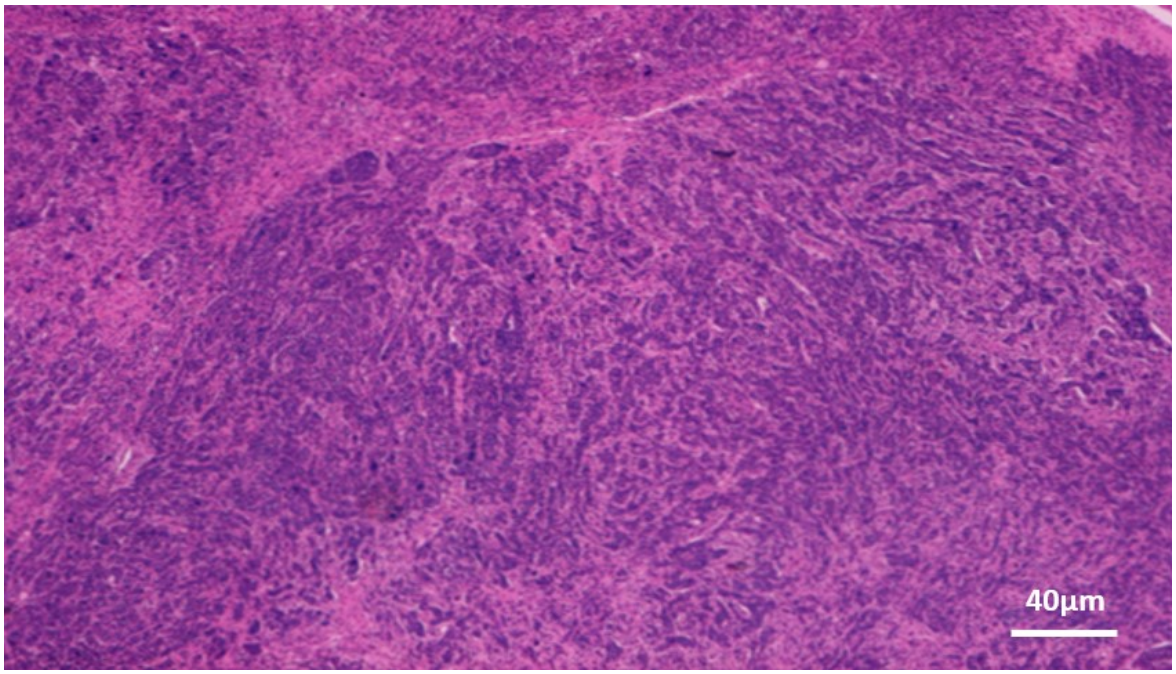

Fig. 6. Magnification frame of an area with a distinct epithelioid appearance. Cells are aggregated in trusses and cords. Mitotic index: 25 × 10 high-power field (HPF).

from native biliary cells and not from a reshaped ductal plate [17, 18, 19]. Cytokeratin 19 is also renowned in the literature as a negative prognostic factor for poorly differentiated hepatocellular carcinoma (HCC) [20]. Due to the rarity of this form, to date it is impossible to define the prognostic impact of this immunophenotype expression in UESL.

A standard treatment strategy for UESL has not been yet established, and there is no specific drug for its treatment [21]. Partial hepatectomy, with adjuvant or neoadjuvant chemotherapy, liver transplantation (LT), and radiation have all been tested, but it remains difficult to define the benefit of each treatment due to its rarity. Wu *et al*. [4] found that radical R0 surgery, combined with chemotherapy, is correlated with improved survival. On the other hand, tumor size and extrahepatic tumor spread seem not to impact disease-free and overall survival. Liver transplantation for UESL has been performed for unresectable cases and hepatic recurrence, with good results in overall survival

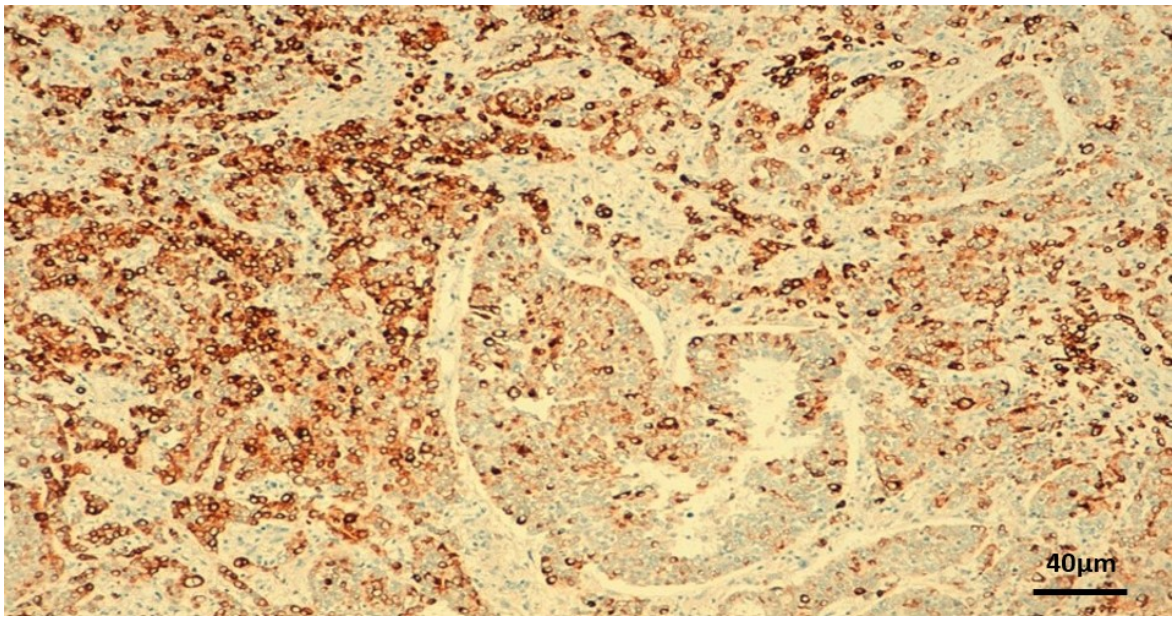

Fig. 7. Epithelioid immunohistochemistry. Epithelioid cells with an immunohistochemistry positivity for CK pool and AE1/AE3 and for CK19 and S100.

[4, 22, 23]. We performed a right hepatectomy with anterior approach, complete hilum lymphadenectomy, and partial diaphragmatic resection for a local infiltration, in order to obtain negative margins of resection. The anterior approach, which includes no liver mobilization and the hanging maneuver, was conceived by Belghiti J *et al* [9], in order to avoid tumor dissemination and to control deep parenchymal bleeds. Indeed, the crucial point during resection of bulky masses is the safe control of the IVC and hepatic veins because these tumors tend to push the right lobe forward and hinder liver mobilization [23]. Currently, the most common drugs used in UESL are vincristine, actinomycin-D, cyclophosphamide (VAC), ifosfamide, doxorubicina, or cyclophosphamide [21].

Our patient was treated with six cycles of Vincristine, doxorubicin ifosfamide, and MESNA. CT scan follow-up at six months was negative for oncological disease.

UESL has a poor prognosis in adults, with a 5-year overall survival (OS) rate of 48.2% compared to 84.4% in children [21], but the real 5-year overall survival of the UESL with epithelioid features remains unclear because this is only the second case reported in the entire literature. The first case described died after 3 months from the hospital discharge for tumor recurrence [6]. Our patient is still alive after 7 months from the diagnosis. They both had a local extrahepatic infiltration (respectively of the omental adipose tissue and of diaphragm), but the first case described refused adjuvant therapy.

Conclusion

UESL is a rare tumor that rarely occurs in adult patients. There are no specific test or signs to diagnose UESL, and multidisciplinary collaboration is fundamental for suspected cases. The histological epithelioid feature has been described in only one other case in the world, and only pathological examination can confirm the diagnosis. UESL is associated with a poor prognosis, especially in adults, but a comprehensive treatment based on radical resection and adjuvant therapy may provide a survival benefit. Surgical excision with negative margins remains mandatory to diagnose and treat UESL. Further studies are needed to clarify pathogenesis, biological behavior, and treatment of this tumor that remains a singularity among rare diseases.

Availability of Data and Materials

All data and any other materials used for the purpose of the manuscript are available from the corresponding author under reasonable request.

Author Contributions

KA and BGr designed and wrote the research study. BGi and CMS provided help and advice on histological examinations. BA, GA, GE, GS and CC analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Helsinki Declaration. Since our study is a case report, it is exempt from ethical approval and the consent was waived. But it was authorized by University of Milan.

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Conflict of Interest

The authors declare no conflict of interest.

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