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Case Report

A Unique Case of the Transformation of a Hepatic Leiomyoma into Leiomyosarcoma with Pancreatic Metastases: Review of the Literature with Case Presentation

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Abstract: Primary hepatic leiomyoma (PHL) is a rare entity, with very few cases reported in the literature. Even more rarely, until now practically undescribed, is the transformation of a hepatic leiomyoma into leiomyosarcoma with pancreatic metastases. Here, we report a single case of the progression of PHL in primary hepatic leiomyosarcoma, with clinical–surgical and histopathological features, and we conducted a review of the literature of related cases that can be found.

Keywords: primitive hepatic leiomyoma; leiomyosarcoma; pancreas; surgery

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1. Introduction

Primary hepatic leiomyoma (PHL) is a rare entity, of which a limited number of cases are described in the literature [1]. In the latest World Health Organization (WHO) "Digestive Tumours" of 2019, leiomyomas of the gastrointestinal (GI) tract are listed as "relatively rare", more commonly found in the esophagus, stomach and colon [2]. Although rare, cases of primary liver leiomyosarcoma have also been reported in the literature, but cases of the malignant transformation of a primary hepatic leiomyoma into its malignant counterpart have practically never been reported. In this paper, we report a case of the malignant transformation of a PHL, provide clinical–radiological and histo-morphological information, and conduct a literature review of similar cases.

2. Material and Methods

This case report was presented after approval from informed patient consent; the samples were taken in the operating room and fixed in 10% buffered formaldehyde, sampled according to national guidelines, processed, dipped in paraffin and cut with a microtome. Sections 5 µm thick were obtained, and stained with hematoxylin–eosin and with antibodies for the immunostaining for smooth muscle actin (1A4, Dako-Agilent, Santa Clara, CA, USA 1:250) Desmin (PA5-16705, ThermoFisher, Waltham, MA, USA 1:200), Ki67 (MIB-1, Dako-Agilent, 1:500).

In addition, we conducted a review of the literature using PubMed and Web of Science (WoS) as search engines, typing the following keywords: "primitive hepatic leiomyoma" OR "hepatic leiomyoma" OR "primitive hepatic leiomyosarcoma" OR "primitive mesenchimal hepatic tumours" in combination with "case report" OR "review" OR "case presentation". Only articles in English were selected. The last search was performed on 28 August 2021. Eligible articles were assessed according to the Oxford Centre for Evidence-Based Medicine 2011 guidelines and rated as level 3 or 4 evidence for clinical research. Case reports, review

articles, meta-analyses, observational studies, letters to the editor, and comments to the letters were all included. Other potentially relevant articles were identified by manually checking the references in the included literature.

An independent extraction of the articles was performed by two investigators according to the inclusion criteria. Disagreements were resolved by discussions between the two review authors. We focused on the histopathological diagnosis of leiomyoma or leiomyosarcoma, on the size and topography of the lesion, and on any symptoms mentioned by the patient. The articles and data obtained are presented in Table 1, and the review was performed according to the PRISMA guidelines (Figure 1).

Table 1. Summary of the reported cases of primary leiomyoma and leiomyosarcoma of the liver in literature.

Year	Author	Localization, Measure (cm)	Symptoms	Histological Diagnosis
1926	Demel [3]	RL/12	RUQ pain	Leiomyoma
1962	BEAIRD JB [4]	Portal vein	RUQ pain	Leiomyosarcoma
1965	Dalenz [5]	LL/NS	RUQ pain	Leiomyoma
1975	Masur [6]	RL/NS	NS	Leiomyosarcoma (2)
1978	Bloustein [7]	RL/3.3	RUQ pain	Leiomyosarcoma
1987	Maki [8]	RL/NS	NS	Leiomyosarcoma
1987	Griffin [9]	Cava vein	NS	Leiomyosarcoma
1987	Shurbaji [10]	RL/NS	RUQ pain	Leiomyosarcoma
1988	Kinoshita [11]	RL/NS	RUQ pain	Leiomyosarcoma
1989	Rummeny [12]	NS	NS	Leiomyoma
1990	Herzberg AJ [13]	RL/19	RUQ pain	Leiomyoma
1990	Little [14]	LL/NS	NS	Leiomyoma
1990	Lee [15]	Hepatic vein	RUQ pain	Atypical Leiomyoma
1990	Spagliardi [16]	RL/NS	None	Leiomyosarcoma
1990	Sundaresan [17]	Portal vein	RUQ pain	Leiomyosarcoma
1991	Bartoli [18]	RL/NS	NS	Leiomyoma
1991	Ishii [19]	34 cases	/	Leiomyosarcoma
1991	Korbi [20]	RL/2.1	None	Leiomyosarcoma
1992	Reinertson [21]	LL/10	RUQ pain	Leiomyoma
1992	Ross J S [22]	RL/3.3	RUQ pain	Leiomyosarcoma (HIV)
1993	Baur [23]	RL/NS	RUQ pain	Leiomyosarcoma
1993	Saint-Paul [24]	RL/9.3	RUQ pain	Leiomyosarcoma
1994	Prévot S [25]	RL/NS	RUQ pain	Leiomyoma in HIV
1995	Hiyama [26]	RL/NS	None	Leiomyosarcoma
1996	Abdelli [27]	RL/NS	RUQ pain and fever	Leiomyosarcoma
1996	Davidoff [28]	RL/NS	RUQ pain	Leiomyoma in transplantation
1998	Yoon [29]	RL/NS	RUQ pain	Myxoid Leiomyoma
1999	Yanase [30]	RL/12	RUQ pain	Leiomyoma with Cystoadenoma
1999	Enoki [31]	Hepatic vein	RUQ pain	Leiomyosarcoma
2000	Mesenas [32]	RL/3.6	None	Leiomyoma
2000	Tsuji [33]	RL/NS	RUQ pain	Leiomyosarcoma
2001	Belli [34]	RL and LL/30	Obstruction	Giant leiomyoma
2002	Torres [35]	RL/NS	RUQ pain	Leiomyosarcoma
2002	Fujiita [36]	RL/NS	RUQ pain	Leiomyosarcoma
2002	Lee [37]	RL/NS	RUQ pain	Leiomyosarcoma
2002	Baek [38]	RL/NS	RUQ pain	Leiomyosarcoma
2004	Beunzen [39]	RL/6	RUQ pain	Leiomyoma
2004	Maruta [40]	RL/13	RUQ pain	Leiomyosarcoma
2005	Lee [41]	RL/NS	RUQ pain	Leiomyosarcoma
2005	Kwon [42]	RL/NS	RUQ pain	Leiomyosarcoma
2006	Surendrababu [43]	RL/NS	RUQ pain	Leiomyosarcoma
2008	Marin [44]	RL/3	RUQ pain	Leiomyoma

Table 1. *Cont.*

Year	Author	Localization, Measure (cm)	Symptoms	Histological Diagnosis
2008	Tsiatis [45]	RL/9.9	RUQ pain	Leiomyosarcoma
2008	Jeong [46]	RL/NS	RUQ pain	Leiomyosarcoma
2009	Giuliante [47]	RL/2.5	RUQ pain	Leiomyosarcoma
2010	Liang [48]	RL/5	RUQ pain	Leiomyosarcoma
2010	Shamseddine [49]	RL/3 cases	RUQ pain	Leiomyosarcoma (3)
2011	Santos [50]	RL/5.5	RUQ pain	Leiomyoma
2011	Shivathirthan [51]	RL/NS	RUQ pain	Leiomyosarcoma
2012	Tsai [52]	RL/2.8	RUQ pain	Leiomyoma
2013	Raber [53]	RL/NS	RUQ pain	Leiomyosarcoma
2013	Chelimilla [54]	RL/4.6	RUQ pain	Leiomyoma
2013	Metta [55]	RL/3.5	RUQ pain	Leiomyosarcoma
2014	Luo [56]	RL/NS	RUQ pain	Leiomyosarcoma
2015	Vyas [57]	RL/8	RUQ pain	Leiomyoma
2015	Wei-Fu Lv [58]	RL/NS	None	Leiomyoma
2015	Navarro [59]	RL/9.1	RUQ pain	Leiomyosarcoma
2016	Ovanesov [60]	RL/NS	None	Leiomyoma
2016	Takashi Iida [61]	RL/NS	RUQ pain	Leiomyosarcoma
2017	Blas Laina [62]	RL/NS	RUQ pain	Leiomyosarcoma
2018	Feretis [63]	RL/13	RUQ pain	Leiomyosarcoma
2019	Jia [64]	RL/7.2	RUQ pain	Leiomyoma
2020	Fraga [65]	RL/19	RUQ pain	Leiomyoma
2020	Coletta [66]	RL/9	RUQ pain	Leiomyoma

RL: Right Liver; LL: Left Liver; NS: not specified; RUQ: Right Upper Quadrant.

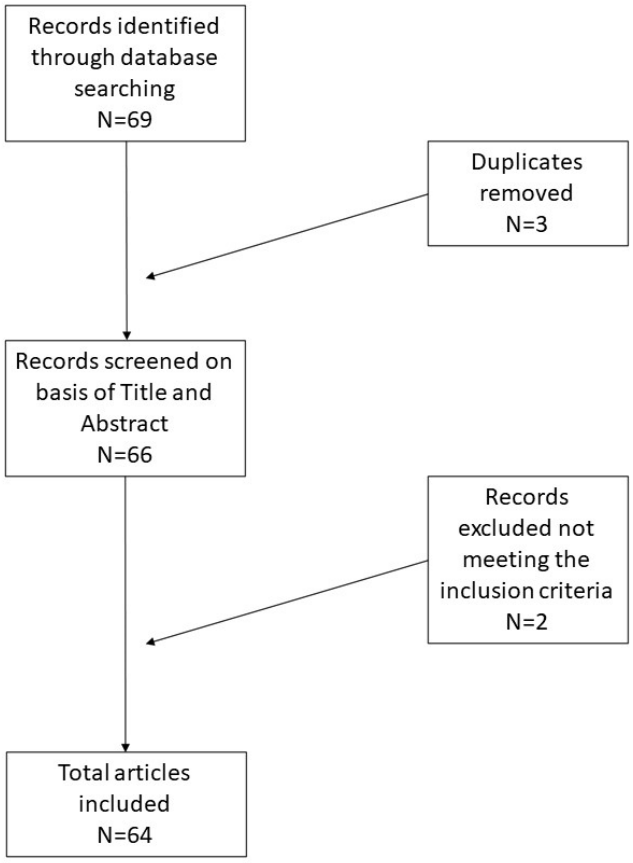

Figure 1. Selection of articles following PRISMA guidelines.

3. Results

3.1. Case Presentation

In 2014, a 53-year-old woman had been suffering from the onset of non-specific gastrointestinal symptoms for some months, including difficulty in digestion, slowed digestion, vomiting and changes in evacuation habits. Following a consultation with the general practitioner, it was decided to refer the patient for a visit to the general surgeon who, on the CT scan, identified the presence of a voluminous neoformation of the cecum, with peri-cecal fluid collection and a suspected metastatic lesion of about 15 mm, between segments 2 and 4 of the liver. Hematological and serum biochemical profiles were within normal ranges. Tumor markers including alpha-fetoprotein (AFP), carcinoembryonic (CEA), carbohydrate antigens 199 (CA199), and carbohydrate antigens 125 (CA125) were also normal.

3.2. Histological Features

A hepatic segmentectomy was performed, and at the post-operative histological examination, a moderately differentiated adenocarcinoma of the large intestine was diagnosed, involving the ileocecal valve, with an expansive growth pattern, which infiltrated the wall up to the proper muscular tunic. There was no vascular invasion in the examined sections, and it was concluded for a staging (pTNM): pT2N0M0. At the hepatic level, on the other hand, a nodular formation was found, well demarcated, consisting of medium–large cellular elements, mainly arranged in an intertwined bundle architecture, with a single focus of central necrosis. There were no cellular elements of the adenocarcinomatous type. Immunohistochemical investigations were positive for smooth muscle actin (Act-mL) and desmin. On the other hand, the reactions for CD117 (c-kit), DOG-1, S-100 protein, CD34 and vimentin were negative. The evaluation of the mitotic index, carried out by measuring the individual mitotic figures on 50 high-magnification fields (HPF, Original Magnification: 40×), was 1 mitosis/50 HPF, a figure confirmed by evaluation of the neoplastic proliferation index (evaluated by Ki67+) which was 1%. On the basis of these data, the diagnosis of primary leiomyoma of the liver was made (Figure 2A,B). The lesion reached close to the Glissoniana, without ever infiltrating it; the surgical resection margins were free from neoplasia. The patient was considered disease-free and continued to have six-monthly follow-ups. In 2019, about 5 years later, at a checkup, a new liver lesion was found on the computed tomography scan, in correspondence with the S3 segment. In agreement with the patient, a hepatic needle biopsy was performed, which revealed a proliferation of leiomuscular elements with mild cytological atypia and low mitotic index (5 mitosis/50 HPF). Additionally, in this case, the immunohistochemical reactions were positive for smooth muscle actin and desmin. The fraction of neoplastic proliferation (again evaluated by Ki67) was, this time, about 10%. A diagnosis of a recurrent smooth muscle tumor of the liver was therefore made. Following this needle biopsy, the patient was again subjected to hepatic segmentectomy (S3.5-8) which revealed a nodular neoformation of 7.3 × 6.3 × 4 cm, whitish in color, and a collated appearance when cut. On this occasion, a consensual cholecystectomy was also performed. The histological diagnosis concluded with mesenchymal malignant neoplasm, with spindle elements with pleomorphic nuclei, arranged in variously intertwined bundles; the mitotic index was equal to 6 mitosis/50 HPF and the proliferative index (Ki67+) was about 20%. Furthermore, multiple and sometimes confluent foci of necrosis were described (Figure 3A–C). However, there were no clear signs of ease of invasion. Additionally, in this case, the immunohistochemical investigations were strongly positive for smooth muscle actin (Figure 3D) and desmin. In consideration of these new data, the diagnosis of primary hepatic leiomyosarcoma, grade 1 (total score: 3), according to the grading system of the French Federation of Cancer Centers Sarcoma Group (FNCLCC), was made. In May 2021, about 2 years after the last diagnosis, the patient was again operated on, focusing on the thyroid gland for the echo-tomography (ETG) detection of a 29 × 16 mm, hypoechoic nodule, located in the middle/lower third of the left lobe. In addition, she underwent pancreatic caudectomy for an expansive formation in the distal

third of the pancreas. The histological diagnosis concluded with an oncocytic adenoma of the thyroid gland and a localization of leiomyosarcoma in the pancreas (Figure 4A,B).

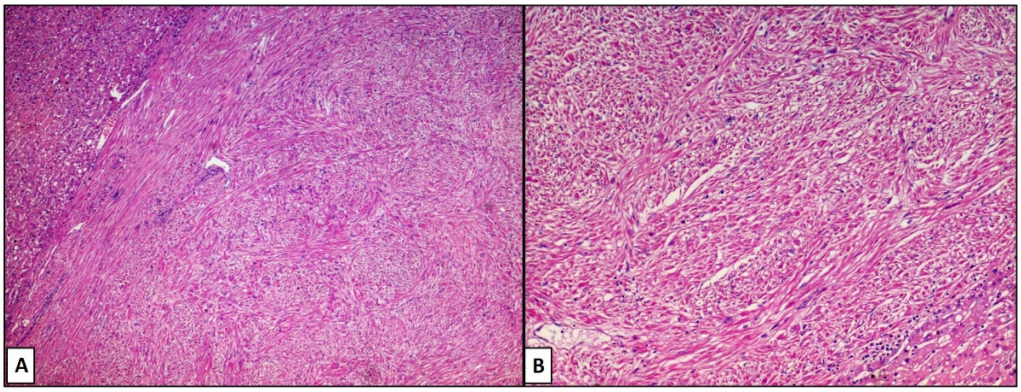

Figure 2. (**A**,**B**). Photomicrograph comprising a proliferation with mesenchymal habitus, consisting of bundles of fibers intersecting with each other, often at right angles, without evident atypia and/or mitotic figures. Note the well-defined and sharp edges of the lesion (hematoxylin–eosin, original magnification: 4× (**A**) and 20× (**B**).

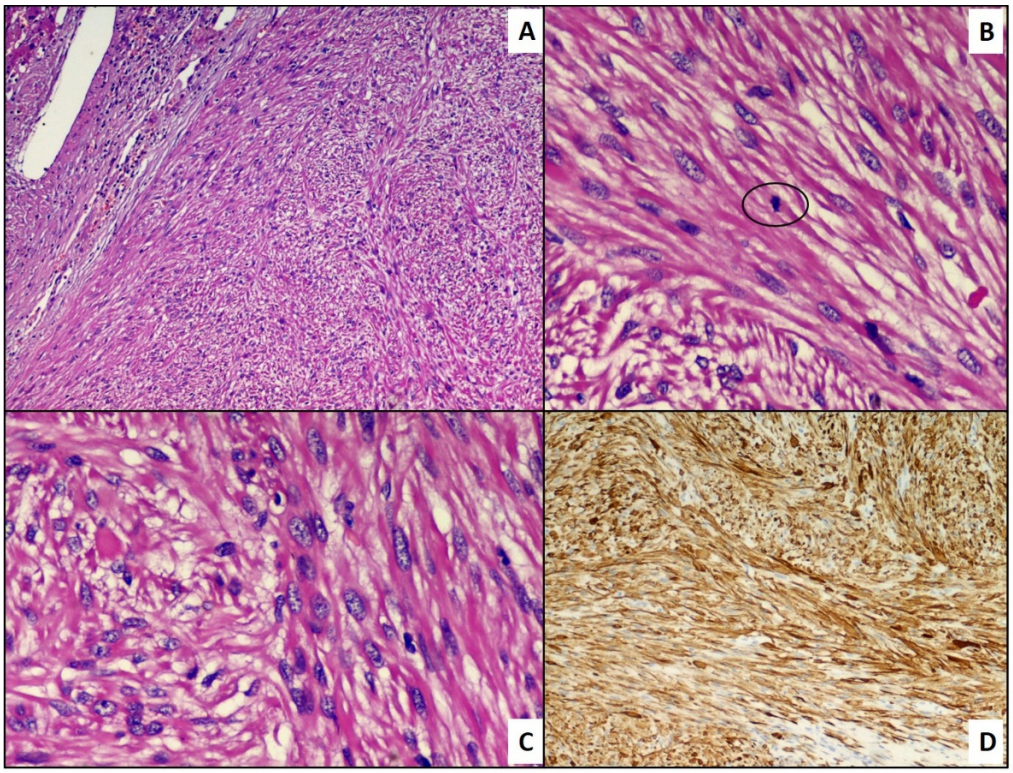

Figure 3. (**A**) Histological preparation including a proliferation of mesenchymal cells more atypical than the previous finding. Note the jagged and less clear and defined edges of the lesion (hematoxylin–eosin, original magnification: 10×). (**B**) Histological detail of a circled atypical mitotic figure (hematoxylin–eosin, original magnification: 40×). (**C**) Histological detail of the lesion: note the greater cellular crowding and nuclear irregularities (hematoxylin–eosin, original magnification: 40×). (**D**) Positive immunostaining for smooth muscle actin (immunohistochemistry, original magnification: 10×).

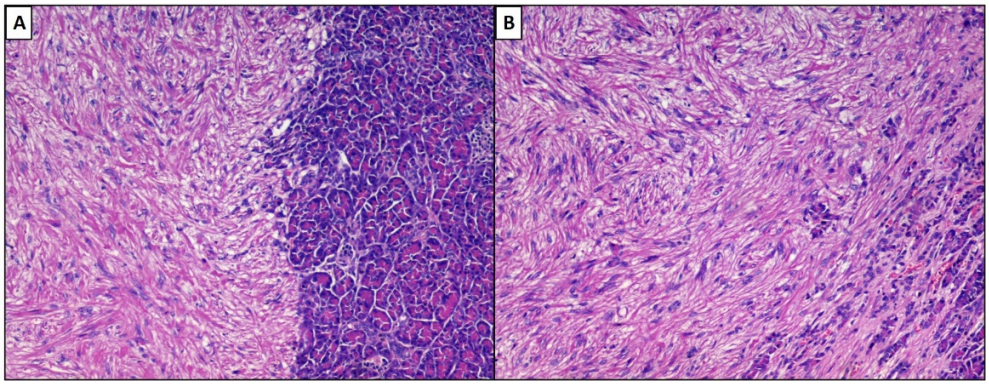

Figure 4. (**A**,**B**). Histological preparation including metastases in the pancreatic parenchyma (left) of PHLeiomyosarcoma. Note the same growth pattern as the primary lesion (hematoxylin–eosin, original magnification: 10× (**A**) and 20× (**B**).

3.3. Review of Literature

We identified 64 publications over a period of time between 1926 and 2020, almost entirely consisting of a single case report each (n = 61) except for three papers comprising 2 cases [6], 3 cases [49], and 34 cases [19]. We included a total of 100 cases, consisting of 24 cases (24%) of primary hepatic leiomyoma, 1 case (1%) of atypical leiomyoma, and the remaining 75 cases (75%) of primary hepatic leiomyosarcoma.

A total of 19 cases (29.6%) consisted of primary hepatic leiomyomas [3,5,12–14,18,21,32,39,44,50,52,54,57,58,60,64–66], whereas 1 case (1.56%) was of leiomyoma in a patient with HIV [25], and 1 case (1.56%) was of leiomyoma in a transplant recipient [28]. Another single case was a myxoid leiomyoma [29], and another case was a leiomyoma close to a hepatobiliary cystadenoma [30]. Finally, 1 case consisted of a giant leiomyoma (>10 cm in maximum diameter) [34] and 1 case consisted of "atypical" leiomyoma [15].

More than half of the lesions (both leiomyomas and leiomyosarcomas) were located in the right lobe of the liver, with the remaining cases located in the left lobe. The symptoms most complained of by patients were right upper abdominal pain, with one case of associated fever [27] and one case of intestinal obstruction due to the size of the lesion [34].

4. Discussion

Primary hepatic leiomyoma is a rare type of mesenchymal tumor originating from the liver, thought to originate from the smooth muscle layer of the intrahepatic blood vessel wall or of the biliar tree [64]. Similarly, primary leiomyosarcoma of the liver is even rarer, with about 70 cases reported in the literature [63]. However, the case of a PHL evolved into PHLeiomyosarcoma has never been reported. In this paper, we report our experience, and, probably, the first case ever described. The first author to describe a case of primary leiomyoma of the liver was Demel [3] in 1926, presenting the case of a patient with a 12 cm lesion to the right lobe of the liver. Conversely, the first official report of primitive leiomyosarcoma of the liver occurred in 1926 by Beaird [4] who described a lesion likely departing from the muscular wall of the portal vein. From that moment, there have been different descriptions with cases rather simple to diagnose, frankly benign, and cases that appeared immediately malignant.

Interestingly, some authors have highlighted how immunodeficiency conditions (congenital or acquired, such as AIDS) can cause or underlie the development of mesenchymal lesions starting from the liver. For example, Ross J.S. [22] and Prevot S. [25] in 1992 and 1994, respectively, reported two cases of primary leiomyosarcoma and leiomyoma of the liver in previously HIV-positive patients. The authors postulated how immune dysregulation could affect the immune system's own immune surveillance function, allowing more such neoplasms to manifest themselves.

Curiously, in 1998, Yoon et al. [29] reported a case of primary myxoid leiomyoma of the liver, providing elements of the morphological analysis of this lesion that had not yet been highlighted in this situation, and tried to explain these modifications as regressive rather than neoplastic progression events.

From careful study of the literature, no one has ever described a malignant transformation of a PHL into a PHleiomyosarcoma, except for the paper by Lee [15] which, in 1990, described a case of atypical leiomyoma of the liver, borrowing certain analogies with lesions of other body districts such as soft tissues or the female gynecological system. This provides a scientific basis for our experience with the reported case.

Traditionally, the histopathological diagnosis of PHL does not require particular effort: a good and clear morphology together with a small number of immunohistochemical markers (actin smooth muscle and desmin) are sufficient to perform the diagnosis. Similarly, even in the case of an overt PHleiomyosarcoma [67], atypia, necrosis and mitotic figures, together with a few markers of IHC, are sufficient. On the other hand, case such as this one presented by us can turn out to be more difficult. Already in the first histological stage, although the lesion did not meet the requirements to satisfy a diagnosis of leiomyosarcoma, characters such as focal necrosis were described, which required a careful follow-up of the lesion. In fact, after a few years, despite the previous removal, progression of the disease took place, with the development of a full-blown picture of PHleiomyosarcoma, recently also metastasized to the pancreas.

5. Conclusions

The meaning of our work is to draw attention to the possibility that in unusual sites, such as the liver, a very rare neoplasm, may, exceptionally, evolve into something frankly malignant. The rarity in the rarity should not be ignored.

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