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REVIEW

Primary Osteosarcoma of the Liver: Case Report and Literature Review

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Abstract

Extraskeletal osteosarcoma is a rare, highly malignant, osteoid formation mesenchymal neoplasm in the absence of bone involvement, associated with exceptionally poor prognosis. It frequently arises in the soft tissues of the extremities or in the retroperitoneum, but rarely in visceral organ. We describe a primary osteosarcoma of the liver in a 70-year-old man who presented with an episode of fever, accompanied by abdominal discomfort, after an accident abdominal strike. Ultrasonography and computed tomography revealed a large heterogeneous mass with areas of dense calcification involving most of the right lobe of liver. Radiography did not show evidence of primary tumor or primary bone lesion at any other site. Histologically, the tumor showed an essentially similar appearance as osteosarcoma originating in the skeleton, comprised of polygonal or spindle shaped cells, along with abundant eosinophilic lace-like osteoids, or irregularly arranged bone trabeculae. Immunohistochemistry showed that the tumor cells were positive for vimentin, CD10, and focally for SMA and CD56, but negative for other lineage-specific markers. Thus, the findings favored a primary hepatic osteosarcoma. This patient received palliative chemotherapy to ease the signs of his sickness due to the large size of the tumor and he died 4 moths later.

Keywords Mesenchymal tumor · Hepatic · Osteoid · Extraskeletal osteosarcoma

Introduction

Extraskeletal osteosarcoma (ESOS) is a rare osteoid-producing malignancy of the soft tissue with histologic similarities to primary bone osteosarcoma, but without attachment to the bone or periosteum [1–5]. It accounts for less than 1% of all soft tissue sarcomas and approximately 4% of all osteosarcomas [1, 2, 6]. Unlike osteogenic sarcoma that most commonly affect children, adolescents, and young adults, most extraskeletal cases occur in patients aged more than 40 years old with a predilection for men [2, 4, 5, 7]. ESOSs are mainly located in the deep soft tissue of the extremity, shoulder, retroperitoneum, neck, and chest, but rarely arise in visceral organ [2, 4, 5]. Osteosarcoma primarily arising from the liver has been rarely reported, and only 11 cases have been described to date [8–18]. We report here additional case in a 70-year-old man who presented with a liver mass incidentally discovered by physical examination after an accident abdominal strike.

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Case Report

A 70-year-old man visited a local hospital with an episode of fever, accompanied by abdominal discomfort, limb weakness, and occasional cough for 4 weeks after an accident abdominal strike. He had no history of liver cirrhosis and chronic hepatitis B virus (HBV) and HCV infection. A physical examination revealed the decrease of breathing sounds in the right lower lung field. His hemoglobin level was 9.9 g/dL. The level of serum alkaline phosphatase was 305 IU/L and serum aspartate transaminase, alanine transaminase and lactate dehydrogenase were within normal limits. Cancer antigen 125 (CA 125) was 59.4 ng/mL, while alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA 19–9) were normal. Computed tomography (CT) scan of the chest and upper abdomen revealed a large heterogeneous mass occupying the right lobe of the liver with solid, cystic components, and areas of calcification, suspected of being a hepatocellular carcinoma (HCC) (Fig. 1a). Chest radiography revealed a right pleural effusion without any other lung lesion. Pleural fluid analysis revealed that it was compatible with transudate. Neither malignant cells nor bacteria were identified. Abdommal ultrasound scan showed an 8.5 × 9.2 cm in size, partially solid, partially cystic, ovoid heterogeneous echogenic mass containing areas of calcification. A

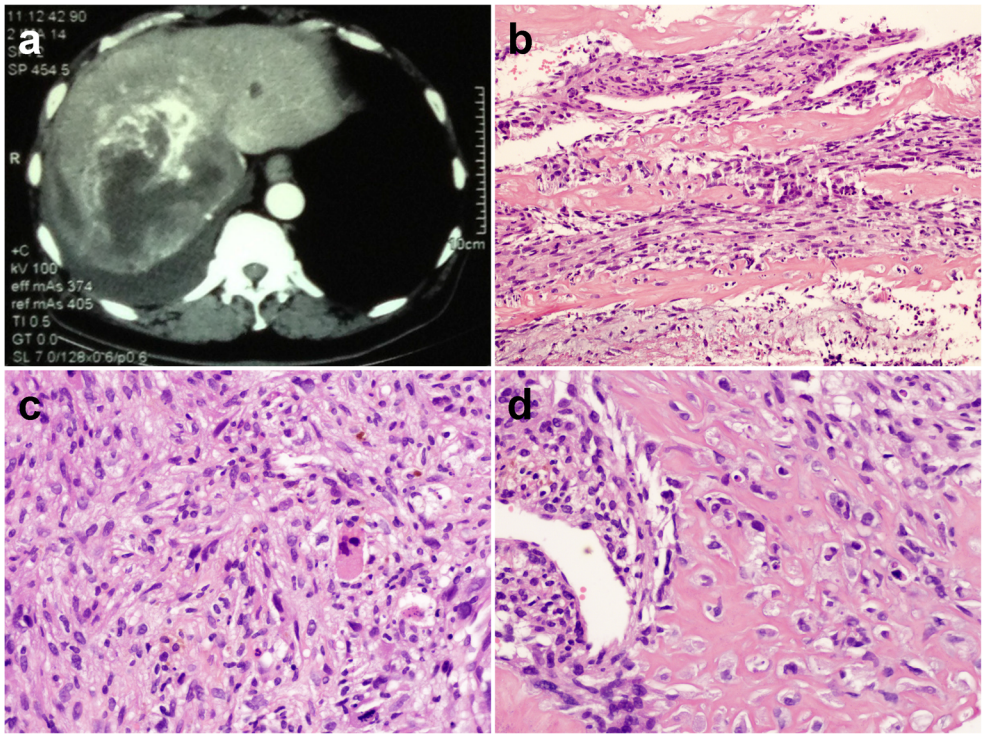

Fig. 1 Radiographic and histiological findings. **a** Computed tomography scan reveals a large, solid mass with large areas of peripheral calcification, measuring 8.5 × 9.2 cm occupying the right hepatic lobe. **b** The liver lesion consists of irregularly arranged bone trabeculae, surrounded by a diffuse proliferation of polygonal or spindle shaped cells, similar to a well-differentiated osteosarcoma (H&E, original magnification, × 200). **c** The malignant cells lying between the osteoid trabeculae have moderate atypia, with irregular, hyperchromatic, round or oval nuclei, inconspicuous nucleoli, and frequent nuclear inclusion (H&E, original magnification, × 400). **d** The spindle to epitheliod cells merge with eosinophilic lace-like irregular osteoid, or calcified osteoid matrix elaborated by atypical osteoblasts (H&E, original magnification, × 400)

bone scan did not reveal any additional bone lesions. Subsequently, a core needle biopsy of multiple sites was performed, and histological examination of the lesion showed considerable osteoid matrix, mixed with polygonal or spindle-shaped tumour cells among the bone trabeculas, which was initially interpreted as a malignant mesenchymoma with osteoid production. Then, this patient was referred to us for consultation.

Materials and Methods

The specimen was fixed in 10% neutrally buffered formalin and routinely processed to paraffin blocks. Tissue sections, 4–5 μm in thickness, were prepared and stained with hematoxylin and eosin (H&E). Additional sections, after antigen retrieval, were immunohistochemically stained using the Dako Envision HRP/DAB detection system on the Roche Ventana BenchMark XT autostainer (Ventana Medical Systems, Tucson, AZ). The primary antibody panel consisted of alpha-smooth muscle actin (SMA) (clone lA4, 1:100, Dako), CD10 (56C6, 1:50; Novocastra, Newcastle, UK), CD34 (QBEnd 10, Ready-to-Use), CD56 (1B6, 1:50, Novocastra, Newcastle upon Tyne, UK), cyclin-dependent kinase 4 (CDK4) (DCS-35, 1:100; Santa Cruz Biotechnology, Santa Cruz, CA), cytokeratin (AE1/AE3, Ready-to-Use), desmin (clone D33, 1:160), epithelial membrane antigen (EMA) (clone E29, 1:100), h-caldesmon (h-CD, 1:50), Ki-67 (MIB-1, 1:100), MDM2 (murine double minute 2) (SMP14, 1:50, Santa Cruz Biotechnology, Santa Cruz, CA), vimentin (V9, 1:100), and S-100 protein (rabbit polyclonal, 1:100, Bio Genex, San Ramon, CA, U.S.A.). All primary antibodies used in this study are murine monoclonal antibodies obtained from DAKO Corporation (DAKO Corporation, Carpinteria, CA), unless otherwise stated. Appropriate positive and negative controls were carried out in parallel. Peroxidase activity was developed using hydrogen peroxide as a substrate and 3,3′-diaminobenzidine tetrahydrochloride (DAB) as chromogen. The sections were counterstained with Harris hematoxylin and mounted in permanent mounting medium.

Results

Microscopic examination showed an osteogenic lesion consisted of diffuse proliferation of polygonal or spindle cells, admixed with abundant eosinophilic osteoids in a lace-like pattern, with partly calcified, reminiscent of a well-

differentiated or low-grade central osteosarcoma (Fig. 1b). Neither carcinomatous nor cartilaginous and other mesenchymal components were identified. The tumor cells had moderate atypia, irregular, hyperchromatic and bizarre nuclei, and indistinct cytoplasmic borders (Fig. 1c). In addition, occasional giant osteoclast-like cells were present, mainly in osteoid areas. Mitotic figures were frequent, with an estimated count of 5 per 10 high-power fields (HPF) in most active areas. Foci of necrosis and hemorrhage were evident within the tumor.

Immunohistochemistry showed that the malignant stromal cells were positive for vimentin (Fig. 2a), CD10 (Fig. 2b), CDK4, weakly for SMA, and focally for CD56 (Fig. 2c), but negative for cytokeratin (AE1/AE3), CD34, desmin, epithelial membrane antigen (EMA), h-caldesmon, MDM2, and S-100. The Ki-67 proliferative index of the tumor cells was approximately 20% (Fig. 2d).

This patient received palliative care to ease the signs of his sickness according to his request without surgery. However, the patient's condition deteriorated rapidly and he died 4 months after chemotherapy.

Discussion

We reported an exceedingly rare case of ESOS arising from the liver in a 70-year-old man without a history of hepatitis or cirrhosis who presented with progressive right upper quadrant pain. CT scan demonstrated a large right hepatic lobe mass with peripheral enhancement. Subsequent liver biopsy showed a tumor composed of spindle cells producing lace-like osteoid matrix. Osteosarcomatous foci in other parts of the body were excluded by performing extensive physical examination and radiologic imaging. The patient underwent palliative chemotherapy due to a large unresectable tumor, however his condition rapidly worsened, finally died of the disease within 4 months.

Osteosarcoma primarily arising from the liver is extremely uncommon condition, with only 11 cases being reported to date [8–18]. These cases and our case are summarized in Table 1. Of these patients, eight cases occurred in men and three in women. The age of patients ranged from 19 to 73 years, with a mean age of 69 years. The symptoms and signs of this neoplasm are not distinctive. Abdominal pain, distention, hepatomegaly, and weight loss were the most frequent clinical features. The liver function tests showed marked impairment. Plain radiographs, CT or magnetic resonance imaging (MRI) usually reveal a large soft tissue mass with variable mineralization. The present case occurred in a 70-year-old man who presented an episode of fever, accompanied by abdominal discomfort after recent abdominal strike, and a liver mass was incidentally discovered by radiological examination. Histological evaluation remains fundamental in the diagnosis of ESOS, like its bony counterparts, relying exclusively on the accurate identification of malignant osteoid or bone, but in absence of other components and lack of association of a bone tumor [6]. The histological appearance of our case, showing polygonal or spindle shaped cells producing abundant osteoid arranged in a lace-like pattern, favored a

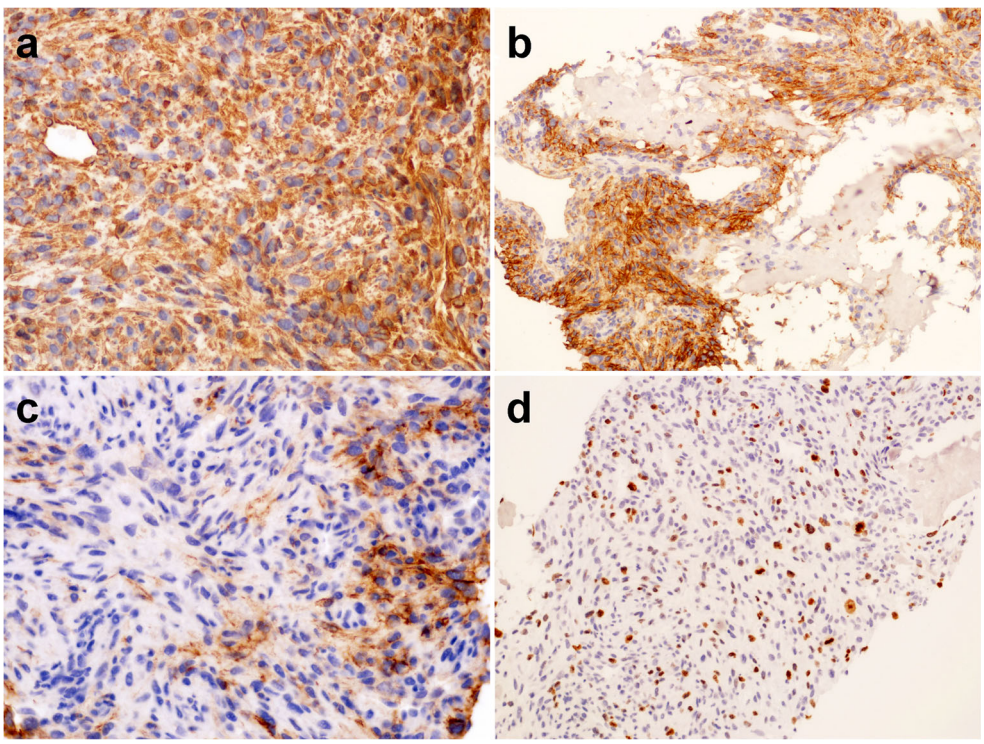

Fig. 2 Immunohistochemistry. **a** The tumor cells are diffusely positive for vimentin in the cytoplasm (Original magnification, × 400). **b** The tumor cells show strong and diffuse positivity for CD10 (Original magnification, × 200). **c** The tumor cells are focally positive for CD56 (Original magnification, × 400). **d** Ki-67 proliferative index is approximately 20% of the tumor cells (Original magnification, × 200). Dako Envision HRP/DAB

Table 1 Primary osteosarcoma of liver

Case	Age/Sex	Tumor size (cm)	Liver disease	Hepatitis status	Therapy	Outcome	Reference
1	61/M	13 × 12 × 11	Cirrhosis, hemochromatosis, alcohol ingestion	Unknown	Unknown	Dead of disease (DOD), 3 weeks after admission	Maynard JH, Fone DJ. [9]
2	52/M	1700 g Multinodular tumor mass	Cirrhosis, Alcohol ingestion	Unknown	None (Autopsy)	DOD, 2 months	Sumiyoshi A, Niho Y. [10]
3	71/M	25 × 20 × 12	No cirrhosis	Unknown	Surgery	DOD, 2 months	von Hochstetter AR, et al. [11]
4	73/F	2100 g	Chronic liver disease; no cirrhosis	Unknown	Unknown	Unknown	Craig JR, et al. [12]
5	67/M	10	Cirrhosis	HBV negative; HCV positive	Transarterial chemotherapy(Autopsy)	DOD.	Kitayama Y, et al. [13]
6	72/M	25 × 19 × 14	No cirrhosis	HBV negative	Autopsy	DOD, 4 months	Govender D, Rughubar KN. [8]
7	45/M	21 × 15 × 9.5	No cirrhosis	HBV and HCV negative	Surgical	Unknown	Krishnamurthy VN, et al. [14]
8	60/F	15 × 13.4 × 4.5	No cirrhosis	HBV, HCV negative	Surgical	DOD, 2 months after surgery	Park SH, et al. [15]
9	19/F	15.0 × 13.8 × 12	No cirrhosis	Unknown	Surgical, chemotherapy	Alive without recurrence 36 months after surgery	Nawabi A, et al. [16]
10	47/M	11 × 10 × 8	Cirrhosis	HBV-positive	Surgical	Alive, 3 months	Jiang RD, et al. [17]
11	50/M	4.4 × 4.8 × 4.8	Cirrhosis	HCV positive	Portal vein embolization	DOD, 2 months	Tamang TG, et al. [18]
12	70/M	8.5 × 9.2	No cirrhosis	HBV, HCV negative	Palliative Treatment	DOD, 4 months	Present case

diagnosis of osteosarcoma. Immunohistochemically, this case were positive for vimentin, CD10, weakly for SMA, and focally for CD56, but negative for S-100, cytokeratins (AE1/AE3), desmin, and EMA, suggesting myofibroblastic differentiation may occur in this tumor. Focal expression of SMA and CD10 has been previously reported in osteosarcomas [19, 20]. Such immunohistochemical profile is obviously not specific, because the same features may be observed in many other sarcomas, but has to be employed to distinguish entities that share overlapping morphologic characteristics. Despite the fact that a core biopsy of a large tumor limited the accuracy in the diagnosis of osteoid formation neoplasm, it becomes a main method for diagnose of these unresectable tumours. To make up this shortfall, multiple site needle core biopsies were taken at one time from the mass, and a collaborative effort in which clinical, radiologic, and pathologic findings have to be considered for a suspected osteoid neoplasm. Also, because liver is known to be a favored site for metastasis, the possibility of metastatic osteosarcoma from a primary osteosarcoma of the bone should be excluded before diagnosing a hepatic tumor as a primary osteosarcoma, as the two entities have different biological behaviors and require different treatments. In our case, the histopathologic and immunohistochemical examinations of multiple sections of the tumor did not reveal any carcinomatous or other mesenchymal components. Furthermore, the possibility of metastasis from a skeletal osteosarcoma was excluded, since no additional skeletal lesions were identified by the bone scan.

Primary osteosarcoma of the liver should be differentiated from other malignancies of the liver that harbor osteosarcomatous foci. Carcinosarcomas are composed of both carcinomatous and sarcomatous components, and an osteoid is sometimes observed in the sarcomatous portion [21, 22]. However, the absence of a carcinomatous component in our case precluded the possibility of a carcinosarcoma. Hepatoblastoma is an uncommon malignant liver cancer occurring in infants and children, and only occasionally in adults. In addition to epithelial component, an osteoid element frequently occurs in the hepatoblastomas of the mixed epithelial and mesenchymal types. In our patient, an osteoid was a main feature, and there were no epithelial elements with an embryonic or fetal pattern of differentiation, which have been reported as being found in the rare adult cases of hepatoblastomas [23]. Also, prior to making a diagnosis of primary liver osteosarcoma, sarcomatous or metaplastic HCC should be excluded, since HCC may exhibit histological features of sarcomatous transformation [13, 24, 25]. However, in sarcoma-like HCCs, components of HCC and a transition between HCC and sarcomatous components are invariably present [13], and these were not found in our case. Although immunohistochemistry plays a limited role in the diagnosis of osteosarcomas, it is important in differentiating primary liver osteosarcomas from sarcomatoid or metaplastic

carcinomas, as the latter is positive for keratin, whereas osteosarcomas are not. The cells from a primary osteosarcoma of the liver are positive for vimentin and further display negativity for hepatocellular markers. Furthermore, malignant mesenchymoma of the liver, another mesenchymal tumor that commonly occurs in childhood, contains osteoid component. A diagnosis of malignant mesenchymoma, in addition to a fibrosarcomatous element, requires that two or more unrelated, differentiated tissues must be identified in the tumor [26]. However, our case failed to meet the diagnostic criteria for a malignant mesenchymoma, as no other sarcomatous component was identified.

The histogenesis of these rare extraskeletal osteogenic tumors remains unresolved, although most authors favor the theory that primary osteosarcomas of the liver may originate directly from primitive, undifferentiated mesenchymal cells. However, monomorphic development of the osteosarcomatous elements of malignant mesenchymoma or osseous metaplasia in malignant mesenchyma of the liver should also be considered alternative possibilities [6]. The pathogenesis of the liver osteosarcoma is also not exactly known. A variety of factors causing DNA alteration or damage, like infection with hepatitis viruses, chemotherapy, ischemic stress, trauma or genetic predisposition, have been implicated in oncogenesis. The role of hepatitis in development of osteosarcoma is uncertain since only 3 of the 12 cases were reported to have hepatitis and the status is not known in four cases. The possible mutability or tumorigenesis of the proliferating mesenchymal tissue in the cirrhotic liver has been suggested, where continuous stimuli for cellular replication may be responsible for oncogenesis in these patients [10]. However, of these cases, only five had underlying liver cirrhosis. The current patient had neither hepatitis nor underlying cirrhosis.

Regarding treatment of ESOS, radical resection has been reported to be the best option for local control of the disease [3], and no effective adjuvant therapy is known [21]. Local recurrence and distant metastasis were common and had usually occurred by 3 years after excision [3]. ESOS, regardless of their sites of origin, have a dismal prognosis even after resection, a 5-year survival rate of 37% has been reported [3, 5]. The prognosis of ESOS depends on the tumor size and site involved. Tumor size (less than 5 cm) has been reported the main prognostic factor [1]. Primary osteosarcoma of the liver, similar to other extra-osseous counterparts, is characterized by its aggressive nature, that is, direct extrahepatic invasion, distant metastases and short survival [8]. Eight previously described cases (8/12) resulted in either quick progression to death after diagnosis or the diagnosis was only established at autopsy. In fact, however, no long-term survivor of primary hepatic osteosarcoma has ever been reported [8, 9, 11]. Although primary osteosarcoma of the liver shares similar histopathologic features with those of osteosarcomas arising in the bone, it should be regarded as a separate disease from its skeletal counterparts both clinically and therapeutically, because of its dismal prognosis and poor response to multimodality therapy [18, 27, 28].

In conclusion, the primary osteosarcoma of the liver is extremely rare disease with a poor prognosis. The diagnosis should be considered when a soft tissue mass that shows abundant malignant osteoid or bone without other malignant components is encountered. Early detection and complete surgical resection of the tumor with concurrent chemo-radiation therapy might be a chance to cure this disease.

References

1. Bane BL, Evans HL, Ro JY, Carrasco CH, Grignon DJ, Benjamin RS, Ayala AG (1990) Extraskeletal osteosarcoma. A clinicopathologic review of 26 cases. Cancer 65(12):2762–2770
2. Chung EB, Enzinger FM (1987) Extraskeletal osteosarcoma. Cancer 60(5):1132–1142
3. Lee JS, Fetsch JF, Wasdhal DA, Lee BP, Pritchard DJ, Nascimento AG (1995) A review of 40 patients with extraskeletal osteosarcoma. Cancer 76(11):2253–2259
4. Lidang Jensen M, Schumacher B, Myhre Jensen O, Steen Nielsen O, Keller J (1998) Extraskeletal osteosarcomas: a clinicopathologic study of 25 cases. Am J Surg Pathol 22(5):588–594
5. McCarter MD, Lewis JJ, Antonescu CR, Brennan MF (2000) Extraskeletal osteosarcoma: analysis of outcome of a rare neoplasm. Sarcoma 4(3):119–123
6. Allan CJ, Soule EH (1971) Osteogenic sarcoma of the somatic soft tissues. Clinicopathologic study of 26 cases and review of literature. Cancer 27(5):1121–1133
7. Hoch M, Ali S, Agrawal S, Wang C, Khurana JS (2013) Extraskeletal osteosarcoma: a case report and review of the literature. J Radiol Case Rep 7(7):15–23
8. Govender D, Rughubar KN (1998) Primary hepatic osteosarcoma: case report and literature review. Pathology 30(3):323–325
9. Maynard JH, Fone DJ (1969) Haemochromatosis with osteogenic sarcoma in the liver. Med J Aust 2(25):1260–1263
10. Sumiyoshi A, Niho Y (1971) Primary osteogenic sarcoma of the liver–report of an autopsy case. Acta Pathol Jpn 21(2):305–312
11. von Hochstetter AR, Hattenschwiler J, Vogt M (1987) Primary osteosarcoma of the liver. Cancer 60(9):2312–2317
12. Craig JR, Peters RL, Edmondson HA (1989) Atlas of tumor pathology: tumors of the liver and intrahepatic bile ducts. Armed Forces Institute of Pathology, Washington, pp 223–255
13. Kitayama Y, Sugimura H, Arai T, Nagamatsu K, Kino I (1995) Primary osteosarcoma arising from cirrhotic liver. Pathol Int 45(4):320–325
14. Krishnamurthy VN, Casillas VJ, Bejarano P, Saurez M, Franceschi D (2004) Primary osteosarcoma of liver. European Journal of Radiology Extra 50(1):31–36
15. Park SH, Choi SB, Kim WB, Song TJ (2009) Huge primary osteosarcoma of the liver presenting an aggressive recurrent pattern following surgical resection. J Dig Dis 10(3):231–235
16. Nawabi A, Rath S, Nissen N, Forscher C, Colquhoun S, Lee J, Geller S, Wong A, Klein AS (2009) Primary hepatic osteosarcoma. J Gastrointest Surg 13(8):1550–1553
17. Jiang RD, Zhang ZL, Li T (2015) Abdominal pain caused by spontaneous rupture of a liver tumor. Gastroenterology 149(1):35–36

18. Tamang TG, Shuster M, Chandra AB (2016) Primary hepatic osteosarcoma: a rare cause of primary liver tumor. Clin Med Insights Case Rep 9:31–33
19. Mechtersheimer G, Moller P (1989) Expression of the common acute lymphoblastic leukemia antigen (CD10) in mesenchymal tumors. Am J Pathol 134(5):961–965
20. Hasegawa T, Hirose T, Kudo E, Hizawa K, Usui M, Ishii S (1991) Immunophenotypic heterogeneity in osteosarcomas. Hum Pathol 22(6):583–590
21. Ojima A, Sugiyama T, Takeda T, Hazama F, Nakakuki F, Uesugi Y et al (1964) Six cases of rare malignant tumors of the liver. Acta Pathol Jpn 14:95–102
22. Leger-Ravet MB, Borgonovo G, Amato A, Lemaigre G, Franco D (1996) Carcinosarcoma of the liver with mesenchymal differentiation: a case report. Hepato-Gastroenterology 43(7):255–259
23. Carter R (1969) Hepatoblastoma in the adult. Cancer 23(1): 191–197
24. Haratake J, Horie A (1991) An immunohistochemical study of sarcomatoid liver carcinomas. Cancer 68(1):93–97
25. Kakizoe S, Kojiro M, Nakashima T (1987) Hepatocellular carcinoma with sarcomatous change. Clinicopathologic and immunohistochemical studies of 14 autopsy cases. Cancer 59(2):310–316
26. Stout AP (1948) Mesenchymoma, the mixed tumor of mesenchymal derivatives. Ann Surg 127(2):278–290
27. Heukamp LC, Knoblich A, Rausch E, Friedrichs N, Schildhaus HU, Kahl P, Tismer R, Schneider B, Büttner R, Houshdaran F (2007) Extraosseous osteosarcoma arising from the small intestinal mesentery. Pathol Res Pract 203(6):473–477
28. Sordillo PP, Hajdu SI, Magill GB, Golbey RB (1983) Extraosseous osteogenic sarcoma. A review of 48 patients. Cancer 51(4):727–734