Hepatic rhabdomyosarcoma in an adult : a rare primary malignant liver tumor. case report and literature review

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Abstract

Rhabdomyosarcomas are malignant tumors that display features of striated muscle differentiation. They are the most common soft-tissue sarcomas among children and young adults. In mature adults however there are very rare. The liver as a primary site in adults has only been described in 12 cases.

We report a case of a primary alveolar rhabdomyosarcoma of the liver in a 59 year old female, confirmed by histological examination using immunohistochemical analysis (positive actin, desmin, vimentin and myogenin staining) and fluorescent in situ hybridization (FISH) analysis (positivity for PAX3/FOXO1A fusion). The patient underwent primary surgical resection, but presented a few weeks after surgery already with recurrent disease in the abdomen and bone metastasis. Despite initial good response to chemotherapy (doxorubicin/ifosfamide) and stable disease at 12 months after diagnosis, the patient died 31 months after the first presentation secondary to complicated abundant abdominal recurrent disease.

We further present a review of the literature on published similar cases since 1979. (Acta gastroenterol. belg., **2011**, 74, **576-581**).

Key words : liver.

Introduction

Primary sarcomas of the liver are extremely rare and their frequency has been estimated at 0,1 % of all primary malignant neoplasms of the liver (1).

The most common primary hepatic sarcomas reported include hemangiosarcoma, epithelioid hemangioendothelioma, undifferentiated (embryonal) sarcoma and embryonal rhabdomyosarcoma of bile duct origin in children. The rarest hepatic sarcomas include fibrosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, as well as embryonal rhabdomyosarcoma of bile duct origin in adults (2,3).

We report a case of primary hepatic rhabdomyosarcoma in an adult and review the literature of all published similar cases since 1979.

Case report

A 59 year old woman was referred to the emergency department with progressive upper abdominal discomfort and heartburn over a 2 weeks period. Her appetite remained good and she experienced no weight loss. Relevant medical background included a history of esophageal ulceration, cholecystectomy, hysterectomy and resection of two benign breast tumors. There was no regular use of medications, nor a history of smoking or alcohol abuse.

Her general clinical condition upon admission to hospital was unremarkable. There was no icterus or fever. Abdominal examination revealed a slightly tense epigastrium with some tenderness upon palpation, but no evidence of peritonitis. Laboratory data was normal, except for an elevated lactate dehydrogenase level. Alpha-fetoprotein (AFP) value was within the normal range.

Ultrasound examination revealed an irregular emarginated, heterogeneous mass with a maximal diameter of 6,5 cm in the left liver lobe. Computed tomography of the abdomen with intravenous contrast medium confirmed the presence of this heterogeneous mass, with a diameter of 6 cm and malignant features, located in the left liver lobe. The mass could focally not be delineated of the stomach.

Additional magnetic resonance imaging showed a large T1 hypo-intense, T2 heterogeneous hyper-/isointense lesion in segment 3 of the left liver lobe (diameter 6 cm) with a rather hypovascular aspect in the arterial phase and progressive contrast uptake during the venous phases. Tumor protrusion from both the anterior and posterior liver border created an imprint on both stomach and pancreas without arguments for actual tumor invasion of these structures. A small lesion with a diameter of 1,5 cm could be delineated under the capsule of segment 2 of the left liver lobe (Fig. 1). Further extensive screening could not reveal any other tumor site in the body.

After multidisciplinary consultation we decided to perform a left hemi-hepatectomy, both because of her young age and the suspicion of a primary malignant hepatic tumor with intrahepatic metastasis. Examination of fresh frozen samples obtained during surgery confirmed the presence of malignancy.

Histological examination of the liver tumor showed a macroscopically pale, bumpy lesion on the surface of the left liver lobe with a diameter of 5,5 cm. At a distance of 8 cm, in segment 2 of the liver, a second lesion was found with a diameter of 1,5 cm. Biopsy samples showed

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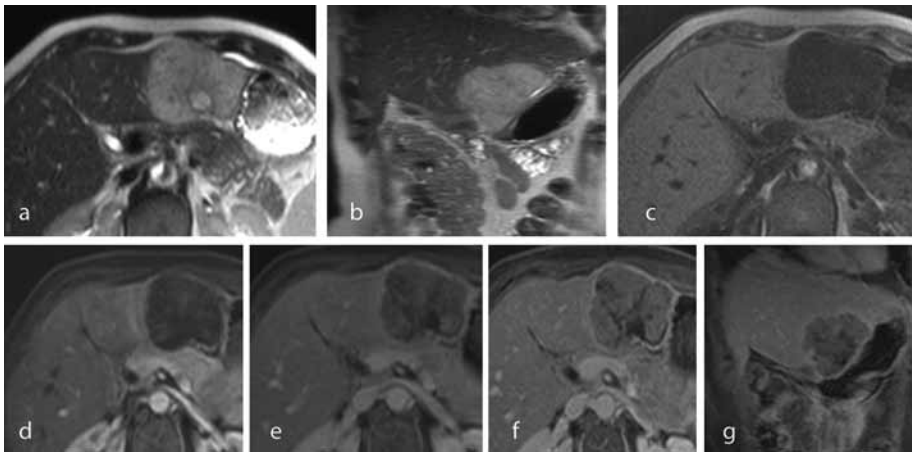

Fig. 1. — Magnetic resonance imaging examination of the liver at initial diagnosis.
(a,b) T2-weighted axial and coronal image of the liver demonstrating a well delineated lesion in the left liver lobe with an intermediate to high signal intensity and a spoke-wheel appearance.
(c) T1-weighted axial image of the liver demonstrating a T1 hypointense lesion in the left liver lobe.
(d-g) T1-weighted VIBE sequences after intravenous Gd showing an hypovascular lesion in the arterial phase (d) with progressive enhancement in the late-venous (e) and delayed phase (f,g).

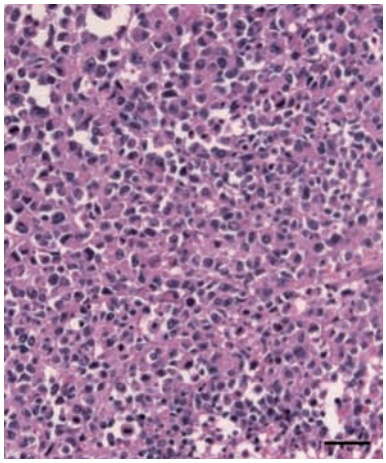

Fig. 2. — Histology features.
Rhabdomyoblasts with eccentric nucleus and bright eosinophilic cytoplasm in a mainly solid growing pattern (hematoxylin-eosin, original magnification ×200, scale-bar = 50 μm).

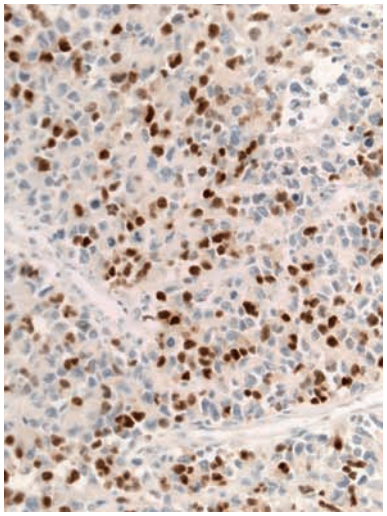

Fig. 3. — Histology sample with immunostaining.
Diffuse nuclear myogenin staining in an alveolar rhabdomyosarcoma (myogenin immunostain, original magnification ×200).

large fields of viable tumoral tissue with areas of central necrosis. The viable tissue had a pseudo-alveolar to solid and nesting growing pattern. The tumor cells were rather round and had a large quantity of eosinophilic cytoplasm with an eccentric nucleus. The cells showed an incohesive-growing pattern. The nuclei ranged in shape from round to oval and even irregular with a granular to vesicular nuclear chromatin. There were a large number of mitotic figures and some cells were multinuclear (Fig. 2). Large areas of tumor necrosis and arguments for diffuse vascular invasion (partially obliterated branch of the portal vein due to tumoral invasion) were seen. All the sections margins were free of tumor.

Immunohistochemical examinations showed a diffuse positivity for desmin, actin and vimentin, and especially nuclear myogenin (Fig. 3). There were no arguments for an epithelial tumor. Based on the growing pattern, the rhabdoid aspect of the cells and the immunohistochemical presentation, the diagnosis of a primary alveolar rhabdomyosarcoma was suggested, which was subsequently confirmed by fluorescence in situ hybridization (FISH) technique, showing a PAX3/FOXO1A fusion characteristic for alveolar rhabdomyosarcoma (Fig. 4).

The postoperative course was uneventful and the patient was subsequently discharged home in good condition. Unfortunately, only a few weeks after surgery

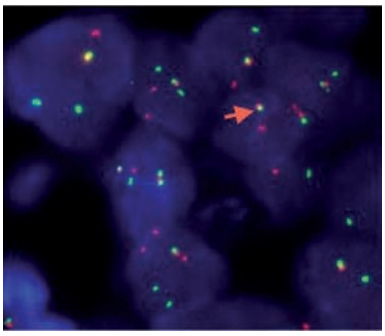

Fig. 4. — Dual-colour FISH analysis.
The PAX3/FOXO1A fusion is evidenced by overlapping red and green signals from biotin-labeled BAC RP11-384O8 (containing *PAX3*/2q35) and digoxigenin-labeled YAC 818B12 (from the CEPH mark 3 Mega YAC library, Paris, France) that contains sequences specific for *FOXO1A*/13q14. The fusion is indicated with a red arrow.

imaging showed already a recurrent tumor in the abdomen and a metastasis in the left iliac bone (Fig. 5a/b). Chemotherapy with doxorubicin (25 mg/m^2) and ifosfamide (3 g/m^2) was initiated, after she had sufficiently recovered from surgery (8 weeks after surgery). Evaluation after 2 cycles (the second with a dose reduction of 80%) showed a very good response with a 50% volume reduction of the abdominal localisation. However, because of poor tolerance to chemotherapy (thrombopenia, neutropenia and fever) and debilitating pain of the left hip, a course of radiotherapy was commenced (5 × 4 gray) for the bone metastasis, before restarting chemotherapy with doxorubicin in monotherapy (75 mg/m^2). Evaluation after 3 cycles showed a good response and chemotherapy was stopped. Twelve months after initial diagnosis, the patient still had a stable disease with no residual tumoral lesions in the abdomen at imaging and a partially consolidated fracture of the left iliac bone. One year later (25 months after initial diagnosis), the patient presented with pain in the right upper abdomen. Imaging studies showed the development of a liver metastasis (Fig. 5c). Because of no abundant tumoral progression nor evidence of visceral disease and her reluctance to restart chemotherapy, we decided to adopt a wait and see attitude. But 2 months later (27 months after initial diagnosis) the patient developed diffuse abdominal pain. Computed tomography showed multiple tumoral lesions in the mesentery, complicated with fistulisation and inflammation of the adjacent bowel (Fig. 5d). Surgery was performed with resection of these visceral lesions and chemotherapy with paclitaxel (80 mg/m^2, 2 cycles) was started. Despite chemotherapy there was significant tumor progression with rapid deterioration of her clinical status (Fig. 5e). Unfortunately the patient died 31 months after initial diagnosis, due to complications of the abdominal tumoral load.

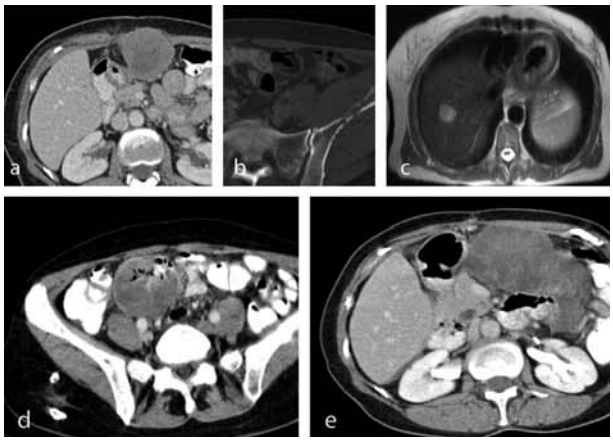

Fig. 5. — Imaging findings of recurrent disease during follow-up.
(a,b) Computed tomography at 2 months after initial diagnosis, demonstrating recurrent abdominal disease and bone metastasis in the left iliac bone.
(c) MRI of the liver (T2-weighted image) 25 months after initial diagnosis showing a liver metastasis.
(d) Computed tomography of the abdomen 27 months after initial diagnosis showing lesions in the mesentery of which one was complicated by fistulisation to the adjacent bowel (intralesional gas bubbles and contrast extravasation).
(e) Abundant recurrent abdominal tumor at 31 months after initial diagnosis.

Discussion

Primary malignant liver tumors can arise from different components of the liver such as hepatocytes, bile duct epithelium, neuroendocrine cells and mesenchymal cells. Of all the primary liver tumors the epithelial group is the largest, with the hepatocellular carcinoma and cholangiocarcinoma accounting for respectively 80% and 5 to 30% of all primary malignant tumors of the liver. Next to the epithelial tumors, there is an important group of mesenchymal tumors accounting for less than 1% of the liver tumors and containing the rhabdomyosarcoma. Rhabdomyosarcomas are tumors that exhibit features of skeletal myogenesis. They may occur in skeletal muscles, but equally elsewhere in the body. Common sites include : the head and neck region (orbita, paranasal sinuses, paraspinal, etc), the genitourinary tract (urinary bladder, prostate, vagina, etc), arms and legs, thoracic and abdominal sites (thoracic/abdominal wall, pleura, lung, retroperitoneum, biliary tract, etc). They are the most common soft-tissue neoplasms among children and young adults, but in adults they are extremely rare (2,3). A PubMed search of the literature for primary hepatic rhabdomyosarcoma in the adult population reveals 12 published similar cases in a time span of 31 years (1979-2010). Data of all these cases, including the one presented in this publication, show a total number of 13 patients (4 females, 8 males, 1 unknown) with a mean age of 55 years (range : 19-76 years) (Table 1) (1,4-13).

Table 1. — **Literature review since 1979 : similar cases of primary hepatic rhabdomyosarcoma in adults (1, 4-13)**

Authors	Mori *et al.* (4)	Watanabe *et al.* (5)	Morimoto *et al.* (6)	Shibata *et al.* (7)	Mc Ardle *et al.* (8)	Zornig *et al.* (9)	Bürrig *et al.* (10)	Tominaga *et al.* (11)	Meyer-Pannwitt *et al.* (12)	Meyer-Pannwitt *et al.* (12)	Nakase *et al.* (1)	McRea *et al.* (13)	Schoofs *et al.*
Year	1979	1983	1986	1987	1989	1992	1994	1995	1996	1996	2003	2005	2005
Publication	Full text	Full text	Abstract	Full text	Full text	Full text	Abs-tract	Full text	Full text	Full text	Full text	Full text	Full text
Language	Eng	Eng	Jap	Eng	Eng	Eng	Ger	Jap	Ger	Ger	Eng	Eng	Eng
Sex	M	M	M	M	M	F	M	N.A.	F	F	M	F	F
Age (years)	76	70	62	68	53	29	69	66	63	29	Elderly	19	59
Nationality	Jap	Jap	Jap	Jap	Aus	Ger	Ger	Jap	Ger	Ger	Jap	Afro-American	Bel
Site	Left lobe	Right lobe	Right lobe	Right lobe	Right lobe, smaller nodules left lobe	Right lobe	N.A.	Right lobe	Left lobe	Right lobe	Right lobe	Right lobe	Left lobe
Liver	Cirr-hosis	Fibrosis	N.A.	N.A.	Normal	Normal	N.A.	N.A.	Normal	Normal	Cirr-hosis	Normal	Normal
Metastases at initial diagnosis	None	None	None	N.A.	None	N.A.	N.A.	N.A.	None	None	None	Right kidney	None
Histology	P autopsy	P	N.A.	A	E	N.A.	P	N.A.	P	P	N.A.	E	A
Treatment	N.A	None	Surgery Chemo-embolisation Chemo	N.A.	None	Surgery Chemo : doxorubicin/ ifosfamide	N.A.	N.A.	Surgery	Surgery, Chemo : doxorubicin/ ifosfamide	Chemo-embolisation	Chemo : Vincristine	Surgery Chemo after recurrence : doxorubicin/ ifosfamide/ paclitaxel
Clinical course	N.A.	Death after 8 months	Death 45 days after surgery	N.A.	Death afterd 3 months	Alive 46 months after therapy	N.A.	N.A.	Alive after more than 14 years	Alive after more than 8 years	Death after 3 weeks	Death after 4 cycles Vincristine due to pneumonia	Death after 31 months
Alpha-feto protein (ng/ml)	167,7	Normal	High	Normal	Normal	Normal	N.A.	47	N.A.	N.A.	N.A.	Normal	Normal

Abbreviations : N.A. : not available ; A : alveolar ; E : embryonal ; P : pleomorphic , Eng : English, Jap : Japanese or Japan ; Ger : German ; Bel : Belgian ; Aus :Australian.

Clinically, hepatic rhabdomyosarcomas, as with other hepatic sarcomas, are often asymptomatic until they become large and even then than they produce nonspecific symptoms. Hence, it is often an incidental finding. They may present with a wide spectrum of symptoms, such as abdominal pain, anorexia, vomiting, weight loss and fatigue. If there is biliary obstruction, they can present with icterus and cholangitis, even early in the course. There are often few significant biochemical abnormalities detected at time of diagnosis. Sometimes there are signs of cholestasis or elevated alpha-fetoprotein (2,3). In the 13 cases we analyzed, there were 3 patients with raised AFP and 6 with normal levels. Of 4 patients there were no data of the AFP levels (Table 1) (1, 4-13).

Imaging findings of mesenchymal liver tumors in adults are variable, with significant overlap between them. This is particularly true with the more common malignant epithelial tumors, as demonstrated in our case where the initial presumed diagnosis was one of cholangiocarcinoma based on the NMR findings. In the case of hepatic rhabdomyosarcomas in adults, the radiologic findings have only been specifically addressed in a few case reports. Therefore, the definitive diagnosis is based on tissue biopsy. Nevertheless, knowledge of radiologic characteristics (especially MRI) of mesenchymal liver tumors in general can be of a great help for narrowing the list of differential diagnoses for the pathologist (14).

The main histological feature of a rhabdomyosarcoma is their resemblance to developing muscle. Based on their cytologic features and their histologic pattern, we can distinguish 3 major subtypes of rhabdomyosarcoma, i.e. the embryonal (ERMS), the alveolar (ARMS) and the pleomorphic type. The pleomorphic type is relatively more frequent in adults and tends to have a poorer prognosis. In children the alveolar type is a predictor for poor outcome, however in adults this seems not to be the case (15). A characteristic cell to recognize by light microscopy is the rhabdomyoblast, a cell with an eccentric round nucleus and variable amount of brightly eosinophilic cytoplasm. Often, however, the tumors are largely or entirely composed of undifferentiated cells with round to oval nuclei with minimal cytoplasm and stellate borders, instead of the typical rhabdomyoblast. Therefore, the use of immunostaining helps to reveal myogenic potential. The tumors are typically positive for muscle-specific markers, such as myogenin, myogenic determination factor (MyoD), desmin, actin, myoglobin and vimentin. These stainings can also be useful to differentiate between an ARMS and an ERMS, as they show respectively a diffuse and focal nuclear myogenin staining.

Although the role of electron microscopy has wandered off in recent years because of the advent of immunohistochemistry, it can still be of value to detect the typical filamentous network of muscle cells (3).

ARMS can also be detected by the typical gene fusions of PAX3 or PAX 7 (on chromosomes 2 and 1, respectively) and the FOXO1A (FKHR) gene on chromosome 13, found in approximately 80% of cases. The fusion is a highly potent activator of a number of downstream events leading to synthesis of cell cycle and apoptosis proteins, as well as myogenesis. Both PAX translocations can be demonstrated by FISH assays, which may be helpful in the diagnosis. Importantly, about 20% of ARMS are translocation negative. Thus, a negative FISH result does not necessarily exclude the diagnosis of ARMS (16,17).

Our case concerned an ARMS with a PAX3/FOXO1A fusion. In the other 12 cases we reviewed, ERMS, ARMS and the pleomorphic subtype represented 2, 1 and 5 cases, respectively. No data of the subtypes were available in 4 cases (Table 1) (1,4-13).

Adult rhabdomyosarcoma has a poor prognosis, with overall survival (OS) rates of 20-40% compared to childhood rhabdomyosarcoma with OS rates of 70%. This is likely in part due to its natural history and its lower sensitivity to chemotherapy and radiotherapy. However, there is definitely a factor of a suboptimal treatment approach, since these results are based on experience with adult soft-tissue sarcomas, treated predominantly by surgery, sometimes complemented by radiotherapy, but usually without chemotherapy. Therefore it is recommended to treat adults with rhabdomyosarcoma following the guidelines developed over the years for childhood rhabdomyosarcoma. This starts with adequate biopsy to obtain sufficient tissue for accurate diagnosis and molecular characterization, followed by extensive assessment for tumor extent. The latter includes MRI/CT of the primary tumor, CT thorax, bone scan, bone marrow examination and imaging of regional lymph nodes. Positron emission tomography is not considered a standard staging tool for rhabdomyosarcoma at present. The first treatment attempt is always to obtain control of the primary site, if possible with complete surgical resection, otherwise with radiotherapy or a combination of both.

All patients with rhabdomyosarcoma are presumed to have micro-metastatic disease at diagnosis, thus all require chemotherapy after control of the primary site. Standard chemotherapy in non-metastatic disease consists of vincristine and dactinomycin, often associated with cyclophosphamide (in Europe substituted by iphosphamide). In the metastatic setting it consists of iphosphamide and doxorubicin. Nevertheless, the survival rates in this last group remain disappointingly poor (16,18).

Regarding localization, there are no specific published guidelines for the treatment of a rhabdomyosarcoma in the liver. Of note, in the pediatric population, the biliary tree is considered as a favorable tumor site (16).

Our patient did not receive adjuvant chemotherapy, in contrast to the pediatric guidelines, because there was already recurrent metastatic disease within a few weeks after surgery. Chemotherapy was then initiated following the metastatic regimen with good response.

In the cases we studied, including our own case, six patients died in a time span of 3 weeks to 31 months after

initial diagnosis. Only 3 patients survived, two of the pleomorphic subtype, one of unknown subtype. The clinical course was unknown in 4 patients. Two patients were treated by surgery, three by combination of surgery and chemotherapy and two received only chemotherapy. The latter was due to extensive local disease and high comorbidity. One patient did not receive any therapy, because of multifocal liver lesions. One patient was diagnosed at autopsy. In 4 patients there were no data concerning the therapy (Table 1) (1,4-13).

In conclusion, rhabdomyosarcoma in adults remains a rare disease with a poor prognosis, however, thanks to evolutions in the pediatric setting (guidelines for diagnosis, classification and therapy ; molecular biology with evolving new therapy targets) the future still looks promising.

References

1. NAKASE H., OKAZAKI K., MATSUURA M., CHIBA T. Hepatobiliary and pancreatic : Primary rabdomyosarcoma of the liver. *J. Gastroenterol. Hepatol.*, 2003, **18** : 105.
2. SURIAWINATA A.A., THUNG S.N. Malignant liver tumors. *Clin. Liver Dis.*, 2002, **6** : 527-54, ix.
3. PARHAM D., ELLISON D. Rhabdomyosarcomas in adults and children. *Arch. Pathol. Lab. Med.*, 2006, **130** : 1454-65.
4. MORI H., MATSUBARA N., FUJII M., KAWAI T., TANAKA T., TAKAHASHI M. Alpha-fetoprotein producing rhabdomyosarcoma of the adult liver. *Acta Pathol. Jpn.*, 1979, **29** : 485-91.
5. WATANABE A., MOTOI M., MIZOBUCHI K., HARA I, NISHIMURA K., NAGASHIMA H. An adult case with rhabdomyosarcoma of the liver. *Jpn. J. Med.*, 1983, **22** : 240-4.
6. MORIMOTO H., TAKADA Y., AKITA T., KATO Y., TANIGAWA N., MURAOKA R., URATA Y. [A resected case of collision tumor of hepatocellular carcinoma and primary liver rhabdomyosarcoma]. *Nippon Geka Gakkai Zasshi.*, 1986, **87** : 456-63.
7. SHIBATA T., HAYAKAWA K., YAMASHITA K., HAMANAKA D., ODORI T., ISHII Y. [Two cases of primary hepatic rhabdomyosarcoma in adults]. *Rinsho Hoshasen.*, 1987, **32** : 653-6.
8. MC ARDLE J.P., HAWLEY I., SHEVLAND J., BRAIN T. Primary rhabdomyosarcoma of the adult liver. *Am. J. Surg. Pathol.*, 1989, **13** : 961-5.
9. ZORNIG C., KREMER B., HENNE-BRUNS D., WEH H.J., SCHRÖDER S., BRÖLSCH C.E. Primary sarcoma of the liver in the adult. Report of five surgically treated patients. *Hepatogastroenterology*, 1992, **39** : 319-21.
10. BÜRRIG K.F., KNAUER S. Rhabdomyosarcoma of the liver in adulthood. Case report and review of the literature. *Pathologe*, 1994, **15** : 54-7.
11. TOMINAGA J., KAWASE S., OCHI T., YOSHIDA M., IZAWA M. A case of primary rhabdomyosarcoma of liver at autopsy-literature review of 7 cases reported in Japan. *Nippon Shokakibyo Gakkai Zasshi.*, 1995, **92** : 255-8.
12. MEYER-PANNWITT U., KUMMERFELDT K., BROELSCH C.E. Primary pleomorphic rhabdomyosarcoma of the liver. *Langenbecks Arch. Chir.*, 1996, **381** : 75-81.
13. MC RAE B., LEE J. Pathologic quiz case : right upper quadrant abdominal mass in young woman. *Arch. Pathol. Lab. Med.*, 2005, **129** : e51-e52
14. KIM K.A., KIM K.W., PARK S.H., JANG S.J., PARK M.S., KIM P.N., LEE M.G., HA H.K. Unusual mesenchymal liver tumors in adults : radiologic-pathologic correlation. *AJR*, 2006, **187** : W481-9.
15. SULTAN I., QADDOUMI I., YASER S., RODRIGUEZ-GALINDO C., FERRARI A. Comparing adult and pediatric rhabdomyosarcoma in the surveillance, epidemiology and end results program,, 1973 to, 2005 : an analysis of 2,600 patients. *J. Clin. Oncol.*, 2009, **27** : 3391-7.
16. BREITFELD P., MEYER W. Rhabdomyosarcoma : New Windows of Opportunity. *Oncologist*, 2005, **10** : 518-27.
17. TANAS M.R., GOLDBLUM J.R. Fluorescence in situ hybridization in the diagnosis of soft tissue neoplasms : a review. *Adv. Anat. Pathol.*, 2009, **16** : 383-91.
18. FERRARI A., DILEO P., CASANOVA M., BERTULLI R., MEAZZA C., GANDOLA L., NAVARRA P., COLLINI P., GRONCHI A., OLMI P., FOSSATI-BELLANI F., CASALI P. Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. *Cancer*, 2003, **98** : 571-80.