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Interdisciplinary Treatment of Primary Hepatic Angiosarcoma: Emergency Tumor Embolization Followed by Elective Surgery

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Abstract
Among primary hepatic malignancies, sarcomas represent a minority of 2 %. Of those, primary hepatic angiosarcoma is the most common one. In the past its incidence has been related to the exposure of certain chemicals like thorotrast, vinyl-chloride or arsenic.

Patients suffering from this aggressive, highly vascular tumor have a poor prognosis in general. Without treatment most of them die after rapid tumor progression with multifocal dissemination. In case of tumor perforation, fatal abdominal hemorrhage has been observed.

We herein report the successful interdisciplinary treatment of an 81 year-old woman with a perforated primary hepatic angiosarcoma of the left hepatic lobe. Initially, tumor bleeding was stopped by emergency interventional coil embolization. After stabilization of the patient, we performed an elective tumor resection. The patient could eventually be discharged in a good clinical condition.

So far, no standard therapy has established for patients with primary hepatic angiosarcoma. Surgery seems to be the treatment of choice. In addition, preoperative interventional embolization of the tumor supplying vessels reduces the risk of pre- and intraoperative bleeding. The value of adjuvant chemotherapy is not yet clarified.

The outcome of most patients with primary hepatic angiosarcoma remains poor and there is a need for clinical studies.

Key words: liver tumors, hepatic angiosarcoma, embolization, resection

Introduction

Primary hepatic sarcomas are rare malignant mesenchymal neoplasms accounting for less than 2% of all primary tumors in the liver. In adults, hepatic angiosarcoma (HAS) is the most frequent primary sarcoma of this site. Its carcinogenesis has been associated with thorotrast, vinyl-chloride or arsenic, though in most patients no risk factors could be identified [1, 2, 3]. Patients usually have a poor clinical outcome and without therapy they die within months. Complete tumor-resection performed at an early stage of disease is the treatment of choice. However, curative surgery often cannot be performed because of a delayed diagnosis with metastatic disease [4, 5, 6, 7, 8].

During the last two decades, liver surgery has become the standard of care for liver sarcomas since surgical techniques have improved and liver resection is a safe procedure.

We report the clinical course of an 81 year-old woman with a primary HAS of the left hepatic lobe that presented with acute hemorrhage to our institution.

Case

An 81 year-old female was transferred to our department from a community hospital, where she presented with severe abdominal pain of sudden onset. During further diagnostics a left hepatic lobe tumor as well as free intra-abdominal fluid was diagnosed by ultrasound and spiral CT-scan. Ascites consisted of blood (hemoglobin: 14.6 g/dl), while serum hemoglobin had fallen to 6.6 g/dl.

On admission to our hospital, stable vital parameters were assessed after previous transfusion of 2 units of blood. The patient complained about strong colic-like pain of the right upper quadrant for a week. Past medical history disclosed persistent thrombocytopenia, splenomegaly and small hepatic cysts for 4 years. Hysterectomy was performed due to descensus uteri 36 years ago. No further co-morbidities were found. There was no exposure to potential risk factors such as thorotrast, vinyl-chloride or arsenic.

Physical examination of the distended abdomen revealed diffuse abdominal tenderness. The patient was not jaundiced and the liver was palpable 1 cm below the costal margin measuring 13 cm.

On laboratory evaluation, serum hemoglobin was 8.7 g/dl. The patient had low platelets of 104 000/ µl while leukocytes, GOT and GPT were within normal limits. CRP was 0.6 mg/dl. The plasma level of CA 12-5 was elevated (344 U/ml). All other tumor markers like CEA and AFP were within normal range.

Computerized axial tomographic scan (CT) of the abdomen showed a large hypervascular solitary mass

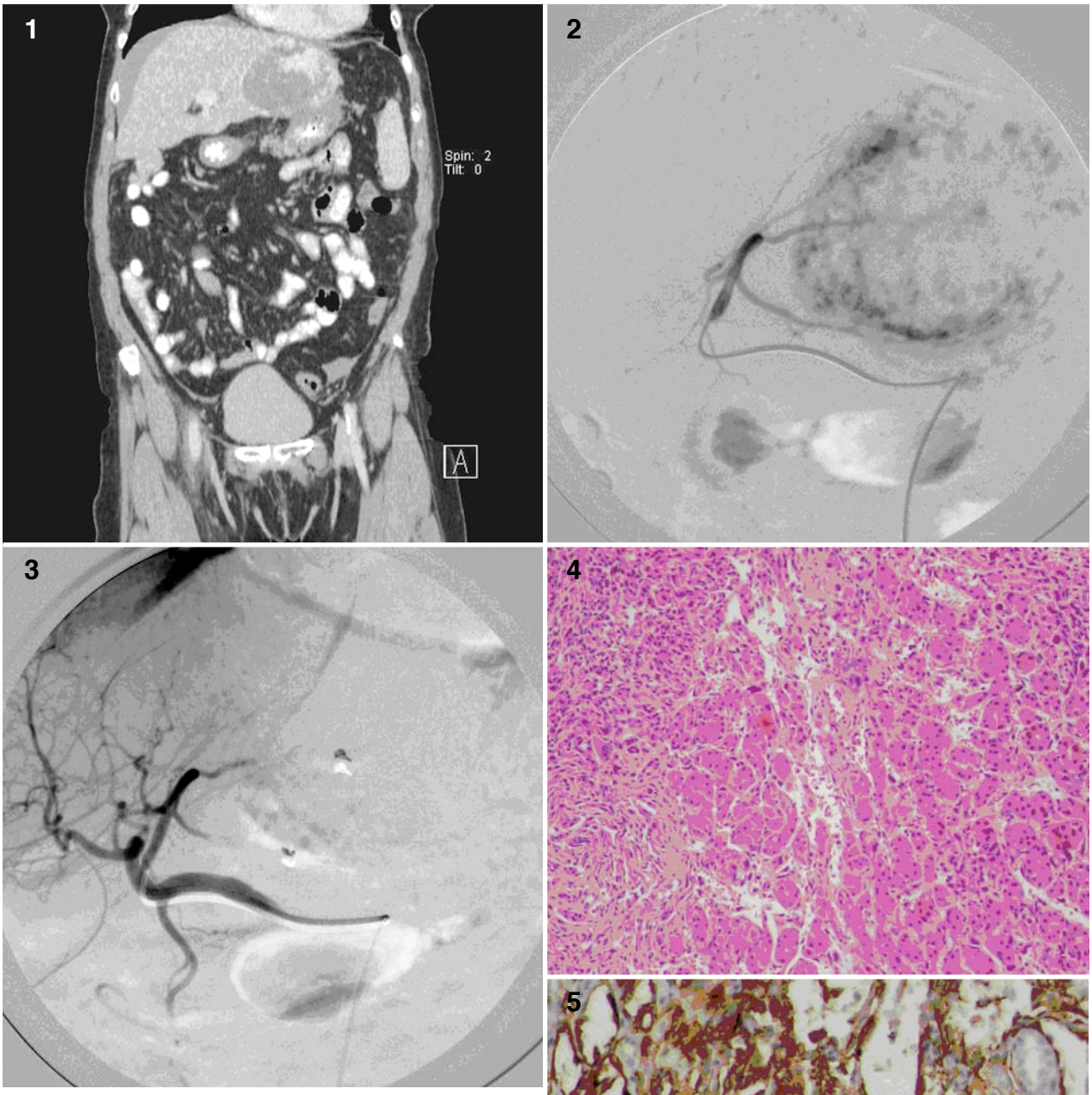

Fig. 1. Contrast enhanced spiral CT showing a large inhomogeneous tumor of the left hepatic lobe.

Fig. 2. Super-selective catheterization of the left liver artery disclosing a pronounced peritumoral enhancement.

Fig. 3. Following embolization with PVA particles and coils angiographic devascularisation was achieved.

Fig. 4. Photomicrographs showing the highly vasculated invasive angiosarcoma (hematoxylin-eosin, original magnification x 100).

Fig. 5. The spindle-shaped cells were highly positive for CD31 (immunhistochemical staining, original magnification x 200).

of irregular texture in the left hepatic lobe involving segments II and III (Fig.1). The maximum diameter was 9 cm. Free fluid of about 1 l was seen on ultrasound.

In order to stop the intra-abdominal bleeding, selective transarterial catheterization was performed. The tumor supplying arteries were embolized with PVA particles and coils (Fig. 2).

A postintervention control CT-scan after 24 hours showed a devascularized tumor with a persistent perfusion of subdiaphragmal parts (Fig. 3). The patient recovered over the following

days an exploratory laparotomy was performed on day 6.

During surgery, large amounts of hematoma were found. Intraoperative ultrasound revealed the tumor clearly demarked in segments II and III while no satellite tumors were found within the liver. Fast frozen sections revealed no involvement of regional lymph nodes. Because of the peripheral localization of the tumor an atypical segmentectomy of segments II and III combined with a cholecystectomy was performed.

The postoperative course was uneventful. Drainages were removed within the usual time frame and the patient was discharged on post-operative day 19.

Gross examination of the resected tumor revealed necrosis and hemorrhage. On histopathologic examination, the tissue presented a vascular pattern with spindle-shaped cells forming vascular channels (Fig. 4). Immunhistochemical staining was strongly positive for CD31 and CD34, supporting the diagnosis of an angiosarcoma (Fig.5). Resection margins proved to be microscopically tumor-free (R0). Therefore, after interdisciplinary discussion of the patient, no chemotherapy was recommended.

Discussion

Hepatic sarcomas represent about 2% of primary hepatic malignancies. Of those, HAS is the most common subtype. Angiosarcoma is a rare agressive tumor of high vascularity predominantly occuring in the skin. HAS occurs predominantly in elderly males and by the time of initial diagnosis most patients are between 50 and 70 years old [4, 5, 6, 7, 8].

Some chemical substances such as thorotrast, polyvinyl-chloride and arsenic were identified as potential risk factors within the last two decades. Therefore, HAS is of distinct interest in occupational medicine: Thorotrast was used as a contrast medium since 1930 and was abandoned 20 years later. Thorotrast related HAS tends to occur 20 to 40 years after exposure. Vinyl-chloride is a component of many plastic products. Since a correlation of vinyl-chloride and HAS is understood, there are restrictions to its use. Arsenic containing Fowler`s solution was used in dermatology and an accumulation of HAS in psoriasis patients was proved [1, 2, 3]. Nevertheless, in most patients - as in our case - none of these risk factors could be identified.

There are no symptoms or clinical parameters clearly indicating the presence of HAS. Finding the correct diagnosis remains difficult. False diagnoses like "hepatic cyst" or "hemangioma" may be followed by fatal clinical courses. Initial symptoms are usually non-specific, e.g. weight-loss, abdominal pain, fever, fatigue and jaundice. Clinical examination may reveal abdominal tenderness with hepatomegaly. Ascites is detectable especially in case of tumor perforation like in our patient [7, 10, 11, 12].

Laboratory abnormalities like thrombocytopenia or elevated alkaline phosphatase are found in some patients. Thrombocytopenia can be explained as a result of local consumption of clotting factors and formed blood elements inside the tumor. Common tumor markers are not elevated in sarcoma patients. We found an increased CA 12-5 plasma level, though intraoperative exploration revealed unsuspicious female pelvic organs.

Due to its various histological composition including areas of necrosis and hemorrhage, HAS presents inconsistent in CT as well as in MR imaging and ultrasound. Furthermore, it is often difficult to differentiate between HAS and other lesions with high vascularity like hepatic hemangioma or hypervascular metastases. Dynamic enhancement may underline the heterogeneous or compartmentalized pattern of this malignant tumor [13, 14]. An inhomogeneous echotexture with areas of hyper- and hypoattenuation was also found in our patient.

In order to diagnose HAS it is inevitable to gain and examine a specimen of the tumor. The use of percutanous biopsy of hepatic tumors is still on debate. On the one hand, malignity cannot be excluded on the basis of tumor-negative samples as there is never a guarantee for a representative probe. A biopsy taken from necrotic areas or perifocal parenchyma may lead to false-negative results. On the other hand, liver puncture may cause severe bleedings, bile duct injuries and is thought to be responsible for metastatic spread [(9)]. We believe that an open biopsy is less dangerous. In addition, explorative laparotomy with intraoperative ultrasonography contributes to an exact staging of the disease.

Only few series with primary HAS are reported in the literature. Therefore, its treatment is not standardized yet. Without therapy, most patients die within months after initial diagnosis due to rapid tumor-growth and tumor-spread. The lung is the most common site of metastasation.

So far, complete resection of the tumor (R0) is the treatment of choice for non-metastatic disease. A survival for more than ten years postoperatively has been observed [19]. Unfortunately, in most cases HAS are diagnosed in an advanced state making curative surgery impossible. Another treatment option may be liver transplantation. However, the postoperative outcome appears to be poor [17, 18]. Doxorubicin- or Ifosfamide-based chemotherapy may stabilize the disease. Especially in childhood a positive effect of cytostatic agents has been observed [15, 16]. Though, the duration of response is usually short. HAS seems to be resistant to radiotherapy which is thought to harm the liver function. Novel molecular strategies (e. g. VEGF antagonists or tyrosine kinase inhibitors) may hopefully support a curative therapy in future.

In spite of advancements in surgical technique and perioperative management, many patients remain at high risk for perioperative morbidity and mortality after major hepatic surgery. Hospitals with high-volume liver resections seem to have better results regarding the patients survival compared to lower-volumes hospitals [20]. Due to their tendency for fatal intraabdominal bleeding, patients with suspicious HAS should be transferred directly to a liver centre.

In our patient, interventional embolization stabilized the patient and reduced the risk of pre- and intraoperative hemorrhage. Therefore, especially for patients with tumor bleeding, interventional embolization seems to be the initial treatment of choice to ac-

quire safe conditions. Also previous studies have outlined the benefit of this procedure [10, 11]. Elective curative surgery can be performed thereafter with reduced risk of severe bleeding.

CONCLUSION

HAS is a rare neoplasm. Unspecific symptoms and the rare occurrence usually delay a definite diagnosis. The treatment is not standardized. Results after liver transplantation were not promising. So far, radical tumor resection seems the only reasonable therapy for HAS. The risk of peri- and intraoperative complications can be reduced by interventional embolization of the tumor-supplying blood vessels. Surgery itself should be performed in experienced medical centres. Nevertheless, most tumors are diagnosed in an advanced stage where the tumor is not resectable.

We report the successful interdisciplinary treatment of HAS after transarterial embolization of the bleeding tumor, followed by elective extended segmentectomy. The outcome of patients with HAS remains poor and further studies are required in order to understand this disease and optimize its therapy.

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