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CASE REPORT

Littoral Cell Angioma and Angiosarcoma of the Spleen: Report of Two Cases in Siblings and Review of the Literature

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Introduction

Littoral cell angioma (LCA), a primary benign tumour of the spleen, was first described by Falk et al. in 1991.[1] Arising from the normal littoral cells lining the sinus channels of the splenic red pulp due to yet unknown stimuli,[2] LCA presents with intermediate features between those of endothelial and histiocytic cells. The most frequent clinical sign is splenomegaly. A malignant transformation to littoral cell angiosarcoma is very rare;[3–5] however, an association with other malignancies has been reported recently.[6]

Primary splenic angiosarcoma (PSAS), first described by Langhans et al. in 1879,[7] is a rare but highly malignant vascular neoplasm[8] with a median survival of 5 months. Splenic rupture (13–32%) is not uncommon.[9] Although the pathogenesis is still unknown, some authors claim that these tumours develop from pre-existing benign lesions (e.g. haemangioma of the spleen).[10]

We herein report the cases of two siblings diagnosed with both primary angiosarcoma and littoral cell angioma of the spleen. In 2003, the brother had died 8 months after splenectomy due to splenic rupture caused by high-grade PSAS. Seven years later, his sister was splenectomized due to multiple vascularized splenic nodules, and diagnosis of LCA was established. Histopathologic re-assessment of the deceased brother's specimen revealed littoral cell differentiation next to splenic angiosarcoma tissue. Family background investigation now evinces another brother with multiple splenic nodules conformable with LCA. To our best knowledge, neither genetic predisposition nor familial clusters between PSAS and LCA have been reported so far.

Case Reports

Case 1

In July 2002, the 62-year-old brother with an unremarkable medical history was admitted to hospital with acute onset of abdominal pain. Abdominal CT scan revealed a fresh subcapsular hematoma of the spleen with bleeding into the peritoneal cavity and several lesions suspect for metastases in the liver. Emergency laparotomy showed a

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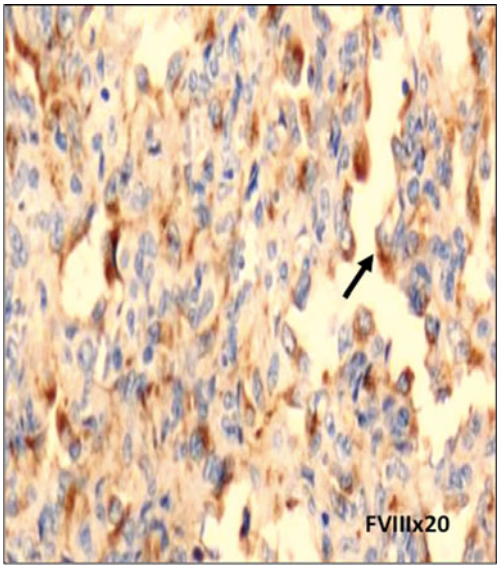

Fig. 1 Angiosarcoma: Cells of angiosarcoma show strong cytoplasmic immunohistochemical staining with an antibody against endothelial cells (*arrow*; CD31; magnification, ×20)

rupture of the spleen, and splenectomy was performed. The surgical specimen (spleen, 110 g; haematoma, 80 g) showed several splenic tumour nodes with dilated vessel proliferations. Histopathology revealed a high-grade angiosarcoma; immunohistochemistry (IHC) staining was positive for CD-31, factor 8 and p53 (Fig. 1). After four cycles, palliative chemotherapy with Etoposid, Iphosphamide and Doxorubicin, re-staging abdominal MRI scan revealed progression of liver metastases. In March 2003, the patient showed further disease progression with diffuse hepatic and spine metastases, as well as local tumour recurrence and died in April 2003, 8 months after first being diagnosed with PSAS.

Case 2

Seven years later in September 2010, his by then clinically asymptomatic 71-year-old sister was admitted to our surgical department due to a progressive deprivation of thrombocytes. Abdominal MRI scan revealed splenomegaly; the spleen was almost completely interspersed with multiple nodular lesions (Fig. 2). As for the positive family history for splenic cancer, splenectomy was performed. Intraoperatively, the spleen was riddled with a multitude of small red- to black-coloured knots of firm texture (Fig. 3). Histopathologic examination revealed a diffuse dissemination of a neoplasm composed of anastomosing vascular channels of sinus-like structures lined by hobnail cells. IHC staining was positive for F VIII R Ag and CD 68; proliferation rate was very low (Ki67, clone MiB1). Diagnosis of littoral cell angioma was established (Fig. 4).

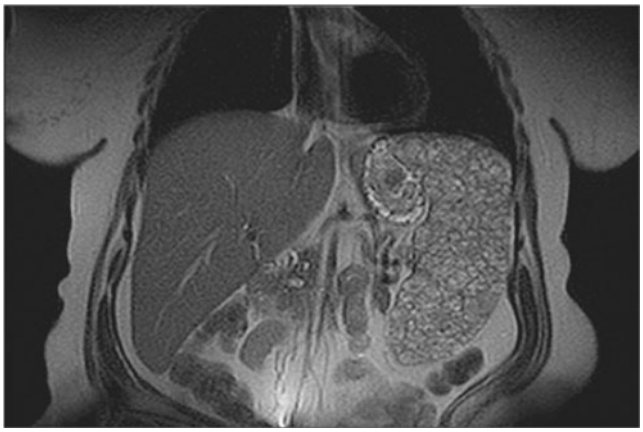

Fig. 2 Abdominal MRI scan (T1- and T2-weighted sequences with contrast enhancement). The spleen is almost completely interspersed with multiple nodular lesions

Histopathologic Re-assessment and Family Background

Current histopathologic re-assessment of the deceased brother's surgical specimen (case 1) revealed residual littoral cell differentiation next to splenic angiosarcoma tissue. Malignant transformation cannot be ruled out. He has three children who are all in healthy condition. The sister with LCA (case 2) has two healthy children and one daughter (age 40) suffering from plasmocytoma. No splenic pathologies were observed until now.

After the diagnosis of LCA was established, two other asymptomatic siblings (male and female, both aged 67) were now referred to abdominal MRI scan. Imaging of the brother revealed multiple splenic nodules without splenomegaly likewise conformable with LCA. Currently, a regular 3-month follow-up is performed. He has four healthy children. The sister's MRI scan was unremarkable; she also has four healthy children.

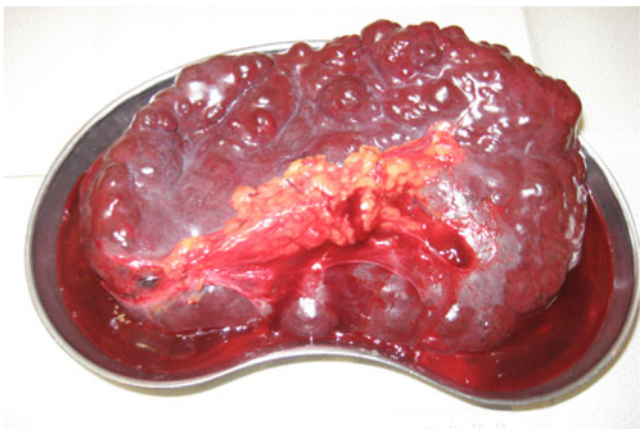

Fig. 3 Surgical specimen. The spleen is riddled with a multitude of small red- to black-coloured knots of firm texture

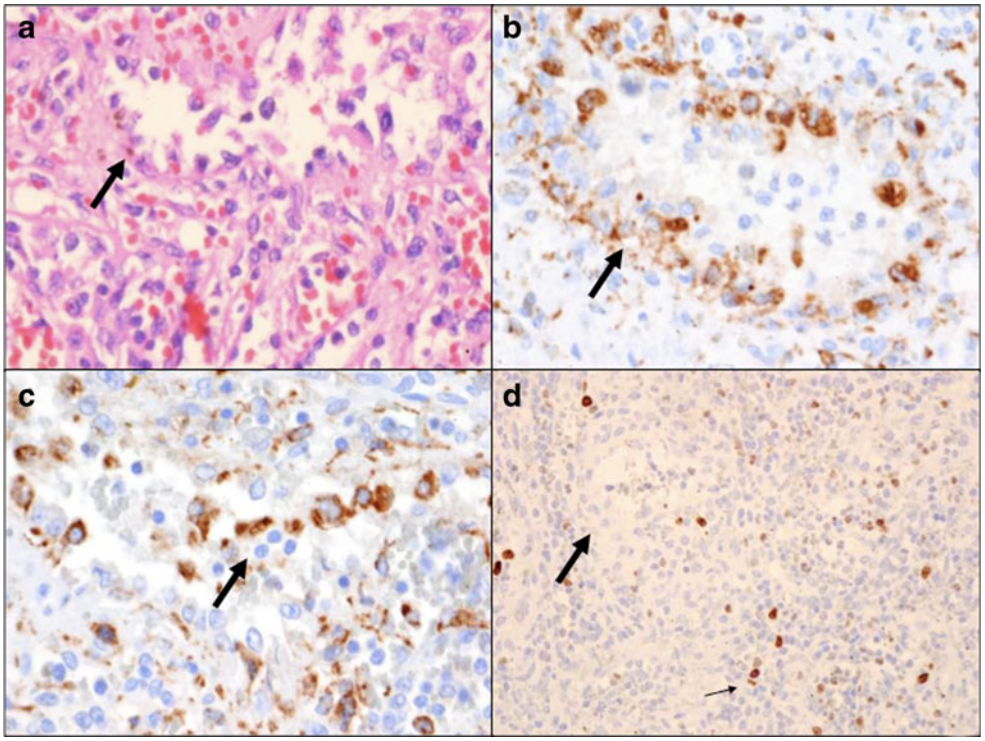

Fig. 4 Littoral cell angioma: splenic vascular sinus-like neoplasm lined by hobnail cells with low to moderate pleomorphism (**a,** *arrow*; HE; magnification, ×40). The same vascular changes show immunohistochemically a characteristic coexpression of endothelial antigens (**b,** *arrow*; FVIII; magnification, ×40) and histiocytic antigens (**c** *arrow*; CD68; magnification, ×40). Proliferation index is low (less than 1%) with no immunopositive tumour cells in the vascular lesion (**d** *arrow*; MiB-1; magnification, ×20), with only some lymphatic cells of the spleen with nuclear staining (**d,** *small arrow*)

The parents of the four siblings had no history of splenic diseases. The father died in the Second World War, the mother due to pulmonary embolism in 2002.

Review of the Literature

For retrieval of genetic predisposition or familial clusters retrieval, we conducted a literature search through the MEDLINE database using the medical subject heading angiosarcoma of the spleen, littoral cell angioma, surgery, survival and genetic predisposition without any restriction to publication date but to published manuscripts with full text articles in the English language. The last search was carried out on January 15, 2011. Whereas for PSAS, over 100 cases have been reported,[11] only a few case reports and reviews[12–15] are published for LCA.

Until now, only scattered reports of malignant differentiation of LCA are available. The most recent review of splenic neoplasm including both PSAS and LCA was conducted in 2010 by Kaza et al.;[13] however, no specific data for genetic predisposition or familial clusters are given by the authors. In 2006, the association between LCA and other malignancies was summarized by Harmon et al.[12] revealing two cases of malignant LCA differentiation.[1, 16] No transformation to angiosarcoma of the spleen was reported. In 1997, Meybehm et al. presented a case of PSAS immunoreactive for both endothelial markers and histiocytic antigens. The authors concluded that the presented angiosarcoma may be regarded as the malignant variant of LCA.[17]

Discussion

Littoral cell angioma is a rare vascular tumour of the spleen arising from the normal littoral cells lining the sinus channels of the splenic red pulp. Although it is a primary benign tumour, newer published literature now classified LCA as having uncertain biological behaviour.[18] A malignant transformation to littoral cell angiosarcoma is very rare;[3–5] however, an association with other malignancies, e. g. colonic and hepatocellular cancer, has been reported recently.[6] As LCA sometimes occurs as paraneoplastic lesion, a differential diagnostic delineation of metastases to the spleen may be required.[19]

LCA most often occurs in middle-aged men and women and has equal sex distribution.[20] Clinically, patients present with splenomegaly, abdominal pain and hypersplenism leading to thrombocytopenia and anaemia.

Histologically, LCA is composed of anastomosing vascular channels resembling splenic sinusoids, irregular lumina (papillary projections) and cyst-like spaces, differentiating it from other primary vascular tumours, including angiosarcoma of the spleen.[15] Tall endothelial cells with histiocytic properties detaching into the vascular lumen are common. IHC staining reveals expression of both endothelial (factor VIII Ag and CD 31/BMA 120) and histiocytic

antigens (CD 68/KP 1 and lysozyme).[21] The typical and characteristic immunohistochemical pattern of the LCA is as follows: CD31, CD68, CD163, CD21, FVIII antigen positive; CD34, CD8 negative.[22]

Primary splenic angiosarcoma (PSAS) is a rare, compulsory malignant tumour entity, which is sometimes difficult to diagnose. It carries a poor prognosis with only 20% of patients surviving for more than 6 months.[1] Neuhauser et al.[9] reported death in over 90% of patients within 2.5 years due to disseminated tumour spread. Metastases are frequently present at the time of diagnosis mainly involving the liver (70%), followed by lung and bone.[23] Clinical features are variable, depending on splenic vascular lesions. Main symptoms are abdominal pain, anaemia and thrombocytopenia; splenic rupture is not uncommon (12–32%),[9] leading to a further decrease of survival probability.[24] Only early splenectomy can improve survival.[25] Hsu et al.[26] reported a disease-free survival of 162 months of one patient after splenectomy, being the longest survivor of splenic angiosarcoma in the literature. Until now, no reliable data on the effectiveness of (neo) adjuvant chemotherapy are available.[27] In the herein reported case, the 62-year-old brother survived 8 months after splenectomy with additive chemotherapy.

Angiosarcomas have a highly variable histology with well-defined nodular appearance and vasoformative components. Most of the tumours express two or more markers of vascular differentiation (CD34, CD31, F VIII R Ag, VEGFR3) and often at least one IHC marker of histiocytic differentiation (CD68 and/or lysozyme).[9]

The pathogenesis of splenic angiosarcoma is still uncertain. Whereas some authors accuse ionizing radiation or chemotherapy,[28] others hypothesize the development of PSAS from previously existing benign vascular tumours (e. g. haemangioma or haemangioendothelioma[10]). The latter complies with our herein reported case of the deceased 62-year-old brother, as re-assessment of the histologic specimen revealed residual littoral cell differentiation within the splenic angiosarcoma tissue.

Since the malignant potential of LCA has not yet been firmly established in the literature, some authors advocate a close clinical follow-up.[29] However, according to the herein reported cases, we would rather recommend splenectomy as treatment of choice, as in one of the patients littoral cell differentiation was found within splenic angiosarcoma tissue and therefore malignant transformation of LCA is highly suspected. Furthermore, blood relatives of patients being diagnosed with either PSAS or LCA should be consequently screened for splenic lesions, as familial exposure is not unlikely.

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