Variants of Hemangioendotheliomas of the Hepatobiliary Tract

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Abstract

Apart from epithelioid hepatic hemangioendothelioma and infantile hepatic hemangioendothelioma/hepatic infantile hemangioma, there are few other endotheliomas that can manifest as primary neoplasms of the liver. Kaposiform hemangioendothelioma is a rare, locally aggressive, vascular spindle-cell tumor that resembles Kaposi's sarcoma. This neoplasm most commonly develops in the skin and the retroperitoneal space of infants and children, but is also observed in the hepatobiliary tract in rare instances. Kaposiform hemangioendothelioma is a well-known cause of Kasabach-Merritt syndrome. Histologically, the neoplasm is characterized by nodules or lobules of rather bland-looking spindle cells which encircle slit-like, CD31- and CD34-positive vascular channels. A further hemangioendotheliomatous neoplasm that develops in the liver as a primary tumor is polymorphous hemangioendothelioma.

Kaposiform Hemangioendothelioma

Introduction

Kaposiform hemangioendothelioma (KFE) is a rare, locally aggressive (borderline), vascular spindle-cell tumor with resemblance to Kaposi's sarcoma, first described in 1993 (Zukerberg et al. 1993). Before the definition as KFH, the

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lesion has anecdotically been described under various names, such as hemangioendothelioma, congenital hemangioendothelioma, Kaposi's-like infantile hemangioendothelioma, and hemangioma with Kaposi's sarcoma-like features (Niedt et al. 1989). The neoplasm seems to be closely related to tufted angioma (TA), and both KFE and TA are now considered neoplasms of intermediate malignancy because of infiltrative growth, local aggressiveness, and variable prognosis. Tumors exhibiting features that are transitional between KFE and TA have been described even in the same specimen of some patients (Brasanac et al. 2003), and a dynamic transformation between both tumors has been reported (Chu et al. 2003), suggesting that KFE and TA may reflect different stages in the evolution of a single entity (Arai et al. 2006). Most commonly, KFE develops in the skin and in the retroperitoneal space of infants and children. The development of KFE in adolescents or in adults is rare (Mentzel et al. 1997; review: Fernandez et al. 2009).

Epidemiology

In a study of 163 patients from North America, the prevalence of KFE in Massachusetts was 0.91 case per 100,000 children (Croteau et al. 2013). Most of KFH present during early childhood (first year of life), and the lesion is more common in males. In the Boston study, KFE manifested in infancy in 93 % of cases, with 60 % as neonate (Croteau et al. 2012). Cases in adults are rare (Mentzel et al. 1997) and may in part have been diagnosed as TA.

Clinical Manifestations and Imaging Features

Apart from the classical sites, i.e., skin and retroperitoneal space, KFH can also occur in visceral locations. Multifocal and particularly internal lesions may, depending on their extension, cause severe complications. Retroperitoneal extensions or manifestations occur in 18 % of the patients. Owing to its distinct angioarchitecture and vascular composition, KFH has a tendency to bleed and to sometimes cause life-threatening hemorrhage. In contrast to infantile and juvenile hemangiomas, KFH shows no tendency to spontaneously regress and involute. Untreated KFH is associated with a rather high mortality rate (up to 30 %), mainly caused by locally invasive effects, large and irresectable visceral manifestations, massive hemorrhage, and KMS (review: Fernandez et al. 2009).

KFH is a well-known cause of Kasabach-Merritt syndrome/KMS (synonym: Kasabach-Merritt phenomenon) (Zukerberg et al. 1993; Walker et al. 2002; Hauer et al. 2007; Drucker et al. 2009; Fahrtash et al. 2010; Veening et al. 2010; Garcia-Monaco et al. 2012), mainly in case of large retroperitoneal lesions. In fact, KMS is closely associated with KFH and TA and not with common infantile hemangioma (Enjolras et al. 1997; Sarkar et al. 1997). KMS was described in 1940 (Kasabach and Merritt 1940) and is characterized by a complex vascular tumor coagulopathy with profound thrombocytopenia (<20,000) and consumptive coagulopathy and hypofibrinogenemia with fibrin degradation products (reviews: Maguiness and Guenther 2002; Rodriguez et al. 2009). KMS in KFH usually develops in the first months of life. The pathogenesis of KMS has not been clarified and is complex, because KMS is not related to the lesion mass or the clinical extent since many large and very large juvenile hemangiomas, vascular malformations with a large internal vessel surface, and disseminated Kaposi's sarcoma never lead to this complication. There is some evidence that KMS preferentially evolves in vascular tumors and tumor-like lesions that have a lymphatic contribution. KMS was found in advanced Kaposi's sarcoma, multifocal lymphangioendotheliomatosis, and TA (Alvarez-Mendoza et al. 2000). KFH was observed to develop on the background of a capillary-lymphatic vascular malformation, followed by Kasabach-Merritt syndrome. KFH may be associated with lymphangiomatosis, characterized by the presence of either diffusely infiltrating lymphangiomas or as lymphangioma involving multiple sites (Zukerberg et al. 1993; Vetter-Kauczok et al. 2008). This association is usually seen in children and only exceptionally in adults (Mentzel et al. 1997).

KFH Involvement of the Hepatobiliary Tract

The liver can be involved by KFH in situations of multifocal tumors, whereby sometimes one dominant extrahepatic lesion is found (Nakaya et al. 2014). KFH has been observed in the choledochus of a 5-month-old male infant with cholestatic jaundice. CT revealed a vascular tumor in the hepatic portal region causing biliary obstruction. The tumor was successfully resected followed by hepatoportoenterostomy (Terui et al. 2010). KFH occurs in the kidney and can invade the inferior vena cava to reach the retrohepatic space (Indolfi et al. 2010).

Pathology

Histologically, KFH is characterized by nodules, solid sheets, or lobules of morphologically rather bland-looking spindle cells, ranging in size from small to large, that are grouped to fascicles and which encircle slit-like capillary channels at the periphery of nodules and lobules. Small areas with densely packed spindle cells may be noted. Dense spindle-cell areas are mainly noted at the periphery of vascular lobules, where the spindle cells stream into the vascular compartment. Central portions of the lobules (the so-called glomeruloid islands), in contrast to the cellular periphery, are composed of hemovascular channels with surrounding clusters of small or epithelioid-looking SMA-positive cells (possibly pericyte-like cells; Lyons et al. 2004). The vascular spaces may look empty, but also contain red blood cells and sometimes microthrombi. Extravasation of erythrocytes and focal hemosiderosis are found.

Immunohistochemically, the endothelial cells of the vascular channels are in part reactive for CD31 and CD34. Staining of these two endothelial markers is diffuse across the vascular lobules, including the circumferential spindle cells at the periphery and the small vascular channels in the center. The endothelial cells of KFH are GLUT1 negative (North et al. 2000; Lyons et al. 2004). More than 90 % of KFH are positive for D2-40 (podoplanin), a marker of lymphatic endothelium (Debelenko et al. 2005; Galambos and Nodit 2005; Arai et al. 2006). D2-40 stains the neoplastic spindle cells and lymphatic channels adjacent to vascular lobules. The staining is typically concentrated at the peripheral part of vascular lobules where D2-40 highlights spindle cells that stream between the lobules and circumscribe the glomeruloid cores. This results in "dark" rings encircling "pale" centers of the vascular lobules. D2-40 staining was observed in 20–70 % of the cellular component of the lesions and 70–90 % of the large spindled cells (Debelenko et al. 2005). Similar to Kaposi's sarcoma and Dabska-type hemangioendotheliomas which have features of lymphatic differentiation, KFH is positive for vascular endothelial growth factor receptor-3 (VEGFR-3), a lymphatic endothelial marker (Folpe et al. 2000; Saito et al. 2009). Part of the cells of KFH express the lymphatic endothelial nuclear transcription factor, Prox1, with a distinct pattern; the mainly peripherally located spindle cells are positive for Prox1, podoplanin, CD31, and CD34, and also the endothelial cells in the glomeruloid foci are Prox1 positive (Le Huu et al. 2010; Miettinen and Wang 2012). It has been proposed that both VEGFR-3 and Prox1 might be superior to D2-40 in identifying endothelial cells of a lymphatic lineage (Castro and Galambos 2009). Prox1 has been found to promote invasion of KFH cells in an experimental murine model (Dadras et al. 2008). In contrast to Kaposi's sarcoma, human herpesvirus 8 was not detected in KFH (Cheuk et al. 2004; Lyons et al. 2004; Robin et al. 2004; Deraedt et al. 2006).

Polymorphous Hemangioendothelioma

Introduction

Polymorphous hemangioendothelioma (PHE) was originally described as a distinctive vasoproliferative lesion developing in lymph nodes, characterized by solid, primitive vascular, and angiomatous patterns and relatively bland cytologic features (Chan et al. 1992). These

authors reported a series of 39 patients with primary vascular tumors of lymph nodes other than Kaposi's sarcoma and identified three cases with the novel phenotype of PHE. The term polymorphous was chosen to emphasize the great variability of histological patterns present in this tumor. PHE is a neoplasm of borderline malignant potential and has both nodal and extranodal manifestations (Rehring et al. 1999; Tadros et al. 2003; Moreno-Ramirez et al. 2004; Falleti et al. 2009). PHE is histologically characterized by a complex mixture of intermingled solid, spindled, retiform, epithelioid, and angiomatous components. The tumor cells are immunoreactive for CD31, CD34, and factor VIII-associated antigen (Nascimento et al. 1997).

Polymorphous Hemangioendothelioma of the Liver

PHE may occur as primary hepatic neoplasm (Cobianchi et al. 2009). A large hepatic mass was detected in 47-year-old female patient suffering from abdominal pain and anemia. Sonography and MRI of the abdomen revealed a large heterogeneous mass ($9 \times 7 \times 7$ cm) in the left lateral hepatic segments (segments II, III, and partially IV). The hepatic resection specimen was almost completely replaced by a nodular, hemorrhagic mass with an expanding growth pattern without encapsulation. Cut sections showed a variegated color from red to yellowish. On histology the tumor displayed a thin inflammatory pseudocapsule and a composite pattern, consisting of angiomatous, retiform, and solid areas. The angiomatous areas showed clefts, branching channels, and dilated vascular spaces lined by plump cuboidal and often hobnailed cells. Pseudopapillary structures were noted, and there were areas mimicking the pattern seen in retiform hemangioendothelioma. The solid areas consisted of oval to spindle cells with vacuolated nuclei and an indistinct, slightly eosinophilic cytoplasm, these cells being arranged in a trabecular to vaguely fascicular pattern. The intervening stroma was sclerotic to fibrocellular to edematous. Only occasional mitotic figures were found. Areas of tumor necrosis were observed. Immunohistochemically, cells of the angiomatous and spindled areas were positive for vimentin, CD31, and factor VIII-associated antigen, but not CD34. The growth fraction (Ki-67) was less than 1 %.

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