We report the case of a Kaposi-like variant of splenic angiosarcoma in a 28-year-old woman. The tumor featured a Kaposi sarcoma–like spindle cell proliferation with slit formation and markedly dilated spongolike vascular channels filled with erythrocytes. Thirteen months following the initial splenectomy, metastatic lesions were found in the patient’s liver and bone marrow. The proliferating cells were positive for factor VIII–associated antigen and CD34. The human herpesvirus 8 genome, which is regarded as a diagnostic feature of Kaposi sarcoma, was not detected by polymerase chain reaction analysis. Although the histologic findings were similar, this Kaposi-like variant of splenic angiosarcoma must be considered distinct from Kaposi sarcoma.

(Splenic Angiosarcoma—Mikami et al 191–194)

Splenic angiosarcomas are the most common malignant primary nonlymphoid tumors, although their occurrence is rare. Microscopic findings are highly variable, both within tumors and between cases. While a spongiform or honeycomb-like proliferation of endothelial cells is the most common finding, Kaposi sarcoma–like proliferation is infrequent. Recently, human herpesvirus 8 (HHV-8) was detected in a case of acquired immunodeficiency syndrome (AIDS)-associated Kaposi sarcoma, and now it is considered to be present in all Kaposi sarcomas, regardless of any association with AIDS. Furthermore, HHV-8 DNA detection using polymerase chain reaction (PCR) or in situ hybridization is now considered to be a critical test for the diagnosis of Kaposi sarcoma. We encountered a case of splenic angiosarcoma showing Kaposi-like spindle cell proliferation. We report here the examination of HHV-8 DNA by PCR analysis and discuss differences between splenic angiosarcomas and Kaposi sarcomas.

REPORT OF A CASE

A 28-year-old housewife without any particular past individual or familial medical history experienced persistent left flank pain.

Abdominal ultrasonography and computed tomography revealed splenomegaly (Figure 1, a), and she was admitted to Kitasato University Hospital, Sagamihara, Japan. Laboratory examination revealed slight anemia (red blood cell count, 3.58 × 10¹²/L; hemoglobin, 107 g/L; hematocrit, 0.32), and because a malignant lymphoma was initially suspected, splenectomy was performed. The resected spleen weighed 530 g and showed diffuse dark-reddish enlargement (Figure 1, b) without nodular lesions. Histologically, the splenic normal structure was entirely replaced by diffuse proliferation of spindle cells arranged in a fascicular pattern with erythrocytes containing slit formations (Figure 1, c). Occasionally, markedly dilated spongolike spaces filled with erythrocytes were seen (Figure 1, d). Nuclear pleomorphism was minimal. Several calcium deposits were found within the remaining splenic trabeculae. The accessory spleen, measuring 1.5 cm in diameter, also exhibited the spindle cell proliferation.

Although Kaposi sarcoma was suspected from the pathologic findings, serologic examination revealed no human immunodeficiency virus infection. After 13 months, follow-up computed tomography and gallium scintigraphy revealed focal hepatic and bone marrow involvement without clinical symptoms except for slight anemia. Liver and bone marrow biopsies were performed. In the liver, spindle cells showed focal nodular proliferation, especially along Gleason sheaths. Occasionally, the spindle cells invaded the sinusoids, replacing the normal endothelium (Figure 2, a). In the bone marrow, the spindle cells were located in the myxoid mesenchyma and were separated from each other (Figure 2, b). She was then treated with adriamycin. Although the metastatic lesions had not completely disappeared, the patient was still alive 21 months after the first operation.

PATHOLOGIC FINDINGS

Immunohistochemistry

Tissue samples from the spleen were fixed in buffered formalin and embedded in paraffin. To investigate the tumor cell character, immunohistochemical staining of tissue sections was performed using the labeled streptavidin-biotin method (commercial kit, Dakopatts, Glostrup, Denmark), with anticytokeratin (monoclonal, clone CÂM 5.2, Becton Dickinson, San Jose, Calif), antilysozyme (polyclonal, clone v9, Dako), anti-factor VIII–associated antigen (polyclonal, Dako), anti-CD34 (monoclonal, clone QBEND 10, Immunotech, Marseille, France), anti-CD68 (monoclonal, clone PG-M1, Dako), anti–α-smooth muscle actin (monoclonal, clone 1A4, Dako), antilysozyme (polyclonal, Dako), and anti–Ki-67 (polyclonal, Dako) primary antibodies. To compare the cell proliferation activity of the tumor with data for vascular tumors, 11 cases of cavernous hemangioma and 15 cases of hemangiosarcoma of scalp were retrieved from the pathology files of Kitasato University Hospital, and immunohistochemistry for Ki-67 an-
tigen was performed. At least 1000 tumor cells were examined for each case, and the percentage of positively stained nuclei was calculated as the labeling index.

Proliferating spindle cells and lining cells of the cavernous spaces showed immunoreactivity for factor VIII-associated antigen and CD34 (Figure 3, a and b). They were negative for cytokeratin, CD68, α-smooth muscle actin (Figure 3, c), and lysozyme. The Ki-67 labeling index for the present case was 5.4%, while the labeling indices of the cavernous hemangiomas and the hemangiosarcomas of the scalp were 1.3% ± 1.5% (mean ± standard deviation) and 20.8% ± 10.9%, respectively.

Electron Microscopy

Electron microscopy was performed with fresh tissues fixed in glutaraldehyde and postfixed in osmium tetroxide. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with a transmission electron microscope (H-600, Hitachi, Tokyo, Japan).

The proliferating spindle cells were observed to form primitive junctional complexes with neighboring cells. Pinocytotic vesicles were found beneath the plasma membranes, and cytoplasmic organelles were sparse, although swollen mitochondria, rough endoplasmic reticulum, lysosomes, and occasional collections of intermediate filaments were noted (Figure 4). Some cells contained intracytoplasmic lumina filled with erythrocytes.

Polymerase Chain Reaction Analysis for HHV-8

DNA was extracted from fresh frozen tumor tissue and sections of formalin-fixed, paraffin-embedded tumor tissues by proteinase K digestion, phenol-chloroform extraction, and ethanol precipitation. Using the primer set (5′-AGCCGAAGGAATTCACCA AT-3′ and 5′-TCGTGTTGTCTACGC CGAG-3′),8 35 cycles of PCR amplification of a section of the HHV-8 genome were carried out. These primers amplify a 233-base pair (bp) fragment located from base pair 987 to base pair 1219 of the reported HHV-8 sequence.5 As a substitute for template DNA, distilled water was added to the reaction solution as a negative control. As a positive control, DNA samples from 3 cases of AIDS-associated Kaposi sarcoma were used.

After electrophoresis, the agarose gels were stained with ethidium bromide and visualized by ultraviolet light. While the PCR product of 233 bp was detected for the 3 samples from Kaposi sarcomas, no product of this size was seen with our present case (Figure 5).

COMMENT

Splenic angiosarcoma is a rare tumor, and most details concerning this tumor have been published in case re-
Figure 2. a, The histology of a liver biopsy specimen. Spindle cells are proliferating in the Gleason sheath (the arrowhead shows a branch of the hepatic artery) (hematoxylin-eosin, original magnification ×200). b, Histology of a bone biopsy. Spindle cells with atypical nuclei are sparsely located in the bone marrow cavity (hematoxylin-eosin, original magnification ×400).

Figure 3. Immunohistochemical findings for the tumor. The spindle cells are immunopositive for (a) factor VIII–associated antigen and (b) CD34. On the other hand, the spindle cells are immunonegative for (c) α-smooth muscle actin (diaminobenzidine and hematoxylin, original magnification ×400).

In 1993, Falk et al reported a clinicopathologic study of 40 collected cases. More recently, Neuhauser et al described the clinicopathologic findings with a detailed immunohistochemical study of 28 cases. According to these 2 articles, the histology of splenic angiosarcoma is highly variable. Although the most common type features a spongiform proliferation of endothelial cells forming irregular capillary networks. Other pseudosinusoidal, pseudodopapillary, and spindle cell sarcoma–like patterns have been documented. Neuhauser et al reported that only 2 of their collected cases showed Kaposi sarcoma–like spindle cell proliferations with slitlike spaces. In the present case, the tumor was composed of 2 characteristic components: spongylar, dilated, thin-walled endothelium and Kaposi sarcoma–like spindle cells. Immunohistochemically, the spindle cells were immunopositive for factor VIII–associated antigen and CD34 and were immunonegative for α-smooth muscle actin, although Kaposi sarcomas generally express α-smooth muscle actin but lack expression of factor VIII–associated antigen. Ultrastructural findings confirmed an endothelial differentiation of the proliferating cells. We therefore concluded that the present case is a rare variant of the splenic angiosarcoma, a Kaposi-like variant.

In the literature, although some controversial findings were reported, most studies were unable to detect HHV-
8 DNA in mesenchymal and vascular tumors other than Kaposi sarcoma, including hemangiomas, hemangiendotheliomas, infantile capillary hemangioma, and hemangiosarcoma. Identification of HHV-8 DNA is now regarded as the diagnostic criterion for Kaposi sarcoma. In the present case, HHV-8 DNA was not detected with PCR analysis. Accordingly, a distinct entity of splenic angiosarcoma—different from Kaposi sarcoma—may exist.

To our knowledge, Sarode et al reported the only case of splenic Kaposi sarcoma to date. The histologic components of the case, judging from the description and the photographs, comprised spindle cell proliferation and thin-walled, dilated vascular channels lined by flattened endothelium. The authors came to a diagnosis of Kaposi sarcoma only from the former component. Their tumor metastasized to the liver, the mesenterium, the pleura, and the lymph nodes. Although the authors did not investigate for HHV-8 DNA (the report was published before the discovery of the virus), we believe that the splenic tumor they reported belongs to the same category as our case because of the similar histologic findings and the malignant behavior.

The symptoms in our patient were slight anemia and left flank pain. According to the collected series of Falk et al, the major symptoms are abdominal pain (83%) and cytopenia (91%), including anemia, thrombocytopenia, and pancytopenia. A rare but important presentation of splenic angiosarcoma is spontaneous splenic rupture (13%). The prognosis of splenic angiosarcoma is poor. Calculated from the cases in the reports of Falk et al and Neuhauser et al, 1- and 3-year survival rates were 52.1% and 13.5%, respectively. The prognosis of the Kaposi-like variant remains to be determined.

In earlier reports, nuclear atypia varied from case to case. In the present lesion, nuclear atypia was minimal, especially in the spongolike component. However, the cell proliferation rate was between those for hemangiosarcomas of scalp and cavernous hemangiomas. Pathologists should bear in mind that splenic angiosarcomas can show minimal nuclear atypia.

In conclusion, we report here a rare variant of splenic angiosarcoma. Although histologically similar to Kaposi sarcoma in part, it appeared to be a distinct entity because HHV-8 DNA was not detected. We conclude that it should be treated as a Kaposi-like variant of splenic angiosarcoma.

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References