An interesting case of angiogenesis in cavernous hemangioma

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Cavernous hemangioma is the most common orbital tumor in adult. There is lot of literatures for clinicopathological features of this tumor. These tumors had been studied for the model of angiogenesis in many of the experimental setups. We present a case of 34-year-old male with this tumor in the left eye with computerized tomography evidence. Postsurgical laboratory findings gave interesting evidence of tumor angiogenesis with tumor endothelial cells and sprouting of the small vessels endothelial cells. Podosome rosette could be conceptualized from the characteristic patterns seen in the tumor.

Key words: Cavernous hemangioma, podosome rosettes, sprouting, tumor endothelial cells

Cavernous hemangioma is the most common tumor seen in adult chiefly in female.[1,2] The pathogenesis of hemangioma, perhaps, poorly understood among the other tumors of the orbit.[3-5] Hemangioma is characterized by proliferation of endothelial cells with multiple laminations of basement membranes (BMs) with gathering of cellular rudiments.[3-6] Endothelial cells in the blood vessels and tumor endothelial cells (TECs) have typical features in physical condition.[5-7] Tumor blood vessels have uneven diameters, and they are delicate, permeable, and have anomalous blood flow.[4-6] In tumor, blood vessel arises from preexisting one by the course of angiogenesis.[6-8] Angiogenesis is characterized by closing of extracellular matrix endothelial cells by mitosis and sprouting.[4-9] It was observed long before that the tumor blood vessels have uncharacteristic morphologically.[6-9]

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TECs are irregular in size and contour extending outward, and tips of some TECs may penetrate the lumen creating an intracellular gap in vessels wall.[6-9] Sometimes nearby tumor cells filled the gap junction.[6-9] Abnormal sprouts resembling pointed tip-like extension and may be there in oxygen scarce stage in the tumor microsurroundings.[6-10] We present a case of unilateral proptosis with intraconal cavernous hemangioma with various interesting macroscopic and microscopic findings.

Case Report

A 34-year-old male presented with proptosis of the left eye (OS) in November 2014 since 2 years with occasional pain and blurred vision. There was no history of trauma, surgery, and any ocular disease. The systemic history was unremarkable. On ophthalmic examination, relative afferent pupillary defect was seen in the OS. Best-corrected visual acuity was 6/6, N6 right eye (OD), 6/18 with pinhole improvement to 6/9, N10 (OS). Axial proptosis was noted with Hertel's exophthalmometry measurement of 14 mm in the OD and 20 mm in OS. There were no ocular motility restrictions in either eye. Slit lamp and fundus examination revealed normal anterior and posterior segments in both the eyes (OU). Intraocular pressure was normal in OU.

Computerized tomography scan of the orbit and brain in OS revealed a retrobulbar mass, well delineated and intraconal in location, displacing the optic nerve medially [Fig. 1]. The lesion was contrast enhanced revealing a provisional diagnosis of intraconal cavernous hemangioma.

Left sided lateral orbitotomy under general anesthesia was planned and carried out under proper consent. The specimen was sent to ocular pathology laboratory where encapsulated bluish black mass measuring (22.1 mm × 16.18 mm × 12.24 mm) was documented [Fig. 1]. Grossly, the tumor showed surface vascularity over the capsule. Surface vessels were in different dimensions and were also seen piercing the capsule. After dissecting a small portion of capsule, numerous TECs were seen, some of which formed a pattern of endothelial podosome rosette which was documented. Sprouting of TEC and the blood vessels with intracellular gap junctions among the TECs was observed. Endothelial cells on the surface of the blood vessels and TEC were seen under high power objective illumination of microscope (Axioskop 40 with AxioCam MRc camera). Microscopic appearance showed capsulated

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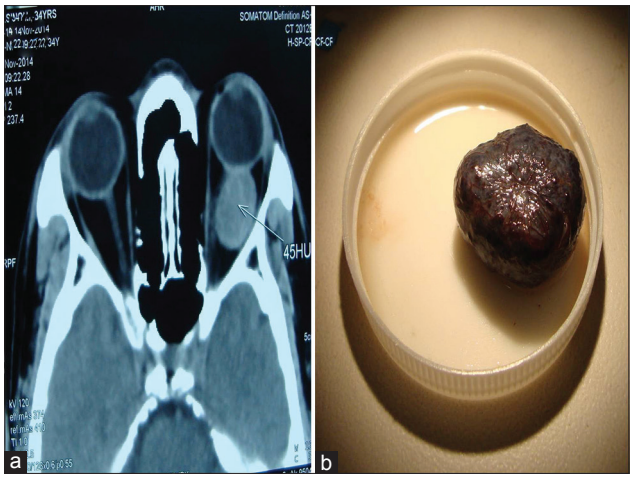

Figure 1: (a) Computerized tomography scan of brain and orbit with intraconal orbital mass and (b) Gross bluish black encapsulated cavernous hemangioma

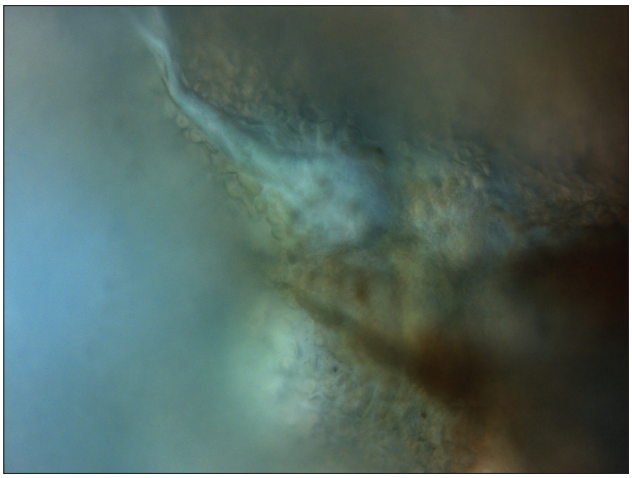

Figure 2: Sprouting of end of small vessels in gross with suspected angiogenesis (×400, unstained specimen)

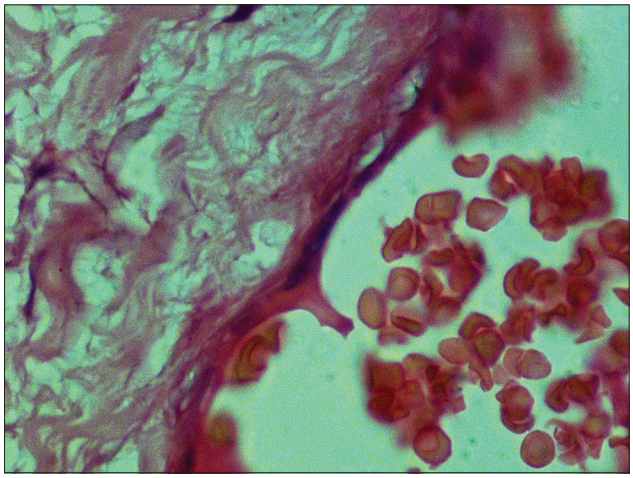

Figure 3: Outgrowth of small twig of sprouting from endothelial surface of blood vessel (H and E × 400)

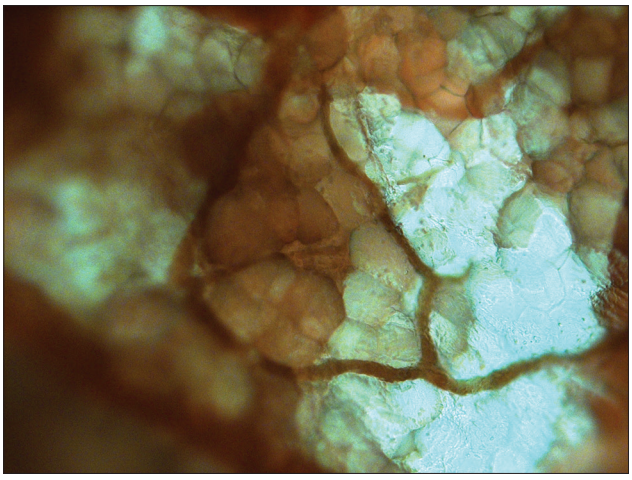

Figure 4: Structure simulating podosome rosette formed by tumor endothelial cell and small blood vessels encircling the rosette

vascular tumor with numerous dilated blood vessels of varying sizes filled with red blood cells and lined by endothelial cells. Some of the endothelial cells showed sprouting of its extension, which were also documented under microscope [Figs. 2 and 3]. Pericytes and fibrocytes with varied morphology were seen in intervening stroma. Some of the lymphocytic collections were seen at the edges of the lumen of the blood vessels. All the microscopic findings were consistent with cavernous hemangioma, and interesting finding of surface blood vessel and TECs was similar to some of the established cell culture tumor model *in vitro* experimental pathology. Immunohistochemistry (IHC) of the tumor showed CD31, CD34, actin, and vimentin positive. Periodic acid-Schiff showed positive for the BM.

Discussion

Sprouting angiogenesis is an enlargement of new capillary blood vessels arising out of preaccessible ones.[1,7-9] It was long being discussed that how a new vessel could arise from the exiting one when the metabolic needs in the adjoining tissue is similar.[7-9] It has been documented in various conditions such as neovascularization in diabetes, pannus in synovium of joints in rheumatoid arthritis, vascular system complications, and in tumor biology.[7-9] In tumors, sprouting angiogenesis is not only seen in primary tumors but also in micrometastasis and obvious metastasis.[2-10] In all these conditions, sprouting angiogenesis was seen in oxygen deficient area where angiogenesis starts with activation of endothelial cells by various growth factors that bind to the specific sites.[7-10] Extracellular matrix and BM surrounding the endothelial cells despoiled locally by activated factors.[7-10] By the process of polarization, the migrating endothelial cells are created within the lumen, and immature blood vessels are formed. The entire development of angiogenesis is firmly prescribed by positive and negative regulators, the stability of which determined the level of ongoing angiogenesis.[7-10]

In 1980, fibroblast growth issue was developed which stimulates major steps in angiogenesis. Thereafter, vascular endothelial growth factor played a major role in prompt of various blood vessels in diverse organs.[7-10]

Our case was a 34-year-old male presented with proptosis in OS for 2 years. After surgery, the specimen was meticulously

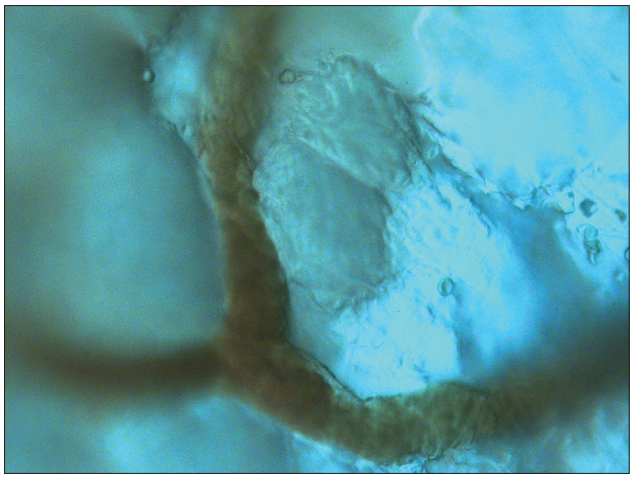

Figure 5: Comparative size of tumor endothelial cell and endothelial cells of small blood cells

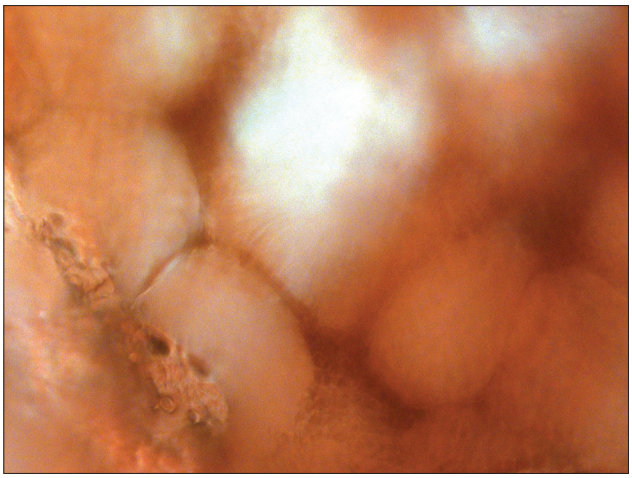

Figure 6: The gap junction of tumor endothelial cell in direct examination of the tissue under high power objective of compound microscope (×400)

examined for its small vascular pattern over that tumor's capsule and its surrounding. TECs were important morphological structures that were documented and compared with the endothelial cells of the surface blood vessels. A pattern of endothelial podosome rosette [Fig. 4] was another pathological structure that was seen and adjoining to them, the TEC showed intracellular gap junctions [Figs. 5 and 6]. Sprouting of blood vessels could be seen in very high power objective of microscope and compare with stained section. IHC for CD34 showed positivity demarcating the structures of endothelial cells of the blood vessels.

We have seen in our case that there was a strong pathological evidence of tumor angiogenesis with sprouting of the blood vessels. TEC which was mostly evident in the model conceptualized for tumor angiogenesis play a significant role in the biology of vascular tumor such as cavernous hemangioma.

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Conflicts of interest

There are no conflicts of interest.

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