Case Report

Incidental in vivo detection of an epithelioid hemangioendothelioma of the mitral valve

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Valvular epithelioid hemangioendotheliomas (EHE) are exceptional. To the authors’ knowledge only four cases have been reported. Herein is described an EHE incidentally detected in the mitral valve of a 69-year-old woman with chronic rheumatic valvular heart disease. The 0.4 cm lesion was situated in the anterior leaflet and was discovered in the pathological study after mitral valve replacement. The patient was alive and well 6 months after operation. Review of the literature including the present report, revealed that the mean age was 60.2 years (range, 49–69 years). Symptomatic patients had clinical features of valvular disease or embolism. Each of the four cardiac valves can be affected. Mean tumor size was 2.4 cm (range, 0.4–8 cm). In 40% of cases the EHE was an incidental finding at autopsy or in a removed valve. In two cases the involved cusp was affected by chronic rheumatic disease. In conclusion, EHE is a rare lesion that can be an incidental finding and it should be considered in the differential diagnosis of valve tumors. Although EHE can present a histologically benign appearance, the correct pathological diagnosis is clinically important because the lesion can be potentially malignant. Regular follow up is suggested due to this potential.

Key words: angiosarcoma, cardiac valves, epithelioid hemangioendothelioma, heart, hemangioma, mitral valve

Primary tumors of the heart are uncommon and, among them epithelioid hemangioendothelioma (EHE) is quite rare.1 Thus, in a series of cardiac tumors covering a period of two decades no case of EHE was observed.2 Most cardiac EHE are asymptomatic but they can be incidentally detected at cardiac surgery3 or at autopsy.4 In contrast, cardiac valve tumors are rare, the great majority of which are papillary fibroelastomas.5

Valve EHE are very rare neoplasms; they are so rare that this location is not mentioned in two recent and authoritative monographs on cardiac tumors.1,6 To the best of our knowledge only four cases of valve EHE, one in the mitral valve, have been described, all in adults.4,7–9 In this report we present a new case incidentally detected in the mitral valve and review the literature on the subject.

CLINICAL SUMMARY

A 69-year-old woman was admitted to Marqués de Valdecilla University Hospital with a 3 year history of increasing exertional dyspnea, orthopnea and edema of the lower limbs. Past medical history was significant for rheumatic heart disease, with mitral stenosis treated with commissurotomy 10 years before. A diagnosis of mitral insufficiency after valvulotomy and severe tricuspid insufficiency was made. Mitral valve replacement with a bileaflet, mechanical device, type Sorin Bicarbon of 33 mm (Sorin Biomedica Cardio, Saluggia, Italy), and a tricuspid De Vega annuloplasty were performed. The posterior leaflet of the mitral valve was left in situ. During operation the mitral valve was noted to be deformed with features of chronic rheumatic disease. Following the operation the atrioventricular valves were sound on function. The patient was discharged in good condition on postoperative day 9. She has remained well without further evidence of neoplastic disease 6 months after operation.

PATHOLOGICAL FINDINGS

The surgical specimen consisted of the anterior leaflet of the mitral valve, measuring $4 \times 3 \times 2$ cm. This leaflet was thick, shrunk and calcified. In addition, the chordae tendinae showed shortening, thickening and fusion. Close to the closure line, at the atrial side and at the center of the leaflet a 0.4 cm reddish nodule was noted. Microscopic examination
showed this small, circumscribed, nodule situated just beneath the endothelial layer (Fig. 1a). The lesion consisted of small capillary-size vessels immature or poorly canalized (Fig. 1b). They were lined by plump endothelial cells with prominent, eosinophilic cytoplasm and ovoid hyperchromatic nucleus with visible, inconspicuous nucleolus. Cytoplasmic vacuoles occasionally forming vascular lumina were present. The intervening stroma was prominent and myxoid (Fig. 1c). Pleomorphism or mitotic figures were not seen.

The immunohistochemical study was carried out with a TechMate 500 automated immunostainer (BioTek, Santa Barbara, CA, USA) using the EnVision+ method (Dako-Cytomation, Glostrup, Denmark). Appropriate controls were included. The antibodies used are summarized in Table 1. Tumor cells stained positively for CD31 and this marker accentuated the vascular nature of the lesion (Fig. 1d). Negative reactivity was noted in these cells for CD34, factor VIII-related antigen, CD68, pancytokeratin, and calretinin. Scant, scattered macrophages were detected among the neoplastic cells with CD68 stain.

The rest of the valve revealed diffuse fibrosis, focal calcification and neovascularization.

DISCUSSION

The term ‘hemangioendothelioma’ was used in the past in an equivocal manner to refer both to benign vascular conditions, often observed in childhood, and to malignant vascular tumors. Currently, the term refers to a heterogeneous group of uncommon vascular neoplasms intermediate in morphological appearance between a hemangioma and a conventional angiosarcoma. At least four subtypes have been characterized including EHE.10

EHE was described by Weiss and Enzinger in 1982 to designate a distinctive vascular tumor composed of epithelioid endothelial cells containing small intracellular lumina, arranged in short strands or solid nests.11 It is a rare entity that has been reported in the soft tissues, bone, and in various organs such as lung, pleura, mediastinum, liver, stomach, peritoneum, breast, brain, meninges, lymph node, skin, spleen, squamous mucosas, salivary glands, and heart.5,12–16 In most cases the tumor appears quite bland with virtually no mitotic activity. This lesion is considered as a low-grade or borderline neoplasm because of an occasional association with local recurrence or metastasis. The condition is different but very close to epithelioid hemangioendothelioma.12,13 EHE of the heart may occur in infancy5 and in adulthood. In the heart the tumor has been present in the left atrium15 and valves.4–7,9

EHE of the cardiac valves are exceptional. Cardiac valves are avascular structures except for one-third of the proximal portion near the valve ring. This fact explains the rarity of the valve hemangioendothelioma and EHE.

As far as we are aware only four cases of valve EHE have been reported, all in adults (Table 2).4,7–9 The case reported by Mariani and De Jaco is a valvular hemangioendothelioma but not an EHE.17 No case of this location has been observed in infant patients. Including the present case the average patient age is 60.2 years (range, 49–69 years). No clear sex predominance has been noted. Most patients are symptomatic. Symptomatic patients have clinical features of valvular disease or embolism. Each of the four cardiac valves can be affected, with a slight predominance of the mitral valve. Average tumor size is 2.4 cm (range, 0.4–8 cm). In 40% of cases the hemangioendothelioma is an incidental finding at autopsy or in a removed valve. In two cases there was neovascularization of the affected cusp as a component of the chronic rheumatic disease.

Histologically EHE can exhibit a solid type of growth or display a prominent stroma hyaline, myxoid or myxochondroid appearance. Immunohistochemically, EHE usually reacts with at least one endothelial marker.18 Although CD31 is highly sensitive and the most specific marker of endothelial differentiation,19 some EHE are negative. Therefore, it is necessary to use a panel of endothelial markers, including CD34 and factor VIII-related antigen, for questionable cases. EHE is typically negative for both epithelial membrane antigen and cytokeratin.13

A recent cytogenetic study has detected an identical chromosomal translocation t(1;3)(p36.3; q25) in two cases of EHE.20

Epithelioid change may represent an unusual functional state of the endothelium. This cell has a superabundance of

<table>
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<th>Antibody for</th>
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<th>Source</th>
<th>Dilution</th>
<th>Pretreatment</th>
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PC, pressure cooker epitope retrieval in 10 mmol/L citrate buffer, pH 6.0.
Figure 1  Microscopic features. (a) Panoramic view of the epithelioid hemangioendothelioma arising from anterior mitral leaflet in subendothelial location. The lesion retains sharp circumscription without encapsulation. (b) Immature pattern of the vascular proliferation with many vessels poorly canalized in a myxoid background. (c) Small capillary-sized vessels lined by epithelioid endothelial cells. These cells show enlarged but uniform nuclei. The intervening stroma is myxoid. (d) Tumor cells are stained for CD31. This marker emphasizes the vascular nature of the lesion.
Mitral valve epithelioid hemangioendothelioma

intermediate filaments, which accounts for its plump shape, is rich in acid phosphatase and lacks alkaline phosphatase. This observation has led some authors to suggest that the cell represents an intermediate form between an endothelial cell and a histiocyte.\textsuperscript{12}

Valvular EHE appears as a tumor of indeterminate prognosis. Patients 1 and 5 (Table 2) had remained well without further evidence of neoplastic disease, respectively, 4 years and 6 months since the time of initial discovery. However, patient 2 developed pulmonary metastasis 4 months after operation. Therefore, prognosis should be guarded. In contrast, a case of non-valvular cardiac EHE developed early distant metastasis.\textsuperscript{15}

It must be noted that the focal presence of epithelioid endothelial cells alone does not imply a diagnosis of an EHE. These cells should make up the entire neoplasm. Thus, the composite hemangioendothelioma tumor possesses a complex admixture of different vascular components including areas of EHE.\textsuperscript{21}

The main differential diagnosis includes epithelioid hemangiofibroma, epithelioid angiosarcoma, metastatic carcinoma and malignant melanoma.

Cardiac epithelioid hemangiofibroma characteristically shows well-developed vascularity lined by hobnail endothelial cells and has a prominent inflammatory infiltrate of lymphoid follicles and eosinophils.\textsuperscript{22} Epithelioid angiosarcoma exhibits overt malignant features including mitotic activity, solid growth, large and hyperchromatic nuclei, with prominent eosinophilic nucleoli, and necrosis.\textsuperscript{23} The stroma can be abundant and hyalinized. However, it must be noted that approximately one-fourth of EHE display atypical features defined as cellular atypia, mitotic activity (>1 mitosis per 10 high-power fields (HPF)), necrosis, or extensive spindling. These cases have a more aggressive course with a higher rate of metastasis and even poor clinical outcome.\textsuperscript{16,18}

Metastatic carcinomas and malignant melanoma generally show significant cytological atypia, mitotic activity and necrosis. Metastatic deposits may be multinodular. However, endocardial metastases are uncommon.\textsuperscript{24} The pattern of reactivity of a panel of antibodies including endothelial markers, cytokeratin, S100 protein, HMB45, and Melan A will help in differentiating EHE from its various mimickers.

In conclusion, we present a case of a primary EHE of the mitral valve and have reviewed the world literature. EHE is a lesion that can be asymptomatic and, despite its rarity, should be considered in the differential diagnosis of vascular lesions of the cardiac valves. Although EHE can present as a histologically bland appearing lesion, a correct pathological diagnosis is clinically important because the lesion can recur and metastasize. Regular follow up is suggested due to this potential.

\section*{REFERENCES}
