Glandular cardiac myxoma: case report with literature review

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[Received 24 November 2013; Accepted 11 January 2014]

Glandular cardiac myxoma is rare, representing only 5% of cardiac myxomas. A 51-year-old female developed embolic events caused by left atrial myxoma. She underwent myxoma resection and had an uneventful postoperative course. Histology of the resected myxoma revealed a glandular cardiac myxoma. In this article, the peculiar case was presented and the origin of cardiac myxoma was discussed. (Folia Morphol 2014; 73, 3: 374–382)

Key words: cell differentiation, heart neoplasms, immunohistochemistry

INTRODUCTION

Cardiac myxomas (CMs) are the most common primary heart tumours in adults, accounting for 50% of the cases [65]. Diverse clinical manifestations and malignant behaviours of this benign neoplasm have attracted considerable interest [33]. Multipotential undifferentiated mesenchymal cells are believed to be the origin of CM [30]. Instant studies revealed that CMs are neoplastic rather than thrombogenic in origin, as mesenchymal cells represent divergent differentiations [1, 14]. Pathological changes representing differentiations, such as chondrification, calcification, ossification, extramedullary haematopoiesis, thymic remnants and mucin-producing glands occasionally found in CM, indicating a neoplastic origin arising from foregut remnants [76]. Immunohistochemical evidences of indifferentiated mesenchymal cells, non-metastatic nature in most cases [16], gland-like, epithelium-lined cystic and tubular spaces with features of the mesothelioma [22], and ultrastructurally proved active secretional structures [21, 23, 32] also supported the neoplastic origin theory. Nevertheless, the organising cardiac intramural thrombi and papillary endocardial lesions of histological features similar to those of CM challenged the neoplastic origin hypothesis [64], and the exact origin of CM still remains disputable [3]. Furthermore, histology, histochemistry and immunohistochemistry of CM have been sufficiently studied; whereas pertinent aspects of glandular CM have not, due to the rarity of the glandular differentiation. As estimated in the literature, glandular CM are rare representing about 5% of CM [38]. The aim of this article is to present the structural and immunohistochemical features of glandular CM by a case report with literature review, and to further discuss the origin of CM.

CASE REPORT

A 51-year-old female had abrupt vision loss 6 months prior to current admission. She was then referred to a nearby hospital and was diagnosed with “top of the basilar” syndrome and cardiogenic shock caused by a left atrial myxoma. She also developed multiple arterial embolisms of her lower extremities involving bilateral anterior tibial, bilateral posterior tibial, right popliteal and bilateral dorsal arteries as evidenced by ultrasonography. Her condition was gradually stabilising after prolonged treatment. She

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was recently referred to this hospital for surgical treatment of left atrial myxoma. After admission, the diagnosis of left atrial myxoma was confirmed by echocardiography and chest computed tomography. Her vital signs were normal. Precordial systolic murmurs were only audible in a sitting position on the 5th morning after admission. She was conscious but apathy, with bilateral blepharoptoses and poor pupillary light reactions. Her left pupil was 4 mm and right pupil was 2 mm in diameter. She showed poorly upward, downward and adducted eye movements, and slightly decreased right lower limb muscle strength but symmetrical deep tendon reflexes.

Left atrial myxoma resection was performed under cardiopulmonary bypass. During the operation, the myxoma was found to be originated from the free wall of the left atrium. The myxoma was resected en bloc, and the iatrogenic atrial wall defect was repaired with an autologous pericardial patch. She had a delayed aesthetic awakening until postoperative hour 13.5 with no new neurological sequelae. She had an uneventful postoperative course and was discharged home on postoperative day 19.

The myxoma was grossly villous, polypoid, and loosely lobulated with smooth, glistening surface, measuring 4.5 × 4.5 × 3.0 cm in size (Fig. 1). The myxoma was brown in colour, uncapsulated and broadbased without a pedicle. On the cut surface, the myxoma was gelatinous and semitransparent with partially haemorrhagic and cystic regions. Microscopically, the myxoma was composed predominantly of scattered stellate, spindle-shaped, or polygonal myxoma cells, with small endothelial vascular channels lying in a loose myxoid stroma.

Glandular structures were focally located at the base of the myxoma dispersed in the loose amorphous stroma (Fig. 2). Some glands had obvious lumina, while others did not. Gland fusions were noted (Fig. 3). In overall, the glandular structures were well-developed by irregularly arranged single columnar, cuboid, or flat cells. There were a few goblet cells with cytoplasmic mucin vacuoles. No obvious atypia, mitosis, or necrosis was present.

The immunohistochemical stains utilised the antibodies against pan-cytokeratin (CK) (AE1/AE3), vimentin, CK7, CK20, epithelial membrane antigen (EMA), smooth muscle actin (SMA), Ki-67, Factor VIII, desmin, S100, oestrogen receptor, c-erbB2, B-cell lymphoma 2 (Bcl-2), myogenin, melanoma marker HMB45, cellular tumour antigen p53, lambda light chain, CD3, CD20, CD34, CD56, CD57, CD68, CD79α, CD99, CD138, proliferating cell nuclear antigen and

![Figure 1. Gross appearance of the myxoma, which was grossly villous, polypoid.](image1)

![Figure 2. Glandular structures were focally located at the base of the myxoma; HE × 25.](image2)

![Figure 3. Gland fusions (arrows); HE × 400.](image3)
cyclin D. The glandular structures were strongly and diffusely immunoreactive to vimentin (Fig. 4) and EMA (Fig. 5), moderately to carcinoembryonic antigen (CEA) (endothelium-lined area) (Fig. 6) and CD34 (glandular epithelium) (Fig. 7) and weakly and scatteredly immunoreactive to CD3 (Fig. 8), CD20 (Fig. 9) and Ki-67 (Fig. 10), but negatively immunoreactive to SMA, Factor VIII, pan-CK, desmin, S100, oestrogen receptor, c-erbB2, Bcl-2, myogenin, HMB45, P53, lambda light chain, CD56, CD57, CD68, CD79α, CD99, CD138, proliferating cell nuclear antigen and cyclin D.

**DISCUSSION**

A comprehensive literature collection of glandular CM was made in PubMed, Google and Baidu search engines, Highwire Press, Airitilibrary, LILACS, sinomed.imicams.ac.cn/jp/ and Chinese Medical Citation Index (CMCI). The search terms included “heart myxoma”, “cardiac myxoma”, “atrial myxoma”, “valvular myxoma”, “glandular component”, “glandular structure” and “gland-like structure”, and the search ended on December 31, 2013. A total of 124 reports were collected including 108 (e-)journal articles, 9 book chapters and 9 web pages. Of them, 54 reports describing CM without any glandular components, or narrating glandular differentiation of CM without patient information, such as review articles, book chapters and majority of the web pages, were excluded from the statistical analysis of this study. Alternative exclusion criteria included duplicate publications [20, 26, 28, 46, 48], and original articles with only patient number [2, 9, 35], or even
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with no patient number [7, 13, 66, 80] of glandular CM without patient information, with 3 intracardiac heterotopia of epithelium [6, 11, 51], and describing a bone metastasis of glandular CM, however, the in situ CM did not show any glandular components [69]. Finally, 54 reports (30 case reports [4, 5, 8, 16, 17, 22, 24, 27, 34, 36-41, 43-45, 52, 53, 55, 58, 62, 63, 65, 66, 68, 70, 74, 77], 23 original articles [10, 12, 14, 15, 19, 21, 29, 30, 47, 54, 56, 59-61, 64, 67, 72, 73, 75, 78, 79, 81, 82] and 1 case series [18]) were included, with 99 patients with a glandular CM (a total of 100 cases including the present patient) representing 7.4% of the 1,351 CM patients under investigation. Of the 100 patients, 24 were males and 39 were females with a male-to-female ratio of 1:1.63, while gender could not be tracked in 37 patients. Their age was 51.2 ± 16.4 (range 10–78; median 53.5) years (n = 40). There was no age difference between male and female patients (51.4 ± 17.3 years vs. 51.0 ± 16.1 years, p = 0.9386). Of the developmental patterns, 24 (80%) were sporadic and 6 (20%) were familial (χ² = 0.0000, p = 1.0000). Locations of the CM were described in 65 patients: 46 (70.8%) in the left atrium, 16 (24.6%) in the right atrium and 3 (4.6%) in both atria (χ² = 67.3, p = 0.0000). The dimensions of the myxomas were 5.9 ± 2.0 (range 2.8–9; median 4.8) cm (n = 30). The left atrial myxoma measured 4.9 ± 1.7 (range 1.5–7.8; median 4.5) cm (n = 17) [1, 15, 17, 18, 24, 27, 34, 36–38, 44, 45, 53, 62, 68, 73], and the right atrial myxomas extended 7.6 ± 3.5 (range 2.5-16; median 7.1) cm (n = 10) [4, 5, 8, 12, 18, 22, 24, 39–41, 58]. The dimensions of the right atrial myxomas were much larger than that of the left (p = 0.0112). The weight of the myxoma was reported in 5 patients which was 41.2 ± 38.7 (range 5–109; median 37.5) g (n = 6) [18, 22, 44, 65, 68] (1 patient had biatrial myxomas weighed). The myxomas were pedicled in 9 patients [1, 22, 24, 34, 36, 37, 40, 68, 73], of whom 4 patients had their pedicles measured with a length of 1.5 ± 1.1 (range 0.3–3.0; median 1.3) cm (n = 4); whereas 4 myxomas were broad-based [8, 24, 39, 44]. The attachment site of the myxomas was described in 40 patients, with atrial septum (fossa ovalis) being the most common attached site (Fig. 11). The locations of the glandular structures were reported in 41 cases: 37 (90.2%) were at the base [1, 8, 30, 37, 40, 44, 56, 60, 65, 73, 75, 79], 2 (5.4%) scattered [36, 60], 1 (2.4%) central [72] and 1 (2.4%) central and at the base of pedicle [39]. The distributions of the glandular structures were expressed in

Figure 8. Weak and scattered immunoreaction to CD3 in glandular structures; En Vision × 400.

Figure 9. Weak and scattered immunoreaction to CD20 in glandular structures; En Vision × 400.

Figure 10. Expression of Ki-67 was only less than 1% in glandular structures; En Vision × 400.
In 1 patient, the glandular CM formed by irregular, angulated contours with cribriform architectures [17]. A CM of another patient showed confluent glandular structures [38]. The present patient had irregular, not very well developed glands, and confluences of glands were seen as well. Mild focal nuclear atypia [1, 65, 73, 81] and occasional atypical mitosis [1, 17, 68, 81] were reported in 4 (4%) patients, each. Besides, epithelial cells with an abrupt transition into myxoma cells were observed in 3 patients [14]. Malignant transformation of glandular structures in a CM was observed in 3 (3%) cases [8, 43, 52].

Histologically, typical myxoma cells are moderate amount of stellate or spindle-shaped myxoma cells, eosinophilic cytoplasm, occasional perivascular aggregates, bubbly to fibrillar stroma with focal haemorrhage, fibrin insudation and haemosiderin-laden macrophages, and absence of nuclear atypia, mitosis, or necrosis [14, 22]. Some of these glands contained luminal mucin [14]. Haemorrhagic areas, haemosiderin laden macrophages, neutrophil, leukocytes and lymphocytes were also observed in myxoid stroma [62].

Immunohistochemical studies of CMs are in 3 ways: surface lining cells, stromal myxoma cells and perivascular cells [17]. Myxoma cells were positively reactive to Factor VIII (focal, endothelium-lined area), SMA [1] and vimentin [1, 8, 37], which was observed in spindle cells of the stroma [36], neuron-specific enolase (NSE) (slightly and focally) [8, 36], S100 (a few dendritic cells) [8, 36] and SMA (slightly and focally, sparse muscular areas) [36], and those with some muscle fibres [37]; but negative to CK, EMA, CEA, Leu 1 and desmin [1]. Negative reaction was also noted in staining with Factor VIII [36]. Matrix showed positivity to vimentin (spindle cells of the stroma) [36], vimentin [38, 40], calretinin [38, 40]; negative to Factor VIII [36], CEA [40], CK [40], CK7 [40] and CK20 [40]. Endothelium-lined capillaries of myxomas were positive to ulex europaeus [14], vimentin (stellate cells) [40], SMA [36], Factor VIII [36, 38], vimentin [37], CD31 [38], CD34 [38], S100 (occasional stellate cells) [40] and CEA (focally, stellate cells) [40]; but negative also to CEA [40], CK [40], CK7 [40] and CK20 [40]. The expressions of pan-CK and CEA are in keeping with the epithelial differentiation in CM. The myxoma cells were positive for SMA, but negative for desmin and S100, and therefore myofibroblastic cells were suggested as the cell of origin [3]. Myxoma cells were positive for calretinin in 75–100% of cases, but had variable positivity for...
The glandular epithelium has been histochemically identified a gastrointestinal or enteric nature of the epithelium. Periodic acid Schiff (PAS)-positive cytoplasmic globules and strong immunoreactivity against cytokeratin were demonstrated in the cuboidal and low columnar simple epithelium [12]. PAS and Alcian blue (AB) stainings were positive in 3 places of glandular structures of myxoma: the gland lumina, the goblet cells and the brush border, where mucus was generated [38]. Basal positivity for PAS and apical positivity for AB and mucicarmine were noted [40].

Immunohistochemically some endothelial markers, such as CD31, CD34 and Factor VIII, are present in myxoma cells. Positive staining has also been reported for S100, calretinin, vimentin, desmin, smooth muscle myosin, CD56, α,-antitrypsin and α,-antichymotrypsin [25], and interleukin-6 [27]. Willebrand factor was only detected in endothelial cells lining vascular channels and deep invaginations of surface papillae [53].

Glandular structures showed positive reactions to CK (50%), EMA (focal, luminal), CEA (50%), Leu 1; Ulex europaeus (epithelial cells and erythrocytes) [1], CK (glandular epithelium) [36, 40, 43], CEA (apical surface cytoplasm) [36, 38, 40], pan-CK [38], CD31 (focal) [38], S100 (focal glands) [40], calretinin [40], CK7 [38, 40], vimentin (cytoplasm) [40], CA19.9 (cytoplasmic membranes, mainly at the apical side and intracytoplasmic vacuoles) [36], mesothelioma marker HBME-1 (focal) [38] and interleukin-8 [27]; while negative to Factor VIII [14], NSE (cytoplasm, slightly) [36], pan-CK [37], CK20 [38, 40], calretinin [38], CEA [37], CD68 [37] and chromogranin A [36, 37]. The histopathology of the present case was compatible with the current literature.

Positivity to CEA is a characteristic of endodermal origin, indicating that the myxoma cells are of capacities of the endoderm cells [29]. The satellite cells express simultaneously S100 and synaptophysin (Syn), suggesting the origin of myxoma may be associated with the endocardial sensory nerve tissue [13]. The staining of CK reactivity was observed mostly in the surface lining cells [19]. In the case with glandular differentiation, the positivity was both within the glandular component and the surrounding myxoma cells [17]. Vimentin, EMA, pan-CK, CK7, CEA and calretinin were positive in the glandular structures and variably in stellate cells and blood vessels [40]. Pan-CK and CK7 were strongly positive along with EMA and CEA, whereas CK20 was negative in the glandular structures, indicating a possibility of entrapped foregut rest origin of CM [40].
p53 protein immunoreactivity could be an indicator for discrimination between neoplastic and reactive mesothelium [49]. Generally, the regular glandular structures showed rare nuclear p53 staining. Foregut remnants, bronchial or alveolar epithelium, mesothelium and germ cells have been supposed as the origin of the glandular structures. Uncommon proliferative activity was considered “reactive” atypia, in the CM with glandular differentiation, the mitotic index and degree of atypia, with striking variation in size and shape of nuclei were more likely an early malignant behaviour than reactive process [17]. Ki-67 represents the proliferation rate, and studies of CM on this aspect revealed a slow proliferative rate [50]. Pucci et al. [48] reported that a very low proliferative activity (< 2%) was detected in glandular cells of case 3 by means of Ki-67 immunoreactivity. Berger et al. [8] noted that the proliferation rate with Ki-67 was less than 10% in the benign glands of CM and about 80% in the malignant glands of the adenocarcinoma and the systemic metastases.

The myxoma cells bear some similarities with mesothelial cells [38]. Expressions of both epithelial and vascular antigens reflect the multipotential nature of myxoma cells. Heterotopia in CM provides evidence to the theory of a pluripotent reserve cell line of origin [42]. Differential diagnoses of CM include intracardiac thrombus, cardiac excrescence and other primary or metastatic cardiac neoplasms [9]. Immunohistochemical study can meet the satisfaction of the differential diagnosis [9]. Glandular CM have to be distinguished from a metastatic carcinoma as small areas of benign glands resemble adenocarcinoma [20, 46]. Nevertheless, atypia and mitosis are rarely present in the former [71]. CM, renal angiofibrolipomas and thyroid adenoma presented considerable atypism at the same time, and therefore CM may be in accord with the hamartoma in view of histogenesis [31]. Side-by-side malignant and benign glands could be detected in the small transitional zone between myxoma and adenocarcinoma, indicating transferable capacities of the myxoma cells [8].

CONCLUSIONS

Glandular CMs are morphologically characterised by base locations, focal distributions and well-developed structures in most cases with low proliferative and metastatic natures. They might derive from entrapped embryonal rests of a precursor cell toward epithelial and mesenchymal lineages. Differentiated glandular structures present in CM cells, other than in the thrombus, support the neoplastic origin of CM. Well-developed glands with basement membranes, junctional complexes and apical secretory granules revealed by ultrastructural studies also support the neoplastic origin of CM.

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