CASE REPORT

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A very rare association between giant right atrial myxoma and patent *foramen ovale*. Extracellular matrix and morphological aspects: a case report

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Abstract

We report a case of sporadic giant cardiac myxoma with a rare localization in the right atrium, operated in our Service, in a 73-year-old female patient who also presented a patent *foramen ovale* and a history of ischemic stroke in the year prior to current admission. Intra-operatively, the tumor had a very friable, gelatinous aspect, with a high potential for embolization due to its reduced consistency. The present paper refers to clinical, histochemical and immunohistochemical particularities, as well as to macroscopic and microscopic characteristics of the cardiac myxoma, emphasizing the extracellular matrix aspects, and without leaving out the cellular components of this rare tumor, with possible inference in the management of this disease. The authors present their own observations related to the data from the literature. Also, there are some particularities of the case which justify the current presentation.

Keywords: cardiac myxoma, myxoid stroma, extracellular matrix, glycosaminoglycan, hyaluronic acid.

Introduction

Soft tissue tumors are complex mesenchymal lesions with vast differentiation possibilities. In this soft tissue tumors group, the *World Health Organization* (WHO) classification includes benign tumors, malignant tumors, and borderline tumors (locally aggressive but non-metastatic tumors) [1]. In the benign tumors group are comprised the entities with a less known or less understood differentiation course. Being such an entity, cardiac myxoma begins to be outlined like a genetic identity, with obvious chromosomal aberrations [1]. The PRKAR1A gene seems to play a role in the development of the so-called syndromic cardiac myxoma from the Carney complex [2]: it codifies the type 1-alpha regulatory subunit of the cAMP-dependent protein-kinase. In the sporadic, common cardiac myxoma, this gene has a less determined role. Now, the literature publishes new data, subsequently to technical progress that allowed the deeper knowledge of these tumors.

Atrial myxoma is the commonest (20–30% of all) primary intra-cardiac tumor in adults and two-thirds of these arise in the left atrium. Other locations are right atrium (next commonest), ventricles, and cardiac valves [3]. Although they are benign, it is recommended their immediate removal as soon as the diagnosis is confirmed, since they are associated with tumor embolization and their harmful consequences [4].

The sufficient and recommended treatment is complete resection of the tumor, associated with the repair of defective area.

Taking into account these considerations, we present the clinical and morphological observations encountered in our case.

Case presentation

A 73-year-old female patient presented in our Service with a four-month history of shortness of breath, accompanied by peripheral edema and palpitations. She also had a history of an ischemic parietal stroke, as well as a radical surgical treatment for duodenal adenocarcinoma in the year prior to her current admission. The cardiovascular, respiratory and abdominal examination was unremarkable and a detailed neurological assessment did not reveal any significant abnormality. The electrocardiogram showed sinus rhythm, with a frequency of 80 bpm (beats per minute), and minor T wave changes in anterior leads.

The trans-esophageal echocardiography (TEE) demonstrated a giant mass (of approximately 65/60/58 mm, with a volume of 63.47 cm^3), which occupies almost entirely the right atrium, prolapsing into the right ventricle, with intermittent obstruction of the tricuspid valve and a very high risk of embolization; the mass was attached to the *ostium secundum* area of the interatrial septum, and also a patent *foramen ovale* with a diameter of approximately 15 mm was present (Figure 1).

The patient accepted the surgical treatment in view of the risks involved, and we performed the complete tumor resection and direct repair (suture) of the atrial septum defect. The surgical approach was made by median sternotomy; we establish the cardio-pulmonary bypass with bi-atrial cannulation, and we tried to avoid tumor

fragmentation and embolization of its parts. Macroscopically, the excised tumor weighted 55 g, and measured 6.5/6/5.8 cm, with a base of implantation of approximately 1.5/1 cm; its coloration was reddish-blue and yellowish, with a slightly fringed surface, and a gelatinous consistence (Figure 2).

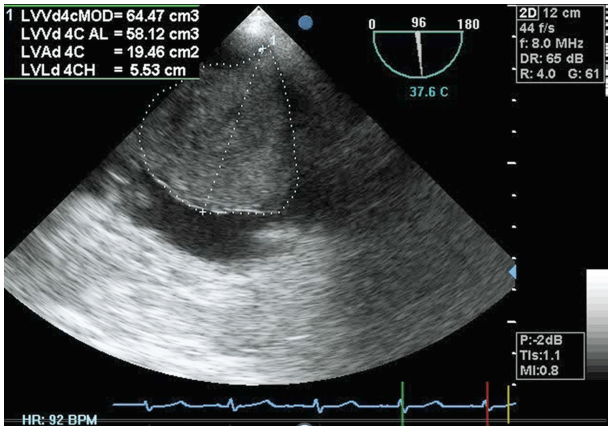

Figure 1 – ***Preoperative image – trans-esophageal echocardiography (TEE): giant mass attached to the ostium secundum area of the inter-atrial septum, occupying almost entirely the right atrium and prolapsing into the right ventricle, with intermittent obstruction of the tricuspid valve.***

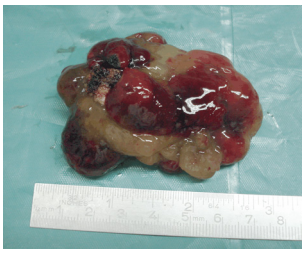

Figure 2 – ***Tumor aspect after surgical removal: gelatinous consistence with a slightly fringed surface, reddish-blue and yellowish coloration, measuring 6.5/6/5.8 cm, with a base of implantation of approximately 1.5/1 cm (arrow).***

We studied multiple fragments from the atrial mass, embedded in paraffin by the routine method; the slices were examined with an Axioskop 40 microscope (Carl Zeiss). The sections were taken at 5 μm, and stained with Hematoxylin–Eosin (HE); we also practiced histochemical and immunohistochemical stains; histochemical stains were Orcein, Masson's trichrome, Alcian blue, Periodic Acid–Schiff (PAS) and Mucicarmine, in order to stand out the particularities of the tumoral matrix. The immunomarking was achieved following multiple steps, one of them being the thermal processing of sections (in a period of 15 minutes, in citrate buffer with a pH of 6). The primary antibodies were applied in the following dilutions: calretinin – 1:100, vimentin, clone 9 – 1:100, desmin – 2:100, Ki67 – 1:100, S100 – 1:4500, CD31 – 5:100. The technique followed the steps of the Streptavidin–Biotin system (the LSAB universal kit), and the chromogenic base for peroxidase was 3,3'-Diaminobenzidine (DAB). For this reason, the positive cells are brownish; the counterstaining was made with watery Hematoxylin, determining the bluish tint of the background.

Microscopically, the multiple tumor fragments analysis showed the presence of a myxoid stroma containing polygonal or stellate cells with eosinophilic cytoplasm and oval nuclei with possible visible nucleolus. The myxoma cells were disposed in a perivascular, annular design, and arranged in groups and strings (Figure 3).

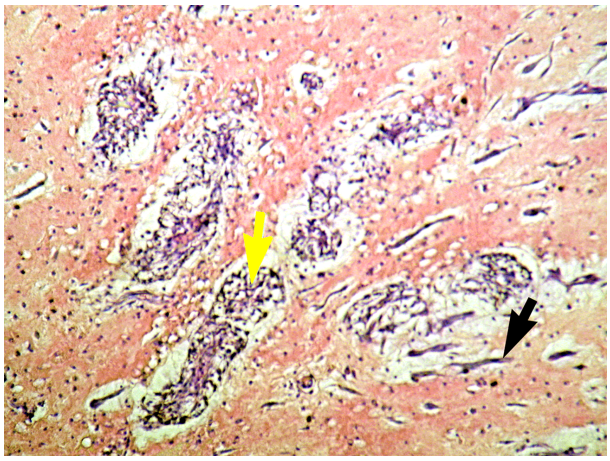

Figure 3 – ***Microscopic aspect of the cardiac myxoma (HE staining, ×100): the cells are arranged in perivascular rings (green arrow), and embedded in a myxoid stroma, some of them being arranged in groups and strings (black arrow).***

The lepidic cells are positive for calretinin, S100, and CD31. By the CD31 antibody, there is evidence of endothelial cells in the vascular structures, surrounded by the mentioned annular structures formed by the myxoma cells (Figure 4).

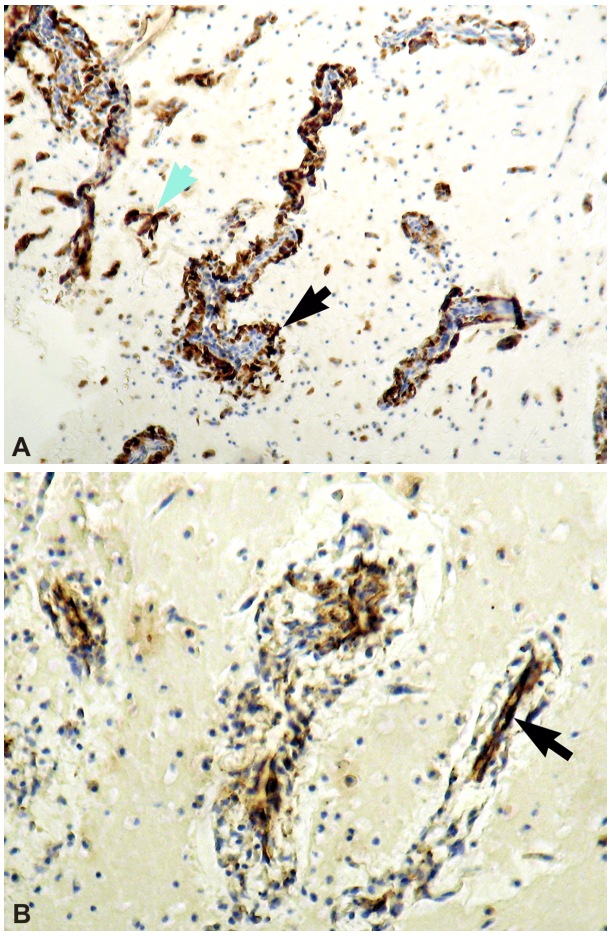

Figure 4 – ***Immunohistochemical stainings for calretinin (A) and CD31 (B). The myxoma cells are positive for calretinin (A): green arrow for groups of lepidic cells and black arrow for rings; the endothelial cells positive for CD31 (B) (black arrow) delineate the vascular channels surrounded by the annular structures composed by myxoma cells.***

The tumoral stroma contains elastic fibers (Figure 5) and is constituted of mucin areas, revealed by Mucicarmine and PAS stainings (Figure 6).

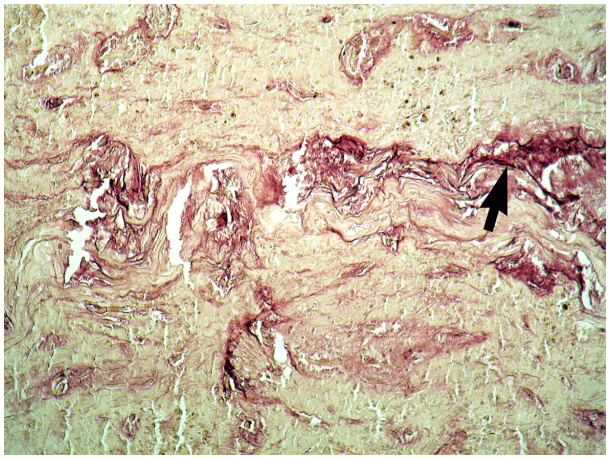

Figure 5 – ***The Orcein staining (×100) reveals the presence of elastic fibers in the myxoma matrix (arrow).***

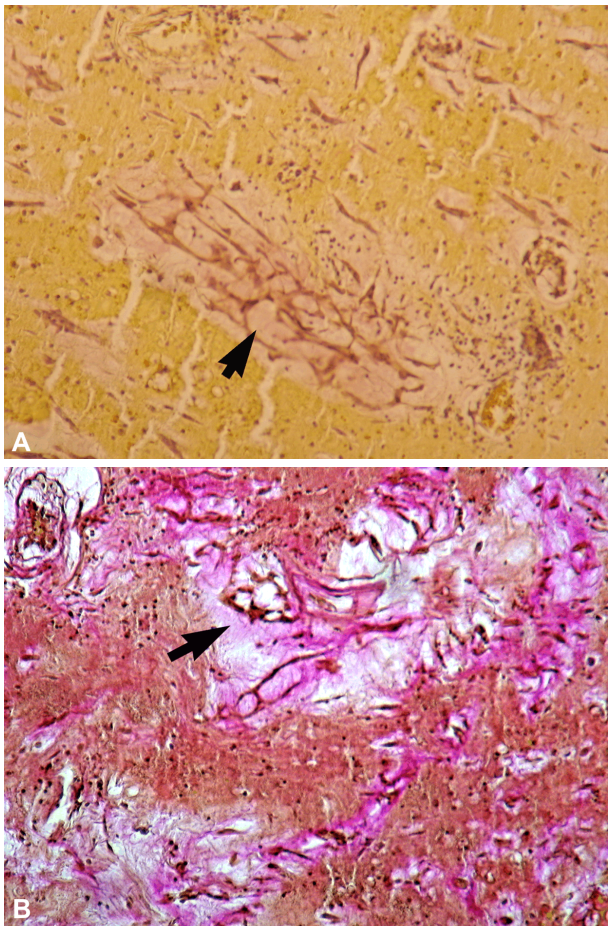

Figure 6 – ***(A) Mucicarmine staining (×100) reveals the central points that contain mucins in the extracellular matrix. (B) PAS staining (×100) performed with the same purpose (arrows).***

Also, the myxoid stroma in our case is very rich in proteoglycans, shown by the Alcian blue staining (Figure 7). Beyond these stromal components, we also identified the presence of lymphocytes and macrophages. The histological exam of the implantation base revealed the complete excision of the myxoma. The Ki67 proliferation factor was less than 5% of the studied material.

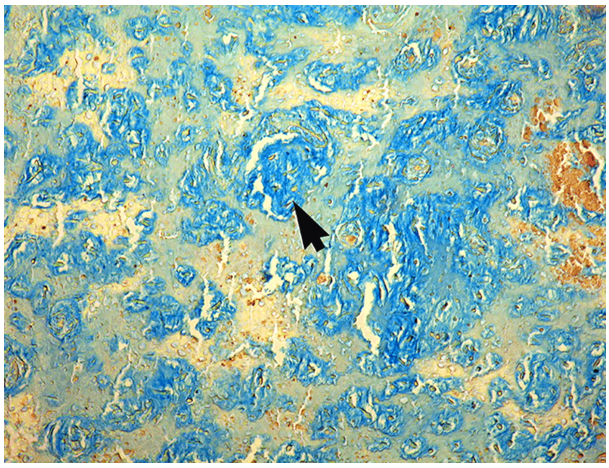

Figure 7 – ***Alcian blue staining (×200) reveals the rich component of proteoglycans in the myxoid tumoral stroma (arrow).***

Discussion

The first mention of a cardiac tumor was made by Realdo Colombo in 1559, but only in 1952 the first antemortem study of an atrial myxoma was published.

The first successful myxoma resection was accomplished in 1954. Based on autopsy findings, the incidence of primary cardiac tumors vary between 0.0017% and 0.25%. Of all primary cardiac tumors, 3/4 are benign and 1/4 are malignant. Of the benign tumors, myxoma is by far the most common, reaching an incidence of about 50%. Regarding the localization, the most frequent is in the left atrium (over 75% of cases), then in the right atrium (15–20% of cases), and the rest could be found in the left ventricle, right ventricle and bi-atrial [5].

In our clinic experience, of 84 cases of myxoma operated between 1991 and 2014, only in 12 cases the myxoma was situated in the right atrium, and only in the presented case the tumor was accompanied by a patent *foramen ovale*.

The term "myxoma" was first introduced by Rudolf Virchow in order to describe the soft tissue tumors structurally resembling the umbilical cord. He used in 1863 the term of myxoma to delineate the tumors he has already described in 1861, as having macroscopic and microscopic characteristics similar to Wharton's gelatin from the umbilical cord [6]. Also, Rudolf Virchow introduced this term as a pathologic entity [7]. The "Medical Lexicon" by Robley Dunglison specifies that the "myxoma" term was first presented by Johannes Müller under the name of "collonema". The term designated a gelatinous tumor, which trembled when being touched [8]. Myxoid tumors are presently classified according to complex clinical and pathologic criteria, and to molecular and cytogenetic characteristics [7].

Presently, there are three theories that explain the myxoma cells' histogenesis: the thrombogenic theory, the neoplasic theory, and the hamartoma theory.

Cardiac myxoma contains a great variety of cells that are believed to originate in the mesenchymal pluripotent stem cells in the *fossa ovalis*, known as Prichard's structures [2]. The myxoma cells, known as lepidic cells, produce the extracellular matrix of the tumor. They are

revealed by the expression of calretinin, as we could see in our case. Calretinin is intensely expressed in the cytoplasm and nucleus of cardiac myxomas, this antibody being proposed as immunohistochemical marker of this tumor since 2003 [9–11]. The lepidic cells can express S100, actin, CD31 and vimentin. Variably, it was demonstrated that there could also be found other positive markers like CD34, myoglobin, desmin, factor VIII, which could be used for explaining the origin of the tumor from mesenchymal pluripotent cells with variable differentiation potential [12–15]. Other cells are represented by lymphocytes, siderophages, plasmacytes, and histiocytes. The blood vessels are numerous and rudimentary, paved by CD31-positive endothelial cells [2]; this aspect is shown in Figure 4B, proving the cellular components of the above-described myxoma.

The histological features necessary for the diagnosis of myxoma are the identification of lepidic cells, surrounded by a gelatinous environment, with rudimentary vascular channels and macrophages with hemosiderin.

The cells are embedded in a gelatinous environment, determining tumor friability, which can embolize spontaneously or during surgical intervention.

Tumor fragment embolization can be produced at any vascular level. The tumor cells are viable and remain attached to the vascular wall [16, 17].

There were some reports on cases with myxoma emboli at pulmonary or cerebral level; the embolized myxoma cells had the ability of multiplying inside the arterial wall where they were quartered, and determining fusiform aneurysm formation.

Cardiac myxoma is not considered a malignant tumor. The myxoma malignancy is determined by its behavior, and not by its histological aspect. Cardiac myxomas were regarded as mild proliferative lesions, with low metastatic potential, and without modulation of oncogenes or tumoral suppressing genes [18].

The lepidic cells produce the myxoid stroma, in which they are embedded, and consequently we granted special attention for this tumoral component.

The extracellular matrix composition was better assessed after introducing the Alcian blue staining in 1950 [7], which identify the presence of glycosaminoglycans in the tissue sections.

The glycosaminoglycans are macromolecules found in the pericellular space and in the extracellular matrix: hyaluronic acid, keratan sulfate, chondroitin sulfate, dermatan sulfate, heparin sulfate, and heparin. The glycosaminoglycans form proteoglycans by specific connections with proteic cores. The proteoglycans are grouped in three families: the lecticans, the small proteoglycans enriched with leukines and the extracellular matrix proteoglycans.

The glycosaminoglycans have specific biophysical characteristics like high viscosity and reduced compressibility. Their rigidity implicates them in maintaining the tissular integrity, by favoring the cellular diffusion and migration. The biochemical characteristics of glycosaminoglycans are mediated by specific connections with other macromolecules in the extracellular matrix.

Besides glycosaminoglycans, the extracellular matrix contains collagen and other molecules as fibronectin and tenascin. In the soft tissue tumors like myxoma, the extracellular matrix is heterogeneous. The cardiac myxoma contains chondroitin-4-sulfate (C4S), chondroitin-6-sulfate (C6S), and hyaluronic acid (HA). The HA seems to be the major component in determining the myxoid aspect of the extracellular matrix [7].

C4S and C6S are glycosaminoglycans that enter in the composition of skin, cartilages and tendons, and play a physiological role in ionic bonding (calcium, copper and iron ions), with anti-oxidative effects and reducing the apoptosis and pro-inflammatory cytokines [7].

By biochemical methods, it was proved that the HA content of cardiac myxoma is 30-times higher than in the normal interatrial septum [19]. The HA is present in the heart during its development and it participates to tissular remodeling, regeneration and reparation processes, embryogenesis, and carcinogenesis [7, 19]. The HA is also abundant in the bones and cartilages. It is involved in early tissular organization by facilitating the migration and condensation of mesenchymal cells; it intervenes in the articular cavity formation, the osteoclastic and osteoblastic functions. It favors the reduction of pain perception and has a suppressing effect on cartilage degeneration [7].

Conclusions

The association between a right atrial myxoma and a patent *foramen ovale* is extremely rare, being mentioned in only six case reports from the English specialized literature. This association, along with the history of an ischemic stroke, the giant tumor size, and the patient's advanced age (knowing the fact that cardiac myxoma usually affects younger patients – less than 50-year-old), constitute particularities that determined us to present and discuss this case. In the mean time, we analyzed the extracellular matrix components in order to understand the causes of its friability and its particular behavior. We consider that cardiac myxoma is a tumor with origin in the pluripotent mesenchymal cells, with differentiation capacity from multiple cell lines. We believe that supplementary studies on the constitutive elements of this rare tumor could bring useful information about the tumor's recurrence mechanisms and behavior, with possible therapeutic consequences.

Conflict of interests

The authors declare that they have no conflict of interests.

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