CASE REPORT

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A rare cause of ischemic stroke: cardiac myxoma. Case report and review of literature

EDME ROXANA MUSTAFA[1)], DIANA RODICA TUDORAŞCU[2)], ALINA GIUCĂ[1)], DESPINA-MANUELA TOADER[1)], MARIA CAMELIA FOARFĂ[3)], ILEANA PUIU[4)], ANCA-MARIA ISTRATE-OFIŢERU[5)]

[1)]*Department of Cardiology, University of Medicine and Pharmacy of Craiova, Romania*
[2)]*Department of Internal Medicine, University of Medicine and Pharmacy of Craiova, Romania*
[3)]*Department of Pathology, University of Medicine and Pharmacy of Craiova, Romania*
[4)]*Department of Pediatrics, University of Medicine and Pharmacy of Craiova, Romania*
[5)]*PhD Student, Department of Histology, University of Medicine and Pharmacy of Craiova, Romania*

Abstract

A 46-year-old female diagnosed several years ago with arterial hypertension and an ischemic stroke with significant recovery was admitted for dyspnea on usual physical activity and fatigue. Physical examination revealed signs of heart failure with crackles on both lung bases, distented jugular veins, accentuated pulmonic valve closure (P2) and tricuspid regurgitation murmur. Echocardiography identified a large tumor in the left atrium, suggestive of atrial myxoma, which caused a severe functional mitral stenosis and produced severe pulmonary hypertension. A cardiac embolic source should always be checked in young patients with stroke. Atrial myxoma can mimic a variety of diseases: rheumatic mitral stenosis, infective endocarditis or autoimmune disease. A review on myxoma's histology, immunohistochemistry and genetics together with clinical aspects is presented.

Keywords: cardiac myxoma, ischemic stroke, echocardiography, immunohistochemistry.

Introduction

Myxoma is the most common primitive cardiac tumor diagnosed in adults; it represents 50–85% of the benign tumors [1]. It has an incidence of 0.5–1 case/10^6 persons/year and it is encountered three times more often in women. It is more common in the 4^{th}–7^{th} decades of life, it is rarely diagnosed in children and it is exceptionally rare in neonates [1]. The name myxoma comes from the abundant myxoid stroma rich in proteoglycans. Myxoma's composition and origin generated debate; initially it was considered an organized thrombus or a chronic inflammatory lesion of endocardial tissue induced by viral infection, then an endothelial cell proliferation caused by turbulent blood flow (Prichard structures) and finally data provided by genetic and immunohistochemical studies confirmed it as a benign tumor originating from subendothelial multipotent mesenchymal heart cells [1–4].

Most myxomas arise in the left atrium (LA), 60–80% of cases, with typical insertion on the *fossa ovalis*, less often they can be found in other locations in LA, right atrium (15–28% of cases), ventricles (12%) or valves [1, 5]. In 90% of cases, myxoma occurs sporadically, while the rest are familial forms as Carney syndrome, in which multifocal myxomas can affect many organs (heart, skin, breast), the patients having abnormal skin pigmentation (lentigines, pigmented nevi) and other types of tumors [1, 6].

Myxomas can grow from a few millimeters to 15 cm, with an average size of 5–6 cm at the moment of diagnosis [1, 5]. Small tumors are usually asymptomatic, while larger masses can cause many symptoms: hemodynamic, due to mechanical interference with mitral valve opening; embolic, due to tumor friability and systemic/constitutional symptoms caused by cytokine release. Atrial myxoma can mimic a variety of diseases: rheumatic mitral stenosis, infective endocarditis or autoimmune disease [2]. Although benign, myxomas can recur in 3% of sporadic cases and up to 20% in familial forms; this can be due to incomplete resection of the interatrial septum or to cell spread at the moment of surgery or previous embolism [1].

We present the case of a young female with previous stroke and symptoms of heart failure with a delayed diagnosis of LA myxoma. A review on myxoma's histology, immunohistochemistry and genetics together with clinical aspects is presented.

Case presentation

Forty-five-year-old female patient, non-smoker, was admitted for dyspnea on usual physical activity and fatigue, symptoms that worsened in the last four months. Previous medical history revealed grade 3 primary arterial hypertension diagnosed four years ago, for which therapy was first discontinuous and an ischemic stroke (in the right carotid artery territory) that occurred four months ago, when the patient presented left side hemiparesis; blood

pressure (BP) was slightly elevated 150/90 mmHg at the moment of stroke and no arrhythmia was detected. Following stroke, the patient received therapy with angiotensin-converting enzyme (ACE) inhibitor, beta-blocker, aspirin, statin, aiming to control BP and reach optimal value of lipids. The recovery was significant, only a minor motor deficit persisted in the upper left limb.

Physical examination (at current hospitalization) showed satisfying general condition, normal body mass index (BMI), crackles in both lung bases, heart rate (HR) 100 beats/min, an accentuated pulmonic valve closure (P2), grade 2/6 systolic tricuspid regurgitation murmur, BP 120/70 mmHg, distended jugular veins, increased muscle tone and minor motor deficit of the upper left limb, exaggerated muscle stretch reflexes and plantar extension on left side.

Blood analysis showed: increased white blood cell count (WBC) and elevated inflammation markers [erythrocyte sedimentation rate (ESR) 33 mm/1 h, fibrinogen 450 mg/dL], optimal value of low-density lipoprotein (LDL)-cholesterol, a slightly decreased high-density lipoprotein (HDL)-cholesterol value (39 mg/dL), increased N-terminal of pro-brain natriuretic peptide (NT-proBNP) 2000 pg/mL, normal D-dimer <0.5 μg/mL and troponin T (TnT) <0.02 ng/mL.

On electrocardiogram (EKG) were noticed sinus rhythm, right atrium (RA) enlargement, decreased QRS voltage in limb leads, nonspecific negative T waves in inferior leads.

On chest X-ray, heart size was increased and dilatation of RA, LA appendage and pulmonary artery trunk were noticed, suggesting a mitral stenosis (Figure 1).

Transthoracic echocardiography (TTE) revealed a left ventricle (LV) with normal volumes and normal global systolic function, ejection fraction (EF) 60%, LA dilatation (volume 34 mL/m^2), an oval mobile echogenic mass of 5.7/3.7 cm with villous aspect was present inside LA, the mass was inserted in the middle part of the interatrial septum – the *fossa ovalis* region – and it protruded through the mitral valve in diastole, causing severe functional mitral stenosis (maximum/medium transvalvular gradients were 16/11 mmHg) and mild mitral regurgitation. The aspect suggested atrial myxoma (Figures 2–4). Right heart chambers were dilated, with moderate functional tricuspid regurgitation and an increased pulmonary artery pressure of 69 mmHg. Carotid and vertebral Doppler sonography did not show atherosclerotic plaques or stenosis.

The patient had an increased risk of embolic and hemodynamic complications. She was urgently transferred to a Cardiac Surgery Center, where atrial tumor was removed with repair of interatrial septum and De Vega tricuspid annuloplasty. Coronary arteriography performed before surgery showed normal epicardial coronary arteries.

Evolution was favorable, with decrease of pulmonary artery pressure to 30–35 mmHg, normalization of right heart chambers dimensions and normal mitral and tricuspid valve function at 30 days postoperatively.

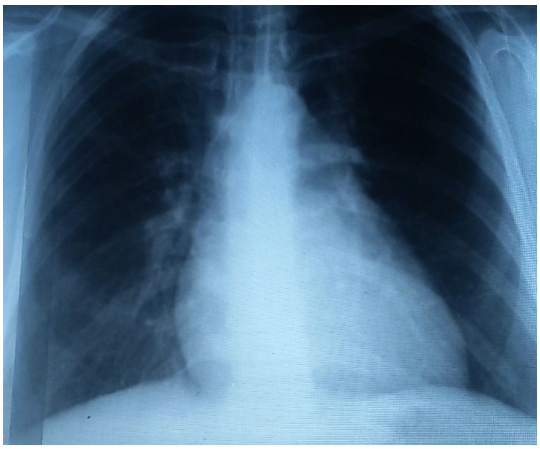

Figure 1 – ***Chest X ray showing dilatation of right atrium, left atrium and pulmonary artery.***

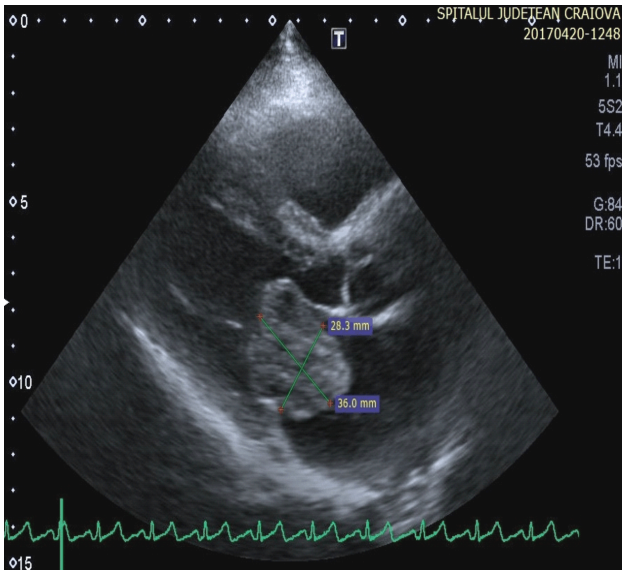

Figure 2 – ***Transthoracic echocardiography (TTE), parasternal long axis view: large atrial tumor (myxoma) passing through the mitral valve in diastole.***

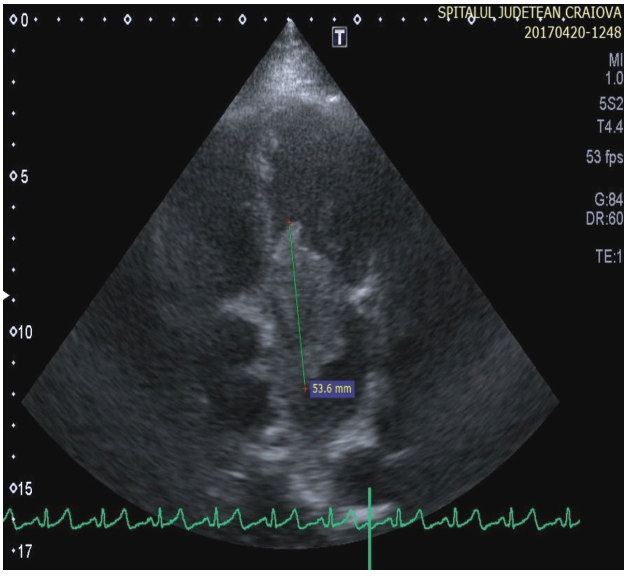

Figure 3 – ***Transthoracic echocardiography (TTE), apical four-chamber view: large atrial myxoma located in the left atrium and inserted on the interatrial septum.***

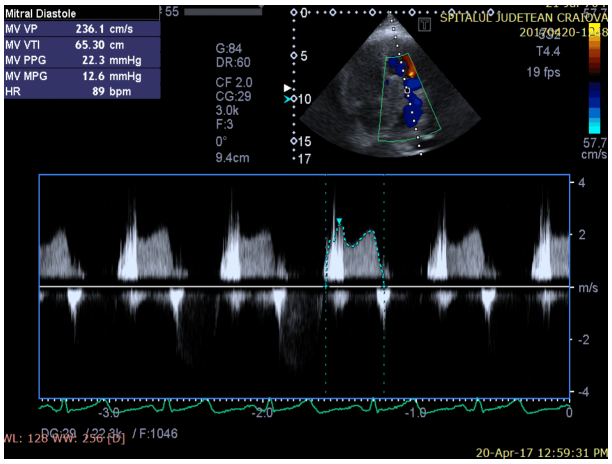

Figure 4 – ***Transthoracic echocardiography (TTE) which highlights high diastolic gradients across mitral valve (severe functional mitral stenosis) on continuous-wave Doppler (CWD).***

In order to establish the positive and differential diagnosis, the surgical resection fragment was sent to the Research Center for Microscopic Morphology and Immunology of the University of Medicine and Pharmacy of Craiova, Romania, where it was fixed in 10% formalin solution and subsequently included in paraffin, according to the usual histopathological techniques. Subsequent 4-µm thick sections were made using a HM350 rotary microtome (Thermo Fischer Scientific, Waltham, MA, USA) equipped with a water-based transfer system (STS, microM), after that they were stained with Hematoxylin–Eosin (HE) and Goldner–Szekely (GS) trichrome. For the immunohistochemical (IHC) study, the following antibodies were used: anti-CD68 (mouse monoclonal antibody, clone KP1, 1:100 dilution, Dako) for highlighting tissue macrophages; anti-CD79a (mouse monoclonal antibody, clone JCB117, 1:50 dilution, Dako) for highlighting B-lymphocytes; anti-S100 (rabbit polyclonal antibody, 1:1000 dilution, Dako) to support the hypothesis that stromal cells originate in mesenchymal cells capable of neuronal differentiation.

On microscopic examination, in HE and GS trichrome staining, various morphological aspects of stromal cells have been identified (*e.g.*, round, stellate, spindle or polygonal), which had aspect of mesenchymal cells or fibroblasts (Figure 5). The cytoplasm of stromal cells was abundant, eosinophilic, and the nuclei were normochromic and increased in size with very rare mitoses. As we said before, the stromal cells were either singular or disposed in islands or elongated cordons, embedded in a slightly eosinophilic and edematous stroma, rich in fundamental substance (Figure 6).

In the tumor stroma, a heterogeneous aspect of the collagen fibers was identified and its features generally warranted for its myxoid appearance, with no glandular appearance (Figure 7). Rarely, in the structure of the cardiac myxoma, areas of hemorrhage were identified (Figure 8). Also, in tumor stroma, areas with strong inflammatory infiltrates, including B-lymphocytes or hemosiderin-laden macrophages (Figures 9–11), have been identified. The positivity for S100 protein of some cells in the tumor stroma suggested that stromal cells originate in mesenchymal cells capable of neuronal differentiation (Figure 12).

Discussions

The case illustrates the polymorphic manifestations of cardiac myxoma and the importance of performing a meticulous cardiac exam in young patients with stroke in search of an embolic source, even if some traditional cardiovascular risk factors are found (like arterial hypertension in this case). Ischemic stroke in young patients is due to cardioembolism (in 15–35% of cases), to atherosclerosis in lesser proportion (15–25%) and up to 35% of cases have undetermined etiology (cryptogenic stroke) [7].

Myxoma originates from multipotent mesenchymal cells usually found in the interatrial septum, in the *fossa ovalis* region and the tumor is located in LA in most cases [1, 2].

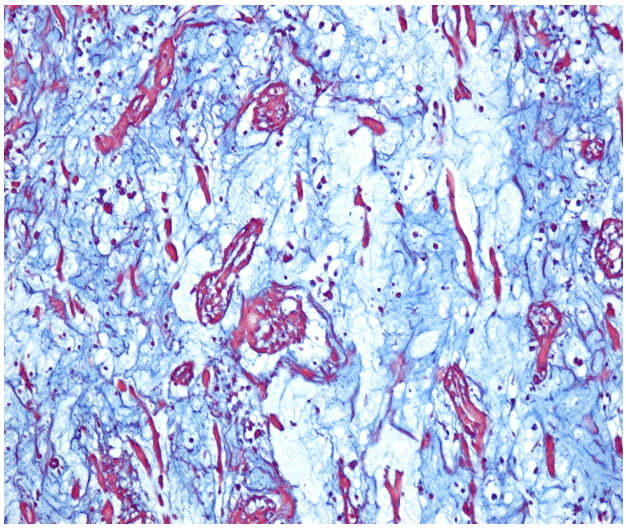

Figure 5 – ***Cardiac myxoma with lepidic, fusiform or stellate cells, arranged isolated or disposed in islands and elongated cordons, in a background myxoid matrix (GS trichrome staining, ×200).***

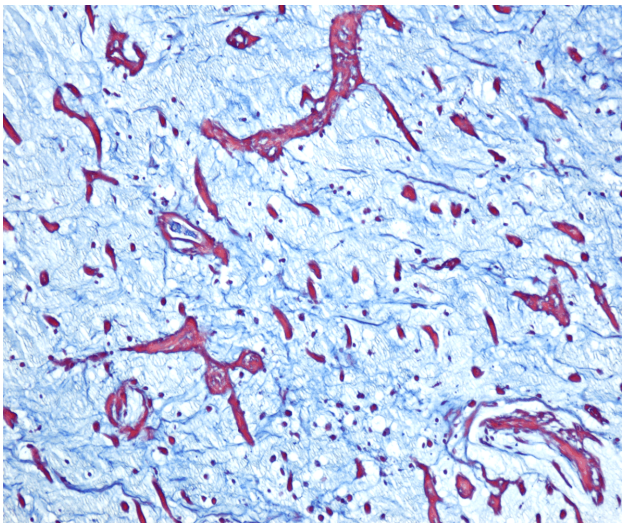

Figure 6 – ***Cardiac myxoma with singular cells or disposed in islands or elongated cordons, embedded in a slightly eosinophilic and edematous stroma, rich in fundamental substance (GS trichrome staining, ×200).***

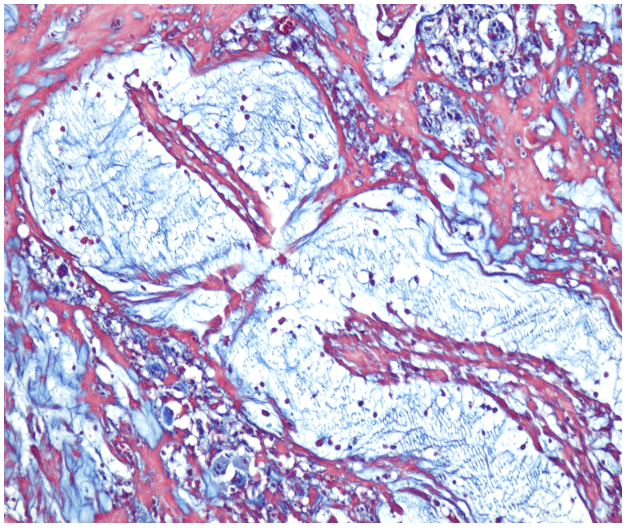

Figure 7 – ***Cardiac tissue destructured by myxoma cells with various morphology in a copious metachromatic myxoid stroma (GS trichrome staining, ×200).***

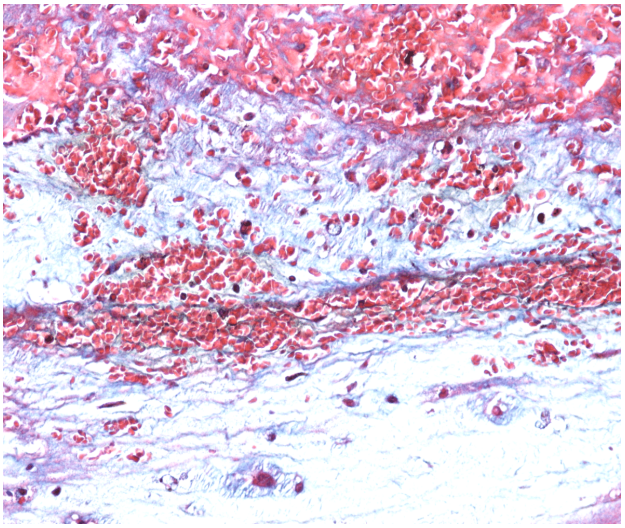

Figure 8 – ***Example of image from cardiac myxoma showing a hemorrhagic focus, with partial red cell hemolysis (GS trichrome staining, ×200).***

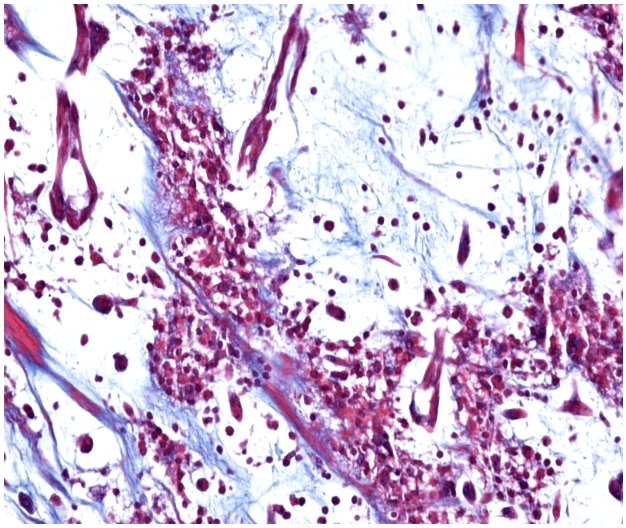

Figure 9 – ***Example of image from cardiac myxoma showing the tumor stroma infiltration with lymphocyte cells (GS trichrome staining, ×400).***

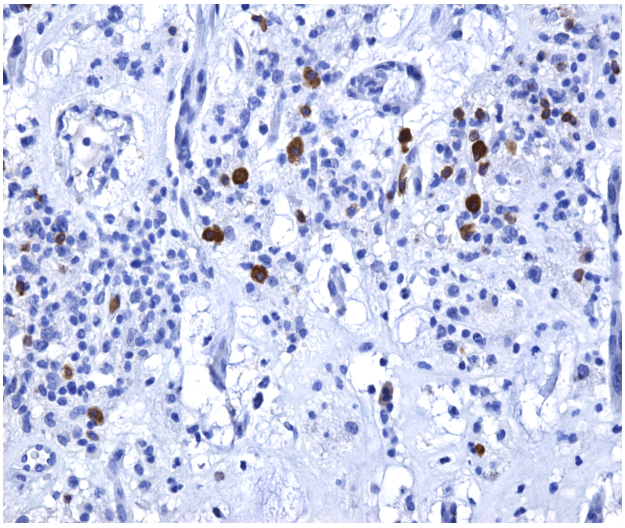

Figure 10 – ***Tumor stroma isolated infiltrated with B-lymphocyte cells (Anti-CD79a antibody immunomarking, ×200).***

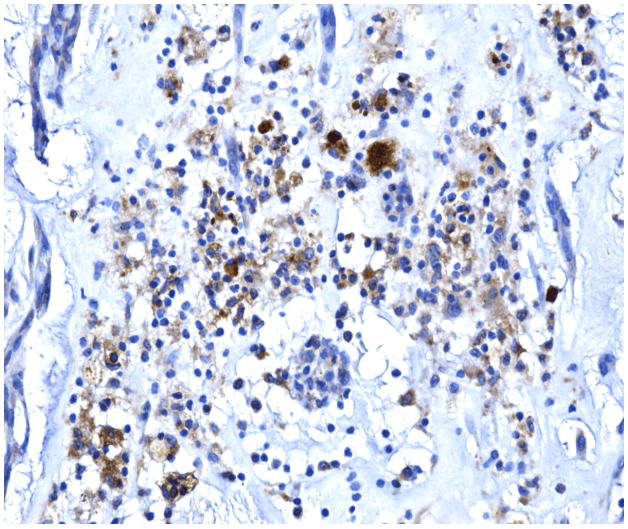

Figure 11 – ***Immunohistochemical staining for CD68 in cardiac myxoma. Rarely, the hemosiderin-laden macrophages are highlighted (Anti-CD68 antibody immunomarking, ×200).***

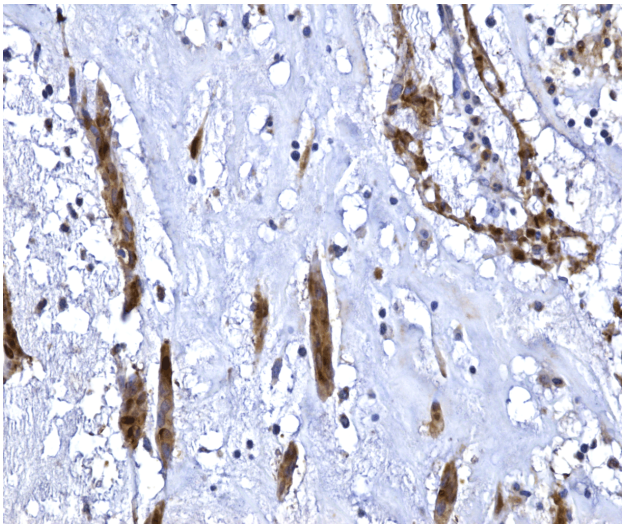

Figure 12 – ***S100 positive stromal cells, isolated and arranged in cordons (Anti-S100 antibody immunomarking, ×200).***

The macroscopic aspect of myxoma varies from an oval mass, smooth or gently lobulated (compact type with a smaller embolic potential) to a mass with villous surface and highly mobile finger like extensions (papillary type very prone to fragmentation and embolism) [1]. It has a gelatinous texture, the color ranges from white, yellow to grey, brown, with hemorrhagic spots and thrombus attached [1]. The tumor can be sessile or pedunculated with a distinct stalk. The histology reveals typical cells with stellate, elongated or polyhedral shape (called lepidic due to resemblance with butterfly wing) placed in an abundant myxoid stroma rich in glycosaminoglycans [2]. These cells have scant pink cytoplasm and an ovoid nucleus [2]. They are isolated or displaced in parallel clusters or multilayered circular structures around thin wall vessels (vasiforme rings). Stroma contains chondroitin 6-sulfate, chondroitin 4-sulfate and hyaluronic acid, elastin, and collagen fibers [8]. Blood proteins like fibrinogen, fibronectin, complement and globulins of plasma origin are bound to the myxoid stroma [8]. An increased amount of matrix metalloproteinases is found in villous tumors and is related to their embolic potential [1]. The myxoma also harbors inflammatory cells – lymphocytes, plasma cells, macrophages – and other cells: erythrocytes, mast cells, fibroblasts, smooth muscle cells, glandular structures, foci of extramedullary hematopoiesis, chondrocytes, osteoblasts [1, 5]. IHC studies in search of tumor's origin revealed variable phenotype of myxoma cells, which can express antigens belonging to several cell lineages, such as endothelial, epithelial, myogenic, myofibroblast and neuroendocrine cells [2]. Myxoma cell expresses transcription factors specific for primitive cardiomyocytes like NKx2.5/CSx and HAND [1, 9], markers of embryonic endothelial to mesenchymal transformation (EMT) [1, 10], mesenchymal markers like vimentin, alpha-smooth muscle actin (α-SMA – primitive myocyte marker expressed during fetal period) and alpha-cardiac actin (α-CA – mostly expressed in adult myocardium and rarely in myxoma) [1, 11]. The rare expression of both CD34–α-SMA (a primitive endothelial marker and a myocyte antigen) can be found in these primitive cells [2]. Endothelial markers [Factor VIII/von Willebrand factor (FVIII/vWF), CD34, *Ulex europaeus* agglutinin (UEA-1)] are expressed in the endothelial layer of vascular like aggregates and in isolated lepidic cells [1, 12]. Neuroendocrine markers like protein gene product 9.5 (PP9.5), S100, neuron-specific enolase (NSE), synaptophysin (SYP), calreticulin/calbindin 2 protein (CALB2) are found in some myxomas [1, 13]. Also, in our study the positivity for S100 protein of some cells in the tumor stroma suggested that stromal cells originate in mesenchymal cells capable of neuronal differentiation as shown in other studies [14–16].

Inflammation is an important actor in myxoma's existence, as showed in different studies [17]. Lepidic cells release cytokines, as interleukin (IL)-6, which attract inflammatory cells, trigger a systemic inflammatory response and also stimulate angiogenesis and tumor growth [1]. IL-6 is also produced by monocytes and lymphocytes infiltrating the myxoma [1]. IL-6 value correlates with initial tumor size, with markers of inflammation, clinical manifestations and can predict tumor recurrence [17–19].

Inflammatory cells (granulocytes, lymphocytes, macrophages) are present in myxoma and have different roles from triggering immune response, induction and resolution of inflammation to stimulation of angiogenesis and tumor growth [20–22]. In Di Vito *et al.* study on innate immunity in cardiac myxoma, different subtypes of macrophages were found: M0 (steady-state polarized macrophage, CD68+), M1 [classically activated with inflammatory functions, CD68+/inducible nitric oxide synthase (iNOS)+], M2 (alternatively activated with anti-inflammatory role, CD68+/CD163+) [20]. M0 cells are most often found, while M2 are abundant in hemorrhagic spots. M0 cells express different chemokines and angiogenic molecules [basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), thymidine phosphorylase (TP), IL-8) [20, 21].

In Zhang *et al.* study, smaller myxomas had higher concentrations of chemokines produced by macrophages and a higher microvessel density (MVD) than larger myxomas [21].

Increased expression of VEGF correlates with higher MVD and smaller tumor size. Smaller tumors have a denser microvessel network in the center part, while larger tumors have more vessels in the periphery [23]. There is a direct correlation between cell proliferation [expressed as proliferating cell nuclear antigen (PCNA) index] and VEGF activity and an inverse correlation between PCNA index and tumor size [24].

Most myxomas receive blood from branches of the right coronary artery and there are reports of a dual blood supply from right coronary and circumflex artery [2].

Chromosomal abnormalities have been described in cardiac myxoma involving chromosomes 2, 12, 17 [1, 2]. In Carney syndrome, there are two major loci where susceptibility genes are found – Carney complex (CNC) 1, located at 17q22-24 and CNC 2, at chromosome 2p16 [2]. For CNC 1, the implicated gene is *PRKAR1A* that encodes the R1α regulatory subunit of cyclic adenosine monophosphate (cAMP)-dependent protein kinase A acting on G-protein receptor signaling pathway [1, 2, 25]. There are 80 different mutations of this protein kinase, mutations that enhance enzyme's activity but the exact mechanism leading to tumor formation is not clear [2]. These mutations are found in the majority of familial cases and only rarely in sporadic cases [1]. Another gene implicated in familial myxoma is located at 17p12-31 and encodes myosin heavy chain 8 (*MYH8*). CNC 2 encodes a gene whose mechanism of action is not clearly established [1]. In sporadic cases, there are clonal and non-clonal structural alterations in chromosomal regions 12p1, 17p1, but no single gene mutations have been incriminated [2].

At diagnosis, small tumors are asymptomatic. Larger and mobile ones located in LA can partially block the mitral valve orifice in diastole, creating a functional mitral stenosis [2]. Most common symptoms are dyspnea, acute pulmonary edema, syncope; these symptoms can change with position [26]. Sudden death can occur [26]. Other symptoms can be due to embolism of tumor fragments and/or superimposed thrombus in different territories with predilection for cerebral and retinal arteries, but coronary arteries, splanhnic circulation or lower limbs can be occluded [2]. Embolic events are found in 39–45% of

patients [27, 28]. Major risk factors for embolism in myxoma are irregular surface, atypical location, while tumor size is not an independent risk factor [26]. Increased mitotic activity correlates with embolic risk [29].

Systemic manifestations like fever, weight loss, myalgias, arthralgias, Raynaud phenomenon, erythematous rash can be present and are caused by IL-6 release [2]. On physical examination in LA myxoma first heart sound (S1) becomes more intense and mitral regurgitation murmur can be heard, together with a diastolic sound called tumor plop and mitral diastolic rumble [2, 30]. Blood analysis can reveal elevated inflammation markers, leukocytosis, thrombocytosis, thrombocytopenia, anemia – sometimes with a hemolytic pattern, hyper-gammaglobulinemia, the presence of antinuclear and anti-phospholipid auto-antibodies [1, 2]. TTE is necessary for diagnosis and gives information about tumor location, dimension, hemodynamic impact [8]. Transesophageal exam and cardiac magnetic resonance imaging (MRI) are useful in cases with atypical location and the presence of multiple tumors [2].

Therapy consists of surgical excision of the tumor together with all *fossa ovalis* and in cases with atypical location a rim of 5 mm of endocardial surrounding the implant site [30–37]. Prognosis is very good after surgery, the survival being 98% and 89% at five years and at 15 years, respectively [31].

Conclusions

Cardiac myxoma is a tumor that can present with different clinical features and often-positive diagnosis can be difficult. Medical imaging investigations, especially echocardiography, allow the identification, localization and impact of the cardiac tumor, but the positive and differential diagnosis is done with the help of the histopathological confirmation exam. The standard therapy is represented by surgical resection and postoperative prognosis is good, with the resumption of structural and functional status of the heart.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Edme Roxana Mustafa and Ileana Puiu equally contributed to the manuscript.

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Corresponding author
Diana Rodica Tudoraşcu, Lecturer, MD, PhD, Department of Internal Medicine, University of Medicine and Pharmacy of Craiova, 2 Petru Rareş Street, 200349 Craiova, Dolj County, Romania; Phone +40763–399 277, e-mail: petridiana@yahoo.com

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