CASE REPORT

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CARDIAC HAMARTOMAS: REPORT OF TWO RARE PRIMARY CARDIAC TUMORS (RHABDOMYOMA AND HAMARTOMA OF MATURE CARDIOMYOCYTES) WITH REVIEW OF THE LITERATURE

D. Metodiev[1,2], A. Gegova[3], M. Ruseva[4], R. Ganeva[4], D. Parvanov[4], R. Marinov[5,6], D. Georgiev[7], D. Staneva-Mitkova[8], G. Stamenov[8]

[1]Department of Clinical Pathology, Nadezhda Women's Health Hospital – Sofia, Bulgaria
[2]Neuropathological Laboratory, University Hospital "Sv. Ivan Rilski" – Sofia, Bulgaria
[3]Department of Anatomy and Histology, Pathology and Forensic Medicine, University "Sv. Kliment Ohridski" – Sofia, Bulgaria
[4]Department of Research, Nadezhda Women's Health Hospital – Sofia, Bulgaria
[5]Department of Cardiology, Nadezhda Women's Health Hospital – Sofia, Bulgaria
[6]Department of Pediatric Cardiology, National Cardiology Hospital – Sofia, Bulgaria
[7]Department of Prenatal Diagnostics, Nadezhda Women's Health Hospital – Sofia, Bulgaria
[8]Department of Obstetrics & Gynaecology, Nadezhda Women's Health Hospital – Sofia, Bulgaria

Abstract. *The most common primary cardiac tumors are myxomas, while cardiac hamartomas are rare. Cardiac hamartomas may constitute manifestation of a genetic disorder such as tuberous sclerosis, or could be diagnosed independently as a solitary lesion. We present two rare cases of primary cardiac tumors detected via diagnostic imaging and subsequent histopathology examination. The first described case is that of a male preterm foetus with multiple rhabdomyomas in the heart, discovered during foetal echocardiography. The finding was later confirmed by autopsy, which also revealed presence of cortical tubers with typical balloon cells constituting well known epileptogenic lesions in the foetal brain. The second case describes an even rarer benign cardiac lesion – a hamartoma of mature cardiomyocytes – which was discovered by chance in a 49-year old female patient during echocardiography. The performed CT scan revealed a 37 x 16 x 12 mm tumor in the right atrium obstructing the superior vena cava inlet. The malformation was surgically removed and examined histologically revealing disorganized hypertrophic mature cardiomyocytes, partly separated by fibrous strands and admixed with mature adipocytes. Differential diagnosis was performed to rule out other benign tumors with myocyte differentiation – cardiac rhabdomyoma, histiocytoid cardiomyopathy and adult cellular rhabdomyoma.* ***Conclusion:*** *The diagnosis of cardiac hamartomas was possible only after pathomorphological examination of material from the tumors. Reporting of rare neoplasms is crucial in order to determine their prevalence and to inform clinical practice.*

Key words: *tuberous sclerosis, rhabdomyoma, hamartoma of mature cardiomyocytes, histiocytoid cardiomyopathy*

Corresponding author: *Dimitar Metodiev, MD, Nadezhda Women's Health Hospital, 3, Blaga vest Street, Bg – 1373 Sofia, e-mail: dimitarmetodievvv@gmail.com*

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INTRODUCTION

Primary cardiac tumors are rare and predominantly benign [1]. Clinical manifestation includes dyspnea, chest pain, heart palpitations, embolisms, cyanosis and others. They are sometimes discovered accidentally through diagnostic imaging, or post-mortem during autopsy examination [2]. The most common primary cardiac tumors are myxomas, constituting 70-80% of all cardiac tumors [3, 4]. Cardiac hamartomas are significantly less frequent [4]. These are primarily hamartomatous formations of the impulse conduction system of the heart (including Purkinje fibers), diagnosed as histiocytoid cardiomyopathy or rhabdomyomas – especially in the context of tuberous sclerosis [5]. Hamartoma arising from mature cardiac myocytes is extremely rare. It was first described by Tanimura et al. [6] in 1988 and to date, only 25 cases have been reported in the literature [7]. It is histologically characterised by the presence of disordered hypertrophic cardiac myocytes admixed with fibrous and adipose tissue.

CASE PRESENTATION

Case 1

A 25-year-old patient with spontaneous first pregnancy was admitted to our hospital for termination of pregnancy at 30 weeks gestation after diagnostic imaging revealed hyperechoic lesions in the fetal heart. These lesions had increased in size in comparison to previous echocardiography scans. In addition, the scan revealed multiple hyperechoic lesions in the fetal cortex with ventriculomegaly (inferior horns of lateral ventricle were 12 mm in diameter) and diminished signal from the cavum septum pellucidum structure. Pathomorphological examination of the fetus and the placental membranes revealed the fetus was male, 42 cm in length and weighed 1800 g. The placenta was 17 x 13 x 3.5 cm in size with paramarginally attached umbilical cord of length 19 cm and with 3 visible vessels. The placental membranes were grey, elastic and tensile.

Necropsy examination of the internal fetal organs revealed presence of multiple intramural unencapsulated greyish nodular masses, that ranged in size from 1 mm to 1 cm.

These were prominent in the cardiac cavities (Fig. 1A) and were composed of enlarged vacuolated cells with clear cytoplasm due to abundant glycogen deposits. An important feature was their so-called spider cell appearance. These cells were positive for the immunohistochemistry (IHC) marker desmin (Fig. 2). The proliferative index was notably low, close to 0%. The necroscopy examination of the lung revealed presence of 4 lobes (Fig. 1B).

Histologic assessment of the brain revealed cortical dyslamination with numerous cortical tubers composed of cells with abundant eosinophilic cytoplasm and large vesicular nuclei (Fig. 3). The described structural characteristics are indicative of balloon cells, typically found in cases of focal cortical dysplasia type IIb in pharmacoresistant focal epilepsy patients.

All remaining organs exhibited histologic features of immaturity as well as autolysis signs.

The observed pathomorphological features of the fetal myocardium and brain were indicative of cardiac rhabdomyomas and cortical tubers which are characteristic of tuberous sclerosis.

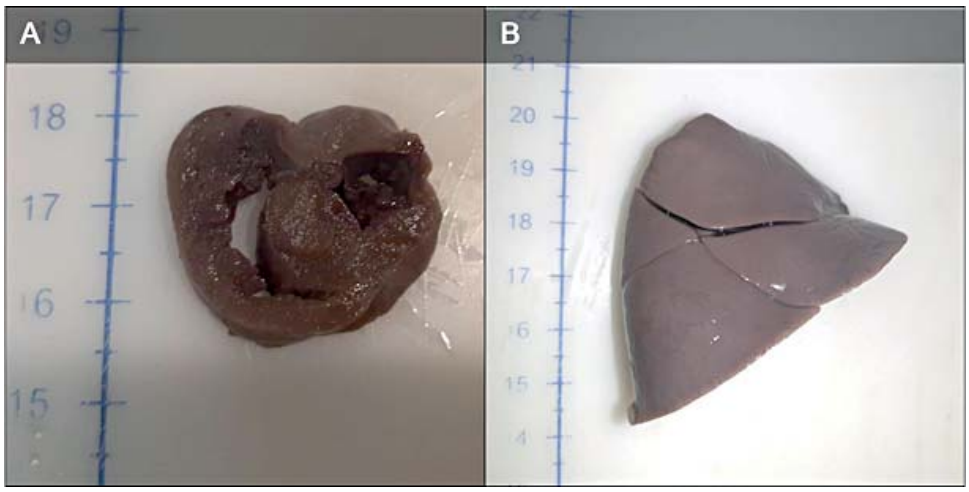

Fig. 1. Macroscopic images of fetal organs with reference scale in cm. **A**: heart – transverse section through left and right ventricle and interventricular septum, demonstrating thickening of the free cardiac walls; **B**: outer surface of the right lung showing abnormal morphology – 4 lobes

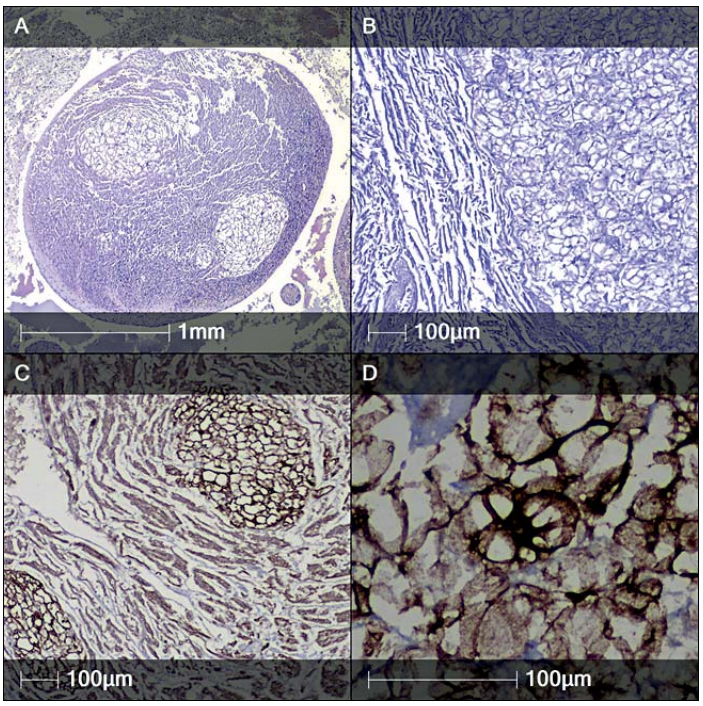

Fig. 2. Fetal cardiac tissue sections stained with hematoxylin-eosin (H&E) and desmin (IHC). **A**: Prominent nodules of cardiac hamartomatous rhabdomyoma formation (H&E); **B**: Rhabdomyoma (right) located in the interventricular septum, in contrast to typical myocardium tissue (left) (H&E); **C**: Desmin staining revealing the nodular character of hamartomatous rhabdomyoma formation (IHC); **D**: Magnified rhabdomyoma nodule with prominent spider-like cell in the middle stained with desmin (IHC)

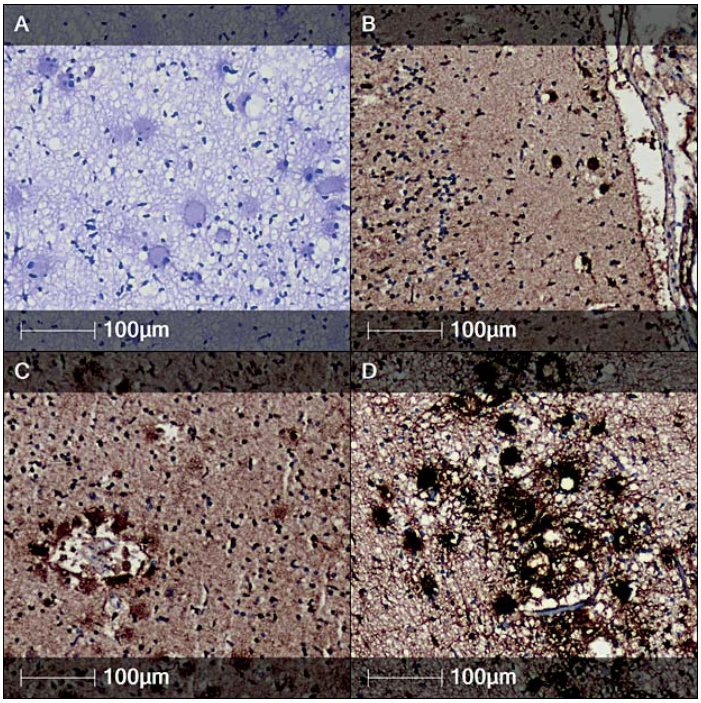

Fig. 3. Fetal brain tissue sections stained with hematoxylin-eosin (H&E) and S100 protein (IHC). **A**: Cortical tuber with typical balloon cells (H&E); **B**: Balloon cells underneath pia matter, positive for S100 protein (IHC); **C**: Perivascular balloon cells, positive for S100 protein (IHC); **D**: Cluster of S100 protein positive balloon cells with abnormal cell protrusions (IHC)

Case 2

A 49-year-old patient with chronic renal failure following glomerulonephritis, undergoing chronic dialysis, was urgently admitted to the hospital after echocardiography revealed a formation in the right atrium. The patient was in an overall satisfactory clinical condition, with normosthenic body habitus, pale skin and visible mucous membranes. Diminished "vesicular" breath sounds, without any wheezes (*rhonci*), unenlarged cardiac silhouette, rhythmic cardiac activity (70 beats per minute), clear cardiac sounds without any murmurs and arterial blood pressure within the reference values range were registered.

Paraclinical tests revealed elevated erythrocyte sedimentation rate (ESR) (73 mm/h), increased serum levels of urea (29.1 mmol/L), elevated creatinine (747 µmol/L) and decreased haemoglobin (8.71 g/dL).

The performed electrocardiographic examination revealed a sinus rhythm of the left position type.

The following echocardiographic examination visualized an immobile formation (37 x 16 x 12 mm) located

within the right atrium, the interatrial septum and the atrial wall. The upper vena cava was affected at the point of its entry in the right atrium. The tricuspid, aortic and mitral valves were intact.

Computer tomography scan confirmed the presence of a formation in the upper half of the right atrium towards the dorsal wall and the septum, obliterating the superior vena cava inlet. Marked venous congestion of v. azygos, v. mammaria, and vv. brachiocephalicae was observed. No thromboembolisms were found in the pulmonary trunk, the two pulmonary arteries, nor in their subsegmental branches.

Due to the intensifying symptoms related to the subtotal superior vena cava obstruction, the patient was subjected to surgical treatment using extracorporeal blood circulation. The part of the tumor formation that engaged the interatrial septum was deemed inoperable. The entry of the upper vena cava was freed by securing a good blood flow. A plastic surgery of the right atrium was performed.

Macroscopically, the removed mass (50 x 37 x 30 mm) had brownish color and fibrillar cut surface resembling muscle tissue.

Pathomorphological assessment revealed abnormal histological elements – primarily scattered hypertrophic muscle fibers containing myocytes with karyomegaly and irregular nuclear contour as well as weakly vacuolated cytoplasm. The cardiac myocytes were partly separated by fibrous strands. Small clusters of adipocytes were also observed. Single large cardiomyocytes with spider-like appearance were found. Sporadic disseminated micronecrosis and haemorrhages were also detected (Fig. 4).

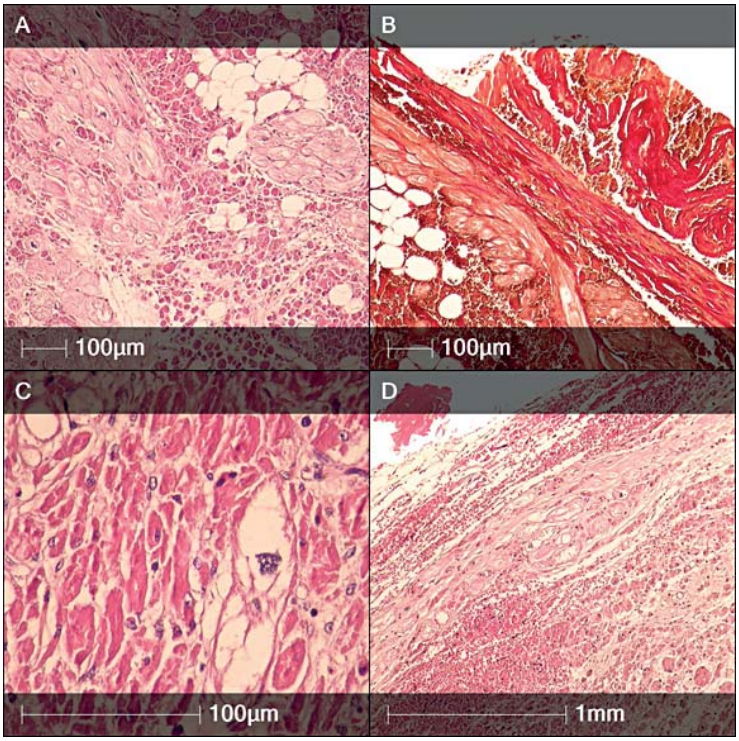

Fig. 4. Post-mortem cardiac sections stained with hematoxylin-eosin (H&E) and elastica van Gieson (EvG). **A**: Cardiomyocytes separated by fibrous strands and adipocytes (white circles) (H&E); **B**: Cardiomyocytes separated by fibrous strands (dark red) and adipocytes (white circles) (EvG); **C**: Gigantic cardiomyocyte with spider-like morphology (H&E); **D**: Cardiac tissue with disseminated micronecrosis and haemorrhages (H&E)

The final diagnosis was hamartoma of mature cardiomyocytes. Despite the uneventful postoperative period, the patient ultimately suffered tachyarrhythmia attacks, which have led to fatal outcome a month after the surgical intervention with a clinical picture of electro-mechanical dissociation.

DISCUSSION

Most cardiac chamber formations are thrombotic masses and vegetations of the valves in endocarditis patients [1, 8]. Although metastases are more common than primary lesions, they are rarely subjected to histologic verification. Cardiac metastases are found in 7-9% of autopsies of patients with malignant tumors [9, 10]. The first case of primary cardiac tumor was described by Bodenheimer in 1865 as an autopsy finding [11]. The prevalence of cardiac tumors amongst the Bulgarian population remains unknown mostly due to the relatively few autopsies performed. Relatives often refuse to give consent for post-mortem investigation which does not facilitate the process of reaching the final diagnosis. This issue is also recognized in other countries leading to a certain degree of variability in the reported frequency of cardiac tumors – from 1:200 to 1:500 [12, 13]. Around 90% of primary cardiac tumors are benign both in the pediatric patient subgroup and in adult patients [12, 14]. Primary cardiac tumors can be classified in three clinico-morphological types: benign congenital tumors, benign acquired tumors and malignant tumors [15]. The first type is usually seen in infancy and early childhood and its prevalence shows a tendency to increase [14]. This can be explained with the improvement of fetal echocardiography methods. Among benign congenital tumors the most common type is rhabdomyoma, while fibromas, teratomas and congenital haemangiomas are becoming increasingly rare [15, 16]. The least common (around 10% of cases) are primary malignant cardiac neoplasms, which are predominantly of mesenchymal origin –

such as angiosarcoma, undifferentiated pleiomorphic sarcoma, leiomyosarcoma, rhabdomyosarcoma and others. Malignant teratomas have been described in the pediatric patient group [17].

The clinical presentation of tumors depends mostly on their size and localization. Tumors located in the right atrium or right ventricle may lead to right heart failure with abnormal pulmonary venous return, later presenting with peripheral oedema, hepatomegaly, ascites, syncope and sometimes sudden death [18]. Tumors affecting the valves may bring about cardiac insufficiency and/or stenosis [19]. The combination of mature cardiomyocytes, some of which gigantic in appearance, separated by fibrous threads and adipocytes is pathognomonic for hamartoma. In the context of the second reported case, differential diagnosis of hamartoma with other benign tumors (cardiac rhabdomyoma, histiocytoid cardiomyopathy and adult cellular rhabdomyoma) with myocyte differentiation was necessary.

Cardiac rhabdomyomas can be solitary or multiple. They are usually associated with tuberous sclerosis and are typically found in the heart chambers. Tuberous sclerosis is an autosomal dominant disorder characterised by development of hamartomas in various organs. It is caused by mutations in tumor suppressor genes TSC1 and TSC2 which lead to loss of expression of the proteins hamartin and tuberin, respectively, which play a role in the mTOR signaling pathway [20]. Multiple rhabdomyomas, as observed in the first presented case, are found exclusively in tuberous sclerosis patients. Macroscopically, rhabdomyomas are well defined non-encapsulated greyish nodular lesions of varying size. Solitary rhabdomyoma is found in only 10% of cases [20]. Histologically, the tumor is composed of large cells with abundant clear vacuolated cytoplasm rich in glycogen. The presence of so-called spider-like cells is a typical hallmark of cardiac rhabdomyoma. Spider cells are characterised by cytoplasmic radial protrusions with contractile myofilament from the central nucleus to the cell periphery. They express immunohistochemical markers for striated muscle tissue (myoglobulin, desmin, actin and vimentin). The spider-like cells were markedly more abundant in the tissues of our case 1 compared to case 2. Partial or complete spontaneous regression of cardiac rhabdomyomas is possible, including in the context of tuberous sclerosis [21].

Histiocytoid cardiomyopathy is a rare finding characterised by a tendency for arrhythmias due to hamartomatous proliferation of structures of the impulse generating and conducting system of the heart – the sinoatrial node, atrioventricular node and Purkinje network [22]. It is diagnosed primarily in the first two years of life. There are no reports of patients diagnosed with such lesion after the age of 25 [5]. Pathomorphological examination of histiocytoid cardiomyopathy demonstrates multifocal poorly demarcated nodular lesions of proliferating polygonal cells with granular eosinophilic cytoplasm, round nuclei, some of which exhibiting prominent nucleoli [20]. The described cells are found in both ventricles, the septum, and rarely in the valve apparatus of the heart [22]. The sinoatrial and atrioventricular nodes are involved in about 28% of cases, however, it should be noted that these structures are not routinely dissected. Hamartomas are characterised by overgrowth of mature differentiated cells in an organ, showing improper arrangement. Although their aetiology is unclear, their presence is associated with abnormal development of embryonic cell lineages [23]. In addition to the hamartoma of the impulse generating and conducting system of the heart, there is also a hamartoma originating from mature cardiomyocytes, as established in the second described case. Hamartomas have been described in 25 patients aged 6 months to 76 years old with a mean age of 24 years [7, 23]. Two thirds of those affected were male. Hamartoma of mature cardiac myocytes occurs in the form of a solitary or multiple tumors in both cardiac atria and ventricles [24]. Those in the atria can cause the development of supraventricular arrhythmias and Wolf-Parkinson-White syndrome, while tumors located in the ventricles cause sudden death. Macroscopically, they are moderately dense, poorly demarcated masses, ranging in size from 0.2 cm to 5.0 cm in their largest diameter [7]. The cut surface is similar to that of the heart muscle. Histologically, hamartomas are composed of disorganised bundles of hypertrophic cardiomyocytes with karyomegaly and irregular nuclear contours. The interstitium shows an increased amount of collagen, dilated venules and a slight thickening of the walls of the intramural arteries. Scattered small groups of adipocytes are also found [25].

Only a few cases of cardiac cellular rhabdomyomas in adults have been described in the literature [25, 26]. This type of neoplastic process is common in the head and neck region (extracardiac rhabdomyomas). Histologically, hypertrophic cardiomyocytes with a light fine-grained cytoplasm are observed and there are no adipocytes, contrary to the the tumor we observed in case 2.

The first case of hamartoma of mature cardiomyocytes was described in 1988 [27]. A crucial component of the diagnostic process of hamartoma is the presence of hypertrophic cardiomyocytes with histoarchitectural damages, mixed with fibrous and adipose tissue in different proportions. The typical mani-

festation of hamartoma of mature cardiomyocytes is the ventricular tachycardia in children and young people [2, 27, 28, 29, 30, 31], whereas our patient (case 2) was 49 years old. In cases with larger tumor sizes and arrhythmias or other complications, surgical treatment is required, which usually leads to permanent healing of the patient.

The presence of hamartomatous formations in childhood and their slow growth point to a possible congenital origin with subsequent hypertrophic changes during the first years of life. Such origin was observed in case 1. The less common slow growing hamartomas may be detected in older individuals, as in the second described case. There is an increased risk of arrhythmias and sudden cardiac death in cases where the impulse generating and conducting system of the heart is involved. In these patients, complete surgical resection of the lesion is impossible. Despite the smooth postoperative period and temporarily improved condition, our second case ended lethally with a clinical picture of electro-mechanical dissociation. Autopsy was not performed due to refusal from the patient's relatives.

CONCLUSION

Cardiac rhabdomyomas are diagnosed primarily in the paediatric group of patients in the context of tuberous sclerosis. Their presence and development can be detected early by intrauterine fetal echocardiography. In such cases, the diagnosis of tuberous sclerosis is confirmed by medical and genetic consultation. It should be noted that in addition to myocardial damage, which is detected in the described case 1, disseminated epileptogenic areas (cortical tubers with balloon cells) are present in the brain, as well as various hamartomatous formations in other organs (kidneys, lungs, eyes).

Hamartomatous formations of the heart are rarely observed. There are two main histological types of hamartoma – one of the structures of the impulse generating and conducting system of the heart (histiocytoid cardiomyopathy) and the less common one of mature cardiomyocytes. While the former occurs mainly in children, the hamartoma of mature cardiomyocytes can be diagnosed in adult patients. Because the cardiac impulse generating and conducting system may be affected, rhythm-conduction disorders are often observed, which can be fatal in these patients. Rarely, sudden cardiac death is their first manifestation. The second described case displays non-specific clinical symptoms. Instrumental examinations proved the presence of a tumor. However, they were unable to determine its type. The diagnosis of hamartoma of mature cardiomyocytes was made only after tumour biopsy.

We found it necessary to describe these rare cases because, despite the declining number of incidences, primary heart tumors do exist and are often associated with significant changes in other vital organs, such as cortical tubers in the brain in the context of tuberous sclerosis.

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REFERENCES

1. Ananiev J, Hadzhi M, Ivanova K. "The Rhythm of Cancer" – Unexpected Autopsy Finding in a Patient with Gastric Ulceration. Acta Medica Bulgarica, 2021;48(3), 38-40.
2. Martínez Quesada M, Trujillo Berraquero F, Almendro Delia M et al. Hamartoma intracardíaco. Caso clínico y revisión de la bibliografía [Cardiac hamartoma. Case report and literature review]. Rev Esp Cardiol. 2005;58(4):450-2.
3. Lamda J, Frishman WH. Cardiac and pericardial tumors. Cardiol Rev. 2012; 20:237-52.
4. Steger CM, Hager T, Ruttmann E. Primary Cardiac Tumours: A Single-Center 41-Year Experience. International Scholarly Research Notices, 2012, Article ID 906109, 7 pages, 2012.
5. Shehata BM, Patterson K, Thomas JE, et al. Histocytoid cardiomyopathy: three new cases and a review of the literature. Pediatr Dev Pathol. 1998; 1:56-69.
6. Tanimura A, Kato M, Morimatsu M. Cardiac hamartoma. A case report. Acta Pathol Jpn. 1988; 38:1481-4.
7. Fealey ME, Edwards WD, Miller DV et al. Hamartomas of mature cardiac myocytes: report of 7 new cases and review of literature. Hum Pathol. 2008 Jul;39(7):1064-71. doi: 10.1016/j.humpath.2007.11.014. Epub 2008 May 27.
8. Butany JW, Nair V, Naseemuddin A et al. Cardiac tumours: diagnosis and management. The Lancet. Oncology, 2005,6(4), 219-28.
9. Amano J, Nakayama J, Yoshimura Y, Ikeda U. Clinical classification of cardiovascular tumors and tumor-like lesions, and its incidences. Gen Thorac Cardiovasc Surg. 2013;61(8):435-47. Erratum in: Gen Thorac Cardiovasc Surg. 2013 Aug;61(8):448.
10. Bussani R, De-Giorgi F, Abbate A, et al. Cardiac metastases. J Clin Pathol. 2007; 60:27-34.
11. Goret CC, Karagoz A, Ozdemir ZT, et al. Histopathological evaluation of 13 cardiac mass biopsy specimens and correlation between clinical prediagnosis. International journal of advanced in case reports, 2015; 2(20):1237-1241.
12. Basso C, Valente M, Thiene G, eds. Cardiac Pathology. New York: Springer, 2013.
13. Patel J, Speppard MN. Pathological study of primary cardiac and pericardial tumours in a specialist UK Centre: surgical and autopsy series. Cardiovasc Pathol. 2010; 19:343-52.
14. Burke A, Virmani R. Pediatric heart tumors. Cardiovasc Pathol. 2008; 17:193-198.
15. Thomas-de-Montpreville V, Nottin R, Dulmet E, et al. Heart tumors in children and adults: clinicopathological study of 59 patients from a surgical center. Cardiovasc Pathol. 2007; 16:22-28.

16. Bielefield KJ, Moller JH. Cardiac tumors in infants and children: study of 120 operated patients. Pediatr Cardiol. 2013; 34:125-128.
17. Padalino M, Vida V, Boccuzzo G, et al. Surgery fir primary cardiac tumors in children: early and late results in a multicenter European Congenital Heart Surgeons Association study. Circulation. 2012; 126:22-30.
18. Grebenc ML, Rosado de Christenson ML, Burke AP, et al. Primary cardiac and pericardial neoplasms: radiologic-pathologic correlation. Radiographics. 2000; 20:1073-1103.
19. Shapiro LM. Cardiac tumors: diagnosis and management. Heart 85: 218-222.
20. Jozwiak J, Sahin M, Jozwiak S, et al. Cardiac rhabdomyoma in tuberous sclerosis: hyperactive Erk signaling. Int J Cardiol. 2009; 132:145-147.
21. Bossi G, Lintermans J, Pellegrino P, et al. The natural history of cardiac rhabdomyoma with and without tuberous sclerosis. Acta Paediatr. 1996; 85:928-931.
22. Shehata BM, Bouzuk M, Sclman SC, et al. Identification of candidate genes for histiocytoid cardiomyopathy (HC) using whole genome expression analysis: analyzing material from the HC registry. Pediatr Dev Pathol. 2011; 14: 370-377.
23. Rizzo S, Basso C, Buja G, et al. Multifocal Purkinje-like hamartoma and junctional ectopic tachycardia with a rapidly fatal outcome in a newborn. Heart Rhythm. 2014; 11:1264-6.
24. Chu PH, Yeh HI, Jung SM, et al. Irregular connexin 43 expressed in a rare cardiac hamartoma containing adipose tissue in the crista terminalis. Virchows Arch. 2004; 444:383-6.
25. Burke AP, Ribe JK, Baja AK et al. Hamartoma of mature cardiac myocytes. Hum Pathol, 1998; 29: 904-909.
26. Eberle MC, Boudousq V, Becassis P, et al. Cardiac rhabdomyoma in an adult: an aspect of Tc-99m sestamibi myocardial perfusion. J Nucl Cardiol. 2002; 9:131-2.
27. Tanimura A, Kato M, Morimatsu M. Cardiac hamartoma. A case report. Acta Pathol Jpn. 1988; 38:1481-4.
28. Wage R, Kafka H, Prasad S. Images in cardiovascular medicine. Cardiac rhabdomyoma in an adult with a previous presumptive diagnosis of diagnosis septal hypertrophy. Circulation. 2008; 117:e469-70.
29. Greenberg HM, Aretz HT. Case 31-1999: a 33-year-old man with wide complex tachycardia and left ventrical mass. N Engl J Med. 1999; 341:1217-24.
30. Minh HT, Dihn BA, Galvin JM. Left ventricular hamartoma associated with ventricular tachycardia. Ann Thorac Surg. 2001; 71:1673-5.
31. Garson A, Smith RT, Moak JP, et al. Incessant ventricular tachycardia in infants: myocardial hamartomas and surgical cure. J Am Coll Cardiol. 1987; 10:619-26.