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Letter to the Editor

Cardiac mesenchymal hamartoma associated with transposition of the great arteries in a neonate

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Dear Editor,

Primary cardiac tumor incidence in pediatric patients is estimated at 0.14-0.20%. Approximately 90% of primary cardiac tumors are benign (1). Hamartoma is a benign tumor-like lesion emerging from residual embryonic tissue of the originating organ, with disorganized growth of differentiated indigenous cells, localized most often near the valvular apparatus or in the ventricular wall (2). Previously described types of cardiac hamartomas include rhabdomyomas, fibroelastomas, hamartoma of the mature cardiac myocytes, vascular hamartoma, histiocytoid cardiomyopathy and, recently, cardiac mesenchymal hamartoma (3,4).

It has been reported that primary cardiac tumors may be associated with cardiac malformations, such as hypoplastic left heart syndrome, transposition of the great arteries (TGA), ventricular septal defect or Ebstein's anomaly (3,4). TGA is a complex cardiovascular malformation characterized by ventriculoarterial discordance, where the pulmonary trunk emerges from the left ventricle and the aorta emerges from the right ventricle. Thus, systemic and pulmonary circulations are not arranged in series but in parallel. TGA incidence is 5-7% of the total cardiac malformations and, without surgical treatment, mortality in the first year of life rises to 90% (5).

Lately, novel histological types of hamartomas have been recognized. In a recent study published in your journal, the authors described a rare case of breast angiomatous hamartoma (6). We report now a case of cardiac mesenchymal hamartoma in a TGA patient, which does not overlap entirely with microscopical and immunohistochemical findings of the previous one.

We present the case of a full-term female neonate, with gestational age of 40 weeks, born by cranial presentation in vaginal delivery. The patient's bodyweight and length were 3500 g and 52 cm, respectively. The patient was transferred to the Emergency Institute for Cardiovascular Diseases and Transplantation of Tîrgu Mureș, where TGA diagnosis was confirmed along with the additional diagnosis of restrictive ostium secundum type of atrial septal defect, patent ductus arteriosus, and an intermittent prolapsing hyperechogenic formation in the left ventricle outflow tract. At thirteen days postpartum, we performed the standard procedure for this condition - the arterial switch operation, in total cardio-pulmonary bypass at 26 degrees. At the level of the left ventricle outflow tract, a tumoral mass of 5x5 cm size of elastic consistency and yellow-red color was found and removed. In the twenty-sixth day, the patient's hemodynamic evolution was complicated by recurrent sustained ventricular tachycardia and sinus bradycardia that required cardiopulmonary resuscitation. In the absence of a cardiac defibrillator of suitable size, external cardiac pacing was considered feasible instead.

The intracardiac mass was submitted to anatomopathological examination. The histological evaluation was performed to establish whether it is a tumor or a non-tissue mass (e.g., thrombus) and revealed the diagnosis of a hamartoma. Microscopically, the cellular rich tissue with benign histology was composed of mature mesenchymal elongated cells which proliferate in a disorganized manner in a fibrous stroma (Fig. 1a). The assessment also revealed the presence of in-

terspersed adipocytes and an increased number of dilated vascular channels contained variable numbers of erythrocytes and were lined by a single layer of well-differentiated endothelial cells (Fig 1b).

Additionally, immunohistochemistry was performed using the characteristic panel to support the hamartoma diagnosis: absence of desmin and myogenin expression, CD31 and CD34 positive for endothelial cells lining the vascular spaces. Ki-67 proliferation index was less than 1%.

There are numerous types of cardiac hamartoma described, where each type presents an increased proportion of a specific structural component (3). Recently, a new form of cardiac hamartoma has been proposed, cardiac mesenchymal hamartoma (7). Compared to other forms, the latter does not have a predominant structural component, as it has a mature mesenchymal morphology with a mixture of mature cardiac myocytes, vascular elements, smooth muscle fibers, and adipose cells. Our case, however, has an immature mesenchymal morphology, as microscopical findings include elongated mesenchymal cells, vascular el-

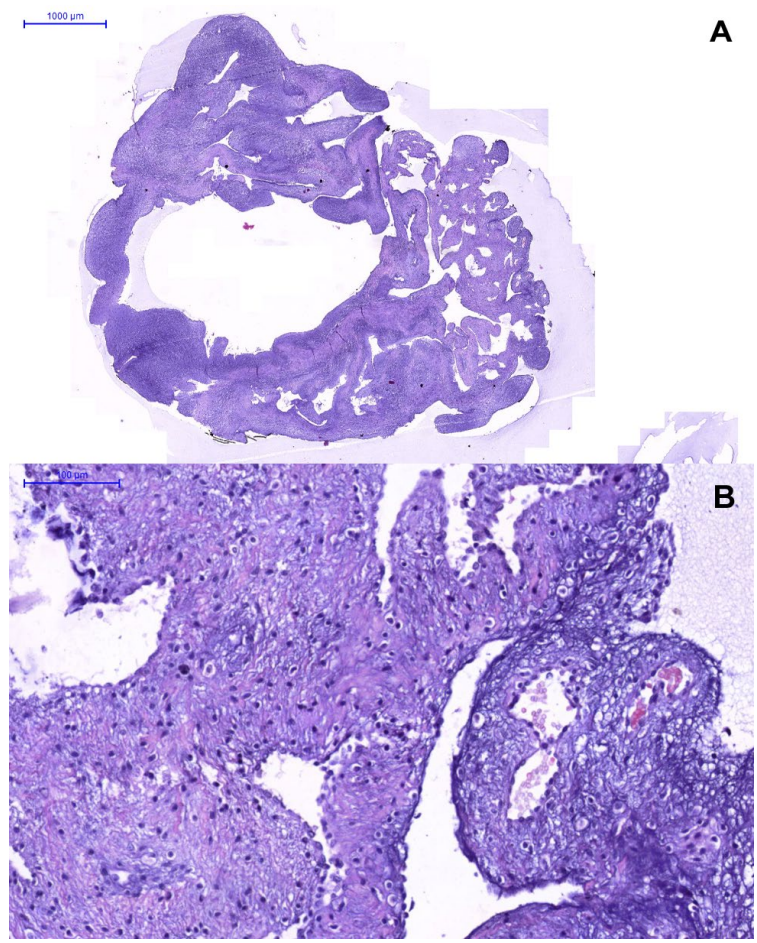

Fig. 1. (A). Cross-sections of the surgical specimen (H&E stain). The 0.4 X magnification highlights a cellular mesenchymal tissue with numerous vascular channels. (B). This tissue is composed of elongated cells surrounding the vascular spaces lined by endothelial cells. No evidence of malignancy (H&E stain, 5 X magnification).

ements, and adipose cells. Immunohistochemical findings revealed desmin negativity, in contrast with the previous case of mesenchymal hamartoma. Lack of myoid differentiation, which can be evaluated by either desmin or actin expression testing, is a novel characteristic for a cardiac hamartoma, as neither of the previous cases reported desmin negativity (Table 1). This characteristic indicates a primitive and undifferentiated hamartoma and implies testing for early regulatory proteins of the myogenic pathway, such as MyoD and myogenin. A rhabdomyosarcoma was specifically excluded by lack of nuclear staining with antibodies for myogenin. Cardiac rhabdomyosarcomas are invariably of immature, embryonal type and expresses myoid markers. A differential diagnosis with rhabdomyosarcoma by myogenin expression testing must always be performed as it is the most common malignant soft tissue tumor in pediatric patients and myogenin positivity is pathognomonic for this tumor. MyoD is less specific and sensitive than myogenin in the diagnosis of rhabdomyosarcomatous lesions (8). A malignant nature of the tumor was excluded by the Ki-67 proliferation index value of less than 1%, further supporting the diagnosis of hamartoma. CD31 and CD34 positivity for the endothelial cells certifies the presence of endothelial cells lining vascular spaces.

Depending on the clinical setting, hamartomas are either congenital, when they appear in fetuses, neonates and pediatric patients, or either adult hamartomas (4). A previous case of mesenchymal hamartoma was diagnosed in a young adult, in contrast to our case. The clinical impact of hamartomas is related to ventricular outflow tracts obstruction or to arrhythmogenic potential of the tumor. There are highly arrhythmogenic hamartomas, such as histiocytoid cardiomyopathy originating from Purkinje cells, that are directly related to sudden cardiac death (2). Our patient also presented multiple episodes of sustained ventricular tachycardia with origin near the excision site. As it may have emerged from the post-surgical myocardial scar, a direct relationship between arrhythmic load and the tumor cannot be drawn. Also, clinical evolution was additionally complicated by association with

Table 1. Types of cardiac hamartomas

	Clinical setting	Multifocal lesions	Microscopic structure	Immunohistochemistry
Rhabdomyoma	Congenital Adult	Possible	Myocytes with large glycogen vacuoles Pathognomonic spider cells	Desmin positive CD31, CD34 negative Ki-67 negative or positive
Histiocytoid cardiomyopathy	Adult	Always	Myocytes with fine vacuoles	Desmin positive Ki-67 negative
Fibroelastic hamartoma	Congenital	No	Fibroblasts Colagen and elastic tissue Calcification	Desmin positive CD34 positive, CD31 negative Ki-67 negative
Hamartoma of the mature myocytes	Adult	No	Resembles hypertrophic cardiomyopathy	Normal cardiac myocyte profile
Mesenchymal hamartoma	Adult	No	Mature myocytes Adipose cells Small blood vessels	Desmin positive CD31, CD34 positive

TGA, a cardiac malformation with high morbidity and mortality.

Although cardiac hamartomas are extremely rare, many histological types have been described. By exclusion diagnosis, this patient is the second reported case of mesenchymal cardiac hamartoma with certain particularities. Our case is a congenital hamartoma with immature mesenchymal morphology and immunohistochemical negativity to desmin, while the previous case is a desmin positive hamartoma with mature mesenchymal morphology in a young adult. Also, it is the first reported association between a cardiac hamartoma and TGA.

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Conflict of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Authors' contribution

V.I.S. – investigation, conceptualization, writing; P.A.C. – investigation, validation, writing; G.A.L. – data curation; C.F.AL. – formal analysis; C.G. – software; A.P. - writing; H.S. – supervision, resources; E.H. – supervision, resources.

Abbreviations

TGA – transposition of great arteries

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