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Evolution of a rare ECG pattern in an aggressive case of neonatal tuberous sclerosis complex

Federica Iezzi*, Andrea Quarti, Alessandro Capestro, Francesca Chiara Surace, Marco Pozzi

Department of Paediatric and Congenital Cardiac Surgery and Cardiology, Azienda Ospedaliero-Universitaria Ospedali Riuniti Ancona "Umberto I, G. M. Lancisi, G. Salesi" Ancona, via Conca n. 71, 60128 Ancona, Italy

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ABSTRACT

INTRODUCTION: Rhabdomyomas are the most frequent cardiac tumors in children. Furthermore, they are often associated to tuberous sclerosis complex, an autosomal dominant neurocutaneous disorder characterized by tumor-like malformations that involve many organ systems.

PRESENTATION OF THE CASE: We describe a rare ECG pattern in a severe case of neonatal tuberous sclerosis complex.

DISCUSSION: In the presence of significant rhabdomyomatosis related to tuberous sclerosis, multiple clusters of rhabdomyoma-like cells can infiltrate the myocardium, with increased fibrosis areas.

CONCLUSION: Considering the fact that rhabdomyomas often show spontaneous regression, close follow-up is sufficient in hemodynamically stable cases. Destruction of the conduction system, with arrhythmias as consequence, can be the presenting feature of diffuse rhabdomyomatosis.

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1. Introduction

Tuberous sclerosis is a neurocutaneous syndrome with autosomal dominant inheritance and has a reported incidence of 1:6.000. In up to 60% of cases, the disease is related to de novo mutations.

It is caused by mutations in either of the two genes, Tuberous Sclerosis Complex 1 (TSC1) or Tuberous Sclerosis Complex 2 (TSC2), which code for the proteins hamartin (chromosome 9q34) and tuberlin (chromosome 16p13), respectively, that act as tumor-growth suppressors. The mutations cause the hyperactivation of the mammalian target of rapamycin (mTOR) signaling pathway, accounting for subsequent abnormalities in numerous cell processes [1,2].

Formerly recognised by the clinical triad of epilepsy, mental retardation, and facial angiofibromatosis, it is appreciated that almost any organ of the body may be affected. The most common cardiac manifestation of the disease is the cardiac rhabdomyoma, which is thought to occur in at least 60% of children with tuberous sclerosis.

Cardiac tumors are extremely rare in children (0.027–0.17%). More than one-half of pediatric cardiac tumors are diagnosed within twelve months of life and are diagnosed both in prenatal and postnatal period. The vast majority of primary cardiac tumors

in children are benign, whilst approximately 10% are malignant. Among the benign, rhabdomyomas are the most common cardiac tumors in children (45%) [3].

Rhabdomyomas appear on ultrasound as round, homogeneous, hyperechogenic, intramural or intracavitary masses, sometimes multiple, predominantly localized within the ventricles but can be observed in the atria or caval veins and may lead to obstruction of cardiac valves or inflow/outflow tracts. They are typically asymptomatic but may also cause atrial or ventricular arrhythmias, sinus node dysfunction, heart block and pre-excitation [4].

The rhabdomyoma ECG pattern depends on the size of tumor and proximity to conduction system. In large rhabdomyomas, ECG shows ventricular hypertrophy and ST-T changes. Conduction system compression by tumor may produce AV block and bundle branch block. Effects of tumor on hemodynamic condition and conduction system involvement predisposed these patients to supraventricular or ventricular tachyarrhythmias. Pre-excitation has also been reported. Rhabdomyomas may regress with time and pre-excitation and other arrhythmias may resolve spontaneously.

Surgical resection is not usually considered unless they cause severe intractable arrhythmias, valvular obstruction or congestive heart failure. If complete surgical resection is not possible because of the location of the tumor, a partial resection can be done and the residual tumor usually regresses. The surgical mortality for cardiac tumors resection in children is reported to be 5%.

* Corresponding author.

E-mail address: federicaiezzi@hotmail.it (F. Iezzi).



Fig. 1. ECG reveals sinus rhythm with short PR, dome-shaped ST segment elevation in V4, V5, V6, I, aVL leads and T waves inversion in the same derivations including inferior limb leads.

2. Case report

A giant cardiac rhabdomyoma was diagnosed at 28 weeks gestational age, in a male foetus. He was born at 35 weeks by vaginal delivery at 2 kg of body weight and showed an Apgars score at 8 and 9 at 5 and 10 min, respectively.

The ECG pattern at third week of age, revealed sinus rhythm with short PR, dome-shaped ST segment elevation in V4, V5, V6, I,

aVL leads and T waves inversion in the same derivations including inferior limb leads [Fig. 1].

The echocardiography revealed multiple echogenic masses embedded into the left and right ventricular myocardium. A giant mass (35 × 45 mm), which extended from the apex of both ventricles to the anterior-lateral wall of left ventricle, was detected. Compared with the usual myocardial aspect, the mass was homogeneous and hyperechoic, including the left coronary artery and involving the pericardial side of left ventricular wall. Multiple



Fig. 2. Echocardiography reveals multiple echogenic masses embedded left (LV) and right ventricle (RV), like rhabdomyoma (Rh) features. LA left atrium, RA right atrium.



Fig. 3. Cardiac Magnetic Resonance images show that the giant rhabdomyoma (Rh) arises from lateral wall of left ventricle (LV). LA left atrium, RV right ventricle.

minor nodular masses were present in the left and right ventricles cavities, atrial aspect of mitral valve and ventricular side of tricuspid valve [Fig. 2].

Doppler's analysis of atrioventricular valves were normal, as well as no evidences of obstruction to ventricular inflow or outflow were detected.

At magnetic resonance, the lesions were homogeneous on all sequences, mildly hyperintense on T2-weighted imaging, isointense to myocardium on T1-weighted sequences, and show minimal or no enhancement after administration of gadolinium-based contrast agents with hypointensity on first-pass perfusion imaging and isointensity on late gadolinium-enhanced sequences [Fig. 3].

Furthermore, radiological examination detected, as extracardiac lesions, a large renal mass characteristic for renal angiomyolipoma, retinal hamartomas, cortical dysplasia and subependymal nodules.

A mutation in the TSC2 gene was identified on genetic investigation.

Everolimus therapy at a dose of 0,3 mg once a day was started, following the guidelines of plasmatic therapeutic range (5–15 mcg/ml).

Everolimus is a derivative of sirolimus, which is approved by the Food and Drug Administration, for the treatment of patients with subependymal giant-cell astrocytomas associated with tuberous sclerosis complex and acts as an inhibitor of mammalian target of rapamycin (mTOR).

During the ten weeks of the everolimus treatment, a significant reduction in the size of the rhabdomyomas was observed without several adverse effects, except mucositis [5].

A strict clinical follow-up with ECG monitoring and periodical echocardiogram examination was carried out. Unfortunately, gradual further evolution of cardiovascular lesions was observed in the first year of life followed by a clinical stabilization, without symptoms or haemodynamic effects. After 20 months, epilepsy was

diagnosed and radiological neuroimaging detected subependymal nodules and cortical dysplasia areas (tubers-related) enhancement.

During this period, the ECG pattern changed, showing abnormal convex ST elevation (maximum 18 mm) in V3–V6, I, II, aVL and specular ST depression in V1, V2 and aVR [Fig. 4].

All these ECG findings were not associated to cardiac troponin elevation. Not evolutive ST segment changes were revealed. Neither angina nor other symptoms have been found.

After 2 years follow-up, thoracic magnetic resonance showed a substantially stability of previous findings. The diameter of par-ventricular mass remained stable at 35 × 16 mm.

3. Discussion

Congenital cardiac rhabdomyomas represent a condition of particular interest for the researcher due to spontaneous regression of the tumors that occurs in more than one-half of cases. To explain the involution tendency we refer to pathological anatomy: tumors consist of pathognomonic spider cells with centrally placed cytoplasm containing the nucleus and myofibrils radiating to the cell wall. These tumors that seem to originate from embryonic myocytes, represent hamartomas of striated muscular fibers occurring solely in the heart. Immunohistochemical immunoreactivity with ubiquitin, associated with the degradation of myofibrils, progression of cytoplasmic vacuolization, enlargement of glycogen vacuoles, apoptosis and myxoid degeneration are the events providing a plausible explanation for the spontaneous regression of rhabdomyoma.

The incidence of primary cardiac tumor in autopsy series ranges from 0.002% to 0.3%. The most common benign tumor is rhabdomyoma. The tumors most commonly involve the ventricular myocardium, projecting into the ventricular cavity or moving freely as a pedunculated mass.

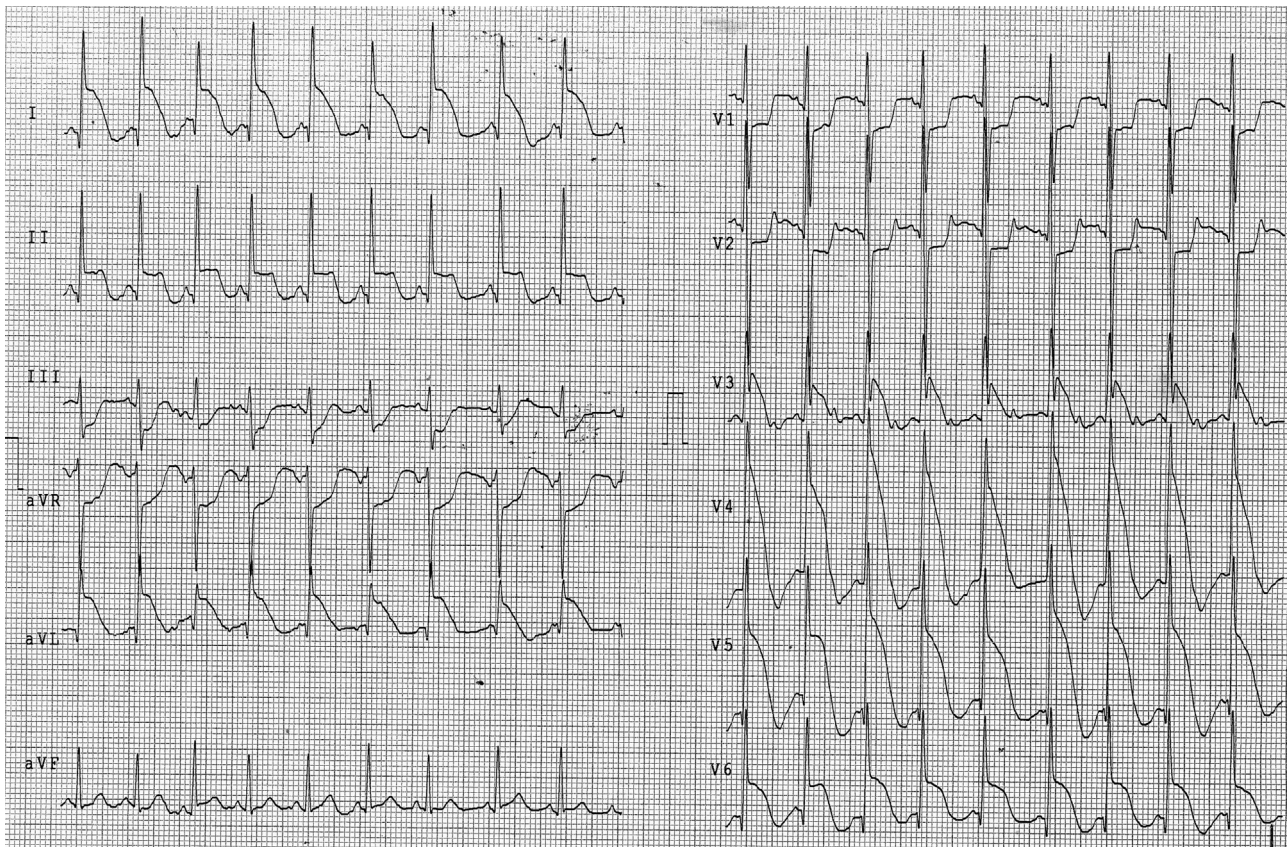


Fig. 4. Patient ECG at three year of age shows abnormal convex ST elevation in V3–V6, I, II, aVL and specular ST depression in V1, V2 and aVR.

The clinical presentation of cardiac rhabdomyomas depends on their number, size and position. They may be detected prenatally on a routine foetal ultrasound scan or may present with hydrops foetalis. Postnatally they may be totally asymptomatic, may present with an asymptomatic cardiac murmur or may present variously as congestive cardiac failure, low cardiac output due to intracardiac flow obstruction, arrhythmias or as sudden infant death.

An early prenatal diagnosis may help for an adequate planning of perinatal monitoring and treatment with involvement of a multidisciplinary team [6].

The natural history of cardiac rhabdomyomas in infants and children shows a propensity for spontaneous regression. The younger the age at diagnosis, the higher is the chance for spontaneous regression, with complete regression being more common in the first 4 years of life [7].

Cardiac rhabdomyomas may alter intracardiac electrical conduction, producing electrical phenomena like pseudopreexcitation or repolarization disturbances resembling ST-elevation myocardial infarction or Brugada's syndrome. These phenomena were supposedly caused by isolated atrial depolarization disturbances due to tumor-caused heterogenous endocardial activation. The seemingly abnormal ventricular repolarization is probably due to atrioventricular electrical activity of the atrial mass, superimposed on the ventricular repolarization.

In a brief review of literature about cardiac rhabdomyoma, ECG anomalies are frequently described. The common findings are arrhythmias, pseudopreexcitation syndrome and repolarization disturbance [8,9].

Partial resolution of the cardiac rhabdomyomas was reported in 50% of cases and complete regression in 18% and added that these tumors have been reported to grow or to appear de novo in 4% of patients with tuberous sclerosis.

In the presence of a significant heart TSC2-associated rhabdomyomatosis, multiple clusters of rhabdomyoma-like cells can infiltrate the near normal myocardium, with increased areas of fibrosis as consequence.

Just few cases of abnormal hypertrophic phenotype on autopsic relief were described, in scientific literature. In all cases, the microscopic pathological analysis revealed heart infiltration by irregularly shaped lesions that replaced the normal myocardium tissue and portion of conduction system [10].

4. Conclusion

The infiltrative nature of diffuse rhabdomyomatosis distinguishes it from the discrete cardiac rhabdomyomas characteristic of Tuberous Sclerosis Complex. Even in cases with large tumors the electric potential might not alter the surface electrocardiogram if the direction of growth of the tumor is towards the ventricular cavity. In many cases, electrocardiographic abnormalities tend to disappear, concomitantly with regression of the tumors. Evolution of inconsistent arrhythmia types suggests that the patient's arrhythmias were not mediated by an embryonic accessory pathway. Destruction of the conduction system has been described in diffuse rhabdomyomatosis that leads to arrhythmias.

Conflict of interest

None.

Sources of funding

None.

Ethical approval

The study has been reviewed and approved by Ethics Board of Azienda Ospedaliero-Universitaria – Ospedali Riuniti Ancona “Umberto I – G.M.Lancisi – G.Salesi”.

All patients sign a consent form, that include the possibility of taking part in scientific studies. All aspects of patient confidentiality have been preserved in this project, following the Helsinki Declaration, translated into regulations for the protection of individuals and into the rules for good research practices.

To all patients are guaranteed protection of the rights, safety and well-being of people taking part in clinical trials.

Consent

Written informed consent was obtained from the patient’s parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Iezzi Federica – Manuscript drawing up.
 Quarti Andrea – Manuscript editing.
 Alessandro Capestro – ECG studies.
 Francesca Chiara Surace – Echocardiography studies.
 Marco Pozzi – Final revision of manuscript.

Guarantor

Dr Iezzi Federica.

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