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CASE REPORT
Cardiac imaging

Ventricular repolarization abnormalities: the electrocardiographic track of cardiac tumoural involvement in an infant with tuberous sclerosis complex. A case report

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Background Primary cardiac tumours are rare in children. Against this backdrop, *Doppler* echocardiogram is the main diagnostic procedure, while electrocardiogram (ECG) usually plays a secondary role, by detecting tumoural consequences as cardiac arrhythmias and chambers overload. We describe a case where an electrocardiographic sign was the cornerstone to diagnosis and surveillance of an infant with a cardiac rhabdomyoma.

Case summary A female infant was referred for cardiac evaluation to elucidate an electrocardiographic abnormality, detected during investigation of seizures. She had recently been diagnosed with epilepsy and was under three different anticonvulsants for appropriate control. Cardiovascular symptoms were absent. Skin inspection revealed hypochromic macules. Respiratory and cardiovascular examinations were normal, as well as laboratorial tests and chest radiography. Electrocardiogram (ECG) showed dome-shaped ST-segment elevation in V2 and V3. Transthoracic echocardiogram unveiled a single hyper-echogenic node (0.4 cm^2) in the interventricular septum. Cardiac chambers had normal size and function and *Doppler* analysis was also normal. No specific medication was used to treat the tumour. During follow-up, she remained free of cardiac symptoms. Eighteen months after her first visit to the cardiologist, routine clinical assessment, ECG, and transthoracic *Doppler* echocardiogram normal results stated the spontaneous and complete involution of the tumoural lesion.

Discussion Convex ST-segment elevation, generally related to myocardial injury, is unusual in paediatric patients. Once it occurs in asymptomatic individuals within this age bracket, exclusion of cardiac tumours is mandatory. However, data regarding the accuracy of such electrocardiographic marker in this clinical setting are still to be defined.

Keywords Cardiac tumours • Rhabdomyoma • Tuberous sclerosis complex • Electrocardiogram • Case report

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Learning points

- Primary cardiac tumours are rare in children; the vast majority of them are benign. Rhabdomyoma, the most common type of primary cardiac tumoural lesion, is often associated with tuberous sclerosis complex, a multi-system autosomal dominant disorder.
- Clinical presentation of cardiac rhabdomyomas depends on their size, number, and location within the heart. The lesions are usually silent and show a propensity for spontaneous regression.
- *Doppler* echocardiography is the primary diagnostic procedure for evaluation of cardiac tumours in paediatric patients.
- Convex and localized ST-segment elevation is a promising marker for diagnosis and surveillance of primary cardiac tumours in infants. However, data regarding its accuracy in this clinical setting are still to be defined.

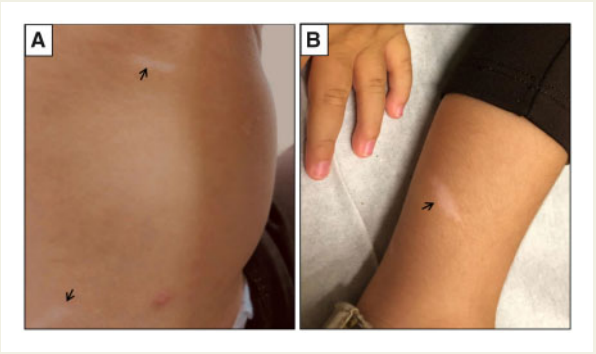

Figure 1 Hypochromic skin macules in our patient's back (*A*) and left leg (*B*).

Introduction

Primary cardiac tumours are rare in the paediatric population[1,2] and overall benign.[2,3] Rhabdomyoma, the most common histopathological finding, is often associated with tuberous sclerosis complex (TSC), a systemic genetic disorder.[1–4] Cardiac rhabdomyomas (CRs) are multiple and usually silent in most TSC patients. Symptoms, when appearing, relate to the lesion number, size and location within the heart.[1–3,5] Haemodynamic compromise is unlikely, but can occur as a consequence of big cardiac tumours or inflow/outflow tract obstruction.[1,3,5] Heart rhythm disturbances are quite more common and a lifelong concern.[1,2,5] Cardiac evaluation is recommended in TSC patients at the time of diagnosis and every 3–5 years for surveillance.[1,4] *Doppler* echocardiography is the imaging modality of choice to assess cardiac tumoural involvement in children with TSC.[1,2] Standard 12-lead electrocardiogram (ECG) is also warranted, usually with the supporting role of detecting tumour consequences as arrhythmias and chambers overload.[1,3,6,7] We describe a case of an infant where an electrocardiographic sign was the cornerstone to a CR diagnosis.

Timeline

Time	Events
18 January 2017	Epilepsy diagnosis
30 March 2017	Single cardiac rhabdomyoma (CR) detection Confirmation of TSC clinical diagnosis
19 June 2018	Multiple bilateral renal cysts observation during investigation of recurrent urinary tract infections
31 October 2018	Brain magnetic resonance imaging unveils tubers, cerebral white matter radial migration lines and ependymal nodules
19 September 2018	CR is no longer detected on echocardiography and ECG normalizes

Table 1 Results and reference values, according to age and sex, of the most relevant laboratorial tests performed in our patient

Laboratorial examination	Results	Reference Value
Haemoglobin	10.7 g/dL	10.3–13.7 g/dL
Creatinine	0.26 mg/dL	0.17–0.42 mg/dL
Potassium	4.3 mEq/L	3.5–5.0 mEq/L
Sodium	137 mEq/L	135–145 mEq/L
Ionic serum calcium	5.39 mg/dL	4.8–5.5 mg/dL
Magnesium	2.07 mg/dL	1.71–2.29 mg/dL
Ammonia	45 µmol/L	21–50 µmol/L
Glucose	83 mg/dL	60–110 mg/dL
TSH	8.27 µIU/mL	0.27–10 µIU/mL
Free T4	1.12 ng/dL	0.93–1.70 ng/dL
CK-MB	3.2 ng/mL	Until 3.8 ng/mL
Troponin	<0.006 ng/mL	Until 0.04 ng/mL

Case presentation

An eight-month-old female was referred for cardiac evaluation to elucidate an electrocardiographic abnormality detected during investigation of seizures. Cardiac symptoms were absent. She was undergoing routine neurological evaluations for epilepsy, controlled with Vigabatrin, Valproic Acid, and Clobazan. Family history was null regarding genetic syndromes. Prenatal, childbirth, and neonatal records were unremarkable. On examination, skin inspection revealed hypochromic macules (*Figure 1*). Respiratory and cardiovascular inquiries were normal, same as laboratory tests (*Table 1*) and chest radiography.

Her first ECG showed sinus rhythm, general parameters within normal range (heart rate: 125 b.p.m.; PR interval: 90 ms; SÂQRS: +50°; QRS duration: 70 ms; QT: 260 ms; QTc: 375 ms, and a pronounced dome-shaped ST-segment elevation in V2/V3 (*Figure 2A*).

The admission's transthoracic echocardiogram detected a single hyper-echogenic regular node in the mid part and right face of the interventricular septum, with 0.4 cm^2 estimated area (*Figure 2B–D*). Cardiac chambers and *Doppler* analysis were normal without evidence of outflow tract obstruction.

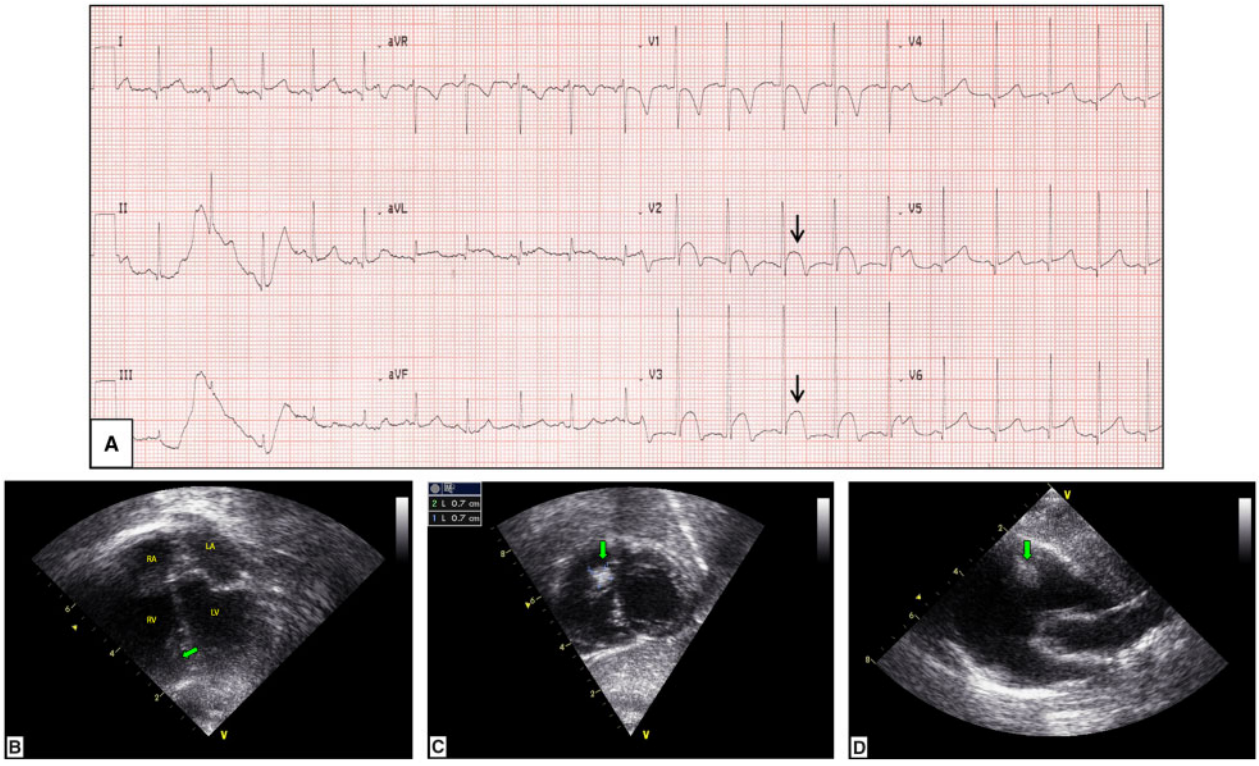

Figure 2 Our patient's first electrocardiogram: observe the dome-shaped ST-segment elevation (black arrows) in the pre-cordial leads (*A*). Transthoracic echocardiography obtained during our patient's first cardiologic evaluation unveiling a single hyper-echogenic nodule in the mid part and right face of the interventricular septum (green arrow)—apical four-chamber view (*B*), apical short-axis subcostal view (*C*), and long-axis view (*D*).

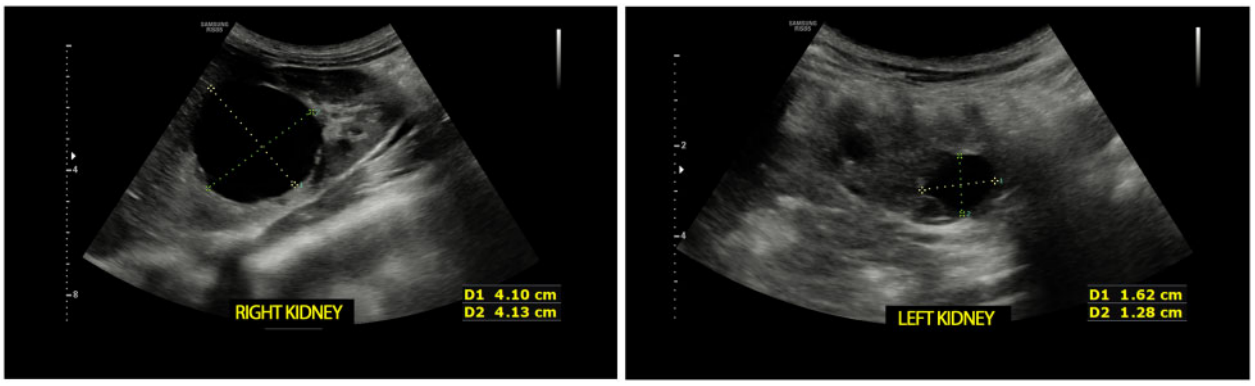

Figure 3 Ultrasonography performed during our patient's evaluation of recurrent urinary tract infections. Hypo-echogenic lesions with regular contours (renal cysts) were detected in both kidneys.

Ambulatory ECG 24 h-*Holter* monitoring displayed sinus rhythm, mean heart rate of 111 b.p.m., normal PR interval, and QRS duration. No arrhythmias were detected.

During follow-up, investigation of recurrent urinary tract infections revealed multiple bilateral renal cysts (*Figure 3*). Epilepsy, confirmed by electroencephalogram, was still controlled with the same medications. Seizures aetiology was elucidated, as brain magnetic resonance imaging unveiled cortical dysplasia and ependymal nodules (*Figure 4*).

Meanwhile, the patient remained free of cardiac symptoms. Given the benign course of the cardiac disease, no specific medication

(mTOR inhibitors) was used to treat the tumour. Cardiologic re-evaluation was performed 18 months after. By then, ECG and echocardiogram had become thoroughly normal (*Figure 5*) documenting the total and spontaneous CR involution.

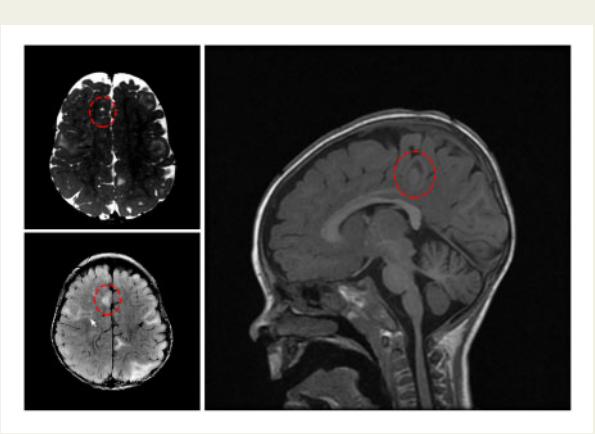

Figure 4 Brain magnetic resonance imaging of our infant patient demonstrates cortical tubers (black arrow), cerebral white matter radial migration lines (right arrows), and ependymal nodules (circled with red-dashed line).

Discussion

Electrocardiogram was requested considering differential diagnosis of seizures in children—given that complex ventricular arrhythmias can manifest as convulsion and thus confound clinical investigation. Moreover, primary neurological disorders—e.g. epilepsy, stroke, brain tumours, cranio-cerebral trauma—may incur substantial autonomic imbalance leading to cardiac alterations commonly disclosed on ECG, such as sub-epicardial ischaemia, ST-segment elevation, and prolonged QTc interval.[8] When resulting from neurologic conditions, ventricular repolarization abnormalities are overall displayed in multiple leads.[8] Hence, although epilepsy diagnosis was beyond question, it could not by itself explain the confined arrangement of ECG observations.

ST-segment elevation is an uncommon finding in infancy. Its most common aetiology in this age bracket is pericarditis.[9] However, the absence of fever and cardiac symptoms, added to the localized ST-segment elevation pattern without PR-segment depression, readily discarded this hypothesis. Normal laboratory tests, respectively, ruled out hydro-electrolytic disturbances and hypothyroidism. Sub-epicardial injury—due to myocarditis, Kawasaki disease, or anomalous left coronary artery—was also precluded, once cardiac size, function, and markers were all normal.[9] The lack of J-waves testified against Brugada syndrome,[9] while literature search revealed that no ventricular repolarization abnormalities had been reported so far in association with any of the drugs our patient was taking.[10,11]

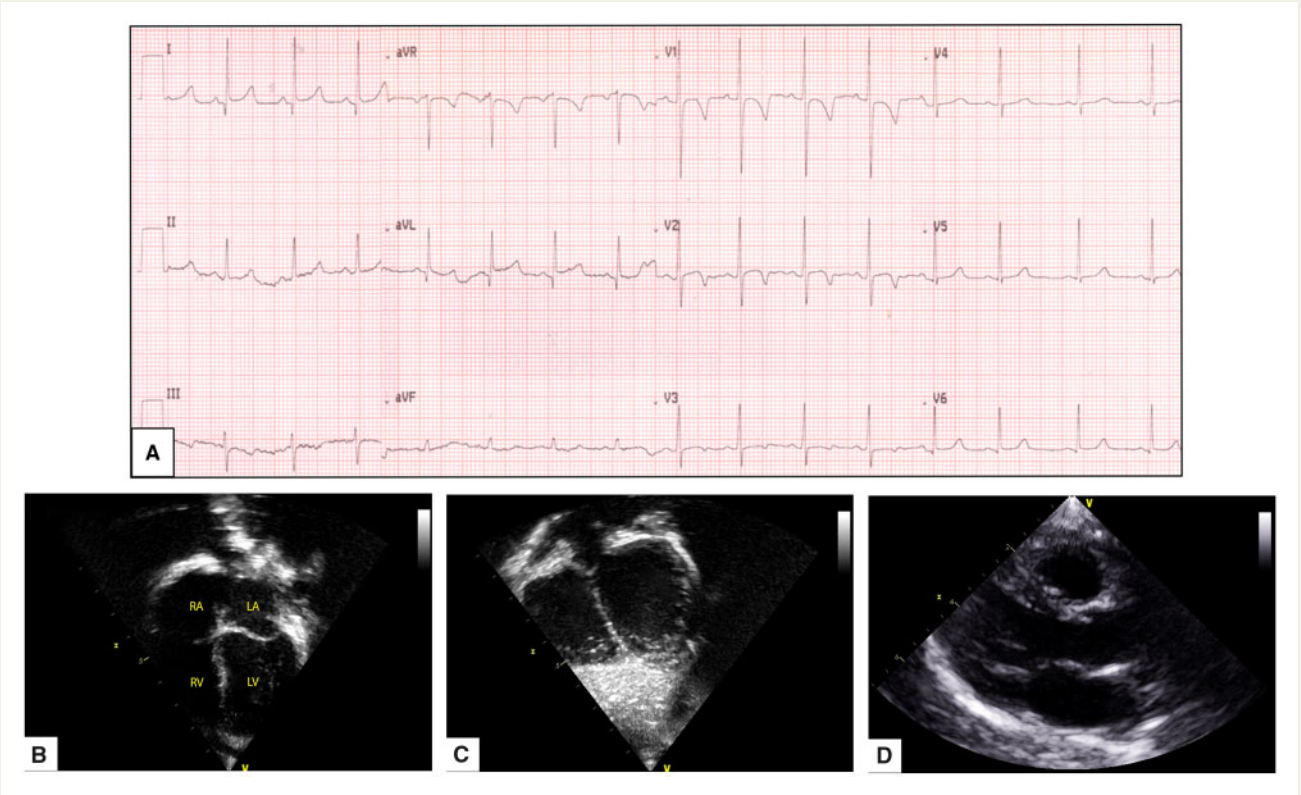

Figure 5 Electrocardiogram obtained almost 20 months after the rhabdomyoma diagnosis with normal findings, considering our patient's age and sex, showing the complete normalization of the ST-segment (*A*). Surveillance transthoracic echocardiogram—apical four-chamber view (*B*), apical short-axis subcostal view (*C*), and long-axis view (*D*). The cardiac rhabdomyoma was no longer detected in our patient.

Table 2 Revised clinical diagnostic criteria[4]

Tuberous sclerosis complex clinical diagnostic criteria	
Genetic diagnostic criteria	
Identification of either TSC1 or TSC2 pathogenic mutations in DNA—note that in 10–25% of patients with TSC, no pathogenic mutation is identified by conventional genetic testing. Hence, a normal result does not exclude TSC diagnosis.	
Clinical diagnostic criteria	
Major features	Minor features
1. Hypomelanotic macules (≥3, at least 5 mm diameter)	1. 'Confetti' skin lesions
2. Angiofibromas (≥3) or fibrous cephalic plaque	2. Dental enamel pits (≥3)
3. Ungueal fibromas (≥2)	3. Intraoral fibromas (≥2)
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Cortical dysplasias[a]	6. Non-renal hamartomas
7. Sub-ependymal nodules	
8. Sub-ependymal giant cell astrocytoma	
9. Cardiac rhabdomyoma	
10. Lymphangioleiomyomatosis (LAM)[b]	
11. Angiomyolipomas (≥2)[b]	

Identification of either TSC1 or TSC2 pathogenic mutations in DNA—note that in 10–25% of patients with TSC, no pathogenic mutation is identified by conventional genetic testing. Hence, a normal result does not exclude TSC diagnosis.
Definite TSC diagnosis: two major features or one major feature with ≥2 minor features. *Possible diagnosis*: either one major feature or ≥2 minor features.
[a]Includes tubers and cerebral white matter migration lines.
[b]A combination of the two major clinical features, LAM and angiomyolipomas, without other features does not meet criteria for a definite diagnosis.

Next, cardiac imaging was performed to clarify the regional distribution of such electrocardiographic abnormalities. Apart from excluding chambers overload and blood flow obstacles, echocardiogram uncovered a small heart tumour, away from coronary courses.

Cardiac tumours have been diagnosed more frequently after the advent of echocardiography.[2] Still, primary cardiac neoplasms are rare in clinical practice, occurring in 0.20% of children presenting to paediatric cardiac referral centres, and in 0.27% paediatric autopsies.[1–3] Cardiac rhabdomyoma is the most common primary cardiac tumour in childhood.[1–3,5,6] Lesions of this sort are multiple in 90% of cases, ranging from few millimetres to several centimetres.[1] The typical echocardiographic aspect of the cardiac single node detected allowed its characterization as a rhabdomyoma.

According to some studies, 70–90% of children with CR have TSC, a multi-system autosomal dominant disorder.[1–4] Tuberous sclerosis complex is reported in 1/6000 to 1/10 000 live births.[4] Mutations in *TSC1* and *TSC2* genes (encoding for *hamartin* and *tuberin*, respectively) account for the majority of cases.[1,4] Abnormal *hamartin-tuberin* tumour suppressor proteins imply in ubiquitous loss of control over cell cycle progression.[4,7] Indeed, TSC most common findings are benign tumours (hamartomas) in the skin, brain, heart, lung, and kidneys.[4] However, clinical spectrum is wide and syndrome's recognition relies on diagnostic criteria (*Table 2*).[4]

Heart involvement with benign tumours befalls in over one-half of TSC patients.[1,2] Although frequently silent, CRs have important implications: often the syndrome's first sign, they can be detected early, are highly specific and a major feature for TSC clinical diagnosis (*Table 2*).[1,2,4]

In this case, detection of a CR in a child with hypochromic skin macules not only certified TSC diagnosis, further endorsed by the unveiling of renal cysts and cerebral cortical dysplasia but also prompted precocious and multidisciplinary assistance.[1,4] Interestingly, the tumour spot correlated spatially to the leads displaying that unusual repolarization pattern—would it be a 'fingerprint'?

Eighteen months after, echocardiogram documented the complete involution of the heart lesion—CRs actually tend towards spontaneous regression or even disappearance during the first 2 years of life.[1,2,4,5] Electrocardiogram normalized concurrently. As drug therapy was unaltered, one could state that the first ECG pattern was not a pharmacologic effect.

The association between heart tumours and electrocardiographic abnormalities has been described in several publications, often case reports on metastatic lesions. Better evidence was provided by two studies demonstrating that, in patients with cancer, localized ST-segment elevation was the most specific electrocardiographic sign of myocardial malignant infiltration.[12,13] Suggested pathophysiologic mechanisms include: (i) direct compression of coronary arteries, (ii) tumour extension/embolization to coronary lumen, (iii) neoplastic pericardium invasion, or (iv) myocardial injury by direct pressure or physiochemical action.[12,13] Otherwise, literature regarding electrocardiographic features of primary cardiac tumours is scarce.[1,3,6,14,15] Few case reports denoted specific ST-T changes in patients with CRs; however, spatiotemporal correlation between ECG and tumours could not be established by the authors.[14,15] In our patient's case, dome-shaped ST-segment elevation, spatial and timely related to the CR, was an important clue during clinical evaluation. More studies are

needed to explore the role of ECG concerning diagnosis and follow-up of primary cardiac tumours, especially in children presenting with other TSC characteristics.

Conclusion

Convex ST-segment elevation, generally related to myocardial injury, is unusual in paediatric patients. Once it occurs in asymptomatic individuals within this age bracket, exclusion of cardiac tumours is mandatory. However, the accuracy of such electrocardiographic marker in this clinical setting still needs definition.

Lead author biography

Mirella Facin graduated in Medicine at Universidade Federal do Paraná (UFPR), had residency training in Internal Medicine (Hospital de Clínicas—UFPR), Cardiology (Instituto Dante Pazzanese de Cardiologia de São Paulo), and Clinical Electrophysiology (Instituto do Coração—InCor-HCFMUSP). She is a specialist in Cardiology (Brazilian Society of Cardiology) and Clinical Electrophysiology (Brazilian Society of Cardiac Arrhythmias), and an ESC and AHA member. Currently, she works as an assistant physician at Instituto do Coração (InCor–HCFMUSP) and as a general physician at São Paulo State Court of Justice.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgement

IRB approval for this report has been obtained.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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