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An uncommon cause of tricuspid regurgitation: three-dimensional echocardiographic incremental value, surgical and genetic insights

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Abstract

Congenital tricuspid valve disease is a rare defect that includes regurgitation, stenosis and Ebstein's anomaly. We report a case of severe tricuspid regurgitation associated with functional mitral regurgitation in a 47-year-old man with congestive heart failure. Transthoracic echocardiography (TTE) ruled out any Ebstein's anomaly. Three-dimensional TTE revealed a 'tricuspid hole' into the anterior leaflet that was only attached to the tricuspid annulus next to both anteroseptal and anteroposterior commissures. There was no sign of leaflet tear or perforation. The surgical repair of the tricuspid and mitral valves was performed with an optimal result. No sign of endocarditis or rheumatic disease was observed during the intervention. Sequence analysis of *GATA4*, *HEY2* and *ZFPM2* genes was performed, but no causative mutation was identified.

Keywords: Tricuspid valve • Valvular heart disease • Echocardiography

CASE PRESENTATION

A 47-year-old man was admitted for asthenia, palpitations and dyspnoea. Past medical history included a decreased exercise tolerance, a loss of 10 kg in the last year without fever and a paroxysmal atrial fibrillation (aFib). There was no family history of heart disease. The clinical examination revealed a 3/6 murmur at the fifth left mid-clavicular intercostal space, a Harzer's sign with jugular vein turgescence and congestive hepatopathy. The electrocardiogram showed atrial fibrillation [Heart rate (HR) = 70 bpm]. Chest X-ray showed a convexity of the second left mediastinal contour with a normal cardiothoracic ratio. B-type Natriuretic Peptide (BNP) was 400 ng/l. C-reactive protein (CRP) and complete microbiological investigations including blood culture were negative. Two-dimensional TTE revealed an left ventricular ejection fraction (LVEF) of 70% with severe functional mitral regurgitation associated with severe tricuspid regurgitation (TR). The right ventricular longitudinal systolic function was severely impaired [tricuspid annular plane systolic excursion (TAPSe) = 10 mm, Doppler tissue imaging (DTI) s′ wave = 8 cm/s and right ventricular outflow tract (RVOT) velocity time integral (VTI) = 7 cm]. There was neither atrial nor ventricular septal defect. Pulmonary valve was normal. We focused on tricuspid valve with three-dimensional (3D) TTE: (i) the septal and posterior leaflets were normal, (ii) there was no apical displacement of the septal leaflet of the tricuspid valve from the insertion of the anterior leaflet of the mitral valve ruling out any Ebstein's anomaly, (iii) the tricuspid annulus was dilated at 55 mm and (iv) concerning the anterior leaflet, we observed a 'tricuspid hole' (TH) [1] corresponding to a defect of attachment of the anterior leaflet to the tricuspid annulus. Anterior leaflet was only attached to the tricuspid annulus next to both anteroseptal and anteroposterior commissures. There was no sign of leaflet tear or perforation (Fig. 1A and Video 1). Given the rareness of this case, a blood sample was obtained after the patient's consent. DNA sequencing and copy number variation analyses were performed. We investigated the genomic DNA of the patient for variation in the entire coding regions, exon–intron boundaries and untranslated regions (3′ UTR and 5′ UTR) of *GATA4*, *HEY2* and *ZFPM2* (also called *FOG2*) genes, which have been already shown to be crucial for atrioventricular valvulogenesis [2–4]. Our analysis revealed the presence of seven variations (Table 1), among these, only one was in the coding region (*GATA4*: c.1129A > G; p.Ser377Gly). After pathogenicity evaluation with prediction tools and variant databases, we conclude that it was likely a polymorphism (between 9.2 and 13.5% in the European population). Moreover, the four identified intronic variations do not appear to have an impact on the splicing. We also screened these three genes for copy number variations by real-time quantitative PCR, and none were found.

[†]The first two authors contributed equally to this work.

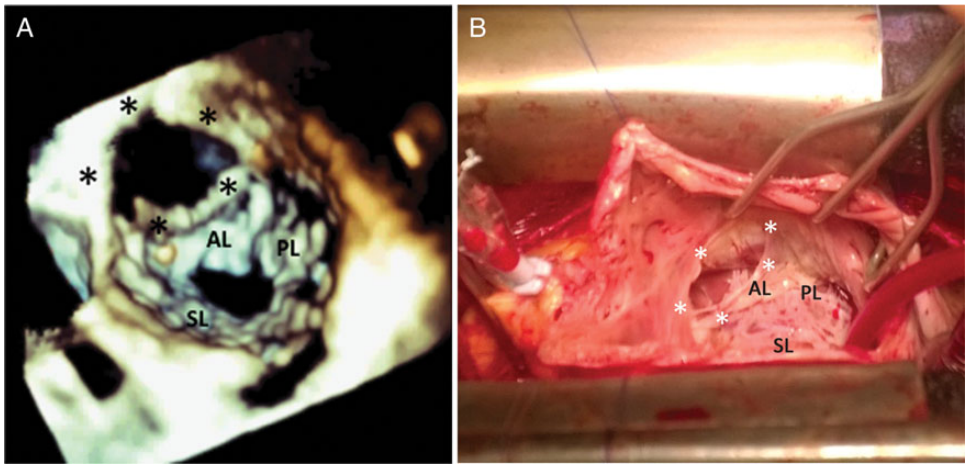
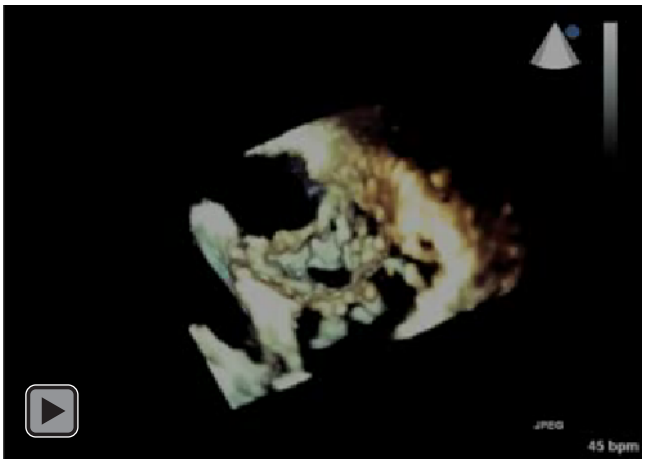


Figure 1: (**A**) Live 3D TTE. 'En face' view of the tricuspid valve showing a hole in the anterior leaflet responsible for severe regurgitation. (**B**) Surgical view after a right atriotomy. AL: anterior leaflet of the tricuspid valve; PL: posterior leaflet of the tricuspid valve; SL: septal leaflet of the tricuspid valve; TTE: transthoracic echocardiography; TH: tricuspid hole. Asterisks delimited the TH.

A cardiac CT scan ruled out any coronary disease. Then, the patient was referred for cardiac surgery. After a left and right atriotomy, we confirmed the 3D echo findings: (i) the mitral annulus was dilated without any anomaly of the valvular and subvalvular apparatus and (ii) a large TH measuring 18 × 23 mm was seen in the anterior leaflet associated with an annulus dilatation (48 mm). No anomaly of the subvalvular apparatus was observed. No sign of endocarditis or rheumatic disease was observed (Fig. 1B). The corrective intervention was undertaken: (i) to close the TH with a xenograft patch, (ii) to perform an undersizing tricuspid annuloplasty with an incomplete rigid ring of 34 mm and (iii) to perform a restrictive mitral annuloplasty with a complete semi-rigid ring of 30 mm. No right ventricular failure occurred postoperatively. LVEF remained stable (65%) with mild residual TR. A pericardial and a right pleural effusion required an urgent drainage at Day 7. The patient was discharged without sequelae at Day 16. Significant clinical improvement was documented at 1-year follow-up without recurrence of congestive heart failure.



Video 1: Live 3D TTE. 'En face' view of the tricuspid valve showing a hole in the anterior leaflet, and a tricuspid annular dilatation.

COMMENTS

Congenital TRs without pattern of Ebstein's anomaly are uncommon. These clinical entities exhibit a morphological heterogeneity that could involve the valvular apparatus, the subvalvular apparatus and/or the tricuspid annulus [4]. Cusp anomalies included cleft, hypoplasia or aplasia of cusp. Chordae anomalies included absence, elongation, shortening or aberrant tendinous chords, whereas other anomalies included commissural deficiency, annular dilatation and double orifice valve. Moreover, several associated lesions, such as pulmonary stenosis, patent ductus arteriosus and patent foramen ovale, have been described, highlighting the wideness of the clinical presentation. Among these anomalies, TH is extremely rare and was reported into a single case report until now [1]. The case reported raises here a number of points:

(i) TH aetiologies are unknown even if congenital origin is strongly suspected in the absence of endocarditic, iatrogenic and traumatic histories.

(ii) Embryological mechanisms leading to TH are unclear. We hypothesize that a too-pronounced delamination or detachment of the right anterior atrioventricular cushion from the ventricular myocardial wall could lead to a defect of connection to the fibrous support apparatus of the tricuspid ring. Interestingly, we support the finding that the epithelial-to-mesenchymal transition could not be involved in the pathogenesis of the TH, as suggested the absence of leaflet anomaly.

(iii) The genes involved in this anomaly could be numerous and remain unidentified. We failed to find causative mutation in the three candidate genes: *GATA4*, *HEY2* and *ZFPM2*. An enrolment of patients with the same default may be relevant in identifying a genetic cause by using new-generation sequencing such as exome or genome sequencing.

(iv) The surgery of TH remains challenging while the superiority of tricuspid repair versus tricuspid replacement has recently been confirmed [5]. To reach this goal, we confirmed that live 3DTTE provided an incremental value in planning the

Table 1: Identified variations in the *HEY2*, *GATA4* and *ZFPM2* genes

Gene	Localization	Nucleotide	Amino acid	dbSNP number	dbSNP frequency (CEU)	ExAC frequency (European)	UMD-predictor prediction	HSF3 prediction
HEY2	5′ UTR	c.1-134T > G	/	rs7764016	55%	/	/	/
	Intron 1	c.84-94C > G	/	rs2875881	44%	/	/	No impact
GATA4	Intron 5	c.997 + 23A > T	/	rs76808439	7.6% (Bushman)	0.06%	/	No impact
	Exon 6	c.1129A > G	p.Ser377Gly	rs3729856	9.2%	13.5%	Score: 16 polymorphism	No impact
ZFPM2	5′ UTR	c.1-64_65insGGCGGGAGC	/	rs71305140	1 individual	/	/	/
	Intron 3	c.302-66delA	/	rs3832566	13 individuals	/	/	No impact
	Intron 3	c.302-13C > T	/	rs3735953	62%	59%	/	No impact

procedure by showing an 'en face' surgical view of this very rare condition.

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Conflict of interest: none declared.

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