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Isolated Tricuspid Insufficiency Revealed by Pernicious Anemia: A Case Report

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SUMMARY:

It is clear that right-sided valvular diseases are much less common than left-sided heart disease. However, in the past two decades, there has been an increasing prevalence of tricuspid valve disorders. Specifically, tricuspid regurgitation has become more frequent, and has drawn attention to its management. Tricuspid regurgitation can be classified as primary, secondary, or isolated tricuspid insufficiency, based on its etiology. Diagnosis is typically established through echocardiographic evaluation, which not only assesses the severity and impact of the condition but also helps determine its underlying cause, in combination with clinical findings. Advancements in three-dimensional imaging techniques have greatly improved the assessment of this previously overlooked valve. These advancements, along with a better understanding of the pathophysiology and prognostic risks associated with tricuspid regurgitation, have led to surgical or even percutaneous intervention to prevent the progression to right ventricular dysfunction and its associated complications.

KEYWORDS: tricuspid regurgitation – tricuspid insufficiency – tricuspid valve – tricuspid repair – atrial fibrillation.

Consent: The authors confirm that written consent for the submission and publication of this case

Publication Ethics (COPE) guidance.

Conflict of interest: None declared.

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FIGURE LEGEND:

1. **And 2: Echocardiographic images in parasternal long-axis view centered on the right cavities showing a dystrophic tricuspid valve, with a diastasis measuring 15 mm and significant regurgitation on color Doppler.**
2. **Echocardiographic image in apical four-chamber view showing a laminar tricuspid regurgitation on continuous Doppler.**
3. **2D echocardiographic image in apical four-chamber view showing dilation of the right cavities with inversion of the RV/LV ratio, which is > 1.**
4. **The etiologies of tricuspid regurgitation.**
5. **Schematic drawing of the different morphologic types of tricuspid regurgitation**
6. **Classification system for tricuspid regurgitation**

INTRODUCTION:

The tricuspid valve has often been considered the "forgotten valve". However, there has been an increase in cases of tricuspid regurgitation, which has resulted in more attention being given to. Tricuspid regurgitation can be categorized as primary, when it occurs as a result of an anomaly in the valve apparatus, or secondary when it is a complication of left heart disease or pulmonary hypertension. It can also be isolated, occurring due to right atrial remodeling following atrial fibrillation. If left untreated, this regurgitation can have a significant impact on patient's survival. The impairment of right ventricular function plays a key role in the progression of the condition, highlighting the importance of surgical intervention before irreversible changes occur. Herein, we present the case of a patient who underwent tricuspid annuloplasty. The procedure was performed after the incidental discovery of isolated lamellar tricuspid insufficiency, which was caused by annular dilation during the patient's hospitalization for pernicious anemia.

CLINICAL CASE:

We present the case of a 47-year-old patient who has a history of former smoking. He has been managed for corticosteroid-responsive autoimmune hemolytic anemia for 2 years and was treated for resolved pericarditis in 2011. The patient was admitted to the internal medicine department for investigation of NYHA class III dyspnea, which was accompanied by sub icterus and vomiting, along with a general deterioration. During the evaluation, the patient was diagnosed with pernicious anemia. Treatment with transfusion, corticosteroids, and intravenous vitamin B12 supplementation result in clinical improvement. However, persistent NYHA class II dyspnea prompted cardiology consultation and echocardiography that has revealed the presence of a systolic murmur at the tricuspid area (2/6 intensity, increasing with deep inspiration, Carvalho sign). There were no sign of heart failure observed during the examination. Pleural pulmonary and abdominal examination did not show any abnormalities. An electrocardiogram indicated irregular atrial fibrillation at a rate of 70 bpm, with a normal cardiac axis and no signs of chamber hypertrophy or repolarization disorders. A chest X-ray revealed cardiomegaly (cardiothoracic ratio 0.65), a concave right heart border, and a straightened left mediastinal border without any parenchymal anomalies.

Transthoracic echocardiography (Figure 1) revealed mild dystrophic thickening of the tricuspid valve, with a 15 mm diastasis causing lamellar regurgitation (Figure 2) that affected the right heart cavities. The right ventricle was dilated and hypertrophied with a basal diameter of 55 mm, RV/LV ratio > 1(Figure 3), and a free wall thickness of 8 mm). However, the right ventricle showed good function with a TAPSE 21 mm, fractional area change of 40% and IVA of 4 m/s². The right atrium was dilated with a surface area of 40 cm², and the inferior vena cava dilated during inspiration in a compliant manner. Whereas, the left ventricle functioned normally with preserved ejection fraction of 68%. The left atrium was dilated with a surface area of 26 cm², with mild mitral valve regurgitation on a thin, pliable valve.

Transesophageal echocardiography confirmed secondary lamellar tricuspid regurgitation due to annular dilation with a 10 mm diastasis, which complicated the severe right ventricular dilation. Preoperative assessment included normal coronary angiography, comprehensive blood work that excluded vitamin B12 deficiency, and ruling out infectious foci.

The patient underwent tricuspid annuloplasty using a 32 mm Sovering band under cardiopulmonary bypass, secured with Ethibond 2/0 U-stitches. The postoperative course was uneventful, and follow-up echocardiography confirmed a well-seated, non-regurgitant, and non-stenotic tricuspid repair.

DISCUSSION:

Etiologies and Pathophysiology:

Tricuspid regurgitation is traditionally classified as primary or secondary. Primary causes include congenital anomalies such as Ebstein's anomaly or acquired abnormalities that affect the valve or subvalvular apparatus. Acquired primary tricuspid regurgitation can occur due to various factors, including tumors (such as carcinoid disease or myxoma), iatrogenic factors (from pacemaker or defibrillator leads, or endomyocardial biopsy), trauma, infection (such as infective endocarditis), medications (such as dopamine receptor antagonists, anorectics), radiation therapy, or systemic and rheumatic diseases.

Secondary tricuspid regurgitation occurs when it is associated with left-sided valvular disease, pulmonary hypertension, or right ventricular pulmonary or ischemic pathology. This typically happens because increased left atrial pressures lead to pulmonary hypertension and increased right ventricular afterload, resulting in annular dilation and subsequent failure of valve coaptation.

However, it has been observed that some patients can be diagnosed with moderate to severe tricuspid regurgitation even if they do not fit into the established causes for this condition. The incidence of tricuspid regurgitation tends to increase with age and the presence of atrial fibrillation. Furthermore, a distinct condition known as isolated tricuspid regurgitation has emerged and is becoming more prevalent. Atrial fibrillation causes the right atrium to dilate and remodel, which lead to annular dilation and eventually creates a defect in the coaptation defect of the valve leaflets.

Isolated tricuspid regurgitation can present clinically with signs of right heart failure, particulary when severe and complicated by right ventricular dysfunction. It may also remain asymptomatic and be incidentally diagnosed during a clinical examination or routine echocardiography, which is usually performed as part of an atrial fibrillation assessment when isolated (Figure 5).

Diagnosis of Tricuspid Regurgitation:

The diagnosis of tricuspid regurgitation primarily relies on imaging, specifically transthoracic echocardiography, which is the main examination. The assessment of tricuspid regurgitation should be multi parametric considering its implications in therapeutic decisions. One of the advantages of echocardiography is its ability to accurately evaluate the severity of tricuspid regurgitation and distinguish between isolated tricuspid regurgitation and signs that suggest primary or secondary causes.

To achieve this, the echocardiographic exam should include several quantitative parameters: regurgitant orifice area, regurgitant volume, and vena contracta. These parameters can be measured using the proximal isovelocity surface area (PISA) method, which is considered the most reliable for quantifying regurgitation. Additionally, 3D echocardiography provides more accurate volumetric measurements and has a higher severity threshold. This is important because it highlights the systematic underestimation of regurgitant areas by the PISA method.

These parameters have contributed to a new classification proposed by Hahn and Zamorano (Figure 6). The purpose of this classification is to better define patient subcategories and estimate improvement post-treatment. It consists of 5 grades and subdivides severe tricuspid regurgitation into three categories: severe, massive, and torrential. This classification also serves prognostic purposes, as the massive and torrential forms are associated with higher mortality rates.

The severity of regurgitation is determined by an EROA greater than 0.45 cm^2 and a regurgitant volume exceeding 45 ml/beat. it is classified as massive if EROA exceeds 0.6 cm^2 and torrential if it surpasses 0.8 cm^2. Due to the challenges in evaluating this regurgitation, it is important to consider other semi-quantitative parameters as well. The tricuspid valve which is made up of at least three leaflets, complicates the use of the PISA method because of the elliptical shape of the regurgitant orifice. Other markers to consider include the evaluation of valve morphology, continuous wave Doppler flow patterns, and hepatic vein flow. Signs such as inadequate leaflet coaptation, triangular and laminar flow defects, reflux in the suprahepatic veins, paradoxical septum, or inferior vena cava dilation indicate severe regurgitation.

To assess the impact of tricuspid regurgitation, it is necessary to evaluate the size of the right heart chambers and the right ventricular systolic function using parameters such as TAPSE, peak systolic velocity, tricuspid S wave, 2D fractional shortening, and 3D ejection fraction. It is also important to assess pulmonary pressures, measure the diameter of the inferior vena cava, and look for systolic flow inversion in the suprahepatic veins. Thresholds indicating right ventricular dysfunction include an effective regurgitant orifice area less than 35%, TAPSE less than 17 mm, S wave less than 9.5 cm/s, longitudinal strain less than 20%, and ejection fraction less than 45%. A right ventricular end-diastolic diameter of 40 mm or an indexed diameter of 21 mm/m^2 indicates severe annular dilation.

Despite the specific anatomical challenges posed by tricuspid valve, echocardiography remains a valuable tool. In complex cases, cardiac MRI can be used as an alternative to, calculate the regurgitant fraction and assess right ventricular systolic function. Synchronized cardiac CT is mainly used preoperatively to determine the feasibility of intracardiac device implantation, such as percutaneous valves.

Treatment:

The surgical treatment of the tricuspid valve is generally a straightforward procedure. It typically consists of anuloplasty for cases where the valve leaflets are intact and regurgitation has occurred due to annular dilation. For valvular lesions, repair or valve replacement with prostheses may be considered. The decision to undergo surgery is based on the specific etiology and clinical context of the regurgitation.

Surgical management for tricuspid regurgitation is well-defined when it is secondary to left-sided valvular disease and requires concomitant surgery. However, it is more limited for functional tricuspid regurgitation. Surgical indication is recommended (Class IIa by ESC and Class IIb by AHA) for late-onset regurgitation post-left valve surgery (25-30% of cases), particularly when the regurgitation is moderate to severe and there is tricuspid annular dilation (antero-posterior diameter $\geq$ 40 mm or 21 mm/m^2), and there is no severe right and/or left ventricular dysfunction or severe pulmonary vascular disease.

The current management of isolated functional tricuspid regurgitation and its natural history when associated with atrial fibrillation are not adequately addressed. Topilsky et al. studied the prognosis and management of severe isolated tricuspid regurgitation, highlighting unfavorable outcomes when it is associated with atrial fibrillation. The study showed 5-year survival and event-free rates of around 60% and 58%, respectively. The study also highlighted the underutilization of tricuspid valve surgery for atrial fibrillation-related regurgitation, despite potential benefits. However, the incidence of cardiac death significantly increases in patients with prior hospitalization for right heart failure (26% at 5 years post-hospitalization).

Wang et al.'s meta-analysis aimed to identify risk factors that exacerbate functional tricuspid regurgitation. The study highlighted atrial fibrillation and the absence of its ablation, age, rheumatic etiology, and tricuspid annular dilation as risk factors. Their retrospective study of 1,568 patients explored the impact of atrial fibrillation on regurgitation progression after mitral valve surgery. Among these patients, 408 underwent atrial fibrillation ablation, compared to 1,160 who did not. The study found higher reoperation rates for regurgitation in patients who did not undergo ablation. At 10 years, patients who underwent ablation had significantly better survival rates, lower reoperation rates (HR 1.85), and less severe regurgitation (HR 1.37). Patients who developed regurgitation following mitral surgery had a poorer prognosis due to higher surgical risk from reintervention and a higher prevalence of right ventricular dysfunction.

Kusajisma et al. demonstrated that tricuspid annuloplasty in grade 2 tricuspid regurgitation limits progression to grades 3 and 4. The study compared two groups with grade II regurgitation: 96 untreated patients and 47 who underwent annuloplasty. Follow-ups at 1 week and 1 year showed a significant reduction in regurgitation severity, although there was progressive worsening over subsequent evaluations (progression to grades 3 and 4 between 7 and 10 years). Conversely, none of patients who underwent tricuspid annuloplasty had regurgitation exceeding grade 1 at 5 years.

Treatment Perspectives:

Studies have shown that managing functional tricuspid regurgitation actively, even if it is only moderate during mitral surgery, leads to positive outcomes. However, there is a lack of research on the risks associated with tricuspid annuloplasty during mitral surgery. Jouan et al. conducted a study on 201 patients undergoing surgery for non-ischemic mitral disease, with 88 of them also undergoing tricuspid annuloplasty. The indication for tricuspid surgery in this group was usually moderate to severe regurgitation often accompanied by annular dilation in two-thirds of the cases. The Postoperative outcomes were similar between the two groups, although the tricuspid surgery group had significantly higher rates of pacemaker implantation.

When atrial fibrillation exacerbates untreated tricuspid regurgitation during mitral surgery, it is important to consider similar surgical indications as functional regurgitation. While published studies support the use of annuloplasty, it is essential to establish therapeutic guidelines in this specific context to ensure widespread treatment and ongoing evaluation in a larger patient population.

CONCLUSION:

Isolated tricuspid insufficiency is a rare clinical entity that can be overlooked due to its often subtle presentation. This case highlights the potential association between pernicious anemia and tricuspid valve dysfunction, suggesting that vitamin B12 deficiency may contribute to valvular alterations through mechanisms such as hematological disturbances, endothelial dysfunction, and hyperhomocysteinemia. Early recognition and correction of pernicious anemia are crucial, as timely vitamin B12 supplementation may help prevent further cardiac complications. This observation underscores the need for a comprehensive cardiovascular assessment in patients with pernicious anemia and calls for further research to better understand the pathophysiological link between vitamin B12 deficiency and valvular disease.

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ILLUSTRATION:

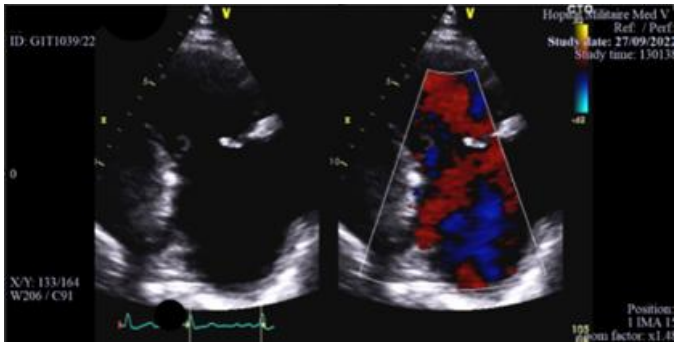

Figure 1: Echocardiographic images in parasternal long-axis view centered on the right cavities showing a dystrophic tricuspid valve, with a diastasis measuring 15 mm and significant regurgitation on color Doppler.

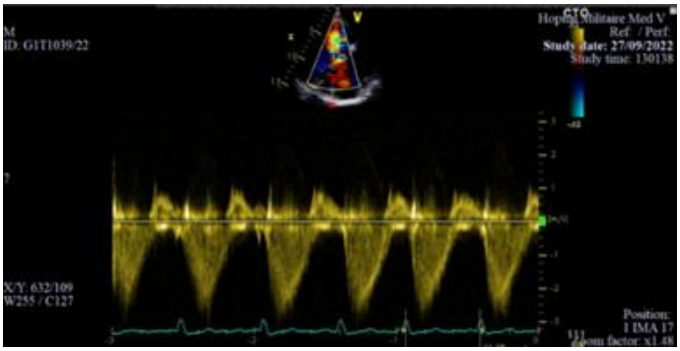

Figure 2: Echocardiographic image in apical four-chamber view showing a laminar tricuspid regurgitation on continuous Doppler.

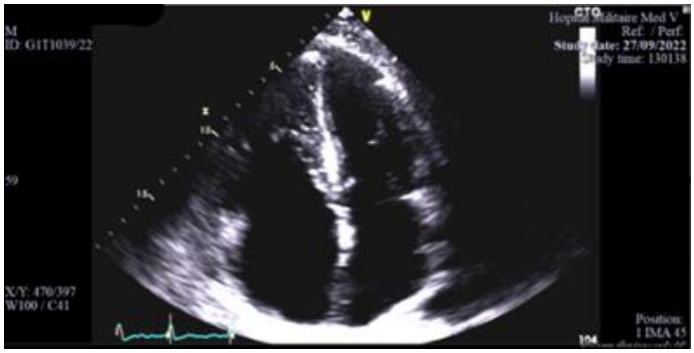

Figure 3: 2D echocardiographic image in apical four-chamber view showing dilation of the right cavities with inversion of the RV/LV ratio, which is > 1.

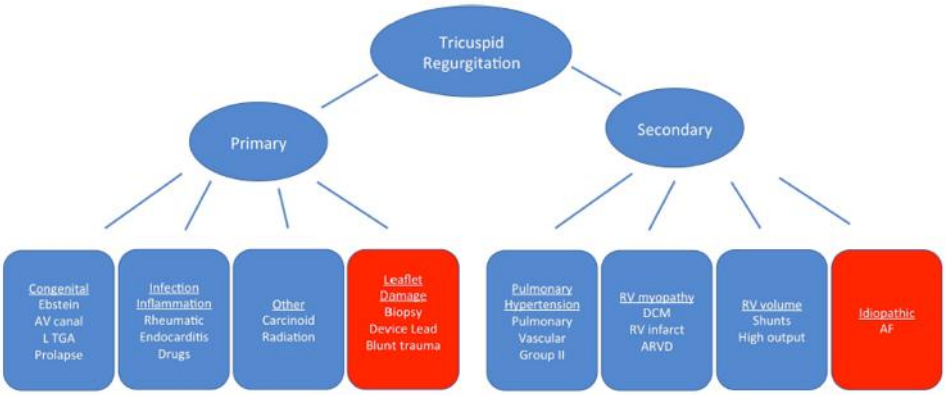

Figure 4: The etiologies of tricuspid regurgitation. AF: atrial fibrillation, ARVD: arrythmogenic right ventricular dysplasia, AV: aortic valve, DCM: dilated cardiomyopathy, LTGA: L-transposition of the great arteries, RV: right ventricle

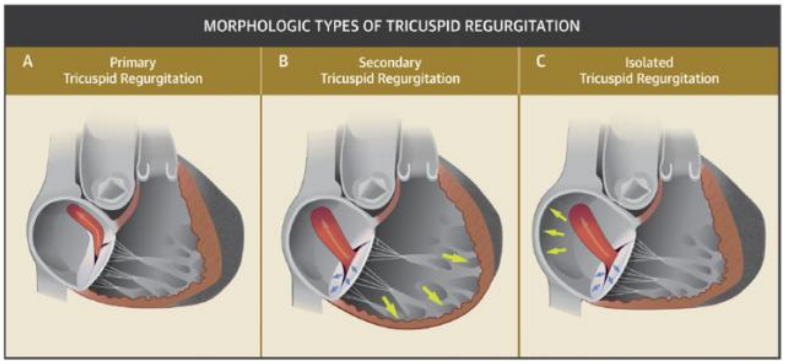

Figure 5: Schematic drawing of the different morphologic types of tricuspid regurgitation.

	Mild	Moderate	Severe	Massive	Torrential
Structural					
TV morphology	Normal or mildly abnormal leaflet	Moderate abnormal	Severe valve lesions	Annular dilation, leaflet tethering	Big coaptation gap, annular dilation, severe tethering
IVC diameter	<20 mm	21–25 mm	>25 mm	Not defined	Not defined
RV and RA	Usually normal	Mild dilation	Dilated	Severe dilation	Severe dilation
Qualitative					
Color flow jet areas	Small, central	Moderate central	Large central jet or	Large central or eccentric	Large central or eccentric
CWD jet	Faint/partial/parabolic	Dense, parabolic, triangular	Dense, triangular	Dense, triangular	Dense, triangular
Semiquantitative					
PISA radius (mm)	≤5	5–9	>9	>9	>9
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic reversal	Systolic reversal	Systolic reversal
Tricuspid inflow	A-wave dominant	Variable	E-wave >1 m/s	E-wave >1 m/s	E-wave >1 m/s
Quantitative					
VC biplane (mm)	<3	3–6.9	7–13	14–20	≥21
EROA (PISA) (mm^2)	<20	20–39	>40–59	60–79	≥80
EROA (quantitative or 3D VCA) (mm^2)	Not defined	Not defined	75–94	95–114	>114
R Vol (ml/beat)	<30	30–44	>44	–	–

Data.[2,10,11,17] CWD, continuous-wave Doppler; EROA, effective regurgitant orifice area; IVC, inferior vena cava; R vol, regurgitant volume; RA, right atrium; RV, right ventricle; VC, vena contracta; VCA, vena contracta area.

Figure 6: Classification system for tricuspid regurgitation

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Author contribution:

MB: Study concept, Data collection, Data analysis, writing the paper.

RL: Study concept, Data collection, Data analysis.

RF: Study concept, Data analysis, writing the paper.

NM: Supervision and data validation

IA: Supervision and data validation

AB: Supervision and data validation

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Competing interests:

None.

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