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Ebstein Anomaly in an Adolescent: A 'Miranda Warning' against Blaming Sickle Cell Cardiomyopathy: A Case-Based Scholarly Update

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Authors' contributions

This work was carried out in collaboration among all authors. Author FAG conceptualized the report, did a literature search and wrote the first draft. Author WSI did the literature search and reviewed the manuscript. Author AIG searched the literature, prepared the images, and reviewed the manuscript. Author IBA analysed and interpreted the patient data regarding the defect and treatment options. Author JNI did a literature search and revised the first draft. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Background: Ebstein's anomaly (EA) is a rare congenital heart disease characterized by apical displacement of the tricuspid valve associated with atrialisation of the right ventricle. The defect arises from failure of the normal process by which the tricuspid valve is separated from the right ventricular myocardium. Most cases are diagnosed in childhood, but asymptomatic ones may remain undiagnosed until adulthood.
Case Summary: We present a rare case of EA diagnosed for the first time in a 13-year-old female sickle cell anaemia patient when she developed biventricular heart failure with severe tricuspid regurgitation and biventricular thrombi which was managed medically; however, patient died 17 days into admission.
Conclusion: The Ebstein anomaly can presents in adolescents for the first time and is usually associated with pericardial effusion and ventricular thrombi. Due to its similarity in presentation to sickle cell cardiomyopathy, it can be missed in sickle cell anaemia patients. Echocardiography can help unravel this diagnostic dilemma.

Keywords: Biventricular thrombi; congenital heart defects; diagnostic dilemma; ebstein's anomaly; echocardiography.

1. INTRODUCTION

Ebstein's anomaly (EA) is a rare congenital heart disease, occuring in approximately one per 20,000 live births and accounts for less than 1% of congenital cardiac diseases [1]. It is characterised by the apical displacement of the septal and posterior leaflets of the tricuspid valve [2]. Ebstein anomaly often features a large, redundant anterior leaflet described as 'Sail-like,' which may include fenestrations contributing to tricuspid regurgitation (TR) [3]. This anomaly results from a developmental failure to properly separate the tricuspid valve from the right ventricular myocardium [2]. The clinical manifestations of EA are highly variable, depending on factors such as the extent of tricuspid valve displacement and the severity of right ventricular outflow tract obstruction, along with associated malformations [4-7]. This variability often leads to delayed diagnosis, with symptoms sometimes not appearing until teenage years or young adulthood. Moreover, the condition's complexities can mimic other cardiac disorders, notably sickle cell cardiomyopathy, due to overlapping clinical presentations such as heart failure.

The apical four chamber view is the preferred echocardiographic plane for evaluation.

2. CASE PRESENTATION

The patient was a 13-year-old female sickle cell anaemia (SCA) patient was diagnosed at 8 years of life but had since defaulted follow-up. She was referred from an NGO facility with a history of recurrent fever and cough of 2 months. Fever was low on and off, cough, which was nonproductive, non-barky or paroxysmal associated with bluish discoloration of the lips and had associated dyspnea on mild to moderate exertion for two months. There was an associated 6-week history of palpitations. The symptoms occurred at rest, 3-4 times per week, with no easy fatigability nor orthopnea. The patient did not report any previous heart disease and had only received folic acid and proguanil since diagnosis of SCA. She had been transfused in a primary health care facility on five different occasions in the past, last transfusion was two weeks prior to presentation. On examination, an acutely ill-looking child, in respiratory distress, afebrile, jaundiced, not pale, cyanosed, not dehydrated, no peripheral oedema, has grade III finger clubbing. She weighs 30kg (below 5th centile) and has a height of 144cm (between 10th and 25th centiles). Dyspneic with flaring of ala nasi and subcostal recession, and tachypneic with RR 30 c/m, SpO_2 of 82% in room air. There was equal chest expansion bilaterally, the percussion notes were resonant and had clear lung fields. Although tachycardic (PR 186c/min), her BP (106/76mmHg) was within normal limits. The JVP was raised, had a hyperactive precordium and the apex was also displaced (6th ICS anterior axillary line). The heart sounds were normal but had associated Grade III holosystolic murmur loudest at the lower left sternal border. Abdomen was slightly distended with moderate ascites demonstrable by shifting dullness and had a firm, smooth andtender liver (hepatomegaly 6cm below the RCM).

The patient was initially evaluated for suspected disseminated tuberculosis (PTB and TB adenitis with moderate pleural effusion in a SCA patient, to rule out sickle cell cardiomyopathy. An electrocardiogram (ECG) revealed normal sinus rhythm, a tall P wave, suggestive of right atrial enlargement, a delta wave due to pre-excitation from an accessory pathway, which along with the widened QRS complex (Fig. 1), raised suspicion for EA. The chest ultrasound showed mild to moderate pericardial fluid collection, supporting the diagnosis of EA over sickle cell cardiomyopathy.

Chest radiograph showed an enlarged cardiac silhouette (cardiothoracic ratio: 0.67), resulting from enlarged right chambers. The pulmonary vascular network was slightly decreased, and the aortic knob was prominent (Fig. 2).

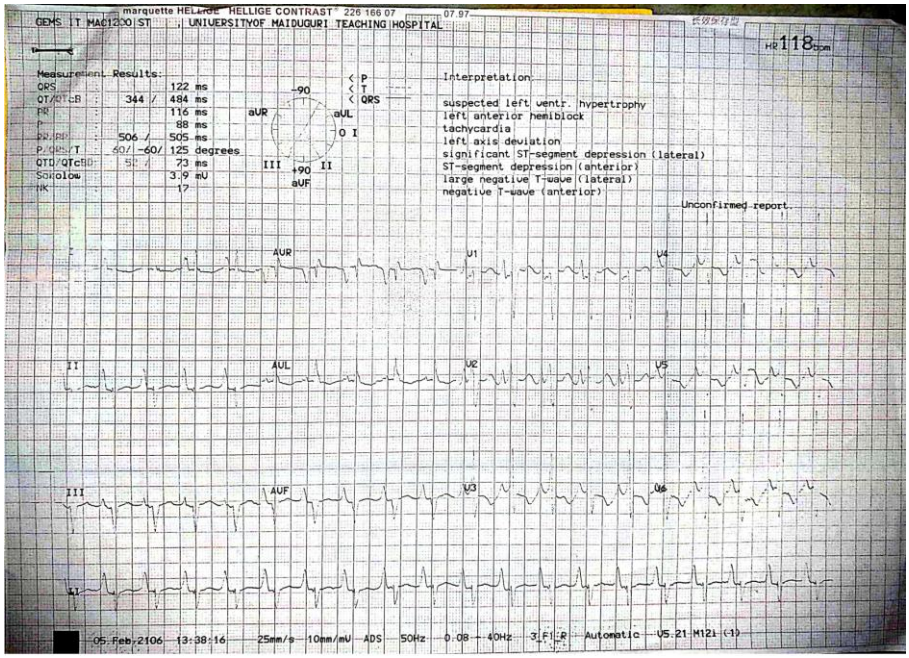

Fig. 1. ECG revealed features consistent with Ebstein's Anomaly

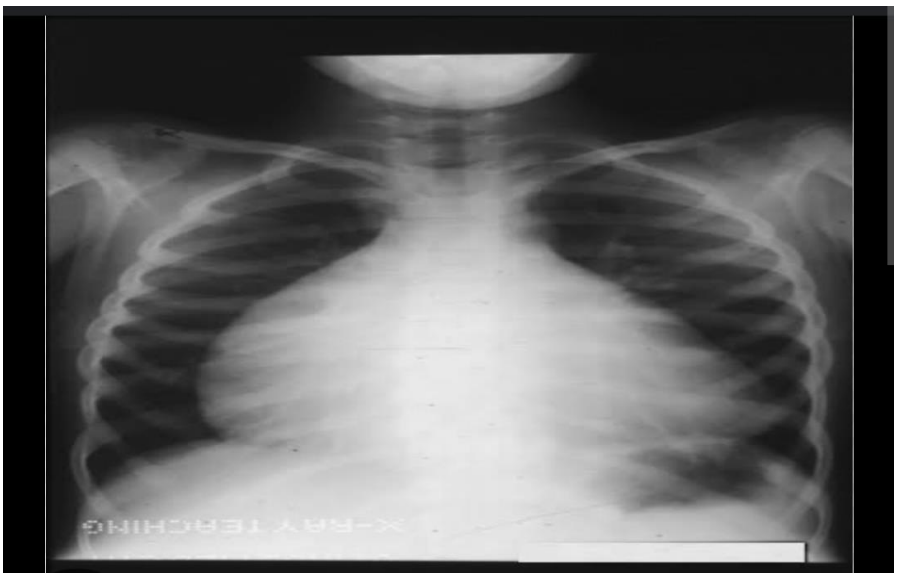

Fig. 2. Chest radiograph showing cardiomegaly with right sided chamber enlargement and prominent aortic knob

Transthoracic echocardiography demonstrated the presence of EA: the tricuspid valve was apically displaced, and formation of an “atrialized” right ventricle. There is an associated left ventricular thrombus (Fig. 3A & 3B).

Other laboratory investigations showed the packed cell volume ranged between 33-37%, INR of 1.1 to 1.9 over the period of admission. All screenings for tuberculosis (sputum gene Xpert MTB/RIF, Mantoux test) were negative.

The patient was placed on treatment for heart failure according to the guideline-directed medical therapy using frusemide, carvedilol and enalapril. Placed on intranasal oxygen and subcutaneous Clexane at 30mg 12hrly X 5/7 and tabs warfarin 5mg od X 2/52 as per protocol [8].

The patient’s condition had clinically improved 16 days into admission and was out of heart failure, clinically. However, the patient developed a sudden episode of breathlessness and collapsed on her way to the bathroom. All resuscitative measures were not successful and was certified death. No permission for autopsy was granted postmortem by the parents; the child probably died from a thromboembolic phenomenon or paroxysmal tachyarrhythmia.

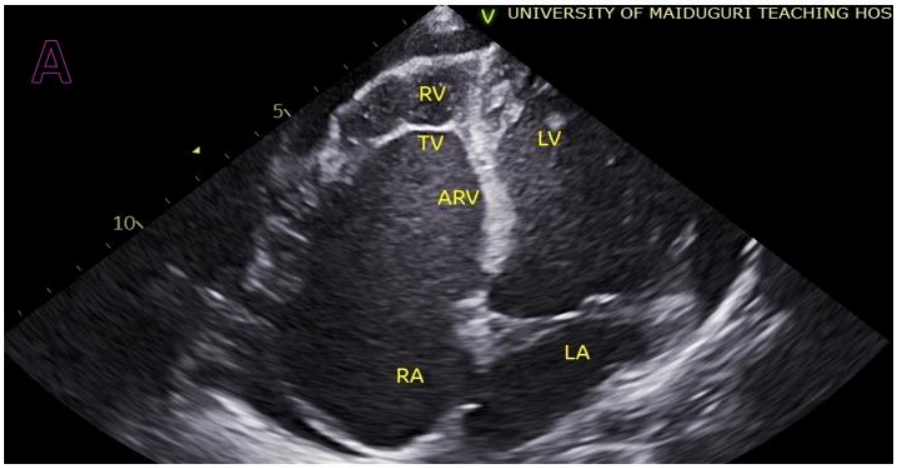

Fig. 3A. Apical 4 chamber view showing Apical displacement of tricuspid valve with enlarged right atrium, "Atrialized" right ventricle and small "functional" right ventricle

RV (Right Ventricle), TV (Tricuspid Valve), ARV (Atrialised’ Right Ventricle), RA (Right Atrium), LA (Left Atrium), LV (Left Ventricle)

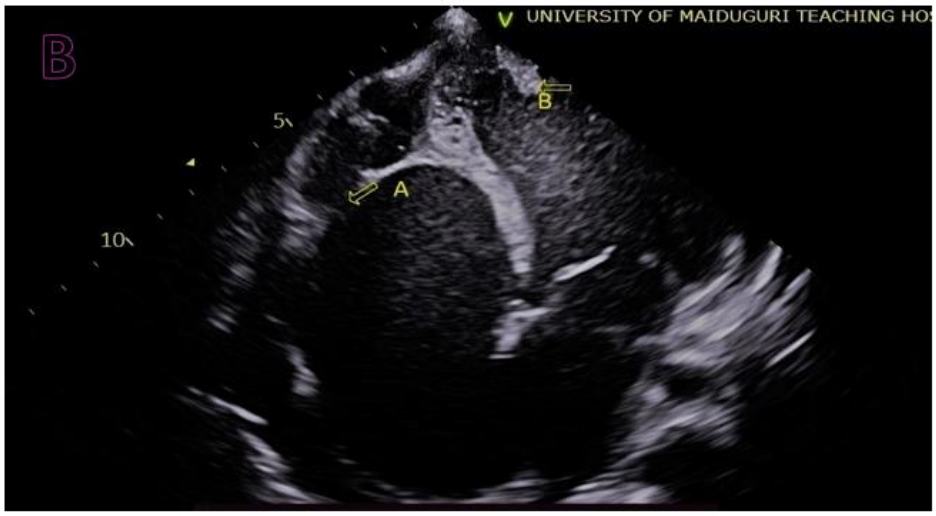

Fig. 3B. A: Tricuspid septal leaflet, B: LV thrombus

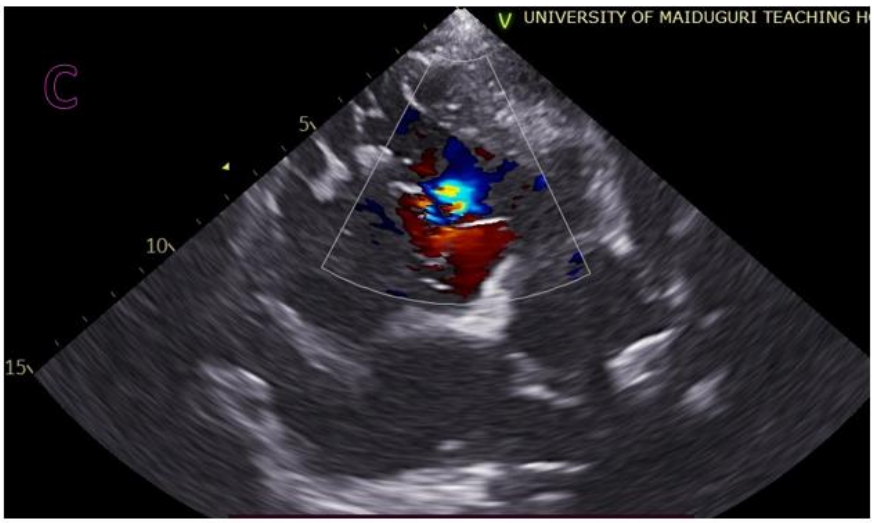

Fig. 3C. Parasternal short axis view at base. Colour doppler through the tricuspid valve showing tricuspid regurgitant jet

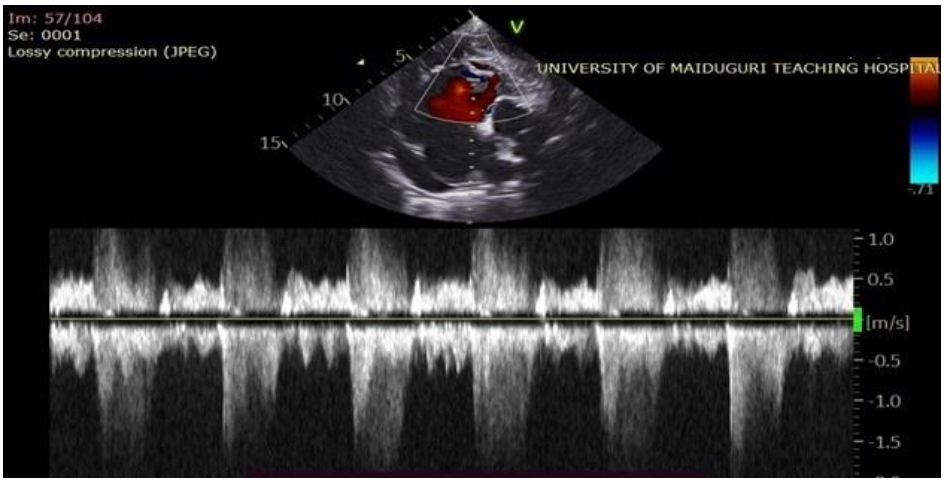

Fig. 3D. Continuous-wave spectral Doppler profiles through Tricuspid valve demonstrating a low-velocity jet with triangular jet profile indicating severe tricuspid regurgitation jet

3. DISCUSSION

3.1 Diagnostic Challenges

This report demonstrates the fact that patients with a long-standing condition and diagnostic dilemma may present to a secondary care facility that lacks appropriate diagnostic tools like Potiskum General Hospital in Yobe State Northeast region of Nigeria that was devastated by insurgency; resulting in a delay in diagnosis and management. Diagnosis of EA is commonly made in younger children, less than one year. It usually presents with features of heart failure and arrhythmia but can also have rare associations like pericardial effusion and biventricular thrombi as was seen in the index case. Diagnosis in older children can be challenging, especially in the setting of comorbid conditions like sickle cell anaemia, because EA can mimic sickle cell cardiomyopathy as seen in our patient. Although very rare, it can present in such patients as a comorbidity. A high index of suspicion and appropriate imaging is important in making the diagnosis.

“Although survival has significantly improved in the last four decades, the diagnosis of Ebstein anomaly is still associated with a 20-fold increased risk of mortality” [9]. “The main pathologic finding of EA is apical displacement of the tricuspid septal leaflet which our patient had.

The diagnosis was confirmed after a thorough review of history, examination, and investigations (including echocardiography) in our patient. Common associations of EA include interatrial communication, patent foramen ovale, ventricular septal defect, and distal right ventricle anomalies" [2]. The index patient had atrial septal defect. Clinical presentation is variable and depends on the degree of tricuspid valve malformation and associated cardiac anomaly. In infants, common presentation is usually an incidental murmur or insipient heart failure while in adolescents, presentation is usually with arrhythmias [10]. Poor prognostic indicators include male sex, cyanosis, Haemoglobin > 15 g/dL, heart failure, CRT ≥ 0.65 (index case had 0.67), atrial arrhythmia, Severe TR, intracardiac thrombi (index case had biventricular thrombi), and coronary artery disease [11]. Prior to our patient's demise, the prognosis was deemed unfavourable based on the aforementioned criteria.

Ebstein anomaly may pose a diagnostic dilemma in SCA presenting for the first time with heart failure in adolescent due to variability in its clinical presentation and rarity hence the clinical suspicion of its alternative diagnosis as SCA cardiomyopathy as suggested in our patient. Furthermore, chronic anaemia with repeated blood transfusions in her clinical history was a pointer to suggest that a causal relationship might exist. "This could have led to iron overload; the excess iron released into the circulation, causing saturation of the carrying capacity of transferrin, and non-transferrin bound iron (NTBI) will appear in the serum. This free iron is taken up by cells of various organs, including the heart: this increases reactive oxygen species production and causes cellular damage" [12]. "Heart damage occurring due to the above-mentioned mechanism causes a unique form of cardiomyopathy. An infiltrative/restrictive cardiomyopathy with defining features such as diastolic dysfunction, LA enlargement, and normal systolic function along with LV dilatation. It is interesting to note here that even though there is a presence of LV dilatation, systolic dysfunction is very uncommon in SCD-related cardiomyopathy" [12]. Nevertheless, echocardiographic findings clearly delineates the anatomic and functional abnormalities of the tricuspid valve and associated defects of the atrial septum proving it to be from EA and thus, assisted in delineating these various pathologies specific to EA rather than sickle cell cardiomyopathy.

Definitive diagnosis of EA is made quantitatively when there is an apical displacement of the septal leaflet hinge point by at least 8 mm/M^2 from the anterior mitral leaflet insertion, assessed in a four-chamber view [13]. Multimodality imaging is key not only for anatomical and functional assessment of tricuspid valve and right-sided chambers but also for identifying associated lesions.

The main pathologic finding of EA is the apical displacement of the tricuspid septal leaflet, which our patient had. Definitive diagnosis of EA is made quantitatively when there is an apical displacement of the septal leaflet hinge point by at least 8mm/M^2 from the anterior mitral leaflet insertion, assessed in a four-chambered view [13]. Multimodality imaging is key for anatomical and functional assessment of tricuspid valve and right-sided chambers as well as for identifying associated lesions.

Transthoracic echocardiography (TTE) is usually the first diagnostic tool that is mostly effective, adequate and is available in our facility, which we utilised. Second-line imaging includes transoesophageal echocardiography and cardiovascular magnetic resonance; the former with particular usefulness in TV assessment, while the latter in right-sided chamber volumes calculation, myocardial characterisation and functional evaluation. The need for anaesthesia, motion artifacts, and the presence of tachycardia limit their usefulness. Our patient had only TTE, other imaging modalities were not available in our centre.

The diagnosis was confirmed after a thorough review of history, examination, and investigations (including echocardiography) in our patient. Common associations of EA include interatrial communication, patent foramen ovale, ventricular septal defect, and distal right ventricle anomalies [2]. The index patient had an atrial septal defect. Clinical presentation is extremely variable and depends on the degree of tricuspid valve malformation and the type of associated cardiac anomaly. In infants, common presentation is usually an incidental murmur or insipient heart failure while in adolescents, presentation is usually with arrhythmias [7].

3.2 Diagnostic Dilemma

Ebstein anomaly poses a diagnostic dilemma in SCA presenting for the first time with heart failure in adolescents, due to variability in its clinical

presentation and rarity hence the clinical suspicion of its alternative diagnosis as SCA cardiomyopathy as suggested in our patient. Furthermore, chronic anaemia with repeated blood transfusions in the patient's clinical history was a pointer to suggest that a causal relationship might exist. This could have led to iron overload; the excess iron released into the circulation, causing saturation of the carrying capacity of transferrin, and non-transferrin bound iron (NTBI), will appear in the serum. This free iron is taken up by cells of various organs, including the heart: this increases reactive oxygen species production and causes cellular damage [9]. Heart damage occuring due to the above-mentioned mechanism causes a unique form of cardiomyopathy. An infiltrative/restrictive cardiomyopathy with defining features as diastolic dysfunction, left atrial enlargement, and normal systolic function along with left ventricular enlargement, these patients may clinically present with congestive cardiac failure similar to EA patients. Nevertheless, echocardiographic findings differentiate it from EA and thus, may assist in delineating the various pathologies specific to each disease state.

3.3 Prognostic Indicators

Although survival has significantly improved in the last four decades, the diagnosis of Ebstein anomaly is still associated with a 20-fold increased risk of mortality.[6] Poor prognosis indicators include male sex, cyanosis, which index patient had, haemoglobin >15 g/dL, heart failure, which index patient also had, CRT ≥0.65 (index case had 0.67), atrial arrhythmias, severe tricuspid regurgitation, intracardiac thrombi (index case had biventricular thrombi), and coronary artery disease [14]. Prior to our patient's demise, the prognosis was deemed unfavourable based on the aforementioned criteria.

3.4 Management Strategies

Multiple specialists evaluated our patient; Paediatric Haematologist, and Cardiologist. The effect of medical therapy on patients with EA has not yet been solidly investigated [13]. Medical therapy is individualised based on the patient's clinical presentation. Our patient had congestive cardiac failure and ventricular thrombi which were treated as per protocol [8]. However, even the decision for a definitive surgical treatment in the index patient with comorbidity of SCA and EA was difficult due to the wide overlapping spectra of the clinical findings complimentary data with cardiac MRI should be provided. It was, however, not possible because of lack of cardiac MRI facility in the resource-limited setting.

3.5 Implications for Resource-limited Settings

Ebstein anomaly is associated with an increased prevalence of atrial arrythmias with or without an accessory pathway, predominantly paroxysmal supraventricular tachycardia. Our patient had pre-excitation as suggested by the ECG. Atrial fibrillation and flutter and a smaller percentage of patients with paroxysmal ventricular tachyarrhythmias are also seen. Sudden cardiac death due to arrythmias has been reported [15]. In the absence of pre-excitation, the severity of the right bundle branch disease is directly related to the abnormal formation of the septal leaflet. In the absence of TTE or better imaging modalities. The highlighted ECG findings should heighten the suspicion of any clinician in resource-limited settings. It is important to note that the absence of cardiomegaly on the chest radiograph does not necessarily preclude the presence of severe disease.

4. CONCLUSION

Ebstein anomaly can be complicated by congestive heart failure and ventricular thrombi and mimic cardiomyopathy in a SCA patient. A multispecialty review for a definitive diagnosis of EA, highlights the importance of accurate diagnosis using echocardiography in the likelihood of close differential diagnoses; earlier presentation would have allowed for prompt care to prevent thrombus formation in resource-limited settings. The use of ECG can raise the index of suspicion for EA and prompt referral to a facility with echocardiography services for definite diagnosis in similar circumstances. Healthcare facilities should know their limit and refer patients to a higher centre as early as possible once doubt is established in what patient condition is.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or University standards written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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