A rare and challenging case:Infective endocarditis and pulmonary hypertension in a patient with Alagille Syndrome and bicuspid aortic valve

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Abstract

Alagille syndrome is a genetic disease with multi-organ involvement and can cause various congenital cardiac lesions. This syndrome is caused by mutations in the JAG1 and NOTCH gene pathways. As a result of these lesions, pulmonary hypertension can be seen in patients. While pulmonary hypertension is observed especially due to pulmonary valve stenosis; It may be due to various causes such as tetralogy of Fallot. Currently, pulmonary hypertension has not been reported in Alagille patients without cardiac anomaly in the literature.

Introduction

Alagille syndrome is an autosomal dominant disease caused by pathogenic mutations in the JAG1 and NOTCH genes. Multiple system involvement is seen in Alagille syndrome. The most frequently involved system is the hepatobiliary system and is seen as a result of insufficiency of intrahepatic bile ducts. In addition, abnormalities can be observed in the cardiac, vascular, ocular, renal system and skeletal muscles.

Pulmonary hypertension may be present and it can be associated with congenital defects such as pulmonary valve stenosis or Fallot tetralogy.

In this case report we described aortic valve infective endocarditis in a patient with Alagille syndrome and group 1 pulmonary hypertension without any cardiac defect.

Case Report

A 26-year-old young man, who was referred to us with complaints of increasing shortness of breath, fatigue, swollen legs and low blood pressure in the last 1 month, also had a history of intermittent fever attacks and irregular antibiotic use. He was referred to cardiology department by the nefrologist who was following him up for his chronic kidney disease, because of coagulase negative staphylococcus growth in the blood culture.

The patient was diagnosed with Alagille syndrome when he was 1 month old and he had been on a hemodialysis program for the last 5 years after developing end-stage chronic kidney disease. In 2016, transthoracic echocardiography demonstrated elevated pulmonary artery pressure, and right heart catheterization was planned and pulmonary artery pressure was measured as 67 mmHg and pulmonary vascular resistance as 27.9 Wood units. The patient was diagnosed with group 1 pulmonary hypertension and endothelin receptor antagonist monotherapy was started. Two years after the diagnosis of pulmonary hypertension, due

to deterioration in functional capacity (FC 4), triple combination therapy consisting of IV epoprostenol + phosphodiesterase 5 inhibitor + endothelin receptor antagonist was started and a subclavian catheter was inserted for continuous infusion of IV epoprostenol. With this treatment strategy, improvement in the functional capacity of the patient was observed.

The patient was admitted to cardiology ward also due to complex underlying syndrome. On admission his temperature was 36.4°C, heart rate was 90 beats/minute, blood pressure was 80/30 mmHg and respiratory rate was 21 / minute. Oxygen saturation in room air was 98%.

He was rhytmic , and had normal first and second heart sounds with a 3/6 Levine systolic murmur in the aortic focus. His lungs were clear with decreased sounds at the basis bilaterally. Bilateral pretibial edema was remarkable(++/++). Peripheral examination findings related to infective endocarditis were not observed.On inspection, the classic findings of Alagille syndrome such as wide forehead, hypertelorism, 'basic' nose and pointed chin were clearly observed.

Laboratory tests showed normal WBC levels , low platelet count, anemia, elevated CRP, procalcitonin, NT-proBNP and creatine levels. Complete laboratory findings are given in Table 1.

Electrocardiogram (ECG) demonstrated sinus tachycardia and signs of left ventricular overload.

Transthoracic echocardiography(TTE) revealed dilatation of all heart chambers, severe global left ventricular hypokinesia with a left ventricular ejection fraction of 35%, severe tricuspid regurgitation with a high estimated pulmonary artery systolic pressure (71+10 mmHg)(Supplementary video 1, Figure 1). TAPSE was measured to be17 mm. Very eccentric aortic regurgitation was observed, which was not seen on previous echocardiograms, but the degree of the regurgitation could not be evaluated clearly due to the poor acoustic window. (Supplementary video 2). An amorphous, mobile mass measuring 12x6 mm was observed on the ventricular face of aortic valve (Supplementary Video 3-4).

Cardiac MRI was performed for quantification of aortic regurgitation. It confirmed severe, global left ventricular hypokinesia with an LVEF of 28%, increased indexed left ventricular volumes, biatrial dilatation, Sievert type 1 bicuspid aortic valve (Figure 2) and eccentric severe aortic regurgitation with a regurgitant fraction of 50%, mild mitral regurgitation and severe tricuspid regurgitation.

Considering Duke criteria, the patient was diagnosed with infective endocarditis. The patient was consulted to infectious diseases for the appropriate antibiotic therapy. As the vegetation was causing severe aortic regurgitation and decompansated heart failure, cardiovascular surgeons assessed the patient too.

After the multidisciplinary evaluation of the patient, emergent aortic valve replacement was the recommended treatment.However, as the operative mortality risk was very high(EuroSCORE II over 40%), the patient and his family refused surgery. He was discharged from the hospital because of their own request. The patient, who continued to receive vancomycin treatment on dialysis days, experienced sudden cardiac death at 4 months after discharge.

Discussion

Alagille syndrome was first described by Daniel Alagille in 1969.The incidence of Alagille syndrome has been reported as 1:30000 live births (1). Various mutations in JAG1 and NOTCH2 genes have been observed in this syndrome(2-3). These genes encode transmembrane ligands and receptors involved in the Notch signaling pathway. Intracellular proteins formed after proteolytic events in the Notch signaling pathway control gene transcription in the cell nucleus(4). The diagnosis of Alagille syndrome can be made clinically or by demonstrating JAG1 and NOTCH2 gene mutations.

The most common cardiovascular abnormalities seen in Alagille syndrome are stenosis or hypoplasia of the pulmonary artery branches. Another frequently observed condition is tetralogy of Fallot. Apart from these pathologies, various anomalies such as atrial and ventricular septal defect, bicuspid aorta and valvular aortic stenosis may also be seen (5) and observation of cardiac involvement in patients with Alagille syndrome significantly increases mortality (6). Although there is no study conducted for the relationship between

Alagille syndrome and pulmonary hypertension; the presence of pulmonary hypertension in these population is described in several case reports. According to literature it is seen that pulmonary hypertension generally develops in the setting of pulmonary stenosis in patients with Alagille syndrome (7-8). However, recent studies have shown that pulmonary hypertension may develop as a result of disorders in the Notch gene pathway (9-11). Presence of NOTCH mutation seen in our patient may have contributed to the development of group 1 pulmonary hypertension without cardiac anomaly.

Infective endocarditis diagnosis is made by the modified Duke criteria (12). The main topics of treatment can be summarized as antibiotic therapy and surgical treatment in people with appropriate indications. Particularly,indications for surgery in people with a diagnosis of infective endocarditis can be classified into three main groups ; development of heart failure, prevention of uncontrollable infections and embolisms. Emergent valve surgery is recommended with a class 1 indication in cases of acute severe mitral or aortic regurgitation and associated refractory pulmonary edema/cardiogenic shock in infective endocarditis cases. Cardiac surgery is urgently recommended for patients with severe aortic and mitral valve regurgitation and in the presence of signs of heart failure or echocardiographic findings showing poor hemodynamic tolerance (13).

Conclusions

Cardiovascular involvement may be in Alagille syndrome.

Pulmonary hypertension in Alagille syndrome can be seen associated with congenital defects such as pulmonary valve stenosis. In patients with and Alagille syndrome who do not have congenital heart defects; pulmonary hypertension could be associated with NOTCH gene mutations

Figure and Video Legends

Figure 1: Continuous wave doppler image shows estimated pulmonary artery systolic pressure of 71 mmHg from severe tricuspid regurgitation

Figure 2: Cardiac magnetic resonance image of Sievert type 1 bicuspid aortic valve

Supplementary video 1: Color doppler image of severe tricuspid regurgitation from apical 4 chamber window

Supplementary video 2: Color doppler image of eccentric aortic regurgitation from apical 5 chamber window. Due to jets eccentricity cardiac magnetic resonance imaging is performed to determine the severity of regurgitation.

Supplementary video 3: Vegetation on ventricular side of aortic valve is shown in apical 5 chamber window. Patients left ventricle ejection fraction is 35%.

Supplementary video 4: Zoomed view of aortic valve vegetation

Patient Consent

Patient in this case report gave written consent to the publication of his case.

Funding Information

None

Conflict of Interest

None

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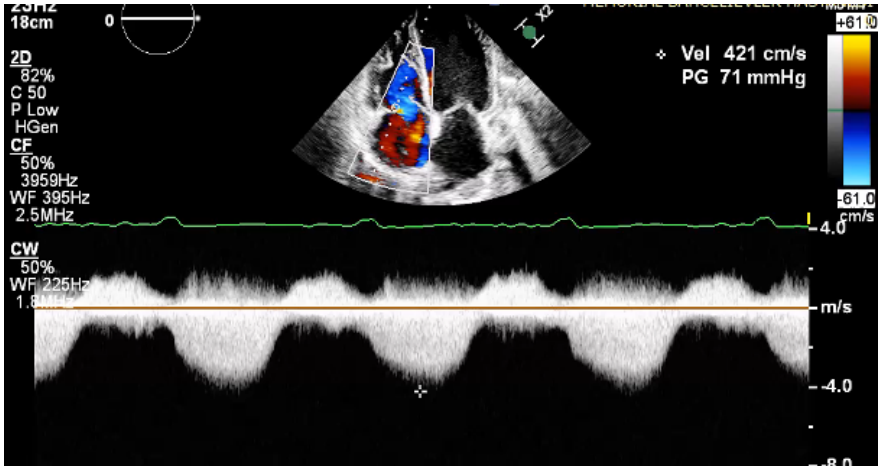

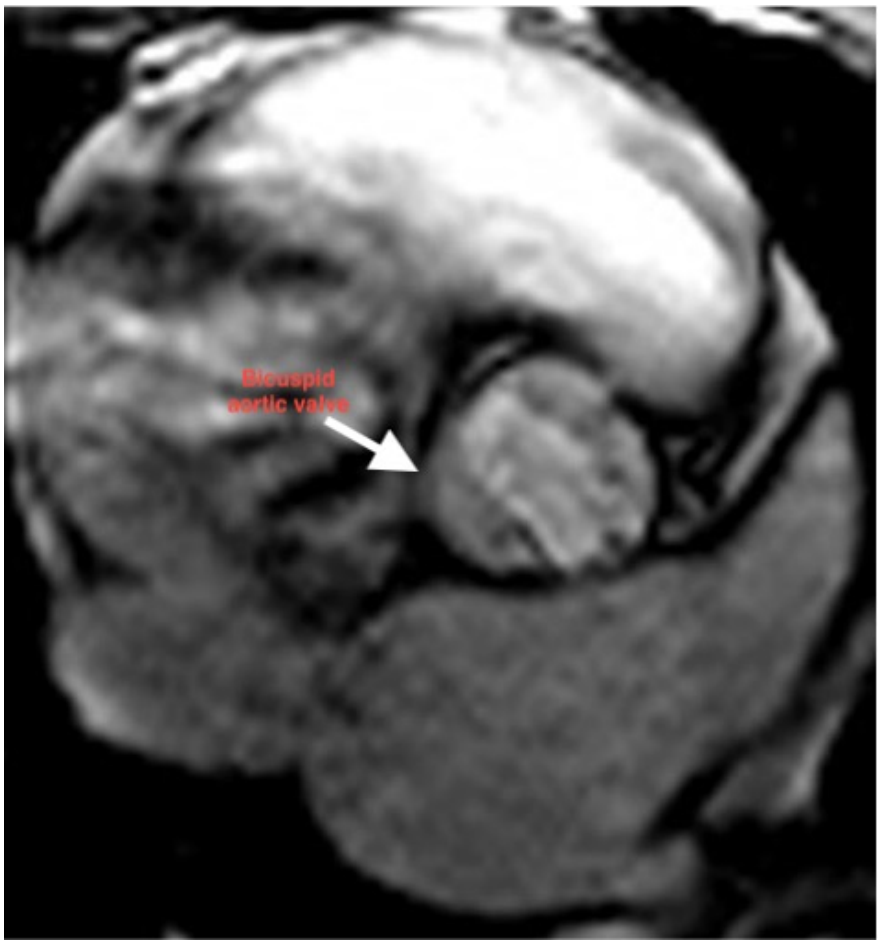

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