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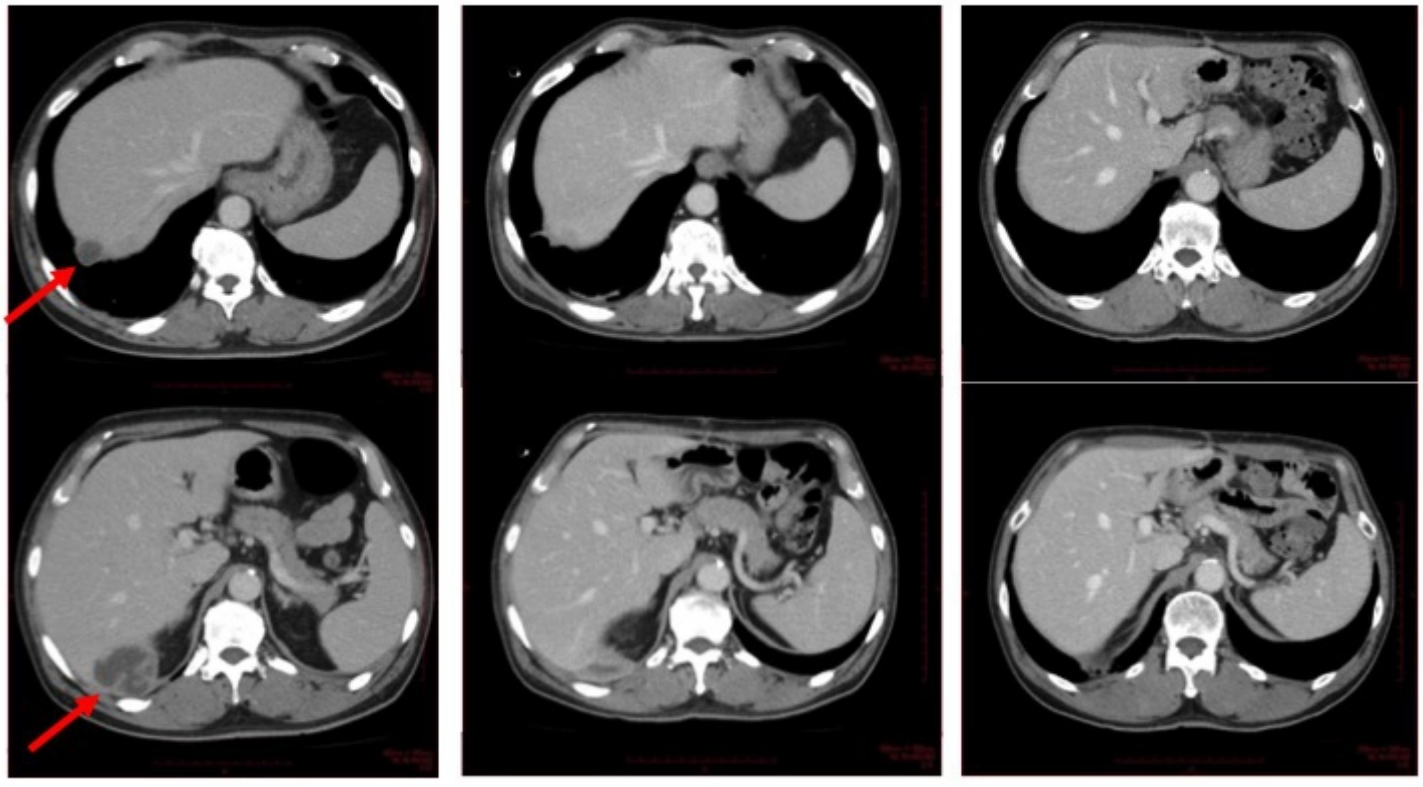

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A Rare Classical Presentation of Bardet-Biedl Syndrome in a Three-Year-Old Male from South East Nigeria: A Case Report

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Abstract

Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive ciliopathy characterized by obesity, post-axial polydactyly, renal abnormalities, mental retardation, pigmentary retinopathy and hypogenitalism. Diagnosis is rare in early childhood, and only few of the features are present at that age. This is because the disease is slow evolving. However, it is possible to find majority of the component of this syndrome in very young children. A 3-year old very obese male presented with clinical features of sepsis and congestive cardiac failure. He is a product of non-consanguineous marriage with unremarkable family history. Both parents are of the Ibo tribe in Nigeria. Polydactyly was noticed at birth. There was delay in some aspects of his developmental milestone. Examination revealed mild hypertelorism and retrognathia, polydactyly of both feet with syndactyly of the big and second toes. Other findings were short broad hands, mottled pigments on the retina, moderate mental retardation, hypogenitalism, nephrotic syndrome, renal tubulopathy, hyperglycaemia and hypopigmented skin lesions. A case of BBS with all the primary features and some secondary manifestations in a very young child is hereby reported. A high index of suspicion for BBS should be shown in any young child with at least one of the features of this syndrome. This will enhance earlier diagnosis and improve disease outcome.

Keywords

Bardet-Biedl Syndrome, Early Childhood, South East Nigeria, Classical Presentation, Case Report

1. Introduction

Bardet-Biedl Syndrome (BBS) is a rare autosomal recessive ciliopathy characterized primarily by obesity, post-

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axial polydactyly, renal abnormalities, mental retardation, pigmentary retinopathy and hypogenitalism [1]-[4]. It is a genetic multisystemic disorder with mutation in 16 different genes [1]. The obesity is mainly truncal, while the retinopathy includes rod-cone dystrophy with childhood onset night blindness and visual loss. Truncal obesity manifests during infancy and remains problematic throughout adulthood. Mental retardation can present with specific learning and behavioral difficulties [1].

The estimated prevalence rate is 1:140,000 - 1:160,000 worldwide [4]. However, higher incidence of 1:1700 - 1:13,500 has been reported from Kuwait and Newfoundland, because of higher consanguinity marriages in these areas [1] [5].

Diagnosis is mainly clinical, and made in late childhood or early adulthood. This is because the disease is slow evolving with gradual loss of night vision and delayed puberty [1]. Significant intrafamilial and interfamilial variations exist in the clinical expression of BBS [4]. Polydactyly may be the only feature at birth [1]-[5].

For ease of diagnosis, the clinical features of BBS are divided into primary and secondary features. The primary features are as aforementioned earlier. The secondary features include developmental delay, behavioral problems, neurological problems, dental anomalies, speech disorders, brachydactyly/syndactyly/clinodactyly, nephrogenic diabetes insipidus, hypertension, diabetes mellitus, anosmia, pigmented naevi, cardiovascular anomalies etc. [1] [3].

A clinical diagnostic criterion of BBS consists of at least four primary features, or three primary features plus two secondary features [1] [3].

I hereby present a case of Bardet-Biedl Syndrome in a 3-year-old male child.

2. Case Report

A 3-year-old male child was referred to us with history of infantile obesity, inability to walk, cough, generalized edema, frequent micturition and difficulty in breathing. There was orthopnoea and paroxysmal nocturnal dyspnoea but no wheezing.

Pregnancy history was uneventful. He was a product of non-consanguineous marriage. Both parents are of the Ibo tribe in Nigeria. He was big at birth but mother could not remember the birth weight. Polydactyly and syndactyly were noticed at birth. His developmental milestone was normal until 12 months of age when it seemed to be halted. He started walking with support at 12 months of life, but yet to walk without support at 3 years of age. His parents attributed this to the infantile obesity. He was yet to speak bi-syllable words or make sentences at 3 years. His appetite was said to be very voracious since infancy, but not to the extent of binging. There was no history of failure to thrive. Family history was not remarkable.

Examination revealed a very obese child (brought in on wheel chair because he could not walk, even with support). He had mild retrognathia and mild hypertelorism. He also had anasarca with short, broad hands (**Figure 1**). There were hypopigmented macular lesions over the neck, shoulders and back, with unilateral genu varus deformity of the right leg. There was also polydactyly (six toes) on both feet with bilateral syndactyly of the big and 2^{nd} toes (**Figure 2**). He was severely dyspnoeic, acyanosed, anictenic, febrile (T-38.2˚C), but not pale.

Weight was 60 kg (>97^{th} centile for age) and height was 99 cm (50^{th} centile for age) with a body mass index of 50.5 kg/m^2 (>97^{th} centile for age). Occipito-frontal circumference was 57 cm, and Mid Upper Arm Circumference was 18 cm (>97^{th} centile for age).

Respiratory rate was 50 cycles/min with decreased air entry both lung fields. There were vesicular breath sounds with generalized coarse crepitation and few rhonchi. Blood pressure was 120/70 mm of Hg, with a heart rate of 140 beats/min. Apex beat was located at 6^{th} LICS–MCL. Only 1^{st} and 2^{nd} heart sounds were heard.

His intelligence quotient, determined by "The Draw-A-Person Test" revealed moderate mental retardation. Muscle tone was normal globally. Abdomen was moderately distended with a tender hepatomegaly of 6 cm. He had micro testis and micro phallus on genital examination.

Dipstick urinalysis showed proteinuria (3^+), haematuria (2^+), glucosuria (1^+), bilirubinuria (1^+), urobilinogenuria (2^+) Urine.

PH was 8.8, with spot urine protein-creatinine ratio of 2.9. Serum urea and creatinine were normal. Thyroid and liver function tests were also normal. Serum cholesterol was 450 mg/dl. All serum electrolytes were normal but for mild hyperkalaemia (K^+ = 5.7 mmol/L) and acidosis (HCO_3 = 18 mmol/L). Total serum protein was 50 g/l while albumin was 24 g/l. Random blood glucose was 7.5 mmol/L.

Complete blood count revealed absolute neutrophilia, while urine culture yielded heavy growth of *Escherichia coli.* Ophthalmological examination revealed mild nystagmus and retinal pigment mottling on both eyes. Abdominal ultrasound was normal, but for moderate hepatomegaly. Chest X-ray showed gross cardiomegaly.

He was admitted at presentation and commenced on Nebulised Salbutamol 5 mg stat, and then Tablet Salbutamol 4 mg 8 hourly for a week, IV Sodium Bicarbonate 30 mmol slowly stat, IV Frusemide 30 mg 12 hourly for 5 days, Tablet prednisolone 30 mg 12 hourly for a month, IV Augmentin 1.2 g 12 hourly for a week, Tab Paracetamol 500 mg 3× daily for 5 days and a 3 day course of oral antimalarial was also given. He was also placed on a "weight reduction" diet by the dietician.

He did well clinically on the above regimen and was able to walk with support again after 5 days of treatment. Most biochemical derangements resolved except the urinary abnormalities (new values were protein 2+, blood 1+) and the serum cholesterol (450 mg/dl). His blood glucose also normalized on the hospital diet. He was discharged after one week of admission on oral prednisolone (60 mg every morning because of the nephrotic syndrome). Parents were also given nutritional counseling concerning his weight.

3. Discussion

BBS varies in its manifestation in different patients [1]-[10]. Apart from the primary features of obesity, postaxial polydactyly, renal abnormalities, mental retardation, pigmentary retinopathy and hypogenitalism; other secondary manifestations exist [1]-[4] [9]. These secondary characteristics include cardiac anomalies, neurological problems, nephrogenic diabetes insipidus, diabetes mellitus, dental anomalies, hypertension, speech disorders, behavioral problems, brachydactyly/syndactyly/clinodactyly, anosmia, lipid disorders, hepatic abnormalities

Figure 1. Truncal obesity with polydactyly/syndactyly of both feet.

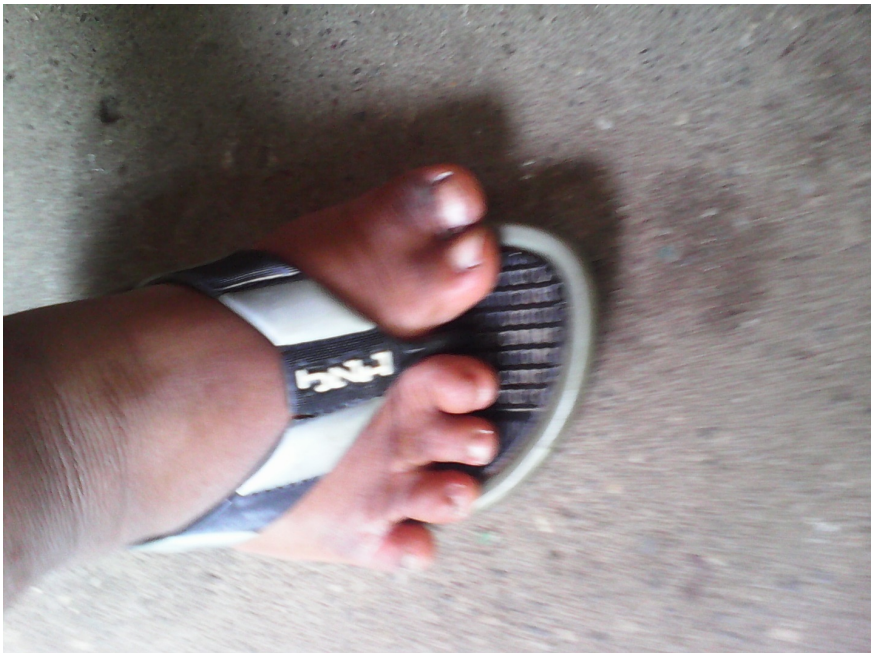

Figure 2. Polydactyly/syndactyly of the right foot.

and skin disorders [1]-[4] [9] [11]. Retrognathia, and hypertelorism are inconsistent features of BBS, and may not be very obvious [1].

At least three primary and two secondary features are enough to make the diagnosis of BBS in a patient [1], [9]. The index patient had all the primary features, plus cardiac pathology and skin lesions. This supports the diagnosis of BBS in our 3-year-old patient [1]-[11]. BBS is the standard term that has replaced the older Laurence-Moon-Bardet-Biedl syndrome after it was found that the phenotypes overlap and may be allelic [1] [12].

The index patient posed a diagnostic challenge initially because of his clinical overlap with syndromes like Alström syndrome and Prader Willi Syndrome (PWS). Alström syndrome shares most features with BBS, however, there is no polydactyly nor cognitive dysfunction in the former [9].

PWS also shares common features with BBS, but unlike in the former, there is no hypotonia, failure to thrive, nor sleeping disturbance in BBS [13]. The patient under discuss has normal muscle tone, and there was no history of feeding difficulties, failure to thrive, nor excessive sleeping. Although the patient's appetite was said to be voracious, there was no history of binging.

Majority of the cases reported in children worldwide were diagnosed either in late childhood or among teenagers [2] [4] [6] [7] [10]. Diagnosis in early childhood is rare [1] [9]. However, few cases have been reported in younger children. Ahmed and Hassan once documented a case of Laurence-Moon-Biedl Syndrome in a 3-year-old Nigerian female who was screened for the disease after the diagnosis was made in her 8 years elder sister [8]. Also, Cristina et al reported a case of BBS with end-stage kidney disease in a 4-year-old Romanian male [9].

Diagnosis is usually not made early because the disease phenotypes are variable and slow evolving [1]. Initial loss of the rod photoreceptors is followed by early macular involvement, with the degeneration of the cone cells. This causes a gradual functional loss of vision [1] [10]. Visual impairment and probably, poor school performance, are the common reasons for coming to hospital in affected patients [1] [4]. The visual pathology then becomes a pointer to the diagnosis in a child with other components of the syndrome.

Our patient presented with sepsis and congestive cardiac failure (CCF). The polydactyly, obesity and mild nystagmus prompted further examination that led to the diagnosis. His parents did not complain about his vision, but were rather worried about the obesity, fever, cough and difficulty in breathing.

Polydactyly and obesity are well documented features of BBS [1]-[10]. Polydactyly when present in BBS, is seen at birth. The incidence of obesity is reported to be 72% - 86% in the BBS population [1] [11] [12] [14]. Although majority of the patients have normal weight at birth, obesity usually sets in by infancy [1] [14]. Polydactyly in a child, more especially with obesity should stimulate a high index of suspicion for syndromic disorders,

including BBS.

The unilateral genu varus deformity found in our patient is likely a complication of his severe obesity. Various types of lower limb deformities result from childhood obesity [15].

Cardiac pathology is a recognized part of BBS [1]-[3]. The CCF in our patient could not be totally explained by the sepsis he had. His cardiac symptoms started 6 months before the onset of cough, fever and frequent micturition. The later symptoms started a week before presentation. Cardiac anomalies, including congenital heart defects and dilated cardiomyopathy, are reported in up to 50% of patients with BBS [1] [2]. Echocardiography was not done for our patient due to financial constraints. Elbedour *et al.* suggested that echocardiographic evaluation be done for all cases of BBS [2].

Liver pathology is found in BBS, though it is considered a secondary feature of the disorder [1] [4] [9] [11] [14] [16]. However, the hepatomegaly in the index patient may be due to the CCF, rather than the BBS. This is because of the normal liver function test, and nil significant hepatic pathology on abdominal ultrasound.

Renal involvement was recently included as a primary feature of BBS [1] [4] [9] [11] [14]. Various kinds of renal pathologies (structural and functional) including nephrotic syndrome and renal tubular acidosis can be found in patients with BBS [1] [4] [8] [10] [11] [17]. End stage renal failure is a major cause of death in these patients [16]. Our patient had both nephropathy and a renal tubulopathy. While Singh *et al*. documented steroid sensitive nephrotic syndrome in a 10-year-old Indian male, Lin & Lin found bilateral dilatation of the renal minor calyces in an 8-year-old female [4] [10].

Skin disorders varying from hyper to hypopigmented lesions and recently multiple pigmented nevi have been reported in patients with BBS [1] [11]. The patches of hypopigmented skin lesions on the index patient may be part of the syndrome. Karaman documented multiple pigmented nevi in a Turkish female with BBS [11].

Early retinal dystrophy, which is slowly progressive in these patients, is the most common component of the syndrome [1] [9] [11]. Mild retinal anomaly is usually the finding in younger patients, while severe retinopathy (retinitis pigmentosa and macular degeneration) is found in older patients. The retinal mottling in our patient depicts early sign of retinitis pigmentosa. Iwuala et al reported nystagmus and retinal mottling in another Nigerian male child with BBS [6].

Although developmental delay and cognitive deficit are common in BBS, mental retardation tends to be variable in these patients [1] [11]. It has been reported that decrease in IQ level correlates with the presence of visual handicap [11] [17].

The hypercholesterolemia in the index patient either reflects the presence of nephrotic syndrome alone, or the deranged hyperlipidaemia that can also occur in patients with BBS [1]. The BBS 5 - 9 and BBS 11 genes are expressed in adipose tissues [11] [18]. Hypercholesterolemia is seen as a secondary feature of BBS.

Both diabetes insipidus and diabetes mellitus are inconsistent findings in some patients with BBS [1] [8] [11]. The index patient had glucosuria and hyperglycaemia.

Hypogenitalism, which is one of the primary features of BBS, is more obvious as the child gets older. Tanner staging in pubertal patients reveals delayed sexual maturation [1] [6]-[11]. In affected children, primary gonadal failure may occur later in life [8]. The index patient, though still very young, has external genitalia that is grossly small for age.

Our patient had financial constraints and this was a major limitation because some important investigations could not be done. Again, his parents were defaulting to the follow-ups. However, the detailed documentations at his initial presentation and the available investigation results made this case report possible.

4. Conclusion

A classical presentation of BBS in very young children is rare. The presence of all the primary features of BBS, along with some of its secondary manifestation in a 3-year-old male, makes this case report very unique. Therefore, the finding of any of the primary features of this syndrome in a younger child should prompt the search for other manifestations of this disorder. This may improve earlier diagnosis of BBS, and possible improvement in disease outcome.

Consent

Written informed consent was obtained from the patient's legal guardian for publication of this case report and

any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing Interest

There is no competing interest.

Funding

There is no funding for this case report.

Acknowledgements

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Costello Syndrome with Congenital Pulmonary Valve Stenosis and Ventriculomegaly—A Case Report

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Abstract

Costello syndrome is an extremely rare genetic disorder with growth delay after birth and typically results in short stature during childhood. It is one of the RASopathy of Ras/MAPK pathway syndromes. It affects the transforming protein p^{21}, an enzyme that in humans is encoded by the HRAS gene. H-Ras is a small G protein and once bound to Guanosine triphosphate, it will activate a Raf kinase like C-Raf, the next step in the MAPK/ERK pathway (mitogen-actvated protein kinase/extracellular signal-regulated kinase) *i.e.*, MEK (mitogen-actvated ERK kinase), a protein that phosphorylate ERK which can directly and indirectly activate many transcription factors. This pathway is also known as Ras-Raf, MEK-ERK pathway, which is a chain of proteins on the cell that communicate a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. Activation of ERK 1/2 is involved in signal transduction pathways associated with cardiac hypertrophy. The developmental syndromes caused by germline mutations in genes that alter the RAS components of the MAP/ERK signal transduction pathway are called "RASopathies". Cardiovascular abnormalities are important features of Costello syndrome and other RASopathies such as Noonan syndrome. Background of this case report described the congenital valvular pulmonic stenosis and ventriculomegaly associated with Costello syndrome by transthoracic echocardiographic imaging in a 9-year-old male boy.

Keywords

Costello Syndrome, Rasopathy, Short Stature, Congenital Valvular Pulmonic Stenosis, Ventriculomegaly

1. Introduction

Costello syndrome is a rare genetic disorder, characterized by distinctive facial features, short stature, flexible

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joints, loose folds of extra skin and structural malformations of the heart present at birth such as valvular pulmonic stenosis and abnormal thickening of the muscular walls of the ventricles (ventriculomegaly). It was discovered by Dr. Jack Costello, a New Zealand paediatrician in 1977 [1]. Costello syndrome is inherited as an autosomal dominant genetic condition due to mutations in the HRAS gene which results in production of H-Ras protein that leads to continuous cell growth and division, causing ventriculomegaly. HRAS is a proto-oncogene and the affected individuals have an approximately 15% lifetime risk to develop tumors such as papillomas, rhabdomyosarcoma, neuroblastoma, transitional cell carcinoma of bladder and hurthle cell carcinoma of thyroid (a follicular carcinoma, oxyphil type). These genetic mutations in HRAS causing Costello syndrome were first reported in 2005 [2] and 200 to 350 cases were reported worldwide.

Isolated pulmonic valve stenosis with dome-shaped pulmonic valve was described in 1761 by John Baptist Morgagni [3]. It occurs with an incidence of 1.5 - 6.5 per 10,000 live births, accounting for 2% to 13% of all congenital heart lesions [4]. In patients with isolated congenital pulmonic valve stenosis (no other valves or congenital cardiac condition), congenital malformations of the valve are two types; dome-shaped acommissural and dysplastic. Acommissuralstenotic pulmonic valve is usually a dome-shaped structure with a central aperture and ridges are visible that mark sites of apparently malformed commissures [5]. In dysplastic pulmonic stenosis, the pulmonic valve is a tricuspid structure and all three cusps are greatly thickened, rubbery and composed of disorganized myxomatous tissue and no commissural fusion but the valve annulus is small and pulmonary trunk is not dilated. Gikonyo and colleagues [6] found that all congenital forms had thickened cusps with or without commissural fusion. Altrichter [7] reported that 58% of stenotic pulmonic valves were bicuspid in 65 patients with Tetralogy of Fallot. The quadricuspid state of the pulmonic valve is seen in 1 in 10,000 cases at necropsy series and the frequency of dysfunctional quadricuspid pulmonic valves range from 4% to 6% [8].

The incidence of isolated congenital pulmonic valve stenosis is uncommon in Costello syndrome and so this case has been reported.

2. Case Report

A 9-year-old male boy was referred from the school with a history of growth retardation from childhood for evaluation. He was asymptomatic and no history of cyanosis at birth. His school performance in studies was not affected compared to other students. His pulse rate was 80 bpm and blood pressure 110/80 mmHg. General examination revealed short stature, low-set ears, prominent head, skin folding below the lower eyelids, teeth abnormalities and skeletal changes such as mild ulnar deviation of elbows and hands, kyphoscoliosis, shortening of arms and thighs, tight tendoachilles and plantar hyperkeratosis , which are consistent with features of Costello syndrome as shown in **Figures 1-4**. Physical examination revealed grade 3/6 systolic murmur over the precordium, most prominent in left 2nd intercostal space. The second heart sound was inaudible. No phasic ejection clicks due to merging of it with 1st heart sound in severe stenosis, Jugular venous pulsation was not present and no parasternal heave. Blood chemistry revealed normal (Haemoglobin—13.7 gm% (normal-12 to 16 g/dl), total count—9000 cells (normal—4 to 11,000 cells) per cubic mm of blood, Differential count-polymorphs—60% (normal—40% to 70%), lymphocytes—30% (normal—20% to 40%), eosinophils—4% (normal—1% to 4%), Erythrocyte sedimentation rate—2 to 4 mm/hour (normal—0 to 9 mm/hour) and platelets—2.56 lakhs (normal—2.5 to 5 lakhs) per cubic mm of blood, ASO (anti-sreptolysin O) titer was negative (<200 IU/ml). ECG revealed right ventricular strain pattern as shown in **Figure 5**. The maximum height of R wave in V_1 is 14 mm (5 mm standardization in ECG) which corresponds to right ventricular systolic pressure of 70 mmHg (14 × 5 = 70 mmHg) and deep S in V_6. X-ray chest revealed prominent main pulmonary artery segment resulting from poststenotic dilatation of the pulmonary trunk and right ventricular hypertrophy as shown in **Figure 6**.

Transthoracic Echocardiographic images in **Figures 7-21** given below revealed thickened, calcified, pulmonary valve with commissural fusion, severe pulmonary valve stenosis with poststenotic dilatation, suprasystemic ventricular systolic pressures and ventriculomegaly.

These features are consistent with isolated congenital valvular pulmonic stenosis and ventriculomegaly in Costello syndrome and the child was advised periodic follow-up. Screening of family members revealed normal.

3. Discussion

3.1. Etiopathogenesis

Costello syndrome is caused by any of at least 5 -different heterogenous germline mutations in the proto-onco-

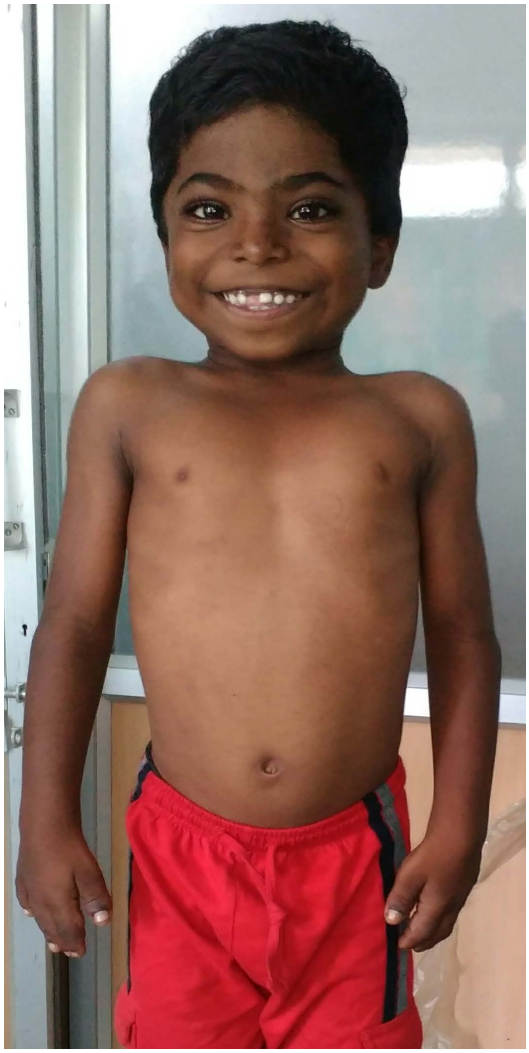

Figure 1. Showing warm, sociable personality and skin folding below the lower eyelids of costello syndrome). Photo image taken with consent.

gene HRAS on chromosome 11, involved in controlling cell growth and division on multiple organ system These mutations produce H-Ras protein which is permanently active and this overactive protein direct cells to grow and divide constantly leading to overgrowth of heart muscle (hypertrophic cardiomyopathy) as shown in **Figure 8**. Infants with Costello syndrome may be large at birth, but grow more slowly than the other children. Later in life, this condition has relatively short stature as shown in **Figure 2** and many have reduced levels of growth hormone and it is a "RASopathy", also called as "Faciocutaneoskeletal syndrome" (FCS syndrome). In some cases, the symptoms and findings of Costello syndrome overlap with two similar disorders known as Noonan syndrome, Cardio faciocutaneous syndrome which are caused by mutations in different genes and characterized by webbing of neck, drooping of upper eyelids (ptosis) and mostly associated with dysplastic pulmonic valve.

The exact embryologic process resulting in pulmonic valve stenosis is not well understood. Maldevelopment of the distal part of the bulbous cordis has been proposed [9], but it appears unlikely that fusion of well-formed pulmonic valve cusps would occur during mid-to late intrauterine development after the ventricular septum has been completed [10]. Fused cusps of varying thickness and rigidity form a fibrous dome in the severest form and contribute the most common form of isolated valvular pulmonic stenosis. Fetal endocarditis has been proposed as a cause but not proven [11]. Maternal rubella infection may be associated with stenosis of the pulmonary artery and its branches. Genetic factors also play a role.

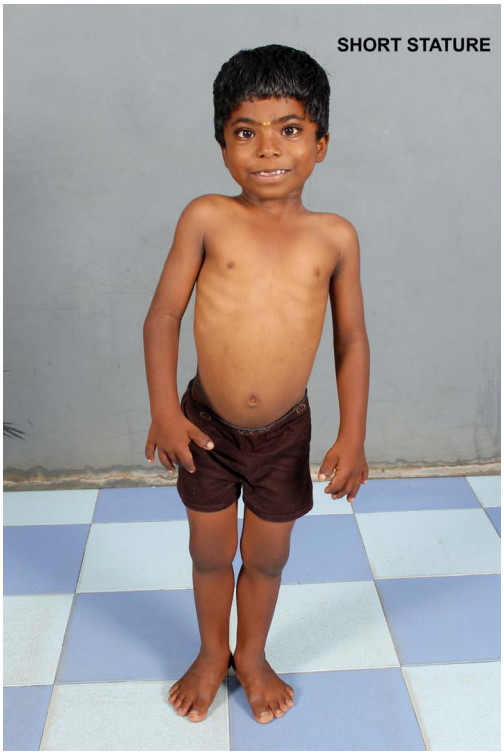

Figure 2. Showing short stature. Photo image taken with consent.

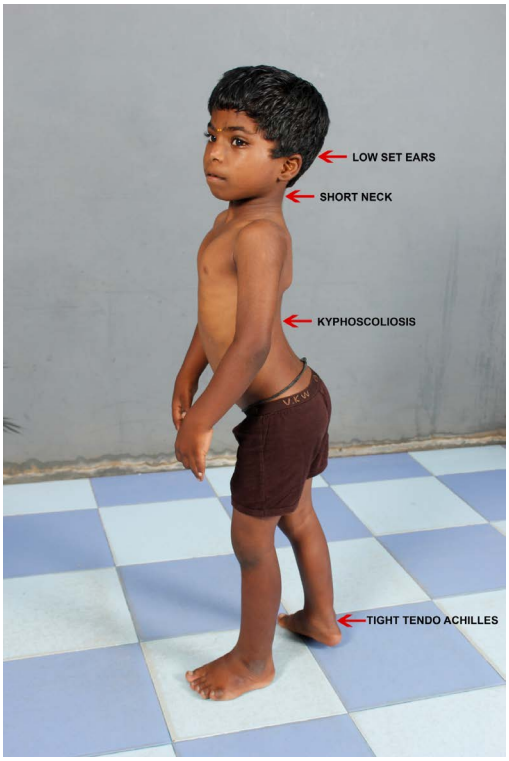

Figure 3. Showing low-set ears, short neck, kyphoscoliosis, tighttendoachilles. Photo image taken with consent.

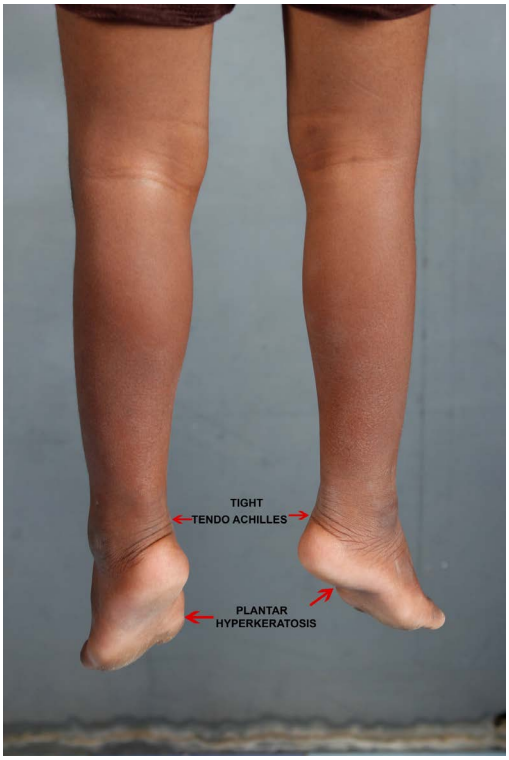

Figure 4. Showing-tight tendoachilles and plantar hyperkeratosis. Photo image taken with consent.

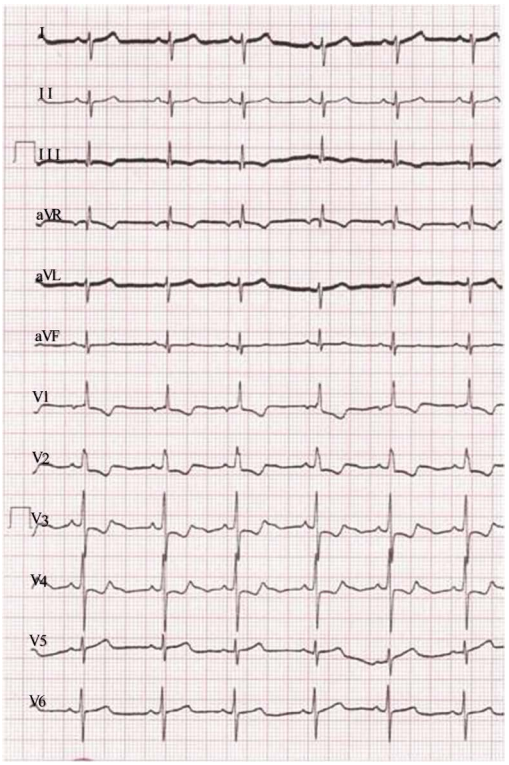

Figure 5. ECG showing RVH (right ventricular hypertrophy) 1 mV = 5 mm standardization.

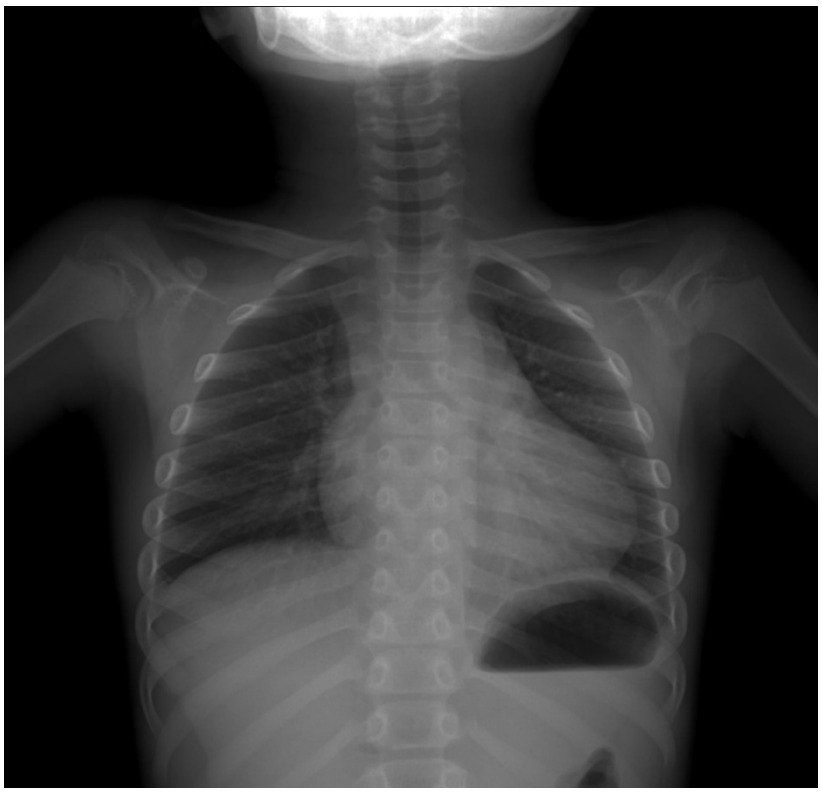

Figure 6. X-ray chest PA view showing main pulmonary artery segment dilatation and RVH (right ventricular hypertrophy). The dilated right ventricle is rounded rather than boot-shaped and its apex is above the left hemidiaphragm.

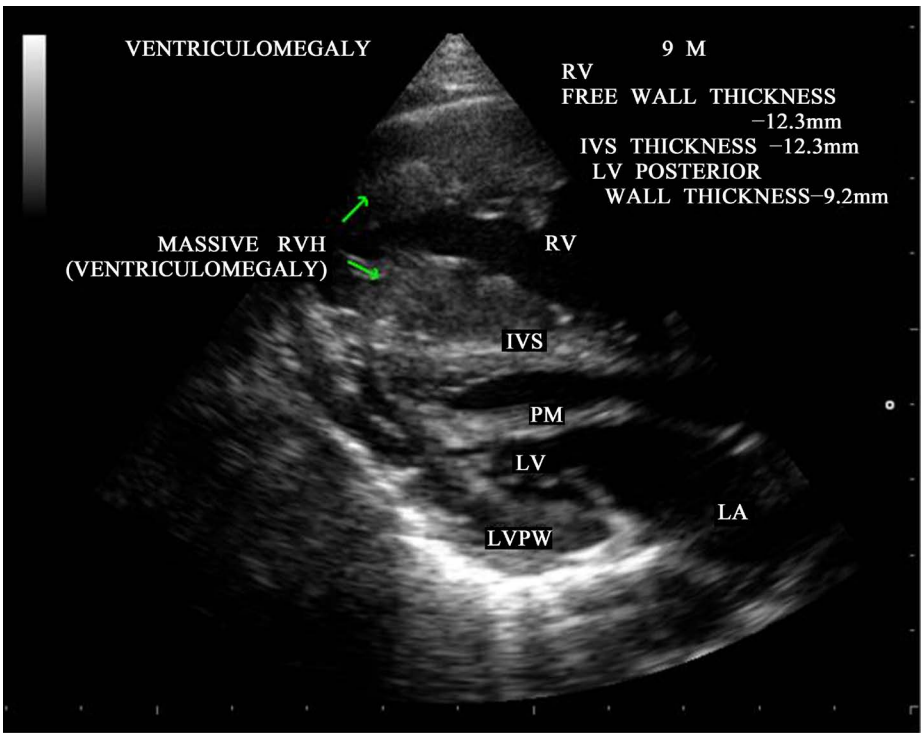

Figure 7. Showing “ventriculomegaly”—massive RVH (right ventricular hypertrophy).

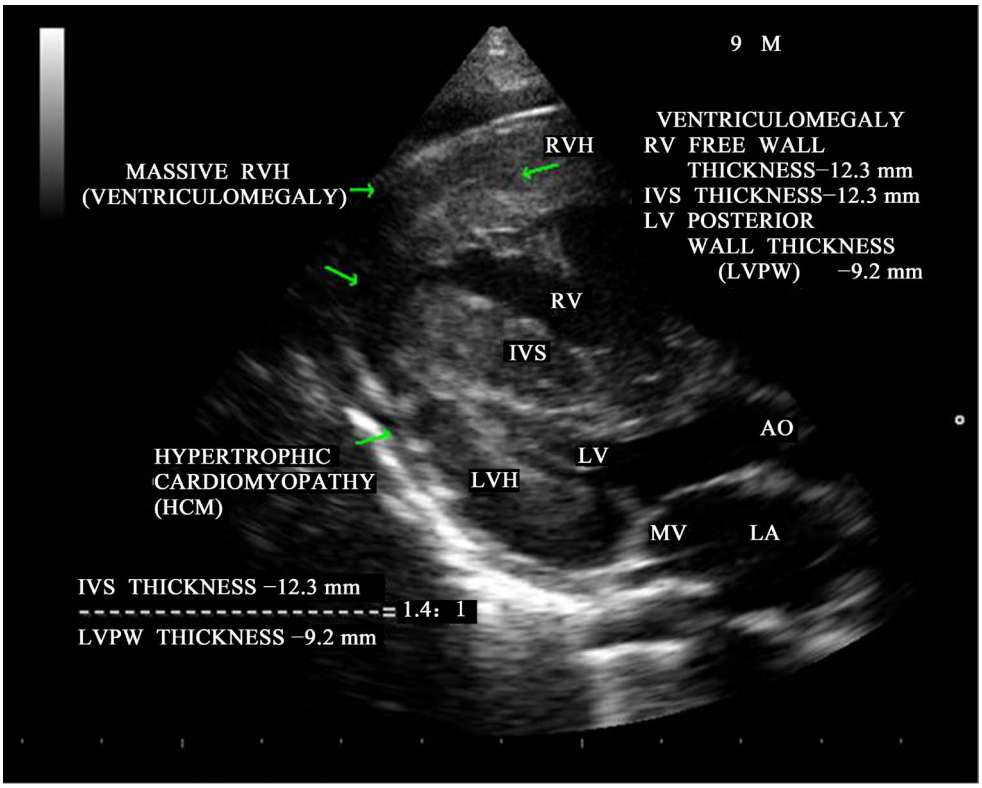

Figure 8. Parasternal long axis view showing HCM (hypertrophic cardiomyopathy).

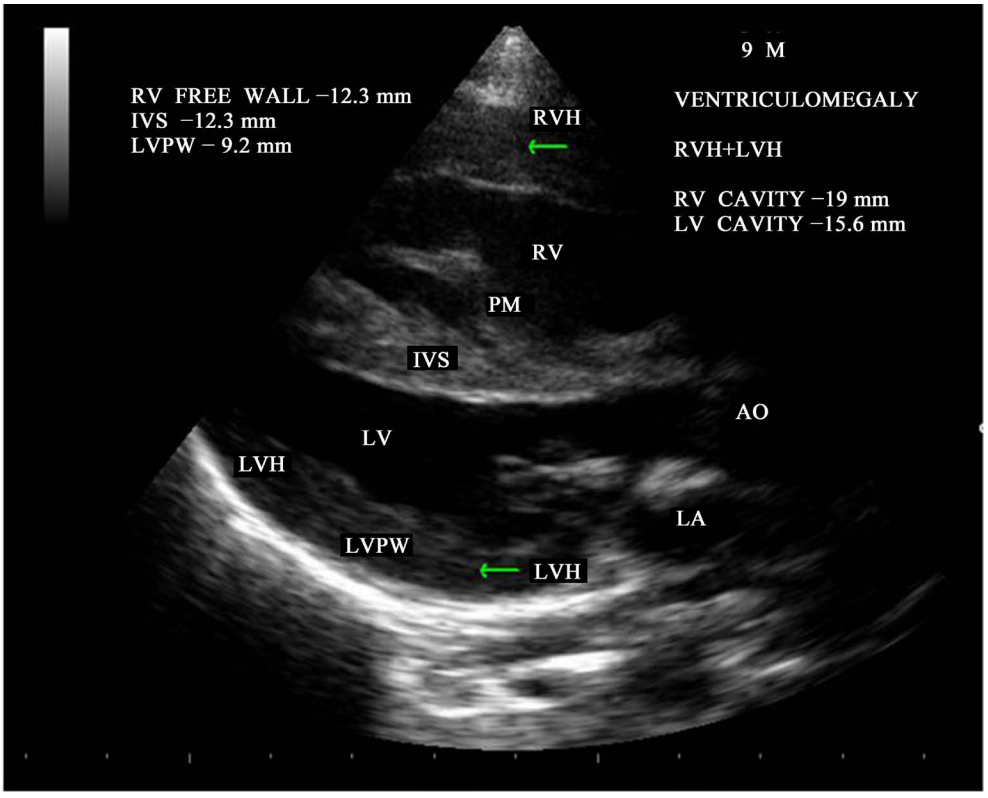

Figure 9. Parasternal long axis view showing dilated RV cavity.

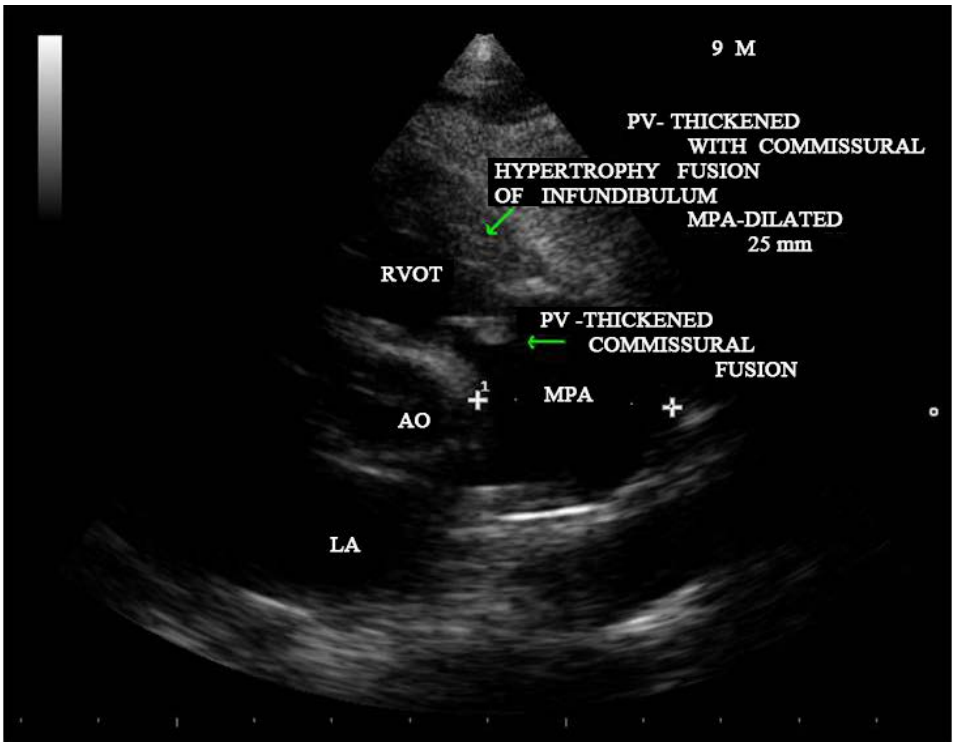

Figure 10. Showing the thickened pulmonary valve with commissural fusion and post-stenotic dilatation.

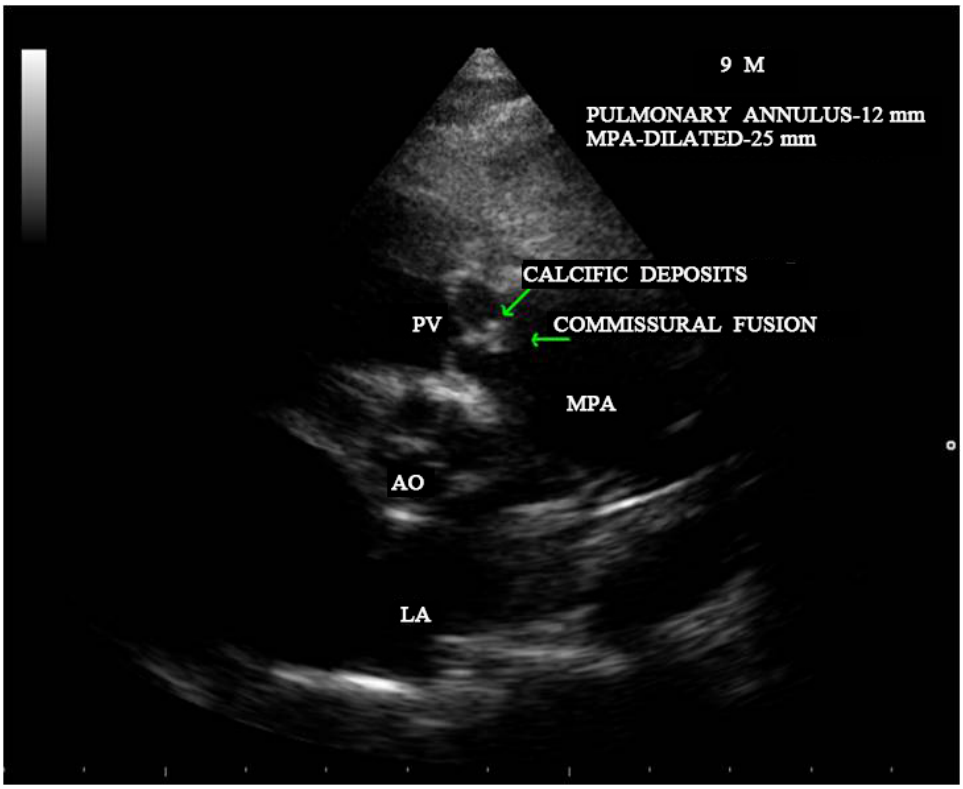

Figure 11. Short axis view showing calcific deposits on pulmonary valve-mimicking as "Lambl's excrescence".

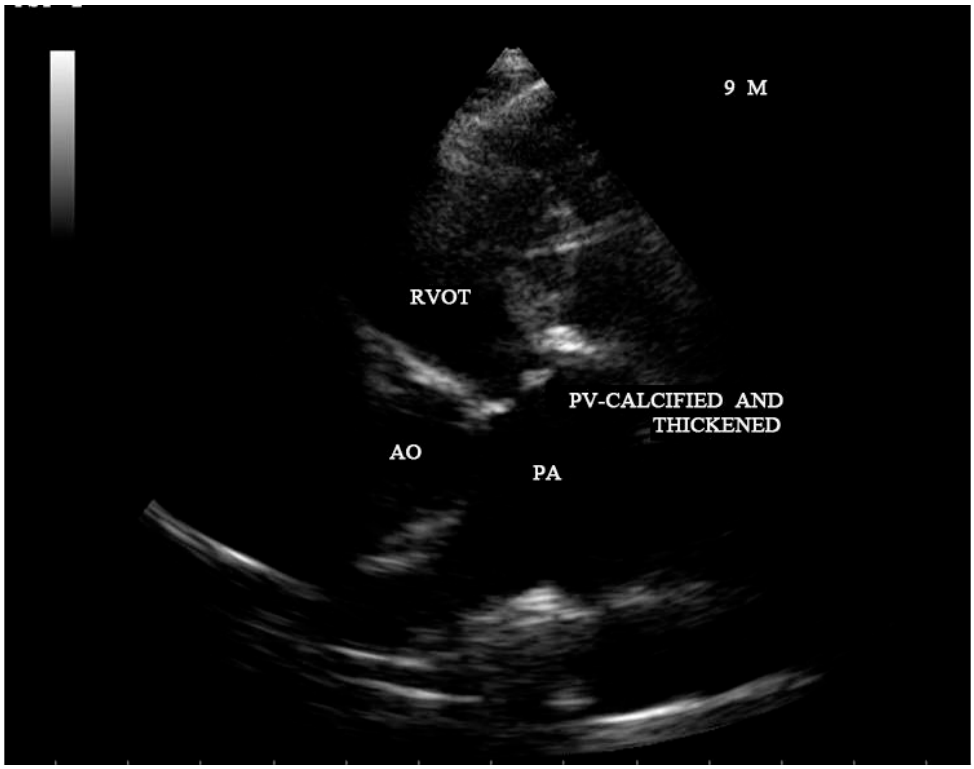

Figure 12. Showing severely thickened and calcified pulmonary valve.

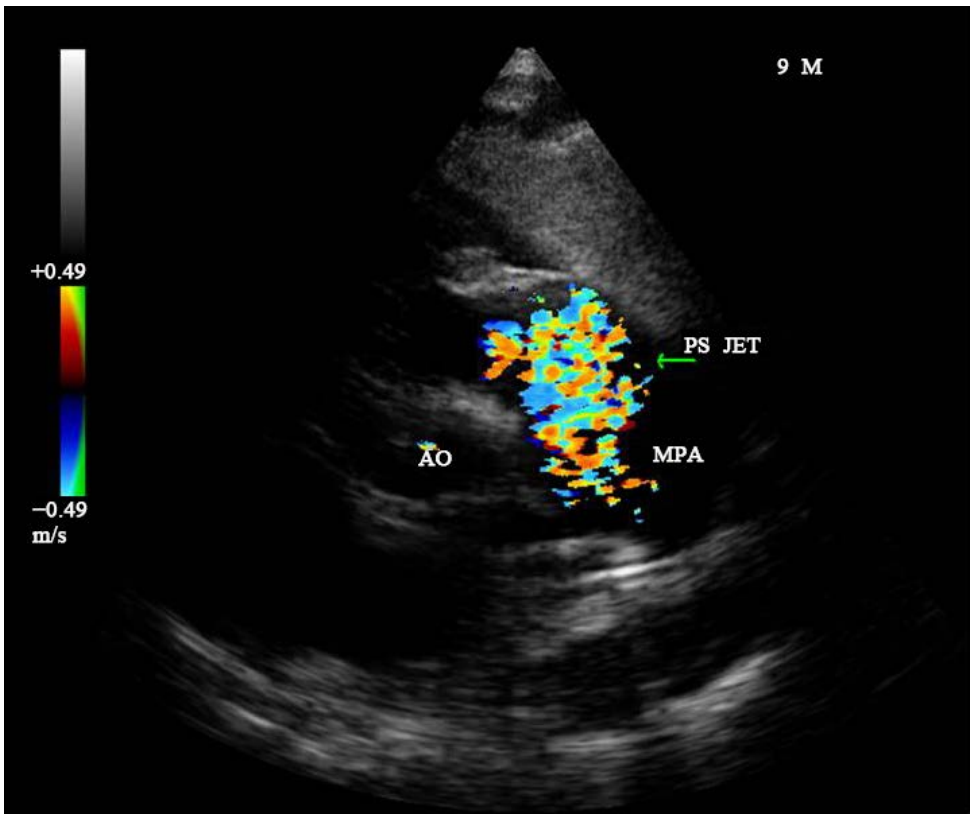

Figure 13. Showing pulmonic valve stenosis jet.

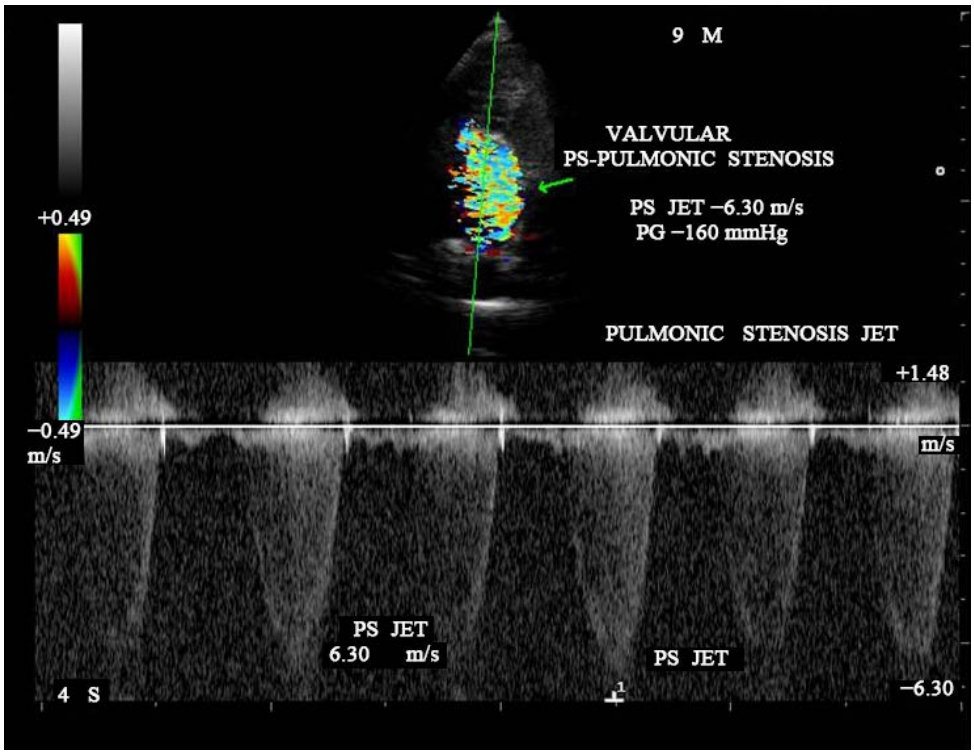

Figure 14. CW (continuous wave) doppler showing the velocity (6.30 m/s) and gradient (160 mmHg) of PS (pulmonary valve stenosis) jet.

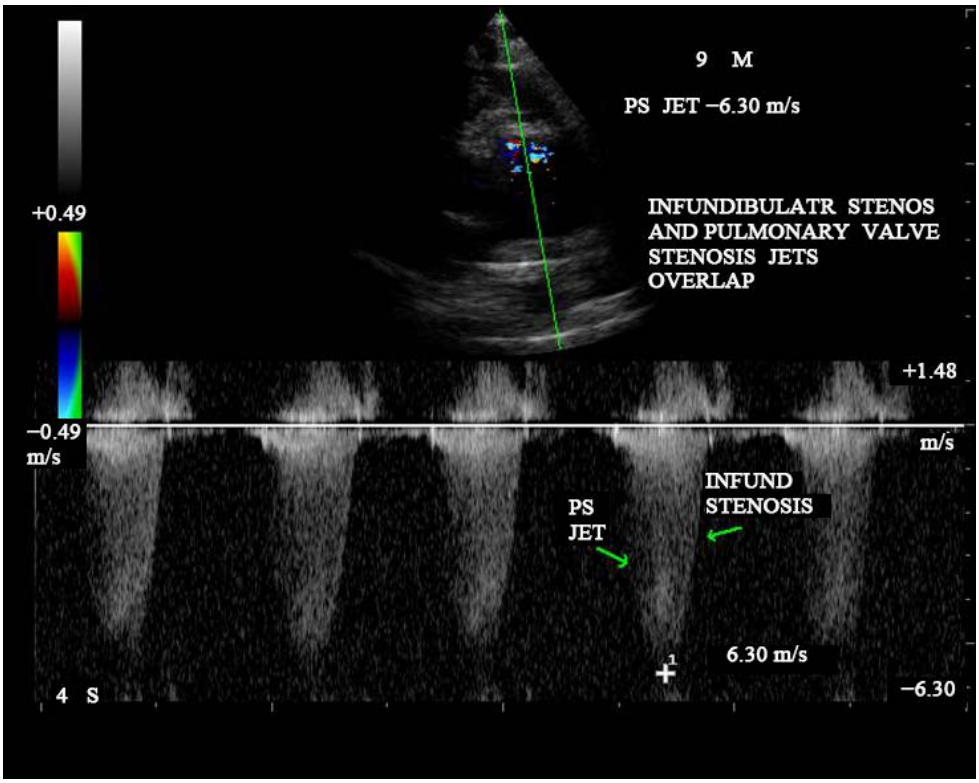

Figure 15. CW (continuous wave) doppler showing the infundibular stenosis jet (dagger-shaped) as an overlap with late systolic peaking in PS jet).

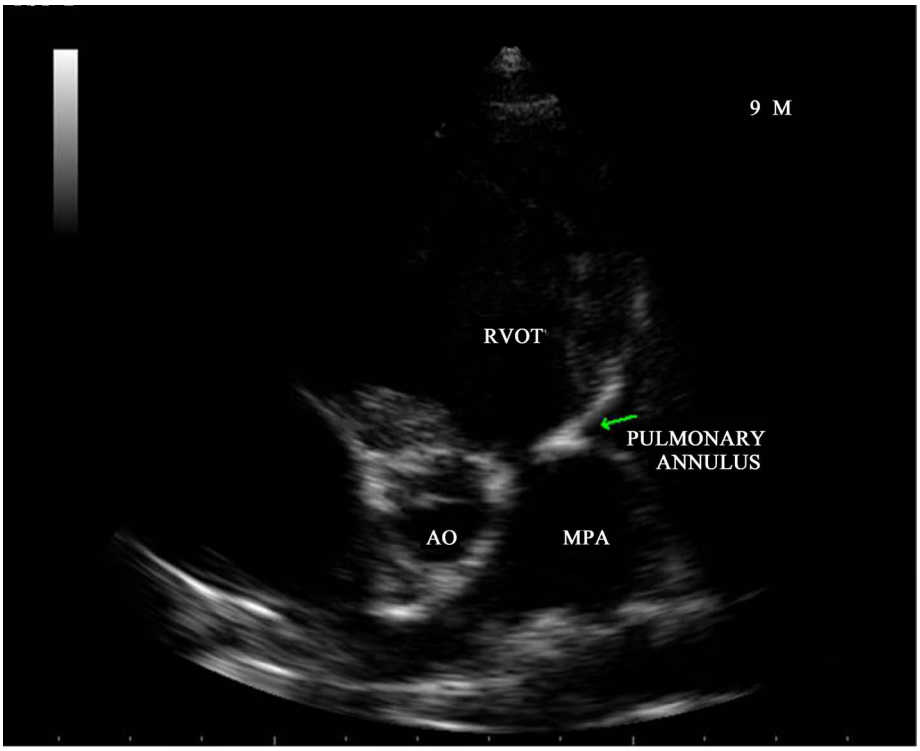

Figure 16. Inflow-outflow view showing pulmonary annulus narrowing and dilated main pulmonary artery.

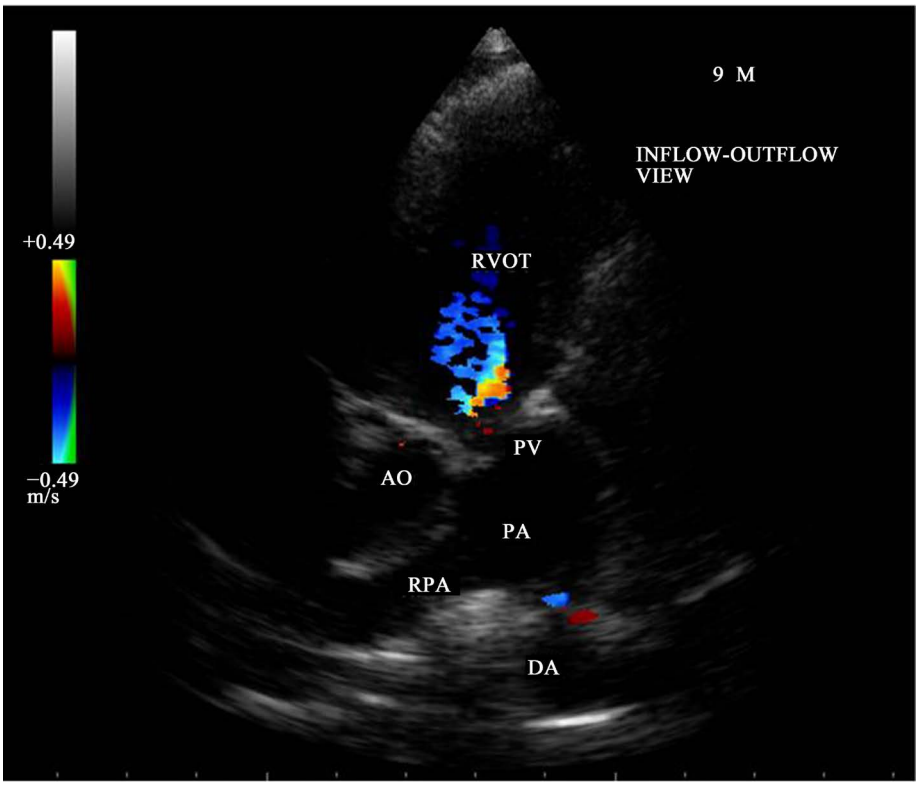

Figure 17. Inflow-outflow view showing no pulmonary regurgitation and dilated pulmonary trunk.

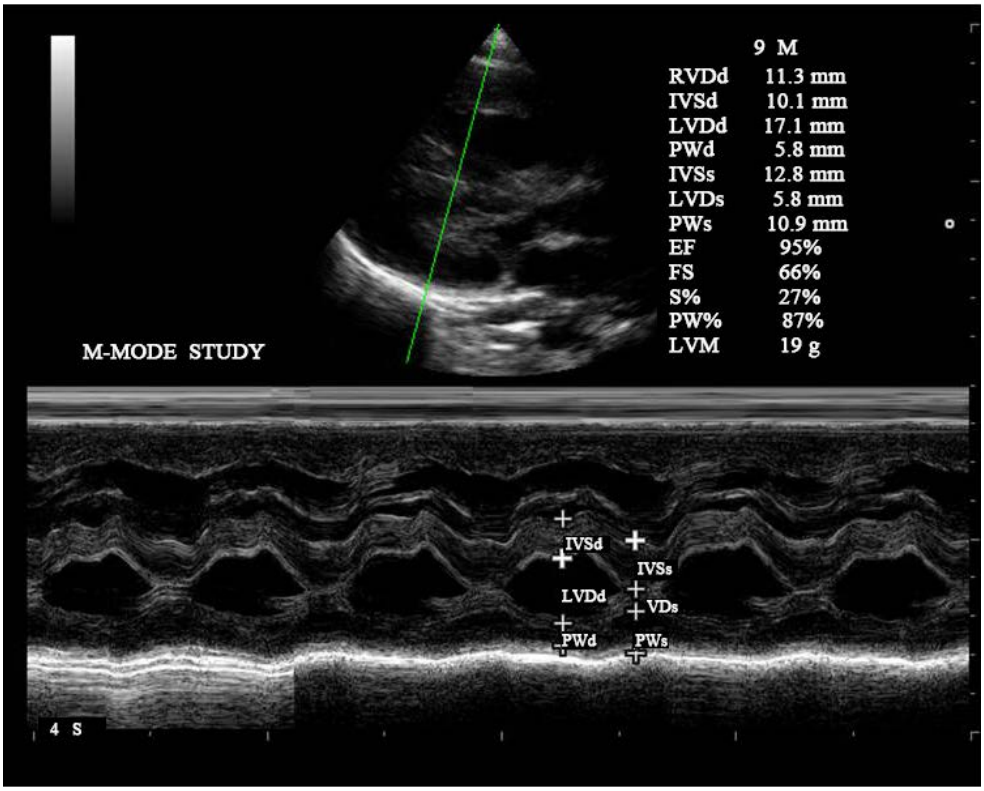

Figure 18. M-mode LV study showing high ejection fraction (EF—95%).

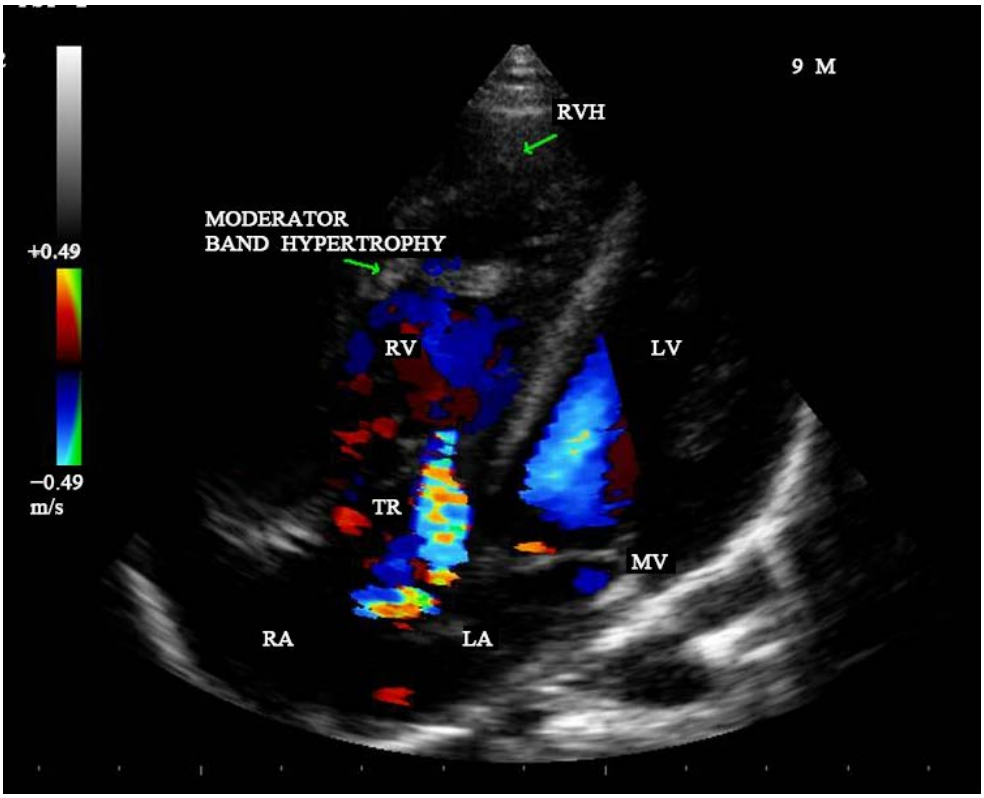

Figure 19. Showing mild to moderate tricuspid regurgitation.

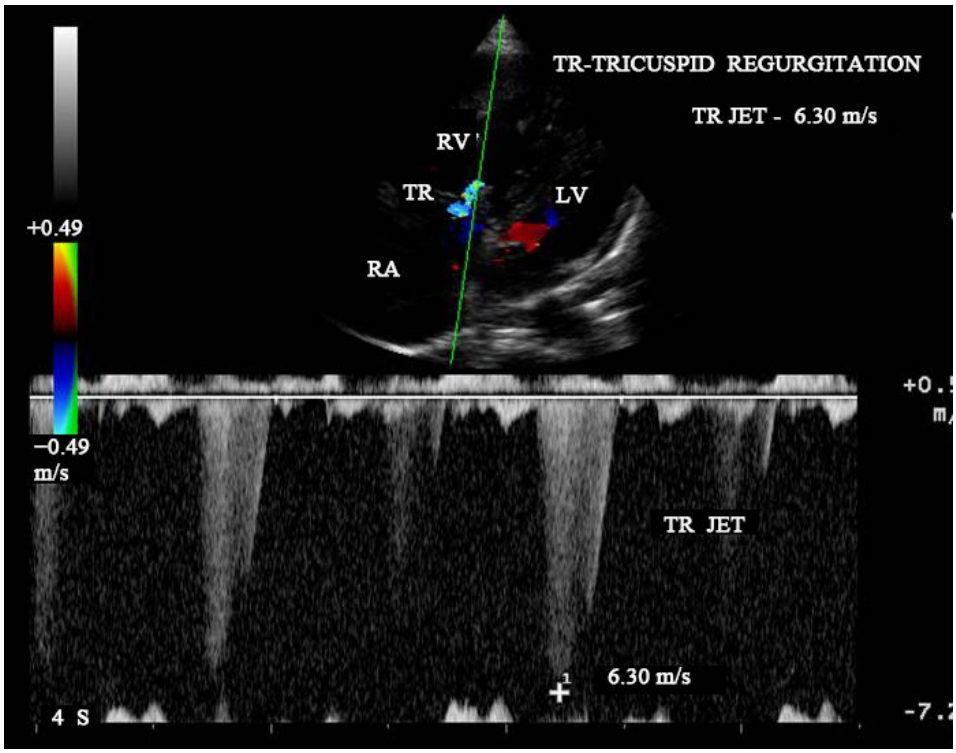

Figure 20. Apical 4 chamber view—CW doppler showing high velocity TR (tricuspid regurgitation) jet with early peaking suggesting high RV pressure at suprasystemic levels—165 mmHg.

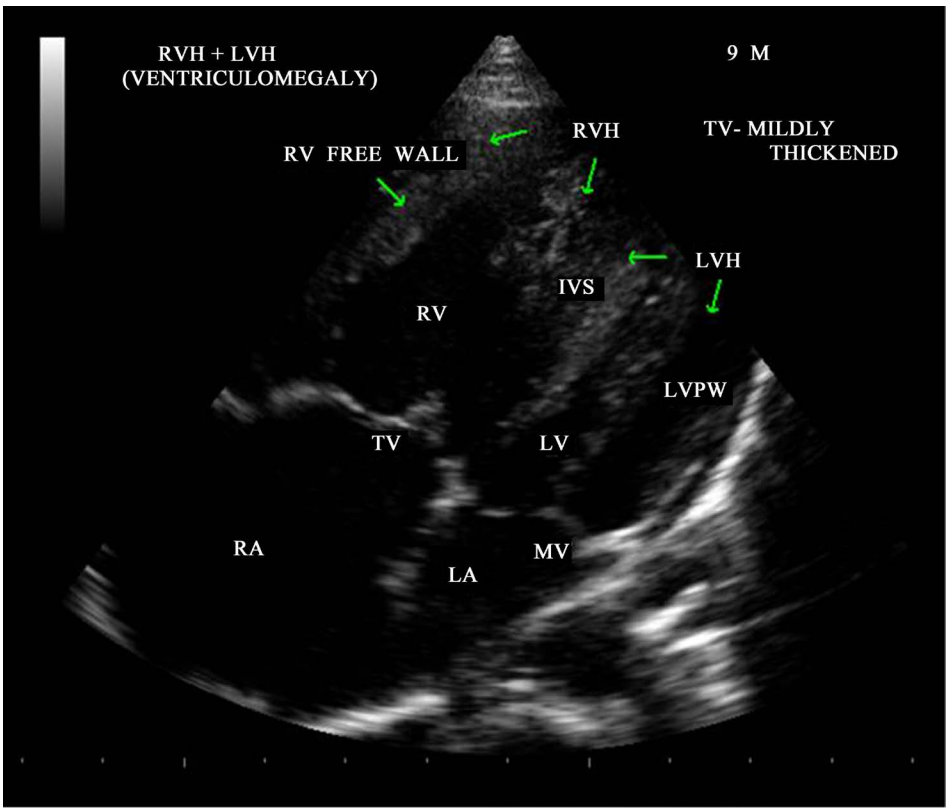

Figure 21. Showing ventriculomegaly (RVH + LVH) and dilated RA, RV.

In the classic form of pulmonic valve stenosis, the valve is conical or dome-shaped and 2 - 4 raphes may be visible, but there is no separation into valve leaflets [12] and separate commissures cannot be identified and sometimes referred as "Functional pulmonary atresia" in neonates. The pulmonary trunk is consistently dilated because of an inherent medial abnormality that is coupled with the morphology of the mobile dome-shaped valve, not with its functional state. Less commonly, the valve may be diffusely thickened, with one, two or three leaflets and commissural fusion.

Hypertrophy of the septal and parietal bands narrowing the right ventricular infundibulum often accompanies the pulmonic valve lesion, especially if it is severe and it is dynamic in nature. The adaptive response of the right ventricle to valvular pulmonic stenosis is characterized by an increase in thickness of the free wall and the ventricular septum [13] with normal cavity size [14]. In neonates with pinpoint pulmonic stenosis, cavity size is diminished. The elevation of right ventricular pressure is accompanied by an increase in muscle mass with a concomitant increase in number of capillaries [15] in the fetus and neonate and thus, the neonatal myocardium may be better adapted to generate the high pressure necessary to overcome the severe obstruction and the increased muscle mass may enable the hypertensive ventricle to maintain a normal stroke volume than in adults in whom no change in capillary network occurs.

If the size of the stenotic orifice remains fixed, however, the degree of obstruction becomes relatively more severe as the person grows. The right ventricle eventually may dilate and fail and this process is exacerbated by the development of tricuspid insufficiency in many patients with severe pulmonic stenosis. The patient may deteriorate rapidly, cardiac output becomes inadequate at rest, leads to right ventricular failure, which is the most common cause of death [16].

Normal birth weight, growth and development are characteristic of mobile dome-shaped pulmonic valve stenosis and experience little or no difficulty in infancy and childhood [17]. Neonates with pinpoint pulmonic valve stenosis confront rapidly progressive condition further and early death.

Critical Pulmonic Stenosis

In utero, when the valvular pulmonic stenosis is severe, right ventricular output decreases and a large right-to-left shunt is established at atrial level and this condition has been termed as "critical pulmonic stenosis" [18]. Right ventricle is hypoplastic due to excessive hypertrophy and affected infants are cyanotic at birth with systemic or supra-systemic right ventricular pressures and the cyanosis persists for months after the stenosis is relieved until the hypertrophy decreases with an increase in right ventricular size.

It is surprising that an appreciable number of patients with moderate to severe pulmonic stenosis are asymptomatic. Patients with right ventricular systolic pressures between 50 and 100 mmHg include New Zealand long-distance runner and an English hockey captain [19]. A 17-year-old boy who played baseball despite a right ventricular systolic pressure of nearly 200 mmHg, and a woman who worked full-time with a right ventricular pressure of nearly 200 mmHg and died at the age of 60 years [20]. In Costello syndrome, the valvular pulmonic stenosis is usually non-progressive and found in 44% of cases and hypertrophic cardiomyopathy is chronic or progressive and found in 61% of cases and atrial septal defect was uncommon [21].

Calcific deposits are rare in congenital stenotic pulmonic valves and thickening of tricuspid valve may be present, and the valve may become regurgitant. The right atrium may be thick and dilated as a result of the increased pressure necessary to fill the hypertrophic right ventricle.

The most common cause of acquired valvular pulmonic stenosis is carcinoid heart disease. Interestingly, calcification of affected valve is rare and may be considered a notable negative echocardiographic feature of carcinoid heart disease [22] and lack of commissural fusion [23].

The etiological differential features of valvular pulmonic stenosis are shown in **Table 1**.

3.2. Clinical Characteristics

3.2.1. General Features

Individuals with Costello syndrome have characteristic craniofacial, musculoskeletal, cutaneous and cardiac abnormalities. Features include relative macrocephaly (abnormally large head), coarse facial feature such as epicanthal folds, full cheeks, low-set ears as shown in **Figure 3** and wide nostrils. Musculoskeletal features include reduced range of mobility of shoulder and elbows, kyphoscoliosis as shown in **Figure 3**, short stature as shown in **Figure 2** and hip dysplasia. Skin may lack elasticity, wrinkled, thickened skin (plantar hyperkeratosis as shown in **Figure 4** thickening of stratum corneum, the outermost layer of epidermis in sole, usually contains

Table 1. Etiological features of valvular pulmonic stenosis.

Congenital	Rheumatic	Carcinoid
Commissural fusion present at birth	After birth	No commissural fusion
Cusps are mobile or fixed, dysplastic	Mostly mobile	Almost fixed and frozen
Valvular regurgitation is uncommon	Frequent	Sometimes more than stenosis
Calcific deposits little. Occasionally dense.	More pronounced	No calcification, bright fibrous plaques on endocardial surface of cardiac chambers and valves (composed of smooth muscle cells embedded in acid mucopolysaccharide rich matrix with sparse of collagen fibers and lack of elastic fibers)
Symptoms at neonatal period with cyanosis or remain asymptomatic	Mostly symptomatic with history of febrile episodes and joint pains during childhood	Symptomatic with episodic cutaneous flushing, prolonged diarrhea lepisodes, bronchospasm and labile hypertension
Right ventricular free wall, septal and infundibular hypertrophy severe	Less severe	Hypertrophy is Uncommon, whitish right ventricular endocardial fibrous plaques present
High right ventricular systolic pressures with suprasystemic levels frequent	Suprasystemic level is uncommon	Right ventricular pressures are not much increased
Isolated or associated with other congenital heart defects	May affect all four valves	Usually right sided valves and occasionally all four valves (primary or metastatic lung carcinoid) affected and may require quadruple valve replacement (mechanical valves preferable for both sides)
Pin-point valvular stenosis is usually progressive. Ventricular hypertrophy get regress after valvuloplasty or valve replacement with bioprostheses if calcific	May regress with treatment. Need valvuloplasty or valve replacement. (Bioprostheses for right-sided lesions and mechanical valves for left -sided lesions)	Symptoms may respond to somatostatinanaloges (octreotide, lanreotide). Oral ketanserin for hypertensive crisis and intravenous octreotide to control hypotension.

increased amount of the protective protein, keratin and associated with an increase in granular layer) and unusual tightening of the fibrous cords on the back of the heels (Achilles tendon) as shown in **Figure 3** and **Figure 4**. Cardiovascular manifestations include ventriculomegaly, valvular pulmonic stenosis, hypertrophic cardiomyopathy and atrial arrhythmias occasionally.

This child is having typical features of large head, skin folding below the lower eyelids as shown in **Figure 1**,

low set ears as shown in **Figure 3**, teeth abnormalities as shown in **Figure 1** and **Figure 2**, short stature as shown in **Figure 2**, ulnar deviation of forearm and cardiac manifestations of ventriculomegaly, valvular pulmonic stenosis, hypertrophic cardiomyopathy as in **Figures 7-21** and warm sociable personalities as shown in **Figure 1**, suggesting the Costello syndrome.

Cardiac examination showed prominent systolic murmur over precordium, with ECG and X-ray features of Right ventricular hypertrophy as shown in **Figure 5** and **Figure 6** are consistent with severe valvular pulmonic stenosis. ECG based R wave height in $V_1 \times 5$ to predict RV systolic pressure ($17 \times 5 = 70$ mmHg) in this case is not correlated with echocardiographic RV (right ventricular) systolic pressure measurements (165 mmHg) and it may be due to chest wall deformity of kyphoscoliosis as shown in **Figure 3**. Interestingly, TR (tricuspid regurgitation) jet velocity (6.30 m/s) correlates with PS (pulmonic valve stenosis) jet velocity of 6.30 m/s as shown in **Figure 14**, **Figure 15** and **Figure 20**.

3.2.2. Echocardiographic Features

Transthoracic echocardiographic images revealed a thickened, calcified, bicuspid pulmonic valve with commissural fusion in 2D imaging as shown in **Figures 10-12**. Color Doppler evaluation showed severe valvular pulmonic stenosis as in **Figure 13** and **Figure 14** and no pulmonary regurgitation as shown in **Figure 17**. Continuous wave (CW) Doppler imaging revealed a high velocity valvular pulmonic stenosis jet (6.30 m/s) with a peak gradient of 160 mmHg as in **Figure 14** and an overlap jet due to infundibular stenosis with a late systolic peaking (dagger-shaped) as in **Figure 15**. Apical 4 chamber view revealed mild to moderate tricuspid regurgitation as in **Figure 19** with a high velocity jet of 6.30 m/s as in **Figure 20** due to increased right ventricular (RV) systolic pressure and a peak gradient of 160 mmHg ($4V^2 - 4 \times 6.30^2 = 160$ mmHg) with an estimated RV systolic pressure of 165 mmHg ($4V^2$ + RA pressure assumed as 5 mmHg since JVP (Jugular venous pressure) is not elevated). Inflow-outflow views revealed poststenotic dilatation of main pulmonary artery segment (25 mm) as in **Figure 10**, **Figure 12**, **Figure 16** and **Figure 17**. Parasternal long axis view revealed ventriculomegaly as massive hypertrophy of right ventricle, hypertrophy of left ventricle with features of hypertrophic cardiomyopathy as in **Figure 7** and **Figure 8** and a dilated RV cavity as in **Figure 9** rather than hypoplastic.

3.3. Treatment

Costello syndrome is a “RASopathy”, characterized by increased growth at the prenatal stage, growth deficiency at postnatal stage with unique cardiovascular features of valvular pulmonic stenosis and hypertrophic cardiomyopathy. Animal models showed G12V mutation may also cause Costello syndrome and it does not appear to develop tumors as reported by Spanish researchers [24], Italian and Japanese researchers [25].

3.3.1. Specific Treatment

Treatment is directed towards the specific symptoms that are apparent in each individual. Bracing and physiotherapy may be used to treat skeletal abnormalities and surgery may be required to lengthen the tight tendoachilles. Cardiac abnormlities such as hypertrophic cardiomyopathy may be treated with beta-blockers or calcium channel blockers. Balloon valvuloplasty or surgical valve replacement may be utilized to relieve the stenotic obstruction of the pulmonary valve.

3.3.2. Investigational Treatment

Farnesyl transferase inhibitor (FTI) affects H-Ras as suggested by Francis Collins at American Society of Human Genetic Meeting in 2005 and Mark Kieras agreed this in 2007 at 1st International Costello Syndrome Research Symposium.

Another medication that affects H-Ras is Lovastatin which helps in children of Costello syndrome with cognition as reported by Alcino Silva in 2007.

MEK (mitogen-actvated ERK kinase) inhibitors such as cobimetinib, relumetinib and trametinib, Raf inhibitors such as sorafenib, encorafenib, dabrafenib and vemurafenib [26] also helps to inhibit the pathway closer to the cell nucleus in Costello syndrome.

Congenital stenotic pulmonic valve rarely contains calcific deposits. Covambias and colleagues [27] reported calcific pulmonic stenosis in a 56-year-old man in whom the isolated stenotic lesion was treated by valve replacement with a bioprosthetic valve.

The valvular pulmonic stenosis is rarely progressive in Costello syndrome and the child was advised periodic

follow-up. Since the stenotic pulmonic valve contains moderate calcification, this child may need valve replacement (bioprostheses) if any symptoms occur on follow up, rather than balloon valvuloplasty. The skeletal abnormalities were not affecting the normal activities and so bracing or physiotherapy was not advised. There are no obstructive manifestations such as syncopal episodes due to hypertrophic cardiomyopathy in this child, beta-blockers or calcium channel blockers were also not advised at this moment.

4. Conclusion

Reported estimate of Costello syndrome prevalence ranges from 1 in 300,000 to 1 in 1.25 million people [28]. This genetically inherited RASopathy with features of valvular pulmonic stenosis and ventriculomegaly and not associated with tumors or neurological lesions was found by Transthoracic 2D echocardiographic imaging in a 9-year-old male boy in 2016 at this hospital in India.

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Rheumatic Aortic Valve Disease with Mitral Stenosis—A Case Report

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Abstract

Congenitally malformed aortic valves are more susceptible to valve injury due to rheumatic fever, mechanical stress of altered flow patterns, atherosclerotic risk factors and degenerative changes. Rheumatic involvement usually occurs in childhood and it is progressive leading to diffuse thickening and fibrosis at leaflet edges and thus differentiated from other patterns of valve damage. Background of this case report revealed the bicuspid nature of the aortic valve due to rheumatic commissural fusion and analysis of echocardiographic parameters in combined lesions of both aortic and mitral valves with severe LV (left ventricular) dysfunction. Left ventricular (LV) and left atrial (LA) dilations predisposing to the formation of smoke (SEC-spontaneous echo contrast) in LV and LA as a consequence of mitral and aortic valve disease are illustrated by 2D echocardiographic imaging in this 41-year-old male.

Keywords

Rheumatic Bicuspid Aortic Valve, Aortic Regurgitation, Mitral Stenosis, Eccentricity Index, Smoke, Water Fall Sign, Bow and Arrow Sign

1. Introduction

Rheumatic heart disease (RHD) is the long-term consequence of acute rheumatic fever (ARF) and continues unabated in tropical nations. At least 15 million people are estimated to be affected by RHD worldwide up to 2005 [1]. RHD predominantly affects the left-sided cardiac valves, causing regurgitation, stenosis, or mixed hemodynamic effects. RHD is still responsible for 95% - 99.3% of all mitral valve stenosis in individuals aged <50 years. Although less common than mitral valve involvement, disease of the aortic valve is a recognized manifestation of RHD. A large study of 10,000 consecutive patients with RHD shows that rheumatic aortic valve disease occurs in 4.5% of individuals aged ≤18 years and in 2.8% of individuals aged >18 years [2]. In smaller

series, the prevalence has been reported to be 0% - 21.4% [3], [4]. Pathological aortic regurgitation in the absence of well defined valvular lesion such as bicuspid aortic valve or dilated aortic root is rare [5] and increased prevalence is likely to represent early RHD. Irregular or focal thickening, coaptation defect and restricted leaflet motion are the echocardiographic features of RHD in aortic valves. Excessive leaflet motion with a prevalence of prolapse constitutes 3.8% - 59% in rheumatic aortic regurgitation.

Review of Literature

Bicuspid aortic valve may be present in as many as 1% - 2% of the population and remain silent, found as an incidental finding on echocardiographic evaluation of the heart. Sir William Osler was the first to identify the bicuspid aortic valve as the commonest congenital anomaly of the heart [6]. The bicuspid aortic valve (BAV) was first characterized in the early 16th century by Leonardo da Vinci [7]. Based on cusp size, three variations have been described as two cusps of equal size, unequal size and a conjoined cusp twice the size of its nonconjoined mate [8]. Thomas Peacock recognized the tendency of a BAV to become stenotic due to mechanical stress by promoting fibrosis and calcification [9]. Two-dimensional echocardiography provides accurate confirmation of a bicuspid aortic valve [10]. Edler was the first to obtain ultrasonic signals from the aortic valve [11] and subsequently Gramiak [12] described the technique of studying the aortic root routinely by echocardiography.

Embryologically, the normal right and left aortic leaflets form at the junction of the ventricular and arterial ends of the conotruncal channel. The nonseptal (posterior) leaflet cusp normally forms from additional conotruncal channel tissue. Abnormalities of this area lead to the development of a bicuspid valve, often through incomplete separation (or fusion) of valve tissue [13]. Proponents of environmental causes believe that abnormal blood flow through the aortic valve during valvulogenesis results in a failure of cusp separation. The extracellular matrix (ECM) proteins help to direct cell differentiation and cusp formation during valvulogenesis. Microfibrillar proteins fibrillin and fibulin [14], act as scaffolding for embryonic cells and regulate tissue formation in the developing aortic valves. Inadequate production of fibrillin-1 during valvulogenesis may disrupt the formation of aortic cusps resulting in a bicuspid aortic valve [15]. Defects in the gene that encode matrix elements have not yet been identified and abnormalities of gene encoding endothelial nitric oxide synthase (eNOS) may result in high incidence of BAV (bicuspid aortic valve) [16].

The bicuspid aortic valve is typically made of two unequal-sized leaflets. The morphologic patterns of bileaflet valve vary according to which commissures have fused. Abnormal neural crest migration resulting in fusion of valve cushions has been suggested as a possible explanation by which bicuspid aortic valve disease develop in humans [17]. The fusion of right and left coronary cusps (RL fusion) is the most common (80%) pattern which is usually associated with coarctation of aorta. Fusion of right and noncoronary cusp (RN fusion—17%) is associated with pathological changes as stenosis or insufficiency [18] in children. The fusion between the noncoronary and left coronary leaflets is less common (2%). The severe the number of cusps, the greater is the chance that the valve is stenotic from birth. The anatomy of the bicuspid aortic valve may also influence the propensity for obstruction. Stenosis is more rapid if the aortic cusps are asymmetrical or in the anteroposterior position [19]. Rarely, the leaflets are symmetrical or there is no raphe, termed as “pure bicuspid aortic valve”. However, two large studies in adults have not identified the leaflet orientation as a risk factor for late adverse events [20], [21] and a modifying role of atherosclerotic and degenerative process encountered for aortic valve disease as mostly of acquired basis. Rheumatic involvement as acquired etiology plays a role in aortic valve disease of children and adults in a similar manner irrespective of the valve leaflet malformation.

Rheumatic involvement of aortic valve results in progressive fibrosis of the leaflets with varying degree of commissural fusion, often with retraction of leaflet edges and in certain cases with calcification. As a consequence, the rheumatic aortic valve is often regurgitant and stenotic [22] and a coexistent mitral valve disease is almost always present and so this case had been reported.

2. Case Report

A 41-year-old male with features of heart failure was referred for echocardiography. He had a history of febrile illness with joint pains during childhood at the age of 6 years, taken penicillin prophylaxis for rheumatic fever and discontinued intermittently. He got married at the age of 26 years and had 3 children in good health. He developed symptoms of heart failure such as exertional dyspnea and orthopnea at the age of 30 years and treated with antifailure measures. He is taking digoxin 0.25 mg once daily, frusemide 40 mg once daily, spironolactone 25 mg twice daily and intramuscular benzathine penicillin G injection 1.2 million units every 3 weeks. His

symptoms get improved and continuing the same medications regularly for the past two years. His pulse rate was 78 bpm, irregular and blood pressure 120/60 mmHg. Physical examination revealed varying intensity of first heart sound, normally heard second heart sound, no additional sounds such as opening snap and third heart sound. He had a heaving apical impulse in the left 7th intercostal space in the mid axillary line and grade 3/6 mid-diastolic murmur at the apex, an early diastolic murmur in the left sternal border most prominent in 3rd and 4th intercostal spaces. He had no ejection click. The peripheral signs of chronic aortic regurgitation such as wide pulse pressure, Corrigan's sign and, Hill's sign were not present due to heart failure. JVP (Jugular venous pressure) not elevated and lung fields were clear at present. Blood chemistry revealed normal and ASO (anti-streptolysin O) titer was negative. ECG revealed atrial fibrillation and LVH (left ventricular hypertrophy) as shown in **Figure 1** and X-ray chest revealed left ventricular enlargement as shown in **Figure 2** and a "double density sign" of LA (left atrial) enlargement in the lower right cardiac border.

Transthoracic echocardiography revealed Rheumatic aortic valve disease with mitral stenosis as shown in **Figures 3-30**.

Echocardiographic features of aortic valve are shown in **Figures 3-17**.

Echocardiographic features of mitral valve are shown in **Figures 18-30**.

3. Discussion

3.1. Etiopathogenesis

Congenitally, unicuspid, bicuspid, tricuspid, or even quadricuspid aortic valves may be the cause of aortic stenosis. In neonates and infants <1 year, unicuspid valve is the most common anomaly with fatal valvular aortic stenosis. Bicuspid aortic valves do not cause significant narrowing of the aortic orifice during childhood. In

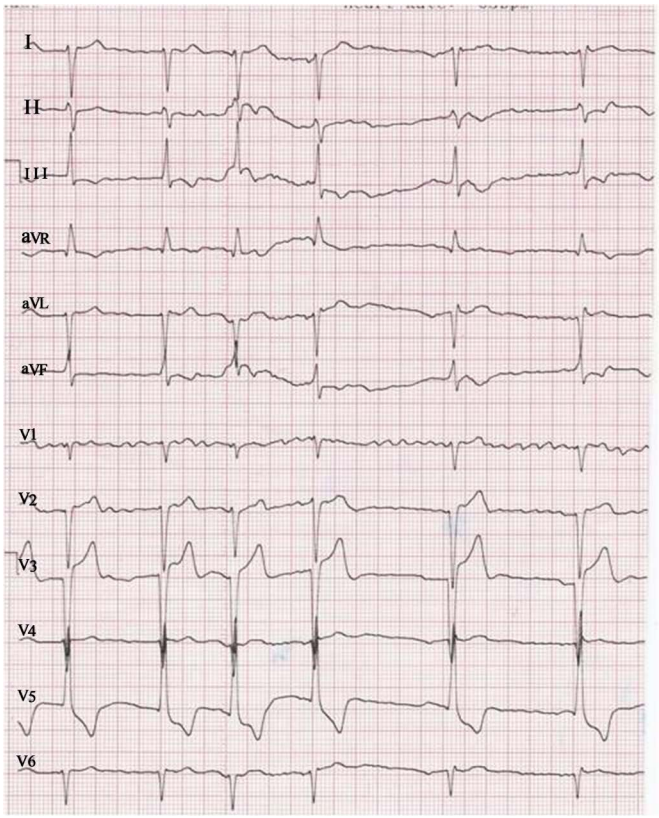

Figure 1. ECG showing atrial fibrillation and LVH and a gross increase in precordial voltage-RV_5 + SV_2 = 70 mm). T waves inverted with ST segment depression-a left ventricular "strain pattern" in V_5 correlates with the presence of dilatation and hypertrophy [23] (1 mV = 5 mm standardization).

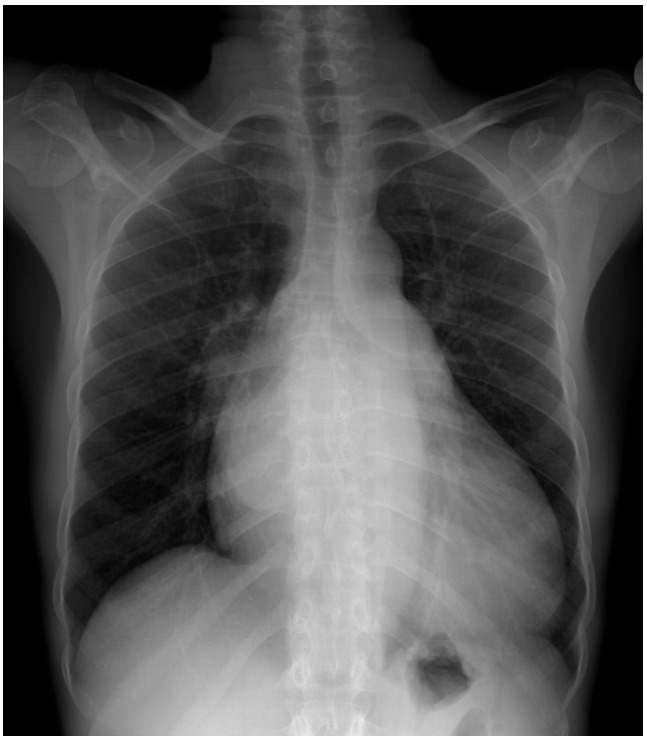

Figure 2. X-ray chest PA view showing LV (left ventricular) enlargement—a large convex left ventricle extending below the left hemidiaphragm and "double atrial shadow" of left atrial enlargement (double density sign) seen in right atrial border.

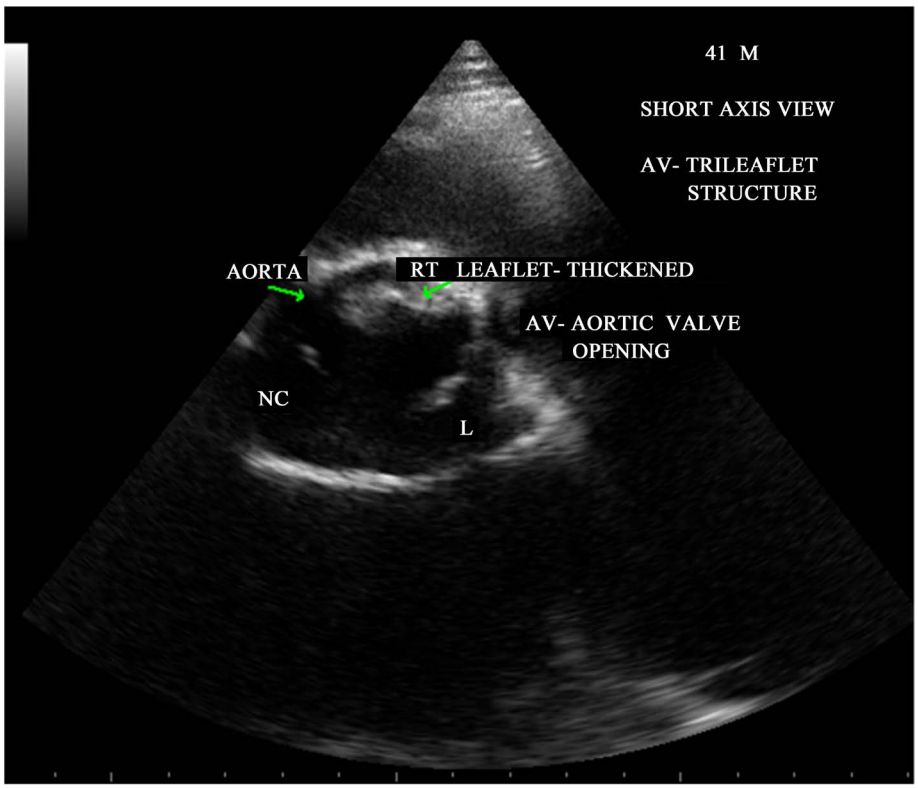

Figure 3. Short axis view showing the aortic valve as a trileaflet structure with unequal cusps.

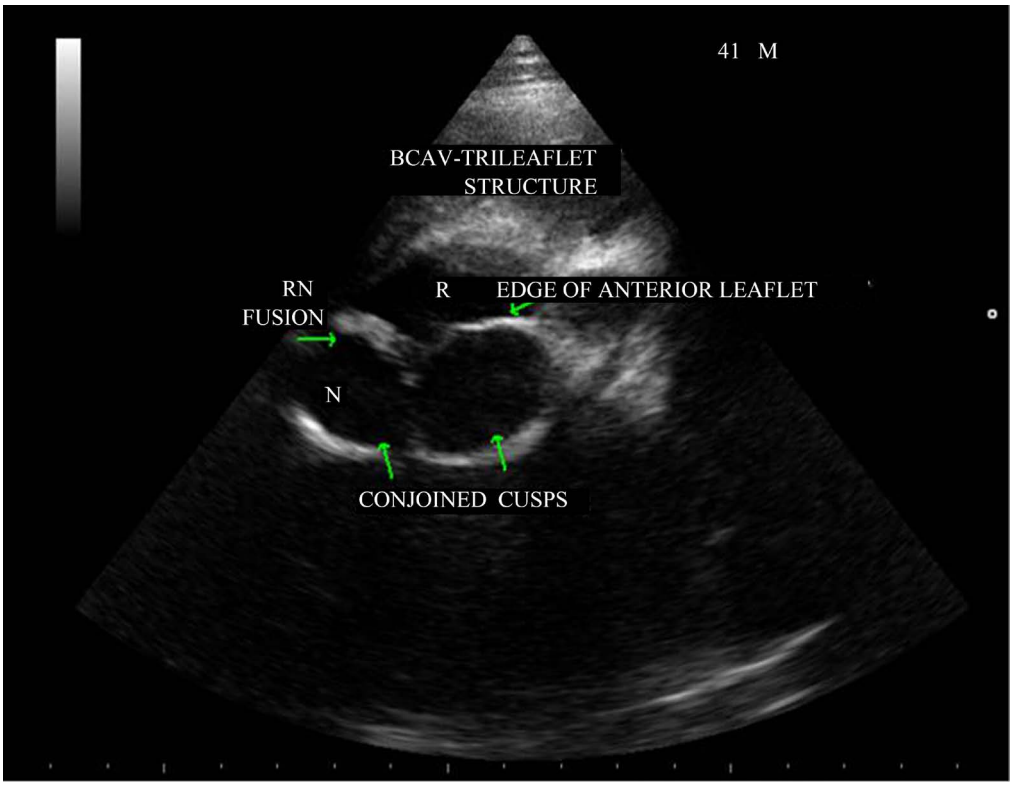

Figure 4. Short axis view showing the bicuspid configuration of the aortic valve.

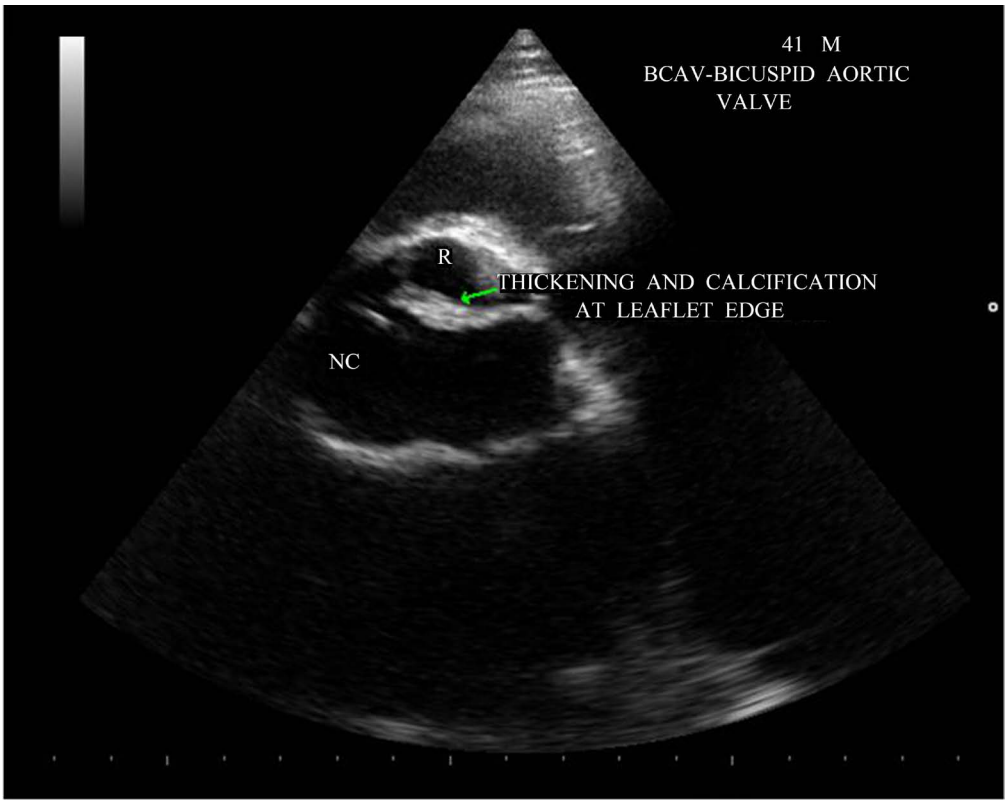

Figure 5. Short axis view showing the thickening and calcification at the anterior leaflet edge.

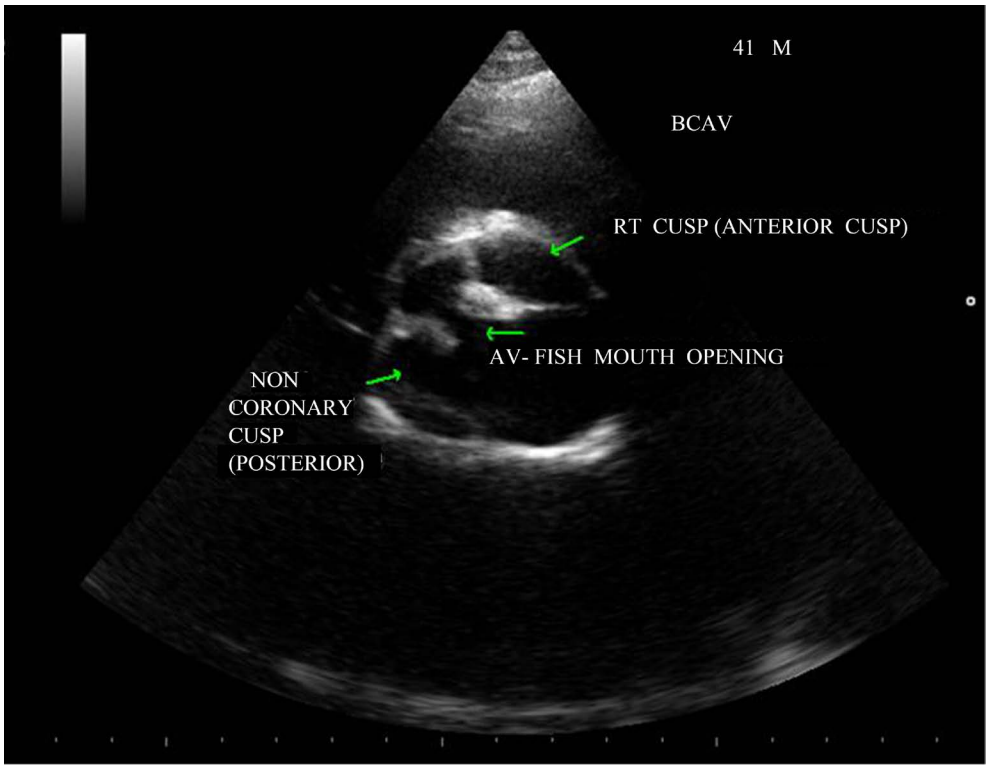

Figure 6. Short axis view showing the "fish mouth" appearance of aortic valve due to thickening and calcification.

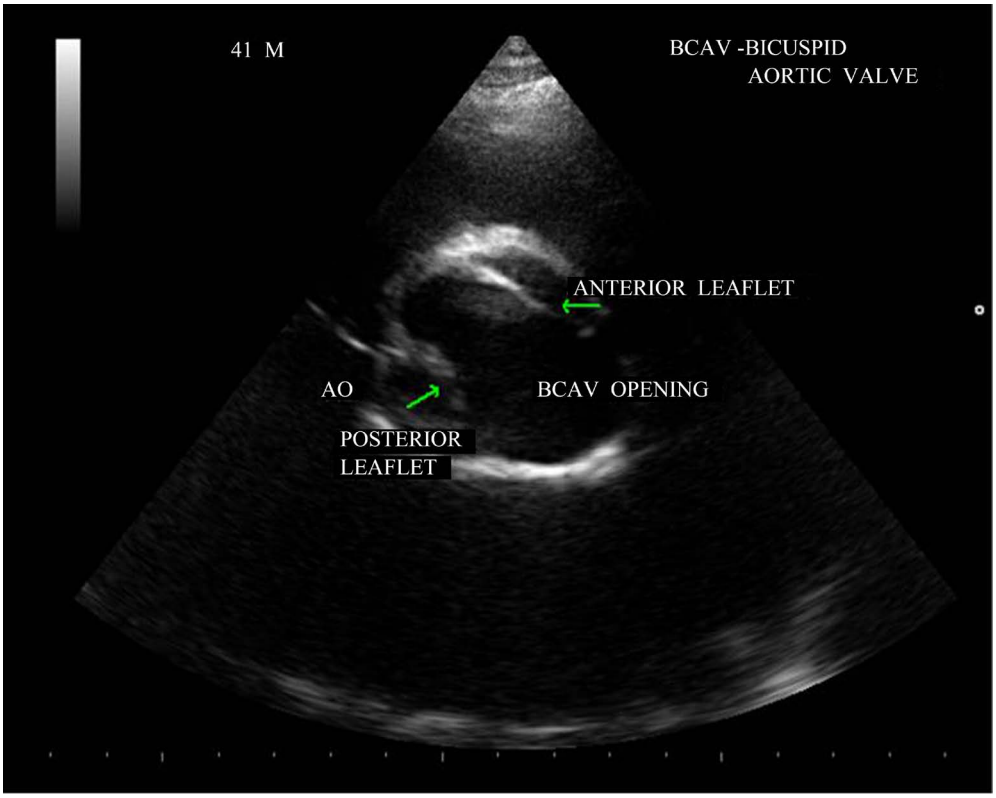

Figure 7. Short axis view showing the opening of the aortic valve with two leaflet structure.

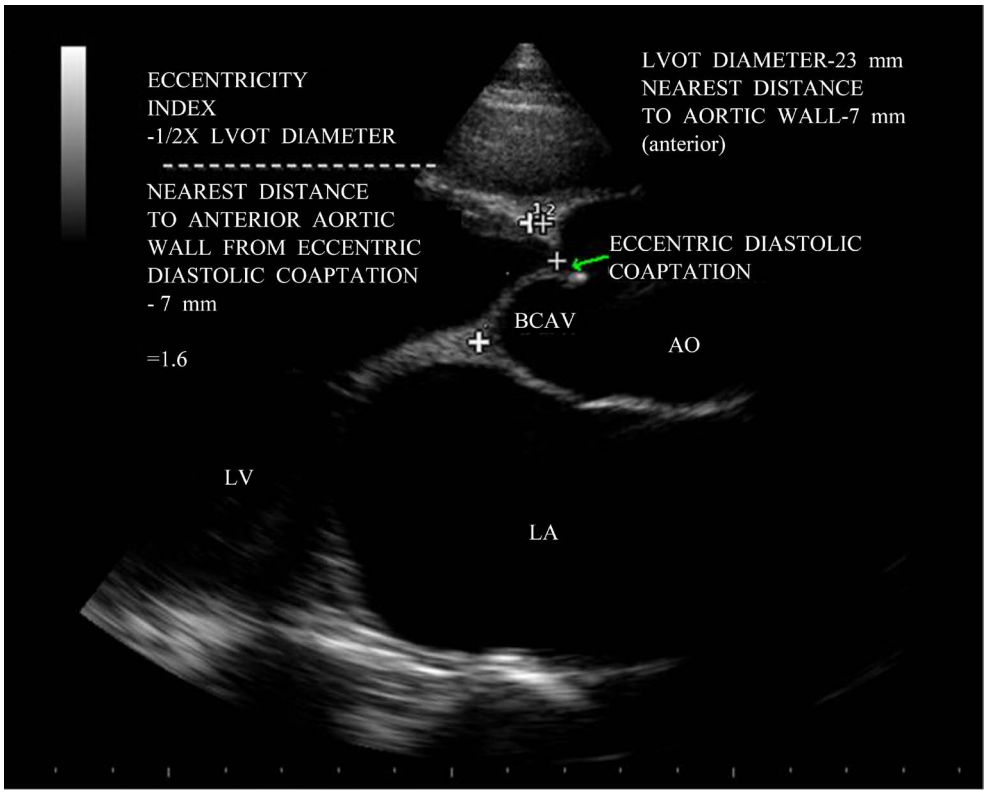

Figure 8. Parasternal long axis view showing the "eccentricity index".

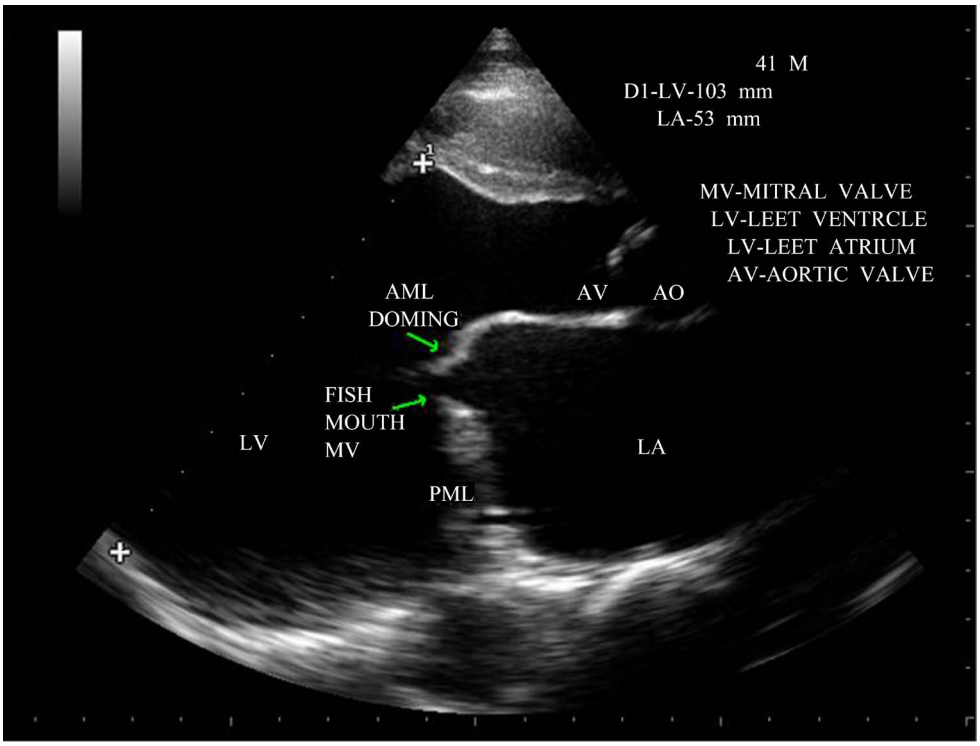

Figure 9. Parasternal long axis view showing the massive LV (left ventricular) dilatation, "doming" motion of anterior mitral leaflet (AML) and" fish-mouth opening" or "buttonhole" deformity of MV (mitral valve).

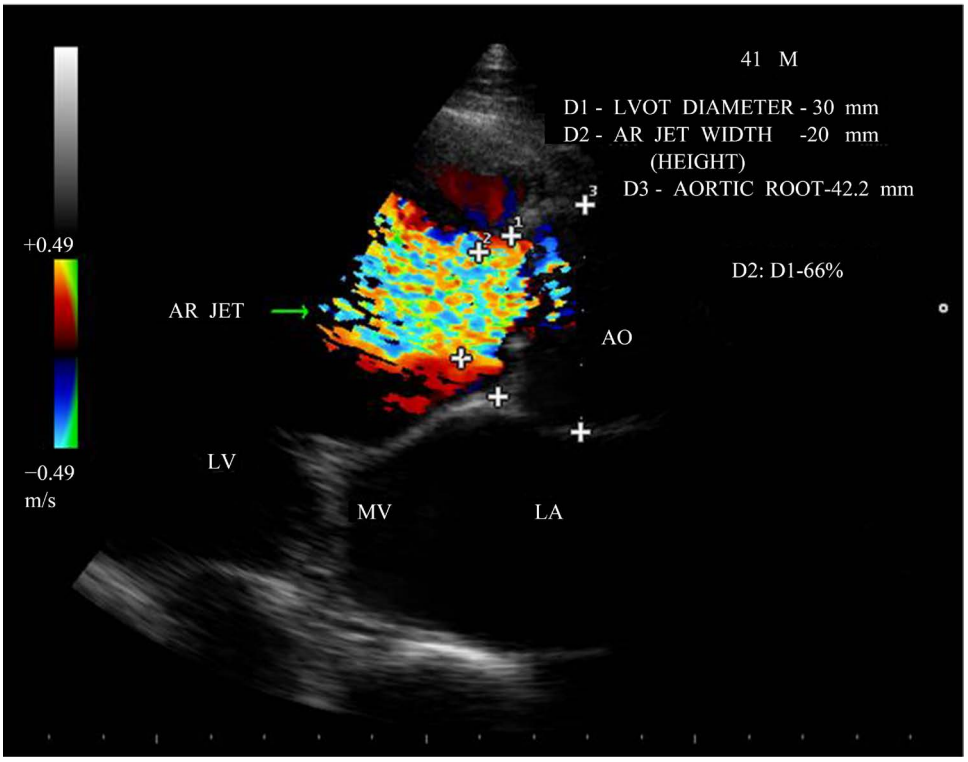

Figure 10. Parasternal long axis view showing the central AR jet in color-doppler imaging—JH/LOVH (Jet height/left ventricular outflow tract height) ratio—66%—severe AR.

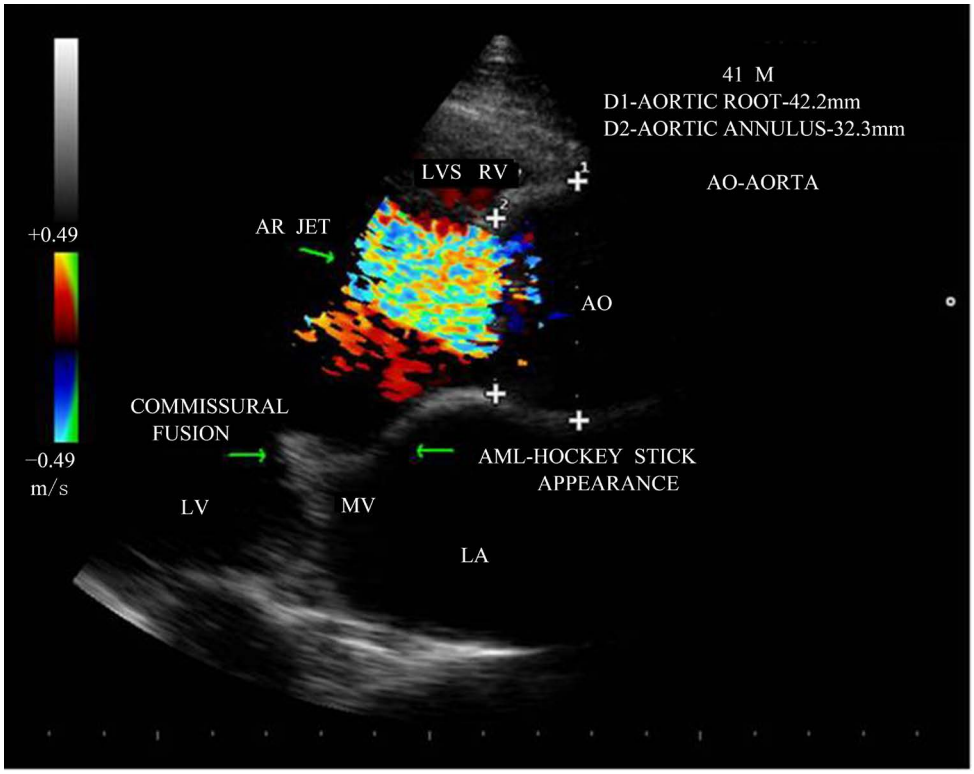

Figure 11. Parasternal long axis view showing the AR jet towards IVS (interventricular septum) and dilated aortic root—42.2 mm, aortic annulus—32.3 mm.

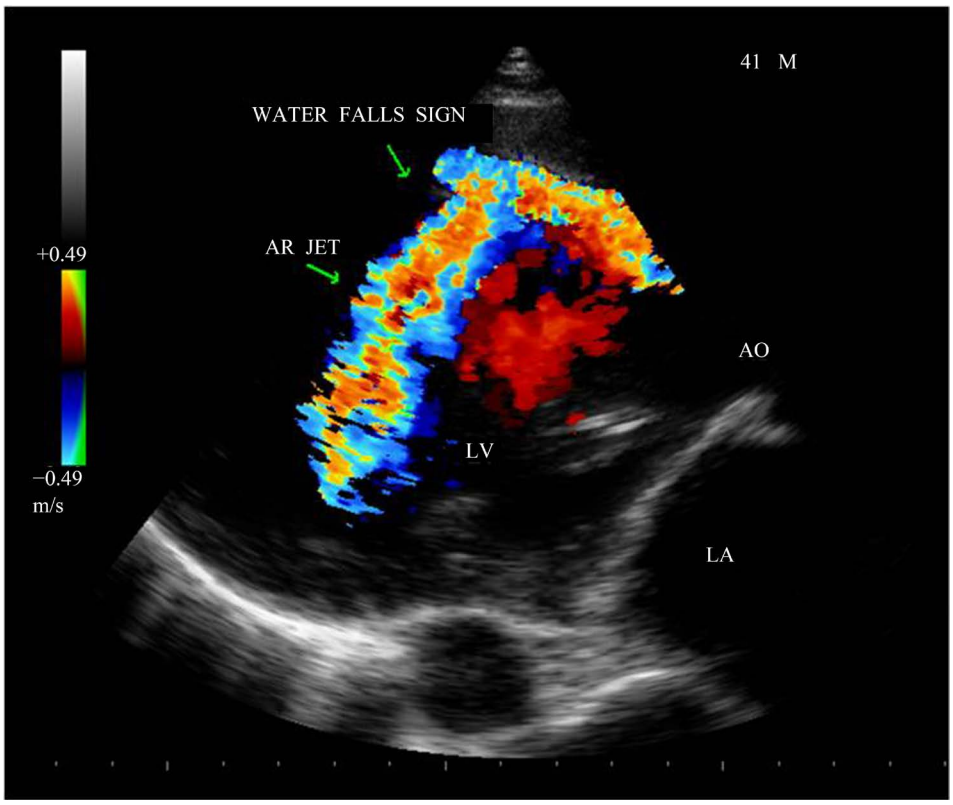

Figure 12. Parasternal long axis view showing the AR jet falling into the LV with a typical appearance of a "water fall".

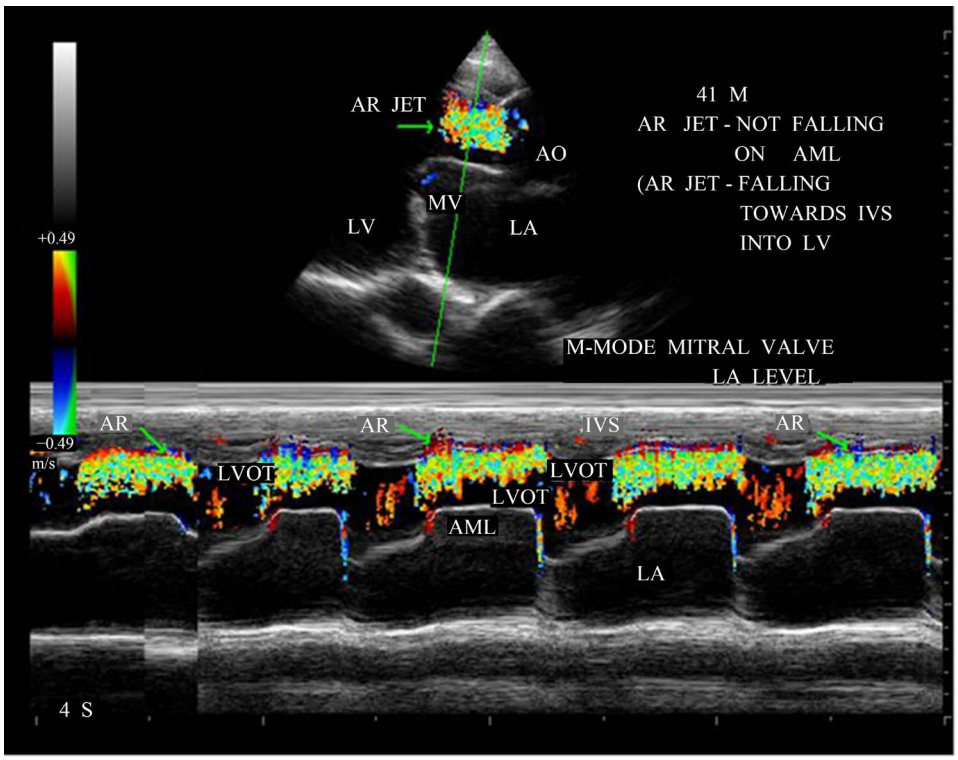

Figure 13. M-mode color doppler AR jet towards IVS at LA (left atrial) level.

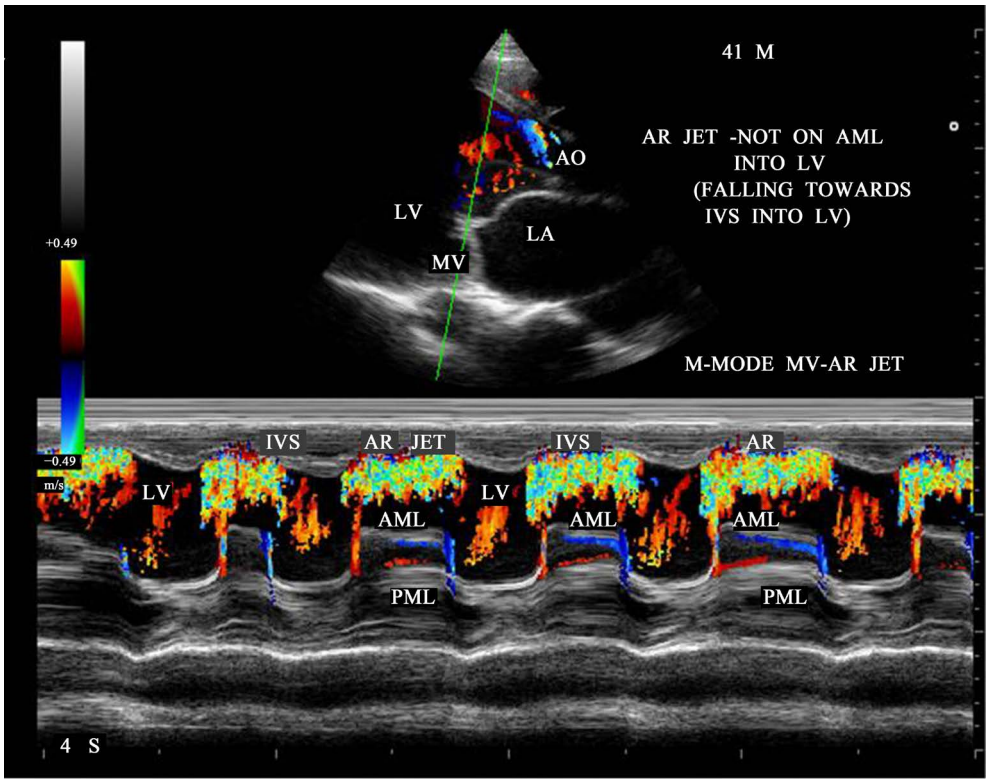

Figure 14. M-mode color doppler showing AR jet towards IVS (interventricular septum) at mitral valve level).

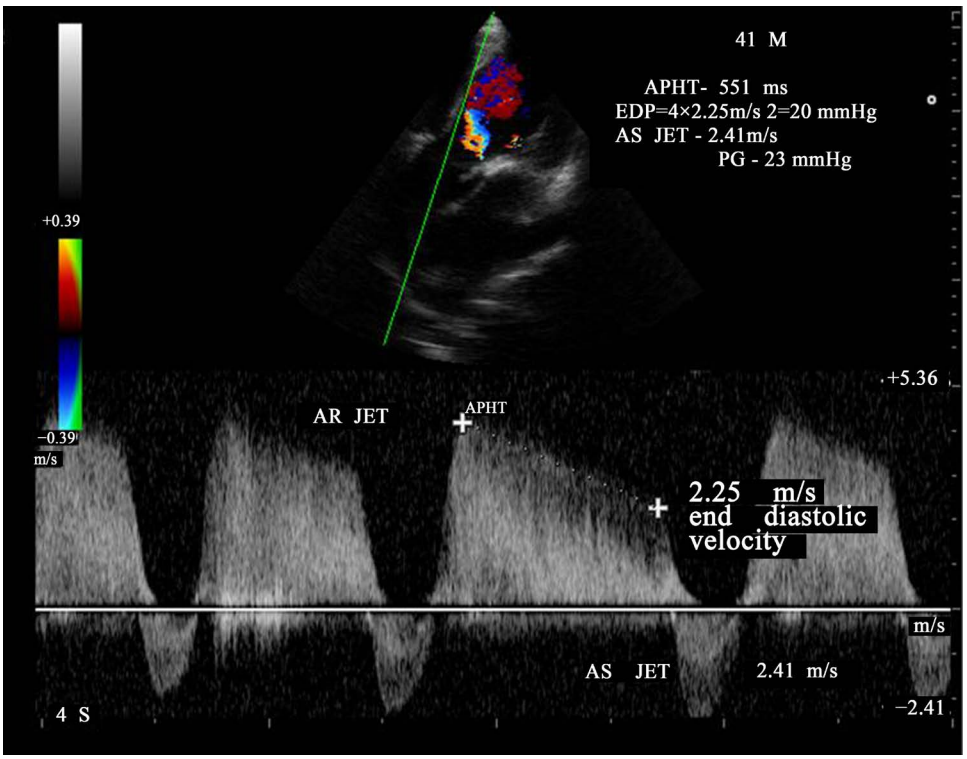

Figure 15. CW doppler imaging showing the AR jet-pressure half-time in long cycle in AF (atrial fibrillation)—flat slope of pressure decay. AS (aortic stenosis) jet.

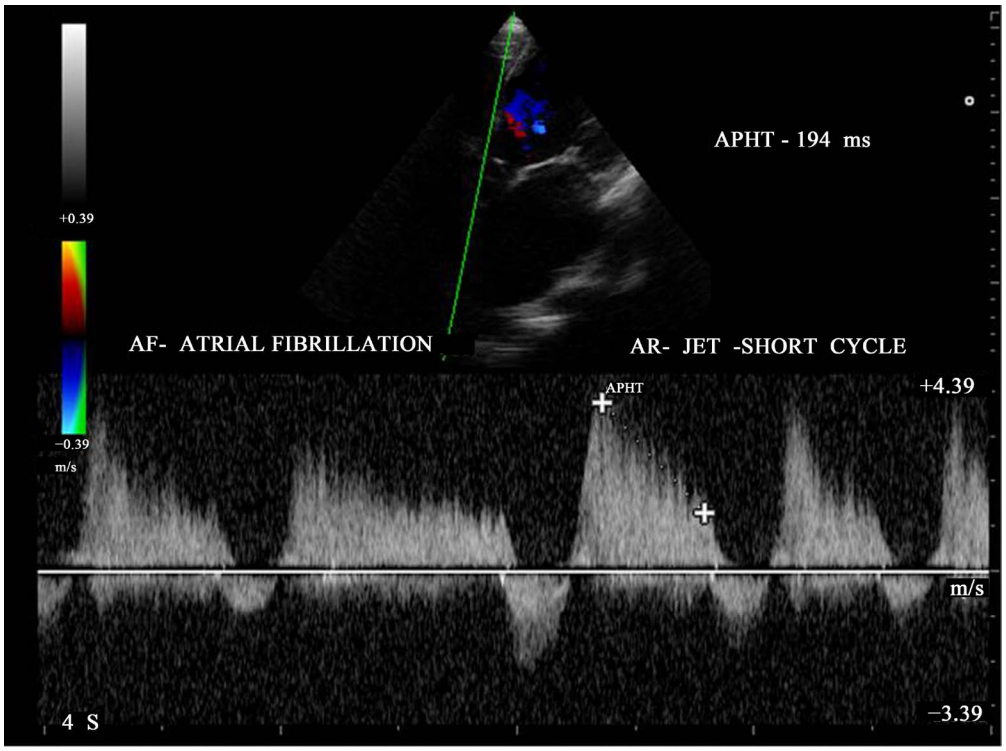

Figure 16. CW doppler imaging showing the AR jet-pressure half-time in short cycle in AF (atrial fibrillation)—steeper slope of pressure decay.

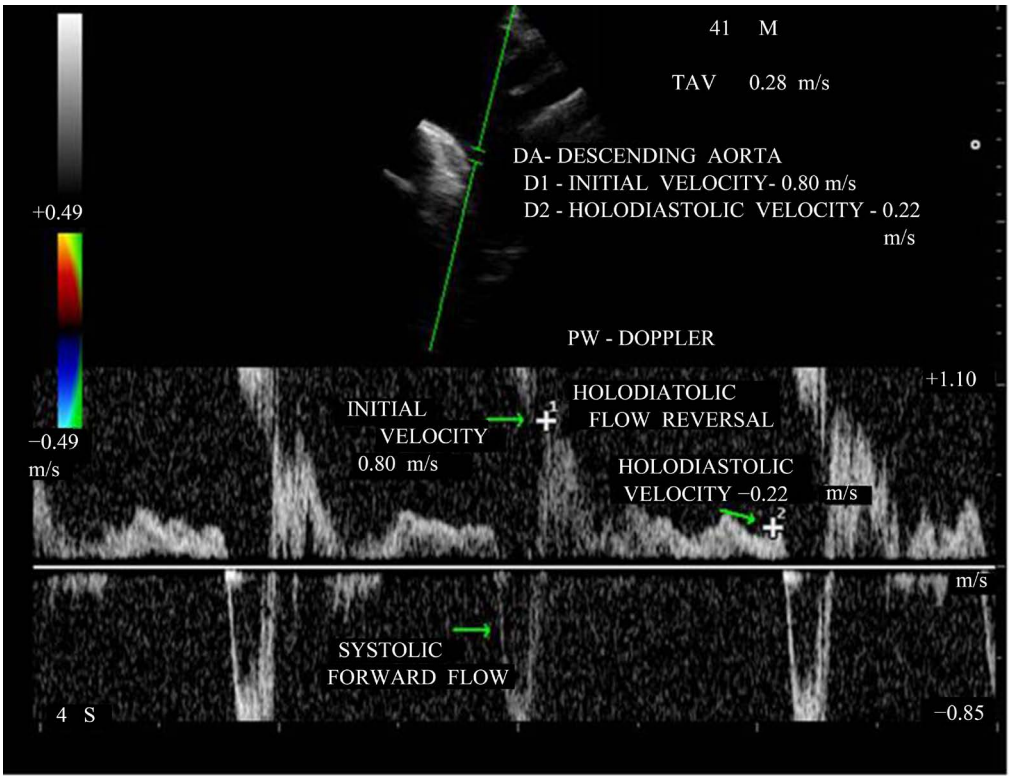

Figure 17. PW doppler showing the "holodiastolic flow reversal" in the descending aorta-suprasternal notch view).

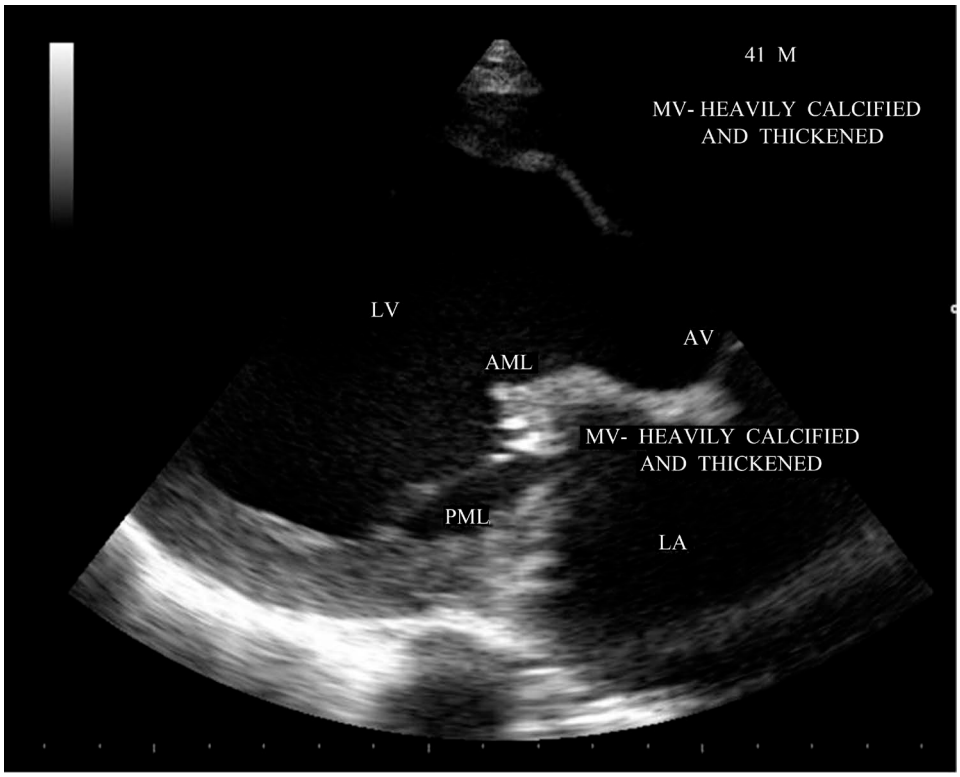

Figure 18. Parasternal long axis view showing the thickened and calcified mitral valve.

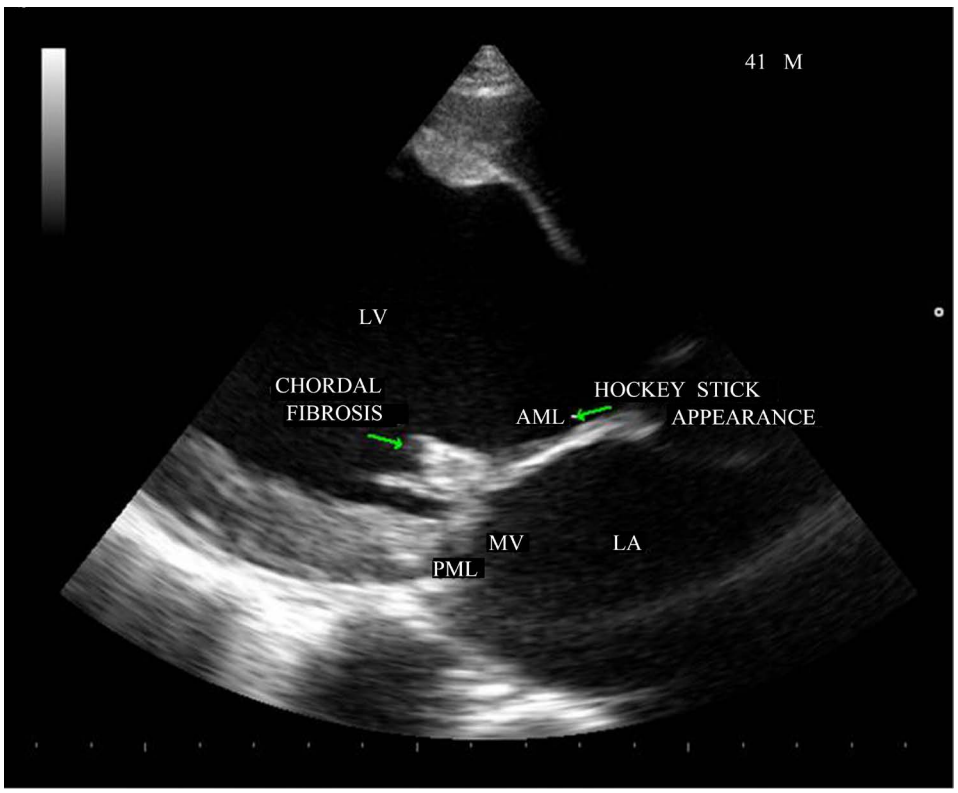

Figure 19. Parasternal long axis view in systole showing the diffuse thickening and fibrosis of chordal apparatus—less amenable to PMC) [24].

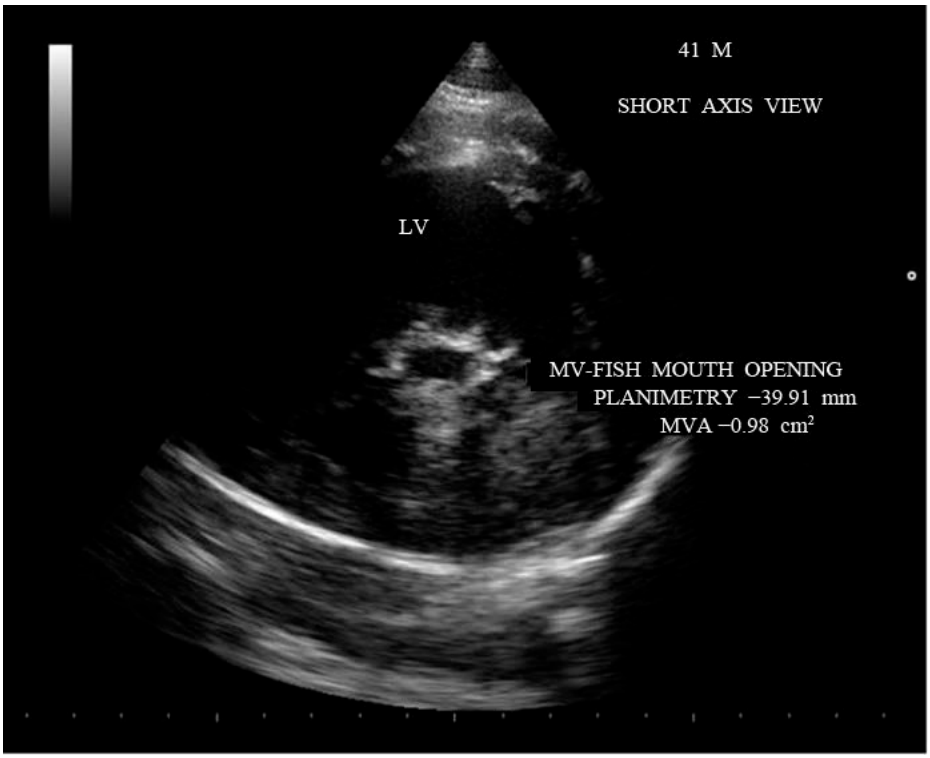

Figure 20. Short axis view showing the planimetry of mitral valve-circular orifice-MVA—0.98 $cm^{2.}$

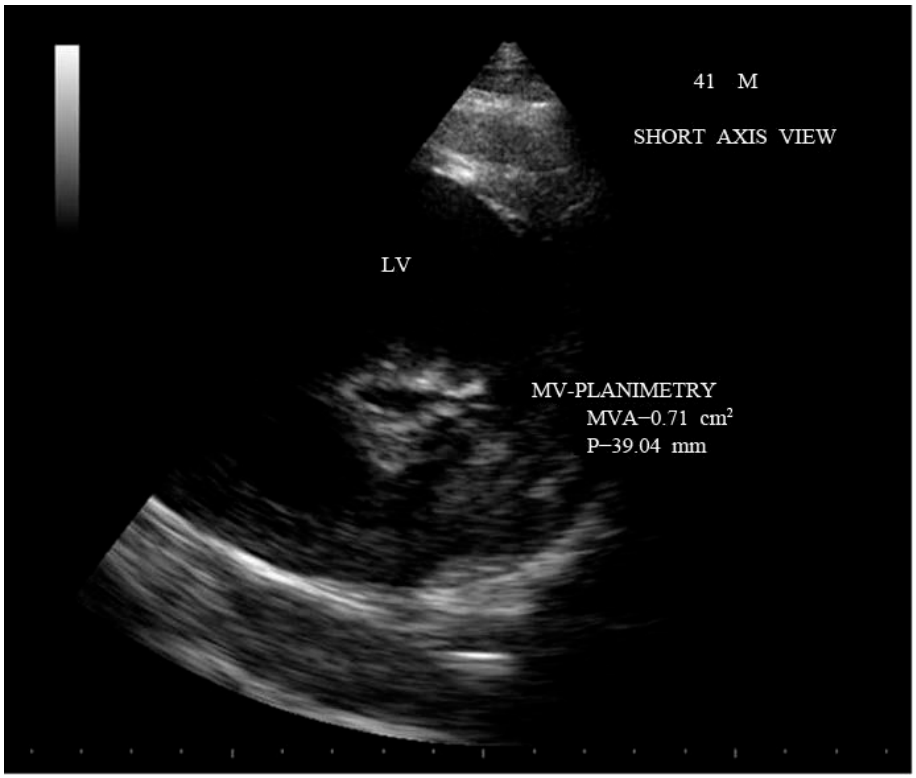

Figure 21. Short axis view showing the planimetry of mitral valve-slit like orifice-MVA—0.71 cm^{2}.

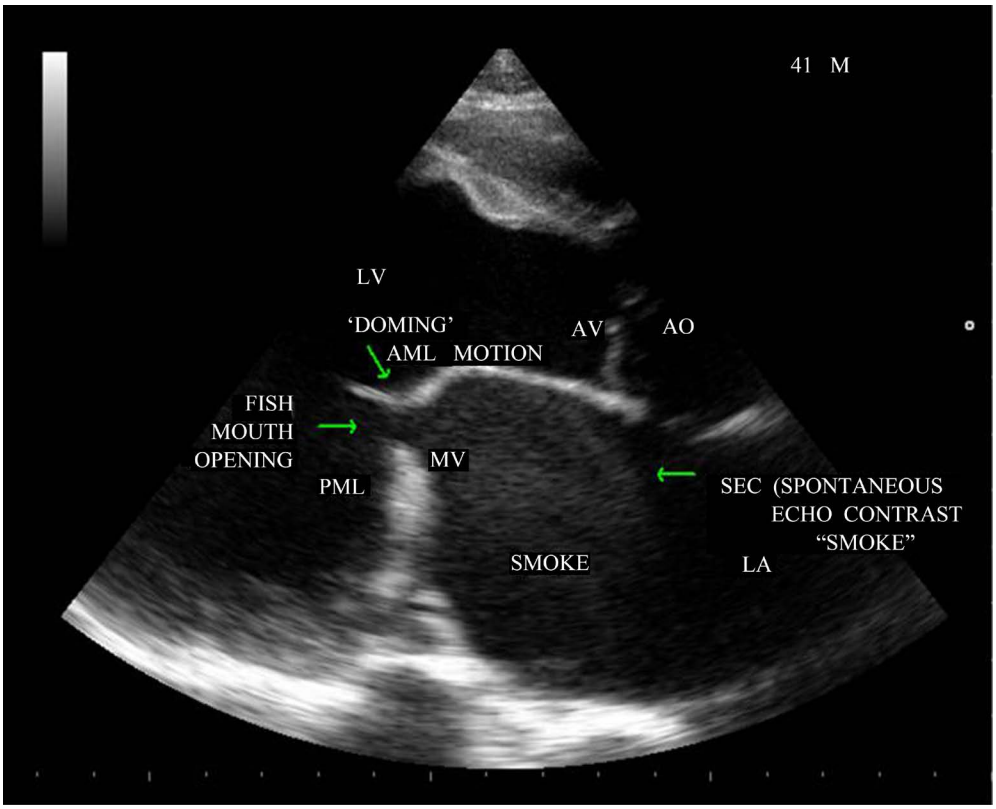

Figure 22. Parasternal long axis view showing the "smoke" in left atrial body.

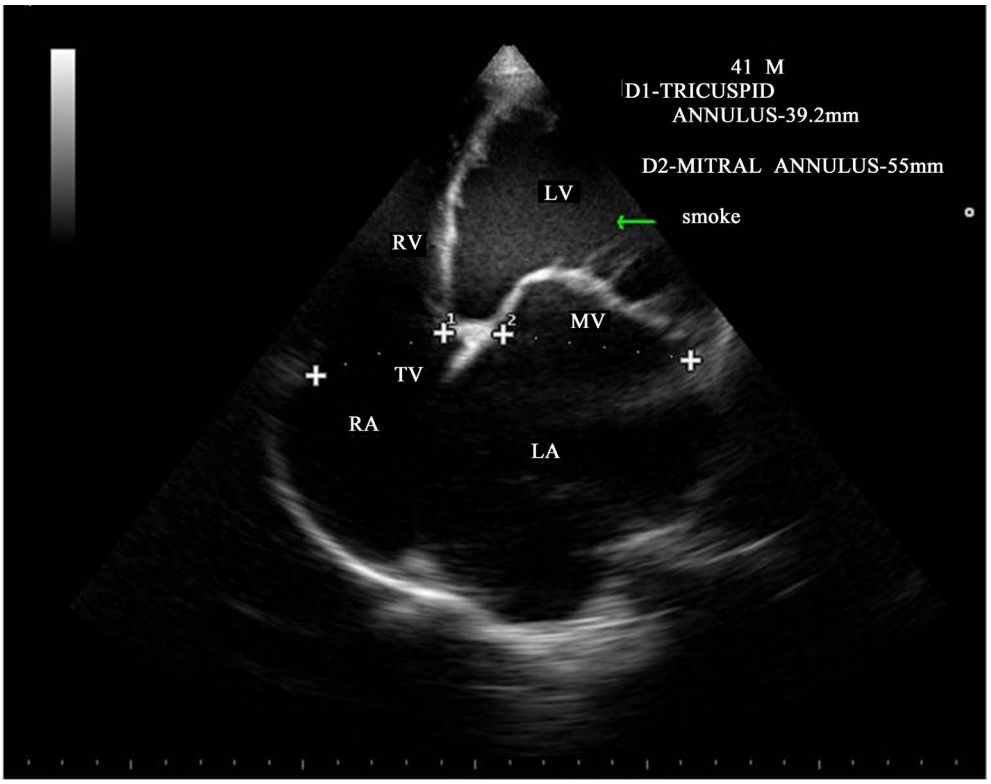

Figure 23. Apical four chamber view showing the "smoke" in the left ventricle.

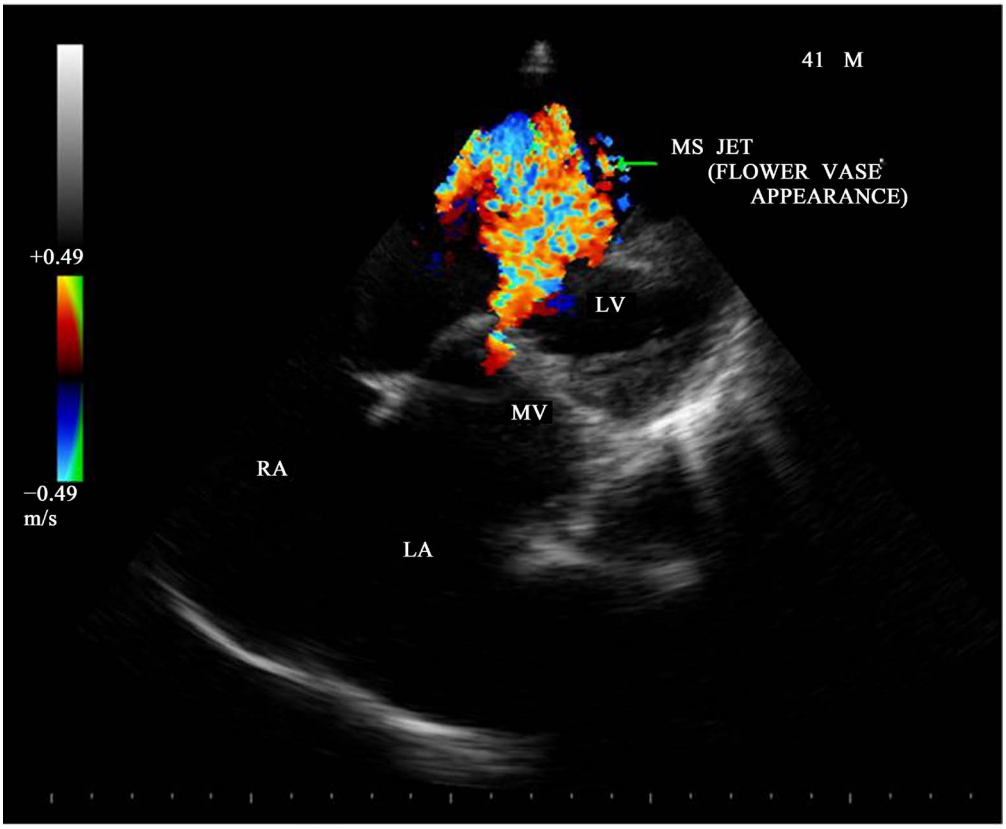

Figure 24. Apical four chamber view-showing the MS jet—"flower vase appearance".

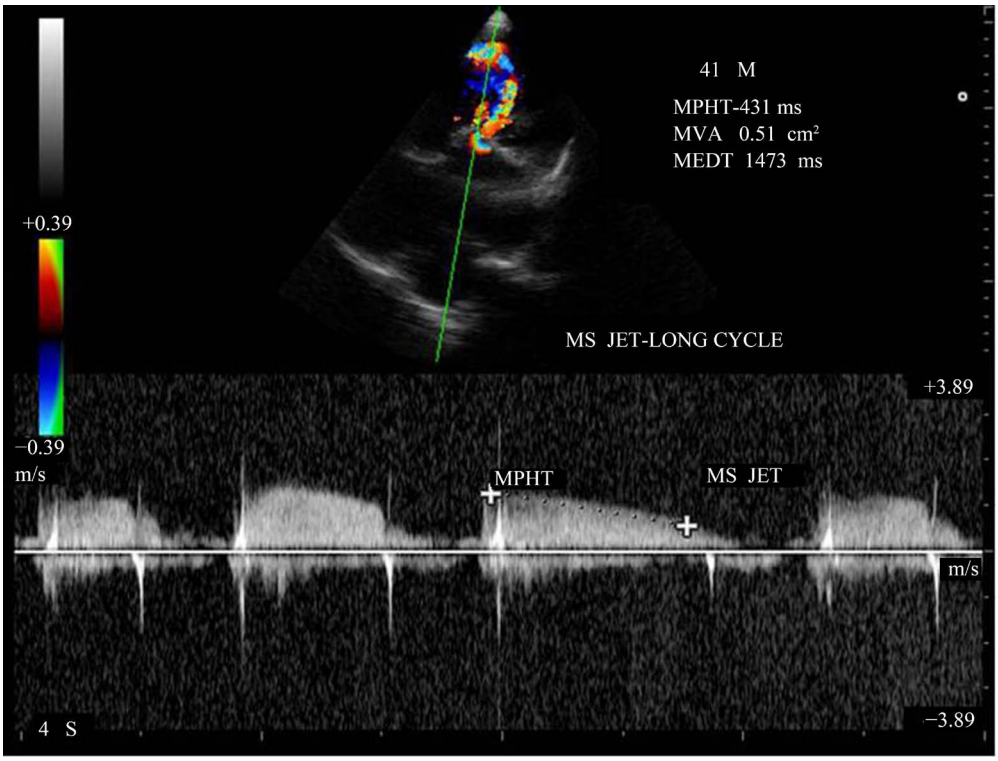

Figure 25. CW doppler showing the MS jet-long cycle pressure half-time.

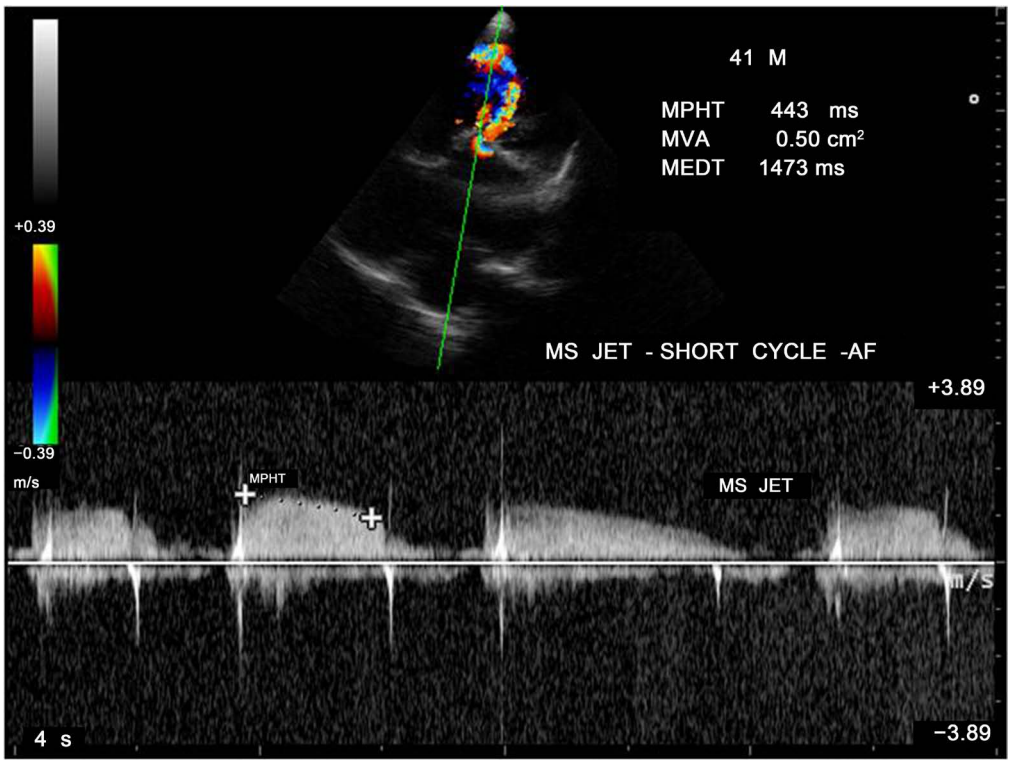

Figure 26. CW (continuous wave) doppler showing the MS jet- short cycle pressure half-time.

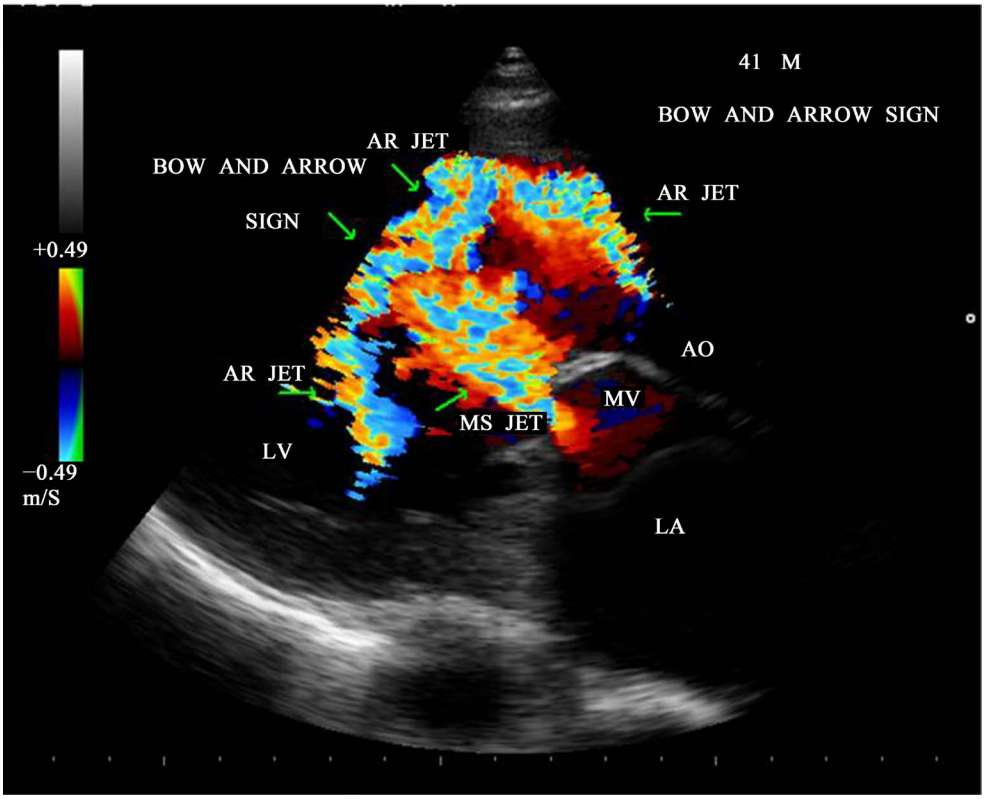

Figure 27. CW doppler showing the MS jet collide with AR jet and a “bow and arrow” appearance in parasternal long axis view.

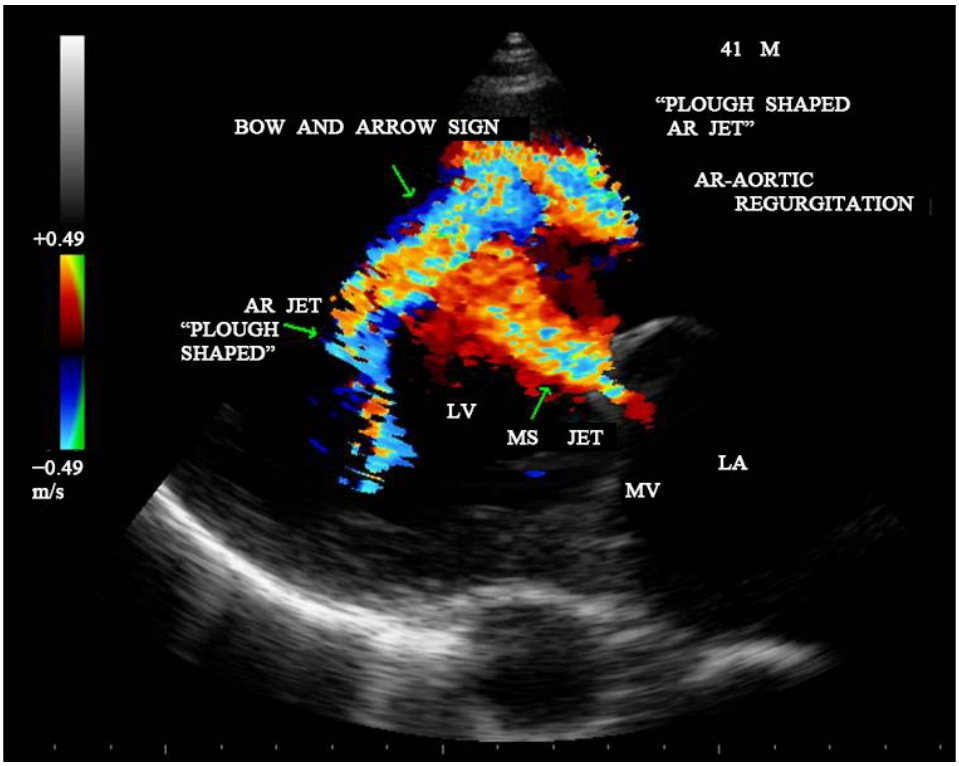

Figure 28. CW doppler showing the MS and AR jets-"bow and arrow sign" in parasternal long axis view—"plough" shaped AR jet.

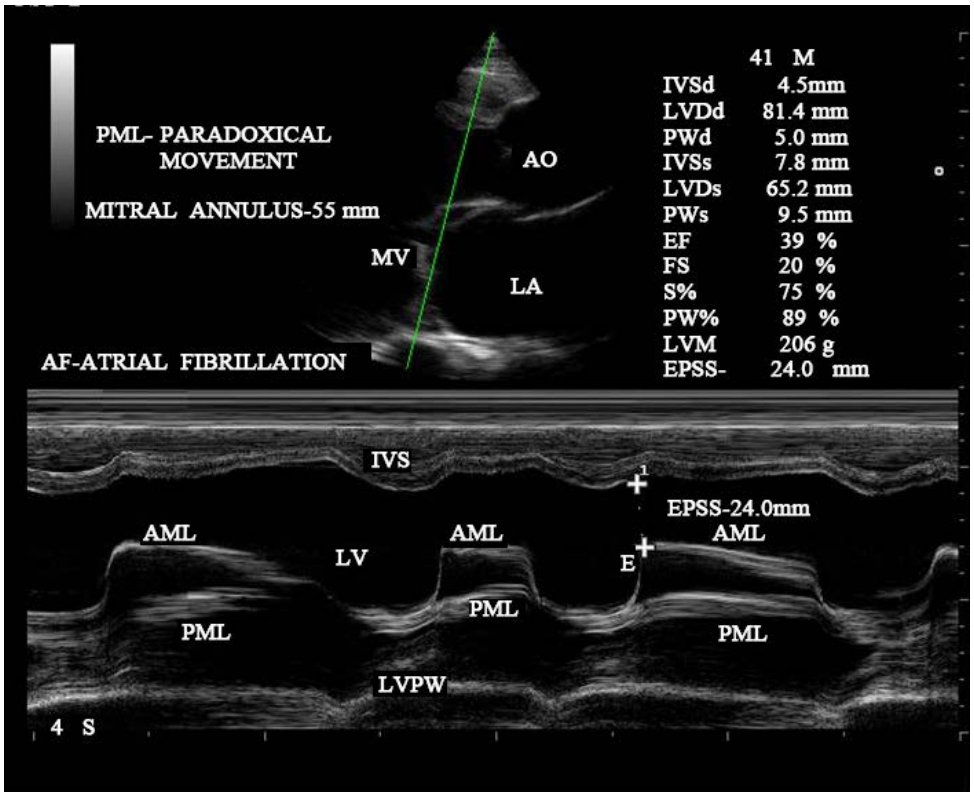

Figure 29. M-mode LV study, EPSS and paradoxical motion of posterior mitral leaflet.

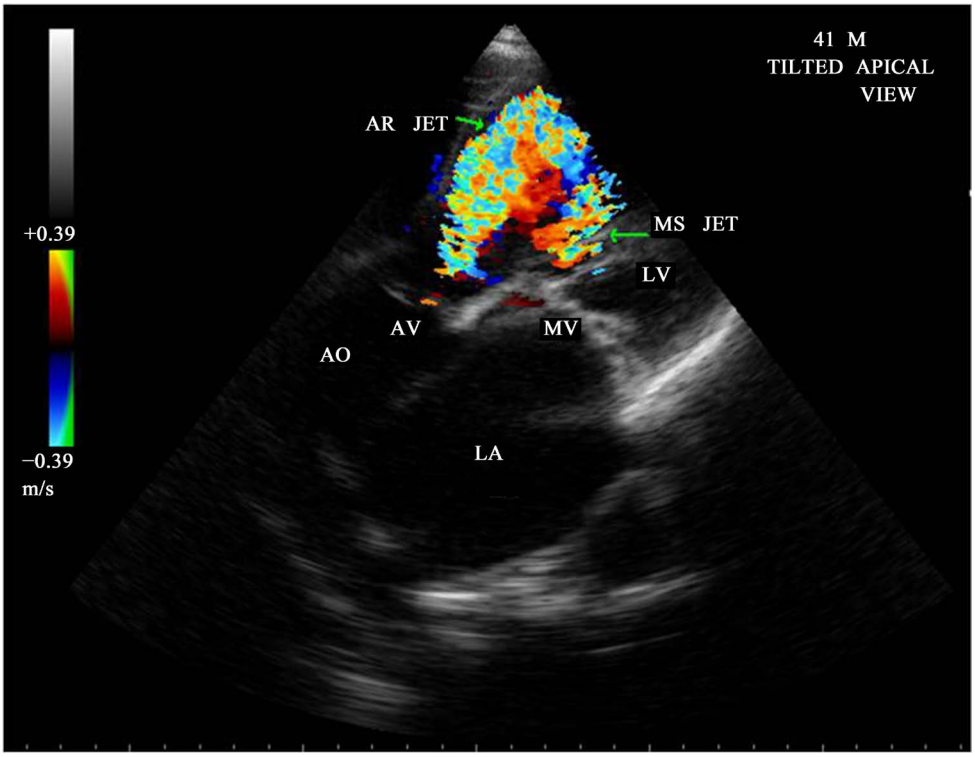

Figure 30. CW doppler showing the MS jet and AR jet in tilted apical view.

congenital bicuspid aortic valve, there are only two functional cusps, usually of unequal size, with the larger cusp having a midline raphe, resulting from incomplete commissural seperation during development. Less frequently, the cusps are of equal size and the raphe is absent. The raphe is frequently a major site of calcific deposits. The altered architecture of the bicuspid aortic valve induces turbulent flow with continuous trauma to the leaflets, ultimately resulting in fibrosis, increased rigidity, calcification and narrowing of the aortic orifice in adulthood [25]. Congenitally malformed tricuspid aortic valves with unequally sized cusps and commissural fusion called as “functionally bicuspid valves”, can also cause turbulent flow leading to fibrosis and, ultimately, to calcification and stenosis. Clinical manifestations of congenital aortic stenosis in adults usually appear after the fourth decade of life. Stenotic bicuspid aortic valve comes to clinical attention at 50 - 70 years and senile calcific aortic stenosis of tricuspid valve at 70 - 90 years. Degenerative calcific aortic stenosis occurs as a consequence of long-standing hemodynamic stress on the valve and usually manifest in individuals older than 75 years with a prevalence of 2% - 9% and occurs most frequently in males [26] having the risk factors of hypertension, hypercholesterolemia, diabetes mellitus, and smoking, due to active disease process at cellular and molecular level that shows many similarities with atherosclerosis, ranging from endothelial dysfunction to, ultimately calcification. The calcification may extend to mitral annulus and conduction system and produce conduction defects. The age-related degenerative (“wear and tear” of either of anatomically normal or congenital bicuspid ones) calcific aortic stenosis, there is dystrophic and passive accumulation of hydroxyapatite, the same calcium salt that is found in bone [27]. Chronic injury due to hypertension, hypercholesterolemia and inflammation in atherosclerosis differs as smooth muscle cell accumulation from the valve injury of calcific aortic stenosis in which abnormal valves contain cells resembling osteoblasts that synthesize bone matrix proteins and promote the deposition of calcium salts. BAV (bicuspid aortic valve) incur greater mechanical stress than the normal tricuspid valves, which may explain why they become stenotic more rapidly. The morphologic hallmark of non-rheumatic, calcific aortic stenosis (with either tricuspid or bicuspid aortic valve) is heaped-up calcified masses within the aortic cusps that ultimately protrude through the outflow surfaces into the sinus of valsalva and prevent the opening of the cusps. The free edges of the cusps are usually not involved and the commissural fusion is not found as in postrheumatic aortic valve stenosis. The calcific process begins in the valvular fibrosa at the point of maximal cusp flexion near the margin of the attachment and the layered architecture of the valve is largely preserved.

Patients with bicuspid aortic valve may be completely asymptomatic. About 30% of individuals with a bicuspid aortic valve develop complications [28]. Occasionally, a congenital bicuspid aortic valve may be the cause of critical aortic stenosis, with symptoms of severe heart failure, developing in early infancy. This critical form of stenosis is more frequently associated with a unicommissural valve (severe form). The bicuspid aortic valve (moderate form) generally functions well in patients with left heart obstructive lesions such as coarctation or interrupted aortic arch and the incidence of bicuspid aortic valve is >50% in these lesions. [29]. Stenosis of a bicuspid aortic valve is more likely to develop in persons older than 20 years and is caused by progressive sclerosis and calcification. High levels of serum cholesterol have been associated with more rapidly progressive sclerosis of the congenitally bicuspid aortic valve [30]. Children who develop early progressive pathologic changes in the bicuspid aortic valve are more likely to develop valve regurgitation than stenosis. Stenotic or partially fused valves may be caused by inflammatory process such as rheumatic fever.

There is a propensity for premature fibrosis, stiffening, and calcium deposition resulting in significant stenosis and cusp prolapse (due to redundancy of conjoined leaflet [31]), fibrotic retraction, or dilatation of the Sinotubular Junction resulting in Regurgitation in abnormally functioning congenital bicuspid aortic valves as "valvulopathy". In addition, patients with poor lipid profile and those who smoke also act as an elevated rik of developing hemodynamically significant bicuspid aortic valve stenosis [32]. Aortopathy refers to dilated aortic root, usually associated with BAV and may lead to aortic aneurysm, dissection (the most feared complication—4%) and rupture due to accelerated degeneration of the aortic media, indicating that BAV disease is an ongoing pathological process and not a discrete developmental event. Certain Gene mutations (NOTCH 1) have been implicated in fibrillin—1 deficiency in tissues. MMPs (matrix metalloproteinases) become activated, degrading the structural support of the aorta and medial weakness, resulting aortopathy in BAV. Recently, it is stated that identification of hemodynamics for leaflet fusion patterns enables detection of specific aortic regions susceptible to dysfunction. Variance in WSS (wall shear stress) and flow displacement are important in aortic leaflet morphology [33]. In BAV, helical and high velocity outflow patterns are consistent with aortic dilatation hemodynamics and RL fusion causes dilation of mid-ascending aorta, while RN fusion is associated with dilation in aortic root [34] as shown in **Figure 11**, distal ascending aorta and transverse arch are not dilated in this patient. Atherosclerotic aortic valve stenosis occur more frequently in patients with severe hypercholesterolemia and is observed in children with homozygous type II hyperlipoproteinemia [35] (total serum cholesterol >800 mg/dl from birth). Immunohistochemical evidence of chlamydia Pneumoniae has been found in early lesions of age related degenerative aortic stenosis [36].

Aortic valve may become bicuspid due to an acquired deformity of rheumatic process and have a fused commissure that produces a conjoined cusp as shown in **Figure 4** and it is twice the size of nonconjoined cusp.

3.2. Echocardiographic Features

BAV is the most frequent congenital cardiovascular malformation in humans [37]. Bicuspid aortic valves are responsible for approximately 50% of cases of aortic stenosis in adults [38]. In bicuspid aortic valve, two cusps are seen in systole with only two commissures framing an elliptical systolic orifice. Diastolic image may mimic a tricuspid valve when a raphe is present. Long axis view shows asymmetric closure line and systolic doming. In children and adolescents, it may be stenotic without extensive calcification. Calcification of tricuspid aortic valve is most pronounced in the central part of each cusp and commissural fusion is absent, resulting in a stellate-shaped systolic orifice. Rheumatic aortic stenosis is characterized by commissural fusion, resulting in a triangular systolic orifice with thickening and calcification most prominent along the edges of the cusps as shown in **Figure 5**.

3.3. Types of Bicuspid Aortic Valve

Bicuspid aortic valve may assume three different types of configuration [39]. Type-1—"Real" bicuspid valve with two symmetric leaflets, Type-II—A tricuspid architecture with a fusion of two leaflets, Type-III—A tricuspid architecture with a fusion of 3 leaflets. Another classification described by Hans Sievens in 2007 based on the number of "cusps" and "raphes" as Type 0—no raphe (pure bicuspid aortic valve), Type-1—1 raphe, Type-II—2 raphes. "Raphe" is the arrow-shaped formation of tissues, also called "false commissures" and refer to the fused areas where the undeveloped cusps form a malformed commissure [40].

Demonstration of marked eccentricity of the aortic valve diastolic echoes with respect to the aortic lumen ap-

pears to be the hallmark of a congenital bicuspid aortic valve. A normal tricuspid aortic valve, on the other hand, closes without cusp folding and therefore does not produce multiple diastolic echo sources along the lines of closure and the diastolic positions of cusp echoes is near the middle of the aortic lumen. In the case of the bicuspid aortic valve, the aortic valve diastolic position would be consistently observed near the anterior or near the posterior aortic margin depending on the location of the dominant leaflet. The eccentricity index denotes the deviation of the diastolic cusp position from the middle of the aortic lumen and takes into account the internal diameter of the aortic root. The index would equal unity if the valve cusps closed exactly in the center of the aortic root, while very high values (3.5 or above) would indicate extreme asymmetry of the cusp images. The eccentricity index was low, ranging from 1.0 to 1.25 in normal tricuspid aortic valve and high (1.5 to 5.6) in all patients with bicuspid aortic valve. The eccentricity index is 1.6 in this patient as shown in **Figure 8** revealed the acquired rheumatic etiology for the bicuspid appearance in parasternal long axis view.

3.4. Spontaneous Echo Contrast (SEC or "Smoke")

Pathologic SEC (spontaneous echo contrast or "smoke") occurs when there is blood stasis due to low-flow velocity as a result of interaction between blood cells and plasma proteins, especially fibrinogen (eg. Rouleau formation) and it has been consistently associated with increased risk of thromboembolism. It is the swirling, hazy echocardiographic appearance as shown in **Figure 22** and **Figure 23**, associated with low blood flow in mitral stenosis, atrial fibrillation and left ventricular failure. SEC usually occurs in the body of left atrium in mitral stenosis a shown in **Figure 22**. Atrial fibrillation in the absence of mitral stenosis is incapable of forming thrombus in the left atrial body [41]. Left atrial SEC is a better predictor of the thromboembolic risk than left atrial size [42]. Spontaneous echo contrast (SEC) is also seen in left ventricle (LV) in this patient as shown in **Figure 23**.

3.5. Atrial Fibrillation

Patients with atrial fibrillation in presence of structural heart disease such as mitral stenosis as shown in ECG in **Figure 1** have high embolic potential and less likely to be maintained in sinus rhythm. The atrial fibrillation, a frequent sequelae of left atrial dilation due to mitral stenosis may cause SEC in LA appendage rather than in the body of left atrium. SEC may also occur in structurally normal heart with LAA (left atrial appendage) emptying flow velocity < 55 cm/s (normal—>50 cm/s) is associated elevated risk of thrombus formation. LAA emptying flow velocity < 35 cm/s in atrial fibrillation is associated with elevated embolic risk (pulsed Doppler sample volume is placed in proximal third of appendage (mouth of appendage) in end-diastole).

3.6. Aortic Regurgitation

Another consequence of functionally normal bicuspid aortic valve is progressive regurgitation, and it is the most common cause of pure congenital aortic regurgitation [43]. Tricuspid aortic valves with cuspal inequality are seldom incompetent in the young, but become incompetent in older patients in whom minor degrees of fibrocalcification exaggerate inherent cuspal inequality and interfere with leaflet coaptation [44]. Rarely, a severely incompetent bicuspid aortic valve becomes stenotic with virtual loss of regurgitation [45]. The echocardiographic diagnosis can be difficult in patients with heavily calcified valves [46] and identification of aortic sinuses in short axis may helpful to predict the leaflet architecture. In normal tricuspid aortic valve, the three lines of coaptation forming a "Y" (sometimes referred to as inverted Mercedes-Benz sign). In bicuspid aortic valve, the raphe can make the valve appear trileaflet during diastole, and a characteristic "fish mouth appearance" of orifice as shown in **Figure 6**. Rheumatic fever produces fibrotic changes, thickening and retraction of the aortic valve leaflets, resulting in central valvular regurgitation [47] as shown in **Figure 10**. Leaflet fusion may occur, leading to concurrent aortic stenosis as shown in **Figure 15**. The pathophysiology depends on whether the regurgitation is acute or chronic. In acute AR (aortic regurgitation), LV (left ventricle) does not have time to dilate in response to the volume overload, the LV end-diastolic pressure increases rapidly and causing an increase in pulmonary venous pressure leading to pulmonary edema and cardiogenic shock in severe cases. In chronic AR, the left ventricle may undergo a series of adaptive changes due to gradual increase in volume overload. LV dilation occurs as shown in **Figure 9** through the addition of sarcomeres in series and as a result, the LV becomes larger and more compliant, with greater capacity to deliver a large stroke volume. Due to increased preload and the Frank-Starling mechanism, the ejection fraction (EF) is normal or even increased during early phase of chronic AR and

the patient may remain asymptomatic during this period. When AR progresses, LV enlargement surpasses preload reserve and the ejection fraction falling to subnormal levels as shown in **Figure 29** (LV EF—39%, the LV end-systolic volume rises and it is a sensitive indicator of progressive myocardial dysfunction. Eventually, the LV reaches its maximal diameter and diastolic pressure begins to rise, resulting in symptoms of dyspnea which may worsen during exercise.

The severity of aortic regurgitation can be assessed by Doppler studies. It is stated that the length of AR jet penetration into the left ventricle is an unsatisfactory indicator of AR severity [48]. Due to massive LV dilation, AR jet falling into the dilated LV from a height of LVOT with an appearance of "water fall" as shown in **Figure 12** and it correlates with severity of regurgitation in this patient. One of the simplest and most reliable is to measure the proximal regurgitation width (height)—immediately within 1 cm below the aortic valve and compared it to LVOT diameter (left ventricular outflow tract) [49] (measured from endocardial septum to anterior mitral leaflet within 0.5 - 1 cm below the aortic valve, parallel to aortic valve plane in mid-systole) and its ratio ≥ 65% defines the severe AR and it cannot be used for eccentric jets. **Figure 10** shows proximal AR jet width 20 mm and LVOT diameter 30 mm and its ratio is 66%, suggesting severe AR in this patient.

3.7. Vena Contracta

It is the smallest neck of flow region at the level of the aortic valve, immediately below the flow convergence region and the threshold of vena contracta width associated with severe AR are 0.5 cm as a highly sensitive, 0.7 cm as a highly specific and 0.6 cm as the threshold with best combination of specificity and sensitivity [50]. To approximately visualize the vena contracta, it is essential to see all the components of the regurgitant flow, *i.e.*, the flow convergence, vena contracta and the jet. The central jet tends to expand fully in the outflow tract as shown in **Figure 10** and may be inconclusive to predict the vena contracta.

3.8. Diastolic Jet Deceleration

The rate of deceleration of diastolic regurgitant jet and the derived pressure half-time reflect the rate of equalization of aortic and LV diastolic pressures, with increasing severity of AR. The aortic diastolic pressure decreases more rapidly. The late diastolic jet velocity is lower and hence pressure half-time is shorter [51] and a ratio <200 - 250 ms is consistent with severe AR and >500 ms with mild AR. On the other hand, pressure half-time can be lengthened or normalized with chronic LV adaptation to severe AR [52] as shown in **Figure 15**. In atrial fibrillation, the steeper slope of pressure decay in short cycle (PHT-194 ms) as shown in **Figure 16** correlates with severity and the flat slope of pressure decay in long cycle (PHT-551 ms) as shown in **Figure 15** is not correlating with severity of AR in this patient.

3.9. Aortic Diastolic Flow Reversal

A brief diastolic flow reversal in aorta is normal and it is best recorded at aortic isthmus level in the upper descending aorta by pulsed-wave doppler. With increasing aortic regurgitant, both the duration and velocity of reversal increase [53]. Therefore, a holodiastolic reversal as shown in **Figure 17** is usually a more specific sign of at least moderate aortic regurgitation. Retrograde flow measured by pulsed-wave Doppler immediately after subclavian artery and if end diastolic flow velocity is <18 cm/s = does not indicate hemodynamically significant AR (grade I and II), >18 cm/s = indicate hemodynamically significant AR (grade III and IV). In severe cases, the initial diastolic flow velocity is >0.6 m/s and TVI backflow signal >15 cm. In this patient, the initial diastolic flow velocity is 0.80 m/s and end diastolic velocity 0.22 m/s correlate with severe aortic regurgitation. Holodiastolic flow reversal can be used to assess the aortic regurgitation following TAVR (Transcatheter aortic valve replacement-paravalvular leak).

Among the echocardiographic parameters, the ejection fraction (EF) and end-systolic dimension are the key determinants of outcome of surgery".

3.10. Coexistent Mitral Stenosis

Acute insult of rheumatic fever on mitral valve leads to the formation of multiple inflammatory foci consists of Aschoff bodies, perivascular mononuclear infiltrate in the endocardium and myocardium. With time, the valve apparatus become thickened, calcified and contracted. Commissural adhesion occurs as shown in **Figure 18** and

ultimately resulting in mitral stenosis after a long latent period of streptococcal infection due to autoimmune mediated inflammation. Due to commissural fusion, the leaflets open with a "doming" motion as shown in **Figure 9** and it results in reduction of the orifice and the conversion of the mitral leaflet-chordal apparatus from a tubular channel to a "funnel-shaped" orifice. The substantial fibrosis and calcification at the orifice of mitral valve limits inflow from left atrium to left ventricle and this limiting orifice is planimetered at the valve tips in mid-diastole as shown in **Figure 20** and **Figure 21**, the orifice area correlate well with hemodynamic data and anatomic valve area [54].

In general, rheumatic mitral stenosis results in a central stenotic orifice with flow directed from the center of the left atrium towards the apex of the left ventricle and collide with AR jet, producing a "bow and arrow" appearance as shown in **Figure 27** and **Figure 28**. The differential features of etiological aspects of mitral stenosis (MS) are shown in **Table 1**.

3.11. Pressure Half-Time

It is defined as the time interval in milliseconds between the maximum mitral gradient in early diastole and the time point where the gradient is half the maximum initial value. The decline of the velocity of diastolic transmitral flow is inversely proportional to valve area (cm^2) and MVA (mitral valve area) is derived by using the empirical formula ($MVA = 220/T_{1/2}$) [55]. The empirically determined constant of 220 is in fact proportional to the product of net compliance (*i.e.*, the combined compliance of left atrium and LV) and the square root of maximum transmitral gradient in a model that does not take into account of active relaxation of LV [56]. In patients with Atrial Fibrillation, tracing should avoid mitral flow from short diastoles and average different cardiac

Table 1. Differential features of etiology of mitral stenosis (MS).

Rheumatic MS	Degenerative MS	Congenital MS
The main lesion is "commissural fusion"	The main lesion is "annular calcification". No commissural fusion	The main lesion is in "subvalvular apparatus". Commissural fusion is rare
Calcification predominates at leaflet tips	At base of leaflets	Chordal fusion with calcification
Planimetry is reliable	Not reliable	Large orifice may be present
Pressure half-time reliable	Unreliable due to impaired diastolic function and should be avoided	Reliable when diastolic jet occurs
Mean Gradient can be used following balloon mitral commissurotomy	Mean Gradient can be used as a marker of severity	Reliable when diastolic jet occurs
Central or commissural jet due to valve stiffness.	No particular orientation	Central jet in symmetric type. Eccentric jet in asymmetric type (anteriorily oriented jet in parachute type)
Orifice is circular or elliptical in short axis view of planimetry.	Unpredictable	Chordal convergence' on a single papillary muscle in short axis view at mid-ventricular level in parachute type
Manifest in younger age group	Manifest in older age group	Seen from birth
Single orifice	Single orifice	May present with "double orifice" type

cycles as shown in **Figure 25** and **Figure 26**, the mitral valve pressure half-time = 431 ms and Mitral valve area is 0.51 cm^2 in long cycle and 443 ms and 0.50 cm^2 in short cycle.

Aortic regurgitation causes the left ventricular pressure to increase more quickly in diastole than would otherwise occur. This can lead to shortening of pressure half-time and an underestimate of mitral stenosis severity. Early diastolic deceleration is prolonged when LV relaxation is impaired while it tends to be shortened in case of decreased LV compliance [57]. Rapid decrease in mitral velocity flow, *i.e.*, short $T_{1/2}$ can be observed despite severe MS in patients who have a particular low atrial compliance [58]. The deceleration slope is sometimes bimodal, the deceleration of mitral flow velocity being more rapid in early diastole than during the following part of the E-wave and in such cases, the deceleration slope in mid-diastole rather than the early deceleration slope be traced [59]. Planimetry is considered as the reference measurement of mitral valve area (MVA) [60]. The mitral valve areas measured by pressure half-time is 0.51 cm^2 and 0.50 cm^2 as shown in **Figure 25** and **Figure 26** are not correlated well with planimetry measurements as shown in **Figure 20** (0.98 cm^2) and 0.71 cm^2 in **Figure 21**. The difference in planimetry measurements is due to positional variations, the point at which the orifice is planimetered [61]. Assessment of valve area using continuity equation and PISA (proximal isovelocity surface area) method are not recommended for routine use.

3.12. M-Mode Findings of Mitral Stenosis

The hallmark of rheumatic heart disease (RHD) was increased echogenicity of leaflets with decreased excursion and reduced separation of the anterior and posterior leaflets. There is "paradoxical" anterior diastolic motion of the posterior mitral leaflet as shown in **Figure 29**, due to tethering at the tips resulted in an obligatory anterior motion of the posterior mitral leaflet tips, that due to commissural fusion, were tethered to the larger anterior leaflet.

EPSS (E-point to septal separation)-EPSS is the distance (mm) from the anterior septal endocardium to the maximal early opening point (E-point) of the mitral valve and it is the first of M-mode findings to predict systolic dysfunction, an indirect measure of a reduced ejection fraction. The normal EPSS is 6 mm and a longer EPSS (24 mm as shown in **Figure 29**) represent a lower ejection fraction (EF-39%). The ESD (end-systolic diameter—65.2 mm and LV dilation is 103 mm in this patient as shown in **Figure 9** and **Figure 29**.

A patient with a low ejection fraction but a resting AS (aortic stenosis) velocity >4 m/s does not have a poor left ventricle. The ventricle is providing a normal response to high after load (severe AS), and ventricular function will improve after relief of stenosis. In this patient, a resting AS (aortic stenosis) velocity of 2.41 m/s (PG—24 mmHg) as shown in **Figure 15** with a low ejection fraction (39%) indicating that the ventricle is poorly responding to high afterload. Absence of contractile reserve (failure to increase stroke volume or ejection fraction > 20%) is a high surgical mortality and poor long-term outcome although valve replacement may improve LV function and outcome even in this subgroup [62].

3.13. Low-Flow Low-Gradient Aortic Stenosis

When LV systolic dysfunction co-exists with severe aortic stenosis, the AS velocity and gradient may be low despite a small valve area, a condition termed "low-flow low-gradient AS" and is characterized by effective orifice area <1 cm^2, LV ejection fraction <40% and a mean pressure gradient <30 - 40 mmHg.

The severity of aortic stenosis may be underestimated because decreased stroke volume due to mitral stenosis reduces the aortic gradient and may result in low cardiac output and therefore, low-flow low-gradient AS as shown in **Figure 15**.

In case of severe AR, the pressure half-time method for assessment of mitral stenosis is not valid. In severe AR, the left ventricle is more likely to become "full" so that the pressure half-time will be short with a poorly tolerated aortic valve insufficiency.

Severity assessment of rheumatic mitral stenosis should rely mostly on valve area (<1 cm^2—severe, 1 - 1.5 cm^2—moderate, >1.5 cm^2—mild) and it is significant and symptomatic when MVA is <1.5 cm^2. It is specific, because of multiple factors influencing other supportive findings such as mean gradient (<5 mmHg—mild, 5 - 10 mmHg—moderate, >10 mmHg—severe) and systolic pulmonary artery pressure (<30 mmHg—mild, 30 - 50 mmHg—moderate, >50 mmHg—severe). However, normal resting value of pulmonary artery pressure may be observed even in severe MS. A diameter of the tricuspid annulus >40 mm seems to be more reliable than quantification of regurgitation to predict the risk of severe late TR after mitral surgery [63]. Tricuspid annulus diameter is 39.2 mm and mitral annulus diameter is 55 mm in this patient as shown in **Figure 23** and reflecting no pulmonary hypertension.

The echocardiographic scoring system (Wilkins score [64]) has been used as a valuable tool for patient selection to PMC (percutaneous mitral commissurotomy/or percutaneous balloon valvuloplasty). Impairment of mitral anatomy is expressed in scores combining different components of mitral apparatus or using an overall assessment of valve anatomy. Leaflet mobility, valvular thickening, valvular calcification, and subvalvular disease are each given a score of 0 - 4 and the total score is the sum of four items and ranges between 4 - 16. A total score of <8 results in good short and long-term outcome with balloon valvuloplasty. With higher scores (>14) indicate more severe involvement and prefer valve replacement.

In Cormier score [65], it is grouped as Group 1 (pliable non-calcified anterior mitral leaflet with mid subvalvular disease *i.e.*, thin chordae ≥ 10 mm long), Group II (pliable non-calcified anterior mitral leaflet and severe subvalvular disease *i.e.*, thickened chordae < 10 mm long), Group III (calcification of mitral valve of any extent, as assessed by fluoroscopy whatever the state of subvalvular apparatus).

Echocardiographic parameters of this patient are shown in **Table 2**.

3.14. Treatment

Since the patient is having significant LV dysfunction and improving with antifailure measures , he was advised to continue the same line of management along with oral warfarin 2.5 mg daily to maintain INR (International normalised ratio) between 2 to 3 and statin therapy (atorvastation 10 mg daily). Patient is taking penicillin prophylaxis regularly every 3 weeks and advised for life long.

3.15. Vasodilator Therapy

Vasodilator therapy may be used to reduce after load in patients with systolic hypertension and chronic aortic regurgitation, in order to minimize wall stress and optimize LV function. However, in normotensive patients, vasodilator therapy is not likely to reduce regurgitant volume (preload) significantly and thus may not be of clinical benefit [66]. Vasodilators such as ACE (angiotensin-converting enzyme) inhibitors were not given due to intractable cough produced by these agents.

3.16. Surgical Therapy

If symptoms worsens, the patient may be referred for double valve replacement (both aortic and mitral valves) with mechanical prostheses since the LVEDD (left ventricular end-diastolic diameter) is >70 mm [67], the EF (ejection fraction) is <55%, ESD (end-systolic diameter) is >55 mm (the “55 rule” [68]—applicable even in asymptomatic patients).

When the diameter of aortic root is >45 mm, concurrent aortic root repair or replacement is indicated and it is not warranted since the aortic root is 43.2 mm. Exclusion of coronary artery disease by angiography may be needed at the time of surgery since the age is 41 years.

Table 2. Echocardiographic parameters.

2D parameters		M-mode parameters		Doppler parameters	
LV size	103 mm	LV end diastolic diameter (LVEDD)	81.4 mm	Aortic valve	Mitral valve
LA size	53 mm	LV end systolic diameter (LVESD)	65.2 mm	AS jet	MS jet
Mitral annulus	55 mm	EPSS	24 mm	AS jet 2.41 m/s PG-23 mmHg	PHT-431 ms-MVA-0.51 cm^2-long cycle
Tricuspid annulus	39.2 mm			AR jet	MS PHT-443 ms-MVA-0.50 cm^2-short cycle
Aortic annulus	32.3 mm			AR-PHT 551 ms-long cycle, 194 ms-short cycle. AREDV-2.25m/s	Planimetry
Aortic root	42.2 mm	EF	39%	AR jet-holodiastolic flow reversal Initial velocity-0.80m/s holodiastolic-ED velocity-0.22m/s	MVA-0.98 cm^2-circular orifice MVA-0.71cm^2-slit-like (elliptical) orifice

4. Conclusion

This patient is having a congenital tricuspid aortic valve with cuspal inequality as shown in **Figure 3** and it is seldom incompetent in the young. Rheumatic involvement of aortic valve creates a bicuspid architecture and the valve is regurgitant severely into the dilated left ventricle (LV) as a central jet falling into the LV with an appearance of a "water fall". It is associated with rheumatic mitral valve involvement creating a "hockey stick" deformity of anterior mitral leaflet with diffuse fibrosis of chordal apparatus resulting in severe stenosis with a central or commissural jet into the left ventricle in diastole and collide with AR (aortic regurgitation) jet and appeared as "bow and arrow" in echocardiography. Massive LV dilation and LA (left atrium) dilation lead to stasis of blood and producing "spontaneous echo contrasts" in both LA and LV is detected by 2D echocardiography imaging. The patient was advised double valve replacement (both aortic and mitral valve) and anticoagulant therapy with penicillin prophylaxis for life long.

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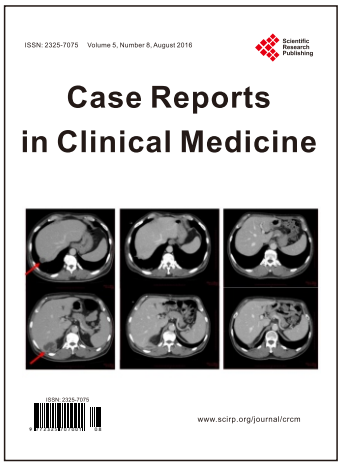

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