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Research Article

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Association Between Histopathological Changes in Mitral Valvular Tissues and Disease Severity in Rheumatic Heart Disease Cases

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Abstract

Background: *Mitral valve leaflets are the most common structures involved in rheumatic disease as a sequele, where long-term inflammation and high degree of fibrosis leads to valve dysfunction. Histopathological examination of surgically excised mitral valve tissue can provide information related to the clinical presentation, insight into pathogenesis and its management; and can prove their association with the disease severity.*

Objectives: *The aim of this study is to evaluate histopathological changes in diseased mitral heart valves in RHD cases by H&E and Masson's trichrome staining to identify the morphological changes, as well as their association with disease severity by observing the echocardiographic findings.*

Method: *A cross-sectional study was carried out in the collaboration of Department of Cardiac surgery and Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from July 2022 to June 2024. A total of 55 patients aged between 18 and 65 years with rheumatic mitral valvular disease were included in this study. The excised mitral valves were histopathologically analyzed and their echocardiography reports were collected.*

Result: *In this study, the mean age of the patients were 37.27 ± 12 years with age ranges from 18 to 65 years. Majority of them are female (61.81%). Mean age of the patients was 37.27 (± 12) years. In gross morphological study, 44% had fibrous stenotic type, whereas 40% had elastic insufficient and 16% had calcific stenotic type valve. 9% had focal and 15% had diffuse calcification. Chordae tendinae was fused in 71% patients. 4% valves had vegetations. Elasticity was increased in 82% & commissures were fused in 100% valves. In microscopic examination, spongiosa layer was thickened in 40% patients. Intensity of inflammation was mild in 9%, moderate in 73% and severe in 18% valves, Pattern of inflammation was focal in 25% patients and diffuse in 75% patients. Aschoff nodule were found in 20% of the valves. Fibrosis was mild in 24%, moderate in 40% and severe in 36% patients. Neoangiogenesis was present in 100%, adipose metaplasia in 9% and edema in 29% valves. Calcification was present as mild in 4%, moderate in 4% and severe degree in 9% valves. In the echocardiography, left atrium was dilated in 93% & right ventricle in 15% patients. Mixed mitral valve disease was present in 73%, multiple valve involvement in 53%, and atrial fibrillation in 31% patients. Mitral valve area was decreased in all 100% patients. IA/IV septa was intact in all patients. Subvalvular change was present in 15%. Mitral valve thickening and commissural fusion were present in 100% of the patients. Calcification was present in 16%, mild MS in 4%, moderate MS in 7% and severe MS in 89% patients. MR*

was mild in 44%, moderate in 24% and severe in 5% patients. LV systolic dysfunction was mild in 13%. Pulmonary hypertension was mild in 49%, moderate in 22% and severe in 18% of the patients. Out of 4 mild MS cases, 2 (20%) cases showed severe inflammation, among 4 moderate MS, 2 (20%) showed severe inflammation and among 47 severe MS cases, 38 (95%) showed moderate inflammation and 6 (60%) cases showed severe inflammation. A chi- square test of independence was performed to examine the relation between inflammation and disease severity. The relation between these variables was significant. P- value was 0.0295.

Discussion: *Observing the histopathological studies of mitral valvular tissues and their association with disease severity can provide new insight to disease presentation and hence can contribute to the development of more specific targeted therapy to halt disease progression.*

List of Abbreviations

- **H&E:** Hematoxylin- Eosin
- **IAS:** Inter Atrial Septum
- **IVS:** Inter Ventricular Septum
- **ICU:** Intensive Care Unit
- **LVEF:** Left Ventricular Ejection Fraction
- **LVP:** Left Ventricular Pressure
- **MMP:** Matrix Metallo Proteinase
- **MV:** Mitral Valve
- **MVA:** Mitral Valve Area
- **MS:** Mitral Stenosis
- **MVR:** Mitral Valve Replacement
- **PM:** Papillary Muscles
- **RHD:** Rheumatic Heart Disease
- **RF:** Rheumatic Fever
- **RV:** Right Ventricle
- **RVP:** Right Ventricular Pressure
- **RHVD:** Rheumatic Heart Valve Disease
- **MVR:** Mitral Valve Replacement
- **PM:** Papillary Muscles
- **RHD:** Rheumatic Heart Disease
- **RF:** Rheumatic Fever
- **RV:** Right Ventricle
- **RVP:** Right Ventricular Pressure
- **RHVD:** Rheumatic Heart Valve Disease
- **WHO:** World Health Organization

Introduction

Rheumatic Heart Disease (RHD) is a condition of global health importance. Every year the disease claims 288,348 lives worldwide. According to WHO, the overall estimate is between 1.96 and 2.21 million cases of rheumatic heart disease in Asian children 5 to 14 years of age. In 2022, the prevalence of RHD in Bangladesh was 0.8/1000 population [1]. Rheumatic heart disease is the most acquired heart disease in people under age 25, and mostly affects children and adolescents of school going age in low and middle income countries, likely due to group A streptococcus transmission among students. First attack can occur in middle to later life. The predominant clinical manifestations are carditis and arthritis, the latter is most common in children [2]. Surgical intervention remains an important treatment modality for those with more severe forms of RHD, yet disparities exist in access to and outcomes following RHD. Factors which have been identified as being associated with outcomes following valve surgery in patients with RHD-related valve disease include age, pre-operative clinical status, pre-existing atrial fibrillation, left ventricular function and the nature of the underlying valve lesions. The valve involved and the nature of the valve lesion (regurgitation versus stenosis) has been shown to influence the outcome of the disease process [3].

Despite the observed progress in research on RHD pathogenesis, several key scientific questions remain unanswered. Specifically, the underlying mechanisms involved in the development of severe valve dysfunction are not completely understood [4]. It is known that long-term inflammation and high degree of fibrosis leads to valve dysfunction due to anatomic disruption of the valve apparatus. This disease shows different natural history and clinical presentations as compared to other degenerative heart valve diseases.

Mitral valve leaflets are the most common structures involved in rheumatic disease; typical pathological features of rheumatic mitral disease come from acute and recurrent inflammation. The rheumatic process includes leaflet thickening, calcification, and retraction, periannular calcification with limitation of annular motion, leaflet fusion, chordal thickening, shortening and fusion as well as papillary inflammation, but the specific immunologic and inflammatory mechanisms leading to the valvulitis are unknown.

Unfortunately, related previous studies on this topic are not very recent. In one of the pioneering studies carried by Nazarian and Aryanpur in 1978, three types of gross pathological features have been described [5]. First is fibrous stenotic type (Type A) which has very thick cusps and extremely short chordae tendineae. It is the most frequent rheumatic valve seen in children. The second is the elastic insufficient type (Type B), which consists of a remarkable elasticity and moderately thickened cusps. The third is the calcific stenotic type (Type C) in which the cusps are moderately thickened, with short chordae tendineae with various degrees of calcification. This type is seen usually in the 4th decades of life and is more frequent in males.

Hence, gross, and microscopic examination of diseased mitral valve by using both H&E and Masson's trichrome staining can enlighten us about the underlying structural changes responsible for valve dysfunction. This can provide information related to the clinical presentation, their association with the severity of disease, and hence, insight into its pathogenesis and management.

So, by doing histopathology of diseased mitral valve, we can identify the morphological changes responsible for the disease progression as well as can understand the cause behind different clinical presentation in each age groups.

Methods

This was a cross-sectional, descriptive, and observational study. A total of 55 patients with RVHD aged between 18 to 65 years were included in this study. Any Cancer patients, covid & dengue positive patients, and patients with cirrhosis of liver & ILD were excluded from the study. The study was conducted at the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, and Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from July 2022 to June 2024.

The valves were collected from the Department of Cardiac surgery immediately after MVR surgery and fixed with 10% neutral buffered formalin for 24 hours. The specimens were subsequently processed and examined at the Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Dhaka for histopathological examination.

After meticulous gross examination, 3 blocks were submitted: 1 block for H&E, 1 for Masson's trichrome and 1 for immunohistochemical examination.

Results

Age Distribution of Patients

Among the 55 patients, 58% cases were from 15-35 years age group, 40% from 36-59 years and 2% were from ≥ 60 years age group.

Table 1: Age Distribution of Patients (n=55)

Age (in years)	Frequency	Percentage
15-35	32	58
36-59	22	40
60- 65	1	2
Total	55	100
Mean ± SD	37.27 ± 10.5417	
Range(min-max)	18-65	

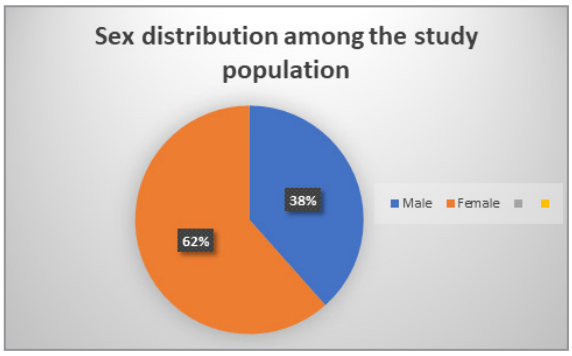

Figure 1: Distribution of the Patients by Sex (n=55)

Among the 55 patients, 32 (62%) of the patients are female, and 23 (38%) of the patients are male

Table 2: Distribution of Patients by Gross Morphological Changes (n=55)

Out of the 55 patients, 24 (44%) patients had fibrous stenotic type valve, whereas 22 (40%) had elastic insufficient and 9 (16%) had calcific stenotic type mitral valve. 42 (76%) valves had no calcification, whereas 5 (9%) had focal and 8(15%) had diffuse calcification. Chordae tendinae was fused in 39 (71%) patients and in 16 (29%) patients it was not fused. Only 2 (4%) valves had vegetations. Elasticity was increased in 45 (82%) valves and were retained in 10 (18%) valves. Commissures were fused in 55 (100%) valves.

Gross Morphological Changes	Frequency (n)	Percentage (%)
Casp Thickness		
Fibrous stenotic type (Type A : 0.4-1 cm)	24	44
Elastic insufficient type (Type B : 0.1-0.3 cm)	22	40
Calcific stenotic type (Type C : 0.3-0.4 cm)	9	16
Degree of Calcification		
No calcification	46	84
Vegetative or ulcerative (focal)	2	4

Marked (diffuse)	7	12
Adhesion of chordae tendineae		
Fused	39	71
Not fused	16	29
Presence of vegetation	2	4
Elasticity		
Normal	10	18
Increased	45	82
Commissure		
Fused	55	100
Not fused	0	0

Table 3: Distribution of Patients by Microscopic Findings (n=55) Out of 55 patients, spongiosa layer was thickened in 22 (40%) patients and normal in 33 (60%) patients. Intensity of inflammation was mild in 5 (9%), moderate in 40 (73%) and severe in 10 (18%) valves, Pattern of inflammation was focal in 14 (25%) patients and diffuse in 41 (75%) patients. Aschoff nodule were found in 11 (20%) of the valves. Intensity of fibrosis was mild in 13 (24%), moderate in 22 (40%) and severe in 20 (36%) patients. Neoangiogenesis was present in 55 (100%) of valves in various degrees. There were adipose metaplasia in 5 (9%) and edema in 16 (29%) valves. Calcification was absent in 42 (76%) valves, whereas it was present in mild degree in 3 (5%), moderate degree in 2 (4%) and severe degree in 8 (15%) valves.

Variables	Frequency (n)	Percentage (%)
Spongiosa layer		
Thickened	22	40
Normal	33	60
Intensity of inflammation		
Absent	0	0
Mild	5	9
Moderate	40	73
Severe	10	18
Pattern of inflammation		
Focal	14	25
Diffuse	41	75
Ashchoff nodule	11	20
Intensity of fibrosis		
Absent	0	0
Mild	13	24
Moderate	22	40
Severe	20	36
Neoangiogenesis	55	100
Calcification		
Absent	46	84
Mild	2	4
Moderate	2	4
Severe	5	9
Adipose metaplasia	5	9
Haemorrhage	0	0
Valvular oedema	16	29

Table 4: Distribution of Patients According to Echocardiographic Findings (n=55) Out of 55 patients, Left atrium was dilated in 51 (93%) patients, Right ventricle was dilated in 8 (15%) patients. Mixed mitral valve disease was present in 40 (73%), multiple valve involvement in 29 (53%), and atrial fibrillation in 17 (31%) patients. Mitral valve area was decreased in all (100%) patients. IA/IV septa was intact in all patients. Subvalvular change was absent in 47 (85%) and present in 8 (15%). Mitral valve thickening and commissural fusion were present in 100% of the patients. Calcification was present in 9 (16%), mild MS in 2 (4%), moderate MS in 4 (7%) and severe MS is present in 49 (89%) patients. MR was absent in 15 (27%), mild in 24 (44%),

moderate in 13 (24%) and severe in 3 (5%) of the patients. LV systolic dysfunction was absent in 48 (87%) and mild in 7 (13%). Pulmonary hypertension was absent in 6 (11%), mild in 27 (49%), moderate in 12 (22%) and severe in 10 (18%) of the patients.

Traits	Frequency (n)	Percentage (%)
Left atrium		
Normal	4	7
Dilated	51	93
Right Ventricle		
Normal	47	85
Dilated	8	15
Mitral valve		
Thickening	55	100
Calcification	9	16
Commissural fusion	55	100
Mixed mitral valve disease	40	73
Multiple valve involvement	29	53
Mitral Valve Area(MVA)		
Normal(4-6 cm^2)	0	0
Increased(>7 cm^2)	0	0
Decreased((<2 cm^2)	55	100
IA/IV septae		
Intact	55	100
Deficit	0	0
Atrial Fibrillation(AF)	17	31
Subvalvular change		
Absent	47	85
Present	8	15
Mitral Stenosis(MS)		
Mild(>1.5 cm^2)	2	4
Moderate(1-1.5 cm^2)	4	7
Severe(<1 cm^2)	49	89
Mitral Regurgitation(MR)		
Absent	15	27
Mild	24	44
Moderate	13	24
Severe	3	5
Double mitral dysfunction	0	0
LV systolic dysfunction		
Normal	48	87
Mild	7	13
Moderate	0	0
Severe	0	0
Pulmonary Hypertension(PAH)	6	11
Absent	27	49
Mild	12	22
Moderate	10	18

Table 5 : Association of Inflammation with Disease Severity Out of 4 mild MS cases, 2 (20%) cases showed severe inflammation, among 4 moderate MS, 2 (20%) showed severe inflammation and among 47 severe MS cases, 38 (95%) showed moderate inflammation and 6 (60%) cases showed severe inflammation. A chi- square test of independence was performed

to examine the relation between inflammation and disease severity. The relation between these variables was significant. P-value was 0.0295.

	Inflammation			
Severity of MS	Mild (%)	Moderate (%)	Severe (%)	p value 0.0295
Mild (4)	1 (20%)	1 (2.5%)	2 (20%)	
Moderate (4)	1 (20%)	1 (2.5%)	2 (20%)	
Severe (47)	3 (60%)	38 (95%)	6 (60%)	
Total	5(100.0%)	40(100.0%)	10(100.0%)	

There is Statistically Significant Association between Inflammation and Disease Severity

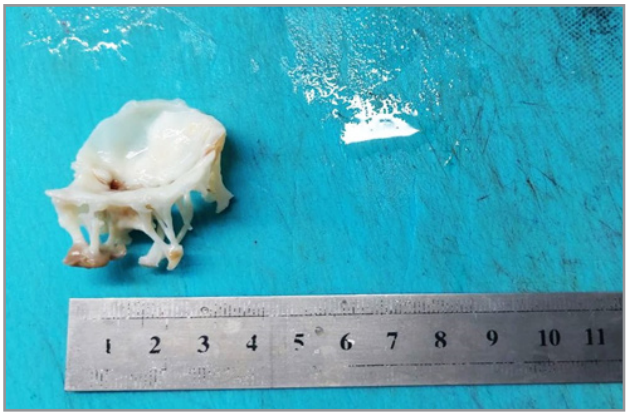

Figure 2: Photograph Showing Excised Mitral Valve

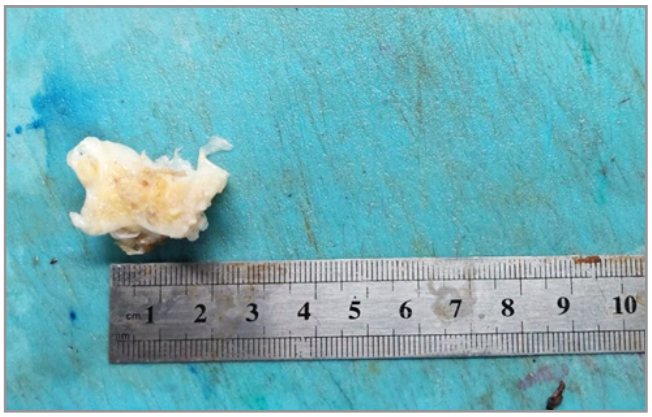

Figure 3: Photograph Showing Calcified Mitral Valve Leaflet

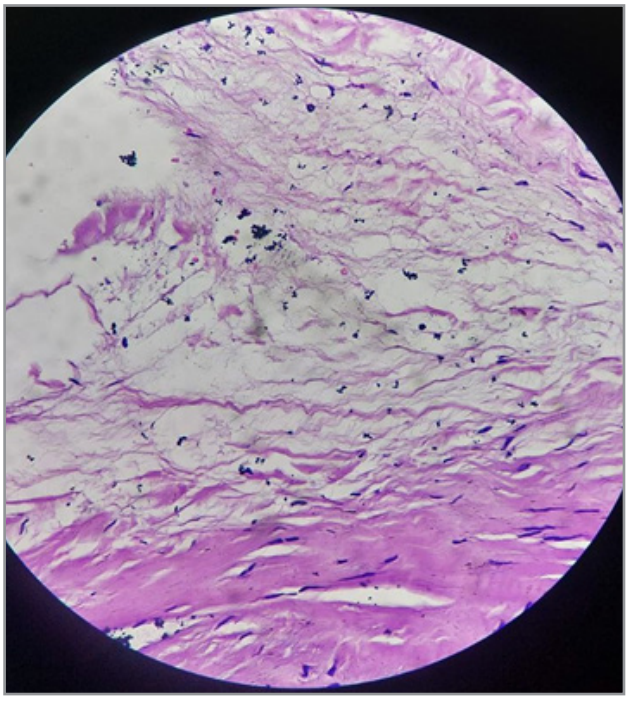

Figure 4: Photograph Showing Edematous Spongiosa (H&E, 40X)

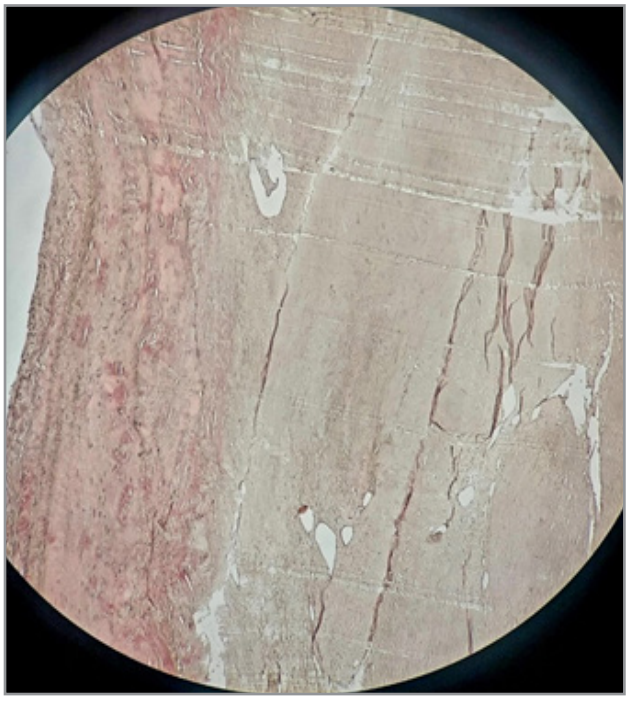

Figure 5: Photograph Showing Edematous Spongiosa (MT stain, 10X)

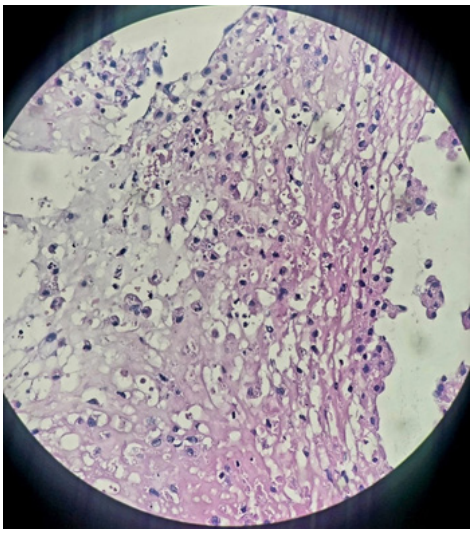

Figure 6: Photograph Showing Vegetation in the Valve caps (H&E, 40X)

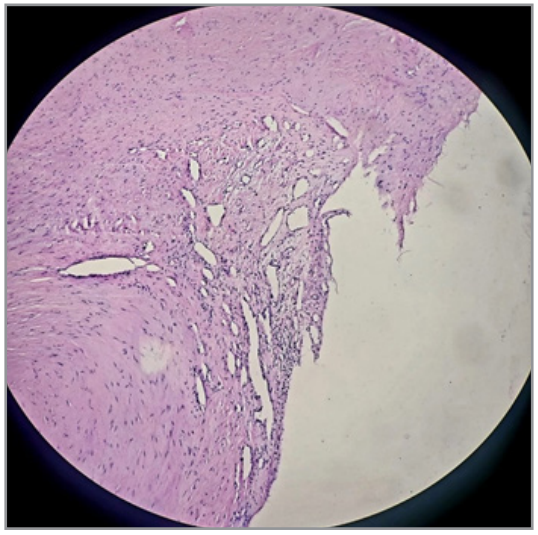

Figure 7: Photograph showing neoangiogenesis in the valve(H&E, 40X)

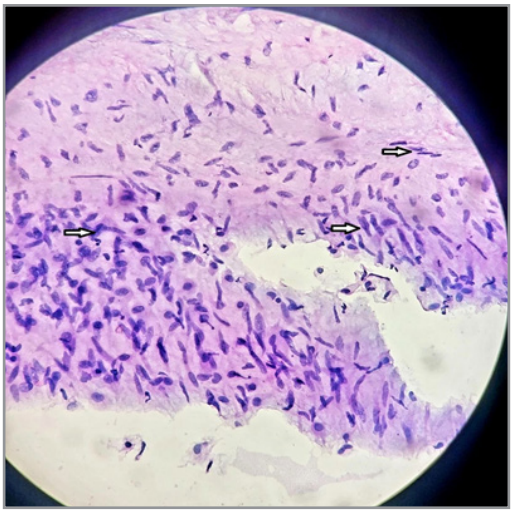

Figure 8: Photograph Showing Anitschkow Cell or Caterpillar Cells in Aschoff Bodies (Arrow, H&E, 40X)

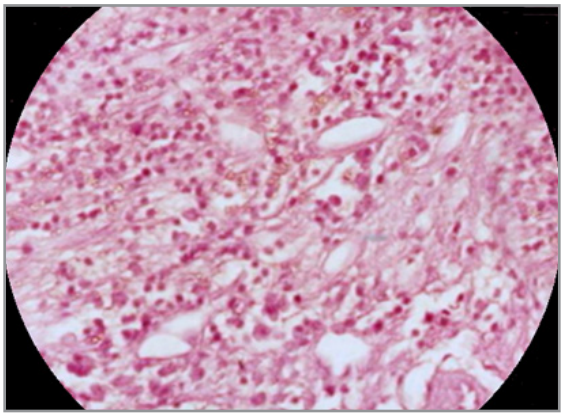

Figure 9: Photograph Showing Aschoff Nodule (H&E, 40X)

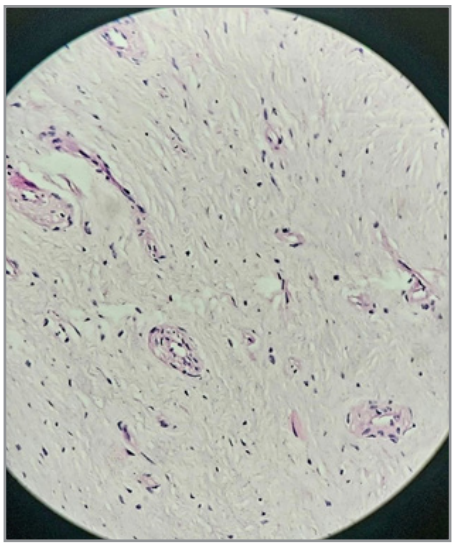

Figure 10: Photograph Showing Moderate Infiltration of Chronic Inflammatory Cells in the Valve caps (H&E, 40X)

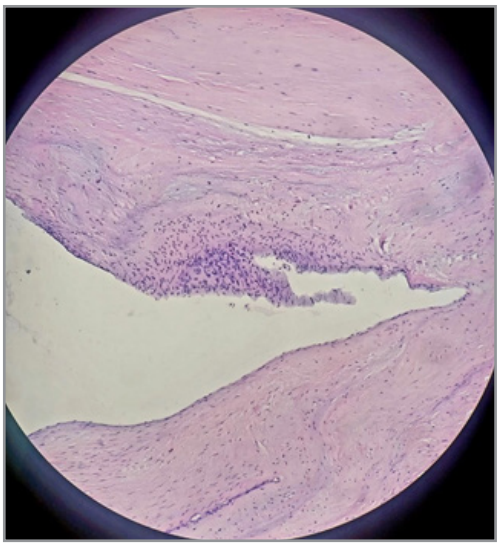

Figure 11: Photograph Showing Dense Infiltration of Chronic Inflammatory Cells in the Valve caps (H&E, 40X)

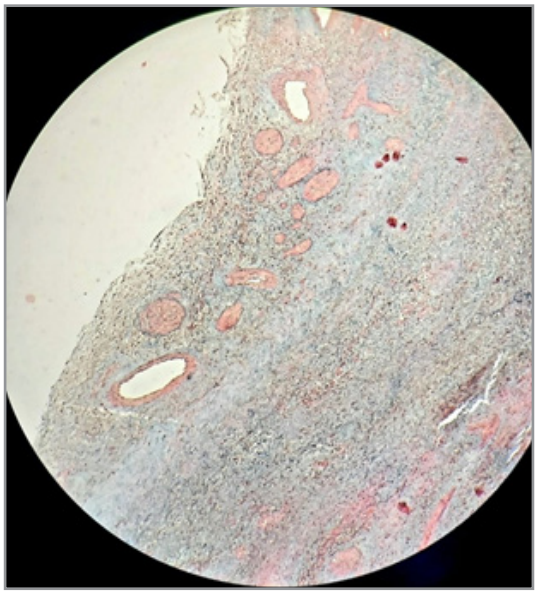

Figure 12 : Photograph Showing Dense Fibrosis in the Valve caps (MT stain, 40X)

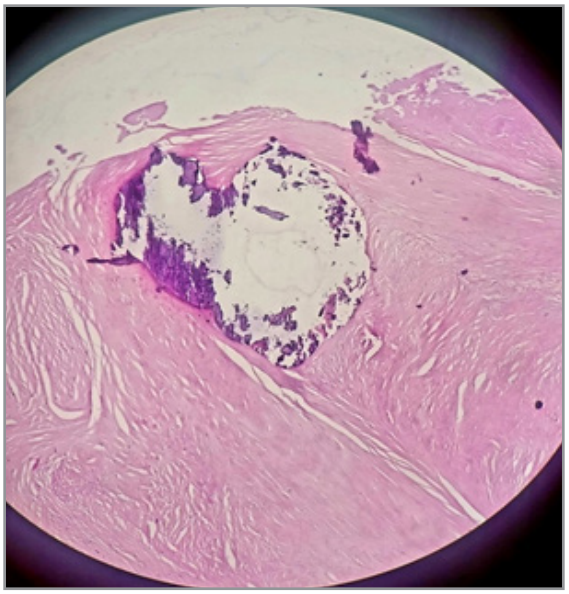

Figure 13: Photograph Showing Diffuse Calcification in the Valve caps (H&E, 40X)

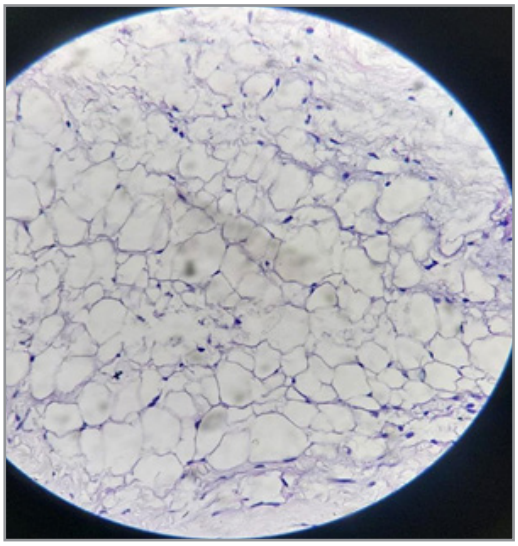

Figure 14: Photograph Showing Adipose Metaplasia in the Valve caps (H&E, 40X)

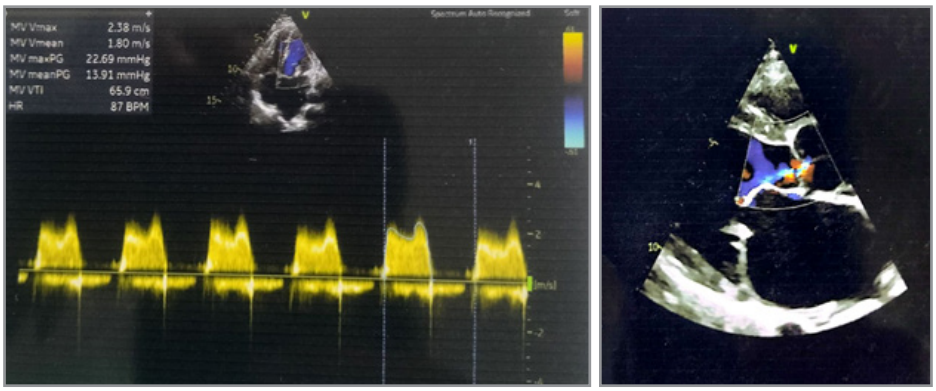

Figure 15: Photograph of Echocardiography Showing Diastolic Doming of Anterior Leaflet, Thickening of Valve Leaflets, Restricted Opening of the Valve & Dilatation of the Left Atrium

Discussion

In this study, the mean age of the patients were 37.27 ± 12 years with age ranges from 18 to 65 years. Majority of them are female (61.81%), and rest are male (38,18%). Mean age of the patients were 37.27 (± 12) years, age ranging from 18 to 65 years. In the study of Agozzino et al., the mean age of the patients was 42 ± 7year, among them female were 64.5% and male were 35.5% [6]. According to Gomez et al., mean age of the patients was 53 ± 13 years, among them 90% were female [7]. In Iran, Nazarian et al., also found female predominance (55%). None of them were more than 49 years old. In the Mutagaywa et al., study, there was a female (63%) predominance among the recruited patients for the study [8]. Their median (range) age was 39 (14–57). All these findings show similarity with the current study.

In the current study, out of the 55 patients, 24 (44%) patients had fibrous stenotic type valve, whereas 22 (40%) had elastic insufficient and 9 (16%) had calcific stenotic type mitral valve. 46 (84%) valves had no calcification, whereas 4 (7%) had focal and 5 (9%) had diffuse calcification. Chordae tendinae was fused in 39 (71%) patients and in 16 (29%) patients it was not fused. Only 2 (4%) valves had vegetations. Elasticity was reduced in 45 (82%) valves and were retained in 10 (18%) valves. Commissures were fused in 55 (100%) valves. According to the study conducted by Nazarian et al., 26% of the valves were fibrous stenotic type, 34% were elastic insufficient and 40% were calcific stenotic type. In my study, I found most valves with fibrous stenosis.

In the present study, spongiosa layer was thickened in 22 (40%) patients and normal in 33 (60%) patients. Intensity of inflammation was mild in 5 (9%), moderate in 40 (73%) and severe in 10 (18%) valves, Pattern of inflammation was focal in 14 (25%) patients and diffuse in 41 (75%) patients. Aschoff nodule were found in 11 (20%) of the valves. Although it is unknown from the available data how long Aschoff bodies last following a clinical episode, they are a characteristic lesion of undetermined cause that can be used as a signal of a recent episode of RF [9]. In the study by Agozzino et al., only 4.41% patients showed scattered lymphohistiocytic infiltrate of the leaflet with or without Aschoff nodule and valvulitis, which contradicts my study. But, in the study by Rashed et al., perivascular lymphocytic aggregates tightly surrounding small & medium sized vessels was present in 16% valves, diffuse interstitial infiltrate of lymphocytes in 28% and mixed lymphocytic infiltrate in 56% valves. These findings completely aligns with my study.

Intensity of fibrosis was mild in 13 (24%), moderate in 22 (40%) and severe in 20 (36%) patients in my study. Gomez et al., found moderate to marked fibrosis in 100% of their cases, in my study which is 76%.

Neoangiogenesis was present in 55 (100%) of valves in various degrees. There were adipose metaplasia in 5 (9%) and edema in 16 (29%) valves. Rashed et al., found out neovascularization in 52% of cases.

Calcification was absent in 46 (84%) valves, whereas it was present in mild degree in 2 (4%), moderate degree in 2 (4%) and severe degree in 5 (9%) valves. Nazarian et al., observed no calcification in 65% of the valves, focal vegetative calcification in 34% and diffuse calcification in 11% of the valves in their study. Gomez et al., found calcification in 35% of valves. Both studies completely align with mine. Rashed et al., observed calcification in 60% of their cases.

In the study conducted in Tanzania by Mutagaywa et al., the proportion of specimens that stained on H&E showed Aschoff nodules and Anitschkow cells is 6 (11.1%), 44 (81.5%) showed leucocytic inflammatory cell infiltrate, 18 (33.3%) neovascularization, 37 (68.5%) edema, 28 (51.9%) haemorrhage, 30 (55.6%) calcification, 37 (68.5%) fibrinoid degeneration, and 39 (72.2%) fibrosis. With von Kossa stain, 35 (64.8%) of the tissues showed evidence of calcification of which 18 (33.3%) were moderate to severe. In the current study, Masson's trichrome stain was used instead of Von Kossa stain and the findings are quite similar.

In the current study, left atrium was dilated in 51 (93%) patients, Right ventricle was dilated in 8 (15%) patients. Mixed mitral valve disease was present in 40 (73%), multiple valve involvement in 29 (53%), and atrial fibrillation in 17 (31%) patients. Mitral valve area was decreased in all (100%) patients. IA/IV septa was intact in all patients. Subvalvular change was absent in 47 (85%) and present in 8 (15%). Mitral valve thickening and commissural fusion were present in 100% of the patients. Calcification was present in 9 (16%), mild MS in 2 (4%), moderate MS in 4 (7%) and severe MS is present in 49 (89%) patients. MR was absent in 15 (27%), mild in 24 (44%), moderate in 13 (24%) and severe in 3 (5%) of the patients. LV systolic dysfunction was absent in 48 (87%) and mild in 7 (13%). Pulmonary hypertension was absent in 6 (11%), mild in 27 (49%), moderate in 12 (22%) and severe in 10 (18%) of the patients. In the study of Manjunath et al., mitral valve was involved in 60.2% patients followed by aortic, tricuspid, and pulmonary valve [10, 11]. Isolated MR was present in 41.1% and multiple valves was involved in 36.8% patients. Nazarian et al., found isolated MS in 62% and mixed mitral valvular disease in 38% of the patients. In Mutagaywa et al.,study, 29 (53.7%) patients had severe MS. According to the study of Rashed et al., isolated MS was present in 56%, double mitral dysfunction in 32% and AF in 68% patie Suresh et al., observed Severe MS in 35%, MR in 25% and double mitral valve disease in 15% of the patients. Agozzino et al., observed mixed MS and mitral incompetence in 58% patients and Gomez et al., observed mixed mitral valve disease in 35% patients.

The Echocardiographic Parameters of the Patients in the Study of GOMEZ et al., is Shown on the Table Below:

Table 5: Echocardiographic Parameters of the Patients in the Study of Gomez et al.,

Parameter	Frequency in the patients
AF	60%
LV end diastolic diameter (mm)	51.7±10.9

LV end systolic diameter (mm)	35.8±8.6
LVEF (%)	60.6±10.5
Mitral valve area (cm2)	1.18±0.37
Left atrial diameter (mm)	55.1±10.5
Pulmonary artery systolic pressure (mm Hg)	46.5±18.3
Right ventricular dysfunction	40%

All the echocardiographic findings of the previous studies mentioned above align with the current study.

In the current study, out of 4 mild MS cases, 2 (20%) cases showed severe inflammation, among 4 moderate MS, 2 (20%) showed severe inflammation and among 47 severe MS cases, 38 (95%) showed moderate inflammation and 6 (60%) cases showed severe inflammation.

A chi- square test of independence was performed to examine the relation between inflammation and disease severity. The relation between these variables was significant. P- value was 0.0295.

Conclusion

In this study, it was evident that various gross and histopathological changes of the mitral valve tissues are associated with RVHD. The severity of the mitral stenosis is also associated with degree of inflammation in the valvular tissue. Thus, the histopathological changes observed in this study can provide new insight to disease presentation and hence can contribute to the development of more specific targeted therapy to halt disease progression.

Declarations

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Author Contributions

Billah M prepared the research protocol and was responsible for data collection, arranging the data analysis and preparing the manuscript. Saba S was responsible for conducting the histopathological analysis, Alauddin M, Rahman M and Hima H A were responsible for conceptualizing the study and assisted in protocol development, manuscript preparation and proofreading.

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Conflicts of Interest

None.

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