Original Article

Lutembacher's syndrome: Is the mitral pathology always rheumatic?

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ABSTRACT

The mitral valve disease (MVD) in Lutembacher's syndrome has been infrequently analyzed from a pathological standpoint. In this study, we have attempted to elucidate the pathology of MVD in this interesting syndrome in 44 autopsied cases of combined non-primum atrial septal defect (ASD) and MVD collected over 16 years. The patients were divided into 3 groups: Group 1: non-primum ASD with clinically diagnosed mitral stenosis (MS) ± regurgitation, Group 2: non-primum ASD with clinically diagnosed mitral regurgitation (MR) and, Group 3: non-primum ASD with no clinically evident MVD, but with mitral valve pathology diagnosed at autopsy. All 44 patients were symptomatic. There were 26 males (59%). The ages ranged from 13 to 73 years. A history of rheumatic fever was available in 2 patients while 16 patients had undergone surgery or intervention for the disease. Of the 18 patients in Group 1, six patients did not show histological features of rheumatic heart disease, although they shared similar gross morphological features. Furthermore, the mitral regurgitation in 12 of 19 patients in Group 2 was non-rheumatic. Also, only one patient had histological evidence of rheumatic activity among seven cases in Group 3. In spite of a high rheumatic load at our center, more than half (54.5%) of patients had "non-rheumatic" mitral valve pathology. Thus, the mitral valvular lesions commonly labeled 'rheumatic' in Lutembacher's syndrome are not always so. The distinction into rheumatic and non-rheumatic MVD in non-primum ASD has to be made on the basis of microscopic criteria.

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1. Introduction

Atrial septal defect (ASD) forms one of the commonest congenital cardiac anomalies. Among them, the ostium primum defects are invariably associated with congenital mitral valvular (MV) malformation, namely a cleaved anterior mitral leaflet with consequent valvular incompetence. However, MV disease that complicates non-primum atrial septal defects, especially the secundum type is rare but of great hemodynamic significance. In most instances, the MV pathology has been attributed to secondary rheumatic heart disease (RHD), especially in developing countries.[1] However, this has not been our observation and hence we sought to ascertain the pathology of MV involvement in our autopsied cases of non-primum atrial septal defects.

2. Methods

One hundred and forty patients of non-complex ASDs were autopsied in a 16-year-period. Nineteen among them were of the ostium primum type and were excluded from the study. Remaining 121 cases were ostium secundum ASDs, of which 52 (42.9%) of them had MV disease. Eight cases from this group were excluded; they were children less than 12 years of age or the ASDs were associated with other left to right shunts or had MVs involved by infective endocarditis/endomyocardial fibrosis. Thus a total of 44 adolescent and adult patients with secundum ASDs and MV disease were available for analysis. The patient demographics and clinical features were available from the hospital records. The heart and lungs specimens had been perfusion fixed with 10% buffered formalin. In all cases, the weight and size of the heart, location and size of the septal defects, degrees of enlargement and hypertrophy of the chambers and valvular status were noted. MVs were assessed with respect to their commissures, leaflets and sub-valvular apparatus, and in the light of their clinical presentations. The cases were then categorized into three groups: Group 1: non-primum ASD with clinically diagnosed mitral stenosis

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(MS) ± regurgitation, Group 2: non-primum ASD with clinically diagnosed mitral regurgitation (MR) and, Group 3: non-primum ASD with no clinically evident mitral valve disease. Sections for microscopy were taken from all valves and chambers, and both lungs. When the valves (particularly mitral and/or aortic valves) showed presence of post-inflammatory features in the form of fibrosis, neo-vascularization, chronic inflammatory cell infiltrates and/or calcification, these changes were attributed to the healing process of rheumatic fever. Mild hypertension was characterized by medial hypertrophy of arteries and muscularization of the arterioles, moderate by cellular intimal eccentric or concentric proliferations and severe by concentric intimal fibrosis with or without plexiform, angiomatoid or dilatational lesions.

3. Results

Of the 44 patients, 17 were 20 years of age or younger. The youngest patients were 13 years old while oldest patient was 73 years. There were 26 males and 18 females. All patients were symptomatic and dyspnea was the predominant feature in all except for the elderly male who presented with neurological deficit. Nine patients were in congestive cardiac failure. A history suggestive of rheumatic fever in the past was obtained in only two patients. Sixteen patients had undergone interventions/surgery for the valvular dysfunction and/or defect.

Eighteen patients had been clinically diagnosed as ASDs with MS or MS/MR (Group 1, Table 1). There was equal gender distribution with an age range of 13–40 years (mean age of 26.6 years); five patients were below 20 years of age. There were 16 secundum defects and one case each with sinus venosus defect, and combined secundum and sinus venosus defects. The size of the septal defects ranged from 2.2 cm × 1.1 cm to 4.5 cm. Of these 19 defects, 11 were closed. In most, there was moderate to marked cardiomegaly (310–660 g), with varying degrees of dilation of the right-sided chambers. In three patients, plexiform lesions were seen, indicating severe pulmonary hypertension (PH). Twelve (66.7%) had underlying RHD with mitral valve replacement or valvotomies in patients. The MVs at autopsy (Fig. 1A) and those which were excised revealed the usual stigmata of rheumatic stenosis in the form of commissural fusion, leaflet thickening and chordal fusion. Histologically, all valves revealed post-inflammatory changes in the form of fibrosis, vascularization and/or focal inflammation. Additional involvement of the tricuspid/aortic valve was present in eight. One case also had active rheumatic pancarditis. Surprisingly, the MVs in the remaining six patients (one adolescent) displayed similar morphological features (Fig. 1B) that are usually ascribed to RHD. However, there was preservation

of the layered architecture with slight distortion produced by deposits of collagen and ground substance on the atrial aspects. There was no inflammation and significant neo-vascularisation. In both rheumatic and non-rheumatic stenosing lesions, there was predilection for involvement of the postero-medial commissural region.

Nineteen secundum ASDs (sizes ranging from 1.6 cm × 1.3 cm to 4 cm × 3.5 cm) had clinically pure MR (Group 2, Table 2) with male preponderance (13 patients). The mean age was 21.9 years. There was moderate to marked cardiac enlargement (300–750 g) with variable degree of dilatation and hypertrophy of the right atrium (RA) and ventricles. Moderate to marked PH was seen in eight. There were seven cases of rheumatic MR, five among which underwent valve replacement. Active carditis and multi-valvar involvement were seen in two cases each. Remaining 12 cases were non-rheumatic (63.2%). Two patients underwent valve replacement. All valves appeared myxomatous. The valvular layers were preserved but distorted by accumulation of increased collagen and ground substance. Other anomalies present were bicuspid aortic valve and persistent left superior vena cava.

Among the seven Group 3 patients devoid of mitral valvular dysfunction, there were four males and three females with ages ranging from 19 to 73 years (mean age of 33.7 years). The defects ranged from 1.5 cm to 3.5 cm × 2 cm in size. Both MV leaflets appeared myxomatous. Healed rheumatic mitral valvulitis was seen in one of them (35 years old male). One other patient had extra-cardiac congenital anomalies and pulmonary stenosis. Plexiform lesions were present in two patients.

4. Discussion

Lutembacher is credited with the first comprehensive account of atrial septal defect with mitral stenosis in 1916.[2] The combination of these two lesions has, since then, been designated as Lutembacher's syndrome. But the earliest description is by the famous anatomist Johann Meckel, which, unfortunately, is considered in clinical literature as the first description of aortic coarctation.[3] Opinions differed with regards to the type of mitral lesions to be included in this syndrome. There is now a tendency to broaden the definition, by including not only MR,[4] but also iatrogenic defects created for balloon mitral valvotomy[5] as well as congenital defects with an intact septum.[1,6] Also, having generated little interest for a few decades, Lutembacher's syndrome is now proving an interesting combination to be treated by interventional means.[7]

The natural history of Lutembacher's syndrome, in general, depends on the size of the inter-atrial communication and severity

Table 1
Group 1: non-primum ASD with clinically diagnosed MS ± MR (*n* = 18).

Valve changes	Rheumatic (*n* = 12, MVR = 04)			Non-rheumatic (*n* = 06)		
	P	A	Both	P	A	Both
Commissural fusion	02 (1[a])	–	06 (3[a], 1[b])	02	01	03 (2[a])
Commissural calcification	01	–	–	01	–	–
Leaflet thickening	–	–	08	–	01	04
Myxomatous leaflets	–	–	–	01	–	–
Leaflet plastering	03	–	–	01	01	–
Leaflet calcification	–	–	01	01	–	–
Leaflet vegetations	–	–	01 (R)	–	–	01 (I)
Chordal thickening	02	01	05	02	–	03
Chordal shortening	02	01	05	02	–	02
Chordal fusion, partial	01	–	05	–	–	01
Chordal fusion, complete	02	01	–	01	–	–

A, anterior leaflet; I, infective; MVR, mitral valve replacement; P, posterior leaflet; R, rheumatic.
[a] Open mitral valvotomy.
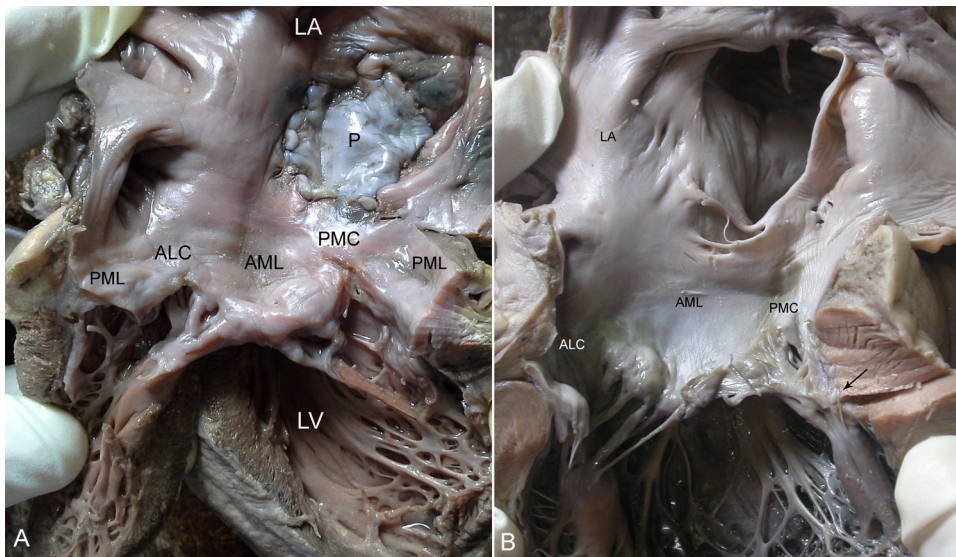[b] Balloon mitral valvotomy.

Fig. 1. (A) Opened out left ventricular inflow tract showing a patch P covering a large secundum atrial septal defect. There was rheumatic mitral stenosis with characteristic leaflet thickening, commissural fusion and accompanying sub-valvular chordal pathology and (B) a large secundum atrial septal defect with a non-rheumatic mitral valvular affliction. Note plastering (arrow) of the posterior leaflet PML to the underlying left ventricular LV endocardium. Both images show predominant involvement of valvular components at its postero-medial region (ALC, antero-lateral commissure; AML, anterior mitral leaflet; LA, left atrium; PMC, postero-medial commissure).

of mitral valvular pathology. Patients with smaller defects and significant valvular lesions would be symptomatic mainly due to the valvular dysfunction. On the other hand in patients with larger defects, the natural history (at least in the early stages) resembles that of a pre-tricuspid shunt despite the presence of even severe valvular pathology. The MV dysfunction in these instances would increase the risk of arterial PH. All the 45 defects in 44 patients had been large. Predictably, features of moderate to severe PH were seen in 14 of the 37 patients with symptomatic MV disease (Groups 1 and 2, 37.9%) and did not correlate with the type or degree of mitral valve disease.

Lutembacher believed that the MS was congenital, but current consensus supports the opposite view, that is, the stenosis is acquired. It is almost always labeled and presumed to be rheumatic, especially in developing countries like India with a high rheumatic case load.[8] Post-inflammatory changes due to rheumatic heart disease resulted in MV abnormality in 20 patients (45.5%), with 12 in Group 1, seven in Group 2 and one in Group 3. The disease affects the entire apparatus rather uniformly. But, with the subset with septal defects, we observed a 'lopsided' involvement in eight patients (42.1%) with more severe changes in

the postero-medial commissural aspect. Another surprising finding was the presence of healed valvulitis in a valve grossly dismissed as merely showing myxomatous change. The patient had no clinical features of mitral dysfunction.

Non-rheumatic etiology for the MV pathology was present in 54.5% of patients (both symptomatic and asymptomatic). The pathology is often explained on the basis of friction occurring between anterior and posterior leaflets at the posteromedial commissure due to abnormal left ventricular motion secondary to right ventricular volume overload.[9,10] The fibrosis that follows leads to improper co-aptation and mitral incompetence ensues, sometimes leading to the morphology of floppy valve. We too found MR to be common among patients in this group, but non-rheumatic stenosis was also found in six patients, with an uncanny resemblance to rheumatic affection on gross examination. None of these mitral valves showed post-inflammatory changes, which could have been attributed to chronic RHD. The brunt was borne by the region around the postero-medial commissure. This has not been documented before. In one of the largest study,[1] there was no histological analysis of the 28 explanted valves among 65 cases of secundum ASDs.

Despite an extremely high rheumatic load at our center, it was surprising to note a non-rheumatic basis for not only for MR but also for even some cases of MS. From our study we can conclude that in association with non-primum atrial septal defects, the MV can be affected in a variable manner. The lesion produced can be stenotic, regurgitant or both, and the etiology can be rheumatic or non-rheumatic. Each of these combinations has different prognostic and management implications. The exact hemodynamic mechanism of non-rheumatic affliction of the mitral valve needs further insight. Additionally, with both rheumatic and non-rheumatic stenosis, the region of postero-medial commissure with adjoining leaflets and sub-valvular apparatus show a more severe pathology. Which combination of lesions should be labeled as Lutembacher's syndrome is debatable and needs a consensus opinion.

Conflicts of interest

The authors have none to declare.

Table 2
Group 2: non-primum ASD with clinically diagnosed MR.

Valve changes	Rheumatic (n = 07, MVR = 05)			Non-rheumatic (n = 07, MVR = 02)		
	A	P	Both	A	P	Both
Commissural fusion	–	–	01	–	02	02
Commissural calcification	–	–	–	–	–	–
Leaflet thickening	01	–	01	–	–	08
Myxomatous leaflets	–	–	–	01	02	02
Leaflet plastering	–	–	05	–	02	–
Leaflet calcification	–	–	–	–	–	–
Leaflet vegetations	–	01 (R)	–	01 (I)	–	–
Chordal thickening	02	–	–	02	01	03
Chordal shortening	02	–	–	01	–	01
Chordal fusion, partial	–	–	–	–	–	–
Chordal fusion complete	02	–	01	–	–	

MVR, mitral valve replacement; A, anterior leaflet; P, posterior leaflet; R, rheumatic; I, infective.

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