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Sudden Death in Association with the Ballooning Posterior Mitral Leaflet Syndrome

The ballooning posterior mitral leaflet syndrome was unrecognized as an anatomic or clinical entity until Barlow's initial description in 1963 [*1*]. Associated sudden death and familial occurrence have been clearly demonstrated [*2-4*], but despite this the significance of the syndrome as a cause of sudden death has not been sufficiently disseminated or appreciated.

Sudden death associated with valvular lesions was first recorded in medical literature over 300 years ago when Rayger reported, in 1672, the sudden death of a man whose heart exhibited an "osseous fusion" of the aortic cusps (quoted by Bonet in 1679) [*5*]. Although there were numerous subsequent descriptions of valvular disease, attempts at clinical pathologic correlation were sparse until Monckeberg's classic description in 1904 of the histology of aortic cusps, and his observations of atherosclerotic changes at their bases [*6*]. Since then there have been a number of statistical studies implicating cardiac valvular disease as a mechanism producing sudden death [*7-12*]. A compilation derived from these studies reveals that approximately 20 percent of sudden deaths due to cardiovascular disease are associated with valvular lesions. In order of frequency, aortic insufficiency, aortic stenosis, mitral insufficiency, and mitral stenosis have been implicated. The pathogenesis of the valvular lesions has been less clearly defined, but a majority have been considered due to rheumatic valvular disease or calcific aortic stenosis. In none of these studies are valvular lesions or clinical patterns suggestive of the ballooning posterior mitral leaflet syndrome described.

The ballooning posterior mitral leaflet syndrome is characterized by symptoms of fatigue, palpitations, chest pain, and faintness in young, fair-haired, light-complexioned females and signs of a midsystolic click or late systolic murmur or both. The pathologic basis of the syndrome is redundancy and myxomatous thickening of the mitral leaflets. During the past year two patients with this syndrome have died suddenly and been necropsied at this medical center. The first case was unique in that the patient was resuscitated successfully after her initial cardiac arrest, and evaluated extensively up to her second, fatal arrhythmia. The second case was diagnosed serendipitously from a medicolegal necropsy. In both instances an extensive familial evaluation was performed to discover other family members with the syndrome. The purpose of this presentation is to describe the clinical and morphologic characteristics of this entity and to emphasize the importance of its diagnosis so that surviving family members can be properly evaluated and followed.

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Case Reports

Case 1

This 27-year-old, fair-complexioned, red-haired female had experienced five syncopal episodes prior to her first cardiac arrest. The first occurred at age 13, the last four years preceding her death. Otherwise she had been entirely well and was asymptomatic until 18 Aug. 1972, when, during a period of emotional excitement, she suddenly fell to the ground. A physician at the scene found her to be cyanotic, pulseless, and flaccid. He immediately initiated external cardiopulmonary resuscitation and she was taken to a nearby hospital where she was found to be in ventricular fibrillation, with fixed and dilated pupils. After multiple resuscitative attempts with countershock, intravenous (IV) bicarbonate, and lidocaine, her rhythm converted to a sinus tachycardia with normal blood pressure. She remained apneic, and deeply comatose, and was transferred to University Hospital under mechanically assisted respiration.

The patient had a prominent midsystolic click and an intermittent, faint, late systolic murmur. Electrocardiograms showed inverted T-waves in leads II, III, and aVF. The Q-Tc interval was slightly prolonged at 0.45 s. Management for control of cerebral edema resulted in dramatic clinical improvement. Ten days later she was alert and ambulatory; the only residuum was a minimal loss of recent memory. Echocardiography and cardiac catheterization with left ventricular angiography revealed a typical ballooning of the posterior mitral leaflet. Despite therapy with IV propranolol and subsequent Dilantin® given to the point of toxicity, the Q-Tc interval remained slightly prolonged. Constant ECG monitoring did not reveal other ECG abnormalities. Five weeks after discharge from the hospital, while on propranolol therapy, the patient collapsed during an argument. Resuscitative measures were unsuccessful.

Case 2

This 36-year-old, fair-complexioned, auburn-haired female had no significant antecedent medical problems. She was an emotionally labile, tense person and had frequent crying episodes. Five years prior to her demise she experienced an apparent episode of tachycardia, associated with cardiac awareness, palpitations, and slight faintness. The episode passed in approximately one minute, and she did not consult a physician. No other such symptoms were ever reported to husband or family. On the day of death the patient was bothered by perianal discomfort while at work. At home that evening she complained about this "hemorrhoid" pain to her husband. Subsequent activities, which included preparing supper, were unremarkable. She again complained to her husband of increasing severity of the hemorrhoidal pain, and sat down in a chair to rest. Within two minutes she slumped over. Her husband saw this, immediately went to her aid, and started resuscitative efforts. These efforts, and subsequent attempts by rescue squads, were unsuccessful, and she was pronounced dead. An autopsy was ordered by the county medical examiner.

Necropsy Examinations

Both subjects were of medium stature and build, with fair skin and red hair. Abnormal findings were limited to the cardiovascular system. There was minimal cardiomegaly and left ventricular hypertrophy. The heart in Case 1 weighed 310 g. The left ventricle was 1.8 cm thick. Case 2's heart weighed 350 g, with a left ventricular thickness of 2.1 cm. Tricuspid, pulmonic, and aortic valves were of normal size and architecture. The mitral valves of both hearts were redundant and exhibited a pearly

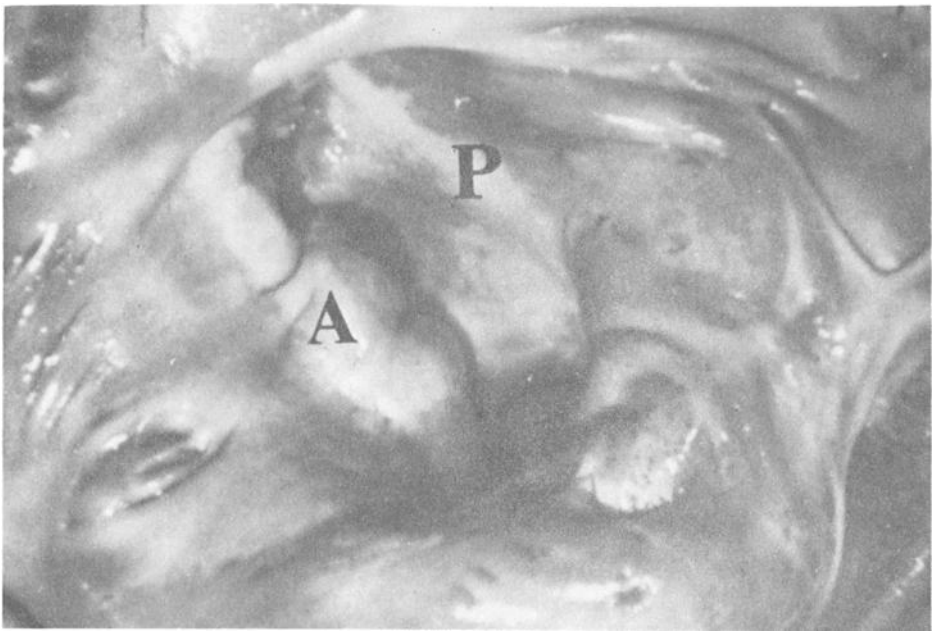

FIG. 1—*The mitral valve from Case 1, viewed from the opened left atrium. The redundancy and thickening of both leaflets can be seen. While the posterior leaflet here is prolapsing into the left ventricular cavity, during life the valve balloons into the atrium during systole:* (A) *anterior leaflet and* (P) *posterior leaflet.*

gray myxomatous thickening (Figs. 1 and 2). The redundant valves sagged into the left ventricular cavity. Both anterior and posterior leaflets were involved, but the latter were more markedly affected. The mitral circumference of Case 1 was 9.7 cm, the posterior leaflet measuring 5.9 cm. There was more severe redundancy in Case 2, where the mitral circumference was 13.5 cm, with a posterior leaflet measurement of 7.0 cm. Valvular commissures were free of adhesions. Chordae tendineae were elongated. On cut surface the valves were firm, with a homogenous, glistening, gray appearance. The conduction systems were dissected [*13*] and found grossly normal. Multiple cut myocardial surfaces were normal except for fresh hemorrhage in Case 1, consistent with the prolonged resuscitative attempts. Coronary arteries in both cases were normal. Both exhibited right coronary artery predominance, with normal appearing S-A nodal arteries arising from the proximal right coronaries. The A-V nodal arteries originated from the genu of the right coronaries as they crossed the crux. The proximal ascending aorta of Case 1 exhibited slight irregular intimal wrinkling. The aorta of Case 2, and the large- and medium-sized muscular arteries of both cases, were normal.

Histopathology

Sections of all valves, conduction system, myocardium, aorta, and muscular arteries were stained with hematoxylin and eosin (H&E); astrablau; alcian blue (pH 2.5); Van Giesen elastica stain; periodic acid-Schiff (PAS), with and without diastase digestion; acid mucopolysaccharide (AMP) (Colloidal Iron) as modified by Rinehart, with and without testicular hyaluronidase digestion; Congo Red; and toluidine blue staining at pHs of 1, 3, and 5. Leaflets of both mitral valves were also stained with aldehyde fuchsin

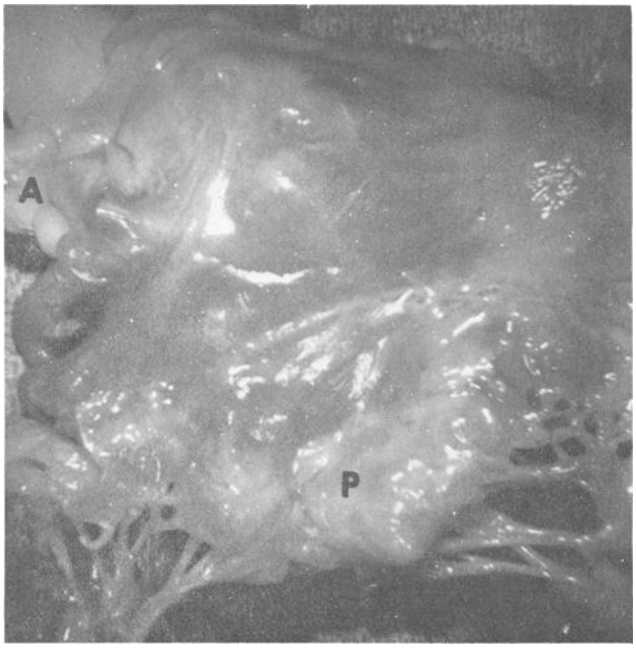

FIG. 2—*The mitral valve from Case 2, viewed after opening of the left ventricle. The myxomatous thickening of the posterior leaflet is readily apparent. The botryoidal configuation of the redundant anterior leaflet can be visualized in the left upper corner:* (A) *anterior leaflet and* (P) *posterior leaflet.*

at pHs of 1.7 and 1.0. (True pH cannot be determined in the alcohol solvent required for this stain, and the pH was empirically read from a pH meter while titrated with HC1).

Leaflets of both mitral valves had extensive deposition of myxomatous, amorphous material within the fibroelastic matrix (Figs. 3-5). Astrablau stains were faintly positive. Alcian blue at pH 2.5, PAS, and AMP stains were intensely positive. The AMP positivity was almost completely lost following hyaluronidase digestion. Toluidine blue staining at pHs 1, 3, and 5 showed faint metachromasia at the lower pH, with increasing metachromasia at pHs 3 and 5. The myxomatous material stained positively with Congo Red, but only small foci exhibited the apple-green fluorescence associated with amyloid. Elastic stains exhibited disruption of the normal matrix, but no significant increase, decrease, or degeneration of elastic fibers was present. There was moderate positive staining by aldehyde fuchsin at pH 1.7, but at pH 1.0 only elastic fibers stained.

Other cardiac valves, the conduction systems, and the myocardium were histologically normal. There was no myocardial hypertrophy, fibrosis, inflammation, or Aschoff bodies. The area of grossly observed aortic intimal wrinkling of Case 1 was microscopically characterized by slight disruption and dissolution of the medial elastic fibers, consistent with minimal cystic medial necrosis.

Discussion

The etiology and pathogenesis of this syndrome are unknown. That it may represent a forme fruste of Marfan's syndrome, particularly when found in conjunction with cystic

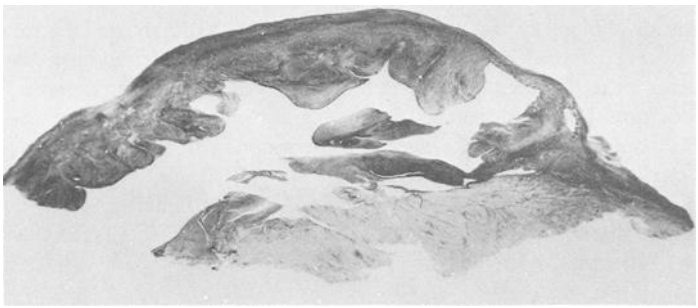

FIG. 3—*A section of the posterior leaflet of Case 1. The light gray areas are the diffuse mucoproteinaceous depositions within the valvular matrix. Van Giesen elastic stain. Original magnification ×4.38.*

FIG. 4—*Section of the posterior leaflet from Case 2. The valvular thickening and myxomatous deposition are apparent. H&E stain, Original magnification ×5.16.*

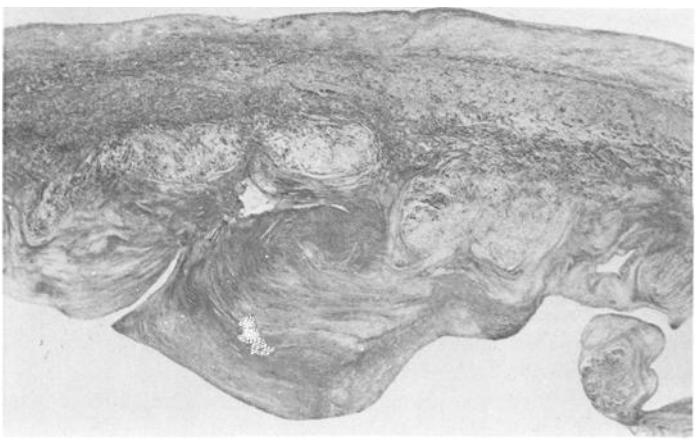

FIG. 5—*A high-power section of the posterior leaflet from Case 1. The dark gray areas are the distorted fibroelastic materix. The lighter shades of gray are the mucoproteinaceous material. Van Giesen elastic stain. Original magnification ×17.0.*

medial necrosis of the aorta, as observed in our Case 1, has been postulated [*14*]. Redundant, thickened mitral valves are relatively common incidental necropsy findings in elderly patients with documented systolic murmurs [*15*]. Except for a predisposition to bacterial endocarditis and spontaneous chordae tendineae rupture, these cases appear benign [*16*]. Ballooning leaflets in the aged are predominantly found in males, while the ballooning posterior leaflet syndrome associated with ECG abnormalities and sudden death show a predilection for young, fair-complexioned females. These significant disparities suggest dissimilar pathogeneses. The ballooning deformity in the elderly is most likely a degenerative senescent process, unrelated to the syndrome under discussion.

The mucoproteinaceous material deposited in the mitral valves is a complex mixture of substances best described as an acid mucosubstance (that is, a protein-acid mucopolysaccharide substance) containing predominantly reactive carboxyl groups of uronic acid, rather than heavily sulfated acid mucopolysaccarides. The histochemical differentiation has been reported elsewhere [*17*], but elaborate histochemical techniques are not required for diagnosis. H&E staining will demonstrate the characteristic myxomatous deposition, and, in contradistinction to other forms of valvular disease such as rheumatic valvulitis, bacterial endocarditis, and calcific aortitis, there is little or no valvular fibrosis, calcification, or commissural fusion.

Moore and Schoenberg, in histochemical studies of human umbilical cords, concluded that fibroblasts are responsible for elaboration of this myxomatous ground substance [*18,19*]. Whether this abnormal accumulation results from excessive synthesis or an inadequate turnover rate is conjectural. The most frequently advanced hypothesis is an excessive production, stimulated by the persistent trauma of mechanical stress.

Involvement of both mitral leaflets occurs in most cases. Fibrosal degeneration and fibroelastic proliferation have been described [*16*] but were not present in our cases, the distortion of the matrix being produced by separation of normal-appearing collagen and elastic fibers by the deposited material.

Although only recognized during the past ten years, it is unlikely that the posterior mitral leaflet ballooning syndrome is a new clinical condition. A lack of appreciation of the clinical and pathologic components of the syndrome is responsible for its exclusion as a diagnostic entity. Although standard criteria for cardiac valvular measurements have long been established, the frequent lack of application of these criteria, particularly in cases of marginal redundancy, has probably contributed to the underdiagnosis of the syndrome in necropsy examinations of patients dying sudden, unexplained deaths. Indeed, the relative lack of chordal abnormalities, and the potential limitation of the process to the posterior mitral leaflet, makes the necropsy diagnosis difficult without a high index of suspicion. Some cases are undoubtedly misdiagnosed as rheumatic valvular disease, and our Case 2 was initially thought to be of rheumatic etiology.

The importance of diagnosis lies not only in the resolution of the medicolegal question of sudden death, but also in recognizing its familial nature to prevent, hopefully, a similar outcome in a family member. The high familial incidence is well established. The detailed family history for Case 1 has been previously reported [*20*]. In Case 2, detailed evaluation showed remarkable familial involvement, including the patient's four sisters, mother, two of three nieces, and the only nephew (Fig. 6).

Once family members with the syndrome have been identified, further assessment of risk can be attained by administering a Minnesota Multiphasic Personality Inventory (MMPI) [*21*]. The emotional lability of testees appears to be able to be estimated by the number of abnormal categories on the MMPI. The greater the abnormal scores for each clinical scale, the greater the risk of a life-threatening arrhythmia.

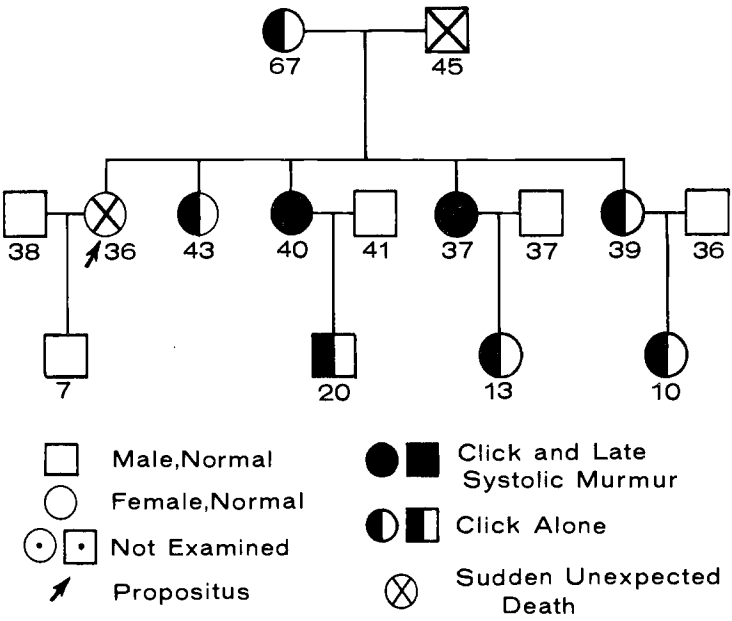

FIG. 6—*Pedigree of Case 2 family, showing that nearly all blood relatives exhibit some evidence of the ballooning posterior leaflet syndrome. The father of the propositus, age 45, died of a myocardial infarction.*

More precise and earlier identification of at-risk individuals initiates with the forensic pathologist, and he should develop a high index of suspicion when confronted with an adult, fair-complexioned female who has died of a sudden, unexplained death. His responsibility does not end with proper diagnosis of the myxomatous posterior leaflet marker. The immediate cause of death in our two patients, and presumably others with the syndrome, is cardiac arrhythmia, and pathologists must alert their clinical colleagues of the need for family evaluation, in order that appropriate attempts can be made to decrease the risk of sudden death. Intensive evaluation of therapeutic agents, including propranolol, Dilantin®, and various tranquilizers, is currently underway in hope of developing an effective combination of pharmacologic and psychotherapeutic preventative measures. Such cooperation between pathologist and clinician will be a significant contribution toward the understanding and prevention of sudden death.

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