Symposium Article

Pathology of inflammatory native valvular heart disease

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Abstract

Rheumatic disease is an important cause of inflammatory native heart valve disease. However, with increased understanding of the pathoetiology of valve disease and valve injury, it is evident that inflammation may play a role in many valve disorders. We are only beginning to understand these complex processes. With increasing knowledge that many of these processes are active, there may be opportunity for intervention or even prevention. © 2006 Elsevier Inc. All rights reserved.

Keywords: Heart valve; Inflammation; Medication; Rheumatic fever

1. Introduction

Rheumatic valve disease, a chronic sequela of rheumatic fever, is the disease most commonly associated with “postinflammatory” valve disease. Rheumatic disease still remains an important concern, especially if one considers a global perspective. However, inflammatory native cardiac valve disease encompasses many disorders and should not be solely equated with rheumatic valve disease (Table 1). With increased understanding of the pathoetiology of valve disease and valve injury, it is evident that inflammation may play a role in many valve disorders. We are only beginning to understand these complex processes. With increasing knowledge that many of these processes are active, there may be opportunity for intervention or even prevention.

2. Rheumatic fever and valve disease

Rheumatic fever is a late inflammatory nonsuppurative complication of pharyngitis that is caused by Group A β-hemolytic streptococci. This multisystem disease is characterized by involvement of the heart, joints, central nervous system, subcutaneous tissues, and skin [1]. Except for the heart, most of these organs are only mildly and transiently affected. No symptom, sign, or laboratory test is pathognomonic of the disease. The Jones criteria, proposed in the 1940s, have stood the test of time and are intermittently revised. Major and minor categories of clinical and laboratory findings may fulfill the criteria for diagnosis [2]. Most pathologists have seen a chronic rheumatic valve disease. Many of us have not recognized an acute case, and this is also true for our clinical colleagues.

Rheumatic carditis is an important and frequently acquired cardiovascular disease in children and adolescents and is an important cause of death from cardiac disease in young people in developing countries. In India, there are an estimated 1 million new cases of rheumatic fever each year. It has been estimated that rheumatic-fever-related heart disease is responsible for 30–40% of cardiovascular-disease-related hospital admissions and is a common indication for cardiac surgery in that country [3]. The pathoetiology of the disease is complex, and its incidence and prevalence vary among countries. Environmental conditions may be a factor, with some climates having an increased frequency of rheumatic fever. In addition, low socioeconomic status, malnutrition, poor hygiene, and poor access to health care have all been associated with increased prevalence and incidence [1,4,5]. Rheumatic fever, which is rare before the age of
5. Myxomatous
4. Dialysis and ESRD
3. Age-related degenerative aortic valve disease
2. Serotonin-related valve disease
1. Rheumatic fever

Table 1
Native valve diseases with an inflammatory component

<table>
<thead>
<tr>
<th>1. Rheumatic fever</th>
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<tbody>
<tr>
<td>(a) Acute</td>
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<td>(b) Chronic</td>
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<td>2. Serotonin-related valve disease</td>
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<tr>
<td>(a) Carcinoid</td>
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<td>(b) Medication-related</td>
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<td>(ii) Anorexogenic</td>
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<td>(iii) Pergolide</td>
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<td>(iv) Other medications</td>
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<td>3. Age-related degenerative aortic valve disease</td>
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<td>4. Dialysis and ESRD</td>
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<td>5. Myxomatous “Floppy” mitral valves</td>
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5 years and after the age of 25 years, is most frequently observed in children and adolescents. The highest incidence is observed in children aged 5–15 years [6]. Genetic studies suggest that there is a vulnerable population with increased risk. Related family members of patients with rheumatic fever have a higher probability of developing the disease. Relationships between the development of rheumatic fever and HLA-DR subtypes have been found. These associations are variable between countries and populations [1,7,8].

Important antigenic structures of the *Streptococcus* include M-, R-, and T-proteins [1]. Streptococcal M-protein, which determines serotype, extends from the cell surface as an α helix with structural homology to myosin and other α helix coiled molecules [9]. The M-protein is a virulence factor with potent antiphagocytic activity [6]. In outbreaks, bacterial colonies isolated from those with rheumatic fever tend to have a mucoid morphology with thick capsules, and certain M-proteins are more common [5,10].

The pathogenesis of rheumatic fever relates to humoral and cellular-mediated immune responses with the development of autoimmunity [7]. The clinical manifestations of rheumatic fever occur 1–3 weeks after the onset of streptococcal infection. After an apparent convalescence of pharyngitis, products of *Streptococcus* display “molecular mimicry” to human tissues and are recognized by the immune system, thus initiating an autoimmune response. Cross-reactivity between the M-protein and cardiac proteins is important [9]. Individuals develop antibodies to the carbohydrate and the M-protein of the streptococcal organism. Anticarbohydrate antibodies cross-react with the valvular endothelium. This produces valve injury or dysfunction with up-regulation of cell adhesion molecules. This facilitates activated lymphocyte infiltration into the valve. M-protein antibodies contribute to the valve disease via molecular mimicry with myosin. Cardiac myosin is not present in the valve, but laminin links myosin in the valve. Antimyosin antibody recognizes laminin, an extracellular matrix α helix coiled protein, which is part of the valve basement membrane structure [7,9].

T-cells that are responsive to the streptococcal M-protein infiltrate the valve through the valvular endothelium, activated by the binding of antistreptococcal carbohydrate antibodies cross-reactive to the endothelium. Within the valve tissue, inflammatory cells are responsible for local cytokine release and interstitial cell damage with neovascularization and chronic inflammation [7]. Within the valve, T-cells produce cytokines, including tumor necrosis factor (TNF) and interleukins. Macrophages are activated and attract T-cells [11]. Local production of TNF is thought to have an important role. Valve destruction may expose more antigens, and the process may be progressive [4].

In support of this mechanism, structural and immunological mimicry between the streptococcal M-protein and cardiac myosin has been shown in the Lewis rat model [9]. T-cells isolated directly from these cardiac valves react with streptococcal M-protein peptides [9]. In addition, T-cells have been isolated from diseased human heart valves and have been found to recognize M-protein peptides and heart-tissue-derived proteins [8,9,11]. Patients with rheumatic fever also have increased serum cytokines (including interleukin 6, interleukin 8, and TNF) and increased CD4 and CD8 lymphocytes in the peripheral blood [12].

The acute involvement of the heart in rheumatic fever gives rise to pancarditis, with inflammation of the myocardium, pericardium, and endocardium. Carditis is the most severe clinical manifestation of rheumatic fever, which can lead to valvular heart disease, heart failure, or death. Carditis occurs in approximately 40–50% of patients on the first attack [6]. Pericarditis occurs in 5–10% of patients and is characterized by chest pain, decreased heart sounds, and pericardial rub [6]. Tamponade is rare. Pericarditis rarely occurs as a sole manifestation; if encountered alone, other causes should be suspected. Myocarditis occurs in 10% of patients and may present with heart failure, arrhythmias, pulmonary edema, and cardiomegaly. Isolated myocarditis is also rare [6].

Endocarditis and acute valve disease may be asymptomatic or may present with a new murmur. In the acute phase, murmurs do not indicate a permanent valve defect and may be transient. The valves most affected by rheumatic fever are the mitral, aortic, tricuspid, and pulmonary valves, in that order. In acute disease, thrombi form along the lines of valve closure. These small thrombi have been termed “verrucous” endocarditis and do not produce valve destruction. Leaflets may have associated edema and inflammatory cell infiltration. CD4 and CD8 T-cell subsets are present within acute rheumatic fever valves, and major histocompatibility complex Class 2 antigens are expressed on vessel endothelium and valve fibroblasts [6,13].

The chronically scarred, inflamed, and neovascularized valve is most commonly encountered by pathologists. Chronically, rheumatic fever leads to neovascularization, chronic inflammation, commissural fusion, valve thickening, and calcification (Fig. 1). Scarring, which is important in the progression of valvular disease, is accompanied by neovascularization of the otherwise avascular valve. Once the valve is inflamed and there is neovascularization, lymphocytes can infiltrate the valve both through the valve...
surface and through neovascularization channels. Even in old calcified rheumatic valves, lymphocytes and neovascularization are still present, indicating progression or persistence of disease in the valve [13].

Grossly chronic rheumatic valves have fibrosis, with or without calcification (Table 2). Commissures are often fused. Valves may be thickened and show scar retraction. The chordae are often thick and shortened. The subvalvular chordal space may seem to disappear, with short thick chords attached almost directly to the papillary muscles. At the commissures of mitral valves, there is often loss of surface endothelium and erosion with overlying thrombus material. This does not seem to be as common in the aortic position. Histology shows neovascularization, chronic inflammation, and fibrosis, with alteration and damage of the underlying valve architecture. Large fibrous endocardial onlays are present.

3. Carcinoid valve disease and serotonin-related valve disease

Serotonin-related valve disorders include carcinoid valve disease and disease associated with serotonin agonists, such as migraine and diet medications. The valvulopathy associated with these agents is hyperplastic in nature, with hyperplastic endocardial lesions [14]. An injured valve may respond by the accumulation of extracellular matrix, increased interstitial cell activity, chronic inflammation, and calcification. The myofibroblast form of interstitial cells is a major participant in valve repair. This cell expresses smooth muscle actin and can proliferate, migrate, make, and remodel the matrix [15,16]. In many adult valve diseases, proliferation and accumulation of myofibroblasts and interstitial cells are common [15–17].

Carcinoid syndrome and the resultant valve disease are thought to relate to increased serum levels of serotonin. Serotonin has been found to induce transforming growth factor (TGF) β expression. Serotonin up-regulates TGFβ expression and increases Erk signaling via mitogen-activated protein kinase [18]. TGFβ can induce valvular endothelial cells and interstitial cells to transdifferentiate into myofibroblasts [17,19].

The pathogenesis of carcinoid valve disease is thought to involve valve serotonin 5HT-2A and 5HT-2B receptors [14,18,20]. The addition of serotonin to cultured valve interstitial cells increases TGFβ expression and increases

<table>
<thead>
<tr>
<th>Chronic rheumatic</th>
<th>Floppy valve</th>
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<td>Valve thickened</td>
<td>Valve thickened</td>
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<tr>
<td>Fibrotic</td>
<td>Soft</td>
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<tr>
<td>Rigid</td>
<td>Rubber, redundant</td>
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<tr>
<td>Scar</td>
<td>Ground substance</td>
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<tr>
<td>Commissures fused</td>
<td>Commissures not fused</td>
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<tr>
<td>Chordae fused</td>
<td>Chordae elongated</td>
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<tr>
<td>Eroded/ulcerated</td>
<td>No erosion</td>
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Fig. 1. (A) Chronic rheumatic mitral valve with fibrosis, calcification, surface erosion, and chordal thickening and shortening. (B) A section from a rheumatic mitral valve with fibrosis, chronic inflammation, and small blood vessels. (C) Myxomatous mitral valve leaflets with thickening and chordal attenuation. Valves are more often repaired; hence, only portions of the valve are now commonly received. (D) A section from a myxomatous mitral valve demonstrating mild chronic inflammation.
extracellular matrix probably through this serotonin receptor mechanism [17, 18]. Addition of serotonin to sheep aortic valve interstitial cells increases TGFβ mRNA and TGFβ activity, with an increase in collagen synthesis [14]. Excised carcinoid valves show increased amounts of latent TGFβ-associated peptide and latent TGFβ-binding protein present in the interstitial cells and extracellular matrix [14].

Carcinoid heart disease is seen in approximately 50% of patients with carcinoid syndrome [21]. The valves commonly affected are the pulmonary and tricuspid valves. Left-sided disease may occur rarely if there is a patent foramen ovale. The valves are grossly white and thickened (Fig. 2). The plaques involve the cusps of the semilunar valves and the leaflets, chords and papillary muscles of atrioventricular valves. Endocardial plaques cause valve thickening and retraction, leading to regurgitation and stenosis. Regurgitant valves are most common, with mixed pulmonary stenosis, pulmonary insufficiency, and tricuspid insufficiency.

Valve thickening is due to the cellular proliferation of myofibroblast-like cells and the accumulation of extracellular matrix in endocardial onlay plaque lesions. These onlays or plaques tend to occur on the arterial surface of the pulmonary valve and both surfaces of the tricuspid valve, but predominantly in the ventricular side. Carcinoid plaques do not destroy the underlying valve architecture. The plaque matrix is rich in collagen and ground substances, and some studies have found small amounts of elastin. In a study of surgically excised carcinoid valves from the Mayo Clinic, 94% had neovascularization, 94% had chronic inflammation (including lymphocytes, plasma cells, and macrophages), and 64% of valves had mast cell inflammation associated with neovascularization [21]. Prior autopsy studies also noted a high degree of neovascularization and the presence of chronic inflammation. An autopsy study of 18 patients with carcinoid syndrome conducted by Thorson [22] found that 94% of valves were neovascularized and 67% had inflammation. Mast cells are variable in number in the reported studies—some find abundant cells, others none. Mast cells tend to be in areas of neovascularization and also may be in adjacent valve tissues and not actually in endocardial plaques.

4. Anorexogenic medications and other drugs

Medications, including anorexogenic drugs and migraine medications (ergotamine and methysergide), have been described as producing a carcinoid-like valve disease. The mechanism is thought to proceed via the activation or the agonist activity of 5HT-2B receptors. Medications have been screened for activity at serotonin receptor subtypes by ligand-binding studies and functional assays [23]. Fenfluramine metabolites, ergotamine, and methysergide have high affinity for these receptors, and these drugs have been associated with serotonin-related valve disease.

Ergot alkaloid drugs include methysergide and ergotamine, which are both used for the treatment of migraine headaches. Ergotamine-associated valve disease chiefly affects the mitral valve and produces a carcinoid-like gross appearance that may be severe. Mitral stenosis and
regurgitation have been seen. Valve leaflets are typically very thick, with chordal fusion, shortening, and commissural fusion. Large “myxoid collagenous” myofibroblast-rich plaques are stuck on the underlying valve proper without underlying valve leaflet destruction [24,25]. Methysergide, a migraine medication, has also had a morphologically similar mitral valve disease described, chiefly causing mitral regurgitation. This medication has also been associated with retroperitoneal and pleuropulmonary fibrosis. With these drugs, inflammatory cell infiltration has been reported as only mild [24,25].

Anorectic diet medications have previously been used as monotherapy for short-duration therapy for many years. The combination of fenfluramine and phentermine (Fen–Phen) was introduced in North America in the mid-1990s. Over a million prescriptions were written, and not all were for severe obesity. There was little knowledge concerning its effectiveness or chronic effects [26]. Connelly et al. [27] reported heart valve disease shortly thereafter in 1997. There is still some debate as to the actual risk and incidence of the valvulopathy associated with anorexogenic agents, but it is probably low [28]. Susceptibility or risk may depend upon the medication dose, the duration of treatment, and individual risk factors, including the presence of preexisting valve disease and concomitant medication use [29].

Grossly and microscopically, the valve disease or valvulopathy associated with anorexogenic drugs has been reported to be similar morphologically to that of carcinoid valve disease [27,30]. The left-sided valves are affected more often, with aortic insufficiency being the most common clinical manifestation [27]. White plaques are noted grossly. There may be chordal encasement and fusion, but not rupture. The commissures are not fused, in contrast to rheumatic disease. Doming or hooding of mitral leaflets is not seen, in contrast to floppy valve disease. By microscopic examination, the valves have myofibroblast and glycosaminoglycan-rich onlay endocardial lesions, with preservation of the underlying valve architecture. These onlay lesions are “neotissues” of glycosaminoglycans, collagen, and myofibroblasts that are superficial to the valve elastic membrane but are deep to the surface endothelium. The “downstream” side of the valve (the ventricular side of the mitral valve and the aortic side of the aortic valve) is described as the most common area involved. The valve proper may have myxoid degeneration with accumulation of glycosaminoglycans. The onlays also may contain chronic inflammatory cells (CD3+ lymphocytes and CD68+ macrophages), and there is neovascularization within the onlay lesions and in the valve proper [31]. Mast cells have been noted [30].

A careful and detailed digital-imaging-assisted study of geometry and composition reported interesting findings to aid in the distinction of anorexogenic disease from floppy mitral valve, rheumatic, and carcinoid diseases [32]. The size and the number of the onlay lesions, the amount of glycosaminoglycans in the onlay lesions and in the valve proper, and the location of inflammation and neovascularization are important in this distinction. Carcinoid valves have large onlays, with preservation of the underlying valve proper architecture. The valve proper and the onlays are glycosaminoglycan-rich, and there may be chronic inflammation throughout the valve. Floppy mitral valves have a medium number of onlays, but these have no significant neovascularization. The valve proper also usually has little neovascularization, but there is accumulation of glycosaminoglycan in the spongiosa layer. Rheumatic valves have few large fibrous onlays. Vascularization of the valve proper is prominent. The valve proper and the onlays show fibrosis [32]. Anorexogenic valves had the most variable findings, perhaps reflecting variability in dose, duration of exposure, and individual susceptibility. These valves had the largest amount of glycosaminoglycans among all valve groups. The onlays were small, numerous, and glycosaminoglycan-rich. Chronic inflammation may be present. Interestingly, both the valve proper and the onlays are neovascularized. There appears to be some similarities between the valve groups, but there are morphological trends and differences to assist in the separation of categories [32].

A similar carcinoid-like valve disease has also been noted recently with Pergolide, an ergot-derived dopamine receptor agonist used for the treatment of Parkinson’s disease [33,34]. Pericardial, retroperitoneal, and pleural fibroses have been reported. Valve disease in these patients has been reported as being fibroproliferative, with preserved underlying valve architecture. Tricuspid valve regurgitation and mitral valve regurgitation have been reported. Valve disease was described in 2002, even though the drug has been marketed for 20 years [33,34]. Pergolide is another medication that has been described to activate serotonin 5HT-2B receptors. It also influences potassium channels in pulmonary artery smooth muscle cells, causing vasoconstriction. Thus, monitoring of individuals taking this drug for pulmonary arterial hypertension (similar to anorexic drugs) has been suggested [34].

The saga of serotonin-related valve disease might continue. “Ecstasy” (3,4-methylenedioxymethamphetamine), an illicit street drug, has been found to induce the proliferative actions of cardiac valve interstitial cells, again via 5HT-2B receptors [35]. To the author’s knowledge, no clinical valve disease has been described yet.

5. Degenerative aortic valve disease

Age-related degenerative change of aortic valves is the most common cause of adult aortic valve stenosis encountered in North America. With an aging population, this will not likely change, and the disease will be commonly encountered at autopsy or as a surgical specimen by many pathologists. Traditionally, valve “degenerative” calcification was thought to be passive in nature, representing dystrophic calcification of degenerated materials. Wear-and-tear of the
valve tissue was postulated. Increasingly, this theory has been shown to be incomplete. An early event appears to be endothelial dysfunction from wear-and-tear, flow, and low-shear stresses. After this, numerous active mechanisms ensue, including lipid accumulation, inflammation, and alteration of cytokines, growth factors, and valve matrix metalloproteinases [36].

The process of valve calcification has much in common with atherosclerosis and bone formation [37–39]. Progression of aortic valvular disease in patients from the general population has been associated with many traditional risk factors for atherosclerotic disease, including systemic arterial hypertension, hyperlipidemia, and diabetes mellitus [40–42]. The calcification process involves the expression of noncollagenous matrix proteins, such as osteopontin, osteonectin, osteocalcin, bone sialoprotein, and bone morphogenetic protein. The expression of these collagenous and noncollagenous matrix proteins has been demonstrated in native cardiac valves and arteries [37,39,43,44]. Calcification of bones is a tightly regulated process that starts with osteoblasts producing a matrix of predominately Type 1 collagen. The collagen is subsequently mineralized by hydroxyapatite, which is thought to initially form within the osteoblasts and move to the matrix via vesicles. The question remains as to how bone cells gain entry into the endothelium and cardiac valves. The myofibroblasts of the valve have been shown to transdifferentiate into osteoblast-like cells [36].

If one histologically examines calcified valves, rather than only examining them grossly, the calcified valves commonly have variable degrees of inflammation, including macrophages, plasma cells, and lymphocytes [39,43]. These cells are capable of synthesizing osteopontin, which may act to hold surrounding cells to the calcified deposits [45]. Osteopontin influences chemotaxis, cellular proliferation, inflammation, and mineralization. It is strongly associated with macrophages and has been reported to influence macrophage invasion, migration, and phagocytosis [46]. The accumulation of T-cells within the cardiac valves is a likely source of cytokines that are important for the recruitment of more inflammatory cells [47]. Expression of cytokines such as TNFα has been noted in stenotic valves [47]. Metalloproteinases are also altered in the valve matrix [48]. Inflammatory cells may activate growth factors such as TNF, which in turn stimulates valve myofibroblasts to proliferate and express matrix metalloproteinases that remodel the valve matrix [47]. Mast cells may influence matrix metalloproteinases, release proangiogenic peptides, and activate cytokines and growth factors [39]. Lymphocytes are found in congenitally bicuspid aortic valves and in degenerative tricuspid valves [38].

Diseased valves may progressively accumulate lipids, and some have postulated a common link between degenerative valve disease and atherosclerosis [40]. Stenotic aortic valves have a larger amount of lipid compared to nonstenotic valves [49]. The lipid may oxidize and attract inflammatory cells. These cells may release cytokines, contribute to neovascularization, and participate in bone morphogenetic protein mechanism. Lipid-lowering therapy with statin medications (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) is thought to stabilize arterial plaques [49–52]. Statins may reduce the proteolytic activity of macrophages, increase plaque collagen content, reduce the size of the lipid core, reduce the degree of inflammation, restore endothelial function, and decrease tissue factor expression, thus decreasing propensity for thrombosis [53,54]. Repression of major histocompatibility complex Class 2 expression, blockage of leukocyte function antigen-1/intercellular adhesion molecule-1 interaction, and inhibition of CD40–CD40L signaling are all molecular mechanisms that have been described to explain the pleiotropic effects of statins [55].

Recent animal studies have demonstrated that hypercholesterolemic rabbits develop valve disease similar to the aortic valve disease of humans [46]. Treatment with statin medications was found to decrease the extent of lipid deposits in animal valves [56,57]. Some have postulated that statins might be useful for the prevention and treatment of valvular heart disease. Clinical trials are underway, and some of those reported are positive, but there are some conflicting results [58–62].

6. Valve disease in end-stage renal disease patients

There is an increased incidence of native valve calcification and stenosis in patients with end-stage renal disease (ESRD) and dialysis patients, compared to the general population [63,64]. Native valve calcification/stenosis seems to progress more rapidly in renal failure patients [65,66]. The presence of multiple risk factors for atherosclerosis may explain the more rapid progression of aortic stenosis; however, a uremic environment, hyperphosphatemia, hypercalcemia, and a high-calcium-phosphate product have also been implicated in the increased risk of cardiac and vascular calcification [63,64,67].

In a recent study conducted to determine if valvular calcification in patients with ESRD is morphologically similar to calcification in patients without ESRD, we examined surgically excised native cardiac valves of hemodialysis patients. While under blind conditions, valves were compared pathologically to age, gender, and valve type controls without renal failure. We found inflammation, neovascularization, and bone morphogenetic proteins in degenerative valves from both the normal and the dialysis populations (Fig. 2). Interestingly, when the results were unblinded, the patients with dialysis seemed to have more neovascularization and chronic inflammation than the nondialysis patients [68]. Enhanced inflammation in patients with ESRD is consistent with the marked elevation of acute-phase reactants in patients with ESRD compared to the general population. The elevation of a reactant, such as C-reactive protein, has been associated with vascular
calcification scores and with an increased risk of death from all-cause and cardiovascular-specific mortality [69,70].

7. Mitral valve prolapse: degenerative, inflammatory, or both?

Mitral valve prolapse may be seen with myxomatous valve degeneration as a degenerative-age-related change or in association with syndromes such as Marfan’s, Ehlers Danlos, or osteogenesis imperfecta. These are the classic, large, redundant, thickened “floppy” valves with endocardial fibrous thickening and accumulation of ground substances (glycosaminoglycans) in the valve spongiosa layer. Mitral valve prolapse may also be seen with Turner’s syndrome, hypertrophic cardiomyopathy, atrial septal defect, ischemic heart disease, and chest trauma. Aortic valve prolapse may be noted in many disorders, including ventricular septal defect, aortoannular ectasia, Marfan’s syndrome, aortic dissection, and infective endocarditis. Tomaru et al. [71] and Tomaru [72] described the entity of “postinflammatory” valve prolapse. They studied 42 aortic and mitral valves that were removed for prolapse and found fibrosis, neovascularization, and chronic inflammation in over 50%. These inflamed valves were scarred.

There may be some overlap between rheumatic changes and floppy myxomatous valves if one takes the effort to examine these valves by histology. By gross examination, one is commonly called upon to distinguish between rheumatic valves and floppy mitral valves (Table 2). The rheumatic valve is fibrotic and firm with thickened and fused leaflets and commissures. The ostium is elongated and funnel-shaped due to chordal fusion. Calcification and rigidity are seen. Chordal ruptures are not common. By contrast, the floppy myxomatous valve is thickened and redundant. The valve remains soft and pliable, and tends to dome above the valve insertion. Chordal rupture and attenuation are common. Ruptured chords may fuse in a random irregular fashion on the underside of valve leaflets. The commissures are not fused [73].

Unfortunately, it is not always simple. In grossly classic rheumatic valves, one sometimes finds some ground substance accumulation. More commonly, in grossly classic myxomatous valves, one sometimes sees some chronic inflammation and neovascularization (Fig. 1). With changes in chordal tension, the valve endothelium may be disrupted, and valve interstitial cells may alter their expression of cytokines and growth factors [48]. Valves may react to injury in a common fashion, and the distinction may not be as clean-cut as we would like.

8. Summary

Inflammatory cardiac valve disease encompasses many disorders and should not be solely equated with rheumatic valve disease. Granted, rheumatic disease remains an important cause, especially if one considers a global perspective; however, with increased understanding of the pathoetiology of valve disease and valve injury, it is evident that inflammation may play a role in many valve disorders. Cellular immunity, humoral immunity, and direct cell activation via pharmacological agents may all contribute.

We are only beginning to understand these complex processes. Pathologists have made many contributions to this field. With increasing knowledge that many of these processes are active, there may be opportunity for intervention or even prevention.

References


