Cartilaginous Metaplasia in Calcific Aortic Valve Disease

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In a 49-year-old man, symptoms of aortic valve stenosis developed that required surgical intervention with valve replacement. Pathologic examination of the valve showed severe calcific aortic sclerosis and foci of hyaline cartilage. The authors believe that these foci are secondary to cartilaginous transformation of mesenchymal valvular tissue. This represents abnormal repair of valvular tissue damaged, in this case, by the nodular calcific process of calcific aortic stenosis. (Key words: Aortic valve; Cartilage; Aortic stenosis; Metaplasia) Am J Clin Pathol 1990;93:809–812

THE USE of surgical aortic valve replacement for symptomatic aortic stenosis has increased the number of valves available for surgical pathology evaluation. The pathologic diagnosis in most of these specimens is calcific sclerosis of the aortic valve.

It has been more than 60 years since cartilaginous transformation in Monckeberg's calcific stenosis has been described. On the other hand, bone and fatty marrow formation in the calcific aortic valve is well recognized. Karsner and Kolletschky described the formation of bone containing fatty marrow in 9 of 200 cases of severe aortic valvular disease. In our experience at The Hospital of the Good Samaritan, we have seen 1 aortic valve with osseous transformation in 101 studied from valvular replacement surgery. We recently had the opportunity to study an aortic valve that had foci of hyaline cartilage as well as severe calcific sclerosis. A description of this case, a review of the literature, and an attempt to explain the mechanism for cartilage transformation are provided.

Materials and Methods

Four-micron sections were prepared from formalin-fixed and decalcified, paraffin-embedded tissue blocks. They were stained with hematoxylin and eosin (H and E) and Alcian blue.

Report of a Case

The patient was a 49-year-old white male who complained of increasing exertional dyspnea, orthopnea, dry cough, and chest pain for one month before admission. He said that for 10-15 years he had been aware that he had a heart murmur and he had been told that he might need aortic valve replacement in 1984 when he was hospitalized for alcoholism.

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At admission, the patient was in congestive heart failure that partially responded to diuresis. He had cardiac catheterization and echocardiography, which showed an aortic valve area of 0.7 cm² with a mean systolic gradient of 35 mmHg, a left ventricular ejection fraction of 20%, and normal coronary arteries. These findings were believed to be consistent with severe calcific aortic stenosis, considered best treated with aortic valve replacement. At surgery, it was noted that the aortic valve was heavily calcified and appeared to be bicuspid.

**Results**

**Gross Examination**

The specimen was submitted as 12 fragments of heavily calcified valve tissue ranging from 2 to 10 mm in size. The external surfaces of the valve were nodular but otherwise smooth and white. The number of cusps could not be evaluated because of the fragmentation and distortion of the valve. No thrombi or vegetations were apparent.

**Microscopic Examination**

Sections of the aortic valve revealed multiple large nodular intramural calcific deposits. These calcific areas showed focal eruption through the endocardial surface. The surrounding valvular stroma demonstrated hyalinized fibrous tissue and small focal collections of mononuclear inflammatory cells. On H and E-stained sections, one of the valve fragments demonstrated a 3.0-mm round focus of mature hyaline cartilage (Fig. 1). The cartilage was composed of uninuclear chondrocytes (Fig. 2). The nuclei were found within lacunae and surrounded by a basophilic matrix, which stained strongly with Alcian blue. The margins were irregular and showed focal calcification, although no well-defined bone formation could be found.

Alcian blue stain revealed two other microscopic foci of cartilage on another section of valve (Fig. 3). These other foci had not been identified on H and E-stained sections because of heavy mineralization. The cartilaginous foci were surrounded by nodular calcifications and hyalinized fibrous tissue. In areas, there appeared to be a gradual transformation from fibrous tissue to cartilage, with cells that appeared intermediate between fibroblasts and chondrocytes in the transformation zone (Fig. 4).

**Discussion**

Cartilaginous foci in the heart, although well described in other mammals, rarely occur in humans. Cartilage is found in the aortic ring of some white rats and mice. The os cordis, composed of cartilage or bone, occurs in the trigonum fibrosum of ruminants. A cartilaginous bar has been described at the base of the semilunar valve of R-Amsterdam rats and Syrian hamsters. The functional significance of these findings is not known, but they appear to be related to aging in some cases and to cartilaginous transformation secondary to mechanical forces in other cases.

In the literature, only two described pediatric cases of cartilage in the heart were found. Small amounts of fibrocartilage were found in the central fibrous body, in close approximation to the conducting tissue in two children, ages six months and two years. These children had sudden unexpected deaths, which were believed to be related to this finding. These cartilaginous foci probably resulted from congenital defects, however, the possibility of reactive metaplasia must still be considered.

The only description of cartilaginous foci of the aortic valve associated with calcific aortic or Monckeberg's stenosis was described by Henke and Labarsh in 1924, as previously mentioned. A more recent description of hyaline cartilage seen in the aortic valve of a 22-year-old male who had endocarditis was described in 1973 by Seemayer and colleagues. This patient presented with migratory arthritis and severe aortic insufficiency. He was treated with antibiotics and then had successful aortic valve replacement surgery. Pathologic examination of the heart valve showed mature hyaline cartilage with focal calcification and osseous transformation. The author postulated that the endocarditis caused destruction of the normal valve, which led to repair by cartilaginous transformation of the primitive mesenchymal spongiosa rather than fibrous replacement.

Induction of chondrogenesis has been performed experimentally in myocardium and other nonskeletal tissue. Devitalized tissue, otocyst implantation, compression and rotational stress, and carrageenan (connective tissue growth stimulant) have all been used to induce cartilaginous metaplasia. The injection of carrageenan into myocardium favored cartilage formation if the tissue was rendered ischemic by coronary artery ligation. The formation of both cartilage and bone in the myocardium has been described with the use of both biologic and synthetic materials as intracardiac grafts in the atrium of dogs. It is theorized that chondrogenesis in all these cases
occurs as a result of the release of a specific inductor sub-
stance, which leads to cartilaginous metaplasia of the tissue
or proliferation of a stem cell into cartilage differentiation.

A recent study by Arbustini and colleagues described
the cartilaginous transformation of bioprosthetic cardiac
valves implanted in the mitral or tricuspid positions in
sheep. Foci of cartilage associated with varying degrees of
calcification were seen in 12 of 120 bioprostheses that
were of porcine aortic valvular or bovine pericardial origin.
Cells that appeared intermediate between fiброblasts and
chondrocytes were seen at the periphery of cartilaginous
foci, similar to that seen in our case. One foci of osseous
transformation was also seen. These changes were only
seen in valves explanted “late” (greater than 13 weeks).
The cartilage was considered to be formed by metaplasia
of devitalized connective tissue of host origin.

It is unlikely that the cartilaginous foci seen in our pa-
tient have an embryonic origin, although, if the valve was
indeed bicuspid, a congenital defect must be considered.
Findings that would suggest acquired cartilaginous trans-
formation of mesenchymal valvular tissue include the late
age of presentation and the multiplicity of foci. The ap-
parent transformation zones seen between the fibrous and
cartilaginous tissue also suggests an ongoing metaplastic
process. We theorize that the aortic valve has become
damaged by the nodular calcific process involved in cal-
cific aortic stenosis. This has led to “abnormal” repair of
devitalized tissue by metaplastic cartilage from mesen-
chymal origin, perhaps as a response to some unknown
inductor substance. The same mechanism is probably re-
 sponsible for osseous transformation seen in the aortic
valve. It would be expected that any type of valvular dam-
age could lead to cartilage or osseous metaplasia and that
with time and additional pathologic examination that
more foci of cartilage will be seen in valves involved with
endocarditis, calcific sclerosis, and other entities, as well
as explanted bioprosthetic valves.

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