Two Necropsy Cases of Hypertrophic Cardiomyopathy in Holstein Cattle

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ABSTRACT. Two cases of hypertrophic cardiomyopathy in Holstein dairy cows are presented. At necropsy, the hearts revealed proportionate hypertrophy of the entire ventricles. The cut surface showed relatively large areas of myocardial scarring scattered throughout the ventricular walls including the septum. Microscopic examination revealed marked disorganization of cardiac muscle cells, intramural coronary arteries with thickened walls and narrowed lumina, and pronounced myocardial fibrosis. These features resemble those of hypertrophic cardiomyopathy in humans, suggesting the presence of a similar primary myocardial disease in cattle. — KEY WORDS: Holstein cattle, hypertrophic cardiomyopathy, sudden death.

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In Japan, at least two forms of hereditary cardiomyopathy in cattle have been reported. One of them is a lethal, idiopathic cardiomyopathy in Japanese black calves. Affected animals, usually less than one month old, die suddenly with multifocal myocardial necrosis and fibrosis [12]. Another form, affecting adult Holstein-Friesian cattle, is a dilated cardiomyopathy in which the heart is enlarged with dilatation of all four chambers. Microscopically, extensive cardiac myocyte degeneration, atrophy and hypertrophy are found, together with diffuse interstitial fibrosis [9].

Hypertrophic cardiomyopathy (HCM) has been studied extensively in humans. HCM is a primary myocardial disease characterized by a hypertrophied but nondilated left ventricle with the microscopic findings of disorganization of cardiac muscle cells, myocardial fibrosis and thick-walled intramural coronary arteries with a narrowed lumen [10, 11], and is genetically transmitted in a pattern consistent with an autosomal dominant trait [3]. Although it is known to occur spontaneously in a few species of animals: cats, dogs [5], and pigs [4], there have been no case reports on HCM in cattle.

Two cases of myocardial disease in Holstein cows are presented in which necropsy examination demonstrated marked ventricular hypertrophy with abnormally oriented cardiac muscle cells typical of HCM in humans.

Case No. 1: A 9-year-old Holstein dairy cow was found dead unexpectedly in a barn. This animal had experienced a clinical episode suggestive of the presence of cardiac disease, namely, syncope that lasted for 2 or 3 min and occurred twice, 7 and 2 weeks before death, but had been completely asymptomatic before the first occurrence of syncope.

At necropsy, the heart weighed 5.1 kg and was globular in shape and firm to the touch. On the cut surface, diffuse, proportionate thickening of both ventricular free walls and the ventricular septum, and slight dilatation of the left atrium were observed. The hypertrophied left ventricular free wall was 6.5 cm thick at the level of the anterior papillary muscle and 4.7 cm thick at the base of the left ventricle. The thicknesses of the hypertrophied ventricular septum and right ventricular free wall, midway between the coronary sulcus and the apex at the midpoint of each wall, were 5.2 and 3.1 cm, respectively. An endocardial fibrous thickening was present on the ventricular septum in the left ventricular outflow tract in apposition to the thickened anterior mitral leaflet (Fig. 1). The slices of the ventricles revealed multiple patchy areas of myocardial scarring, which were varied in size and were frequently <1.0 cm in diameter and occasionally >2.0 cm in diameter (Fig. 2). These sites of myocardial scarring were found throughout the left and right ventricular walls inclusive of the septum, but not in the left or right atrial wall. The coronary arteries were grossly normal and freely patent, and no structural defect such as congenital malformation was seen.

Microscopic examination of the heart revealed a markedly disordered arrangement of numerous cardiac muscle cells in which adjacent cells were oriented obliquely or perpendicularly to each other (Fig. 3). These disarrayed cardiac myocytes were extremely hypertrophied, included bizarre triradiate and stellate forms with increased side-branching and frequent side-to-side junctions, and often contained large, hyperchromatic and bizarre-shaped nuclei. Disarrayed myocytes were distributed extensively throughout both ventricular walls and the septum. Disarray was also observed in the left and right atria, but was less obvious there than in the ventricles. In transverse plane sections of each ventricular wall, abnormally arranged cells were most commonly observed in the middle and inner layers of the wall.

Disorganization of cardiac muscle cells was associated with extensive interstitial fibrosis. In relatively small areas of interstitial fibrosis, it was generally of a plexiform pattern in which the widened interstitium was composed of loosely arranged connective tissue (Fig. 3). Larger areas of interstitial fibrosis were observed not infrequently as replacing numerous cardiac myocytes. This type of fibrosis was restricted to the ventricular walls, and its distribution was consistent with macroscopically observed sites of myocardial scarring.

Changes in the intramural coronary arteries, namely, thickening of the vessel walls and a decrease in luminal

size, were frequently observed. The wall thickening was due mainly to proliferation of smooth muscle and fibrous tissue in the intima (Fig. 4). These abnormal vessels were more common within and around areas of replacement fibrosis distributed in the ventricular walls, although they were also present in the atrial walls.

Case No. 2: This animal, a 7-year-old Holstein dairy cow that was unrelated to the cow in case No. 1, was physically well developed. Its unexpected and instantaneous death was witnessed by the owner, and was regarded as the first definitive manifestation of cardiac disease.

At necropsy, the heart revealed diffuse ventricular hypertrophy and decreased left ventricular cavity size, weighing 6.0 kg (Fig. 5). The left ventricular free wall was 6.7 cm thick at the level of the anterior papillary muscle and 5.5 cm thick at the base of the left ventricle, and the ventricular septum and right ventricular free wall were 5.8 and 4.0 cm thick, respectively, midway between the coronary sulcus and the apex at the midpoint of each wall. The cut surface showed numerous patchy lesions of myocardial scarring scattered throughout both ventricular free walls and the septum, ranging in diameter from 0.5 to 2.5 cm. There was no anatomic involvement of the heart valves or coronary arteries.

Microscopy revealed widespread fibrosis of the left and right ventricular free walls and the septum with a high degree of myocardial cellular disarray, and intramural coronary arteries of abnormal morphology. The degree of fibrous-tissue formation in the ventricular myocardium ranged from relatively small areas of interstitial or replacement fibrosis to extensive and massive scars (Fig. 6). The histologic features of cardiac muscle cell disorganization and abnormal intramural coronary arteries and their distribution were similar to those observed in case No. 1 (Fig. 7).

This report describes morphological features of spontaneously occurring primary myocardial disease in 2 cows. The cardiac structural abnormalities observed in these cases were consistent with the morphologic hallmarks described in human patients with HCM: massive ventricular hypertrophy, disorganization of cardiac muscle cells, myocardial fibrosis, and occlusive changes in the intramural coronary arteries [10, 11]. This suggests that a primary myocardial disease that appears phenotypically similar to HCM in humans also occurs in cattle. Compared with universally verified cases of HCM in humans, however, there were a few aspects unique to our bovine cases. (1) Proportionate thickening of the left and right ventricular free walls and the septum (symmetrical hypertrophy of the heart) was found, and disorganized cardiac myocytes were distributed extensively throughout the thickened ventricular walls. (2) The areas of fibrosis were much larger than those usually observed in human patients with HCM [1, 6].

Asymmetrical septal hypertrophy has been accepted as the most common pattern of left ventricular hypertrophy in human HCM [10, 11]. Quantitative histologic analyses have shown that some cellular disorganization is present in the ventricular septum in about 95 percent of human patients dying of HCM, and disorganization characterizes at least 5 percent of the septal myocardium in about 90 percent of such patients [7]. Myocyte disarray is also seen in the left and right ventricular free walls, however, usually to a lesser extent than is seen in the septum [11]. The fibrosis in human HCM is usually present as plexiform fibrosis [1]; severe fibrosis characterized by extensive replacement scarring occupying substantial portions of the myocardium is therefore very rare [6].

In our bovine cases, the heart showed a symmetrical pattern of ventricular hypertrophy, and cardiac muscle cell disorganization and massive myocardial fibrosis involved extensive regions of the walls of the left and right ventricles including the septum, representing a diffuse cardiomyopathic process. Thus, it seems that HCM in cattle may be somewhat different in terms of degree in a few morphological aspects from HCM in humans.

In this connection, Liu *et al.* [5], who compared morphologic findings of HCM in 38 humans, 51 cats and 10 dogs, obtained the following findings: asymmetrical septal hypertrophy was more common in humans (81%) and dogs (80%), than in cats (31%), and marked septal disorganization was present in 92% of the human patients, but in only 27% of the cats and 20% of the dogs. Thus, they concluded that there was substantial morphologic variability in HCM among the species.

Another striking microscopic finding in the present cases is the presence of abnormal intramural coronary arteries with a thickened wall and narrowed lumen. These abnormal vessels tended to be localized to the areas of myocardial

Fig. 1. The left ventricular inflow and outflow tracts of case No. 1. Severe endocardial thickening forming a white patchy lesion on the ventricular septum below the aortic valve (arrow). Bar=2 cm.

Fig. 2. A formalin-fixed tissue slice of the full thickness of the left ventricular free wall of case No. 1, showing multiple sites of myocardial scarring. Bar=1 cm.

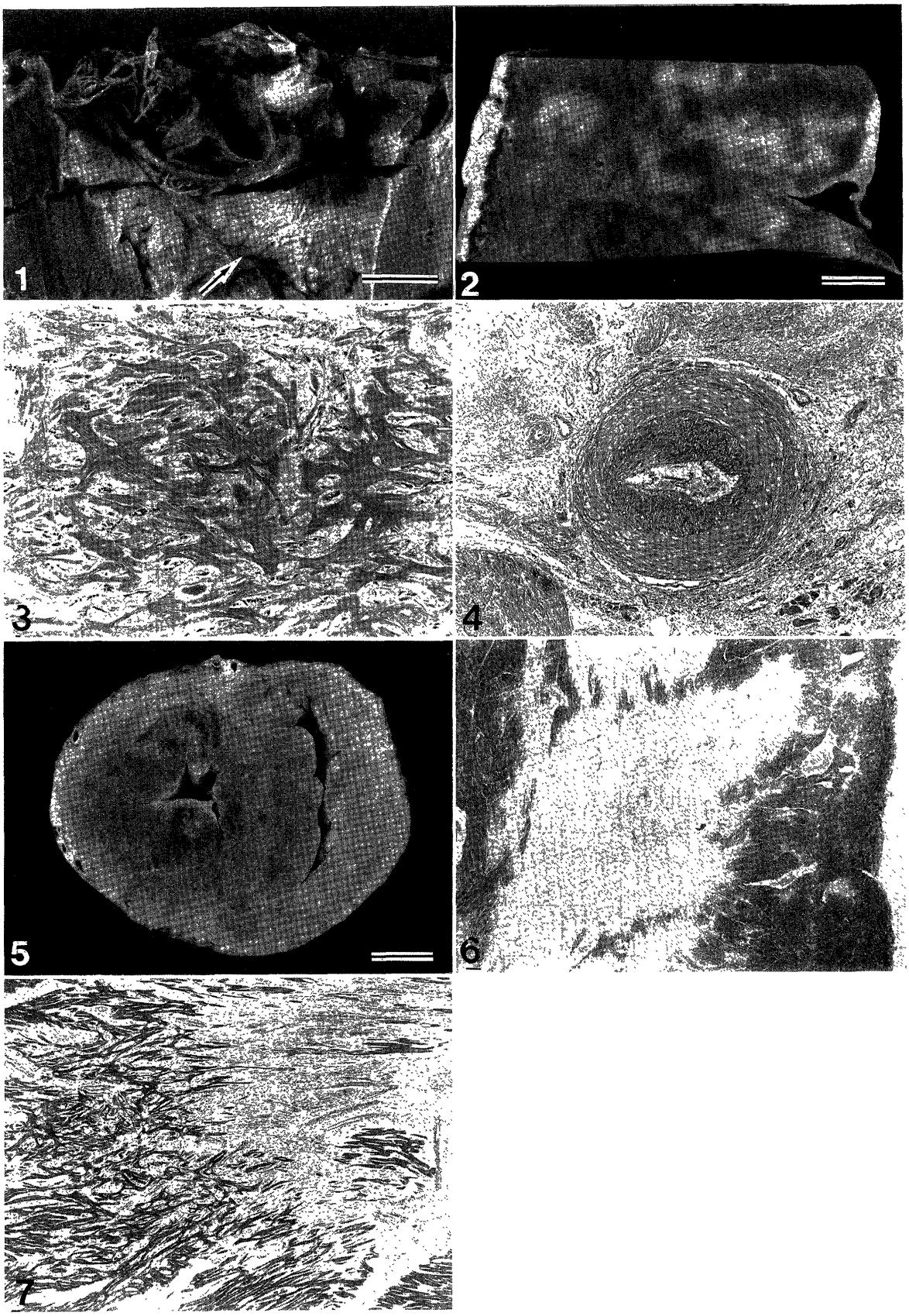
Fig. 3. Microscopic section taken from the ventricular septum of case No. 1, showing a typical area of marked disorganization of cardiac muscle cells with plexiform fibrosis. HE × 117.

Fig. 4. Representative photomicrograph of an intramural coronary artery within an area of myocardial scarring in the left ventricle of case No. 1, showing a thickened wall and narrowed lumen. Elastica van Gieson × 77.

Fig. 5. Cross-sectional slice of the heart of case No. 2, showing proportionate hypertrophy of the entire ventricles. Bar=3 cm.

Fig. 6 Photomicrograph of section of the right ventricular wall of case No. 2, showing areas of substantial scarring. Masson's trichrome × 5.

Fig. 7. Microscopic section taken from the ventricular septum of case No. 2, showing representative myocardial area of disorganized cardiac muscle cells in contanct with a lesion of myocardial fibrosis. Masson's trichrome × 30.



scarring. It is well known that the intramural coronary arteries in areas of substantial myocardial fibrosis may show marked wall thickening with luminal narrowing in human patients with HCM [8]. Maron *et al.* [8] postulated that the abnormal intramural coronary arteries might constitute an independent marker of HCM and a component of the cardiomyopathic process.

One of our 2 cases showed an endocardial fibrous plaque-like lesion on the ventricular septum adjacent to a thickened anterior mitral leaflet. Such a sclerotic plaque is seen in 38 percent of human HCM patients [2]. This lesion is regarded as evidence of systolic contact between the anterior mitral leaflet and the ventricular septum and is believed to be of considerable diagnostic importance at autopsy [2].

In conclusion, it is evident that a primary myocardial disease, with pathologic features similar in many respects to those of HCM in humans, occurs in cattle.

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