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CASE REPORT

PATHOLOGY/BIOLOGY

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Sudden Death Due to Infiltration of Left Bundle Branches by Interventricular Septal Cardiac Fibroma

ABSTRACT: Cardiac fibromas are benign conditions; however, their location and size may cause ventricular arrhythmias and sudden cardiac death. We report a case of a 68-year-old female who died suddenly. Postmortem investigation detected a huge cardiac fibroma in the pars muscularis of the interventricular septum, occupying almost the entire muscular septum, and restricting the volume of left ventricular chamber. Histological examination revealed numerous foci of calcification in the alternating complex interlacing or strictly parallel collagenous fiber mass. Tumor mass was mainly demarcated, but in some places, fibrous infiltration of surrounding working cardiac muscle was found. We present a case when direct tumor involvement in the descending left bundle branches was evidenced. Mainly, the branches of septal fascicle were disrupted, entrapped, and degenerated by the tumor mass. This case report emphasizes that postmortem histological examination of conduction system in all sudden cardiac death cases may substantially improve the accuracy of postmortem diagnosis.

KEYWORDS: forensic science, cardiac fibroma, tumor, sudden death, conduction system, left bundle branches, interventricular septum, autopsy

The prevalence of primary cardiac tumors at autopsy ranged from 0.001 to 0.3% and benign primary neoplasms are more common (75%) than malignant neoplasms (1). Cardiac fibromas, the second most frequently occurring benign cardiac tumors, usually arise from the left ventricular free wall or ventricular septum (2). Fibromas are composed of connective tissue fibroblasts interspersed among large bundles of collagen fibers. Patients with fibromas may manifest with heart failure, ventricular arrhythmias, and sudden cardiac death (3). It is supposed that conduction abnormalities in cardiac fibromas may be due to a direct involvement of the conduction system or conduction disturbances are secondary to intramyocardial tumor growth and may cause fatal arrhythmia; however, collection of pathomorphological evidences needs a very careful postmortem investigation.

We present a sudden cardiac death case with cardiac fibroma in the interventricular septum of a 68-year-old woman.

Case Report

Autopsy Findings

A 68-year-old female died suddenly on a train during journey without any previous symptoms or well-known illnesses. The resuscitation made by the ambulance was not successful. Postmortem investigation detected mild coronary sclerosis and brain edema. The heart weighted 480 g. In the interventricular septum, a single brown-white fibrous mass ranging 5 × 4 × 3 cm was found. It was mainly ovoid with few irregular projections, at gross appearance without a distinct capsule (Fig. 1). Proximal part of the fibrous tumor approached the base of the heart but did not reach the membranous ventricular septum. The posterior surface of the muscular ventricular septum instead of curving with the convexity toward the right ventricle bulged into the left ventricular chamber. There were no intervening cardiac muscle cells between the tumor and the endocardial lining on the left side of the superior part of the muscular interventricular septum (Fig. 1—on the right). The cut surface of the tumor was firm and solid, and there were no areas of hemorrhage or necrosis. Blood alcohol concentration test showed slight (49.6 mg/100 mL) alcohol level. Toxicology had negative result.

Histology

To examine the tumor and cardiac conduction system including regions of the HIS and left and right bundle branches, 11 blocks were fixed in 10% formalin buffer, routinely processed for light microscopy, and stained with hematoxylin–eosin, Krutsay's trichrome stain, Verhoeff's elastic stain, and von Kossa's calcium stain. Microscopic investigation revealed in some places increased amount of dense fibrous tissue among the cardiomyocytes as extensions from the tumor (Fig. 2*A*). However, most of the tumor circumference was demarcated from the myocardium. The fibroma was composed primarily of coarse collagenous fiber bundles interlaced or oriented strictly parallel displaying few fibrocytes and poor vascularization (Fig. 2*C*). Beside collage-

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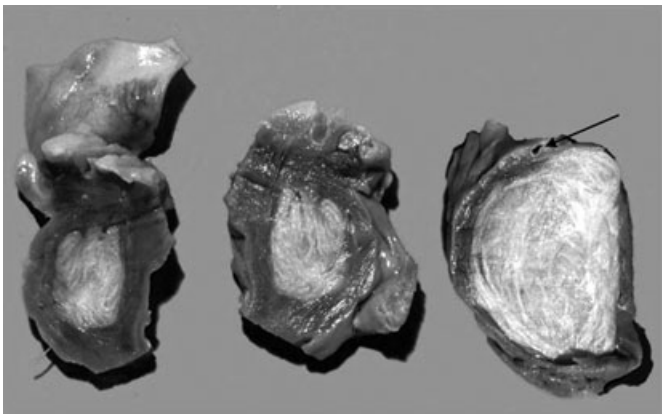

FIG. 1—*Gross appearance of tumor mass in the interventricular septum. Three sections of interventricular septum cut parallel with the plane of the septum. No working cardiac muscle or only a thin layer of it remained at the maximal extension of fibroma. Proximally, the fibroma approaches the level of coronary sulcus (black arrows).*

nous fibers, numerous elastic fibers (Fig. 3*A*,*B*) are also evidenced by specific elastic staining, and foci of calcium deposits, identified by von Kossa stain (Fig. 3*C*), were present both in the central and peripheral portions of the tumor. In the peripheral regions of the tumor, completely entrapped working cardiac muscle cells were observed (Fig. 2*D*). The wall of intramural arteries often displayed focal thickening of tunica intima and media that contained increased amount of collagen fibers (Fig. 2*B*). At the tumor–myocardium interface, there were areas where lymphocytes accumulated around the arterioles and venules. No evidence of malignancy was detected. The conduction system was identified in vicinity of the tumor, close to the upper edge of the muscular interventricular septum, that is, in the area of the distribution of ventricular conducting branches. HIS bundle and its bifurcation were not altered by the tumor (Fig. 4*B*–*D*). Similarly, the right bundle branch (Fig. 4*A*) passing subendocardially toward the apex exhibited intact histological features. However, the branches of trifurcating left Tawara bundles were displaced by the tumor (Fig. 5*A*). Furthermore, the fibroma invaded the spreading branches of the septal fascicle, and some entrapped conducting myocardial fibers (Fig. 5*C*) displayed signs of cellular degeneration, fragmentation of myofibrils (Fig. 5*B*).

Discussion

Sudden death because of septal cardiac fibroma is a known fatal outcome; however, the direct infiltration of conduction system is rarely found (4,5). Conduction abnormalities in cardiac fibromas may be due to direct infiltration of the conduction system by the tumor, or to compression of the conduction system, or to accessory conduction pathways located within the tumor (4). James et al. (5) reported a case with cardiac fibroma compressing the His bundle. Therefore, the postmortem collection of pathomorphological evidences for conduction system involvement also has a great importance in ascertaining the cause of sudden death. Dissection of the cardiac conduction system involves the examination of sinoatrial node, the atrioventricular node, HIS bundle, the left and the right bundle branches (6).

To our knowledge, this is the first report presenting histopathological evidences for the direct infiltration of a cardiac fibroma

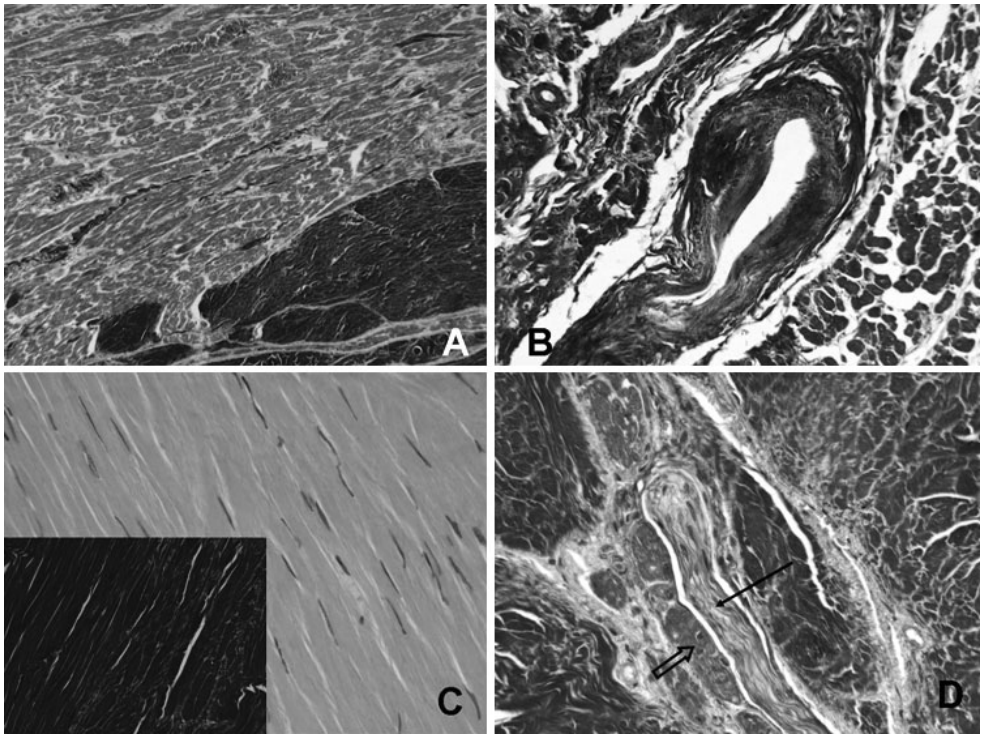

FIG. 2—*Section through the fibroma showing (A) increased fibrosis in the vicinity of the tumor mass, Krutsay's trichrome staining (obj 4×); (B) thickening of the tunica intima and media by focal accumulation of collagen fibers in an intramural artery, Krutsay's trichrome staining (obj 10×); (C) collagen bundles oriented mostly strictly parallel with flattened nuclei of fibrocytes, H&E staining (obj 20×), insert: Krutsay's trichrome staining (obj 20×); and (D) longitudinal section of a peripheral nerve (black arrow) and oblique section of working cardiac muscle cells (open arrow) embedded into the tumor mass, Krutsay's trichrome staining (obj 20×).*

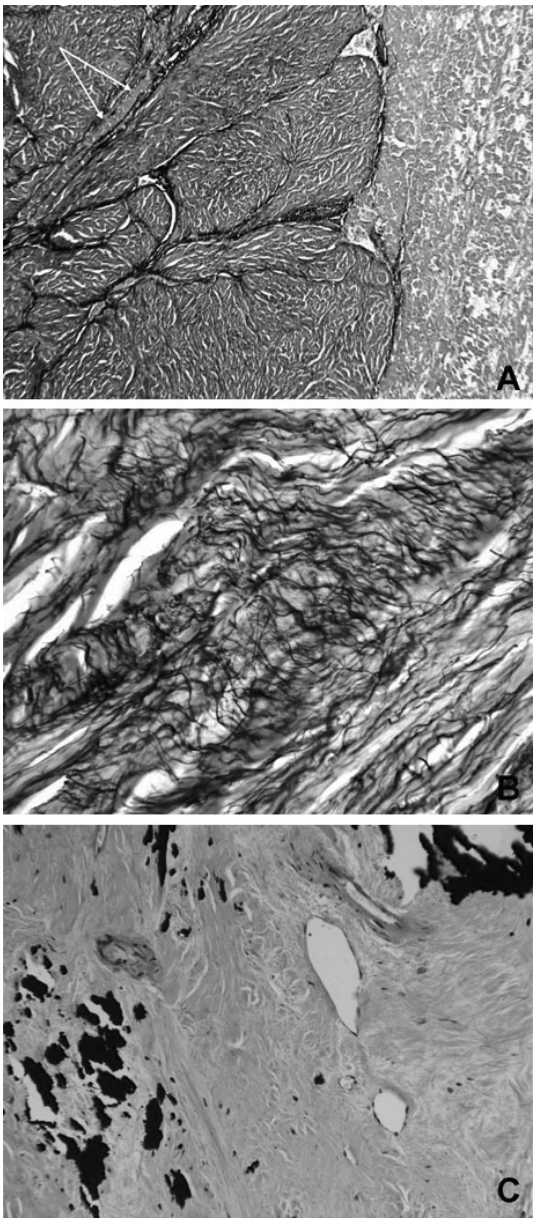

FIG. 3—*(A) Specific staining demonstrates besides collagen fiber bundles (red) a substantial amount of elastic fibers (black) in the tumor. White arrows label cardiac muscle cells compressed by the tumor mass, Verhoeff's elastic stain (obj 4×); (B) higher magnification micrograph displays a dense elastic fiber network (obj 20×); and (C) von Kossa's staining manifests calcification in the fibroma, calcium deposits stained black (obj 10×).*

grown in the interventricular septum into the left bundle fascicle disrupting and damaging the ramifications of septal fascicle. Proximally on the septal surface, facing the left ventricular cavity, the bulging tumor was covered only by a thin endocardial sheath. Thereby, the fibroma replaced and/or displaced both the subendocardially coursing fascicles of left bundle branch of HIS (mainly the septal fascicle) and the working cardiac muscle fibers. Accurate histological examination of conduction tissue in serial sections uncovered the direct invasion of the spreading septal fascicle of the left bundle branch. Near to the proximal margin of the fibroma, entrapped conducting cells could be recognized, some of them showed signs of cellular degeneration, that is, fragmentation of myofibrils. Above this region, the divergent spreading of left bundle branches has yet been evidenced. In contrast, the right bundle branch displayed normal course and histology along the right septal surface. These histopathological findings suggest that degeneration of the invaded conduction tissue and alternating compression, overstretching of the left bundle branches by the rigid tumor critically compromising conduction could lead to partial or complete left bundle branch block, ventricular arrhythmia evolving to fibrillation, and sudden death. Moreover, the fibroma itself as a "scar tissue," compressing and/or stretching and damaging the surrounding cardiac myocytes might trigger a re-entry mechanism of ventricular arrhythmia.

Cardiac fibroma was described in 1855, and the first successful surgical excision was performed in 1962 [in 3]. The vast majority occurs in children, but presentation in adulthood is also recognized (7). Fibromas are solitary, white fibrous well-circumscribed or infiltrative masses, ranging in size from 2 to 10 cm, and occurring primarily within the ventricular free wall or interventricular septum (2,8). Fibromas in adults become progressively poorly cellular and poorly vascularized; therefore, they are composed predominantly of collagen as it was observed in our case. Cardiac fibroma is a rare benign tumor that occurs primarily in infants and children, with no numerical disparity by sex. The most common cardiac tumor in infants and children is rhabdomyoma, followed by fibroma and teratoma. Cardiac fibroma has been documented but has received little attention. The propensity of cardiac fibroma to cause arrhythmias is becoming increasingly evident. Echocardiography is the investigative method of choice, to determine the potential for resection (9). These tumors are solitary, occur exclusively within the ventricle and the ventricular septum, and affect the sexes equally. Few tumors have been reported, and most are diagnosed below the age of 2. These tumors are not associated with other diseases nor inherited (10).

The described histological pattern of fibromas shows differences in the reported cases. In some reports (11,12), the cellular fibroblastic component is abundant, however, in others (13,14) the collagen and elastic fibers are prominent. Fibromas are nonencapsulated, firm, nodular, gray-white tumors that can become bulky. They are composed of elongated fibroblasts in broad spiral bands and whirls mixed with collagen and elastin fibers. Calcium deposits or bone may occur within the tumor and occasionally are seen on roentgenography (10).

However, the richly cellular fibromas were diagnosed mainly in infants or children <10 years of age. We confirmed results that numerous foci of calcification, identifiable with special stains, are found in fibromatous mass, furthermore, in our case numerous elastic fibers were observed beside abundant collagen fibers (1,15). Dystrophic calcification of the central portion of the tumor is common, reflecting poor blood supply to the mass. Histopathology of cardiac fibroma in Gorlin syndrome displays the same features as that of noninherited cardiac fibroma.

The most frequent tumors involving the heart as metastases are carcinomas of the lung and breast, melanomas, leukemias, and lymphomas. Metastases can reach the heart and pericardium by retrograde lymphatic extension, hematogenous seeding, by direct contiguous venous extension. Myocardial metastases are usually clinically silent or have nonspecific features. Primary tumors of the heart are rare, metastatic tumors to the heart occur in about 5% of patients dying of cancer. The most common primary tumors in descending order of frequency are myxomas, fibromas, lipomas, papillary fibroelastomas, and other sarcomas. The five most common tumors are all benign and collectively account for 80–90% of primary tumors of the heart. Myxomas (benign neoplasia) are the most common primary tumors of the heart in

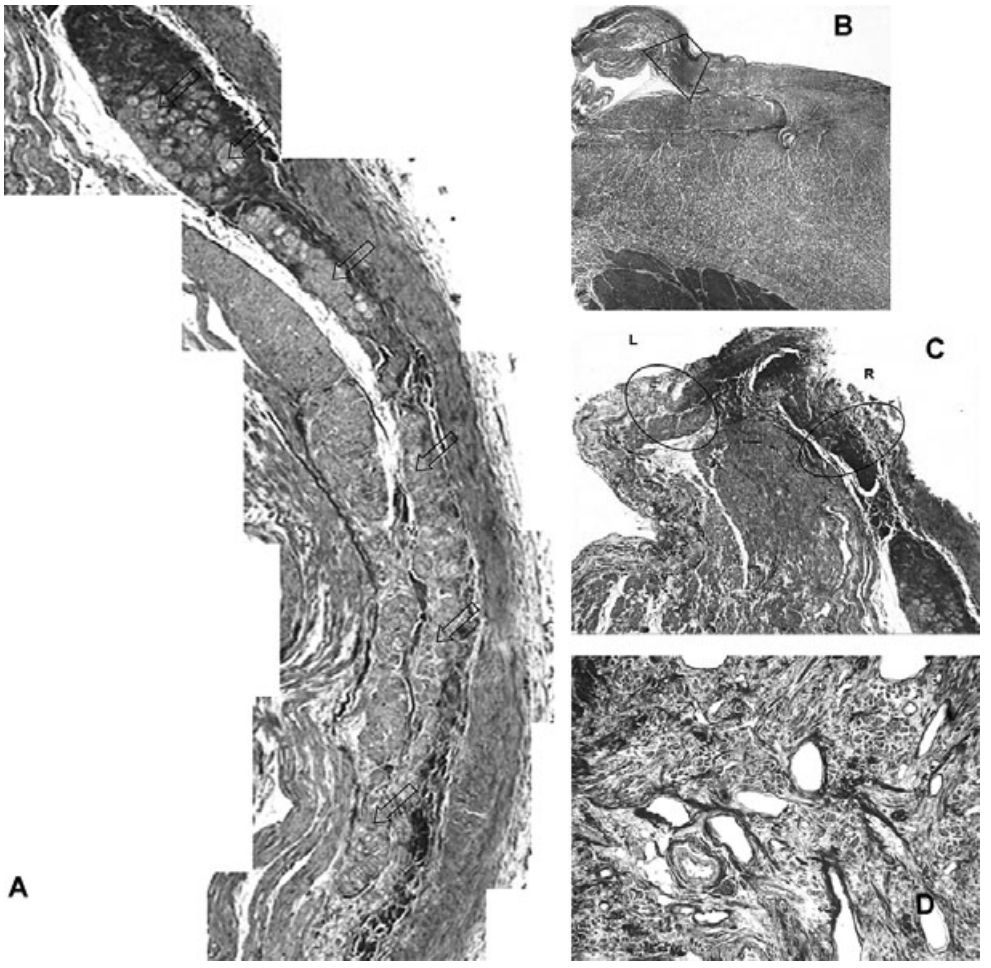

FIG. 4—*(A) Montage of six microphotographs displaying the right bundle branch of HIS passing subendocardially toward the apex. Purkinje fibers (open arrows) are insulated by collagenous connective tissue, which is not related to tumor mass, Krutsay's trichrome staining (obj 10×); (B) montage of four microphotographs showing topographic relation of tumor mass and the membranous interventricular septum (rectangular frame), Krutsay's trichrome staining (obj 1×); (C) division of His bundle into left (L) and right (R) bundle branches, Krutsay's trichrome staining (obj 4×); (D) richly vascularized region above the crest of muscular interventricular septum showing the ramifying left bundle branches, Krutsay's trichrome staining (obj 10×).*

adults, 90% are located in the atria. Histologically, myxomas are composed of stellate or globular myxoma cells, endothelial cells, smooth muscle cells, and undifferentiated cells embedded within an abundant acid mucopolysaccharide ground substance and covered on the surface by endothelium. Cardiac fibromas are connective tissue tumors derived from fibroblasts (16).

Although most cardiac tumors are benign, displaying slow and continual growth, they may cause conduction defect or obstruction or may spread to the ventricular free walls, leading to life-threatening arrhythmias and ventricular fibrillation (17–19). Damaged cardiac tissue may cause conduction block with ventricular fibrillation based on the abnormal electrical impulses that are initiated and fibrillation perpetuated through a phenomenon of re-entry. Clinical investigations detected complete AV block and supraventricular tachycardia in association with cardiac fibroma, and ECG may show partial or complete bundle branch block and ST-T wave abnormalities (20,21). Most of the fibromas are accompanied by cardiac symptoms (18–20); however, it is estimated that 10% of patients with cardiac fibroma may present with sudden death (3,22).

The clinical manifestations of cardiac tumors are diverse, nonspecific, and depend on location and size. Some cardiac tumors remain clinically silent and have been diagnosed postmortem, others present with symptoms relating to intracardiac obstruction and interference with conduction pathways (23). During the diagnostic procedures, imaging techniques play a central role in the evaluation of suspected cardiac tumor. Cardiac magnetic resonance provides an unrestricted field of view in the characterization of cardiac masses, and multidetector computed tomography is especially useful for detecting calcification (7). Despite the fact, that high quality imaging is a common available method for the correct diagnosis, sudden death may occur without any previous symptoms as happened in our case (24,25).

Cardiac fibroma may occur as an inherited manifestation with nevoid basal-cell carcinoma, the syndrome was described by Gorlin (Gorlin syndrome) (26). Cardiac fibroma is more commonly encountered in patients with Gorlin syndrome (3%) than the general population (27). It is transmitted as an autosomal dominant trait and is caused by mutation in the *PTCH1* gene at 9q22.3 (28). Its estimated prevalence is 1 in 57,000, and approximately 3% of cases are associated with cardiac fibromas, which may present later during adulthood rather than the typical infancy or childhood period (29,30). Cardiac fibromas rarely cause symptoms in patients with Gorlin syndrome, although they can reach significant size. Occasionally, tumor growth may impede blood flow or displace or directly involve mitral and aortic valves and result in hemodynamically significant valvular stenosis or regurgitation or may be associated with arrhythmias

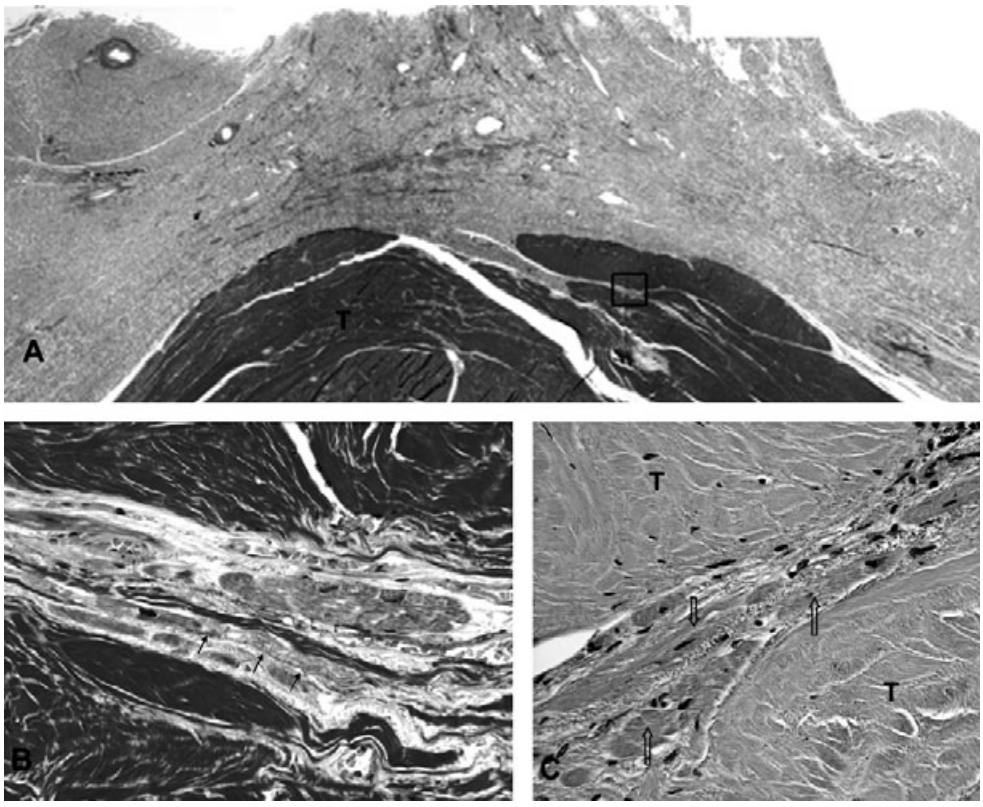

FIG. 5—*(A) Montage of seven microphotographs showing the septal region where the left bundle branch splits into three fascicles and immediately below it, the fibrous tumor mass (T) is seen, Krutsay's trichrome staining (obj 1×). (B) and (C) These microphotographs have been taken in the area labeled with black rectangular frame (in panel A). (B) Section through the tumor demonstrating entrapped degenerating conducting cardiomyocytes. Black arrows indicate fragmentation and decomposition of myofibrils, Krutsay's trichrome staining (obj 20×). (C) This section is adjacent to that showed on microphotograph "B." The photographed area locates in the right half of the rectangular frame labeled area on microphotograph "A." Between masses of dense fibrous tissue (T) some apparently intact Purkinje cells are labeled (open arrows), H&E staining (obj 20×).*

(27). Histopathology of cardiac fibroma in Gorlin syndrome presents proliferation of spindle cells, hyalinized collagen, and focal calcifications. No cytological atypia, necrosis, or mitotic activity was identified (31).

As the routine forensic autopsy does not include the examination of the conduction system, significant pathomorphologic abnormalities of conducting system may remain unrevealed. We first present a case when direct tumor involvement in the descending left bundle branches was evidenced by detailed histological demonstration of cardiac conducting elements. In our case, a voluminous fibroma displaced disrupted and destroyed the left septal bundle fascicle. Accurate histopathological study of possible alteration of the cardiac conduction system is recommended in all cases of sudden unexpected death for providing more complete medico-legal documentation (5), thereby reducing the number of "unexplained" cases. On the basis of our findings, we suppose that disorders of conduction system disrupted and damaged by cardiac fibroma may cause fatal dyskinesia or arrhythmia because of tumor compression. This case report emphasizes that postmortem histological examination of conduction system in all sudden cardiac death cases may substantially improve the accuracy of postmortem diagnosis and the cause of death.

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