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**Histiocytoid cardiomyopathy and ventricular noncompaction presenting as sudden death in an adult male**

Short form of the title:

**Histiocytoid cardiomyopathy and ventricular noncompaction in a man**

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A B S T R A C T

Histiocytoid/oncocytic cardiomyopathy (HCM) is a rare, distinctive arrhythmogenic disorder that presents as

arrhythmia or sudden death in infants and children. Ventricular noncompaction (VNC) is a rare cardiomyopathy characterized by a thickened endocardial layer of noncompacted myocardium and a thin epicardial layer of compacted myocardium. Only six cases of the association of both cardiomyopathies have been reported previously in the literature. All these cases were in children. To the best of our knowledge, a case of HCM has not been described in the adult. We report the case of a 45-year-old man with an increased heart weight and involvement of both ventricles by HCM and VNC cardiomyopathy. Besides, multiple foci of myocardial disorganization were detected. He died suddenly while hiking. The association of both processes HCM and VNC was an unexpected finding at autopsy. The death was linked to functional abnormalities of the cardiac histiocytoid cells, and it was favored by a state of abnormal development of the heart.

*Keywords*: Histiocytoid cardiomyopathy, Ventricular noncompaction, Myocardium disarray, Sudden death

## 1. Introduction

Histiocytoid or oncocytic cardiomyopathy (HCM), also known as Purkinje cell hamartoma, is a congenital multicentric hamartomatous proliferation of cardiac cells with oncocytic characteristics [1]. The condition is very uncommon, the age range at presentation is birth to 4 years (mean, 10-13 months), and there is a female predominance of 75%. The most common presenting features are arrhythmias and electrical disturbances, followed by sudden death [1-3].

Ventricular noncompaction (VNC) is defined by excessively prominent ventricular trabeculations, deep intertrabecular recesses, and a thin compacted layer. The diagnosis is established when the ratio of noncompact inner myocardial layer to compact subepicardial layer is >2 [4-6]. This rare cardiomyopathy is more common in men than in women with male patients accounting for about 71% [7]. Clinical presentation is highly variable. It may be asymptomatic or it may lead to heart failure, arrhythmias, including sudden cardiac death, and systemic embolic events [6].

Association of HCM and LVNC has been rarely reported. We are aware of only six cases documented, all in infants or children [4,8,9-11].

To the best of our knowledge, a case of HCM has not been described in the adult. We report herein a case of HCM in an adult male associated with VNC presenting as sudden unexpected cardiac death.

## 2. Case report

A 53-year-old Caucasian man was found dead on a trail while hiking. Two years before he suffered several episodes of dizziness with normal electrocardiograms and without consequences. Past medical history also revealed chronic asthma treated with bronchodilators and gastroesophageal reflux. The family denied smoking, alcohol or intravenous drug abuse.

At autopsy, the heart weighed 420 g. Grossly, both ventricles showed a two-layer myocardium. This was thin and compacted next to the epicardium, and thick, noncompacted next the endocardium. The luminal surfaces of both ventricles showed excessive number of abnormally conspicuous coarse trabeculations with deep intertrabecular recesses from the basal segments to the apices (Fig. 1A).

There were multiple raised, yellowish endocardial nodules in both ventricles with a clear predominance in the left ventricle. These endocardial nodules were present circumferentially in all walls of the left ventricle (Fig. 1B). The thick trabeculae simulate papillary muscles (Fig. 1C). The size of the yellow nodules ranged from 1 mm to 5 mm (Fig. 1D). The noncompacted layer in the left ventricle involved 84.2% of the thickness. This layer in the right ventricle involved 81.9% of the thickness. Measurements were made in the middle third of both ventricles and histologically confirmed.

Microscopically the noncompaction layer showed anastomosing muscle bundles separated by irregularly branching recesses, sometimes with a staghorn appearance, covered by endocardium (Fig. 2A). In this noncompaction layer, there was focal fibroelastosis of the endocardium, and replacement fibrosis, and adipose infiltration of the subendocardium (Fig. 2B). The left ventricle exhibited deep recesses extending more the 50% of the left wall thickness. In the right ventricle, the recesses extended more than 75% of the wall thickness. Besides, the endocardial yellowish areas identified macroscopically were constituted by well-circumscribed, collections of large, polygonal, oncocytic or histiocytoid cells with centrally located round to oval nuclei. These nuclei were dark, or vesiculous with visible nucleoli. The cytoplasms were occasionally vacuolated (Fig. 2C). The nodules of histiocytoid cells were scattered in the subendocardium of both ventricles (Fig. 2D). Histiocytoid cells showed diverse morphologic aspects. Thus, cells were pale (Fig. 3A), oncocytic (Fig. 3B), or elongated recalling Purkinje cells (Fig. 3C). All these cells stained faintly with the periodic acid Schiff (PAS) procedure. This staining highlighted cell membranes.

Masson´s trichrome and Van Gieson´s stains showed absence of significant collagen fibers among the cells and clear reduction in the number of myofibrils. These were displaced to the periphery of the cells (Fig. 3D). Additionally, trichrome stains demonstrated focal endocardial sclerosis overlying the lesions. There was no inflammatory infiltrate. Cardiac valves were not affected. No connections were observed between the histiocytoid nodules and the sinoatrial or atrioventricular nodules, or with the His bundle. One aggregate of foam cells without a necrotic core or fibrous cap (xanthoma) was found in the intima layer of the left anterior descending coronary artery (Fig. 4A). There were multiple foci with myocytes showing disorganized fascicles on the wall of both ventricles (Fig. 4B).

Immunohistochemically, the histiocytoid cells showed positivity for desmin (Fig. 5A), anti-mitochondrial antibody (Fig. 5B), myoD1 (Fig. 5C), muscle specific actin (HHF35) (Fig. 5D), and myoglobin (Fig. 6). These cells showed no reactivity for S100, lysozyme, alpha-1-antitrypsin, CD68, and smooth muscle myosin heavy chain (SMMS-1).

Mild atherosclerosis of the aorta and coronary arteries was observed. The lungs showed diffuse congestion and multiple foci of recent alveolar hemorrhage. The liver presented generalized acute congestion and mild macrovacuolar steatosis. The rest of the organs showed no significant alterations.

The forensic study did not detect drugs of abuse in urine.

## 3. Discussion

HCM is a rare disorder usually affecting female infants under the age of 2 years. HCM is more common in Caucasian

(75%), followed by African-American (15.6%), Latin-American (6.3%) and Asian infants (3.1%) [3]. The disease has diverse clinical presentations. Most reported patients (70%) experienced arrhythmias and electrical disturbances including ventricular fibrillation. Other infants were healthy except for undergoing a flu-like illness of short duration before their death. Approximately 22% of patients presented as sudden death without prior clinical manifestations [3]. Some authors consider HCM a form of mitochondrial cardiomyopathy [12,13]. Thus, ultrastructural study of cases has revealed striking mitochondrial hyperplasia with disarranged cristae and reduced numbers of myofibrils [14]. On the other hand, it has been confirmed that the disease is genetically heterogeneous [14].

Prominent cardiomegaly was present in 95% of cases. After the opening of the heart chambers multiple, small, yellowish, grossly visible nodules can be observed on the endocardial surface. The nodules ranged from 1-15 mm and were composed of well-defined clusters of large polygonal histiocytoid myocytes with abundant eosinophilic or foamy cytoplasm. The nuclei were round to oval, sometimes with evident nucleoli. These cells have been observed in all layers of the heart including the cardiac valves. The conduction system was involved in 28% of cases [3]. The cells of the HCM are believed to be transformed myocytes akin to Purkinje cells with an accumulation of mitochondria. The multicentric aggregates of these modified cells and the observation in infants are data in favor of HCM to be a hamartomatous lesion [1].

In VNC, the left ventricle is always affected. Right ventricular involvement is variably present. VNC affects both children and adults. Pediatric LVNC can frequently co-

exist with (a) other cardiac anatomical abnormalities including ventricular septal defect, anomalous pulmonary veins, coronary ostial stenosis, histiocytoid cardiomyopathy, polyvalvar dysplasia, and pulmonary stenosis [4]; (b) neuromuscular disorders; (c) metabolic diseases; and (d) genetic syndromes. The prevalence of isolated VNC in adults has varied from 0.01 to 0.26 of all adults referred to an echocardiography laboratory [15]. The histopathologic diagnosis is established when the noncompacted/compacted ratio, histologically verified, is >2. Besides, the papillary muscles are not well-formed [4]. Characteristic histologic features are anastomosing or polypoid endomyocardial trabeculation with endocardial fibroelastosis, deep intertrabecular recesses (sinusoids) communicating with the ventricular cavity, and thin compacted layer. The resultant endocardial-lined recesses are staghorn-shaped [4]. Due to the normally increased trabeculation in the right ventricle, the noncompacted layer should involve at least 75% of the thickness in order to consider right ventricle involvement. The lesion is postulated to result from an intrauterine developmental arrest that stops the process of normal trabecular compaction [16]. The weight of evidence supports this hypothesis. However, there is a controversy if LVNC can also be acquired as complete lesion is not always present at birth [17]. VNC seems to be a distinct myocardial phenotype with genetic heterogeneity. LVNC does not necessarily describe a disease; it rather describes an anatomical variant of ventricular structure. Thus, it may be a morphological trait or morphological expression of many different cardiomyopathies [18,19].

The presence of both HC and VNC occurring concurrently has only been previously reported six times all in infants or

children [4,8,9-11]. However, no case has been described in the adult.

The present is a case of sudden cardiac death in a 45-year-old man with an increased heart weight and multifocal involvement of both ventricles by HCM and VNC cardiomyopathy. He died suddenly while hiking. The association of both processes was an unexpected finding at autopsy. The death was linked to functional abnormalities of the cardiac histiocytoid cells, and it was favored by a state of abnormal development of the heart.

Our case presents features of congenital lesion, namely: (1) the hamartomatous histiocytoid cells appeared widely disseminated as subendocardial groups; (2) VNC cardiomyopathy has origin in an abnormal cardiac development; (3) this lesion was also associated with multiple disorganization zones of the myocytes. These zones have been observed in some cases of VNC cardiomyopathy [5].

In conclusion, the presence of both HCM and VNC occurring concurrently suggests an embryogenic defect of development in which noncompaction phenotype represents a trait shared by different cardiac conditions. The association of both cardiomyopathies although rarely can occur in the adult.

**The authors declare no conflict of interest**

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Color should be used for any figures in print

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**Figure captions**

**Fig. 1.** Cardiac gross appearance. (A) Biventricular noncompaction. In the left ventricle, a compressed spongy parenchyma can be seen. In the right ventricle, the pattern is of anastomosing broad trabeculae. There is absence of well-formed papillary muscles. (B) Raised, yellowish endocardial nodules are seen predominantly in the left ventricle. (C) The trabeculae simulate papillary muscles. Close up view of prominent endocardial yellow nodules are seen in (D).

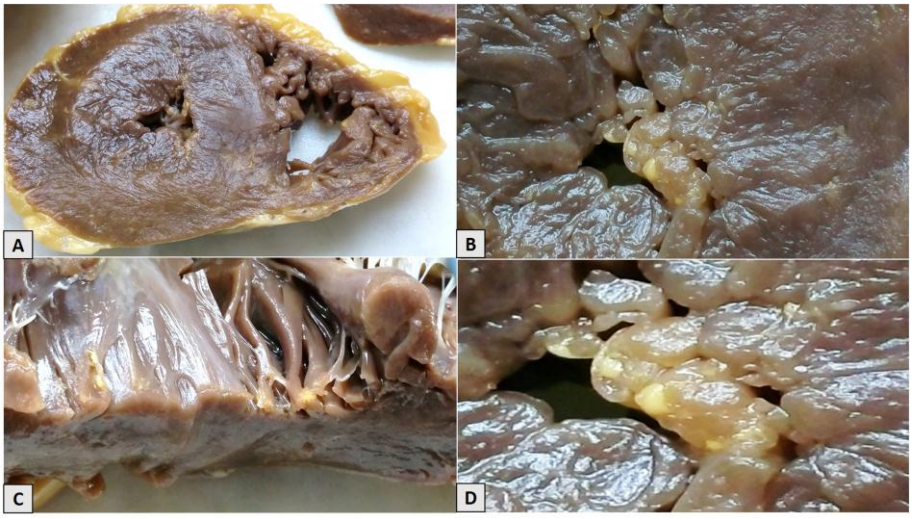

**Fig. 2.** Ventricular noncompaction associated with histiocytoid cardiomyopathy. (A) Anastomosing trabeculae resulting in irregular endocardial lined spaces (H&E, x40). (B) Groups of adipocytes replace the lost myocardial cells (H&E, x40). (C) Subendocardial well-defined collections of characteristic histiocytoid myocytes can be observed (H&E, x200). (D) There is a fairly demarcation between normal myocardium and histiocytoid cells (H&E, x400).

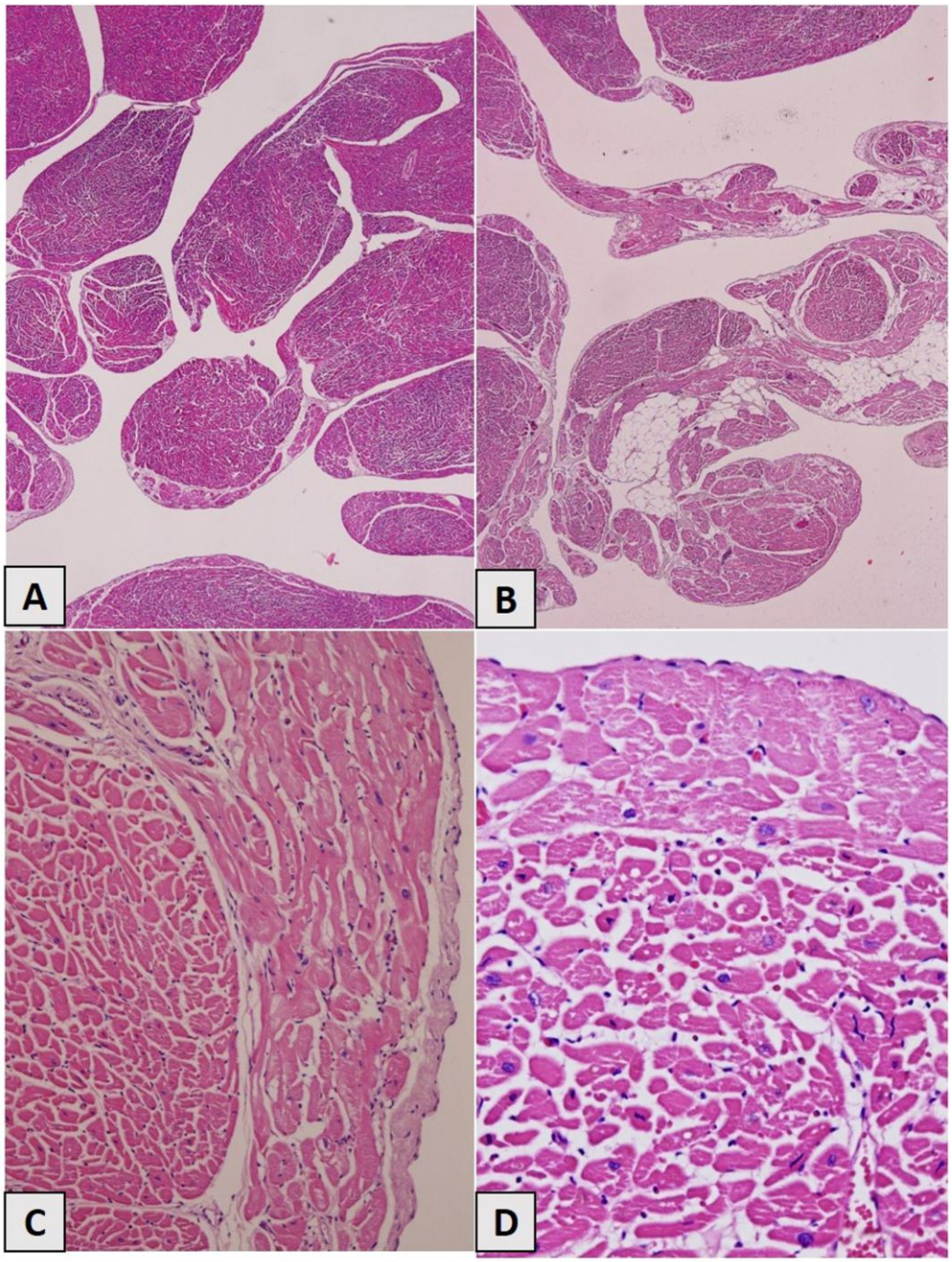

**Fig. 3.** Morphology of the histiocytoid cells. (A) Top: Subendocardial well-delimited cluster of histiocytoid pale cells making prominence towards the cardiac cavity (H&E, x10). Bottom: Cytoplasmic limits are inconspicuous. Nuclei are large with visible nucleoli (H&E, x40). (B) Large polyhedral cells with oncocytic transformation (H&E, x20). (C) Elongated cells remembering Purkinje cells (H&H, x40). (D) Cells are larger than cardiac muscle cells but have fewer myofibrils. Contractile filaments are displaced to the periphery of the cells (Masson trichrome, x40).

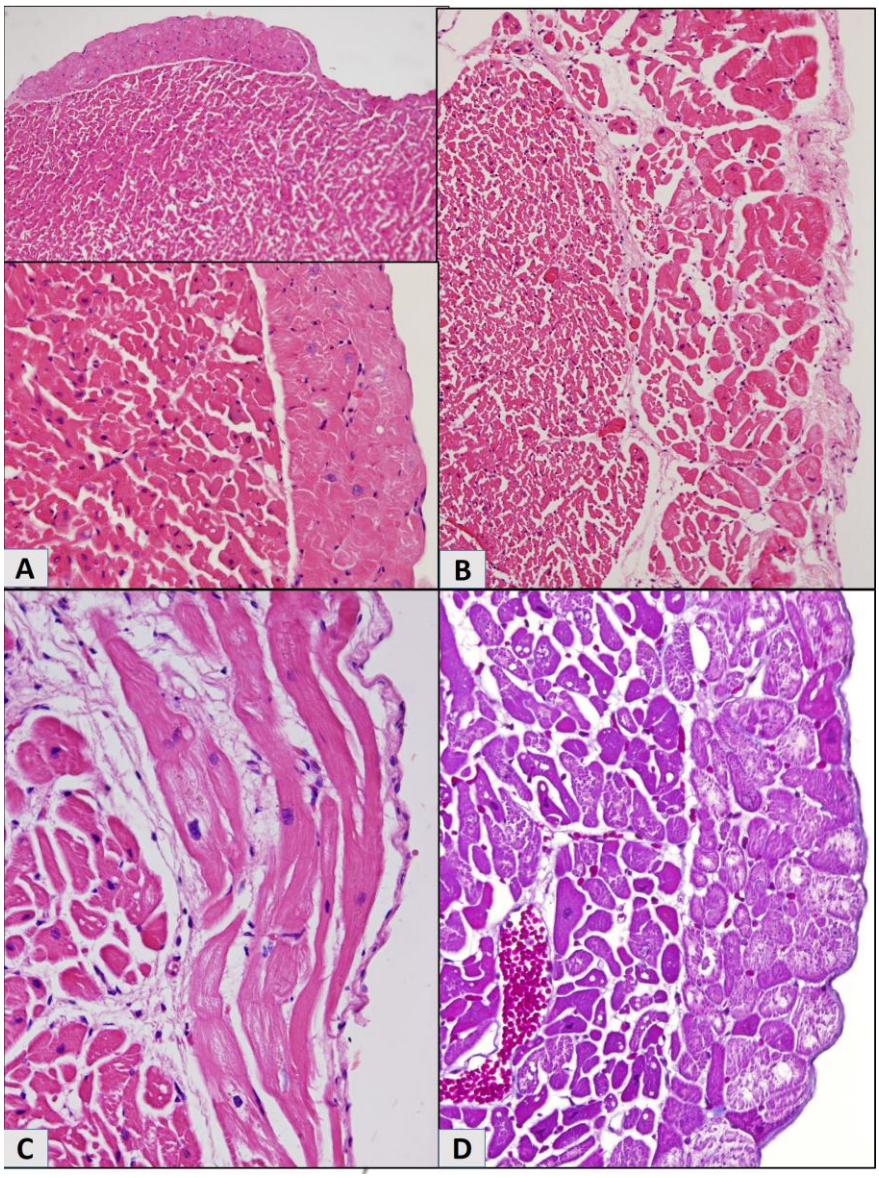

**Fig. 4.** Coronary intimal xanthoma and myocardial disorganization. (A) Left anterior descending coronary artery showing a focal accumulation of fat-laden macrophages in the intima (H&E, x200). (B) Area of myocardial disorganization (H&E, x200).

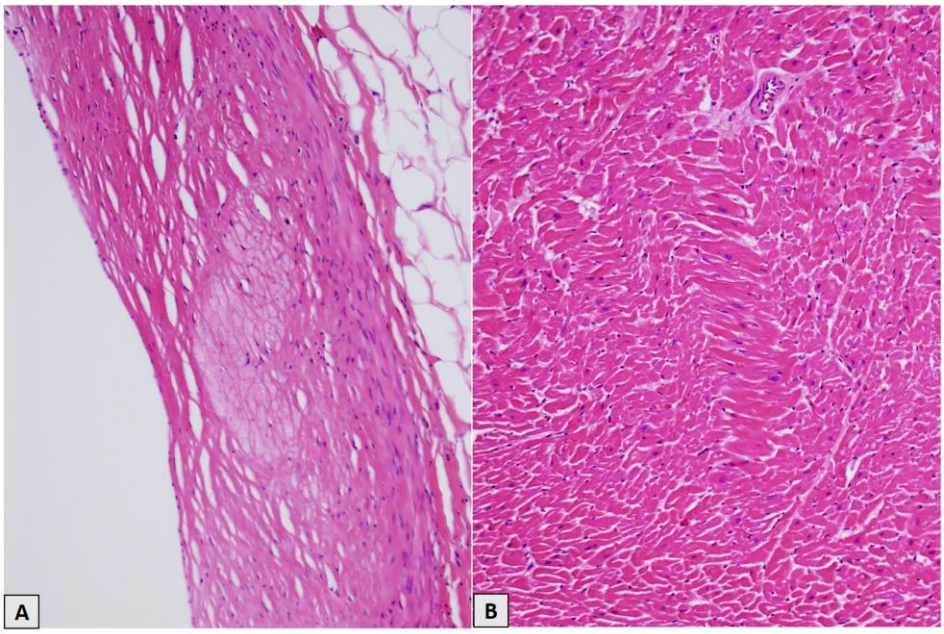

**Fig. 5.** Immunohistochemical study. Subendocardial nests of histiocytoid cardiomyopathy. These cells are reactive for (A) desmin (x200), (B) antimitochondrial antibody (x200), (C) myoD1 (x200), and (D) muscle specific actin (x400).

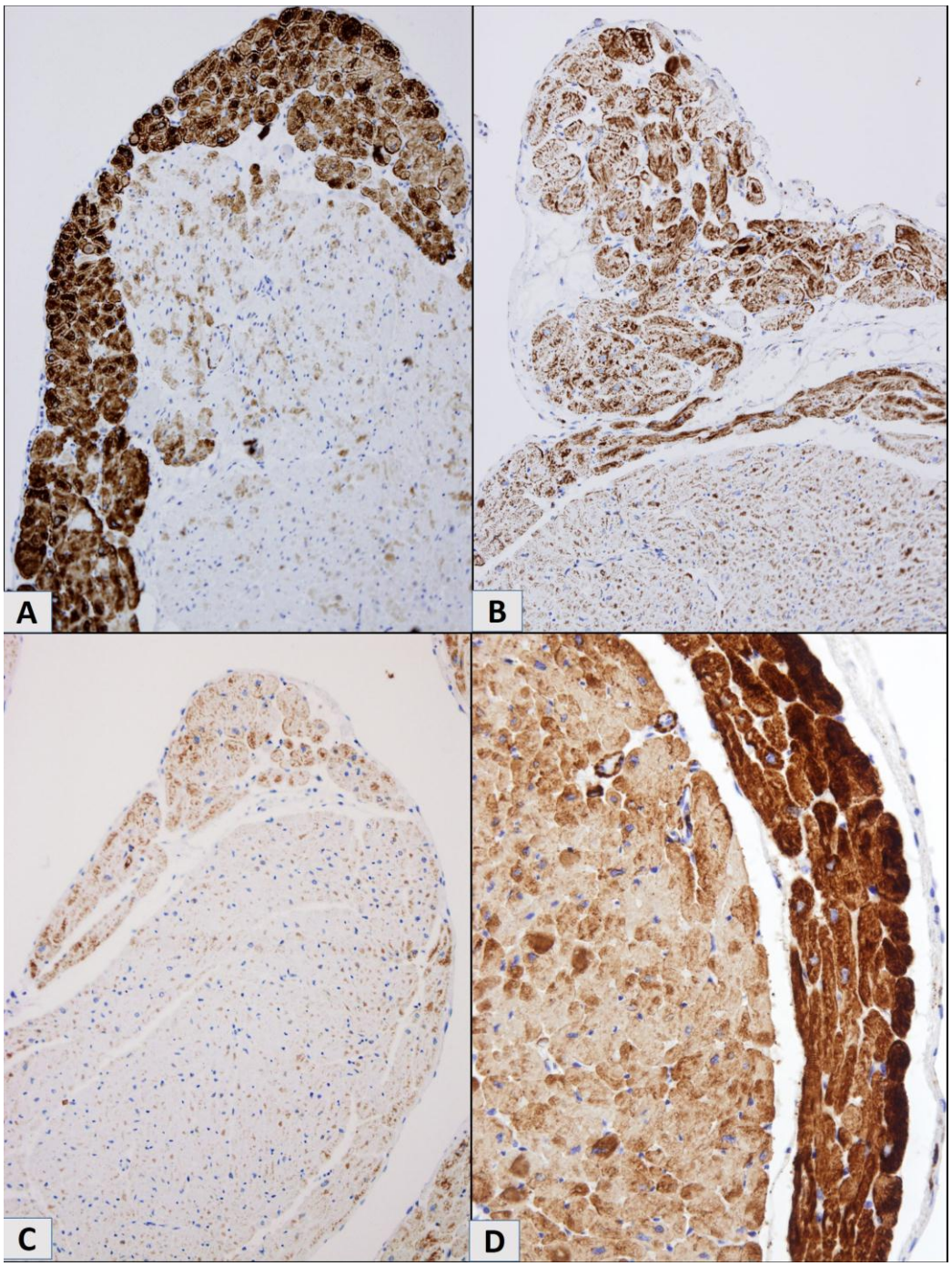

**Fig. 6.** Histiocytoid cells are intensely positive for myoglobin (x400).