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# A phenotypic variant of bovine dilated cardiomyopathy expressing lipofuscin-pigmented autophagic vacuoles in cardiomyocytes

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**Case Report**

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# Abstract

*Bovine dilated cardiomyopathy* (BDCM) has been described predominantly in the Holstein-Friesian breed worldwide, whereas *autophagic vacuolar cardiomyopathy* (AVCM) has been less frequently reported in humans. Of comparative pathologic significance, both consistently exhibit sarcoplasmic vacuoles in cardiomyocytes. Pathologic examination was conducted on an 8-year-old Holstein-Friesian slaughtered dairy cow that was clinically diagnosed with idiopathic heart failure. Grossly enlarged with prominent dilation of the right ventricle, the heart histopathologically exhibited distinctive myocardial lesions characteristic of CM. Among a variety of regressive morphologic changes observed in cardiomyocytes were sarcoplasmic deposition of autofluorescent lipofuscin and substantial appearance of lipofuscin-pigmented vacuoles that were considered to be autophagic ones. There was also a marked interstitial fibrosis associated with infiltrates of small numbers of $CD3^+$ T cells and macrophages that phagocytosed lipofuscin pigments. Viewed from a histopathogenetic perspective, the myocardial lesions were likely to be relevant to an autophagy-related process involved in lipofuscinogenesis. Although a disease entity of AVCM was a consideration, this bovine case would be most appropriate to be categorized as a phenotypic variant of BDCM, on the basis of the breed occurrence, clinical characteristics, gross findings, and nature/severity of the histopathologic lesions in the myocardium.


# Background

In veterinary medicine, *bovine dilated cardiomyopathy* (BDCM) is a condition that is associated with an unfavorable prognosis and has long been recognized as a subgroup of primary heart diseases. BDCM has been described in cattle worldwide, principally in the Holstein-Friesian breed (Nart et al. 2004; Leifsson and Agerholm 2004; Ohfuji 2016, 2020) and occasionally in other specific breeds (Nart et al. 2003; Riedi et al. 2018). Studies have verified that BDCM is an autosomal recessive genetic disorder (Dolf et al. 1998; Guziewicz et al. 2007; Owczarek-Lipska et al. 2009). Histopathology of BDCM consistently comprises a variety of myocardial lesions, characterized by a mixture of atrophied and hypertrophied cardiomyocytes with vacuolated and necrotic changes and interstitial fibrosis (Nart et al. 2003, 2004; Leifsson and Agerholm 2004; Ohfuji 2016, 2020).

In human medicine, among a wide spectrum of primary heart diseases are 2 distinct subgroups: one is DCM; the other, *autophagic vacuolar cardiomyopathy* (AVCM). DCM is the most common form of myocardial disease in humans (van der Klooster et al. 2015; Saito et al. 2016; Mitrut et al. 2018; Kanamori et al. 2022) and has many histomorphologic similarities to BDCM. Known to develop as a hereditary determined or drug-induced condition, on the other hand, AVCM have been less frequently reported in which autophagic vacuoles (AVs) accumulate in cardiomyocytes as a common histopathologic hallmark (Nishino et al. 2000; Daniels et al. 2013). According to current understanding, these AVs play a major role in a catabolic pathway (autophagy) via lysosomal degradation for cytoplasmic material in cardiomyocytes (Terman and Brunk 2005; De Meyer and Martinet 2008; Gatica et al. 2022). Occurrence of myocardial diseases identical with AVCM has been documented in experimental animals (Tanaka et al. 2000; Miyata et al. 2006) but not in livestock including cattle.

Herein reported is a bovine case of idiopathic heart failure, a variant BDCM, which had not only clinical signs, gross and histopathologic features characteristic of BDCM, but also such AVs as those in AVCM.

## Case presentation

A Holstein-Friesian dairy cow that had been raised at a farm showed a 10-day history of idiopathic heart failure at the age of 8 years. Clinical signs and symptoms began abruptly and progressed rapidly. A poor prognosis was predicted by the referring veterinarian, and then the cow was slaughtered at the owner's request. Antemortem examination revealed lethargy, exercise intolerance, a wide-based stance of the forelegs, subcutaneous edematous swelling of the dewlap, jugular venous engorgement, and tachycardia (120 beats/minute). The animal was processed according to the guidelines for the disposal of animals on the basis of the Act on Welfare and Management of Animals in Japan (Act No. 105 of October 1, 1973). At postmortem examination, subcutaneous edema in the thoracic and abdominal regions, subserosal edema in the alimentary tracts (particularly the abomasum, small and large intestines), and ascites were observed. The heart was enlarged with all the chambers dilated. The right ventricle was more prominently dilated with thinner ventricular wall, and the myocardium looked diffusely paler. Additionally found were hepatic congestion and edematous swellings of lymph nodes attached to the thoracic and abdominal visceral organs. For histopathologic examination, tissue samples including heart, other representative visceral organs, and thigh muscles (biceps femoris, semimembranosus, semitendinosus) were fixed in 10% neutral-buffered formalin and processed to paraffin blocks. All sections were stained with hematoxylin and eosin (HE) and periodic acid-Schiff (PAS).

Histopathologically, the heart exhibited distinctive myocardial lesions characteristic of CM. Myocardial lesions were more severe in the right ventricular free wall than in other areas and consisted of a wide range of regressive changes in large numbers of cardiomyocytes. These morphologically altered cardiomyocytes displayed a disarrayed arrangement, pronounced variation in cross-sectional sarcoplasmic area due to varying degrees of atrophy or hypertrophy, scarcity (decrease in number) of myofibrils, hyalinization (homogenous hypereosinophilia without demonstrable cross-striations), lipofuscin deposition, or sarcoplasmic vacuolation (Fig. 1a). Occasionally necrotic cardiomyocytes with macrophage were present and nuclear pleomorphism – variation in nuclear size and bi- or multinucleation – was observed in a few cardiomyocytes.

The sarcoplasmic vacuoles in cardiomyocytes were the most frequently recognized noticeable finding, such that many cardiomyocytes in severely affected myocardial lesions had vacuolated sarcoplasm, typically up to 26% of cardiomyocyte population per x 200 field. These sarcoplasmic vacuoles were characterized by variably sized, usually clear, round or slightly elongated spaces (< 50 μm in diameter). Cardiomyocytes had varying numbers of such vacuoles that made a single, multiple discrete, or overlapped arrangement (Fig. 1b). Occasional vacuoles were partially demarcated from sarcolemma by a membranous structure (Fig. 1c). Some of the sarcoplasmic vacuoles were nonstaining (empty), but the others contained varying amounts of lipofuscin granules (Fig. 2). No matter whether sarcoplasmic or

intravacuolar deposition, the lipofuscin showed PAS-positive staining (Fig. 2, inset top) and emitted, in fluorescence microscopy, yellow-orange autofluorescence under ultraviolet light (not shown).

The interstitial connective tissue of the lesional myocardium exhibited marked fibrosis characterized by a diffuse collagen-fiber deposition that was shaped into an abundant fibrillar background (Fig. 1a, Fig. 2). In these fibrotic interstitial areas, there was a proliferation of fibroblasts and fat cells admixed with small numbers of interspersed macrophages and lymphocytes. Immunohistochemistry (IHC) with a mouse monoclonal anti-human CD3 antibody (clone F7.2.38, dilution 1:50; Dako, Glostrup, Denmark) was performed using an EnVision horseradish peroxidase (HRP)-labeled polymer immunoperoxidase staining technique (Dako) and revealed the lymphocytes to be $CD3^+$ T cells (Fig. 2, inset bottom). Sections of a mixed thymoma in a cow (Ohfuji 2014) and intestinal epithelial cells within the case section were used as positive and negative controls, respectively. Some macrophages phagocytosed lipofuscin pigments (Fig. 2). The endocardial layer partially showed degenerate elastic fibers that exhibited multifocal segmental swellings and fragmentation. Intracardiac blood vessels and autonomic nerve bundles were unremarkable.

Extracardiac visceral lesions consisted of congestive liver, edematous distension of the hepatic and renal hilar connective tissue, and acute focal bronchiolitis. The thigh muscles had no any aberrations.

## Discussion and conclusion

Most but not all the clinical signs, gross, and histopathologic features of this bovine heart were consistent with those of previously reported descriptions of BDCM (Nart et al. 2003, 2004; Leifsson and Agerholm 2004; Riedi et al. 2018; Ohfuji 2016, 2020). Among a variety of histopathologic changes in cardiomyocytes were sarcoplasmic vacuoles that are considered important in terms of pathologic differential diagnosis. Several authors (Takemura et al. 2017) alluded to cardiomyocyte vacuolation as follows: “By itself, this finding has little diagnostic value, but may have important clinical implications when the vacuolar contents are of etiological significance (e.g., accumulation of abnormal metabolites), ….” The sarcoplasmic vacuoles were different from fatty change inasmuch as they were not necessarily empty but contained lipofuscin. Taking into account that the PAS-positive reaction can be demonstrated by various kinds of intracellular storage materials other than lipofuscin, another differential to consider, which was ruled out, is glycogen storage disease. Unlike the present bovine case, glycogen storage disease may usually involve not only myocardium but also skeletal muscle (Reichmann et al. 1993). In human cases of DCM, several authors regarded sarcoplasmic vacuoles as hydropic change (Mitrut and Stepan 2018). Substantial meaning of vacuolated cardiomyocytes has not necessarily been clarified for most reported cases of BDCM. One ultrastructural study on BDCM revealed mitochondrial vacuolation due to partial loss of cristae in cardiomyocytes (Furuoka et al. 2001). This finding was probably identical with mitochondrial vacuolar degeneration in cardiomyocytes of human patients with heart failure (Chaanine 2019). As it turned out, the observed sarcoplasmic vacuoles that were occasionally membraned would be most likely to be consistent with AVs (Terman and Brunk 2005; De Meyer and Martinet 2008; Gatica 2022).

The appearance of myocardial autophagy was similar to if not identical with what is known about human DCM which is associated with substantial cardiomyocyte involvement by AVs (van der Klooster et al. 2015; Saito et al. 2016; Kanamori et al. 2022). In those cases of DCM, which were studied by using light and/or electron microscopy, large numbers of cardiomyocyte AVs were identified and proved to contain glycogen granules, ribosomes, damaged mitochondria, and other degenerated organelles. The available evidence suggests that myocardial autophagy is involved in both the progression and prevention of many human heart diseases (De Meyer and Martinet 2018; Gatica et al. 2022). It has been shown that myocardial autophagy, an important cellular process thereby cardiomyocytes degrade and recycle their own components at molecular levels, is involved in the development of important cardiac pathologies, including CM, myocardial hypertrophy, ischemic heart disease, and cardiac remodeling (Terman and Brunk 2005; Nishida et al. 2009; Zech et al. 2020; Gatica et al. 2022; Bielawska et al. 2023).Taking this commonly held and prevailing view into account, there is a likelihood that this myocardial autophagic pathway was implicated in the development of CM described here.

Myocardial lipofuscinosis, especially lipofuscin-pigmented AVs in cardiomyocytes, was another noticeable finding in CM of the cow reported here. Lipofuscin accumulates within a long-lived, post-proliferative cell types, including cardiomyocytes, neurons, and retinal pigment epithelial cells (Porta 2002; Höhn and Grune 2013; Dontsov and Ostrovsky 2024). Investigations have indicated that age-related decline in autophagy favors an accumulation of lipofuscin that may directly impair cardiomyocyte function (De Meyer and Martinet 2008; Walter et al. 2025). Therefore, ageing may be taken into consideration for the cow (aged 8 years) of this study. Also suggested is that under pathologic environments such as conditions of oxidative stress, aggregated intracellular proteins may be taken up by autophagy and react further with other cellular components, forming lipofuscin, which accumulates in the lysosomal system over time (Keller et al. 2004; Walter et al. 2025). The light-microscopically identified lipofuscin-pigmented AVs in cardiomyocytes would likely to be an uncommon finding in heart diseases of cattle, being only once reported in a cow that suffered from BDCM with concurrent myocarditis (Ohfuji 2020). In that cow, however, not only did lipofuscin-pigmented AVs contain a lesser amount of lipofuscin pigments and/or amorphous materials, but AVs-associated cardiomyocytes also appeared to indicate a much lesser severity and extent than those seen in the presently described cow.

With the frequent occurrence of AVs in cardiomyocytes, a differential is AVCM. Some authors have investigated patients with AVCM and myopathy caused by a primary deficiency of LAMP2 (lysosome-associated membrane protein 2), providing evidence that AVs in cardiomyocytes contained cytoplasmic degradation products and glycogen (Nishino et al. 2000). Other authors have made ultrastructural analysis of cases with chloroquine- or hydroxychloroquine-induced AVCM and revealed that some patients exhibited a marked increase in AVs which contained electron dense material, lamellated membrane structures, and curvilinear bodies (Daniels et al. 2013). Both, though, demonstrated no finding of lipofuscin-pigmented AVs. Morphologically identical heart diseases with AVCM have been described in experimental animal models, such as LAMP2-deficient mice (Tanaka et al. 2000) and cardiomyopathic hamster (Miyata et al. 2006). Likewise, AVs in these animals lacked a finding of lipofuscin deposits. What seems to be more important is that pathology of AVCM may be so monotonously uniform. With the

exception of AVs, cardiomyocytes in AVCM are otherwise unremarkable or minimally diseased (Nishino et al. 2000; Tanaka et al. 2000; Miyata et al. 2006; Daniels et al. 2013), contrasting with pathology of human DCM (van der Klooster et al. 2015; Saito et al. 2016; Mitrut et al. 2018; Kanamori et al. 2022), BDCM (Nart et al. 2003, 2004; Leifsson and Agerholm 2004; Riedi et al. 2018; Ohfuji 2016, 2020), and CM presented in the current cow, all of which have represented a wide variety of regressing features in cardiomyocytes. This difference in the nature and severity of cardiomyocyte involvement may fail to substantiate the present bovine case to be a distinct entity of AVCM. On the basis of the histomorphologic and comparative pathologic features, it is most appropriate to consider the presently reported CM to be more similar in expression profile to BDCM than to AVCM.

Most likely interstitial fibrosis associated with infiltrates of T cells and macrophages, as seen in this cow, is rare in BDCM, with only 2 published reports of the condition presenting with T-cell infiltrated fibrotic interstitial connective tissue of the myocardium (Nart et al. 2003, 2004). Contrastively, interstitial fibrosis representing these immune-cell infiltrates has been observed more frequently in human cases of DCM (Noutsias et al. 2002; Cojan-Minzat et al. 2021; Jeyalan et al. 2023; Angelotti et al. 2026). Of prime clinical significance, an increased infiltration of T cells and macrophages is acknowledged to actually promote adverse remodeling and myocardial fibrosis in hearts with DCM (Noutsias et al. 2002; Cojan-Minzat et al. 2021; Jeyalan et al. 2023; Angelotti et al. 2026), so that it may be a formidable change impairing heart function and increasing morbidity and mortality in patient with DCM (Cojan-Minzat et al. 2021; Kayvanpour et al. 2024). In the presently described CM, there was evidence that macrophages phagocytosed lipofuscin. Even though it remained unproven whether lipofuscin undergoing phagocytosis arose from necrotic cardiomyocytes with sarcoplasmic lipofuscinosis or was derived from collapsed lipofuscin-pigmented AVs, or both, it may be noteworthy that activated macrophages played a pivotal role in engulfing unnecessary substance and removing it from the lesional myocardium.

In conclusion, the breed occurrence, clinical presentations, gross findings, and histopathologic lesions of the heart associated with interstitial fibrosis infiltrated by macrophages and T cells are considered supportive of the likelihood that the presently described CM would be categorized as a phenotypic variant of BDCM. Viewed from a histopathogenetic perspective, this variant BDCM, which was characterized by substantial appearance of lipofuscin-pigmented AVs in cardiomyocytes, appears to be associated with an autophagy-related process that is involved in myocardial lipofuscinogenesis.

# Declarations


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### Declaration of competing interests

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# Figures

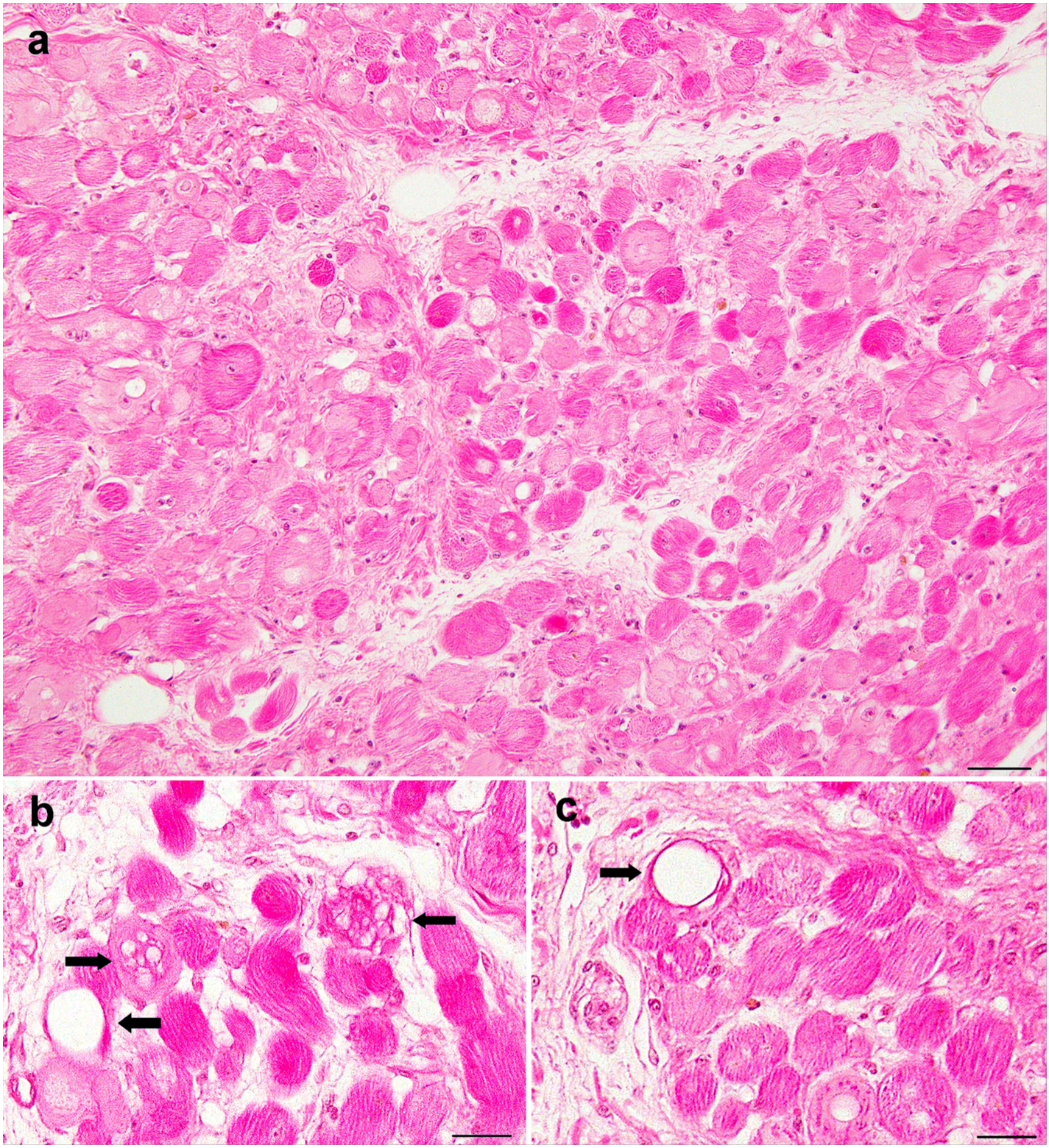



**Figure 1**

Histopathologic findings of a cow with cardiomyopathy. (a) Cardiomyocytes show variable sizes, hypereosinophilic sarcoplasm or autophagic vacuoles. Collagen fiber deposition with scattered cell infiltrates is seen in the interstitial connective tissue. Hematoxylin and eosin (HE). Bar, 80 μm. (b) Variable numbers of autophagic vacuoles (arrows) in cardiomyocytes. HE. Bar, 50 μm. (c) Note membraned autophagic vacuole (arrow). Bar, 50 μm.

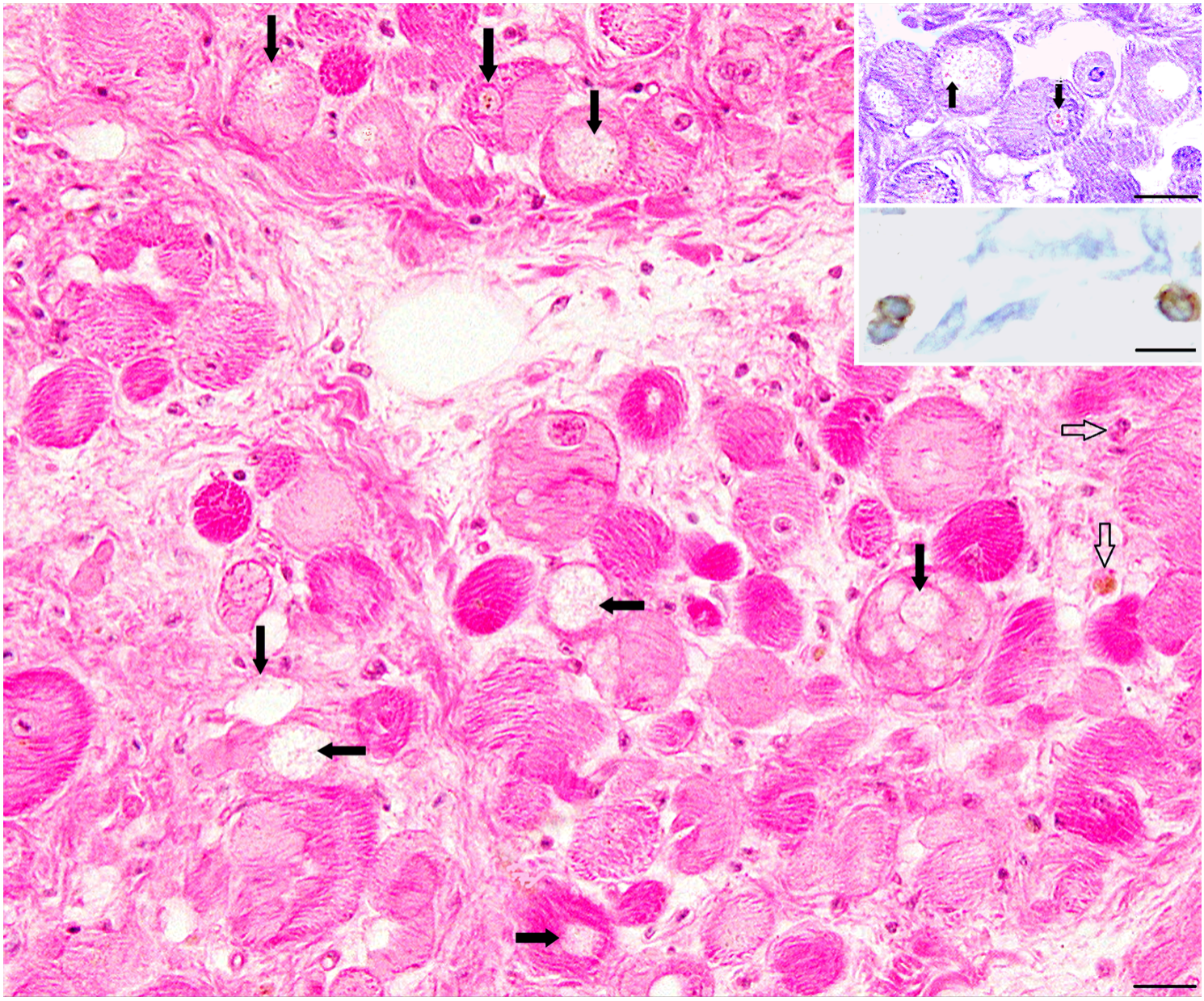


**Figure 2**

Histopathologic findings of a cow with cardiomyopathy. Higher magnification of Fig. 1(a). Variably-sized cardiomyocytes have autophagic vacuoles that contain lipofuscin granules (closed arrows). A few T cells and macrophages (open arrows) phagocyting lipofuscin are seen in the interstitial connective tissue that presents with collagen fibre deposition. HE. Bar, 40 µm. Inset top: lipofuscin granules (arrows) are positive for periodic acid-Schiff (PAS). Bar, 40 µm; Inset bottom: immunolabelling of T cells for CD3. IHC. Bar, 20 µm.