Short Communication

Cardiac myxoma in the pulmonary trunk of a canine: presence of mesenchymal stem-like cells

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Abstract

Cardiac myxoma is a rare disease in dogs. Its histogenic origin has not yet been established, but the involvement of mesenchymal stem cells has been suggested in humans. Here we report an encapsulated and benign cardiac myxoma located at the entrance to the pulmonary trunk of the heart of an 8-year-old male Yorkshire Terrier dog presenting sudden death in the absence of clinical symptoms related to cardiac alterations. Hematoxylin/eosin staining demonstrated the mixoid origin of the myxoma, showing abundant hypocellular stroma with polygonal cells, while immunohistochemistry (IHC) corroborated its mesenchymal lineage with the detection of vimentin and α-SMA positive cell populations. In addition, IHC showed some cell populations in the stroma to be immunoreactive to the pluripotency markers Oct4 and ALDH1. In conclusion, this is the first report of the presence of mesenchymal stem-like cells with an Oct4 and ALDH1-positive IHC profile in a canine cardiac myxoma.

Keywords: canine cardiac myxoma, mesenchymal tumor, mesenchymal stem-like cells

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Introduction

Primary and secondary neoplasms in canines are uncommon (Aupperle *et al*., 2007), with controversy over the frequency of persistence. Ware found that 83% were primary neoplasms (Ware and Hopper, 1999), while others reported 66% of metastasis cases (Aupperle *et al*., 2007). Neoplasms can occur in any area of the heart (Treggiari *et al*., 2017), but, unlike humans, almost all of primary origin affect the right side of the heart, especially the right atrium (Ware and Hooper, 1999) and rarely affect the left ventricle (Fernandez-del Palacio *et al*., 2011). Hemangiosarcoma is the most common tumor in canines, and cardiac myxoma has only been sporadically reported (de Nijs *et al*., 2016; Treggiari *et al*., 2017).

The World Health Organization defines myxoma as a neoplasm composed of stellate and globose mesenchymal cells within a myxoidstroma (Di Vito *et al*., 2015). The origin of these tumors is not yet clear. Although it is accepted that the histogenesis is endocardium-like (Di Vito *et al*., 2015), in light of the current knowledge available, it is very likely that cardiac myxomas are derived from a pluripotent mesenchymal stem cell or a subendothelial vasiform reserve cell located around the oval fossa and the surrounding endocardium (Raith, 2010). These tumors are rare and benign (Akkoc, 2007) and were first reported in canines in 1959 (Roberts, 1959). The few cases described to date mainly involve the right atrial ventricular valve (Machida *et al*., 2003).

In humans it is known that benign cardiac myxomas originate from pluripotent (Vaideeswar& Butany, 2008) or multipotent mesenchymal cells (Grubb *et al*., 2018); however, these are sporadic or familial, the embolism and tumor presentation are associated with recurrent obstructive and constitutional symptoms and the tumor is only incidentally diagnosed by echocardiography. (Vaideeswar& Butany, 2008). Here we describe for the first time the involvement of mesenchymal stem-like cells in a cardiac myxoma of a dog.

Materials and Methods

This study was conducted in an 8-year-old male Yorkshire Terrier dog weighing 3.5 kg. The clinical history over the previous year described the presence of pruritic dermatitis with extensive alopecia. Cytology reported *Demodex canis*, dermatophytes and bacteria that were treated with oral ivermectin according to doses recommended by the manufacturers (200 mcg/kg/week/4dose), plus ketoconazole (10mg/kg/15d) and oral cephalexin (20mg/kg/12hr). The animal had no previous history of heart disease. The dog died suddenly at the owner's house and necropsy was performed immediately following a routine protocol.

When the heart was opened, a 2.5 cm long conical and semi-hardened tumor mass was found at the entrance to the pulmonary trunk (Figure 1-A) A 0.5x1 cm; a biopsy of the tumor was obtained and fixed in 10% buffered formalin.

The histological section was stained with hematoxylin/eosin for histopathological evaluation, which showed abundant hypocellular myxoid stroma, star-shaped and other polygonal scattered cells with dense irregular nucleii and some mononuclear inflammatory cells (Figure 1-B). These characteristics are consistent with the diagnosis of cardiac myxoma as reported by Machida (2003) (Machida *et al*., 2003). Blood clots were evident in blood vessels in the lung (Figure 1-C).

To identify the constituent cells within the tumor mass, immunohistochemistry (IHC) was performed using monoclonal antibodies for vimentin (Sigma)(Figure 2-A) and alpha-smooth muscle actin (α-SMA)(Millipore, Sigma) (Figure 2-B), demonstrating their mesenchymal origin. Positive reactivity to the monoclonal antibody ALDH1(Sigma) (Figure 3-A) and Oct4 (Invitrogen)(Figure 3-B) markers determined the presence of cells with a pluripotent phenotype in the hypocellular stroma of the tumor. Paraffin-embedded tissue sections were pre-treated by boiling in citrate buffer (pH 6.0) for 20 minutes to perform the IHC following the protocol suggested by the manufacturer of the Super PictureTM 3rd Gen IHC kit (Novex Life Technologies).

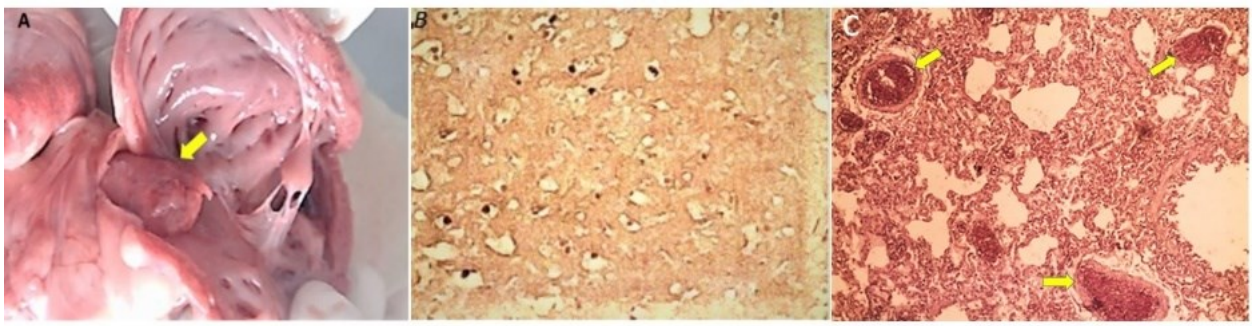

Figure 1 Tumor in the trunk of the lung. (A) conical tumor at the entrance to the pulmonary trunk (yellow arrow), (B) tumor histology showing the characteristic stroma of this type of tumor; (C) lung with clots in blood vessels. 10X. H/E.

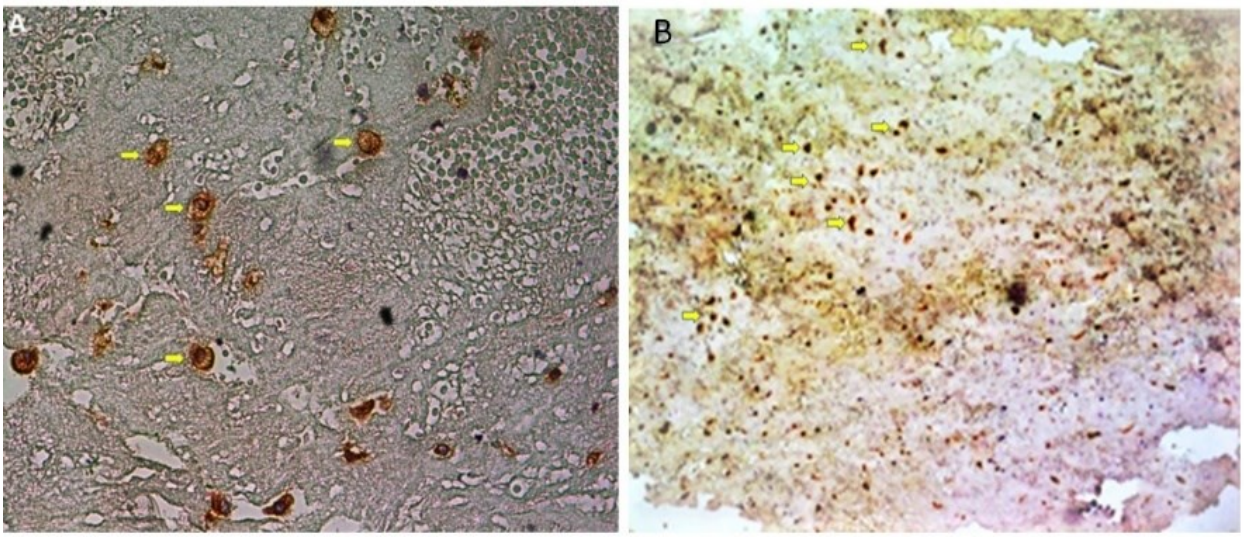

Figure 2 (A) Vimentin+ cells (yellow arrow), 20X and (B) α-SMA+ in the tumor stroma (yellow arrow). Immunohistochemistry (peroxidase) 10X.

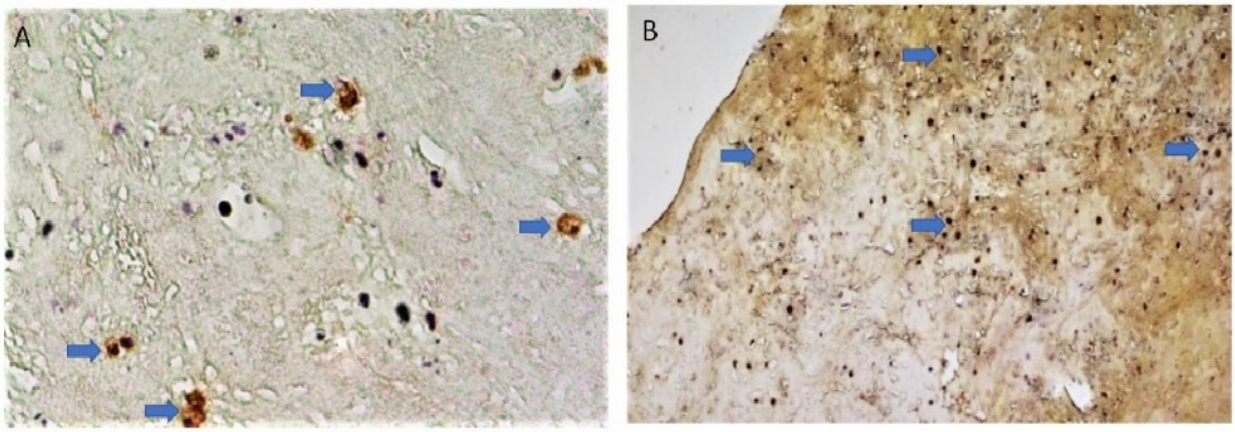

Figure 3 (A) ALDH1+ cells. 20X (arrows) and (B) Oct4+ cells in the tumor stroma (arrows). Immunohistochemestry (peroxidase). 10X.

Results and Discussion

The clinical presentation of cardiac myxoma in dogs is that of a highly sporadic tumor (Treggiari et al., 2017), which is most frequently found in the right atrium (Akkoc et al., 2007). It has a variable clinical presentation with non-specific constitutional symptoms and clinical signs which may not be evident until sudden death, as described in the present case. The myxoma in this case was considered to be a primary tumor due to the absence of evidence of neoplasms in other organs at necropsy. There is debate in this regard, since some authors have reported that 84% of cardiac myxomas are primary tumors (Ware & Hopper, 1999) while other studies conclude that only 41% are primary (Aupperle *et al*., 2007).

The histogenesis of cardiac myxoma is not yet clear, with histology showing different cell types including epithelial, endothelial, myogenic, myofibroblastic and neural cells (Roy *et al*., 2011). Recent studies indicate that cancer stem cells are responsible for cancer initiation and metastasis (Wang *et al*., 2015).

In the present study, the involvement of mesenchymal stem-like cells in the tumor structure was determined by the presence of cells expressing positive immunoreactivity to the pluripotency markers Oct4 and ALDH1. This suggests that these cells are mesenchymal stem-like cells because of their phenotype and that they play an important role in the origin and/or progression of cardiac myxoid tumor in canines, coinciding with the suggestion that this tumor is derived from a pluripotent mesenchymal cell (Raith, 2010). Nonetheless, according to other authors, the origin of this type of tumor is not well defined (Di Vito *et al*., 2015).

In humans (Song *et al*., 2016) the presence of cell surface markers CD19, CD45 and CD44 has been reported in the mucopolysaccharide rich matrix of the myxoma by IHC study, thereby ratifying that this tumor could originate from mesenchymal stem cells. Although there is no agreed set of markers for this type of tumor, the present results confirm the mesenchymal origin of the tumor with one cell population being vimentin-positive and α-SMA-positive. On the other hand, transcription factor Oct4 is considered the universal marker of pluripotency and, therefore, its expression in the tumor cells suggests the participation of mesenchymal stem-like cells in the genesis of this tumor.

The IHC results of the present study demonstrate the mesenchymal origin of a primary cardiac myxoma located at the entrance of the pulmonary trunk in a dog, due to the presence of vimentin and α-SMA in the cell population and the expression of positive immunoreactivity for the multipotency markers Oct4 and ALDH1.

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