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Case Report

Primary paraganglioma-like dermal melanocytic tumor in a dog

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Abstract

Melanocyte-derived tumors are common in humans and dogs. Their natural presentation in dogs is comparable to that of humans. Therefore, the dog has been proposed as a model in comparative pathology. Melanocyte-derived tumors are highly heterogeneous neoplasms considered the great mimickers because, in rare presentations in humans, their histopathology may include other distinct, unexpected tissue images. The term paraganglioma-like dermal melanocytic tumor refers to a rare neoplasm with a neuroendocrine (paraganglioma) pattern documented in human beings. Twelve cases have been registered to date. A case with these characteristics is herein described in a dog's skin. To the best of the authors' knowledge, this is the first case of a dermal melanocytic tumor with the paraganglioma-like pattern described in veterinary pathology.

Keywords: dog, paraganglioma-like dermal melanocytic tumor, chromogranin A, HMB45, Melan A.

Introduction

The study of spontaneously occurring melanocyte-derived tumors in dogs has been emphasized in comparative oncology (9). Melanocyte-derived tumors have a high potential to develop unexpected divergent differentiation patterns (1). Remarkably, rare melanomas registered in men have also been recognized in dogs (10). The paraganglioma-like dermal melanocytic tumor (PDMT) has been included as a benign melanocyte-derived tumor subtype in humans (3,11). This tumor is rare, with few cases reported in humans (16). Herein, the first case of this neuroendocrine pattern is described in a dog.

Case Description

The clinician revised a six-year-old Siberian husky male due to a rapidly growing mass over the right scapula region. The lesion was an ovoid subcutaneous mass, mostly firm, and moveable, which appeared during an estimated 6 months by the date of clinical attention but with rapid enlargement during the last three weeks. The dog appeared to feel some pain in the site during exploration. The cytology informed a mesenchymal mass with neoplastic characteristics. Regional lymphatic nodes were not involved. Besides this suspicious mass, the dog was clinically healthy. The mass was excised in block. Its dimensions were 6 x 5 x 4 cm. The mass was firm at section, with a fleshy aspect and reddish pink color. Representative sections in all the mass were collected and fixed by immersion in 10% buffered formalin solution for 48 h and then routinely processed for histology. Subsequently, 4 µm sections were stained with H&E. Microscopically, the tumor was a moderate cellular multilobular mass, partially demarcated, unencapsulated, invading deep dermis and subcutaneous tissue. There was a focal area in which the neoplasm caused protrusion of the

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superficial dermis, provoking an ulcer on the epidermis. The excision was incomplete. The tumor was composed of numerous conglomerates of epithelioid cells tightly accommodated in small nests or long trabeculae. These organoid structures were circumscribed by fine strands of fibrous connective tissue (Fig. 1a,b). A different pattern, which included still nested but palisading spindle cells, appeared in some areas (Fig. 1c). The limiting fibrous connective tissue appeared hyaline in some zones. In these hyaline zones, an isolated and small focus of necrosis contained several necrotic cells with coarse melanin (Fig. 1d). Conversely, in the nested arranged pattern, the melanin contained in epithelioid cells was extremely scarce, occurring as small cytoplasmic granules or tiny, dust-like deposits hard to be encountered (Fig. 1f). The neoplastic cells were large and polygonal, with clear cytoplasm. The pleomorphism was moderated, mainly mild anisokaryosis (Fig. 1b). The mitosis count was low (2/10 HPF). A single focus with mature osseous matrix deposition was also recognized (Fig. 1e).

Furthermore, additional sections were labeled by immunohistochemistry (IHC) employing the two-step OptiView DAB IHC Detection kit, using the automated platform BenchMark-XT (Ventana/Roche Diagnostics; Comercial Biomédico JR, Monterrey, Mexico). The primary antibodies included those recommended for melanocyte tumors IHC diagnosis in humans, anti-SOX10 (SP267, rabbit monoclonal); -Melan A (A103 CONFIRM, mouse monoclonal); -melanosome (HMB45 CONFIRM, mouse monoclonal) and -S100 (4C4.9 CONFIRM, mouse monoclonal). The positive controls for all the mentioned immune assays were human melanoma tumors, whereas normal striated muscle was the internal negative tissue control, as recommended for negative controls in IHC (15). Furthermore, those IHC assays for neuroendocrine tumors in humans comprised anti-synaptophysin (MRQ-40, rabbit monoclonal) and -chromogranin A (LK2H10, mouse monoclonal). For these latter, the positive control was human paraganglioma tumor, and the internal negative tissue control was fibrous connective tissue. All the primary antibodies employed were ready to use (pre-diluted). The procedure was in accordance with the supplier recommendations (Ventana/Roche Diagnostics; Comercial Biomedico JR, Monterrey, Mexico). The rationale for using these primary antibodies was to identify this neoplasm as neuroendocrine or melanoma due to the carcinoid/neuroendocrine pattern on routine H&E and the rare, nested cells with melanin. Others have used these primary antibodies for the same purpose (1,5).

The immunoreactivity of the tumor to chromogranin A was graded with intermediate distribution (++) and moderate cytoplasmic immunostaining in dispersed cells (Fig. 2a; the positive control for comparison is presented in Fig. 2b). Synaptophysin resulted negative (Fig. 2 c, and the corresponding positive d). S100 also resulted negative (Fig. 2 e, and the positive control f). HMB45 showed intermediate (++) distribution with moderate immunostaining in nested cells (Fig 3. a, and positive reaction in the control b). Melan A also resulted in intermediate (++) distribution immunoreactivity and weak immunostaining in nested cells (Fig 3. c and the positive control d). Finally, SOX10 resulted negative (Fig. 3. e, and the positive control f).

Discussion

Despite recent advances in molecular biology, histopathology remains the gold standard for melanoma diagnosis (1,6,14). However, pathologists may encounter discrepancies in the diagnosis of melanocyte-derived neoplasms (6). Melanoma may appear to mimic other tumors of non-melanocyte origin, in which case there may also be an aberrant expression of antigens, particularly in amelanotic neoplasms (8). The melanocyte-derived primary tumors and their metastasis include a high potential for trans-differentiation (divergent differentiation), such as chondroid, osseous, rhabdoid, angiomatoid, and carcinoid-neuroendocrine patterns, among others (4,14). Therefore, the PDMT is a subtype with rare divergent characteristics (1,14). At least twelve cases with this pattern have been reported nowadays (16).

Most PDMT cases show immunoreactivity compatible with melanocyte-derived neoplasm markers. However, not all cases immunoreacted with all the markers. For instance, in the original description of eight cases of PDMT, only 4 of 8 cases resulted positive for Melan A, still the total was positive for other melanocyte markers (4). On the other hand, in the case of a 13-year-old girl and another in a 60-year-old man, both tumors resulted in negative for HMB45 but positive for other melanocytic markers (2,11). Therefore, these melanocytic tumors may occur with variable immunoreaction to melanocyte markers, such as the case herein described in a dog. The presence of melanin in the cytoplasm of the neoplastic cells is the undoubted mark of melanocytic tumor origin. However, in most cases, the pigment is absent or barely encountered in PDMT (4,16). These finding in the case herein described was the initial suspect of a melanocytic tumor because in some isolated areas (< 2%) the tumor showed rare cells with coarse melanin or others with scarce dust-like pigment as shown. Therefore, these tumors are mostly amelanotic. It has been described that melanin synthesis in selected types of amelanotic tumor cells (cell line Ab hamster melanoma) may drive these cells to an apoptotic cycle in vitro (12). That condition could have happened in this case because the zone with more melanin synthesis was a small necrotic focus with pyknotic nuclei. Moreover, focal or faint immunoreactivity to chromogranin A and/or synaptophysin occurred in cases of cutaneous melanomas in which the neuroendocrine pattern included pseudo rosettes formation (7). It has been mentioned that 37% of melanocytic skin tumors result weakly and focally positive to either chromogranin A and/or synaptophysin (5). Furthermore, primary cutaneous

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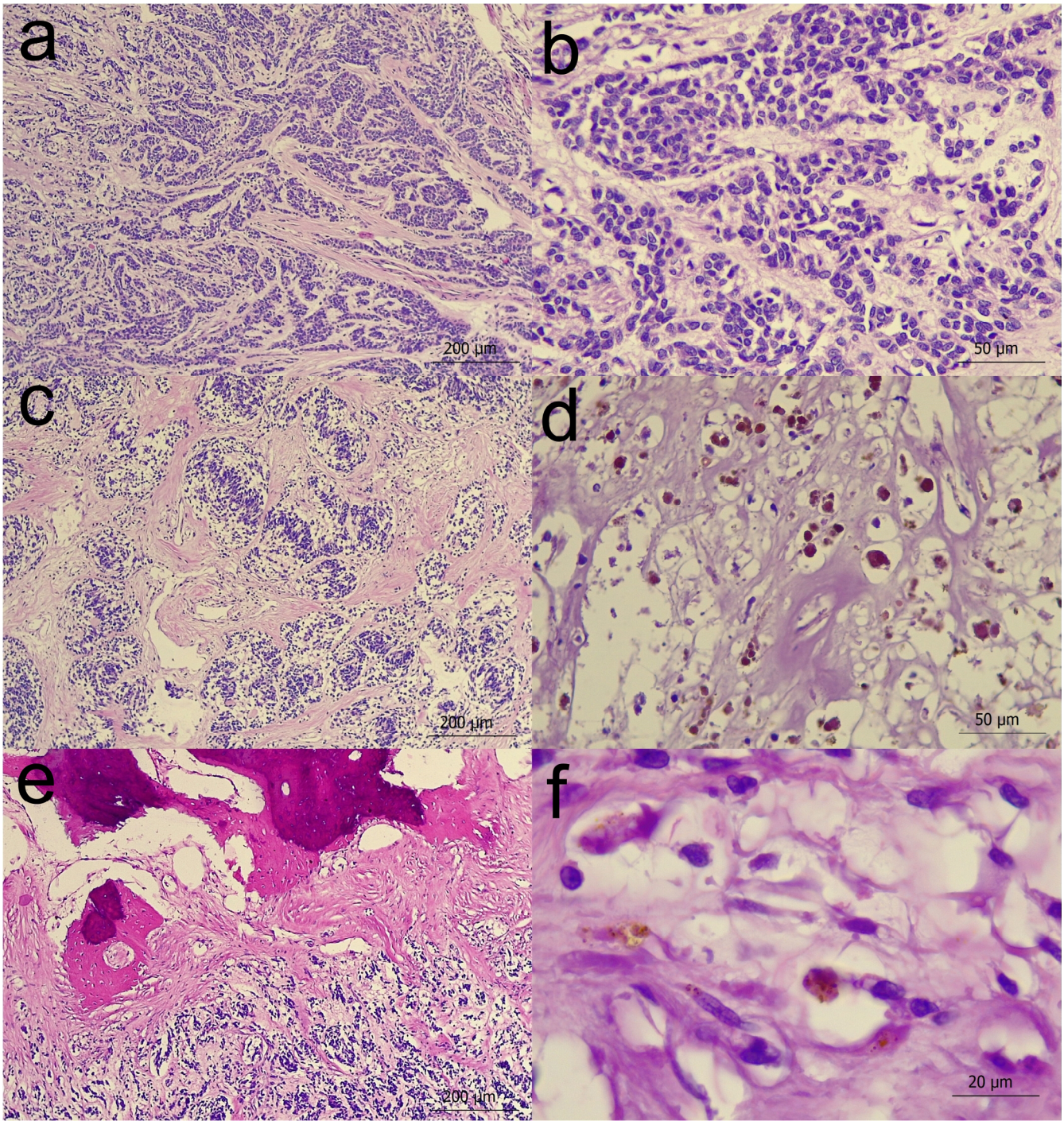

Figure 1. Dog, skin and subcutaneous tissue, paraganglioma-like dermal melanocytoma. 1a. A well-defined neuroendocrine/carcinoid pattern is recognized. There is an irregular proliferation of fibrous connective tissue intervening the neoplasm (H&E stain, Bar 200 µm). 1b. A closer view of the carcinoid arrangement where cells appear nested enclosed by slender projections of fibrous connective tissue. The neuroendocrine/carcinoid pattern characteristic of paraganglioma is evident (H&E stain, Bar 50 µm). 1c. In some areas the nested cells were forming palisades. This pattern is reminiscent of nerve tissue tumors. The limiting fibrous connective tissue is more abundant (H&E stain, Bar 200 µm). 1d. In an isolated necrotic focus, the cells expressed abundant melanin (H&E stain, Bar 50 µm). 1e. Also, a peripheral single focus with metaplastic well differentiated bone tissue was recognized. The peripheral connective tissue in this zone was hyaline with evidence of precursory osseous trans-differentiation (H&E stain, 200 µm). 1f. In the nested cells the melanin synthesis was barely identified, and when occurred was scant and mostly as delicate dust-like granules (H&E stain, Bar 20 µm).

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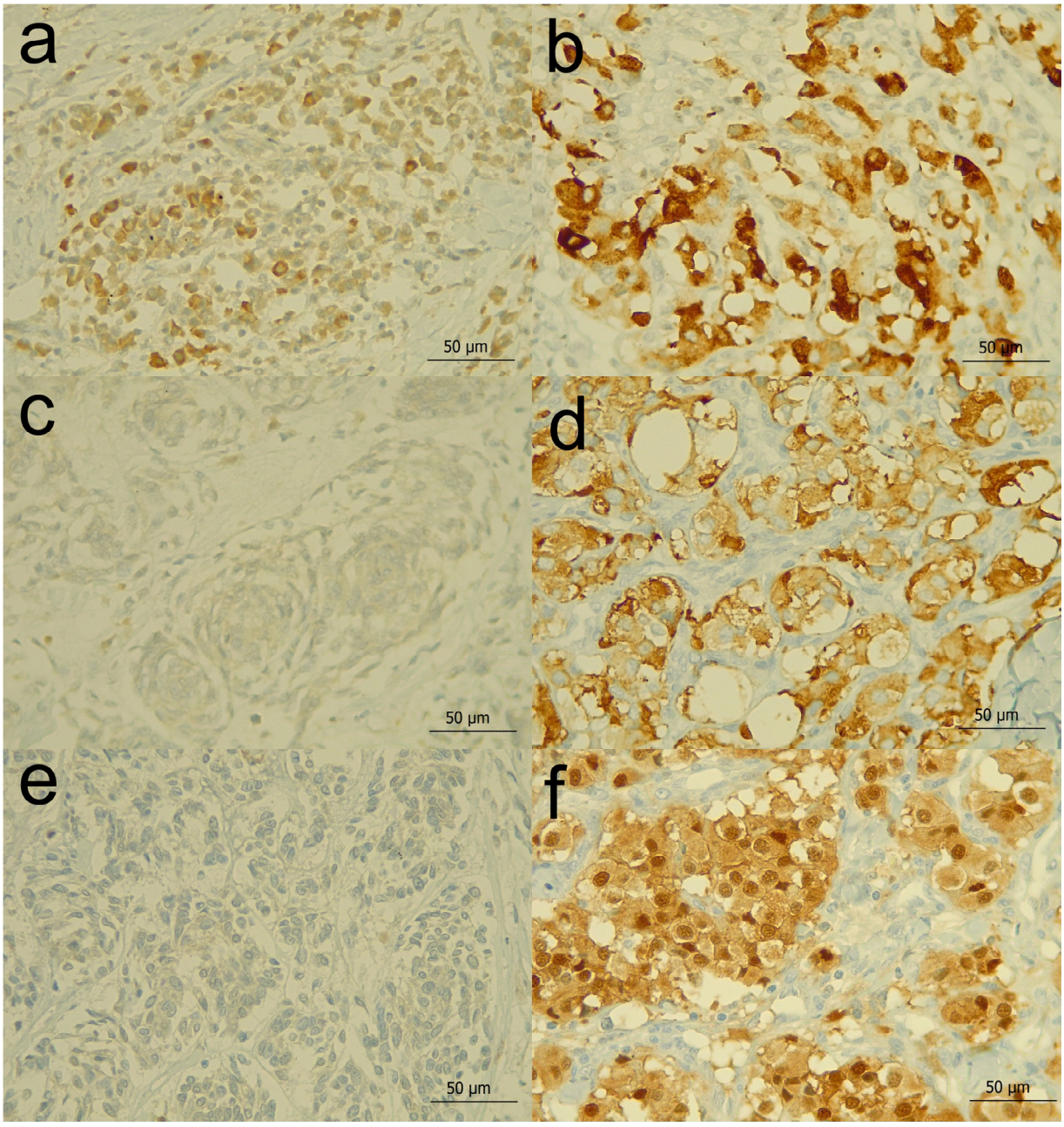

Figure 2. Dog, skin and subcutaneous tissue, paraganglioma-like dermal melanocytoma. 2a. Chromogranin A immunoreactivity resulted in intermediate distribution and dispersed cells with strong immunostaining. 2b. The positive tissue for comparison corresponds to human paraganglioma tumor. Immunoreactivity demonstrated with diaminobenzidine chromogen and slightly counterstained with hematoxylin (Bar 50 µm). 2c. Synaptophysin immunoreactivity resulted negative. 2d. The positive tissue for comparison was a human paraganglioma tumor. Immunoreactivity demonstrated with diaminobenzidine chromogen and slightly counterstained with hematoxylin (Bar 50 µm). 2e. The S100 marker resulted also negative. 2f. The comparative positive control was a human melanoma tumor. Immunoreactivity demonstrated with diaminobenzidine chromogen and slightly counterstained with hematoxylin (Bar 50 µm).

melanomas with ganglioneuroblastic differentiation included chromogranin A and synaptophysin immunoreactivity (13). The explanation could be that both neuroendocrine tissues and melanocytes emerge from the neural crest and their pluripotent histogenesis remains (5,13). Finally, the focus of bone associated with the tumor described here is evidence of divergent differentiation (1,4,14). In no other case of PDMT has been informed of the presence of osseous tissue.

The case presented here confirms that the rarest melanoma subtypes occurring in humans also happen

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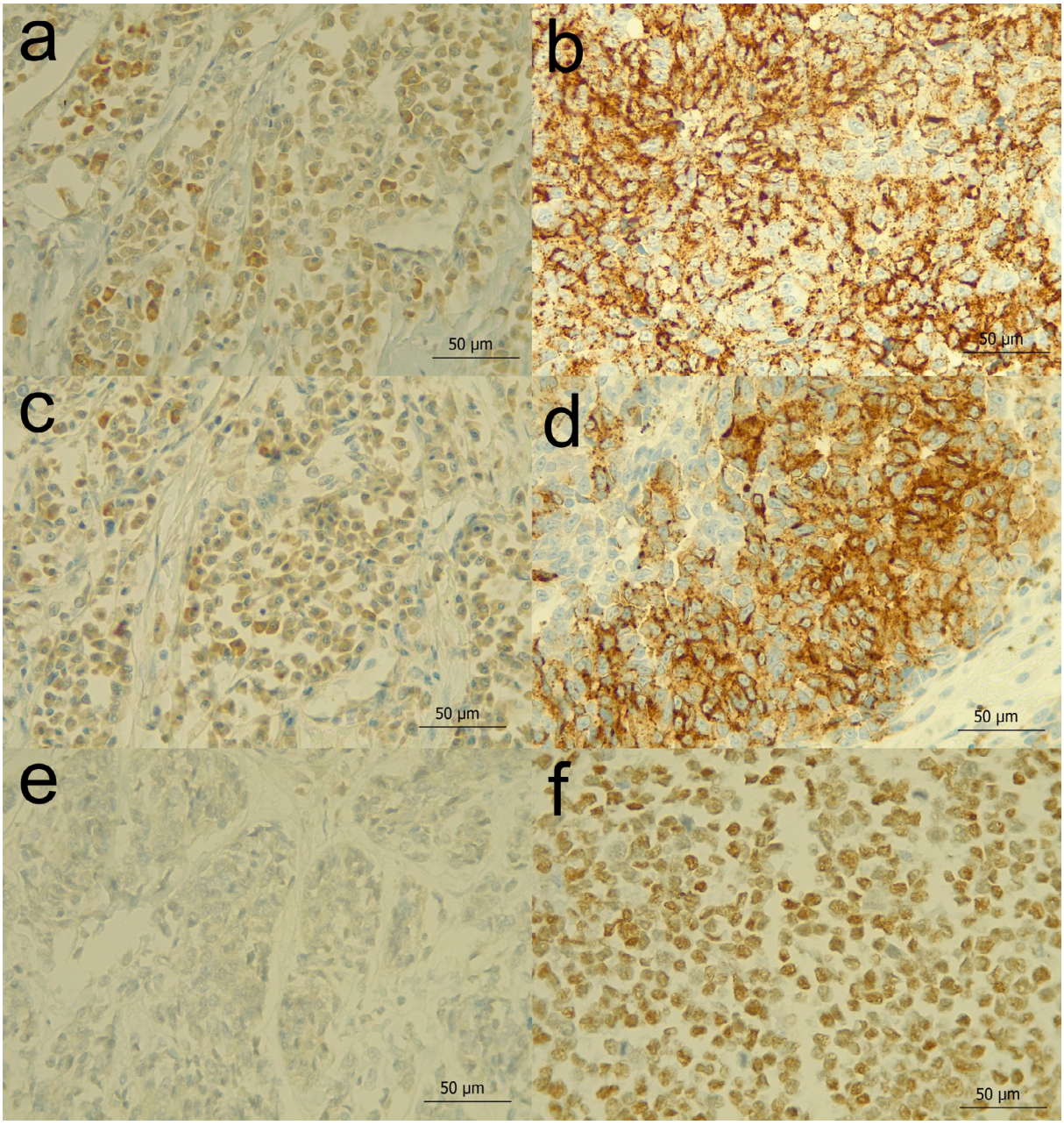

Figure 3. Dog, skin and subcutaneous tissue, paraganglioma-like dermal melanocytoma. 3a. The HMB45 marker resulted positive with intermediate distribution and moderate immunostaining in nested cells. 3b. The positive control tissue was human melanoma. Immunoreactivity demonstrated with diaminobenzidine chromogen and slightly counterstained with hematoxylin (Bar 50 µm). 3c. The Melan A marker was also positive with moderate distribution and weak immunoreactivity. 3d. Corresponds to human melanoma tumor included as the positive control tissue. Immunoreactivity demonstrated with diaminobenzidine chromogen and slightly counterstained with hematoxylin (Bar 50 µm). 3e. The Sox10 marker resulted negative. 3f. The positive control tissue was human melanoma. Immunoreactivity demonstrated with diaminobenzidine chromogen and slightly counterstained with hematoxylin (Bar 50 µm).

spontaneously in dogs. This case was considered a melanocytoma because, despite divergent differentiation, no malignant evidence was identified. Most of the cases reported in humans have been classified as benign or with low malignant potential (1,11,16). Furthermore, evidence supports that the de-differentiation/trans-differentiation in melanocytic tumors in humans does not necessarily confer more aggressive tumor behavior (4). The dog with the excised neoplasm herein described has a satisfying restoration (18 months ago) with no other clinical manifestation.

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Declaration of Conflicting of Interests

The authors declare no conflict of interest in any form related to the publication of this report.

Authors' contribution

The authors contributed in the following way: C R-H and R R-R, diagnosis, original conceptualization, acquisition of data, materials, procedures, and writing of the original draft; CE C-V supervised the hospital attention and surgical excision and oversaw the clinical progress of the dog. JL G-V and LJ G-M provided a conceptualization of the project, critically reviewed, and edited the draft, took some pictures, and provided supportive references and arguments.

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