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CASE REPORT

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Multiple cutaneous plasmacytosis with multilobated (clover-leaf shaped) nuclei cells in a dog

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Abstract

A 12-year-old female Shih-tzu dog was presented with a 2-month history of cutaneous non-pruritic multiple ulcerated or crusted nodules of less than 1.5 cm in diameter on eyelids, lips, abdomen, groin, thighs and perianal region. Several diagnostic tests were performed, including fine needle aspiration and skin biopsy of the cutaneous nodules. Cytologic interpretation was round cell neoplasm with multilobated (clover-leaf shaped) nuclei. Histopathology revealed round neoplastic cells with prominent anisocytosis and anisokaryosis, and numerous mitotic figures; however, the origin of the cells was not identified. Immunohistochemical evaluation indicated that these cells were positive for CD79a and MUM-1, but negative for CD3, CD20 and Pax 5. The patient was treated with chemotherapy, and the skin condition improved. Despite good response to chemotherapy, the patient was euthanized due to poor general health.

KEYWORDS

clover-leaf shape, cutaneous plasmacytosis, cytology, dog, multilobated, plasmacytoma

1 | INTRODUCTION

Extramedullary plasmacytomas are relatively common plasma cell tumours in dogs, and usually occur in the skin (86%), oral mucocutaneous junction (9%) and rectum and colon (4%) in the absence of bone involvement (Lucke, 1987; Rakich, Latimer, Weiss, & Steffens, 1989). Cutaneous plasmacytomas are most commonly solitary and look like an alopecic, pink, raised, round mass approximately 1–2 cm in diameter with a distinct border, and they are frequently observed in the skin of the head and limbs but other locations can be affected (Cangul, Wijnen, Garderen, & Ingh, 2002; Rakich et al., 1989).

Cutaneous plasmacytosis (CP) in humans is characterized by multiple cutaneous plasmacytomas that have well-demarcated reddish-brown nodules or plaques without systemic plasmacytosis or multiple myeloma, and they occur significantly more frequently in patients of Asian or Pacific Islander descent (Honda et al., 2013; Kodama et al., 1992). In most reported cases of canine CP the lesions have been similar to solitary cutaneous plasmacytomas, and 71% of affected dogs (15/21) had more than 10 lesions (Boostrom et al., 2017). "Multiple cutaneous plasmacytoma" was reported in 2.2% of 406 dogs in one study (Goldschmidt & Shofer, 1992).

The dog breeds that are reportedly most commonly affected by CP are golden retrievers and Labrador retrievers (38%), but the condition has also been reported in American cocker spaniels, English cocker spaniels and West Highland white terriers (Lucke, 1987). The initial diagnosis of CP can be made via fine needle aspiration cytology, but confirmation via histopathology with plasma cell-specific immunohistochemical markers including multiple

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myeloma oncogene-1 (MUM-1) and lambda light chains is optimal, especially in cases of poorly differentiated round cell tumours (Kyriazidou, Brown, & Lucke, 1989). Although cases of CP have been reported in both humans and veterinary medicine, cytomorphology of CP including multilobated clover-leaf shaped nuclei visualized in aspirated samples has not been reported. Herein, we describe such highly unusual cells aspirated from skin nodules in a dog with multiple CP.

2 | CASE REPORT

A 12-year-old female Shih-tzu dog with a 2-month history of multiple cutaneous non-pruritic papules and nodules with frequent crust formation of less than 1.5 cm in diameter on the eyelids, lips, abdomen, groin, thighs and perianal region was presented. On physical examination the dog was mildly lethargic but there was no evidence of generalized lymphadenopathy. Complete blood count and chemistry data revealed normocytic, normochromic, non-regenerative anaemia (haematocrit 15%, reference range 37%–55%) without reticulocytosis (31 × 10^9/L, reference range 8–65 × 10^9/L), mild thrombocytopenia (174 × 10^9/L, reference range 200–500 × 10^9/L), hypoalbuminaemia (1.5 g/dl, reference range 2.9–4.2 g/dl), and hyperglobulinaemia (10 g/dl, reference range 5.4–7.4 g/dl). In serum electrophoresis there was a prominent monoclonal band in the gamma region. SNAP 4Dx Plus Test (IDEXX Laboratories, Inc.) results were negative for infectious diseases such as ehrlichiosis and dirofilariasis, and urinalysis was unremarkable. Radiography of the thorax, abdomen, spine and all four limbs was unremarkable, as was abdominal ultrasonography. Fine needle aspirates of the cutaneous nodules were stained with Diff-Quik for cytologic evaluation.

Aspirates from the skin nodules were highly cellular and contained monomorphic populations of discrete cells larger than two to three times the diameter of a red blood cell, with highly unusual nuclei (Figure 1). The cells had multilobated clover-leaf shaped nuclei and exhibited diffuse finely stippled chromatin, and occasionally one to three small nucleoli. The cytoplasm was scant and had a distinct border, and it contained occasional punctate clear vacuoles and was mildly to moderately basophilic. The cells exhibited mild anisocytosis and anisokaryosis, and there were one or two mitotic figures per high-power (x400) microscopy field. The cytologic interpretation was undifferentiated malignant round cell tumour. The main differentials were cutaneous lymphoma, cutaneous plasmacytoma and histiocytic sarcoma.

Three sites of skin masses that had been aspirated for cytology were evaluated and the dermis and subcutis were infiltrated by solid aggregates and sheets of neoplastic round cells. Round shaped tumour cells were observed with amphophilic cytoplasm and round to ovoid nuclei with small nucleoli. Prominent anisocytosis and anisokaryosis with numerous mitotic figures were observed (Figure 2). Immunohistochemical staining was negative for CD3, CD20, and paired box 5 (Pax 5), and positive for CD79a and MUM-1 (UC Davis, CA, USA) (Figure 3). The PCR for antigen receptor rearrangement was consistent of B-cell lineage. These findings were consistent with a plasma cell tumour origin.

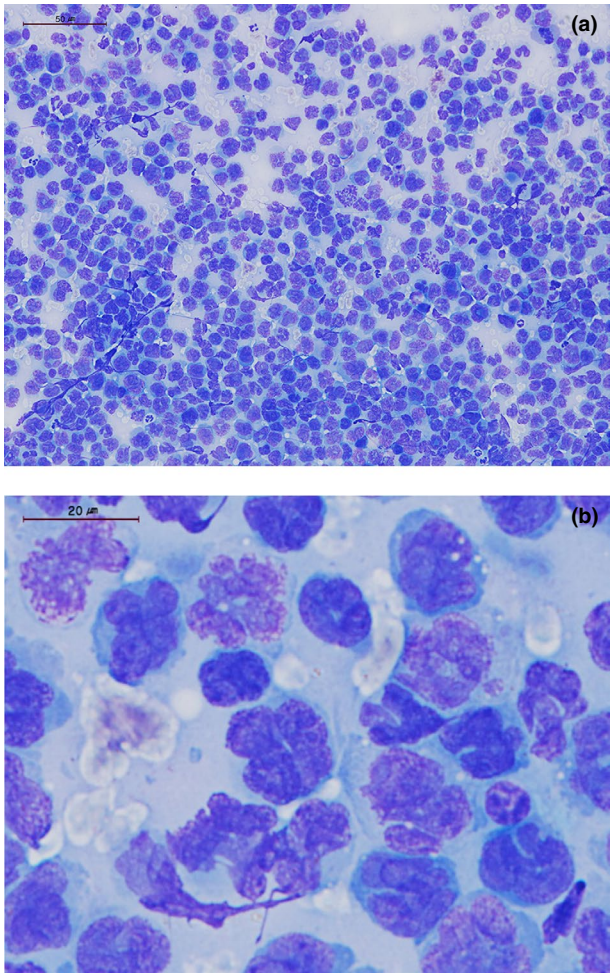

FIGURE 1 Aspirates of cutaneous nodules in a 12-year-old female dog. Monomorphic populations of discrete cells larger than two to three times the diameter of a red blood cell with multilobated clover-leaf shaped nuclei, diffuse finely stippled chromatin, and occasionally one to three small nucleoli were found. The cytoplasm was scant, had a distinct border, contained occasional punctate clear vacuoles, and was mildly to moderately basophilic. Diff-Quik, ×40 objective (a), ×100 objective (b)

Bone marrow biopsy was performed under local anaesthesia, then chemotherapy was initiated. There was no bone marrow infiltration of any neoplastic cells, similar to that found in skin nodules. The dog was treated with three cycles of L-asparaginase, cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy. The skin lesions improved markedly, but her general health status continued to gradually deteriorate. She was euthanized at the owner's request 65 days after initial presentation. Necropsy and further histopathological analysis revealed that the parenchyma of the spleen contained numerous haematopoietic cells, including clusters of blastic cells and megakaryocytes as well as clusters of hemosiderin-laden macrophages consistent with splenic extramedullary haematopoiesis. The small intestine exhibited erosive enteritis. In the lymph nodes, lungs, stomach, liver and spleen, there were no

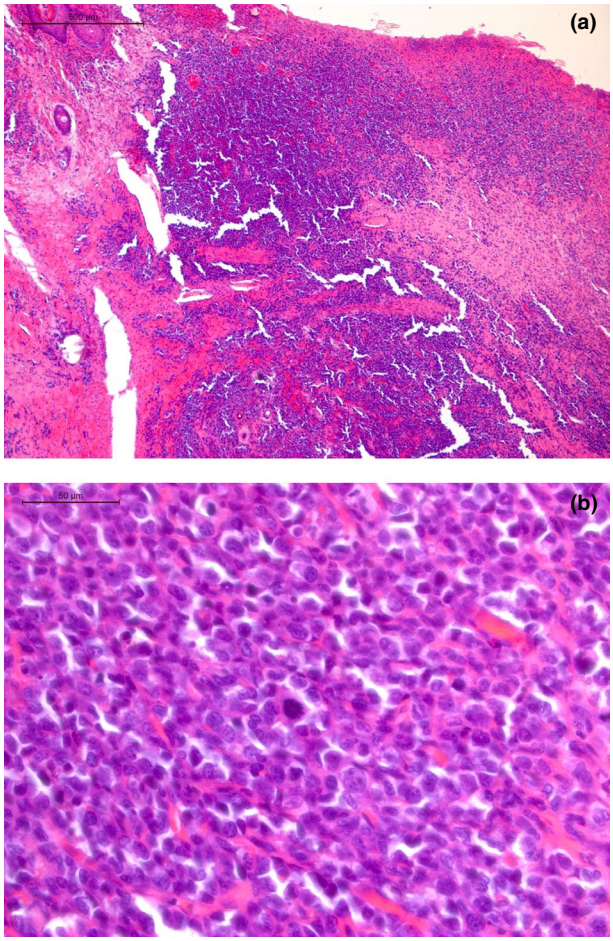

FIGURE 2 Histologic section of a skin nodule. Diffuse, nonencapsulated, and uncircumscribed masses were observed in the dermis and subcutis, showing that the nodules consisted of proliferating round cells in sheets with prominent anisocytosis and anisokaryosis, nuclear polymorphism, and variable amounts of eosinophilic cytoplasm. H&E stain, ×4 objective (a), ×400 objctive (b)

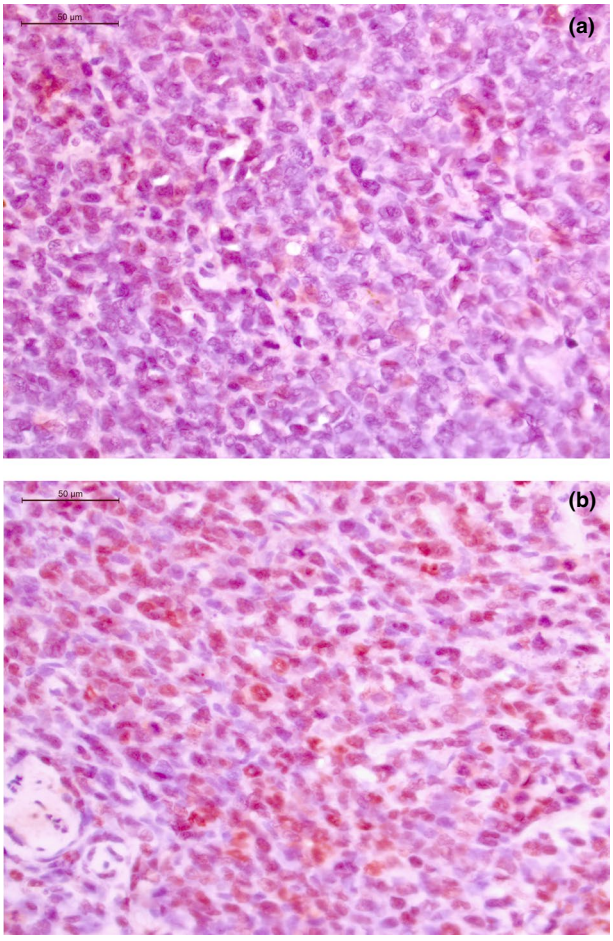

FIGURE 3 Immunohistochemistry showing that the tumor cells were positive for CD79a (a) and MUM-1 (b)

neoplastic infiltrates that corresponded morphologically with the neoplastic infiltrate in the skin.

3 | DISCUSSION

Cutaneous plasmacytosis is an uncommon skin neoplasm typically involving multiple cutaneous plasma cell tumours, and it is differentiated from systemic plasmacytosis and multiple myeloma by the absence of disseminated disease in lymph nodes, bone marrow, liver and spleen. Cases of CP have been anecdotally reported in human and veterinary medicine, but they have recently been described in detail in the veterinary literature (Boostrom et al., 2017). Histopathologically, CP in humans is characterized by dense superficial and deep perivascular and periadnexal infiltrates of mature plasma cells that are typically polyclonal but include very few atypically shaped cells or none at all (Georgesen, Kheterpal, & Pulitzer, 2017; Uhara et al., 1994). In dogs however, nuclear atypia, substantial anisocytosis or anisokaryosis or both, and multinucleated cells were reportedly distinct features observed in most cases of CP (Boostrom et al., 2017). These findings are similar to those of solitary cutaneous plasmacytoma and cytologic features of plasmacytoma in dogs (Baer, Patnaik, Gilbertson, & Hurvitz, 1989; Raskin, 2016).

Some authors have hypothesized that multilobated nuclei may be associated with a sample aging effect (Dunn, D'Agorne, & Twigg, 2003), but changes in cellular morphology due to sample aging are not likely to occur in a large population of the cells as was observed in the present case. Multilobated cells have been associated with dysgranulopoiesis, cobalamin deficiency, myelodysplastic syndrome and lymphoid or myeloid neoplasia (Fyfe, 2000). To the authors' knowledge however, plasma cells with multilobated clover-leaf shaped nuclei identified in cytology examination of samples from animals with CP have not been reported in the veterinary literature, although atypical plasma cells with cerebriform or multiple lobular nuclei have been observed in plasma cell neoplasms such as plasma cell leukaemia and anaplastic atypical myeloma (Fukumoto et al., 2012; Rout et al., 2017; Webb & Robat, 2010). In the cytology of these cases with systemic disease, there were mixed populations of plasmatoid cells and atypical cells with multilobated or bizarre nuclei. Multilobated cells described as 'flower cells' that resemble the cells identified in

the present case have previously been described in a cat (Fritz et al., 2005), but in that case the cells were of a B-cell lymphoma lineage. In another report describing myelodysplastic changes multilobated nuclei similar to those observed in the present case were described, but those host cells were a polymorphic population and exhibited other dysplastic changes (Raskin & Krehbiel, 1985). In the current case >90% of the plasma cells had monomorphic clover-leaf shaped nuclei.

In humans, cells with multilobated clover-leaf shaped nuclei have been associated with T-cell-derived neoplasias such as adult T-cell leukaemia-lymphoma, peripheral T-cell lymphoma not otherwise specified, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, and mycosis fungoides/Sezary syndrome (Jaffe, Harris, Stein, & Vardiman, 2001). In cytologic preparations these cells have been described in lymphoproliferative disorders affecting the gastrointestinal tract, central nervous system, lung, and kidneys, and in malignant pleural effusion with or without lymphoma (Jaffe et al., 2001).

'In the present case, the initial histopathologic and immunohistochemical analyses indicated suspected cutaneous B-cell lymphoma due to the CD3 (negative) and CD79a (partially positive) results.' Plasma cell tumour was not ruled out though, and additional staining for MUM-1, Pax 5 and CD20 was performed. Because morphology is not specific for a particular cell origin, immunophenotyping with a variety of markers is mandatory for the definitive determination of cell lineage. Notably however, characteristic cytomorphology can contribute to an early putative differential diagnosis of CP while waiting for the results of immunohistochemistry, which can be time consuming and costly. In some cases, chemotherapy could be pre-emptively initiated before the results of immunohistochemistry are known.

Although hypergammaglobulinemia is a common clinicopathologic feature in humans with CP, increased globulin concentrations were detected in 15% (3/20) of patients in one report (Kodama et al., 1992) and all dogs had polyclonal gammopathy in a veterinary CP report (Boostrom et al., 2017). The present case exhibited monoclonal gammopathy as has been previously reported in the context of metastatic extramedullary plasmacytoma (Trevor, Saunders, Waldron, & Leib, 1993).

Necropsy of the spleen and small intestine were performed. Microscopy of the spleen revealed that the parenchyma contained numerous hematopoietic cells including clusters of blastic cells and megakaryocytes. This was likely reflective of a secondary response to anaemia and bone marrow depression. The small intestine exhibited erosive enteritis, which was potentially associated with the observed anaemia and hypoalbuminaemia. Anaemia can be caused by this erosive enteritis, chronic illness associated with CP, and hypergammaglobulinaemia.

This case report describes canine CP with monomorphic population of multilobated (clover-leaf shaped) nuclei cells in cytology, which is occasionally observed in other plasma cell neoplasms. The prognosis for this patient was poor despite improvement in skin lesions with aggressive chemotherapy.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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