Unique cytologic and histologic features of a suspected cutaneous xanthoma in a dog

Elise B Russell

Natalie F Courtman

U-Vet Werribee Animal Hospital and Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, Werribee, VIC, Australia

Correspondence
E. Russell, Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, 250 Princes Hwy, Werribee, Victoria 3030, Australia
Email: elise.russell@unimelb.edu.au

ABSTRACT

A 4-year-old spayed female American Staffordshire terrier presented to the U-Vet Animal Hospital, Werribee, Australia, with a cutaneous mass that had been slowly growing over 12 months. Cytologic evaluation showed cohesive to individualized, vacuolated spindled cells often arranged in a perivascular pattern. The mass was completely excised, and the histopathologic examination demonstrated sheets of vacuolated spindled to round cells expanding the full thickness of the dermis. The cells demonstrated both Iba1 and CD18 antibody binding, leading to an initial interpretation of histiocytic sarcoma. Given the discordance with the clinical presentation, further immunohistochemistry (IHC) was performed. The cells demonstrated strong CD204 antibody binding and did not bind the E-cadherin antibody, consistent with dermal macrophage origin. Ki-67 antibody binding was regionally variable from <5-25%, with more regions that had low Ki-67 expression.
28 Fasted serum biochemistry revealed hypertriglyceridemia and persistent hypercholesterolemia.
29 Based on clinical, microscopic, biochemical, and IHC results, the final interpretation was an indolent
dermal histiocytic proliferation of macrophage origin, with a preference for cutaneous xanthoma or
reactive dermal fibrohistiocytoma.

KEYWORDS
Benign fibrohistiocytoma, foam cells, histiocytic, hyperlipidemia, immunohistochemistry,
xanthogranuloma

CASE PRESENTATION
A 4-year-old female spayed 35.6kg American Staffordshire Terrier was presented to the U-Vet
Animal Hospital, Werribee, Victoria, Australia, for routine vaccination and evaluation of a mass on
the ventral thorax which had been slowly growing over the preceding 12 months. The dog had
otherwise been clinically well but was overweight (BCS 8/9). Physical examination demonstrated an
8mm firm raised alopecic cutaneous mass in the right pectoral region. Fine-needle aspiration (FNA)
of the mass was performed.

Cytopathology revealed highly to poorly cellular smears comprising apparently cohesive to
individualized round to spindled cells often present in a striking perivascular arrangement, amongst
a pale blue proteinaceous background with abundant fine, clear vacuoles (Figure 1A). The cells had
round to oval nuclei with coarsely stippled chromatin and 1-3 variably distinct nucleoli. The
cytoplasm was abundant, often highly vacuolated, and pale blue with indistinct cell borders. The
cells displayed mild anisocytosis and mild to moderate anisokaryosis with occasional irregular
nuclear borders. Occasional large irregular nucleoli were noted. Rare inflammatory cells comprising
small lymphocytes, plasma cells, and eosinophils were also noted (Figure 1B).

The cytologic interpretation was soft-tissue sarcoma, likely liposarcoma, based on the high
cellularity, striking perivascular pattern, spindle cell morphology, and marked vacuolation.
Differentials included perivascular wall tumor (PWT) or sebaceous carcinoma. An excisional biopsy
with wide margins was recommended.

Excision was performed 10 days later, and histopathology demonstrated a highly cellular,
unencapsulated, mildly infiltrative proliferation of sheets of spindled to round cells, which infiltrated
and expanded the full thickness of the dermis (Figures 2A and 2B). The cells had moderate amounts
of vacuolated pink cytoplasm and indistinct cell borders. Vacuoles were small and numerous, clear,
and had distinct borders. The nuclei were plump to ovoid with lacy chromatin with a single nucleolus
(Figure 2C). Mitoses were two per ten 400x fields. There was mild to moderate anisokaryosis.
Multifocally, and throughout the mass, were small numbers of plasma cells and lymphocytes.

Excision was complete with 6mm lateral margins and 12mm deep margins.

Immunohistochemistry with CD18 (mouse monoclonal, CA16.3.C10; Peter Moore, Davis, CA, USA) and ionized calcium-binding adapter molecule 1 (Iba1, rabbit polyclonal; Metagene, Brisbane, QLD, Australia) antibodies, using canine lymph nodes as positive controls, demonstrated moderate diffuse membranous binding of the CD18 antibody and strong diffuse membranous binding of the Iba1 antibody, reflecting a histiocytic origin (Figure 3). Given the histologic and IHC results, an initial diagnosis of histiocytic sarcoma was made, and screening for metastasis was recommended.

Thoracic radiographs and abdominal ultrasound were performed; both were unremarkable. Focused ultrasonographic examination of the right axillary lymph node, however, demonstrated moderate enlargement (width: 1.28cm), with normal echogenicity and margins. FNA was performed, and smears demonstrated an unremarkable lymph node cytologically; however, slides were noted to be of low cellularity, and thus the cause of the lymphadenopathy was not determined. Fasting serum biochemistry results, at this time, revealed a moderate hypercholesterolemia (348.0mg/dL; reference interval (RI) 150.8-301.6mg/dL). The CBC demonstrated mild hyperhemoglobinemia (19.2g/dL; RI 12.0-18.0g/dL) and moderate reticulocytosis (209 x 10³/μL; RI 10-110 x 10³/μL) in the absence of anemia (HCT 52%; RI 37-55%) with moderately hemolyzed plasma.

Formalin-fixed samples were submitted to the University of California, Davis, CA, USA for further immunohistochemistry. The round to spindled cells demonstrated strong CD204 antibody binding, and no E-cadherin antibody binding, suggesting a dermal macrophage origin for the mass. Ki-67 antibody binding was highly and regionally variable, from below 5% to 25%, though the well-expressed regions were less frequent than the poorly-expressed regions.

A year later, fasted serum cholesterol and triglyceride testing demonstrated moderate hypertriglyceridemia (407.4mg/dL; RI 8.9-141.7mg/dL), and persistent moderate hypercholesterolemia (351.9mg/dL; RI 150.8-301.6mg/dL). The serum total thyroxine concentration was within normal limits (2.03μg/dL; RI 1.01-3.96μg/dL). There was no evidence of recurrence at the surgical site, and no additional masses were noted. The dog remained clinically well, with only a single episode of self-limiting gastrointestinal upset eight months after biopsy. Given the clinical and immunohistochemical findings, the mass was diagnosed as an indolent dermal histiocytic proliferation of macrophage origin, with a preference for cutaneous xanthoma or, less likely, reactive dermal fibrohistiocytoma. The dog subsequently re-presented 18 months after initial biopsy for the presence of a 1cm diameter firm raised erythematous haired mass on the medial aspect of
the first digit of the left forepaw and right-sided otitis externa. Cytology of the digital mass was non-diagnostic due to poor cellularity, and the mass resolved spontaneously.

**DISCUSSION**

Cutaneous xanthomas have been described in a variety of veterinary species, most frequently in avian species, but also rarely in cats, and very rarely in dogs, horses, rabbits. They are non-neoplastic masses composed of large foamy lipid-laden macrophages and are usually associated with defects in lipid metabolism or with metabolic disorders such as diabetes mellitus, hypothyroidism, or hyperadrenocorticism. Rarely, solitary xanthomas have been reported in the absence of abnormalities in lipid metabolism.

The dog, in this case, had persistent fasting moderate hypercholesterolemia and hypertriglyceridemia. Hyperlipemia in dogs may be primary or secondary to underlying nephrotic syndrome, hypothyroidism, cholestatic disease, or pancreatitis. Hypothyroidism was considered unlikely based on normal serum thyroxine concentrations, and other secondary causes were considered unlikely given the lack of supportive biochemical or clinical findings; however, obesity might have been a predisposing factor. As such, a low-fat diet and weight loss were recommended.

Initial moderate reticulocytosis in the absence of anemia was attributed to hemorrhage associated with surgical biopsy two weeks prior, post-operative carprofen administration, and/or excitement/splenic contraction; however, hemolysis could not be excluded. Given the normal red cell count (8.4 x 10⁹/dL; RI 5.5-8.5 x 10⁹/dL), the hyperhemoglobinemia was likely an artifact of moderate sample hemolysis or could have reflected concurrent hyperlipidemia masked by hemolysis.

Hemogram monitoring was not performed; however, the dog remained clinically well, and there was no clinical evidence of hemorrhagic or hemolytic disease on subsequent follow-up examinations.

Commonly affected sites for cutaneous xanthomas are species-dependent, and in dogs, cutaneous xanthomas have been reported on the face, ears, and ventrum. In humans, the tuberous and eruptive forms characteristically form at sites of pressure and minor trauma. This is postulated to be due to histamine release causing increased vascular permeability facilitating accelerated xanthoma formation. While there was no history of trauma to the affected site, in this case, it is interesting to note that the single report of a solitary cutaneous xanthoma in a dog was also present on the ventral thorax. In that case, cutaneous mast cell tumors were also present, and it could be
speculated that histamine-mediated mechanisms could have increased susceptibility to xanthoma formation. There was no evidence of mast cell neoplasia in this case.

While the cytologic and histologic preparations demonstrated the characteristic and prominent vacuolation observed in cutaneous xanthomas, there were several unique microscopic features in this case. Firstly, the striking perivascular arrangement of cells noted on cytology, a common feature of perivascular wall tumors, liposarcomas, and Leydig cell tumors on cytology\textsuperscript{18-20}, has not previously been reported in xanthomas and led to the initial incorrect cytologic interpretation. This pattern has been reported in diffuse normolipemic plane xanthoma in humans, a type of xanthoma that occurs secondary to perivascular immunoglobulin deposition associated with plasma cell neoplasia, monoclonal paraproteinemia, leukemia, and lymphoma\textsuperscript{21}, but to the authors’ knowledge, has not been reported in other forms of xanthoma. Previous studies in humans have demonstrated that endothelial cells appear to play a role in xanthoma development, by increasing von Willebrand factor and E-selectin expression and undergoing proliferation to promote macrophage migration into xanthomatous lesions\textsuperscript{22}. If this also occurs in animals, it could explain the perivascular arrangement observed in this case. Additionally, the frequent spindled morphology of histiocytes, both cytologically and on histopathology, initially resulted in an erroneous interpretation of a sarcoma. The additional finding of diffuse immunohistochemical binding of CD18 and Iba1 antibodies further confused the preliminary interpretation by suggesting a histiocytic sarcoma was present, a more common malignant cutaneous neoplasm of dogs\textsuperscript{23}. While the high cellularity, spindled morphology, and perivascular pattern on cytology could have supported a PWT; however, these tumors do not typically bind the CD18 antibody\textsuperscript{24}. The spindled morphology of histiocytes has been reported in solitary reticulohistiocytoma and cellular spindled histiocytic pseudotumor complicating fat necrosis in humans, and reactive fibrohistiocytic nodules in humans and dogs\textsuperscript{17,25}. To the authors’ knowledge, spindled histiocytes have not been reported in cutaneous xanthomas, which are typically characterized by the presence of large round macrophages filled with lipid, sometimes termed “foam cells”.

Reactive fibrohistiocytic nodules are uncommon in dogs and, as such, are poorly characterized. They are described as solitary or occasionally multiple small cutaneous nodules that predominantly affect dogs less than three years of age. Histologically these nodules comprise predominantly histiocytic cells with round to polygonal to plump spindle morphology that contain variable numbers of vacuoles. Fibroblasts and mixed lymphocytic, neutrophilic, and eosinophilic infiltrates might also be present. These lesions are postulated to be reactive, with excision being curative.\textsuperscript{25} While the spindled morphology of the histiocytes, in this case, was most consistent with a reactive
This article is protected by copyright. All rights reserved


This article is protected by copyright. All rights reserved


264 **FIGURE LEGENDS**

**Figure 1.** Photomicrographs of a fine-needle aspirate from a cutaneous mass in a dog. Features consist of a marked perivascular cellular arrangement and cytoplasmic vacuolation, with indistinct cell borders. Wright-Giemsa stain. (A) x20 objective and (B) x50 objective.

**Figure 2.** Photomicrograph of histopathology of the excised cutaneous mass in a dog. Expansion of the dermis is characterized by a highly cellular, unencapsulated, infiltrative proliferation of sheets of spindled to round cells with vacuolated eosinophilic cytoplasm and indistinct cell borders. Mitoses were two per ten high power fields (400x magnification). H&E stain, (A) x4 objective, and (B, C) x10 objective.

**Figure 3.** Photomicrograph of immunohistochemical antibody binding in the excised cutaneous mass from a dog. Cytoplasmic binding with both (A) CD18 and (B) Iba1 antibodies. H&E stain, x10 objective.
Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Russell, EB; Courtman, NF

Title:
Unique cytologic and histologic features of a suspected cutaneous xanthoma in a dog

Date:
2019-11-25

Citation:

Persistent Link:
http://hdl.handle.net/11343/286658