Case Report

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Cutaneous Xanthoma in a Dog

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Abstract A 2-year-old, 12.5 kg, castrated male, mixed-breed dog was presented with a 1-year history of pruritus and progressive alopecia. On physical examination, no remarkable findings were detected including body condition score (5/9). A dermatological examination of the dog revealed generalized erythema, papules or plaques, especially on the face, auricle, dorsum, and shoulder. A fine-needle aspiration of the dorsum and face lesions revealed various numbers of macrophages with foamy cytoplasm and multinucleated giant cells. A bacterial culture test showed the growth of *Staphylococcus pseudintermedius*. A complete blood cell count was unremarkable and biochemical abnormalities included hyperglobulinemia (4.8 g/dL, reference interval 2.5-4.5 g/dL), mild hypertriglyceridemia (277 mg/dL, reference interval 10-100 mg/dL) and mild hypercholesterolemia (383 mg/dL, reference interval 110-320 mg/dL). Additional diagnostic tests were performed to identify the underlying cause of hyperlipidemia. Canine pancreatic lipase immunoreactivity (<50 ng/mL, reference interval 0-200 ng/mL) and total T4 (1.4 μg/dL, reference interval 1.1-5.6 μg/dL) were within the reference intervals. For a definitive diagnosis, skin biopsy specimen was collected from the papular lesions on the dorsum by using a 4 mm biopsy punch. A histopathological examination revealed numerous large macrophages with abundant foamy cytoplasm in the dermis. The foamy macrophages were located diffusely between the collagen fibers. Extracellular amorphous lipid deposits were also presented in the dermal tissue. A definitive diagnosis of cutaneous xanthoma was made based on clinical signs and cytological and histopathological results.

Key words cutaneous xanthoma, dog.

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Introduction

Cutaneous xanthomas are generally benign multifocal granulomatous skin lesions that contain lipoprotein-derived deposits and lipid-laden macrophages (6). Although the precise mechanism of lipid accumulation in skin lesions is not completely understood, xanthomas are commonly associated with lipid metabolism disorders (12,13). Cutaneous xanthomas are reported in the veterinary literature, most frequently in birds, rarely in cats, and very rarely in dogs (13). Cutaneous xanthomas have been reported in dogs with diabetes mellitus and those given high-cholesterol diets (1,4). The cutaneous lesions of xanthomas are represented by multiple white-to-yellow papules, nodules, and plaques with erythematous borders (1,6). The skin lesions can be alopecic, pruritic, and painful (10). The typical sites for cutaneous xanthomas are the face, ears, extremities, ventrum, and bony prominences (10,13).

The presumptive diagnosis of the xanthomas requires clinical presentation and the existence of macrophages with foamy cytoplasm on a cytological examination of the lesions (1,4). Foam cells develop from macrophages due to the progressive intracellular deposition of lipids taken up by particular receptors or by the process of phagocytosis (15,17). A definitive diagnosis can be made based on the histopathological findings of a skin biopsy (4). The common histopathological features of xanthomas are diffuse infiltration of vacuolated macrophages and variable amounts of multinucleate histiocytic giant cells (6,10,12). Vacuolated macrophages may diffuse throughout the collagen fibers, and large lakes of extracellular amorphous lipid deposits may be present in the tissue (6). The treatment of cutaneous xanthomas involves identifying and correcting the underlying problem and surgical treatment (11). The lesions resolve spontaneously with successful treatment of the underlying disease (10,11). On the other hand, surgical excision without treatment of the underlying cause commonly results in relapse (10,11). To the best of our knowledge, there has been no case report of cutaneous xanthoma of dogs in Korea. The purpose of this case report is to describe a cutaneous xanthoma occurring with hyperlipidemia in a dog and its diagnosis and treatment.

Case Report

A 2-year-old, 12.5 kg, castrated male, mixed-breed dog presented with a 1-year history of pruritus and progressive alopecia. On physical examination, no remarkable findings were detected including body condition score (5/9). The dermatological examination of the dog revealed generalized erythema, papules or plaques, especially on the face, auricle, dorsum, and shoulder (Fig. 1). The lesions were symmetrical, erythematous, and lichenoid. The skin was also oily and greasy. Acetate tape preparations on lesions revealed mild degenerative neutrophils, and intra-cellular cocci. Follicular casts were mildly presented on the trichogram. The bacterial culture and sensitivity test showed the growth of *Staphylococcus pseudintermedius* susceptible to amoxicillin-clavulanate. Amoxicillin-clavulanate at 25 mg/kg orally twice daily (Amoclan Duo; Hanmi Pharm) was prescribed to treat bacterial infection for 2 weeks. However, the skin lesions did not improve.

In the complete blood count (CBC), red blood cell ($7.29 \times 10^{12}/\mu L$, reference interval $5.65\text{-}8.87 \times 10^{12}/\mu L$), hematocrit (48.3%, reference interval 37.3-61.7%), neutrophil ($7.57 \times 10^3/\mu L$, reference interval $2.95\text{-}11.64 \times 10^3/\mu L$), lymphocyte ($3.15 \times 10^3/\mu L$, reference interval $1.05\text{-}5.1 \times 10^3/\mu L$), monocyte ($0.57 \times 10^3/\mu L$, reference interval $0.16\text{-}1.12 \times 10^3/\mu L$), eosinophil ($0.48 \times 10^3/\mu L$, reference interval $0.06\text{-}1.23 \times 10^3/\mu L$), basophil ($0.08 \times 10^3/\mu L$, reference interval $0\text{-}0.08 \times 10^3/\mu L$), and platelet ($224 \times 10^9/\mu L$, reference interval $148\text{-}484 \times 10^9/\mu L$) were within the reference range. The fasting serum biochemistry test revealed hyperglobulinemia (4.8 g/dL, reference interval 2.5-4.5 g/dL), mild hypertriglyceridemia (277 mg/dL, reference interval

Fig. 1. Two-year-old, 12.5 kg, castrated male mixed-breed dog presented with (A) yellow to pink plaques on the head and (B) yellow to pink papules on the ear pinna, dorsum, and shoulder.

10-100 mg/dL), and mild hypercholesterolemia (383 mg/dL, reference interval 110-320 mg/dL). Glucose (90 mg/dL, reference interval 74-143 mg/dL), creatinine (0.8 mg/dL, reference interval 0.5-1.8 mg/dL), blood urea nitrogen (7 mg/ dL, reference interval 7-27 mg/dL), total protein (7.4 g/dL, reference interval 5.2-8.2 g/dL), albumin (2.3-4 g/dL, reference interval 2.3-4 g/dL), alanine aminotransferase (79 U/L, reference interval 10-125 U/L), alkaline phosphatase (70 U/L, reference interval 23-212 U/L), gamma-glutamyl transferase (0 U/L, reference interval 0-11 U/L), and total bilirubin (0.6 mg/dL, reference interval 0-0.9 mg/dL) were within the reference range. A fine-needle aspiration (FNA) of the dorsum and face lesions was performed for a cytology evaluation. Cytopathology revealed various numbers of macrophages with foamy cytoplasm (Fig. 2A), and multinucleated giant cells (Fig. 2B). Considering the cytopathologic results, the differential diagnosis that can be included are cutaneous xanthomas, panniculitis, sterile pyogranuloma/granuloma syndrome and fat necrosis. For a definitive diagnosis, skin biopsy specimen was collected from the papular lesions on the dorsum by using a 4 mm biopsy punch.

A histopathological examination showed extensive infiltration of numerous and large lipid-laden macrophages and multinucleated giant cells in the dermis (Fig. 3). Large amounts of foamy macrophages were compactly organized and located between the collagen fibers (Fig. 3A). Extracellular amorphous lipid droplets were also observed in the dermal tissue (Fig. 3B). These histological characteristics were deemed consistent with a diagnosis of cutaneous xanthoma.

Additional diagnostic tests were performed to identify the underlying causes of hyperlipidemia and the treatment of cutaneous xanthoma. Canine pancreatic lipase immunoreactivity (<50 ng/mL, reference interval 0-200 ng/mL) and total T4 (1.4 μg/dL, reference interval 1.1-5.6 μg/dL) were in reference ranges. Urinalysis results were also unremarkable. Abdominal radiography and ultrasound were performed, but no significant abnormalities were observed. Ultrasound scans of the thyroid gland was also unremarkable. Hyperlipidemia was considered the primary cause based on the history, clinical signs, CBC, serum biochemistry, and additional diagnostic test results.

Treatment was started with a low-fat diet to manage the hyperlipidemia. After 2 weeks, the skin lesions were not improved. A serum biochemistry test was repeated at that time.

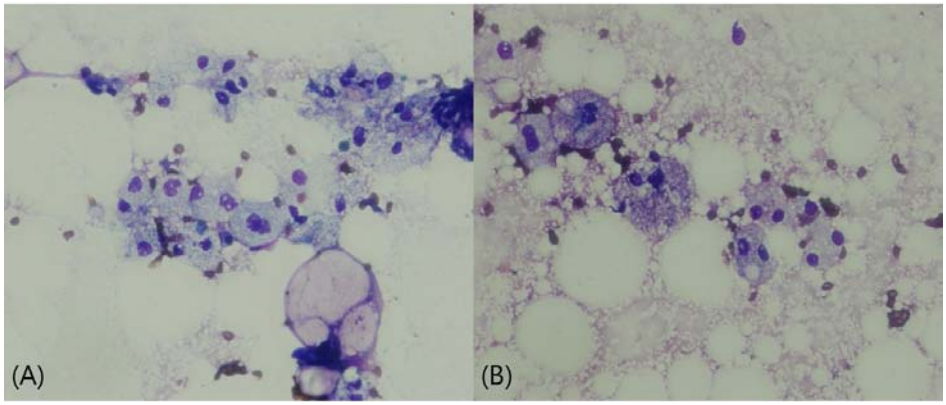

Fig. 2. Fine-needle aspirate from a cutaneous lesion in a dog. (A) Numerous macrophages with foamy cytoplasm were noted. (B) Multinucleated giant cells and many lipid droplets were observed. Modified Romanowsky stain (Diff-Quik), ×400 (A) and (B).

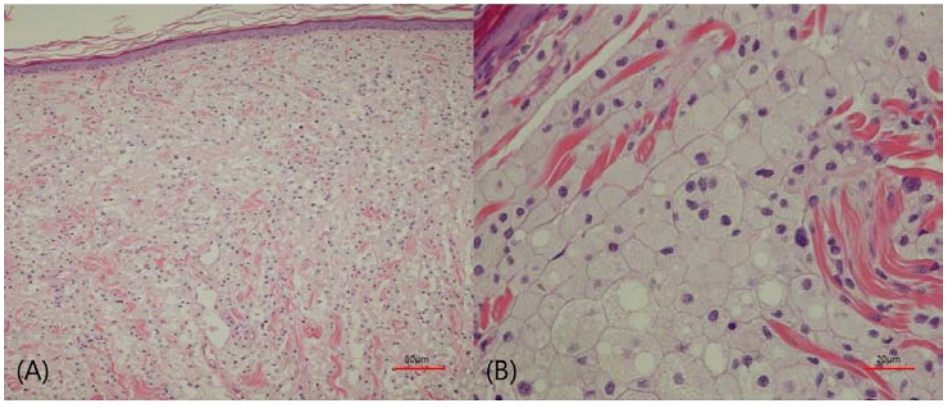

Fig. 3. Histopathology of canine cutaneous xanthoma. (A) Extensive infiltrates of numerous lipid-laden macrophages and multinucleated giant cells are identified in the dermis (scale bar 80 μm). (B) Large amounts of foamy macrophages and lipid droplets are diffused between collagen fibers (scale bar 20 μm): H & E, ×100 (A) and ×400 (B).

The results showed that the dog was still hyperlipidemic, with mild hypertriglyceridemia (207 mg/dL, reference interval 10-100 mg/dL) and mild hypercholesterolemia (412 mg/dL, reference interval 110-320 mg/dL). The patient was continued on the low-fat diet for an additional 2 weeks. On the other hand, omega-3 fatty acids supplementation was started concurrently due to the insufficient clinical improvement after 4 weeks of a low-fat diet. One month after omega-3 fatty acids supplementation was initiated, the skin lesions still did not improve. The serum biochemistry test was reexamined and revealed mild hypertriglyceridemia (167 mg/dL, reference interval 10-100 mg/dL) and mild hypercholesterolemia (435 mg/dL, reference interval 110-320 mg/dL). The dog was prescribed simvastatin (Simvastatin Tab; Myungmoon Pharm, Korea) at 20 mg/dog every other day to control hyperlipidemia for one month. No clinical resolution of skin lesions was evident after one month of treatment with simvastatin. In addition, mild hypertriglyceridemia (165 mg/dL, reference interval 10-100 mg/dL) and mild hypercholesterolemia (416 mg/dL, reference interval 110-320 mg/dL) were still observed. Therefore, treatment with simvastatin was discontinued. The dog has been managed with a low-fat diet and omega-3 fatty acids supplementation.

Discussion

Cutaneous xanthomas are granulomatous inflammatory lesions usually associated with hyperlipidemia or metabolic diseases, such as hypothyroidism, hyperadrenocorticism, or diabetes mellitus (7,9,16). The term hyperlipidemia describes an increased concentration of cholesterol, triglycerides, or both in plasma (16). When the plasma concentrations of either cholesterol or triglyceride are elevated, one or more of the lipoproteins transporting these lipids may also elevated (9). Canine lipoproteins can be classified into 4 major classes based on their size and density: chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL) (6,16). Chylomicrons and VLDL are the primary carriers of serum triglycerides, while LDL and HDL comprise mainly cholesterol (16). In dogs, hyperlipidemia is common and presents as a primary or secondary to underlying diseases (7,9,13). Secondary hyperlipidemia is most common and can result from endocrine diseases, cholestatic liver disease, pancreatitis, protein-losing nephropathy, high-fat diets, obesity, and treatment with corticosteroids (16). Primary hyperlipidemia is uncommon and is usually related to hereditary in certain breeds of dogs (16). In this case, the clinical suspicion of primary hyperlipidemia was made by excluding secondary hyperlipidemia based on the clinical signs, CBC, serum biochemistry analysis (mild hypertriglyceridemia and mild hypercholesterolemia), and additional diagnostic tests.

The pathogenesis of xanthoma formation in veterinary species is not fully understood (8,12). On the other hand, inflammation, heat, and local trauma may induce the release of lipids within tissues, leading to cholesterol deposition in those tissues (8,12). In humans, the development of xanthomas has been reported to be associated with oxidized low-density lipoprotein (ox-LDL) (15,17). Ox-LDL is the major modified type of native LDL, and increased serum lipid levels lead to the accumulation of ox-LDL (15,17). Ox-LDL attracts monocytes from the blood flow, impairs macrophage motility, and inhibits the return of macrophages to the blood flow (15,17). The phagocytosis of ox-LDL by macrophages via scavenger receptors leads to the formation and accumulation of foam cells in the tissue, which results in the development of a xanthoma (15,17). This pathological process involves several factors that contribute to the formation of a xanthoma (17). The factors include increased local levels of lipids in the connective tissue, the existence of different types of lipoproteins in normal plasma lipid concentrations, increased leakage of lipids due to elevated vascular permeability, lipid synthesis and their accumulation in histiocytes, and impairment of the reverse cholesterol transport (17). This aetiopathogenesis has not been fully elucidated in veterinary species, and more research is needed.

For histological diagnosis of xanthoma, the use of supportive diagnostic methods such as oil red O staining and immunohistochemical staining have been reported (3,6,8,13). Oil red O is used for staining lipid contents and is very helpful in confirming the presence of lipids in the vacuoles of macrophages and giant cells (2). In a previous study, immunohistochemical staining was used to confirm the origin of cells such as macrophages (3). The present case has limitations as follows. Frozen tissue samples necessary to perform oil red O stain and tissue samples for immunohistochemical staining were not collected in biopsy procedure. Therefore, the oil red O staining and immunohistochemical staining was not performed.

The treatment options for cutaneous xanthomas include resolving the underlying cause and surgical excision. In this case, the dog had persistent fasting, mild hypercholesterolemia, and hypertriglyceridemia. Therefore, the treatment of cutaneous xanthoma was started by managing hyperlipidemia. The initial treatment approach for hyperlipidemia includes a low-fat diet and management of the underlying disease in secondary hyperlipidemia cases (5). Lipid-lowering medications are required for primary hyperlipidemia, secondary hyperlipidemia that fails to respond sufficiently to

the management of the underlying disease, or low-fat diet management is ineffective (5,16). Lipid-lowering drugs, such as omega-3 fatty acids, niacin, fibrates, and statins, should be administered based on underlying disturbance causing hyperlipidemia (5,16).

Statin is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor used widely as a lipid-lowering agent in humans (14,16). In humans, statins specifically reduce the LDL-cholesterol levels with fewer effects on the triglyceride metabolism (16). This makes statins considered less effective in treating hypertriglyceridemia in humans and dogs (16). Adverse effects of statin treatment include myopathy, rhabdomyolysis, and hepatotoxicity in humans (14,16). In dogs, hepatotoxicity and the deterioration of myocardial stunning have been reported as adverse events (14,16). There are no standardized dosages for simvastatin in dogs. Therefore, the dosage can only be extrapolated from human medicine (16). Because the increase in the ox-LDL concentration is associated with the development of xanthoma in humans, and LDL contains a higher proportion of cholesterol in dogs, it was inferred that simvastatin, which is mainly a cholesterol-lowering drug, would be effective in the current case.

Conclusions

This case report describes the clinical, cytological, and histopathological features of cutaneous xanthoma in a dog with primary hyperlipidemia. Cutaneous xanthoma in dogs is very rare disease. Nevertheless, in this case, we diagnose cutaneous xanthoma through a thorough diagnostic tests. The pathogenesis of cutaneous xanthoma in dogs has not been fully elucidated, so further investigation will be required. Treatment with simvastatin was ineffective, and further studies will be needed to examine the safety and cholesterol-lowering effects of statins in dogs.

Conflicts of Interest

The authors have no conflicting interests.

References

1. Albanese F. Cytology of canine and feline non-neoplastic skin diseases. In: Albanese F, editor. Canine and feline skin cytology. Cham: Springer. 2017: 116-121.
2. Albanese F. Techniques of sampling, preparation and staining of cytological specimens. In: Albanese F, editor. Canine and feline skin cytology. Cham: Springer. 2017: 71.
3. Balme E, Thuilliez C, Lejeune T, Chateau-Escoffier L, Bernex F. Multiple atypical mucosal xanthomas in a dog similar to human verruciform xanthoma. J Vet Diagn Invest 2009; 21: 124-128.
4. Barachetti L, Fanton N, Savov S, Cancelli I, Miller PE. Lipemic aqueous humor and suspected xanthomas associated with primary hypertriglyceridemia in a cat. Vet Rec Case Rep 2021; 9: e123.
5. De Marco V, Noronha KSM, Casado TC, Nakandakare ER, Florio JC, Santos EZ, et al. Therapy of canine hyperlipidemia with bezafibrate. J Vet Intern Med 2017; 31: 717-722.
6. Gross TL, Ihrke PJ, Walder EJ, Affolter VK. Noninfectious nodular and diffuse granulomatous and pyogranulomatous diseases of the dermis. In: Gross TL, Ihrke PJ, Walder EJ, Affolter VK, editors. Skin diseases of the dog and cat: clinical and histopathologic diagnosis. 2nd ed. Oxford: Blackwell Science Ltd. 2005: 330-333.
7. Hargis AM, Myers S. The integument. In: Zachary JF, editor. Pathologic basis of veterinary disease. 6th ed. St. Louis: Elsevier. 2017: 1111.
8. Harvey AM, Teixeira LBC, Dubielzig RR. A clinicopathological study of 17 cases of ocular surface xanthogranuloma in dogs. Vet Ophthalmol 2020; 23: 190-198.
9. Johnson MC. Hyperlipidemia disorders in dogs. Compend Contin Educ Vet 2005; 27: 361-370.
10. Miller WH, Griffin CE, Campbell KL. Endocrine and metabolic diseases. In: Miller WH, Griffin CE, Campbell KL, editors. Muller and Kirk's small animal dermatology. 7th ed. St. Louis: Elsevier. 2013: 542.
11. Paterson S. Endocrine and metabolic skin disease. In: Paterson S, editor. Manual of skin diseases of the dog and cat. 2nd ed. Oxford: Blackwell Science. 2008: 161.
12. Ravens PA, Vogelnest LJ, Piripi SA. Unique presentation of normolipaemic cutaneous xanthoma in a cat. Aust Vet J 2013; 91: 460-463.
13. Russell EB, Courtman NF. Unique cytologic and histologic features of a suspected cutaneous xanthoma in a dog. Vet Clin Pathol 2019; 48: 716-720.
14. Satoh K, Takaguri A, Itagaki M, Kano S, Ichihara K. Effects of rosuvastatin and pitavastatin on ischemia-induced myocardial stunning in dogs. J Pharmacol Sci 2008; 106: 593-599.
15. Soslowsky LJ, Fryhofer GW. Tendon homeostasis in hypercholesterolemia. Adv Exp Med Biol 2016; 920: 151-165.
16. Xenoulis PG, Steiner JM. Canine hyperlipidaemia. J Small Anim Pract 2015; 56: 595-605.
17. Zak A, Zeman M, Slaby A, Vecka M. Xanthomas: clinical and pathophysiological relations. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2014; 158: 181-188.