Artykuł przeglądowy *Review*

Xanthoma in different species – an unusual tumor with many faces

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Summary

Xanthoma is an interesting, inflammatory, noncancerous lesion that is rarely diagnosed in companion animals, although it has been reported in a number of domestic and wild species. Macroscopically, it can range from a few millimeter plaques or nodules to even several-centimeter masses. It usually occurs within the skin, but has been diagnosed in almost all other internal systems and organs. As the name suggests, xanthoma most often is of yellow color, but whitish and red forms are also encountered. Although inconspicuous, the presence of xanthoma is often reflected in disorders of lipid and lipoprotein metabolism, which affects the entire body. Therefore, in patients with even a small xanthoma on the skin, coexisting metabolic and endocrine disorders should be excluded, such as: hyperlipidemia, hypercholesterolaemia, hypothyroidism, hyperadrenocorticism and diabetes.

Keywords: xanthoma, animals, dog, cat, lipid disorders

Xanthomas or xanthogranulomas (also called xanthomatosisor xanthelasmas) are granulomatous multiple nodular inflammatory lesions of a non-cancerous nature quite rarely diagnosed in small animal practice (13, 24, 27). Their name comes from the Greek xanthos, meaning „yellow". Their specific, usually yellow color, is due to the large amount of lipids and/or cholesterol accumulated in macrophages and giant cells (1, 22, 27). They can take various shapes and sizes of a soft consistency, are movable and usually not painful. However, over time they may undergo partial mineralization and the lipids contained therein induce a productive local inflammatory reaction with the formation of granulomas. Clinically, they usually take the form of yellowish nodules, papules or plaques (1, 3, 40). Although, they can be found in every organ or anatomical area, they show specific predilection towards the skin and subcutaneous tissue (1, 3, 5). Xanthomas are classified as benign (noncancerous) lesions (5, 22). In both humans and animals, multiple xanthomas can often be the only visible symptom of an ongoing systemic disease associated with alterations in lipid and lipoprotein metabolism (dyslipidemia): diabetes, hypothyroidism, hyperadrenocorticism, obesity (1, 3, 5, 22, 27, 34). If they are single they usually do not reflect comorbidities and are referred to as idiopathic (27, 34). They can also appear after taking certain medicines from the group of corticosteroids, oestrogens, progesterone (1, 22, 38) and some beta-blockers (40). The presence of xanthomatous lesions is an important clinical indicator of some underlying conditions such as hypercholesterolaemia and hyperlipidemia (3). Excess lipoproteins circulating in the blood penetrates between vascular endothelial cells and is deposited in the dermis, subcutaneous tissue and tendons. The resulting lipid deposits are then phagocytosed by phagocytic cells, thus forming characteristic of the histopathological picture of xanthomas: lipid-laden macrophages (foamy cells or xanthoma cells) observed among the connective tissue stroma (3). Xanthomatous lesions have been described in a variety of species: birds, cats (5, 13, 29, 35), dogs (1, 13, 34, 35), horses (1, 12), domestic cattle and goats (28), reptiles and amphibians (1, 8, 13, 32). In the available literature in human medicine skin

xanthomas have been described as flat, pale pink and yellow spots or nodules located on the skin of the ears, hands or face (mainly eyelids, medial canthus). They can also take the form of hard, red-yellow nodules that characteristically develop at sites of skin pressure and minor trauma over the heels, knee and elbow joints – co called the tuberous or eruptive forms of xanthoma (22, 34, 40). Outside the integumentary system, xanthomatous masses have been reported at many other sites in human body, including the reproductive system (ovary, fallopian tube, endometrium), respiratory system (lungs, larynx), oral cavity and digestive system (esophagus, stomach, appendix, colon), as well as in skeletal muscles, Achilles tendons or hand extensor tendons (1, 13, 26, 33). Xanthomas can also occur in internal organs: spleen, liver, kidney, gallbladder, heart muscle, lymph nodes, bones, parotid gland, ocular and periocular tissues (13, 33). On the basis of reviewed veterinary literature cutaneous xanthomas in animals have been reported on the head and neck, ears, and ventral area of the body (34, 38), groins (22, 40), distal extremities, in particular on footpads and over bony prominences (5, 38), ocular and periocular tissues (13, 27, 41). Disseminated, nodular xanthomatous granulomas affecting the liver, kidneys, spleen, adrenal glands, esophagus, stomach, small intestine, mesentery and colon were also observed (1, 5, 33).

Pathomechanism of xanthoma formation and its influence on lipid metabolism

The cause of the formation of xanthomas has not been fully established. Solitary lesions, especially on the skin, are considered idiopathic. In the case of disseminated, multiple xanthomatous changes in the skin and other internal systems, the cause of their formation is thought to be associated with lipid metabolism disorders (1, 3, 5, 27, 34). While the general mechanisms of tissue lipid deposition are well known, the pathomechanism of lipid accumulation leading to xanthoma is not entirely understood (31).

Lipids are a heterogeneous group of organic compounds that are the main energy substrate and an important component of the body's cell membranes. The hydrophobic nature of lipids means that their transport in the blood is possible only in the form of plasma-soluble complexes with proteins as the so-called apolipoproteins. These complexes, apart from the structural function in lipoproteins, also regulate the processes of cholesterol esterification and its transport to body cells. The lipoprotein fraction includes: chylomicrons (CM), VLDL (very low density lipoprotein), LDL (low density lipoprotein) and HLD (high density lipoprotein) (9, 40). Chylomicrons are formed in the wall of the small intestine and play a major role in the transport of triglycerides from the gastrointestinal tract to peripheral tissues. VLDL formed in the liver are responsible for the transport of lipids from the liver to the tissues while LDLs are the main transporter of cholesterol. Receptors for LDL are mostly found on hepatocytes, and their number is regulated according to the demand of the body's cells for cholesterol. When the amount of circulating lipoproteins increases, the number of their receptors decreases. Another mechanism of cellular uptake of LDL is endocytosis, in which the so-called scavenger receptors of monocytes and macrophages play a vital role. As a result of excessive uptake of LDL by macrophages, characteristic xanthoma foam cells (macrophages containing intracytoplasmic lipids) are formed (11, 41). This process is believed to contribute to the formation of cutaneous xanthomas or later larger, diffuse or nodular lesions in body cavities (13). Interestingly, foam cells can also be formed as a result of *in situ* lipid synthesis by macrophages. In addition, lipids that have diffused out of the blood vessels can recruit further macrophages to the already formed xanthoma (31).

All conditions that are referred to as dyslipidemias, i.e. disorders of lipid metabolism, such as: hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hyperlipoproteinemia, and/or hyperchylomicronemia can develop in conjunction with xanthomas formation (5, 13). Physiological hyperlipidemia occurs after ingestion of fat-containing meals (so-called postprandial). Pathological increase in lipids, both primary and secondary, may result from excessive synthesis or ineffective removal of lipids from the blood serum (5, 34). In both humans and animals, primary hyperlipidemia is often hereditary in origin (familial) (2). In cats, it is characterized by pathological accumulation of serum chylomicrons and LDL and mild elevation of cholesterol (5, 17, 40) or lipoprotein lipase deficiency (40). In this species, hyperlipidemia, apart from cutaneous xanthomatous changes, may cause peripheral neuropathies, i.e. Horner's syndrome, tibial or radial nerve paralysis (22). In dogs, primary idiopathic hyperlipidemia has a breed predisposition and is common in Miniature Schnauzers and Beagles (9, 13). Hereditary hyperlipidemia (The Watanabe Heritable Hyperlipidemia; WHHL) has also been observed in rabbits. Watanabe et al. described the cases of young rabbits aged 2-3 months old diagnosed with xanthomas of the skin and finger joints, as well as spontaneously developing atherosclerosis of the aorta and large arteries. It was shown that the concentration of cholesterol and triglycerides in the blood serum of these animals was 8-14 times higher than in healthy rabbits (39). Secondary hyperlipidemia often develops in dogs and cats and accompanies metabolic diseases such as diabetesmellitus, hypothyroidism, and hyperadrenocorticism (1, 16) or is a consequence of taking medications, including estrogens, progesterone, corticosteroids and retinoids (38, 40). According to some sources, xanthomas are caused by genetic mutations in the proteins that make up lipoproteins, resulting in the formation

of defective apolipoproteins, which in turn accumulate in the blood, causing the state of hyperlipoproteinemia or hypercholesterolemia (3). An example of congenital hyperchyloromicronemia and systemic xanthomosis is the case of a 4-month-old domestic cat described by Chunut et al. As a consequence of an excess of circulating serum lipids, the animal developed multiple xanthomas in the skin of distal extremities, ears and chin as well as disseminated, nodular granulomas affecting the liver, kidneys, spleen, adrenal glands, mesentery and colon (5). Due to the extent and large number of lesions, the cat was euthanized. Histopathological examination of the post-mortem nodules showed the presence of foamy macrophages containing lipoprotein deposits (5). Eating a high-fat diet is another factor that contributes to disorders in lipid metabolism in animals (11, 23, 34, 38). An example is the case of a 9-month-old domestic longhair cat described by Volgenest, that was diagnosed with multiple cutaneous xanthomas. Marked hypercholesterolaemia, hypertriglyceridaemia and hyperglycaemia were subsequently confirmed (38). Studies conducted by Vogelnest have shown that the introduction of an elimination, low-fat diet resulted in significant alleviation of skin lesions (22, 38). However, accidental consumption of fatty foods several times and concurrent glucocorticoid therapy have caused recurrence of the disease and xanthomas development (38).

Xanthoma localization in different species

In most cases of xanthoma, the disease is initially characterized by the appearance of yellowish patches and yellowish or reddish-orange papules and nodules that coalesce into hardened plaques with time (31). The size and number of skin lesions usually increase over time or with each recurrence of the disease (31). An example of a cutaneous form of xanthoma in a 7-year-old Labrador dog in the lateral area of the thigh is shown in Figure 1 (authors' own clinical case).

Fig 1. Cutaneous form of xanthoma in a 7-year-old Labrador dog in the lateral area of the thigh

In humans, xanthomas are very often visible on the skin of the eyelids (in the form of single or multiple papules located symmetrically on the eyelids or in the region of the corneoscleral limbus) and around the eyes – both extraocularly and intraocularly. Most often they accompany metabolic disorders or endocrine diseases (13). Similar changes were observed in 3 cases of Miniature Schnauzer dogs aged 9-13 years that underwent enucleation because of glaucoma (41). The presence of an intraocular, solid mass pressing on the remaining intraorbital structures was found that was later diagnosed as intraocular xanthogranuloma. The histological examination confirmed the presence of lipid-laden macrophages (foam cells) with birefringent crystals inside. Additionally, the animals were found to have advanced diabetes mellitus or hyperlipidemia, which was considered a direct cause of xanthomas (41).

A similar localization of xanthoma was described in a in 10-year-old female spayed American Pit Bull Terrier (27). A slow growing mass was located on the temporal limbus area of the eye. In this case, unlike in analogous cases in humans, serum cholesterol and triglyceride concentrations were within reference limits. There were also no other endocrine diseases such as diabetes or hypothyroidism. Apart from the presence of xanthomatous lesions, the dog showed no other clinical signs. Unfortunately, the lesion was constantly growing and was resistant to pharmacological treatment with 1% prednisolone and 0.03% tacrolimus. To prevent the potential invasion of the xanthoma into the cornea and the development of granulomatousepisclerokeratitis, the nodular mass was surgically removed. Lamellar sclerokeratectomy was performed with good cosmetic results without further recurrence. The author suggests that in the differential diagnosis of eyelid and limbal nodules that are resistant to topical treatment, xanthoma should always be taken under consideration (27).

Xanthomas around the eyes were also confirmed by Harvey and colleagues in 17 dogs of different breeds, neutered and intact males and females, aged from 0.7 to 14 years, examined in 1993-2018 (13). The changes were in the form of small nodules within the cornea, sclera, episclera, conjunctiva the third eyelid. As in the studies by Ota-Kurki, the majority of dogs (14/17) did not have any metabolic and lipid disorders (27). Only two of the dogs were reported to have diabetes mellitus, and one was reported to have hypercholesterolemia. Surgical removal of the nodules has proven to be the most effective treatment without recurrence (13). According to the literature, although xanthomas around the eyes in humans were correlated with lipid disorders in the blood, such a correlation, however, was not found in most cases of analogous changes in dogs. As described in the cases presented above, xanthogranulomas have also been reported to develop in normolipidemic animals (3, 34). This indicates the need for more thorough research to determine the etiology

Fig 2. Multiple xanthoma of the lower eyelid margin, third eyelid and in medial canthal area in an 8-year-old mixed breed dog

of canine xanthomas around the eyes. An example of multiple xanthoma of the lower eyelid margin, third eyelid and in medial canthal area in an 8-year-old mixed breed dog is shown in Figure 2 (photo of the authors' own clinical case).

A clinically different type is verruciform xanthoma, which in humans has been observed in many tissues and organs lined with stratified squamous epithelium, such as the oral cavity, esophagus, genital mucosa and skin (1, 4, 14, 30). This type of xanthoma takes the form of pedunculated formations with a granular surface resembling warts and is not associated with disorders of lipid metabolism. Lesions clinically resembling verrucous xanthoma were also diagnosed in a dog (1). According to Balme et al. a 14-year-old neutered male Shi-tzu was diagnosed with multiple, yellow 1-8-mm-diameter papillary proliferations on the dorsal and ventral side of the tongue and upper lip. Similar numerous granular lesions were also present on serosal and muscular layers of the esophageal and gastric mucosa. Histologic examination of all papillary nodules showed characteristic accumulations of foamy cells. Hyperlipidemia, hypothyroidism and hyperadrenocorticism were excluded in this patient (1). Although the macro- and microscopic appearance of the nodules was characteristic of xanthomas diagnosed in humans, in the described case significant differences were found as to the number of lesions and their location. In the case described in the dog, the number of pathological changes was large, while in humans, multiple lesions of verruciform xanthomas are described quite rarely. Secondly, verruciform xanthomatous lesions were observed in the gastric mucosa which has not been reported in humans (1).

Xanthomas located on the mucous membrane of the digestive tract in humans were recognized as early as 1997 (25). Unlike gastric and esophageal xanthomas, which most commonly present as nodules or papules, those in the large intestine clinically resemble a polyp (24, 25). Differences were also demonstrated in the color of xanthomas of the gastrointestinal tract depending on their location. Most rectosigmoid xanthomas were reddish or whitish, which was probably the result of capillary proliferation just below the surface of the epithelium (25). On the other hand, xanthomas of the esophagus and stomach were seen endoscopically as yellow granules or slightly raised lesions, often misdiagnosed as gastric adenocarcinoma (15, 24). Researchers looking for the causes of xanthomas of the gastrointestinal tract suggested that the predisposing factor for the appearance of xanthomas in the intestine are previous damage or injuries to the mucous membrane. Whereas the formation of xanthomas in the esophagus or stomach was associated with chronic inflammation of the mucous membrane, peptic ulcer disease or gastroduodenal reflux (10, 24, 25). Some have proven that gastric xanthomas are useful markers for predicting the development of early stomach cancer (10, 19, 24, 36). Disseminated xanthomas within the gastrointestinal tract were also found in a dog. Romanucci et al. described the case of a 12-year-old male American Staffordshire Terrier diagnosed with disseminate xanthogranulomatous inflammation of the small intestine and its mesentery. The dog was presented with anorexia, weight loss and chronic diarrhea unresponsive to pharmacologic treatment. The dog underwent diagnostic laparotomy. During the surgery, the presence of small nodules, 2-3 mm in diameter, scattered in the serosa of the small intestine and the mesentery was observed (33). The histopathologic examination of a tissue sample taken from the small bowel showed characteristic for xanthoma foamy cells with vacuolated cytoplasm (33). A similar case of disseminated mesenteric xanthoma of the small intestine in a 12-year-old mixed breed dog is presented in Figure 3 (autopsy photo of the authors' own case).

Various forms of xanthomas have also been diagnosed in both wild and domesticated birds (6, 20, 37). As in other species, lipid metabolic disorders, nutritional disorders and, to a large extent, injuries may contribute to its formation (6). Xanthomas may be small nodules located on the eyelids (37), atypical, pedunculated and covered with intact epithelium nodules of non-feathered parts of the skin (16, 29) or may form tumors up to 10 cm in diameter in the subcutaneous tissue (6). It has been proven that a high fat diet influences the formation of lesions in domestic birds (16,

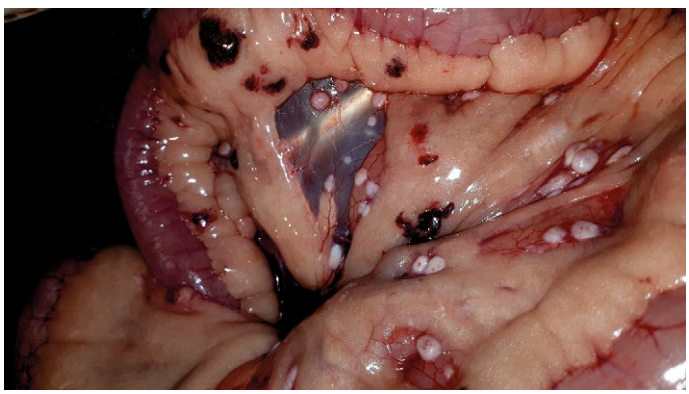

Fig 3. Disseminated mesenteric xanthoma of the small intestine in a 12-year-old mixed breed dog

20, 29). Jeansen et al. analyzing lipids and lipoproteins in geese with xanthoma, showed the presence of hypercholesterolemia and hypertriglyceridemia in the blood serum (16). Similar results were obtained by Souza et al. dealing with a case of conjunctival xanthoma in a blue-and-yellow macaw. In the biochemistry panel, in addition to elevated cholesterol, he also found leukocytosis, increased AST and creatinine levels. After surgical removal of the xanthoma and reduction of fats in the parrot's diet, he did not find recurrence of skin lesions (37). In the case of wild birds, e.g. pelicans, which feed mainly on fish and varied food, injuries turned out to be the presumed cause of skin xanthomas (6). The large weight of the bird's body and difficult access to feeding places on the rocks expose the birds to repeated injuries in the area of the sternum and may contribute to the formation of subcutaneous xanthomas in this area (6). Repeated microtrauma causes a local increase in vascular permeability through the release of histamine and other intrinsic vasoactive compounds, and consequent excessive infiltration of plasma lipids and lipoproteins into the connective tissue (23, 34). The formation of xanthomas in the skin and subcutaneous tissue at sites exposed to pressure, usually over bony prominences, or as a tissue response to repeated microinjuries has also been described in humans (5, 34, 38).

Xanthomas have also been diagnosed in amphibians and reptiles (snakes and lizards). Nodular cholesterol clusters and lipid-laden macrophages were found post-mortem in the lateral brain ventricles of 5 hydrocephalic geckos (8) and in the coelomic cavity of a leopard gecko (32). Since the lesions occurred mainly in female reptiles, the authors speculated that xanthomatosis appeared to be sex-related. Increased blood cholesterol levels in these animals may have arisen because of alterations in cholesterol metabolism secondary to folliculogenesis, follicular degeneration, and/or yolk coelomitis (8).

Xanthoma diagnosis

Fine-needle biopsy helps in the initial diagnosis, however, the final diagnosis requires histopathological examination. The microscopic image shows characteristic foamy macrophages, cholesterol and lipid deposits. Multinucleated giant cells and low numbers of neutrophils, eosinophils, lymphocytes and plasma cells may also be present (1, 22, 27).

Xanthoma therapy

In addition to direct surgical removal of xanthomatous masses, the treatment of patients with xanthoma should also include the treatment of metabolic and endocrine diseases that contribute to the formation of these lesions (9, 38). Treatment of hyperlipidemia-related diseases requires the identification of the underlying lipoprotein disorder and other possible exacerbating factors. Thus, metabolic diseases such as diabetes mellitus, hypothyroidism and hyperadrenocorticism should be excluded (1, 34). It should be remembered that in the treatment of xanthomas, the goal is to optimize the patient's lipid profile. It is advisable to evaluate the diet in terms of fat content and periodically monitor the concentration of cholesterol and triglycerides in the blood serum. In animals, treatment of xanthomas should begin with a low-fat diet. It is generally recommended that diets should contain less than 20% fat on a metabolizable energy basis for dogs and less than 25% for cats (7). In addition, the introduction of lipid-lowering pharmacological agents may be considered. Agents used in humans, such as: niacin, omega 3 acids, chitosan, fibric acid derivatives or statins, give good therapeutic effects (9, 18, 22). These agents have been used in animals, but due to their dubious effectiveness and a large number of undesirable side effects, such as weakness and muscle pain, gastrointestinal disorders, and vision and taste disorders, their use is limited (9). Surgery, including laser surgery and cryosurgery should be instituted if dietary changes or treatment of comorbidities prove insufficient significantly reduce the size of the tumors (3, 13, 16, 31, 32). Small, individual yellow spots that do not adversely affect the comfort and functioning of the animal should be only monitored for growth.

Based on our own experience and a review of the literature, it has been shown that xanthomas occur in various species of animals and humans. The macroscopic appearance of xanthomas is not unambiguous and skin lesions may have a different shape, size and external structure. Xanthomatous changes also appear outside the integumentary system and are often a reflection of systemic diseases associated with disorders of lipid metabolism. Therefore, in order to ensure optimal results in the diagnosis and treatment of xanthomas, close cooperation of an interdisciplinary team (surgeons and internists) is necessary (3).

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