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RESEARCH ARTICLE

Cutaneous angiomatosis-like presentation in koi carp (*Cyprinus carpio* koi): Clinical–pathological investigations

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Abstract

The skin represents an indicator of an animal's health status. Causes of cutaneous diseases in fish most often trace back to biological agents. However, fish skin diseases can also arise from a complex interaction of infectious and non-infectious causes, making it more difficult to identify a specific aetiology. In the period between April and September of the years 2019–2022, four koi carp (*Cyprinus carpio* koi) from two European countries presented with multifocal, irregularly round, few mm to 1 cm, variably raised cutaneous reddened areas. The fish displayed good general condition. Cutaneous samples, investigated by microbiological and molecular methods and microscopy, did not indicate a primary pathogenic agent. Gross and histological findings of the cutaneous biopsies were consistent with a multifocal/reactive process centred on dermal vessels. The histological features were reminiscent of angiomatosis, a benign proliferative condition affecting the dermal vessels of mammals, including human patients. The clinical–pathological presentation and the dermatologic condition that affected the koi carp are discussed and compared with the veterinary and human literature.

KEYWORDS
angiomatosis, cutaneous disease, koi carp, ornamental fish, skin

1 | INTRODUCTION

Koi carps (*Cyprinus carpio* koi) are an ornamental fish variety frequently kept as pets in domestic ponds worldwide (Ott Knüsel et al., 2016). Fish diseases usually arise from a complex interaction of a variety of factors. The majority of problems affecting ornamental fish have multifactorial causes involving stress as a result of poor husbandry, poor water quality, overcrowding, and overfeeding. In a closed water system, such as a pond or aquarium, water quality analysis is an important procedure. The routine investigation should involve checking levels of ammonia, nitrite, nitrates, and pH; additional parameters such as hardness and dissolved oxygen may be required in some circumstances (Wildgoose, 2001). As an example of environmental causes of disease related to the pond, sunburn causes petechiation and patches of erythema on white and non-pigmented dorsal surfaces of exposed fish, and often occurs in shallow ponds where there is no shade and the water is exceptionally clear.

In such cases, fish may become susceptible to opportunistic pathogens ubiquitous in the water that target skin as a primary portal of entry. Additionally, the skin plays a crucial role in maintaining homeostasis and damage can result in osmoregulatory dysfunction and death. Skin changes may also reflect systemic disease processes, such as septicaemia, manifested as reddening due to hyperaemia of the fins and other areas. Gram-negative bacteria, such as aeromonads, pseudomonads, and vibrios are often the cause of such septicaemic events (Hunt, 2006; Wildgoose, 2001). Among viral agents, *Cyprinid herpesvirus 1* (CyHV1), *Cyprinid herpesvirus 3* (CyHV3), *Carp Sprivivirus* and *Carp edema virus* (CEV) can be associated with cutaneous manifestations (McDermott & Palmeiro, 2020; Su & Su, 2018). In addition, some ectoparasites such as *Lernaea cyprinacea*, and the inflammatory tissue reaction that they produce, may be grossly visible (Wildgoose, 2001). However, rare conditions that are not infectious in nature also exist and need to be taken into consideration.

Four cases of koi carp (*Cyprinus carpio* koi) showing similar cutaneous disorders are presented in this work. The clinical–pathological presentation and the dermatologic condition, based on the current knowledge in veterinary and human medicine, and the possible causes of the disorder, are discussed.

2 | CASE REPORT

2.1 | Animals

In the period between April and September of the years between 2019 and 2022, four koi carp from two European countries presented with multifocal, reddened skin areas. Details of the investigated cases are provided in Table 1. The carp were reared in ponds supplied with water at an uncontrolled temperature, ranging between 18 and 25°C; carp of two ponds had previously been treated with drugs (praziquantel) against gyrodactylosis. The water parameters of two cases (#1 and #3) were measured and compared with normal reference values (Table 2).

3 | DIAGNOSTIC INVESTIGATIONS

3.1 | Parasitological investigation

Skin scrapes and gill clips were sampled by practitioners and evaluated for the presence of parasites. Wet mounts were slip-covered and viewed at 400× magnification with an optical microscope.

3.2 | Bacteriology

Cutaneous swabs from cases #1, #2, and #3 were cultured on Columbia blood agar at 28°C for a minimum of 36 h. The material from dominant colonies was grown on AD plates (ampicillin dextrin agar, Tritium Microbiologie, Eindhoven, the Netherlands). The

TABLE 1 Details of investigated cases.

Case number#	Year	Country	Variety	Sex	Age-size	Housing	History	Follow-up
1	2019	Belgium	Ginrin ochiba	Female	2 years/50–55 cm	In a pond with some trees or plants around that might give some shade	Originally imported from Japan, purchased in a koi shop; presented with cutaneous lesions, mostly ventral, but had completely normal behaviour, good appetite	Full recovery
2	2019	Belgium	Ginrin Chagoi	Female	2 years/50–55 cm	In tanks in covered buildings	Recently imported from Japan, presented with skin lesions, normal behaviour, good appetite	Slow and gradual (weeks) healing; the fish returned to the wholesale
3	2019 and 2022	Belgium	Beni Kikokuryo	Male	>10 years	In a pond without any shading	Originally imported from Japan, clinically referable to multifocal ulcerative dermatitis	Recurrence in 2022; euthanasia requested
4	2019, 2021 and 2022	Italy	NAD	Female	14 years/65 cm	In a tank with artificial shading	Originally imported from Japan, presented with multifocal pinpoint reddened areas, extending craniocaudally, no elective site	Recurrence in 2021 and 2022; euthanasia requested

Abbreviation: NAD, not available data.

TABLE 2 Water quality parameters of two cases (#1 and #3) and normal reference values for koi carp (T. Barbé personal communication).

Parameters (unit of measurement)	Case 1	Case 3	Normal value range
Potential of hydrogen—pH	7.5	7.7	7–8.5
Dissolved oxygen—0_2 (mg/L)	9	n.a.d.	>6
Temperature (°C)	25.1	n.a.d.	2–30
Electrical conductivity—EC (µs/cm)	780	1060	200–500
Total Dissolved Solids—TDS (ppm)	390	530	½ EC
Sodium chloride—NaCl (ppt)	0.4	0.5	<0.5
Carbonate hardness—KH (°DH)	7–8	10	>5
General hardness—GH (°DH)	10–16	11–16	6–25
Free chlorine—Cl (mg/l)	0	0	<0.15
Total ammonia nitrogen—NH3/$NH4^+$ (mg/L)	0	1.5	<0.15
Nitrite—NO_2^- (mg/L)	0	0	<0.1
Nitrate—NO_3^- (mg/L)	0	50	<50
Phosphate—PO_4^- (mg/L)	0	0.5	<0.4

Abbreviation: n.a.d., not available data.

culture selection was made on the basis of the morphology, growth, pigmentation, and odour. The identification was done phenotypically by growth on Kligler–Iron agar, oxidase test, and API 20 NE (BioMèrieux, Schaerbeek, Belgium). In 2021, cutaneous and gill swabs from case #4 were cultured on Trypticase Soy Agar (TSA, Oxoid, Basingstoke, UK) at 25°C for a minimum of 36 h. The material from a few randomly chosen dominant colonies was inoculated onto TSA and incubated at 25°C for 24 h to obtain pure cultures. Molecular identification through 16S rDNA amplification and sequencing were conducted. Briefly, DNA was extracted from pure colonies through the boiling method, and the amplification of 16S rDNA was performed with primers P0F and P6R using 100 µL of each lysed cell suspension according to a previously described procedure (Caccamo et al., 1999). Polymerase chain reaction products were purified and sequenced for bacterial identification. Sequences were obtained through the Bio-Fab Sequencing Service (Rome, Italy) and then analysed using the online Basic Local Alignment Search Tool (BLAST) (2023) web interface provided by the National Center for Biotechnology Information (NCBI) to confirm bacterial identity.

3.3 | Molecular analyses

The presence of the following pathogens was investigated through PCR assays: CyHV1, responsible for carp pox, CyHV3 otherwise known as koi herpesvirus (KHV), Carp edema virus (CEV), and Rickettsia-like organism (RLO).

A gill sample from case #1 was tested for KHV and CEV presence using the iiPCR tests (IQ Plus kit, GeneReach, Taiwan) and following the manufacturer's instructions.

RLO and CyHV1 DNA presence was investigated in cutaneous tissues. Total DNA was extracted from formalin-fixed, paraffin-embedded (FFPE) samples of cases #1, #2, and #4 and from an alcohol sample of case #3 using the Purelink Genomic DNA kit (Invitrogen; Carlsbad, CA, USA) following the manufacturer's instructions with minor modifications. For FFPE samples, excess paraffin was removed from the samples using sterile scalpels, and 10–15 mg of sliced FFPE tissue was placed in 1 mL of xylene (JT Baker, Deventer, and the Netherlands). A previously described method was used as a pre-extraction step to remove paraffin from the samples (Sirri et al., 2018). Samples were deparaffinized in xylene for 5 min; following centrifugation, samples were washed twice in 100% ethanol. The pellet was dried at 37°C for 10 min, and DNA extraction was subsequently undertaken using the aforementioned kit. The DNA quality was evaluated for all samples through a PCR assay targeting a fragment of the thyroid-stimulating hormone (TSH) gene according to a protocol previously described (Sirri et al., 2018). Positive samples for the TSH gene PCR were further analysed to detect the presence of RLO and CyHV-1 DNA. RLO presence was investigated with a nested PCR targeting the 16S rRNA gene as previously described (Galeotti et al., 2021). For CyHV1 DNA detection, a previously described method targeting the thymidine kinase gene was used (Crossland et al., 2018). Positive and negative controls were run along with all PCR reactions.

3.4 | Histology

Four bioptic samples of affected skin (one for each animal examined) were collected and preserved in 10% neutral buffered formalin and alcohol. After 48 h, formalin-fixed specimens were dehydrated in ethanol series and paraffin-embedded. Tissues were cut at 4 µm and stained with routine haematoxylin–eosin (HE) to study the morphology of the skin lesions. To assess the presence of intralesional bacteria, the Warthin–Starry stain was performed using a commercial kit (Histoline Laboratories, Milan, Italy), including an archived case of canine cutaneous bacillary angiomatosis as a positive control. The slides were evaluated by means of a Leica DM1000 (Leica Microsystems) optical microscope. An archived HE slide of healthy koi carp skin was included for comparative purposes.

3.5 | Ultrastructural analysis (transmission electron microscopy)

Samples were placed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer, post-fixed with 1% osmium tetroxide, dehydrated, and

embedded in Durcupan ACM resin (Sigma-Aldrich). From toluidine blue stained semi-thin sections (0.7 Lm), selected ultrathin sections (60 nm) were obtained and stained with uranyl acetate and lead citrate. The ultrastructural observations were made with a Philips EM 208 transmission electron microscope (Philips; Eindhoven, Holland) operating at 80 kV.

4 | RESULTS

4.1 | Animals

The fish displayed good general condition, normal behaviour and appetite. In one animal (case #4), the cutaneous lesions recurred in June 2021 and May 2022, and similarly to what happened 2 years earlier, small red foci appeared starting from the head, and then progressively extending to the caudal part of the body.

Out of the four carp, one (#1) is currently in a good health, one (#2) was returned to the wholesaler at the time of sampling, whereas cases #3 and #4 were euthanized at the owner's request due to recurrent presentation.

Grossly, the skin of the four koi carp presented a similar aspect, with multifocal, irregularly round, few mm to 1 cm, variably raised cutaneous reddened areas (Figure 1a), located on the dorsal, lateral, and ventral body aspects (Figure 1b), without any apparent association with the normal coloured areas. In case #4, the reddened areas were more prominent at the level of the face (Figure 1c); the site of the cutaneous biopsy, performed ventrally and near the opercular opening, is shown (Figure 1d).

4.2 | Parasitological and bacteriological investigations

Observation of wet mounts from scrapes did not show the presence of parasites.

Motile *Aeromonas* sp. and *Enterococcus* sp. were isolated from cases #1 and #3. Case #2 resulted negative for bacteriological examination. *Flavobacterium* sp. was isolated from the skin and gills of case #4. Furthermore, *Shewanella xiamenensis* was identified from a colony isolated from the cutaneous swab of case #4.

4.3 | Molecular analyses

The gill sample from case #1 resulted negative to the tests for KHV and CEV. Regarding cutaneous samples, only the DNA from two (cases #1 and #3) out of four samples were suitable for further molecular investigation. The presence of RLO DNA or CyHV1 DNA was not detected in the investigated samples.

4.4 | Histology

All the biopsies included the epidermis and dermis and displayed similar histologic features among the cases investigated. In comparison with a histological sample of healthy koi carp skin (Figure 2a), the superficial dermis was expanded by an inflammatory/reactive process, characterized by the presence of multifocal dilated small vessels (Figure 2b), sometimes engorged with erythrocytes or a

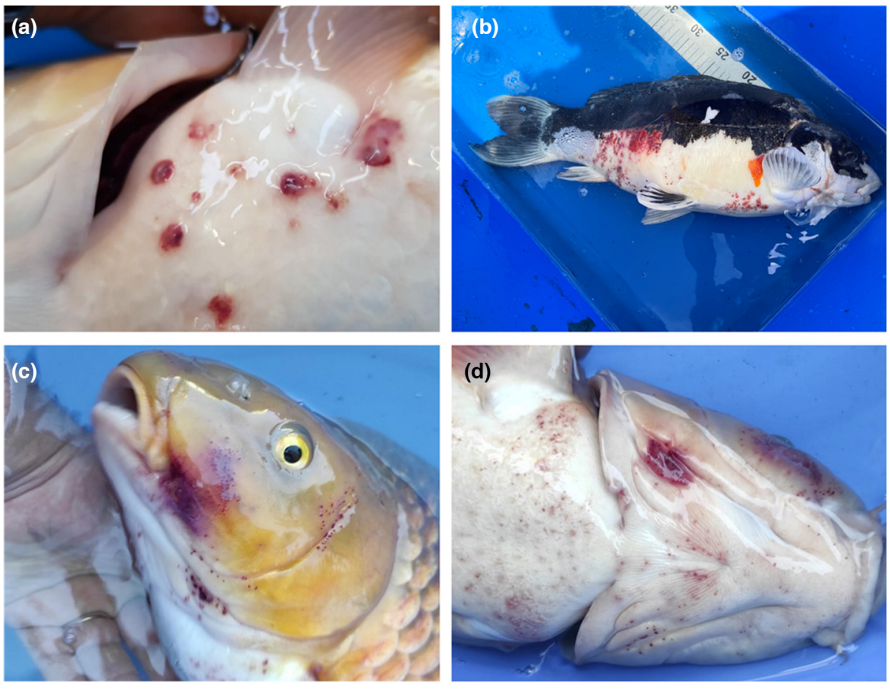

FIGURE 1 Macroscopic appearance of the skin lesions in the affected koi carp. (a) Case #2: Multifocal, irregularly round, few mm to 1 cm, variably raised cutaneous reddened areas, (b) Case #3: The reddened areas were located on the dorsal, lateral, and ventral body aspects, without any apparent association with the normal colour. (c) Case #4: The reddened areas were more prominent at the level of the face, and (d) at the site of cutaneous biopsy near the opercular opening.

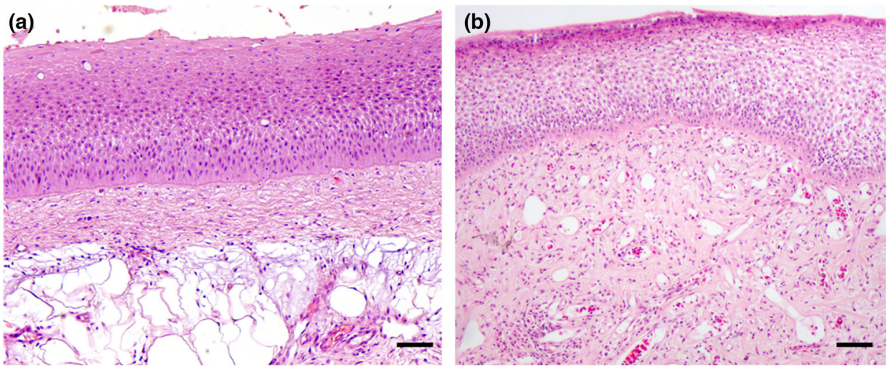

FIGURE 2 Histological presentation common to the four koi carp (HE stain). (a) Skin of a healthy koi carp (left) in comparison with (b) a case affected by the angiomatosis-like condition (right), which is characterized by multiple dermal vessels expanding the superficial dermis. Bar = 50 μm.

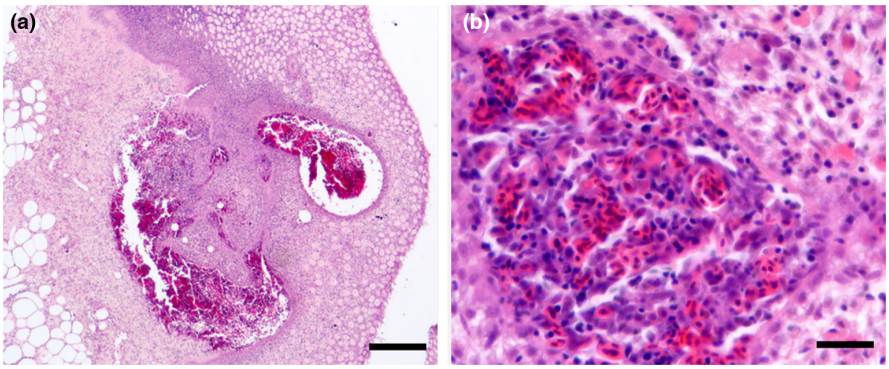

FIGURE 3 (a) Vascular changes affecting the superficial dermis, well reflecting the gross presentation. (b) At higher magnification in some areas of the tissue, the coexisting presence of dermal capillaries, alternated with basophilic nests of cells, produced a glomerular-like tuft appearance. Bar = 200 and 40 μm.

pinpoint, multifocal to diffuse, dermal hyperaemia, characterized by a more evident vessel ectasia. At higher magnification, multifocally, well-demarcated round to oval clusters measuring 30–400 μm in diameter, composed of densely packed vascular structures filled with erythrocytes, were detected. In particular, in case #2, at low magnification, the vascular changes affecting the superficial dermis were evident (Figure 3a) and reflected the gross presentation; at higher magnification, the coexisting presence of dermal capillaries, alternated with basophilic nests of cells, produced a renal glomerular-like tuft appearance (Figure 3b). As additional findings, in association with the dermal vascular lesions, but not sparing the epidermis, there was an inflammatory component represented by eosinophilic granular cells (EGCs), together with lymphocytes and macrophages, to a lesser extent. The surrounding dermis showed diffuse, moderate oedema and the epidermis overlying the vascular lesions was either focally ulcerated or hyperplastic. The small vessels, interpreted as capillaries, were lined by a single layer of flat, well-differentiated endothelial cells (Figure 4a).

4.5 | Semi-thin section findings

In the semi-thin sections, there was a poorly circumscribed proliferation of disorganized, variably-sized, vascular structures in the dermis. The redundant small vessels (capillaries) were lined by a single layer of flat, well-differentiated to plump endothelial cells. Most of the vessels were engorged with erythrocytes and mononuclear inflammatory cells; occasional clusters of seemingly empty, dilated vascular channels were also observed. Interspersed and surrounding the capillaries were proliferating spindle to plump ovoid to stellate cells with ellipsoid and occasionally indented nuclei (activated fibroblasts or pericytes). Intense inflammatory infiltrate (lymphocytes, plasma cells, histiocytes, and EGCs), and multifocal amorphous material (myxoid matrix) separating the vessels were also observed (Figure 4b). Unfortunately, artefacts occurred in the ultrathin sections, even though in case #4, the sampling was made with proper measures, which did not allow the development of a meaningful interpretation of the sample.

5 | DISCUSSION

In the koi carp investigated, the endothelial cells, or less probably pericytes, were thought to be the main elements involved in the pathologic process. The cutaneous presentation suggested considering granulation tissue formation, which constitutes a key step during wound healing (Jiang & Scharffetter-Kochanek, 2020). Granulation tissue is a highly plastic tissue, composed of new connective tissue, fibroblasts, myofibroblasts, inflammatory cells, and newly formed capillaries (Sveen et al., 2020) with abundant oedema. The granulation tissue formation can be elicited by infectious and non-infectious factors such as chronic trauma. Histologically, it is characterized by plump fibroblasts and small-calibre blood vessels, with hypertrophied endothelial cells, arranged perpendicularly to the overlying epithelium (Hurley-Sanders et al., 2016). In the cases here described, there was an inflammatory cell component, however,

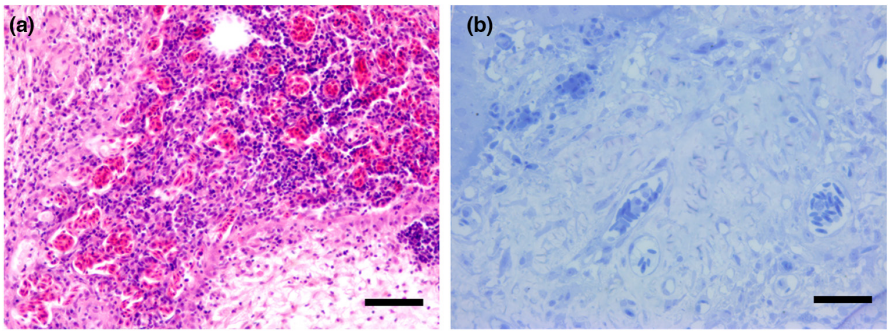

FIGURE 4 Histological findings of the cutaneous biopsies. Case #2: (a) HE and (b) Toluidine Blue semi-thin section. The capillaries are lined by hypertrophic endothelial cells filled with several red blood cells. Bar = 200 and 100 μm.

the findings were represented by several dermal capillaries lined by hypertrophied cells, interpreted as endothelial cells; the capillaries did not show any specific orientation toward the epithelium, and the presence of newly deposited connective/collagen material was not noted. For these reasons, the hypothesis of granulation was ruled out. On a whole, the multifocal distribution of small-calibre vessels, the lack of cellular atypia of the elements, constituting the vessels and their cellular precursors, were reminiscent of a vasoproliferative condition, known in human and veterinary medicine as angiomatosis.

Angiomatosis includes a heterogeneous group of non-neoplastic vascular diseases that can affect cutaneous and visceral tissues. It belongs to the cutaneous disorders centred on dermal vessels that may affect veterinary patients and human beings (Gross et al., 2005; Weedon, 2002).

Specifically, bacillary angiomatosis is a vasoproliferative tumour-like lesion in human patients. It usually affects immunocompromised individuals and is caused by a bacillus belonging to the genus *Bartonella*. The pro-angiogenic and pro-inflammatory response of the tissue to this bacillus explains the gross appearance (Lima et al., 2014). At histology, *Bartonella* bacilli are black with the silver impregnation Warthin–Starry stain. In our koi carp, this staining did not demonstrate the presence of bacteria.

In human dermatopathology, cutaneous reactive angiomatoses encompass a distinct group of rare benign vascular proliferations. The aetiology of these conditions, often associated with either localized or systemic diseases, is poorly understood; at least six forms with different histopathological patterns have been described. Histologically, they are associated with a proliferation of endothelial cells, either intravascular or extravascular, and a lobular or diffuse distribution, together with pericytes or histiocytes (Corti et al., 2013). The common characteristic is the tendency to develop either a vasculopathic occlusive process or an inflammatory vascular reaction that generates a localized hypoxic stimulus causing endothelial neovascularisation. Endocrinopathies (i.e. hypothyroidism), an increasing hypercoagulability status, cirrhosis, other chronic liver diseases, and general local or systemic diseases should be considered as predisposing conditions. No specific treatment is available for cutaneous reactive angiomatosis; it is usually managed by treating the underlying systemic disorder. Antibiotics for occult infections and systemic steroids for their suppressive effect on neoangiogenesis have also been used in cases where no apparent underlying aetiology has been found. Some cases can resolve spontaneously (Bin Saif et al., 2015). This diagnosis should be based on the clinical–pathological correlation, rather than the pure morphology of the cells involved (Enzinger & Weiss, 1983).

In veterinary medicine, angiomatosis can affect various organs and tissues of domestic and wild animal species, including, cats, horses, cows, llamas, and dolphins (Cerri et al., 2019; Leitzen et al., 2020). Cutaneous angiomatosis is a proliferative lesion of the vascular tissue involving the dermis and subcutis of dogs (Koo et al., 2021). It is considered rare, with little information on its causes, clinical behaviour, and treatment options. In dogs, there are reports of angiomatosis as a congenital problem, secondary to the use of immunosuppressive doses of prednisolone or as a complication of sepsis (Marchis & Veiga-Parga, 2019). Clinically, the angiomatosis lesions are progressive and can expand into surrounding tissues, mimicking the behaviour of low-grade malignancies, such as fibroma, haemangioma, and lipoma (Baron et al., 2020; Gross et al., 2005). As a whole, data on signalment, clinical presentation, and follow-up are able to support the histopathological diagnosis but are rarely sufficient to differentiate angiomatosis from neoplasia (Abramo et al., 2018). Nevertheless, the current view of the condition is that it is hamartomatous rather than neoplastic, in consideration of the multifocal arrangement of the vascular foci, the different nature of the vessels involved, and the prominent monolayered endothelial lining (Olivieri et al., 2010).

In dogs, cutaneous progressive angiomatosis is well known (Abramo et al., 2018, 2022); recently, 11 histopathological criteria were analysed in 31 cases and 11 primary cutaneous hemangiosarcomas in dogs. The absence of plump/prominent endothelial cells, lack of atypia, and lack of mitoses constituted significant factors differentiating it from hemangiosarcoma.

The clinical–pathological investigation performed on these koi carp is the first report of such a condition in fish and provides a description of gross and histological findings. However, several questions remain open. The water parameters, while limited to two of the four cases, were within the normal range; this, in association with the general good health of the animals suggests a quite limited role that environment and aquatic microorganisms could have played in triggering the disease. As a matter of fact, microbiological and molecular investigations reported no major pathogens potentially associated with the described condition. Regarding the fish investigated, a direct effect produced by improper sunlight exposure was excluded, since the skin was indifferently involved on the dorsal,

lateral, and ventral aspects of the fish; moreover, most of the ponds were adequately shaded.

One of the investigated animals (case #4) was treated with dexamethasone; the use of dexamethasone in human patients may have played a role in vascular regulation and the disappearance of the cutaneous lesions in some cases (Bin Saif et al., 2015). Regarding the pharmacological effect of dexamethasone, Katychev et al. (2003) demonstrated that pericytes, in particular, undergo apoptosis in response to this corticosteroid, suggesting that the regulatory function of this steroid may be important in vascular development and that pericyte apoptotic cell death may accompany vascular regression. The authors of the above-cited paper concluded that the deregulation of pericytes involved in vascular homeostasis may result in clinical disease.

The identification of the cells, interpreted as endothelial cells or pericytes, was one of the aims of this study. Unfortunately, the quality of the tiny biopsies was not adequate to obtain a good morphology for ultrastructural studies. Only semi-thin sections supported the histological findings in the unique case from which a sample was obtained, highlighting flat endothelial cells surrounding capillaries and reinforcing the concept of the plasticity of these cells. Indeed, the ability of endothelial cells to undergo cell fate changes has been seen throughout development, during injury repair, and within different disease pathologies. This indicates that endothelial cells are not only plastic during embryonic stages but also into adulthood, where they can respond to changes in local signals and hemodynamic forces (Greenspan & Weinstein, 2021).

In all the cases observed in the present study, the endothelial cells, under the influence of still unknown causes, were part of a vascular reaction that could have generated a hypoxic stimulus causing the endothelial activation.

Some limitations resulting primarily from the inconsistent collection of the anamnestic data about the koi carp, which are of fundamental importance to set up a correct interpretation, were present in this study. The different places of origin of the animals were a logistic complication, which on the other hand, permitted comparison among cases living in two European countries. Another weakness of the study was represented by the tiny size of the cutaneous biopsies, explainable by the economic and emotional value of the fish studied. This made it necessary to choose certain investigations at the expense of others, which could lead to the definition, for example, of the vessel wall composition. Unfortunately, the ultrastructural study did not allow any meaningful contribution to the identification of the cells that were prone to the reactive process. This technique, never employed in mammalian studies, could add significant information about the cells actively involved in the process, and its use could be emphasized among veterinarians and research laboratories.

6 | CONCLUSIONS

This study, carried out on cutaneous bioptic samples of four koi carp, identified an angiomatosis-like vascular condition, which showed similarities with that reported in mammalian and human patients.

The lack of mammalian anatomical structures, such as the cutaneous adnexa and the different constitutive architecture of the dermis of fish does not allow adaptation of the histopathological criteria recently identified in the retrospective study of canine cutaneous progressive angiomatosis (Abramo et al., 2022).

For the koi carp studied, we prefer to use the more general term angiomatosis-like, without focusing on its possible 'progressive' connotation, although the clinical course, of at least two cases, suggests this eventuality. The recurrence in two out of four analysed cases suggests a less benign clinical course compared with that observed in mammals.

Being aware of the limitations of this study, the authors wish to contribute by pointing out the existence of cutaneous angiomatosis-like, a benign vasoproliferative, non-neoplastic condition centred on dermal vessels in koi carp. We encourage collaboration among veterinarians in collecting information and sharing cases to widen the knowledge about this condition and provide the basis for future studies.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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