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RESEARCH ARTICLE

Branchial Arteritis in Rainbow Trout, *Oncorhynchus mykiss* (Walbaum, 1792): A Novel Pathology Associated With Environmental and Infectious Stressors

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ABSTRACT

The frequency and impact of non-infectious cardiac and vascular diseases in salmonids have increasingly been recorded in the recent literature. Among others, case collections reported enlarged and round-shaped heart, vessels misalignment, epicarditis, coronary and ventral aorta arteriosclerosis, and myocardial fibrosis, degeneration, and necrosis, highlighting their potential influence on fish wellness, performance, and mortality and raising considerable attention in the field. In the present cases, peculiar histopathologic lesions involving the branchial arteries, bulbus arteriosus and ventral aorta developed after intense rainfalls in rainbow trouts. The morphological changes encompassed a spectrum of inflammatory arterial lesions of varying severity, ranging from mild inflammation to severe arteritis with fibrinoid necrosis and thrombosis, thus differing substantially from those previously reported. The context is further compounded by the presence of a severe and systemic form of proliferative kidney disease in a few subjects. Given the importance of cardiovascular pathology in farmed salmonids, these novel and unusual findings are relevant for understanding the spectrum of cardiovascular lesions potentially affecting these species. Moreover, the impairment of cardiovascular and respiratory function likely entailed by these lesions could compromise fish welfare by reducing their ability to cope with stressful events or adverse climatic environmental conditions.

1 | Introduction

Cardiovascular diseases pose a major threat to the welfare of salmonids and could be responsible for production losses of 10%–20% in salmonid aquaculture (Mercier et al. 2000; Brocklebank and Raverty 2002; Poppe et al. 2007; Brijs et al. 2020).

Since heart morphology and function are strictly linked to the overall animal performance, the high degree of morphological and physiological cardiac plasticity in response to environmental and anthropogenic factors is of specific concern in salmonids (Farrell 2002; Poppe et al. 2003; Gamperl and Farrell 2004; Claireaux et al. 2005; Ferguson 2006; Johansen et al. 2017). Moreover, the heart in salmonids is composed of the inner spongy layer, supplied by the oxygen of the venous blood present in the heart chamber and of the outer compact myocardium, supplied by the oxygen of the coronary vessels. This architecture renders the heart highly sensitive to variations in blood oxygenation, flow and pressure as well as water temperature (Farrell 1991; Ferguson 2006; Ekström et al. 2019). While highly selective breeding programs and intensive rearing conditions have prioritized traits such as rapid growth and late sexual maturation, other traits related to the functional morphology of organs have likely been overlooked (Farrell 2002; Poppe et al. 2003;

Gabrita De Zan's present address is different from where the work was carried out and holds co-primary authorship.

Brijs et al. 2020). A recent study (Brijs et al. 2020) on prevalence and severity of cardiovascular diseases in farmed rainbow trout found that the hatchery of origin was the main contributing factor towards the variability of cardiovascular diseases observed and specifically, of coronary arteriosclerosis. The authors concluded that cardiac abnormalities could potentially lead to significant negative consequences on the cardiac oxygen supply in metabolically demanding activities and on the cardiac electrical activity. They also emphasized the importance of their findings towards not only the improvement of selective breeding and rearing strategies and the reduction of the production losses in salmonid aquaculture, but also in the view of the increasing global temperature and heat waves, thus raising ethical concerns.

Given the impact on salmonid aquaculture, knowledge and reports of cardiovascular diseases and malformations have expanded in the last years. The spectrum of reported lesions includes several conditions that occasionally overlap: enlarged and round-shaped heart, vessels misalignment, coronary and ventral aorta arteriosclerosis (Eaton et al. 1984; Farrell 2002; Claireaux et al. 2005; Dalum et al. 2017; Brijs et al. 2020), coronary myointimal proliferation (Poppe et al. 2007), bulbus arteriosus epicarditis (Dalum et al. 2017), myocardial fibrosis and degeneration/necrosis (Poppe et al. 2007, 2021), anomalies in the heart rate (Mercier et al. 2000; Brijs et al. 2020), hypoplasia/aplasia of septum transversum (Poppe et al. 1998; Brocklebank and Raverty 2002), situs inversus of the heart (Kaada and Hopp 1995), hypoplasia of the outer, compact ventricular myocardium (Poppe and Taksdal 2000), cardiac hernia with myocardial hypoplasia (Poppe et al. 2002), aneurysm and infarct (Mercier et al. 2000) and round-shaped heart with increased fat deposition (Poppe et al. 2003; Gamperl and Farrell 2004).

Additionally, the inherent heart plasticity of salmonids may result in abnormal and maladaptive changes such as cardiac hypertrophy, remodelling and dysfunction associated with chronically increased cortisol levels in stressful conditions (Johansen et al. 2011, 2017). Moreover, intensive rearing strategies and dietary composition have been investigated as potential risk factors for cardiac diseases (Farrell et al. 1986, 1990; Saunders et al. 1992; Farrell 2002; Gamperl and Farrell 2004; Seierstad et al. 2005, 2008).

Systemic arterial necroinflammatory changes, segmentally involving small to medium-sized arteries and mainly targeting branch points, are described in polyarteritis nodosa (PAN) of both humans and animals. In humans, this disease displays different stages of vasculitis coexisting in different vessels or even in the same vessel, often with the presence of aneurysm and/or thrombosis, suggesting ongoing vascular injury. Although occasionally associated with hepatitis B antigen, the underlying cause remains unknown in most cases (Robbins and Cotran 2021). Based on shared histologic morphologic features with the human disease, PAN has been described sporadically in all domestic animal species (Robinson and Robinson 2015) and frequently in aging rats, where it particularly targets the mesenteric vessels (Barthold et al. 2016).

In the present cases, distinctive vascular inflammatory lesions of rainbow trout, mainly involving the branchial arteries, bulbus arteriosus and ventral aorta, were characterized by degenerative, necrotic and inflammatory changes of both endothelium and vessel wall, with the development of severe fibrinoid necrosis and thrombosis. These features clearly differentiate these lesions from the cardiovascular diseases and malformations previously reported in salmonids, suggesting a novel pathological entity in this field.

2 | Materials and Methods

Two episodes of mortality (10%–15%) affecting adult rainbow trout weighting approximately 150–200 g occurred after periods of intense rainfall in an Italian farm located in the Friuli Venezia Giulia region.

This land-based farm was supplied by river water with a documented history of recurrent episodes of viral haemorrhagic septicaemia and proliferative kidney disease (PKD), as well as water quality issues associated with intense rainfall events.

A total of 25 individuals were sampled during the two episodes of mortality for further diagnostic investigations and distributed as follows: 6 fishes in the first episode and 19 fishes in the second one. The individuals sampled were chosen from among the early dead fishes and the moribund fishes giving priority to those displaying macroscopic lesions. The fishes were euthanized either by spinal severance or anaesthetic overdose according to the legal requirements then in force.

Fresh Smears From Skin and Gills Were Immediately Collected for Parasitological Examination.

Histological samples were fixed in 4% neutral buffered formaldehyde or Bouin's solution and paraffin-embedded. Four-µm-thick tissue sections were routinely stained with haematoxylin and eosin and additional histochemical stains were carried out on selected tissues (Gram, Periodic acid-Schiff, Wright-Giemsa, Alcian PAS, Van Gieson, Masson's trichrome and Ziehl-Neelsen standard techniques). Conventional immunohistochemistry on skeletal muscle, liver, kidney, spleen, gills and sites of lesions was performed using monoclonal antibody against *Tetracapsuloides bryosalmonae* (AquaMAb-P01, Aquatic Diagnostics) according to the literature (Morris et al. 1997, 2000). The specimens were examined under an optical microscope (Nikon Eclipse Ni) equipped with a digital camera (Nikon DSFi3, Nikon Instruments Italia) and the software NIS-Elements BR (Nikon Instruments Italia) for image acquisition.

3 | Results

3.1 | Clinical Findings

The affected fishes appeared darker, lethargic and stayed near the water raceway grates or at the bottom of the tanks. The farm veterinarian noted the presence of dark red nodular lesions protruding from the gill arches. Individuals with the gill lesions were overrepresented in the daily mortality. However, since they were removed during daily routine raceways cleaning by farm technicians, it was not possible to determine their exact proportion in the total daily mortality. These branchial

lesions and the increased mortality apparently recurred randomly over the years at this farm and specifically in association with water quality deterioration following intense rainfall events. Moreover, they were not observed in the other farms owned and managed by the same farmer.

3.2 | Macroscopic Findings

In both episodes, all individuals displayed variably severe gill lesions including gill pallor (anaemia) and increased thickness with glistening surface, consistent with gill hyperplasia and oedema, respectively. In addition, diffuse presence of superficial and interfilamental mucoid and turbid material on gills (excessive gill mucus production) associated with excessive particulate debris on both gills and skin surfaces was observed.

A peculiar branchial lesion was detected in fish 24: an irregularly nodular (about 1 × 1.5 cm), exophytic, whitish and opaque mass, with fibrous consistency was present on branchial filaments displaying areas of continuity and fusion with both adjacent filaments and branchial arches.

Frequently, round to oval (diameter ranging from 0.2 to 1.5 cm), non-infiltrative, demarcated, exophytic lesions protruded from the ventral aspect of the gill arches, at the base of filaments, extending both caudally to the emergence of the ventral aorta and rarely cranially to the ventral aspect of the oral cavity. These masses were brown-red, soft, single or multiple, occasionally adjacent and associated with mild to moderate peripheral haemorrhages (Figures 1A,B, 2A,B and 3A).

Additionally, one individual (fish 12) displayed moderate bilateral nephromegaly characterized by altered renal architecture due to multifocal to coalescing, poorly demarcated, whitish nodular lesions observable both superficially and on cut surface, likely consistent with granulomatous nephritis due to *T. bryosalmonae* infection.

In the liver of one individual (fish 16), irregular, well-demarcated, brown to red, flat lesions with a multifocal to coalescing distribution pattern and with both subcapsular and intraparenchymal localization were also noted. These lesions were interpreted as possible telangiectasia.

3.3 | Microscopic Findings

No cutaneous or branchial ectoparasites were detected on fresh smears taken from skin and gills.

Microscopically, the main lesions were located on gill arches epithelium and vascular system. The gills examined (24 out of 25 fishes) displayed variably severe lesions of chronic proliferative/hyperplastic branchitis.

Superficially, there was the presence of amorphous, brown to grey, occasionally abundant, refractile exogenous material (particulate debris) in association with numerous microorganisms compatible with different stages of algal organisms. The lamellae epithelial stratigraphy was multifocally to diffusely, moderately to severely altered with tissue disarray. Epithelial cells displayed hypertrophy and hyperplasia with piling up of cells in multiple layers and multifocal fusion/synechiae of filaments and lamellae. Epithelial cells appeared multifocally swollen with increased volume and clearer cytoplasm (ballooning/hydropic degeneration); frequent leukocyte exocytosis and occasional single cell necrosis were also evident. Mild deposition of amorphous eosinophilic material, consistent with fibrin, was occasionally evident at the junction of the epithelial layer and fibrovascular axis (basement membrane necrosis). Aspects of hypertrophy, as well as degeneration and necrosis, were observed in the chloride cells. Multifocally, fibrovascular axes displayed a moderate to severe, chronic mixed inflammatory infiltrate composed of lymphocytes, plasma cells and occasional macrophages, mast cells and eosinophilic granular cells, these latter being occasionally prevalent. Areas of moderate to severe stromal reaction were also multifocally evident and characterized by marked fibrovascular hyperplasia and neovascularization. Occasionally, similar inflammatory and stromal proliferative changes involved also the oesophageal chamber and the skin of the cephalic region. Gill lamellae capillaries were frequently characterized by moderate to severe ectasia and congestion with multifocal haemorrhages (telangiectasias/aneurism) and thrombi.

Loma salmonae and monogeneans were also rarely identified (1/24 and 3/24 respectively) in the gill samples. Concerning the single exophytic lesion observed macroscopically in fish 24, it resulted histologically comparable with a 2 mm in diameter branchial nodular lesion observed in fish 5: both were composed of massive lamellar epithelial and fibrovascular proliferation in association with the presence of extrasporogonic *T. bryosalmonae*-stages (Figure 4B).

The nodular lesions observed macroscopically ventrally to the gills arches microscopically resulted targeted on the main gill arteries (afferent branchial artery, recurrent and concurrent branches and filament arteries) and less frequently, on the bulbus arteriosus and ventral aorta (Figures 1C, 2C and 3B).

These lesions were characterized by a spectrum of variably severe, degenerative, necrotic, inflammatory and fibrovascular proliferative arterial changes, displaying different stages of development and distribution, even in the same fish and/or vascular tract, and occasionally occurring abruptly. The spectrum of arterial lesions, starting from the vascular lumen, included:

- Endothelial cell degeneration (swelling and protrusion) and necrosis with mild to moderate chronic inflammation (mainly lymphocytes and plasma cells) in the endothelial layer (chronic non-leukocytoclastic vasculitis/endothelitis) (Figure 2D);
- Denuded endothelial layer with deposition of amorphous and intensely eosinophilic material (basement membrane damage) (Figure 2E) up to the development of thrombi, multifocally laminated with lines of Zahn, occlusive or recanalized (Figures 1C, and 3D); occasionally, thrombi caused severe alteration of the vascular course profile with no longer identifiable wall stratification and abrupt dilations that, in few individuals, were visible macroscopically and corresponded to the nodules described above (Figures 1C, 2C and 3B);

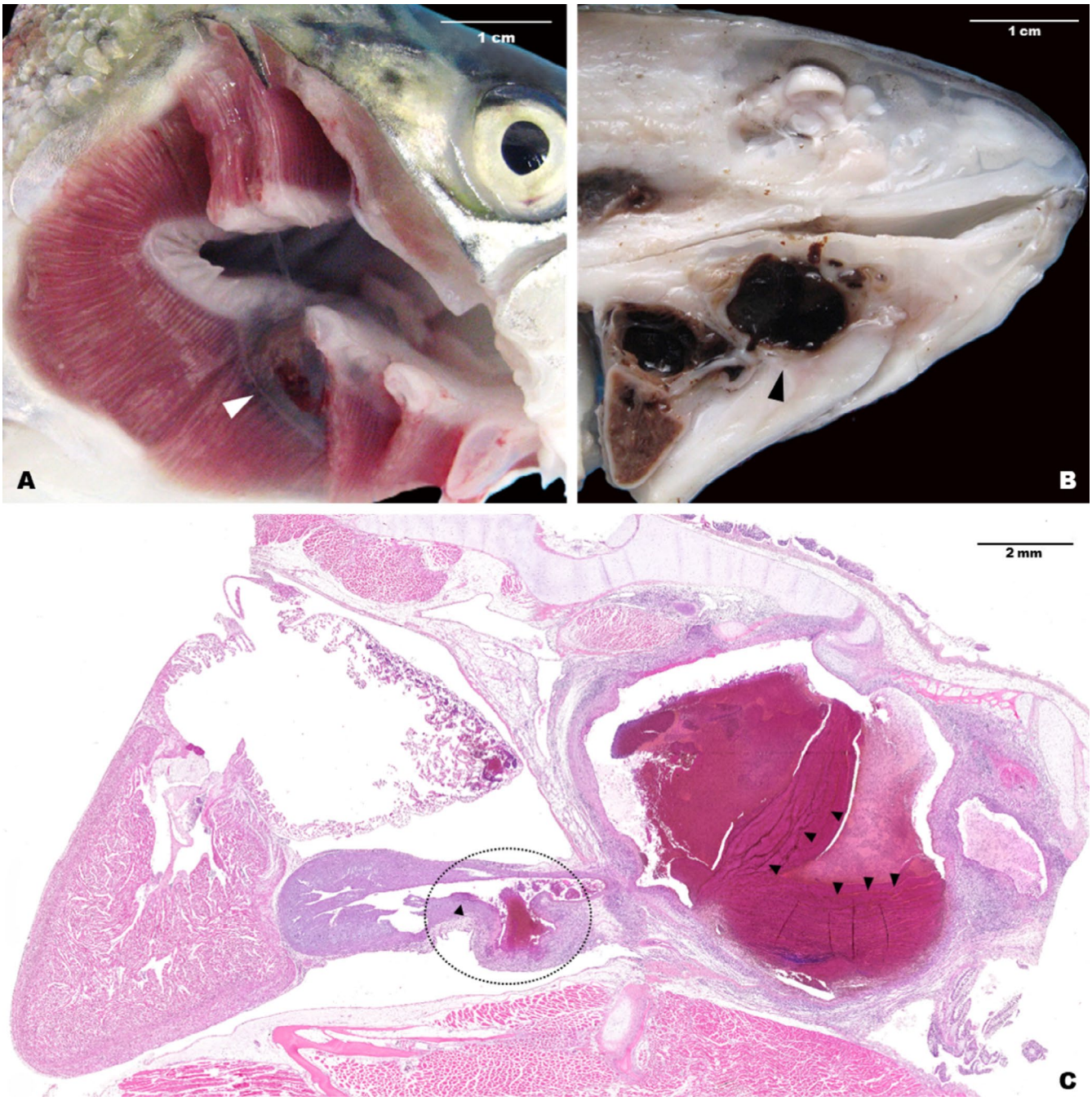

FIGURE 1 | Branchial arteritis in rainbow trout (*Oncorhynchus mykiss*). (A) Fish 1: About 1 cm in diameter, round, brown-red, soft, single, non-infiltrative, demarcated, exophytic lesion on the gills arches, at the base of filaments (arrowhead). (B) This nodular lesion extends both caudally, to the emergence of the ventral aorta and cranially, to the ventral aspect of the oral cavity (arrowhead) with mild peripheral haemorrhages. (C) The nodular lesion corresponds to areas of arteritis of branchial circulatory system extending to bulbus arteriosus and ventral aorta with hernia-like lesion (dotted circle), abrupt arteritis (arrowhead), laminated thrombus with lines of Zahn (arrowheads) and moderate peripheral chronic mixed inflammation with bone resorption/lysis on the upper right (H&E).

- Focal endothelial papillary hyperplasia;
- Internal elastic lamina disarray (wrinkling, dissociation and disruption) and/or mucinous matrix interstitial deposition and/or fibrinoid necrosis (Figure 2E);
- Moderate to severe vascular and/or perivascular chronic mixed inflammation composed of lymphocytes, plasma cells, macrophages and occasional Mott cells and eosinophilic granule cells (chronic mixed non-leukocytoclastic arteritis and periarteritis) (Figures 2D,E and 3C,D);
- Peripherally to the foci of inflammation and vasculitis, severe fibrovascular proliferation with fibroblastic hypertrophy/hyperplasia, neovascularization and vascular remodelling occurred; these inflammatory and proliferative changes extended multifocally to the adjacent soft tissues

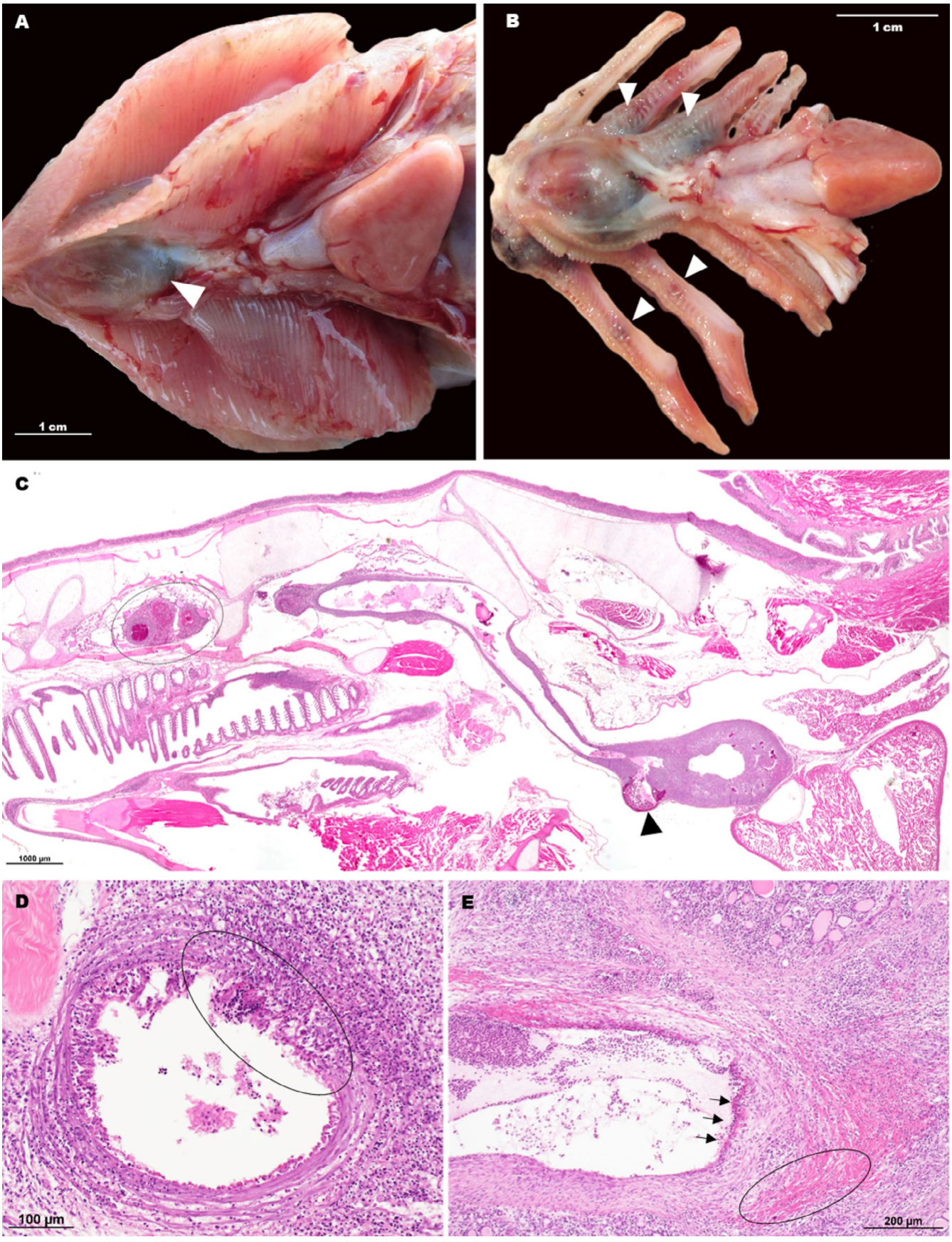

FIGURE 2 | Legend on next page.

FIGURE 2 | Branchial arteritis in rainbow trout (*Oncorhynchus mykiss*). (A) Fish 17: About 1.5 cm in diameter, round, brown-red, soft, single, non-infiltrative, demarcated, exophytic lesion on the gills arches, at the base of filaments, close to the emergence of the ventral aorta. (B) The same nodular lesion after gill lamellae cutting with evidence of similar but less severe alterations on the branchial arches (arrowheads). (C) Fish17: Hernia-like lesion (aneurysm) of the bulbus arteriosus (arrowhead) and foci of milder arteritis of the branchial afferent circulation (dotted circle) (H&E). (D) Chronic non-leukocytoclastic vasculitis with endothelial cells degeneration (swelling and protrusion) and necrosis and moderate chronic mixed inflammation (mainly lymphocytes and plasma cells) (circle) (H&E). (E) Chronic non-leukocytoclastic vasculitis with basement membrane necrosis (arrows), fibrinoid necrosis (circle) and peripheral chronic mixed inflammation extending to the thyroid gland on the upper right (H&E).

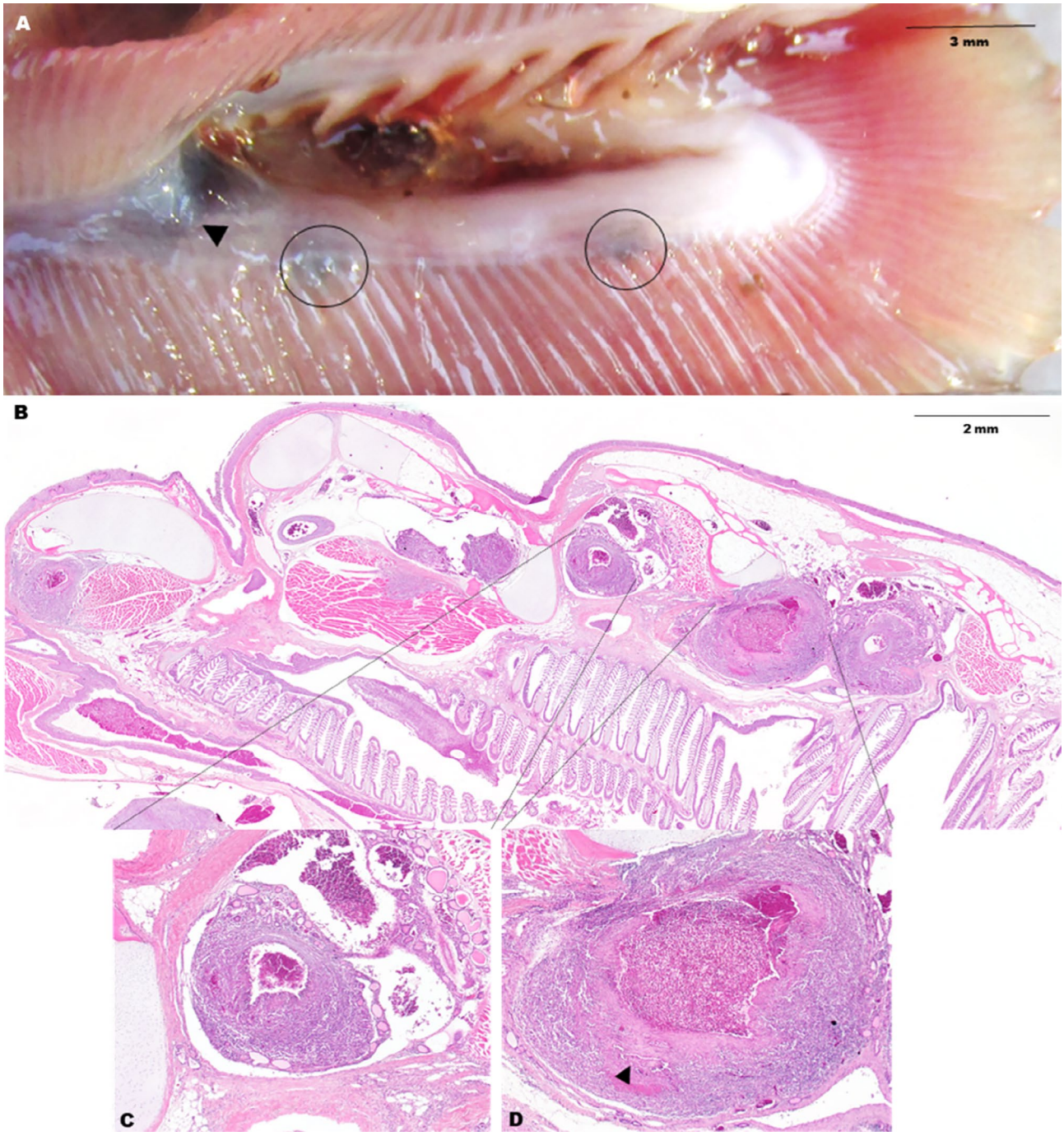

FIGURE 3 | Branchial arteritis in rainbow trout (*Oncorhynchus mykiss*). (A) Foci of severe (arrowhead) and subtle arteritis (circles) at the base of filaments. (B) Foci of less severe arteritis with chronic non-leukocytoclastic vasculitis (C) and thrombosis with recanalization (arrowhead) (D) (H&E).

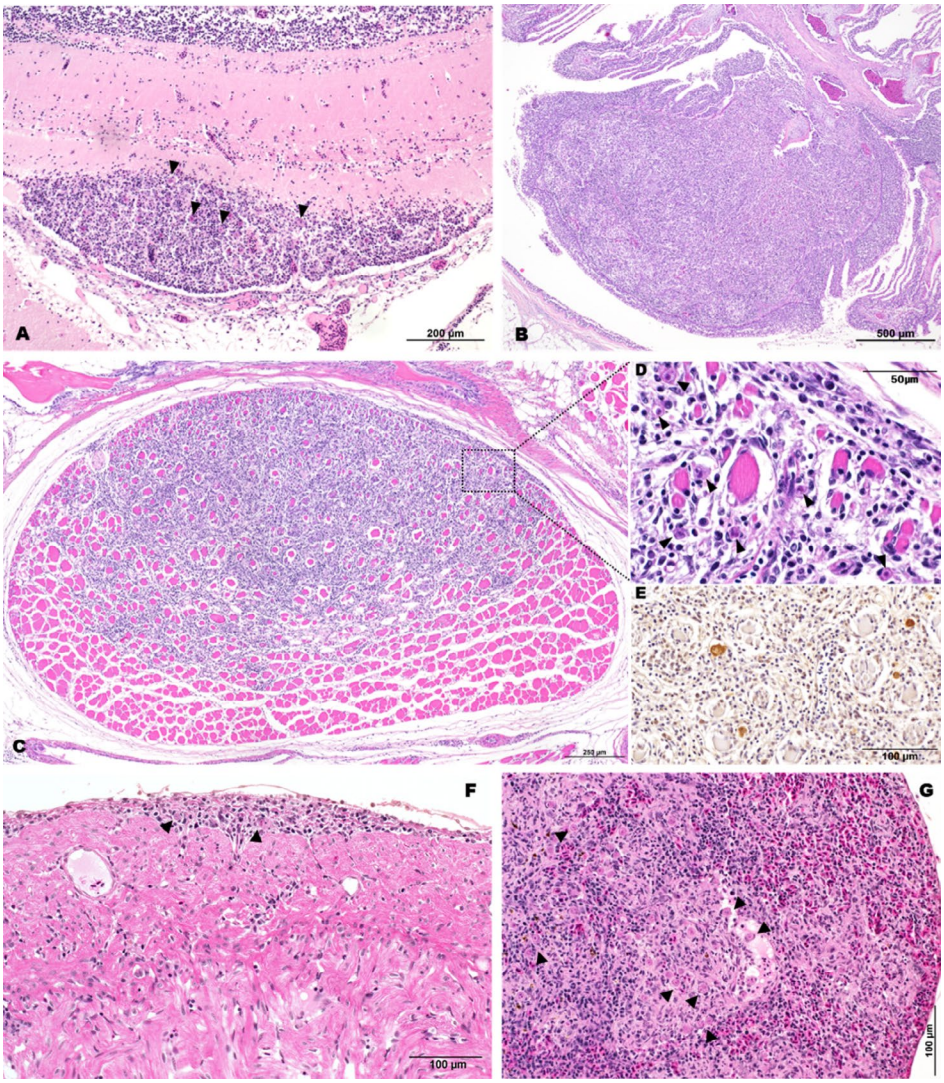

FIGURE 4 | Visceral lesions of systemic proliferative kidney disease in rainbow trout (*Oncorhynchus mykiss*). (A) Moderate, locally extensive, chronic mixed meningitis with rare extrasporogonic *T. bryosalmonae*-stages (arrowheads) (H&E). (B) Fish 5: Massive lamellar epithelial and fibrovascular proliferation with intralesional extrasporogonic stages (H&E). (C) Cephalic skeletal muscle: Effacing almost the entire muscular fascicle and dissecting myocytes is a severe chronic inflammation, mainly composed of lymphocytes and plasma cells, with myocyte atrophy and frequent, intralesional extrasporogonic stages (H&E). (D) Higher magnification of intralesional extrasporogonic stages (arrowheads) (H&E) and (E) positive immunolabelling of extrasporogonic stages in the muscle. (F) Fish 12: Moderate, locally extensive, chronic mixed epicarditis with intralesional extrasporogonic stages (arrowheads) (H&E). (G) Moderate granulomatous splenitis with numerous intralesional extrasporogonic stages (arrowheads) (H&E).

(e.g., thyroid) (Figure 2E) and/or hard tissues with degeneration/lysis/resorption of the osteocartilagineous tissues (Figure 1C).

In 11 out of 13 fishes examined, we observed cardiovascular lesions that, in the heart, occasionally displayed areas of continuity with the branchial arterial lesions detailed above and similarly exhibited different patterns of distribution and severity, as follows:

- Chronic mixed epicarditis, myocarditis and endocarditis with rare areas of myocardial and endocardial (valvular) necrosis and multifocal extension to the ventral aorta (peri/endoarteritis); occasionally, endocarditis/endothelitis arose abruptly (Figure 1C), extrasporogonic *T. bryosalmonae*-stages were observed in the context of epicarditis (fish 12) (Figure 4F);
- Severe and focal alteration of the profile of the bulbus arteriosus wall, in proximity to the emergence of the ventral aorta, with segmental dilation and arteritis (hernia-like lesion, fish 1) (Figure 1C) or protrusion of the intimal layer into the muscular wall (aneurysm, fish 17) (Figure 2C);
- Multifocal visceral papillary endothelial hyperplasia (Figure 5A).

Further significant histopathologic alterations are discussed below.

3.3.1 | Skeletal Muscles

Chronic mixed myositis was frequently observed (11 out of 12 fishes examined). Multifocally, muscle fibres or entire muscle

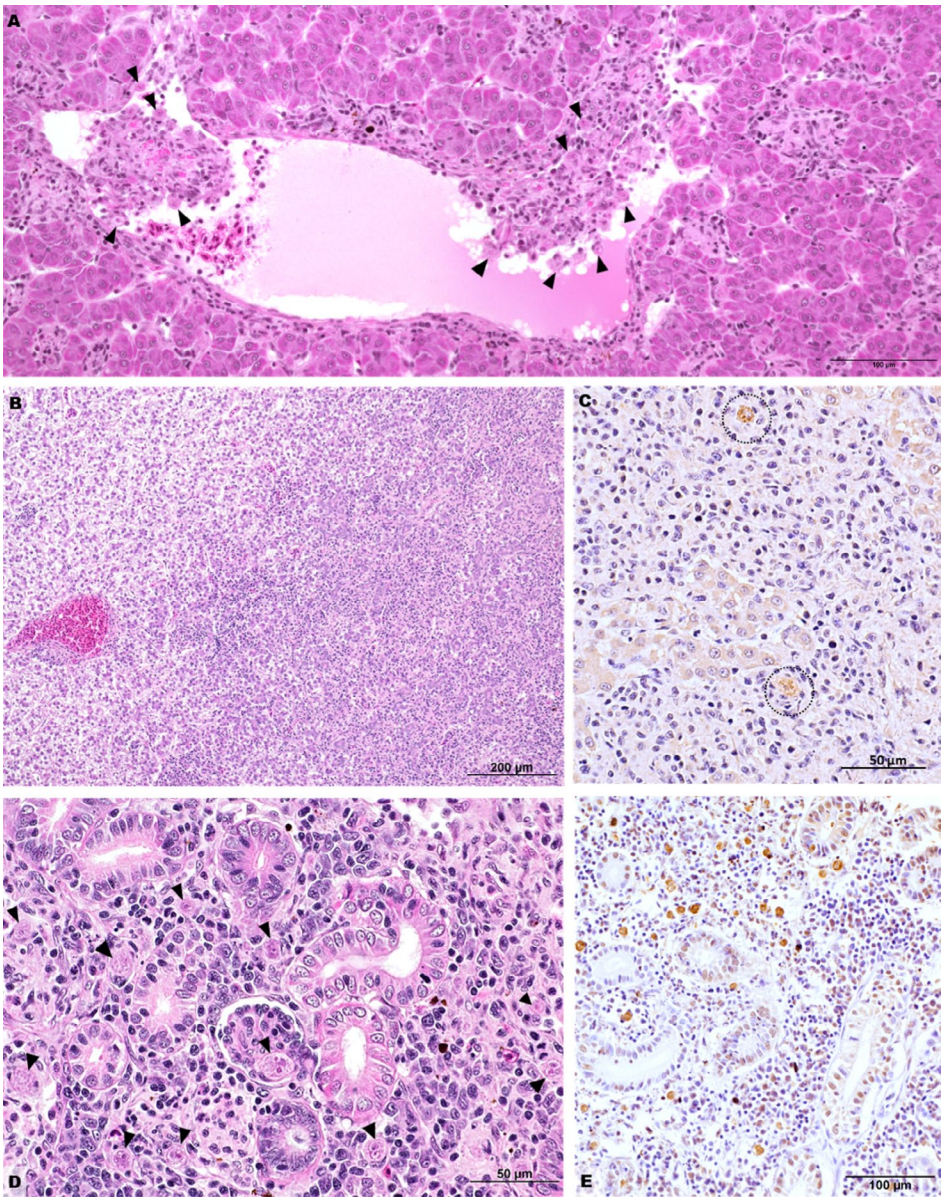

FIGURE 5 | Visceral lesions of systemic proliferative kidney disease in rainbow trout (*Oncorhynchus mykiss*). (A) Liver, multifocal endothelial papillary hyperplasia with mild chronic mixed inflammation and numerous intralesional extrasporogonic *T. bryosalmonae*-stages (arrowheads) (H&E). (B) Fish 22: Liver, severe, locally extensive hepatobiliary and stromal hyperplasia with occasional intralesional extrasporogonic stages. (H&E). (C) Positive staining of hepatic extrasporogonic stages detected at immunohistochemistry in the hepatobiliary and stromal hyperplasia shown in B (dotted circles). (D) Moderate granulomatous nephritis with numerous intralesional extrasporogonic stages (arrowheads). Note the presence of the parasite in the glomerulus in the centre of the image (H&E). (E) Positive immunolabelling of renal extrasporogonic stages.

fascicles exhibited variably severe mononuclear inflammation, mainly composed of lymphocytes and plasma cells, dissecting myocytes and occasionally accompanied by myocyte atrophy, degeneration and necrosis (Figure 4C). These lesions were more severe on the head epaxial muscles and milder in the branchial and periesophageal muscles. Extrasporogonic *T. bryosalmonae*-stages were associated with myositis in 4 individuals (Figure 4D).

3.3.2 | Central Nervous System

Multifocal, moderate, chronic mixed meningitis was observed in 4 out of 4 individuals examined. Occasionally, areas of grey matter colliquative necrosis were present and characterized by Nissl substance lysis and neuronal pyknosis/necrosis, as well as white matter vacuolation. Rare extrasporogonic *T. bryosalmonae*-stages were identified within inflammatory areas (fish 1) (Figure 4A).

3.3.3 | Liver

Multifocal, peripherally located, irregularly nodular, unencapsulated, non-infiltrative, delimitated lesions characterized by severe hepatobiliary and stromal hyperplasia were observed in 2 individuals (fishes 5 and 22) (Figure 5B). The suspected telangiectasia was confirmed histologically in fish 16. Extrasporogonic *T. bryosalmonae*-stages were present with a vascular localization

in 2 individuals (fishes 12 and 13) (Figure 5A) and within the context of hepatobiliary and stromal hyperplasia in fish 22 (Figure 5B).

3.3.4 | Spleen

Multifocal, moderate to severe granulomatous splenitis was observed in fish 12 and extrasporogonic *T. bryosalmonae*-stages presence was detected in 2 individuals (Figure 4G).

3.3.5 | Kidney

Multifocal to coalescing, moderate to severe, granulomatous nephritis win fishes 12 and 13, and presence of extrasporogonic *T. bryosalmonae*-stages (fish 12—tubular and glomerular localization; fishes 13, 17 and 22—tubular localization) (Figure 5D).

3.4 | Immunohistochemical and Histochemical Findings

Extrasporogonic *T. bryosalmonae*-stages identification was confirmed by immunohistochemistry in skeletal muscle, liver, kidney, gills and spleen (Figures 4E and Figures 5C,E).

Besides *T. bryosalmonae*, no other infectious agents were observed with histochemical stains in the samples examined.

4 | Discussion

In the present cases, distinctive vascular inflammatory, degenerative and necrotic lesions were observed in rainbow trout, mainly targeting the branchial arterial vascular system and, to a lesser extent, the bulbus arteriosus and the ventral aorta. Based on the morphology and distribution of these lesions, they are consistent with a form of non-leukocytoclastic, segmental and polyphasic vasculitis of unknown aetiology occurring in the presence of poor water quality due to heavy rains and, in few individuals, in association with a severe systemic *T. bryosalmonae* infection. These lesions were reported as recurrent and associated with moderate mortality but occurred in only one of the fish farms operating under the same management practises. Moreover, the feedback received during presentations of these cases at national and international conferences (SIPI 2008 and 2015, EAFP 2019) indicated that practitioners and technicians were unfamiliar with this type of vascular lesions. This information initially led to the hypothesis that these vascular lesions could be potentially linked to the conditions and characteristics unique to this farm. However, comparable lesions were documented at different time points, in other two farms located in different geographic areas of the same region and belonging to different owners therefore, making a farm-restricted phenomenon unlikely. Similarly to our case, these farms utilized river water supply systems and lesions developed following periods of intense rainfall (Beraldo P., personal communication). In addition, given the anatomical location of the lesions (lesions are not visible unless opercula are opened and evaluated from a ventral point of view) and the potential for subtle gross changes or early histological alterations (e.g., perivasculitis), underestimation of this pathological condition cannot be excluded.

Concerning the specific morphological characteristic of these lesions, they appear distinctive, stereotyped and with features different from those of cardiovascular diseases and malformations previously reported in salmonids. Characterized predominantly by degenerative, necrotic and inflammatory vascular changes of variable distribution and severity, and occasionally exhibiting abrupt onset, these lesions are not consistent with either malformations nor with the spectrum of other cardiovascular diseases previously described (Eaton et al. 1984; Farrell et al. 1986, 1990; Kaada and Hopp 1995; Poppe et al. 1998, 2002, 2003, 2007, 2021; Mercier et al. 2000; Poppe and Taksdal 2000; Farrell 2002; Brocklebank and Raverty 2002; Gamperl and Farrell 2004; Claireaux et al. 2005; Dalum et al. 2017; Brijs et al. 2020). Specifically, the vascular lesions that have recently attracted attention in the field, such as arteriosclerosis and coronary myointimal proliferation, differ substantially from the findings herein described (Farrell 2002; Poppe et al. 2007; Dalum et al. 2017; Brijs et al. 2020).

Segmental necrotizing arteritis, a hallmark of PAN in humans and other mammals, shares striking similarities with the vascular lesions observed in our study. Specifically, arterial vasculitis in PAN displays different stages of development and severity, in different vessels or even in the same vessel, and preferentially in branch points. This characteristic pattern has been interpreted as evidence of recurrent damage (Robbins and Cotran 2021). The specific localization of the lesions in our cases (mainly gill arteries and main heart vessels) is significant. In fish, these localisations represent major circulatory branch points that are subjected to high blood flow turbulence and pressure compared to low-pressure peripheral circulatory beds (Ferguson 2006). If on the one hand, both the localization and the morphology of the lesions described here could be considered compatible with a form of spontaneous/idiopathic polyarteritis, on the other, the specific targeting of branchial and, to a lesser extent, major heart vessels, while apparently sparing other visceral sites, is not consistent with the systemic diffusion pattern of PAN. Concerning the hernia-like lesion and aneurysm observed in fishes 1 and 17, respectively, these may fall in the lesions pattern of PAN, which often includes aneurysm and/or thrombosis (Robbins and Cotran 2021). However, the presence of these types of lesions could also suggest a high cardiovascular workload, as previously hypothesized in brown trout during summer seasons with unfavourable environmental conditions (Mercier et al. 2000). This latter interpretation appears more appropriate in our cases.

In addition to these considerations, other factors present at this farm could have likely contributed to the deterioration of fish health status. Specifically, the presence of a form of chronic, severe and proliferative branchitis, in association with water turbidity and rainfall events, is suggestive of significant respiratory compromise, consistent with ongoing overload of the cardiorespiratory system and probable overstretching of this specific vascular site. This site is in fact particularly susceptible to overstretching and mechanical injury during periods of high oxygen and metabolic demand, which could potentially overwhelm the huge morphological vascular plasticity of fish (Farrell 1991;

Poppe et al. 2003; Gamperl and Farrell 2004; Claireaux et al. 2005; Ferguson 2006; Johansen et al. 2017). Also, acute stress favours activation of haemostatic mechanisms and could be involved in thrombus formation (Tavares-Dias and Ragonha de Oliveira 2009). Considering all these elements, it is therefore possible that Virchow's triad (stasis, endothelial injury and hypercoagulability) was fulfilled, leading to the development of vascular damage and thrombosis (Robbins and Cotran 2021).

Although investigations for infectious agents within vascular lesions were limited, morphologically, a primary infectious aetiology seems unlikely, as supported also by negative histochemical stains and by the absence of identifiable pathogens on routine histological examination. As a note, attempts of bacteriological and mycological cultures performed in a previous episode of branchial arteritis occurred in another farm resulted negative (Beraldo P., personal communication).

Severe and systemic visceral infection with *T. bryosalmonae* involving gills, heart, central nervous system, skeletal muscle, kidney, liver and spleen was present in few individuals. Following initial infection through epithelial gill cell junctions, myxosporean sporoplasms that successfully penetrate the branchial capillaries are able to disseminate via blood circulation to the target organs. In severe cases, multiple visceral sites are potentially involved. Specifically, *T. bryosalmonae* frequently infects the endothelium of the renal portal vessels, leading to parasitic thrombi formation and dissemination not only in the kidney but also in other visceral sites, such as liver and skeletal muscles (Fernández-de-Luco et al. 1997; Ferguson 2006). Correspondingly, the extrasporogonic stages were identified in multiple visceral sites and in association with visceral papillary endothelial hyperplasia in our cases. However, severe vasculitis affecting major vessels, such as that herein described in branchial arteries and heart, is apparently not compatible with the spectrum of lesions typically reported in PKD. Although the parasite was not morphologically identified within the vascular lesions, the limited sensitivity of histological, histochemical and immunohistochemical stains cannot entirely exclude the presence of the parasite. Molecular biology techniques would provide greater diagnostic sensitivity for parasite detection. Nevertheless, given that such severe arteritis in major vessels has not been previously described as a characteristic feature of PKD, a direct causal relationship appears unlikely.

T. bryosalmonae may have also contributed to the severity of branchitis in our cases, since the parasite was identified in sites of severe epithelial and stromal chronic inflammatory and proliferative changes (fishes 5 and 24).

Finally, it is noteworthy the identification of *T. bryosalmonae* stages in the kidney with both a vascular/glomeral and tubular localization since traditionally, rainbow trout is considered unable to release spores as it has not co-evolved with the European strains of *T. bryosalmonae* (Sudhagar et al. 2019).

5 | Conclusions

Given the increasing attention focused on cardiovascular pathology in salmonids, the present findings contribute to the expanding spectrum of cardiovascular diseases in these species, as they appear to represent a novel pathological entity apparently arising in a complex farm condition related to both water quality deterioration and systemic PKD. Moreover, considering the severe involvement of major vascular sites, such as the branchial and cardiac ones, the negative impact on the respiratory and cardiac functions, and consequently on fish welfare, performance and production, could potentially be significant. Further investigations from other research groups are needed to further elucidate the distribution, prevalence, health impact and possible causes of these lesions.

Author Contributions

Gabrita De Zan: conceptualization, visualization, investigation, writing – original draft, data curation. **Paola Beraldo:** conceptualization, visualization, investigation, writing – review and editing, methodology, resources, validation, supervision.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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