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Spontaneously arising disease

Fatal cerebrovascular accident in a captive red panda (*Ailurus fulgens fulgens*) with concurrent amdoparvovirus infection

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ABSTRACT

We report the pathological and molecular findings in an adult male Himalayan red panda (*Ailurus fulgens fulgens*) whose death was attributed to parenchymal brain haemorrhage (PBH) of the thalamus. Post-mortem examination revealed severe, acute PBH and intraventricular haemorrhage with major involvement of the thalamus, as well as scattered chronic microinfarctions. Vascular disease in the brain and other organs was suggestive of systemic hypertension. Histological lesions included arteriolar hyalinosis and varying degrees of arteriosclerosis, arterial tunica media hypertrophy and hyperplasia and infiltration of arterial walls by lipid-laden macrophages. Other relevant findings included marked myocardial fibrosis, lymphoplasmacytic tubulointerstitial nephritis, lymphoplasmacytic meningoencephalitis and chronic mitral valve degeneration. The changes in the cerebral vasculature were consistent with hypertensive encephalopathy and a cerebrovascular accident, specifically PBH, which has not been previously reported in this species. Additionally, polymerase chain reaction analysis for red panda amdoparvovirus (RPAV) was positive in the brain and kidneys. Preceded by hypertensive vascular changes and brain microinfarctions, sudden death in this animal likely resulted from fatal PBH with intraventricular haemorrhage. The clinicopathological role of RPAV infection is unknown in this case, although its contribution to the chronic renal disease is considered possible in the context of our current understanding of RPAV-associated pathology.

Red pandas (*Ailurus fulgens*) are native to central and eastern Asia and are listed as an endangered species [1]. As such, they are subject to substantial conservation efforts that include breeding programmes and disease monitoring of captive populations. Retrospective analyses of mortality in captive red pandas highlight cardiovascular disease, predominantly myocardial fibrosis and hypertrophic cardiomyopathy, as the most common cause of death in adult and geriatric animals. Renal and gastrointestinal diseases are additional common findings at necropsy [2–4]. Recent studies also suggest the possibility that red panda amdoparvovirus (RPAV) may contribute to morbidity and mortality in this species [5–7]. We now describe a case of sudden death associated with cerebrovascular disease (CVD) in a red panda concurrently infected with RPAV.

A 7-year-old male Himalayan red panda (*A. fulgens fulgens*) was submitted in October 2022 for post-mortem examination after sudden death. Relevant clinical history included general anaesthesia in May 2019 for a general health and dental check. At this time, a mildly decreased body condition score was noted. During general anaesthesia, heart rate averaged 100 bpm and systolic blood pressure averaged 80–90 mm Hg. Oral examination revealed moderate dental calculus, gingivitis and uncomplicated crown fractures. Biochemistry and a complete blood count were performed; abnormalities found included mild uraemia (22 mmol/L; reference interval 4.3–19.6 mmol/L) [8].

A post-mortem examination was performed and selected tissues were collected and fixed in 10% buffered formalin or stored at −80°C. Samples of brain, heart, trachea, lungs, liver, kidneys,

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urinary bladder, testes, spleen, stomach, small intestine, large intestine, pancreas, thyroid and parathyroid glands, skeletal muscle, sciatic nerve and one eye were saved in 10% neutral buffered formalin; additional samples of kidneys, liver, brain, lungs, spleen, blood and small intestine were frozen. Selected fixed tissues (lung, liver, kidney, thyroid, stomach, small and large intestine, heart, and brain [cerebral cortex, pons, cerebellum, thalamus, hippocampus]) were processed via standard methods for microscopic review with haematoxylin and eosin (HE) staining.

Gross examination of the central nervous system (CNS) revealed a 1 cm diameter, focally extensive, well-demarcated dark red haemorrhagic focus that expanded the left side of the thalamus communicating with the third and lateral ventricles, and a similar 3 mm diameter focus within the right thalamus (Fig. 1). Clotted blood was present within the lateral, third and fourth ventricles.

Bilaterally, the kidneys had marked loss of corticomedullary distinction, with frequent pale tan corticomedullary streaks and frequent, pinpoint to 1 mm diameter pale tan–red foci scattered within the cortex. The free edges and the central smooth zone of the mitral valve cusps were expanded with a few, discrete, white to yellow, firm, pinpoint to 1 mm diameter nodules. Pleural and peritoneal serous effusions and hepatic and pulmonary congestion were also seen. Other macroscopic findings included bilateral, moderately prominent thyroid glands (approximately $3 \times 1.5 \times 0.8$ cm) and dark red duodenal contents.

Histological examination of the CNS confirmed severe, acute, locally extensive haemorrhage and neuroparenchymal disruption in the thalamus, with vacuolation and oedema of the adjacent neuroparenchyma. Haemorrhagic foci were characterized by arborizing and coalescing dissection of the thalamic parenchyma by erythrocytes admixed with a few strands of poorly organized fibrin and rare leucocytes (Fig. 2). Within the adjacent grey and white matter, including the internal capsule, multifocal vascular hyalinosis with regional hemosiderosis, gliosis and parenchymal rarefaction (chronic microinfarcts) was present (Fig. 2, left inset). Congo red staining was performed on these brain sections and the hyaline material within vessel walls did not fluoresce under polarized light. Multifocally throughout the cerebrum, brainstem and cerebellum, a variably prominent, perivascular lymphoplasmacytic and histiocytic infiltrate expanded the leptomeninges and occasionally the Virchow–Robin spaces in the parenchyma, consistent with chronic meningoencephalitis (Fig. 2, right inset).

Within the heart, subendocardial coronary arteries had multifocal, irregular medial and subintimal thickening, consisting of hypertrophy and hyperplasia of medial smooth muscle cells, rare accumulations of cholesterol clefts and foam cells, mineralization and neointimal hyperplasia (Fig. 3). Multifocally, the myocardium had moderate to marked interstitial fibrosis, which was most severe within the left ventricular free wall and interventricular septum (Fig. 3). The grossly visible nodular changes in the mitral valve corresponded with chronic valvular fibrosis and thick and tortuous vessels (Supplementary Fig. 1), abundant capillary profiles and rare haemosiderin-laden macrophages. Rare, loosely dispersed clusters of lymphocytes and plasma cells infiltrated the myocardium.

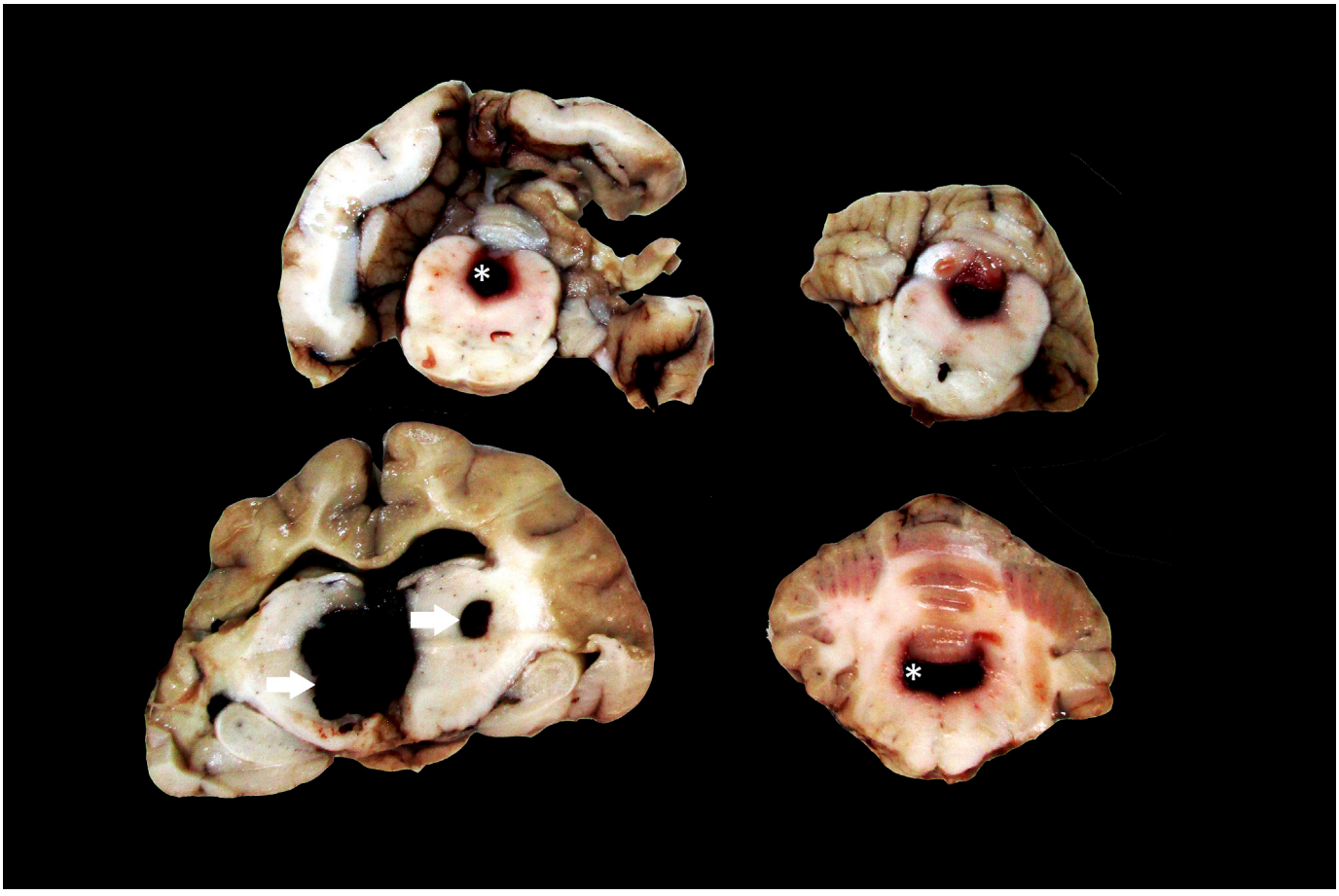

Fig. 1. Cerebrovascular accident, brain, red panda. Multifocal haemorrhage expands the thalamus (arrows) and ventricular system (*).

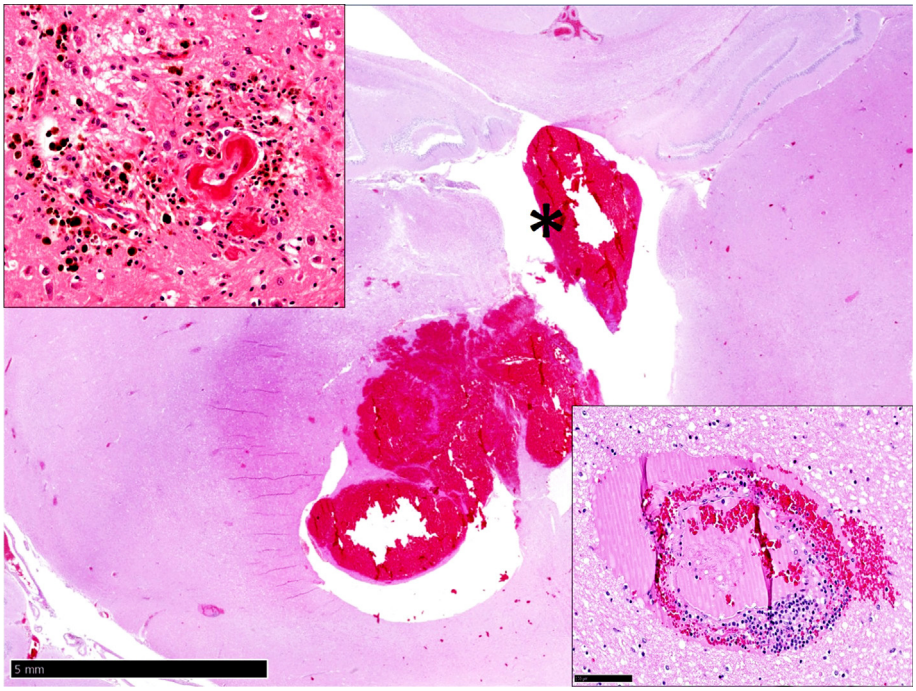

Fig. 2. Cerebrovascular accident, thalamus, red panda. Neuroparenchyma at left medial thalamic nuclei disrupted by acute haemorrhage, which extends into third ventricle (*). HE. Bar, 5 mm. Left inset: hyalinized and obliterated arterioles in thalamus accompanied by haemosiderophages and gliosis (chronic microinfarct). HE. Right inset: partial lymphoplasmacytic and histiocytic perivascular cuff with oedema and haemorrhage. HE. Bar, 120 μm.

The kidneys had multifocal, locally extensive areas of interstitial fibrosis associated with lymphoplasmacytic interstitial nephritis, extensive nephron loss with glomerulosclerosis, as well as marked tubular proteinosis and tubuloepithelial regeneration. Lobar and interlobar renal arteries and the vasa vasorum supplying them were undergoing varying degrees of degeneration with associated subintimal and mural lipid-laden macrophages (Fig. 4), tunica media hypertrophy and hyperplasia, hyalinosis and obliteration. Rare vessels were replaced by fibrin (Supplementary Fig. 2). Arteries within other organs, including the submucosa of the gastrointestinal tract, and perilymph nodal soft tissues had prominent tunica media thickening due to hypertrophy and hyperplasia and occasional mural mineralization. Intestinal submucosal arteries frequently had expansion of the subintimal space with amorphous eosinophilic material (Supplementary Fig. 3). However, the pathological significance of this change is uncertain given the degree of autolysis of the surrounding tissues. The thyroid glands had diffusely dilated and mildly hyperplastic colloid follicles, consistent with moderate colloid goitre. Although no clear ulceration of the duodenal mucosa was seen, a mild granulocytic duodenitis with abundant superficial coccobacilli was present. Bacterial culture of the small intestinal contents resulted in isolation of a mixed growth of normal enteric commensals, including enterococci, non-haemolytic *Escherichia coli* and *Clostridium perfringens*.

Fresh brain and kidney samples were analysed by polymerase chain reaction (PCR) for the presence of RPAV DNA. Ten percent suspensions of these samples were prepared and used for DNA extraction using the MagMAX CORE Nucleic Acid Purification Kit on the KingFisher Flex System (Thermo Fisher Scientific; www.thermofisher.com) according to the manufacturer's instructions. The extracted DNA was used for PCR as described [5]. RPAV DNA was detected in both tissues.

CVD encompasses the neuropathology that results from lesions within the cerebral blood vessels [9,10]. Stroke or cerebrovascular accident (CVA) is the most common clinical manifestation of CVD and the second or third most leading cause of death in humans [10–12]. CVAs are subclassified into ischaemic or haemorrhagic presentations, with the latter also encompassing parenchymal brain haemorrhage (PBH) [13–15].

Sudden death in this red panda is believed to have been the result of acute, fatal PBH with subsequent intraventricular haemorrhage, preceded by hypertensive vascular disease. This case represents the first description of a haemorrhagic CVA in a red panda. Hypertension is one of the most common risk factors for the development of CVAs in humans, especially the subset of CVAs presenting with PBH [16,17]. Although hypertension was not confirmed clinically with blood pressure measurements in this case, vascular changes consistent with those observed in patients with clinical hypertension were identified within the coronary arteries, CNS, gastrointestinal system and kidneys. Hypertension was suspected in this case, possibly induced or exacerbated by severe renal disease and culminating in a suspected fatal CVA. The heart rate and blood pressure of the animal recorded during general anaesthesia 3 years prior to death were not indicative of hypertension and blood biochemistry at the same time revealed only minimal changes in renal function parameters [8,18,19]. More recent bloodwork and blood pressure measurements were not available and the clinical correlations therefore remain speculative.

Descriptions of cerebral vascular changes in animals associated with hypertension are rare outside the laboratory setting. The most consistently recorded histological change in cats with hypertensive encephalopathy is arteriolar hyalinosis, characterized by thickening and replacement of the arteriolar walls with deposits of hyaline material [20]. Arteriolar hyalinosis and fibrinoid vascular necrosis is also an important feature of small vessel disease associated with chronic hypertension in humans [13,16]. The presence of cerebral arteriolar hyalinosis associated with localized neuroparenchymal rarefaction with gliosis and haemosiderophages (chronic microinfarctions) in this case supports

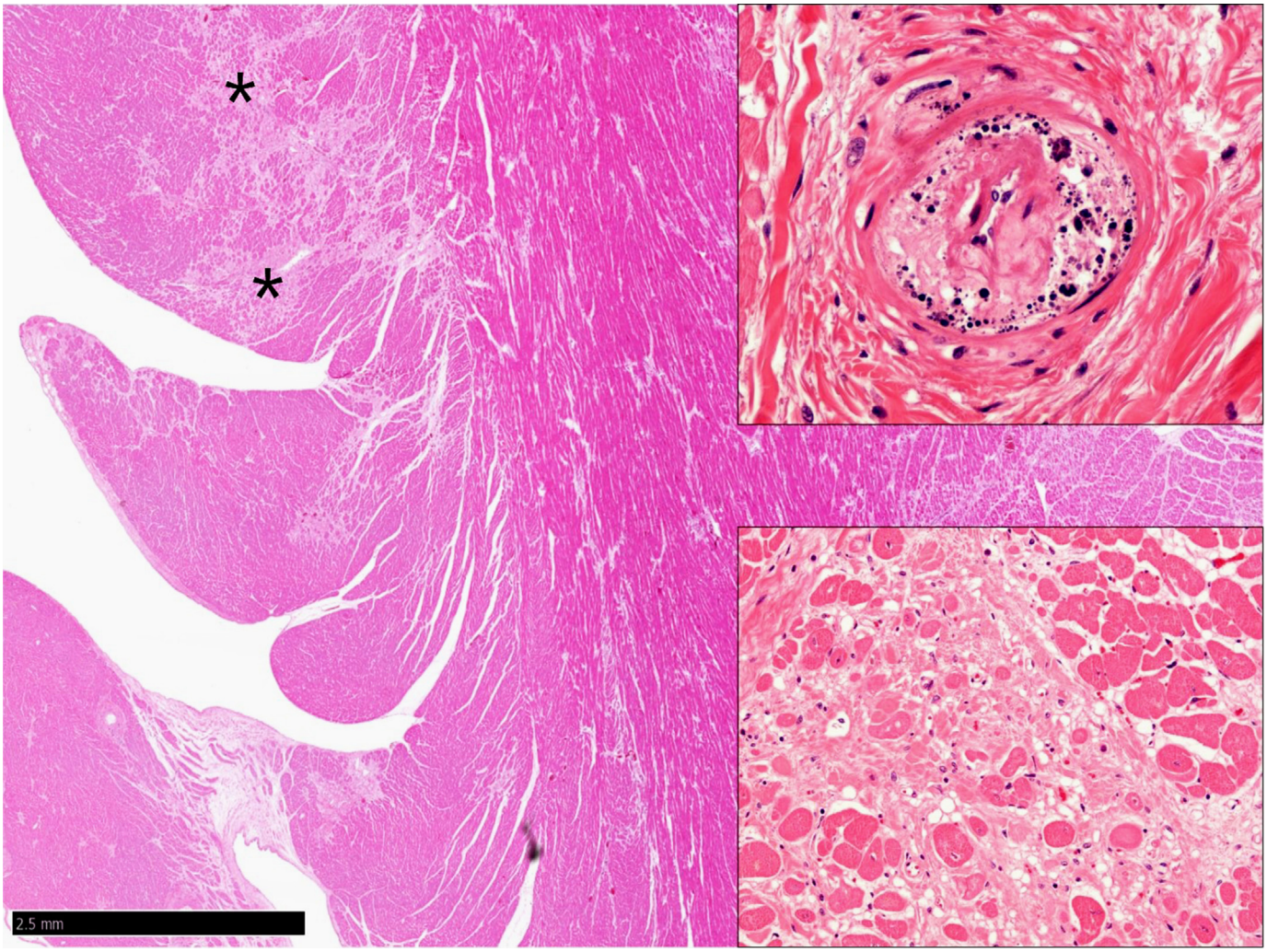

Fig. 3. Myocardial fibrosis and degenerative vascular changes, heart, red panda. Multifocal areas of myocardial fibrosis (*). HE. Bar, 2.5 mm. Upper inset: arterial degeneration with mineralization. HE. Lower inset: focal myocardial fibrosis with marked cardiomyocyte size variation, including atrophy and loss. HE.

the theory that the CVA in this animal was preceded by hypertension [16,21]. The changes in the tunica media and tunica intima of the coronary arteries were also suggestive of hypertension, as described in humans and dogs [22,23].

CVAs have been considered rare in pet animals. However, they are becoming increasingly recognized as a common cause of acute neurological dysfunction, in particular in dogs, due to advanced imaging modalities [24]. PBH, as we suspect occurred in this case, can result from rupture of vessels within the brain; this can be secondary to systemic hypertension, amyloid angiopathy (excluded in this case by negative Congo red fluorescence under polarized light), anticoagulants, tumours or vascular anomalies, including arteriovenous malformations, angiomas and aneurysms [13]. It is often difficult to determine the exact cause of PBH. Although a significant association between systemic hypertension and cerebral infarction has not been definitively established in dogs, 8/28 dogs with brain infarctions in one study had clinically elevated blood pressure [25]. In that study, the most commonly infarcted regions of the brain included the rostral cerebellum, caudal thalamus and rostral brainstem. In humans, the most common location for hypertension-associated PBH is the deep cerebral grey matter, including the putamen and thalamus [13]. The features observed in this red panda supported thalamic PBH and subsequent intraventricular haemorrhage as described in humans.

Comorbidities associated with brain infarctions in dogs and cats include chronic kidney disease, hypothyroidism-induced or idiopathic atherosclerosis and hyperthyroidism [10,20]. The renal changes in this case highlighted chronic tubulointerstitial nephritis, which is reported to be common in older red pandas [2,4,8]. Regardless of the aetiology, chronic kidney disease is both a common cause and a complication of hypertension in many species via several mechanisms including sodium retention, activation of the renin–angiotensin–aldosterone system and sympathetic nerve stimulation [26,27]. It is highly plausible that severe renal disease played a role in the apparent hypertensive vascular changes in this case. The vascular changes in the renal and coronary arteries may also have contributed to hypertension due to stenosis of the vascular lumina. In humans, hypertension is also considered a major risk factor for the development of atherosclerosis, although localized lipid retention and inflammatory mediators are also necessary pathogenetic components [28,29]. Coronary artery disease (CAD; arteriosclerosis and atherosclerosis) is a common condition in humans that has been associated with an increased probability of major adverse cardiac events, such as myocardial

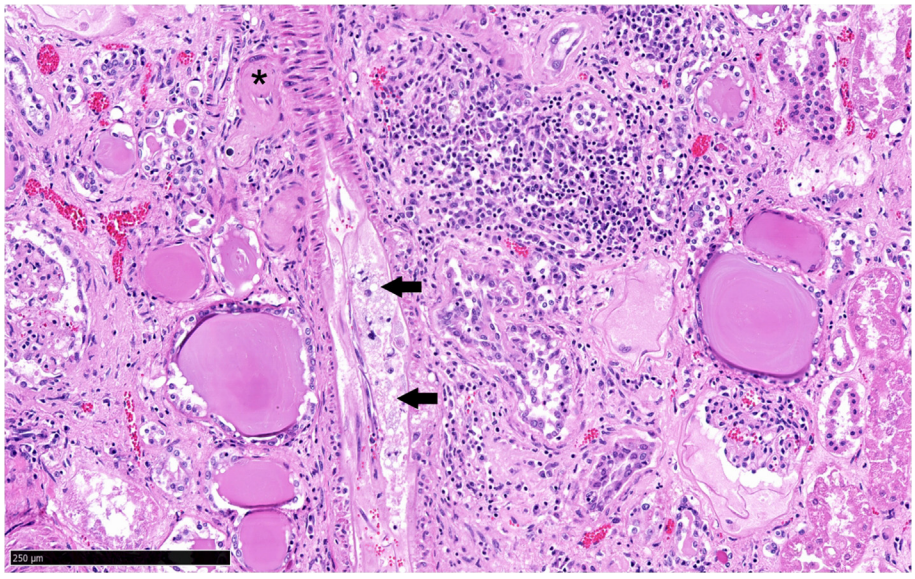

Fig. 4. Chronic interstitial nephritis and degenerative vascular changes, kidney, red panda. Intima of a post-lobar arteriole segmentally expanded by foamy macrophages (arrows); smaller arteriole completely obliterated (*). Interstitial lymphoplasmacytic infiltrate, fibrosis, segmental tubular dilatation with epithelial simplification, luminal proteinosis and segmental nephron atrophy and loss in adjacent parenchyma. HE. Bar, 250 µm.

infarctions [30]; speculatively, CAD may have played a role in the development of myocardial fibrosis in this case. The causal relationship between the cardiovascular and renal conditions and the PBH remains speculative.

Colloid goitre, as seen in this case, can occur in adult animals with decreased thyroid hormone requirements and is not necessarily suggestive of hypothyroidism; clinical thyroid values were not available in this case and the potential contribution of thyroid hormone dysregulation could not be evaluated.

Additional cardiac changes included nodular accumulations of fibrovascular tissue with rare haemosiderophages within the smooth zone of the mitral valve, and the presence of thick, tortuous vessels near the site of atrial attachment within the same valve. Neovascularization of the heart valves is typically associated with rheumatic heart disease or healed endocarditis [31], although neovascularization and the presence of large-calibre veins in the mitral valve has also been associated with non-inflammatory, age-related degenerative changes in humans [32]. The valvular changes were chronic and may, speculatively, represent healed sites of prior endocarditis. It is possible that the thickened vessels may have reflected a degenerative change, and further investigation into the vascularity of heart valves in this species is needed to fully interpret these changes.

The clinicopathological significance of the RPAV infection in this red panda is uncertain but the detection of viral DNA in kidney and brain tissue correlated with inflammatory lesions within both of these organs. The prototypical and best described amdoparvovirus, Aleutian mink disease virus, is a well-established cause of chronic kidney disease characterized by both glomerulonephritis and interstitial nephritis [33,34]. It has also been suggested as a cause of meningoencephalitis and fibrinoid necrosis of cerebral arterioles [35,36]. RPAV is one of a growing list of unique amdoparvoviruses recently discovered in carnivores, and while persistent asymptomatic infections appear to be common, a growing body of evidence suggests that these infections may be associated with various pathological outcomes [37]. Amdoparvoviruses in red pandas (RPAV) and skunks (skunk amdoparvovirus, SKAV) have been detected by PCR and in-situ hybridization (ISH) in lesions of tubulointerstitial nephritis, arteritis and myocarditis, and SKAV has also been detected in inflammatory CNS lesions in skunks [38,39]. Further testing (eg, immunohistochemistry or ISH) would be needed to draw a more definitive conclusion about the association of the inflammatory lesions in this case and the presence of RPAV. Based on the enclosure and the husbandry of this species, canine distemper virus was not regarded as a likely differential diagnosis for the inflammatory changes in the brain.

Preceded by presumed hypertensive vascular changes and brain microinfarctions, sudden death in this animal probably resulted from the PBH with intraventricular haemorrhage. Given the mesencephalic location of the PBH, compression of the cardiorespiratory centres and subsequent cardiorespiratory failure was, plausibly, the ultimate cause of death. The proposed pathogenesis is similar to that in humans, where sudden death is a common consequence of CVA due to disturbance of the central autonomic control centres [40]. We propose that CVA should be included as a differential diagnosis for sudden death in red pandas, particularly in those with potential underlying vascular disease and hypertension.

In conclusion, this case represents the first description of a fatal CVA in a red panda and one of the first documentations of the lesions potentially associated with RPAV in a zoo within the UK [41]. Growing evidence of RPAV's worldwide distribution underlines the importance of developing monitoring plans to better inform management decisions in zoo populations of these endangered species [42]. Further research is warranted to assess this virus's relevance to morbidity or mortality in zoo-housed populations of red pandas, particularly with regard to the development of systemic hypertension associated with renal disease.

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Declaration of competing interests

The authors declared no conflicts of interest in relation to the research, authorship or publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcpa.2023.06.006.

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