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NOTE

Pathology

Surveillance of amyloidosis in stranded and bycaught cetaceans off Hokkaido, Japan

Shotaro NAKAGUN[1,2)]*, Kenichi WATANABE[1)], Takashi MATSUISHI[3)], Mari KOBAYASHI[4)] and Yoshiyasu KOBAYASHI[1)]

[1)]Laboratory of Veterinary Pathology, Department of Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Obihiro, Hokkaido 080-8555, Japan
[2)]United Graduate School of Veterinary Sciences, Gifu University, Gifu, Gifu 501-1193, Japan
[3)]Division of Marine Bioresource and Environmental Science, Faculty of Fisheries Sciences, Hokkaido University, Hakodate, Hokkaido 041-8611, Japan
[4)]Department of Ocean and Fisheries Sciences, Faculty of Bioindustry, Tokyo University of Agriculture, Abashiri, Hokkaido 099-2493, Japan

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ABSTRACT. Systemic amyloidosis is rarely reported among cetaceans, and a surveillance dedicated for its occurrence across a certain geographic location has not been reported. Between 2013 and 2018, comprehensive gross and histopathologic examinations were conducted on 54 animals comprising 11 species of stranded and bycaught cetaceans in Hokkaido, Japan. Systemic amyloidosis was diagnosed in 2 out of 3 Stejneger's beaked whales (*Mesoplodon stejnegeri*), through Congo red staining and immunohistochemistry for amyloid A. The kidney and gastrointestinal tract had the largest amounts of amyloid deposits, representing a previously undescribed organ distribution in the species. The current study demonstrates the possibility of Stejneger's beaked whales being prone to the development of systemic amyloidosis, and highlights the need for further investigations.

KEY WORDS: epidemiology, pathology, prevalence, Stejneger's beaked whale, systemic amyloidosis

Amyloidosis refers to a collection of debilitating proteopathies in which misfolded amyloid fibrils accumulate and deposit in extracellular spaces of organs and tissues [4]. There are about 10 types of amyloid fibril proteins recognized in animals to date, each having a distinct precursor protein [15]. Deposition can either be systemic or localized, and out of the 6 reported systemic types in animals, the predominant form is amyloid A (AA) amyloidosis [15]. With AA amyloidosis, an increase in the circulating acute phase protein serum amyloid A (SAA) level triggers the accumulation and subsequent deposition of AA in tissues, usually following chronic inflammation [4]. The disease has been diagnosed occasionally in a variety of species, both domestic and wild [5, 7, 9, 18]. In wild mammals, the island foxes (*Urocyon littoralis*) are known to show an unusually high prevalence of AA amyloidosis at the population/species level, signifying potential detrimental effects to the species' survival [5].

Marine mammals are no exception to being affected by systemic amyloidosis. The condition has been reported sporadically in a total of 3 Stejneger's beaked whales (*Mesoplodon stejnegeri*) [14, 16], while a more in-depth study has been conducted in bottlenose dolphins (*Tursiops truncatus*) [2] and California sea lions (*Zalophus californianus*) [1]. Out of these 3 species, stranding records have indicated that Stejneger's beaked whales are the only regular residents around Hokkaido, Japan. Although the previous cases of amyloidosis in this species have been reported in detail especially on the histopathology of selected organs [14, 16], a thorough investigation on its tissue tropism has not been described. Furthermore, epidemiologic assessments of amyloidosis among various species of marine mammals occurring in a certain geographic location through comprehensive gross and histopathologic examinations have never been conducted. The objective of this study was to investigate the incidence of amyloidosis in cetaceans around Hokkaido, Japan, where prior information on cetacean health is scarce, and to further describe the pathology with its detailed organ distribution.

During 2013 to 2018, 366 cetacean strandings were reported along the coast of Hokkaido. Many of these animals were unsuitable for histopathologic examinations due to decomposition and hence not included in this study, but comprehensive gross and histopathologic investigations were attainable on 54 cetaceans comprising 11 species (Table 1), which include a fin whale (*Balaenoptera physalus*), 2 common minke whales (*Balaenoptera acutorostrata*), 1 pygmy sperm whale (*Kogia breviceps*), 6 Hubbs' beaked whales (*M. carlhubbsi*), 3 Stejneger's beaked whales, 3 killer whales (*Orcinus orca*), 3 Pacific white-sided dolphins (*Lagenorhynchus obliquidens*), 1 Risso's dolphin (*Grampus griseus*), 6 striped dolphins (*Stenella coeruleoalba*), 12 Dall's

*Correspondence to: Nakagun, S.: snakagun@gmail.com

Table 1. Details of the animals examined with their representative morphologic findings

Species	SNH[a] ID	Sex	Length (cm)	Age class	Location	Representative morphologic findings
Fin whale (*Balaenoptera physalus*)	SNH16040	Female	498.6	Calf	Setana	Fetal distress
Common minke whale	SNH16022	Male	263.5	Calf	Tomari	Pseudohermaphroditism with testicular hypoplasia
(*Balaenoptera acutorostrata*)	SNH16044	Female	460.0	Subadult	Koshimizu	Peritonitis
Pygmy sperm whale (*Kogia breviceps*)	SNH14045	Male	245.2	Adult	Toyokoro	Myocardial degeneration
Hubbs' beaked whale	SNH15011	Male	493.0	Adult	Samani	Hepatic trematodiasis; Pulmonary nematodiasis
(*Mesoplodon carlhubbsi*)	SNH16003	Male	436.4	Juvenile	Hakodate	Myocardial degeneration
	SNH17030	Female	278.0	Calf	Shinhidaka	Hepatic lipidosis; Adrenal lipidosis
	SNH17037	Female	248.3	Calf	Shinhidaka	Esophageal ulcer; Sinus histiocytosis
	SNH18033	Female	548.0	Adult	Samani	Multiple lymphadenitis;
	SNH18034	Female	510.0	Adult	Kushiro	Hepatic trematodiasis; Pulmonary cestodiasis
Stejneger's beaked whale	SNH17015	Female	495.5	Adult	Hakodate	Systemic AA amyloidosis; Renal crassicaudiasis
(*Mesoplodon stejnegeri*)	SNH17034	Male	410.0	Juvenile	Betsukai	Granulomatous myocarditis; Renal crassicaudiasis
	SNH18001	Male	448.0+[b]	Adult	Rumoi	Systemic AA amyloidosis; Renal crassicaudiasis
Killer whale (*Orcinus orca*)	SNH16006	Male	219.8	Calf	Kushiro	Neonatal weakness
	SNH16035	Female	227.3	Calf	Rebun	Neonatal weakness
	SNH17011	Male	712.5	Adult	Toyokoro	No remarkable changes
Pacific white-sided dolphin	SNH17020	Female	203.4	Adult	Hakodate	Pulmonary fibrosis; Pancreatitis
(*Lagenorhynchus obliquidens*)	SNH17024	Male	102.9	Calf	Hakodate	Pulmonary nematodiasis
	SNH17056	Male	228.3	Adult	Esashi	Myocarditis
Risso's dolphin (*Grampus griseus*)	SNH16032	Male	288.7	Adult	Shari	Meningoencephalitis
Striped dolphin (*Stenella coeruleoalba*)	SNH15032	Male	250.0	Adult	Urahoro	Meningitis
	SNH16002	Female	147.0	Juvenile	Kushiro	Encephalitis; Lingual ulcer
	SNH16019	Male	244.0	Adult	Oshamambe	Pulmonary aspiration
	SNH18025	Male	216.9	Subadult	Tomakomai	Meningoencephalomyelitis
	SNH18038	Male	212.5	Subadult	Samani	Meningitis; Multiple myocardial necrosis
	SNH18043	Male	224.3	Adult	Noboribetsu	Meningitis; Epididymo-orchitis; Multiple hepatic abscess; Pulmonary nematodiasis
Dall's porpoise (*Phocoenoides dalli*)	SNH14017	Male	118.0	Calf	Abashiri	Hepatic lipidosis
	SNH14018	Female	118.5	Calf	Abashiri	Hepatic lipidosis
	SNH14024	Male	108.5	Calf	Saroma	Hepatic lipidosis
	SNH14026-1	Male	219.5	Adult	Rausu	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH14026-2	Male	207.7	Adult	Rausu	Pancreatic trematodiasis; Pulmonary nematodiasis
	SNH14026-3	Male	210.5	Adult	Rausu	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH14030	Female	118.8	Calf	Ishikari	Hepatic lipidosis
	SNH14031	Female	179.3	Subadult	Ishikari	No remarkable changes
	SNH14034-1	Male	193.5	Subadult	Rausu	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH14034-2	Male	199.5	Subadult	Rausu	Pancreatic trematodiasis; Pulmonary nematodiasis
	SNH14034-3	Male	198.6	Subadult	Rausu	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH18005	Male	211.0	Adult	Matsumae	Bronchopneumonia; Pancreatic trematodiasis
Harbor porpoise (*Phocoena phocoena*)	SNH13012	Male	131.0	Subadult	Rausu	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH14011	Female	182.8	Adult	Rausu	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH16201	Male	135.0	Subadult	Rausu	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH16011-2	Male	127.2	Subadult	Hakodate	Hepatic trematodiasis; Pulmonary nematodiasis; Lingual papillomatosis
	SNH16023	Female	186.5	Adult	Urahoro	Aspiration pneumonia; Hepatic trematodiasis; Pulmonary nematodiasis
	SNH16031	Male	138.3	Subadult	Erimo	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH17002	Male	133.0	Subadult	Hokuto	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH17003	Male	139.5	Subadult	Otaru	Hepatic trematodiasis; Pulmonary nematodiasis; Intrapancreatic accessory spleen
	SNH17004	Male	127.0	Subadult	Otaru	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH17005	Female	133.1	Subadult	Tomakomai	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH17007	Female	138.6	Subadult	Tomakomai	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH17046	Male	116.9	Juvenile	Shiranuka	No remarkable changes
	SNH18009	Male	143.0	Subadult	Otaru	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH18011	Female	131.8	Subadult	Hakodate	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH18012	Female	152.2	Adult	Hakodate	Hepatic trematodiasis; Pulmonary nematodiasis
	SNH18015	Male	134.4	Subadult	Muroran	Hepatic trematodiasis; Pulmonary nematodiasis

a) SNH refers to 'Stranding Network Hokkaido', where the first 2 digits after the letters indicate the year of stranding and the following numbers indicate the chronological order of event. b) Individual had a broken maxilla, making accurate measurements unattainable.

porpoises (*Phocoenoides dalli*) and 16 harbor porpoises (*Phocoena phocoena*). Most of the Dall's and harbor porpoises were obtained from bycatch. The approximate age class was determined through a combination of body length, coloration, teeth eruption

for beaked whales, size of thymus and histologic features of gonads, where the 4 age classes in this study were each defined as follows: calf (newborns and those with a similar body length), juvenile (larger than a calf but obviously smaller than a subadult with an immature body coloration), subadult (reaching or slightly falling below a full grown body length but reproductively immature) and adult (fully grown and reproductively mature) [6, 8]. All postmortem examinations were carried out systematically in the same manner including morphometry, necropsy and histopathology. For histopathology, tissue samples of the liver, spleen, kidney, heart, lung, thyroid gland, pancreas, adrenal gland, stomachs, intestine, urinary bladder, gonad, thymus (for immature individuals), various lymph nodes, laryngeal gland, brain, and others such as the skin and spinal cord when noted with gross abnormalities were fixed in 10–15% neutral buffered formalin and processed routinely. The above complete list of tissue collection was restricted to certain tissues in a small number of animals due to logistic constraints. Sections were stained with hematoxylin and eosin (HE), while an additional Congo red (CR) stain was performed for the definitive diagnosis of amyloidosis. All CR-stained sections were viewed under polarized light. Whenever deemed necessary, a selection of other special stains such as periodic acid Schiff (PAS), Gram, and Ziehl-Neelsen (ZN) stains were also conducted for tissues of some animals.

Immunohistochemistry using a mouse monoclonal antibody against AA (1:600, clone KM268; Kyowa Medex, Tokyo, Japan) was conducted on all collected tissues of Stejneger's beaked whales in order to determine the nature of the deposited amyloid. The same immunohistochemistry was also applied in cases where amyloid deposition was suspected by the HE stain in other species. Briefly, antigen retrieval was performed by incubating the slides with pronase E (Kaken Pharmaceutical, Tokyo, Japan) for 60 min, while endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 min, both reactions performed at room temperature. The antigen was detected using a Histofine Simple Stain MAX-PO kit (Nichirei Biosciences, Tokyo, Japan) and labeling was visualized with 3′3-diaminobenzidine chromogen (Nichirei Biosciences). The sections were counterstained with Meyer's hematoxylin. Tissue sections in which the primary antibody was replaced by normal mouse serum served as negative controls and a liver section of a Holstein cow (*Bos taurus*) with AA deposits was used as a positive control.

Out of the 54 animals across 11 species, amyloid deposits were found only in the adult male and female Stejneger's beaked whales (SNH17015, SNH18001). In these 2 animals, although prominent gross abnormalities suggestive of amyloidosis were difficult to detect, slight hepatomegaly and splenomegaly were noted. The edges of the livers were slightly rounded, and the parenchyma appeared friable. With histopathology, deposits of amorphous pink material that stained positive on the CR stain and by birefringence were identified in multiple tissues. In particular, amyloid deposits were found in the vascular walls of various organs such as the liver (including the space of Disse) and choroid plexus, follicles of the spleen, glomeruli and medullary interstitium of the kidney, and lamina propria and muscularis of the stomachs and intestine (Fig. 1, Table 2). Additionally, in the adult female whale, amyloid was also detected in the pericellular spaces of the myocardium, endometrial mucosa of the uterus, and interstitium of the thyroid gland, adrenal gland and pancreas. The degree of amyloid deposition in each organ was assessed using a semi-quantitative scale [18], showing that the kidney and gastrointestinal tract had the largest amounts of deposits (Table 2). Through immunohistochemistry, all these deposits showed affinity to the anti-AA antibody. The 2 adult Stejneger's beaked whales were diagnosed as systemic amyloidosis, while the juvenile male Stejneger's beaked whale (SNH17034) did not have any discernible amyloid deposits in the examined tissue sections.

Other pathologic changes shared among the 3 Stejneger's beaked whales were moderate renal crassicaudiasis characterized by granulomatous inflammation and fibrosis. Furthermore, the 2 adults showed moderate polyglucosan body deposition in the cerebellum and intracytoplasmic lipofuscin in the neurons of the brainstem, while the juvenile had multiple granulomas in the heart. These granulomas did not reveal any associated pathogens with HE, PAS, Gram and ZN stains.

The current patho-epidemiologic study is a first of its kind to assess the occurrence of amyloidosis in cetaceans over a particular geographic area during a set time period. It is worthy to note that the individuals included in this study were not based on the kind of species or other biological factors, and that the majority of fresh to moderately decomposed individuals reported within the study period were covered. Amyloidosis was diagnosed only in adult Stejneger's beaked whales, while none of the others, including the juvenile and the closely related Hubbs' beaked whales, exhibited this condition. Amyloid deposits were detected in multiple tissues of adult Stejneger's beaked whales, whilst the kidney and gastrointestinal tract were affected the most. It is noteworthy that neither of the kidney, stomachs nor intestines demonstrated obvious gross changes to suspect amyloidosis such as the classic renal enlargement [9], emphasizing the need of histopathologic examinations to diagnose this disease in cetaceans. The kidney is a commonly affected organ in humans and many other reported animals with systemic amyloidosis [9, 11], and hence extensive involvement of the kidney was to be expected. Meanwhile, prominent deposits in the stomachs and intestine were previously undescribed findings in the systemic amyloidosis of this species. Since heavy amyloid burdens in the kidney and gastrointestinal tract can potentially cause renal failure [11] or malabsorption through the alimentary system [19], respectively, future investigations to correlate these histopathologic findings with clinical presentations will be ideal.

Systemic amyloidosis in marine mammals is a disease still needing much research attention. The type of deposited amyloid has only been immunohistochemically confirmed as AA in California sea lions [1] and proposed as AA in Stejenger's beaked whales and bottlenose dolphins by pretreatment of CR stains with potassium permanganate and sulfuric acid [2, 16]. Our immunohistochemistry results for AA follow these previous propositions, and also, the rather similar systemic deposition patterns compared to well studied species with AA amyloidosis such as dogs (*Canis lupus*) and cattle [9], suggest that systemic amyloidosis in Stejnger's beaked whales is likely to be of the AA type.

AA amyloidosis usually occurs as a result of chronic inflammatory disease through the persistent elevation of SAA or due to a genetic factor [4, 15]. Assuming that the amyloid deposits in Stejneger's beaked whales are formed from SAA-derived protein, the only common causative factor of chronic inflammation was renal crassicaudiasis. However, all 3 Stejneger's beaked whales,

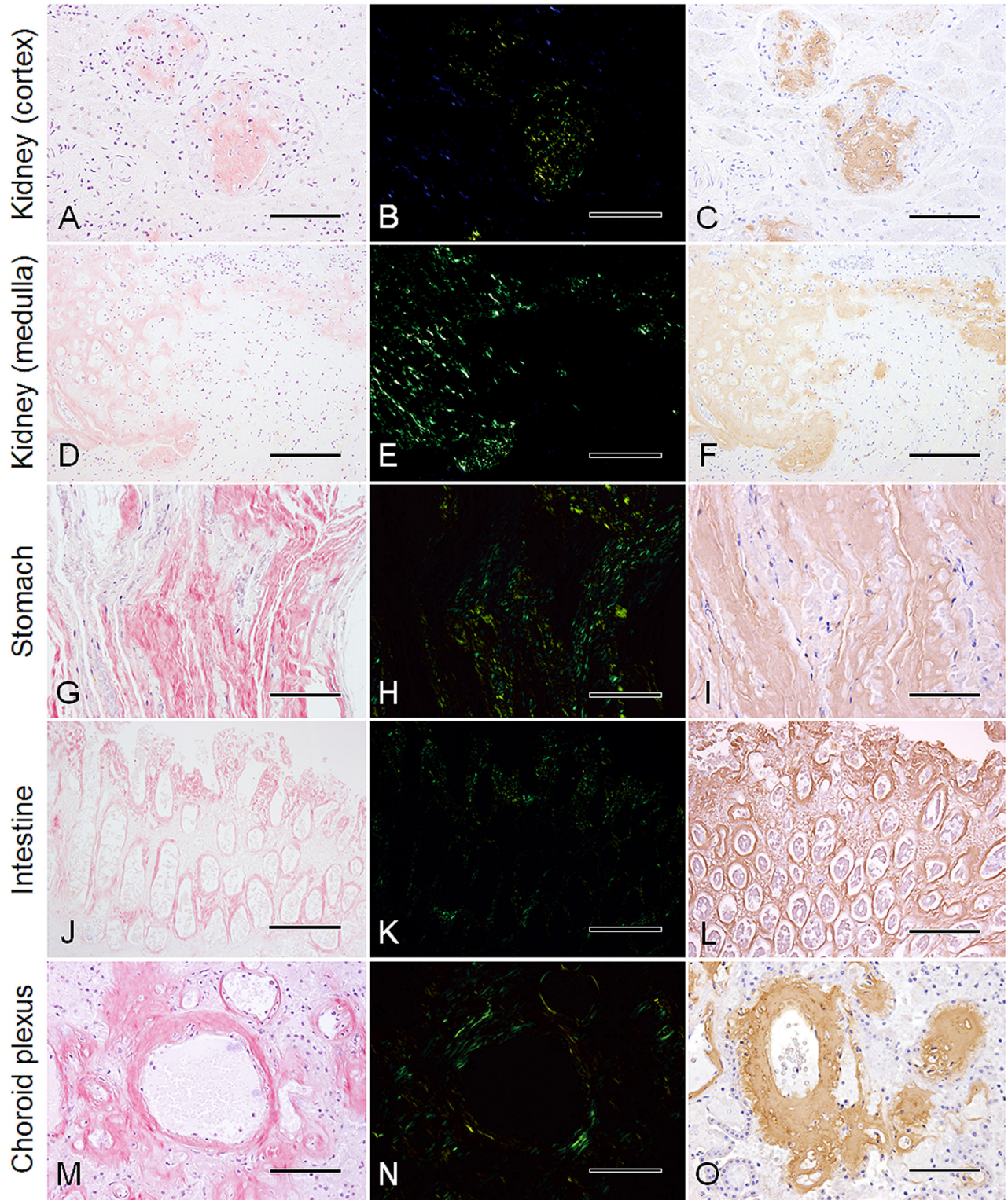

Fig. 1. Histologic features of systemic amyloidosis in Stejneger's beaked whales (*Mesoplodon stejnegeri*). Columns: left, Congo red; middle, Congo red under crossed polars; right, immunohistochemistry for amyloid A with Mayer's hematoxylin counterstain. (A)–(C) Cortex of kidney (serial sections). Segmental amyloid deposits expand the glomeruli (SNH18001). Bar=100 μm. (D)–(F) Medulla of kidney (serial sections). Marked amyloid deposits in the tubular basement membrane and interstitium at the renal papilla (SNH17015). Bar=200 μm. (G)–(I) Main stomach. Prominent amyloid deposits in the interstitium of the lamina propria (SNH18001). Bar=100 μm. (J)–(L) Intestine. Striking amyloid deposits with a periglandular pattern and at the tip of the lamina propria (SNH17015). Bar=200 μm. (M)–(O) Choroid plexus. Marked amyloid deposits expanding the vascular walls while nodular deposits intersperse within the interstitium (SNH17015). Bar=100 μm.

Table 2. Severity of amyloid deposition in various tissues of 3 Stejneger's beaked whales (*Mesoplodon stejnegeri*)

	Liver	Spleen	Kidney (cortex)	Kidney (medulla)	Heart	Lung	Thyroid gland	Pancreas	Adrenal gland	Stomachs	Intestine	Urinary bladder	Mammary gland	Uterus	Gonad	Brain	Choroid plexus
SNH17015 (adult female)	++	++	++	++	+	+	++	++	+	+++	+++	−	−	+	−	−	++
SNH17034 (juvenile male)	−	−	−	−	−	−	−	−	−	−	−	−			−	−	−
SNH18001 (adult male)	+	++	+++	+++	N. E.	N. E.	N. E.	N. E.	N. E.	+++	+++	−			N. E.	−	++

−=no amyloid detected, +=mild, ++=moderate, +++=severe (see Terio *et al.* [18] for details of the grading criteria, a) N. E.: not examined.

including the individual without amyloidosis were affected with the same parasite, and inflammatory lesions including those owing to parasitic infections were a common finding among the examined cetaceans (34 out of 40 animals excluding Stejneger's beaked whales and calves of other species; Table 1). On the other hand, genetic predisposition may be a contributing factor in the development of amyloidosis in Stejneger's beaked whales, as genetic pleomorphism seems to be rather limited in this species [10]. This condition is comparable to that of the island foxes, where its high prevalence of AA amyloidosis is suggested to be due to a lack in heterozygosity, owing to their isolated insular habitat [5, 13]. Nonetheless, confirmation of the amyloid precursor protein in Stejneger's beaked whales at this point seems premature since recent studies have suggested that immunohistochemistry alone is not enough and additional proteomic and/or genetic analyses are required, especially for little-studied wildlife species [5, 7].

The Stejneger's beaked whale is a species with even the most basic biological information yet to be revealed [17]. Virtually nothing is known on their status of abundance, but like other beaked whale species, they are probably prone to anthropogenic threats such as loud acoustic exposure and ingestion of plastic, making them already vulnerable to the ever changing marine environment [3, 12]. Although it is unlikely that stranded animals represent disease prevalence in an entire population, the result of this study implies that systemic amyloidosis may be a substantial factor contributing to morbidity and mortality in adult Stejneger's beaked whales. Our sample size of Stejneger's beaked whales is limited, but the presence of earlier sporadic reports of amyloidosis in adult individuals is supportive of these conclusions [14, 16]. Stejneger's beaked whales may possibly be more prone to the development of systemic amyloidosis among various cetaceans, and therefore, further pathologic research focusing specifically on the species is necessary to elucidate the pathogenesis of amyloidosis and its true prevalence in a population.

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