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Metastatic gastric adenocarcinoma in a grey seal *Halichoerus grypus*: clinicopathological and immunohistochemical characterization

Gonçalo Nogueira Marques[1,*], Bernat Marti-Garcia[2], Miriam Oliveira Leal[1,3], Nuno Urbani Ramos da Silva[1], Carla Anne Flanagan[1], Alejandro Suárez-Bonnet[2]

[1]Zoomarine Portugal, 8201-864 Guia, Portugal
[2]Department of Pathobiology and Population Sciences, The Royal Veterinary College, Hatfield AL9 7TA, UK
[3]MARE-ISPA – Marine and Environmental Sciences Centre / ARNET – Aquatic Sciences Network, 1149-041 Lisbon, Portugal

ABSTRACT: A 33 yr old female grey seal *Halichoerus grypus* presented with inappetence and progressive weight loss. Medical management included blood analysis, imaging, and fecal evaluation, along with multimodal supportive therapy, which periodically improved the overall medical condition. Six months after the initial presentation, the clinical condition deteriorated significantly, including severe hyporexia, hematemesis, and marked neutrophilic leukocytosis, which led to the decision to euthanise based on welfare grounds. Necropsy findings included severe thickening of the distal esophagus, cardia, and proximal gastric fundus, as well as multiple nodular to cystic structures over the stomach's serosa, omentum, and mesentery. Histologically, a mucinous gastric adenocarcinoma was diagnosed, with metastasis to the gastric lymph nodes and prominent carcinomatosis involving the omentum, mesentery, and diaphragm. Immunohistochemically, the gastric adenocarcinoma was positive for cytokeratin AE1/AE3, weakly positive for COX-2 and E-cadherin, and negative for vimentin. The Ki-67 proliferative index was low (0.8). Although rare, this case offers further insights into the clinical presentation, histopathology, and immunohistochemical profile of gastric tumors in pinnipeds.

KEY WORDS: *Halichoerus grypus* · Grey seal · Gastric carcinoma · Carcinomatosis · Immunohistochemistry

1. INTRODUCTION

The grey seal *Halichoerus grypus* is the only member of the genus *Halichoerus* in the family Phocidae, and is listed as 'Least Concern' on the IUCN Red List of Threatened Species (Hall & Thompson 2009, Bowen 2016). Reports of neoplasms in wild grey seals primarily focus on uterine leiomyomas, with incidences varying from 43 to 64% (Mawdesley-Thomas & Bonner 1971, Bergman 1999, Bäcklin et al. 2003). The available literature on gastric neoplasia in pinnipeds is scarce. Documented cases include a gastric carcinoma in a spotted seal *Phoca largha*, a metastatic multicentric ganglioneuroblastoma in a northern fur seal *Callorhinus ursinus*, and a carcinoma in a South American sea lion *Otaria flavescens* (Honma et al. 2001, Spraker & Lander 2010, Yamazaki et al. 2016). To our knowledge, there are no reports of gastric tumors in *H. grypus*. The present study describes the clinicopathological and immunohistochemical features of a metastatic gastric adenocarcinoma in a grey seal housed under professional care.

*Corresponding author: gnmarques1205@hotmail.com

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2. MATERIALS AND METHODS

A 33 yr old female grey seal housed in an outdoor pool complex at Zoomarine Portugal had an irregular appetite since January 2023. As part of the zoological collection, this individual was included in a routine preventative medicine program, grounded on voluntary medical and welfare behaviors. A varied dietary plan included species such as herring, capelin, mackerel, smelt, sardine, sprat, blue whiting, and squid. The medical history of this seal included bone marrow aplasia due to hyperestrogenism, with a subsequent laparoscopic ovariectomy in 2003.

Medical management involved blood sampling when deemed clinically needed for diagnostic and follow-up purposes, including a complete blood count and general biochemistry panel (Table S1 in the Supplement at www.int-res.com/articles/suppl/d161p125_supp.pdf). Imaging studies included thoracic and abdominal radiographs, and abdominal ultrasound. Fecal analyses comprised direct microscopy, as well as parasitology and bacteriology studies.

From March 2023 onward, the seal experienced gradual weight loss and sporadic episodes of diarrhea. Multimodal treatment throughout the clinical course included antibiotic therapy (metronidazole 10 mg kg^{-1} administered orally [PO] twice a day [BID], enrofloxacin 5 mg kg^{-1} PO BID), sucralfate (1–2 g PO BID), probiotics (SivoMixx® 1 sachet PO BID; Antibiophilus® 2 capsules PO once a day [SID]-BID), diazepam (5 mg intramuscularly [IM]), and cannabidiol support (WeConfort® 3 tablets PO SID). The severity of clinical signs fluctuated with partial responsiveness to support therapy. However, in May–June 2023, the seal's clinical status deteriorated critically, including marked hyporexia, an episode of hematemesis, and general discomfort characterized by reduced activity, prolonged periods spent in dry areas, postural changes, shallow breathing, and closed eyes. Due to the continued decline of the seal's medical condition, poor medical prognosis, poor compliance with medications, and need for involuntary medical procedures, as well as unresponsiveness to further support treatment (including prednisolone 5 mg PO BID, metamizole 575 mg PO BID, and tramadol 100 mg PO BID), the seal was euthanized based on welfare grounds (midazolam 0.6 mg kg^{-1} IM, propofol 2 mg kg^{-1} intravenously [IV], and pentobarbital 200 mg kg^{-1} IV).

A complete necropsy was performed shortly after death. Tissue samples were collected and fixed in 10% neutral buffered formalin, routinely processed, embedded in paraffin wax, sectioned (4 µm), and stained with hematoxylin and eosin. Histopathological examination was carried out by 2 board-certified pathologists. Periodic acid-Schiff (PAS), Ziehl-Neelsen (ZN), Gram, Giemsa, and Warthin-Starry stains were performed on selected tissues. Immunohistochemistry was performed on the stomach and gastric lymph nodes using anti-cytokeratin AE1/AE3, anti-vimentin, anti-cytokeratin 20, and anti-Ki-67 antibodies (Table 1). External (canine stomach) and internal positive controls (seal stomach) and a negative control (omission of the primary antibodies) were employed. PCR testing for *Mycobacterium* spp. (primers MYC1p/MYC2p) was performed on paraffin-embedded lung tissue.

Table 1. Summary of immunohistochemical methodology. All antibodies were monoclonal and all antigens were retrieved in citrate buffer

Antibody	Source	Host	Clone	Dilution
AE1/AE3	Dako	Mouse	AE1 and AE3	1 in 100
Vimentin	Dako	Mouse	V9	1 in 100
Cytokeratin 20	Dako	Rabbit	Ks20.8	1 in 20
COX-2	Thermo	Mouse	SP21	1 in 50
E-cadherin	Dako	Mouse	NCH-38	1 in 100
Ki-67	Dako	Mouse	MIB-1	1 in 200

3. RESULTS

Blood results obtained in May 2023 included neutrophilic leukocytosis (22 800 × 10^6 l^{-1}) with no left shift (Table S1). Fecal studies were clinically unremarkable. Thoracic radiographs revealed a mild interstitial and bronchial pattern, more pronounced in the right lung. Additionally, there was gas accumulation in the upper left quadrant of the abdomen, accompanied by blurring of the gastric contour and loss of cranial abdominal detail. Ultrasonographic examination showed an irregular gastric wall outline, along with several variably sized anechoic pockets (up to 1.8 × 2.3 cm) in the cranial abdomen, with posterior acoustic enhancement.

Post mortem examination revealed a large volume of free abdominal serosanguineous fluid (ascites) and a moderate amount of free thoracic fluid (hydrothorax). *Acinetobacter lwoffii* was cultured from both the abdominal and thoracic fluids. *Kytococcus sedentarius* was cultured from the abdominal fluid. The esophageal wall was markedly thickened (2–3.5 cm) at its distal end, at the junction with the

gastric cardia. The cardia and the first third of the fundus were prominently thickened (2–3.5 cm). The abdominal diaphragmatic surface had multifocal white, firm, irregular nodular lesions, ranging from 1 × 1 cm to 4 × 1 cm. Multifocally, the gastric serosa, omentum, and small intestine serosa were effaced by approximately 40 irregular nodules and cystic structures filled with serohemorrhagic fluid. The gastric lymph nodes were firm and moderately enlarged. The pancreas was severely hemorrhagic. The liver had a superficial whitish coloration along the margins of the hepatic lobes, with a thickened Glisson's capsule (2 mm). The hepatic lymph node was normal in size and congested. Additional gross lesions included a firm lung parenchyma with 2 ill-defined nodules (2 × 1.5 cm), 2 cystic structures (8 mm in diameter) in the parenchyma of the left thyroid, and a small amount of purulent discharge covering the internal uterine wall and vaginal mucosa. *Kocuria rosea* and *Kocuria varians* were cultured from the uterus and vagina, respectively.

Histologically, the distal esophageal and gastric masses consisted of a mucinous gastric adenocarcinoma (Fig. 1). The tumor, originating from the gastric chief cells, was highly infiltrative, poorly demarcated, transmural, and moderately cellular, with associated ulceration. The neoplasm extended into the serosal, omental, and mesenteric fibroadipose tissues (carcinomatosis), eliciting a prominent desmoplastic fibrous (scirrhous) response and associated suppurative peritonitis. The neoplastic cells were haphazardly arranged in tubuloacinar structures containing large amounts of basophilic to amphophilic, PAS-positive homogeneous material (mucin) and were supported by pre-existent fibrovascular stroma. Neoplastic cells were cuboidal to polygonal, with eosinophilic to amphophilic homogeneous cytoplasm and a single, parabasal, round to oval nucleus with coarsely stippled chromatin and a single prominent nucleolus. Moderate anisocytosis and marked anisokaryosis were noted. There was 1 mitotic figure in 10 high-power fields (2.37 mm^2). Extensive areas of necrosis were observed throughout the tumor, often forming microabscesses and accompanied by hemosiderin-laden macrophages. In the distal esophagus, the neoplasia showed similar morphological characteristics as in the stomach. The superficial esophageal epithelium was multifocally attenuated or extensively eroded, with no evidence of mucinous metaplasia (Barret's esophagus) in the normal esophageal mucosa. The gastric lymph nodes and perinodal fibroadipose tissue were multifocally and extensively effaced by a similar carcinoma, which markedly expanded the subcapsular and medullary sinuses, and distorted the normal nodal architecture. The remaining lymphoid tissue was hyperplastic, with prominent cortical germinal centers. The nodules found on the diaphragm corresponded with multifocal areas of carcinomatosis.

Immunohistochemically, the neoplasm had strong cytoplasmic and membranous labeling for cytokeratin AE1/AE3, weak cytoplasmic immunolabeling for COX-2, and weak to absent membranous E-cadherin expression. Vimentin strongly labeled the stroma and infiltrating inflammatory cells, while neoplastic cells were consistently negative. The Ki-67 index was low (0.8). Cytokeratin 20 did not cross-react with seal tissues.

Microscopically, the lung had multifocal to coalescing, subpleural to peribronchial/-bronchiolar granulomas. These granulomas consisted of large central cores of lytic necrosis admixed with degenerate neutrophils, surrounded by mature fibrous tissue containing intermingled multinucleated giant cells, lymphocytes, plasma cells, and fibroblasts that merged with the surrounding alveolar septa. PAS and ZN special stains did not reveal fungal or acid-fast bacterial organisms, and PCR using MYC1p/MYC2p primers did not detect mycobacterial DNA in the lung samples.

Incidental or age-related histological findings included diffuse follicular collapse with lack of colloid (atrophy) and multifocal cysts in the thyroid gland, adrenocortical hyperplasia of the left adrenal gland with scattered interstitial lymphocytes, occasional renal tubular mineralization, multifocal vaginal polyps, cystic hyperplasia of the gallbladder, capsular hepatic fibrosis with multifocal mild ductular reaction, and mild hepatocellular lipofuscinosis.

4. DISCUSSION

Gastric carcinoma is a rare form of cancer in veterinary oncology, accounting for <1% of reported neoplasms in dogs (Hardas et al. 2021). In contrast, gastric tumors are one of the leading causes of cancer-related deaths in humans (Hugen et al. 2016). Adenocarcinoma is the most common type of gastric neoplasm reported in both humans and dogs, comprising 50–90% of all canine gastric malignancies (Patnaik et al. 1977). Few epidemiological studies have been conducted on pinniped neoplasia, with no reports of gastric tumors in grey seals and only 3 documented cases of gastric carcinoma in other pinniped

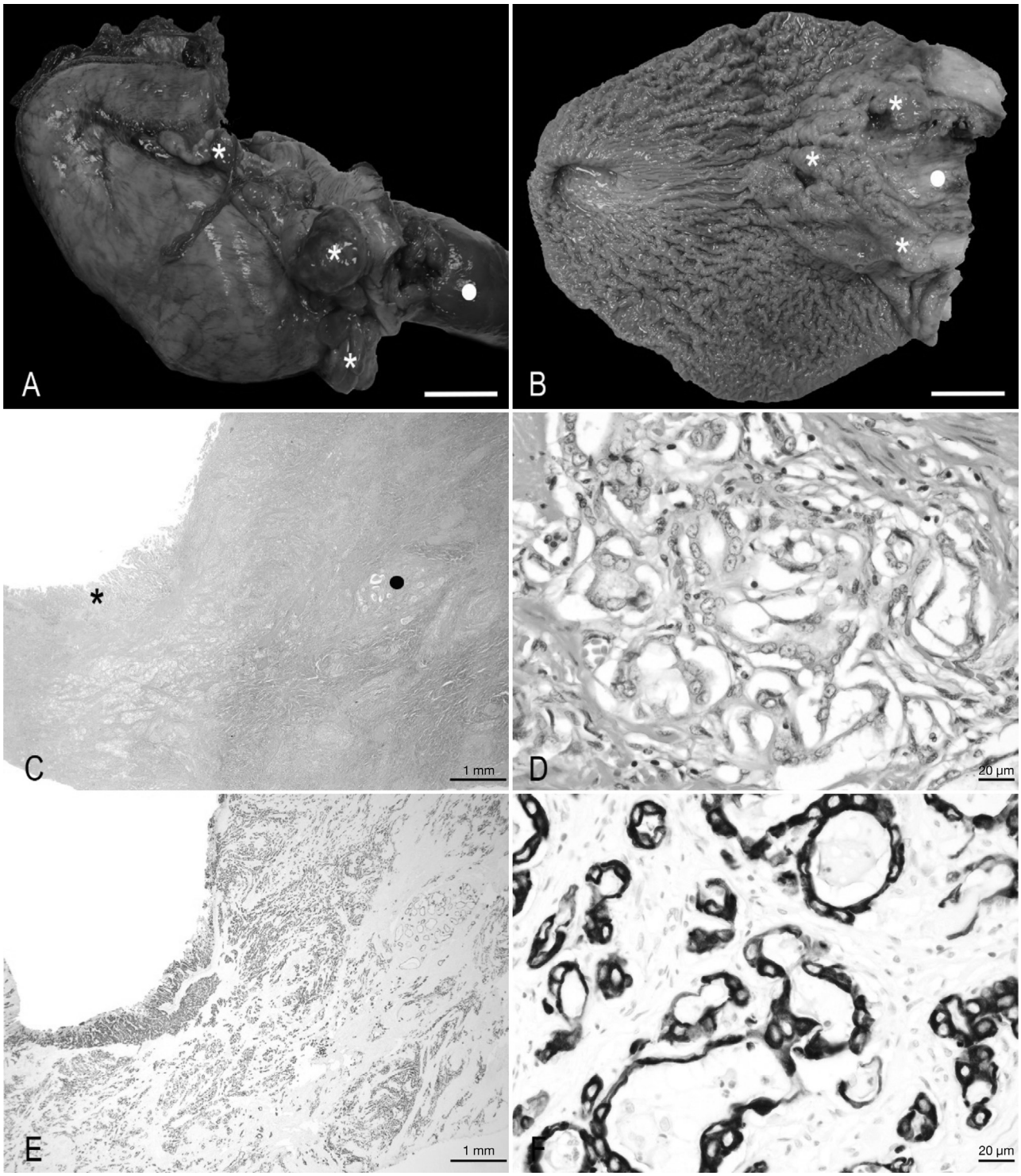

Fig. 1. Grey seal (*Halichoerus grypus*) metastatic gastric adenocarcinoma with carcinomatosis. (A) External surface of the stomach. Gastric wall and serosa exhibit multifocal firm nodules (asterisks). Distal esophagus is segmentally thickened (white dot). Scale bar = 5 cm. (B) Cardia is locally ulcerated (white dot). Mucosa is extensively thickened and irregular, with multifocal areas of erosion and ulceration (asterisks). Scale bar = 5 cm. (C) Low-power magnification of gastric wall. An area of normal gastric mucosa (asterisk) blends with a markedly infiltrative malignant glandular neoplasm that invades all layers of the gastric wall. A group of neoplastic glands is observed within tunica muscularis (black dot). Scale bar = 1 mm. (D) Neoplastic cells form irregular acini. Scale bar = 20 µm. (E) Cytokeratin AE1/AE3 labels the normal gastric mucosa and all neoplastic cells infiltrating the gastric wall. Scale bar = 1 mm. (F) Cytokeratin AE1/AE3 strongly labels all neoplastic cells. Scale bar = 20 µm

species (Honma et al. 2001, Spraker & Lander 2010, Yamazaki et al. 2016).

The etiology of gastric adenocarcinoma is not yet completely understood, though a variety of factors contributing to chronic inflammation and its role in carcinogenesis have been thoroughly studied in both humans and animals (Hardas et al. 2021). Potential risk factors in the precancerous cascade leading to human gastric adenocarcinoma include gastroesophageal reflux disease, *Helicobacter pylori* infection, dietary factors, obesity, use of antacids, smoking and occupational tobacco exposure, as well as demographic, genetic, and epigenetic factors (Carr et al. 2013, Abdi et al. 2019). The pathogenesis of canine gastric carcinoma remains elusive, although a strong environmental component has been suggested (Terragni et al. 2014). Moreover, a higher prevalence of these tumors in certain dog breeds suggests an underlying genetic influence (Terragni et al. 2014).

Several studies have explored the etiology and pathogenesis of metastatic carcinomas of urogenital origin in *Zalophus californianus* (Newman & Smith 2006, Browning et al. 2015). However, no research has specifically addressed the pathogenesis and the specific role of chronic inflammation in the development of gastric tumors in pinnipeds. Although *H. pylori* infection is a well-established contributor to gastric carcinoma in humans, promoting an immune microenvironment of chronic gastritis (Zavros & Merchant 2022), there was no histological evidence of *Helicobacter* spp. in the present study. Furthermore, this seal had no previous clinical signs associated with gastroesophageal reflux disease (e.g. decreased appetite, difficulty swallowing, changes in vocalizations, chronic cough, generalized discomfort) or chronic gastritis, nor was there a history of antacid prescription, except for rare, short periods of omeprazole (<7 d) preventively administered with nonsteroidal anti-inflammatory therapy. PCR or culture should be considered in further cases to completely rule out *Helicobacter* spp. involvement. Regarding dietary factors, the seal diet primarily consisted of fish sourced from open seas, subjected to stringent quality-control assessments. Upon arrival at Zoomarine, the fish underwent detailed organoleptic and chemical analyses, including key parameters such as peroxide index, total volatile basic nitrogen, thiobarbituric acid reactive substances, moisture content, protein, ash, fat, glucose, and caloric value. The nutritional plan of the seal was continuously tailored to its metabolic needs during different growth stages and physiological demands (e.g. molting season). Furthermore, particular attention was given to preventing abrupt weight fluctuations, reducing the risk of obesity.

The advanced stage of the gastric adenocarcinoma presented only with late, nonspecific, and inconsistent clinical signs, including a gradual onset of hyporexia, weight loss, and gastrointestinal discomfort. This mirrors the challenges faced in both human and small-animal oncology, in which gastric tumors are often asymptomatic or manifest with subtle signs in their early stages, delaying detection and overall clinical management (Hugen et al. 2016).

Regarding diagnostic methodologies, hematological and biochemical findings in dogs with gastric carcinoma are typically minimal or absent. When present, they may include panhypoproteinemia, microcytic hypochromic anemia, increased liver enzymes, hypoglycemia, and prolonged clotting times (Terragni et al. 2014, Hugen et al. 2016). In the seal in the present study, hematological findings were unremarkable overall, though neutrophilic leukocytosis was noted later. Similar to canine gastric carcinomas, abdominal radiographs showed a loss of cranial abdominal detail with no other specific abnormalities (Hugen et al. 2016). However, technical difficulties with the radiographic equipment may have hindered a thorough assessment of the gastric wall. Moreover, while ultrasonography is a valuable diagnostic tool for gastric neoplasia, its diagnostic sensitivity in canine cases has been reported to be only 50–58% (von Babo et al. 2012). Endoscopy with biopsy remains the gold standard for early confirmation of gastric neoplasms (Terragni et al. 2014). Laparoscopy with peritoneal washings is also part of the initial workup for gastric carcinoma in human medicine, as carcinomatosis is identified in approximately 20% of patients without imaging evidence of peritoneal disease (Ikoma et al. 2016).

Systemic chemotherapy, radiotherapy, surgery, immunotherapy, and targeted therapy all have demonstrated efficacy in managing human gastric adenocarcinomas (Hugen et al. 2016). However, in dogs, the most established potential treatment for gastric carcinoma is surgical resection, while chemotherapeutic interventions are still in early stages, and limited to case report series (Hugen et al. 2016). In dogs, the median survival time following a diagnosis of gastric carcinoma is 35 d, with metastasis occurring in 70–90% of cases (Sullivan et al. 1987).

Given the advanced age of the seal in the present study, surpassing the mean lifespan of 15–25 yr for wild individuals, along with the inherent risks of anesthesia in geriatric animals, the expected prognosis associated with metastatic disease, and the postoper-

ative quality of life and the need for involuntary medical procedures to ensure drug compliance, ethical considerations on medical management arose (MacDonald 2009). Considering the balance between animal welfare and the potential benefits of invasive diagnostics and extensive surgery, a conservative clinical approach was ultimately chosen.

A unique feature of this seal's case in comparison with previous pinniped reports is the presence of carcinomatosis and metastases in the abdominal cavity. Yamazaki et al. (2016) reported a similar gross thickening with scattered ulcers at the cardia of a South American sea lion, and although those authors mentioned transmural thickening, their case did not extend beyond the serosa, invading the omentum, or produce metastasis in lymph nodes. Interestingly, our case exhibited a very low mitotic count and Ki-67 index, indicating a low tumor growth rate, likely leading to more widespread dissemination and a silent clinical course. Similarly, the case described by Yamazaki et al. (2016) was diagnosed as an undifferentiated carcinoma, which differs from the mucinous type in the seal in the present study, characterized by tubuloacinar structures and mucin production, as described in other species (Hugen et al. 2016).

The immunohistochemical profile in the present case is in accordance with previous studies (Yamazaki et al. 2016, Hardas et al. 2021). E-cadherin is an adhesion molecule that maintains cell integrity, and its loss in malignant transformation favors invasion and metastasis. In this case, the neoplastic cells had weak to complete loss of expression, supporting the advanced stage of the tumor. COX-2 was expressed in areas of normal gastric mucosa, in comparison with the neoplastic cells that had weak expression. COX-2 overexpression in cancer is associated with high malignancy, invasion, and metastasis, and COX-2 inhibitors are used as adjuvant therapy in some neoplasms (Hashemi Goradel et al. 2019) The weak COX-2 expression in the present case may indicate that COX-2 inhibitors would have minimal palliative effect (Mao et al. 2007). The significance of COX-2 in seal gastric physiology requires further investigation.

Although rare, this seal's case offers further insights into the clinical presentation, histopathology, and immunohistochemical profile of gastric tumors in pinnipeds.

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