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Corneal Fibropapilloma in Loggerhead Turtles (*Caretta caretta*) in Mediterranean Sea

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ABSTRACT

Fibropapillomatosis (FP) is a panzootic and neoplastic disease. In the current study, we aimed to characterize a tumour-like mass and reveal spirorchid-like parasitic eggs in the ocular tissues of *Caretta caretta* turtles. In this study, seven ocular tissue samples, including six eye/eyelid tissues taken from Loggerhead turtles (*C. caretta*) with healthy-looking animals and one tumour-like ocular mass obtained from a *C. caretta* turtle with a clinical lesion, were used as study material. Unilateral spirorchid-like parasite eggs were detected in the tissue samples of only two healthy-looking animals. The characterization and identification of a tumour-like mass were performed using histopathology, PCR and immunohistochemistry, respectively. Unilateral corneal scarring, spirorchid-like parasite eggs and papilloma virus by PCR were detected in the ocular tumour-like mass evaluated as fibropapilloma. However, in immunohistochemical staining, Ki-67, p16, pan-cytokeratin, vimentin and herpesvirus showed positive staining, whereas p53 showed negative staining. Koilocytosis was observed in some cells. Our findings indicate that papillomavirus, herpesvirus and spirorchid-like parasite eggs may have a predisposing role in the occurrence of FP. This study provides the first research data on spirorchid-like parasite eggs and FP in loggerhead turtles (*C. caretta*) in the Mediterranean Sea in Türkiye.

1 | Introduction

Fibropapillomatosis (FP), a neoplastic disease of marine turtles, is a panzootic chronic disease characterized by occasionally involving visceral fibromas and single to multiple fibroepithelial growths of the skin (Herbst 1994). A benign tumour of the epithelium and connective tissue in which multilayered squamous epithelial growth is accompanied by at least as much or more growth of the underlying connective tissue (Erer and Kıran 2021). FP was initially discovered in green sea turtles (*Chelonia mydas*) in Florida in 1938, Hawaii in 1958 and the Grand Cayman Islands in 1980 (Jacobson et al. 1989; Smith and Coates 1938). FP has been reported in green sea turtles, loggerhead (*Caretta caretta*), leatherback (*Dermochelys coriacea*), hawksbill (*Eretmochelys imbricata*), flatback (*Natator depressus*), olive ridley (*Lepidochelys olivacea*) and kemp's ridley (*Lepidochelys kempii*) turtle species. Due to FP's recent emergence of panzootic distribution, disease has gained importance in green turtles (Herbst 1994; Jones et al. 2016; Work et al. 2015). FP is now considered a disease that has spread globally (Herbst 1994). The species having the highest prevalence of FP (Blackburn et al. 2021; Jones et al. 2016), which is commonly seen in the orbital, periorbital and oral cavities (Brooks et al. 1994; Herbst 1994), is the green sea turtle (*C. mydas*). Moreover, the prevalence

of papillomas, fibromas and fibropapillomas is believed to be increasing worldwide in green sea turtles (Casey et al. 1997).

Corneal and/or ocular FP has previously been recorded in Florida, USA (Jacobson et al. 1989), Queensland, Australia (Flint et al. 2010), Itaipu, Brazil (Tagliolatto et al. 2016), Unhocomo and Unhocomozinho islands of the Bijagos Archipelago, Guinea-Bissau (Monteiro et al. 2021) and Mabul Island, Malaysia (Robben et al. 2023). However, FP in loggerhead turtles has been sporadically reported and is not very common (Page-Karjian et al. 2015). Although the etiological agent of fibropapilloma is yet to be confirmed (Work et al. 2017), many studies suggest that fibropapilloma cases in marine turtles have a viral aetiology, including papillomaviruses (Herbst 1994; Mashkour et al. 2021), herpesviruses (Manire et al. 2008; Mashkour et al. 2021), retroviruses (Casey et al. 1997) and papova-like virus (Lu et al. 2000).

Spirorchids are a family of blood parasites that can cause various inflammatory reactions in the vascular system of their hosts, often leading to the death of sea turtles worldwide (Santoro et al. 2020). It has been reported that spirorchid eggs, which settle in small vessels and spread through the blood circulation, cause the development of multifocal granulomas in different tissues (Gordon et al. 1998).

The most common sea turtle species in the Mediterranean Sea is the loggerhead sea turtle (*C. caretta*) (Gentile et al. 2021). Although sea turtles can be found all over the Mediterranean Sea, their main nesting areas are Greece, Türkiye, Cyprus and Libya. In other Mediterranean countries, nesting is rare (Casale and Margaritoulis 2010; Sozbilen and Kaska 2018). The Samandag coast of the Mediterranean Sea is the easternmost nesting site of the loggerhead turtles (Casale and Margaritoulis 2010). Nevertheless, research on FP and spirorchid infection in loggerhead turtles (*C. caretta*) in Türkiye has not been described. The objective of the present study was to characterize a tumour-like mass by histopathological and virological analyses and to reveal the presence of spirorchid-like parasitic eggs in the ocular tissues of loggerhead turtles (*C. caretta*) with a healthy appearance and a tumour-like mass. To the best of our knowledge, this is the first etiologic detection of corneal FP in loggerhead sea turtles in Türkiye.

2 | Materials and Methods

The materials of this study consisted of seven ocular tissue samples: one ocular tumour-like mass and six eye/eyelid tissues taken from healthy-appearing animals. Turtles and tissue samples were brought to the Department of Pathology for histopathological examination from the Samandag coast in the Mediterranean Sea in Türkiye. A part of the ocular tumour-like mass was fixed in 10% formalin. The other part of ocular tumour-like mass was sent to the Department of Virology for molecular identification.

Total viral DNA extraction was performed using a high-purity viral nucleic acid kit (Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocols. First, viral DNA was amplified using oligonucleotide FAP59/64 degenerate primers (forward primer 5′-TAACWGTIGGICAYCCWTATT-3′ and reverse primer 5′-CCWATATCWVHCATITCICCATC-3′) targeting a 478-bp fragment amplifying the L1 gene of the papillomavirus, as described by Ogawa et al. (2004). The amplification process was performed in a 20 μL reaction mixture by adding 2 μL of template DNA to 18 μL of PCR master mix containing a final concentration of 0.5 μM of each primer using a commercial master mix solution (5x HOT FIREPol Blend PCR Master Mix; Solis BioDyne, Tartu, Estonia), which included Hot FIREPol DNA polymerase as a proofreading enzyme. As a negative control, DNA extracted from Madin–Darby bovine kidney cells was used. The BPV-1 strain was used as a positive control, which was confirmed by sequencing in our previous study (Ataseven et al. 2016). PCR products were visualized under ultraviolet light using a transilluminator after electrophoresis in 1% agarose gel with a nucleic acid dye (Applied Biological Materials, Canada).

P53, Ki-67, p16, pan-cytokeratin (Pan-CK) and vimentin immunohistochemical markers were used to confirm the presence of fibropapilloma. Moreover, a mouse monoclonal anti-Marek disease virus antibody (NB110-599908) was used for immunohistochemical diagnosis of herpesvirus. Six eye/eyelid tissues taken from healthy-looking animals that underwent systematic necropsies and died as a result of injury and one ocular tumour-like mass were fixed in 10% formalin, routinely processed and embedded in paraffin. After being sliced to a thickness of 5 μm, the paraffin blocks were stained with haematoxylin and eosin (Kanat 2024). All the sections were deparaffinized, and heat-induced antigen retrieval was performed on positively charged slides. The slides were stained with an immunohistochemical staining system (Autostainer Link 48 and Dako's premier reagents). The slides were incubated with primary antibodies that used mouse monoclonal anti-human Ki-67 antibody (1:300), mouse monoclonal anti-human p53 protein antibody (1:100), mouse monoclonal anti-human p16 antibody (1:150), pan-cytokeratin (Pan-CK) monoclonal antibody (1:200), vimentin (1:350) and mouse monoclonal anti-Marek disease virus antibody (1:150). PBS was used instead of primary antibody in negative control. A light microscope (Olympus DP12BSW, Tokyo, Japan) was used to evaluate all samples. In addition, a digital imaging system was used to acquire microscopic images of the specimens (Olympus BX50-F4, Tokyo, Japan).

3 | Results

The moderately pigmented ocular tumour-like mass had a thick stalk that extended from the medial region of the right eye, gradually narrowing as it reached its apex. Macroscopically, the ocular tumour-like mass had a slightly soft consistency (Figure 1). Papillomavirus DNA was detected using FAP59/64 degenerate primers in an ocular tumour-like mass characterized as a fibropapilloma on histopathological examination; however, the papillomavirus type could not be identified by sequence analysis due to the low-quality sample.

Histopathologically, unilateral spirorchid-like parasite eggs were detected in the tissue samples of two healthy animals (Figure 2a). FP or spirorchid-like parasite eggs were not detected in the ocular samples of the other four healthy animals. In the ocular tumour-like mass determined to be a fibropapilloma, unilateral corneal scarring and spirorchid-like parasite eggs were visualized using histopathological techniques. Atypical cell features in mucinous

FIGURE 1 | Macroscopy. Moderately pigmented ocular mass, gradually narrowing and slightly soft consistency.

columnar and squamous cells, hyperaemia, mononuclear cell infiltration with particularly dense lymphocytes, and numerous parasitic cysts and foreign-body giant cells were observed in the dermis (Figure 2b), and Langhans giant cells and macrophages developing against parasitic cysts were also observed (Figure 2c). Moreover, histopathologically, apart from moderate stromal hyperplasia, it was seen to have a papillary pattern, epithelial hyperplasia, prominent epithelial pegs due to hyperplasia, acanthosis, hyperkeratosis, perinuclear halo and intranuclear (Figure 2d) and intracytoplasmic eosinophilic inclusion bodies (Figure 2e). Dark reddish-brownish black pigments similar to melanin were observed in the sections. Atypical cell features were observed in some transitional epithelial cells. It was observed that the nuclei of some cells were enlarged and swollen and had different structures. In the upper spinous layer, cells referred to as koilocytes, are characterized by a perinuclear halo and eccentric pyknotic nuclei. Koilocytosis was observed in some cells (Figure 2f). Differentiation of superficial goblet cells was observed.

In immunohistochemical staining of tumour-like mass, Ki-67 expression was found in some places in the basal layer of the epithelium. No dysplasia was observed. Immunostaining for p16 showed a distribution in the squamous epithelium, particularly in koilocytic cells (Figure 3a). Vimentin expression was seen in the dermis (Figure 3b). Furthermore, Pan-CK showed positive staining (Figure 3c), whereas p53 showed negative staining (Figure 3d). Additionally, for herpesvirus, IHC was implemented on the sections of ocular tumour-like mass, and herpesvirus-positive reactions were detected on the nucleus and cytoplasm of epithelia as yellowish-brownish granules (Figure 3e). The negative control showed no positive reaction (Figure 3f).

4 | Discussion

Many researchers have held responsible some viral etiological agents such as papillomavirus, papova-like virus, retrovirus and herpesvirus for the development of FP in sea turtles (Casey et al. 1997; Lackovich et al. 1999; Lu et al. 2000; Manire et al. 2008). Furthermore, spirorchid eggs, first reported by Smith and Coates (1938), were later reported in fibropapilloma cases by Balazs (1986). In the present study, the presence of spirorchid-like parasite eggs in two of the sampled *C. caretta* turtles' eye tissues and the presence of both corneal FP and spirorchid-like parasite eggs in a single tumour tissue were revealed. The most prominent histological findings regarding the aetiology of FP are eosinophilic inclusions and spirorchid-like parasite eggs (Chaves et al. 2013; Jacobson et al. 1989). In this study, both spirorchid-like parasite eggs and intranuclear eosinophilic inclusions were detected in tumour tissue, whereas inclusion bodies were not observed in tissues in which only spirorchid eggs were identified. Additionally, papillomavirus DNA was also detected in the tumour-like tissue characterized as FP using PCR. Furthermore, immunohistochemically, herpesvirus-positive reactions were seen in the cytoplasm and nucleus of ocular tumour-like mass epithelia.

In a previous study, corneal FP masses were sessile and multinodular with less arborization (Brooks et al. 1994), whereas corneal FP in this study was multinodular and pedunculated. Moreover, the tumour-like masses in the research were not sessile, and indications of superficial damage and secondary bacterial colonization have been reported (Flint et al. 2010). In our study, no evidence of secondary bacterial colonization was found, contrary to what the researchers reported. It is thought that this situation may change according to the genetic makeup of populations and environmental and regional factors affecting the living conditions of turtles.

In the present study, other than foreign-body and Langhans giant cells in the dermis, the histopathological findings of tumour-like mass in this turtle had a similar appearance to those previously described in cutaneous and ocular sites (Brooks et al. 1994; Flint et al. 2010; Rodenbusch et al. 2012). Histopathologically, as reported by some researchers (Jacobson et al. 1991; Work et al. 2015), degeneration and intranuclear inclusion bodies in epidermal cells were interpreted as herpesvirus-related lesions in our study. Moreover, in this study, koilocytic cells were observed in the epidermis. Identification of these cells can be an important finding in diagnosing various papillomavirus-associated lesions. Our findings indicate that papillomavirus and spirorchid-like parasite eggs may have played a predisposing role in the occurrence of FP. However, future epidemiologic, antigenic and histopathologic studies detailed on turtle papillomaviruses are needed to evaluate their clinical history and interactions with different factors such as parasites, bacteria or viruses.

Immunohistochemically, the epithelial component of the lesion was stained with pancytokeratin and the mesenchymal component with vimentin. The papillary lesion was diffusely stained with Pan-CK, indicating the epithelial nature of the lesion. The mesenchymal component of the lesion was immunopositive for vimentin. Prominent epithelial pegs were observed due to acanthosis. However, no dysplasia was observed. Supporting the viral infection, the expression of p16 showed a distribution in the squamous epithelium and rarely in koilocytic cells in immunohistochemical staining. The p53 gene is essential in the cell cycle and plays a vital role in cell division (Özgür et al. 2006; Şevik 2013). It is also involved in the synthesis and repair of DNA, cell differentiation and programmed cell death (Özgür et al. 2006). However, the p53 staining performed in this study yielded a negative result. It

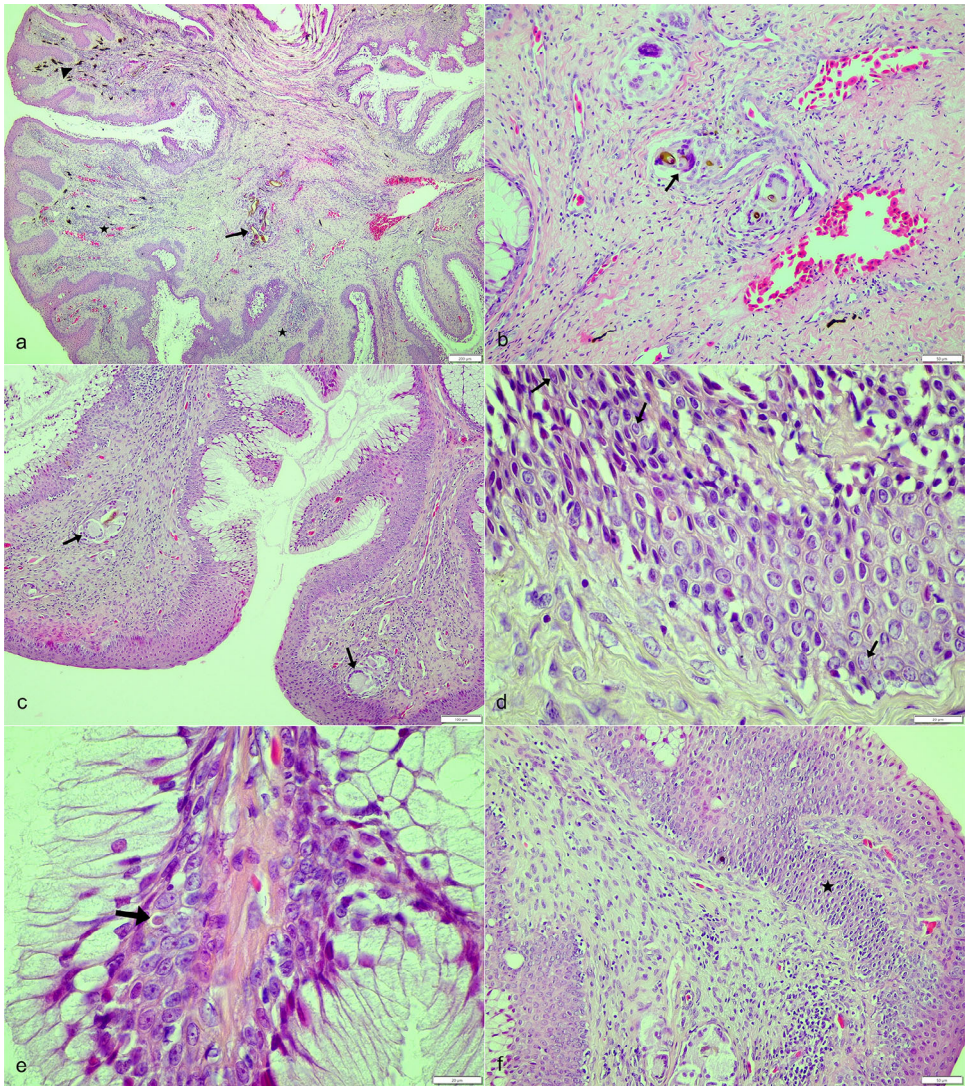

FIGURE 2 | Histopathologic findings. (a) Epithelial pegs, spirorchid-like parasite eggs (arrow), mononuclear cell infiltration (stars) and dark reddish-brownish pigments similar to melanin (arrowhead). (b) Hyperaemia, spirorchid-like parasite eggs and foreign-body giant cell (arrow). (c) Acanthosis and Langhans giant cells (arrows). (d) Intranuclear inclusion bodies (arrows). (e) Intracytoplasmic eosinophilic inclusion bodies (arrow). (f) Koilocytosis in cells (star). HE staining.

was thought that the reason for the negative staining might be the difference between the animal species. In herpesvirus immunostaining, despite the observation of intranuclear inclusion bodies in the study by Work et al. (2015), some researchers reported that mostly intracytoplasmic with some intranuclear and free staining was observed in the parenchyma of many tissues, such as the liver, kidney and lung in herpesvirus immunostaining (Yavuz and Erer 2017). Contrary to the researchers, the presented study observed both significant intranuclear and intracytoplasmic positive expressions. Positive staining in the cytoplasm in IHC herpesvirus stainings was thought to be viral genetic material released during cell degeneration. Intranuclear and intracytoplasmic inclusion localizations thought that the viruses may play an important role in viral spread while exhibiting an active, more pronounced cytopathogenic effect on tumour cells. In extant vertebrates, melanins are dark to rusty pigments that are found in the integument, eyes and internal tissues and underpin critical functions (visual signalling, photoprotection, immunity, mechanical strengthening etc.) in physiology and behaviour. Melanomacrophages that derive immunity in fish, amphibians and reptiles contain abundant melanocytes (McNamara et al. 2021). Therefore, dark reddish-brownish black pigments observed in the dermis were physiologically evaluated as melanin pigments in this study.

5 | Conclusion

In conclusion, spirochid-like parasite eggs can also be detected in healthy animals, and this study represents the first report on the detection of spirorchid-like parasite and papillomavirus and herpesvirus in loggerhead turtles (*C. caretta*) in the Mediterranean Sea in Türkiye. However, it has also been reported that the risk of spirorchid infection in the Mediterranean Sea is lower than that in other geographical regions and that differences in the prevalence of infection may be related to differences in spirorchid intermediate hosts in regional habitats (Santoro et al. 2020). To our knowledge, although this is the first detection of herpesvirus in

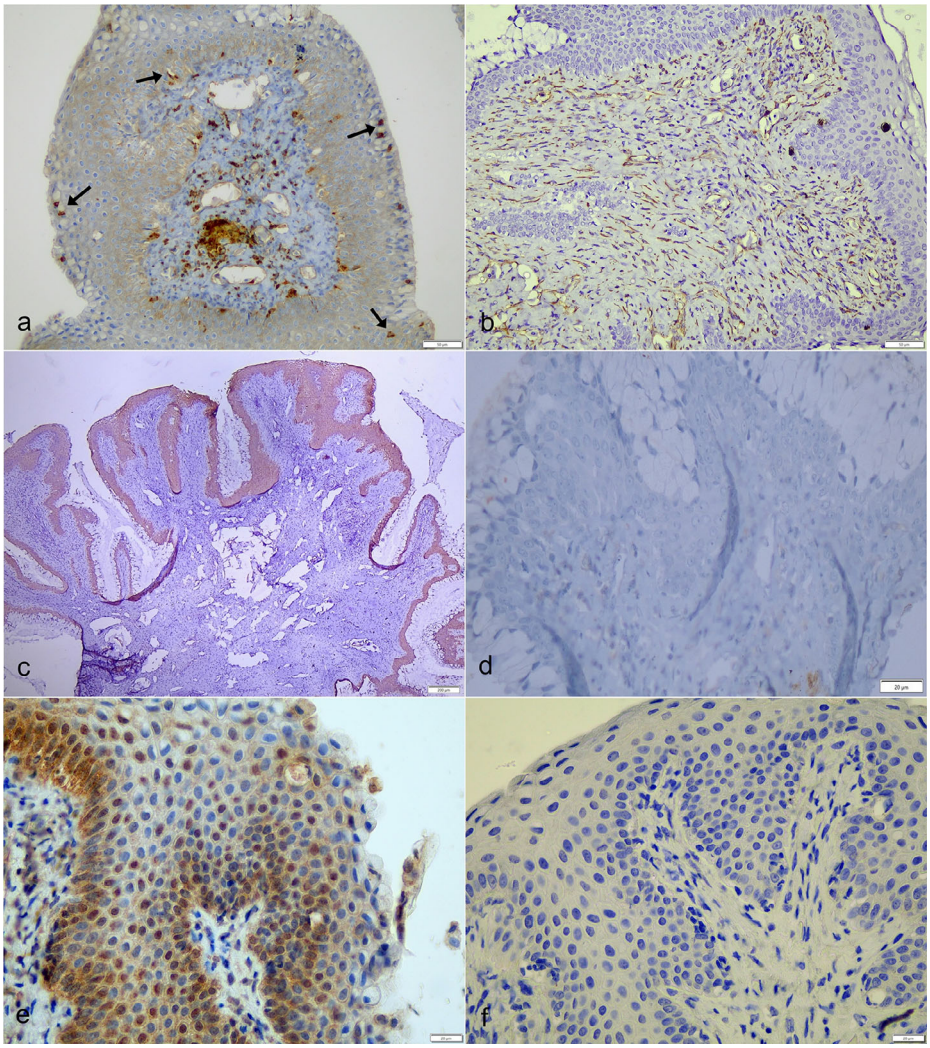

FIGURE 3 | Immunohistochemical staining. (a) p16 positive staining in koilocytic cells (arrows). (b) Vimentin positive staining. (c) Pan-cytokeratin positive staining. (d) p53 negative staining. (e) Intranuclear and intracytoplasmic herpesvirus-positive staining. (f) Negative control for herpesvirus staining.

Loggerhead sea turtles (*C. caretta*) in the Mediterranean Sea in Türkiye, future large-scale epidemiological and histopathological studies on the papillomavirus, herpesvirus and spirorchid-like parasite in the Loggerhead turtle (*C. caretta*) population in the Mediterranean Sea will provide a better understanding of the prevalence, transmission and lesion characteristics in this population.

Author Contributions

Özgür Kanat: conceptualization, methodology, investigation, visualization, writing-original draft, writing – review and editing. **Veysel Soydal Ataseven**: conceptualization, methodology, investigation, visualization, writing – original draft, writing – review and editing. **Pınar Karabağlı**: conceptualization, methodology, investigation, writing – review and editing.

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Ethics Statement

All procedures in this study were approved by the Animal Ethical Committee of Hatay Mustafa Kemal University (2021/06-23).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analysed during this study are mentioned in this manuscript.

Peer Review

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