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Research

Odontogenic hamartomas in cultured angelfish (*Pterophyllum scalare*)

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ABSTRACT

Background: Odontogenic tumors present diverse clinical and histopathological behaviors that range from benign odontoma or hamartoma lesions to malignant tumors. In angelfish *Pterophyllum scalare*, findings of tumorous masses have been reported in the frontal region of the mouth, encompassing both the maxilla and mandible. Histologically, oral tumors have been characterized as angelfish lip fibroma or ameloblastoma.
Methods: In this report, we describe the occurrence of a compound odontoma/hamartoma in 60 angelfish from a population of 300, all of which were collected from a Mexican ornamental fish farm.
Results: All fish presented a tumor-like mass on the rostral part of the mouth. Histological analyses revealed the tumor-like mass was covered by a hyperplastic stratified squamous epithelium, with fully differentiated denticles in various states of organization, immersed among normal dental tissues and showing a mild disorganized pattern. Radiograph analysis revealed radiopaque denticles in a radiolucent protuberance. Bacterial and viral isolation procedures and electron microscopy analysis revealed no presence of these microorganisms.
Conclusion and clinical relevance: Although findings of odontogenic tumors in the mouth of angelfish are reported as sporadic, our study detected odontogenic mouth tumors in 60 angelfish, but the possible cause of alteration is not yet clarified. Further research is needed to clarify pathogenesis and to identify possible genetic abnormalities.

Introduction

Neoplastic processes have long been omnipresent in vertebrate organisms [1]. Tumor research has mainly focused on higher vertebrates, but among inferior organisms (e.g., fish, amphibians, and reptiles), fish have the highest number of neoplastic alterations. Furthermore, fish present the same variety of tumors as described in mammals and birds [2], although reports are limited [3].

Tumorous diseases, or neoplasms, generally have multifactorial causes associated with genetic susceptibility, such as situational stressors (e.g., overcrowding, malnutrition, trauma), exposure to contaminants and carcinogens, and viruses [4,5]. Regarding viruses, members of the *Retroviridae* family are considered carcinogenic in fish [6,7]. *Papillomaviridae* produce papillomas, *Iridoviridae* fibromas [8], and *Herpesviridae* cause cell hyperplasia or hypertrophy, but are not carcinogenic, one exception is the *Oncorhynchus massou* virus (Herpes virus 2) that produces epitheliomas in various salmonid fish. Seasonal incidences of tumors are also suspected for wild fish [9,10].

Odontogenic tumors are related to alterations in epithelial and/or mesenchymal tissues involved in the formation and development of teeth. This means that these tumors are found in mandibular bones or soft tissues covering the teeth. While these tumors are generally benign, there is some evidence of aggressive, invasive growth, and high recurrence rates [11].

Some researchers classify odontomas as hamartomas rather than as tumors. Histological classification as a compound odontoma occurs when the epithelial and mesenchymal tissues are fully differentiated, including all dental tissues (i.e., enamel, dentin, and cementum) [12,13]. Complex odontomas are defined by structures of dental tissues having no resemblances to a tooth; such structures generally present as radiopaque areas of varying densities [1,12,13].

Fish odontomas were initially described in higher species [14–20]. In small fish species, oral tumors have almost exclusively been described in freshwater angelfish *Pterophyllum scalare* and ocellaris clownfish *Amphiprion ocellaris* [21], but only as sporadic findings or isolated cases, not as an epizootic tumor, such as observed in *Oncorhynchus tshawytscha* [5]. Oral tumors are macroscopically characterized as a nodular mass

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located in the frontal regions of the mouth at the mucocutaneous junction, encompassing both the maxilla and mandible. In angelfish, these tumors can be described as lip fibroma (in captive specimens), evidencing retroviral particles [4,7], or as ameloblastomas (in wild specimens) [22]. However, ameloblastomas were classified as odontomas in ocellaris clownfish [21]. In this study, we describe tumorous-like lesions in the rostral region of 60 angelfish collected from a fish farm in Morelos State (Mexico). Techniques in histopathology, radiology, electronic microscopy, and microbiology were employed to evaluate possible inflammatory and/or infectious or neoplasic origins for this pathological condition.

Materials and methods

Fish culture conditions and sampling

In April 2016, a total of 60 angelfish (aged three months old) with tumors on the frontal part of the mouth were transported by ornamental fish farmers located in Morelos, a central state in Mexico, for complete pathological, bacteriological, and virological workup using routine diagnostic methods at the Centro de Investigación y Estudios Avanzados en Salud Animal facilities, Universidad Autónoma del Estado de México. Specimens were retrieved from an ornamental fish farm employing an intensive system (i.e., 50 angelfish pairs and 45,000 offspring), in a greenhouse system containing 7 m^3 circular plastic ponds maintaining a density of 50 angelfish/m^3. The farm employed spring water with a temperature of 25° C, oxygen of 8 mg /L, pH 7.8, and a cycle of natural light. Fish were fed daily with commercial tilapia food (El Pedregal®, Toluca, Mexico) at approximately 3% body weight.

As reported by the farm that provided the samples, the 60 angelfish specimens (7 g average weight) were collected from a batch of 300 angelfish; all of which were offspring from a single mating pair. The collected 60 specimens were the only angelfish presenting tumors, characterized as outgrowths on the frontal part of the mouth, affecting both the superior maxilla and mandible. The fish showed no apparent signs of disease or injury on the body surface and/or in the internal organs.

Bacteriology

All fish were sacrificed via anesthetic overdose with 240 mg/L tricaine methanesulfonate 222 (Sigma) for 30 minutes to ensure death [23]. Thereafter, the specimens were immediately subjected to postmortem examination, following the recommendations of the FMVZ-UAEM Commission of Bioethics. Samples were taken from the tumorous area of ten fish for initial bacteriological analyses and streaked in replicates onto trypticase soy agar, Cytophaga agar, and Columbia agar with 5% sheep blood (AES laboratories). All plates were aerobically incubated at 15° C and 28° C for 7 days. Imprints of the maxilla and mandible were Gram-stained and stained for acid-alcohol resistant bacteria.

Histopathology

Samples of the mouth nodules, kidney, liver, and spleen were fixed in 10% neutral buffered formalin for posterior dehydration via an increasing ethanol series. Following dehydration, the samples were diaphanized in xylol and embedded in paraffin. Each tissue was sectioned at 5 μm and stained with hematoxylin and eosin to describe histopathological alterations by light microscopy at different magnifications.

Cell cultures

To isolate any virus implicated in the pathogenesis of odontomas, 20 fish were used to establish 4 sample pools, each using 5 fish. Each pool contained approximately 1 mL of mouth nodules and kidney and spleen tissues deposited in 15 mL Falcon tubes containing 9 mL of Leibovitz's L-15 Medium (Gibco BRL). Subsequent viral isolation procedures were carried out according to the methodology of the OIE Manual of Diagnostic Tests for Aquatic Animals [24]. The samples were macerated and centrifuged at 4000 *g* for 15 minutes at 4° C. The obtained supernatant was recovered and filtered at 0.22 µm. Each sample was diluted to 1:10 and 1:100 and inoculated, in duplicate, at a ≥90% confluence in 12-well multiwell plates containing cell monolayers of cell lines Chinook salmon embryo (incubated at 18° C) and bluegill fry (incubated at 20° C), as well as epithelioma papulosum cyprinid (incubated at 25° C). The inoculated cells were examined daily under an inverted Axiovert 40 C/40 CFL ZEISS microscope to establish the presence of the cytopathic effect. At 7 days postinoculation, the supernatant of plates with a negative cytopathic effect were recovered, inoculated again in the same cell lines, and incubated as previously described to confirm negative classification. Negative controls consisted of duplicate sets of wells containing monolayers of the cell lines inoculated with 0.1 mL of filter-sterilized (0.45 µm pore diameter) Hank's balanced salt solution.

Electron microscopy and radiography

To detect the potential presence of viral particles, samples of the tumor-like masses were collected from ten fish specimens for electron microscopy analysis. Tissue samples were fixed in 2.5% glutaraldehyde in a 0.1 M sodium cacodylate buffer (pH 7.4) and post-fixed in 2% osmium tetroxide for 1 hour at room temperature. Samples were rinsed in distilled water, dehydrated with ascending concentrations of acetone, and then embedded in epoxy resin (Epon 812, Electron Microscopy Sciences) and acetone (1:1), followed by immersion in molds with 100% fresh resin. Semi-fine slices (0.25–0.5 μm) were cut with glass knives and contrasted with toluidine blue-O as a guideline to determine the areas of interest and further cutting the embedded tissue block (Electron Microscopy Sciences). Ultrathin sections (150 nm) were obtained using an ultra-microtome. Finally, samples were observed using a Jeol 1010 electron transmission microscope at 60 kV.

For radiograph (x-ray) analyses, images were obtained using digital x-ray equipment (CMR) at 41 KVp and 10 mAs.

Results

Macroscopic findings

The 60 angelfish specimens presented spherical or semispherical protuberances measuring approximately 0.2–0.4 cm. The nodules were semisolid in consistency and were located on the frontal region of the maxilla and mandible. Nodules on the superior maxilla were notably larger than those on the mandible, which were barely evident or absent altogether (Fig. 1A, B). The nodules were multilobed in 45 angelfish (Fig. 1B and C) and single-lobed in the remaining 15 (Fig. 1A). The nodules were sessile edematous and whitish, pink, or reddened in color (Fig. 1B and C). No ulcerations were observed. Skin, gill, and abdominal-organ samples did not show evidence of tumors or other injuries or abnormalities.

Bacteriology and histopathology

Microscopic examination of smears from the mouth nodules of affected fish found no detectable bacteria; similarly, no growth was observed in any of the culture media used (trypticase soy agar, Cytophaga agar, and Columbia agar). All of the analyzed mouth nodules showed an exophytic sessile protuberance covered by a stratified hyperplastic squamous epithelium. Inside of each nodule, numerous fully differentiated dental structures (denticles) were observed (Fig. 2A), but in different stages of development. The denticles were oriented towards the epithelial surface, but without projecting into or being exposed to the stratified squamous epithelium (Fig. 2A). The dental structures were composed of ameloblastic cells over a layer of enamel. Below these structures was a layer of dense eosinophilic dentin supported by odontoblastic cells. The dental papilla was centrally positioned at a deeper

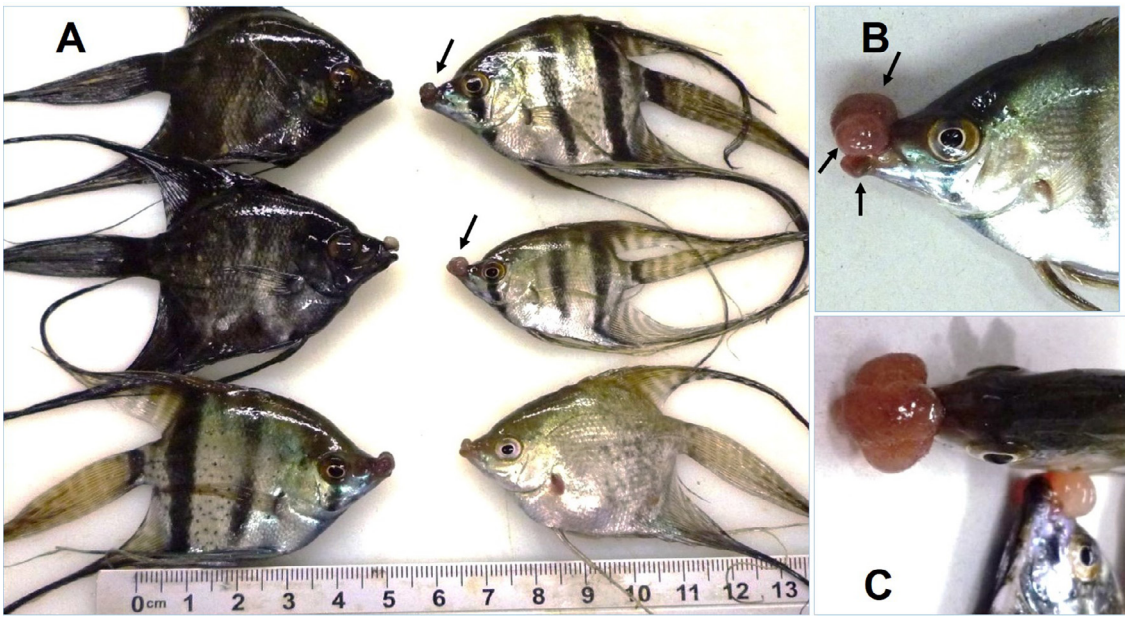

Fig. 1. Angelfish with tumor masses on the frontal region of the mouth. (A) Six angelfish with tumors of varying aspects and sizes. (B) Specimen with multi-lobed tumor masses in the maxilla and mandible, notice the appearance of the mass redness; (C) Superior view of a multi-lobed tumor mass shown in B. Arrows highlight the changes described.

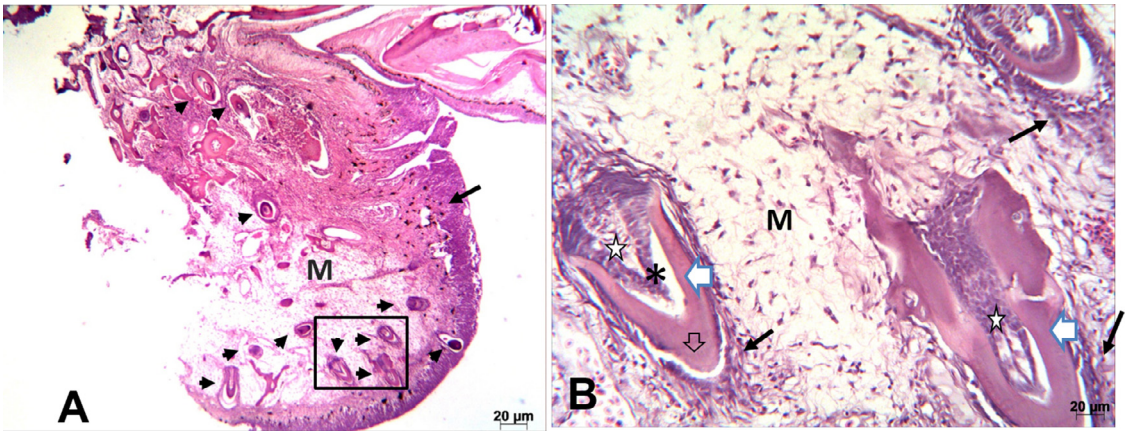

Fig. 2. Histopathology of a tumor mass on the frontal surface of an angelfish mouth. (A) Shown is a rounded nodular protuberance of hyperplastic stratified squamous epithelium (arrow), with various denticles (arrowhead) dispersed in loose mesenchymal stroma (M). (B) Detail of A, showing three denticles dispersed. The denticle presented ameloblasts (black arrow) over a layer of enamel (arrowhead), under which can be seen a layer of dense eosinophilic dentine (empty black arrow) supported by odontoblastic cells (asterisk). Centrally located at a deeper level is the dental papilla (star).

level. All of these odontogenic structures were embedded into a nonencapsulated, hyperplastic, loose mesenchymal stroma characterized by a low cellularity of stellate or fusiform cells with scant fine collagen fibers (Fig. 2B). Due to the characteristics, composition, and organization of the observed structures, the oral masses were diagnosed as a compound odontoma according to the World Health Organization. Histological Classification of Tumors of the alimentary system of Domestic Animals and the Armed Forces Institute of Pathology [25]. None of the odontoma showed evidence of peripheral or interior tissue inflammation, the presence of any infectious agent, anisocytosis, or metastasis. The presence of mitosis was very low, being scarcely observed in the myxomatous fibrous tissue.

Radiography

Nearly all of the specimens presented a radiopaque protuberance with smooth edges on the front of the mouth, concordant with the tumor mass observed macroscopically. Inside the tumor mass, irregular areas with greater radiopacity were found. These corresponded to the multiple denticles recorded histologically (Fig. 3). Furthermore, some fish presented with maxillary shortening.

Viral isolation in cell cultures and electron microscopy

Tumor, kidney, and spleen tissue samples inoculated in the Chinook salmon embryo, bluegill fry, and epithelioma papulosum cyprinid cell cultures did not show any evidence of the cytopathic effect or microbial and viral presence. Additionally, no viral or microbial particles were detected by electron microscopy.

Discussion

In this study, all mouth outgrowths assessed in the angelfish specimens were histologically diagnosed as compound odontomas/hamartoma. This determination was made based on observations of normal

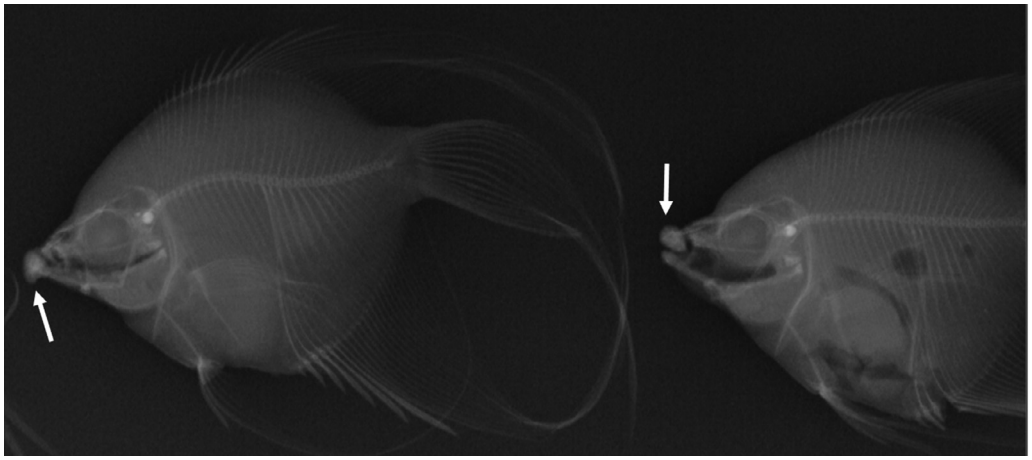

Fig. 3. Radiograph of two angelfish with an odontoma. Radiopaque protuberances are observable on the rostral region of the fish. These correspond to the macroscopically observed tumorous mass in the mouth (arrow).

pulpal, enamel, dentin, and cementum tissues with normal structures in the maxilla and mandible and the lack of evidence for inflammatory reactions or any infectious agent. The term hamartoma can be applied to compound odontomas that have complete odontogenesis with the development of denticles, as is our case. Some authors suggest that this lesion should be considered as a hamartoma rather than a neoplasm [25]. The denticles did not show external projections, although they were oriented towards the surface, as also found by Francis-Floyd et al. [7]. Similar macro- and -microscopic lesions in a non-angelfish species have, to our knowledge, only been found in two individual cases of odontoma affecting ocellaris clownfish [21]. In these cases, x-rays revealed radiopaque protuberances in the rostral region, similar to those described here; however, the radiopacity in ocellaris clownfish was intense due to diffuse bone formation with scarce denticles. In the present study, denticles were abundant, and osseous tissue was nonexistent.

Cases of odontogenic tumors in angelfish [7,22] and ocellaris clownfish [21] report localization in only the frontal zone of the mouth. In larger species, however, odontomas can develop in any or all of the oral surfaces where teeth are normally located (i.e., dental plaque, hyoid bone, and vomer) [5,16–18]. Occurrences have also been reported in the gill rakers of Chinook salmon [15]. Odontogenic tumors have likewise been described in areas normally devoid of teeth [20]. In the present study, the compound odontomas of the mouth were the only observed abnormality, and no mortalities due to these reasons were recorded.

Compared with other types of tumors, the incidence of odontomas in fish are sporadically reported. In pickhandle barracuda *Sphyraena* spp., for example, reported incidences range from 0.37% [26] up to 12.1% [18]. In angelfish, Francis-Floyd et al. [7] reported a prevalence of less than 1%. This low incidence rate has subsequently been supported by Videira et al. [22], who reported only one affected fish and, more recently, by Vorbach et al. [21], who reported two independent cases in ocellaris clownfish. The 60 fish examined in the present study were reported by farm workers to be the only specimens affected in a population of 300. Therefore, the true proportion of animals affected, the moment of manifestation, and possible predisposing factors are unknown.

Regarding etiology, odontogenic tumors in angelfish have been associated with a retrovirus [7,9] and iridovirus [8], but virus isolation has not been achieved, nor have tumors been reproduced when extracts are inoculated in healthy fish [7]. However, retrovirus infections occur as seasonal epizootics, and most lesions heal spontaneously and induce immune resistance to reinfection for life [9]. This clinical-pathological and epidemiological presentation did not occur in our case, where this pathological condition appeared and persisted in only one of the aquarium ponds, and there was no spontaneous recovery or new outbreaks. The behavior of this pathological condition together with the histopathological, electron-microscopy, and laboratory results did not suggest the involvement of any infectious agent. Although electron microscopy of the nodules from mouth showed no evidence of viral particles, we cannot rule out the existence of some virus as an infective agent. While isolation was tried, it is probable that the cell lines our laboratory routinely uses for this purpose were insufficiently specific for any virus implicated in the development of odontomas in angelfish.

According to Kaur et al. [27], odontogenic tumors originate at a genetic level. This could involve alterations in the genes involved in dental development or bone metabolism [28], but it is difficult to determine the phenomenon that triggers development. Despite ample knowledge on the spatiotemporal expression of specific genes during the formation of teeth, no gene has been directly related to ontogenesis. Developmental defects normally occur as a result of mutations in genes that code for signaling molecules and transcription factors [29]. Given that the odontomas described for the 60 angelfish in this study were, according to farm workers, an isolated incident in a single spawning group, tumor origin might have occurred at the genetic level and on a hereditary basis. Similar situations have been previously reported by Francis-Floyd et al. [7]. Such phenomena could warrant greater attention. Vorbach et al. [21] recently described an ocellaris clownfish descendent that presented a tumorous mass similar to previous reports, but the specimen was not analyzed further.

The hypothesis of a genetic origin for the tumors reported herein is supported by the fact that odontomas were initially thought to only occur in fish maintained under farm-aquarium conditions, where density and environmental stressors could play a role [7,19]. However, Videira et al. [22] later reported this tumor in wild angelfish, and it occurs in other wild fish species as well [15–17]. Further research is needed to clarify pathogenesis and to identify possible genetic abnormalities. More specifically, appropriate studies of transmissibility [30] are needed to determine if exposed fish develop odontomas.

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Conflicts of Interest

The authors declare no conflict of interest.

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