CHARACTERIZATION OF A FOLLICULAR CELL CARCINOMA OF THE THYROID IN A YELLOWBAR ANGELFISH (POMACANTHUS MACULOSUS)

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Abstract: Histopathologic diagnosis of thyroid neoplasia in teleosts is complicated, because thyroid tissue is unencapsulated, and normal tissue can have wide ectopic extensions. Assessment of thyroid hormone concentrations in conjunction with histologic evaluation of thyroid carcinoma has not been reported in teleosts, even though routinely performed in other species. A yellowbar angelfish (Pomacanthus maculosus) presented with a mass that extended beyond the gill arches. Partial surgical resection was performed, and a histologic diagnosis of thyroid carcinoma was made. Plasma from the affected fish and two control Pomacanthus were used to assess thyroid hormone concentrations using a domestic mammalian assay. Thyroid-stimulating hormone and throxine were undetectable in two of three fish. Triiodothyronine was lower in the affected fish than in controls. The tumor did not appear to be actively secreting hormone. This is the first characterization of thyroid tumors and corresponding thyroid hormones in teleosts, which may assist in diagnosis of this disease.

Key words: Angelfish, histopathology, Pomacanthus maculosus, teleost, thyroid carcinoma, thyroid hormone.

BRIEF COMMUNICATION

Thyroid hormones (TH) are responsible for roles in growth, development, and metamorphosis in teleost species. They play a part in pigment deposition during smoltification, and help control osmoregulatory functions during seawater adaptations.\(^6\) Thyroxine (T\(_4\)) is the major hormone released from the thyroid gland, and is controlled by thyroid-stimulating hormone (TSH). Peripheral monodeiodination to produce the active form, triiodothyronine (T\(_3\)), takes place in the liver and kidneys.\(^6\)

Reports of both thyroid hyperplasia and neoplasia in fish are likely underdiagnosed. Postmortem decomposition is more rapid in fish than in mammals. The thyroid gland in teleost fishes is normally diffuse, with follicles scattered along the aorta and between the branchial arteries.\(^6\) Follicles contain colloid, but the thyroid gland does not have a defining capsule, which can make histopathologic diagnosis of thyroid tumors difficult. Assessment of TH in conjunction with histologic evaluation has not been reported in teleosts, even though TH evaluation is routinely performed in other species with thyroid tumors.\(^1,10\)

This case describes a thyroid carcinoma in a yellowbar angelfish and presents information on associated TH concentrations to begin to characterize relationships between TH concentrations and thyroid neoplasia.

An adult yellowbar angelfish (Pomacanthus maculosus) greater than 20 yr of age was housed in a natural seawater, indoor multispecies reef exhibit. The system was well seasoned, was not ozonated, and nitrates were maintained below 3 parts per million. Iodide concentrations were not routinely evaluated. The animal presented with a slowly progressive, solid brown mass with an irregular surface that extended beyond the gill arches and displaced both opercula. No other fish in the system were affected. After monitoring for 3 mo, the animal began to show signs of lethargy, hiding behavior, and increased frequency and depth of respiration. On 13 September 2012, the fish was anesthetized with 65 mg/L MS-222 (tricaine methane sulfonate, Argent Chemical, Redmond, Washington 98052, USA) and placed in lateral recumbency with oxygenated water passing over the gills. Because of its invasive nature, the entire mass was not excised. A portion approximately 3 × 2 × 2 cm was removed and submitted for biopsy evaluation. Electrocautery was used to achieve hemostasis, and the wound was left open to heal by secondary intention. The anesthetic recovery and immediate postoperative period were uneventful, and the animal was clinically normal for 2 wk. At 14 days postop, it developed erythematous patches along the pe-
duncle bilaterally, and became anorexic. A ciprofloxacin bath treatment (6.6 mg/L) was performed for 8 hr daily for 5 days for treatment of apparent septicemia. It declined despite antibiotic and supportive therapy, and was euthanized because of poor prognosis 19 days postsurgery.

THs were measured in the plasma from the case animal (Pomacanthus maculosus) and two Pomacanthus controls (P. semicirculatus and P. paru; both adults). Whole blood was collected in sodium heparin tubes at approximately the same time of day (mid-day) in all three fish. Plasma was submitted to Antech Diagnostics (Irvine, California 92614, USA) for analysis, using a commercially available thyroid panel validated for canine, feline, and equine blood. Quantification of T4 was performed using an Immulite chemiluminescence assay (Siemens, Tarrytown, New York 10591, USA), and T3 and TSH were performed with a Beckman enzymatic immunoassay (Beckman Coulter, Brea, California 92821, USA).

Necropsy revealed a remaining mass measuring 3.5 × 2 × 2 cm that extended ventromedially from the gill arches (Fig. 1). The mass caused visible expansion of cervical region. Tissue extended from the primary mass to the heart base, but did not invade the cardiac muscle. Histopathologic examination revealed a moderately cellular, nonencapsulated, infiltrative mass composed of thyroid follicular epithelium in various stages of activity generally forming follicles and often exhibiting disorganized patches. Moderate anisocytosis and anisokaryosis were noted; mitoses were rare. All other organs were unremarkable on both gross and histologic examination. A diagnosis of a well-differentiated thyroid carcinoma was made on the basis of the heterogenous growth pattern, as well as cellular pleomorphism and mitotic figures. The invasive nature of the tumor was not a factor for the diagnosis of carcinoma because of the nonencapsulated and extensive nature of the normal teleost thyroid gland.2

T3 was detectable in the affected fish (59 ng/dl), but the two control fish had concentrations more than twofold higher than the case animal (110 and >600 ng/dl, respectively) (Table 1). Total T4 concentrations were below the detectable limit (<0.5 μg/dl) for the case animal as well as for P. paru, whereas P. semicirculatus had a detectable T4 concentration of 0.7 μg/dl. TSH concentrations in all fish were below the detectable limit for the assay (<0.03 ng/ml).

Gross and histologic descriptions of thyroid hyperplasia, colloid goiter, and carcinoma have been well documented in salmonids since 1912.3 Thyroid hyperplasia has been reported in both wild and captive populations of teleosts, and prevalence may reach 90% in populations that are exposed to goitrogens or have altered iodine metabolism.7 Spontaneous thyroid carcinomas appear to be rare, although thyroid carcinomas have been induced with carcinogens such as N-methyl-N9-nitro-N-nitrosoguanidine.5,9 In the case study there was no evidence of elevated nitrate or ozone concentrations, and although iodide was not evaluated, no other fish that died in the system were found to have evidence of thyroid enlargement on gross necropsy. This makes causes such as exposure to goitrogens or carcinogens less likely, although the role, if any, iodide played in tumor development in this case is unknown. The cause of this tumor was presumed to be spontaneous in nature.

Histopathologic diagnosis of thyroid neoplasia can be complicated, because thyroid tissue in teleosts is unencapsulated. Normal tissue can have wide ectopic extensions, and follicles can extend into normal tissues. Fournie et al.2 determined diagnostic criteria for proliferative thyroid lesions using mainly small fish species such as Japanese medaka (Oryzias latipes) or zebrafish (Danio rerio), and included lesions submitted to the National Cancer Institute’s Registry of Tumors in Lower Animals (Experimental Pathology Laboratories, Inc., Sterling, Virginia).

To standardize the diagnosis of carcinoma, the following previously determined criteria were used for a well-differentiated follicular carcinoma: exhibition of anaplastic features such as cellular pleomorphism and nuclear atypia; exhibition of
heterogenous growth patterns; and densely packed follicle-like structures of a nonuniform size with small amounts of colloid. Indeed, diagnoses of follicular cell hyperplasia or adenoma must be considered in this case, because these lesions can show evidence of proliferation in ectopic sites, can compress adjacent tissues, and contain an increase in the number of follicles. In the described lesion, anaplastic features were noted, but mitotic figures were rare. Characterization of the relationship between TH concentrations and thyroid neoplasia may help lead the clinician to one diagnosis over another when a histologic diagnosis is complex or inconclusive. Tumor hormone activity varies by species, such as in felines, where thyroid hyperplasia is typically associated with elevated circulating TH, as opposed to in canines, where thyroid tumors typically are not associated with elevated TH concentrations. The relationship between plasma TH concentrations and thyroid neoplasia has not been defined in teleosts, which led the authors to sample TH in the case animal and two congeneric angelfish.

The differences in circulating T3 concentrations in the control fish may have been due to species differences or differences in growth stage or reproduction. These hormone values suggest that this thyroid tumor was not actively secreting hormone. It is unclear whether the low T3 concentration in the affected fish was due to 1) suppression from the tumor; 2) indicative of a goiter secondary to insufficient iodine intake or elevated environmental nitrate concentrations, and thus decreased T3; or 3) within normal limits for the animal's age and reproductive status.

The biologically inactive form of TH, T4, is found in similar concentrations to T3, but would have been expected to be near or below the detection limit for the mammalian assay. The T3 values that were documented for all fish in this study are within the range of seasonal variation reported in a study in coho salmon with and without thyroid hyperplasia.

The commercial assay was also unable to either detect or measure the TSH hormone. In humans, low TSH concentrations may predispose to the onset of differentiated thyroid carcinoma, whereas T3 concentrations are not associated with thyroid carcinoma risk. Baseline values of teleost TSH are likely well below the detection limit of the mammalian assay.

The limitations of this study are the lack of available TH assays validated for teleosts and the small sample size (N = 3). A larger sample size is needed before the conclusion can be made that measurement of circulating plasma hormone concentrations, using assays for mammalian species, will aid in distinguishing between thyroid neoplasia and hyperplasia in fish. On the basis of our very limited data set, T3 concentrations may provide clinical information about thyroid tumors in teleosts, but further investigation is necessary to gauge the utility of these diagnostic tests.

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**LITERATURE CITED**

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**Table 1.** Thyroid hormone plasma concentrations in a yellowbar angelfish diagnosed with thyroid carcinoma (*Pomacanthus maculosus*) and two clinically healthy fish of the same genus.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>P. maculosus</th>
<th>P. semicirculatus</th>
<th>P. paru</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (ng/ml)</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>T3 (ng/dl)</td>
<td>59</td>
<td>110</td>
<td>&gt;600</td>
</tr>
<tr>
<td>T4 (μg/dl)</td>
<td>&lt;0.5</td>
<td>0.7</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

*TSH indicates thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine.*


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