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J Case Rep Images Surg 2020;6:100076Z12YA2020.
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Case of primary thyroid rhabdomyosarcoma in children with literature review

Yohana Azhar, Hasrayati Agustina

ABSTRACT

Primary thyroid embryonal rhabdomyosarcoma (ERMS) is an extremely rare tumor. Diagnostic and management of these cases can be challenging. This report presents cases of 7- and 8-year-old girls with non-orbital of non-parameningeal rhabdomyosarcoma (RMS), which is a new, seldom-reported variant of RMS in the head-neck region. These pediatric patients suffer from large swelling in the anterior neck that clinically resembles a thyroid mass. In the anterior neck, the entire thyroid lobe is replaced by a heterogeneous mass as shown from the results of a computed tomography (CT) scan. Usually, fine-needle aspiration cytology is non-diagnostically mistaken with an undifferentiated thyroid cancer. Total thyroidectomy with neck dissection in one patient was done and final histopathological results turn out to be ERMS; the diagnosis was confirmed by positive reactions to MyoD1 and myogenin. The children were subsequently treated with chemotherapy. Despite the rarity of these conditions, they remain an important part of the differential diagnosis for any thyroid nodule. Awareness of their presentation, work-up, and management is critical for oncologist and head and neck surgeons.

Keywords: Children, Primary rhabdomyosarcoma, Thyroid

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Received: 24 May 2020
Accepted: 15 July 2020
Published: 12 August 2020

How to cite this article

Azhar Y, Agustina H. Case of primary thyroid rhabdomyosarcoma in children with literature review. J Case Rep Images Surg 2020;6:100076Z12YA2020.

Article ID: 100076Z12YA2020

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doi: 10.5348/100076Z12YA2020CS

INTRODUCTION

A case of true sarcoma of the thyroid was known for a long time. In 1817, Alibert (quote by Bircher) had already reported the true sarcoma of the thyroid body. Similar report delivered by Raynaud, in 1838, under the title "Thyroscaromie," depicted an encephalic sarcoma with metastatic foci in the lungs and liver, but no additional specific description of this microscopic findings. In 1860, Forster provided an accurate and careful description of one of this class of neoplasms. Further, Virchow discussed the malignant tumors of the thyroid but no data provided to support their occurrence. He confirmed to observe one sarcoma of the thyroid gland [1].

Primary thyroid sarcomas (PTSs) are uncommon tumors, accounting for less than 1% of all thyroid malignancies. Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children, with approximately 350 cases diagnosed per year in the United States. As per the system information report of Hasan Sadikin General Hospital, there were approximately 57 new cases of RMS in children. Diagnosis and treatment of PTSs is a challenging problem. They belong to one the most rapidly proliferating tumors (duplication time of the tumor mass can only 14 days). There is tremendous variability in primary tumor site, subgroups histology, and clinical behavior of these tumors and new understanding of the molecular biology has helped refine risk stratification and appropriately tailor therapy. Adding to the complexity, the choice of local control option with

surgery and/or radiotherapy requires thoughtful decision from pathologist, oncologist surgeon, medical oncologist, and radiation oncologist, emphasizing the need for strong multidisciplinary involvement to achieve the optimum result [2, 3].

CASE SERIES

Case 1

An 8-year-old girl presented to us at thyroid clinic for evaluation of left anterior neck mass. It had been gradually enlarging for the last two months, extending from the root of the neck to above the sternal notch. She was not in pain initially and became complained of mild pain for last one month. The size of mass was about 9 × 9 × 8 cm. It was firm, tender at certain points, and lobulated with well-defined margin (Figure 1). Clinically it resembled a thyroid mass although due to the huge size, its movement with deglutition could not be satisfactorily demonstrated. There were no history of respiratory distress, difficulty in swallowing, and change of voice. Indirect laryngoscopy revealed normal movements of vocal cords and free piriform fossae. There were also palpable lymph nodes at left lateral neck along jugular chain, firm confluence with well-defined margin. There was no history of radiation in the past.

Computed tomography (CT) scan of the neck revealed a large lobulated and heterogeneously enhancing mass (7.3 × 8.2 × 8.1 cm in its greatest dimensions) with a relatively well-defined margin occupying the surrounding structures, such as the left jugular vein, completely replacing the left of thyroid. The right lobe and the isthmus were normal. The trachea was shifted to the right and there were bilateral cervical lymph node enlargement suggesting metastases (Figure 2).

Fine-needle aspiration cytology (FNAC) from left thyroid showed clusters and some diffuse of round, oval to spindle, and intermediate to large cells. The nuclei are pleomorphic, have coarse chromatin, and some nucleoli are prominent. The FNAC report was carcinoma of the left thyroid (Bethesda category 6) (Figure 3).

Due to the suspicious nature of the lesion and the diagnostic was carcinoma from needle biopsy, total thyroidectomy with bilateral neck dissection was performed. Intraoperative findings revealed a large mass occupying the entire left side of the neck, also encroaching to the level 2 cervical lymph node, internal jugular vein, deep to the strap muscles, left sternocleidomastoid, and omohyoid muscle. The left lobe of thyroid was absent and was replaced totally by the mass. The left recurrent laryngeal nerve was saved, and the mass was removed. The excised mass measured approximately 11 × 7 × 3 cm (Figure 4). All specimens were sent to pathology laboratory.

The early postoperative period was uneventful. Six days after surgery, the patient was discharged with a planned rehabilitation program. Histopathology revealed hyperplastic, nested, round, oval cells arranged in solid nests and some parts showing trabecular pattern with pleomorphic and hyperchromatic nuclei, scanty eosinophilic cytoplasm, and mitotic figures in a hyalinized background, with scattered lymphocytes, suggestive of carcinoma with differential diagnosis ERMS (Figure 5).

Immunohistochemistry showed positive expressions for Myo-D1 and myogenin (Figure 6); staining with cytokeratin, and TTF-1 turned negative.

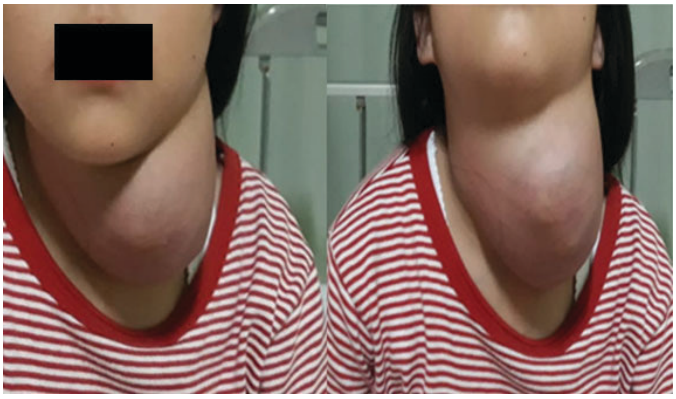

Figure 1: The huge mass in front of the neck, more toward the left, before surgery (Case 1).

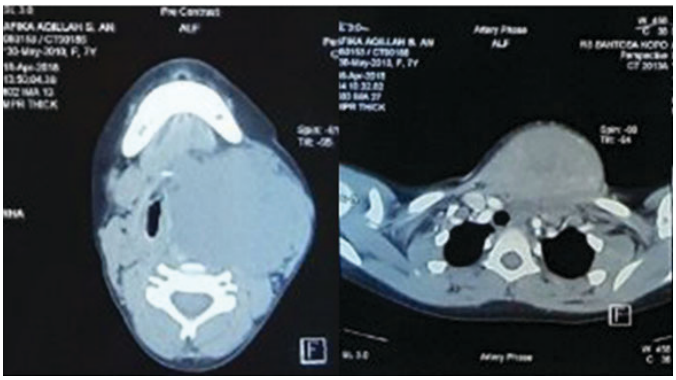

Figure 2: Computed tomography scan of the neck (axial section) shows a heterogeneous enhancing mass in the anterior neck arising from the left lobe of the thyroid gland with severe mass effect to the surrounding structures (Case 1).

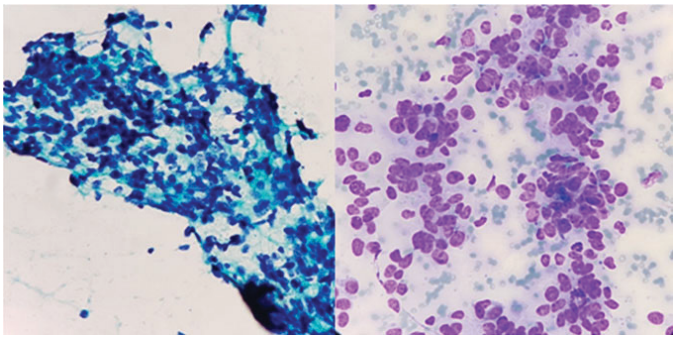

Figure 3: Cytology of the left thyroid shows clusters and some diffuse of round, oval to spindle and intermediate to large cells. The nuclei are pleomorphic, have coarse chromatin, and some nucleoli are prominent (Case 1) (left: Papanicolaou 400×, right: Diff-Quik 400×).

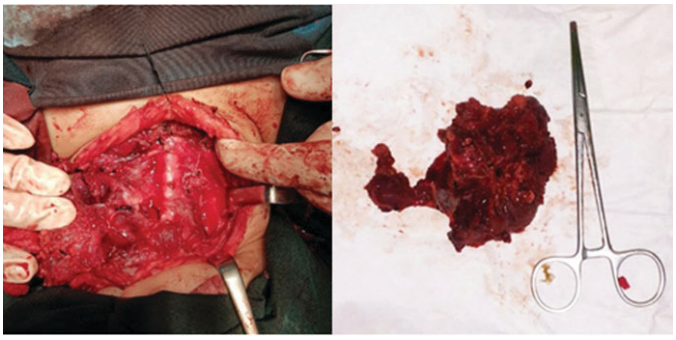

Figure 4: Clinical photograph showing large mass occupying the entire left side of the neck. The excised mass measured approximately 11 × 7 × 3 cm (Case 1).

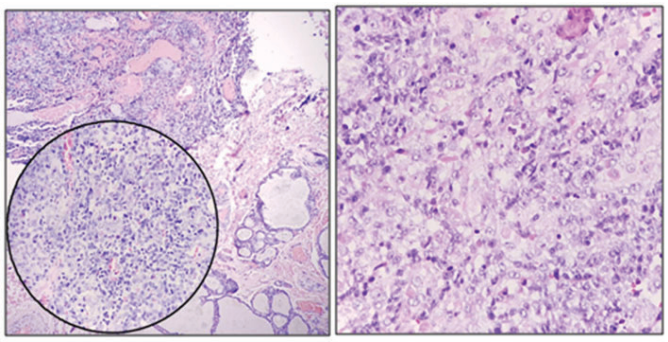

Figure 5: Histopathology picture of Case 2 shows hyperplastic, nested, round, oval cells arranged in solid nests with pleomorphic and hyperchromatic nuclei, scanty eosinophilic cytoplasm, and mitotic figures in a hyalinized background [H & E staining, left 100×, islet 200×, right 400×].

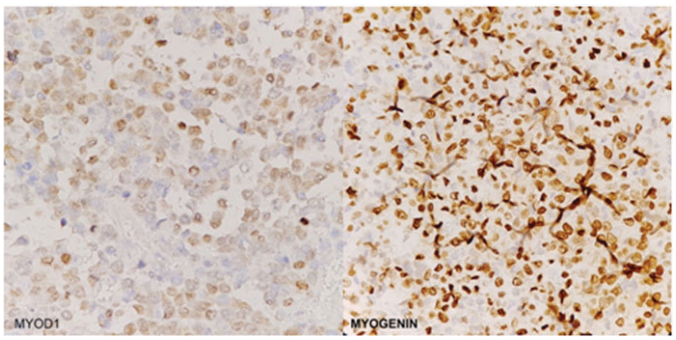

Figure 6: Immunohistochemical analysis is positive for MyoD1 and myogenin (400×) (Cases 1 and 2).

This case was diagnosed histopathologically and immunohistochemically as ERMS thyroid.

Subsequent whole-body CT scan and bone marrow examination revealed no evidence of distant metastasis. The patient had received thyroid hormone replacement and six cycles of chemotherapy with doxorubicin, ifosfamide, and mesna. We did not use radiotherapy in effort to prevent its long-term complications.

Fourteen months after initial surgical resection and ten months after completion of chemotherapy, the child remained without evidence of local recurrence or distant metastasis.

Case 2

A 7-year-old girl visited our clinic for evaluation of left anterior neck mass which is detected three weeks ago and had been growing rapidly. The patient denied pain, hoarseness, dyspnea, and dysphagia. He had no familial disease. There was about 3 × 2 × 2 cm palpable left thyroid mass without lymph node enlargement. An ultrasonography of the neck with needle biopsy was performed. The result suggested spindle cell neoplasm, reasonable finding for RMS with differential diagnostic anaplastic thyroid carcinoma. She was admitted to Department Oncology, Head and Neck Surgery and underwent operation. A CT scan of the neck demonstrated 3 cm mass in the left thyroid without lymph node metastasis. Total thyroidectomy was done because the result of intraoperative frozen section could not conclusive. A size of 2.6 × 2.1 × 2.0 cm mass adhered to the left thyroid without invasion into tracheal cartilage. During resection the recurrent laryngeal nerves were saved without tumor invasion. The parathyroid was identified and also preserved.

Histologic examination showed a malignant lesion composed by proliferation of spindle cell with rhabdomyoblastic differentiation, there was also shown normal thyroid. On immunohistochemistry examination, myogenin and desmin were clearly seen in tumor cells. This case was diagnosed histopathologically and immunohistochemically as ERMS.

After surgery, the patient had replaced thyroid hormone and calcium supplement due to temporary hypoparathyroid. We did not evaluate bone and bone marrow because the size of tumor was <5 cm and no evidence of nodal involvement. There was some debate at our multidiscipline meeting regarding the utility of molecular testing to stratification disease and guide further management for this patient, but at the end the molecular testing canceled. We planned to give her adjuvant chemotherapy but her parents refused further treatment. Nine months after initial surgical resection, she remained without evidence of local recurrence or distant metastasis and then loss of follow-up.

DISCUSSION

Primary thyroid sarcoma is an exceedingly rare condition that comprises less than 1.5% of all thyroid malignancies. It often represents as a thyroid nodule without any additional symptoms until the disease becomes advanced. The diagnosis algorithm involves thyroid ultrasound, followed by FNA. On ultrasound these lesions exhibit a nonspecific hypo-hyperechoic pattern. It is important for pathology team to recognize that certain subsets of sarcoma, can often be mistaken with moderate to undifferentiated thyroid malignancies [2].

The most striking feature shared between these two cases is the involvement of the thyroid gland. Both

preoperative imaging and intraoperative findings suggested that the anterior neck mass was contiguous with the thyroid in an extent so as to entirely replace one of its lobes. Whether there were separate malignancies in the anterior neck and thyroid is debatable. Rhabdomyosarcoma in the thyroid has rarely been described before; as such, sarcomas constitute only <1% of thyroid malignancies. Rather, it seemed from the clinic radiologic profile that the anterior neck and the thyroid were involved by a single malignant tissue bulk, and there was no way to determine the tissue of origin. However, Furze et al. noted one case in which RMS originating from the anterior neck tissue in an adult failed to invade the thyroid, even when it presented in an advanced stage. This could support the fact that the tumor in the present case was actually originated from the thyroid itself, rather than the thyroid being invaded [3].

The diagnosis of pediatric solid tumors requires an extensive panel of immunohistochemical markers as many entities exhibit a non-characteristic of "small round cell tumor" phenotype. Several studies have examined the use of immunohistochemical staining with MyoD and myogenin in the diagnosis of RMS [4]. All RMS samples showed nuclear immunoreactivity for MyoD1 but background cytoplasmic was stained with this antibody that makes interpretation to be more difficult. Cui et al. reported nuclear expression of MyoD1 and myogenin was about 80% of RMS cases. MyoD1 generally is expressed in small, primitive tumor cells, whereas the larger cells are showing morphological evidence of negative skeletal muscle differentiation. Positive nuclear expression of myogenin was stronger than MyoD1 in cases with differentiated tumor cells, but was less prominent in cases in which small, primitive tumor cells predominated [5].

Molecular testing (FISH, reverse transcription PCR, or Next Generation Sequencing) results may be used to decide proper treatment choices, based on risk stratification. Examination PAX/FOXO1 fusion may impact treatment decisions. For example, Alveolar RMS lacking FOXO1 translocation behave similarly with ERMS. The diagnosis subtypes are important because alveolar RMS is reported to have a worse prognosis, with a greater frequency of disseminated metastases [6–8].

It has been proven yet needs more study that sarcoma patients in general may harbor underlying germline mutations. There is also growing evidence to recommendations of genetic screening for seeking several cancer predisposition syndromes including neurofibromatosis type 1, Gorlin, Beckwith–Wiedermann, and Li–Fraumeni syndromes. These examinations have important implications for patients and their siblings or other family members. For example, in Li–Fraumeni syndrome, germline TP53 mutation was found in <2% of 213 intermediate risk RMS. The incidence may be higher in patients diagnosed with RMS in younger age. It begins reasonable to make referral genetic counseling patient who are younger at diagnosis [9, 10].

Rhabdomyosarcoma cases accounted for 3% of all soft tissue sarcomas [11], with alveolar, embryonal, and pleomorphic classification. Alveolar and embryonic variants are often found in pediatric patients. It can originate from any mesenchymal tissue, except bone, and has long been regarded as cancer arising from skeletal muscle. The 2013 World Health Organization (WHO) classification system for RMSs includes four subgroups: embryonal rhabdomyosarcoma (ERMS), alveolar rhabdomyosarcoma (ARMS), pleomorphic, and spindle cell/sclerosing.

Embryonal rhabdomyosarcomas are seen commonly in children, younger than 10 years of age (mean age: near 7 years), but it also occurs in adolescents and young adults. Because of the aggressive behavior of tumor, prognosis is generally poor in RMSs. Primary RMS of the thyroid gland is a truly rare malignancy. Up to now, only four cases have been reported, these include two cases with anaplastic thyroid carcinoma exhibiting RMS differentiation and two cases who were children, in whom thyroid gland tissue was detected within anterior cervical tissue and diagnosed as RMS. These tumors also exhibited aggressive tumor characteristics as it invaded the surrounding tissue. The large/bulky/massive mass and compression of the surrounding tissue are the characteristics of RMS. Previous studies reported that RMS was detected in one of 77 children, in whom the etiology of thyroid nodules was evaluated [12–14].

Rhabdomyosarcomas usually have a very high mitotic rate, explaining the aggressive behavior and poor prognosis of these tumors. Histologically, common features to most of the EMRS are the followings: varying degrees of cellularity with alternating densely packed, hypercellular areas and loosely textured myxoid areas; a mixture of poorly oriented, minor, undistinguishable, hyperchromatic round or bar-shaped cells; and an erratic differentiated cells with rhabdomyoblasts eosinophilic cytoplasm features.

From immunohistochemistry examination, only vimentin is present in the cytoplasm of the most primitive cells, and desmin and actin are acquired by developing rhabdomyoblasts. Antibodies against MyoD1 and myogenin are highly specific and sensitive for RMS and are currently used for diagnosis [15]. Differential diagnosis includes anaplastic thyroid carcinoma with rhabdoid variant due to the presence in each variant of spindle cell elements. The common of anaplastic undifferentiated thyroid cancers exhibited "sarcoma-like" features, with spindle-shaped neoplastic cells set in a fascicular or rounded pattern of growth. Positive immunohistochemical result for keratins verifies the epithelial nature of the tumor. Immunohistochemical evaluations disclosed positive staining for MyoD1 and myogenin, whereas negative staining for keratin thus, rhabdoid variant of anaplastic thyroid carcinoma was excluded in our case.

The imaging has no specific feature in RMS. On CT scan, it is similar to skeletal muscle and there is an

increased attenuation. However, imaging is usually helpful in staging as 44% of RMS cases have metastasis at the time of diagnosis. Magnetic resonance images show a homogeneous mass characterized by an increase in signal intensity compared to muscle and fat as depicted on T1-weighted. Detection of iso-intensity and hypersensitivity can be done by comparing the muscles as shown in T2 [16].

A complete surgical removal, combined with chemotherapy using vincristine actinomycin-D and cyclophosphamide, is recommended standard for treatment by the Intergroup Rhabdomyosarcoma Study IV (IRS-IV). This is also recommended by National Comprehensive Cancer Network (NCCN) guidelines to perform primary surgery in combination with chemoradiation therapy for patients where resection has inadequate margins. Chemoradiation therapy will become the foundation of treatment with subsequent surgical intervention for patients with unresectable disease or undesirable functional outcomes with surgery. It is decisively important to consider negative margins with surgery for any sarcoma. It is recognized that challenge on head and neck surgery is obtaining 1–4 cm margin clearance around the cancer to diminish local recurrence rates. The balances between local recurrence rates and functional outcomes after reconstruction must be considered by surgeon.

In cases where marginal margins are uncertain to be obtained, presurgical chemotherapy or radiation should be performed in each individual case. The literature on whole-body sarcoma has not fully construed the role of multi-modality treatment order, precisely in regard to improve margin control and local recurrence rates. It is obvious that the most predictive factor in controlling local disease is negative margin and overall sarcomas respond volumetrically to presurgical treatment. However, the optimization of margin control with multi-modality treatment will need to be further studied.

Radiation therapy is used as an adjuvant for incomplete tumor resection, residual disease suspicion, or tumor recurrence. Radiation is often avoided in children because it can cause severe abnormality growth and may lead to second malignancy. In our case, we decided to postpone radiotherapy on the first patient, even though the size of tumor was relatively big. We performed bone marrow aspiration biopsy to asses metastatic spread since the patient showed the locally advanced disease thus the risk to have metastatic spread was higher. With combined modality therapy, the overall survival rate for all pediatric RMSs is 71%. However, younger patients tend to have a more favorable prognosis, for unknown reason [2].

CONCLUSION

Primary RMS of anterior neck involving and replacing the thyroid tissue is extremely rare which clinically presents as a rapidly growing painless neck mass that can be easily misdiagnosed as thyroid carcinoma. Histological features and immunohistochemical stains are crucial to establish the diagnosis. Surgery plays a significant role in the management of this malignancy with a combination of radiotherapy and chemotherapy. It should be emphasized that management must be interdisciplinary at the time of diagnosis. With precautionary consideration the adjuvant radiotherapy for pediatric patient can be enacted later.

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Author Contributions

Yohana Azhar – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Hasrayati Agustina – Conception of the work, Acquisition of data, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.