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A Rare and Intriguing Case of A Solitary Thyroid Neurofibroma in a Non NF1 Patient - A Case Report and Review.

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Abstract
Swellings in the neck are a common presentation in adults in ENT OPD however, midline neck swellings in adolescents often raise concerns for congenital anomalies, benign thyroid nodules or rarely malignancies. Peripheral nerves sheath tumours especially Neurofibromas are the last to be suspected and more so a large multinodular swelling involving the whole gland with a woody hard consistency and short duration of history poses a diagnostic challenge. We present a case of a 14-year-old girl with a solitary large multinodular neurofibroma of the thyroid, highlighting the clinical presentation, diagnostic challenges, surgical management, histopathological findings and Immunohistochemistry. This case underscores the importance of considering neural origin tumours in paediatric thyroid swellings and the role of histopathology and immunohistochemistry in reaching a definitive diagnosis.

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I. Introduction

Peripheral nerve sheath tumours (PNSTs) are a group of primary neurogenic tumours that are neuroectodermal in origin arising usually from the peripheral neural sheath cells.[1] The vast majority are benign, however, malignant transformation is seen particularly in large tumours and those associated with neurofibromatosis type 1 (NF1).[2] The benign PNSTs can further be classified into Neurofibroma, Schwannoma and perineuroma based on their histopathology.[2,3]

Neurofibromas are basically benign peripheral nerve sheath tumours mainly composed of Neoplastic cells showing Schwannian differentiation admixed to a minor component of cells with fibroblastic and perineurial differentiation.[4] In 90% of cases, they are found as single solitary or sporadic neurofibroma while the remainder are found in persons with neurofibromatosis type I (NF1), an autosomal-dominant genetically inherited disease.[5] These neurofibromas can be classified further based on their anatomical location, growth pattern and their relationship to nerve and pathogenesis.[6] However, most prefer to classify them according to their growth pattern into localized/nodular, diffuse, plexiform and ANNUBP (atypical neurofibromatosis neoplasms with certain biologic potential).[7,8] The diffuse and plexiform are more commonly seen in children rarely occurring after age 5 and are associated with neurofibromatosis in about 10% of the cases whereas localized/ nodular are seen in adults.[4]

Usually, Neurofibromas occur in the skin arising from the small sized nerves,[7] they can also develop in the deep soft tissues from a major or small sized nerve, however there have been possibilities that the anatomic association with a nerve cannot be demonstrated and neurofibroma may present as a soft tissue mass involving tissues and organs underneath the dermis frequently involving the skin and subcutaneous cellular tissue of the head and neck.[5]

II. Review Of Literature

Historical background

It was in 1803 the term neuroma was introduced by Odier[9] to the involvement of nerve associated with soft tissue tumours followed by Schwann[10] in1830 describing the predominance of peripheral nerve sheath cells in neurofibromas. In 1847, Rudolf Virchow[9], a pioneering German pathologist, first described neuromas in several members of a single family and later in 1863 classified these tumours arising from the peripheral nerves into true neuromas (which contained nerve elements) and false neuromas (originating in the connective tissue of the nerve sheath). Following which, many other researchers and clinicians reported additional cases of neuromas, contributing to a deeper understanding of their nature, causes, and classifications.

However, it was not until 1882 that Friedrich Daniel Von Recklinghausen recognized neurofibromatosis (NF) as a distinct nosological entity, describing two cases of multiple neurofibromatosis. He proposed that tumours along major peripheral nerves, as well as false skin neuromas, originated from the connective tissue of the nerve sheaths and nerve plexuses, particularly the perineurium and endoneurium. His groundbreaking research paved the way for further exploration by physicians and surgeons worldwide in the study of these nerve tumors.[9]

In 1911, Greggio was the first to report the presence of mast cells in neurofibromas.[11] Later, in 1976, Isaacson conducted a study on 132 cases of benign tumours derived from the nerve sheath, finding a high concentration of mast cells that were diffusely distributed in neurofibromas.[12] Following this, in 2001, Antonio Jr.'s doctoral thesis suggested that mast cells could contribute to the growth of these tumours.[13] In 2006, Lim et al. reported that superficial neurofibromas displayed distinct characteristics on MRI when compared to deep neurofibromas in NF1 patients.[14] Finally, in the 2021 edition of the WHO Classification of Tumours of the Central Nervous System, six distinct entities of peripheral nerve sheath tumours were officially listed.[15]

Among the benign soft tissue tumours, the estimated incidence of neurofibromas is 5.3% being the most prevalent benign peripheral nerve sheath tumours affecting patients of all ages, races and genders with most localized lesion appearing in adults with a variable onset between the 20 to 40 age group.[16]

Neck

In a retrospective study conducted at Lousiana State University Health Sciences Center (LSUHSC) between 1969-1999, out of the 91% (361) benign PNSTs most were Branchial plexus tumours (140) comprising of 62% (87) neurofibromas, and 38% (54) Schwannomas. And among these neurofibromas, 63% (55) were solitary neurofibromas and 37% (32) were associated with neurofibromatosis Type 1 (NF1). The other most predominated region was the neck in the Supraclavicular tumours with 62% (32 of 55) solitary neurofibromas, 69% (37 of 54) Schwannomas and 59% (19of 32) were associated with neurofibromatosis.[17]

It was in 2002, Anagnostouli et al[18] reported the first case of thyroid neurofibroma in a NF1 patient. He reported a 55-year-old man with typical symptoms with NF1 with a neurofibroma of the thyroid gland and abdominal carcinomatosis. He discussed the rarity of thyroid neurofibromas, emphasizing the early detection and NF1 complications.

Following this in 2008 Severo et al[19], reported a patient with NF1 with a nonfunctional thyroid nodule and obstructive symptoms who underwent surgical resection and on histopathology was compatible with neurofibroma of thyroid.

Then in 2013, Doulias etal[20] presented a case report of a thyroid neurofibroma in a female patient with neurofibromatosis 1. He reported a plexiform neurofibroma in thyroid gland in a 14-year girl previously diagnosed with NF1 highlighting that the management is primarily surgical and thyroidectomy remains the mainstay of treatment when thyroid tissue is involved with any local invasion with a substantial risk of recurrence especially in Plexiform Neurofibromas.

Later Bulut et al[21] in 2024 reported the fifth case of thyroid neurofibroma in a 60-year woman who was previously treated with Graves' disease underwent Right Lobectomy followed by radioactive thyroid ablation and then enlarged heterogenous left thyroid lobe. Patient underwent thyroidectomy and the histopathology revealed neurofibroma with positive immunohistochemistry for S-100, CD 34. He reported a Solitary Thyroid neurofibroma in the absence of neurofibromatosis 1.

And now in 2025 Feller et al[22] has reported an intrathyroidal neurofibroma. This case was unique as it has been reported in a 6-year-old child with NF1. The tumour was adhered to the larynx and trachea with the

recurrent laryngeal nerve entering the tumour. The patient underwent hemithyroidectomy and histopathology confirmed the presence of plexiform neurofibroma with intrathyroidal origin.
Thyroid Neurofibromas are extremely rare, with only a few handfuls reported cases in medical literature.

We report a case of Neurofibroma of thyroid gland in a 14-year girl with an unusual presentation arising from the Thyroid Tissue.

III. Case Report

A 14-year-old girl presented to the ENT outpatient department Of Venkateshwara Institute of Medical Sciences with a painless, progressively enlarging mass in the neck over 7 months. The mass in spite of being large was not associated with any history of dysphagia, dyspnea, voice changes, fever or weight loss.

On examination- A multibosselated mass firm to woody hard painless mass with well-defined margins of size 11x9cm was palpable in the anterior midline part of neck appearing as a thyroid Swelling. The mass moved on deglutition. The overlying skin was nonadherent with no changes in skin texture or any ulceration. There was a mild deviation of trachea to left with no cervical lymphadenopathy. On Video laryngoscopy vocal cord, appeared normal in appearance with normal mobility and mild deviation of trachea to left.

Pre-operative – Thyroid mass

Post operative

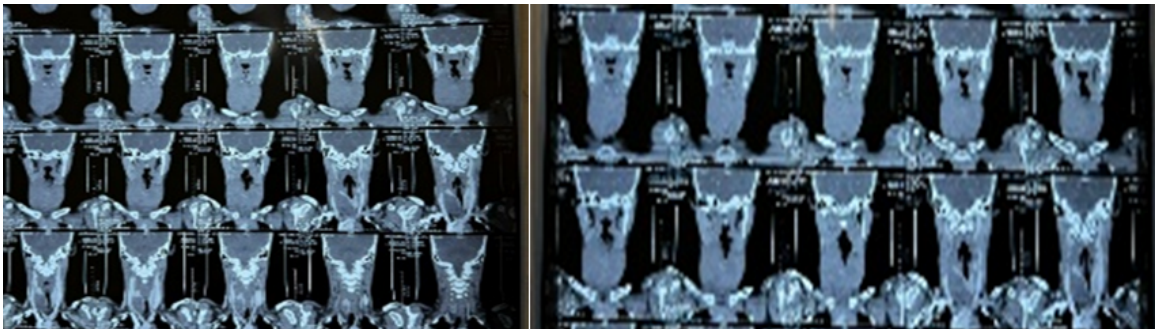
Due to the unusual presentation of the painless rubbery mass of the thyroid and the age of the patient a thorough personal & family history was taken and systemic examination was done. In the personal history the child had not had here menarche and family history also revealed a late onset menarche in all the siblings and mother. Interdepartmental consultation with pediatrician, orthopaedic and dermatologist was sought to rule out syndromic condition especially in reference to neurofibromatosis. Cutaneous cafe au lait macules, axillary/ inguinal freckling, Iris Lisch nodules were ruled out. An Orthopedic consultation was done for kyphoscoliosis.

The child was investigated thoroughly, thyroid function tests reported euthyroid state, with no biochemical evidence of thyroid dysfunction TSH 1.11, T3 1.36, T4 9.67. TPO antibodies were negative. PTH was 33.44pg/ml and S. cortisol was 9.50µg/dl

An Ultrasound revealed few heterogeneously hyperechoic nodules largest measuring 6.0x 3.0cm with internal vascularity on colour doppler involving right lobe of thyroid and normal right thyroid tissue could not be visualized. Lesion upper end was extending into submandibular region and lower end could not be delineated. Few hyperechoic lymph nodes with maintained fatty hilum in right cervical region seen. Findings were suggestive of thyroid nodule (TIRADS III)

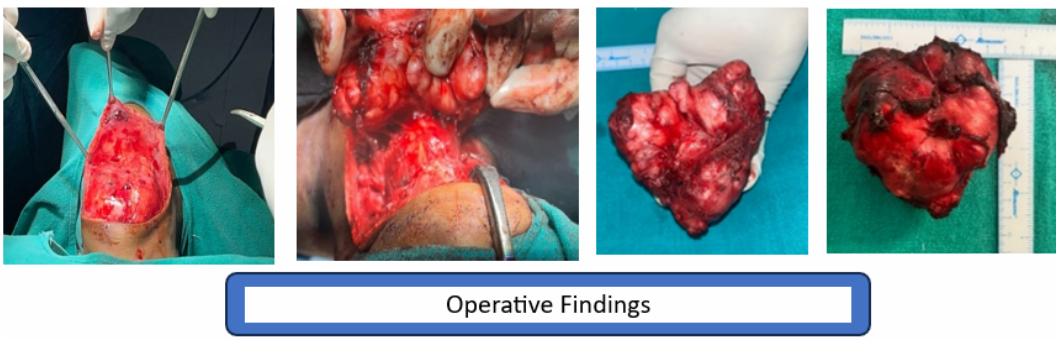
FNAC- showed scanty cellular and spindle cells varying from bland appearing fibroblast with a uniform pale nucleus and moderate eosinophilic cytoplasm. Also seen are few thyroid follicles in clusters and mostly in singles. Background showed thin colloid and inflammatory cell infiltrates comprising predominantly of lymphocytes and few neutrophils. Cytological findings were suggestive of nodular goiter with fibrosis. The Bethesda system for reporting thyroid cytology was TBSRTC category II. In view of dense fibrosis, excision biopsy was advised to rule out Riedel's Thyroiditis and to make a complete diagnosis.

CECT neck- showed few Hypodense nodules with minimal enhancement in right lobe of thyroid resulting into gross enlargement of right lobe. Superiorly right lobe was reaching up to submandibular space, inferiorly reaching into supraclavicular space approx. 4.7 mm above right clavicle, medially lesion crossing the midline and displacing trachea towards left side with mild narrowing of trachea. Laterally thyroid was seen displacing the carotid and jugular vessels. Findings were suggestive of a multinodular goiter.

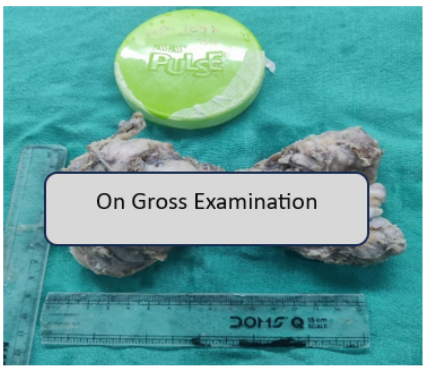


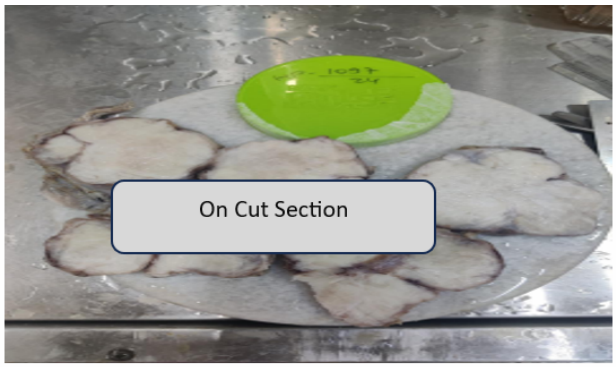
Due to the inconclusive FNAC and CECT Scan and progressive growth which may eventually lead to compressive symptoms a Thyroidectomy was planned.

Intraoperatively, a well encapsulated, firm to hard multibosselated mass firmly adherent to the underlying laryngeal cartilage framework was seen. The left thyroid lobe was pushed posteriorly and on the right side only a small strip of normal thyroid tissue was preserved. During resection the thyroid mass exhibited poor vascularity with minimal bleeding. The bilateral recurrent laryngeal nerve, bilateral carotid sheath and all the parathyroid glands were well preserved with no infiltration into any deeper tissue noted. The mass/tumor was removed in toto and sent for histopathological examination.

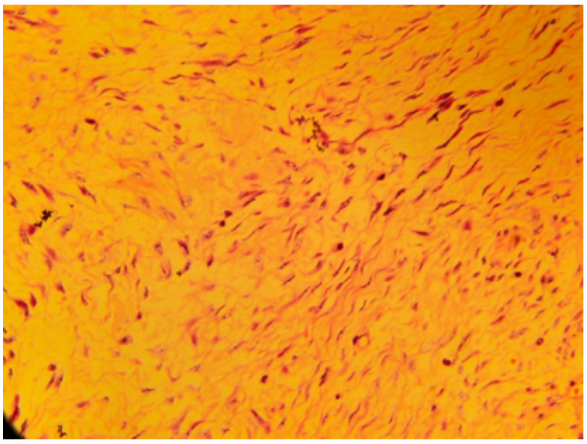


On gross examination the specimen consisted of single irregular grey white to grey brown soft tissue mass measuring 8.0 x 5.5 x 4.0cm. The external surface was bosselated. On cut section an encapsulated grey white soft tissue seen.



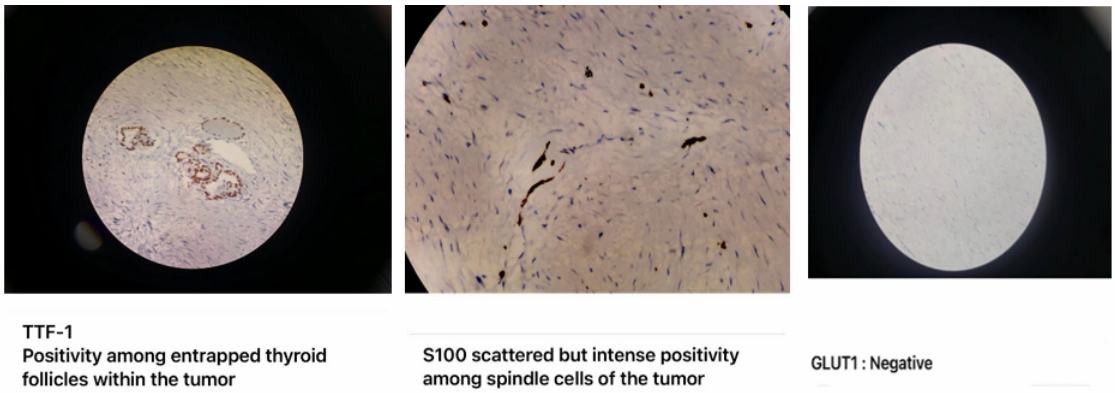


Microscopically the sections showed encapsulated tumor with whorling, fascicular and diffuse pattern of growth with entrapped normal thyroid follicles and adipose tissue. Tumor compromising of spindle cell with wavy nuclei, spindle cells with plump to oval nuclei. Myxoid and collagenous areas with hypercellular and hypocellular areas. Prominent small vessels with mast cells. The findings were suggestive of benign nerve sheath tumor with a differential diagnosis of neurofibroma or peri neuroma.



On Microscopic Examination

To confirm the definitive diagnosis immunohistochemistry was advised. On Immunohistochemistry, S-100 was scattered with intense positivity in the spindle cells confirming neural origin, TTF-1 positive in entrapped follicles within the tumor confirming thyroid origin. SOX10 positive (supporting peripheral nerve sheath differentiation), CD34 variable positivity (seen in neurofibromas) and GLUT I was negative ruling out peri neuroma.



TTF-1
Positivity among entrapped thyroid follicles within the tumor

S100 scattered but intense positivity among spindle cells of the tumor

GLUT1 : Negative

And the Final diagnosis of solitary neurofibroma of the thyroid gland (without NF1 association) was made. The Patient has been followed up since last 9 months with no recurrence.

IV. Discussion

Neurofibromas of the thyroid is an exceptionally rare entity with only a few reported cases in the literature. Neurofibromas are basically benign peripheral nerve sheath tumors arising from Schwann cells, Fibroblasts and perineural cells.[11] They originate from the endoneurium of peripheral nerves and are typically nonencapsulated, allowing them to infiltrate into the surrounding tissues. The Schwann cells provide myelin support to peripheral nerves and are the primary neoplastic component along with the fibroblasts and perineural cells that contribute to the collagenous and extracellular matrix of the tumor. Mast cells are often present and play role in tumor growth and fibrosis and along with the fibroblast and perineural cells contributing to the firm rubbery consistency of the tumor.

They are most frequently found in the skin, peripheral nerves and deep soft tissues and are strongly associated with NF1, an autosomal dominant disorder characterized by mutations in the NF1 gene on chromosome 17q11.2.[23,24]

As solitary Lesions most cases are reported on the skin as superficial neurofibromas, along the trunk especially in the subcutaneous tissues also common sites particularly along the nerves in the arms and legs. Neurofibromas can also appear along the nerves in the head and neck region, including the face with most being reported near the branchial plexus.

Primary neurofibromas of the thyroid gland are extremely rare, with most reported cases occurring in patients with NF1.

The thyroid is an unusual site for neural derived tumors, making this case unique. Due to the rarity of thyroid neurofibromas, they are often misdiagnosed as benign thyroid nodules, schwannomas or sarcomas, leading to diagnostic uncertainty.

Histologically, neurofibromas show spindle cells with poorly defined cell borders with a collagenous matrix consisting of coarse collagen bundles of low to moderate cellularity. Presence of mast cells scattered in the stroma with absent to minimal mitosis. These histopathological features were in accordance to our presented case report where the tumour was encapsulated. The encapsule seen was basically the thyroid capsule.[25,26]

Also, the role of immunohistochemistry cannot be be ruled out in making a definitive diagnosis of neurofibroma, as it help's in distinguishing it from other spindle cell lesions such as Schwannoma, fibromatosis or even malignancies like sarcoma. Immunohistochemistry plays a major role in confirming their neural lineage by detecting specific markers like the S100 protein which shows patchy positivity in neurofibroma whereas in schwannoma shows diffuse positivity. The S100 protein is found predominantly, but not exclusively, in the nervous system. This protein is expressed by Schwann cells and is very useful for the identification of tumours composed of these cells.[27] And the presence of CD 34 in the stromal component aids in differentiation from schwannoma. NF1 should be considered for any patient presenting with a plexiform neurofibroma. Plexiform types are also the most common precursor to malignant peripheral nerve sheath tumors.[28,29]

Patients with multiple localized neurofibromas should be considered for further neurofibromatosis testing**,** as the presence of multiple tumours may suggest an underlying genetic condition like neurofibromatosis type 1 (NF1)**.**

For the evaluation of a solitary soft tissue tumour**,** the process often begins with a physical exam and/or an excisional biopsy for microscopic examination**.** However, to arrive at a definitive diagnosis of the specific type of peripheral nerve sheath tumour**,** immunohistochemistry plays a crucial role. This technique helps differentiate between various tumour types by detecting specific markers at the molecular level.

In addition to biopsy and histological analysis, imaging (typically CT **or** MRI) is essential for assessing the extent of tumour involvement. This allows for the planning of complete surgical excision to remove the tumour while minimizing risk to surrounding structures.

Although all types of neurofibromas are generally benign, regular follow-up of these patients is important. Despite their benign nature, there remains a small risk of malignant transformation into malignant peripheral nerve sheath tumours (MPNSTs)**.** Therefore, monitoring for changes in the size, characteristics, or symptoms associated with neurofibromas is essential for early detection and management of any potential malignancy.

The thyroid is an unusual site for neural derived tumors, making this case unique. Due to the rarity of thyroid neurofibromas, they are often misdiagnosed as benign thyroid nodules, schwannomas or sarcomas, leading to diagnostic uncertainty.

This report discusses a rare case of solitary thyroid neurofibroma in an adolescent girl, focusing on its clinical presentation, diagnostic workup, surgical management and histopathological confirmation.

V. Conclusion

It is widely noted that 90% of neurofibromas occur as solitary or sporadic cases in adults. However, the occurrence of a solitary neurofibroma in the thyroid of a 14-year-old girl without neurofibromatosis type 1 (NF1) is an extremely rare event. This underscores the importance of considering thyroid neurofibromas and other peripheral nerve sheath tumours (PNSTs) in the differential diagnosis of thyroid nodules, especially when there are atypical clinical features and unusual cytological findings.

To confirm the diagnosis, histopathology and immunohistochemistry are essential, as they provide detailed information at the cellular and molecular level, helping to distinguish between different types of tumours.

Surgical excision remains the primary treatment approach, ensuring complete removal of the tumor and minimizing the risk of malignancy. In this case, careful monitoring post-surgery is essential to exclude any potential for malignant transformation, although this remains rare in benign neurofibromas.

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