Case study

A Rare Case Of SETTLE Tumor In Pregnancy: A Case Report And Literature Review

ABSTRACT

Spindle epithelial tumour with thymus-like differentiation (SETTLE) is a rare tumour of the thyroid. It is even rarer when it occurs in pregnancy. In this case report, we present a case of a 30 year old pregnant patient diagnosed with SETTLE tumour. She initially presented a lump on her neck during her third trimester, she was clinically euthyroid. The biopsy of the neck lump revealed a SETTLE tumour . As the best time for surgery for this situation is unclear, the management is a challenge for both doctors and patient. In view of the indolent nature of the tumour and her condition, decision was made for a delayed Computed Tomography (CT) scan for complete assessment and for total thyroidectomy post-partum. A total thyroidectomy was successfully performed 2 months after delivery with no immediate maternal or foetal complication. In patients with SETTLE tumour, it appears safe to delay the thyroidectomy until after the post-partum period. To the author's knowledge, this is the only SETTLE tumour in a pregnancy that has ever been reported.

Keywords : Case report, SETTLE, Thyroid cancer, Pregnancy, Total thyroidectomy

Introduction

Pregnancy-associated cancer was defined as a malignancy detected during pregnancy or within 2 years of delivery (38). While enlargement of the thyroid gland in pregnancy is commonly a physiological change related to pregnancy, in rare occurrences it can be due to thyroid malignancy. The reported incidence rates of differentiated thyroid cancer in pregnancy vary from 3.6 to 14 per 100,000 live births. The majority of thyroid cancers are classified as papillary thyroid cancer (88%)

and follicular thyroid cancer (9%). Thyroid cancer in pregnant patients is not unusual. Approximately 10% of thyroid cancers are diagnosed during pregnancy or during the post-partum period. The diagnosis of a thyroid tumour during pregnancy can cause anxiety about the optimal timing of recommended treatments. Management of thyroid cancer during pregnancy is a challenge. American Thyroid Association (ATA) guidelines recommended surgery after delivery for patients diagnosed with thyroid cancer during pregnancy that do not present any aggressive features, total thyroidectomy with or without lymph nodes dissections is recommended during second trimester if aggressive features are present.

SETTLE was first formally characterized by Chan and Rosai in 1991 as family of tumour arising from either ectopic thymus or rudimentary brachial pouches that retained their potential to differentiate along the thymic line. Predominantly it affects children and young adults, and best classified as low grade malignant neoplasm due to its indolent growth, low mitotic activity, rare focal necrosis and delayed blood-borne metastases at the time of diagnosis. Its malignant potential can be underestimated because of the lack of long-term follow-up in published literature. Herein, we report a case of SETTLE in Pregnancy. Ethical approval from Clinical Research Centre of Hospital Putrajaya and written consent from patient were obtained. This study aims to discuss the severity of SETTLE in pregnancy and offer recommendations on the management based on our experience and literature review.

Case History

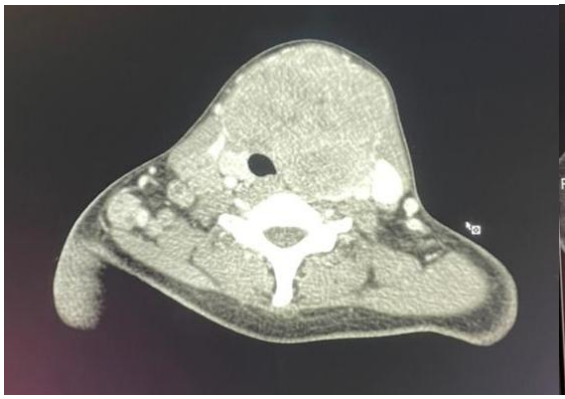
A 30 year old patient in her fourth pregnancy with three previous life births at 32 weeks of gestation. She does not have any medical illness. She presented to the outpatient clinic with a history of 2 years of anterior neck swelling, present since her third pregnancy, but she did not receive any treatment. This neck swelling was persistent and progressively increasing in size over the past 2 months. She did not experience any compression or direct infiltration symptoms, or any

hyperthyroid or hypothyroid symptoms. On physical examination, there is a hard, non mobile anterior neck swelling measuring around 8cm by 7cm which extends to the left side of her neck. Laboratory evaluation revealed normal thyroid hormone levels. Fine-needle aspiration cytology (FNAC) from another center was consistent with medullary carcinoma and patient was investigated for evidence of MEN-II syndrome for which the relevant investigations were negative. Subsequently, she defaulted follow up until 2 months post-partum at which point she was referred to our centre as she developed ptosis of the left eye. Otherwise, She reported that her neck swelling did not increase or decrease in size since her last appointment.

Upon physical examination in our centre, neck examination showed a hard, non mobile, nodular anterior neck swelling measuring 8 by 7 cm extending to the left side of the neck. Eye examination showed slight ptosis of the left eye, otherwise her visual axis, iris and pupil are normal. Fundoscopy showed a normal bilateral funds macula and peripheral retina. Magnetic resonance imaging (MRI) of the brain was done which showed no significant changes. Lumbar puncture was done to rule out leptomeningeal metastasis and was negative. She was diagnosed to have isolated 3rd nerve palsy and was decided for conservative management.

Ultrasound guided left thyroid mass biopsy was done which revealed a spindled tumour cells with intervening fibrovascular stroma. The spindle cells have elongated nuclei with scant cytoplasm. The cytoplasmic border is ill-defined. Mitotic figures are inconspicuous. Few glandular structures are noted. Immunohistochemical study shows the tumour cells are negative for Calcitonin, Chromogranin, Synaptophysin, TTF-1, Thyroglobulin, CK7 and CK20. The biopsy was interpreted as spindle cell lesion with differential diagnosis of SETTLE and synovial sarcoma.

Computed Tomography (CT) scan post biopsy revealed a large heterogeneous mass with cystic components within at the left side of the neck, arising from the left thyroid gland, measuring 7.0cm x 8.0cm x 10.5cm with enlarged, matted right cervical (level III, IV and V) and supraclavicular lymph nodes. The largest at level III measures 2.2 x 1.8cm, sub-centimetre left cervical and sub-mental nodes. (Referrence with Figure 1 and 2)



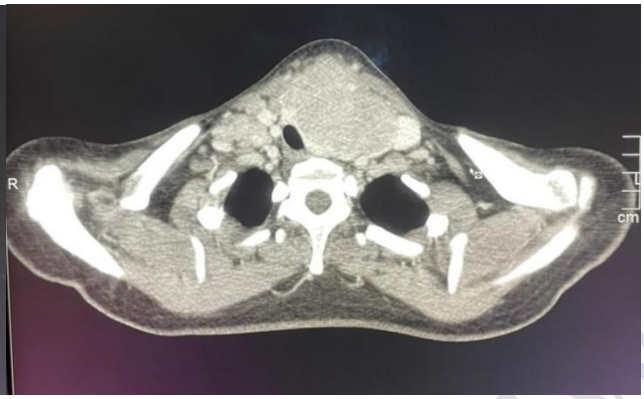


Figure 1 Figure 2

(Figure 1 and 2 show the computed tomography of patient with large heterogenous mass with some cystic components within)

Patient underwent total thyroidectomy with left modified radical neck dissection. Intra-operative findings showed left thyroid adhering to infrahyoid muscles anteriorly and to sternocleidomastoid muscle laterally and to cricothyroid muscle posteriorly. Enbloc resection of the muscles was done. Level II left cervical lymph nodes was removed. Because her right thyroid gland was only adhered to the strap muscle, enbloc resection was also done. Patient was discharged well about a week after surgery with thyroid and calcium supplements. There is no oncologic treatment given and she was on a 6 monthly follow up in our centre. Patient remained disease-free to date, 3 years following surgery.

Pathological Findings

Gross and Histological Appearances

The resection consisted of a total thyroidectomy and a modified radical node dissection. The thyroid gland weighed 288.2g. The left thyroid measuring around 135mm x 100mm x 60mm, and the right thyroid gland measuring around 55mm x 22mm x 10mm with muscle attached to its lower pole, measuring 65mm x 50mm x 8mm. The isthmus measuring 15mm x 12mm x 5mm.

Generally, the left thyroid is grossly enlarged, firm and multi-lobulated. There are muscles attached at the anterior part of the left thyroid gland which measure around 52mm x 22mm. The capsule of the left thyroid gland is intact. The right gland is normal in size, and the capsule of the right thyroid gland is intact. The cut section of left thyroid gland shows a pale yellowish solid grey- whitish tumour. Fibrous septa is noted within the tumour which shows firm to hard in consistency. There is a minimal [illegible] the posterior part of the left thyroid gland.

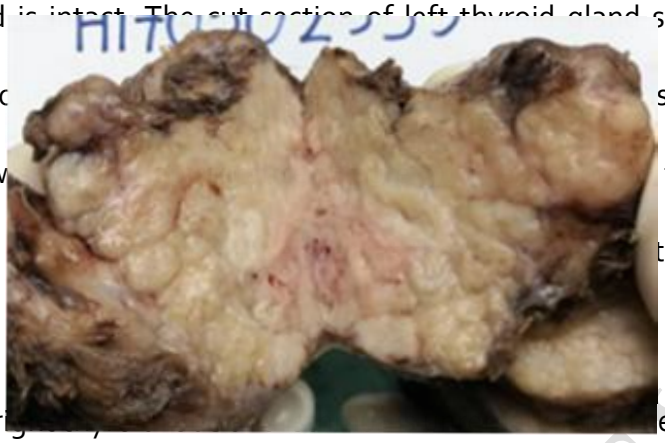


Figure 3. Total thyroidectomy specimen: Cut section of tumour shows solid and nodular gray-whitish tumour with intact capsule.

The cut section of ri[illegible]ere were no gross infiltration seen in the muscle. There is also a level II left central lymph node measuring 11mm in its widest dimension with homogenous brownish cut surface.

Histologically, from the thyroid gland, the sections of the left thyroid lobe show a fairly circumscribed tumour surrounded by a thick fibrous capsule. The tumour is composed of highly cellular spindle cells tumour separated by thick and thin sclerotic bands of collagen which formed a nodular appearance. The spindle shaped cells are arranged in sheets, interlacing bundles, short fascicles, herring bone in some areas and show slightly attenuated storiform pattern. The tumour cells are fairly uniformed exhibiting an elongated or oval nuclei with fine chromatin and inconspicuous nucleoli. The cytoplasm is eosinophilic (Figure 4). In certain areas, the spindle cells merge into tubulo-papillary pattern of epithelial component (Figure 5).

Mitoses are 2-3/10hpf. Foci of necrosis are noted. A few benign thyroid follicles are present at the surrounding fibrous capsule. Hyalinized stroma and myxoid area with less cellularity are also noted. Lymphovascular invasion is present. Tumour is less than 0.5mm from the nearest surgical margin. Sections from right lobe and isthmus show various sized follicles. No tumour cells infiltration is seen.

Immunohistochemistry study shows the tumour cells are positive toward CK MNF116, CK19, Vimentin (focal), CD99, and SMA (focal). However, are negative for EMA, TTF-1, Thyroglobulin, Calcitonin, S100, CD34, Chromogranin, Synaptophysin, Desmin, CD68, PAX8 and STAT6. The level II left central lymph node showed a reactive lymph node, there is no tumour cells infiltration seen.

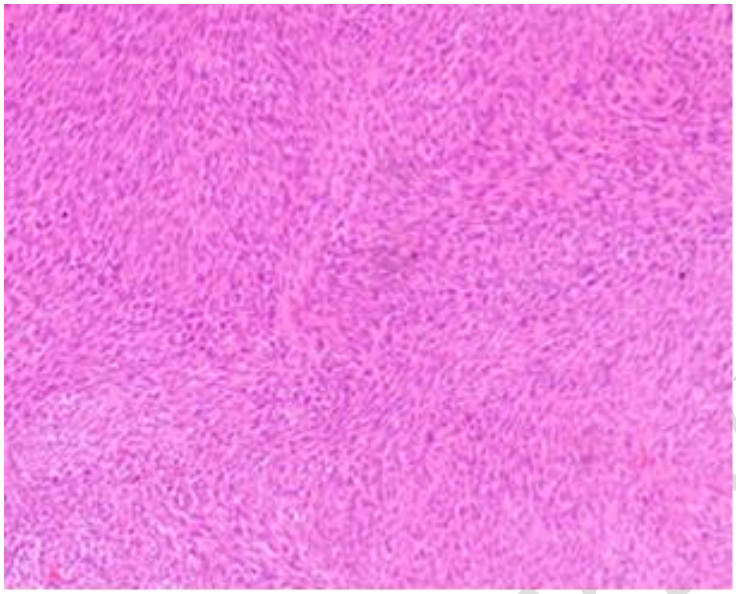


Figure 4. Microscopy shows biphasic tumour components. Tumour composed of predominantly cellular spindle cells tumour arranged in sheets, interlacing bundles, short fascicles, herring bone in some areas and show slightly attenuated storiform pattern. The tumour cells are fairly uniformed exhibiting elongated or oval nuclei with fine chromatin and inconspicuous nucleoli. The cytoplasm is eosinophilic.

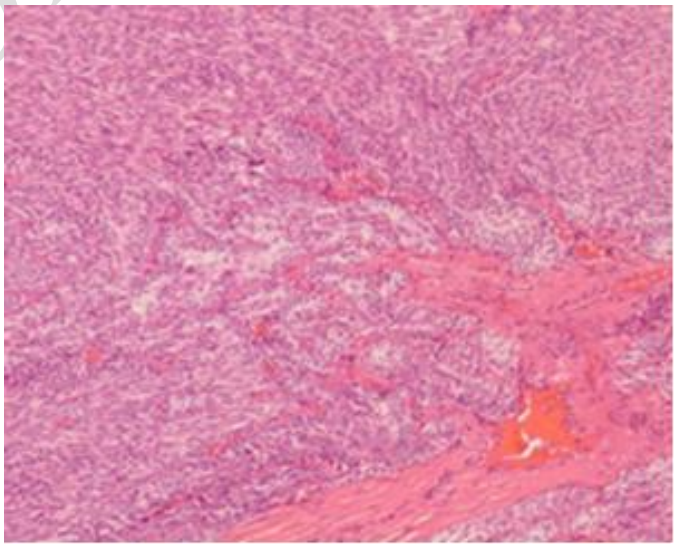


Figure 5. In certain areas, the spindle cells merge into tubulopapillary pattern of epithelial component (arrow).

Discussion

SETTLE was first formally characterized by Chan and Rosai in 1991 as a family of tumours arising either from ectopic thymus or from remnants of brachial pouches that retained their potential to differentiate along the thymic line (1). The aetiology of this disease was first coined by Harach et. al. in 1985 under the term "thyroid spindle cell tumour with mucous cyst". During embryogenesis, at 3-4 weeks of gestation, the median anlage of the thyroid arises at the foramen caecum of the tongue which then migrates to the anterior neck, attached to the tongue by the thyroglossal duct whereas the lateral thyroid is derived from ultimobranchial body which then fuses with the medial anlage. Others that derivate from the ultimobranchial body include the thyroid C cells, parathyroid, thymic and salivary gland tissues and it is this cascading events that lead to the presence of ectopic tissues in the thyroid gland, including thymic remnants which can undergo neoplastic transformation (15).

SETTLE predominantly affects children and young adults with a mean age of 19 at diagnosis, ranging from 2 to 59 years and a male to female ratio of 1.4:14. In nearly all cases this disease presents only as a painless neck mass or enlarged thyroid and rarely presented with symptoms of obstruction. Though SETTLE predominantly is an indolent tumour, according to Gonzalo et. al., patients with follow up exceeding 5 years have a rate of metastasis up to 41% with the commonest site being cervical lymph nodes, lungs and mediastinum and others include pancreas pleura, kidney, bone and peritoneum (4).

The differentials include CASTLE, a highly lethal immature teratoma of soft tissues of the neck and thyroid, dedifferentiated thyroid carcinoma, spindle cell variant of medullary thyroid carcinoma, columnar cell thyroid carcinoma, and synovial sarcoma of the neck (7,16). Spindle cell

neoplasm is rare in thyroid cancer and has wide range of differential diagnoses. Therefore, it needs a combination of clinical and radiological information together with morphological and immunohistochemical study to reach a diagnosis. Fine-needle aspiration cytology normally shows a cellular spindle cell proliferation with mild pleomorphism which may cause a few differential diagnoses that are more common than SETTLE such as medullary thyroid carcinoma with spindled morphology and synovial sarcoma. Thyroid biopsy and further immuno-histochemical study enable us to narrow down the diagnosis. SETTLE is usually composed of spindle cells of epithelial nature forming fascicles, merging into glandular structures with tubulopapillary epithelial structures (2,7). In some cases, cysts or glands can be lined by mucinous or respiratory epithelium which are reminiscent of glandular structures found in the thymus (canals of Kursteiner), believed to represent remnants of the thymic duct, or alternatively, interpreted as derivates of the medullary duct epithelium (1,2,7,17-21). While other differential diagnosis, for example a cervical thymoma is an encapsulated lesion with a jigsaw puzzle appearance to the lobules and consists of plump epithelial cells, it may also be a spindled shape, and is often admixed with lymphocytes. SETTLE, on the other hand, is a biphasic tumour which shows typical merging of the spindle and epithelial cells, and lack of lymphocytes. In synovial sarcoma, another differential diagnosis which is also a biphasic tumour, the spindle cells are generally more monomorphic, hyperchromatic with mild pleomorphism but manifest more mitoses (25, 38). The Anaplastic carcinoma with predominant spindled sarcoma-like features is also another differential, however, it will manifest marked pleomorphism and high mitotic activity (40). Another differential diagnosis will be Solitary fibrous tumour which is a well circumscribed tumour and composed of bland spindle cells proliferation with whorl pattern (39).

SETTLE disease is typically positive for cytokeratin and vimentin and often positive to alpha-SMA and negative to TTF-1, thyroglobulin, calcitonin, S100, CD5, CEA (2,9,16-30). Ideally, SETTLE must be distinguished from sarcomatoid anaplastic carcinoma due to it being an aggressive tumour with poor prognosis and histologically it reveals overt nuclear atypia, frequent

mitoses, and necrosis. Spindle cell variant of medullary carcinoma should also be excluded as it may mimic SETTLE and negative immunostaining for calcitonin and chromogranin are the elements that exclude it from this diagnosis. In synovial sarcoma, the immunopositivity for cytokeratin has patchy distribution; however, in SETTLE, the cytokeratin staining is strong and diffuse. In addition, epithelial membrane antigen (EMA) positivity is regarded as a reliable marker for synovial sarcoma (38). In Solitary fibrous tumour, which is another differential diagnosis, it shows a positive result for BCL-2, CD34 and STAT6 and negative for CK (39).

In our patient, the morphology is typical of SETTLE where it is a fairly circumscribed tumour surrounded by thick fibrous capsule and shows highly cellular spindle cells which merge into tubulopapillary pattern and the immunohistochemistry study shows the tumour cells are positive to cytokeratin and vimentin as well as SMA.

Surgical resection is the mainstay of therapy for SETTLE and includes resection of the primary and oligometastatic disease. This is a common and successful strategy in many slowly growing cancers. There is no known role for adjuvant chemotherapy or radiotherapy. Gonzalo Recondo et. al. studies show that in the rare cases where data are available, SETTLE is uniformly responsive to radiotherapy and first-line chemotherapy, demonstrating that radiation is a good therapeutic option. On the basis of the available data, a combination of cisplatin, etoposide, and ifosfamide or of carboplatin, paclitaxel, and ifosfamide are options for metastatic disease (41).

It is well known that papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy found in the population and also in the pregnant patients' cohort. The issue in treating SETTLE during pregnancy, as evidenced in our case, is the timing of surgery, taking into consideration the maternal and neonatal outcome. SETTLE can be considered as a low grade malignancy due to the comparative long period between initial treatment and diagnosis of metastasis. A planned premature delivery of gestation before term may also predispose the child to multiple morbidities related to prematurity. As the patient was presented to us during her third trimester, decision in unison was made to time the surgery after delivery. There is no

recommendation from the ATA guideline for the optimal timing of surgery for SETTLE in pregnancy. However, it is recommended that surgery is strongly considered as delay in treatment can adversely affect outcome depending on tumour behaviour and timing of patient presentation (31). It is also postulated that pregnancy on its own could promote growth of multi-nodular goitre. Rosen et. al. concluded that pregnancy may accelerate growth of thyroid cancers (32). Kung et. al. studied the effect of pregnancy on thyroid nodule formation and found that there were no significant differences in size of nodule diameter but a significant difference in increasing nodule volume during pregnancy (33). Some study subjects who had pre-existing solitary nodule developed new nodules as their pregnancy advanced. According to the ATA guidelines, surgery is generally safe during the second trimester, but it applies only for differentiated thyroid cancer. Uruno et. al. had retrospectively reviewed 45 patients who had differentiated thyroid cancer during pregnancy (34) of which 24 patients underwent total thyroidectomy during second trimester and there were no immediate or long term complications from the surgery or anaesthesia. They concluded that surgery can be safely performed in the second trimester and surgery after delivery is also acceptable and recommended for non aggressive differentiated thyroid carcinomas.

Prophylactic lymph-node dissection remains a debatable issue. A study done by Franc et. al. has shown that even with extensive lymph node dissection, recurrences are still possible. Biochemical recurrence can still occur even when patient was operated at an early stage; thus, close follow-up on CT scans to detect recurrence should be emphasized. However, in a study by Yen et. al., compartment oriented surgery (COS) could reduce rates of disease recurrence even in the later stages of the disease (35). This was followed by a study by Dralle et. al., that summarized cases of patients who had undergone systemic lymphadenectomy where survival rates were much better than patients who had selective lymphadenectomy.

Conclusion

SETTLE can be considered as a low grade malignancy due to the comparative long period between initial treatment and onset of metastasis. Based on our study, total thyroidectomy after delivery was found to have no immediate adverse outcome to maternal and neonatal well-being so far. Long term observation on both mother (patient) and child should be performed, as the disease can be fatal, eventhough SETTLE is initially indolent. The malignant potential of this tumor might be underestimated due to the lack of long-term follow-up. In cases where a complete surgical resection is not possible, radiotherapy or combination chemotherapy can be effective and beneficial for the patient.

Reference

1. Chan JK, Rosai J. Tumours of the neck showing thymic or related branchial pouch differentiation : a unifying concept. Hum Pathol 1991; 22:349-67

2. Wah Cheuk, M.D., Avram A. Jacobson, M.D., John K.C Chan, M.D. Spindle Epithelial Tumour with Thymus-Like Differentiation (SETTLE) : A Distictive Malignant Thyroid Neoplasm with Significant Metastatic Potential. (Mod. Pathol 2000;13(10) : 1150-1155)

3. Aleksandr Yu. Abrosimov and Virginia A. LiVolsi. Spindle Epithelial Tumour with Thymus- like Differentiation (SETTLE) of the thyroid with Neck Lymph Node Metastasis : A case Report.(Endocrine pathology, vol.16 no. 2 139-144, Summer 2005)

4. Gonzalo Recondo, Jr, MD, Naifa Busaidy, MD, Jeremy Erasmus, MD, Michelle D. Williams, MD, Faye M. Johnson, MD, PhD. Spindle epithelial tumour with thymus-like. Differentiaton : A case report and comprehensive review of the literature and treatment options.(Journal of science speciality of head and neck ,Vol 37 , Issue 5 . 747-756)

5. Bing Xu, MD, PhD, Mitsuyoshi Hirokawa, MD, PhD, Katsuhiko Yoshimoto, MD, PhD, Hitoshi Miki, MD, Masanori Takahashi, MD, Seiji Kuma, MD, and Toshiaki Sano, MD, PhD. Spindle Epithelial Tumour with Thymus-like Differentiation of the thyroid : A case report with pathological and molecular genetics study (Human Pathology, Elsevier, Volume 34, Issue 2:190-193.0

6. R. Chetty, S. Goetsch, S Nayler & K Cooper. Spindle epithelial tumour with thymus-like element (SETTLE) : the predominantly monophasic variant. (Histopathology, 1998 Jul;33(1) 71-4)

7. Shintaro Satoh, Shuji Toda, Keita Narikawa, Keiko Watanbe, Kuniyoshi Tsuda, Yuichiro Kuratomi, Hajime Sugihara and Akira Inokuchi. Spindle epithelial tumour with thymus-like differentiation (SETTLE) : Youngest reported patient (Human Pathology: Case Report, Elsevier, Volume 11, March 2018, Pages 60-64)

8. Kazunori Iwasa, MD, Miwa Akasofu Imai, MD, Masakuni Noguchi, MD, Shigehiro Tanaka, MD, Tadashi Sasaki, MD, Shogo Katsuda, MD, Ei Kawahara, MD, Yuji Mizukami, MD. Spindle epithelial tumour with thymus-like differentiation (SETTLE) of the thyroid (Journal of the Sciences and Specialities of the Head and Neck, August 2002, Volume 24, Issue 9, Page 888-893)

9. A. Nihan Haberal, Hakan Aydin, Ergin Turan, and Beyhan Demirhan. Unusual Spindle Cell Tumour of Thyroid (SETTLE) (Thyroid, August 2008, Volume 18, Issue 1)

10. Sophie Giusiano-Councambeck, Anne Denizot, Veronique Secq, Catherine De Micco and Stephane Garcia. Pure spindle cell follicular carcinoma of the thyroid ((Thyroid, 2008 Sept 18(9):1023-5

11. Serena Ippolito, Claudio Bellevicine, Debora Arpala, Carmela Peirce, Gluseppe Ciancia, Elena Vigliar, Glancarlo Troncone, Bernadette Biondi. Spindle epithelial tumour with thyrmus like-differentiation (SETTLE) : clinical pathological features, differential pathological diagnosis and therapy (Endocrine, 51(3), 402-412)

12. Noriko Kusada, Yasuo Hara, Shunzo Kobayashi, Tang Weihua, Yasushi Nakamura, Kenichi Kakudo, and Hiromitsu Yuasa. A case of aggressive carcinoma showing thymus-like differentiation with distant metastases. (Thyroid, 15(12), 1383-1388)

13. S.M.Chow, J.K.C.Chan, L.L.Y. Tse, D.L.C Tang, C.M.Ho, S.C.K Law. Carcinoma showing thymus-like element (CASTLE) of thyroid : combined modality treatment in 3 patients with locally advance disease. (European Journal of Surgical Oncology (EJSO), 33(1), 83-85)

14. Stephane Yerly, Johannes-Alexander Lobrinus, Massimo Bongiovanni, Minerva Becker, Maryam Zare, Perrine Granger, and Marc Pusztaszeri. A carcinoma showing thymus-like elements of the thyroid arising in close association with solid cell nests : evidence for a precursor lesion ? (Thyroid, 23(4), 511-516

15. LiVolsi Va. Brnachiah and thymic remnants in the thyroid and cervical region : an explanation for unusual tumours and microscopic curiosities. (Endocrine Pathology 1993;4:115-119)

16. Kirby PA, Ellison WA, Thomas PA. Spindle epithelial tumour with thymus-like differentiation (SETTLE) of the thyroid with prominent mitotic activity and focal necrosis. Am J Surg Pathol 1999;23:712-16

17. Gilmour JR. The embryology of the parathyroid glands, the thymus and certain associated rudiments. The Journal of Pathology and Bacteriology 1937;45:507-22

18. Willis RA. The borderland of Embryology and Pathology, 2nd edn. London : Butterworths, Volume 50, Issue 221, November 1962, Page 348

19. Henry K. Mucin secretion and striated muscle in the human thymus. Lancet 1966;1:183-5

20. Shier KJ. The thymus according to Schambacher: Medullary ducts and reticular epithelium of thymus and thymomas. Cancer 1981;48:1183-99

21. Suster s, Rosai J. Histology of the normal thymus. Am J Surg Pathol 1990;14:283-303

22. Harach HR, Saravia Day E, Franssila KO. Thyroid spindle-cell tumour with mucous cysts. An intrathyroid thymoma? Am J Surg Pathol 1985;9:525-30

23. Hogman P, Mainguene C, Michiels JF, Pagas A. Thyss A. Thyroid spindle epithelial tumour with thymus-like differentiation (the 'SETTLE' tumour). An immunohistochemical and electron microscopic study. Eur Arch Otorhinolaryngol 1995;252:316-20

24. Su L, Beals T, Bernacki EG, Gidordano TJ. Spindle epithelial tumour with thymus-like differentiation : A case report with cytologic, histologic, immunohistologic, and ultrastructural findings. Mod Pathol 1997; 10:510-14

25. Chetty R, Goetsch S, Nayler S, Cooper K. Spindle epithelial tumour with thymus-like element (SETTLE) : The predominantly monophasic variant. Histopathology 1998;33:71-4

26. Iwasa K. Imai MA, Noguchi M et al. Spindle epithelial thymour with thymus-like differentiation (SETTLE) of the thyroid . Head Neck 2002;24:888-93

27. Xu , Hirokawa M, Yoshimoto K et al. Spindle epithelial tumour with thymus-like differentiation of the thyroid : A case report with pathological and molecular genetics study. Hum Pathol 2003;34:190-93

28. Raffel A, Cupisti K, Rees M et al. Spindle epithelial tumour with thymus-like differentiation (SETTLE) of the thyroid gland with widespread metastases in a 13 year-old girl. Clin Oncol 2003;15:490-95

29. Abrosimov AY, LiVolsi VA. Spindle epithelial tumour with thymus-like differentiation(SETTLE) of the thyroid with neck lymph node metastasis : A case report. Endocr Pathol 2005;16:139-43

30. Erickson ML, Tapia B, Moreno ER, McKee MA, Kowalski DP, Reyes-Mugica M. Early metastasizing spindle epithelial tumour with thymus-like differentiation (SETTLE) of the thyroid. Pediatr Dev Pathol 2005;8:599-606

31. Sophia SY, Bischoff LA. Thyroid cancer in pregnancy. Paper presented at: Seminars in reproductive medicine 2016.

32. Rosen IB, Walfish PG. Pregnancy as a predisposing factor in thyroid neoplasia. Archives of surgery. 1986;121(11):1287-1290.

33. A.W.C Kung, M.T. Chau, T.T.Lao, S.C.F. Tam, L.C.K. Low. The effect of pregnancy on thyroid nodule formation. *The Journal of Clinical Endocrinology & Metabolism*, Volume 87, Issue 3, 1 March 2002, Pages 1010–1014

34. Uruno T, Shibuya H, Kitagawa W, Nagahama M, Sugino K, Ito K. Optimal timing of surgery for differentiated thyroid cancer in pregnant women. World journal of surgery. 2014;38(3):704-708.

35. Hanzali Jumastapha, YL Tan, Sadhana Mahamad. Medullary Thyroid Carcinoma in Pregnancy: A Case Report and Literature Review on Maternal and Neonatal Outcome of Delayed Surgery Post-Partum. *Hanzali J., et al Surg Chron 2020; 25(1): 32-34.*

36. Association BT. Guidelines for the management of thyroid cancer.2007.

37. Lawrence A. Shirley, Natalie B. Jones, and John E. Phay. The role of central neck lymph node dissection in management of papillary thyroid carcinoma. (Frontiers in Oncology, Volume 7, June 2017, Article 122)

38. Radhika Kottu and Aruna K Prayaga. Synovial sarcoma with relevant immunochemistry and special emphasis on the monophasic fibrous variant. Journal of Cytology, 27(2), 47.

39. Bita Geramizadah, Mahsa Marzban, and Andrew Churg. Role of immunohistochemistry in the diagnosis of solitary fibrous tumour, a review. July 2016 Iranian Journal of Pathology 11(3):195-203

40. Moira Ragazzi, Alessia Ciarrocchi, Valentina Sancisi, Greta Gandolfi, Alessandra Bisagni and Simonetta Piana. Update on Anaplastic Thyroid Carcinoma : Morphological, Molecular and Genetic Features of the Most Aggressive Thyroid Cancer. (International Journal of Endocrinology, 2014 1-13)