Metachronous Dual Primary Tumors ; Thymoma with Papillary Thyroid Carcinoma : Report of a Case and Review of Literature.

Abstract:

Introduction: A second primary malignancy (SPM) in a case of papillary thyroid carcinoma is a rare finding.

Case presentation: We report here a known case of papillary thyroid carcinoma (PTC) who presented with cervical lymph node enlargement along with a large mass in anterior mediastinum (retrosternal part) both clinically suspected to be metastatic thyroid disease. However, on histology the mediastinal mass was diagnosed as Thymoma type B2 and lymph nodes showed metastases of PTC.

Conclusion: To the best of our knowledge, a total of 39 cases of thymoma with thyroid cancer have been reported in the published English world literature till date. Hence, we considered it prudent to document this rare occurrence.

Keywords: Mediastinal mass, thymus, thyroid metastases.

Introduction:

Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the thyroid gland. It can occur at any age but most commonly is seen in 3rd to 5th decade and is more common in females. It is known for its excellent prognosis and survival [1]. A second primary malignancy (SPM) in papillary thyroid carcinomas is rare. Very few studies have reported second primary malignancy (SPM) in cases of primary thyroid cancer [2-6]. We report herein a follow through case of PTC who presented with cervical lymphadenopathy along with a large anterior mediastinal mass.

Case Report:

A 46-year-old male patient presented to our CTVS department in January 2021 with complaints of weight loss (~8 kg) and loss of taste for 11 months.

His past history revealed that he had undergone total thyroidectomy 2.5 years back at a tertiary care government referral institution. On histology, it was reported as papillary carcinoma thyroid. After surgery he was administered radioiodine therapy; 100 mCi of I-131 was given orally on 22/11/2018, 150 mCi on 29/05/2019, 100 mCi on 16/12/2019; total dose of 350 mCi.

During follow up he reported to the same institution with symptoms in November 2020 where he was advised CECT neck and chest and also whole body PET scan which showed the anterior mediastinal mass in the retrosternal part along with right sided central compartment level VI lymph nodes. Radiologist suggested possibility of recurrence of thyroid carcinoma with retrosternal extension and patient was advised surgery.

For further surgical management the patient came to our hospital. The review of his **CECT Neck and Chest** showed a 6.5x5.2x7.1 cm (APxMLxCC) sized heterogeneously enhancing solid cystic lesion in anterior mediastinum (retrosternal part) closely abutting the SVC, ascending aorta and right atrium. **18F–FDG whole body PET CT** study revealed a heterogeneously FDG avid (SUV max – 6.21) soft tissue mass lesion in anterior mediastinum (measuring 6.9x4.3x7.2 cm) on right side, medially it is abutting pericardium, right atrium, SVC and ascending aorta. FDG avid (SUV max – 4.48) right cervical VI lymph nodes noted (measuring 1.2 x 1.7 cm). After relevant investigations and pre anaesthesia clearance, the patient underwent excision of the mediastinal mass via median sternotomy along with right neck node dissection. Lymph node resection of FDG avid nodes was done. Central compartment clearance was not done in order to avoid injury to recurrent laryngeal nerve considering that the patient was undergoing a re-do thyroid surgery .

Histopathological examination of the lymph nodes showed metastases of PTC in five out of eight (5/8) lymph nodes.

The resected mediastinal mass on gross examination was lobulated and well encapsuled measuring 11.5 x 8.5 x 4.0 cm. External surface showed

multiple dilated blood vessels. Cut surface showed lobulated grey white fleshy areas along with occasional cystic spaces.

Light microscopy revealed an encapsulated and circumscribed lobulated tumor separated by thick fibrous bands. The tumor was composed of large atypical cells disposed in sheets, as well as bordering the peri-vascular spaces. These atypical cells had large oval vesicular nuclei with small nucleoli with ill-defined cell borders. Intervening areas showed lymphocytes. Occasional mitosis and scanty necrosis was seen. Normal thymic tissue with cystic spaces, occasional Hassall's corpuscles and focal calcification was identified at the periphery. Histological differential diagnoses of Thymoma, Lymphoma and Germ cell tumor were considered for immunohistochemistry work up.

A panel of immunohistochemistry markers ; LCA, CD3, CD20, Cytokeratin, CD117, CD30, Tdt, CD68 and Ki67 was done. The large atypical looking cells were positive for Cytokeratin (epithelial cells) and the infiltrating lymphocytes were positive for LCA, CD3, and Tdt (immature lymphoid phenotype). Ki 67 showed low proliferative index in tumor cells and 45% in Tdt positive lymphoid cells. CD 117, CD 30, CD 20 and CD 68 were negative in tumor cells.

The final histological diagnosis of Thymoma, type B2, pT1a was rendered on the anterior mediastinal mass.

After 6 months of follow up, the post operative period was uneventful.

Discussion :

The present case was a diagnostic surprise to us on histology (a case of dual malignancy; PTC metastatic to lymph nodes and Thymoma B2). The patient reported to us as a follow through case of operated PTC with radio-iodine therapy. On PET CT there was FDG avid uptake in cervical lymph nodes with uptake in an anterior mediastinal mass (retrosternal part) with thyroid

fossa free of the gland. This finding clinically suggested that it could be a retrosternal thyroid tumor with little inkling of a second malignancy.

Review of literature shows that among thyroid cancers, differentiated papillary thyroid cancers account for majority of cases and these have an excellent prognosis with 10 year survival rate exceeding 90%. Definitive therapy for these differentiated cancers is complete or partial surgical thyroidectomy, with adjuvant radioiodine ablation/therapy used for residual, unresectable, and/or metastatic disease. The use of radioiodine in cancer treatment has caused concern about the potential for development of secondary malignancies (4,5).

In 2008, Brown AP et al [4] conducted a large population database study with longest period of follow up of any study of second primary tumors after thyroid cancer diagnosis. They utilised Surveillance, Epidemiology and End Result program (SEER) database from 1973 to 2002 and the follow up was upto 30 years. They concluded that the overall risk of second primary malignancies is slightly increased for thyroid cancer survivors over that of the general U.S. population and the risks are modified by age at diagnosis, radioisotope use, and latency period. The risk of SPM was increased with the use of radioisotopes. The greatest risk occurred within 5 year of diagnosis and was elevated in younger patients.

In 2013, using a SEER 9 database consisting of 52,103 patients, Kim et al. [6] demonstrated an increase of second cancers in all sites, and the most commonly elevated second cancers were the salivary gland and kidney.

In 2018, using SEER 13 database Endo at el [5] presented the most updated incidence rates of second primary malignancy from original diagnosis of PTC. In their study, 3,200 patients developed second primary malignancy, a substantially higher number than in the reference population of 2,749 with observed to expected ratio (O/E) of 1.16. The authors observed an increased SPM risk of many sites particularly salivary gland, bone, kidney, ureter, and

hematologic malignancies. Males had a higher incidence of SPM than females. Radiation therapy including radioiodine therapy was associated with increased risk of SPM in cases of PTC.

Other studies included a European study which suggested that second cancers were elevated 27% compared to cancer rates in general population, and treatment may play a role in future second cancer risk [2]. In a pooled analysis of 13 registries, 31% increase was discovered by a UK group [3].

In our case, the second primary malignancy was histologically proven thymoma, developed approximately 2.5 years after the initial diagnosis of Papillary Thyroid Carcinoma. The patient had received three doses of Iodine-131. Development of second primary in our case is in corroboration with other studies that have reported increased risk of second primary malignancy after radioiodine therapy [2,4,5,6].

Thymoma is a thymic epithelial neoplasm exhibiting organotypic features, which include lobulation, medullary differentiation, perivascular spaces, and presence of immature T lymphocytes. All thymomas, irrespective of histologic type, are potentially malignant [7]. In 50 % of cases, thymoma is detected as an incidental finding on imaging as it is a relatively slow growing tumor and may be asymptomatic for long. It constitutes about 20 % of the mediastinal tumours and in 95 % of cases, it presents as an anterior mediastinal mass [8]. The 2015 WHO Classification of Tumors of the Thymus classified Thymomas as Type A thymoma, including atypical variant, Type AB thymoma, Type B1 thymoma, Type B2 thymoma, Type B3 thymoma, micronodular thymoma with lymphoid stroma, metaplastic thymoma and other rare thymomas including microscopic thymoma, sclerosing thymoma and lipofibroadenoma. Type B2 thymoma shows increased numbers of single or clustered polygonal or dendritic epithelial cells intermingled with abundant immature T cells[9].

The coexistence of thymomas with numerous paraneoplastic syndromes and second primary cancers is also well documented. There is an increased incidence of second cancers irrespective of the histology of the thymic epithelial tumour [8].

A study conducted at Johns Hopkins Hospital [10] found additional neoplasms in 31% of thymoma patients at some time during their follow-up. Many other large series [11-17] have also reported association of thymomas with non-thymic neoplasms with incidence rates ranging from 8% to 21%.

In a series of 46 thymomas, four additional neoplasms (9%) were found [18]. Two male patients had papillary thyroid carcinomas accompanied with myasthenia gravis. Notably, the thyroid malignancies preceded the diagnosis of thymomas by 1.5 and 9 years, respectively. Few other case reports describe the association of thyroid carcinomas with thymomas [19,20,21]. Tables I and II summarise cases of thymoma associated with thyroid cancers and summarises cases of head and neck cancers that were reported before thymoma respectively [22].

Theories on the causes of extrathymic tumor before or after thymoma have been debated till date. Extrathymic tumors following thymoma is widely recognized, however tumors before thymoma are rare and there has been relatively little investigation of possible causes. According to Doumas et al [23], a plausible pathogenic explanation of the association of thymomas with other cancers taking into account the facts that associated cancers occur before, with or after the diagnosis of thymomas and are independent of thymoma treatments. It is possible that these patients have altered immunity related to immunologic cancer surveillance that predisposes them to develop second malignancies.

In the present case, diagnosis of thymoma was made 2.5 years after the diagnosis of papillary thyroid carcinoma. Since thymomas are asymptomatic

and slow growing tumors, there is a possibility that thymoma might have existed before the development of papillary thyroid carcinoma and however was detected later during follow up of PTC.

Conclusion:

Correct timely diagnosis and awareness regarding the occurrence of synchronous or metachronous dual or multiple malignancies are important for management of such cases. This was an interesting case of metachronous dual malignancy who presented to us with lymph node metastases of papillary thyroid carcinoma and Thymoma B2 type with a history of treated papillary thyroid carcinoma 2.5 years back. In view of rarity of such cases in published world literature, we considered it prudent to document.

Patient Consent Statement:

Written informed consent was obtained from the patient.

Declaration of Competing Interest:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contribution:

Shweta Katiyar carried out the literature search and prepared the draft manuscript. Akriti Saxena helped in preparing and editing the manuscript. Niti Singhal and Madhu Mati Goel conceived the study and edited the final manuscript. Gauranga Majumdar ; the Cardiothorcic Surgoen and

Subraharsh Singh ; the Surgical Oncologist were involved in patient's surgery , post surgery follow up and editing of the final manuscript.

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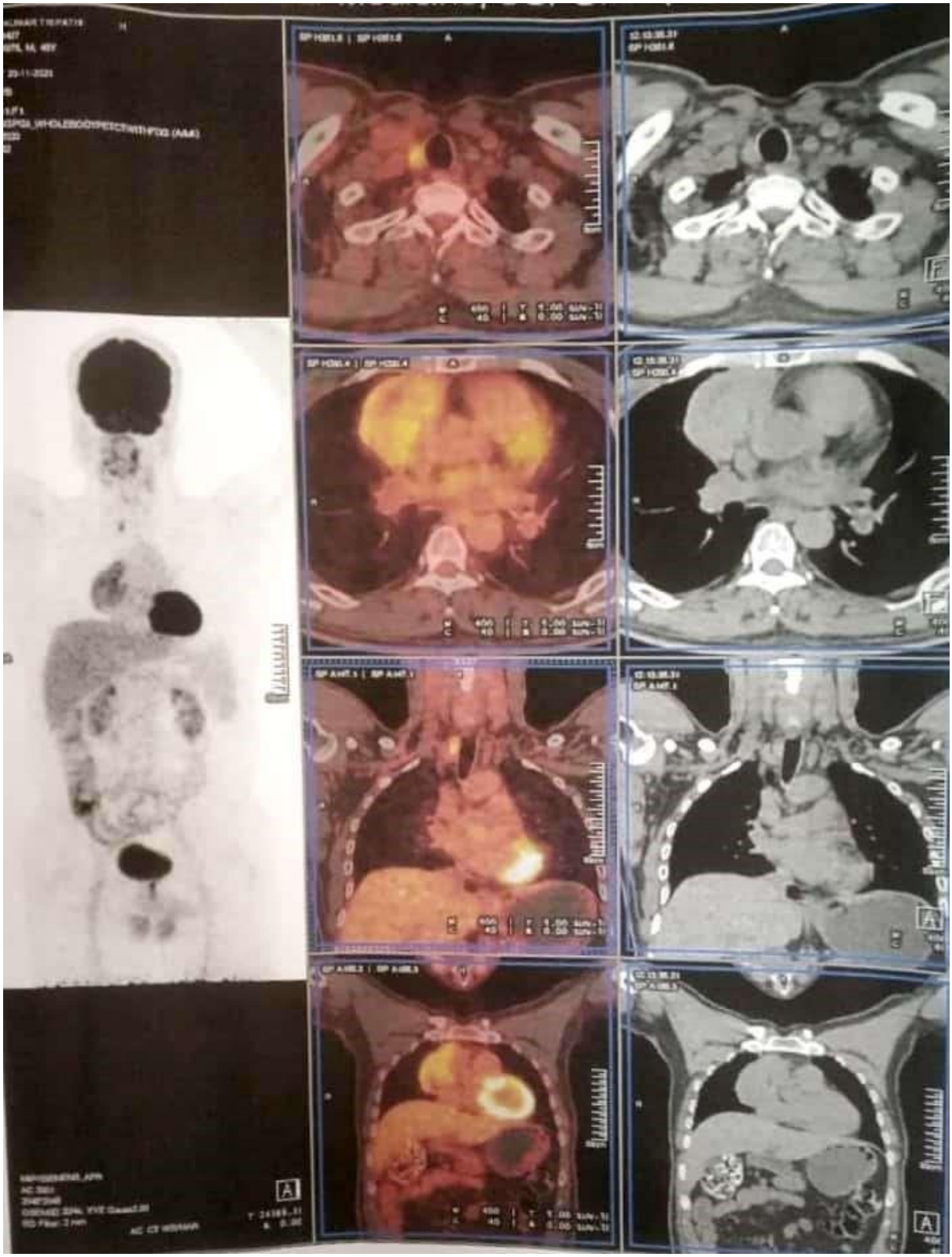

Figure 1- Whole body CT scan

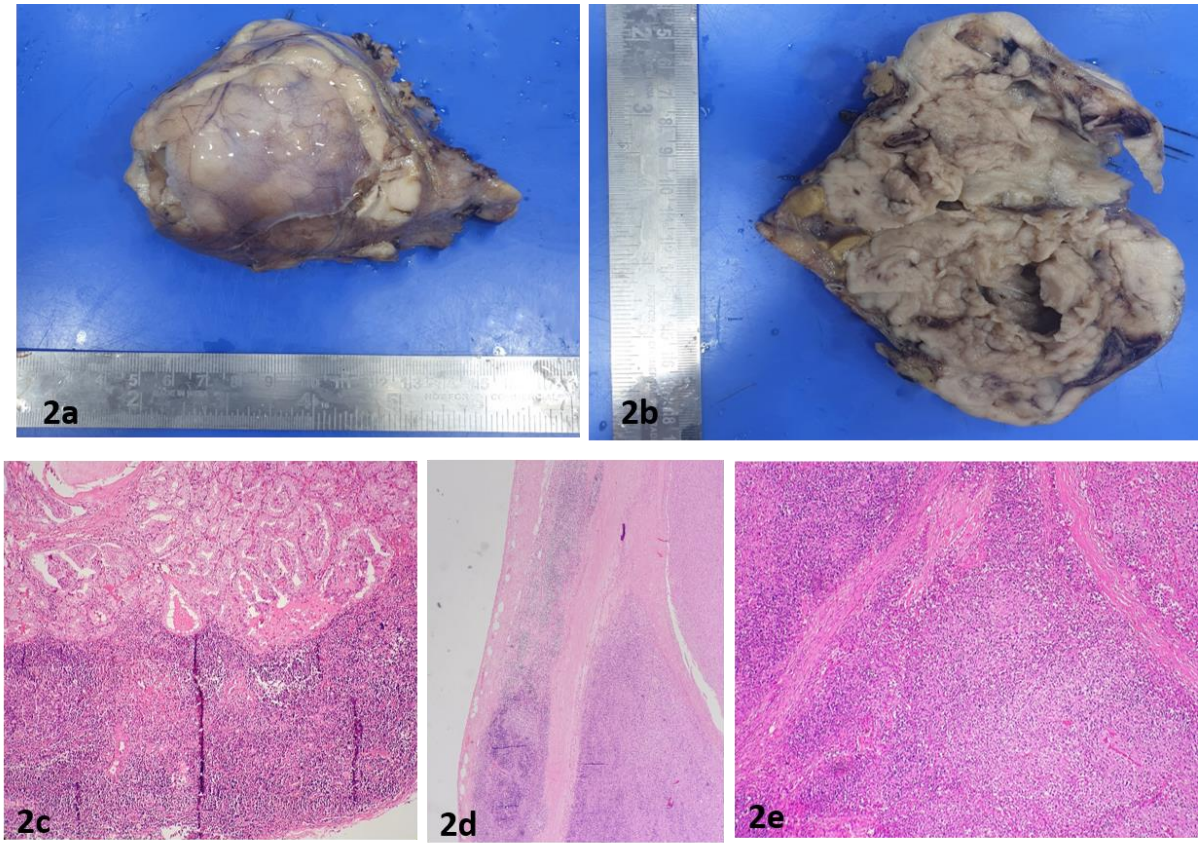

Figure 2-Gross and microscopy

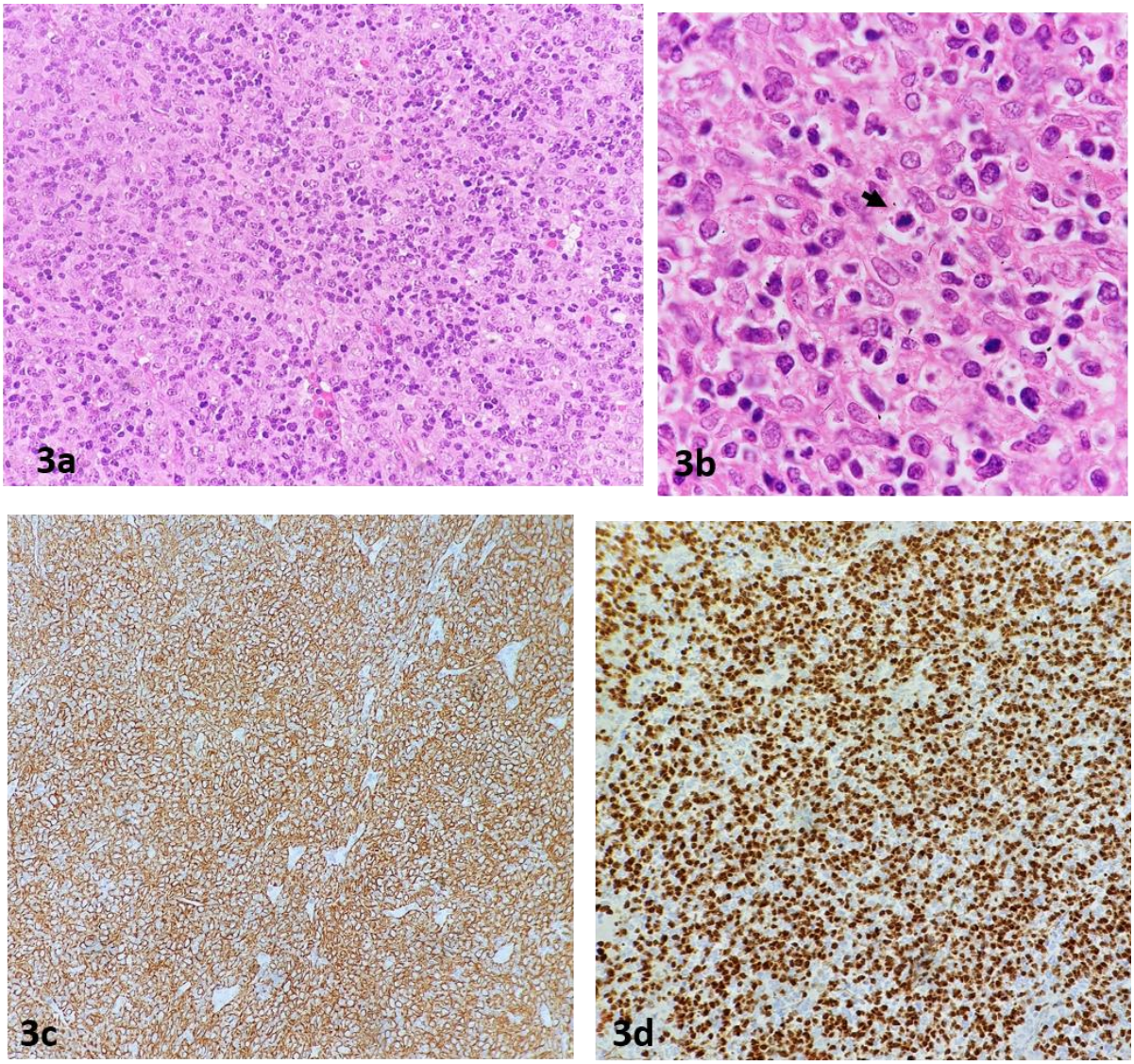

Figure 3-Immunohistochemistry markers

Table I: Cases of combined thymoma and thyroid cancer.

Year	Age/Sex	1st cancer	2nd cancer	3rd cancer	4th cancer	5th cancer	Time interval b/w thymoma and thyroid cancer

1962	NA/NA	Thymoma	Thyroid and rectal cancer	_	_	_	NA
1968	NA/NA 3 cases	Thymoma	Thyroid cancer	_	_	_	NA
1977	NA/male 2 cases	Papillary thyroid cancer	Thymoma	_	_	_	NA
1983	58/F	Endometrial adenocarcinoma	Thymoma (7 years after the 1st cancer treatment)	Papillary thyroid cancer	_	_	Synchronous thymoma and thyroid cancer
1990	NA/NA	Laryngeal cancer	Thyroid cancer (follicular)	Thymoma	_	_	Within 1 year (from 1st and 2nd cancer to thymoma)
1992	48/F	Thymoma	Papillary thyroid cancer and b/l jugular lymph node metastasis	_	_	_	10 days
1995	NA/NA	Thymoma	Thyroid cancer	_	_	_	NA/NA
1999	NA/NA (5 cases)	Thymoma	Thyroid cancer	_	_	_	NA/NA

2002	NA/NA (2 cases)	Thymoma	Thyroid cancer	Breast cancer	_	_	Synchronous
2003	85/F	Gliosarcoma of brain	Poorly differentiated adenocarcinoma cecum	Follicular variant of papillary thyroid carcinoma	Meningioma	Malignant (invasive) thymoma	NA
2004	NA/NA	Thymoma	Papillary thyroid carcinoma	Breast cancer	_	_	Tumor order unknown
2004	NA/NA	Thymoma	Papillary thyroid carcinoma	_	_	_	Tumor order unknown
2008	42/male	Malignant Thymoma	Papillary thyroid carcinoma	_	_	_	Within 12 months
2012	42/female	Papillary thyroid carcinoma	Thymic carcinoma	_	_	_	Synchronous
2012	59/female	Breast cancer	Thymoma (3 years after breast cancer)	Papillary thyroid carcinoma	_	_	Synchronous (thymoma and thyroid carcinoma)
2012	38/female	Follicular carcino	Thymoma	_	_	_	Synchronous

		ma - thyroid					
2013	NA/NA (3 cases)	Thymoma	Thyroid carcinoma	_	_	_	NA
2013	NA/NA	Thymoma	Thyroid carcinoma	_	_	_	Synchronous
2013	NA/NA (2 cases)	Thyroid carcinoma	Thymoma	_	_	_	NA
2014	NA/NA (5 cases)	Thyroid cancer (2 cases), H&N cancer (3 cases)	Thymoma	_	_	_	NA
2016	63/female	Papillary thyroid carcinoma	Thymoma	Undifferentiated Thymic carcinoma	_	_	Synchronous in same mass (left anterior mediastinum)
2018	NA/NA	Thyroid cancer	Thymoma	_	_	_	NA
2018	NA/NA	Thyroid cancer	Thymic carcinoma	_	_	_	NA
2018	49/female	Thymoma	Thyroid cancer	_	_	_	43 months

2021 (present case)	46/male	Papillary Thyroid cancer	Thymoma	-	-	-	2.5 years

NA: Not Available