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Original Research Paper

Histopathology

PAPILLARY THYROID CARCINOMA WITH NODULAR FASCITIS -LIKE STROMA: A CASE REPORT WITH REVIEW OF LITERATURE

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ABSTRACT Papillary thyroid carcinoma (PTC) is a common malignant tumor and has multiple variants, some of which occur very rarely. Papillary thyroid carcinoma with nodular fasciitis-like stroma (PTC-NFS) is one such rare variant composed of foci of malignant epithelial components showing the features of Papillary thyroid carcinoma and abundant stromal components. We report a case of PTC-NFS, a malignant tumor characterized by an abundant stroma with an intervening epithelial component with the morphologic features of PTC (conventional type). We have reviewed the literature on this rare entity, discussed the need for a thorough examination of epithelial components in a case of fibroproliferative lesion of the thyroid, and addressed the diagnostic difficulties due to the tumor's excessive stromal component.

KEYWORDS : PTC, Nodular fasciitis-like stroma, IHC

INTRODUCTION

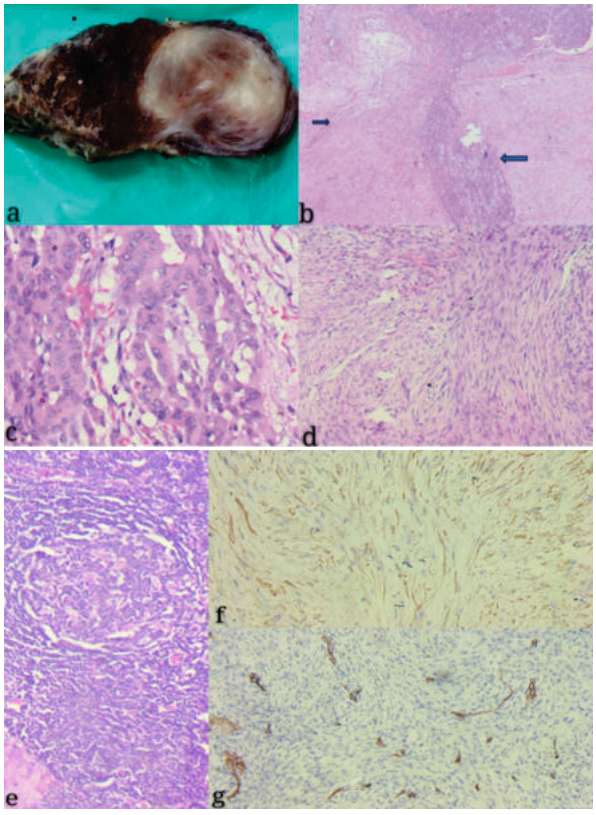
Papillary thyroid carcinoma (PTC) is the most commonly encountered malignant tumor of the thyroid. Among various variants of PTC, Papillary thyroid carcinoma with nodular fasciitis-like stroma(PTC-NFS) is a rare variant composed of foci of malignant epithelial components showing the features of PTC and abundant stromal components. PTC-NFS was first discovered by Chan et al. in the year 1991. [1] PTC-NFS can be challenging to diagnose on both fine-needle aspiration (FNA) and histopathologic examination due to its unusual morphology. To date, 71 cases of PTC-DTF have been reported. We report a case of PTC-NFS with lymph node metastasis and extrathyroid extension.

Case Report

A 65-year-old woman presented with midline neck swelling for 6 months. The patient was hypothyroid and was put on a tablet thyronorm 100 mcg. Physical examination revealed non-tender, nodular, solitary firm to hard swelling of size 5x5 cm gradually increased and moved with deglutition with no dysphagia hoarseness, or dyspnea. USG thyroid showed a well-defined heterogeneously hypoechoic solid lesion with increased internal vascularity and suggestive of neoplastic etiology-TIRADS-IV. FNAC attempted thrice yielded only blood and was inadequate for opinion. Other routine laboratory investigations were within the normal unit. A total thyroidectomy was performed and sent for histopathological examination.

The thyroid gland measured 5x4x2 cm. On gross examination, a well-circumscribed nodule measuring 2.8x2.5 cm was noted in the right lobe. The cut surface of the nodule was firm, grey-white, well-circumscribed, and with a fibrous appearance. **(Fig. a)**

Microscopically, the tumor was composed of a predominant stromal component and foci of the epithelial component**. (Fig. b)** The stroma consists of myofibroblastic cells arranged in a storiform pattern with a few scattered lymphocytes in between. **(Fig. d)** An epithelial component consists of patchy nodular foci of papillary thyroid carcinoma; cells are arranged in a follicular and papillary pattern with large oval nuclei, foci of nuclear clearing, and few intranuclear grooves. **(Fig. c)** On IHC stromal cells show positivity for Smooth muscle actin(SMA) and epithelial cells for TTF-1. **(Fig. f&g)** Based on the morphologic features, a diagnosis of PTC-NFS was given. One out of two lymph nodes showed metastatic carcinoma. **(Fig. e)** An extrathyroid extension was noted. The patient has received post-operative radioactive iodine therapy and is free of disease at 6 months of follow-up.



a. Gross Findings: well-circumscribed Nodule of size 2.8x2.5 cm, Grey-white, solid, involving Isthmus and part of the Right lobe of the thyroid. b. The tumor consists of two distinct components: The abundant stromal component and foci of

epithelial component(PTC) (arrows). (H&E stain x100). C. . Foci of papillary thyroid carcinoma; cells are arranged in a follicular and papillary pattern with large oval nuclei, foci of nuclear clearing, and few intranuclear grooves. (H&E stain,x 400). d. Stroma consists of myofibroblastic cells arranged in a storiform pattern with a few scattered lymphocytes in between. (H&E stain, x200). e. Lymph node with metastatic carcinoma. (H&E stain,x 400). f & g. IHC-stromal cells show positivity for Smooth muscle actin (SMA) and epithelial cells for TTF-1.

DISCUSSION

Papillary thyroid carcinoma with nodular fasciitis-like stroma is a rare variant and was first described by Chan et al in the year 1991. [1] Mizukami et al later described it as Papillary thyroid carcinoma with fibro myxoid stroma.[2] The pathogenesis of this phenomenon is not yet fully understood. The WHO classification used PTC with nodular fasciitis-like stroma or fibromatosis-like stroma as synonyms.[3]

In terms of clinical manifestations, PTC-NFS shows similar features to classic PTC, but it has a higher risk of local infiltration and lymph node metastasis.[4-5] In the literature total of 71 cases of PTC-NFS have been published. Most of the Patients presented with a right neck mass with a duration ranging from 1 to 18 months. The age at presentation ranges from 20 to 82 years, with a mean age of 44.5 years. (In our case it was 65 years) ; a female preponderance has been observed, Most commonly seen in females with the M: F ratio of 3:1. [6] TFT results were not available for all patients; however, out of 24 cases, 23 cases showed normal values, and one case with elevated thyroglobulin levels and none were hypothyroid, however in our case patient was hypothyroid. Most case reports show Normal Thyroid function tests. Around 50 patients underwent radiology investigations out of which 36 showed well-defined hypoechoic nodules. (Table 1) Na and Kumiko et al. described ultrasound findings of PTC-NFS, where the thyroid nodule frequently revealed a decreased echogenicity and increased vascularity, consistent with our case.[7]

Pre-surgical fine-needle aspirations were performed on 33 cases, 24 of which were diagnostic of PTC, 2 of which were reported as atypical cells, 3 were benign neoplasm and malignant neoplasm with myxoid stroma, FVPTC, atypical cells, and AUS/ Follicular lesions of undetermined significance one case each. The extensive proliferation of fibroblasts can obscure the neoplastic cells of PTC, causing difficulties in cytologic diagnosis and may lead to an incorrect diagnosis if true neoplastic cells are scanty and overlooked in the sample. [1] This extensive stromal proliferation explains the inadequacy or diagnostic difficulties encountered on FNAC, despite multiple attempts in the present case.

Subtotal thyroidectomy or total thyroidectomy is the treatment of choice for PTC-NFS. One should ensure negative margins, as the stroma of PTC-NFS shares characteristics of fibromatosis, including susceptibility to recurrence and local infiltrative growth. Surgical findings showed that the nodules are often indistinct from the normal thyroid and can range in size from 0.5 to 10 cm. [8]

In the present case, the tumor consisted of prominent spindle cell proliferation and few foci of conventional PTC. The stromal component markedly resembled nodular fasciitis, and it occupied more than 70% of the tumor. There were no mitoses or atypia in stromal spindle cells. The stromal component accounts for more than 65% of the tumor volume and exceeds 80% in most reviewed cases. [9-10] Immunohistochemistry has shown that spindle cells in PTC-NFS showed the characteristics of myofibroblasts with immunopositivity for SMA; consistent with the present case.

The proliferation of myofibroblasts is observed in the inflammatory process and the stroma of invasive, malignant neoplasia as a host reaction. In the present case, and other reported cases, these stromal cells proliferate significantly to form a nodule, which is apparently beyond the limit of usual stromal reactions. It is necessary to differentiate between the benign component of stromal cell proliferation and stromal sarcoma, carcinosarcoma, and anaplastic carcinoma because the present tumor shows a good prognosis, while anaplastic carcinoma is a fatal disease. [11]

Roth et al. reported a case of PTC with extrathyroid extension of desmoid-type fibromatosis.[12] In the published literature, till now 71 cases of PTC-NFS have been reported. (Table 1) Lymph node metastasis was mentioned for 36 cases; out of which 21 cases showed LN metastasis. The extrathyroid extension was mentioned for 35 cases, out of which 25 cases showed ETE. (Table 1) Huang et al reported five cases of PTC primarily composed of small neoplastic epithelial components distributed in vast mesenchyme with infiltrative borders that invaded the peri thyroidal/extranodal soft tissue. Due to its rare incidence and short follow-up of PTC-NFS, there is currently insufficient data on distant metastasis. [8] H Haung, Wong, and Tarabichi et al. reported that BRAF mutations may drive interstitial proliferation in PTC.

The coexistence of mutations in the mesenchymal CTNNB1 gene and the epithelial NRAS gene may lead to highly aggressive behavior and distant metastasis. [8,13-14]

An immunohistochemically SMA showed positivity in 27 cases, Beta-catenin in 8 cases and CK in 10 cases. In molecular study *CTNNB1* mutations have been identified in 11 cases, BRAF in 7 cases, and TTF1 in cases of PTC with DTF/NFS. (Table 1) Post-operative radioactive iodine therapy is essential adjuvant therapy for reducing the recurrence, especially in differentiated thyroid cancer (DTC) and PTC with CTNNB1, BRAF V600E, or NRAS mutations.[15]

In conclusion, the present case highlights cytological and histopathological diagnostic challenges and aggressive behavior of this rare variant of PTC.

Table 1. Clinical information, pathological features and IHC findings of 71 patients with PTC-NFS.

Sr No.	Literature	Age/ Gender	size	TFT	Radiology	FNAC	LN +	ETE	IHC	Molecular study	Follow-up
									Epithelial Stromal		
1	Chan et al.,1991	20/F	2 cm	NM	NM	PTC	NM	NM	TG; CK Vimentin, SMA	NM	Well at 12 months
		35/F	4 cm	NM	NM	PTC					
		20/F	3 cm	NM	Cold nodule	NM	NM	NM			
2	Mizukami et aL.1992	67/F	2 cm	NM	Cold nodule	NM	No	No	TG ;CK Vimentin	NM	well at 20 months
3	Mizukami et aL.1995	43/F	3 cm	NM	NM	NM	yes	yes			well at 12 months

4	M Parkhi et al.2021	20/F	3.6 cm	NM	Well-defined heterogeneous nodule	NM	NM		BRAF +;beta-catenin-	TTF1,TG;BRAF, SMA	NM
5	Nandeesh et al. 2011	46/F	3 cm	Normal	NM	Paucicellular; Few benign Follicular cells	NM	No	NM	NM	NM
6	Na et al. 2013	49/F	2.3 cm	Normal	Well-defined nodule with increased vascularity	PTC with spindle cells	yes	No	TGF-beta ,beta-catenin,desmin,SMA	NM	
7	H Huang et al.2023	33/M	6 cm	Normal	Solid nodule	NM	No	yes	TTF1,TG, vimentin SMA	TTF1,TG;BRAF, SMA	NM
		53/M	1 cm	NM	Hypoechoic nodule with vascularity	PTC	yes	yes	TTF1,TG,beta catenin vimentin	NRAS;CTNNB1 mutation	NM
		66/F	4 cm	NM	Hypoechoic nodule	NM	No	yes	TTF1,TG,beta catenin vimentin	BRAF;CTNNB1 mutation	NM
		51/F	4 cm	NM	Hypoechoic nodule	Atypical cells	No	yes	TTF1,TG,beta catenin vimentin	BRAF	NM
		56/F	0.5 cm	NM	NM	NM	No	yes	CK; Vimentin;SMA	NM	NM
8	Inaba et al. 2002	65/F	3.5 cm	Normal	Well-defined solid nodule	PTC	No	No	TG;CK SMA		well at 24 months
		26/F	3.2 cm	Tg elevated	Well-defined solid nodule	PTC	NM	No			well at 6 months
9	US-Krasovec et al 1999	52/F	1.9 cm	Normal	NM	PTC probably sclerotic variant	No	No	Vimentin, SMA		NM
10	Naganuma et al.2002	52/M	6 cm	Normal	NM	NM			TGF-beta negative		NM
11	Roth et al. 2019	20/M	3.2 cm	NM	Hypoechoic nodule with vascularity	Atypical spindle cell neoplasm	No	yes	,beta-catenin,desmin,SMA	BRAF V600E Negative	NM
12	Wong et al.2019	58/M	5 cm	NM	Hypoechoic nodule with vascularity	Suspicious for PTC	yes	yes	beta-catenin, SOX11	CTNNB1 mutation	well at 8 months
13	Zhou et al 2018	48/F	1.2 cm	NM	Irregular Hypoechoic nodule	NM		yes			
14	Terayama et al. 1997	57/F	4 cm	Normal	Well demarcated nodule	PTC			NM Vimentin,SMA		well at 22 months
15	Acosta et al. 1998	41/F	3 cm	Normal	Hypoechoic nodule	PTC	No	yes	NM Vimentin	NM	NM
16	Sarma et al.1998	50/F			NM						NM
17	Toti et al.1999	73/M	4 cm	Normal	NM	PTC	yes	yes	TGF-beta Vimentin,SMA		NM
		24/F	2 cm	Normal	Well demarcated nodule	PTC	yes	yes			NM
18	Yang et al. 1999	82/M	7 cm	NM	Equivocal	Malignant neoplasm f/s/o myxoid stroma			TG;CK Vimentin,SMA		NM
		40/M	5 cm	Normal	NM	positive for cancer cells					NM
19	Andres et al. 2005	35/F	0.8 cm	Normal	Well demarcated nodule	PTC with spindle cells	yes	yes	TG; CK Vimentin, SMA	NM	NM
20	Lee et al. 2006	40/F	2.5 cm	Normal	Well demarcated nodule	PTC			TG; CK Vimentin, SMA	NM	well at 7 months
21	Basu et al. 2006	35/F		NM							NM

22	Leal et al. 2006	34/F	10 cm	NM	NM	PTC			TTF-1;PR SMA		well at 12 months
23	Lee et al. 2008	45/F	1 cm	NM	Hypoechoic nodule with calcification	Suspicious for PTC	yes	NM	NM		NM
24	Lee et al.2010	35/F	6.5 cm	Normal	Hypoechoic nodule	PTC	No	No	NM	NM	NM
25	Khalil et al. 2010	29/F	NM	NM	NM	NM			NM	NM	Recurrence in subsea pregnancy
28	Wu et al. 2013	42/F	3 cm	Normal	NM	NM			Vimentin, SMA		Well at 5 year
29	Ginter et al. 2013	44/F	3.5 cm	Normal	Hypoechoic complex nodule	PTC	yes	No	TTF1;CK;EMAT GF-beta ,beta-catenin,desmin ,	NM	NM
30	Mardi et al. 2017	38/F	3 cm	Normal	Heterogenous echotexture	Possibility of FVPTC	NM	NM	TG Vimentin, SMA	NM	NM
31	Rebecchini et al.2017	34/M	2 cm	Normal	Partly cystic nodule - microcalcification	AUS/ Follicular lesion of undetermined significance			CK; beta-catenin;Vimentin;SMA	NM	NM
		48/M	2.8 cm	Normal	ill-defined nodule - microcalcification	Suspicious for PTC			CK; beta-catenin;Vimentin;SMA	NM	NM
32 Takada et al. 2017			mean age= 49.3	1.6 cm-	Normal	High suspicion= 11	Suspicious for Malignancy=12	yes(12 cases)	beta-catenin	NM	NM
			F=9; M=5	7.9 cm							
	(14 cases)					Intermediate suspicion=3			Benign=1		
33	Takada et al. 2018	mean age=44.8	3.6 cm	Normal	NM	NM	yes	NO		BRAF;CTNNB1 mutation	NM
		F=5;M=3									
	(8 cases)										
34	Suster et al.2020	20/M	4.2 cm	NM	NM	PTC	NM		beta-catenin, SMA	CTNNB1 mutation	NM
	(7 cases)	34/M	2 cm	NM		PTC	NM		beta-catenin, SMA	CTNNB1 mutation	NM
		53/M	3.6 cm	NM		NM	NM		beta-catenin, SMA	CTNNB1 mutation	NM
		48/M	2.8 cm	NM		PTC	NM		beta-catenin, SMA	CTNNB1 mutation	NM
		65/M	NM	NM		NM	NM		beta-catenin, SMA	BRAF	NM
		58/M	NM	NM		NM	NM		NM	CTNNB1 mutation	NM
		30/F	NM	NM		NM	NM		beta-catenin, SMA	CTNNB1 mutation	NM
35	M Parkhi et al.2021	20/F	3.6 cm	NM	Well-defined heterogeneous nodule	NM	NM		BRAF +;beta-catenin-ve	TTF1,TG; BRAF, SMA	NM
36	Christofer et al. 2022 39	39/F	4 cm	Normal	NM	PTC-bethesda category-six	NM	NO	TTF1,TG;BRAF, SMA	NM	NM
37	A Toniato et al. 2023	41/F	4 cm	Normal	Hypoechoic nodule	Compatible with TIR 3B nodule				NM	NM
38	Michal et al.,1992	49/F	5 cm	NM	NM	NM	yes	yes	TG;CK Desmin;,SMA	NM	well at 12 months
		33/F	3 cm	NM	NM	NM			TG;CK Desmin;,SMA	NM	well at 24 months

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