PATHOLOGICA 2017;109:162-167

Case report

Tall cell variant of papillary breast carcinoma: an additional case with review of the literature

A. PITINO[1], S. SQUILLACI[2], C. SPAIRANI[1], P.C. RASSU[3], M.F. COSIMI[1]
[1] Division of Anatomic Pathology, Hospital "San Giacomo", Novi Ligure (AL), Italy; [2] Division of Anatomic Pathology, Hospital of Vallecamonica, Esine (BS), Italy; [3] Division of Surgery, Hospital "San Giacomo", Novi Ligure (AL), Italy

Key words

Breast tumor • Tall cell variant • Papillary breast carcinoma • Papillary thyroid carcinoma

Summary

Papillary lesions of the breast can be one of the most challenging aspects of mammary pathology because of a wide morphologic spectrum that may be encountered in these lesions. An unusual breast tumor has been first classified as "breast tumor resembling the tall cell variant of papillary thyroid carcinoma" and subsequently renamed "tall cell variant of papillary breast carcinoma". To our knowledge, only 13 cases of this neoplasm have been reported so far. Metastasis to the breast is not an uncommon event and about 5% of all such cases are of the thyroid origin. We report the clinico-pathological and immunohistochemical features, together with a molecular screening for BRAF mutations, of an additional case of tall cell variant of papillary breast carcinoma occurring in a 65-year-old woman. The immunohistochemical and molecular clues leading to the correct diagnosis have been correlated with the data of the literature. Tall cell variant of papillary breast carcinoma represents a unique histologic subtype of mammary carcinoma of probably low malignant potential which has to be recognized to avoid misdiagnosis as metastatic carcinoma from the thyroid.

Introduction

Malignant papillary lesions of the breast are a nonexceptional finding in the practice of surgical pathology, with most of them being papillary ductal carcinomas in situ, intracystic (encapsulated) papillary carcinomas, or solid papillary carcinomas, all of which may or may not be associated with unequivocal invasive tumors. The characteristic feature of all these lesions is the presence of an expansile epithelial proliferation composed of fibrovascular cores covered by rows of epithelial cells with no or minimal myoepithelial cell partecipation. Although phenotypic variations mirroring the differences in the growth pattern of tumor cells have been described, including a solid, cribriform or micropapillary arrangement, the epithelial component more frequently features one or more layers of columnar elements with a variable degree of nuclear stratification [1]. This latter morphological appearance is not unique to these neoplasms but is also shared with papillary carcinomas arising in other sites, including papillary thyroid carcinoma, which characteristically displays nuclear clearing and stratification. Tall cell variant of papillary breast carcinoma is an unusual histologic type of breast carcinoma which morphologically closely mimics the tall cell variant of papillary thyroid carcinoma. Following the original description in 2003 by Eusebi et al. [2] as a series of 5 cases of "breast tumor resembling the tall cell variant of papillary thyroid carcinoma", only further 8 cases have been described so far [2-7]. Here we report the fourteenth of these peculiar tumors of the breast, focusing on its histologic and immunohistochemical profile, together with a molecular screening for BRAF mutations, which have been identified in a high proportion of papillary thyroid carcinomas [8].

Case report

A nodule in the right breast was discovered during a screening program at the Hospital "San Giacomo", Novi Ligure, Italy in a 65-year-old woman with a past medical history significant of: (a) hypertension; (b) diabetes; (c) hypercholesterolemia; (d) hormone treatment (oestrogen/progestagen) for 6 years ; (e) abdominal hysterectomy (uterine prolapse). In April 2013, mammography

Acknowledgements

The authors would like to thank Prof. Juan Rosai for his consultative opinion on this case. This work was presented in abstract form (poster presentation) at the Annual Italian SIAPEC-IAP Congress of Anatomic Pathology, Firenze, Italy, 22-25 October 2014.

Correspondence

Salvatore Squillaci, Division of Anatomic Pathology, Hospital of Vallecamonica, via Manzoni 142, 25040 Esine, Italy - Tel: +39 0364 369256 - Fax. +39 0364 369257 - E-mail address: salvatore.squillaci@outlook.it

Fig. 1. (A) Preoperative ultrasound image shows a hypoechoic mass in the upper inner quadrant of the right breast. (B) Periphery of the tumor with expansive growth pattern; the neoplastic cells were arranged in cribriform structures.

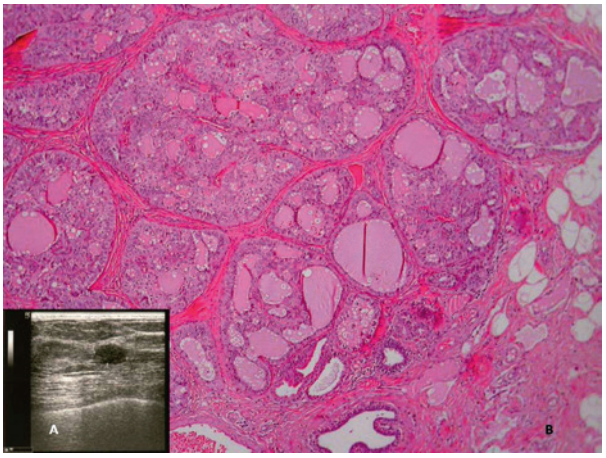


Fig. 2. (A) Focally packed follicles and papillae are often observed. (B) Follicles and papillae are constituted of columnar to cuboidal cells with papillary thyroid carcinoma-like nuclei.

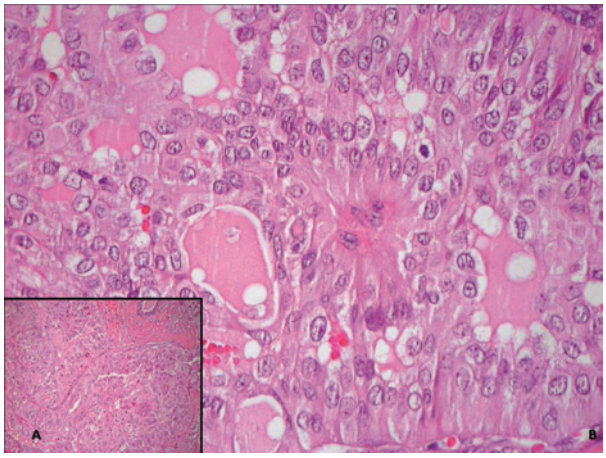


Fig. 3. (A) Negative TTF-1 immunostaining of the tumor cells; (B) The neoplastic elements do not stain for thyroglobulin, whereas aspecific staining of intraluminal amorphous material may be noted; (C) GCDFP-15 is expressed by tumor cells; (D) The cytoplasm of the neoplastic cells is filled with mitochondria highlighted by the corresponding antibody.

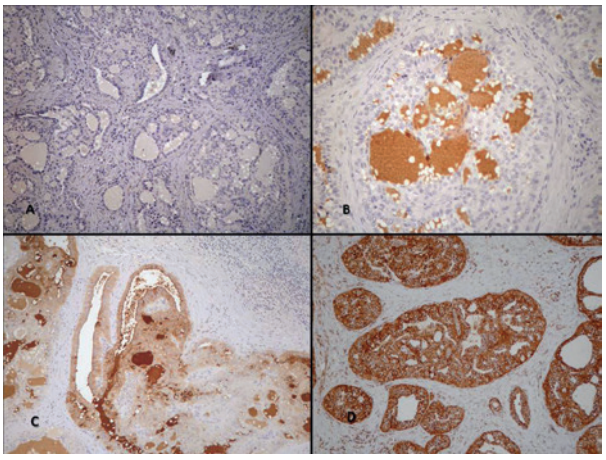
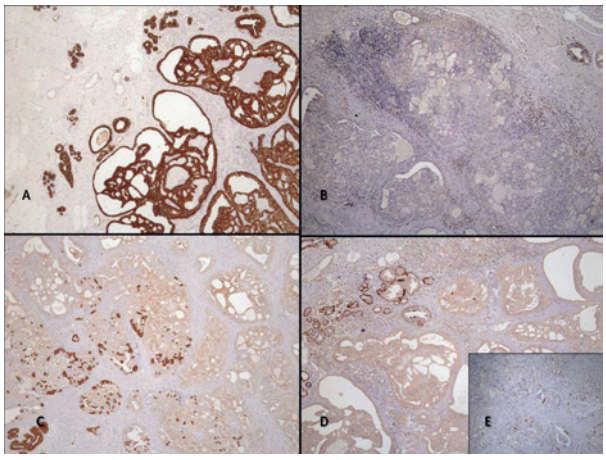


Fig. 4. (A) Diffuse and intense staining of cytokeratin 7; (B) No evidence of myoepithelial cells within the neoplastic growth is observed in p63 immunostaining; (C) Focal cytokeratin 19 expression of the tumor cells; (D) The neoplastic cribriform and packed follicular structures do not stain for cytokeratin 14: (E) Only focal nuclear expression of estrogen receptor in the tumor cells.



demonstrated the presence at the upper inner quadrant of the right breast of a 0, 8 cm well-circumscribed mass. A subsequent ultrasound exam showed a hypoechoic structure of this lesion (Fig. 1A). The patient underwent core needle biopsy and the diagnosis of malignancy was established leading to quadrantectomy and excision of two sentinel lymph nodes. There was no evidence of a mass in the thyroid gland and enlargement of regional lymph nodes on ultrasonography and computed tomography (CT) of her neck, and thyroid function tests were normal. Postoperative follow-up, including CT scan, at 34 months revealed no sign of recurrence or metastatic disease.

The right quadrantectomy specimen disclosed an irregular mass, 0.7X0.6X0.5 in size, with a gray-whitish, solid cut surface. Microscopic examination revealed, at low-power magnification, a relatively well-demarcated lesion from the surrounding mammary parenchima (Fig. 1B). The majority of the tumor consisted of aggregates of neoplastic cells showing a cribriform to papillary architecture. Closely packed follicles, papillae, and trabeculae were focally admixed (Fig. 2A). Characteristically, the luminal spaces of these structures surrounded by a dense fibrous stroma were filled with eosinophilic amorphous colloid-like material showing scalloped borders. The neoplastic nests were made up of columnar to cuboidal cells with moderate amounts of eosinophilic cytoplasm and round to oval nuclei with clear chromatin, grooves and occasional eosinophilic nuclear pseudoinclusions (Fig. 2B). Patchy lymphoid aggregates, focal

hemorrhagic zones, and pools of foamy histiocytes were present too. Significant mitotic activity was absent. No psammoma bodies or granular calcifications were observed. No metastasis was identified in sentinel lymph nodes. Immunohistochemically, the neoplastic cells were diffusely positive for cytokeratin 7, HBME-1 (cytoplasmic and luminal membrane staining), and mitochondria; focal staining for GCDFP-15 and cytokeratin 19 was also detected (Fig. 3C, 3D; Fig. 4A, 4C). Estrogen receptor (ER) was weakly positive and expressed in < 10% of the neoplastic cells (Fig. 4E). Tumor cells did not show any immunostaining for TTF-1, PAX-8, progesterone receptor, thyroglobulin and HER2/neu (Fig. 3A, 3B). No abnormal expression of β-catenin was noted. All the neoplastic cribriform structures were negative for cytokeratin 14 and p63, demonstrating the malignant and invasive nature of this tumor (Fig. 4B, 4D). The MIB-1 index was 3%. Mutation status in the BRAF gene was tested using polymerase chain reaction and reverse dot blot for V600A, V600D, V600E, V600G, V600K, V600M, V600R, K601E [8]. No mutation was detected in the neoplastic cells. Based on the light microscopic morphology, immunohistochemical profile and molecular features, the neoplasm was classified as tall cell variant of papillary breast carcinoma (TCVPC).

Discussion

Breast tumor resembling the tall cell variant of papillary thyroid carcinoma is an unusual histological variant of mammary carcinoma not included in the current WHO classification of breast tumors and is a matter of debate within the pathologists' community. The striking cytoarchitectural findings featured by the present case and those previously reported (Tab. I) prompt differential diagnosis with a breast metastasis from a papillary thyroid carcinoma [2-7]. Metastasis of thyroid carcinoma to the breast is not an uncommon event and has been documented in about 5% of all mammary metastatic malignancies (usually associated to widespread neoplastic diffusion) [9]. Nevertheless, nonimmunoreactivity to TTF-1, thyroglobulin and HBME-1 (membranous/basolateral staining) would strongly argue against breast metastasis from papillary thyroid carcinoma [10 11]. Besides, extensive clinico-pathologic investigation in the 14 patients of the present review, including ours, failed to reveal any suspicious abnormality in the thyroid [2-7]. In addition, further molecular studies, with results analogous to those of our case, have suggested that the mechanism leading to distinct nuclear pictures in these breast carcinomas may be different from the molecular pathway leading to analogous features in papillary thyroid carcinoma since RET/PTC rearrangements and BRAF mutations were absent in these primitive mammary tumors [1 3 12]. Furthermore, the presence of cytoarchitectural features distinctive of papillary thyroid carcinoma is not restricted to this entity, as papillary carcinomas of the breast also display such features to a variable extent [1]. For all these reasons, it has been recently proposed that cases reported previously as "breast tumor resembling the tall cell variant of papillary thyroid carcinoma" most likely represent "tall cell variant of papillary breast carcinoma" (TCVPBC) to remove confusion about a possible association with papillary thyroid carcinoma and simplify the technical terms used to name this rare entity [6].

From the published data, including those of our patient, TCVPBCs are neoplasms that are diagnosed in woman aged from 45 to 80 years (mean = 62 years) with a median of 61 years. Follow-up information was available in 12 patients with TCVPBC for a mean period of 28.1 months (range = 3 months to 9 years) [2-5 7]. Reported follow-up revealed that the majority of patients pursued an indolent clinical course [2 4 5]. Two patients had metastatic disease: one patient was found to have lymph node and osseous metastasis and the other had metastasis to an intramammary lymph node [3 7]. Both of these cases were stage pT2 neoplasms. The majority of tumors were invasive (50%) as was the case mentioned above. Macroscopic examination of the resected specimen generally showed a solid whitish to tan mass, with well-demarcated margins, a common macroscopic appearance of breast carcinoma [6 7]. However, in a case the macroscopic appearance of the brownish translucent multinodular tissue bore resemblance with thyroid hyperplastic parenchima [5]. This macroscopic appearance, as well as the microscopic features with cystically dilated ducts containing eosinophilic secretion, closely resembled to what Guerry et al. [13] described in cystic hypersecretory hyperplasia of the breast. In all patients tumor dimensions were documented, the median size was 2.6 cm (range = 0.7-8.5 cm) [2-7]. Microscopically, our case was similar to the previously reported cases; a tumor with a striking follicular, papillary and cystic architecture with areas of complex cribriform growth composed of columnar to cuboidal cells with nuclear clearing, grooves and pseudoinclusions. Aggregates of microcalcifications reminescent of psammoma bodies were sometimes observed [2 4 6 7]. The presence of peculiar nuclear clearings and a cribriform pattern have also been reported in the cribriform-morular variant of papillary thyroid carcinoma [3]. Some data suggest that somatic mutation in exon 3 of the β-catenin gene resulting in nuclear translocation of β-catenin contributes to the development of the cribriform-morular variant of papillary thyroid carcinoma and intranuclear inclusions were found to be β-catenin positive in papillary thyroid carcinoma [3]. Nevertheless, in two cases of the present review, including ours, abnormal nuclear localization of this marker was not found [3].

Most of the reported cases of TCVPBC, including the current case, were immunohistochemically studied, and the neoplastic cells were consistently negative for TTF-1 and thyroglobulin, two markers that together characterize almost 100% of papillary thyroid carcinomas. On the contrary, a variable expression was reported of gross cystic disease fluid protein-15 (GCDFP-15), estrogen,

Tab. I. Clinicopathologic characteristics, immunohistochemical profile and molecular findings of the present case and the previously reported ones.

No.of case	Authors (Ref)	Age (years)/Gender	Tumor size (cm)	Location	In situ/invasive	Treatment	Follow-up	Negative immunohistochemical features	Positive immunohistochemical features	Molecular analysis
1	Cameselle-Teijeiro et al. [3]	64/F	4.1	Right breast/ lower quadrants	Invasive	Mastectomy with axillary lymphadenectomy, chemotherapy, irradiation and tamoxifen	Alive with bone and lymph node metastases, 32 months	TTF-1, Thyroglobulin, TPO, Galectin-3, β-catenin, calcitonin, chromogranin, synaptophysin, vimentin, S100 protein, p53, HER2/neu	GCDFP-15 (focal), EMA (focal), CK7, CK19, CK34βE12 (rare cells), α-estrogen R, β-estrogen R, Progesterone R, Androgen R, CEA, bcl-2, MIB1 index (31%)	BRAF -
2	Chang et al. [4]	66/F	1.1	Left breast/ upper inner quadrant	Invasive	Segmental mastectomies and sentinel lymph node excision	ANED at 12 months	TTF-1, progesterone receptors, HER-2, p63, calponin, Androgen R, CK20	Estrogen receptor (< 10% of tumor cells), CK7, CK19, GCDFP-15	ND
3	Colella et al. 5	79/F	8.5	Right breast/ retroareolar mass	Microinvasive	Retroareolar quadrantectomy, mastectomy with axillary lymphadenectomy	ANED at 18 months	TTF-1, thyroglobulin, estrogen receptor, progesterone receptor, HER-2	GCDFP-15, collagen IV (focal), p63 (focal), caldesmon	ND
4	Eusebi et al. [2]	58/F	1.2	Left breast/ lower inner quadrant	Microinvasive	Wide excision	ANED at 26 months	TTF-1, thyroglobulin, CK19, estrogen and progesterone receptors.	Mitochondria, GCDFP-15 (focal), CK7, EMA (focal), androgen R (rare cells), SMA, laminin, collagen IV	RET/ PTC -
5	Eusebi et al. [2]	70/F	1.3	Right breast/ upper outer quadrant	In situ and synchronous invasive ductal carcinoma of the contralateral breast	Right quadrantectomy and left mastectomy	ANED at 54 months	GCDFP-15, TTF-1, thyroglobulin, CK19, estrogen and progesterone receptors, androgen R	Mitochondria, EMA (focal), CK7, SMA, laminin and collagen IV	RET/ PTC -
6	Eusebi et al. [2]	57/F	1.6	Left breast/ upper outer quadrant	Invasive	Wide excision	ANED at 28 months	GCDFP-15, TTF-1, thyroglobulin, estrogen and progesterone receptors, androgen R, SMA, laminin, collagen IV	Mitochondria, CK7, CK19 (rare cells), EMA (focal)	RET/ PTC -
7	Eusebi et al. [2]	74/F	2	Right breast	Invasive	Wide excision	ANED at 9 years	GCDFP-15, TTF-1, thyroglobulin, CK19, estrogen and progesterone receptors, androgen R, SMA, laminin, collagen IV	Mitochondria, CK7, EMA(focal)	ND

Tab. I. Clinicopathologic characteristics, immunohistochemical profile and molecular findings of the present case and the previously reported ones.

No.of case	Authors (Ref)	Age (years)/Gender	Tumor size (cm)	Location	In situ/invasive	Treatment	Follow-up	Negative immunohistochemical features	Positive immunohistochemical features	Molecular analysis
8	Eusebi et al. [2]	56/F	0.8	UK	Microinvasive	UK	UK	UK	UK	UK
9	Masood et al. [6]	57/F	3.7	Left breast/ upper quadrants	Invasive	Mastectomy with axilllary dissection	UK	HER-2, TTF-1, thyroglobulin	Estrogen and progesterone receptors	ND
10	Tosi et al. [7]	80/F	2.5	Right breast/ lower outer quadrant	In situ	Quadrantectomy and axillary dissection	Alive with metastasis to an intramammary lymph node at 3 months	CK14, CK19, estrogen and progesterone receptors, androgen R	Mitochondria, GCDFP-15, CK7, EMA (rare cells), p63 (focal)	ND
11	Tosi et al. [7]	45/F	5	Right breast/ upper outer quadrant	Invasive	Quadrantectomy and axillary dissection	ANED at 5 months	CK14, EMA, androgen R, p63	Mitochondria, GCDFP-15, CK7, CK19, estrogen and progesterone receptors	ND
12	Tosi et al. [7]	61/F	2	Right breast	Unknown	Quadrantectomy and axillary dissection	ANED at 8 months	GCDFP-15, progesterone receptor	Estrogen receptor (rare cells)	ND
13	Tosi et al. [7]	47/F	2.3	Right breast	In situ	Quadrantectomy and axillary dissection	ANED at 10 months	GCDFP-15, CK7, CK14, androgen R	Mitochondria (rare cells), CK19, EMA, estrogen and progesterone receptors, p63	ND
14	Pitino et al. [current case]	65/F	0.7	Right breast/ upper inner quadrant	Invasive	Quadrantectomy and excision of two sentinel lymph nodes	ANED at 34 months	TTF-1, PAX-8, progesterone receptor, thyroglobulin, HER-2, CK14, p63	CK7, HBME-1 (cytoplasmic and luminal membrane staining), mitochondria, GCDFP-15 (focal), CK19 (focal), estrogen receptor (rare cells)	BRAF-

Ref = reference; F = female; M = male; ND = not done;UK = unknown; ANED = Alive with no evidence of disease; R = receptor; TPO = thyroperoxidase.

progesterone and androgen receptors. The nature of the eosinophilic cytoplasm of the columnar neoplastic epithelium was explored by both Eusebi et al. [2] and Tosi et al. [7] who showed the presence of abundant mitochondria and diffuse positive staining for the specific antibody in most tumors. Analogous findings were observable in our case. The indolent clinical course of these tumors was attributed to their mitochondrion-rich cytoplasm and this finding is in keeping with the harmless clinical behavior of the reported cases of breast oncocytic carcinoma [2].

Of interest, rare neoplastic lesions having thyroid-like features have been also reported in the kidney and in the liver [14 15]. In the kidney the several cases described were superimposable to follicular thyroid carcinoma [14]. The unique case reported in liver was very similar to a follicular variant of papillary thyroid carcinoma [15].

In summary, we describe a case of a rare breast epithelial neoplasm (TCVPBC) bearing striking resemblance to tall cell variant of papillary thyroid carcinoma. The tumor cells were negative to thyroid markers and had no molecular expression of BRAF mutations. Beyond its absolute histologic distinctiveness, at this time the main importance of recognition of this primary tumor of the breast with most likely low malignant potential lies in its distinction from metastatic carcinoma from thyroid, which is usually widespread by the time it involves the

breast and carries completely different prognostic and therapeutic implications. To better define this type of breast carcinoma, more cases with clinicopathologic, as well as genetic studies, should be accumulate.

References

[1] Hameed O, Perry A, Banerjee R, et al. *Papillary carcinoma of the breast lacks evidence of RET rearrangements despite morphological similarities to papillary thyroid carcinoma*. Mod Pathol 2009;22:1236-42.

[2] Eusebi V, Damiani S, Ellis IO, et al. *Breast tumor resembling the tall cell variant of papillary thyroid carcinoma. Report of 5 cases*. Am J Surg Pathol 2003;27:1114-8.

[3] Cameselle-Teijeiro J, Abdulkader I, Barreiro-Morandeira F, et al. *Breast tumor resembling the tall cell variant of papillary thyroid carcinoma: a case report*. Int J Surg Pathol 2006;14:79-84.

[4] Chang SY, Fleiszer DM, Mesurolle B, et al. *Breast tumor resembling the tall cell variant of papillary thyroid carcinoma*. Breast J 2009;15:531-5.

[5] Colella R, Guerriero A, Giansanti M, et al. *An additional case of breast tumor resembling the tall cell variant of papillary thyroid carcinoma*. Int J Surg Pathol 2015;23:217-20.

[6] Masood S, Davis C, Kubik MJ. *Changing the term "breast tumor resembling the tall cell variant of papillary thyroid carcinoma" to "tall cell variant of papillary breast carcinoma".* Adv Anat Pathol 2012;19:108-10.

[7] Tosi AL, Ragazzi M, Asioli S, et al. *Breast tumor resembling the tall cell variant of papillary thyroid carcinoma: report of 4 cases with evidence of malignant potential*. Int J Surg Pathol 2007;15:14-19.

[8] Afkhami M, Karunamurthy A, Chiosea S, et al. *Histopathologic and clinical characterization of thyroid tumors carrying the BRAF(K601E) mutation*. Thyroid 2016;26:242-7.

[9] Fiche M, Cassagnau E, Aillet G, et al. *Mètastase mammaire d'un carcinome papillaire à cellules hautes de la thyroïde*. Ann Pathol 1998;2:130-2.

[10] Bejarano PA, Nikiforov YE, Swenson ES, et al. *Thyroid transcription factor-1, thyroglobulin, cytokeratin 7, and cytokeratin 20 in thyroid neoplasms.* Appl Immunohistochem Mol Morphol 2000;8:189-94.

[11] Nasr MR, Mukhopadhyay S, Zhang S, et al. *Immunohistochemical markers in diagnosis of papillary thyroid carcinoma: utility of HBME1 combined with CK19 immunostaining*. Mod Pathol 2006;19:1631-7.

[12] Eusebi V, Tallini G. *Nuclear alterations and RET/PTC activation.* Am J Surg Pathol 2004;28:974-5.

[13] Guerry P, Erlandson RA, Rosen PP. *Cystic hypersecretory hyperplasia and cystic hypersecretory duct carcinoma of the breast. Pathology, therapy, and follow-up of 39 patients*. Cancer 1988;61:1611-20.

[14] Alessandrini L, Fassan M, Gardiman MP, et al. *Thyroid-like follicular carcinoma of the kidney: report of two cases with detailed immunohistochemical profile and literature review*. Virchows Arch 2012;461:345-50.

[15] Fornelli A, Bondi A, Jovine E, et al. *Intrahepatic cholangiocarcinoma resembling a thyroid follicular neoplasm*. Virchows Arch 2010;456:339-42.