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Tumor carcinóide neuroendócrino da mama - Estudo clínico-patológico de seis casos

Neuroendocrine carcinoid tumors of breast - Clinicopathologic study of six cases

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Resumo

O tumor carcinóide primário da glândula mamária é uma neoplasia muito rara, de existência controversa. Sua histogênese ainda é discutida, sendo a origem mais reconhecida as células basais primitivas ductais. No estudo retrospectivo de 243 carcinomas infiltrativos e "in situ" de tipo ductal e lobular, seguindo estritos critérios de seleção, foram achados seis tumores carcinóides. O material correspondia a mulheres com idade média de 43 anos, que apresentaram-se com massas palpáveis notadamente nos quadrantes externos da glândula mamária direita. Não foram comprovadas metástases axilares nem síndrome carcinóide. A mamografia mostrou opacidades densas de contornos regulares. A punção citológica com agulha fina sugeriu células neoplásicas de tipo lobular em três casos; hiperplasia lobular atípica em um caso e presença de mucina não específica no resto. No estádio II da doença foi realizada mastectomia de tipo Madden em todos os casos. Macroscopicamente os tumores tinham uma média de 29,8 mm de diâmetro, aspecto sólido em quatro casos e cístico-gelatinoso em dois, e margens bem definidas. O padrão histopatológico mais freqüente foi o basalóide e presença de mucina extracelular compondo 28% do tumor em três casos. Não foram comprovadas mitoses. Os diagnósticos diferenciais incluíram: o carcinoma lobular, o carcinoma mucinoso e as metástases mamárias de carcinóides de outras topografias. Na evolução pós-operatória não foi comprovada recorrência local, disseminação a distância ou óbito numa média de 3,8 anos, sendo que em nenhuma das pacientes realizou-se rádio, químio ou hormonioterapia. Baseados nesses dados propõe-se a quadrantectomia com esvaziamento axilar como primeira forma de tratamento, reservando a mastectomia para um segundo momento.

Palavras chaves: glândula mamária; carcinóide; tumor argirofílico; tumor neuroendócrino; tumor mucinoso

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Abstract

Primary carcinoid tumor of the breast is a very rare tumor which existence and histogenesis are still controversial. Ductal basal stem cells seem to be a possible source. In a retrospective study of 243 invasive and in situ, ductal and lobular mammary carcinomas, following strict criteria of selection, six carcinoids were identified. All of the patients were females, mean age of 43 years, disclosing palpable nodules into upper outer quadrants mainly from right breast. Axillary involvement and carcinoid syndrome were not detected. Mammography showed dense opacities with regular outlines. Fine needle aspiration cytology suggested lobular neoplastic cells in three cases, atypical lobular hyperplasia in one and non-specific mucin (probably mucoid carcinoma) in the rest. As stage II of disease modified radical mastectomy was performed in all of the cases. Gross appearance showed tumors with 29.8 mm in average size, solid aspect in four cases and cystic gelatinous in two with pushing margins. Microscopically, basaloid was the most frequent pattern, with extracelullar mucin in three cases up to 28%. Mitosis were not observed. Differential diagnosis included lobular carcinoma, coloid carcinoma and carcinoid breast metastasis. Follow-up data indicate absence of local spread distant metastasis or death upon a mean of 3.8 years. None of the patients received radio, chemo or hormone therapy. We propose that quadrantectomy and axillary lymph nodes dissection should be the first choice of treatment. Radical surgery would be reserved for a second time surgical approach.

Key words: *breast; carcinoid tumor; neuroendocrine tumor; mucoid tumor; argyrophilic tumor*

Introduction

It is now widely accepted that neuroendocrine tumors of the breast include two major varieties: carcinoid tumors (also known as argyrophilic carcinomas) and the small cell neuroendocrine (oat cell) carcinoma[1, 2].

Although carcinoid tumor was described more than a century ago by Langhans[3], it was not until 1977 when Cubilla and Woodroff[4] reported its occurrence in the breast. Nevertheless, the existence of true carcinoids of the mammary gland is still a controversial issue[5-15]. Several reports published during the past years, mainly concerning the histopathological and immunohistochemical features seem to confirm its existence as a single and distinct clinicopathologic entity[4, 16-23].

The purpose of the current study was to examine six cases of carcinoid tumors and correlate relevant clinical data with those published in the literature. Follow-up data and therapeutic considerations are also discussed.

Material and method

A retrospective study of 243 specimens of ductal and lobular invasive and "in situ" mammary carcinomas, diagnosed between January 1990 and December 1995 was performed in the Departamento Ciências Morfo-Biológicas da FURG (Rio Grande).

Selected criteria of the available hematoxylin/eosin slides was based upon two or more of the following findings: a) basaloid, tubular or festooned histological pattern. b) little variation in cell morphology, nuclear grade 3, according to Black[24]. c) absent or scant mitotic activity. Only 11 cases satisfied our selection as strongly suspected of carcinoids or pseudocarcinoids. Essential criteria for diagnosis were: a) presence of cytoplasmatic argyrophilic granules into neoplastic cells; b) absence of cytoplasmatic argentaffin substances; c) in some cases pools of mucin intermingled with the epithelial component up to 33% of the tumor[22]. According to these features 6 out of 11 were considered true carcinoids.

Clinical records from each patient was reviewed in regard to the following parameters: age, race, presenting symptoms, duration of symptoms, TNM stage, urinary excretion of 5-hidroxiindol acetic acid, mammography and fine needle aspiration cytology (FNAC) results, treatment, incidence of local recurrences or distant metastasis and follow-up data.

Additional slides from selected cases were stained with periodic acid-Schiff (PAS) with and without distase digestion and with Alcian Blue (pH 2,5) for mucinous substance; Grimelius[25] and modified Grimelius

method[26] for detection of argyrophilic granules; and Masson-Hamperl for argentaffin substances. When axillary lymph nodes were 10 mm or more, they were sliced into multiple sections to improve assessment of micrometastasis (less than 2 mm). A mean of 30 serial sections per lymph node were analyzed.

Survival rates and time free of symptoms were calculated from the date of diagnosis to the end date for follow-up, because none of the patients have showed distant metastasis or death.

Results

Clinical characteristics are summarized in Table 1. Tumors corresponded to six Caucasian women, with average age of 43 years (range 30 to 51 years). A palpable breast mass was present in all of them associated with pain in two cases, and hemorraghic nipple discharge in one. Duration of symptoms was between 3 and 9 months. Right breast was mostly affected, specially into outer quadrants (five cases). The tumor size ranged from 22 mm to 44 mm, with a mean of 34.8 mm. Only in one case axillary lymph nodes were palpable without clinical signs of malignancy. Carcinoid syndrome was not detected.

Mammography (Table 1) detected dense opacities with regular outlines in five cases. The remaining had smooth round outlines indistinguishable from a benign tumor. Mammographic tumor size ranged from 20 mm

Table 1 - Clinical characteristics in carcinoid tumors of the breast.

	1_0	2_0	3_0	4_0	5_0	6_0
Race/age (years)	w/38	w/42	w/42	w/40	w/50	w/47
Presenting symptom(s)	lump	lump	lump pain	lump	lump pain	lump hnd
Symp. Duration (months)	6	4	5	3	5	9
Breast location	R/uoq	R/boq	R/loq	L/uoq	R/loq	R/buq
Tumor size (mm)	30	40	44	22	31	42
Metastasis at diagnosis	no	no	no	no	no	no
Carcinoid syndrome	no	no	no	no	no	no
Mammography						
Appearance	ro/mt	ro/mt	ro/mt	ro/mt	ro/mt	so
size (mm)	28	32	36	20	29	37
Clinical stage (UICC)	II	II	II	II	II	II
Treatment	m.r.m.	m.r.m.	m.r.m.	m.r.m.	m.r.m.	m.r.m.
Postoperative treat.	no	no	no	no	no	no
Follow-up data	well	well	well	well	well	well
Follow-up period (years)	2	4	2.5	4.5	5	3.8

W: white; hnd: hemorraghic nipple discharge; R: right breast; L: left breast; uoq: upper outer quadrant; boq: both outer quadrants; loq: lower outer quadrant; m.r.m.: modified radical mastectomy; ro: regular outlines; so: smooth outlines; mt: malignant tumors.

to 37 mm (average 30.3 mm). FNAC (Table 2) showed neoplastic lobular cells in three cases, atypical lobular hyperplasia cells in one, and non-specific mucoid material (probably mucoid carcinoma) in two.

Modified radical mastectomy, Madden type, was performed in all of the patients. None received postoperative adjuvant treatment. Follow-up data indicate that none of the patients have had clinical evidence of local recurrence or metastatic disease, 2 to 6 years (average 3.8 years) after surgery.

The pathological features are summarized in Table 2. The average tumor size was 29.8 mm (range 18 mm to 37 mm). Gross appearance showed white to tan nodular solid masses in four cases, and cystic formation with solid areas and mucinous content in two. Most had pushing or circumscribed contours (margins); one disclosed a mixed pattern (pushing and infiltrative). Number of dissected axillary lymph nodes range from 18 to 31.

Microscopically, basaloid was the most frequent pattern following by tubular differentiation (Figure 1). PAS and Alcian Blue positive extracelullar mucin was observed in three cases composing about 15% to 28% of the neoplasm (Figure 2). Moderate to marked amount of positive argyrophilic granules, with no argentaffinity were seen into the neoplastic cells (Figure 3). Accor-

Table 2 - Pathological features of carcinoid tumors of the breast.

	1_0	2_0	3_0	4_0	5_0	6_0
FNAC	mec	mucoid	mucoid	alh	mec	mec
Gross appearance						
size (mm)	28	33	34	18	29	37
aspect	nod	cys/g	nod	nod	nod	cys/g
colour	w	tan	gw	w	gw	w/tan
margins	push	push	push	mixed	push	push
axillary nodes	18	23	21	28	22	31
Histopathology						
domin. pattern	bas	tub/crib	bas/tub	bas/tub	tub	bas/crib
e.c.m.(%)	no	20	15	no	no	28
argyrophilia	+++	++	+	+++	++	++
argentaffinity	(-)	(-)	(-)	(-)	(-)	(-)
mitosis (*)	(-)	(-)	(-)	(-)	< 3	(-)
monon. infilt.	(-)	(-)	+	++	(-)	(-)
tumor necrosis	(-)	++	++	(-)	+	+
axillary metastasis	0	0	0	0	0	0

mec: malignant epithelial cells; alh: atypical lobular hyperplasia; ecm: extracellular mucin; nod: nodular; cys/g: cystic-gelatinous; push: pushing; w: white; gw: graywish; bas: basaloid; tub/crib: tubular-cribriform; (-): not present; (+): minimal presence; (+++): maximal presence. (*): number of mitosis per 10 high power field.

ding to Fisher's classification[17] 3 cases were diagnosed as solid carcinoid tumors and the others were carcinoid tumors, mucinous type. Mitosis were not present in five cases; a single case showed less than 3 mitosis per 10 high-power field, without atypical mitosis. Lymphocyte/plasma cell infiltration was observed in two cases, in the cystic cases.

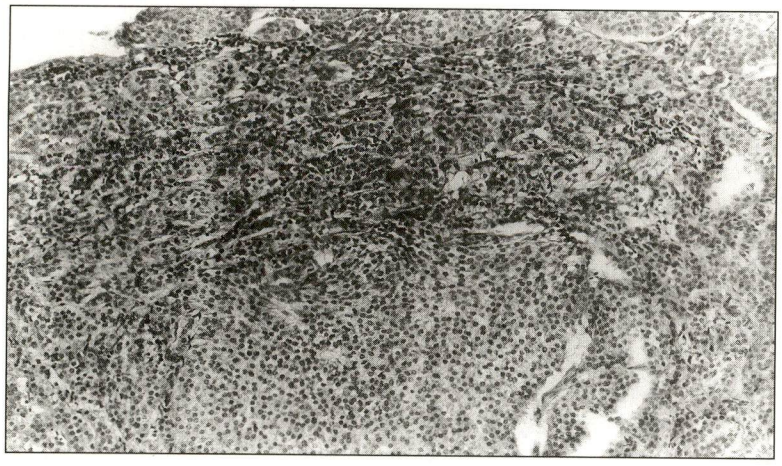

Figure 1 - Solid type of carcinoid tumor with predominant basaloid pattern. (HE; 200X).

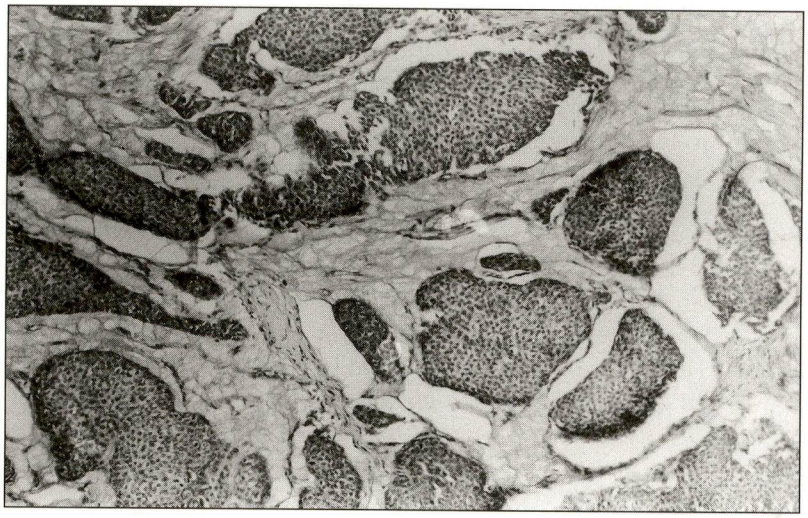

Figure 2 - Mucinous type of carcinoid tumor. Lakes of extracelullar mucin are intermingled with the basaloids type of the tumor. (Alcian blue staining; 100X).

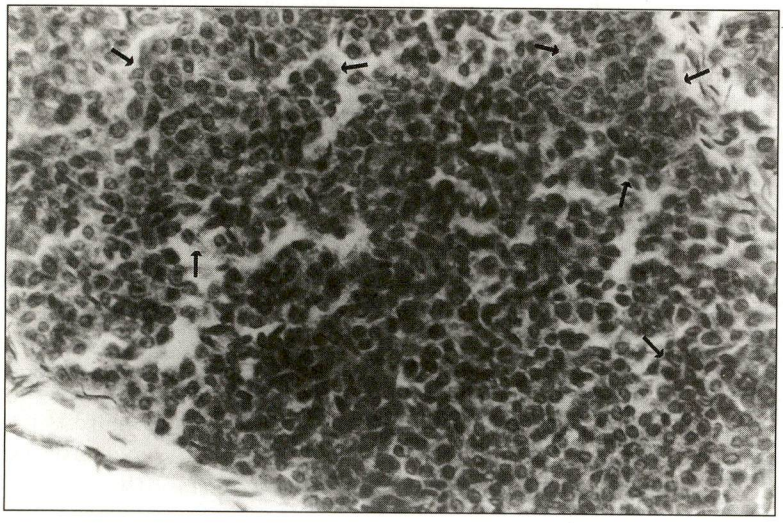

Figure 3 - A diffusely positive argyrophilic granules are showed (arrows), confirming euroendocrine differentiation of the tumor. (Grimelius staining; 400X).

Discussion

During the second half of the last century several authors described a tumor they believed a new pathological entity. Despite Langhans'[3] report in 1867, Lubarsch[27] is quoted the first to describe a detailed description of carcinoids, considering as a variety of adenocarcinoma. Ranson[28] in 1890 noted the occurrence of diarrhea and wheezing with hepatic metastasis secondary to a ileal carcinoid, establishing the clinical course of carcinoid syndrome. Nevertheless, it was just in 1907 when Oberndorfer[29] coined the term "Karcinoid" to describe a subset of intestinal tumors with histologic resemblance of adenocarcinoma but with less aggressive clinical behavior. Gosset and Masson[30] in 1914 showed the argyrophilic properties of tumor cells suggesting they originate from Kulchitsky cells. In addition of these cell types in the gastrointestinal tract, populations of functionally and morphologically similar cells have been described in a variety of other sites, like thymus, lung, urogenital tract. During sixties, Pearse[31] created the concept of APUD cells, that corresponded in large measure to Masson's argentaffin-argyrophil cell system[30], and to the diffuse endocrine system described by Feyter[32]. Over the years, the term carcinoid was extended to inclose several extraintestinal neoplasms, which share some of the clinical, histologic and histochemical features of intestinal carcinoids. Hence, carcinoid tumors could be considered a heterogeneous group derived from the diffuse endocrine system which have been reported in various organs[33] like thymus[34, 35], uterine cervix[36], ovary[37], kidney[38], pancreas[39] and lung[40].

Although the existence of primary carcinoid tumors of the breast is debated, World Health Organization classification on breast tumors[9] have suggested restrict the term for those neoplasms with one or more of the recognized histological patterns of intestinal carcinoids.

Carcinoid tumors of the breast, also called argyrophilic carcinoma were first reported by Feyter and Hartmann[41] more than three decades ago. They described two tumors they encountered among 170 mammary cancers, both showing argyrophilic reaction, and benign clinical course. As they also detected some amount of mucin, designation of "carcinoma solidum gelatinosum" was proposed. In 1977 Cubilla and Woodroff[4] reported on clinical and pathologic features of ten patients with irrefutable carcinoid tumors. Subsequent studies[17] have proved the occurrence of two histologic varieties: solid and mucinous. In a consecutive series of 35 pure mucoid mammary carcinomas Capella et al.[22] identified a subtype with argyrophilic cells they believed endocrine differentiation. Recently, van-Laarhoven et al.[10] described large and small cell types on carcinoid tumors, with no difference on clinical behavior.

Carcinoid tumors and small cell neuroendocrine (oat cell) carcinoma of the breast close relationship has been proposed lately[1, 2]. However, clinical course and the presence of axillary and hepatic spread at the time of diagnosis suggest the tumor behaves on an aggressive fashion analogous to other small cell neuroendocrine carcinoma opposite to an indolent course of carcinoids. Ruffolo et al.[42] have recently described a variant of primary endocrine tumor predominantly formed by cytologically bland spindle cells with argyrophilic granules.

Our clinical data have revealed some interesting points. While our patient's average age was 43 years, several reports have mentioned a mean age of 54 years, mostly on menopausal period[4,13,17,25]. A single case in a male was described by Papotti et al.[43]. Most tumors were located on right breast, especially into outer quadrants. We believe this is an incidental finding not related to any special breast morphology. A palpable mass noted 6 months earlier was the most frequent clinical presentation. Pain was present in patients with lower outer quadrants tumors; hemorraghic nipple discharge was the most conspicuous finding in one of cystic cases.

Size is one of the most important prognostic factors on breast cancer as statement on TNM classification. Mean pathological tumor size in our cases was 29.8 mm, meanwhile the average clinical size was 34.8 mm. This apparent discrepancy is explained by the Leborgne's law[6]: a malignant tumor usually feels considerably larger on palpation than on radiological or pathological examination, whereas a benign lesion has a similar clinical and radiological size. Tumors larger than 30 mm are strongly associated with metastasis as Cubilla and Woodroff[4] established in four

of their cases. Although period of follow-up in our cases is short (2 to 5 years after surgery) none of the patients have local recurrence and are alive without evidence of disease.

Carcinoid syndrome was not detected in any case. As a matter of fact, only those tumors with hormone production or metastatic spread were accompanied by carcinoid syndrome, as Kaneko et al.[44] reported. However, some of Cubilla and Woodrof's[4] metastatic cases, had no carcinoid syndrome. Identification of urinary 5-hidroxiindol acetic acid or other vasoactive amines or hormones is a reliable method to confirm secretory nature of the tumor, not detected in our cases.

Carcinoids have been classified according to embryologic origin into derivates of foregut, midgut and hindgut by Williams[45], in 1962. From the histological point of view breast carcinoids are similar to those derivatives from the foregut (like thymus, bronchus, stomach). As in these locations, tumors disclosed argyrophilic reactions without argentaffinity. That is the reason why presence of argyrophilic granules is an essential issue on diagnosis of carcinoid, hence some authors called this tumor "argyrophilic carcinomas"[16,20].However, Rosen[13] considers this tumor as a variant of mammary carcinoma with biochemical and structural metaplasia.

As in Fisher's cases[17] the solid variety was only composed of cells arranged on basaloid or tubular patterns. The presence of extracellular mucin is essential to consider the tumor as the mucinous variety of carcinoids. Capella et al.[22] established the mucin amount up to 33% to consider the tumor as mucinous carcinoid or mucoid carcinoma. This feature was also found in three cases, but despite Fisher's considerations[17] we were unable to find any clinical or biological difference between those two varieties. Rosen[13] has established that patients with argyrophilic mucinous carcinomas were more likely to have axillary nodal metastasis(48%) than those with Grimelius-negative tumors (26%). However, in Rasmussen's[46] study, the presence or absence of argyrophilic granules did not influence the prognosis of patients with mucinous carcinoma.

Pathological differential diagnosis include invasive lobular carcinoma[19], coloid carcinoma[17,22], and breast metastasis from a primary carcinoid located outside the gland[47,48]. Accurate diagnosis of breast metastasis is important to avoid unnecessary mastectomy and to implement an appropriated systemic therapy[49]. In 3 cases neoplastic cells from probably lobular carcinoma was suspected by FNAC, not confirmed by histopathology. Something similar also occurred with atypical lobular hyperplasia cells. Further, five cases selected in the prior identification, finally corresponded to invasive lobular carcinoma after histochemical study. Two previously reported cases of carcinoid tumors of the breast were cytologically diagnosed as poorly-differentiated carcinomas[50,51].

Nuclear grade, tumor necrosis, mitotic activity and lymphocyte/plasma cell infiltrate are valuable prognostic factors in current subtypes of breast carcinomas, but much less is known on carcinoids. Nuclear grade set on grade 3, seems not to be important, since most metastatic and non-metastatic carcinoids disclosed little variation in nucleus morphology. Only one patient showed less than 3 mitosis per 10 high power field; however, follow-up not revealed any difference with the others.

It appears that the stage at diagnosis is the major determinant of prognosis[12]. Following UICC classification[52], all of the patients were included on stage II of disease (five T2 N0 M0 and one T2 N1a M0) and treated by modified radical mastectomy. None received radio, chemo or hormonal therapy. Follow-up indicates all are alive free of disease on an average of 3.8 years. These results prompt us consider radical surgery as one of the therapeutic methods, but not the best. Absence of intraglandular spread, lymphatic vessels invasion, local involvement or axillary metastasis allow suggest quadrantectomy with axillary nodes dissection as first treatment, specially for those tumors less than 30 mm. Mastectomy would be maintained when lymph nodes metastasis or vascular invasion are demonstrated by histopathology or tumor size is larger than 30 mm. Since indolent course was recognized, chemotherapy would seem not to be indicated.

On the other hand, Birsak et al.[53] have shown that all of the cases of carcinoids of the breast (nine cases) were estrogen receptor (ER) po-

sitive, while five cases expressed progesterone receptor (PR) and five androgen receptor (AR). This similarity in sex steroid receptor expression pattern in carcinoids of the breast and the more common categories of breast cancer suggests an identical responsiveness to endocrine therapy.

Somatostatin analogs are presently approved for treatment of gastrointestinal endocrine cancer such as carcinoids or vipomas. As neuroendocrine tumors often express somatostatin receptors, labelled analogues may be useful for tumor assessment and for the prediction of tumor response to therapy[54].

In conclusion, carcinoid tumor of the breast, no matter the variety, is a malignant tumor with excellent prognosis and could be treated in first instance by a conservative method, due to oncological, esthetical and psychological reasons.

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