Primary neuroendocrine carcinoma of the breast:
a 5-year experiences

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PURPOSE: *Breast neuroendocrine carcinomas constitute approximately 0.3-0.5% of all breast cancers. In this study, we aimed to evaluate the data of patients diagnosed with primary breast neuroendocrine carcinoma.*
METHODS: *Patients with more than 50% neuroendocrine differentiation identified in the histopathological examination between January 2010 and January 2015 and who had no other focus on imaging were evaluated retrospectively from the hospital registry system. Patients with secondary neuroendocrine tumor of the breast and male patients were excluded from the study. All patients gave informed consent. Patients were staged according to TNM classification.*
RESULTS: *During the study period, 425 patients were operated for breast cancer. Eleven patients were included in the study. The mean age of the patients was 68 (range 49-86). Immunohistochemical examinations revealed positive staining with neuron-specific enolase, synaptophysin and chromogranin in all patients. Ten patients had strong positive estrogen and progesterone receptors and receptor status was not specified in one patient. Distant organ metastasis was detected in 1 patient during the follow-up period, no local recurrence and mortality were seen in any patient.*
CONCLUS ON: *The most widely used specific markers of neuroendocrine differentiation are chromogranin and synaptophysin. There is no standard treatment protocol for primary breast neuroendocrine tumors. Most of the treatments reported in the literature and in this study are breast sparing surgery or mastectomy, followed by anthracycline and taxane-based chemotherapy and/or hormonotherapy, similar to the treatment of ductal carcinoma. The distinction of primary metastases in breast neuroendocrine tumors is important, so the presence of neuroendocrine tumors should be investigated in other organs. In this case the treatment is changed. The issue of how neuroendocrine differentiation affects clinical outcome is yet to be debated.*

KEY WORDS: Chromogranin, Neuroendocrine tumor, Synaptophysin

Introduction

Neuroendocrine carcinomas are a rarely seen heterogeneous group of neoplasms. They may localized in many sites such as stomach, pancreas, adrenal, thyroid and breast [1]. Breast neuroendocrine carcinomas constitute approximately 0.3-0.5% of all breast cancers [2]. Approximately 200 cases described in the literatüre [3]. Primary breast neuroendocrine breast tumors are diagnosed by the expression of neuroendocrine markers in more than 50% of tumor cells, no other primary focus, and presence of in situ component in the histological examination [4]. Since primary neuroendocrine tumors of the breast are rarely seen, unfortunately only the case reports and case series are available in the literatüre [5]. In addition, there is no standard treatment for the management of these tumors. Therefore, in this study we aimed to evaluate the data of patients diagnosed with primary breast neuroendocrine carcinoma in order to provide contribution to the literature about diagnosis, treatment and prognosis of these carcinomas.

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Material and Methods

Patients with more than 50% neuroendocrine differentiation identified in the histopathological examination between January 2010 and January 2015 and who had no other focus on imaging were evaluated retrospectively from the hospital registry system. Patients with secondary neuroendocrine tumor of the breast and male patients were excluded from the study. All patients gave informed consent. Patients were staged according to TNM classification. Ki-67 index is rated low if ≤ 15%, intermediate if between 16-30% and high if 30%.
Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 22 software. When evaluating study data, in addition to descriptive methods (mean, standard deviation, frequency, ratio and median) Mann Whitney U test and Chi-square test were used for the comparison of variables. Statistical significance was set at $p<0.05$.

Results

During the study period, 425 patients were operated for breast cancer. Eleven patients with more than 50% neuroendocrine differentiation identified in the histopathological and having no other focus on imaging were included in the study. The mean age of the patients was 68 (range 49-86).
The diagnosis was established with a palpable mass in 9 patients with complaint of breast pain in 5 patients and incidentally during the controls in 3 patients. When the ultrasound (US) reports are evaluated; malignancy suspected, irregular contoured masses were found in 10 patients, while the mass was normal in one patient. Four patients underwent mastectomy and 7 patients underwent breast conservating surgery.
Invasive ductal carcinoma in 5 patients, solid papillary carcinoma in 4 patients, neuroendocrine difference in 1 patient, and invasive mucinous adenocarcinoma in 1 patient detected in biopsy examination previous operating.
Immunohistochemical examinations revealed positive staining with neuron-specific enolase, synaptophysin and chromogranin in all patients. Ten patients had strong positive estrogen and progesterone receptors and receptor status was not specified in one patient. In all patients c-erb B2 was negative. Ki 67 index was high (>30%) in 6 patients, intermediate (16-30%) in 3 patients and low (≤15) in 2 patients.
According to the staging status, 5 of the patients were stage 1A, of 1 stage 1B, of 1 stage 2A, of 1 stage 2B, of 1 stage 3A, of 1 stage 3B and of 1 was stage 3C. Distant organ metastasis was detected in 1 patient during the follow-up period, mortality was seen in 1 patients and no local recurrence was seen in any patient (Table I).

Discussion

Breast neuroendocrine tumors constitute less than 1% of neuroendocrine tumors [6]. In a retrospective study by Wang et al [7], histopathological examination of 381,786 patients with invasive breast carcinoma performed between 2003 and 2009 reported neuroendocrine breast carcinoma only in 142 patients and most of the patients were in the 6th decade. In our study, according to the literature, the mean age of the patients was 68 (range 49-86), consistently with the literature.
The most widely used specific markers of neuroendocrine differentiation are chromogranin and synaptophysin. Neuroendocrine tumors are stained with argentafine in the histochemical examination and neuroextreate granules are detected in electron microscopic examination. Breast neuroendocrine tumors are diagnosed by detecting positivity in at least one of neuroendocrine markers chromogranin, synaptophysin and neuron-specific enolase in more than 50% of tumor cells [4,8]. Estrogen receptor positivity is often found in neuroendocrine breast

Table I - *The patient's receptor status, type of operation and recurrent / metastatic status*

	Age	Estrogen reseptor	Progesterone receptor	c-erb B2	Ki 67 (%)	Stage	Operation	Recurrence/ Metastasis	Mortality
1	51	+	+	-	70	1B	mastectomy	-	-
2	60	+	+	-	15-20	2A	breast conservating surgery	-	-
3	86	+	+	-	10	1A	mastectomy	+	+
4	69	+	+	-	13	3C	breast conservating surgery	-	-
5	70	+	+	-	20	1A	breast conservating surgery	-	-
6	81	+	+	-	30	1A	mastectomy	-	-
7	65	+	+	-	80	1A	breast conservating surgery	-	-
8	49	+	+	-	80	3A	mastectomy	-	-
9	85	+	+	-	70	2B	breast conservating surgery	-	-
10	55	+	+	-	60	3B	breast conservating surgery	-	-
11	77	None	None	-	80	1A	breast conservating surgery	-	-

carcinomas [9]. In our study, estrogen receptor positivity was detected in all patients in accordance with the literature. Ki-67 was accepted as a prognostic parameter and classified in treatment approaches in the St Gallen 2009 consensus [10].

Kawasaki et al. examined the pathology of 89 patients admitted to the hospital with bloody nipple discharge, and 24 (27%) of these patients had neuroendocrine carcinoma. Neuroendocrine breast carcinoma may explain a significant portion of breast diseases associated with bloody nipple discharge [11].

No specific finding can be detected in the differential diagnosis from other breast cancers in breast ultrasonography and mammography studies [12,13]. There is no standard treatment protocol for primary breast neuroendocrine tumors [14]. Most of the treatments reported in the literature and in this study are breast sparing surgery or mastectomy, followed by anthracycline and taxane-based chemotherapy and/or hormonotherapy, similar to the treatment of ductal carcinoma [15]. The prognosis is controversial. The most important factor in prognosis is thought to be the histopathological examination, as well as tumor size, stage at the time of the diagnosis and estrogen and progesteron receptor status [16,17].

Conclusions

In conclusion; the distinction of primary metastases in breast neuroendocrine tumors is important, so the presence of neuroendocrine tumors should be investigated in other organs. In this case the treatment is different. The issue of how neuroendocrine differentiation affects the clinical outcome is yet to be debated.

Riassunto

I carcinomi neuroendocrini della mammella rappresentano lo 0,3-0,5% di tutti i carcinomi mammari. Con questo studio abbiamo analizzato i dati riferiti a pazienti cui è stato diagnosticato un carcinoma neuroendocrino mammario primitivo.

Si tratta di uno studio retrospettivo eseguito sui registri ospedalieri nel periodo compreso tra Gennaio 2010 e Gennaio 2015 riferito a pazienti affette da cancro mammario che presentavano all'esame istopatologico una differenziazione neuroendocrina superiore al 50%, e senza altri foci all'imaging. Dallo studio sono state escluse le pazienti con tumore neuroendocrino secondario della mammella, oltre ai pazienti di sesso maschile.

Tutte le pazienti hanno dato il loro consenso informato e sono state stadiate secondo la classificazione TNM.

Nel periodo di studio considerato 425 pazienti sono state operate per cancro della mammella, ed undici di queste sono state incluse nello studio. L'età media è risultata di 68 anni (da 49 a 86). Lo studio immunoistochimico ha rivelato colorazione positiva con enolasi neuroendocrina-specifica, sinaptofisina e cromogranina in tutte questa pazienti. Dieci di esse hanno presentato forti recettori per estrogeni e progesterone; dell'undicesima non è stato specificato lo stato recettoriale. n una paziente è stato evidenziata una metastasi in organo distante nel successivo follow-up, ma nessuna recidiva locale nè mortalità in nessuna delle undici pazienti.

In conclusione i markers specifici di maggior uso diffuso per la differenziazione neuroendocrina sono la cromogranina e la sinaptofisina. Non esiste un protocollo standard di trattamento per i tumori primitiva neuroendocrini della mammella: la maggior parte dei trattamenti riferiti in letteratura e in questo stesso studio sono la chirurgia conservativa o la mastectomia, seguite dal trattamento chemoterapico adiuvante con antracicline e a base di Taxane, e/o ormonoterapia, come per il trattamento del cancro duttale.

La distinzione di metastasi primitiva nei tumori neuroendocrini della mammella è importante, e pertanto va indagata la presenza di tumori neuroendocrini in altri organi, in che comporta un cambiamento del trattamento.

La prognosi della differenziazione neuroendocrina del cancro mammario necessita uno specifico dibattito.

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