Small cell carcinoma of the breast.
Report of a case

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Manuela Cesaretti**, Alfredo Guarnieri*, Ilaria Gaggelli*, Andrea Tirone*, Niccolò Francioli*, Anton Ferdinando Carli *

**U.O.C. Chirurgia 2, AOU Senese, Siena, Italy*
***Department of Surgery, DICMI, "San Martino" Hospital, Genoa, Italy*

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The recognition of undifferentiated forms of endocrine tumors in the extrapulmonary sites is considered as extremely infrequent. Immunohistochemical patterns of this tumor are similar to small cell neuroendocrine cancer of the lung and as the pulmonary one, it is more aggressive than carcinoma without neuroendocrine differentiation.
We report a case of a 68 years old woman with a primary small cell carcinoma of the breast gland presented as a palpable and mobile 2 cm mass, located in the upper outer quadrant of her right breast. It was treated with surgery and the diagnosis was made after surgical treatment, thanks to the immunohistochemical studies of tissue.

KEY WORDS: Breast, Small cell carcinoma

Introduction

Undifferentiated endocrine tumors (UETs) represent an heterogeneous group of neoplastic diseases whose existence has been largely underestimated because they are often reported as mixed, un-differetiated or anaplastic forms. UETs may arise from any organ or tissue **undertaking** to neuroendocrine regulation, such as respiratory, gastro-enteric, and urinary tracts as well as secretory glands such as prostate, breast and pancreas [1], and present common phenotypic and functional features. UETs clinically manifest themselves with different modalities such as paraneoplastic syndrome and/or hormone activity and with different clinical-biologic aggressivity and prognosis [2,3]. Small cell carcinoma (SmCC) belongs to this large family and similarly to them it may arise from many different sites, such as salivary glands [4], vagina [5], cecum [6], pancreas [7], stomach [8], urinary bladder [9], gallbladder [10], hypopharinx [11], paranasal sinuses[12], larynx [13], cervix [14], thymus [15], prostate [16], skin [17], epididymis [18], esophagus [19], kidney [20] and breast [21] even thought it preferentially derives from broncho-pulmunary stem cells [1].
The recognition of undifferentiated forms of endocrine tumors in the extrapulmunary sites could have critical prognostic as well as therapeutic implications. These tumors are in fact, much more aggressive than the epithelial as well as glandular counterparts, and at the same time, they are much more responsive to specific platinum based anticancer treatments and somatostatin analogues. Extrapulmonary Small cell carcinoma and UETs, may be very sensitive to chemo- [22, 23] and chemohormone-therapy [24].
Their recognition and diagnosis for highly un-differentiated forms however may be very challenging considering that they miss specific neuro-endocrine markers and for this reason their incidence is largely underestimated. The Authors report on a case concerning a 68 years old woman with a small cell carcinoma of the breast gland.

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Corrispondence to: Dr. Andrea Tirone, Policlinico "Le Scotte", U.O.C. Chirurgia 2, Viale Bracci 53100 Siena, Italy (e-mail:andrea.tirone@alice.it)

Case report

A 68 year old woman consulted our institute in Gen 2008 for evaluation of a mass in the right breast which she had noticed in October 2007.
Physical examination showed a painful, solid and regular lump of 2 cm in size, in the upper outer quadrant of her right breast. The skin over the lesion was erythematous. She had no signs or symptoms of paraneoplastic syndrome.
There was no nipple discharge but a mobile lymph node was palpable in right axilla.
Family history's patient reported a case (her sister) of breast benign tumour (fibroadenoma).
The past history of the patient was unremarkable.
The Mammography and Ultrasonography showed a 1,5 - 2 cm solid lump with ill-defined borders and specular formation in right upper outer quadrant, with axillary lynphoadenopathy.
Blood chemistry test, liver function test, urinalysis and full blood count were in normal range.
A chest X-ray showed no abnormality and excluded other primary lung sites.
A cytological analysis with fine-needle aspiration biopsy of the lump demonstrated neoplastic cells and classified the tumour as: "Invasive Ductal Carcinoma".
A segmental mastectomy of the right upper outer quadrant was performed with axillary nodes clearance.
The tissue obtained from the quadrantectomy was fixed in 4% formalin and cut into 5mm slices. The speciment revealed a ill-defined, hard, grey lump, 1,1 cm in maximum dimension.
Histologically, the tumour showed infiltrative borders, peritumoural vascular invasion; adjacent breast tissue revealed a Fibrocystic Mastopathy. None of the 19 right axillary lymph nodes showed any evidence of metastasis. The histology diagnosis was: "Neuroendocrine carcinoma of the breast, G2" (Figg. 1, 2).
Immunohystochemical studies exhibited cells positive reaction for Cytokeratin (AE-1/AE3), GCDFP-15, Chomogranin A, Synaptophysin, Neuron specific enolase (NSE), E-cadherin.
The oestrogen receptor was positive in 95% , progesterone receptor in 95%.
There's no high proliferative index evidenced by positive nuclear staining for Ki67 in 7% of the neoplastic cells. C-erb-2 (DAKO) immunoreactivity was not documented.
The TNM staging was pT1cN0Mx.
These immunohistochemical results of tissue from mammary carcinoma drove us to undergo the patient a further work-up, which included chest CT, abdominal ultrasonography, and they resulted negative for both metastatic disease and other primary sites disease. Neuron-specific enolase (NSE), serotonin, tryptophan, indoleacetic acid, chromogranin A and tumour markers such as carcinoembryonic antigen (CEA), Ca19-9 and Ca 15-3, were measured in serum, and they resulted in normal range. The patient performed an octreotide total body scan that demonstrated no pathological tracer accumulation. After the surgical resection, patient received both radiation to the breast (cobalt-60) and hormonal therapy in form of tamoxifen (20 mg/die for 2 years) and anastrazole (1 mg/die for 3 years). Our follow-up con-

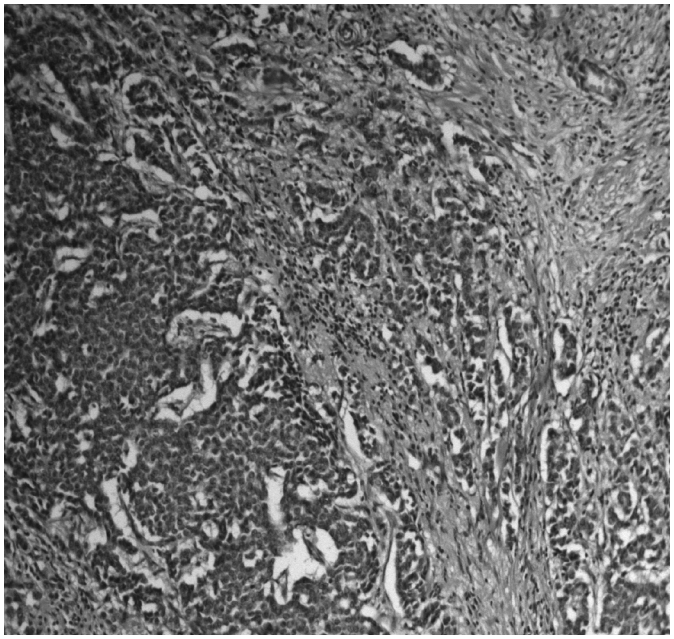

Fig. 1: Alveolar pattern with rounden solid nests of spindle cells invading a dense collagenous stroma (EE, 10x).

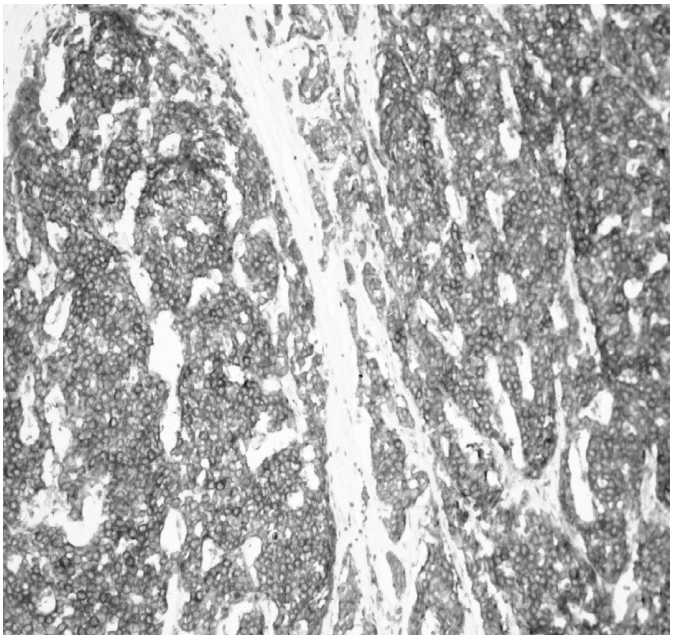

Fig. 2: IHC staining is positive for chromogranin (IHC, 10x).

sisted of blood tests (tumour markers) and medical visit every 3 months, abdominal sonography every 6 months and CT total body, mammography and bone scintigraphy every 12 months. On December 2009, there was a increase of Chromogranin A (305 ng/ml), so she underwent a PET-CT TOTAL BODY, showed a tracer accumulation (Infiammatory disease). This diagnosis was confermated by CT and X-Chest.
The patient was alive and free of local recurrence or extramammary metastatic disease at last follow up to 34 months after treatment.

Discussion

The recognition of pure primary small cell carcinoma of the breast is considered as extremely infrequent. They were initially described in 1983, event though at that time a contaminating non-mammary primary could not be excluded [25]. Histologically, as the reports suggest, they are more aggressive than carcinoma without neuroendocrine differentiation.
In 1984 was also described the first case involving a male breast [26]. A review of the literature revealed fewer than 30 cases, with the largest series of nine patients reported by one Autor [27], identified by a consultation of reports.
We report a new case of mammarian carcinoma with neuroendocrine features, revealed to our knowledge by immunohistochemical analisys performed after surgical procedure.
Primary small cell carcinomas of the breast are uncommon (1% of primary breast cancers [28]), in fact this tumour is nearly always localized in the lungs and characterized by a rapid progress, which often results in death within a short period of time under the clinical picture of generalized tumour spread [29]. In our experience, this is the first case of neuroendocrine breast carcinoma, and the diagnosis was only made after surgical treatment, thanks to the immunohistochemical studies of tissue. This tumour can produce hormone products, which can give particular clinical manifestations, however, this is unusual, indeed. In our case it presents in the same way as adenocarcinoma of the breast. The differentiation between primary and metastatic neoplasms is essential for planning therapeutic treatment and it is possible performing an immunohistochemical study and an accurate instrumental diagnostics [30]. Due to the rarity of this tumour, there was no standard therapy until these tumors started to be recognized of five/ten years.
Literature reports cases that had undergone radical or modified radical mastectomy [31] with axillary clearance, lumpectomy and quadrantectomy [32], and we performed a segmental mastectomy because of our early tumour's staging. Subsequently, patient received adjuvant radiotherapy and hormonal therapy, because the tumour was oestrogen and progesterone receptors positive [33]. We believe that an accurate follow-up, consisting of measuring neoplastic and neuroendocrine markers and instrumental diagnostics, is the crucial point of the carcinoma therapy with neuroendocrine features, because every modification from reference values could point up a recurrence of the disease, both local and metastatic. In conclusion, primary small cell carcinoma of the breast presented nonspecific instrumental features and a multimodality approach to treatment should be performed because of its rarity and its poor prognosis.

Riassunto

Il reperto di forme indifferenziate di tumori endocrine in sedi extrapolmonari è considerate un'evenienza straordinariamente rara. Le caratteristiche immunoistochimiche di questo tumore sono simili a quelle del tumore neuroendocrino a piccolo cellule del polmone, e come quello a sede polmonare è molto più aggressivo del carcinoma privo di differenziazione neuroendocrina.
Si riferisce qui il caso di una donna di 68 anni portatrice di un tumore primitivo a piccole cellule della ghiandola mammaria, rivelatosi come una massa palpabile e mobile di 2 cm, localizzata nel quadrante supero esterno della mammella destra. Essa fu trattata chirurgicamente, e la diagnosi fu fatta dopo l'intervento chirurgico grazie allo studio immunoistochimico del tessuto.

References

1) Rovera F, Masciocchi P, Coglitore A, La Rosa S, Dionigi G, Marelli M et al.: *Neuroendocrine carcinomas of the breast.* Int J Surg, 2008; 6 Suppl 1:S113-5.

2) Moertel CG: *An odyssey in the land of small tumors.* J Clin Oncol, 1987; 5:1503-22.

3) Buchanan KD, Johnston CF, O'Hare MM, Ardill JE, Shaw C, Collins JS et al.: *Neuroendocrine tumors. An European view.* Am J Med, 1986; 81(6B):14-22.

4) Walters DM, Little SC, Hessler RB, Gourin CG: *Small cell carcinoma of the submandibular gland: A rare small round blue cell tumor.* Am J Otolaryngol, 2007; 28(2):118-21.

5) Crowder S, Tuller E: *Small cell carcinoma of the female genital tract.* Semin Oncol, 2007; 34(1):57-63.

6) Demellawy DE, Samkari A, Sur M, Denardi F, Alowami S: *Primary small cell carcinoma of the cecum.* Ann Diagn Pathol, 2006; 10(3):162-65.

7) Wang RF, Chou YH, Hwang JI, Tiu CM, Chiou HJ, Chen SP, et al.: *Primary small cell carcinoma of the pancreas with an unusual sonographic appearance.* J Clin Ultrasound, 2007; 35(2):82-84.

8) Namikawa T, Kobayashi M, Okabayashi T, Ozaki S, Nakamura S, Yamashita K, et al.: *Primary gastric small cell carcinoma: Report of a case and review of the literature.* Med Mol Morphol, 2005; 38(4):256-61.

9) Petrescu A, Berdan G, Hulea I, Gaitanidis R, Ambert V, Jinga

V, et al.: *Small cell carcinoma of the urinary bladder. A new case report.* Rom J Morphol Embryol, 2007; 48(3):309-14.

10) Zachos I, Papatsoris AG, Sountoulides P, Podimatas T, Politis P, Repanti M, et al.: *Primary small cell bladder carcinoma: A case report and review of the current literature.* Tumori, 2006; 92(6):552-54. Review.

11) Sano M, Kitahara N, Toma M: *Hypopharyngeal small cell carcinoma: A case report.* Auris Nasus Larynx, 2005; 32(3):319-22.

12) Babin E, Rouleau V, Vedrine PO, Toussaint B, de Raucourt D, Malard O, et al.: *Small cell neuroendocrine carcinoma of the nasal cavity and paranasal sinuses.* J Laryngol Otol, 2006; 120(4):289-97.

13) Hamid O, El Fiky L, El Arab LE, El Beltagy Y, Amin R: *Small cell carcinoma of the larynx: A case report.* Otolaryngol Head Neck Surg, 2005; 133(4):647.

14) Crowder S, Tuller E: *Small cell carcinoma of the female genital tract.* Semin Oncol, 2007; 34(1):57-63.

15) Mirza IA, Shahab N: *Small cell cancer of the pleura, kidney, and thymus.* Semin Oncol, 2007; 34(1):67-69.

16) Palmgren JS, Karavadia SS, Wakefield MR: *Unusual and underappreciated: Small cell carcinoma of the prostate.* Semin Oncol, 2007; 34(1):22-29.

17) Renner G: *Small cell carcinoma of the head and neck: A review.* Semin Oncol, 2007; 34(1):3-14.

18) Chen JW, Yuan L, Hu HH: *Small cell undifferentiated carcinoma in the epididymis.* Chin Med J (Engl), 2005; 118(16):1402-404.

19) Alici S, Ozen S, Kotan C: *Small cell carcinoma of the esophagus: Report of a case with review of the literature.* J Buon, 2002; 7(2):161-64.

20) Miyake M, Fujimoto K, Tanaka M, Matsushita C, Tanaka N, Hirao Y: *A case of small cell carcinoma of the kidney.* Hinyokika Kiyo, 2007; 53(4):235-40.

21) Shaco-Levy R, Dyomin V, Kachko L, Sion-Vardy N, Geffen DB, Koretz M: *Small cell carcinoma of the breast: Case report.* Eur J Gynaecol Oncol, 2007; 28(2):142-44.

22) Langley K: *The neuroendocrine concepts today.* Ann NY Acad Sci, 1994; 733:1-17.

23) Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufié P, Aparicio T, et al.: *Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin.* Br J Cancer, 1999; 81(8):1351-55.

24) Correale P, Sciandivasci A, Intrivici C, Pascucci A, Del Vecchio MT, Marsili S, et al.: *Chemo-hormone therapy of non well-differentiated endocrine tumors from different anatomic sites with cisplatinum, etoposide and slow release lanreotide formulation.* Br J cancer, 2007; 96(9):1343-47.

25) Wade PM, Millis SE, Read M, Cloud W, Lambert MJ 3rd, Smith RE: *Small cell neuroendocrine (oat cell) carcinoma of the breast.* Cancer, 1983; 52(1):121-125.

26) Jundt G, Schulz A, Heitz PU, Osborn M: *Small cell neuroendocrine (oat cell) carcinoma of the male breast. Immunocytochemical and ultrastructural investigations.* Virchows Arch A Pathol Anat Histopathol, 1984; 404(2):213-21.

27) Shin SJ, DeLellis RA, Ying L, Rosen PP: *Small cell carcinoma of the breast: A clinicopathologic and immunohistochemical study of nine patients.* Am J Surg Pathol, 2000; 24(9):1231-38.

28) Mirza IA, Shahab N: *Small cell carcinoma of the breast.* Semin Oncol, 2007; 34(1):64-66.

29) Miremadi A, Pinder SE, Lee AH, Bell JA, Paish EC, Wencyk P, et al.: *Neuroendocrine differentiation and prognosis in breast adenocarcinoma.* Histopathology, 2002; 40(3):215-22.

30) Mariscal A, Balliu E, Diaz R, Casas JD, Gallart AM: *Primary oat cell carcinoma of the breast: Imaging features.* AJR Am J Roentgenol, 2004; 183(4):1169-71.

31) Yamasaki T, Shimazaki H, Aida S, Tamai S, Tamaki K, Hiraide H, et al.: *Primary small cell (oat cell) carcinoma of the breast: Report of a case and review of the literature.* Pathol Int, 2000; 50(11):914-18.

32) Adegbola T, Connolly CE, Mortimer G: *Small cell neuroendocrine carcinoma of the breast: a report of three cases and review of the literature.* J Clin Pathol, 2005; 58(7):775-78.

33) Sengoz M, Abacioglu U, Salepci T, Eren F, Yumuk F, Turhal S.: *Extrapulmonary small cell carcinoma: Multimodality treatment results.* Tumori, 2003; 89(3):274-77.