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Synchronous primary papillary breast cancer, medullary thyroid carcinoma and neuroendocrine tumor in postmenopausal woman

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Case Report

Abstract

Multiple endocrine neoplasia are syndromes involving two or more endocrine tissues, often correlated to RET proto-oncogene mutations. We herein present the first reported case of a 57-years-old woman with three synchronous primary cancers of breast (papillary), thyroid (medullary) and pancreas (neuroendocrine), the latter with liver metastasis. The patient first underwent surgery for papillary breast cancer with axillary lymph nodes metastases. A staging whole body computerized tomography (CT) showed a right lateral cervical lymph node, pancreatic inhomogeneity, peri-pancreatic nodes and a single liver metastasis. The poor response to an antracycline and taxane-based chemotherapy, the good performance status of patient, and associated symptoms, suggested a different origin for pancreatic and hepatic lesions. A careful re-evaluation of clinical history, an octreotide-labeled scan and an immunohistochemical analysis, on both hepatic and pancreatic tissues and on laterocervical lymph node, determined the diagnosis of synchronous papillary breast cancer, pancreatic neuroendocrine tumor (pNET) with liver metastasis and an occult medullary thyroid carcinoma in a patient who had proto-oncogene RET wild type.

Keywords: Breast Cancer; Neuroendocrine Tumors; Medullary Thyroid Carcinoma; MEN Syndromes; RET Oncogene

Introduction

Multiple endocrine neoplasia (MEN) are autosomal dominant syndromes characterized by tumors involving two or more endocrine tissues. Two, among these syndromes, have been clinically and genetically well characterized: the MEN type 1 (MEN1) and type 2 (MEN2), which are caused by germline mutations in the MEN1 tumor suppressor gene and in the RET (Rearranged during Transfection) proto-oncogene, respectively.[1] However, uncommon situations of multiple synchronous cancers, without evident correlation with a particular genetic mutation, can also occur, such as atypical MENS. We herein present a clinical entity of three synchronous primary cancers of the breast (papillary), thyroid (medullary) and pancreas (neuroendocrine), the latter with liver metastasis.

Case presentation

On February 2001, a well-being 57-year-old woman underwent left mastectomy and axillary lymph nodes dissection. Histology revealed a completely excised, 11 mm of diameter, grade 2, invasive breast papillary carcinoma with metastatic involvement of 2, among the 17 examined, axillary lymph nodes. The TNM classification was pT1c pN1 (2/17) pMx; estrogen receptor (ER) and progesterone receptor (PR) were negative, Ki 67 index was 20%, Her2 was negative, as well as synaptophysin.

Staging radiological examinations were performed and a computerized tomography (CT) scan showed metastatic involvement of a right lateral cervical lymph node, inhomogeneity of the pancreatic head with loco-regional lymph nodes involvement and the presence of a single large (8 cm in diameter) hepatic metastasis on the left hepatic lobe. The patient received a first line chemotherapy for metastatic breast cancer, with an antracycline and taxane-based regimen, and she reached only a stable disease.

She was then suffering persistent heartburn and emesis, responsive only to anti H2 antagonists, flushing and

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neck swelling. Therefore, an esophagogastroduodenoscopy was carried out, which resulted negative. Serological evaluation of CEA (carcinoembryonic antigen), neuron specific enolase (NSE), 5-hydroxyindoleacetic acid (5-HIAA) and thyroglobulin was negative, but the patient presented high serum levels of calcitonin (58 pg/ml, normal range < 15 pg/ml) and weakly positive chromogranin A values (126 ng/ml, normal range 0-90 ng/ml).

Somatostatin receptor scintigraphy (Octreoscan), a sensitive method for the detection of neuroendocrine tumors and metastases bearing the somatostatin receptor subtypes 2 (SSTR2) or SSTR 5, demonstrated high density of somatostatin receptors in the right thyroid-parathyroid area, in the right neck, in duodeno-pancreatic region and in a focal hepatic site.

We then performed a fine needle aspiration of the enlarged lateral cervical lymph node, and a liver and pancreatic biopsy. Lateral cervical lymph node cytological examination revealed numerous singly arranged cells of plasmacytoid appearance, immunoreactive for calcitonin: these findings were consistent with a metastatic thyroid medullary carcinoma. Histopathological evaluation of the pancreatic and liver biopsies established a diagnosis of primary pancreatic well-differentiated neuroendocrine tumor, grade 2 according to WHO (2010), with metastatic involvement of the liver. The tumor showed a low mitotic count (2/10 high- power field HPF).

Immunohistochemical analysis of both tissues showed a Ki67 index of 5%, diffuse synaptophysin and focal chromogranin A (Figure 1a) expression in the tumor cell component (Figure 1b). Yet, RET resulted wild type. The patient underwent radical thyroidectomy and lateral cervical lymph node dissection and histology showed a medullary carcinoma, measuring 2.5 cm diameter, with > 25% calcitonin immunopositive cells in the thyroid. Additionally, 2 out of the 10 examined loco-regional nodes were involved by metastatic disease (TNM classification pT2 pN1 pMx).

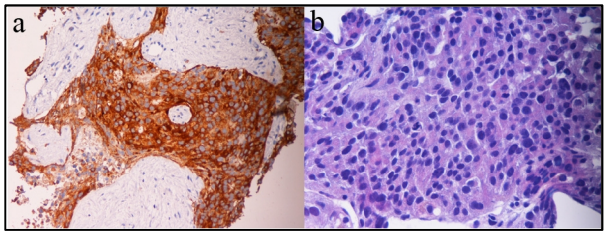

Figure 1: a) Cromogranin A immunoperoxidase staining of metastatic liver. b) Higher magnification histology of metastatic tumor cells into the liver.

Surgery of the pancreatic neuroendocrine tumor was contraindicated, due to the liver metastasis extension and location. Therefore, the patient received a chemotherapy regimen based on streptozotocin and 5-fluorouracil for 6 cycles, achieving a clinical partial response.

In relation to the histological and immunohistochemical features of the pancreatic tumor (mitotic count of 2/10 HPF, Ki67 index of 5%, synaptophysin +, chromogranin A+/-) and to the high density of somatostatin receptors on Octreoscan analysis, the patient was also started to a treatment with long-acting Octreotide (LAR) 30 mg intramuscularly every 28 days, without toxicities and maintaining clinical partial response. Presently, she is still alive, with a good performance status and preserving a good quality of life. Continuing treatment with long-acting Octreotide did not result in systemic toxicities, and allowed for good control of metastatic neuroendocrine carcinoma, with biochemical and symptomatic responses.

Discussion

We present an intriguing clinical entity of a combined synchronous primary papillary breast carcinoma, thyroid medullary carcinoma and pancreatic well-differentiated neuroendocrine tumor that has not, to our knowledge, previously been reported.

Our patient was affected by an unusual variety of ductal carcinoma, the papillary histotype. Its incidence ranges from 0, 5 to 2% of all newly diagnosed breast cancers. It usually occurs in women aged between 50 and 70 years, and it is characterized by a good prognosis with a long term survival.[2] Antracyclines and taxanes are some of the most active agents against advanced breast cancer; the obtainment of a stable disease instead than an objective response to this chemotherapy in the present case called into question the diagnosis, so we decided to undergo further examinations for a better evaluation of the patient's disease.

In breast cancer patients a high prevalence of thyroid diseases, particularly Hashimoto's thyroiditis, has been described, whose relationship and coincidence is still a subject of extensive debate and controversy.[3] To a more careful evaluation of the literature we found two cases of synchronous breast and medullary thyroid cancer.[4] These patients presented high serum CEA levels, and were affected by the usual ductal-type variety of breast carcinoma, differently from the present case. Therefore, the finding of a synchronous thyroid medullary carcinoma was rather unexpected.

Medullary thyroid carcinoma is an APUDoma (Amine Precursor Uptake and Decarboxylation) arising from the parafollicular C cells. It is sporadic in 75% of cases, and familial in 25%, due to RET proto-oncogene germinal mutations. The familial form of medullary thyroid carcinoma can also be a component of multiple endocrine neoplasia (MEN) IIA or IIB. Serum calcitonin value is an important diagnostic tool for thyroid cancer

and high levels are usually found in the medullary thyroid cancer.[5]

Neuroendocrine tumors (NETs) are rare neoplasms, with an incidence of about 1 case per 100,000 in the population per year, with variations due to their histotype.[6] Recently, an increase in the incidence of these tumors has been observed, from 1.09 to 5.25 cases per 100,000 in the USA population per year.[7] In 70% of the cases, NETs are highly differentiated tumors, and are characterized by long patient's survival. They can be sporadic or familial diseases.[6]

The peculiar association of such unusual tumors, suggested a careful genetic evaluation, despite her negative family history, that revealed no first-degree relatives with history of cancer. RET proto-oncogene analysis surprisingly indicated that the patient expressed wild type RET, ruling out a MEN syndrome, not excluding a case of atypical MEN. However, as medullary thyroid cancer has a common origin with neuroendocrine tumors, this patient could harbor genetic alterations other than RET germinal mutations. Recent literature reported, for example, the expression of Kit protein and CD34 and the mutation of Kit receptor tyrosine kinase gene in multiple endocrine neoplasia.[6]

Gastro-entero-pancreatic neuroendocrine tumors can be associated to other synchronous or metachronous primary epithelial malignancies, accounting for about 10% of cases, and, even less frequently (1.3% cases), they can be associated to non-epithelial neoplasms.[7]

Nuclear imaging by Octreoscan plays a key role in the diagnosis of NETSs. Therapy with somatostatin analogs, such as long-acting repeatable octreotide (LAR), can improve symptoms and stabilize tumor growth in many patients. Results from the PROMID study showed that LAR octreotide is an effective molecule for patients with newly diagnosed, functionally active or inactive, well-differentiated metastatic midgut NETs.[8] CLARINET study conducted on 200 patients with metastatic enteropancreatic neuroendocrine tumors treated with lanreotide demonstrated a significantly prolonged progression-free survival.[9]

The use of LAR octreotide instead of standard octreotide demonstrated an improvement in tumor mass decrease and survival prolongation with long acting molecules.[10] This new formulation requires only one monthly intramuscular injection, and shows better acceptability and patient compliance to therapy, so it seems preferable in clinical practice. Indeed, minimal adverse effects of somatostatin analogs permitted to our patient a prolonged treatment period without alteration of her quality of life.

Conclusion

Our case report highlights an unusual association of multiple synchronous tumors, all characterized by low incidence. This case suggests that sometimes atypical forms of MEN with wild type RET can remain undiagnosed and that a neuroendocrine tumor should be kept in mind when facing with a patient with an extensive disease, not responsive to key-drugs.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Lodish MB, Stratakis CA. RET oncogene in MEN2, MEN2B, MTC and other forms of thyroid cancer. Expert Rev Anticancer Ther. 2008; 8:625-32.
2. Pal SK, Lau SK, Kruper L, *et al*. Papillary carcinoma of the breast: an overview. Breast Cancer Res Treat. 2010; 122:637-45.
3. Tanaka H, Tsukuma H, Koyama H, *et al*. Second primary cancers following breast cancer in the Japanese female population. Jpn J Cancer Res. 2001; 92:1-8.
4. Andry G, Wildschutz T, Chantrain G, *et al*. Elevated CEA in breast cancer patients with overlooked medullary thyroid carcinoma. Eur J Surg Oncol. 1993; 19:305-8.
5. Costante G, Meringolo D, Durante C, *et al*. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab. 2007; 92: 450-5.
6. Cirillo F. Neuroendocrine tumors and their association with rare tumors: observation of 4 cases. Eur Rev Med Pharmacol Sci. 2010; 14: 577-88.
7. Yao JC, Hassan M, Phan A. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008; 26: 3063-72.
8. Rinke A, Müller HH, Schade-Brittinger C, *et al*. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol. 2009; 27:4656-63.
9. Caplin ME, Pavel M, Ćwikła JB, *et al*. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014; 371: 224-33.
10. Dogliotti L, Tampellini M, Stivanello M, *et al*. The clinical management of neuroendocrine tumors with long-acting repeatable (LAR) octreotide: comparison with standard subcutaneous octreotide therapy. Ann Oncol. 2001; 12Suppl 2:S105-9.