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Multiple endocrine neoplasia type 1 and breast cancer. An association to consider☆

Neoplasia endocrina múltiple tipo 1 y cáncer de mama. Una asociación a tener en cuenta

Multiple endocrine neoplasia type 1 (MEN1) is an uncommon syndrome with an autosomal dominant hereditary pattern. The genetic basis of MEN1 consists of a mutation of the MEN1 gene located in chromosome band 11q13, resulting in germ line functional loss. This gene encodes for a protein called menin that acts as a tumor suppressor.[1] Multiple endocrine neoplasia type 1 syndrome is characterized by the association of primary hyperparathyroidism (PHP), enteropancreatic neuroendocrine tumors and pituitary adenomas. Primary hyperparathyroidism is the first and most common of these components to develop, exhibiting a penetrance of approximately 100% by 40–50 years of age.[2] Enteropancreatic neuroendocrine tumors have a prevalence ranging from 30% to 75% depending on the series,[3] and are the main cause of morbidity and mortality in patients with MEN1. Pituitary adenomas are present in 30–40% of the patients.[3]

However, the acknowledged clinical spectrum of MEN1 is widening as a result of the appearance of other neoplasms in both endocrine and non-endocrine tissues, including carcinoid tumors, adrenal gland adenomas, lipomas, angiofibromas, collagenomas and meningiomas.[3]

In recent years, several studies have indicated that MEN1 syndrome may be implicated in the development of breast cancer. Menin protein may be related to the development of breast cancer due to its estrogen receptor-stimulating role.[4] We present the case of a woman diagnosed in 2004, at 41 years of age, with a left breast lesion detected on the occasion of a routine examination. The mammographic image was suggestive of malignancy; a cytological study was therefore carried out, with the identification of carcinoma. The personal history included menarche at 9 years of age, mild smoking (4 cigarettes a day) and two offspring (first delivery at 21 years of age). The family history included a mother with PHP and multifocal papillary thyroid carcinoma (tall cell variant and follicular variant). There was no family history of breast cancer. A left upper quadrantectomy and axillary lymphadenectomy were performed. The histopathological study revealed hormone receptor-negative infiltrating ductal carcinoma of nuclear grade 2 measuring 1.8 cm in diameter, with a MIB-1 proliferative index 3%, HER-2 negativity and p53 negativity. Ten lymph nodes without metastatic disease were removed. The patient received 6 cycles of chemotherapy according to the FEC scheme (5-FU, epirubicin and cyclophosphamide), with adjuvant radiotherapy. Following the diagnosis of breast carcinoma and during follow-up, the recorded albumin-corrected plasma calcium levels were between 11.3 and 12.1 mg/dl, with plasma phosphorus 1.8–3.4 mg/dl, intact PTH 120–170 pg/ml and hypercalciuria. After the biochemical diagnosis of PHP, sestamibi scintigraphy was performed, showing uptake in the right inferior parathyroid gland. Surgery was carried out, a unilateral approach being adopted, with the exploration of both right parathyroid glands and the removal of a right inferior parathyroid adenoma. However, the pathology report indicated parathyroid hyperplasia. Following first surgery, the patient continued to show biochemical evidence of persistent PHP. Repeat surgery was therefore carried out, with the adoption of a unilateral approach to remove the right superior gland. The pathology report indicated adenoma. In view of the maternal history of PHP and multiple glandular involvement, a genetic study was performed, with detection of the variant p.C421R/p.426R in the MEN1 gene. At present, after the second operation in 2006, the patient is asymptomatic, with no data suggestive of PHP relapse. During follow-up there has been no evidence of a recurrence of her breast carcinoma. In addition, biochemical tests and imaging studies were performed to detect possible enteropancreatic neuroendocrine tumors and pituitary adenomas, with all the study results proving normal. After the diagnosis, a family study was made, with positive findings for MEN1 in a sister, two maternal nephews, and one of the daughters. We do not know whether the sister has developed breast cancer, though to date the daughter has not presented this type of tumor.

In recent years there have been descriptions of the association of MEN1 syndrome with breast cancer in patients without germ line mutations of the BRCA1 and BRCA2 genes, associated with hereditary breast cancer.[5,6] Furthermore, there have been reports of women with MEN1 who also have mutations of the BRCA1 and BRCA2 genes.[7,8] In our case, mutations of these genes were not determined at the time of diagnosis, though according to the current recommendations genetic counseling is indicated, since the patient was diagnosed with triple-negative breast carcinoma (negative

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progesterone and estrogen receptors and HER-2 negativity) before 50 years of age.[9]

The Dutch MEN1 study group recently published a study comprising over 90% of the Dutch population with MEN1, with a mean follow-up of 20 years, which assessed the risk of women with this syndrome developing breast cancer.[10] In this study, 73% of the women with MEN1 and breast cancer had no family history of this type of tumor. In addition, no differences were found in the prevalence of risk factors associated with the development of breast cancer (age at menarche and menopause, parity, age at first delivery, breastfeeding, use of oral contraceptives, obesity, smoking or alcohol consumption) between patients with MEN1 and breast cancer and the control group. Likewise, no associated prolactinomas were recorded. The relative risk of breast cancer in women with MEN1 was 2.83 in this cross-sectional study, which classifies the MEN1 gene as a moderate risk factor. Furthermore, no increases in other types of tumors were recorded. These data are consistent with the findings in three other cohorts with MEN1 in the United States, Tasmania and France, comprising a total of 675 patients. The incidence of breast cancer on evaluating the combined data of all three cohorts was 1.96 (95%CI 1.33–2.88).[11] On the other hand, in the Dutch cohort the mean patient age at diagnosis was 48 years, which is 10 years earlier than in the Dutch general population. In our case, the patient age at diagnosis was also early, since breast cancer in the Spanish population is typically seen in women over 50 years of age.[9] Finally, in the Dutch cohort, most tumors were luminal lesions associated with a favorable prognosis, with a single case of triple-negative breast cancer, as in our patient. The authors concluded that in women with MEN1, there was sufficient justification for starting screening for tumors of this kind from 40 years of age and with a periodicity of every two years.

In conclusion, although there appears to be a link between MEN1 and breast cancer, no clear causality has been established due to the limitations of the published series and the possibility of an association between MEN1 syndrome and mutations of the BRCA family of genes. The clinical practice guidelines on the management of MEN1 published in 2012 made no mention of breast cancer screening, since the potential association had not been reported at that time,[3] though this subject has been addressed by more recent publications.[12] Further studies are needed to clarify the relative risk of these tumors in women with MEN1 and the impact of breast cancer screening in this population. Nevertheless, it seems reasonable to intensify screening in women with MEN1 at an earlier age than in the general population and with a periodicity that should be established on an individual basis.

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