Etiopathogeny of Multiple Myeloma Associated With Breast Cancer: Case Reports

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Abstract- The association between multiple myeloma and solid cancers is rarely described in the literature. Some authors report that multiple myeloma increases the risk of developing some cancers such as breast cancer. We report three cases of multiple myeloma and breast cancer metachronous in order to study the etiopathogenesis of this association. Such a big spectrum of these studies should be done to understand whether there is a relation between causes of these two diseases or the risk factors behind this rare association. Our objective is to be able to define patients with high and low risk of developing secondary cancer in order to adapt the therapies and propose possibly screening for colon and breast cancers every two years for patients with high-risk multiple myeloma.

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Keywords: Multiple myeloma; Breast cancer; Association; Etiopathogeny

Introduction

The association between multiple myeloma and solid cancers are rarely described in the literature. Some authors report that the existence of multiple myeloma increases the risk of developing cancers such as breast cancer. We report three cases of multiple myeloma and metachronous breast cancer to investigate the etiopathogenesis of this association.

Case Report

Case report No. 1

Mrs. R.M, 84 years old, with a history of hypertension under treatment, had been followed since 2004 for multiple myeloma stage I IgG Kappa chain according to the Salmon and Durie classification. The patient was monitored on a regular basis. Ten years later, the clinical examination showed a 1 cm hard left breast nodule with nipple retraction. The investigations revealed that there was, infiltrating ductal carcinoma, the hormone receptors were positive for estrogen and progesterone, and Her 2 neu was negative. The patient refused surgery. She was on hormone therapy alone with tamoxifen. The evolution was marked by the stability of her breast cancer and myeloma then the patient was lost sight of.

Case report No. 2

Mrs. W. N, 50 years old, was followed since 2010 for a multiple myeloma IgA type I Lamda chain stage III according to the Salmon Durie classification. The discovery pattern was spinal cord compression in relation to the 3rd lumbar vertebra. She had decompressive radiotherapy. The patient was treated with 4 blocks of velcade, thalidomide and dexamethasone with complete remission of her disease. After two years, the screening mammogram showed an ACR5 right breast injury. The patient had a mammectomy, and histopathological examination concluded that had invasive ductal carcinoma, hormone receptors were estrogen and progesterone positive, and her 2 neu was positive. Bone scintigraphy showed D12 hyperfixes and hyperfixations in the anterior arches of the 5th, 6th straight sides. The treatment included hormone therapy with letrozole with bisphosphonate and right chest wall radiotherapy for breast cancer, and 4 cycles included velcade and dexamethasone for multiple

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myeloma. The patient is currently in complete remission of her breast cancer and myeloma with a four-year follow-up since the end of treatment.

Case report No. 3

Mrs. B.O, 65 years old, was followed since 2001 for multiple myeloma stage III A kappa chain IgG according to the Salmon Durie classification. The patient received 12 cycles of Melphalan, Prednisone and Thalidomide with a partial response, followed by consultation with biological stability. The evolution was marked by the discovery, 6 years later, of a breast nodule. The explorations concluded that there was infiltrating lobular carcinoma of the upper quadrant of the right breast with positive hormone receptors. The extension assessment showed hyperfixation of the 6th right side, sternum and dorsal spine with negative tumor markers. A straight mastectomy with ipsilateral axillary lymph node dissection was performed. In view of the underlying hematological malignancy and the immunodeficiency field, the patient was receiving only Tamoxifen hormone therapy initiated in November 2007 for breast cancer and Melphalan and Prednisone-based chemotherapy for recurrence of hematological malignancy with correct response. In July 2011, she had right inguinal pain. The examination noted the presence of a fixed hard right inguinal mass. The inguinal biopsy was inconclusive. The patient was receiving palliative analgesic radiation therapy. The evolution was marked by the alteration of its general state. The patient died 3 months later in a septic shock table.

Discussion

The association between multiple myeloma and solid tumor is rare or even exceptional (1). In recent years, the survival of patients with multiple myeloma is improved due to improved therapeutic means. However, the risk of secondary cancer has increased because of environmental factors related to the disease and treatment (2). A prospective study published in 2016 showed a delay of 2.7 years between the treatment of multiple myeloma and the appearance of a second cancer (3). In our observations, the time to onset of breast cancer was 10, 2 and 6 years, respectively. Several hypotheses have been raised concerning the appearance of breast cancer after treatment of multiple myeloma: the carcinogenic effect of myeloma treatment, the immune deficiency in myeloma patients, the genetic predisposition with p53 gene expression and the alteration of the microenvironment with dysfunction of breast cancer resistance protein (BCRP/ABCG2) by plasma cells. It has long been known that among the side effects of chemotherapy is the appearance of a second cancer. Melphalan, a potent alkylating agent, is one of the chemotherapy agents at risk of causing secondary neoplasia. Only one patient in our observation received melphalan. Indeed, the alkylants are recognized as strongly carcinogenic agents and the delay of three to four years, in this case, is sufficient for the appearance of a secondary cancer (4). In three randomized studies, one in elderly patients treated with melphalan, prednisone and thalidomide (5,6) and two in patients receiving thalidomide as autograft maintenance therapy for multiple myeloma (7,8), there was an increase in the risk of secondary cancers four times higher in the thalidomide arm compared to the control arm. These cancers were haematological, but also various solid tumors, mainly gastrointestinal and mammary. It should be noted that these secondary cancers occurred late, the median time between the start of thalidomide treatment and the diagnosis of secondary cancer was more than two years. This was the case of our second observation, which had received thalidomide two years before the discovery of breast cancer. However, according to a large Swedish retrospective study (9), other non-treatment factors may also play a role. This Swedish study showed that patients with multiple myeloma have a significantly increased risk of developing secondary cancers compared to the general population, mainly hematologic cancers (chronic myeloid leukemia, myelodysplastic syndrome), but also solid tumors (stomach, non-melanocytic skin cancers). In addition, this study reported that patients with monoclonal gammopathy of undetermined significance (GMSI), a precursor disease of multiple myeloma, also had an increased risk of developing these cancers compared to the general population. The increased frequency of some cancers among previously untreated GMSI patients suggested that non-treatment factors may contribute to the development of secondary cancers in patients with plasma cell dyscrasias such as multiple myeloma.

One of the non-treatment-related factors that may contribute to the development of secondary cancers in patients with multiple myeloma is immunosuppression related to the myeloma process (1). Indeed, multiple myeloma leads to predominantly humoral immunodepression, but also cellular, especially in cases of leukopenia. A brief reminder of the role of anti-tumor immunity is needed here. The immune system can thwart and prevent tumor development by three main mechanisms. First, it protects the host from viral

infections (in particular by EBV and HPV) and thus the tumors they favor. Second, it eliminates pathogenic organisms, reducing the inflammatory response itself potentially carcinogenic. Finally, it detects and eliminates tumor cells. This is the case of the first observation that developed breast cancer 10 years after the diagnosis of multiple myeloma while it was not taking any treatment. Another hypothesis that could explain the association between multiple myeloma and breast cancer is the mutation of p53 that could be found in different types of solid and hematological cancer. The p53 tumor suppressor gene is involved in the control of normal cell proliferation, differentiation, and apoptosis (10). Inactivation of p53 by mutation or allelic loss was observed in many solid tumors, and the results suggested a relationship between the presence of a p53 gene mutation and tumor development or progression (11,12). In addition, alterations in the p53 gene have been reported as a prognostic factor in breast cancer (13). On the other hand, multiple myeloma is one of the few neoplasia in which the mutation of p53 is very rarely found at the time of diagnosis (1). Overall, p53 mutation has been found in less than 20% of patients with multiple myeloma, those who typically have advanced and aggressive forms of the disease, including leukemic cells in the blood (1-14). The conclusion from these studies was that p53 mutations represented a late event in the progression of multiple myeloma and are not considered an important prognostic factor. In addition, genotype studies have shown that germline mutations in the CDKN2A gene may predispose to multiple myeloma and other cancers (15). In clinical practice, and for most patients, multiple myeloma remains an incurable hematologic malignancy and therefore, the overall risk of death is significantly greater than the risk of developing a second cancer (16).

The rare association between multiple myeloma and breast cancer should not be due to chance. The problem of identifying causes of secondary cancers in treated multiple myeloma is related to the small number of cases reported in the literature. New studies based on a large number of patients should be conducted to understand whether there is parallelism between the etiologies of these two diseases or the risk factors behind this rare association. The goal is to be able to define patients at high and low risk of developing secondary cancer in order to adapt therapies and possibly offer screening for colon and breast cancers every two years in patients with high-risk multiple myeloma.

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