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Multiple Myeloma Mimicking Bone Metastasis: The Contribution of Biochemistry Laboratory to Differential Diagnosis

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Abstract: Breast carcinoma is a tumor that tends to metastasize to various organs. The hasty diagnosis of metastasis in patients treated for breast carcinoma who report symptoms for another malignant tumor, may be the cause of diagnostic and therapeutic delay. We report the case of a patient with breast ductal carcinoma, having completed her therapeutic protocol, she came in 3 years later with severe bone pain, epistaxis and headache in a context of asthenia and anorexia, suggesting a relapse of her breast cancer with bone metastasis. On clinical examination, the patient presented with cutaneous and mucosal pallor. She had no other signs of secondary localization, the performance of electrophoresis and immunofixation of serum proteins, led to a diagnosis of multiple myeloma. This observation highlights the diagnostic difficulty that can arise in patients treated for breast carcinoma who present with a malignant hemopathy mimicking a metastasis of the initial cancer, or other cases where the multiple myeloma is synchronous with other malignancies. This clinical similarity may delay treatment and worsen the patient's condition. This situation can be avoided by the simple performance of protein electrophoresis, which is a relevant method of diagnosis and follow-up of monoclonal gammopathies thanks to the efficient separation of serum proteins and quantification of monoclonal peaks.

Keywords: Multiple Myeloma, Breast Carcinoma, Serum Protein Electrophoresis, Immunofixation

1. Introduction

Breast carcinomas are tumors with a high metastatic potential, especially to the lung, brain and bone, with variable periods of occurrence from a few months to several years [1, 2].

However, diagnostic difficulties may arise in cases of hematological malignancies clinically mimicking a bone metastasis presentation, such as patients presenting with severe bone pain and lytic bone lesions on the MRI.

The reported case presents an illustration of this difficulty in a patient initially treated for ductal carcinoma of the breast, who presented multiple myeloma three years after finishing her cure.

2. Case Report

We report the case of a 68-year-old patient, hypertensive under treatment, with a history of infiltrating ductal carcinoma of the breast (IDC) grade II SBR (3+2+1), Hercept test was

negative, with pulmonary and hepatic metastases, without secondary bone localization, for which she benefited from surgery with lymph node curage, chemotherapy, hormonal therapy and radiotherapy.

Having completed her therapeutic protocol in March 2018. She came in 3 years later (March 2021) with severe bone pain, epistaxis and headache in a context of asthenia and anorexia, suggesting a relapse of her breast cancer with bone metastasis. On clinical examination, the patient presented with cutaneous and mucosal pallor. She had no other signs of secondary localization. Given the history of breast cancer, a spinal MRI was performed showing diffuse spinal infiltration, the biological workup revealed normocytic anaemia with HB=6.1 g/dl and a smear test showing red blood cells in rolls. In order to rule out an etiology other than bone metastases, a serum protein electrophoresis (SPE) performed by capillary electrophoresis technique (MINICAP FLEX PIERCING; SEBIA®) was performed, and showed a monoclonal peak migrating in the beta globulin zone estimated at 118 g/l. Immunofixation electrophoresis (IE) of the serum was performed on a semi-automatic device (HYDRASYS; SEBIA®) with agarose gel as migration support, revealed a monoclonal gammopathy of IgG Lambda type. An immuno-fixation electrophoresis (IE) of urinary proteins revealed the presence of a Bence Jones type Lambda proteinuria, thus reorienting the diagnosis towards a multiple myeloma.

The patient underwent an osteo-medullary biopsy (difficult aspiration even in the ilium) which revealed a diffuse plasma cell infiltration >30%. Renal function and blood calcium levels were normal.

The patient was put on a weekly VTD protocol (Bortezomib- Thalidomide - Dexamethasone), with partial remission after 3 courses. The patient continued the same protocol for 3 additional courses with a very good partial response, then was put on maintenance treatment with Bortezomib. The patient did not receive a hematopoietic stem cell transplant because she was not considered eligible according to local guidelines.

Table 1. *Biochemical Test Results.*

Test	Result	reference values
Total protein (g/l)	152	62 - 87
Proteinuria (mg/l)	1202, 8	< 100
Microalbuminuria (mg/l)	29	< 20
Proteinuria / Creatinuria (mg/mmol)	117	< 20
Albumin (g/l)	21, 17	35 - 50
Free lambda (mg/l)	157, 08	5, 71 - 26, 30
Free Kappa (mg/l)	10, 83	3, 30 - 19, 40
Free Kappa/λfree ratio	0, 07	0, 26 – 1, 65
β2 microglobulin (mg/L)	5, 43	0, 7 – 1, 8
Proteinuria/Creatinuria (mg/mmol)	117	< 20
Creatinine (umol/l)	63, 27	50 - 90
Alkaline phosphatase (U/l)	106	35 - 104
LDH (U/l)	244	135 - 214
Calcium (mg/L)	68	86 - 103

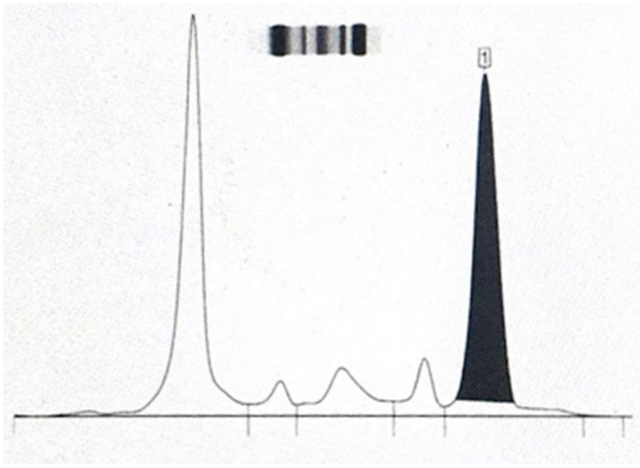

Figure 1. *Serum Electrophoresis Showing a Peak Migrating in the beta 2 Globulin Zone Estimated at 118 g/l+ Decrease in Gammaglobulins.*

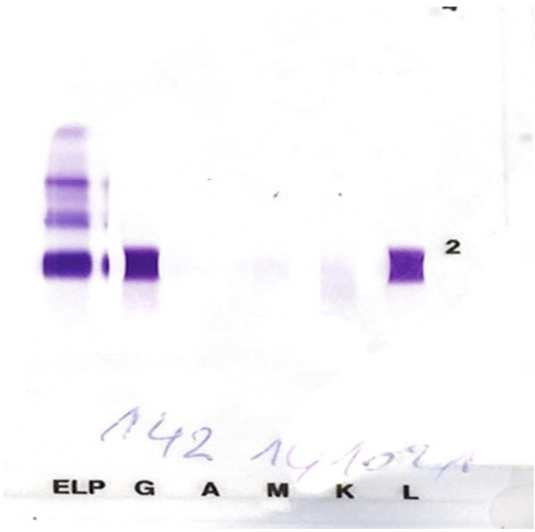

Figure 2. *IE of the Serum Showing a Monoclonal Gammopathy of IgG Lambda Type.*

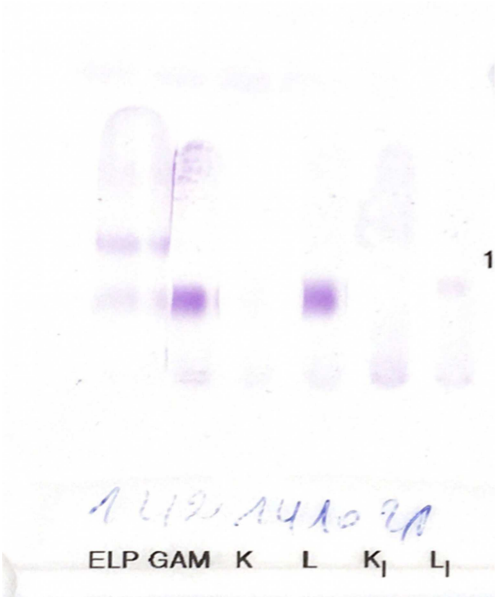

Figure 3. *IE of Urine Sample Showing the Presence of a Bence Jones Proteinuria Type Lambda.*

3. Discussion

This case illustrates the diagnostic complexities of multiple myeloma. Given the history of a treated breast cancer three years before symptomatology, breast cancer relapse was the most likely diagnosis. There are clinical and radiological similarities between these two cases, notably the lytic images on MRI, which are present in 80% of multiple myeloma [3]. However, the presence of normocytic normochromic anemia, rouleaux of red blood cells and normal alkaline phosphatase levels were suggestive of another cause.

Indeed, alkaline phosphatase (ALP) are elevated in 2/3 of patients with bone metastases, and only in 4-17% of patients with multiple myeloma [4] Serum protein capillary electrophoresis, a simple and non-invasive test, has provided a major diagnostic orientation by showing a monoclonal peak, helping to adjust the diagnosis. Capillary electrophoresis of serum proteins, immunofixation and free light chain assay increase the diagnostic sensitivity of multiple myeloma to 97%. Currently, it is the recommended screening method for suspected multiple myeloma [3].

There are several similar cases in the literature of diagnostic difficulties of multiple myeloma in patients with a history of osteophilic cancers, such as breast cancer, which, even when diagnosed at an early stage, has a risk of bone metastasis of 22% over an average period of up to 8.4 years [5].

Savage D et al [4] report the cases of two patients aged 73 and 56 years initially treated for breast cancer, who presented respectively 8 and 11 years later with bone pain, the diagnosis of metastasis was retained and treatment with radiotherapy was started without clinical improvement, causing a diagnostic delay.

Tomono et al [6] reported on a 72-year-old patient treated for breast cancer who presented with a fracture of the 8th thoracic vertebra complicated by paraplegia, and was treated with radiotherapy before the diagnosis was rectified on osteo-medullary biopsy.

Rossi D et al [7] reported the case of a 51-year-old patient who presented 15 years after treatment for breast cancer with bone pain, the diagnosis of bone metastases being retained, she was put on hormonal therapy before a bone-medullary biopsy was performed following persistent alteration of renal function.

Chandra et al [8] reported the case of a 63 year old patient previously treated for breast carcinoma, who presented 15 years later with scapular pain with a lytic lesion on imaging suggesting a bone metastasis.

Mastroianni et al [9] reported the case of a 67-year-old patient treated for breast cancer who presented 4 years later with bone pain diagnosed as bone metastasis for which she was put on hormonal treatment (Fulvestrant and Palbociclib), before undergoing a biological workup in view of the lack of clinical improvement, showing a monoclonal peak of migration in the gamma zone on plasma protein electrophoresis, which was of the IgG Kappa type on immunofixation.

Vennepureddy et al [10], reports the case of a A 77-year-old female with history of hypertension, diabetes mellitus type II, dyslipidemia, and chronic kidney disease who presented to the hospital after a fall, Her clinical examination and lab tests on admission showed an irregularily shaped mass on the outer quadrant of the left breats, an acute kidney injury, normocytic normochromic anemia, and multiple bony lesions on the MRI. The patient had a synchronous diagnosis of multiple myeloma, breast cancer, and monoclonal B-Cell Lymphocytosis.

These literature data show similarities regarding the history of breast cancer: the age of the patients (mean age = 63.6 years), the clinical presentation (since they all showed up to consultation for bone pain), with intervals ranging from 4 to 15 years after the end of treatment. This is consistent with the reported case, aged 68 years, presenting with the same symptoms 3 years after the end of treatment, but unlike the cases cited in the literature, the patient was able to benefit from adequate treatment thanks to an early biological workup.

These cases highlight the diagnostic difficulty that can arise in patients treated for breast carcinoma who present with a malignant hemopathy mimicking a metastasis of the initial cancer, or other cases where the multiple myeloma is synchronous with other malignancies. [11-13] This clinical similarity may delay treatment and worsen the patient's condition. This situation can be avoided by the simple performance of protein electrophoresis, which is a relevant method of diagnosis and follow-up of monoclonal gammopathies thanks to the efficient separation of serum proteins and quantification of monoclonal peaks, and which demonstrates a monoclonal peak in 82% of cases. The sensitivity of the test increases to 93% when combined with serum protein immunofixation and to 97% when a free light chain assay or 24-hour proteinuria is performed. [3, 14, 15]

The second interesting feature of this case is the occurrence of multiple myeloma after treatment for breast cancer, which raises the question of the possibility of multiple myeloma secondary to adjuvant chemotherapy, but there are currently no data concluding that there is a causal link between these two entities, unlike acute myeloid leukemia and non-Hodgkin's lymphoma [7, 16].

4. Conclusion

Multiple myeloma has various clinical presentations. In cases of bone pain or skeletal lesions in patients previously treated for breast cancer, the hasty conclusion of a bone metastasis may lead to a delay in the diagnosis and treatment of multiple myeloma. This situation can be avoided by performing a biological workup with electrophoresis and immunofixation of serum proteins, as accessible and non-invasive tests for rapid and sensitive screening of multiple myeloma.

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