Vertebral bone metastasis in breast cancer: a case report

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Abstract

Background: We report here a case of a 66-year-old woman with a very aggressive form of breast carcinoma, having both liver and bone dissemination points. Case Description: The patient was admitted for a rapid onset disk-herniation-like syndrome, but which on further investigation proved to be in fact a metastatic case of breast cancer. We found evidence of disseminations at least in the lumbar vertebral bodies and the liver. Pathological analysis of the available vertebral metastasis revealed a HER2+ molecular pattern, according to the newly evolving molecular typing of breast cancers. Despite a rapid treatment instauration, the patient reacted poorly to taxanes and osteoclast inhibitors, and died after less than 11 months from admitting to the hospital. Conclusions: This is a rare case of an aggressive breast carcinoma identified initially after the vertebral metastases themselves that induced a non-specific symptomatology.

Keywords: breast cancer, HER2 only positive, vertebral metastasis.

Introduction

Breast cancer is the most common cancer in women and the leading cause of cancer mortality worldwide [1, 2]. Approximately 95% of all breast tumors are carcinomas, meaning that they arise from the epithelial cells of ducts and of lobules [3]. Although classical histopathology describes breast carcinomas as either non-invasive (as intraductal carcinoma, intralobular carcinoma, or Paget’s disease of breast) or invasive (invasive ductal carcinoma, invasive lobular carcinoma, medullar carcinoma, colloid carcinoma); breast cancer phenotypes are extremely heterogeneous and very frequently pathological staging or tumor grading are not accurate predictors for the therapeutic strategy or overall prognostic.

Considerable efforts have been made to establish a consensus and molecular characteristics of distinct subclasses. Wide scan gene-expression studies started more than a decade ago, and the first study that approached this methodology found four main molecular patterns spread among many breast tumor types: luminal-like, basal-like, HER2-positive and normal-like [4]. In time, the target gene spectrum narrowed and the luminal-like type was subdivided in types A, B, and C [5, 6]. Now it seems that most commonly accepted are five molecular types: ER+ (luminal-like types A and B), and ER- (HER2-positive, basal-like and normal-like (or unclassified)); as demonstrated by genetic and immunohistochemical testing [7–9].

Basal-like carcinoma is the third most frequent and is characterized by the expression of basal cytokeratin 5, EGFR (not necessarily), and the absence of ER, PR and HER2. Because of these three missing transcripts, this subtype is also known in the literature as the “triple negative” tumor. Basal-like breast carcinoma is known to generate mostly secondary disseminations to brain and lungs. The phenotype is in generally centered on an aggressive, poor differentiated tumor that has a tendency for high recurrence and high mortality in the first years after the treatment [9, 10].

Luminal-like carcinoma is the most frequent molecular pattern, being characterized by the expression of ER/PR, cytokeratin 8/18, HER2 and Bcl-2. Subtype A has a strong expression of ER, while subtype B tumors express les ER and mostly EGFR-1 and cyclin E1. While the phenotype of the subtype A is mostly represented by in situ lobular carcinoma and lobular invasive carcinoma, and have a good prognostic; subtype B reflects a higher tumor grading and a poor prognostic [9, 10].

HER2 carcinoma (the second most frequent form), besides strongly expressing HER2 may or may not express ER. Luminal cytokeratins may be expressed. The phenotype of the ER negative cases reflects mostly high grade carcinomas, which have a poor evolution.
despite a relative good response to taxanes and anthracyclines [9–11].
Unclassified carcinomas express luminal cytokeratin, but are negative for ER, PR, HER2, basal cytokeratins and EGFR. The phenotype is again that of “triple negative” tumors with, that is an aggressive evolution but with an overall better prognosis compared to basal-like tumors [9, 10].

Despite all the current new advances in molecular pathology and widespread patient screening methods, a significant proportion of women still present with advanced breast cancer. In particular, breast cancer skeletal metastases have unique characteristics, and although being only rarely silentious (usually associated with severe and refractor bone pain), they occur in more than half of patients with breast cancer [12].

In the present report, we present the case of a patient admitted initially in the Clinics of Neurosurgery from the Emergency County Hospital Valcea for a lumbar disc herniation symptomatology. Consecutive imaging and paraclinical investigations revealed a breast carcinoma, which had already spread to liver and to lumbar vertebral bodies. Aspirative punctation localized a tumor on the left infero-lateral region of the left breast, and the immunohistochemical profile of the vertebral metastasis revealed a HER2 only profile. Treatment approach and patient evolution are then discussed, relating this patient with the literature data on bone metastases secondary to breast cancer tumors.

**Patient, Methods and Results**

**Initial clinical and imaging assessment**

Patient L.A., female, aged 66 years, retired, is presented in the Neurosurgery Department of the Emergency Hospital Valcea, accusing pain at the level of the lumbar spinal cord with irradiation on the pathway of the left sciatic nerve and paresthesia in the lower left limb. This symptomatology had an abrupt onset with pain in the lower left lumbar region and irradiation to the aneromedial region of the left calf; and paravertebral contracture.

General and neurological clinical examination found a normostenic patient, with normal weigh, as well as a slight decrease of the muscular force of the left lower limb, paresthesia at the same level, stoppage gate, Neri, Bonnet and Lasegue (at 45°) signs positive for the left inferior limb, diminished achilean reflex on the left foot, hypoesthesia of the anterolateral region of the left calf. Altogether, these data suggested an initial diagnostic of left lumbar disc herniation at the level of L4.

MR scanning on the lumbar spinal cord confirmed a disc herniation at the level of the left L4 radicular root, and also multiple non-compressive vertebral tumors at the level of L4, L5, S1 and S2. No familial history of any tumoral disease could be recorded. In these conditions, the patient was referred for a surgical procedure in order to correct the spinal nerve root compression symptomatology and to further explore the tumors.

Serological investigations found that the erythrocyte sedimentation rate (ESR) was increased three times over normal, and the blood cell count was not modified. Presurgical systemic clinical examination revealed no obvious neoplasic disease.

Five days after being admitted in the hospital, the patient undergoes surgery, with discectomy at the L4 level by L4/L5 fenestration, and exophytic tumoral biopsy at the level of S2.

**Tissue processing for histopathology**

The biopsy was fixed in 10% buffered neutral formalin and then processed for mild decalcification in a 5% formic acid solution. Decalcification process was checked daily for a week, with an equal volume of 3% of ammonium oxalate until no precipitate was formed. Next, the tissue was dehydrated and routinely processed for paraffin inclusion. The block was cut on a rotary microtome and serial sections were collected on poly-L-Lysine coated slides (Sigma, Medicalkit, Craiova, Romania). A few intercalate slides were stained with Hematoxylin–Eosin, and other sections were processed for immunohistochemistry as described below.

Briefly, after deparaffination and antigen retrieval, sections were cooled to room temperature and incubated for 30 minutes in 1% hydrogen peroxide solution. Sections were next washed in PBS, followed by a blocking step of 30 minutes in 1% skim milk. A panel of primary antibodies was selected in order to characterize the molecular subtype of the tumor (Table 1).

Table 1 – The antibodies utilized in this study

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Host</th>
<th>Clone</th>
<th>Dilution</th>
<th>Retrieval</th>
<th>Source</th>
<th>Metastatic cells' reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth muscle actin (SMA)</td>
<td>Mouse</td>
<td>1A4</td>
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<td>0.1 M Citrate pH 6</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>Bcl-2</td>
<td>Mouse</td>
<td>124</td>
<td>1:100</td>
<td>Tris-EDTA, pH 9</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>BRCA-1</td>
<td>Mouse</td>
<td>GLK-2</td>
<td>1:50</td>
<td>0.1 M Citrate pH 6</td>
<td>Dako</td>
<td>+</td>
</tr>
<tr>
<td>CA125</td>
<td>Mouse</td>
<td>M11</td>
<td>1:50</td>
<td>0.1 M Citrate pH 6</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>CD10</td>
<td>Mouse</td>
<td>56C6</td>
<td>1:100</td>
<td>Tris-EDTA, pH 9</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>CD117</td>
<td>Rabbit</td>
<td>–</td>
<td>1:500</td>
<td>Tris-EDTA, pH 9</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (CEA)</td>
<td>Rabbit</td>
<td>–</td>
<td>1:400</td>
<td>Proteinase K digestion</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>Cytokeratins 1/5/10/14</td>
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<td>34BE12</td>
<td>1:50</td>
<td>Proteinase K digestion</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>Cytokeratins 5/6</td>
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<td>D5/16 B4</td>
<td>1:50</td>
<td>Tris-EDTA, pH 9</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>Mouse</td>
<td>OV-TL 12/30</td>
<td>1:100</td>
<td>Tris-EDTA, pH 9</td>
<td>Dako</td>
<td>-</td>
</tr>
<tr>
<td>Cytokeratin 18</td>
<td>Mouse</td>
<td>DC 10</td>
<td>1:50</td>
<td>0.1 M Citrate pH 6</td>
<td>Dako</td>
<td>+</td>
</tr>
</tbody>
</table>
were incubated overnight at 4°C. Next day, slides were slipped after a light Hematoxylin with DPX (Fluka, Medicalkit). Positive tissue reactivity was considered as with 1% BSA (Sigma). Finally, the slides were cover-

PBS, pH 7.2, and all antibodies were diluted in PBS step with a 30 minutes incubation time. The signal was dissected the spongious bone architecture (Figure 1).

E-cadherin

Epidermal growth factor receptor (EGFR)

Human epidermal growth factor receptor 2 (HER2)

Epithelial membrane antigen (EMA)

Estrogen receptor (ER)

Ki-67

P53

P63

Progesterone receptor (PR)

Thyroid transcription factor (TTF-1)

Vimentin

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The primary antibodies were added and the slides were incubated overnight at 4°C. Next day, slides were washed and the signal amplified utilizing a biotinilated species-specific secondary antibody (diluted as 1:500, Dako, Medicalkit) and an ABC HRP kit (Dako), each step with a 30 minutes incubation time. The signal was finally detected with 3,3’-diaminobenzidine (DAB) (Dako).

All intermediate washing steps were done in 0.1 M PBS, pH 7.2, and all antibodies were diluted in PBS with 1% BSA (Sigma). Finally, the slides were cover-slipped after a light Hematoxylin with DPX (Fluka, Medicalkit). Positive tissue reactivity was considered as the expected cytoplasmic/nuclear localization pattern together with the accepted relative percentage of cell reactivity [13].

Lastly, the sections were imaged with a Nikon 90i microscope (Nikon, Apidrag, Bucharest, Romania) equipped with a 5-megapixel CCD camera, and the images were grabbed with apochromatic objectives, as uncompressed TIF files utilizing the NIS Elements BR software (Nikon).

Histopathological characterization of the tumor

Anatomo-pathological examination of the Hemato-
yxin–Eosin stained slides revealed an undifferentiated epithelial tumor, which together with its stroma dissected the spongous bone architecture (Figure 1).

Among remaining bone lamella, tumor cells were plasmomorph, with nuclei ranging form flat elongated shapes to round and lobulated silhouettes. Very rare abnormal mitotic figures could be noted. On an average, the nuclei comprised most of the cells’ areas, but this was difficult to appreciate as no clear-cut inter-cellular delimitation could be made. This heterogeneous mass of cells was organized as trabeculae and irregular nests of cells that did not seem to be clearly delimited from the tumor stroma. A moderate desmoplastic stroma contained these tumor cells, with a minimum inflammatory reaction and erythrocyte extravasation. Rare formation of tubular entities was also noted (Figure 1).

As the above images pointed toward a carcinoma-tous (and later on proved by the cytokeratin profile) metastasis with an unknown origin, a large panel of antibodies was further utilized in order to characterize this tumor.

In order to asses the histopathological subtype of the tumor and its possible origin we pursued to characterize the expression of the following markers (Table 1): for breast as the origin (BRCA-1, CK5/6, CK7, CK18, CK20, 34βE12, ER, PR, p63, and alpha-actin); for lung (TTF-1, ER, CK7, CK20); for the genitourinary tract (ER, PR, p63, vimentin, CD117, CK7, CK18, CD10, CEA, CA125), for the liver (EMA, VIM, CEA), and for the gastrointestinal tract (ER, vimentin, ER, PR, CK7, CK20, CDX2, CA125). In addition, some of the markers were also intended as prognostic markers for the disease (ER, PR, Ki67, Bcl-2, EGFR, HER2, BRCA-1).

Molecular characterization by immunohisto-
chemistry showed only very rare ER positive cells within the tumor nests, while PR was completely negative (Table 1, Figures 1 and 2). In both cases, the percentage of positive cells was thus below the positivity threshold of at least 10% of all the tumor cells. On the other hand, HER2 was strongly positive in all tumor cells, the expression pattern being represented by the membranes and to a lesser extent by the cytoplasm itself. Also, the tumor was completely negative for the anti-EGFR antibody. From the cytokeratins panel, only luminal cytokeratin 18 was strongly expressed by the tumor cells’ cytoplasm, while basal cytokeratins and in fact all other anti-cytokeratin antibodies utilized were not present at all.

In addition, the tumor showed no expression of Bcl-2 and p53, with a moderate membrane presence of E-cadherin, and the cytoplasmic and to a lesser extent nuclear expression of breast cancer type 1 susceptibility protein (BRCA-1). In fact, it was in a serial section stained for anti-E-cadherin that we noticed that the tumor cells could be also arranged as very rare and discrete tubular structures (Figure 2A). No reactivity could be noted for p63, CD117, TTF-1 and CA125. Less than 10% of the tumor cells expressed vimentin, while this was present in fibroblasts, smooth muscle cells and endothelial cells in the stroma. Less than 5% of the tumor cells’ nuclei were positive for Ki-67. Smooth muscle actin was expressed only by smooth muscle cells and stromal miofibroblasts.
Figure 1 – Histopathological assessment of the vertebral metastasis: (A) The tumor invades and replaces the bone tissue, in the upper right of the image a remnant trabecula is visible; (B) Pleomorphism of the tumor cells; (C) very rare ER positive cells; (D) PR was completely absent; (E) 3+ reactivity for HER2 scoring; (F) and (G) No expression of EGFR and other cytokeratins rather than CK18 (H). Scale bars represent 50 µm.
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Figure 2 – Histopathological assessment of the vertebral metastasis – continuation: (A) E-cadherin was expressed by the tumor cells (membrane pattern); (B) BRCA-1 positive tumor cell nests; (C) Very rare Ki-67 positive cells; (D) Together with the stroma cells, a small fraction of the tumor cells were expressing vimentin; (E) Only the stromal cells were positive for an anti-SMA antibody; (F) Echo-guided fine needle aspiration from the breast tumor showed frequent red blood cells and relative frequent groups of epithelial cells with increased nucleo-cytoplasmic index, hyperchromatic and dyskariotic nuclei. Scale bars represent 50 µm.

Post-surgical management

Histopathological data recommended a complete re-evaluation of the case in order to update the diagnostic, to identify the tumor of origin and the therapeutic approach.

Clinical re-examination did not reveal obvious changes that would suggest an original tumor site. At the examination of the breasts, the patient accused bilateral discomfort, but mostly in the left breast, without any palpable tumor mass. ECOG (Eastern Cooperative Oncology Group Performance Status Scale) performance score was appreciated as 2 out of 5.

Serological investigations at 10 days post-surgery showed an increasing ESR (now more than seven times the normal value), GPT was twice the normal value (2×N) and GOT was 1.5 more than normal (1.5×N). Ferritin was 3.5×N, total calcium was 1.5×N, and alkaline phosphatase was 1.5×N. Circulating tumoral antigens investigated were CEA (1.5×N), CA15–3 (2×N) and AFP (=N).

Thoraco-pleuro-pulmonary radiography showed no abnormal changes and a gynecological examination revealed no abnormality.

When a mammary echography was performed, it showed a hypoechochogenic image of 0.3×0.2 cm behind
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the left nipple, with irregular border, with posterior attenuation, and a non-homogenous structure given by the presence of inclusions with increased echogenicity. No abnormal images were detected in the right breast. No images that would have suggested an adenopathy could be identified in the axillas. Mammography of the left breast characterized the tumor further as having a diffuse border, with a 0.5×0.5 cm and with a few microcalcifications. The right breast had no abnormal changes.

Echo-guided fine needle aspiration from the tumor showed frequent red blood cells and relative frequent groups of epithelial cells with an increased nucleocytoplasmic index, with hyperchromatic and dyskariotic nuclei (Figure 3).

Abdominal echography showed a liver with a regulated contour, homogenous, normal size, but with a nodular image in the liver’s seventh segment (Figure 3). Biliary ducts, pancreas, spleen, both kidneys and internal genital organs were all normal. No ascitic liquid and no retroperitoneal adenopathies could be viewed.

Abdominal CT-scan revealed on the visceral side of the left hepatic lobe a spontaneous hypodense image with a diameter of 2.63 cm, with a discrete contrast increase during the arterial time, and becoming isodense during the portal time (Figure 4). The patient had normal spleen, pancreas and kidneys, with cholecystectomy in the past. Multiple osteolitic type of images were recorded at the level of L4, L5, S1, S2 vertebral bodies, paralleling initial MR scan results.

All the clinical, histopathological and imaging data together indicated the final and most probable diagnostic: liver and vertebral bodies metastases with a breast tumor as the most probable point of origin. An L4 disc herniation was over-imposed on the tumor pathology.

Thus the case is reconsidered after two weeks from the initial presentation, as a stage IV left breast neoplasm (central portion), with liver and bone metastases (T1aN0Moss, hep).

The patient was thereafter treated with sequences of osteoclast inhibitors, polychemotherapy and based on the particular symptomatology. As osteoclast inhibitor therapy, the patient received Bondronat (Acidum ibandronicum), as 6 mg once at 28 days. The polychemotherapy consisted of Docetaxel (TXT), 75 mg/sqm/hour once at three weeks, ×6 series; and Xeloda (Capecitabinum), 1250 mg/sqm twice a day in the days 1–14 of each of the six series. The antialgic symptomatic treatment consisted of NSAID and analgesic drugs (Tramadol) administrated as 100 mg twice a day when needed. Although HER2 was positive on IHC, ECOG status did not recommend beginning of a Herceptin based therapy. No hormonotherapy was indicated as estrogen and progesterone receptors were negative on immunohistochemistry.

During the treatment period, clinical examination revealed the evolution of the disease, with intense bone pain, oligoanuria, nausea, bilious vomiting, and finally leading to hepato-renal failure.

The patient died following a cardio-respiratory arrest, after 10 months and 21 days from the initial presentation.

Figure 3 – Abdominal echography. The liver shows a regulated border, is relatively homogenous, with normal dimensions, and with a nodular image in the seventh segment of the liver, suggestive for a metastasis.

Figure 4 – Native abdominal CT. Hypodense image with a diameter of 2.63 cm is present in the left hepatic lobe, together with osteolytic lesions at the level of the vertebral body.
Discussion

When discussing cancer evolution, most of the patients die mostly due to tumor dissemination rather than due to the effect of the primary tumor. Bone metastases are a frequent target for tumor spreading, and occur in as much as 70% of the patients with breast and prostate cancers, and in 15–30% of the patients with lung, gastro-intestinal, genital tract, kidney and bladder cancers [14]. That is bone is the preferred site of metastasis for cancers in women. Carcinomas are more likely to metastasize to bone compared to sarcomas. The approximate incidence of deaths with bone metastasis in USA is estimated at around 350,000 people each year [15].

The axial skeleton is more likely to be a site of metastasis, and this is thought to occur due to the persistence of red bone marrow in these locations. Usually the ribs, the pelvis, and the spine are the first bones to be involved [14]. The consequences of bone metastasation are severe and often life-threatening. Osteolytic metastases may cause severe pain, pathologic fractures, hypercalcemia, spinal cord and peripheral nerves’ compression. Mechanisms responsible for bone pain are not well understood [16] but seem to be the consequence of osteolysis and bone destruction. There is data in the literature showing that inhibitors of bone resorption like osteoproterogen or bisphosphonates may be utilized to decrease bone pain [17]. Osteolysis brings also increased bone fragility, this also increasing the incidence of pathological fractures because of bone metastasation. Patients with osteoblastic metastases on the other hand, have bone pain and pathologic fractures because of the poor quality of the newly replaced bone. For the patients with breast cancer, it is estimated that once the tumor reaches to bone, less than 20% of these patients will still be alive after five years [18].

As the most frequent form of cancer in women, in breast cancer, bone metastasis incidence is also as high as 65% [19]. It has been reported that bone metastases are more common in well-differentiated primary tumors [14]. That is tumors with tubular formation on at least 10% of the tumor area, nuclei with moderate to minimal variations in size and shape, and less than 10 mitotic figures per 40× microscopic fields (which in fact gather together grades 1 and 2 of the Nottingham–Bloom–Richardson system [20]), show bone metastasation in ~60% of the cases [14]. The spine is the most frequent site for bone metastasis in breast cancer patients, and 17% to 50% of these patients would sustain a vertebral fracture [21].

Lung cancer is the third most common site of origin for bone metastases, after breast and prostate cancers. Small cell undifferentiated carcinomas, adenocarcinomas, and large cell undifferentiated carcinomas have a tendency to spread much more compared to squamous carcinoma (which accounts only for 25–35% of lung cancers) [22].

From the digestive tract cancers, in 10.7% of the colorectal primary tumors have been described bone metastases. The incidence of bone metastases in colorectal carcinomas ranges between 5.6–7.9% [23]. Signet-ring cell carcinoma showed a high incidence of bone metastasis, and especially if located in the cecum and rectum [24]. Poorly differentiated adenocarcinomas, and especially those showing a high degree of lymphatic permeation in the submucosal layer constitute the most frequent forms of gastric carcinomas that metastasize to bone [25].

Most of the patients with cervical cancer metastasizing to axillary skeleton had been shown to have squamous cell carcinomas, although other forms may also metastasize to bone [26].

For urothelial bone metastasizing tumors (as most of the urothelial tumors are transitional cell carcinomas), grades II–IV transitional cell carcinomas are the most prone for local and distal invasion. Infiltration of lamina propria, muscle wall, or blood vessels had been reported as predictive factors [27]. Bone metastasizing cases of renal adenocarcinomas have been also reported in the literature [28].

As already discussed, nowadays it seems that most commonly accepted molecular types of breast cancer are: ER+ (luminal-like types A and B), and ER–HER2-positive, basal-like and normal-like (or unclassified); as demonstrated by genetic and immunohistochemical testing [7–9]. Published data shows the basal-like carcinomas had a higher rate of recurrences compared to the other types of breast cancer [4]. Basal-like breast cancers also have a tendency for visceral (cerebral and pulmonary) metastases rather than bone disseminations [29, 30].

We described here the case of a 66-year-old patient, initially admitted for a disk-herniation-like syndrome, but which later on proved to be in fact a disseminated case of breast cancer. We found evidence of disseminations at least in the lumbar vertebral bodies and the liver. Pathological analysis of the vertebral metastasis revealed a HER2 molecular pattern that expressed CK18, but was negative for ER, PR, CK5/6 and EGFR. In addition, this secondary tumor expressed E-cadherin and BRCA-1. Together with stromal mesenchymal cells, only a fraction of the tumor cells expressed vimentin, but since this is expressed also in carcinomas, it cannot help in narrowing the disease pattern. On the other hand, this was a proof of an epithelial-mesenchymal transition in these tumor cells as they acquired a metastasizing profile; and it correlated with an aggressive profile of an estrogen receptor-negative tumor.

Only very few of the tumor cells were Ki-67-positive, so the metastasis itself was not characterized by an increased proliferative index. However, the evolution was extremely rapid, the patient dying after less than 11 months from the initial presentation. While we could not obtain immunocytochemistry data from the fine needle biopsy, we could not find out the actual molecular profile of the primary tumor.

There is data in the literature aiming at assessing the molecular profiles of different metastases compared to the molecular profiles of the originating breast tumors [31]. While it seems that HER2 status is not lost between the primary tumor and the metastasis, ER and PR expression has a tendency to be lost in the metastases in less than 10% of the cases [31]. According
to the same study, brain metastases were most frequently HER2+ type, liver metastases were predominantly ER+ or PR+/HER2+, and bone metastases showed mostly a triple negative or a ER+ or PR+/HER2- pattern. Altogether, it could very well be that our case had also a HER2+ pattern in the primary tumor, with uncertain ER/PR status. The presence of this factor itself and the rapid evolution of the disease parallels data showing that HER2+ status predicts the presence of circulating tumor cells, and thus the potential spread of the disease [32], and our case showed at least liver and vertebral metastases.

The disseminated tumor showed a strong cytoplasmic and rarely nuclear immunoreactivity to an anti-BRCA-1 antibody (Clone GLK-2, Dako), a pattern previously demonstrated to be present in BRCA-1 gene exon 11 mutations but also in patients with no BRCA-1 mutations at all [33]. BRCA-1 is a tumor suppressor gene, and together with BRCA-2, mutations in these genes have been proved to be linked to hereditary breast and ovarian cancers. Although the risk of developing breast and/or ovarian cancer is increased by the presence of harmful mutations in these genes, a familial history of multiple cases of breast and/or ovarian cancers might be a stronger predictor, as not even every patient with a harmful BRCA mutation is prone to develop a tumor. In fact it has been showed that the inheritance of mutations in these two genes increase the chances of developing a breast tumor five folds over the rest of the population, thus modulating mechanisms or activated cofactors must play an important role [34]. Our patient had no familial history of breast/ovarian cancers, but a genetic screening of BRCA-1 would have brought more information in this matter.

E-cadherin is a calcium-modulated adhesion molecule expressed by most of the normal epithelial cells [35]. It is thought it is important during gland formation and epithelial cell polarization [35]. Multiple studies have found loss of E-cadherin expression to cause de-differentiation and invasivity in esophageal ovarian and gastric tumors [36]. Although most studies on breast tumors showed a reduced expression of E-cadherin to be associated with high histological grade, there is no clear-cut correlation with lymph node spreading, the hormonal status or a prognostic value [37, 38]. Thus, the only established role is in pinpointing an invasive lobular carcinoma (which does not express E-cadherin) versus an invasive ductal carcinoma (witch express it more or less, but there are not completely negative) [36]. In our case, E-cadherin immunoreactivity correlated well with a low proliferative index, somehow illustrating a not-very-aggressive invasion profile of the metastasis itself. Moreover, this poor outcome of the disease was independent to the lymph node involvement and the size of the primary tumor.

Although with a rapid onset, and a not typical symptomatology, this was a case of a metastatic bone tumor, which reacted poorly to taxanes and osteoclast inhibitors. As the primary tumor could not be initially pinpointed, these forms of very aggressive and rapid evolving breast carcinomas would need a very precise, rapid and accurate diagnostic scheme for the best possible treatment administrated in the shortest possible period.

Large studies have performed gene expression profiling from the RNA extracted from fine needle aspirate material and proved that different molecular classes of breast cancer showed variable sensitivities to different chemotherapy materials, and this probably is the future for cancer rapid management [39–42].

Conclusions

In conclusion, this paper presents a case report that follows an advanced but locally silentious breast cancer form, which is diagnosed only in the late phase of metastasation. The particularity of the case consists in that it presented as a classical disc herniation with no localized or systemic tumor suspicion. In the future, molecular profiling of breast carcinomas together with their pathological forms will ensure a rapid and correct assessment of the patient, while wide scan microarray-type of genetic analysis will correctly evaluate the inherited background of each patient, and thus the susceptibility of disease spreading, response to the treatment, and best treatment option.

References

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Received: June 2nd, 2011
Accepted: August 20th, 2011