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Case Report
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Peritoneal Metastasis as Extramedullary Myeloma

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Abstract

A 71 year old woman with a prolonged history of cured breast cancer after lumpectomy and radiation in 1991. She presented with unspecific symptoms of fatigue, increased abdominal size. Her labs showed acute renal failure and the imaging demonstrated innumerable deposits on omentum, serosa of intestine, pleura and pericardium. Tumor markers of the gynecologic and mammary malignancies were high [CA-125 of 94 units/ml (0-35) and CA15-3 of 788.6 units/ml (1-30)]. Cytology of the ascetic fluid is suspicious for carcinoma but not definitive. Omental biopsy demonstrates poorly differentiated malignant cells; however immunostaining indicates diffuse positivity for CD138 with restricted kappa light chains the marker of plasma cells disorders. Bone marrow is involved with plasma cells in 5% and Multiple Myeloma (MM) profile was positive to monoclonal IgG Kappa. Patient initiated treatment with Velcade, Cyclophosphamide and Dexamethasone (CyBorD). Resultantly, FISH showed Del 17p (TP53) in 49% and repeat CT scan showed progressing disease after the first cycle of CyBorD. Treatment was switched to Daratumumab, Velcade and Dexamethasone. The patient's nutrition continued to be poor and her breathing worsened due to pleural effusion. Finally, palliative care was consulted and hospice was chosen.

Case Presentation

A 71-year-oldfemalepresents with abdominal symptoms of nausea, retching, increased abdominal girth and general symptoms of poor appetite and unintentional weight loss of 10 pounds over 6 weeks. Her past medical history is significant for right partial mastectomy and radiation for breast cancer in 1991. Most recent mammography was normal just 1 year prior to her current presentation in 2016. Current blood work, with normal reference ranges shown, demonstrates the following: hemoglobin 10.3 g/dL (11.9-15.5), creatinine 12.3 mg/dL (0.6-1.1), BUN 79 mg/dL (8-25), potassium 7 mmol/L (3.3-4.9), calcium 8.4 mg/dL (8.5-10.3) and total protein 9.7 g/dl (6.5-8.5). Urine output is less than 400 ml in 24 hours. Renal ultrasound demonstrated no obstruction or abnormalities. She was placed on Renal Replacement Therapy (RRT) after conservative treatment failed for oliguric acute kidney injury.

CT scans of chest, abdomen and pelvis demonstrate a uterus mass, innumerable omental deposits and multiple serosal implants along the large and small bowel without evidence of bowel obstruction. Additionally, CT scans demonstrate moderate ascites and metastatic soft tissues deposits on the pericardium, pleura, and serosa. PET scan reveals extensive hypermetabolic masses and deposits in the same areas as the CT scans in the uterus, bowel loops, cervical spine and lymph nodes in the chest, abdomen and pelvis (Figures 1-3).

The above findings are most suspicious for diffuse metastases, likely secondary to primary gynecologic-type or mammary malignancy. Abnormal tumor markers are significant for a CA-125 of 94 units/ml (0-35) and CA15-3 of 788.6 units/ml (1-30). CA19-9 and CEA tumor markers were within normal reference range; however, other malignancies of the small bowel, melanoma and lymphomas could still be considered. Cytology of the ascetic fluid is suspicious for carcinoma but not definitive.

CT-guided omental biopsy demonstrates poorly differentiated malignant cells; however immunostaining is diffusely positive for CD138 with restricted kappa light chains. Kappa to lambda ratio is greater than 10:1. Notably, CD99 is negative, arguing against a diagnosis of PNET/Ewing's sarcoma. Furthermore, CAM 5.2 and cytokeratin 19 are also negative, arguing against a diagnosis of carcinoma. Lastly, positive CD56 and negative cyclin D1 argue against a diagnosis of lymphoma.

Subsequently, work-up for plasma cell disorders is completed. Serum Protein Electrophoresis

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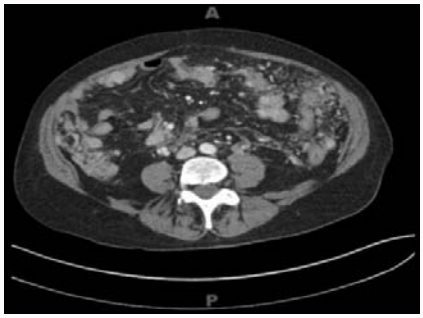

Figure 1: CT scan shows peritoneal deposits along with small intestine.

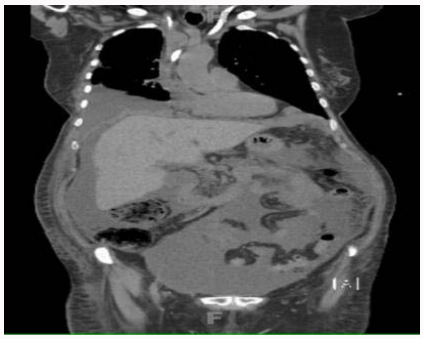

Figure 2: MRI: shows large ascites with uterine mass and numerous deposits.

(SPEP) and Urine Protein Electrophoresis (UPEP) demonstrate a gamma-restricted peak. Serum protein immunofixation demonstrates a monoclonal IgG Kappa. Serum free light chain studies are as follows: kappa 374 mg/dL (0.33-1.94), lambda 0.6 mg/dL (0.6-2.6), kappa/lambda ratio 603.2. Serum IgG is elevated at 3,644 mg/dL (700-1,600). B2 Microglobulin (B2MG) is elevated at 31.3 mg/L (1.0-2.5). Additionally, IgA and IgM are low. Skeletal survey is negative for any lytic lesions. Bone marrow is involved with plasma cells in 5%.

SPEP completed 5 years in 2012 ago demonstrated a mildly elevated peak gamma of 1.9 and IgG kappa monoclonal. The SPEP was repeated in 2015, demonstrating an increase in gamma from 1.9 to 2.1 with the same immunofixation finding.

In light of the above findings, the patient was told she has monoclonal gammopathy of undetermined significance (MGUS). Therapy was initiated with VCD/ CyBorD: Velcade, Cyclophosphamide and Dexamethasone. Resultantly, FISH showed Del 17p (TP53) in 49% and repeat CT scan showed progressing disease after the first cycle of CyBorD. Treatment was switched to Daratumumab, Velcade and Dexamethasone. The patient's nutrition continued to be poor and her breathing worsened due to pleural effusion. Finally, palliative care was consulted and family chose hospice.

Case Discussion

We are writing a case of an Extramedullary Myeloma (EMM) which presented as implants on the soft tissues and lymph nodes in the entire pelvis, abdomen and chest. Our patient is a woman with a longstanding, invasive history of treated breast cancer with recently elevated CA-125 and CA15-3. Conclusively, the carcinogenic nature of the primary malignancy is pinpointed to the breast or ovary. The staining of the omental cells demonstrates positive CD 138 and the kappa restricted population points to a plasma cell pathology.

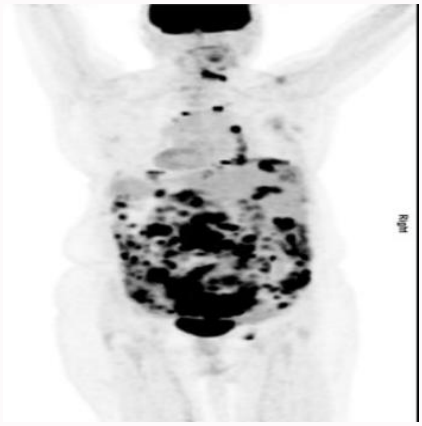

Figure 3: PET scan shows numerous metastasis in chest, abdomen and pelvis.

Multiple Myeloma (MM) is defined by the presence of 10% or more of clonal Plasma Cells (PCs) in the bone marrow (or a biopsy-proven extramedullary plasmacytoma) and by the evidence of end-organ damage attributed to the PC disorder (CRAB: hypercalcemia, renal insufficiency, anemia, and bone lesions) [1]. In most cases of MM, the PC proliferation is restricted to the bone marrow. However, a subset of MM patients develops Extramedullary Myeloma (EMM), defined by the presence of clonal PCs outside the bone marrow [2].

In our patient, Multiple Myeloma (MM) profile was positive to monoclonal IgG Kappa. Bone marrow is involved with plasma cells in 5% which is less than 10% the required percentage for MM diagnosis. Nevertheless, patchy involvement of bone marrow makes less than 10 % involvement acceptable for diagnosis of MM in the context of presence other MM criteria.

Prevalence

At the time of myeloma diagnosis, EMM is found in 6% to 8% of patients (as in our patient) [3,4]; however, this increases to 10% to 30% as the disease progresses [2,5]. Interestingly, it has been noticed that the incidence of EEM relapses is increasing, possibly due to novel treatments or allogeneic stem cell transplantation [4]. EMM may present in different patterns [2,6,7]:

1. Local soft-tissue growth from adjacent bone lesions.
2. Hematogenous spread with:

a) Large subcutaneous plasmacytomas.

b) Metastatic-like nodules in the skin or in organs such as liver, spleen, kidney, breast or lymph nodes.

c) CNS involvement (meningeal myelomatosis).

3. Develop at the site of surgical scars or even at the sites of catheter insertions.

Mechanism

Plasma Cells (PCs) are heavily dependent on the bone marrow microenvironment. Stromal cells and extracellular matrix prompt the PCs' growth, survival, drug resistance, and migration in the bone marrow milieu [8]. However, the ultimate mechanisms in which PCs become stromal cells, independently favoring their proliferation and

survival in the absence of the BM microenvironment, still remains unclear [9].

In a cohort study of 14 multiple myeloma patients with EMM disease, DNA sequencing is done for a targeted panel of 50 tumor suppressor and oncogenes, which are often mutated in cancer. Most samples contain only a single mutation, with a maximum of three mutations in one sample. These somatic mutations are found in NRAS, KRAS, Kit c840, ATM, PAC, TP53 and BRAF. Extramedullary PCs also demonstrate up regulation of a Focal Adhesion Kinase (FAK) [9]. Furthermore, in different studies PCs show a high frequency of p53 and Ras mutations and up regulation of a FAK [10]. In our patient, FISH showed Del 17p (TP53). In terms of molecular pathogenesis, PCs in EMM are characterized by a decreased expression of the CD56 adhesion molecule and an increased expression of CD44, which is involved in cell proliferation and migration [2,11]. The increased expression of CXCR4 and its ligand CXCL12 have also been implied to contribute to the dissemination of PCs through the activation of an epithelial-mesenchymal transition pattern [12].

Prognosis

Extramedullary spread in multiple myeloma likely points to aggressive myeloma or disease relapse. The presence of EMM, excluding bone-related plasmacytomas, at the time of diagnosis is associated with an adverse prognosis [4]. However, at the time of relapse, extramedullary disease, excluding the bone-related plasmacytomas, has an even worse prognosis with an overall survival of less than 6 months [13].

In our case, the patient had MGUS in 2012 and 2015 and normal kidney function and Complete Blood Count (CBC) at that time just 2 years before presentation. Her response to the chemotherapy was poor approved by clinical deterioration and imaging where repeated-CT scan after the first cycle of CyBorD demonstrated progressed disease. The patient was doing poorly regarding her nutrition even with TPN (Total Parenteral Nutrition). Her breathing was gradually deteriorating due to fluid accumulation in her chest and bilateral pleurocentesis confirmed the malignant nature of pleural effusions. Unfortunately, she ended up in hospice care.

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