HEMATOLOGY, TRANSFUSION AND CELL THERAPY

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Case Report

Spontaneous spleen rupture: an unusual presentation of extramedullary multiple myeloma

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Case report

A 50-year-old female, previously diagnosed with systemic arterial hypertension and peripheral arterial occlusive disease, presented with an acute onset of intense abdominal pain. She denied previous symptoms (including B symptoms, asthenia or bone pain) and was promptly evaluated and diagnosed with acute abdomen, demanding urgent surgical intervention. During the procedure spontaneous rupture of the spleen was noted and a splenectomy was performed. Concurrently, she presented some laboratorial abnormalities as follows: hemoglobin 10.3 g/dl, white blood cell count 15,700/mm^3 with 7% of plasma cells, platelets 63,000/mm^3, creatinine 5.7 mg/dl, corrected calcium 9.6 mg/dl (reference value: 8.4–10.2 mg/dl), lactate dehydrogenase (LDH) 3885 U/L (reference value: 313–618 U/L).

Based on the unusual presence of plasma cells in the peripheral blood and other findings, the patient underwentbone marrow evaluation. The bone marrow aspirate had 11% of plasma cells, which were characterized as clonal (CD20-/+, CD38++, CD45+/++, CD138-/+, Kappa-/+, negative CD56) by the flow cytometric immunophenotyping. The karyotype showed the following aberrations in ten of the twenty metaphases analyzed: 38~41,XX,del(1)(q?21),-2,-4,-5,-6,-7,-9,add(12)(q24.3),-13,-14,add(16)(p13.3),add(17)(q25),add(19)(p13)X2,-21,-22,+mar1,+mar2,+mar3,+mar4,+mar5,inc[cp10]/46,xx[10].
The bone marrow trephine biopsy histology evidenced a cellularity of 90% due to diffuse infiltration by plasma cells (Figure 1), positive for CD20, CD138 and Kappa in the immunohistochemical study. The spleen histology showed atypical plasma cell infiltration and the immunostaining results confirmed clonality (CD20+, CD138+, Ki67 60%, Kappa+) (Figures 2 and 3).

Some additional exams included serum protein electrophoresis that contained a 3.5 g/dl monoclonal protein peak and a serum immunoelectrophoresis that distinguished IgG 4606 mg/dl and Kappa 1850 mg/dl. The imaging exams did not show bone or visceral involvement.

Because of the aggressive behavior, we started the treatment with the DT-PACE protocol. The patient presented severe infectious complications after the chemotherapy, leading us to discontinue the treatment until the infection was managed.

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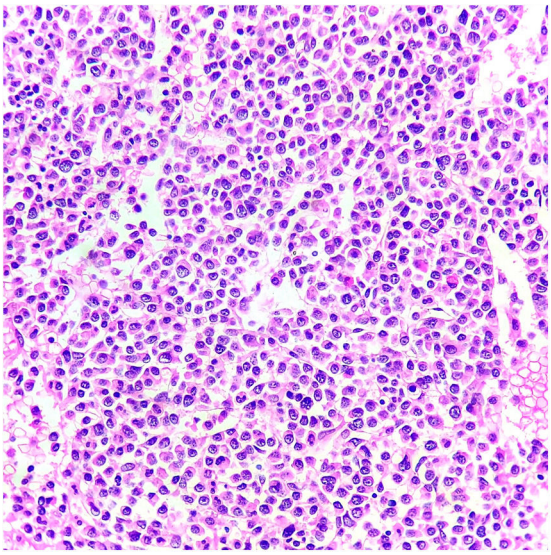

Figure 1 – Bone marrow trephine biopsy shows diffuse and massive infiltration by plasma cells with cytologic atypia. Hematoxylin & eosin, ×400.

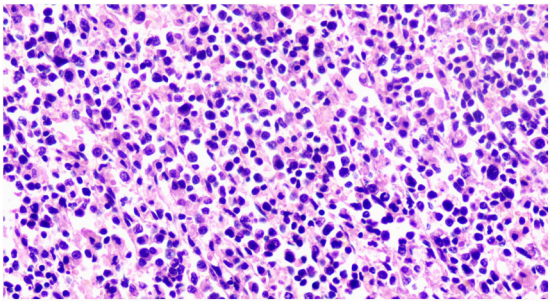

Figure 2 – Splenectomy specimen with architectural effacement due infiltrating plasma cells. The neoplastic cells are CD138 positive (membrane).

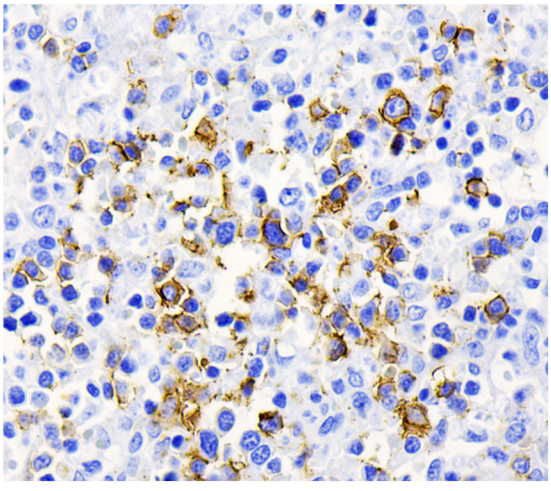

Figure 3 – Splenectomy specimen with architectural effacement due infiltrating plasma cells. The neoplastic cells are CD138 positive (membrane).

We proceeded treatment with the cyclophosphamide, thalidomide and dexamethasone (CTD) protocol. After six cycles the patient achieved partial response and will be submitted to autologous stem cell transplantation (ASCT) as consolidation therapy.

Unlike the other cases of spontaneous splenic rupture in newly diagnosed myeloma reported, our patient did not have a fatal outcome within the initial presentation, despite its aggressiveness, and after the resolution of the infectious complications we have been able to treat her with the usual protocol of the institution for multiple myeloma.

Literature review

Multiple myeloma accounts for 13% of all hematologic malignancies and is the result of clonal plasma cell proliferation, which is restricted to the bone marrow in most cases.[1] A small portion of patients with multiple myeloma develops extramedullary disease (EMD), defined as the presence of clonal plasma cells infiltrating distant sites from the bone marrow through hematogenic dissemination.[2] This form of presentation is found in 6–8% of the recently diagnosed multiple myeloma and 10–30% of the patients with relapsed or refractory disease.[3] Curiously, the dissemination of the plasma cells may be induced by a bone fracture or even some invasive procedures, such as surgery or catheter insertion.

The presence of EMD correlates with a more aggressive presentation and higher risk disease, usually with very elevated LDH, being more frequent the presence of poor prognostic factors, such as the del 17p and clonal mutations (genes TP53, RB1, FAK and RAS). The molecular mechanism that explains the hematogenic propagation of the plasma cells is not well understood, involving the altered expression of adhesion molecules, with reduced expression of CD56 and P-selectin (molecules that promote adhesion of the plasma cell to the bone marrow), increased expression of CD44 (the molecule implicated in the cell migration and proliferation) and increased angiogenesis-promoting factors (VEGF, CD31, MMP-9). In the EMD, the histology findings show that the clonal plasma cells have, more frequently, an immature/plasmablastic appearance.[4] All these features contribute to lower rates of progression-free survival and overall survival, even in the era of novel agents.[5]

In 2018, the European Society for Blood and Marrow Transplantation conducted a retrospective trial that included 3744 patients with multiple myeloma, among them just 3.7% presented involvement of sites not related to the skeleton. These extramedullary sites, in decreasing order of prevalence, were: kidneys (27.3%); skin (23%); lymph nodes (17.3%); central nervous system (10.1%); lungs and respiratory tract (6.5%); liver and gastrointestinal tract (5.8%); pleura and heart (5%), and; spleen, ovaries and testicles (5.3%). Spleen infiltration, followed by its pathological rupture as the initial presentation of multiple myeloma, is extremely rare, with only three cases reported so far,[6–8] two of them associated with fatal outcomes.

Some direct mechanisms have been used to explain the splenic rupture in multiple myeloma, such as extramedullary hematopoiesis, which is an uncommon finding in this disease; the tumoral pressure effect of multiple plasmacytomas

on the splenic tissue; amyloid deposition in the spleen, leading to capsular distension and increased vascular fragility, and; spleen infiltration by plasma cells, that can invade vessels and capsular walls, especially seen in plasma cell leukemias.[9] Despite not meeting the criteria for plasma cell leukemia, our patient's multiple myeloma presented with an aggressive behavior, by the presence of plasma cells in the peripheral blood, the absence of CD56 in the immunophenotyping examination, a complex karyotype and a very high LDH level; hence, this may account for a similar presentation, the patient having experienced spleen rupture due to infiltration of the spleen by plasma cells.

Plasma cell leukemia is distinct from multiple myeloma as for the clinical behavior, affecting younger patients, with a higher tendency for the development of EMD and an inferior propensity of causing lytic bone lesions and bone pain. It has been previously documented that plasma cell leukemia can present with splenic rupture. In addition, a subgroup of aggressive multiple myelomas may have a similar tendency for this complication. A recent Mayo Clinic study compared outcome results between multiple myeloma patients based on their percentage of circulating plasma cells.[10] They found outcomes much poorer in the group with ≥5% of circulating plasma cells compared to the other group with <5% and these outcomes were similar to those in cases traditionally defined as plasma cell leukemia (≥20% of circulating plasma cells in the peripheral blood or absolute plasma cell count $\geq 2 \times 109/L$).[11] They also noticed that survival rates were the same between patients with 5–19% and ≥20% of circulating plasma cells at diagnosis.

There is no prospective clinical trial focused on patients with EMD treatment and the expert opinion is favorable to considering this presentation as an aggressive form of multiple myeloma that requires intensive treatment. In this context, the ideal therapy for a patient eligible for autologous stem cell transplantation (ASCT) consists in the induction triple therapy containing immunomodulatory drugs and proteasome inhibitors, followed by the ASCT with high-dose melphalan conditioning, triple therapy consolidation and maintenance treatment with lenalidomide. For the non-eligible patients, the treatment choice with better responses consists in the triple therapy containing an alkylating agent plus proteasome inhibitors and a corticoid or continuous lenalidomide plus dexamethasone.

More clinical and laboratory trials are needed in cases of multiple myeloma with an EMD presentation for a better understanding of its true incidence, pathogenic mechanisms, prognostic information and for the definition of the best therapeutic strategy.

Conflicts of interest

The authors declare no conflicts of interest.

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