Testicular Plasmacytoma Masking as Epididymo-orchitis in a Known Multiple Myeloma Patient

URWAT TIL VUSQA1, PALASH ASAWA1, SALMAN FAZAL2 and YAZAN SAMHOURI2

1Department of Internal Medicine, Allegheny Health Network, Pittsburgh, PA, U.S.A.; 2Division of Hematology and Cellular Therapy, Allegheny Health Network Cancer Institute, Pittsburgh, PA, U.S.A.

Abstract. Background/Aim: Extramedullary plasmacytoma (EMP) is defined as a localized plasma cell neoplasm that arises in tissues other than the bone. The most common sites of involvement of EMP are the upper airways followed by lymph nodes, gastrointestinal tract, thyroid gland, skin, brain, liver, and lungs. Testicular plasmacytoma has a very rare occurrence with about 70 cases reported in literature to date. Case Report: We describe a 52-year-old male with a diagnosis of multiple myeloma presenting with lytic lesions of the axial skeleton. He had lambda light chain restricted, R-ISS stage II with high risk cytogenetics as he tested positive for t(4;14). He underwent four cycles of cyclophosphamide, bortezomib and dexamethasone followed by auto-peripheral stem cell transplantation. He was kept on ixazomib, lenalidomide and dexamethasone maintenance therapy, but relapsed soon after and was diagnosed with plasmacytoma of the left lung. Therapy was switched to daratumumab, carfilzomib and dexamethasone and the patient received radiation of his left lung. He then developed left painless testicular mass which was treated with six weeks course of antibiotics. However due to persistence of concerning features on scrotal ultrasound post-treatment, the patient underwent radical orchiectomy with pathology coming back positive for plasma cells. Conclusion: The testes serve as a sanctuary site for hematological malignancies due to the presence of the testicular-blood barrier. Hence, it is imperative to keep a high index of suspicion for testicular plasmacytoma in the right clinical context when evaluating a patient with known multiple myeloma.

Multiple myeloma (MM) is defined as monoclonal neoplastic proliferation of plasma cells within the bone marrow (1, 2). It accounts for 10% of all hematological malignancies and 2% of newly diagnosed cancers, with the median age of diagnosis being 66-70 years (2, 3). Extramedullary disease (EMD) is seen in one third of patients; 6-8% present with EMD at the time of diagnosis and an additional 10-30% in relapsed/refractory disease (2, 4). These figures are much higher in autopsy studies where extra-skeletal involvement is reported to be as high as 70% (5).

Extramedullary plasmacytomas are defined by the World Health Organization as localized plasma cell neoplasms that arise in tissues other than the bone (6). The median age of presentation for extramedullary plasmacytoma (EMP) is 55-59 years, which is lower when compared to multiple myeloma (7, 8). The most common site for involvement of EMP is the upper airways (80%). Other sites include lymph nodes, gastrointestinal tract, thyroid gland, skin, brain, liver, and lungs. Testicular plasmacytoma is a very rare occurrence, with about 70 cases being reported in literature so far (1). There is conflicting evidence of what EMP means in terms of prognostication. Moreover, there are no clear guidelines on how to treat EMP. Herein, we report a case of an extremely rare occurrence, testicular plasmacytoma in a 52-year-old gentleman who had a prior diagnosis of MM.

Case Report

The patient was a 52-year-old male with past medical history of hypertension, coronary artery disease, gastroesophageal reflux disease who was diagnosed with multiple myeloma in April 2019. He presented to the outpatient clinic for concerns of neck and upper back pain and increasing fatigue. He
subsequently had X-rays of the spine performed which showed a C2 fracture and T6 and T11 compression deformities. Pertinent lab values at the time of diagnosis were as follows: Corrected calcium 12.4 mg/dl, creatinine 0.9 mg/dl, hemoglobin 8.1 g/dl. SPEP showed bicalon gammapathy with M-spike 0.4 g/dl and 4.8 g/dl. Immunofixation confirmed bicalon IgG lambda and free lambda light chain monoclonal gammapathy with IgG levels of 7,053 mg/dl with immunoparesis. Free lambda chain levels were 128.52 mg/dl. Lactate dehydrogenase level was 249 U/l, B2 microglobulin level 3.8 mg/l and albumin 2.2 g/dl. A skeletal survey revealed lytic lesions in the calvarium, thoracic spine, pelvis, femurs, and bilateral humeri. A PET/CT scan showed innumerable mixed lytic lesions scattered throughout the axial and appendicular skeleton. Bone marrow biopsy performed showed hypercellular bone marrow. Immunostain for CD138 performed on biopsy estimated the plasma cells at 80-90%. In-situ hybridization for kappa and lambda showed that the plasma cells were lambda light chain restricted. Cytogenetics was positive for FGFR3/IGH fusion variant also commonly described as t(4;14). He was classified as R-ISS stage II with high-risk cytogenetics. He underwent one cycle of cyclophosphamide, bortezomib and dexamethasone (CyBorD), followed by four cycles of induction therapy with lenalidomide (Revlimid), bortezomib (Velcade), dexamethasone (RVAD). He underwent auto-peripheral stem cell transplantation (auto-PBSCT) with melphalan conditioning. The patient was maintained on ixazomib, lenalidomide and dexamethasone. However, after about five months into therapy, the patient developed an increased M-spike. He also complained of chest pain, and a CT chest with contrast showed a large left pleural effusion. He underwent bone marrow biopsy which showed 10-20% lambda restricted plasma cell infiltrate. He underwent thoracocentesis and left pleural fluid cytology was consistent with plasmaclotoma. There was evidence of atypical plasma cells with the presence of CD138 and CD56 with lambda light chain restriction. He was subsequently managed with left-sided chest tube placement which was later exchanged with PleurX catheter. He received radiation to his left lung and mediastinum for 2400 cGy. He was then switched to daratumumab, carfilzomib and dexamethasone. PET/CT scan 6-8 weeks post radiation showed significant improvement in left pleural effusions. Five months after switching therapy, patient noticed painless swelling of his left testicular mass, which was evaluated by Urology. Initial scrotal ultrasound (US) showed heterogenous and hypervascular left testes with associated minimal left complex hydrocele and hypervascular left epididymis. These findings were initially attributed to epididymo-orchitis, and the patient was treated with a 6-week course of Levaquin. However, patient’s swelling failed to resolve. A repeat scrotal US showed an interval increase in size of left testis with persistent abnormal heterogenous infiltration throughout the testes, concerning for underlying left testicular neoplasm. No tumor markers were collected at that time and patient decided to proceed with radical orchietomy. The pathology of the resected sample came back positive for plasma cell neoplasm. The plasma cells were lambda-restricted and positive for CD138, MUM-1, CD79a and CD56. The patient underwent PET/CT scan which showed new hypermetabolic foci in the right internal mammary lymph nodes, new soft mass anterior to the right 3rd rib, soft tissue extension along right pleural and mediastinal borders, new soft tissue paravertebral focus on the T6 rib, all pointing towards disease progression. Moreover, to assess leptomeningeal involvement by MM, an MRI brain, MRI cervical/thoracic and lumbar spine were performed which was negative for disease involvement. Patient treatment was switched to carfilzomib, pomalidomide and dexamethasone. Patient also underwent central nervous system prophylaxis with intrathecal methotrexate and hydrocortisone. He also received radiation 3,000 centigray to his right chest wall as he had disease progression. Patient had interval development of symptomatic large right pleural effusion which was drained. He was subsequently enrolled in BITE trial and was initiated on elranatamab monotherapy. However, he was again noted to have disease progression with appearance of new left pleural soft tissue mass with involvement of spinal canal/tecal sac with compression. He was immediately started on high dose steroids and was switched to carfilzomib, dexamethasone, and selinexor. He also received 2,600 centigray of palliative radiation to his left chest wall. Patient continues to be on systemic chemotherapy till date.

Discussion

Extramedullary plasmacytomas are less common than bone marrow involvement by plasma cells as bone marrow provides a favorable microenvironment for plasma cell proliferation (9). The incidence of solitary bone plasmacytoma (SBP) is 5% and even lesser in solitary soft tissue plasmacytoma. 25% of SBP have evidence of systemic disease and have a high incidence of progression to MM if the systemic disease is not present on initial presentation. Contrarily, SEP is associated with a better prognosis (9). A retrospective review analyzing the response to treatment in SEP reported favorable outcomes: 85% of cases remained disease-free and 78% were alive in 15 years (7). The scenario where EMD is present in an existing MM patient is quite different; the prognosis of such patients is dismal. Rosenberg et al reported post-orchietomy survival to be around 5 weeks to 48 months. Moreover, patients who relapse without EMD involvement have a much longer overall survival than patients with evidence of EMD (109 vs. 38 months; p<0.001). Also, when doing a comparison within EMD, bone-related EMD is associated with better overall survival compared to soft-tissue EMD (45 vs. 30 months; p=0.022) (10).
Testicular plasmacytoma is a rare occurrence and accounts for 0.03% to 0.1% of all primary and secondary testicular neoplasms. Testicular plasmacytomas usually occur in patients with systemic multiple myeloma, either at diagnosis or at relapse (11). It is proposed that the testes serve as a sanctuary site for hematological malignancies because of the presence of testicular-blood barrier (1). Hence it is imperative to keep a high index of suspicion for testicular plasmacytoma in the right clinical context when evaluating a patient with known MM. Even in our case, patient’s testicular plasmacytoma was initially mistaken for epididymo-orchitis and was treated with antibiotics.

This is reminiscent of acute lymphoblastic leukemia (ALL) where up to 17% of patients in complete remission present with testicular involvement of ALL, making the male sex a negative prognostic factor (12). Historically, testicular involvement of ALL has been well-described and well researched. Possible mechanisms for chemotherapy resistance in the testes include: i) Presence of different leukemic clone in the testes compared to the bone marrow; ii) Tight junctions between the myoid cells and Sertoli cells preventing large chemotherapeutic molecules from penetrating into the seminiferous tubules; iii) Lower concentration of chemotherapy in the interstitium where the leukemic cells are situated in the testes; iv) Cooler temperature of the testes which makes the chemotherapeutic agents less effective; v) Testes being an immune-privileged site due to the presence of prostagladin E2, anti-inflammatory cytokines and complement inhibitors (13). With the introduction of high-dose methotrexate and improves systemic chemotherapy, orchiectomy and irradiation is rarely needed in ALL involving the testes (13). Moreover, the rates of testicular relapse have significantly reduced with modern intensive chemotherapy. Lessons learnt from ALL can be incorporated into testicular plasmacytoma as well.

Some factors may be associated with soft tissue EMD. IgD associated MM has often been associated with an increased incidence of EMD (14). Moreover, allogeneic transplantation (Allo-T) with dose reduced-intensity-conditioning has a higher frequency of EMD occurrence when compared with autologous stem-cell transplantation (ASCT) (15). Thirty-two percent of patients who underwent Allo-T for MM relapsed with EMD involvement in patients who underwent Allo-T for MM relapsed with EMD involvement in 25 patients. This percentage was 9-14% after ASCT (16). There are several theories to suggest why EMD occurs after Allo-T. Firstly, young, sicker patients with poor prognostic factors are usually the population who is offered Allo-T which inherently increases the risk for EMD relapse. Secondly, the graft-vs-myeloma effect is more effective in the bone marrow than extramedullary sites (16). Whether novel agents used for treatment of MM contribute to the development of EMD remains a topic of much debate.

However, the literature available on this topic does not seem to support this hypothesis. Pour et al looked at 226 patients with MM, and they did not find an association between EMD relapse and novel agents used for treatment of MM (lenalidomide/bortezomib). It is possible that treatment leads to increase in lifespan which then leads to an increased risk of EMD (11). Interestingly, one of the things that can trigger plasmacytomas are surgical site incisions. Hence, they can be seen in laparotomy scars and catheter site insertions (15).

The pathophysiology behind the extramedullary spread of MM has been described in the literature. Plasma cells adhere to the bone-marrow endothelium by means of adhesion molecules which include VLA-4 and CD44. Down-regulation of these molecules has been proposed as a possible mechanism of hematogenous spread of plasma cells. Moreover, chemokine receptors like CCR1, CCR2 and CXCR4 that enable these adhesion molecules to work can also be downregulated, which too can lead to the extramedullary spread of disease (15).

An important thing to note in our case report was that we ruled out CNS involvement of MM after our patient was found to have testicular plasmacytoma. Our patient had a high myeloma burden, evidence of EMD, lambda subtype MM, high-risk cytogenetics, all of which are features associated with leptomeningeal myelomatosis. Other characteristics that are associated include Salmon Duire stage III disease, IgD MM, plasma cell leukemia, plasmablastic morphology, increased LDH levels and p53 deletion. (17). There are no clear guidelines on CNS prophylaxis in high-risk MM. However, some authors do suggest chemotherapy and/or irradiation in high-risk patients (18).

The treatment for testicular plasmacytoma involves radical inguinal orchiectomy. If surgery alone cannot remove the entire tumor burden, local radiation may be considered (19). For patients with known multiple MM who present with EMD on relapse, there are only case reports highlighting the efficacy of bortezomib in treating EMD (15). However, in patients who present with newly diagnosed plasmacytomas with evidence of systemic disease, PETHEMA trial suggests that bortezomib/thalidomide/dexamethasone (VTD) followed by high dose therapy/ASCT is the recommended first-line therapy for younger patients with MM (15).

**Conclusion**

This case adds to the few cases of testicular plasmacytoma reported in the literature. It adds to the knowledge about the treatment modalities available and the course that the disease takes after testicular plasmacytoma appears. Our case also highlights the importance of ruling out leptomeningeal myelomatosis in high-risk multiple myeloma patients. Another learning point is to keep a high index of suspicion for testicular plasmacytoma in the right clinical context, and
ruling malignancy out before treating testicular swelling as epididymo-orchitis.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors’ Contributions

Urwat Til Vusqa: Conceptualization, methodology, investigation, writing – original draft, review and editing, visualization. Palash Asawa: Writing – original draft, review and editing, project administration. Yazan Samhouri: Conceptualization, methodology, writing – review and editing. Salman Fazal: Conceptualization, methodology, investigation, resources, writing – review and editing, visualization.

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