Multiple Myeloma Following Bladder Cancer Successfully Treated With Bortezomib: A Case Report and Review of Literature

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Abstract

The incidence of Multiple Myeloma (MM) following other malignancies is extremely rare. To our knowledge, only 23 cases of this condition have been reported. This study is the first to report on an incidence of MM following bladder cancer after treatment with intravesical Pharmorubicin RD instillation in a 71-year-old male patient. The etiopathology of this specific condition is discussed with an emphasis on two pathogenic features, namely, anthracyclines and gene mutation, which may have been involved in MM development. Regimen consisting of bortezomib may be used as a clinical basis for future treatment of MM following other malignancies.

Keywords: Multiple myeloma; Bladder cancer; Gene mutation; Bortezomib

Introduction

Multiple myeloma (MM) following other malignancies is a rare type of malignant plasma cell disorder. To the best of our knowledge, only 23 cases of MM following other malignancies and its coexisting symptoms have been documented in PubMed MEDLINE [1–23] (Table. 1). MM can occur after the appearance of solitary tumors, such as those in lung cancer and gastric cancer, or hematological malignancies, such as MyeloProliferative Neoplasm (MPN) and lymphoma. We report the first case of a patient with MM following bladder cancer. The satisfactory clinical recovery of this patient after treatment with bortezomib is also discussed.

Case report

A 71-year-old male patient was admitted to the Second Affiliated Hospital of TianJin Medical University in January 2010 after being diagnosed with approximately one-month totally painless gross hematuria. The patient did not have a history of dysuria, urinary urgency, or urethral discharge that could indicate an infectious or inflammatory process. No fever was evident, but the patient occasionally complained of blood clot discharges and flank pain. B-scan ultrasound revealed multiple hypoechoic masses or nodules in the anterior bladder wall and bladder neck. Complete blood count, renal function, and globulin levels were normal. No other evidence of metastatic disease was found elsewhere in the body. Transurethral Resection of Bladder Tumor (TURBT) was performed. The pathological diagnosis was low-grade papillary transitional epithelium carcinoma (Figure. 1). After four cycles of intravesical Pharmorubicin RD instillation (50 mg/m², day 1; one week/cycle) after surgery, the patient exhibited satisfactory clinical recovery. However, a follow-up B-scan ultrasound evaluation five months after chemotherapy revealed multiphypoechoic masses or nodules in the anterior bladder wall and bladder neck. Complete blood count, renal function, and globulin levels were normal. No other evidence of metastatic disease was found elsewhere in the body. Transurethral Resection of Bladder Tumor (TURBT) was performed. The pathological diagnosis was low-grade papillary transitional epithelium carcinoma (Figure. 1). After four cycles of intravesical Pharmorubicin RD instillation (50 mg/m², day 1; one week/cycle) after surgery, the patient exhibited satisfactory clinical recovery. However, a follow-up B-scan ultrasound evaluation five months after chemotherapy revealed hyperechoic uplifted shapes on both sides of the bladder neck, which suggested relapse of bladder cancer. No symptoms and abnormalities were found upon laboratory examination. Cystoscopic examination and TURBT were again performed. Pathological analysis revealed intrinsic-fibrous tissue hyperplasia, as well as chronic inflammation in the tissue overlying the transitional epithelium. No
evidence of recurrence was observed, and no further therapy (including chemotherapy) was provided for four months after the last surgery.

In July 2011, the patient was again referred to the hospital with major complaints of intermittent fever and pain in both lower limbs. The blood count [hemoglobin (Hb) 81 g/L; mean corpuscular volume, 81.7 fl; mean corpuscular hemoglobin concentration, 328 g/L; white blood cell and platelet counts, normal] indicated normocytic, normochromic anemia. The bone marrow contained an excess of plasma cells (40.0%) (Figure 2). Immunohistochemical analysis of the bone marrow showed that the tumor cells were positive for monoclonal κ light chains, CD38, and CD138, but negative for CD79a, CD5, and CD10. Flow cytometric results are as follows: R5 2.0%: CD38 (47.8%), CD138 (31.1%), CD56 (40.2%), and CD20 (-). Immunoelectrophoresis and immunofixation showed a spike in the γ globulin region corresponding to a monoclonal protein (M protein) in the serum and in the urine. The patient had hyperglobulinemia (IgA 3570.0 mg/dL, κ light chain 2810.0 mg/dL), with a noticeably high κ/λ ratio of 30:1. The creatinine level was 108 μmol/L. Plasma albumin (ALB) and lactate dehydrogenase levels were normal (37 g/L and 128 U/L, respectively). The β2M level was increased (6.56 mg/dL). Serum C-reactive protein concentration was 2.98 mg/dl.

A skeletal survey revealed multiple lytic bone lesions in ribs 4, 7, and 8. The adjusted serum calcium concentration was 2.69 mmol/L. Both cytogenetic and FISH analysis indicated a normal karyotype (46, XX [9]). Both ras and p53 gene mutations were detected in the bone marrow mononuclear cells by reverse transcription-polymerase chain reaction.

A diagnosis of multiple myeloma (IgA κ) was given (Durie–Salmon Clinical staging IIIA, ISS stage III). The patient was then treated with one cycle of “VDZ” (1.3 mg/m² bortezomib, d 1, 4, 8, and 11; 40/m² dexamethasone, d1, 8, 15, and 22; and 4 mg/m² zoledronic acid, d1) for chemotherapy. CBC was normal. Bone marrow aspiration and biopsy showed 3% plasma cell. Serum protein electrophoresis and immunofixation indicated the presence of IgA κ monoclonal protein. Bence–Jones proteinuria was again detected (806 mg/dl IgA, 1080 mg/dl κ light chain, and 7.1:1 κ/λ ratio), and good partial remission was achieved based on the evaluation. The patient further received two regular cycles of “VDZ” chemotherapy.
| Authors, year | Age/sex | Malignancies before MM | Treatment before MM | Malignancies-MM interval | SPE/IE | Treatment after MM | Outcome | Abnormal chromosome/gene |
|--------------|---------|------------------------|---------------------|-------------------------|--------|-------------------|---------|--------------------------|
| Drasin H et al., 1979 | 50 F | Lung Lymphocytic lymphoma | Radiation therapy | 9 years | IgG | MOP | Died after 28 months | NS |
| Claudia W et al., 1999 | 57 M | T-cell lymphoma | PUVA + INFa2b | 2 years | IgG λ | alkeran+ decortin | Died after 28 months | NS |
| Muzaffer K et al., 2013 | 68 M | Colon adenocarcinoma gastrointestinal stromal tumor lung cancer | folinic acid 5-fluorouracil irinotecan bevacizumab | 15 months | IgG κ | Chemotherapy and biphosphomate | Died after 18 months | K-RAS mutation t(4;14),17p13, |
| Vassilia G. et al., 2005 | 68 M | CML | INF α Imatinib | 18 months | IgG λ | MP + Imatinib | Alive after 8 months | t(9;14;22) (q34;q24;q11) |
| Frances C et al., 1995 | 74 F | ET | INF α2b P32 | 61 months | IgA λ | MP | Died after 3 months | NS |
| Philip M et al., 1995 | 94 F | ET | Alkylating + thiotepa | 11 years | IgA κ | MP | NA | NA |
| Montserrat R et al., 1990 | 38 F | CNL | Without any therapy | 7 years | κ | MP | Alive after 5 months | 46XX; Ph(-) |
| Michalis M et al., 2009 | 63 F | CML | Imatinib | 65 months | IgA κ | TD + Imatinib VAD Velcode | Alive after two years | NS |
| Pérez LM et al., 2007 | 63 M | Prostate adenocarcinoma | NA | NA | NA | NA | NA | NS |
| Rogulj IM et al., 2011 | NA | CLL | NA | 11 years | Without any therapy | NA | NA | NS |
| Prósper F, et al., 1992 | NA | ET | NA | 5 years | NA | NA | NA | NS |
| Dorn GW et al., 1984 | NA M | Hodgkin's disease | NA | NA | NA | NA | NA | NS |
| Tzilves D et al., 2007 | 74 M | gastrointestinal stromal tumor | Imatinib | 1 month | IgA κ | MP + Imatinib | Died after 6 months | NS |
| Nowakowski et al., 2007 | 65 M | Penile myeloid sarcoma | NA | NA | NA | NA | Died after 16 months | NS |
| Monique A, 2010 | 71 M | Merkel cell carcinoma CLL | RFC | 14 years | κ | CTX+P | Died after 6 months | NS |
| Hashimoto S et al., 1992 | 71 M | Diffuse large B cell malignant lymphoma | CHOP | 32 months | IgA κ | Combination chemotherapy | alive | NS |
| Derghazarian et al., 1974 | 65F | CML | busulphan | 3 years | IgG κ | L | NA | 46XX;22q--;Ph (+) |
| Zoumbos et al., 1987 | 57M | CNL | busulphan | 5 years | κ | NA | NA | NS |
| Majhail NS et al., 2003 | 85 M | ET | hydroxyurea | 50 months | IgG λ | Without any therapy | Refuse any treatment | NS |
| Majhail NS et al., 2003 | 54M | ET | Hydroxyurea | 29 months | IgG κ | MP DOP | Died after 5 years | NS |
| Derghazarian C et al., 1974 | 65 F | ET | busulfan | 7 years | IgG κ | Radiotherapy L + busulfan | Alive after 2 years | NS |
| Kough RH et al., 1978 | 75F | CLL | Chlorambucil | 80 months | IgAk | MP CTX | Died after 3 year | NS |
| Kough RH et al., 1978 | 58 M | CLL | Chlorambucil | 4 years | κ | MP | Died after 1 year | NS |

Table 1. Clinical data from cases of MM following other malignancies

CTX, cyclophosphamide; L, Phenylalanine mustard; MP, melphalan + prednisone; TD, Thalidomide + dexamethasone; VAD vincristine + liposomal doxorubicin + dexamethasone; MOP, MP + Vincristine; DOP, vincristine + doxorubicin + dexamethasone; RFC, fludarabine + cyclophosphamide + rituximab; CHOP doxorubicin + cyclophosphamide + vincristine + prednisolone; F, female; M, male; NA, not available; NS, not stated; SPE, serum protein electrophoresis; IE, immunoelectrophoresis; + combined with; - negative; ↑ increased; CNL, chronic neutrophilic leukemia; CLL, chronic lymphocytic leukemia; CML, Chronic myeloid leukemia; ET, essential thrombocytopenia; L, Phenylalanine mustard; INF, interferon
developed MM after 18 months of treatment with Pharmorubicin RD alone. However, our patient received localized intravesical Pharmorubicin RD instillation with no systemic chemotherapy for four cycles (total accumulated dose of 200 mg) without receiving any prior treatment for bladder cancer. Furthermore, no chromosomal abnormality was found in our patient. Therefore, evidence to prove that anti-bladder cancer therapy could possibly cause myeloma development was insufficient in this case.

The development of MM and bladder cancer involves genomic instability. Therefore, the patient may have possessed a genetic defect predisposing the development of frequent neoplasia. Both ras and p53 genes are carcinogenic genes that are closely related to MM and bladder cancer. Mutations of these genes were also detected in our patient. These two genetic mutations may have triggered the occurrence of the two distinct malignancies. Another possible explanation for the biological mechanism of MM is that one genetic mutation (ras or p53) occurred at the onset of bladder cancer in the first stage, consequently creating a possible preneoplastic state for MM. The other gene (p53 or ras) mutated in the second stage under immune-deficient conditions and resulted in overt MM. This condition is called a “two-hit phenomenon.” However, the genetic mutations in bone marrow were undetected during biopsy and diagnosis of bladder cancer. However, the most likely explanation for the development of MM is predisposition to genetic defects.

In this report, our patient received bortezomib treatment. Bortezomib reversibly inhibits the 26S proteasome, which disrupts various cell signaling pathways and leads to cell cycle arrest, apoptosis, and inhibition of angiogenesis. Bortezomib has been approved and widely used as the first therapeutic proteasome inhibitor for patients with relapsed or refractory MM and mantle cell lymphoma [26]. Successful treatment of simultaneous MM and bladder cancer by bortezomib has not yet been reported. Nevertheless, in vitro and in vivo data from cell cultures and clinical trials support the hypothesis that bortezomib induces bladder cancer cell death and inhibits angiogenesis [27–30]. Bladder cancer rapidly relapsed and progressed because of the absence of a sensitive therapy, including TURBT and Pharmorubicin RD, at the early stage. Therefore, bortezomib was administered to our patient with MM and bladder cancer. Good clinical response was achieved for 20 months. Relapse of MM and bladder cancer occurred after discontinuation of bortezomib therapy. Complete remission was again achieved after three cycles of
bortezomib. Although direct evidence of the efficacy of bortezomib as a targeted therapy for bladder cancer is currently lacking, administration of bortezomib may be feasible because this drug is cytochrome independent. Further studies are required to improve the management of this rare case of coexisting multiple neoplasia.

To the best of our knowledge, this study is the first to report on an MM case following bladder cancer treated with Pharmorubicin RD alone. Genetic mutations may have been involved in the development of MM. The successful treatment of the condition with bortezomib may be used as a clinical basis for future treatment of concomitant MM and other malignancies.

Authors’ Contribution
YH. Wang and FP. Peng have contributed equally to this work.

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Disclosure
The authors do not have any conflict of interest.

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