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Case Reports

Development of Diffuse Large B-Cell Lymphoma and Sarcoidosis In The Course Of Multiple Myeloma: A Case Report with Literature Review

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Abstract

Despite significant survival increment due to treatment improvement, multiple myeloma (MM) remains an incurable disease. We herein describe a unique patient that is not only a MM long survivor despite adverse features, such as the occurrence of extramedullary disease at relapse, but also developed, sixteen years after MM diagnosis, an extranodal diffuse large B-cell lymphoma (DLBCL) of the small intestine. The patient eventually achieved cure but developed sarcoidosis two years later that regressed with corticosteroids. Today, after 26 years of follow-up the patient is in remission and in good clinical condition.

INTRODUCTION

Multiple myeloma (MM) and Diffuse B cell lymphoma (DLBCL) are two very different B-cell disorders. MM is a relatively frequent hematological disorder of terminally differentiated malignant B-cell, the plasma cells, that infiltrates the bone marrow and secrete paraprotein; the disease is accompanied by morbid manifestations such as bone pains, spontaneous fractures, renal failure, fatigue due to anemia and other. In spite of the tremendous therapeutic improvements, MM is usually incurable. Diffuse large B-cell lymphoma (DLBCL) is the most prevalent subtype of B-cell non-Hodgkin lymphoma (NHL) and accounts for approximately 30% of all new NHL diagnoses. It exhibits considerable heterogeneity, despite its typical appearance. Two primary DLBCL subgroups were classified according to their cell of origin: germinal center B-cell (GCB) and activated B-cell (ABC). DLBCL cells usually infiltrate lymph nodes or extranodal sites and more rarely the bone marrow. Patients with MM have been reported to have a higher risk of developing secondary hematological malignancies [1]. In this report, we present an exceptional case of a MM patient who not only defied the odds by surviving well for a very prolonged period but also developed an aggressive form of extranodal diffuse large B-cell lymphoma (DLBCL) of the small intestine Owing to the implementation of advanced treatment strategies, the patient was ultimately able to attain complete remission; however, he subsequently developed sarcoidosis.

CASE REPORT

In 1997, a 45-year-old man presented with back pain worsening during exercise. An IgAλ MM, staged IIA and 1 according to Durie and Salmon and the International Staging System (ISS) respectively, was diagnosed. He presented multiple osteolyses and three plasmacytomas originating from the 3rd right rib, the 7th left rib and left pelvis respectively confirmed by fine needle aspiration. Bone marrow (BM) aspiration and smears revealed a borderline (12%) plasma cell infiltration combined with low paraprotein level (IgA 627 mg/dl). He received a Melphalan-containing regimen, radiation therapy targeting the plasmacytomas and adjuvant aminobisphosphonate (pamidronate) monthly, achieving long-lasting complete remission (CR). The patient relapsed in 2007, presenting with swallowing difficulty. Physical examination and imaging showed a tumor mass at the base of the tongue. Initial laboratory work-up was normal. Histological examination of the tumor revealed a plasmacytoma; malignant plasma cells expressed CD56, were lambda restricted and negative for Cyclin D1, CD20, CD3. BM biopsy showed 12% plasmacytic infiltration but paraprotein was undetectable along with serum free light

chains and their ratio within normal range. The patient received 5 cycles of bortezomib-dexamethasone and re-entered CR. He subsequently underwent high dose therapy with autologous stem cell transplantation (ASCT) and received a thalidomide-based maintenance. The patient remained in CR until December 2013. He complained at that time of acute abdominal pain, the investigation of which by ultra sound and magnetic resonance imaging, revealed a tumor mass and significant wall thickening involving the terminal ileum (Figure 1). Laboratory examinations demonstrated only mild anemia (Hgb 10, 6 g/dl), and increased LDH (476 U/L, upper normal value 220U/L). Biopsy of the lesion showed infiltration by middle sized B-cells with a high mitotic index of 99%, expressing CD20, CD79a, BCL6, CD10, LCA, BCL2 and not CD138, CD3, cyclinD1, CD56, CKIT, DBA44 while further PCR analysis revealed no c-myc rearrangement. Diagnosis was consistent with DLBCL, staged IE according to Ann Arbor as whole body computed tomography scan showed no other lesions. BM aspiration and smears showed plasma cell infiltration (60%) although paraprotein was undetectable in the serum. The R-IPI score was low-intermediate. The patient received three cycles of R-EPOCH regimen (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) but experienced obstructive ileus, and CTs revealed persistent disease. He then received lenalidomide-rituximab (RR regimen) and entered CR. After completion of 12 cycles, he underwent a second ASCT with previously frozen harvested cells and remained in CR thereafter. In July 2016, the follow-up PET-CT-scan showed inflammatory activity in the mediastinum. Transbronchial biopsy revealed sarcoidosis, while serum angiotensin converting enzyme was increased (128, 4 U/L). The patient initially received low-dose corticosteroids; he is currently alive with both MM and DLBCL in CR.

DISCUSSION

Our patient was diagnosed with symptomatic MM, presenting with multiple osteolysis and plasmacytomas at a relatively young age. At the time of diagnosis, he was treated conventionally with a melphalan–prednisone-based regimen, radiotherapy, and aminobisphosphonates, hopefully achieving long-lasting remission. Our patient's presentation with multiple plasmacytomas and low tumor burden, reminds macrofocal multiple myeloma, a relatively indolent subtype [2,3]. In fact, our patient achieved a 10-year remission, exceeding by far the 85-month overall survival recorded in similar patients. Reports on patients with relapsed macrofocal myeloma are extremely limited. Rache et al. reported in their study of ten patients with relapse macrofocal myeloma, four patients relapsing with extramedullary disease [4]. MM relapse manifested by extramedullary plasmacytoma (EMP) only, is relatively unusual. EMP incidence ranges from 6 to 16% [5], although definitive frequency has not been established yet probably due to the increase of cases observed during the last decades [5]. Liver is the most common site of EMP in the course of MM, while the lingual

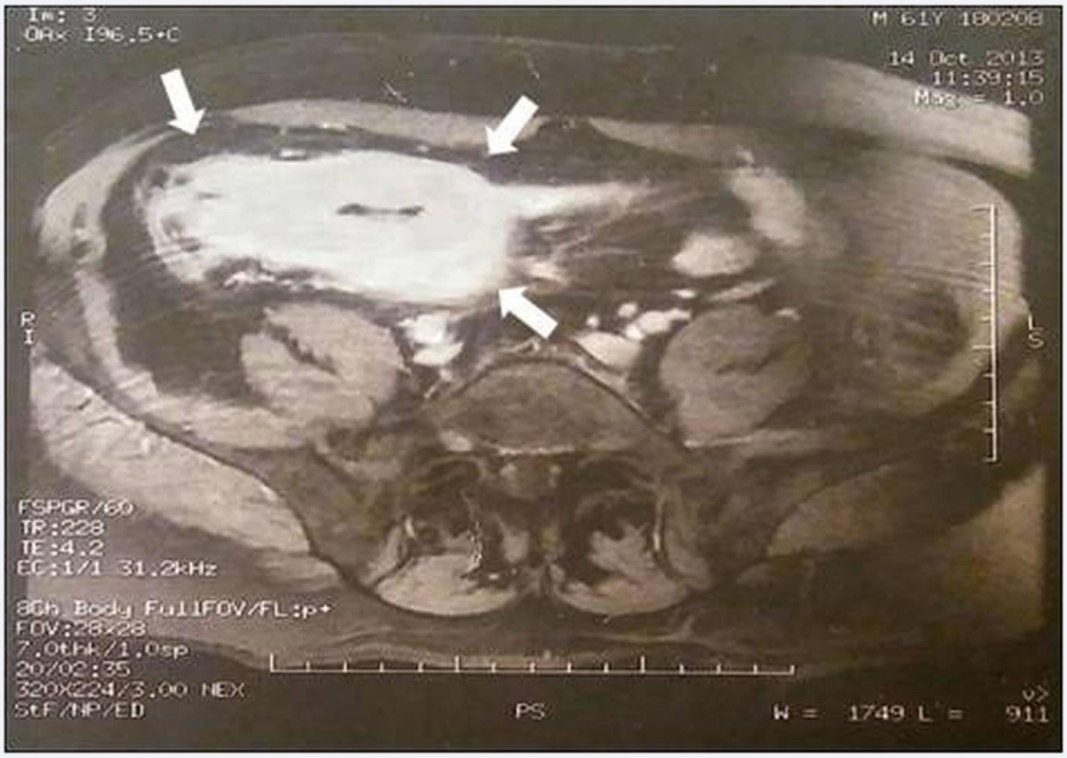

Figure 1 Magnetic resonance image showing enormous abdominal mass emerging from the terminal ileum.

region is extremely rare. Many studies have shown that the presence of EM involvement negatively affects prognosis [5,6,7]. Increased LDH levels, lower hemoglobin and M-protein values were reported in these patients. Presence of CD56, observed also to our patient eventually constitutes a marker of better disease behavior in this context. Papa Nikolaou et al, reported an increased frequency of bone plasmacytoma occurrence at the time of MM diagnosis in patients who further developed EMP [7], as this is the case here. Interestingly, the capacity of myeloma cells for migration to other sites preferring a particular site over another, is regulated by complex process including decreased expression of adhesion molecules, homing receptors, dysregulation of cytokines, angiogenic factors and chemokine receptors [6]. Another aspect of our patient's first relapse, was that he became non secretory, a phenomenon described as "dedifferentiation"; a subtype of aberrant immunoglobulin secretion involving also free light or heavy chain escape and conferring adverse prognosis [8]. Despite initial treatment with melphalan, peripheral stem cells could be successfully abundantly harvested; this may suggest that the deleterious effect of alkylators on stem cells [9] could be reversed after a long-time period (ten years).

In addition, our patient developed second malignancy. The prevalence of any secondary malignancy is generally low across studies, with an incidence of 5-7% [1,10.11]. The development of secondary hematological and solid malignancies depends on the prolonged use of alkylating agents, IMIDs, stem cell transplantation, and radiotherapy. Hematological malignancies are more frequent than solid malignancies with higher incidence rates in myelodysplastic syndromes/myeloid leukemias (MDS/AML), following acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and non-Hodgkin lymphoma (NHL) [11,12,13]. Following a four-year period of remission, our patient was diagnosed with DLBCL that presented at an unusual location in the small intestine. This rare occurrence is associated with a poorer overall survival prognosis [13-16]. According to Hans algorithm for subtype molecular discrimination (Active B Cell and Germinal Center B-like), our patient had the GCB-like type, which was correlated with a better prognosis. GC (GCB subtype) shows a unique gene expression profile and expresses GC markers according to immunohistochemistry. DLBCL that arises from post-GC B cells of the activated B-cell-like (ABC) subtype, is characterized by dependence on B-cell receptor (BCR) and nuclear factor kappa B (NFκB) signaling, as well as the expression of interferon regulatory factor 4/ mutated gene 1 (IRF4/MUM1). These tumors also exhibit enrichment for mutations in the BCR pathway (e.g., MYD88, CD79B, and PIM1) and PRDM1/BLIMP1 mutations or deletions [14,15]. Categorization of the cell of origin (COO) of diffuse large B-cell lymphoma (DLBCL) should be retained because of its potential prognostic impact according to the ICC and WHO (WHO-HAEM5). Immunohistochemistry is currently the most widely used method in routine practice owing to its simplicity. However, it is unable to recognize the "unclassified" category. Concerning our patient, c-myc rearrangement was negative, so both "double hit" and Burkitt lymphomas were excluded. Dual immunohistochemical expression of Bcl2 and Bcl6 was observed; such coexistence has been described to occur in only 3% of DLBCL [14] and its clinical importance remains unclear. According to a recent meta-analysis, BCL 6 positivity is an independent adverse prognostic factor in DLBCL and survival does not correlate with BCL 2 status [15,17,18]. In addition, BCL-2 expression alone is associated with poor prognosis [19]. Development of DLBCL and MM is an extremely rare event; all cases reported so far have been summarized (Table 1). A concomitant diagnosis of DLBCL, multiple myeloma, or monoclonal gammopathy often shows an immunoblastic phenotype arising from post-germinal center B cells (ABC type). However, the differentiation of DLBCL with the secretion of paraprotein and coexistence of two malignancies has been established by different immunophenotypes (pan – B cell markers vs cd20 negative plus cd138 positive cell). DLBCL was diagnosed after MM in three of the cases reported. In our patient, DLBCL was diagnosed years after MM and arose from the germinal center. Therefore, we hypothesized that DLBCL is not a clonal evolution from the first malignancy, but a second primary malignancy. The treatment is mostly conventional. In one case, CAR-T cell therapy was administered with a four-month follow-up. Immunohistochemically, BCL-6 protein was expressed in three cases. Almost all patients died. Owing to the aggressiveness of our patient's lymphoma, we opted therapeutically for the R-EPOCH regimen; however, in interim CTs, stable disease was observed. Given the underlying diagnosis of myeloma, we prescribed lenalidomide, an immunomodulatory drug that had not yet been approved for DLBCL in 2013. The drug enhances immune-mediated cytotoxicity and tumor suppressor gene expression but also inhibits the production of pro-angiogenic factors in lymphoma cells. Lenalidomide has demonstrated promising results in combination with rituximab for relapsed/refractory aggressive DLBCL, especially ABC type [20]. Currently, clinical studies on frail elderly patients with DLBCL aim to develop chemo-free therapy (lenalidomide – rituximab) and other clinical studies combining three immunotherapy agents to treat relapsed/refractory DLBCL.

Despite achieving CR in both malignancies, our patient developed pulmonary sarcoidosis. Sporadic cases of sarcoidosis have been described after ASCT (three months to ten years) [21] with two of the reported patients having lymphoma (follicular and DLBCL). In our case, sarcoidosis occurred 12 months after ASCT. All patients, including ours, responded to steroids without lymphoma recurrence. The correlation between sarcoidosis and lymphoma includes lymphoma occurring after sarcoidosis diagnosis, known as sarcoidosis-lymphoma syndrome (SLS), which is the most common type [21], concurrent presentation, or lymphoma preceding sarcoidosis development. Only a few cases of sarcoidosis occurring after DLBCL exist in which excessive immune response against lymphoma cells might be responsible, considering that remission occurred shortly before the onset of sarcoidosis. In our case the immune response might have been boosted by lenalidomide. However, safe conclusions cannot be drawn. In conclusion, we described a unique case of two hematological malignancies complicated by sarcoidosis.

Table 1: Published Cases of Multiple Myeloma (MM) and Diffuse Large B-Cell Lymphoma (DLBCL)
*Article in Japanese, F=Female, M=Male, NHL=non Hodgkin lymphoma, ISS: International Staging System, R-CHOP= rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, DCEP=Dexamethasone, cyclophosphamide, etoposide and cisplatin, ECHOP=endostatin, cyclophosphamide, doxorubicin, vincristine and prednisone , CHOP= cyclophosphamide, doxorubicin, vincristine and prednisone, VD: Bortezomib-Dexamethasone, RD: Lenalidomide-Dexamethasone, VRD: Bortezomib -Lenalidomide-Dexamethasone, MPT : Melphalan -prednisone-thalidomide, NA=not applicable

Author	*Age/ Gender*	*MM Diagnosis*	*MM (Type/ISS Stage)*	*NHL (Diagnosis/ Location)*	*Immunohistochemistry of NHL*	*Treatment of NHL & MM*	*Outcome*
Mitra S, Mukherjee S, Mehta J, Bhattacharyya M, Chakraborty H, et al. Indian J Pathol Microbiol. 2016; 59(3): 427.	65/M	NA	IgAκ/stage I	synchronous testicular DLBCL	CD20(+), CD3(-), CD5(-), CD10(-), CD23(-), CD38(-), MIB-1 labeling index > 50%	R-CHOP, 2 cycles	lost to follow-up
Zhou S, Ma Y, Bi L, Shen Z, Yu K, et al. Oncol Lett. 2014; 8(2): 908–910.	75/M	2009	IgGλ/NA	2009/ascending colon DLBCL	CD20(+), CD79a(+), CD10(+), BCL-6(+), melanoma associated antigen (mutated)-1,EBV-encoded small RNA and the Epstein-Barr virus, Ki-67 80%, CD138(-), CD38(-)	DCEP, 6 cycles	2012, ECHOP 1 cycle, died abdomen infection.
* Iwakiri R, Mikoshiba M, Tsutsumi H, et al. Nihon Ronen Igakkai zasshi. Japanese journal of geriatrics. 2001; 38(5): 678-681.	75/F	1998	IgGλ/NA	1990/ NA DLBCL		DLBCL□CHOP MM□melphalan & prednisolone.	
*Nagamura F, Goto S, Iseki T, et al. [Rinsho ketsueki] The Japanese journal of clinical hematology. 1995; 36(10): 1182-1187.	49/M	1989	IgGκ + IgAκ/ NA	1990/ right cervical lymph node, diffuse, mixed, B cell type		MM□modified M2 regimen, CHOP for both diseases	1991, died of respiratory failure.
* Hashimoto S, Kawano E, Hirasawa A, et al. [Rinsho ketsueki] The Japanese journal of clinical hematology. 1992; 33(5): 671-676.	71/M	1988	IgAκ/ NA	1986/ right cervical lymph node DLBCL	Positive B cell markers, IgG, kappa type	DLBCL□CHOP MM□Combination chemotherapy	improved
Drasin H, Blume MR, Rosenbaum EH, Klein HZ, et al. Cancer. 1979; 44(1): 215–220.	50/F	1975	IgG/NA	1965/DLBCL abdominal tumor & pulmonary lymph nodes		DLBCL□ radiation MMmelphalan, vincristine, prednisone	1977, Died
Li T, Tan J, Chen L, Kuang D, Mao X, Lou Y, Zhou J, Zhou X. Medicine (Baltimore). 2020 Apr;99(16):e19739	50/M	2016	Biclonal IgG and IgA/R-ISS 2	2016/DLBCL mediastinal lymph nodes, retroperitoneum, mesentery, and hepatic portal area lymph nodes/bone marrow.	CD20+, CD22+, Kappa+, intracellular Kappa+, intracellular CD79+, CD38– CD20+, CD30+, CD3-, PAX5+, OCT-2+, BOB.1+, CD10-, BCL6+, MUM1+, ALK–, LMP1+	DLBCL : RCHOP CD19-CAR T cells combined with BCMA-CAR T MM : VD, RD, VRD, MPT	2016, 4 months follow up , disappearance of monoclonal B and plasma cells in the bone marrow,M protein undetectable

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