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Original Article

Refractory multiple myeloma with extramedullary plasmacytoma of the spleen and suspicious teratoma: a rare case report and literature review

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Abstract: Multiple myeloma (MM) is a type of malignant disease that is characterized by a clonal proliferation of plasma cells within the bone marrow. Relapsed and refractory multiple myeloma (RRMM) is a subtype of MM that is unreactive to salvage therapy and progresses during treatment or within 60 days of the last therapy in patients who achieved a minimal response before progression of disease. This usually results in a poor prognosis. Extramedullary plasmacytoma (EMP) occurs when MM occasionally develops in tissues other than bones marrow. To the best of our knowledge, case studies of the presence of EMPs in the spleen have rarely been reported. Teratoma is a type of congenital tumor that consists of tissue that arises from pluripotent embryonic cells. Here we report a case of refractory immunoglobulin G (IgG) MM with both splenic plasmacytomas and a suspicious teratoma. To investigate the clinical and treatment features of patients under similar conditions, we also reviewed the available literature supporting the useful information in the pathogenesis, diagnosis and treatment of RRMM with EMP.

Keywords: Multiple myeloma, primary extramedullary plasmacytomas, teratoma

Introduction

Multiple myeloma (MM), also known as symptomatic plasma cell myeloma, is a plasma cell malignancy. It is defined by proliferation of malignant bone marrow plasma cells that can secrete a monoclonal paraprotein and cause organ damage, such as splenomegaly [1]. Patients with MM can present with a wide range of symptoms, mainly including anaemia, hypercalcaemia, renal impairment, bony lytic lesions and recurrent infections. MM may occur in other tissues, even though it usually presents in the bone marrow. Presentation of MM in other tissues is known as extramedullary plasmacytoma (EMP) [2]. A teratoma is a type of benign tumor that contains a mixture of differentiated tissues and organotypic derivatives of the three germ layers [3]. Relapsed and refractory multiple myeloma (RRMM) occurs when the disease is unreactive to salvage therapy and progresses during treatment or within 60 days of the last therapy in patients who achieved a minimal response before the progression of disease [4]. Patients with RRMM have poor prognoses [5], and despite the recent developments in the treatment of MM, relapse of MM is mostly unavoidable [6]. Cases of RRMM that co-exist with splenic plasmacytoma have rarely been reported.

In this study, we present a rare case of immunoglobulin G (IgG) κ MM with both EMP of the spleen and a suspicious teratoma that was refractory to nearly 10 regimens. We also present a review of the literature that pertains to RRMM and MM with EMPs, and we further summarize the clinical features and treatments of these diseases.

Case presentation

A 46-year-old female patient with a primary complaint of fatigue and poor appetite was admitted to our hospital in January 2014. The physical examination results demonstrated anemia and splenomegaly. Her labs were posi-

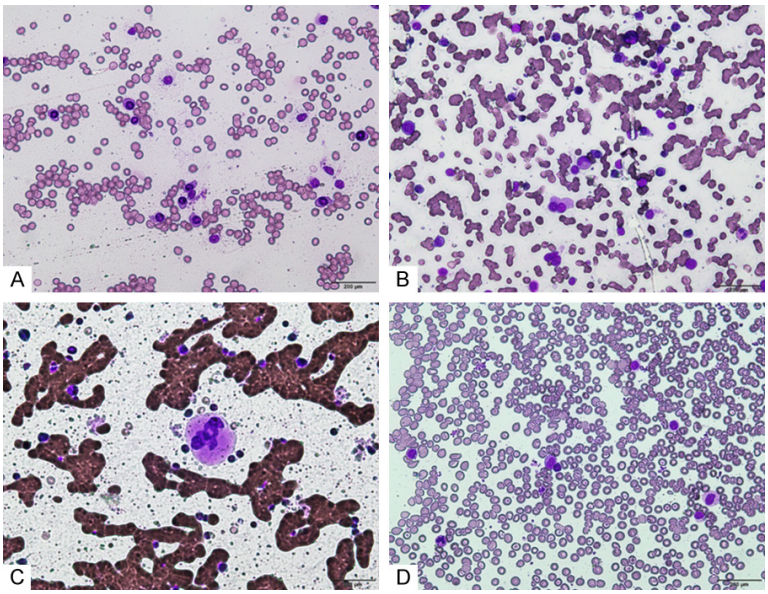

Figure 1. Bone marrow cytology. A: The first bone marrow cytology in January 2014 showed 29% plasma cells, Wright staining × 400; B: Bone marrow cytology in June 2014 showed 50% plasma cells, Wright staining × 400; C: Bone marrow cytology in August 2014 showed 55% plasma cells, Wright staining × 400; D: Bone marrow cytology in September 2014 showed 26% plasma cells, Wright staining × 400.

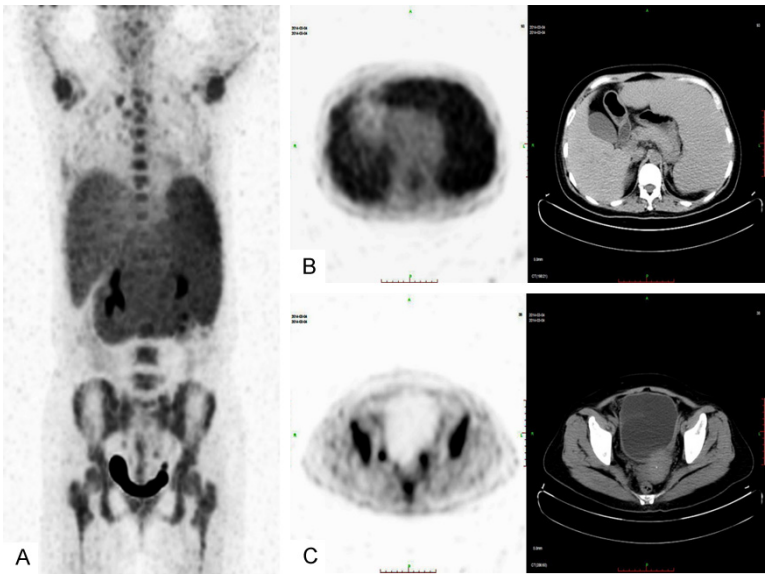

Figure 2. PET-CT of the whole body. A: Systemic bone diffuse lesions; B: Splenomegaly; C: Pelvic cystic mass.

tive for severe anemia with an Hb level of 39 g/L, coagulation disorders, and elevated fibralbumin and β2-MG. Protein electrophoresis showed an elevated IgG level of 101.2 g/L, along with serum and urinous κ light chains. A bone marrow biopsy in January 2014 revealed extremely active plasma cell proliferation, and 29% of the cells in the sample were monoclonal plasma cells (**Figure 1A**). Myeloid leukemia immunophenotyping showed that 92% of cells were CD38+, 99% were CD117+, 89% were CD20+ and 92% were CD-138+. Computed tomography (CT) and ultrasound revealed splenomegaly and a pelvic placeholder that likely contained a teratoma. The initial fluorescence in situ hybridization (FISH) of the bone marrow was negative and did not detect amplification of 1q21, deletion of 13q14, 13q14.3 and p53, or translocation rearrangement of IGH. The karyotype was normal, and other examinations revealed no abnormalities. Therefore, using the International Staging System (ISS), a diagnosis of IgG κ MM in stage III was established, and the patient accepted a cycle of VTD (bortezomib, thalidomide, and dexamethasone).

However, due to an unsatisfying efficacy of the treatment (the test result of her fibralbumin was 90.4 g/L), the patient continued a cycle of VCTD (bortezomib, cyclophosphamide, thalidomide, and dexamethasone) in February 2014. Then, she received a positron emission tomography-computed tomography (PET-CT) scan one month later, which showed systemic bone diffuse lesions, splenomegaly with diffuse increased glucose metabolism and a pelvic cystic mass demonstrating a glucose metabolism defect (**Figure 2A-C**). Because the treatment was ineffective, the regimen was successively changed to a cycle of VCD (bortezomib, cyclophosphamide, and dexamethasone) with lenalidomide and a cycle of DVD (liposome doxo-

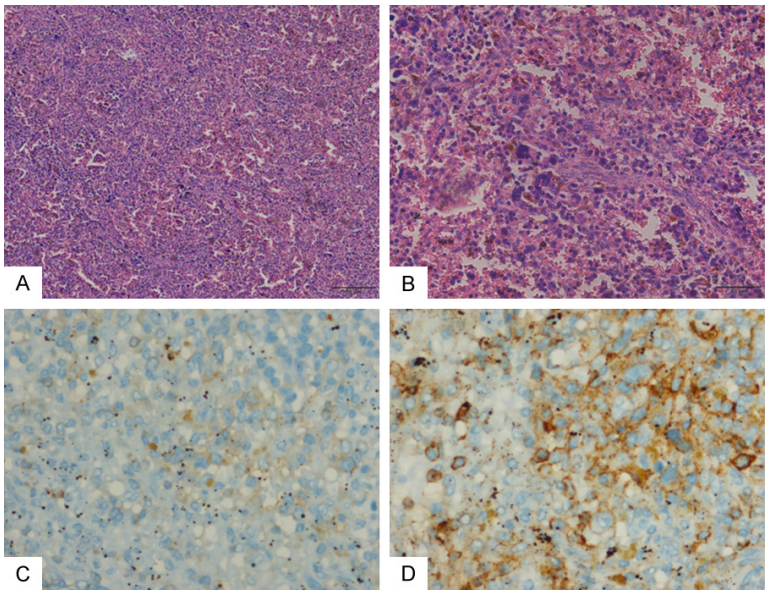

Figure 3. Biopsy of spleen and immunohistochemical results. (A, B) Biopsy of spleen showed chronic splenic congestion and splenomegaly; (C, D) The immunohistochemical findings were positive for CD38 (C) and CD138 (D). ((A) H&E staining; × 100; (B) H&E staining, × 400; (C, D) Immunohistochemical staining, × 400).

rubicin, bortezomib, and dexamethasone) with lenalidomide.

In May 2014, the patient suffered from concurrent acute renal damage and pulmonary infection and was treated several times with hemofiltration. Her bone marrow cytology was positive for cyclin D1. Then, she received one cycle of R (rituximab) -VTD (bortezomib, thalidomide, and dexamethasone). Reexamination of fusion genes in June 2014 showed an abnormal IGH/CCND1 gene (data not shown), and the bone marrow cytology showed 50% plasma cell concentration (**Figure 1B**).

In July 2014, following doctors' advice, the patient underwent a splenectomy with a postoperative pathology reporting chronic splenic congestion and splenomegaly. The immunohistochemistry panel was positive for both CD38 and CD138 and was negative for CD19, indicating splenic plasmacytoma (**Figure 3A-D**). Because of the high tumor burden with 55% plasma cells in the bone marrow (**Figure 1C**), the patient accepted various treatment regimens, including one cycle of R(rituximab) - VATD (bortezomib, liposome doxorubicin, thalidomide, and dexamethasone), after which the plasma cell concentration decreased to 26% (**Figure 1D**). The patient then received one cycle of VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, liposome doxorubicin, cyclophosphamide, and etoposide), one cycle of PLD-VTD (bortezomib, liposome doxorubicin, thalidomide, and dexamethasone) and two cycles of MP (melphalan, and dexamethasone). After a cycle of VDT-PACE, the patient developed a fever, and blood cultures suggested an Escherichia coli infection. After the corresponding treatments, the level of bone marrow plasma cells was 73.5% in November 2014. In February 2015, the patient began a cycle of VTD that led to decreased fibralbumin. However, since intravenous chemotherapy was refused by the patient, the oral treatment of MP was performed for approximately another ten cycles and was then stopped in September 2016.

In October 2016, the patient experienced repeated fevers, where the thermal peak was 39.5°C. Cytology revealed 2.96% peripheral plasma cells in the sample. A biopsy showed reduced bone marrow hyperplasia hematopoietic tissue into a focal distribution with increased plasma cells, which was considered a result of specimen dilution. The MM multigene combined detection revealed deletion of 13q14 (RB1). The chromosome karyotype analysis reported 49-53, X, Xq+, 3p+, +5q-, +7, +11, 12q+, +18 and +19. Abdominal CT revealed a teratoma. The patient accepted three rounds of plasmapheresis during this period of hospitalization, and as a result, her fibralbumin level was reduced to 22.6 g/L. After detailed communication with the patient and her family, further treatment, including new drugs such as CD138 or allogeneic hematopoietic stem cell transplantation, was refused and the patient left the hospital.

Discussion

Here we describe a rare case of refractory IgG MM with both splenic plasmacytoma and suspicious teratoma. Tests from this MM case

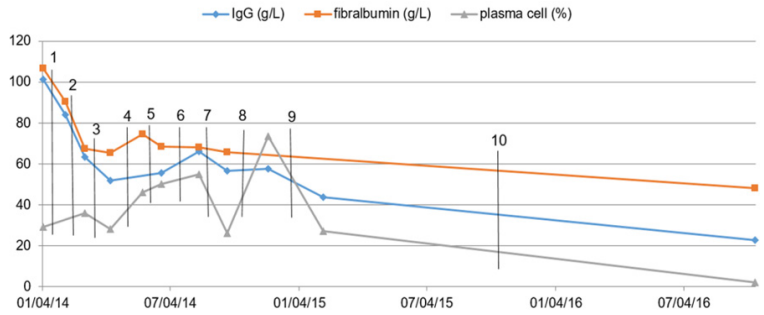

Figure 4. IgG, fibralbumin and plasma cell levels over two years of treatment. 1: VTD; 2: VCTD; 3: VCD + lenalidomide; 4: DVD + lenalidomide; 5: R(rituximab) - VTD; 6: Splenectomy; 7: R(rituximab) - VATD; 8: VTD-PACE; 9: 1* PLD-VTD & 2*MP; 10: 1*VTD & 10*MP & 3* plasmapheresis.

revealed positive expression of CD20 and clylind1, which confused the diagnosis of mantle cell lymphoma (MCL). However, in the present case, the lymph nodes of the patient were not enlarged, and the cell morphology did not match with the cell morphology observed in MCL. In addition, there have been reported MM cases with positive CD20 expression [7]. Additionally, the spleen biopsy, combined with the histology results (positive CD38 and CD138 expression and negative CD19 expression), excluded the diagnosis of lymphoma. Taken together, MCL was ruled out as a possibility.

In this case, the patient had tried various treatment regimens (including a splenectomy) while the MM continued to progress (**Figure 4**). Even after multiple treatment regimens, the disease was unstable. From our data, we concluded that the disease was relieved after three different treatment regimens. However, the disease slowly progressed from April to July 2014. After a splenectomy, the patient's IgG, fibralbumin and plasma cell levels decreased significantly. Both changes of index and her postoperative pathology demonstrated the existence of EMP of the spleen. However, even with many different therapies, the disease still failed to achieve complete remission (CR). Furthermore, various imaging examinations revealed a pelvic mass likely to be a teratoma and was thusconsidered another EMP. However, this was an assumption since the patient refused to participate in further examination.

Of note, the fact that genetic abnormalities were found later in the progression of the disease that had not been observed in the initial stages of the disease suggested progression of the disease [8]. Although deletion of RB1 induces both cell proliferation and death [9] and has no obvious correlation with disease progression when it has already appeared in the first biopsy [10], the appearance of EMP still indicates poor prognosis in patients with conventional chemotherapy [11].

Since MM is a treatable but incurable malignancy with an incidence of 6.3 cases per 100,000 persons per year in the United States [12, 13], it is necessary to develop more effective treatments for patients, especially those with RRMM. Therefore, it is important to gather information from the literature before treatment of patients with RRMM. **Table 1** [5, 14-17] contains a summary of known cases of RRMM, including a brief summary of the clinical features of those patients. Patients with RRMM are generally middle-aged or elderly, and there is no obvious gender bias. However, it is interesting that in Case 5 [17], all of the RRMM patients with severe renal impairment were female. Whether women with RRMM are more susceptible to renal damage than men remains unclear. Initial diagnoses of RRMM were at relatively high stages (stage III), which demonstrates that more attention is needed for those MM patients with high stages. Furthermore, we determined that prior treatment regimens for patients with RRMM before attempting new treatments were variable. Of note, SCT was very common in the management for RRMM, which reflected the importance of HSC to some degree. A variety of novel methods were utilized to attempt to determine sequence-specific treatments for RRMM. For example, Chari A [15] reported a patient with RRMM that received the single agent, CNTO 328, an anti-IL-6 monoclonal antibody, and achieved durable remission. We noticed that outcomes of RRMM patients with severe renal impairment [17] were worse that those without renal impairment, which demonstrated the negative impacts of organ dysfunction on the prognosis of the patients. However, the positive efficacy of the pomalidomide-based therapy is worth noting, and this kind of therapy could become

Table 1. Summary of clinical features of patients with RRMM

Case	Age	Sex	Stage	Ig subtype	Remark	No. prior regimens	Recom-mended treatment	Outcome
1 [14]	54	F	IIIA	NA	1 × SCT	5	Bortezomib	nCR
2 [15]	42	M	IIIA	NA	1 × SCT	8	CNTO 328	CR for 1 y
3 [16]	58	F	IIIA	IgG	1 × SCT	2	Lenalidomide + Bortezomib	PR
4 [5]	40	M	NA	IgD	2 × SCT	5	Daratumumab	VGPR
5 [17]	39	F	IIIB	IgG	Severe renal impairment and four fifths had SCT	4	pomalidomid-based therapy	PR
	64	F	IIIB	NA		7		PR; died
	59	F	IIB	NA		3		PR; died
	62	F	IIIA	IgG		3		VGPR
	68	F	IIIB	NA		8		PR; DP

CR: complete response; DP: disease progression; F: female; M: male; NA: not available; nCR: near complete response; PR: partial response; SCT: stem cell transplantation; VGPR: very good partial response.

Table 2. Summary of clinical features of MM with EMPs

Case	Age	Sex	MM stage	Sites of EMPs	Treatments	outcome
6 [26]	55	F	NA	Right breast, forehead, left clavicular region, nasopharynx	RT, CT	DP, died
7 [27]	57	M	IIIB	Colon	CT, HSCT	died from complication
8 [25]	71	F	I	Right sternoclavicular joint, chest, cervical backbone	RT, CT	CR
9 [28]	43	M	NA	Testicle	Surgery	NA
10 [29]	50	F	NA	Nasolacrimal duct	Surgery, CT, RT	CR
11 [30]	54	F	IIIA	Mediastinum, lungs, pancreas, psoas muscle, epigastrium	Dialysis, CT	SD
12 [31]	54	F	NA	Small bowel	Surgery	DP, died
13 [32]	60	F	III	Neck, right eyelid	CT, RT	SD

CR: complete response; CT: chemotherapy; DP: disease progression; F: female; M: male; NA: not available; RT: radiotherapy; HSCT: hematopoietic stem cell transplantation; SD: stable disease.

an alternative option for RRMM patients with renal damage. Additionally, Asou N [18] reported a case of refractory MM that responded well to a combination therapy with oral melphalan, dexamethasone, and thalidomide (MDT). This is similar to the patient in this presentation who received MP as maintenance therapy. Both Tsuda H [19] and Nakazato T [20] separately reported a case of refractory MM treated with RD (lenalidomide and dexamethasone), which remarkably decreased the patient's myeloma protein level and induced osteogenesis, demonstrating the positive effects of lenalidomide. Moreover, there have been numerous advances in pharmacotherapy for patients with RRMM. For instance, both carfilzomib and pomalidomide have been approved by the FDA [21], and histone deacetylase inhibitors, such as vorinostat [22] and panobinostat, have been shown to be effective in RRMM and have been further studied [4]. However, despite the development of novel agents for RRMM, older drugs still should be kept as options for treatment when new ones fail [23].

Due to uncontrolled plasma cell proliferation and monoclonal plasmacytic infiltration, EMP is a rare malignant neoplasm that infiltrates into extramedullary tissues [2]. **Table 2** is a summary of the clinical features of MM with EMPs; from these data, we determined that the age of patients with MM and EMPs is similar to those with RRMM (most were over 50). Due to limited information, we were unable to determine if there was a relationship between MM with EMPs and the stage of the patient.

EMPs are predominantly located in head and neck regions [24] and the upper respiratory tract [25] in the form of either isolated tumors

or coexistence with MM. As noted in **Table 2** [25-32], most sites of EMPs were located in the head and neck regions. The clinical symptoms caused by EMPs are related to the location of the EMP [2], which increases the difficulty of its diagnosis. Although EMP can be viewed as a subtype of MM relapse, EMP rarely converts to MM, and there are some significant immunophenotypic differences between the two diseases, which may become the diagnostic tool to distinguish between them [33, 34]. For example, CD56 is frequently expressed in MM but is usually absent from EMP, which leads to the hypothesis that there are true biological differences between these two diseases. Additionally, cyclin D1 is not normally expressed in EMP, while it is often overexpressed in MM; thus, any presence of cyclin D1 in EMP may strongly indicate an underlying MM [33]. Furthermore, EMPs showed a CD19+/miR-223$^-$ phenotype, which distinguished it from the CD19-/miR-223$^+$ phenotype of MM [35]. Additionally, nuclear p53 immunoreactivity was also associated with extramedullary progression of MM [36].

Currently, there are no consensus guidelines for treatment of EMP or EMP with MM. Therefore, there are a variety of treatment options for EMP, including surgery, radiotherapy and chemotherapy [37]. For EMP that presents with MM, treatment is much more likely to be a combination of these options (**Table 2**). For example, Kalyani, A [26] described a patient with recurrent MM that presented as EMPs of the breast, forehead, left clavicular region and nasopharynx. The patient accepted radiotherapy and chemotherapy successively despite her poor outcome due to the rapid progressing disease. Kakati BR [27] reported a case of MM with EMP of the colon that was treated with the combination of radiation therapy, systemic chemotherapy and autologous hematopoietic stem cell transplantations to achieve CR, yet the patient succumbed to treatment-related complications. Splenic EMPs have been rarely reported, and treatment was mainly surgical resection [24, 38, 39], which was similar to the option for the patient we presented. Since our patient refused further examination, her pelvic mass, which was probably a teratoma, still remains unknown, and the possibility of pelvic plasmacytoma cannot be ruled out.

Furthermore, outcomes of MM with EMPs were generally worse, which suggested that the presence of EMPs in MM may have negative impacts on the prognosis. This could be attributed to the fact that EMP is the MM end-phase [40], and the presence of EMPs in MM is associated with aggressive disease [30]. Consistent with this, patients with extramedullary relapse have poor outcomes and lower overall survival than those without extramedullary relapse [34]. With a splenic plasmacytoma and another suspicious pelvic plasmacytoma, the RRMM patient we presented in this article hardly achieved stable and continuous remission.

The presence of RRMM together with EMPs, no matter where the EMPs occur, may have detrimental effects on prognosis. Therefore, more effective treatments or novel agents are required for this disease.

Conclusion

In this article, we describe a very rare case of refractory IgG MM with both splenic plasmacytoma and a suspicious teratoma that we considered to be a pelvic EMP relapse. The patient received various treatment regimens and a splenectomy but still failed to achieve durable clinical relief. Furthermore, the diagnosis of teratoma or pelvic EMP lacked pathological support because the patient rejected further therapy. We will provide further observation for this patient. Cases containing EMP of the spleen and RRMM with EMP of the spleen are rare, and there has been no unified consensus of treatment. Therefore, this case may aid in the diagnosis and treatment of future cases.

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Disclosure of conflict of interest

None.

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