Title: Spontaneous Regression of Multiple Solitary Plasmacytoma Harboring Epstein-Barr Virus: A Case Report and Literature Review

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New findings: We report a first case of spontaneous regression (SR) in an elderly untreated patient with multiple solitary plasmacytoma. Detailed clinicopathologic studies potentially

indicate that host immune response as well as EBV infection contribute to the SR rarely seen in plasma cell neoplasms.

Abstract

We report a rare case of spontaneous regression (SR) in an elderly untreated patient with multiple solitary plasmacytoma (MSP). Diagnosis of MSP was confirmed through surgical resection of the left nasal cavity mass and subsequent biopsy of the right humerus. The patient was considered ineligible for chemotherapy due to poor performance status. At 3 months post-diagnosis, the patient's condition worsened with deteriorating bone lesions and emergence of a new serum monoclonal protein. However, these clinical findings completely disappeared at 6 months, and positron emission tomography-computed tomography at one year confirmed complete metabolic remission. Notably, peripheral blood lymphocyte counts were inversely correlated with tumor progression and remission. Pathological re-evaluation of the initial biopsy specimens revealed programmed cell death protein 1 (PD-1) expression in tumor-infiltrating $CD8^+$ T-cells. Additionally, tumor cells were infected with Epstein–Barr virus (EBV) but were negative for programmed cell death ligand 1 (PD-L1) expression, which is the most potent immune escape mechanism in tumor cells. While the mechanism underlying SR remains unclear, our findings suggest that host immune response as well as EBV infection may contribute to SR. Further studies are needed to elucidate the clinicopathologic mechanisms of tumor regression in plasma cell neoplasms.

Introduction

Multiple solitary plasmacytoma (MSP) is a rare form of plasma cell neoplasm (PCN) characterized by multiple sites of neoplastic monoclonal plasma cells in the bone and/or soft tissue without evidence of multiple myeloma (MM) [1, 2]. Approximately 5% of patients with solitary plasmacytoma progress to MSP [1]. Typically, solitary plasmacytoma (bone or extramedullary) is managed with radiation therapy (RT) [3, 4], whereas MSP is managed with chemotherapy, similar to the treatment of symptomatic MM [5, 6].

Spontaneous regression (SR), defined as the partial or complete, temporary or permanent disappearance of malignant tumor without appropriate treatment [7], remains a rarely observed phenomenon in various cancers, including carcinomas and hematopoietic tumors [8-11]. Although the mechanism of SR is not fully understood, several hypotheses have been proposed, including immune system modulation of the tumor microenvironment by concurrent bacterial/viral infections or tumor biopsy, tumor suppression by growth factors and cytokines, angiogenesis inhibition, and apoptosis [8-11]. To the best of our knowledge, there have been two reports of SR in patients with solitary plasmacytoma [12, 13], but no reports of SR in those with MSP. We herein describe the first case of SR occurring 6 months post-diagnosis in a patient with MSP who had bone and extramedullary plasmacytomas.

Case Report

An 83-year-old Japanese male was referred to the Department of Otorhinolaryngology of our institution for a 2-month history of persistent left nasal obstruction without epistaxis or rhinorrhea. He had a significant past medical history of paroxysmal atrial fibrillation, pacemaker implantation for complete atrioventricular block, carotid endarterectomy for internal carotid artery stenosis, and cervical laminoplasty for cervical spondylitis myelopathy. Routine laboratory tests, including in hemoglobin, lactate dehydrogenase, creatinine, and calcium levels, were all unremarkable. Gadolinium-enhanced, T1-weighed, paranasal sinus magnetic resonance imaging revealed a mass in the left middle nasal conchae (Fig. 1A, red arrowheads). On nasal endoscopic examination, a circumscribed reddish mass was found in the left nasal cavity (data not shown). Biopsy was subsequently performed, and histological examination using hematoxylin and eosin staining demonstrated a dense proliferation of large cells with atypical nuclei (Fig. 1B). Further immunohistochemistry staining identified these cells as CD3−, CD20−, CD138+, and immunoglobulin kappa (Igκ)+ (Fig. 1C, D). Additionally, the Ki-67 labeling index was 70% (data not shown). Based on these findings, an initial diagnosis of extramedullary plasmacytoma was made, prompting referral to our Department of Hematology.

The patient's detailed clinical course with imaging and graphs of laboratory findings are shown in Fig. 2A. Further laboratory testing at the time of diagnosis showed no evidence of serum or urine monoclonal protein, abnormal free light chain ratio, or human immunodeficiency virus antibodies, although Epstein–Barr virus (EBV) antibody titers were suggestive of prior infection (data not shown). Bone marrow examination via aspiration and flow cytometry analysis revealed no abnormal plasma cells (Fig. 2B–D); however, positron emission tomography-computed tomography (PET-CT) showed fluorodeoxyglucose (FDG) uptake in the right humerus, bilateral ribs, and vertebra (Fig. 2E). This prompted a CT-guided biopsy of the right humerus (Fig. 2A), and examination of the specimens revealed the presence of scant malignant plasma cell infiltration (CD19−, CD56+, and Igκ+) (Fig.2F–H, red frame). Based on these results, the diagnosis of MSP was confirmed. Despite undergoing cervical laminoplasty at another hospital 3 months prior, the patient had persistent lower limb motor function loss, resulting in an Eastern Cooperative Oncology Group performance status of 3 [14]. Therefore, he was deemed ineligible for chemotherapy. The patient was put on observation and consideration for RT if his bone lesions caused clinical symptoms.

At 3 months after diagnosis, the patient developed new bone lesions in the right clavicle and left femur but presented without clinical symptoms (Fig 2I, J, red arrows). Laboratory studies showed elevated IgG levels and free light chain ratio, and detection of the

IgG-κ-type monoclonal protein on immunofixation electrophoresis (IFE) (Fig 2A). However, 6 months after diagnosis, all bone lesions, including the right clavicle and left femur had completely disappeared (Fig 2K, L, red arrows), and laboratory studies showed normalized IgG levels and free light chain ratio, and absence of the IgG-κ-type monoclonal protein on IFE (Fig 2A). PET-CT at 1 year after diagnosis revealed no lesions with FDG uptake (Fig 2M). Interestingly, peripheral blood (PB) lymphocyte counts were closely inversely correlated with MSP exacerbation and remission during the clinical course (Fig. 2A). While data before SR were unavailable, normal proportions of $CD8^+$ T-cells and NK cells were observed ($CD8^+$: 31.6%, reference range: 23.0–56.0%; $CD56^+$: 13.9%, reference range: 9.0–43.0%), and EBV-DNA was not detected in peripheral blood studies. At the time of writing this report, the patient remains in good general condition without any evidence of PCN recurrence.

To explore the underlying mechanisms of this rare case, we performed further analyses with immunohistochemistry staining and *in situ* hybridization. Immunohistochemistry staining showed T-cell infiltration, with a slight predominance of $CD8^+$ T-cells, surrounding the tumor cells (Fig. 1E, F). Notably, the infiltrating T-cells expressed programmed cell death protein 1 (PD-1), while the tumor cells did not express programmed cell death ligand 1 (PD-L1) (Fig. 1G, H). Furthermore, *in situ* hybridization

showed expression of Epstein–Barr virus-encoded small RNA within the tumor cells (Fig. 1I). These results were consistent with previous reports on the mechanisms of SR in diffuse large B-cell lymphoma (DLBCL), albeit with differences in the underlying disease [15, 16].

Discussion

In this study, we reported a rare case of a patient with MSP who experienced SR 6 months after diagnosis. Although the underlying mechanism of SR remains uncertain, immunomodulation has been proposed as a relevant key factor [8-11].

The incidence of SR in patients with low-grade lymphoma is relatively high (approximately 10–20%), whereas SR incidence in those with intermediate-grade lymphoma, high-grade lymphoma, or PCN are extremely rare [9, 12, 13, 17-20]. In cases of DLBCL that develops as other iatrogenic immunodeficiency associated lymphoproliferative disorders (OIIA-LPD), temporary or permanent SR has been observed in approximately 40–80% of patients after withdrawal of immunosuppressants alone [21-23]. Conversely, among the few cases of PCN have developed from patients treated with immunosuppressants (except for after organ transplantation), there have been no reports of SR after withdrawal of immunosuppressants [24-28]. Previous studies suggest that methotrexate withdrawal plays a crucial role in the higher SR incidence of patients with OIIA-LPD compared to those with *de*

novo DLBCL due to the increase in PB lymphocyte counts (mainly $CD8^+$ T-cells and NK cells) [29-32]. This signifies that improvement of the immune system may partially be responsible for SR development. The reason why PB lymphocyte counts of our patient without immunosuppressants decreased at 3 months and increased at 6 months after diagnosis is unclear, but the phenomenon observed in this case, which PB lymphocyte counts were inversely correlated with tumor progression and remission, is similar to that observed in patients with OIIA-LPD [31], suggesting that host immune response has contributed to SR. Additionally, DLBCL that develops as OIIA-LPD exhibits a higher incidence of EBV infection than *de novo* DLBCL [21-23, 33, 34]. Thus, it is also possibly indicated that the heightened immunogenicity in OILA-LPD due to the expression of EBV latency-associated proteins may serve as a target for the immune system, resulting in SR [35]. However, the relationship between EBV infection and SR in patients with OIIA-LPD may be not as robust as the increase PB lymphocyte counts after withdrawal of immunosuppressant, since this relationship has been suggested to be related to histology types of lymphoma [21, 36]. Based on the above, this case suggests that host immune response as well as EBV infection may contribute to SR even in patients with PCN. Since only two cases of patients with PCN that develops as OIIA-LPD have been reported to be pathologically associated with EBV

infection [25, 27, 37], further studies with a larger number of cases are warranted to clarify this possibility.

Given the role of PD-L1 expression as one of the most potent and common immune escape mechanisms in PCN [38], we also focused on the significance of the PD-1/PD-L1 axis in SR. Previous studies have associated PD-L1 expression with increased tumor cell proliferation and resistance to chemotherapy, resulting in poor clinical outcomes among patients with PCN [39, 40]. In our patient, biopsy examination of the left nasal mass revealed a predominant presence of tumor-infiltrating $CD8^+$ T-cells. Additional immunohistochemical analyses revealed that the majority of these T-cells expressed PD-1, whereas tumor cells did not express PD-L1. This absence of PD-L1 suggests the inability of the tumor cells to evade immune responses, resulting in apoptosis and potentially contributing to the development of SR.

To further our understanding on the clinical presentation of the patient, we performed a literature search in the PubMed and Google Scholar databases using the following search terms: "spontaneous regression" or "spontaneous remission" and "plasmacytoma" or "myeloma". Our search yielded only five English-written case reports, including our own (Table 1) [12, 13, 19, 20]. Among these cases, three were noted to be elderly (i.e., age of 65 years or older according to World Health Organization criteria). Unfortunately, none of the

previous cases mentioned any preceding infections prior to SR, and the presence of EBV infection were unknown. In addition, one case of MM (case 3) attributed SR to the cytolytic activity exerted by pamidronate-stimulated γδT cells, although the remaining three cases provided no clear explanations aside from immune dysregulation due to aging and immune status enhancement due to tumor biopsy. SR occurred within 6 months of diagnosis for all cases, including our own, and four of those with documented outcomes (case 1 was unknown due to self-interrupted follow-up) were reported to be alive without signs of recurrence.

In conclusion, we encountered a rare case of SR in a patient with MSP, providing us with the opportunity to explore its clinicopathological mechanisms. We observed that host immune response as well as EBV infection might have contributed to the development of SR in this case. Further investigations involving similar cases are warranted to validate these findings and elucidate the clinicopathologic mechanism of tumor regression in patients with PCN.

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Data availability statement

The data are available from the corresponding author upon reasonable request.

Author contributions

W.K. collected clinical and histological data and wrote the original draft. H.K. and M.N. performed review and editing. A.I. and Y.K. performed histological diagnosis. Y.M. and S.K. performed supervision, review, and editing. All authors approved the final manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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Figure legends

Fig. 1 Gadolinium-enhanced T1-weighed paranasal sinus magnetic resonance imaging shows a mass lesion in the left middle nasal conchae (A, red arrows). Hematoxylin and eosin staining of the left nasal mass reveals the dense proliferation of large cells with atypical nuclei (B, ×200; scale bar: 100μm). These cells are positive for CD138 (C, ×200; scale bar: 100μm) and immunoglobulin kappa (D, ×200; scale bar: 100μm) on immunohistochemistry staining. A pathological review of the initial biopsy specimens reveals an infiltrate of $CD4^+$ T cells (E, ×200; scale bar: 100μm) and $CD8^+$ T cells (F, ×200; scale bar: 100μm) around the tumor (slightly predominant $CD8^+$ T cells). These T cells are positive for programmed cell death protein 1 (PD-1) (G, ×200; scale bar: 100μm). The tumor cells are negative for programmed cell death ligand 1 (H, ×200; scale bar: 100μm) and positive for Epstein–Barr virus-encoded small RNA *in situ* hybridization (I, ×200; scale bar: 100μm).

Fig. 2 The clinical course with imagings and graphs of laboratory findings (A). Flow cytometry analysis of the bone marrow aspiration shows no evidence of abnormal plasma cell population (B). Histological examination of the bone marrow biopsy specimens using anti-CD138 and immunoglobulin kappa (Igκ) staining reveals no abnormal plasma cells (C, D, ×200; scale bar: 100μm). Positron emission tomography computed tomography (PET-CT) on

diagnosis with plasmacytoma demonstrates the uptake of fluorodeoxyglucose (FDG) in the right humerus, both ribs, and vertebra (E, red arrows). Flow cytometry analysis of the right humerus specimens shows small malignant plasma cell population (F, red frame). Histological examination of the right humerus using anti-CD138 and Igκ staining reveals abnormal plasma cell population (G, H, ×200; scale bar: 100μm). CT after 3 months from diagnosis demonstrates new bone lesions in the right clavicle and left femur (I, J, red arrows), but those after 6 months from diagnosis shows spontaneous regression of these bone lesions (K, L, red arrows). PET-CT after 1 year from diagnosis reveals no FDG uptake in the bone lesions (M). Abbreviations: IFE, immunofixation electrophoresis