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Case Report

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Refractory Myeloma Developed with Multiple Extramedullary Tumors and Myelofibrosis

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Abstract

The use of novel drugs has improved prognosis in multiple myeloma (MM). However, as the pathophysiology of primary Extramedullary Myeloma (EM) is not well defined due to its rarity, effective treatment for EM is not yet established. We report the case of a 63-year-old man with MM who presented with back pain and fever following the development of extramedullary disease, including subcutaneous tumors accompanied by marrow fibrosis. CT at presentation revealed subcutaneous tumors, mediastinal lymphadenopathy, and pleural involvement with pleural effusion. Peripheral blood exhibited leukoerythroblastosis. Bone marrow biopsy showed diffuse fibrosis and infiltration of large or small atypical cells with high N/C ratio that did not resemble plasma cells, and were positive for CD138 and cytoplasmic IgG/κ immunoglobulin. Biopsy of subcutaneous tumors showed an infiltration of small atypical cells similar to those of bone marrow. The diagnosis was MM with primary EM that was refractory to chemotherapy with bortezomib and progressed with multiple subcutaneous tumors. Intriguingly, molecules related to proliferation including p53, cyclin D1, and Ki-67 were differentially expressed between bone marrow tumor cells and soft tissue tumor cells. In addition, the simultaneous occurrence of primary EM and diffuse myelofibrosis at diagnosis is peculiar.

Keywords: Refractory, Multiple Myeloma, Extramedullary Disease, Myelofibrosis, Poor Prognosis

1. Introduction

Multiple Myeloma (MM) is a mature B-cell tumor that occurs mainly in the elderly. Multiple Myeloma is characterized by neoplastic proliferation of clonal plasma cells in the bone marrow that causes the production of monoclonal protein and related organ impairment including multiple osteolytic lesions, anemia, renal failure, and hypercalcemia. However, extramedullary disease at the initial presentation is rare, and its pathobiology is not well defined. Extramedullary Myeloma (EM) is classified into either primary EM that develops at the time of initial diagnosis or secondary EM that develops during the course or at the time of recurrence. EM is further classified into bone–related EM (EM-B) that extends directly from osteolytic bone lesions and extraosseous EM (EM-E) that arises in extraosseous regions such as soft tissue or viscera as a result of hematogenous spread not related to the involved bone lesions [1,2]. The incidence of primary EM-E and EM-B at diagnosis of MM has been estimated as 1.7–4.5% and 7–34.2%, respectively [3]. We experienced a case of atypical IgG/κ-type MM that presented initially as EM-E with subcutaneous tumor masses and diffuse marrow fibrosis. To the best of our knowledge, primary extramedullary-extraosseous myeloma with synchronous myelofibrosis at the initial presentation has not been reported. Here we discuss EM with coincidence of myelofibrosis, along with a literature review.

2. Case Presentation

A 63-year-old man who developed fever and back pain admitted to our hospital. Physical examination revealed body temperature of 38.8°C and an immobile tumor of diameter 3 cm that was palpable subcutaneously on the anterior chest. Whole-body CT showed subcutaneous masses on anterior to the sternum and the right chest wall, a right intrathoracic mass, right pleural effusion, mediastinal lymphadenopathy, and splenomegaly without osteolytic lesions (Figure 1 A-C). Peripheral blood showed a hemoglobin level of 8.6 g/dL, platelet count of 4.2×10^9/L, and white blood cell count of 1.19×10^9/L with leukoerythroblastosis, including blasts of

0.5% and erythroblasts of 28%. Biochemical examination revealed lactate dehydrogenase of 448 IU/L (reference range, 142–246), soluble IL-2 receptor of 1520 IU/mL, creatinine of 0.9 mg/dL, calcium of 9.1 mg/dL, albumin of 2.9 g/dL, and β2-microglobulin of 5.6 mg/L. Serum immunological test revealed CRP of 20.37 mg/dL, IgG of 1933.1 mg/dL, IgA of 11.1 mg/dL, and IgM of 2.3 mg/dL. Immuno-electrophoresis detected IgG and κ-type monoclonal protein in serum but not in urine.

Fig.1

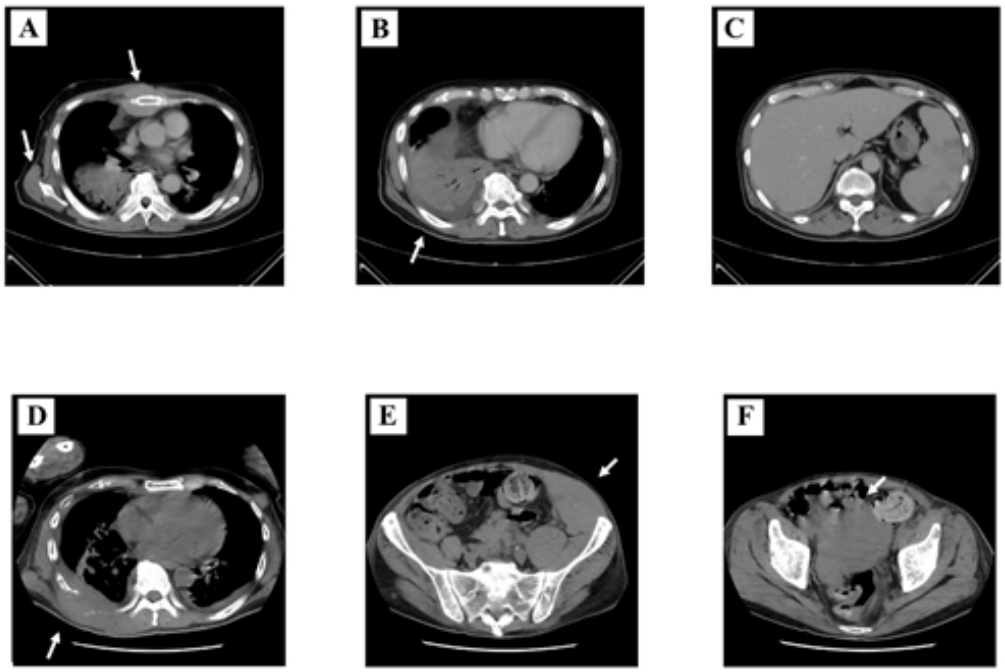

Figure 1: Whole-Body CT
Subcutaneous masses are seen surrounding the sternum and in the right chest wall (arrows, A) in addition to a right intrathoracic tumor (arrow, B) and splenomegaly (C). Despite receiving chemotherapy, the tumor in the right chest wall increased in size (arrow, D) and new intraabdominal tumors appeared (arrows; E, F).

Bone marrow aspirate was a dry tap and biopsy showed a diffuse infiltration of immature tumor cells that did not resemble typical plasma cells, comprising large atypical cells with eccentric lobulated nuclei and small round cells with a high nuclear–cytoplasmic ratio and diffuse fibrosis (Figure 2 A, E). On immunohistochemical staining, tumor cells were negative for LCA, CD2, CD3, and CD56; but positive for CD138, with weak staining of cytoplasmic IgG and κ (Figure 2 B–D). In addition, partial expression of c-Myc and cyclin D1, aberrant nuclear expression of p53, and strong expression of Ki-67 (labeling index 45%) were demonstrated in tumor cells (Figure 2 F-I).

Fig.2

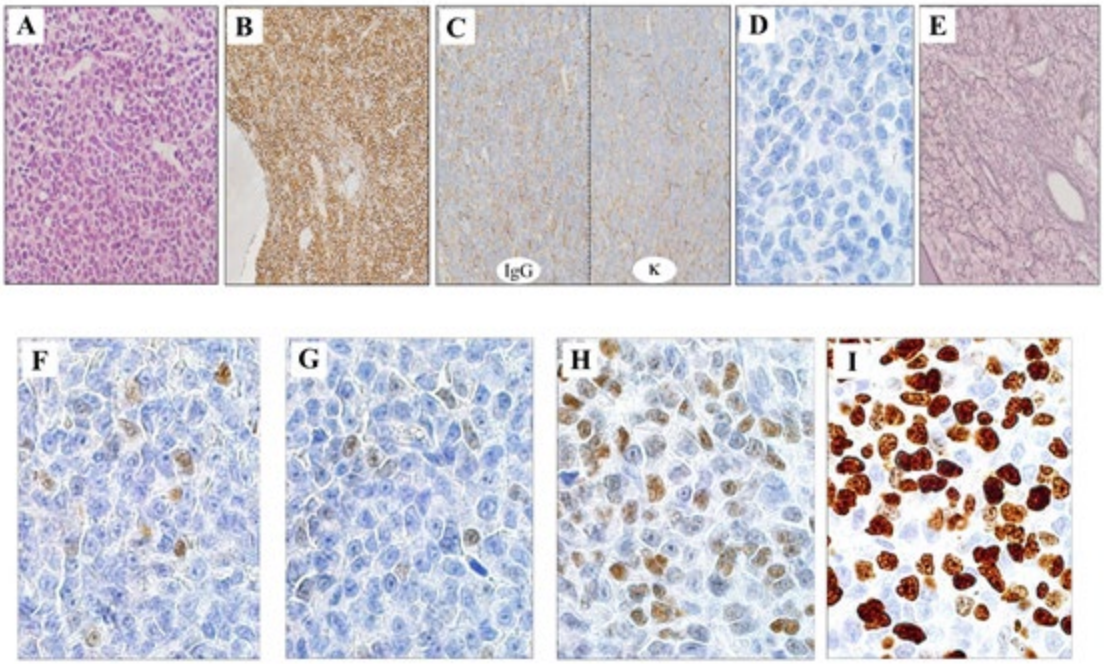

Figure 2: Histological Findings, Immunohistochemical Analysis of Cell Proliferation and Survival of Biopsy Samples of Bone Marrow on Admission.
Bone marrow biopsy tissue (H-E stain x100) shows a diffuse infiltration of immature tumor cells (A) that do not resemble typical plasma cells, comprising large atypical cells with eccentric lobulated nuclei. Immunohistochemical staining of bone marrow shows positivity for CD138 (B) and IgG/kappa (C), but not CD56 (D). Small round cells show a high nuclear–cytoplasmic ratio and moderate diffuse fibrosis (Ag stain) (E). Expression of c-Myc (F) is low, but that of cyclin D1 (G) is seen to a lesser extent. Expression of p53 (H) is significantly high, and the labeling index of Ki 67 is 45% (I).

Biopsy of the subcutaneous mass on the right chest wall showed sheet-like proliferation of small round tumor cells that showed the same immunophenotype as the bone marrow tumor cells (Figure 3 A-D). In contrast to bone marrow, no expression of c-Myc or cyclin D1 and lower expression of p53 and Ki-67 (labeling index 25%) was found in tumor cells (Figure 3 E-H).

Fig.3

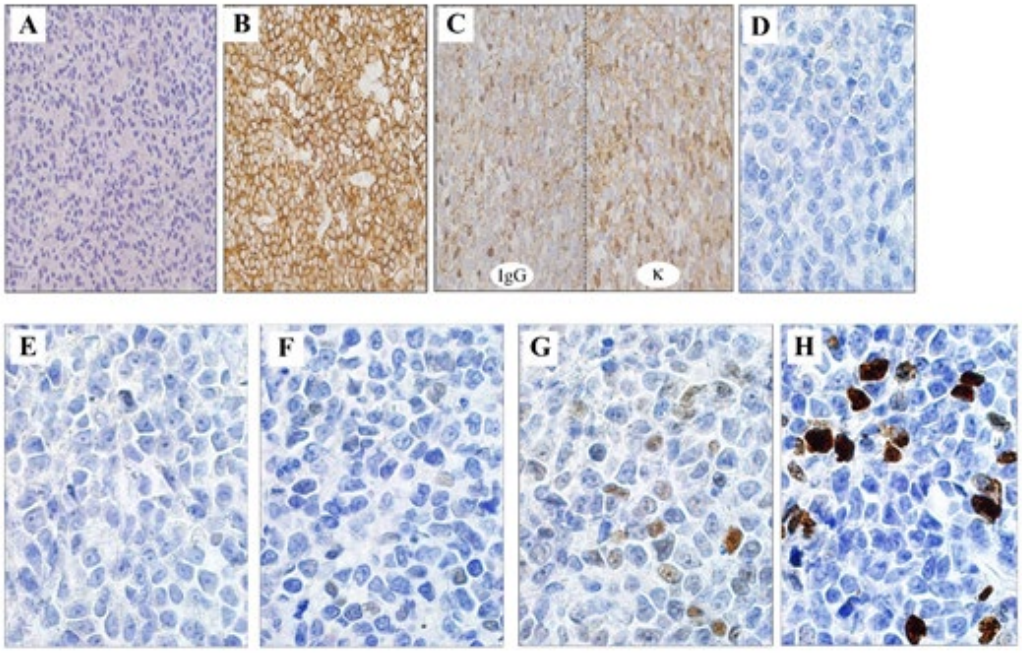

Figure 3: Histological Findings, Immunohistochemical Analysis of Cell Proliferation and Survival of Soft Tissue Tumors on Admission. Biopsy tissue of the subcutaneous mass in the right chest wall shows sheet-like proliferation of the same small round tumor cells seen in the bone marrow (H-E stain, x100) (A) and shows positivity for CD138 (B) and IgG/kappa (C), and negativity for CD56 (D). There is almost no expression of c-myc (E) and cyclin D1 (F). There is low expression of p53 (G) and the labeling index of Ki 67 is 25% (H).

These findings suggested a diagnosis of primary EM-E accompanied by myelofibrosis (Durin & Surmon, stage IIIA; ISS, stage III). He was treated with chemotherapies including the VAD regimen (vincristin 0.4 mg, adriamycin 14 mg, and dexamethasone 40 mg, days 1–4) and the VD regimen (bortezomib 1.95 mg, days 1, 4, 8, 11; and dexamethasone 40 mg, days 1, 2, 4, 5, 8, 9, 11, 12) but the mass on the right chest wall continued to grow and appeared multiple new subcutaneous tumors (maximum size 5 cm). The new tumors were diagnosed as high-grade plasma cell tumors based on examination of biopsy tissue, which showed diffuse infiltration of plasmablastic tumor cells (data not shown), indicating progressive disease. The patient was further treated with the M-2 protocol (melphalan 14 mg, cyclophosphamide 540 mg, ramunistine 100 mg) that resulted in shrinkage of the subcutaneous tumors, but his therapy was interrupted due to prolonged myelosuppression. Bone marrow examination showed severely hypoplastic marrow with a reduction in tumor cells and improved fibrosis. Chromosomal analysis revealed complex karyotypic abnormalities of 69, X, -X, -Y, add(1)(p11)x3, -2, -2, add(2)(p11.2), del(6)x2, add(8)(p11.2), add(9)(p13), -12, -13, add(14)(q32)x2, -15, -16, -17, add(17)(q25), +18, der(19), t(1;19)(q21;p13)-20, -20, -20, -22, +12mar. The patient died 10 months after the initial presentation following progression of the subcutaneous and intra-abdominal tumors (Figure 1 D–F).

3. Discussion

The present patient was diagnosed with primary EM-E accompanied by myelofibrosis. He showed only a small amount of IgG/κ and M-protein, no renal impairment, no osteolytic lesions, and no hypercalcemia. Intriguingly, biopsies of bone marrow and the subcutaneous mass revealed diffuse infiltration of two types of tumor cells, comprising large anaplastic-like cells and small blastic cells which were completely different from typical plasma cells. Extramedullary infiltration in myeloma can occur in various organs including the lymph nodes, soft tissues, liver, pancreas, kidneys, lungs, central nervous system, genitourinary system, and skin [4]. The prognosis of EM is generally very poor, with median survival ranging from 0.5 to 1.6 years in EM-E [5]. Anemia, thrombocytopenia, high LDH level, low level of M-protein, high β2-MG level, and complex karyotypic abnormalities including deletion of 17, which are poor prognostic factors in myeloma as well as EM [6], were seen in the present patient. It is generally considered that EM develops from preexisting bone marrow myeloma cells, and that the tumor morphology differs between bone marrow myeloma and EM. Thus, an abundance of immature or plasmablastic cells in EM tissue with typical plasma cells of bone marrow suggests that extramedullary lesions are subclones of bone marrow myeloma cells. Interestingly, the present patient displayed two types of immature tumor cells: anaplastic-like cells in bone

marrow and small round blastic cells in both bone marrow and EM, which is a different morphological pattern to typical myeloma with EM. Furthermore, proliferative index with immunostaining of tumor cells revealed a distinction in pattern between bone marrow and EM. Nuclear p53, cyclin D1, and Ki-67 were more strongly expressed in bone marrow than in EM, which suggests a greater proliferative capability of the bone marrow tumor cells. This finding is contrary to previous reports in which nuclear p53 expression and higher proliferative index as determined by Ki-67 was more predominant in EM than bone marrow, corresponding to clonal progression of EM from bone marrow [5,7]. The reason for the discrepancy in our case is unclear. Considering single karyotypic abnormality obtained from bone marrow aspirate obtained after treatment, it cannot be ruled-out that aggressive myeloma clones (large anaplastic cells) in bone marrow have been derived from subclone (small round cells) in both bone marrow and the extramedullary site.

In the present case, diffuse marrow fibrosis with leukoerythroblastosis was observed at the time of diagnosis. Only one similar case has been reported, in which myelofibrosis resembled essential thrombocythemia with JAK2V617F mutation that preceded myeloma [8]. We did not perform driver mutation analysis of JAK2, CALR, or MPL; however, improvements in both marrow fibrosis and bone marrow tumor cell infiltration following chemotherapy support the diagnosis of myelofibrosis secondary to myeloma. In the two studies that have reported myelofibrosis complicated with myeloma, increased myelofibrosis was present at diagnosis of myeloma in 9/44 and in 5/42 of patients (grades 2 and 3, respectively) [9,10]. In these studies, myelofibrosis was associated with immature plasma cell morphology, proliferative ability, and refractoriness to therapy; and median survival was 11 months for grade 2 or higher fibrosis. Although successful treatment of myeloma appears to correlate with improvement in myelofibrosis, [11] , progression of EM despite the improvement in fibrosis after chemotherapy indicates that EM was a stronger prognostic factor than myelofibrosis in the present case.

Our patient was refractory to treatment including bortezomib and multiple chemotherapies. At present, a standard therapy for EM has not yet been established. Regimens containing proteasome inhibitors, immunomodulatory drugs as well as monoclonal antibodies of daratumumab and elotuzumab, chimeric antigen receptor-T cell therapy, and ASCT have shown promising results in EM [3,12]. However, the efficacy of these novel agents or SCT has not been confirmed in long-term follow-up. The effect of therapy containing novel agents can vary depending on biological factors such as morphology, cytogenetic aberration, and proliferative capability of EM. Thus, future clinical studies that include assessment of these factors are warranted.

4. Conclusion

We experienced a case of atypical IgG/κ-type multiple myeloma with subcutaneous tumor masses as primary EM-E, accompanied by distinct immature tumor cells occupying both bone marrow and soft tissue, and diffuse marrow fibrosis. The patient was refractory to several chemotherapies and died 10 months after the initial presentation. Considering that the primary EM-E has a poor prognosis and usually refractory to chemotherapy, an effective treatment method for EM based on biological factors such as EM morphology, cytogenetic abnormalities, and proliferative capacity is awaited.

References

1. Pour, L., Sevcikova, S., Greslikova, H., Kupska, R., Majkova, P., Zahradova, L., ... & Hajek, R. (2014). Soft-tissue extramedullary multiple myeloma prognosis is significantly worse in comparison to bone-related extramedullary relapse. *Haematologica, 99*(2), 360.
2. Sevcikova, S., Minarik, J., Stork, M., Jelinek, T., Pour, L., & Hajek, R. (2019). Extramedullary disease in multiple myeloma–controversies and future directions. *Blood reviews, 36,* 32-39.
3. Chen, Y., Tao, S., Zheng, X., Shi, Y., Zhang, L., Chen, K., ... & Yu, L. (2021). Research progress on treatment of extramedullary multiple myeloma. *Hematology, 26*(1), 985-994.
4. Bladé, J., Fernandez de Larrea, C., Rosiñol, L., Cibeira, M. T., Jiménez, R., & Powles, R. (2011). Soft-tissue plasmacytomas in multiple myeloma: incidence, mechanisms of extramedullary spread, and treatment approach. *Journal of Clinical Oncology, 29*(28), 3805-3812.
5. Usmani, S. Z., Heuck, C., Mitchell, A., Szymonifka, J., Nair, B., Hoering, A., ... & Barlogie, B. (2012). Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents. *haematologica, 97*(11), 1761.
6. Bhutani, M., Foureau, D. M., Atrash, S., Voorhees, P. M., & Usmani, S. Z. (2020). Extramedullary multiple myeloma. *Leukemia, 34*(1), 1-20.
7. Sheth, N., Yeung, J., & Chang, H. (2009). p53 nuclear accumulation is associated with extramedullary progression of multiple myeloma. *Leukemia research, 33*(10), 1357-1360.
8. Badelita, S., Dobrea, C., Colita, A., Dogaru, M., Dragomir, M., Jardan, C., & Coriu, D. (2015). The simultaneous occurrence of multiple myeloma and JAK2 positive myeloproliferative neoplasms-Report on two cases. *Journal of Medicine and Life, 8*(1), 55.
9. Subramanian, R., Basu, D., & Dutta, T. K. (2007). Significance of bone marrow fibrosis in multiple myeloma. *Pathology, 39*(5), 512-515.
10. Babarović, E., Valković, T., Štifter, S., Budisavljević, I., Seili-Bekafigo, I., Duletić-Načinović, A., ... & Jonjić, N. (2012). Assessment of bone marrow fibrosis and angiogenesis in monitoring patients with multiple myeloma. *American journal of clinical pathology, 137*(6), 870-878.
11. Kawauchi, K., Mori, H., Sugiyama,H., Oshimi,K., & Hirayama, A. (1991). Multiple myeloma with coexistent

myelofibrosis: improvement of myelofibrosis following recovery from multiple myeloma after treatment with melphalan and prednisolone. *Japanese Journal of Medicine, 30*(5), 483-486.

12. Jagosky, M. H., & Usmani, S. Z. (2020). Extramedullary disease in multiple myeloma. *Current Hematologic Malignancy Reports, 15,* 62-71.