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# Anaplastic multiple myeloma with MYC rearrangement

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ABSTRACT

A 52-year-old man with rapidly progressive paraplegia was presented to us with paravertebral tumors. Laminectomy with tumor resection was performed, and pathological analysis of the tumor revealed compact proliferation of anaplastic plasmacytoid cells. G-band analysis of the tumor revealed a complex karyotype, including IgH/MYC translocation. The patient was diagnosed with anaplastic multiple myeloma (AMM) with MYC arrangement, and cytotoxic chemotherapy followed by autologous hematopoietic stem cell transplantation resulted in long-term disease-free remission. This is the first report describing a case of de novo AMM with MYC rearrangement, suggesting that conventional chemotherapy could be a treatment option for this formidable disease.

## 1. Introduction

Anaplastic multiple myeloma (AMM), also described as plasmablastic myeloma, is considered as a rare variant morphological form of multiple myeloma (MM) with an aggressive clinical course, which is characterized by massive proliferation of undifferentiated plasma cells with extensive extramedullary diseases [1]. A part of relapsed/refractory myeloma can progress into such an aggressive variant. Only few de novo AMM cases have been reported in recent years [2–4], and their clinicopathological features are yet to be elucidated. Here, we report a case of de novo AMM harboring the rearrangement of MYC oncogene, which was successfully treated with conventional chemotherapy. To the best of our knowledge, this is the first report describing the case of de novo AMM with MYC rearrangement.

## 2. Case report

A 52-year-old male with no relevant past medical history experienced a sudden onset of progressive numbness and weakness of both lower limbs, which rapidly developed into paraplegia within a month. He was admitted to the department of orthopedic surgery in our hospital because paravertebral tumors, which spread into the spinal canal and compressed the spinal cord, were detected on computed tomography (CT) and magnetic resonance imaging (MRI) (Fig. 1). Laminectomy with tumor resection was promptly performed without complications; however, his neurological deficits did not improve.

Several days after the operation, pathological analysis of the tumor revealed a compact proliferation of large abnormal cells with distinct nucleoli, which formed solid cell nests (Fig. 2a). The deviation of nuclear localization was also observed. On immunohistochemistry, they were positive for CD38, CD138, and MYC (>95% positivity), and negative for CD3, CD19, CD20, CD30, CD45, CD56, CD79a, ALK, and cyclin D1 (Fig. 2c-g). Immunoglobulin light chain restriction was observed (λ>>κ). Epstein-Barr virus-encoded RNA (EBER) was negative on fluorescence in situ hybridization (Fig. 2h). The Ki-67 labeling index was as high as >90% (Fig. 2i). Although bone marrow aspiration resulted in a dry tap, bone marrow biopsy revealed the massive infiltration of the same abnormal cells as described above (Fig. 2b). From these findings, the pathological diagnosis was anaplastic plasma cell neoplasm, and he was introduced to our department a week after the operation.

At presentation, he complained of severe malaise in addition to neurological deficits. A complete blood test revealed normocytic anemia (hemoglobin, 8.0 g/dL), mild thrombocytopenia (130,000/μL), and a normal white blood cell count with some myeloid immature cells (7800/μL, with neutrophils 71%, lymphocytes 16%, monocytes 8%, metamyelocytes 3%, myelocytes 1%, and blasts 1%). Biochemical analysis

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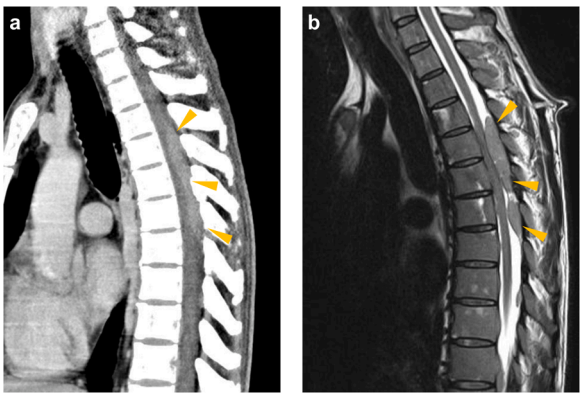


**Fig. 1.** Radiological findings on CT (**a**) and MRI (**b**) of the paravertebral tumors. The arrowheads indicate the paravertebral tumors compressing the spinal cord. CT, computed tomography; MRI, magnetic resonance imaging.

revealed an extremely elevated level of lactate dehydrogenase (LDH, 5842 U/L; normal range: 124–222); this rapid increase occurred within one week before (554 U/L). His renal function, which was normal a week before, worsened (creatinine, 1.86 mg/dL). Although serum immunoglobulin concentrations were heterogeneously low (IgG, A, M, and D; 1039, 91, 29, and 0.6 mg/dL, respectively), a monoclonal band could not be detected by immunoelectrophoretic analysis of serum and urine. Serum free light chain analysis indicated no deviation of the kappa/lambda ratio (κ-chain, 50.8 mg/L; λ-chain, 110 mg/L). The antibody for human immunodeficiency virus was negative.

Based on the established anaplastic plasma cell neoplasms, aggressive development of paravertebral tumors, and significant elevation of LDH levels, the patient was diagnosed with non-secretory AMM. G-band analysis of the paravertebral tumor revealed a complex karyotype including IgH/MYC translocation and 1q21 aberration (Fig. 3a) in all the evaluable eight cells. Additionally, fluorescence in situ hybridization with paraffin-embedded tissue sections of both paravertebral tumor and bone marrow biopsy specimens also showed positive split signals of the MYC gene (Fig. 3b).

The patient was promptly treated with cytotoxic chemotherapy using the EPOCH regimen (etoposide, doxorubicin hydrochloride, vincristine, prednisolone, and cyclophosphamide), which resulted in rapid improvement of malaise and remarkable decrease in serum LDH levels. However, his neurological deficits did not improve, and rehabilitation continued. Three weeks after the initiation of chemotherapy, the bone marrow could be aspirated, although hypocellular marrow was observed. No abnormal plasma cells were detected via flow cytometry. A bone marrow biopsy also revealed hypoplastic marrow without the infiltration of plasma cells.

Thereafter, he received three additional courses of the EPOCH regimen, which resulted in sustained disease remission. High-dose chemotherapy (melphalan, 200 mg/m$^2$) with autologous peripheral blood stem cell transplantation was sequentially performed as consolidation therapy. An infusion of 5.0 × 10$^6$/kg of CD34$^+$ cells was administered, and neutrophil engraftment was confirmed on day 11. No severe regimen-related toxicities were observed. Thereafter, as of the time of this report, disease relapse has not been experienced for more than 2.5 years without any chemotherapeutic intervention. He has been well with gradual improvement in neurological deficits due to rehabilitation.

## 3. Discussion

AMM is considered a form of aggressive transformation of myeloma, which can be observed as a de novo disease, as well as during the course of multiple myeloma. Although the clinicopathological definition of AMM has not been fully established, conspicuous features such as aggressive disease progression with significant elevation of serum LDH levels, extramedullary tumors, and massive proliferation of immature plasma cell-like aberrant cells, have been frequently reported in AMM case reports in the literature [2, 5-7]. The cellular origin of AMM is speculated to be immature plasma cells, and it could be a key point in distinguishing AMM from the neoplasm of plasmablasts, namely plasmablastic lymphoma (PBL) [8]. PBL is a rare histological subtype of B-cell lymphoma with a CD20-negative plasmacytoid phenotype [9]. Inversely, PBL usually presents as an extranodal mass of the head and neck (especially the oral cavity) or gastrointestinal tract [9]. Additionally, PBL occurs predominantly in immunocompromised hosts, and EBER-ISH positivity is frequently observed. In the present case, we diagnosed the patient with AMM rather than PBL, considering the absence of an immunodeficiency history, the negativity of EBER-ISH, the lesion sites of paravertebral tumors, and the bone marrow findings. Additionally, according to the recently proposed diagnostic algorithm for tumors with a plasmablastic morphology [8], this case could also be categorized as a plasma cell neoplasm based on the negativity of EBER and ALK. Although human herpes virus-8 (HHV8) could not be evaluated in this case, HHV8-asociated large B-cell lymphoma is deniable because multicentric Castleman disease and human immunodeficiency virus infection were absent in this case.

The cytogenetic and molecular characteristics associated with anaplastic change in MM have not been elucidated. The rearrangement of MYC is reported to be present in a part of MM, which is considered a late progression event in clonal evolution and associated with poor prognosis [10, 11]. However, the association between MYC rearrangement or overexpression and AMM development has not been reported in the literature. Although it has been reported that MYC overexpression is significantly correlated with advanced disease with marked proliferation, plasmablastic morphology, high calcium level, and abnormal karyotype [12], its association with anaplastic change of myeloma has not

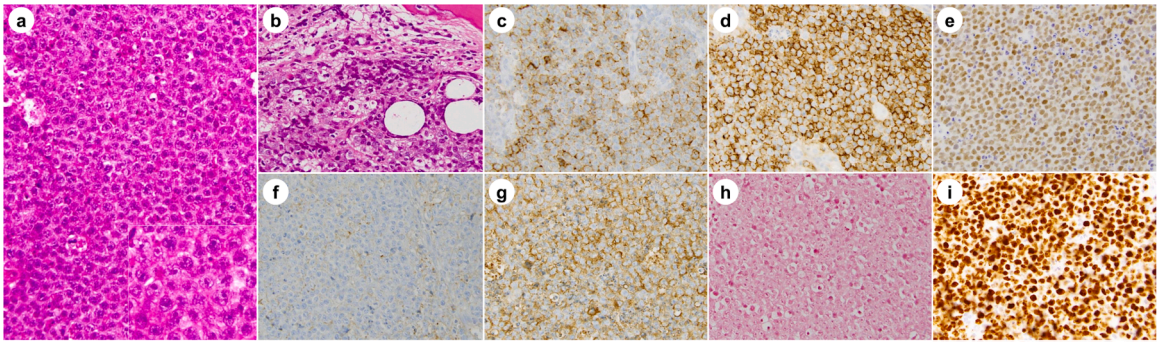


**Fig. 2.** Pathological findings. (**a, b**) Hematoxylin-eosin staining of the paravertebral tumor (***a***× 20, inlet × 40) showing a compact proliferation of large abnormal cells with distinct nucleoli, which infiltrated the bone marrow (***b***× 20). **(c-g)** Immunohistochemical staining of the paravertebral tumor showing CD38$^+$ (**c**), CD138$^+$ (**d**), MYC$^+$ (**e**), Igκ$^-$ (**f**) and Igλ$^+$ (**g**). (**h**) Cells negative for Epstein-Barr virus-encoded small RNA via situ hybridization. (**i**) The Ki-67 labeling index is high (>90%).

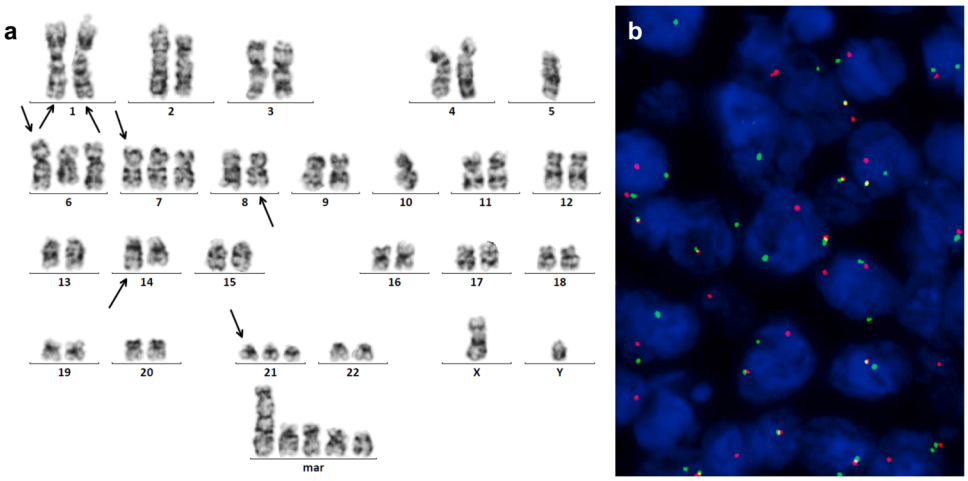


**Fig. 3.** Cytogenetic findings. **(a)** G-band analysis of the paravertebral tumor. The karyotype was 50~53,XY,ins(1;?)(q21;?) × 2,+6,+7,t(8;14)(q24;q32),−10,+21,+3~5mar [cp8]. The arrows indicate aberrant chromosomal findings. **(b)** FISH analysis using paraffin-embedded tissue of the paravertebral tumor showing split signals of the MYC gene. The green and red spots indicate signals from probes on the telomere and centromere sides of the MYC gene (chromosome 8q24), respectively.

been documented. On the other hand, amplification or gain of chromosome 1q21 (1q21+), on which the CKS1B gene is located, is frequently observed in AMM, and CKS1B amplification can be considered a hallmark of AMM [13]. However, it should be noted that many other genes at the 1q21 locus could be associated with poor prognosis and resistance to chemotherapy [14]. 1q21+ is also observed in non-anaplastic MM and is likely to be associated with the disease progression of MM [15]. Moreover, it was recently reported that 1q21+ is strongly associated with MYC rearrangement, which is associated with poor prognosis in MM [16, 17]. Although it is not clear whether the combination of 1q21+ and MYC rearrangement is associated with the anaplastic phenotype of MM, this is the first documented case of de novo AMM harboring MYC rearrangement and 1q21 aberration.

The therapeutic strategy for AMM has not yet been established. Some reported cases were successfully treated with myeloma-targeting agents such as proteasome inhibitors and/or immunomodulatory agents [5, 7]; in contrast, other cases have been reported to be refractory to such novel agents [6, 18]. Although conventional chemotherapy is effective for short-term disease control [2], it is scarcely results in long-term remission. In this case, lymphoma-targeting aggressive chemotherapy, combined with high-dose chemotherapy and autologous hematopoietic stem cell transplantation, resulted in long-term disease-free survival for more than two years. This suggests that conventional cytotoxic agents, as well as novel agents, could be a treatment option for AMM. However, the optimal combination or sequence of treatments is uncertain.

In summary, we report a case of AMM with MYC rearrangement, that was successfully treated with conventional chemotherapy. Further accumulation of clinical experiences of similar cases is urgently required to elucidate the clinicopathological features, development of treatment strategies, and amelioration of the poor prognosis of AMM.

## Statement of ethics

Written informed consent to publish the case report was obtained from the patient. This study was approved by the Ethics Committee of Tohoku University Hospital.

## CRediT authorship contribution statement

**Satoshi Ichikawa:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **Noriko Fukuhara:** Data curation, Formal analysis. **Ko Hashimoto:** Data curation, Formal analysis. **Fumiyoshi Fujishima:** Data curation, Investigation. **Ryo Ichinohasama:** Data curation, Investigation. **Hideo Harigae:** Data curation, Formal analysis, Supervision.

## Declarations of Competing Interest

The authors declare that there are no conflicts of interest relevant to this study.

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