Clinical and histopathological analyses of anaplastic myeloma

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As a morphological sub-type of multiple myeloma (MM), anaplastic myeloma (AM), which includes “anaplastic multiple myeloma” and “anaplastic plasmacytoma”, is a rare disease that aggressively progresses. It is reported to be very resistant to chemotherapy and exhibits a poor prognosis.1,3 Although AM was detected in 2.6% of patients in a large series of cases,2 there have only been some case reports since AM was first reported in 1983.3 Therefore, AM lacks detailed descriptions and strict definitions. To further analyze the clinical and pathological features of AM patients and to provide some suggestions for diagnosis and treatment, we retrospectively analyzed four AM patients who were admitted to the Affiliated Hospital of Qingdao University.

A total of 269 patients were admitted to the Affiliated Hospital of Qingdao University with a definite diagnosis of MM from January 2015 to August 2019. Four patients were diagnosed with AM by pathology.

The first case of a 36-year-old woman presented with bone pain and weakness in the lower limbs. Blood tests showed the following: hemoglobin, 78 g/L; β2-macroglobulin (β2-MG), 6.89 mg/L; lactic dehydrogenase (LDH), 1429.1 U/L; free λ light chain, 1429 mg/L; and immunofixation electrophoresis (IFE), λ isotype. Immunoglobulin (Ig) levels were below normal. The computed tomography scans showed an intraspinal mass with extraosseous extension involving the T7 and T8 vertebrae. Bone marrow biopsy revealed that 53.5% of cells were round and similar to the malignant cells found in sarcoma. Immunohistochemistry showed CD38(+), MUM1(+), CyclinD1(+), Ki-67 60%, Kappa(−), Lambda(−). Fluorescence in situ hybridization (FISH) confirmed 1q21 gain, immunoglobulin heavy chain (IGH) rearrangement, and del (13q14.3). Karyotyping revealed multiple abnormalities, including del (1q25), −13, and −14. The patient received a cycle of the VTD (bortezomib, thalidomide, and dexamethasone) and a cycle of VDD (bortezomib, liposome doxorubicin, and dexamethasone) regimens, but there was no response. Then, she was treated with one cycle of the V-DECP (bortezomib, cisplatin, cyclophosphamide, etoposide, and dexamethasone) regimen and achieved partial remission (PR). However, the patient had severe bone marrow suppression and died of infection and dyscrasia, with a 5-month survival.

The second case of a 58-year-old man presented with back pain and weakness in both lower limbs. Blood tests showed the following: hemoglobin, 99 g/L; LDH, 693 U/L; and IFE, λ isotype. Ig levels were below normal. Imaging showed multiple osteolytic lesions and a mass with extraosseous extension involving the T1 and T2 vertebrae. Bone marrow biopsy revealed that 53.5% of cells were round and similar to the malignant cells found in sarcoma. Immunohistochemistry showed CD38(+), MUM1(+), CD20(−), epithelial membrane antigen(−), CD79a(−), CD56(−), Kappa(−), Lambda(−), and Ki-67 90%. The patient received one cycle of the VAD (vindesine, epirubicin, and dexamethasone) regimen, without response. He had repeat fever, which was not responding to broad-spectrum antibiotics. Then, he progressed aggressively and eventually died of infection, with a total survival of 3 months.

The third case of a 47-year-old woman presented with rib pain. Blood tests showed the following: hemoglobin, 78 g/L; LDH, 444 U/L; β2-MG, 9.46 mg/L; IFE, IgG-κ type; and IgG, 125.19 g/L. The proportion of plasma cells in the bone marrow was 27.5%. She received nine cycles of the VTD regimen. One month later, the patient was admitted to the emergency department due to severe abdominal...
pain. Imaging showed multiple intraperitoneal masses, osteolytic lesions, and effusions. Blood work showed IgG-κ paraproteins and a serum IgG level of 3.99 g/L. The pathological examination of the masses showed anaplastic cells. Immunohistochemistry revealed CD38(+), CD138(+), MUM1(+), CD20(+), CD3(-), Kappa(+), Lambda(-), and Ki-67 85% [Figure 1]. She received two cycles of thalidomide-VAD and a course of radiotherapy, without any therapeutic response. This patient died of disease progression, with the survival of three months since she was diagnosed with AM.

The last patient of a 57-year-old woman complained of “a skull mass.” Blood tests showed the following: hemoglobin, 87 g/L; IFE, IgG-κ type; and IgG, 30.90 g/L. A total of 32.5% of myeloma cells were seen in the bone marrow, and del(TP53) was found with FISH. The pathological results of the resected skull mass revealed plasmacytoma. Immunohistochemistry revealed CD38(+), CD138(+), CD56(+), MUM1(-), CD20(-), CD79a(-), CyclinD1(-), Kappa(+), Lambda(-), and Ki-67 25%. After she received four cycles of the VCD (bortezomib, cyclophosphamide, and dexamethasone) regimen, she suddenly complained of paraplegia in both lower limbs. Imaging showed a mass in the spinal canal involving the T3-T5 vertebrae. Blood work showed IgG 2.48 g/L. She had an operation to remove the mass. The pathological results revealed that the nucleus in the anaplastic cells was vacuolated, with prominent nucleoli and additional common mitotic figures. Immunohistochemistry revealed like her skull mass, but MUM1(+) and Ki-67 80%. After treatment with a cycle of the V-DECP regimen and five cycles of thalidomide plus the VAD regimen, she had reached PR and was still alive when the manuscript was finished, with a survival of more than nine months since she was diagnosed with AM.

The clinical and pathological features of AM have yet to be fully elucidated because of its rarity. AM patients are relatively young; usually complicated by anemia or pancytopenia, significantly decreased serum levels of Ig, IgA isotype, and rapidly growing extramedullary masses.[5]

As we reported, all four patients were younger than 60 years of age. They all had anemia, decreased serum Ig levels, and extramedullary masses. However, all patients did not have IgA isotypes, which may be related to the small number of patients.
AM cells are diffusely distributed atypical plasmacytoid differentiated cells. They exhibit the following distinct morphological features: pleomorphic cells with substantially enriched cytoplasm; more than one large and irregular nucleolus; nucleoli with many scattered vacuoles. Sometimes AM cells are similar to “immunoblasts,” and they are often misdiagnosed as other low-differentiated cancers, such as malignant melanoma, Burkitt lymphoma, and sarcoma.

Therefore, immunohistochemistry is very important for differential diagnosis. AM cells usually express CD38, CD138, and MUM1 and have restricted expression of the light chain, while the lymphocyte markers CD20, CD19, and CD3 are not expressed. This is consistent with our report.

However, it is very difficult to differentiate AM from plasmablastic lymphoma (PBL). Because PBL is very similar in morphology and immunophenotype to AM. 75% of patients with PBL have obvious immunodeficiency, such as human immunodeficiency virus (HIV) infection. The current identification of PBL and AM is focused on the difference in clinical manifestations, such as M-protein levels, HIV infections, and osteolytic changes. Additionally, with the widespread application of FISH and next-generation sequencing, the chromosomal and genetic abnormalities of AM have been increasingly reported. Multiple chromosomal and gene abnormalities often occur in AM, the majority of which are aneuploidy, 1q21 amplification, del (TP53), t (4;14), and chromosome 13 abnormality.

Most AM patients have an inadequate response to conventional chemotherapy and radiotherapy. In our research, we found that patients described an unsatisfactory response to treatment with novel agents, that is, bortezomib and thalidomide. However, bortezomib combined with the DECP regimen was effective in two patients. Thus, a combination of intensified chemotherapies and novel agents may improve the response. Of course, immunotherapy, including chimeric antigen receptor T-cell immunotherapy, monoclonal antibodies, and even hematopoietic stem cell transplantation, may provide new therapeutic hope for these patients.

In summary, we presented four cases of AM, which is a highly malignant sub-type of myeloma that is resistant to conventional therapy. Another treatment strategy may be necessary to cure AM. Accumulation of new clinical experience is needed to better understand the pathophysiology, develop treatment strategies, and improve the prognosis of AM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

References


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