LETTER TO THE EDITOR

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Ring-Like Nuclear Morphology in Cerebrospinal Fluid Plasma Cells in Central Nervous System Myeloma

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To the Editor,

A 57-year-old man was diagnosed with κ light-chain multiple myeloma (MM), ISS stage IIIA, four years before the current presentation. He initially received one cycle of PAD therapy (bortezomib, doxorubicin, and dexamethasone) on February 8, 2022, followed by three cycles of VRd therapy (bortezomib, lenalidomide, and dexamethasone) on March 15, April 25, and May 24, 2022. After achieving measurable residual disease (MRD) negativity, he underwent stem-cell mobilization with high-dose cyclophosphamide on June 24, 2022, followed by autologous hematopoietic stem cell transplantation on August 15, 2022. Four additional cycles of VRd were administered from November 2022 to March 2023, followed by maintenance therapy with bortezomib and lenalidomide. Approximately one year before the current presentation, the patient developed extramedullary relapse, with repeat biopsies performed at an outside hospital confirming anaplastic plasmacytoma involving the right upper arm and pharynx. Notably, the patient remained MRD-negative in both the bone

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marrow and peripheral blood during this period, despite the development of biopsy-proven extramedullary disease. The relapsed extramedullary lesions showed a markedly high Ki-67 proliferation index, consistent with a highly proliferative and clinically aggressive disease phenotype. He subsequently received salvage therapy with KPD (carfilzomib, pomalidomide, and dexamethasone), beginning on August 15, 2025, with a second cycle initiated on September 15, 2025. This was followed by daratumumab plus dexamethasone (DD) on October 28 and November 4, 2025, and subsequently by DPD (daratumumab, pomalidomide, and dexamethasone) from November 11, 2025, through February 8, 2026. He then received DECP chemotherapy on March 6, 2026, with a further cycle administered on March 31, 2026.

The patient subsequently developed headache. Cranial magnetic resonance imaging (MRI) revealed multiple enhancing skull lesions without definite dural, leptomeningeal, or parenchymal involvement. These findings alone were insufficient to establish central nervous system (CNS) involvement. Repeat bone marrow examination showed no morphologic evidence of plasma cell infiltration, consistent with the persistently negative marrow MRD status. However, cerebrospinal fluid (CSF) smears revealed numerous atypical plasma cells characterized by large cell size, abundant cytoplasm, eccentric nuclei, and prominent perinuclear hof. Notably, CSF MRD had previously remained negative, making the detection of morphologically overt plasma cells in the CSF particularly striking.

On careful review of high-power fields, the ring-shaped structures were confirmed to represent the nuclei themselves rather than prominent nucleoli or other intranuclear inclusions. These cells showed dense peripheral nuclear chromatin surrounding a relatively pale central area, producing a distinctive ring-like configuration. Among 112 morphologically evaluable atypical plasma cells, 45 (40%) displayed this unusual nuclear morphology (Figure 1A–D). CSF analysis showed a white blood cell count of 6 cells/μL (6×10^6/L), elevated protein of 1.22 g/L, and glucose of 5.18 mmol/L. The CSF red-cell count was zero, indicating that the specimen was not contaminated by peripheral blood, and no circulating plasma cells were identified in the peripheral blood around the time of lumbar puncture—arguing against a peripheral-blood source for the CSF findings.

Flow cytometry identified an abnormal plasma cell population comprising 7,334 of 8,915 acquired CSF cellular events (82.3%). Because the patient had received daratumumab, the abnormal plasma cells were CD38-negative; plasma-cell identification therefore relied on combined CD45/SSC and CD38/CD138 gating rather than CD38 or CD138 alone. These cells demonstrated a clonal immunophenotype: CD138+CD56+CD38−CD19−CD33+CD14−CD15−CD117−CD3−cκ−cλ−CD45− (Figure 1E–N). The absence of detectable CD38 expression was likely attributable to recent daratumumab exposure, which can interfere with flow cytometric CD38 detection for several months after treatment.[1] Thus, despite the absence of definite radiological leptomeningeal or parenchymal involvement and morphologically detectable marrow disease, the identification of clonal plasma cells in CSF established CNS involvement by multiple myeloma.

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CNS involvement in multiple myeloma is uncommon, occurring in approximately 1% of patients, and is associated with extramedullary disease, relapse, and poor prognosis.[2] CSF cytology and multiparameter flow cytometry provide complementary information, with flow cytometry particularly valuable for demonstrating clonality in paucicellular specimens.[3] To the best of our knowledge, ring-shaped nuclei have not previously been described in plasma cells from CSF or bone marrow smears in multiple myeloma. The ring-shaped nuclear configuration observed in the CSF plasma cells should be distinguished morphologically from nuclear pseudoinclusions, Dutcher bodies, folded or multilobated nuclei, and signet-ring plasma-cell variants, which exhibit distinct nuclear or cytoplasmic features.[4] The biological basis and prognostic significance of this configuration remain unknown. Recognition of this distinctive finding may aid cytological identification of myeloma involvement in CSF and broadens the recognized spectrum of plasma cell morphologic abnormalities in extramedullary disease. The patient received intrathecal chemotherapy combined with oral lenalidomide and dexamethasone, with subsequent improvement in neurological symptoms, and was discharged.

Keywords: Multiple myeloma, Central nervous system involvement, Cerebrospinal fluid, Ring-shaped nuclei, Flow cytometry

Declarations

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Authors' contributions All authors contributed to the paper conception and design. Clinical and histological data were collected by Fang Chen. Histological diagnosis and study design were performed by Fang Long. The draft of the manuscript was written by Ting Li and Yingdong Xu, and all authors read and approved the final Manuscript

Conflict of Interest The authors declare that they have no conflicts of interest.

Informed consent Written informed consent for publication was obtained from the patient

Ethical approval Ethics approval was not required for this single-patient case report.

Consent for publication Informed consent was obtained from the publication.

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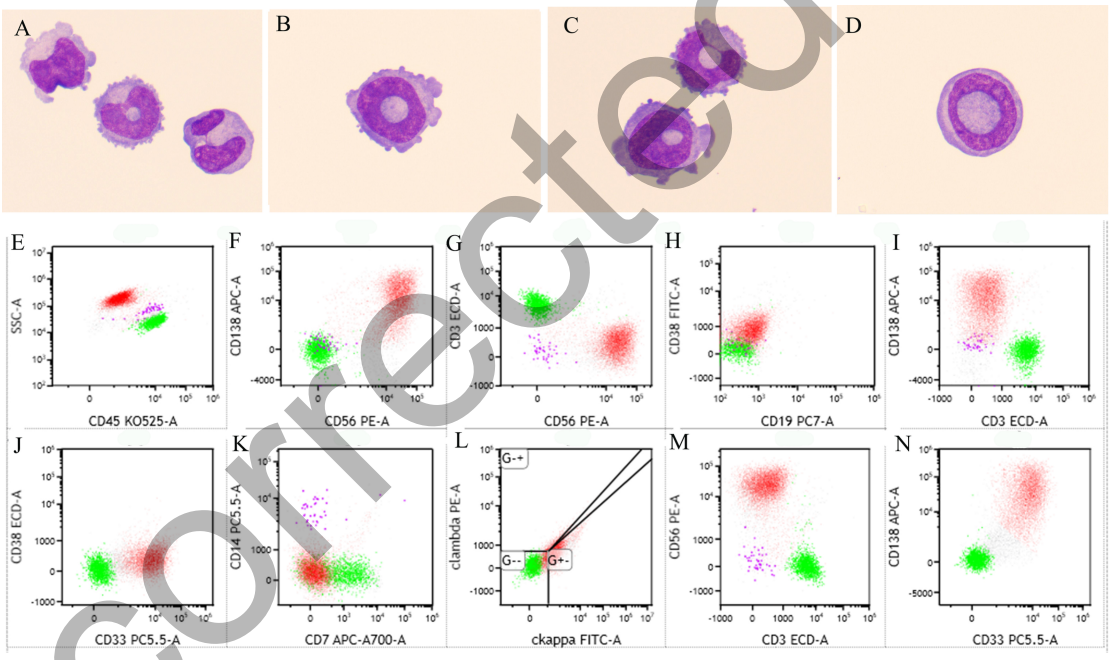


Figure 1. A-D Wright–Giemsa-stained cerebrospinal fluid smears showing atypical plasma cells with abundant cytoplasm, eccentric nuclei, and prominent perinuclear hof. The ring-shaped feature represents the nuclear configuration itself rather than a prominent nucleolus, with peripheral chromatin surrounding a relatively pale central nuclear area (Wright-Giemsa stain, ×1000).

E-N Because the patient had received daratumumab, the abnormal plasma cells were CD38-negative; plasma-cell identification therefore relied on combined CD45/SSC and CD38/CD138 gating rather than CD38 or CD138 alone. Red blood cell fragments and platelets were first excluded using FSC/SSC, followed by exclusion of residual debris using FSC-A/SSC-A and of doublets using FSC-A/FSC-H. For this CSF specimen (100 µL), approximately 8,915 viable nucleated events were acquired per tube.

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Abnormal plasma cells with the immunophenotype CD138+CD56+CD38−CD19−CD33+CD14−CD15−CD117−CD3−cκ−cλ−CD45− accounted for 82.3% of acquired events (7,334/8,915), shown as red dots in panels E–N. Antibody clones used were as follows: CD138 (B-A38), CD38 (HB7), CD19 (SJ25C1), CD56 (N901), kappa (TB28-2), and lambda (HP6054).

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