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Monoclonal Gammopathies & Multiple Myeloma

CIRCULATING PLASMA CELLS DRIVE DISEASE DISSEMINATION IN MULTIPLE MYELOMA, INDEPENDENT OF CLONALITY

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Multiple myeloma (MM) is a hematologic malignancy defined by clonal proliferation of plasma cells (PCs) within the bone marrow (BM), with occasional migration into peripheral blood (PB) as circulating plasma cells (CPCs). Despite substantial advances in therapy and improved patient (pt) outcomes, relapse remains common, possibly due to the capacity of BM-resident PCs to detach from the marrow niche and generate CPC clones that facilitate extramedullary spread and disease dissemination. This study assessed the relationship between CPCs and disease dissemination using imaging (DWI and PET), and evaluated biological and clinical differences between pts with monoclonal CPCs (mCPCs) and polyclonal CPCs (pCPCs). A total of 140 newly diagnosed MM pts were enrolled. BM aspirates, PB samples, imaging, and genomic data were collected at diagnosis. Multiparametric flow cytometry (sensitivity $\geq 10^{-5}$) was employed to enumerate and characterize CPCs; pCPCs were defined by a cytoplasmic Igκ/Igʎ ratio between 0.5 and 4. CPCs were detected in 112/140 pts (80%) with a median frequency of 0.02% (range 0.002–17.84%), while 28 pts (20%) had no detectable CPCs. Among CPCs-presenting pts, 83 (74%) harbored mCPCs (median 0.025%) and 29 (26%) had pCPCs (median 0.018%). CPCs presence correlated with higher-risk genomic profiles (IMWG-CGS; p=0.044) and unfavorable biochemical parameters—lower hemoglobin, reduced albumin, elevated beta-2 microglobulin (p<0.004)—indicating a more aggressive disease phenotype regardless of CPC clonality. Imaging data confirmed this aggressive phenotype: CPCs-presenting pts exhibited diffuse BM uptake by PET (p=0.028), positive DWI patterns (p=0.01), more osteolytic lesions (p=0.013), and elevated PET uptake values (p=0.043). They also showed greater numbers of DWI focal lesions (4–10, p<0.001; >10, p=0.004), with preferential extremity involvement (p<0.001), corroborated by PET (p=0.014). Pts with mCPCs had significantly worse clinical, biochemical, and imaging findings than those with pCPCs—focal DWI lesions (p=0.027), higher FDG uptake (p=0.041), and greater CGS risk (p=0.032)—confirming the aggressive nature of monoclonal dissemination. Within the mCPC group, higher mCPC levels (>0.02%) were associated with increased CGS risk (p=0.026), PET positivity (p=0.025), and extremity focal lesions on DWI (p<0.0001). Lack of CD56 expression correlated with this high-risk subset (p=0.022). Interestingly, pts with pCPCs also demonstrated adverse imaging profiles relative to CPCs-negative cases (p=0.035). Despite limited follow-up, CPCs presence—monoclonal or polyclonal—was associated with increased relapse incidence (p=0.057). In conclusion, CPCs detection at diagnosis correlates with extensive skeletal involvement, higher genomic risk, and systemic disease spread, supporting their role as drivers of MM dissemination. Even polyclonal CPCs indicate a poorer clinical condition compared with pts lacking CPCs.

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