EDITORIAL

MULTIPLE MYELOMA, GAMMOPATHIES

Solitary but not simple—a call for precision risk stratification and individualized treatment in solitary plasmacytoma

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Solitary plasmacytoma is a localized manifestation of plasma cell neoplasia and is a distinct clinical entity from multiple myeloma (MM). Solitary plasmacytoma is defined by the presence of a single bone or extramedullary lesion without evidence of systemic disease as confirmed by laboratory testing, advanced imaging and bone marrow assessment to exclude MM [1]. The presence of a solitary lesion does not automatically mean solitary plasmacytoma, and 3 distinct clinical entities can be differentiated based on the presence and extent of bone marrow involvement namely—true solitary plasmacytoma [without clonal bone marrow plasma cells (BMPCs)], solitary plasmacytoma with minimal marrow involvement (clonal BMPCs with <10% involvement), and multiple myeloma (10% or greater clonal BMPCs) (Table 1) [1]. The prognosis varies markedly across these three disorders, affecting follow up and management [1–4]. Prognosis also varies based on whether the solitary lesion involves bone (solitary bone plasmacytoma; SBP), or is extramedullary (solitary extramedullary plasmacytoma). Besides bone marrow involvement, other adverse prognostic factors for recurrence or progression are persistent monoclonal protein or abnormal serum free light chain ratio a year or more following localized therapy [5].

Traditionally, the therapeutic mainstay of solitary plasmacytoma and solitary plasmacytoma with minimal marrow involvement has been localized radiotherapy or in selected instances complete surgical excision (mainly in small extramedullary lesions). While many patients experience durable remissions with radiotherapy alone, a substantial proportion either recur at a different site or progress to overt MM, often unpredictably [6]. A key challenge in solitary plasmacytoma is identifying patients at risk for progression to systemic disease. The role of systemic therapy, especially in cases with minimal marrow involvement, remains unclear, with retrospective data suggesting benefit but no prospective trials to guide standardized treatment approaches [6].

Against this backdrop of clinical uncertainty, the study by Burroni et al. represents a pivotal contribution to our understanding of the molecular underpinnings of SBP [7]. In one of the most comprehensive genomic characterizations of SBP to date, the authors performed targeted next-generation sequencing (NGS) and immunohistochemical profiling on diagnostic tumor samples from 47 patients with biopsy-proven SBP across multiple French centers. Their findings bring to light the striking molecular heterogeneity of SBP and provide the foundation for risk-adapted clinical strategies. The prognostic value of high-risk cytogenetic abnormalities (HRCA) has been demonstrated in SBP, with a median time-to-progression to MM of just 8 months in patients harboring high-risk features [8]. The study by Burroni et al. further refines this by adding molecular alteration data. Among the most important insights from this study is the high prevalence of MAPK pathway mutations, identified in nearly 60% of cases, underscoring the biological proximity of SBP to MM [9, 10]. *KRAS* mutations in particular emerged as an independent adverse prognostic factor, with patients harboring *KRAS*-mutated tumors demonstrating significantly shorter progression-free survival (PFS). Furthermore, mutations in *TP53* and genes involved in DNA damage repair (*ATM, ATR, DIS3*) also predicted inferior outcomes, particularly when co-occurring with *KRAS* mutations. The authors also identified the use of adjuvant system therapy as a predictor of favorable PFS, with progression defined as the development of a second SBP or MM. When the cytogenetic information was combined with mutational profiling, particularly the absence of *KRAS* and *TP53* mutations, a refined two-tiered classification system was proposed, delineating a "molecularly favorable" subgroup with a 5-year PFS of 79%, versus only 36% in those with high-risk features.

One of the limitations of this study is that it does not clearly separate SBP from SBP with minimal marrow involvement which could confound many of the findings. Nevertheless, the findings suggest a markedly different progression risk based on the molecular profile, especially if this can be confirmed independently in separate cohorts of patients with true SBP and SBP with minimal marrow involvement. This work reinforces the need for prospective, biomarker-driven studies to define the role of adjuvant systemic therapy in patients at high risk of recurrence or progression.

Solitary plasmacytoma presents a unique clinical challenge. Even though the management of solitary lesions with or without minimal marrow involvement may be simple localized therapy, the prognosis differs based on the presence or absence of marrow involvement, presence of HRCAs, molecular alterations like *KRAS* and *TP53* mutations detected on the malignant tissue sample, and presence of residual paraprotein after completion of localized therapy. The estimated risk of recurrence or progression based on these variables affect counseling and intensity of follow-up. The rarity of the conditions and the various subsets make it also very challenging to conduct clinical trials in this setting. Hence, real-world studies may be the foundation to inform optimal clinical care.

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Table 1. Clinical Spectrum of Solitary Plasmacytomas [2–4, 6].

Entity	Definition	3-year progression-free survival[a]
Solitary Bone Plasmacytoma	Presence of a solitary bone-associated lesion with clonal plasma cell infiltrate without evidence of clonal BMPCs.	64–94%
Solitary Bone Plasmacytoma with Minimal Marrow Involvement	Presence of solitary bone-associated lesion with clonal plasma cell infiltrate and presence of less than 10% clonal BMPC infiltrate.	28–37%
Solitary Extramedullary Plasmacytoma	Presence of solitary soft tissue/visceral clonal plasma cell infiltrate with no evidence of clonal BMPC infiltrate.	85–94%
Solitary Extramedullary Plasmacytoma with Minimal Marrow Involvement	Presence of solitary soft tissue/visceral clonal plasma cell infiltrate and presence of less than 10% clonal BMPC infiltrate.	56-80%
Multiple Myeloma	Presence of solitary bone-associated or extramedullary plasmacytoma and ≥10% clonal BMPC infiltrate	Not Applicable

[a]Progression to multiple myeloma or recurrence of solitary bone/extramedullary plasmacytoma, with approximate ranges derived from key selected studies.
BMPCs bone marrow plasma cells.

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AUTHOR CONTRIBUTIONS

SZ and SVR conceived the study, wrote the manuscript draft, and both authors approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.