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Lenalidomide-associated reversible TP53-mutated clonal hematopoiesis in plasma cell neoplasms

Running Title

Reversible TP53-mutant hematopoiesis

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C.B.G and M.P. wrote the manuscript; L.P.G and A.E.Z edited manuscript and gave critical input into clonal hematopoiesis and myeloid malignancies; P.H.I, S.A.A, and C.A.H contributed multiple myeloma expertise and edited the manuscript. C.D.G contributed expertise in NGS and edited the manuscript.

Disclosure of Conflicts of Interest

There are no conflicts of interest to declare.

Data sharing

Data will be made available upon reasonable request from the corresponding author.

Lenalidomide has become a key component of induction, consolidation and maintenance therapies, significantly improving outcomes for the vast majority of multiple myeloma (MM) patients. The incorporation of lenalidomide into treatments for MM clearly improves overall survival but also increases the risk of developing secondary primary malignancies (SPMs).(1–4) Thus, a deeper understanding of the clinical circumstances and the underlying mechanisms by which lenalidomide might promote carcinogenesis is essential. Notably, the large Myeloma XI trial recently demonstrated that the risk of SPM appears to be particularly high in MM patients who are exposed to lenalidomide for prolonged periods (e.g., during both induction and maintenance rather than either alone).(5) Despite the increased incidence of SPMs in populations of lenalidomide exposed patients, the risk of dying from MM still appears to be higher if lenalidomide is discontinued.(6) Therefore, the overall risk-benefit profile clearly favors continuation of lenalidomide for patients who are tolerating the therapy. Early identification of markers for patients at ultra-high-risk of developing a deadly SPM might prompt either discontinuation of lenalidomide or closer monitoring that might prevent the development of devastating consequences. Although relatively uncommon, myeloid neoplasms-post cytotoxic therapy (MN-pCT), formerly known as therapy-related myeloid neoplasms, are among the most significant SPMs due to their high morbidity and mortality. In a recent report it was demonstrated that *TP53*-mutated MNs tend to cluster specifically in lenalidomide-exposed patients. Further, lenalidomide exposure resulted in a selective pressure on normal hematopoietic stem cells that allowed for expansion of *TP53*-mutant clones.(7) However, it remains unclear if cessation of lenalidomide will halt or even reverse the selective expansion of *TP53* CH. Here we describe two patients with plasma cell neoplasm who were treated with lenalidomide, developed cytopenias, and were found to have *TP53* CH that subsequently decreased or resolved after cessation of lenalidomide. The presentation of these cases and data within were approved by the Johns Hopkins Institutional Review Board.

Case 1: A 63-year-old previously healthy Caucasian female presented with nephrotic syndrome, monoclonal gammopathy, and a normal complete blood count (CBC). A subsequent kidney biopsy demonstrated renal AL amyloidosis. Bone marrow (BM) examination revealed approximately 20% clonal plasma cells without significant myeloid or erythroid dysplasia. Computed tomography revealed multiple lytic bone lesions consistent with a concomitant diagnosis of multiple myeloma (MM). The patient underwent six cycles of lenalidomide, bortezomib, and dexamethasone followed by lenalidomide maintenance for

approximately four months at which time she developed pancytopenia (hemoglobin (Hgb) 7.1 g/dL, absolute neutrophils 570/mm^3, platelets 15,000/mm^3), prompting lenalidomide discontinuation. Repeat BM examination revealed a normocellular marrow with all hematopoietic elements identified with no morphologic evidence of residual myeloma, dysplasia, or increased blasts, and a normal metaphase karyotype. Next generation sequencing (NGS) on unsorted whole bone marrow aspirate using a custom pipeline covering SNVs and indels in 87 genes at a depth average of >1000X after PCR duplicate removal uncovered a pathogenic somatic *TP53* R248L mutation at a variant allele frequency (VAF) of 5.37% (Table 1; only variants are reported). The patient subsequently remained off all anti-MM therapy for 2 years, with normalization of peripheral blood counts. NGS of peripheral blood (PB) failed to detect the previously identified *TP53* mutation (limit of detection ~0.3% VAF). Recent data demonstrate a strong correlation between CHIP clone size in PBMCs and CD138-depleted BM in MM patients (8). Therefore, even without matched BM samples, PB provides an appropriate surrogate for overall CHIP clone dynamics, and likely indicates a true decrease in the patient's overall clonal burden.

Case 2: An 84-year-old African American male with a history of rheumatoid arthritis (previously managed with methotrexate), diabetes, and chronic kidney disease, was found to have a monoclonal gammopathy with a serum free light chain ratio of 24. BM examination revealed 50% kappa-restricted plasma cells. Although the CBC demonstrated mild anemia (Hgb 12 g/dL), this preceded the diagnosis of smoldering MM and was concluded to be likely a consequence of chronic kidney disease. A kidney biopsy demonstrated no evidence of paraprotein-related disease. Initiation of single agent lenalidomide for high-risk smoldering MM resulted in a partial response that lasted approximately 2 years. At that time the patient developed worsening anemia (hemoglobin of 8.8 g/dL) without significant increases in serum FLC levels or changes in his BM plasma cell percentage (now 30-40%). NGS testing on the BM aspirate revealed a pathogenic somatic *TP53* V173M mutation at a VAF of 7.43% (Table 1). Subsequent testing on unsorted PB showed a similar VAF of 6.86% and absence of plasma cells on the differential (Table 2), indicating that the mutation was present in myeloid cells rather than the plasma cell clone. A metaphase karyotype was normal. Lenalidomide was discontinued and 4- and 7-months later repeat PB testing revealed VAFs of 3.75% and 1.5%, respectively, as well as corresponding improvement in his Hgb to 12 g/dL and stable disease by serum FLC measurement. Monitoring of CBCs during and after lenalidomide treatment showed stable counts on lenalidomide, at 4- and

7-months after discontinuation respectively, reducing the likelihood that observed changes in clone size are driven by alterations in PB composition (Table 2).

The selective expansion of TP53-mutant clones observed in our cases is consistent with the established mechanistic effects of lenalidomide on hematopoietic stem and progenitor cells. Lenalidomide alters cereblon E3 ubiquitin ligase substrate specificity to degrade CK1α, thereby activating p53 and inducing apoptosis in TP53–wild-type cells. In contrast, TP53–mutant cells evade this apoptosis and gain a selective growth advantage under lenalidomide pressure.(7) This selective pressure is uniquely specific to lenalidomide and has not been observed with other immunomodulatory drugs used in myeloma treatment, such as pomalidomide.(7)

Emerging clinical data increasingly link lenalidomide to expansion of TP53-mutant clones. In a cohort of 416 t-MN cases, TP53 mutations were significantly associated with prior thalidomide exposure, and prolonged lenalidomide therapy in MM correlated with higher incidence of TP53-mutated t-MN compared to wild-type TP53. (7) A subsequent study demonstrated the temporal relationships between lenalidomide treatment and TP53-mutant clone expansion, showing that under maintenance therapy these clones expand, while discontinuation leads to stabilization in approximately half of cases and regression in 29% of patients (9). Our cases align with these observations and importantly suggest that clonal outgrowth may be reversible. Notably, both patients had relatively short lenalidomide exposure times (less than 1 year in case1 and approximately 2 years in case2). Similar reversibility has been reported in myelodysplastic syndromes, where lenalidomide-associated *TP53* CH disappeared after switching from lenalidomide to decitabine maintenance.(10) In both patients, low levels of *TP53* CH likely predated lenalidomide initiation, consistent with reports showing CH can be present years before myeloid neoplasm development. (11,12) Thus, early recognition and prompt therapeutic modifications may prevent the development of MN-pCT. These findings suggest that knowledge of underlying clonal hematopoiesis, particularly TP53-mutated clones, could inform clinical decision-making to prevent selective expansion of premalignant clones and subsequent transformation to MN-pCT.

While prior studies demonstrate a net benefit of continuing lenalidomide in MM patients with underlying CH (6), the majority of these cases involved somatic variants not considered high-risk for progression to MN-pCT, unlike TP53 CH. The Myeloma XI trial clearly demonstrated a significant association between the

duration of lenalidomide exposure and the development of a SPMs.(13) The potential reversibility of TP53 clone expansion, particularly with shorter exposure periods, raises the possibility that discontinuation of lenalidomide could be considered in patients with TP53 clonal hematopoiesis. Early recognition and prompt therapeutic modifications may be critical, since prolonged lenalidomide exposure increases opportunities for loss of the wild-type TP53 allele through biallelic mutation or loss of heterozygosity. Once this occurs, the process likely becomes irreversible and evolution to MN-pCT inevitable.(12) It is important to emphasize that not all TP53-mutated cases of clonal hematopoiesis progress to hematological malignancy, so even with continued lenalidomide exposure alone, these patients might not have developed myeloid neoplasms or other blood cancers.(14) The combination of lenalidomide with DNA-damaging chemotherapy, either concomitantly or sequentially, may be more leukemogenic than lenalidomide monotherapy. Therefore, consideration of pre-existing *TP53* CH should be taken into account prior to and after autologous stem cell transplantation to preempt development of MN-pCT. (15)

Several important limitations must be acknowledged in interpreting these findings. The small sample size (two cases), relatively low variant allele frequencies, and short lenalidomide exposure limit generalizability. Clones with higher frequencies and patients with longer exposure may not exhibit similar regression upon discontinuation. Although intra-patient BM vs PB comparisons may introduce bias due to PB-BM discordance in VAF sizes, case 2 demonstrates persistent PB clone decline across multiple timepoints, supporting a true regression. Importantly, this regression occurred despite a normal white blood count and differential over time. While we cannot exclude artificially elevated baseline clone size due to cytopenias corrected by hematopoietic normalization, the decline observed with stable blood counts makes this less likely. Lastly, CD138+ cell depletion would strengthen the clonal hematopoiesis observation.

These cases highlight the need for rigorous investigations into whether the early detection and dynamic monitoring of *TP53*-mutations, particularly in patients who are in deep remission, could help guide therapeutic modifications that might prevent an often-lethal myeloid neoplasm.

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Tables

Table 1. NGS data for patient cases 1 and 2.

Case	Days since 1st NGS test	Source	Chr:Pos	Base Change	Reference Database ID	Gene	AA change	VAF (%)
1	0†	BM	chr17:7577538	C>A	rs11540652; COSM6549	**TP53**	p.R248L	**5.37**
			chr17:5485199	G>A	rs149535960	NLRP1	p.T211M	43.85
			chr11:3720413	T>C	rs201011075	NUP98	p.E1303G	46.83
	930	PB	chr17:7577538	C>A	rs11540652; COSM6549	**TP53**	p.R248L	**ND***
			chr17:5485199	G>A	rs149535960	NLRP1	p.T211M	46.25
			chr11:3720413	T>C	rs201011075	NUP98	p.E1303G	47.2
2	0	BM	chr17:7578413	C>T	rs876660754; COSM11084	**TP53**	p.V173M	**7.43**
	46‡	PB	chr17:7578413	C>T	rs876660754; COSM11084	**TP53**	p.V173M	**6.86**
	207	PB	chr17:7578413	C>T	rs876660754; COSM11084	**TP53**	p.V173M	**3.75**
	305	PB	chr17:7578413	C>T	rs876660754; COSM11084	**TP53**	p.V173M	**1.5**

† *lenalidomide stopped on day -14*

‡ *lenalidomide stopped on day +101*

**ND=not-detected, limit of detection <0.3%.*

BM = bone marrow, PB = peripheral blood, VAF = variant allele frequency

Table 2. CBC of patient case 2

Days since 1st NGS test	46 ‡	207	305
WBC (10^3/µL)	5.84	6.29	6.54
RBC (10^6/µL))	3.16	3.94	3.79
Hemoglobin (g/dL)	9.9	12.2	11.5
HCT (%)	30.9	37.7	36.1
Platelet Count (10^3/µL)	234	275	316
Differential			
Neutrophil %	50.2	47.8	45
Immature Gran %	0.3	0.3	0.3
Lymphocytes %	41.4	42	43.1
Monocytes %	3.6	7.5	9.2
Eosinophil %	3.1	1.4	1.5
Basophil %	1.4	1	0.9
Neutrophils Absolute (10^3/µL)	2.93	3.01	2.94
Lymphocytes Absolute (10^3/µL)	2.42	2.64	2.82
Monocytes Absolute (10^3/µL)	0.21	0.47	0.6
Eosinophil Absolute (10^3/µL)	0.18	0.09	0.1

‡ *lenalidomide stopped on day +101*