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Short Communication

Correlation of bone marrow morphologic assessment and genetic aberrations in plasma cell myeloma with clinical outcomes

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Abstract

Plasma cell myeloma is a hematopoietic neoplasm with morphologic and genetic heterogeneity. Genetics have been shown to play an important role in risk stratification of plasma cell myeloma however the correlation between genetic aberrations and morphologic features is not well studied. In performing a systematic study of 266 multiple myeloma bone marrow biopsies from 329 patients, we initially investigated the association between bone marrow morphology, conventional cytogenetics, gene expression profiling and gene mutations. It is the first known study demonstrating the correlation between high tumor burden, diffuse sheet growth pattern, immature cell morphology, high mitotic index, and increased reticulin fibrosis with high risk disease determined by MyPRS gene expression profiles. Furthermore, the MyPRS risk stratification showed significant correlation of high risk cases with chromosomal alterations and specific gene mutations. In this more recent analysis, we demonstrate that poor prognostic histomorphologic features, genetic aberrations including high risk score of MyPRS and TP53 alterations do in fact have a negative effect on patient survival.

Introduction

Plasma cell Myeloma is a hematopoietic neoplasm arising from the malignant proliferation of mature post-germinal center plasma cells. These neoplasms show a spectrum of morphologic and genetic features in addition to the diversity of clinical presentations and survival. Risk categorization of each plasma cell myeloma (PCM) case is crucial as patients with high-risk disease require treatment and additional monitoring in compared to those with low-risk disease. It is as a result of this consensus that many efforts have been made to standardize and characterize risk stratification to therefore maximize clinical outcome. The histomorphologic spectrum has been previously studied to determine significant histopathologic and cytomorphologic features associated with poor clinical outcome [1-4]. Of these, Bartl et al. studied histologic variables with clinical correlation to determine factors of value in predicting PCM prognosis [1-2]. They studied the prognostic significance of bone marrow histomorphologic features including, plasma cell mass, proliferation pattern, reticulin fibrosis, lymphocytic infiltration and degree of plasma cell maturation with nuclear features on clinical survival. Uniquely, they developed a tumor burden classification system by quantifying plasma cell mass into three stages based on quantity of plasma cell infiltration vol %; stage 1(<20 vol%), stage 2 (20-50 vol%), and stage 3 (>50 vol%) [1-2]. These 1987 studies demonstrated outstanding prognostic significance of histologic features including cell maturity, quantity of infiltration, growth pattern, and fibrosis. Goasquen et al. later modified the Bartl study to provide a new methodology for the assessment of plasma cell morphology through the incorporation of bone marrow aspirate smears. With the progressive evaluation of three criteria; nucleolus, chromatin and nuclear-cellular ratio (N/C), they developed an algorithm which demonstrates the degree of maturation of plasma cells, a sensitive prognostic factor. In the algorithm, Goasquen et al. were able to distinguish immature plasmablastic cells (presence of a nucleolus, fine chromatin, N/C ratio>0.6), from mature plasma cells (inconspicuous nucleoli, coarse chromatin, N/C ratio<0.6) [13].

Along with the morphologic heterogeneity however, PCM demonstrates clinical and genetic heterogeneity. This heterogeneity has resulted in molecular genetic advances identifying and providing important independent prognostic indicators for myeloma patients. These investigations

initially included conventional cytogenetics, with the current diagnostic guidelines recommending the use of fluorescence in situ hybridization (FISH)-based assessment of chromosomal alterations. The examination for lesions involving the immunoglobulin heavy chain (IgH), light chain (IgL) gene regions and hyperdiploidy (HD), including t(14;20), t(14;16), t(4;14), del(1p11) and/or del(17p13), are used to determine a patient's risk status [5,7].

More recently, molecular subtyping has been introduced through gene expression profiling (GEP). Specifically, the University of Arkansas for Medical Science (UAMS) has used GEP to develop seven PCM subtypes. These subtypes are strongly influenced by known genetic lesions, such as c-MAF– and MAFB-(Group MF), CCND1-(Group CD-1) and CCND3-(Group CD-2), and MMSET- (Group MS) activating translocations, hyperdiploidy, or increased expression of proliferation-associated genes (Group PR). Additional subtypes included cases with a low number of bone lesions (LB), or the largest group (HY) containing HD cases [6,7]. Furthermore, using GEP data, Weinhold et al. identified 70 genes linked to early disease-related death, contributing to the GEP 70 risk score. The integration of the UAMS subtypes, in conjunction with the GEP70 risk score and individualized "virtual karyotype" lead to the creation of the Myeloma Prognostic Risk Signature (MyPRS). From this, studies have shown that the molecular subtypes and this 70-gene prognostic risk score significantly correlated with prognosis in myeloma patients [5-8].

Despite the many reports studying morphologic and genetic parameters in isolation, very few studies have performed a combinational analysis. As a result, we were interested in further investigating this correlation of bone marrow histological features with specimen matched cytogenetic and molecular data. We performed a multi-step systematic study, with initial histomorphologic evaluation of the bone marrow trephine biopsies to assess for cellularity, plasma cell burden (Bartl staging, as previously mentioned), plasma cell infiltration patterns (interstitial, microclusters, nodules, diffuse sheets), mitotic activity per high power field (HPF), and fibrosis. The monoclonal plasma cell populations were highlighted using CD138, kappa and lambda immunohistochemical staining. Assessment of bone marrow fibrosis was performed with reticulin staining to evaluate reticulin fiber content and graded as follows: grade 0/ MF0 (none), grade I/MF1 (mild), grade II/MF2 (moderate) and grade III/MF3 (severe). The accompanying aspirate smears were assessed for percentage of plasma cells based on a 200-cell differential count and cytologic features. The cytomorphologic assessment for degree of maturation was performed based on the modified quantitative Bartl grading system [13]; as grade 1 (mature) defined as biopsies with >70% of plasma cells showing small-medium cell size, eccentric nucleus, coarse clumped chromatin and inconspicuous nucleolus, grade 2 (intermediate) in biopsies with <50% plasma cells showing nuclear atypia, open chromatin, lack of significant pleomorphism and small nucleoli, and grade 3 (immature) with biopsies composed of >50% of plasma cells with marked cytologic atypia showing open chromatin, pleomorphism, and prominent nucleolus.

The next step involved the investigation of cytogenetic and molecular aberrations in the patient-matched samples through metaphase karyotyping (conventional cytogenetics). The MyPRS prognostic risk score was divided into high and low risk group and calculated based on 70 gene expression profiling, while the molecular subtype analysis was calculated through 700 gene expression profiling. A Virtual karyotype of 13 distinct chromosomes or sub-chromosomal regions was also created, based on the expression levels of 816 genes [5,15,16]. Results from targeted next-generation sequencing studies were used for gene mutation and translocation analysis.

Finally, in this extension of our previous study [3], we investigated the clinical follow-up by comparing patient survival in high risk cases/ prognostic significant features with low risk cases/ non-prognostic significant features, one year following initial data collection. The morphologic parameters investigated were tumor burden (stage 1-2 vs stage 3), pattern of infiltration (sheet vs non-sheet), mitotic rate (<3/ HPF vs >=3/HPF), fibrosis (MF0-1 vs MF2-3), and modified Bartl grade (grade 1-2 vs grade 3). The one year patient survival comparison was then performed for significant genetic aberrations. For completion, the overall patient survival of the MyPRS high risk cases in the study were compared to the survival of the low risk cases in the study.

Results

In the first known comparative analysis of histomorphologic features of bone marrow trephine biopsies with MyPRS risk stratification revealed statistically significant features seen in high risk groups compared to low risk groups. These features were neoplastic plasma cell cellularity, high tumor burden, diffuse pattern bone marrow infiltration, severe bone marrow fibrosis, and immature cytomorphologic features (Table 1). Interestingly, many of these

		MyPRS High Risk	MyPRS Low Risk	P-value
Bartl Stage	1	41.3%	66.9%	0.0001
	2	25.0%	25.2%	
	3	33.7%	7.9%	
Growth Pattern	Non-sheets	77.1%	90.4%	0.0065
	Sheets	22.9%	9.6%	
Modified Bartl Grade	1	47.9%	48.4%	0.0001
	2	38.5%	50.8%	
	3	13.5%	0.8%	
Fibrosis	MF 0-1	85.9%	95.7%	0.0096
	MF 2-3	14.4%	4.3%	
Mitosis/ HPF (mean)		2.5	1.4	0.0267
Light Chain	Kappa	52.0%	68.7%	0.0137
	Lambda	48.0%	31.3%	

Table 1: Histologic features of the MyPRS high risk and MyPRS low risk cases. Modified from Hao et al. 2019.

findings observed in high risk patients, match those histologic factors reported by Bartl et al. to predict unfavorable prognosis. Specifically, the statistical significance of neoplastic plasma cell cellularity on both the bone marrow biopsy and the bone marrow aspirate smear were p=0.0026 and 0.0084, respectively. Bartl staging showed higher plasma cell burden (Bartle stage 3) exists more often in high risk cases when compared to low risk cases (p-value=0.0001). The diffuse sheet pattern of infiltration into the bone marrow of high risk disease showed a p-value=0.0065 when compared to non-sheet infiltrations patterns (interstitial, microclusters, nodules). Fibrosis, a feature often seen in PCM, is a well-known PCM feature associated with prognostic significance. Our study, however, not only showed prognostic significance, but also noted statistical significance of moderate to severe fibrosis between high and low risk PCM cases (p=0.0096). Degree of maturation of neoplastic plasma cells has also been previously studied in

association with prognostic significance, where it is well-understood that more immature nuclear features, such as marked cytologic atypia, open chromatin, pleomorphism, and prominent nucleoli, are associated with an unfavorable prognosis. Our study's comparison of nuclear features between high and risk groups mirrored the previous studies with statistical significance observed in the association of immature tumor cells with high risk cases (p=0.0001). The 200 cell differential of bone marrow aspirate smear showed a similar cellular composition seen in all cases studied, both high and low risk, with the exception of blast quantity, which was identified less in high risk cases (p=0.0041). The final parameter observed to have significance was interestingly, lambda light chain restriction, seen more often in high risk cases (p=0.0137). Although mitotic activity can often been used as a prognostic parameter in solid tumors, in comparing the low risk and high risk groups of this study, the average mitotic index only approached statistical significance, a p-value=0.071.

Following the morphologic association with MyPRS risk stratification, our study next looked to compare the same risk stratification with genetic aberrations. Conventional cytogenetic analysis through both FISH and the virtual karyotype showed that MyPRS high risk groups were more often associated with 1q gains, 13q losses and t(4;14)(IGH-FGFR3). The identification of the IGH-FGFR3 translocation correlates to those reports whose aim was the study of poor prognostic cytogenetic lesions. In fact, UAMS molecular subgroup MS, was reported as the subgroup with the worst survival with the presence of a t(4;14) [5,7]. Although plasma cell morphology and molecular/genetic correlations have rarely been reported outside of this study, there are few such studies that have been successful. As t(11;14)(q13;q32) is the most common structural abnormality in PCM to date, it is frequently the focus scientific investigations. Fonseca et al. reported that multiple myeloma with the t(11;14)(q13;q32), not only showed evidence of higher plasma cell proliferative activity, such as a high labeling index and extensive bone marrow involvement, but also showed lymphoplasmacytic morphology in nearly one half of cases. The study additionally discovered that these cases with t(11;14)(q13;q32), were characterized by higher prevalence of low-concentration monoclonal proteins, no association with an unfavorable outcome, and greater likelihood of being pseudodiploid or hypodiploid than hyperdiploid [10,11]. As previously mentioned, UAMS classified seven PCM molecular subtypes based on hierarchal clustering of gene expression. We further studied those molecular subtypes through the comparison of high and low risk MyPRS groups [5-8,16,25-27]. Our molecular comparison found that, as expected, the poor prognostic subtypes (MF, MS, PR) were associated with MyPRS high risk groups, whereas the good prognostic subtypes (CD1, CD2, HY, LB) were associated with MyPRS low risk groups (p=0.0001). These findings were in agreement with those identified by Weinhold et al. The consistency of these findings demonstrates the natural history of the molecular subgroups, which as stated in original reports, can be used to optimize PCM treatment strategies [7]. To further the molecular assessment, we used targeted Next Generation Sequencing which demonstrated higher genetic alteration rate of both mutations and translocations in high risk cases compared to the low risk cases (p=0.0012). In focusing on the top 10% translocations and top 10% mutations to identify significant mutations, there were no significant translocations seen between the high and low risk cases. Among the most frequent mutations, however, TP53 and CD36 mutations were significantly associated with high risk cases (p=0.0068 and p=0.0473). Of particular interest was the mutated gene TP53. TP53 mutation has been frequently documented to contribute with poor prognosis [19-22]. Chang et al. studied this with the use of both hemizygous TP53 deletions identified by interphase fluorescence in situ hybridization and nuclear p53 immunohistochemical protein expression on bone marrow biopsies. They determined that the overall survival of p53 immunoreactive patients was significantly less than the survival of p53 non-reacting patients [21]. Deng et al. uniquely studied extramedullary disease (EMD) of PCM to investigate the association of TP53 deletion and poor survival. Their group demonstrated that PCM patients with EMD at the time of diagnosis showed remarkably greater prevalence of P53 deletion in FISH analysis and additionally, higher LDH levels [22]. Another related study, conducted by Hideshima et al. on TP53-related receptor kinase (TP53RK) showed that not only does TP53RK increase with progression from smoldering PCM to active PCM, but also increases within PCM to identify patients with particularly poor prognosis [20]. Our own research group recently reported on this same mutation, in association with immature plasma cell morphology. In comparing aspirate smears with >30% plasmablastic/immature morphology (P/IM) and smears with <30% P/IM, it was observed that there was statistical significance of TP53 gene mutations (gains/losses) in association with P/IM [12]. In following the extensive previous documentation of the TP53 gene, this current study not only identified the TP53 mutated gene association with MyPRS high risk cases, but furthermore, we found that in conjunction with 17p deletion, the two aberrations have a combinational effect on cell morphology including diffuse sheet like infiltration, immature neoplastic cellular features, and high mitotic index (Table 2). In addition to TP53 and CD36, other recurrent gene mutations were observed (KRAS, NRAS, BRAF, DNMT3A, TET2, DNMT3A, and TET2), however, the frequency of mutations showed no statistical significance between high and low risk cases.

In this most recent extension of our original study, we further

Genetic alteration		Control	TP53 mutation only	17p loss only	TP53 mutation & 17p loss
Sheet		15.6%	27.3%	50.0%	60.0%
	p-value		0.3903	0.0063	0.0372
Modified Bartl Grade	1	41.1%	45.5%	38.5%	20.0%
	2	54.0%	54.5%	53.8%	40.0%
	3	8.4%	0.0%	7.7%	40.0%
	p-value		0.6034	0.9711	0.037
Mitosis/HPF		1.6	2.9	2.1	4.8
	p-value		0.133	0.4767	0.0068

Table 2: Histological features in wild-type cases and cases with TP53 mutations and/or 17p loss. Modified from Hao et al. 2019.

		Death Rate 1-year follow-up	p-value
Bartl Stage	1-2	9/177 (5.8%)	0.0005
	3	10/41 (42.9%)	
Growth Pattern	Non-Sheets	13/202 (6.4%)	0.007
	Sheets	8/37 (21.6%)	
Modified Bartl Grade	1-2	12/207 (5.8%)	0.0002
	3	6/14 (42.9%)	
Fibrosis	MF 0-1	12/221 (5.4%)	0.0019
	MF 2-3	6/21 (28.6%)	

Table 3: Histologic features with patient survival 1-year following initial collection.

	MyPRS Low risk	MyPRS High risk	P value
Death rate	5/151 (3.3%)	17/115 (14.8%)	0.0012

Table 4: Patient mortality rate in MyPRS high risk and MyPRS low risk cases.

Genetic alteration		Control	TP53 mutation only	17p loss only	TP53 mutation & 17p loss
Death rate		9/118 (7.6%)	3/11 (27.3%)	2/15 (13.3%)	2/5 (40.0%)
	p-value		0.0666	0.359	0.0629
		Control	**TP53 alteration**		
Death rate		9/118 (7.6%)	7/31 (22.6%)		
	p-value		0.0439		

Table 5: Patient mortality rate in wild-type cases and cases with TP53 mutations and/or 17p loss.

analyzed the effect that these unfavorable morphologic and genetic parameters have on the survival of patient's in high risk groups when compared to the low risk group. The MyPRS score is a tool developed to identify patients with high risk disease. The importance is demonstrated here by the significant difference in death rate 1 year following initial data collection between cases with MyPRS-scored high risk disease from those with low risk disease (p=0.0012) (Table 4). This is in agreement with previous documentation of which five year overall survival rate between high risk score cases and low risk score cases are dramatically different [9]. We observed that the biopsies which showed unfavorable histologic features (sheet pattern, tumor burden, severe fibrosis, immature cytologic features), were associated with statistically significant reduction in patient survival (p=0.007, p=0.005, p=0.0019, p=0.0002, respectively) (Table 3). We found particular interest in the TP53 gene, as there was statistical significance of the gene mutation present in high risk disease both alone and in conjunction with 17p loss. In further studying the death rates of these patients in comparison to wild-type control patients, the survival approached significance with TP53 mutation alone (p=0.0666) and TP53 mutation with del17p (p=0.0629), and was not statistically significant with the 17p deletion alone (Table 5).

Discussion

Overall, PCM is the most frequent lymphoid disorder of the marrow, with over 30,000 new cases estimated, and contributing to 13,000 new deaths in 2019 [34]. With this prevalence, accurate and consistent risk stratification is therefore crucial. Recent studies have demonstrated the superior role that gene expression profiling with prognostic risk score through MyPRS has on risk stratification reproducibility [5,15,16]. Our goal for the initial study was, for the first time, to provide better risk stratification by performing a systematic study using a combinational approach, to review bone morphologic features and genetic aberrations in correlation with the high regarded MyPRS risk stratification. This extended study was established to observe how the high risk-associated features ultimately affect patient survival. This study was limited to the inclusion of both initial diagnostic and relapse biopsies. Additionally, patient follow-up was performed one year after initial data collection. Future projects will focus on diagnostic biopsies, test reproducibility, lengthier clinical outcome analysis, as well as increasing the cohort size. The ultimate goal being to allow establishment of a risk stratification criteria for the integration into clinical practice.

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