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A differentiated effector T cell repertoire defines a functionally high-risk group of smoldering myeloma patients

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To the Editor:

Smoldering multiple myeloma (SMM) is a precursor to active multiple myeloma (MM) characterized by a higher plasma cell burden than monoclonal gammopathy of undetermined significance (MGUS) but without evidence of the end-organ damage that defines MM [1, 2]. Current SMM guidelines advocate for close observation for progression to symptomatic progression to MM, with some studies suggesting the benefit of early intervention for patients with a high risk (HR) of progression [3]. Current methods to prognosticate SMM outcomes, including the Mayo 2/20/20 model, rely primarily on methods of tumor-burden assessment to assign risk scores and identify which patients are at HR of progression [4]. As SMM is an asymptomatic condition, great consideration must be made for who to select for systemic therapy, as many SMM patients may never progress to MM in their lifetimes [5].

While some studies have investigated patient immune features that correlate with response to systemic therapy in SMM patients [6, 7], there has been no investigation into these features in SMM patients on observation, which remains the standard of care at this time. Furthermore, these prior studies have used samples from patients on therapeutic trials involving drugs known to affect immune cell characteristics. Using plasma proteomics and high-dimensional spectral cytometry analyzed with algorithm-assisted and artificial intelligence (AI) tools, we performed comprehensive peripheral blood (PB) immune profiling in a cohort of risk-matched SMM patients with and without early progression (EP) to identify T cell signatures predictive of early progression to active MM. We focused our analysis on T cell populations given their sensitivity to tumor cell populations and their association with clinical outcomes in other MM contexts.

We identified 466 patients diagnosed with SMM at Memorial Sloan Kettering Cancer Center (MSKCC) between 2002 and 2019 with follow-up until 12/31/2024, among which nine patients with EP to MM (median time to progression of 2.1 years, range 0.85–3.3), had PB samples collected and cryopreserved within 100 days of SMM diagnosis. All EP patients had advanced imaging at SMM diagnosis (7/9 with PET/CT, 2/9 with WB MRI), and 8/9 patients had a myeloma-defining CRAB event at progression (2/8 anemia, 6/8 lytic bone lesion), with the remaining patient having >80% bone marrow plasmacytosis as the myeloma-defining event. Mayo 2/20/20 risk scores were calculated at diagnosis for EP patients and a “Mayo-matched” 9 SMM patient cohort (Total N = 18), matched by clinical risk score but distinguished by long term outcome, with non-progression (NP) to MM, with a median clinical follow-up time of 8.6 years (range 5.1–12.8), with PB samples banked within 100 days of diagnosis was assembled.

None of the SMM patients with NP have had progression to myeloma as of the data cutoff (Table 1).

This study was performed in accordance with the Declaration of Helsinki, Belmont Report, and received approval from the MSKCC IRB (IRB #s 06-107, 14-276, 18-143).

PB samples were isolated, separated into the plasma and mononuclear cell (MC) fractions, and cryopreserved per institutional guidelines [8]. High-dimensional spectral cytometry experiments on PBMCs were conducted using a 37-color T cell-focused panel inclusive of T cell lineage markers, activation and exhaustion markers, and intracellular transcription factors and granzymes (Supplementary Methods A1, Table S1). Data were analyzed using FlowJo Software version 10.8.2. Spectral cytometry experiments captured 1.49 million live singlet T cells across all 18 patients (range 26089 – 192698 T cells per patient, Supplementary Methods A2, Fig. S1). Plasma proteomics experiments were performed using the Olink® Target 96 inflammation panel (Supplementary Methods A4, Table S2).

Following T cell isolation, dimensionality reduction was performed via Uniform Manifold Approximation and Projection (UMAP), and algorithm-assisted cell clustering was performed using Phenograph (Supplementary Methods A3) [9].

Immune signatures were extracted by training a random forest (RF) classifier to predict if a given cell belonged to an SMM patient with EP [10]. The model was trained on live singlet T cells using normalized fluorescence intensity values for spectral cytometry markers as input features, irrespective of cell type (Table S1).

Table 1. Baseline patient characteristics.

	Early Progressors (N = 9)	Non-progressors (N = 9)
Age – median (range)	64 (45–74)	61 (43–73)
Male (%)	4 (44%)	6 (67%)
Risk of progression according to Mayo 2018 risk criteria (%)		
Low – no. (%)	1 (11%)	1 (11%)
Intermediate – no. (%)	4 (44%)	4 (44%)
High – no. (%)	4 (44%)	4 (44%)
Time from SMM diagnosis to progression / last follow-up – years median (range)	2.1 (0.9–3.3)	8.6 (5–12.7)
Myeloma defining event	Not applicable	
Bone lesion	6 (67%)	
Anemia	2 (22%)	
>60% bone marrow plasma cells	1 (11%)	

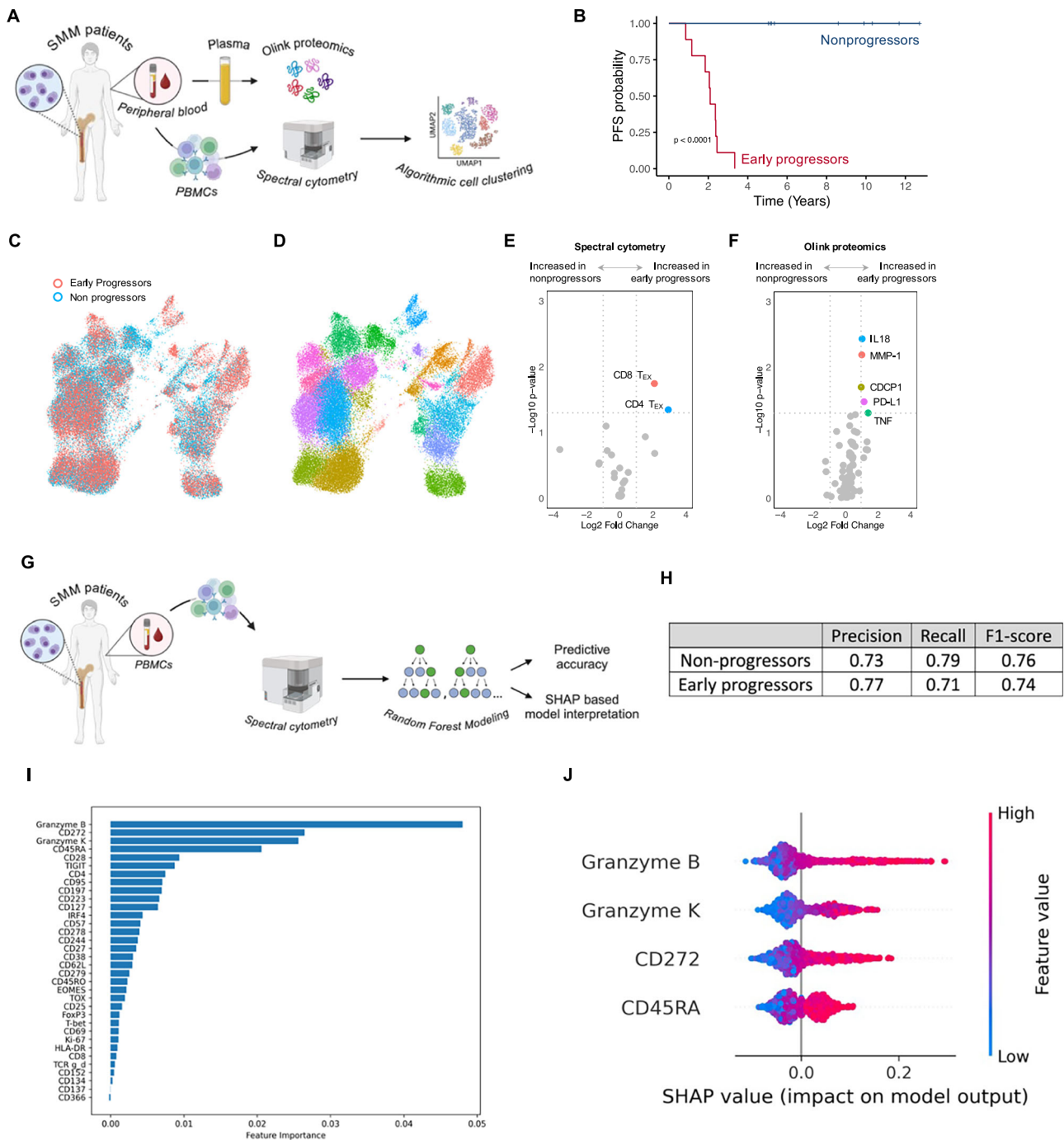


Fig. 1 Smoldering patients with early progression have more differentiated T cell profiles. **A** Peripheral blood (PB) was collected from smoldering multiple myeloma (SMM) patients with PB mononuclear cells (PBMCs) being used for high-dimensional spectral cytometry-based T cell characterization using algorithm-assisted cell clustering and PB plasma being used for immunoproteomic analysis with Olink. **B** SMM patients were divided into early progressors ($n = 9$, median PFS 2.1 years) and non-progressors ($n = 9$, median follow-up 8.6 years). **C–E** Dimensionality reduction analysis and algorithm-assisted cell clustering identified that early progressors had enrichment for $CD8^+CD45RA^+CCR7^+CD62L^-$ T cells with high relative expression of CD57 and TOX ($CD8^+T_{EX}$) and $CD4^+CD45RA^+CCR7^+CD62L^-$ T cells with high relative expression of CD57 ($CD4^+T_{EX}$). **F** PB plasma from SMM patients with early progression showed ~2-fold higher concentrations of IL-18, MMP-1, CDCP1, soluble PD-L1, and TNF. **G** Spectral cytometry data was additionally used for random forest (RF) modeling. **H** A table showing model performance for the non-progressors versus non-progressors cells is shown. The model's overall accuracy after five-fold cross-validation was 0.75. **I** A feature importance plot from RF modeling shows that Granzyme B, CD272, Granzyme K, and CD45RA expression values most heavily contribute to outcome predictions using the RF method. **J** SHAP analysis of the top four features shows that high expression values of all four proteins are associated with progression. In this figure, each dot represents a cell from a subset of the testing cohort.

Feature importances were computed using the permutation importance method associated with RF classification, and results were five-fold cross-validated. A leave-one-out analysis was done to ensure no singular subject's cells had an outsized influence. To understand the directionality of feature importances, we utilized Shapley Additive Explanations (SHAP) via the SHAP toolbox (Figure 2 A) [11]. All code is available on GitHub at github.com/aksimhal/smm-tcell-signature.

Algorithm-assisted analysis of spectral cytometry data identified 25 unique T cell clusters, 21 of which comprised at least 0.5% of the total T cell population across all patients. Among these, SMM patients with EP had enrichment for a cluster corresponding to CD8⁺CD45RA⁺CD62L⁺CCR7⁺ T effector cells re-expressing CD45RA (T_{EMRA}), with high relative CD57 and TOX expression, when compared to SMM patients with NP (4.3-fold increase, $p = 0.018$, Figs. 1A–E, S2). This cluster had the highest mean expression level of TOX among all algorithm-defined clusters (Figure S3), demonstrating similar phenotypic characteristics to terminally exhausted effector T cells. There was also enrichment for a cluster corresponding to CD4⁺ T_{EMRA} cells with similar CD57 expression (7.6-fold increase, $p = 0.045$, Figs. 1E, S2). When performing this analysis, comparing SMM patients by Mayo risk criteria instead of clinical outcomes, there were no statistically significant differences in relative cluster abundance among all algorithm-defined T cell populations. Plasma proteomics (Fig. 1F) identified increased markers of inflammation in SMM patients with EP, with a 2-fold increase in plasma IL-18 ($p = 0.0037$) and MMP-1 ($p = 0.0065$) among other markers of inflammation and T cell differentiation (Table S2).

The RF model had an overall accuracy of 75%; the F1-score was 0.76 for non-progressors, and 0.74 for early progressors (Figure 2B). A leave-one-subject-out analysis did not show any significant performance differences (Fig. S6) with any patients omitted. A UMAP analysis of cells misclassified by their patient's progression status did not reveal any obvious patterns (Fig. S4).

Permutation-based feature importance analysis of the RF model identified Granzyme B, CD272 (BTLA), Granzyme K, and CD45RA as the four most influential features. SHAP analysis showed high feature expression for all four proteins was associated with progression (Figures 2C, 2D), regardless of T cell subset (Fig. S5). Repeating the SHAP analysis using only cells positive for CD45RA that were predictive of EP continued to demonstrate that high expression of Granzyme B, CD272, and Granzyme K predicted progression, indicating CD45RA expression reflected terminal differentiation as opposed to T cell naivete.

In this study, we have demonstrated that patient-specific peripheral blood immune phenotypes can stratify SMM patients by clinical outcome and may offer a method of prognosticating SMM outcomes in a manner separate from tumor burden quantification. Both the algorithm-assisted clustering-based analysis, which identified a population of exhausted effector T cells in SMM patients with EP, and the RF modeling, which identified higher expression of granzymes and exhaustion markers in SMM patients with EP, demonstrate that a more differentiated T cell phenotype associates with early progression in SMM. Recent studies have shown that patients with active MM, when compared to those with MGUS or SMM, demonstrate a more differentiated T cell phenotype, with this being associated with a loss of anti-tumor immunity, allowing for progression from precursor diseases to active MM [12, 13]. Therefore, the increased T cell differentiation and exhaustion we observed in SMM patients with EP may define a "myeloma-like" immune signature indicative of immune surveillance loss and predictive of progression to MM shortly after diagnosis. Furthermore, plasma proteomics identified increased IL-18, among other markers of immune activation and T cell differentiation that were enriched in SMM patients with EP. As dysregulated IL-18 has been shown to drive the immunosuppression associated with progression to active MM, our results

further support that SMM patients with "myeloma-like" immune dysfunction are at high risk for EP [14, 15].

Our dataset involves using "mayo-matched" patient cohorts with identical estimated risks of progression at diagnosis but with drastically different clinical outcomes. This suggests that the immunophenotype associated with SMM with EP is not merely reporting on known risk factors, which rely on tumor burden estimates, and instead represents a novel functionally high-risk feature of SMM. This dataset is certainly limited by its exploratory nature and narrow sample size, thereby requiring prospective validation in large clinical datasets. However, given that our RF analysis demonstrated high accuracy when predicting clinical outcomes, these observations could be clinically translatable. As expression levels of only 4 T cell markers carried the most predictive potential in our model, a conventional flow cytometry panel focused on these markers could be applied to clinical practice settings. Future study could incorporate T cell receptor sequencing to determine if T cell populations reporting on clinical outcomes are tumor-specific.

SMM represents a challenge for clinicians as it presents as an asymptomatic condition with a possibility of progression to a life-threatening malignancy. As a recent prospective clinical trial has demonstrated possible survival benefits to treating SMM with systemic therapy, it is now even more necessary to distinguish which patients can be spared therapy altogether due to the low risk of progression from those that may benefit from early intervention. Furthermore, as our dataset involves PB profiling, it offers a potential minimally invasive method of immune profiling not requiring evaluation of the BM microenvironment. Our work demonstrates that incorporating patient-specific immune characteristics can inform clinical decision-making in this vulnerable patient population.

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DATA AVAILABILITY

All data are available on request from the corresponding authors.

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AUTHOR CONTRIBUTIONS

RSF and MH conceived the project. RSF, TS, KHM, SM, CT, NK, AML, HH, UAS, NK, CRT, SR, HH, AML, SZU, and MH collected samples or recruited patients. RSF, DM, and KH designed and executed all experiments. RSF and AKS designed the methodology and analyzed the data. AKS developed the software. JHO and JJG contributed to data analysis. RSF, AKS, and MH wrote the manuscript, and all authors reviewed the manuscript.

COMPETING INTERESTS

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ADDITIONAL INFORMATION

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