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Myelodysplastic Syndromes

FROM HAEMATOLOGICAL DISORDERS TO IMMUNE DYSREGULATION: THE ROLE OF EXTENDED IMMUNOPHENOTYPING TO GUIDE THE DIAGNOSIS TOWARDS INBORN ERRORS OF IMMUNITY

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Introduction: Haematological disorders with immune dysregulation may conceal unrecognised inborn errors of immunity (IEIs). These conditions, often presenting with autoimmunity, cytopenias, lymphoproliferation, or bone marrow dysfunction rather than recurrent infections alone, frequently remain undiagnosed. This study integrated clinical, immunophenotypic, and molecular analyses to identify immune signatures suggestive of IEIs in patients with haematological diseases of suspected immune origin.

Methods: In this prospective observational study, 87 adult patients were enrolled at the Immunology and Haematology Units of Tor Vergata University Hospital (Rome) between January 2020 and September 2025: 13 patients with autoimmune cytopenias (AIC), 7 with bone marrow failure (BMF), and 39 with lymphoproliferative disorders (LPD), both therapy-naïve (n=22) and post-therapy (n=17), alongside 37 controls. All underwent extended immunophenotyping of T-cell, B-cell, and NK-cell subsets by multiparametric flow cytometry, and genetic testing by targeted next-generation sequencing and whole-exome sequencing. Principal component analysis (PCA) was used to identify immune clustering and discriminative variables.

Results: Distinct immunophenotypic profiles emerged across the study groups. AIC patients showed reduced switched-memory and plasmablast B-cells, whereas T-cell analysis revealed decreased CD4⁺ naïve and RTE, and increased CD4⁺ CM cells, reflecting a skewing towards T-cell differentiation. BMF cases exhibited marked reduction of total B and NK cells but largely preserved B-cell subset architecture. The T-cell compartment showed a trend towards CD4⁺ EM enrichment and CD8⁺ remodelling, consistent with chronic activation and marrow failure. Therapy-naïve LPD patients showed an overall preserved B-cell maturation profile whereas, a significant reduction of CD4⁺ RTE was observed in the T-cell compartment, as compared to controls. Post-therapy LPD patients showed a therapy-related remodelling signature, with persistent depletion of switched-memory and marginal zone like B cells, reduced plasmablasts, relative enrichment of naïve B cells, and loss of CD4⁺/CD8⁺ naïve T cells, with expansion of memory subsets, driving a clear separation in PCA from controls and other groups **(Fig 1)**.

We identified two genetic defined IEIs: a STAT3 gain-of-function syndrome and a GATA2 deficiency, both with direct therapeutic implications. Additional variants of uncertain significance were also detected and are pending further functional validation.

Conclusions. A prospective, immunophenotype-driven strategy coupled with genetic testing effectively revealed hidden immune regulatory defects across diverse haematological contexts. Extended immunophenotyping emerged as a key tool for early recognition of immune dysregulation, guiding molecular prioritisation and personalised management, and reinforcing the clinical intersection between immunology and haematology.

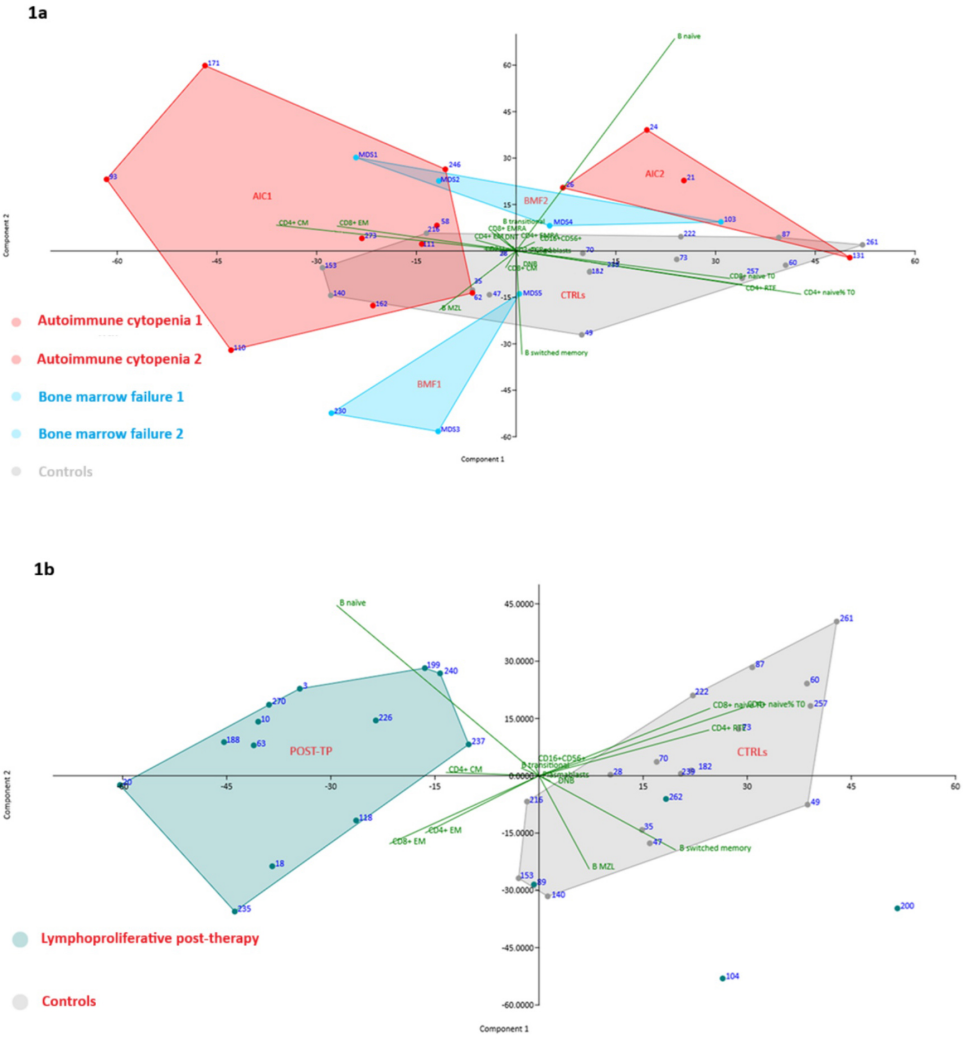

Fig 1. Principal component analysis (PCA) of extended lymphocyte immunophenotyping in patients with haematological disorders and controls. **(1a)** The PCA demonstrates distinct immunophenotypic clustering among patients with autoimmune cytopenias (AIC) and bone marrow failure (BMF) compared with healthy controls. Both AIC and BMF cohorts were subdivided into two groups (AIC1/AIC2 and BMF1/BMF2) due to clearly divergent clustering patterns. **(1b)** PCA of lymphoproliferative patients post-therapy (POST-TP) reveals a distinct cluster separate from controls, indicating persistent immune perturbation following chemo-immunotherapy.