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POSTER ABSTRACTS

637.MYELODYSPLASTIC SYNDROMES - CLINICAL AND EPIDEMIOLOGICAL

UBA1 Mutations Identify a Rare but Distinct Subtype of Myelodysplastic Syndromes

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Background

Mutations in *UBA1* are associated with VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome, an adult-onset inflammatory disorder (Beck DB et al. NEJM 2020). Approximately 40% of VEXAS patients are also diagnosed with myelodysplastic syndromes (MDS). We previously profiled *UBA1* p.M41 mutations in a select subset of the International Working Group for MDS (IWG-PM) cohort (Bernard E et al. NEJM Evid 2022) including 375 male patients lacking disease-defining mutations or established disease classification by WHO guidelines, and identified 28 patients (7%) with *UBA1* p.M41T/V/L mutations (Cohort A, Sirenko M et al. Blood 2022). However, the prevalence and characteristics of *UBA1* mutations in MDS have not been systematically evaluated in a representative MDS population.

Methods

We used targeted next-generation sequencing of the full *UBA1* locus to profile 2027 diagnostic and treatment-naive MDS samples (Cohort B, 61% male) ascertained through the IWG-PM (Figure 1). Clinical associations of *UBA1* mutations were evaluated and clinical history was reviewed for inflammatory conditions when available.

Results

In Cohort B, 35 *UBA1* mutations in 34 (1.7%) patients were identified, of which 20 (0.97%) had likely pathogenic variants and 14 had variants of unknown significance (VUS). Likely pathogenic variants included 13 p.M41T/V/L mutation (variant allele fraction [VAF] range 0.013-0.94), and 7 non-p.M41 mutations where 6/7 had VAF>0.35: 2 with p.S56F (VAF 0.87 and 0.93), 2 p.A478S (VAF 0.72 and 0.80), 2 p.S621C (VAF 0.80 and 0.82) and 1 p.Y55H (VAF 0.025). Three VUS were in female patients. 204 cases were profiled by both assays and of those, all 8 ddPCR positive cases were identified by NGS with concordant VAF ($R2=0.999$ $p<0.0001$).

Integration of Cohort A and B (n=2,198) yielded 40 patients (all male, median age 72; range 44-89 years) with pathogenic *UBA1* variants. The WHO 2016 classification (available for n=38 of 40) was MDS-SLD/MLD (25), MDS-EB1 (4), MDS-U (3), CMML (2), MDS-RS-MLD (1), aCML (1), MDS/MPN-RS-T (1), MDS/MPN-U (1). Patients had a median of 1 myeloid gene mutation in addition to *UBA1* (range: 0-4) with most frequent co-occurring events in *TET2* (n=12), *DNMT3A* (n = 10), *ASXL1* (n=3), *SF3B1* (n=3) and loss of the Y chromosome (n=5). In 8 patients with pathogenic *UBA1* > 2% VAF and co-occurring *DNMT3A* mutations, *DNMT3A* and *UBA1* VAF were correlated (slope = 0.88, r = 0.87, p = 0.0005), suggesting that co-mutation may lead to clonal expansion. Conversely, *TET2* co-mutations were either subclonal (n=4) or clonal (n=8) to *UBA1*.

Among patients with pathogenic *UBA1* variants, the majority had IPSS-M Very-Low/Low risk (73% 27/37). In contrast, patients with VUS were more likely to have Moderate or High risk (64% 7/11).

Partial clinical history was available for 33 cases with pathogenic *UBA1* variants. 50% (9/18) had inflammatory-rheumatic disease (IRD) including psoriatic arthritis, relapsing polychondritis, Sweet syndrome, bronchiolitis obliterans with organizing pneumonia, ear chondritis, and rosacea. 3 patients had more than one IRD. 8 were treated for IRD with steroids (n=6) or methotrexate (n=2). 4 patients had MGUS. Other manifestations included vacuoles (4/8), thromboembolic disease (5/16), non-infection fever (5/14), weight loss (4/14), ocular symptoms (5/15), arthralgia (3/16), chondritis (5/15), and other inflammation (6/14). IRD diagnosis usually preceded MDS (average time 0.28 years; range 16.5 years prior to 1.4 years after).

Three patients transformed to acute myeloid leukemia (AML). One patient had a low VAF *UBA1* p.M41V (0.0002 by ddPCR) and *TET2*, *SF3B1*, *FLT3*, and *ASXL2* co-mutations at baseline. The second had *UBA1* p.S56F (VAF 0.868) and a Chr 7q deletion. The third had VUS *UBA1* p.R869L (VAF 0.222) and *IRF1*, *NFE2* and *RRAS* co-mutations. Among the other *UBA1*-mutant patients that died or were censored after 1 year (n=37), none transformed to AML.

Conclusion

Within the large, representative, diagnostic and well-characterized IWG-PM MDS cohort, we find likely pathogenic *UBA1* mutations in 1% of patients, with enrichment in male patients with few or no mutations in myeloid driver genes (7%). *UBA1*-mutant patients were predominantly IPSS-M low risk with a median of 1 additional mutation, usually in *DNMT3A* or *TET2*. *UBA1* mutations may define a distinct subset of MDS and its recognition in future guidelines will improve the management of patients with MDS/VEXAS overlap.

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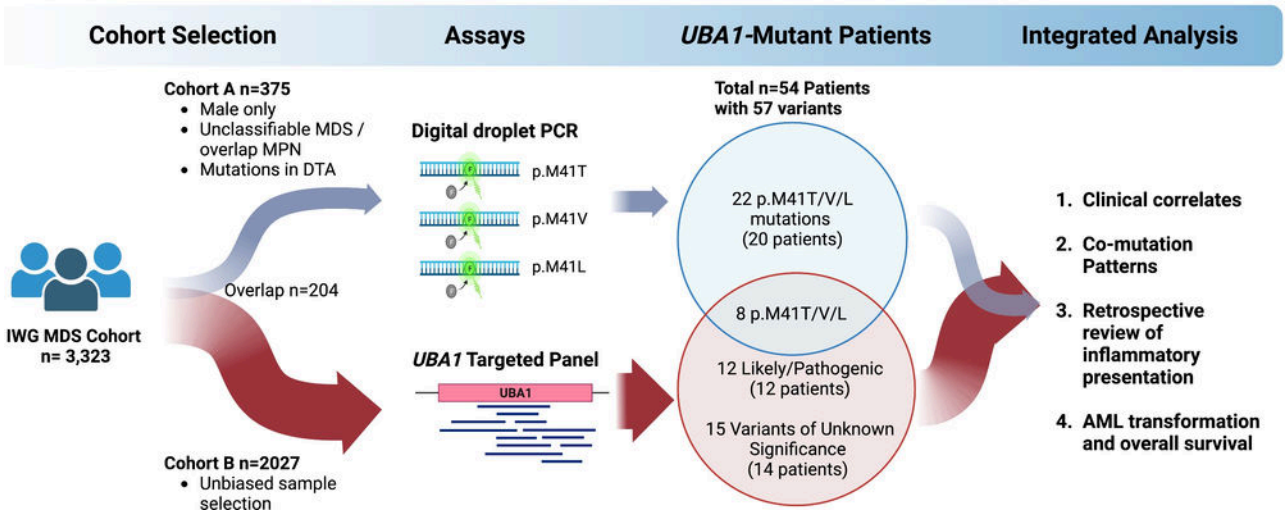

Figure 1

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