

Prevalence of *UBA1* mutations in MDS/CMML patients with systemic inflammatory and auto-immune disease



Lin-Pierre Zhao*^{1,2}, Berenice Schell*^{2,3}, Marie Sébert^{1,4}, Rathana Kim³, Pierre Lemaire³, Maxime Boy², Stephanie Mathis³, Lise Larcher^{3,4}, Clémentine Chauvel³, Mohamed Bedis Dhouaieb³, Valéria Bisio², Claude Preudhomme^{5,6}, Alice Marceau-Renaut^{5,6}, Raphaël Itzykson^{1,4}, Arsène Mekinian⁷, Olivier Fain⁷, Antoine Toubert^{2,8}, Pierre Fenaux¹, Nicolas Dulphy^{2,8}, Emmanuelle Clappier^{3,4}, Lionel Adès¹

* These authors contributed equally to this work

Background

Systemic inflammatory and auto-immune diseases (SIAD) are observed in 25% of patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemias (CMML). In a cohort of **85 MDS/CMML patients with SIAD**, we recently found that *TET2*, *IDH1/2* and *SRSF2* mutations were more prevalent in MDS/CMML patients with SIAD compared with 319 MDS/CMML patients without SIAD, suggesting a common pathogenesis for the 2 disorders (1).

Mutations in *UBA1* have recently been described, defining a new syndrome called **VEXAS** in patients with autoinflammatory manifestations (2), including relapsing polychondritis (RP) and Sweet syndrome (SwS).

The prevalence of *UBA1* mutations in MDS and CMML patients remains unknown, as is its implication in all MDS/CMML associated inflammatory disorders.

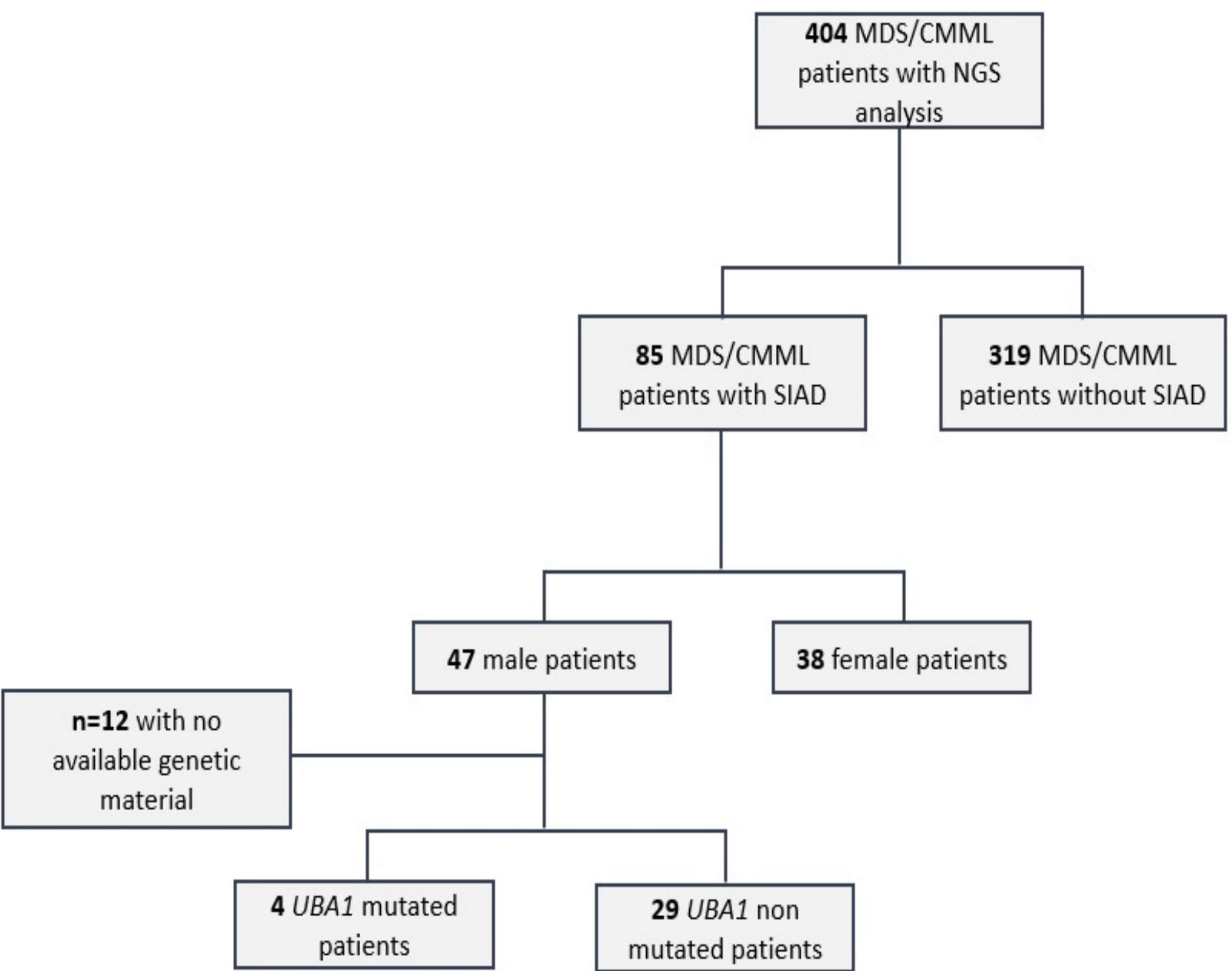
Objective

To explore the prevalence of *UBA1* mutations and the characteristics of mutated patients in our cohort of MDS/CMML with SIAD.

Materials & Methods

- From our cohort of 85 patients with MDS/CMML and SIAD, all male patients (n=47) for whom material was available (n=33) were analyzed for the presence of *UBA1* mutations (**Figure 1**).
- DNA was obtained from peripheral blood or bone marrow mononuclear cells and Sanger sequencing of exons 2 and 3 as well as exon-intron junctions was performed.

Figure 1: Flow chart of the study



Results

4 patients out of 33 (12%) had *UBA1* mutations.

Cytomorphologic review of bone marrow smears showed numerous vacuoles in myeloid and erythroid precursors in all 4 cases (**Figure 2A and B**), which were not specific of *UBA1* mutated patients, as vacuoles were also observed in 9 of 13 *UBA1* wild type MDS with associated SIAD (**Figure 2C and D**).

All 4 patients had MDS without excess of blasts. Karyotype was normal in 3 of them, and patient #3 had deletion 9q (**Table I**).

Mutations in *UBA1* affected methionine-41 in patients #2, #3 and #4, while patient #1 had a mutation at a splice site, predicted to have similar consequence on UBA1 protein. Patient #3 and #4 also had somatic mutations in *DNMT3A* and *TP53*, and *TET2* respectively.

Three patients in our MDS/CMML SIAD cohort (n=85) had RP, and 2 of them (patients #1 and #2) had *UBA1* mutations, while 6 patients from our initial SIAD cohort had a diagnosis of SwS, including 2 (patients #1 and #4) with *UBA1* mutations.

Patients #1, #2 and #3 had steroid refractory SIAD and were heavily treated with other immunosuppressive therapies. Patients #1, #3 and #4 received azacytidine (AZA) for the treatment of SIAD associated with MDS, based on our previous experience in patients with MDS and SIAD where SIAD was improved in 19 of 22 cases (3). In the present work, only patient #1 achieved a partial response, allowing steroids decrease without total discontinuation. The number and intensity of episodes of acute febrile neutrophilic dermatosis persisted in patient #4 despite AZA treatment, while response was not evaluable in patient #3 in whom AZA was quickly withdrawn due to suspected treatment related interstitial lung disease.

At last follow up, none of the 4 patients with *UBA1* mutations had MDS progression, and one of them (patient #2) had died from a stroke, 2.4 years after MDS diagnosis.

Figure 2: Precursors morphology with vacuoles (red arrows) in MDS patients with (A; B) or without (C; D) *UBA1* mutations. Cells were observed on May Grunwald Giemsa stained Bone Marrow smears at x500 magnification.

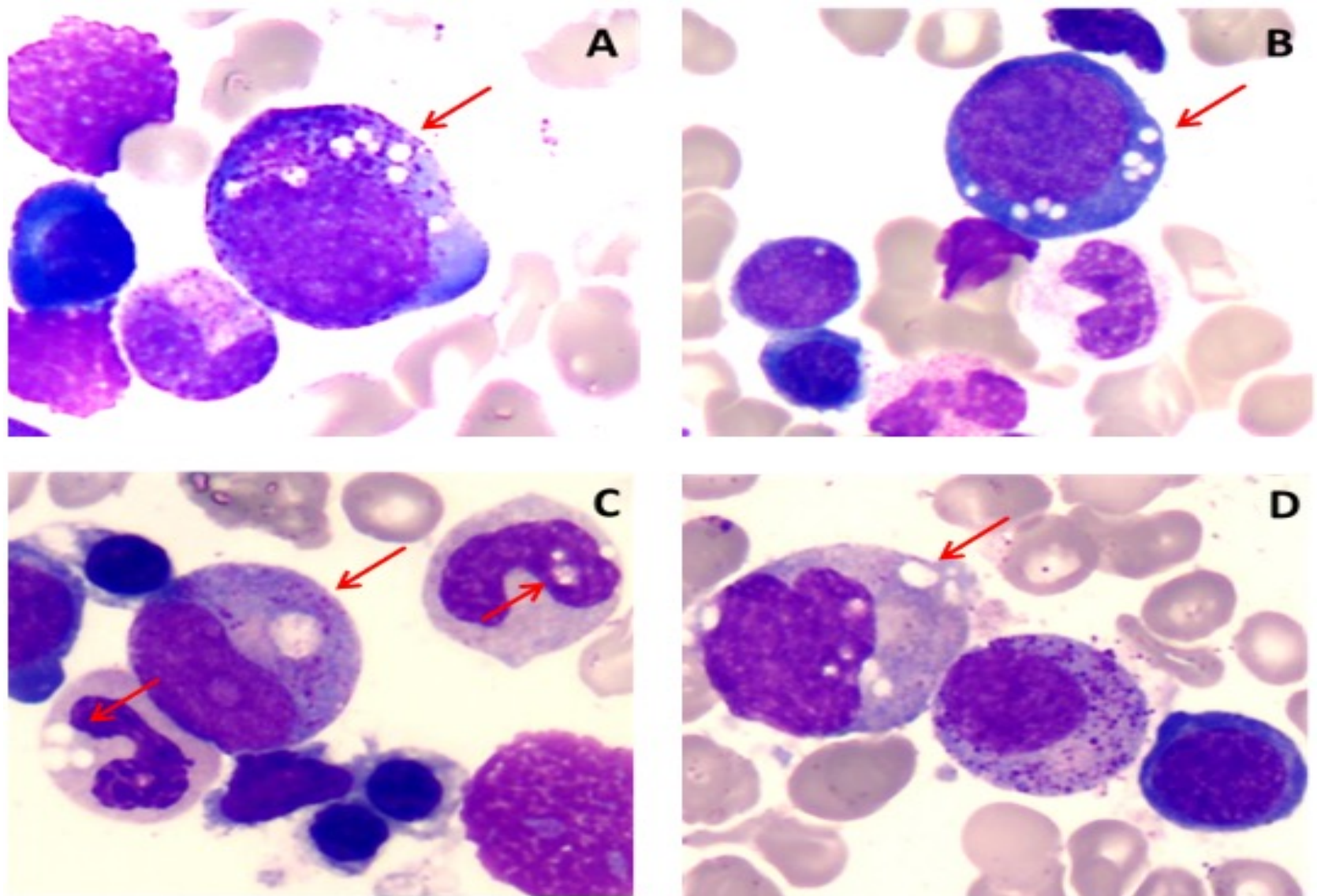


Table I: Patients main clinical and biological characteristics

Variables	Patient #1	Patient #2	Patient #3	Patient #4
Age at MDS/CMML diagnosis	74	78	66	57
Gender	Male	Male	Male	Male
Hematological diagnosis	MDS SLD	MDS MLD	MDS SLD	MDS MLD
Karyotype	normal	normal	del9q	normal
IPSS-R risk category	low	high	high	low
Mutations (myeloid NGS panel)	none	none	DNMT3A (VAF 11%), TP53 (VAF 2%)	TET2 (VAF 18%)
SIAD diagnosis	relapsing polychondritis, Sweet syndrome	relapsing polychondritis, Hashimoto	giant cell arteritis	Sweet syndrome, undifferentiated inflammatory arthritis
UBA1 mutations	c.118-1G>C	c.T122C:p.Met41 Thr	c.A121G:p.Met41 Val	c.T122C:p.Met41 Thr
Treatment	hydroxychloroquine, steroids, thalidomide, azathioprine, anti IL1R, anti IL6R, AZA, low dose IL-2	MTX, steroids	steroids, azathioprine, MTX, anti-IL6R, AZA, anti-IL1R, TNF inhibitor	AZA

Conclusion

This retrospective analysis represents to our knowledge the **first assessment of *UBA1* mutations among patients with myeloid malignancies**, selected for male gender and the co-occurrence of SIAD.

Other pathological mechanisms may drive inflammation in MDS/CMML patients with associated SIAD, including our own hypothesis of common genetic susceptibilities with mutations in epigenetic regulators *TET2/IDH* and *SRSF2* (1).

References

1. **Zhao L-P** et al. Genomic landscape of MDS/CMML associated with systemic inflammatory and autoimmune disease. *Leukemia*. 2021.
2. **Beck DB** et al. Somatic Mutations in UBA1 and Severe Adult-Onset Autoinflammatory Disease. *NEJM*. 2020.
3. **Fraison J-B** et al. Efficacy of Azacitidine in autoimmune and inflammatory disorders associated with myelodysplastic syndromes and chronic myelomonocytic leukemia. *Leuk Res*. 2016.