**Supplementary Data:**

**Supplementary Methods**

**NGS MDS Panel:**

Molecular analysis for MDS was performed with the Oncomine™ Myeloid Research Assay using the Ion Torrent S5 instrument. It covers 40 relevant myeloid genes, and with a sensitivity of 5% VAF (variant allele frequency), and which is not error corrected. The following genes were analyzed:

ABL1 (Exone 4-9), ASXL1 (Exone 11-12), BCOR, BRAF (Exone 11, 15), CALR, CBL (Exone 8-9), CEBPA, CSF3R (Hotspots in Exone 14, 17, 18), DNMT3A (Exone 11-23), ETV6, EZH2, FLT3 (Exone 8, 11, 14-16, 21), GATA2 (Hotspots in Exone 4, 5), HRAS (Exone 2, 3), IDH1 (Hotspot in Exon 4), IDH2 (Hotspot in Exon 4), IKZF1, JAK2 (Exone 12-15), KIT (Hotspots in Exone 8. 9, 10, 11, 13, 17), KRAS (Hotspots in Exone 2, 3, 4), MPL (Hotspots in Exone 3, 4, 10, 12), MYD88 (Exone 3, 5), NF1, NPM1 (Exon 11), NRAS (Hotspots in Exone 2, 3, 4), PHF6, PRPF8, PTPN11 (Hotspots in Exone 3, 12, 13), RB1, RUNX1, SETBP1 (Hotspot in Exon 4), SF3B1 (Hotspots in Exone 14, 15, 16, Exone 17-21), SH2B3, SRSF2 (Exon 1), STAG2, TET2, TP53, U2AF1 (Hotspots in Exone 2, 6), WT1 (Exone 6, 8), ZRSR2.

**Supplementary Tables:**

**Supplementary Table 1: Overview of laboratory parameters and autoimmune serologies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter (Unit)** | **Normal range** | **Patients’ max.** | **Patients’ min.** |
| CRP (mg/L) | < 3 | 343 | <3 |
| Ferritin (ug/L) | 20 - 250 | 3008 | 355 |
| Hemoglobin (g/L) | 135 - 168 | 112 | 66 |
| MCV (fl) | 80 - 98 | 120 | 99 |
| Thrombocytes (Giga/L) | 150 - 450 | 251 | 85 |
| Leukocytes (Giga/L) | 3.00 - 10.50 | 10.8 | 1.95 |
| Neutrophils (Giga/L) | 1.60 - 7.40 | 11.96 | 0.71 |
| Rheumatoid Factor IU/ml | < 3.50 | 0.5 |  |
| ACPA | neg. | neg. |  |
| ANA | < 1:80 | < 1:80 |  |
| Anti-PR3 Abs. (IU) | < 5 | < 0.5 |  |
| Anti-MPO Abs. (IU) | < 6 | < 1 |  |

**Supplementary Table 1**: Laboratory parameters and autoimmune serologies. Only normal range, minimal and maximal values are listed**.**

**Supplementary Table 2: Formal review of the literature, describing VEXAS patients with concomitant clonal hematologic disorders**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author (Reference)** | **MDS** | **MDS-associated somatic mutations** | | | **Other diseases** | **Comments** |
|  |  | *TET 2* | *DNMT3A* | Other |  |  |
| Oganesyan et al. 03/2021 (23) | 1 |  | 1 | 1 *EP300* |  | *EP300* concomitant with *DNMT3A* |
| Rieu et al. 03/2021 (22) | 1 |  |  |  |  | MDS, no additional somatic mutations |
| Tsuchida et al. 03/2021 (20) | 6 |  |  |  |  | RP-VEXAS and MDS in 6 subjects, no additional somatic mutations |
| Huang et al. 03/2021 (10) | 1 |  |  |  |  | MDS, no additional somatic mutations |
| Sakuma et al. 04/2021 (21) | 1 |  |  |  |  | MDS, no additional somatic mutations |
| Staels et al. 04/2021 (9) | 1 |  | 1 |  |  |  |
| Van der Made et al. 05/2021 (16) | 4 |  | 1 |  |  |  |
| Lytle et al. 06/2021(18) | 1 |  |  |  |  | MDS with *CCND1-IGH* |
| Templé et al. 07/ 2021 (19) | 2 |  |  | 1***PPM1D*** |  | 2 Subjects with MDS; Atypical UBA1 splice site mutation; NO vacuoles |
| Obiorah et al. 08/2021 (6) | 6 |  | 2 | ***1 GNA11+CSF1R***  *(1 EZH2)* | 2 MM  2 MBL  2 MGUS | 2 MGUS (1 with concomitant MM)  MBL: monoclonal B-Cell lymphocytosis  EZH2 in subject without MDS diagnosis |
| L.Zhao et. al. 08/2021 (3) | 4 | 1 | 1 | *1 TP53* |  | *TP53* concomitant with *DNMT3A* |
| Dupuy et al. 09/2021(8) |  |  |  |  |  | *No UBA1 mutations in a cohort of 108 CMML Patients* |
| Shaukat et al. 09/2021 (2) | 1 |  | 1 |  |  | Review of the literature: 31% of VEXAS patients with MDS, 7% with MGUS, 1% with MM |
| Li et al. 10/2021 (13) | 0 |  |  | 1***PRPF40B*** |  | 2 subjects without MDS; germline origin suggested (VAF 48%) |
| Muratore et al. 10/2021 (14) | 5 |  |  |  |  | 5 subjects with MDS and no cytogenetic changes; all with vasculitis |
| Raaijmakers et al. 10/2021 (1) | 3 | 1 | 2 |  |  | 3 additional patients in cohort, but no specific details provided |
| Georgin-Lavialle et al. 10/2021 (4) | 52 | 6 | 11 | 1 unclear | 12 MGUS (all with MDS) | 52 MDS (out of 116 VEXAS Patients)  Identification of 3 clusters as well as phenotype association for *UBA1 p.MET41Leu* (less inflammatory, better prognosis) |
| Pamies et al. 10/2021 (12) | 1 |  |  |  |  | RP-VEXAS with MDS + IgA Vasculitis |
| Diarra et al. 10/2021(5) | 5 | 2 | 1 | *1(CBL, KRAS*  *NRAS, ZRSR2)*  *1 RUNX1* | 1 Myelofibrosis | 6 HSCT Patients, retrospective analysis  all with additional mutations (*TET2, CBL, KRAS, NRAS, ZRSR2*) in 1 Patient with *TET2+* MDS  RUNX1 in Patient with *DNMT3A* mutation |
| Roy L. Kao et al. 11/2021 (11) | 0 |  | 1 |  |  | no MDS |
| Gurnari et al. 2021 (7) | 2 |  | 1 |  |  | Retrospective analysis of subjects with vacuolization on bone marrow examination |
| Koster et al. 2021 (15) | 1 | 1 |  |  | 1 MM |  |
| Grey et al. 2021 (17) | 1 |  |  |  |  | MDS, no additional somatic mutations |
| Bourbon et al. 2021 (24) | 6 |  |  |  |  | 6 MDS, no additional somatic mutations |
| Lötscher et al. 12/2021 | 1 | 1 |  |  |  |  |
| **24 Publications**  **including presented case-report** | **106** | **12** | **23** | **Combined w. TET2 or DNMT3A: 4**  **Isolated: 3** | **14 MGUS (13 with MDS, 1 with MM)**  **3 MM**  **1 Myelofibrosis** |  |
|  |  |  |  |  |  |  |

**Abbreviations:** VAF: variant allele frequency; MDS: myelodysplastic syndrome; MGUS: monoclonal gammopathy of undetermined significance; MBL: monoclonal B-Cell lymphocytosis; CMML: chronic myelomonocytic leukemia; MM: multiple myeloma; RP-VEXAS: relapsing polychondritis VEXAS. The literature search was performed via pubmed (search term: VEXAS syndrome) on 10 December 2021: 59 manuscripts were identified and each manuscript was screened for patients with clonal heamatologic diseases.

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