Successful allogeneic hematopoietic stem cell transplantation in patients with VEXAS syndrome: a 2-center experience

Ava Diarra, Nicolas Duployez, Elise Fournier, Claude Preudhomme, Valérie Coiteux, Leonardo Magro, Bruno Quesnel, Mael Heiblig, Pierre Sujobert, Marie Balsat, Quentin Scanvion, Eric Hachulla, David Launay, Ibrahim Yakoub-Agha, and Louis Terriou, on behalf of the French VEXAS study group

The recently described vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is caused by somatic mutations in UBA1. Patients with VEXAS syndrome display late-onset autoinflammatory symptoms, usually refractory to treatment, and hematologic abnormalities. The identification of an easily-accessible specific marker (UBA1 mutations) is of particular interest as it allows the convergence of various inflammatory and hematological symptoms in a unique clinico-biological entity and gives the opportunity to design specific treatment strategies. Here we retrospectively identified 6 patients with VEXAS syndrome who underwent allogeneic hematopoietic stem cell transplantation (ASCT). To date, no treatment guidelines have been validated. In 4 patients, ASCT was guided by life-threatening autoinflammatory symptoms that were refractory to multiple therapies. Three patients are in durable complete remission 32, 38, and 37 months after ASCT. Two others are in complete remission response after 3 and 5 months. One unfortunately died post-ASCT. This report suggests that ASCT could be a curative option in patients with VEXAS syndrome and severe manifestations. Considering the complications and side effects of the procedure as well as the existence of other potential treatment, clinical trials are needed to define the subgroup of patients who will benefit from this strategy and its place in the therapeutic arsenal against VEXAS syndrome.

Introduction

Beck et al recently identified a specific somatic molecular alteration targeting the UBA1 gene, located on the X chromosome, defining the vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. Patients with VEXAS syndrome are men (rarely women with acquired monosomy X) with a late-onset, treatment-refractory autoinflammatory syndrome and hematologic abnormalities, especially macrocytic anemia and characteristic vacuoles in myeloid precursors from bone marrow (BM). The UBA1 gene encodes the E1 ubiquitin-activating protein, which is critical for the first step of ubiquitylation. The vast majority of UBA1 mutations involve the methionine 41 in exon 3 (which initiates the translation of the canonical cytoplasmic isoform UBA1b) and lead to the production of a shorter cytoplasmic catalytically-deficient isoform (UBA1c, initiated from methionine 67). This results in decreased

Key Points

- Allogeneic hematopoietic stem cell transplantation is a curative option in patients with VEXAS syndrome and severe manifestations.
ubiquitylation and activation of innate immune pathways, elevated serum cytokine levels, and severe inflammatory effects. Other mutations affecting the acceptor-splice site of exon 3 or the serine 56 have also been rarely described. The identification of VEXAS syndrome is of particular interest for clinical practice as it provides a strong diagnostic marker, giving the opportunity to design specific treatment strategies in patients whose inflammatory symptoms are usually refractory to most therapies. Here, we retrospectively diagnosed VEXAS syndrome in 6 patients who underwent allogeneic hematopoietic stem cell transplantation (ASCT) for the treatment of severe inflammatory symptoms ($n = 4$) or myelodysplastic syndromes (MDS, $n = 2$). Patients’ characteristics, BM examination, and $UBA1$ screening are summarized in Table 1, Figure 1, and supplemental Appendix.

Case description

The first patient (#UPN1, briefly depicted in ref 6) was a 43-year-old man diagnosed with polyarteritis nodosa and Sweet’s syndrome. Clinical manifestations included fever, orchitis, myalgia, erythema nodosum, and chemosis. Blood cell count revealed persistent macrocytic anemia, and BM examination revealed a MDS with multilineage dysplasia and multiple vacuoles in myeloid precursor cells. The patient received multiple therapies without remission of the vasculitis symptoms. ASCT was considered 2.7 years after initial diagnosis due to uncontrolled autoinflammatory manifestations. Following reduced-intensity conditioning, he underwent ASCT from an HLA-matched unrelated donor. Despite chronic GVHD, the patient remains in complete remission of both hematological and inflammatory diseases 32 months after ASCT. Retrospective sequencing (supplemental Methods) demonstrated the $p$.Met41Val mutation in $UBA1$, leading to the diagnosis of VEXAS syndrome.

The second patient (#UPN2) was a 56-year-old man who presented with inflammatory symptoms including fever, arthritis, and Sweet’s syndrome with neutrophilic dermatosis. After 1 year, he experienced diffuse purpura related to immune thrombocytopenia, bilateral episcleritis, and splenomegaly. Splenectomy was performed for refractory immune thrombocytopenia. Analysis of spleen histopathology revealed signs of extramedullary hematopoeisis. BM trephine biopsy showed hyperplasia of all lineages, megakaryocytic dysplasia, vacuoles in myeloid precursor cells, and grade II fibrosis, leading to the diagnosis of myelofibrosis. The patient received multiple therapies without remission of the vasculitis symptoms. ASCT was then performed, more than 3 years after initial diagnosis, from a related donor after reduced-intensity conditioning. He developed extensive chronic cutaneous GVHD treated by cyclosporine, corticosteroids, and ruxolitinib. He is still in remission from hematological and autoinflammatory diseases 67 months after ASCT. Retrospective sequencing showed the $UBA1$ $p$.Met41Val mutation.

The third patient (#UPN3) was a 63-year-old man with a chronic inflammatory syndrome with fever, arthralgia, and myalgia who was referred to our department for chondritis, anterior uveitis, Sweet’s syndrome, and mild cytopenia. BM examination led to the diagnosis of MDS with major dysgranulopoiesis and vacuolization of erythroid and granulocyte precursor cells. Multiple therapies, including 5-azacytidine, did not result in clinical improvement of the Sweet’s syndrome. ASCT was then performed with peripheral blood stem cells from an HLA-matched unrelated donor after reduced-intensity conditioning. He subsequently developed BK virus–related hemorrhagic cystitis, cytomegalovirus replication, and acute cutaneous GVHD treated with corticosteroids. The patient is still in complete remission of the hematologic disease and Sweet’s syndrome 38 months after ASCT. Retrospective Sanger sequencing revealed the $UBA1$ $p$.Met41Leu mutation.

The fourth patient (#UPN4) was a 48-year-old man diagnosed with deep venous thrombosis, asthenia, fever, chondritis, Sweet’s syndrome, macrocytic anemia, polyadenopathy, and pulmonary infiltrate. BM examination showed dysmyelopoiesis and vacuolization of erythroid and granulocytic precursor cells. Several therapies were ineffective. The diagnosis of VEXAS syndrome with the $UBA1$ $p$.Met41Thr mutation was made (prior to ASCT). ASCT was performed 2 years after the first symptoms with peripheral blood stem cells from an HLA-matched unrelated donor after myeloablative conditioning.

In addition to the 4 previously described patients who underwent ASCT because of severe refractory inflammatory symptoms, we identified 2 other patients with a retrospective diagnosis of VEXAS syndrome for whom ASCT was performed because of hematological diseases. The fifth patient (#UPN5) was a 56-year-old man concomitantly diagnosed with multilineage dysplasia, mouth and genital ulcers-inflamed cartilage syndrome, and large vessel vasculitis. The patient received multiple therapies including 5-azacytidine and ruxolitinib with insufficient response. ASCT was finally performed with a related donor after reduced intensity conditioning allowing complete response (5 months of follow-up). The sixth patient (#UPN6) was a 50-year-old man who had atypical vasculitis associated with sinusitis, orchitis, arthritis, and concomitant pancytopenia that led to the diagnosis of MDS with excess blasts type 1. Treatment with 5-azacytidine was initially successful, but relapse of the autoinflammatory symptoms occurred after 30 months, and the patient was treated with glucocorticoids. He finally underwent ASCT due to reoccurrence and worsening of cytopenia with peripheral blood stem cells from an HLA-matched unrelated donor 5 years after the first symptoms but died of infectious severe hypoxic pneumonia 4 months after ASCT.

Methods

After the Beck et al., paper describing VEXAS, French centres of the Medecine Interne, HEmato et ONco (MINHEMON) group analysed $UBA1$ mutation in samples from their patients with similar unexplained symptoms, while several Groupe Francophone des Myelodysplasies (GFM) centres analysed systematically this mutation in MDS with concomitant autoimmune/autoinflammatory disease, yielding a total of 116 patients (between December 2020 and May 2021). In all, 6 of them underwent ASCT. One of them has previously been reported. The present study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. Data collection Collected data at baseline and during the follow-up included patient demographics, MDS characteristics (WHO classification, karyotype), clinical and laboratory features of VEXAS, and additional somatic mutations by next-generation sequencing analysis. Statistical analysis Data were expressed as median (range) for quantitative variables and number (percentage) for categorical variables.

Results and discussion

Because of its recent description, there are no guidelines for the treatment of VEXAS syndrome. We present here 6 patients
Table 1. Characteristics of UBA1-mutated patients

| Patient ID | #UPN1 | #UPN2 | #UPN3 | #UPN4 | #UPN5 | #UPN6 |
|------------|-------|-------|-------|-------|-------|-------|
| Sex        | M     | M     | M     | M     | M     | M     |
| Age at onset (years) | 43    | 56    | 63    | 48    | 56    | 50    |
| UBA1 mutation | c.121A>G, p.Met41Val (VAF 73%) | c.121A>G, p.Met41Val (VAF 88%) | c.121A>G, p.Met41Leu (VAF 43%) | c.122T>C, p.Met41Thr (VAF 87%) | c.121A>G, p.Met41Val (VAF: NA) | c.121A>G, p.Met41Val (VAF: NA) |
| Key clinical features | Neutrophilic dermatosis | + | + | + | + | – |
| | Polyarteritis nodosa | + | – | + | – | – |
| | Chondritis | – | – | + | + | + |
| | Pulmonary involvement | – | – | – | + | – |
| | Deep vein thrombosis | – | – | – | + | – |
| Laboratory findings* | Hemoglobin concentration (g/l) | 96 | 92 | 102 | 78 | 110 | 131 |
| | Mean corpuscular volume (fl) | 102 | 98 | 104 | 105 | 91.2 | 113.7 |
| | Platelet count (×10^9/l) | 225 | 67 | 157 | 341 | 268 | 153 |
| | Neutrophil count (10^9/l) | 2.1 | 11.8 | 4.0 | 4.6 | 5.5 | 1.2 |
| | Bone marrow vacuoles | + | + | + | NA | NA | NA |
| | Additional genetic aberrations (HTS and cytogenetics) | Normal karyotype | Normal karyotype | Normal karyotype | Normal karyotype | Normal karyotype | Trisomy 8 |
| | | No additional mutation | DNMT3A p.Trp795Ser (VAF 43%)† | RUNX1 p.Gly165fs (VAF 2%) | CBL c.1228-2A>G (VAF 9%) | KRAS p.Gly12Arg (VAF 2%) | No additional mutation | No additional mutation |
| | | | DNMT3A p.Trp795Ser (VAF 43%)† | RUNX1 p.Gly165fs (VAF 2%) | CBL c.1228-2A>G (VAF 9%) | KRAS p.Gly12Arg (VAF 2%) | No additional mutation | No additional mutation |
| Hematologic diseases | Myelodysplastic syndrome | + | – | + | + | + | + |
| | Myelofibrosis | – | + | – | – | – | + |
| | Number of prior lines of therapy | 6 | 8 | 7 | 6 | 5 | 4 |
| | | GC, anakinra, dapsone, canakinumab, AZA, HCQ | GC, CP, IVig, rituximab, danazol, anakinra, dapsone, canakinumab | GC, MTX, anakinra, canakinumab, tocilizumab, IVIG, 5-AZA | GC, dapsone, colchicine, anakinra, canakinumab, sirolimus | GC, tocilizumab, adalimumab, 5-AZA, ruxolitinib | GC, MMF, colchicine, 5-AZA |
| | Reaction at anakinra injection | – | – | + | + | NA | NA |
| Allogeneic HSCT | Age at time of HSCT | 46 | 59 | 65 | 50 | 58 | 55 |
| | Conditioning | fludarabine, busulfan, ATG | fludarabine, busulfan | fludarabine, busulfan | fludarabine, busulfan, ATG | fludarabine, busulfan, thiopeta | busulfan, OPAT, ATG |

*At time of first bone marrow examination.
†The somatic state of the DNMT3A mutation was confirmed by sequencing on a skin biopsy.
‡Sanger sequencing only.

5-AZA, 5-azacytidine; ATG, antithymocyte globulin; AZA, azathioprine; CP, cyclophosphamide; CR, complete remission; CSA, cyclosporine; GC, glucocorticoid; GVHD, graft-versus-host disease; HCQ, hydroxychloroquine; HSCT, hematopoietic stem cell transplantation; IVIG, intravenous immunoglobulin; M, male; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; VAF, variant allele frequency.
## Table 1. (continued)

| Patient ID | #UPN1 | #UPN2 | #UPN3 | #UPN4 | #UPN5 | #UPN6 |
|------------|-------|-------|-------|-------|-------|-------|
| Donor      | Unrelated donor | Related donor | Unrelated donor | Related donor | Unrelated donor | Related donor |
|            | Pheno-identical 10/10 |                   | Pheno-identical 10/10 |                   | Pheno-identical 10/10 |                   |
| Graft origin| Peripheral blood | Bone marrow | Peripheral blood | Peripheral blood | Peripheral blood | Peripheral blood |
| GVH prophylaxis | CSA, MMF | CSA, MTX | CSA, MMF, CP | CSA, MTX | CSA, MMF, CP | CSA, MTX |
| Infectious complications | None | None | E. coli bacteremia, BK virus-related hemorrhagic cystitis, CMV replication | Bacterial catheter related infection | Bacterial catheter related infection | Bacterial catheter related infection, fusariosis |
| Immune complications | Chronic cutaneous GVHD, hepatic GVHD | Chronic cutaneous GVHD | Acute cutaneous GVHD grade I | None | Acute gastrointestinal GVHD grade II | Cutaneous GVHD grade I |
| Clinical response | CR | CR | CR | CR | CR | CR |
| Follow-up (months) | 32 | 67 | 38 | 3 | 5 | 4 |
| Alive at end of follow-up | + | + | + | + | + | – |

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*At time of first bone marrow examination.
†The somatic state of the DNMT3A mutation was confirmed by sequencing on a skin biopsy.
‡Sanger sequencing only.
with VEXAS syndrome who underwent ASCT after multiple therapies. Three patients with sufficient follow-up were still in complete remission 32, 38, and 67 months after ASCT, and 1 died of infectious complications. The 2 remaining patients were still alive with a shorter follow-up (3 and 5 months, respectively). In 4 patients, ASCT was guided by life-threatening autoinflammatory symptoms that were refractory to multiple biologics/anti-rheumatic drugs and immunosuppressants. This condition represents a rare indication for ASCT in our practice (no other case identified in our institution). However, because the selection of our patients was retrospectively made according to the severity of the disease and indication for ASCT, it cannot be excluded that some patients with VEXAS syndrome with moderate symptoms may have a favorable outcome with other therapies. Notably, Bourbon et al recently reported the retrospective study of patients with VEXAS syndrome in which they identified 1 patient with an indolent course without specific treatment. Interestingly, the authors observed a potential effectiveness of JAK inhibitors and hypomethylating agents in some patients. Overall, further studies are needed to identify predictive factors of response. Some variability may be related to additional somatic aberrations. For example, the study of variant allele frequencies in #UPN2 and #UPN3 strongly suggests that the UBA1 mutation was concomitant to mutations in DNMT3A or TET2. Another patient reported by Hage-Sleiman et al demonstrated under therapy the selection of an UBA1-mutated clone, outcompeting a CALR-mutated clone, both developing after a preexisting DNMT3A founding clone.

In conclusion, the present report suggests that ASCT could be a curative option in patients with VEXAS syndrome and severe manifestations. Considering the complications and side effects of the procedure (as demonstrated by our last case) as well as the...
existence of other therapeutic options, clinical trials are required to define the subgroup of patients who will benefit from this strategy and its place in the therapeutic arsenal against VEXAS syndrome.

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Authorship
Contribution: A.D. and L.T. conceived the study; N.D., E.F., C.P., and P.S. performed cytomorphological examinations and molecular analyses; A.D., E.H., I.Y.-A., V.C., L.M., B.Q., Q.S., D.L., M.H., F.B., M.B., and L.T. managed the patients and provided samples and clinical data; A.D., N.D., and L.T. wrote the manuscript, which was approved by all the authors.

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