Allogeneic hematopoietic stem cell transplantation for VEXAS syndrome - UK experience

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VEXAS (Vacuoles, E1-ligase, X-linked, Auto-inflammatory, Somatic) syndrome, is an acquired, progressive systemic auto-inflammatory disorder with overlapping rheumatological and haematological features(1, 2). It is caused by myeloid-restricted somatic mutations in *UBA1*, the gene which encodes E1 ubiquitin ligase. VEXAS is associated with significant morbidity and reduced life expectancy. Current treatment options are limited to symptomatic control, with corticosteroids being universally effective and JAK inhibitors showing promising results. Allogeneic hematopoietic stem cell transplantation (HSCT) has been proposed as potentially curative option in selected patients. The experience of HSCT in VEXAS is limited to few case reports(3, 4). Here, we describe four additional cases of VEXAS in whom HSCT was performed. We also report on the incidence of undiagnosed VEXAS in patients with MDS and chronic myelomonocytic leukaemia (CMML) who underwent BMT for haematological indications.

Clinical features of four VEXAS patients who underwent HSCT (mean follow up 13.5 months; range 0.4-40 months) are summarised in Table 1 (detailed clinical vignettes provided in supplements). Three patients P1, P2 and P3 were diagnosed with VEXAS prior to transplantation, with the transplant indication being severe and poorly controlled inflammatory illness. Patient 4 was identified retrospectively, after undergoing HSCT for what was thought to be MDS. Patients 1 and 3 were also included in a recent cohort study, although this did not report on their outcomes following HSCT (1, 2).

The average age of disease onset for these patients was 59 years (range 49-64), which is younger than expected for VEXAS, as described in two recent, large cohort studies which demonstrated an average age of 66 and 67 years (2, 5). Patients 1 and 2 had a UBA1 p.Met41Val variant recently found to be associated with a worse outcome (2). Patients 1, 3 and 4 were also transfusion dependent, a feature associated with more severe disease (2). All three patients transplanted for an inflammatory indication had previously failed multiple DMARD's, whilst patient 4 had only received corticosteroids. Outcomes following HSCT were variable. Patient 1 died from sepsis and multiorgan failure in the early post-transplant period (day +11). Patient 2 survived the transplant with good engraftment and full donor chimerism, but recovery was complicated by hemophagocytic lymphohistiocytosis, aseptic encephalitis and Epstein Barr Virus reactivation within 2 months of transplant, and subsequent chronic skin graft versus host disease and recurrent bacterial infections, the sequelae of which have

resulted in a Karnofsky performance score of 40. Patient 3 achieved disease control with no molecular evidence of VEXAS, however developed severe post-transplant myelitis resulting in paraplegia, urinary and faecal incontinence, and passed away 11 months post-transplant from infectious complications. Patient 4 is the only one who at the time of writing (40 months post-transplant) remains alive and in good health.

Previous studies have reported VEXAS patients being transplanted in the absence of a prior diagnosis, including one of the patients we report here (P4). We therefore speculated about the incidence of undiagnosed VEXAS cases amongst patients with myeloid disorders who had undergone HSCT. To this end, we studied patients from a single centre, with a diagnosis of MDS or CMML, who were transplanted in the last 10 years, for whom historical pre-HSCT bone marrow DNA samples were available.

We identified 44 patients in total, 34 MDS and 10 CMML. Historical, pre-HSCT bone marrow DNA samples were available for all patients. We performed deep sequencing of the whole *UBA1* gene (for method please see supplements). To date, all pathogenic mutations associated with VEXAS have been confined to exon 3, with Methionine-41 (Met41) being a particularly important site (1, 2). No patients demonstrated any of the known pathogenic mutations in *UBA1*, but 4 patients were found to have rare variants outside exon 3 that have not been previously reported and have unknown functional consequences. The variants identified (and variant allele frequencies) were: c.2554-1G>T (0.5), c.2554-8C>T (0.4), c.2374C>T:p.Gln792Ter (0.14) and c.1321G>A:p.Glu441Ter (0.8). However, none of the patients carrying these variants had any inflammatory symptoms. Three had a diagnosis of MDS, whilst the patient with c.1321G>A, p.Glu441Ter variant was diagnosed with CMML.

A failure to find any typical cases of VEXAS across the entire transplanted cohort was likely predictable. Very few patients had any inflammatory symptoms or disease manifestations classically associated with VEXAS (Table 2). The MDS features were also different. Ferrada et al. reported that MDS was diagnosed in 31% of the total cohort, who were retrospectively found to have VEXAS (2). On review, these patients typically had low risk disease, have a much lower frequency of MDS associated gene mutations and show no evidence of progression to acute myeloid leukaemia (2, 6) consistent with UBA1 mutations being the main driver of cytopenias and bone marrow morphological changes not a distinct MDS. The other haematological manifestations which are almost universal in VEXAS, such as

macrocytic anaemia (close to 100%), were seen in only 32% of patients in our cohort, although other types of anaemia (e.g. microcytic) were more common.

We report variable outcomes of HSCT in our VEXAS case series with 50% (2/4) overall survival but only 25% event free survival at current follow up. There are several potential explanations for this. Patient 1 underwent HSCT as a 'treatment of last resort' for a rapidly progressive, recalcitrant inflammatory disorder. The risk of poor outcome in such circumstances is invariably high, as reflected in his HCT-CI score of 6. Patient 2 was transplanted three years after the onset of symptoms and had received continuous immunosuppressive therapy including corticosteroids during this time. Patient 3 was transplanted almost 10 years after disease onset, during which time he had already developed several complications including renal impairment and steroid toxicity. In addition, he was exposed to several immunosuppressive therapies and had experienced several serious infections. It is unclear to what degree post-transplant complications were influenced by these factors. Nevertheless, the purported benefit of reduced corticosteroid use as a result of better control of his inflammatory illness was significantly offset by his pre-existing, iatrogenic adrenal insufficiency.

What these cases illustrate is the current lack of evidence informing the selection of VEXAS patients who will benefit from HSCT. The tools currently utilised in "classical" MDS and CMML to identify transplant candidates (IPSS, IPSS-R) would not be applicable in patients with VEXAS given the distinct bone marrow pathology and clinical manifestations. The only way to address these issues is through well-designed trials, alongside collection of detailed outcome data for all transplanted patients. An example of such a trial has been proposed by a team from the National Institutes of Health (USA) who are now recruiting patients for a Phase II study of allogeneic HSCT for subjects with VEXAS syndrome (7). An essential design of this trial could be adopted by other transplant centres internationally. This could lead to a larger platform trial to recruit more patients, test more treatment arms and provide results sooner.

Table 1. Clinical characteristics and outcome of HSCT in VEXAS patients

Patient ID	P1	P2	P3	P4
Genetics				
UBA1 mutation	p.Met41Val (c.121A>G)	p.Met41Val (c.121A>G)	p.Met41Thr (c.122T>C)	p.Met41Leu.(c.121A>C)
VAF (5%)	50	24	50	40
Demographics				
Gender	Male	Male	Male	Male
Age of onset	49	64	52	59
Key inflammatory features				
Fever	Yes	Yes	Yes	Yes
Weight loss	Yes	Yes	Yes	No
Skin involvement	Yes (Nodular)	Yes (Nodular)	Yes (Nodular)	Yes (Jessners Infiltrate)
Chondritis	No	No	No	Yes (Ear)
Arthritis	No	No	No	No
Pulmonary infiltrates	Yes	No	Yes	No
PE	No	Yes	No	No
DVT	No	No	No	No
Other	None	Periorbital oedema	Tubular interstitial nephritis	No
Rheumatological diagnosis	None	None	uSAID	Relapsing polychondritis
Haematological disease				
MDS	Yes	No	No	Yes
Myelofibrosis	No	No	No	No
MGUS/MM	No	No	No	No
Transfusion dependent	Yes	No	Yes	Yes
R-IPSS score	3	N/A	N/A	2.5
Laboratory findings				
Macrocytic anaemia	Yes	Yes	Yes	Yes
Thrombocytopenia	Yes	Yes	Yes	No
Neutropenia	No	No	No	No
Lymphopenia	No	Yes	Yes	No
Elevated CRP	Yes	Yes	Yes	Yes
Bone marrow vacuoles	Yes	Yes	Yes	No
Additional genetic aberrations (HTS and cytogenetics)	No	No	No	No
Treatment prior to HSCT				
Total number of previous treatments	4	3	6	1
Type	CS,TOC, Anakinra, BAR, Colchicine	CS, MTX, HCQ	CS, MTX, AZA, MMF, anakinra, TOC, BAR	CS
Complications	None	None	Severe injection site reaction to anakinra, infections (pneumonia, menigitis)	None
Allogeneic HSCT				
Age at transplant	51	67	61	62
Karnofsky performance scale (PS)	70	80	70	90
Seattle HCT-CI score	6	3	3	N/A
Comorbidities	Single kidney with CKD, Deranged liver function, type II diabetes (on oral hypoglycaemics)	TLCO 63%	Moderate pulmonary, mild hepatic impairment, obesity	Chondritis
Conditioning regiment	FLU/BU, Thiotepa	FLU/MEL/CAM	FLU/TREO/CAM	FLU/BU/ATG
Donor	Haplo (son)	MUD	Sibling	MUD
Graft origin	PBSC	PBSC	PBSC	PBSC
GVH prophylaxis	CYC, TAC, MMF	CSA	CAM, CSA & MMF	ATG/CSA
Infectious complications	Salmonella houtenae in blood cultures, pseudomonas in sputum	EBV reactivation	Bacterial, C difficile, SARS-CO-V2	No
Immune complications/ GVHD	N/A	HLH, aseptic encephalitis, GvHD	Metabolic acidosis peri-transplant, myelitis & optic neuropathy	Grade 1 GvHD
Day 100 Donor chimerism CD3	N/A	100%	99%	100 (whole blood)
Day 100 Donor chimerism CD15	N/A	100%	100%	100 (whole blood)
Duration of follow-up post HSCT	11 days	5 months	11 months	40 months
Alive	No	Yes	No	Yes
Cause of death	Sepsis, multiorgan failure, cardiac arrest	N/A	Infection	N/A
Event free survival (EFS)			11 months	40 months
Current status	Died	Karnofsky 40	Died	Alive in remission

ATG-Anti-thymocyte globulin; AZA-azathioprine; BAR-baricitinib; BU-busulfan; CAM-campath; CKD-chronic kidney disease; CRP-C reactive proteine; CS-cortcosteroids; CSA-ciclosporin; CYC-cyclophosphomide; EBV-Epstein-Barr virus; DVT-deep vein thromosis; FLU-fludarabine; GvHD- graft versus host disease; HCQ-hydroxychloroquine; HCT-CI-Hematopoietic cell transplantation-specific comorbidity index; HLH-hemophagocytic lymphohistiocytosis; HTS-High-throughput sequencing; MDS-myelodysplastic syndrome; MEL-melphalan; MGUS-monoclonal gammopathy of undetermined significance; MM-multiple myeloma; MMF-mycophenolate mofetil; MUD-matched unrelated donor; PBSC-Peripheral blood stem cell; SARS-CO-V2-Severe acute respiratory syndrome coronavirus 2; PE-pulmonary embolus; R-IPSS- Revised International Prognostic Scoring System; TAC-tacrolimus; TLCO-transfer factor for carbon monoxide; TOC-tocilizumab; TREO-treosulfan; uSAID-undiffentiated Systemic Autoinflammatory Disorder; VAF-Variant allele frequency

Table 2. Clinical characteristics of patient cohorts			
	Cohort 1 Ferrada et a (n=83)	Cohort 2 Georgin-Lavialle et al (n=116)	Cohort 3 Present study (n=44)
Demographics			
Age of disease onset, median (range)	66 (41-80)	67 (62.5-73)	57 (22-72)
Male sex n (%)	83 (100)	111 (95.7)	25 (58.1)
Clinical Diagnosis			
Relapsing polychondritis n (%)	43 (52)	N/A	0 (0)
Undifferentiated Fever Syndrome n (%)	19 (23)	N/A	0 (0)
Sweets syndrome	18 (22)	N/A	0 (0)
MDS	26 (31)	58 (50)	34 (79)
CMML	0 (0)	0 (0)	10 (4.3)
Clinical Manifestations n (%)			
Fever	69 (83)	75 (64.6)	0 (0)
Skin involvement	68 (82)	97 (83.6)	6 (13)
Arthritis	48 (58)	33 (28.4)	3 (7)
Pulmonary infiltrates	47 (57)	47 (40.5)	0 (0)
Ear chondritis	45 (54)	37 (31.9)	0 (0)
Unprovoked deep vein thromosis (DVT)	34 (41)	41 (35.3)	0 (0)
Nose chondritis	30 (36)	18 (15.5)	0 (0)
Periorbital edema	25 (30)	10 (8.6)	0 (0)
Hearing loss	24 (29)	N/A	3 (7)
Ocular inflammation	20 (24)	43 (37)	0 (0)
Pulmonary embolism	11 (13)	N/A	0 (0)
Pleural effusion	11 (13)	11 (9.5)	3 (7)
Orchitis	10 (12)	N/A	0 (0)
Airway chondritis	1 (2)	0 (0)	0 (0)
Hematologic Manifestations			
Macrocytic anemia n (%)	81 (97)	N/A	14 (32)
Thrombocytopenia n (%)	40 (83)	N/A	34 (77)
R-IPSS Score* n (%) (MDS patients only)			
Very low risk	9 (39)	N/A	1 (3)
Low risk	12 (52)	N/A	4 (12)
Intermediate risk	0 (0)	N/A	6 (18)
High risk	2 (4)	N/A	16 (47)
Very high risk	0 (0)	N/A	7 (20)
MDS-associated mutations	7/17 (41)	N/A	19/24 (79)

Cohorts 1 and 2, VEXAS patients decribed in Ferrada et all, and Georgin-Lavialle et all respectively. Cohort 3 patients from this study who were transplanted for Myelodysplastic syndrome (MDS) or Chronic myelomonocytic leukemia (CMML) and found not to have VEXAS. R-IPSS- Revised International Prognostic Scoring System

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SS, AK and JP, conceived and design the study; AA, DM, AMSR, SE, HE, CC, CJAD, MB, VB collected data; JA, AA and SS performed data analysis; SS wrote first draft of manuscript; All authors read, edited and approved manuscript. SS provided funding the study.

Conflict of interest
Authors have no conflict of interest to declare

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