VEXAS Syndrome: A Call for Diagnostic Awareness Based on a Case Series of Seven Patients

Síndrome VEXAS: Alerta para o Diagnóstico Baseado numa Série de Sete Casos em Portugal

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Dear Editor,

VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) is a recently described disease caused by somatic myeloid mutations in *UBA1*,[1] a gene with critical importance in ubiquitylation (the addition of ubiquitin residues to a protein in order to mark it for degradation by the proteosome). Patients, mostly male and middle-aged or older, present with multisystemic inflammatory clinical manifestations (recurrent fever, neutrophilic cutaneous and pulmonary infiltrates, chondritis, vasculitis, eye and ear, nose, and throat involvement). Hematologic findings are common: macrocytic anaemia, myelodysplasia, plasma cell dyscrasia,[2] vacuolization of myeloid and erythroid precursors in the bone marrow (BM) and thrombosis.[1] The true prevalence rate of VEXAS remains unknown, but mounting evidence suggests that it may be much more common than initially anticipated. The aim of this case series is to raise awareness to the importance of earlier diagnosis and treatment of this entity. All patients authorized the publication of their anonymous case reports. Approval by the Ethics Committee was not necessary since these clinical reports were not part of a study/trial.

We reviewed the clinical and laboratory features of seven patients with VEXAS syndrome (Table 1), with confirmed somatic mosaicism (i.e., the presence of two genetically distinct cell populations within an individual, resulting from postzygotic mutations cell populations with a different genotype, as a result of a post-zygotic mutational event) for variants in exon 3 of the *UBA1* gene (by Sanger sequencing), followed at our tertiary university hospital centre. All seven patients were male, with a median age of 74 years (range 68 - 84) at diagnosis, 72 at disease onset and with five years of symptomatic onset (range 0.5 - 6.0). One patient died due to infectious complications (p.Met41Leu variant). Corticosteroid dependence led to treatment escalation with tocilizumab (n = 3), with rapid and sustained clinical improvement that also allowed for corticosteroid dose reduction.

Table 1 – Demographic and clinical characteristics of patients with VEXAS

Current age (y)	Time since symptoms onset (y)	Inflammatory manifestations	Hematologic findings	Thrombotic findings	*UBA1* Variant*	Treatment	Outcome
68	2	Polyarthritis, recurrent exanthema	Macrocytosis without anaemia or cytopenia; MG IgG/Kappa/Lambda and IgG/Lambda	No symptoms	c.121A>C (p.Met41Leu)	CCT	Stable disease
74	6	Leucocytoclastic vasculitis, chondritis, episcleritis	MDS-MLD (IPSS-R 2.5) Macrocytic anaemia MGUS IgG/Kappa	DVT	c.121A>C (p.Met41Leu)	EPO	Remitting-remission of chronic CCT; On demand transfusions.
78	5	Neutrophilic dermatosis, panuveitis	MDS-SLD (IPSS-R 3) Macrocytic anaemia MG IgM/Kappa	No symptoms	c.121A>C (p.Met41Leu)	EPO CCT MTX	Died from infection
85	5	Migratory polyarthritis, oral aphthae, chondritis	Macrocytic anaemia (without BM study)	No symptoms	c.121A>C (p.Met41Leu)	CCT TCZ	Stable disease
74	0.5	Recurrent fever, chondritis, pulmonary infiltrates	Macrocytic anaemia (without BM study)	Recurring thrombophlebitis	c.121A>G (p.Met41Val)	CCT TCZ	Stable disease
78	6	Non-infectious retropharyngeal phlegmon, constitutional syndrome	MDS EB Type 2 (IPSS-R 6/7), t (9;22) (Vacuoles in myeloid precursors) Macrocytic anaemia MG IgG/Kappa	DVT	c.121A>G (p.Met41Val)	EPO CCT Imatinib	Stable disease; No transfusions needed.
74	3	Recurrent fever, orchitis, Sweet-like dermatosis, labyrinthitis, chondritis	MDS-MLD (IPSS-R 2.5) (Vacuoles in myeloid and erythroid precursors) Macrocytic anaemia	No symptoms	c.122C>T (p.Met41Thr)	CCT TCZ	Stable disease

BM: bone marrow; CCT: corticotherapy; DVT: deep venous thrombosis; EB: excess of blasts; EPO: erythropoietin; IPSS-R: Revised International Prognostic Scoring System; MDS: myelodysplastic syndrome; MG: monoclonal gammopathy; MGUS: monoclonal gammopathy of undetermined significance; MLD: multilineage dysplasia; MTX: methotrexate; SLD: single lineage dysplasia; TCZ: tocilizumab; (**UBA1* reference sequence: NM_003334.4).

VEXAS syndrome presents with debilitating and progressive inflammatory symptoms. Our patients' features are concordant with the most recent literature.[1,3,4] As an X-linked disease, it occurs predominantly in male patients, but has also been diagnosed in women,[5] with lower somatic variant frequencies. New techniques such as quantitative digital polymerase chain reaction may allow for diagnosis in cases of low-level mosaicism (< 20% of cells) which can be undetectable by conventional Sanger sequencing. Myeloid precursors with *UBA1* variants have a high risk of progression to myelodysplastic syndrome (MDS). It is still unclear if this is due to a survival advantage of mutated cells with subsequent clonal expansion or to a highly inflammatory altered microenvironment.[4] There are still no national or international guidelines for screening and treating patients with VEXAS. Patients are frequently steroid-dependent, and we have good results with tocilizumab add-on therapy.

Due to its complexity and heterogeneity, diagnostic awareness is of utmost importance, as patients may seek physicians working in different medical specialties before a diagnosis is established. Physicians should consider a diagnosis of VEXAS in patients aged 40 years or older presenting with inflammatory and/or thrombotic manifestations, particularly when found to have macrocytic anaemia/myelodysplasia.

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AUTHOR CONTRIBUTIONS

FRP, AL: Data collection and analysis. Drafting, critical review and approval of the manuscript.

DGO, MEO, RF: Critical review and approval of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

DGO has received payments from Novartis for attending meetings and/or travel.

RF has received consulting fees from GSK and AstraZeneca; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from GSK; individual payments from GSK, AstraZeneca and Abbie for the participation on a Data Safety Monitoring Board or Advisory Board.

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REFERENCES

1. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic mutations in UBA1 and severe adult-onset autoinflammatory disease. N Engl J Med. 2020;383:2628-38.
2. Obiorah IE, Patel BA, Groarke EM, Wang W, Trick M, Ombrello AK, et al. Benign and malignant hematologic manifestations in patients with VEXAS syndrome due to somatic mutations in UBA1. Blood Adv. 2021;5:3203-15.
3. Georgin-Lavialle S, Terrier B, Guedon AF, Heiblig M, Comont T, Lazaro E, et al. Further characterization of clinical and laboratory features in VEXAS syndrome: large-scale analysis of a multicentre case series of 116 French patients. Br J Dermatol. 2022;186:564-74.
4. Koster MJ, Kourelis T, Reichard KK, Kermani TA, Beck DB, Cardona DO, et al. Clinical heterogeneity of the VEXAS syndrome: a case series. Mayo Clin Proc. 2021;96:2653-9.
5. Barba T, Jamilloux Y, Durel CA, Bourbon E, Mestrallet F, Sujobert P, et al. VEXAS syndrome in a woman. Rheumatology. 2021;60:e402-3.

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