Further Characterization of Clinical and Laboratory Features in VEXAS Syndrome: Large-scale Analysis of a Multicentre Case Series of 116 French Patients

S. Georgin-Lavialle, B. Terrier, A.F. Guedon, M. Heiblig, T. Comont, E. Lazaro, V. Lacombe, L. Terriou, S. Ardois, J.-D. Bouaziz, et al.

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Further characterization of clinical and laboratory features occurring in VEXAS syndrome in a large scale analysis of multicenter case-series of 116 French patients

Sophie Georgin-Lavialle[1*], Benjamin Terrier[2*], Alexis F. Guedon[3], Mael Heiblig[4], Thibault Comont[5], Estibaliz Lazaro[6], Valentin Lacombe[7], Louis Terriou[8], Samuel Ardois[9], Jean-David Bouaziz[10], Alexis Mathian[11], Guillaume Le Guenno[12], Achille Aouba[13], Roderau Outh[14], Aurore Meyer[15], Murielle Roux-Sauvat[16], Mikael Ebbo[17], Lin Pierre Zhao[18], Adrien Bigot[19], Yvan Jamilloux[20], Vivien Guillotin[12], Edouard Flamarion[21], Patrick Henneton[22], Guillaume Vial[12], Vincent Jachiet[23], Julien Rossignol[24], Stephane Vinzio[25], Thierry Weitten[26], Julien Vinit[27], Christophe Deligny[28], Sebastien Humbert[29], Maxime Samson[30], Nadine Magy-Bertrand[29], Thomas Moulinet[31], Rim Bourguiba[1],Thomas Hanslik[32], Claude Bachmeyer[1], Marie Sebert[18], Marie Kostine[33], Boris Bienvenu[34], Pascal Biscay[35], Eric Liozon[36], Laurent Sailler[37], François Chasset[38], Alexandra Audemard-Verger[19], Eugenie Duroyon[39], Guillaume Sarrabay[40], Fabrice Borlot[41], Celine Dieval[42], Thomas Cluzeau[43], Paola Marianetti[44], Hervé Lobbes[12], Guilaine Boursier[40], Mathieu Gerfaud-Valentin[4], Juliette Jeannel[21], Amélie Servettaz[44], Sylvain Audia[30], Marion Larue[45], Basile Henriot[46], Benoit Faucher[17], Julie Graveleau[47], Benjamin de Sainte Marie[12], Joris Galland[48], Laurence Bouillet[25], Constantin Arnaud[37], Lionel Ades[18], Fabrice Carrat[3], Pierre Hirsch[49], Pierre Fenaux[18], Olivier Fain[23], Pierre Sujobert[29], Olivier Kosmider[39], Arsene Mekinian[23], French VEXAS group, and on behalf GFEV, GFM, CEREMAIA and MINHEMON.

[1]Sorbonne Université, AP-HP, Hôpital Tenon, service de médecine interne, CEREMAIA, F-75020, Paris, France

[2]University of Paris, AP-HP, Cochin Hospital, Department of Internal Medicine, F-75014, Paris, France.

[3]Sorbonne Université, Inserm, Institut Pierre-Louis d'Epidémiologie et de Santé Publique, Département de Santé Publique, Hôpital Saint-Antoine, APHP, Paris.

[4] University Hospital of Lyon, Hospices Civils de Lyon, Department of Haematology, Lyon, France.

[5]University Hospital of Toulouse, Department of Internal Medicine and Clinical Immunology, Toulouse, France.

[6]Department of Internal Medicine and Infectious Diseases, Hôpital Haut-Lévêque, Bordeaux, France

[7]Department of Internal Medicine, Angers University Hospital, Angers, France

[8]Department of Internal Medicine, Lille University Hospital, Lille, France

[9] Service de médecine interne, CHU de Rennes, Rennes, France

[10]Université de Paris, Service de dermatologie, Hôpital Saint Louis, APHP, INSERM U944, Paris, France.

[11]Assistance Publique–Hôpitaux de Paris, Groupement Hospitalier Pitié–Salpêtrière, French National Referral Center for Systemic Lupus Erythematosus, Antiphospholipid Antibody Syndrome and Other Autoimmune Disorders, Service de Médecine Interne 2, Institut E3M, Paris, France

[12]University Hospital Centre of Bordeaux, Saint Andre Hospital, Department of Internal Medicine and Clinical Immunology, F-33000 Bordeaux, France.

CHU de Clermont-Ferrand, Hôpital Estaing, service de médecine interne, Clermont-Ferrand, France

[13] Caen Université, Hôpital de Caen, Department of Internal Medicine, Caen, France

[14]Service de médecine interne et générale, Centre Hospitalier de Perpignan, Perpignan, France

[15]Service d'immunologie clinique et médecine interne, Nouvel Hôpital Civil, CHU Strasbourg

[16]GHND, Centre Hospitalier Pierre Oudot, 30 avenue du Médipôle, BP 40348, 38302 Bourgoin-Jallieu Cedex

[17]Aix Marseille Université, AP-HM, Hôpital de la Timone, Department of Internal Medicine, Marseille, France

[18]APHP, Hematology department, CHU of Saint Louis, Paris, France

[19]University of Tours, Tours, France, Department of Internal Medicine and Clinical

[20] University Hospital of Lyon, Hospices Civils de Lyon, Department of Internal Medicine and Clinical Immunology, Lyon, France.

[21]Université de Paris, Service de médecine interne, HEGP Paris, France.

[22]Service de Médecine Vasculaire, CHU Montpellier, 80 Av Augustin Fliche, Montpellier 34090

[23]Sorbonne Université, AP-HP, Hôpital Saint Antoine, service de médecine interne et Inflammation-Immunopathology-Biotherapy Department (DMU i3), F-75012, Paris, France

[24]Université de Paris, Service d'hématologie, Necker Enfants Malades, Paris, France.

[25]Univ. Grenoble Alpes, Inserm, U1036, CHU Grenoble Alpes, CEA, IRIG-BCI, 38000, Grenoble, France

[26] Service de médecine interne, Centre Hospitalier (CHICAS), GAP, France

[27] Service de médecine interne, Centre Hospitalier, Chalons, France

[28] Service de Rhumatologie - Médecine Interne 5D · CHU de Martinique - Hôpital P. Zobda-Quitman, France
[29]CHU de Besançon, Service de Médecine Interne, Besançon, France
[30]Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, Dijon, France
[31]Department of Internal Medicine and Clinical Immunology, Regional Competence Center for Systemic and Autoimmune Rare Diseases, Nancy University Hospital, UMR 7365, IMoPA, Lorraine University, CNRS, Vandoeuvre-lès-Nancy, France
[32]AP-HP, Hôpital Ambroise Paris, service de médecine interne, Paris, France
[33]Department of Rheumatology, Hôpital Haut-Lévesque, Bordeaux, France
[34] Hôpital Saint Joseph, service de médecine interne, Marseille, France
[35]Clinique Mutualiste Pessac Médecine Interne, Pessac, France
[36] Service de Médecine Interne, CHU Dupuytren, Limoges, France
[37] University Hospital of Toulouse, Department of Internal Medicine, Toulouse, France.
[38]Sorbonne Université, Hôpital Tenon, service de dermatologie et allergologie et Inflammation-Immunopathology-Biotherapy Department (DMU i3), F-75020, Paris, France
[39]Service d'Hématologie Biologique, DMU BioPhyGen GH AP-HP. Centre-University de Paris
[40]Laboratory of Rare and Autoinflammatory Genetic Diseases and Reference Centre for Autoinflammatory Diseases and Amyloidosis (CEREMAIA), CHU Montpellier, University of Montpellier, Montpellier, France
[41] Service de médecine Interne, CH Béziers, Béziers, France
[42] Service de médecine interne et hématologie, CH régional, Rochefort, France
[43]Hematology department, CHU of Nice, Cote d'Azur University, Nice, France
[44]CHU de REIMS, Service de médecine interne, maladies infectieuses, immunologie clinique
[45] APHP, Service de rhumatologie, Hôpital Henri Mondor, Créteil, France
[46] Service de médecine interne, Centre Hospitalier René Pleven, Dinan, France
[47]CHU de Nantes Hôtel Dieu, Service de Médecine Interne, Nantes, France
[48]Service de médecine interne, hôpital Fleyriat, Centre hospitalier Bourg-en-Bresse, France
[49]Sorbonne Université, AP-HP, Hôpital Saint Antoine, service d'hématologie biologique, F-75012, Paris, France

*: Both authors contributed equally to this work

VEXAS Collaborators

Limoges : Sylvain PALAT

Bordeaux : Emmanuel RIBEIRO, Pierre DUFFAU, Marie-Elise Truchetet

Paris Pitié : Julien Haroche, Zahir AMOURA, Micheline PHA, Miguel HIE

Lyon : Pascal Sève, Jean-Christophe Lega, Arnaud Hot, Thomas Barba, Cécile-Audrey Durel, Arthur Bert

Saint Antoine : Mehdi HAGE-SLEIMAN, Noémie Abisror, Amir Adedjouma, Maria Chauchard, Sébastien Riviere, Francois Delhommeau, Marjolaine Morgand, Delphine Gobert

Cochin: Marie Templé, Chloé Friedrich, Loria Zalmai, Didier Bouscary, Justine Decroocq, Jerome Tamburini, Lise Willems, Benedicte Deau Fisher, Luc Mouthon, Marguerite Vignon, Costedoat-Chalumeau

Necker: Olivier Hermine

HEGP : Adrien MICHON, Jean Benoit ARLET, Brigitte RANQUE

Saint Louis: Eve Zakine

HIA BEGIN: Care Weniko

Toulouse: Odile Beyne-Rouzy

Rennes : Antoinette Perlat, Clémence Saillard, Jean-Sébastien Allain

Trousseau: Irina Giurgea

Béziers: Eric Oziol

Nancy: Paul Decker, Roland Jaussaud, Fabien Pontille, Maud D'Aveni, Julien Broseus

Correspondence and reprint requests to:

Arsene Mekinian, MD, AP-HP, Hôpital Saint Antoine, service de medicine interne and Inflammation-Immunopathology-Biotherapy Department (DMU i3), F-75012, Paris, France, Phone: + (33) 1 49282387 Fax: + (33) 149282652. E-mail: arsene.mekinian @aphp.fr

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Abstract

Background. A new autoinflammatory syndrome related to somatic mutations of *UBA1* was recently described and called VEXAS syndrome.

Objective. To describe clinical characteristics, laboratory findings and outcomes of VEXAS syndrome.

Design. Case-series.

Setting. Patients referred to a French multicenter registry between November 2020 and May 2021.

Patients. 116 patients with VEXAS syndrome.

Measurements. Frequency and median of parameters and vital status, from diagnosis to the end of the follow-up.

Results. Main clinical features were skin lesions (83.5%), non-infectious fever (63.6%), weight loss (62%), lung involvement (49.6%), ocular symptoms (38.8%), relapsing chondritis (36.4%), venous thrombosis (34.7%), lymph nodes (33.9%), and arthralgia (27.3%). Hematological disease was present in 58 cases (50%), considered as myelodysplastic syndrome (MDS, n= 58) and monoclonal gammapathy of unknown significance (n=12).*UBA1* mutations included p.M41T (44.8%), p.M41V (30.2%), p.M41L (18.1%), and splice mutations (6.9%). After a median follow-up of 3.0 years, 18 patients died (15.5%), from infectious origin (n=9) and MDS progression (n=3). Unsupervised analysis identified 3 clusters: cluster 1 (47%) with mild-to-moderate disease; cluster 2 (16%) with underlying MDS and higher mortality rates; cluster 3 (37%) with constitutional manifestations, higher C-reactive protein levels and less frequent chondritis. Five-year probability of survival was 84.2% in cluster 1, 50.5 % in cluster 2, and 89.6% in cluster 3. *UBA1* p.Met41Leu mutation was associated with a better prognosis.

Conclusion. VEXAS syndrome displays a large spectrum of organ manifestations and shows different clinical and prognostic profiles. It also raises a potential impact of the identified *UBA1* mutation.

Introduction

A new autoinflammatory disease characterized by somatic mutation of the *UBA1* gene has been recently described in males and named “VEXAS syndrome”; an acronym for “Vacuoles, E1 Enzyme, X-linked, Autoinflammatory, Somatic syndrome” (1). *UBA1* encodes for the major E1 enzyme that initiates protein ubiquitination in the cell cytoplasm. *UBA1* is located on the X chromosome, and most patients displayed mutations at methionine-41 (p.Met41) in the original description (1). VEXAS syndrome occurs in adults presenting with fever, cytopenia, vacuoles in myeloid and erythroid progenitors, dysplastic bone marrow, neutrophilic dermatosis, pulmonary infiltrates, chondritis and/or vasculitis, and the disease frequently shows a treatment-refractory course with high mortality rates (2). Most of the initial 25 patients met clinical criteria for inflammatory disease such as relapsing polychondritis, Sweet's syndrome, polyarteritis nodosa or giant cell arteritis. Additionally, a study on relapsing polychondritis patients showed that *UBA1* somatic mutations were present in 7.6% (3). *UBA1* somatic mutations-related relapsing polychondritis presented an onset in the fifth decade or later and showed higher mortality rate compared to patients with relapsing polychondritis in the absence of *UBA1* mutation (3, 4). The treatment of VEXAS syndrome includes glucocorticoids, conventional Disease-modifying antirheumatic drugs (DMARDs) and biological-targeted drugs. A small case-series recently raised the potential benefit of JAK inhibitors in patients with VEXAS syndrome (5). More recently, VEXAS syndrome has been described in woman, all presenting an X acquired monosomy (6, 7). Large case-series of VEXAS syndrome, especially describing clinical phenotypes, prognosis and overall survival are still lacking.

Based on a French multicenter registry, we aimed to describe clinical presentation and laboratory features of VEXAS syndrome, determine clinical and prognostic phenotypes; analyze phenotype-genotype correlations, overall survival and factors associated with death.

Patients and Methods

Study design

A retrospective multicenter study was conducted in France between November, 2020 and May, 2021. All cases of VEXAS syndrome, defined as an autoinflammatory disease with the presence of *UBA1* somatic mutations on genetic sequencing were included. All French laboratories performing *UBA1* mutation at the time of the study beginning were asked to identify the *UBA1* mutated patients. Data were collected in a Redcap database by clinicians belonging to the French file for rare autoinflammatory/autoimmune diseases (FAI2R), French Vasculitis Study Group (GFEV), French group of myelodysplastic syndromes (GFM), national reference center for autoinflammatory diseases (CEREMAIA) and/or French group for immunohematological disorders (MINHEMON).

Data collection

Clinicians fulfilled a standardized electronic case report form including clinical and laboratory parameters, outcome and treatments. Clinical parameters included constitutional signs (fever, weight loss, fatigue), ocular, skin, joint, gastrointestinal, kidney, peripheral and central nervous system, lung and heart involvements, hepatomegaly, splenomegaly and lymph node enlargement, at diagnosis of first symptoms and the follow-up. Laboratory data included hemoglobin, lymphocytes, neutrophils, platelets, C-reactive protein levels, creatininemia, immunological screening (antinuclear antibodies, ANCA, rheumatoid factor), gammaglobulin levels and presence for monoclonal protein. Analysis of bone marrow, presence of vacuoles in the progenitors, karyotype and additional somatic mutations by NGS were also recorded when available. Diagnosis of myelodysplastic syndrome (MDS) was made according to WHO criteria. Treatments, especially the use of glucocorticoids, conventional DMARDs, targeted biological drugs, azacytidine, JAK inhibitors and allogeneic hematopoietic stem cell transplantation, were recorded during the follow-up. Death and cause of death were collected for each patient.

UBA1 mutation genetic screening

Genomic DNA extracted from bone marrow (n=50) or blood samples (n=66) were extracted and analyzed by Sanger sequencing (n=84) or next generation sequencing (n= 32) to detect mutations of *UBA1*.

Some case reports from this study have been previously reported (5-10).

Ethical considerations

This study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles and received approval from the Cochin Hospital Institutional Review Board (CLEP Decision N°: AAA-2021-08040).

Statistical analysis

Data are expressed as medians with interquartiles and numbers with frequencies. Qualitative variables and quantitative variables were compared using Fisher and Kruskal-Wallis tests, respectively.

In order to define homogeneous clusters, a Hierarchical Clustering on Principal Components (HCPC) was performed using FactoMineR (11). HCPC approach allows to combine the results from a factor analysis with the hierarchical and k-means clustering. First, we used clinical and laboratory variables from patients, listed in **Figure 1** to perform a factor analysis of mixed data (FAMD) on the individuals. Missing data were handled in the HCPC analysis by multiple imputation using the R "missMDA" version 1.18 (12). Then, we performed a hierarchical cluster analysis on the FAMD results using Euclidean distance and the Ward agglomerative method. The optimal number of clusters was the one with the higher relative loss of within-cluster inertia. Finally, we performed K-means clustering on the partition obtained from the hierarchical cluster analysis to get the final partitioning solution. Kaplan-Meier estimator were used to generate survival curves and to compute survival rates. Log-rank test were used to compare overall survival across the three clusters obtained with the HCPC approach, between MDS and non MDS patients and between different *UBA1* mutation types. The follow-up was considered from the first symptom consistent with VEXAS syndrome.

We used unadjusted logistic regression to obtain odds ratios (OR) and 95% confidence intervals (95% CI) (1) for risk factors associated with death, accounting for missing values using multiple imputations with the R “MICE” package (version 3.5.0). Two-sided testing was used, with $P < .05$ considered statistically significant. All analyses were performed using R software 3.6.0 version for Mac (Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical presentation and laboratory findings

One hundred and sixteen patients with VEXAS syndrome were included. Most patients were males (n=111; 96%), with a median age of 67.0 years [62.5, 73.0] at the onset of symptoms and 71.0 years [66.25, 76.0] at diagnosis of VEXAS syndrome.

Patients' clinical characteristics are detailed in **Table 1**. Main clinical features were skin lesions (n=97, 83.6%), non-infectious recurrent fever (n=75, 64.7%), weight loss (n=62, 54.5%), lung involvement (n=57; 49.1%), ocular symptoms (n=47, 40.5%), relapsing chondritis (n=42, 36.2%), unprovoked venous thrombosis (n=41, 35.3%), lymph node enlargement (n=40, 34.5%), and arthralgias (n=33, 28.4%), peripheral nervous system involvement (n=17, 14,7%) and gastrointestinal involvement (n=16, 14%).

Skin lesions were classified as neutrophilic dermatosis (n=46, 39.7%), with pathological confirmation in 22 cases, cutaneous vasculitis (n=30, 26%), with pathological confirmation in 14 cases. Other cutaneous features included erythematosus papules (n=25, 21.6%) and injection-site reactions (n=9, 7.8%). Lung involvement mainly consisted in pulmonary infiltrates (n=47, 40.5%) and pleural effusion (n=11, 9.5%). Ocular inflammation included uveitis (n=11, 9.5%), scleritis (n=10, 8.6%) and episcleritis (n=14, 12.1%), and periorbital oedema (n=10, 8.6%). Gastrointestinal involvement consisted in abdominal pain (n=10, 8.6%), chronic diarrhea (n=8, 6.9%), gastrointestinal bleeding (n=1); digestive perforation (n=1); and digestive stenosis (n=2).

Nine patients (all men with age of 79 years old (ranging from 55 to 83) displayed injection-site reactions. The injection-site reactions were neutrophilic dermatitis-like cutaneous lesions presenting as erythematous papules (n=5), and 4 had x lesions with vasculitis on skin biopsy. These subset of patients experience venous thrombosis (2 superficial and 2 profound), with 6 of them with monoclonal gammopathy.

Laboratory data are summarized in **Table 1**. Hematological disease was present in 58 cases (50%) and was considered by physicians as myelodysplastic syndrome in 58 (MDS, 50%) and monoclonal gammopathy of unknown significance in 12 patients (MGUS, 9.6%)(all MGUS patients have also a MDS). MDS subtypes included mainly MDS with ring sideroblasts (MDS-RS) (n=16) and MDS with multilineage dysplasia (n=10).

UBA1 somatic mutations included p.Met41Thr (c.122T>C) in 52 patients (44.8%), p.Met41Val (c.121A>G) in 35 (30.2%), p.Met41Leu (c.121A>C) in 21 (18.1%) and splice mutations in 8 (6.9%). Screening for additional somatic mutations by NGS was performed in 75 patients and

revealed associated somatic mutations in 18 cases (14.9%), mostly DNMT3A (n=11, 9.1%) and TET2 (n=6, 5.0%).

Comparison of VEXAS patients with and without associated MDS

In comparison to patients without MDS, VEXAS-MDS patients had more frequent non-infectious recurrent fever (76% vs 55%; p=0.02), gastrointestinal tract involvement (22.4% vs 5.2%; p=0.015), pulmonary infiltrates (53.6% vs. 29.3%; p=0.025) and arthralgia (39.7% vs 17.2%; p=0.009). VEXAS-MDS patients had lower platelets count, higher medullar blasts and more frequently received glucocorticoids (82.8% vs 65.5%; p=0.04) and azacytidine (**Table 2).** Overall survival rates did not differ between VEXAS-MDS and VEXAS without MDS, with a 5-year probability survival of 83.0% [95% CI 70.3; 97.9] and 76.3% [60.35; 96.54], respectively (log rank p= 0.90).

Therapeutic management and outcome

Therapeutic management of patients with VEXAS syndrome at the time of inclusion included glucocorticoids in 86 (74.1%), conventional DMARDs in 30 (18.2%) and biological targeted therapies in 49 cases (33.1%). Conventional DMARDs included methotrexate in 20 (17.2%), cyclophosphamide in 6 (5%) and mycophenolate mofetil in 4 (3.4%). Biological targeted therapies consisted in anti-IL-6R in 22 (19%), IL-1 receptor antagonists in 19 (16.4%), TNFα inhibitors in 8 (6.6%) and rituximab in 3 (2.5%) patients. JAK inhibitors and azacytidine were used in 15 (12.9%) and 14 (12.1%) cases, respectively. Glucocorticoid-dependency was noted in 53 (45.7%) patients, at a median prednisone dose of 20 mg/day [IQR 10; 30].

After a median follow-up of 3.0 years (1.64; 5.92) since the onset of VEXAS-related symptoms, 18 patients died (15.5%), from infectious origin in 9 cases (bacterial in 7 cases, COVID-19 in 2 cases), MDS progression in 3 cases, cardiovascular events in 2 cases and other cause in the remaining cases.

Factors associated with death were the presence of gastrointestinal involvement (OR 3.7 [95% CI 1.14; 12.19], p=0.028), lung infiltrates (OR 3.3 [95% CI 1.12; 10.12], p=0.03) and mediastinal lymph node enlargement (OR 7.73 [95% CI 2.47; 24.17], p<0.001).

Cluster analysis of VEXAS patients

To dissect potential heterogeneity in VEXAS syndrome, we performed an unsupervised hierarchical analysis and identified 3 clusters detailed in **Table 2 and Figure 1A-B**.

VEXAS patients in cluster 1 (n=54, 47%) had mild-to–moderate disease with fewer constitutional symptoms such as recurrent fever (32.7%) or weight loss (15.1%), and fewer lung involvement (31.5%), lymph node enlargement (20.4%) and unprovoked venous thrombosis (16.7%). Median neutrophils counts and C-reactive protein levels were lower in comparison in patients with other clusters. UBA1 p.M41Leu (c.121A>C) mutation was significantly more frequent in this cluster (29.6% vs 1.05% in cluster 2 and 7% in cluster 3, respectively; p=0.01). VEXAS patients in cluster 2 (n=19, 16%) had more relapsing chondritis (52.6%), gastrointestinal (36.8%) and heart (47.4%) involvement, and the presence of pulmonary infiltrates (68.4%). These patients had lower platelets count, with significantly more frequent MGUS (26.3%). MDS was noted in 68.4% of patients of this cluster, and infections were more frequent (47.4%).

Finally, cluster 3 (n=43, 37%) was characterized by older patients, more frequent weight loss (97.7%) and cutaneous vasculitis (38%), less frequent relapsing chondritis (20.9%), and higher median C-reactive protein levels.

Treatments received and prognosis differed between the three clusters. Patients in cluster 1 received significantly less frequent immunosuppressive drugs (35.2%), especially glucocorticoids (24.1%), and mortality rate was lower (11.5%). In contrast, patients in cluster 2 more frequently received azacytidine (31.6%) and had the highest mortality rates (36.8%).

Analysis of overall survival according to the 3 clusters (**Figure 2A**) showed an increased mortality rate of cluster 2. Five-year probability of survival in cluster 2 was 62.7 % (95% CI 41.3; 95.1) compared to 87.4% (74.9; 100.0] in cluster 1 (p=0.03 vs. cluster 2) and 93.1% (84.3; 100.0) in cluster 3 (p=0.04, vs. cluster 2). No difference was found between clusters 1 and 3 (log rank p=0.80).

VEXAS phenotype according to type of *UBA1* mutation

To assess phenotype-genotype correlations, we compared VEXAS patients according to the type of *UBA1* mutation (**Table 3**). Patients with *UBA1* p.Met41Leu had less frequent fever and lung involvement (19% and 9.5%, respectively). VEXAS patients with *UBA1* p.Met41Val mutation showed less frequent chondritis (14.3%), higher C-reactive protein levels and more frequent MDS (68.6%). *UBA1* p.Met41Leu was more frequent in patients with mild-to-moderate disease (cluster 1, 29.6%). Overall survival according to the 3 main *UBA1* mutations (**Figure 2B**) showed a better 5-year survival of patients with *UBA1* p.Met41Leu (100% [95% CI 100; 100]), compared to 76.7% (58.8; 100.00) for p.M41Val (p=0.04) and not different from

p.Met41Thr with 83.1% [70.5; 98.0] (p=0.1). No difference was found between p.Met41Val and p.Met41Thr (log rank p=0.50).

Discussion

From this French nationwide cohort of patients, we expand the clinical phenotype of VEXAS syndrome. In the princeps publication by Beck et al., main clinical features included fever (92%), chondritis (64%), pulmonary infiltrates (72%) and venous thromboembolism (44%), and the disease was restricted to males (1). A recent study on VEXAS in patients with criteria for relapsing polychondritis reported different frequencies of arthralgias (46%) and periorbital oedema (32%) in this particular subset of patients (3). In the present study, we add other clinical key features into the spectrum of VEXAS syndrome, such as lymph node enlargement, joint and gastrointestinal involvements. Joint involvement in VEXAS syndrome was reported in two cases, the first showing severe and refractory erosive joint involvement mimicking rheumatoid arthritis (9) and the second presenting with HLA-B27 spondyloarthritis (13). Finally, from our study the main clinical features of VEXAS patients remain recurrent fever (64.7%)(vs 72% in original description by Beck et *al*), skin lesions (83.6%)(vs 88%), lung infiltrates (49.1%)(vs 72%), unprovoked thrombosis (35.5%)(vs 44%), whereas we report new features such as arthralgia (28.4%), ocular involvement (40.5%) or lymph node enlargement (34.5%), expanding the previous clinical phenotype of VEXAS syndrome (1). In this study, the VEXAS syndrome in women was also confirmed, and thus the possibility of VEXAS syndrome should be thus considered independently from sex, even remain more prevalent in males. The potential selection bias should be important to consider when describing a cohort study, and we used several important French networks and the laboratories performing *UBA1* testing to avoid these errors.

We identified 3 clusters, including a MDS-related phenotype close to the original description showing recurrent fever, chondritis and venous thromboembolism. We add two other clinico-biological phenotypes, including one with mild-to-moderate disease and less fever, chondritis and thromboembolism, and one with more “inflammatory” profile characterized by cutaneous vasculitis lesions and relapsing profile. However, the clinical utility of this clustering has to be validated in external cohorts and the limited number of deaths restrict the definite conclusion about the risk of death according to the cluster.

We also analyzed potential phenotype-genotype association and observed that *UBA1* p.Met41Leu was associated with less “inflammatory” and mild-to-moderate phenotype possibly explaining a better overall prognosis. Given the absence of external validation and limited number of deaths, these data would have to be confirmed in other cohorts of VEXAS, but it could represent important data to adapt the therapeutic management and identify low-risk VEXAS patients.

Previous studies linked autoimmune/inflammatory features to MDS or chronic myelomonocytic leukemia, in particular recurrent fever or Crohn's-like disease associated to trisomy 8 (14, 15). Studies evaluated the frequency of *UBA1* somatic mutations in patients with MDS-related inflammatory disorders, showing a relatively low prevalence of VEXAS syndrome (16) [unpublished personal data]. Our study showed a similar rates of underlying MDS in VEXAS syndrome, ranging from 25% to 55% in previous reports (17). Interestingly, our study do not show any new association with other hematological malignancies. However, the screening for associated hematological malignancies, especially the accurate classification of MDS, would have to be analyzed in detail, including centralized review of bone marrow evaluation.

In accordance with other studies, VEXAS syndrome is a severe and life-threating disease with high mortality rates and a 5-year survival of 63% (5) (2). Majority of deaths are related to disease progression or treatment-related severe adverse events (1). Gastrointestinal involvement is considered as a potential severe life-threating condition, in particular in polyarteritis nodosa related or not to underlying MDS or CMML and in MDS-related Behcet's-like disease. Here, gastrointestinal involvement, lung infiltrates and mediastinal lymph node enlargement were significant risk factors associated with mortality. These data will probably contribute to the better stratify the management of patients with VEXAS syndrome.

Lastly, our study has some limitations, especially the retrospective design what is mainly explained by the very recent description of the disease, and the lack of homogenized clinical evaluation and therapeutical management related to the absence of yet available recommendations and treatment guidelines in such a "new" disease. Therefore, the efficacy of treatments could not be ascertained in the present study. The limited number of death also restrict the conclusions about the survivals according to the clusters and mutation status. Despite these limitations, this cohort provides new important insights into the clinical phenotypes and prognostic factors.

Overall, we expand the newly described VEXAS syndrome, and report different clinical phenotypes, especially according to the clinico-biological profiles and the type of *UBA1* mutation. Prospective studies will be required to confirm some data and determine the optimal management of VEXAS syndrome.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article.

Arsène Mekinian and Sophie Georgin-Lavialle had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of data analysis.

Study conception and design. French VEXAS group members designed the study, Sophie GEORGIN-LAVIALLE, Isabelle MELKI, Thibault COMONT, Louis TERRIOU,
Pierre FENAUX, Lionel ADES, Olivier FAIN, Alexandra AUDEMARD-VERGER, Mikael EBBO, Achille AOUBA, Philippe GUILPAIN, LAZARO Estibaliz , Yvan JAMILLOUX, Guillaume SARRABAY, Odile BEYNE-RAUZY, Alexander BELOT, Pierre SUJOBERT, Olivier KOSMIDER, Rim BOURGUIBA, Raphaël BORIE , Alexis MATHIAN, Laurent ARNAUD, Francois CHASSET, Jean-David BOUAZIZ, FAIN Olivier, Benjamin TERRIER, Arsene MEKINIAN.

Acquisition of data. All coauthors.

Analysis and interpretation of data. All coauthors.

Data availability: data are available from Arsene Mekinian and Sophie Georgin-Lavialle.

Table 1. Clinical characteristics of VEXAS syndrome patients (n=116).

Characteristics	All patients (n=116)
Male gender	111 (95.7)
Age at diagnosis (years)	71.00 [66.25, 76.00]
Weight loss	62 (54.5)
Fever	75 (64.7)
Chondritis	42 (36.2)
Auricular chondritis	37 (32.0)
Nasal chondritis	18 (15.5)
Skin lesions	97 (83.6)
Neutrophilic dermatitis	46 (39.7)
Vasculitis	30 (26)
Erythema nodosum	15 (12.5)
Urticaria	10 (8.6)
Erythematosus papules	25 (21.6)
Injection site reactions	9 (7.8)
Periorbital oedema	10 (8.6)
Gastrointestinal tract	16 (14.0)
Abdominal pain	10 (8.6)
Diarrhea	8 (6.9)
Gastrointestinal bleeding	1 (0.9)
Digestive perforation	1 (0.9)
Peripheral nervous system involvement	17 (14.7)
Sensory neuropathy	6 (5.2)
Multiple mononeuropathy	3 (2.6)
Ocular involvement	47 (40.5)
Uveitis	11 (9.5)
Scleritis	10 (8.6)
Episcleritis	14 (12.1)
Orbital mass	4 (3.4)
Heart involvement	13 (11.2)
Pericarditis	5 (4.3)
Myocarditis	3 (2.6)
Lung involvement	57 (49.1)
Pulmonary infiltrates	47 (40.5)
Pleural effusion	11 (9.5)
Arterial involvement	12 (10.3)
Aortitis	2 (1.7)
Aneurysms	4 (3.4)
Lymph node enlargement	40 (34.5)

Cervical	8 (6.9)
Axillary	3 (2.6)
Mediastinal (n; %)	16 (14.0)
Abdominal (n; %)	3 (2.6)
Inguinal (n; %)	3 (2.6)
Spleen / liver enlargements	16 (13.8) / 9 (7.8)
Kidney involvement	11 (9.5)
Unprovoked thrombosis	41 (35.3)
Arthralgias	33 (28.4)
Laboratory data	
Hemoglobin (g/dl)	10.10 [9.00, 11.50]
VGM	101 [94.08, 106.75]
Platelets (n/mm3)	204 [138.25, 260.25]
Leucocytes / mm3	4400 [2972 , 6222]
Neutrophils / mm3	2600 [1640 , 4185]
C-reactive protein (g/L)	61 [30.00, 128]

Data are medians with interquartile and number with frequencies.

Table 2. Cluster analysis of VEXAS syndrome and comparison of patients' characteristics among the three clusters.

Characteristics	Cluster 1 (n=54)	Cluster 2 (n=19)	Cluster 3 (n=43)	p
Sex Male (n; %	50 (92.6)	18 (94.7)	43 (100.0)	0.198
Age at diagnosis (years)(median [IQR])	70.00 [66.00, 74.00]	71.00 [69.00, 76.00]	73.00 [68.50, 78.50]	0.067
Fever	17 (32.7)	18 (94.7)	40 (93.0)	<0.001
Weight loss	8 (15.1)	15 (78.9)	42 (97.7)	<0.001
Fatigue	29 (55.8)	19 (100.0)	43 (100.0)	<0.001
Chondriti*s*	23 (42.6)	10 (52.6)	9 (20.9)	0.023
Auricular chondritis	21 (40.4)	10 (52.6)	6 (14.0)	0.003
Nasal chondritis	11 (21.2)	3 (15.8)	4 (9.3)	0.288
Skin lesions	42 (77.8)	17 (89.5)	38 (88.4)	0.282
Neutrophilic dermatitis	20 (37.7)	9 (47.4)	17 (39.5)	0.761
Vasculitis	11 (20.8)	8 (42.1)	11 (25.6)	0.191
Infusion site reactions	1 (1.9)	2 (10.5)	6 (14.0)	0.081
Periorbital inflammation	3 (5.7)	1 (5.3)	6 (14.0)	0.302
Gastrointestinal tract	4 (7.4)	7 (36.8)	5 (11.6)	0.005
Abdominal pain	2 (3.8)	5 (26.3)	3 (7.0)	0.011
Diarrhea	3 (5.8)	4 (21.1)	1 (2.3)	0.026
Digestive perforation	0 (0.0)	1 (5.3)	0 (0.0)	0.080
Ocular involvement	21 (38.9)	11 (57.9)	15 (34.9)	0.222
Uveitis	5 (9.6)	2 (10.5)	4 (9.3)	0.989
Scleritis (n ; %)	6 (11.5)	2 (10.5)	2 (4.7)	0.476
Episcleritis (n ; %)	4 (7.7)	5 (26.3)	5 (11.6)	0.105
Heart involvement	4 (7.4)	9 (47.4)	0 (0.0)	<0.001
Pericarditis	0 (0.0)	5 (26.3)	0 (0.0)	<0.001
Myocarditis	1 (1.9)	2 (10.5)	0 (0.0)	0.053
Lung involvement	17 (31.5)	14 (73.7)	26 (60.5)	0.001
Lymph nodes	11 (20.4)	9 (47.4)	20 (46.5)	0.012
Spleen enlargement	7 (14.0)	4 (22.2)	5 (12.2)	0.595
Kidney involvement	2 (3.7)	6 (31.6)	3 (7.0)	0.001
Unprovoked thrombosis	9 (16.7)	10 (52.6)	22 (51.2)	<0.001
Infections	8 (14.8)	9 (47.4)	8 (18.6)	0.010
Hemoglobin	10.50 [9.50, 11.80]	10.10 [8.95, 11.50]	9.90 [8.90, 10.90]	0.109
Platelets (n/mm3)	196.00 [136.00, 230.00]	147.00 [69.50, 197.00]	249.50 [169.75, 309.00]	<0.001
Neutrophils / mm3	1900.00 [1202.50, 2570.00]	2800.00 [1985.00, 3995.00]	3790.00 [2200.00, 4970.00]	0.001
C-reactive protein	41.00 [21.50, 82.00]	44.00 [26.50, 80.00]	133.00 [68.00, 190.00]	<0.001
MDS / MGUS	25 (46.3) /2 (3.7)	13 (68.4) /5 (26.3)	20 (46.5)/ 5 (11.6)	0.214/ 0.02
UBA1 somatic mutations p.Met41Thr (c.122T>C)				
p.Met41Val (c.121A>G)				
p.Met41Leu (c.121A>C)				
Splice mutations				

Relapse	2 (3.8)	3 (15.8)	4 (9.3)	0.232
Deaths	6 (11.5)	7 (36.8)	5 (11.6)	0.022
Steroid dependence	22 (42.3)	11 (57.9)	20 (46.5)	0.507
VEXAS therapy				0.050
No treatment	19 (35.2)*	0 (0.0)	7 (16.3)	
Steroids	13 (24.1)	9 (47.4)	16 (37.2)	
Azacytidin	5 (9.3)	6 (31.6)	3 (7.0)	0.016
Jak inhibitors	10 (18.5)	0 (0.0)	5 (11.6)	0.112

Data are medians with interquartile and number with frequencies.

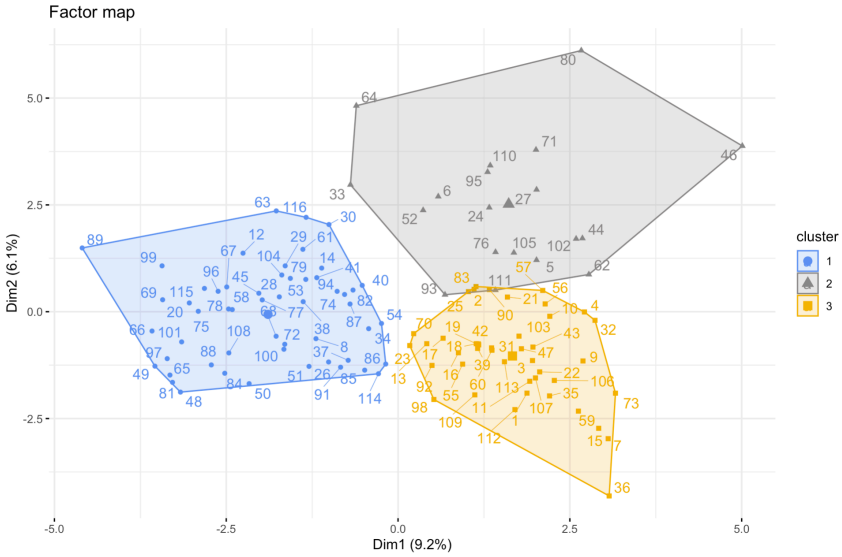
Table 3. Patients' characteristics according to the type of *UBA1* mutation.

Characteristics	Splice mutations (n=8)	UBA1 p.Met41Leu (c.121A>C) (n=21)	UBA1 p.Met41Thr (c.122T>C) (n=52)	UBA1 p.Met41Val (c.121A>G) (n=35)	p
Sex Male	8 (100.0)	19 (90.5)	51 (98.1)	33 (94.3)	0.452
Age at diagnosis	74.00 [68.00, 76.50]	68.00 [60.00, 72.00]	72.50 [68.75, 77.25]	70.50 [68.00, 74.75]	0.022
Fever	7 (87.5)	4 (19.0)	36 (70.6)	28 (82.4)	<0.001
Weight loss	5 (62.5)	9 (42.9)	28 (54.9)	23 (65.7)	0.396
Chondritis	5 (62.5)	11 (52.4)	21 (40.4)	5 (14.3)	0.006
Skin lesions	7 (87.5)	17 (81.0)	44 (84.6)	29 (82.9)	0.969
Gastrointestinal tract	3 (37.5)	1 (4.8)	6 (11.5)	6 (17.1)	0.123
Peripheral nervous system involvement	2 (25.0)	1 (4.8)	12 (23.1)	2 (5.7)	0.057
Ocular involvement	5 (62.5)	8 (38.1)	24 (46.2)	10 (28.6)	0.220
Heart involvement	2 (25.0)	1 (4.8)	7 (13.5)	3 (8.6)	0.405
Lung involvement	5 (62.5)	2 (9.5)	26 (50.0)	24 (68.6)	<0.001
Lymph nodes	4 (50.0)	3 (14.3)	22 (42.3)	11 (31.4)	0.102
Spleen enlargement	3 (37.5)	3 (14.3)	6 (12.2)	4 (12.9)	0.303
Unprovoked thrombosis	2 (25.0)	6 (28.6)	20 (38.5)	13 (37.1)	0.785
Arthralgias	4 (50.0)	9 (42.9)	10 (19.2)	10 (28.6)	0.105
Infections	4 (50.0)	2 (9.5)	12 (23.1)	7 (20.0)	0.125
Hemoglobin	9.90 [9.45, 10.75]	11.60 [10.05, 13.70]	10.20 [9.15, 11.53]	9.65 [9.00, 10.45]	0.019
VGM	107.45 [105, 113]	102.00 [95.25, 109.58]	100.75 [96, 106]	99.90 [91.42, 103]	0.084
Platelets (n/mm3)	129.00 [90.50, 178]	196.00 [162, 245]	206.00 [127.50, 254.50]	221.00 [149, 268]	0.388
Neutrophils / mm3	800.00 [460, 1180]	735.00 [402.50, 887.50]	910.00 [795, 1345]	1100.00 [650.00, 1327.50]	0.056
C-reactive protein	29 [19, 102]	45 [27.50, 60.50]	50 [29, 104]	131 [79.50, 162]	<0.001
MDS	5 (62.5)	7 (33.3)	22 (42.3)	24 (68.6)	0.031
Relapse	1 (12.5)	1 (4.8)	3 (6.0)	4 (11.4)	0.714
Deaths	1 (12.5)	0 (0.0)	9 (18.0)	8 (22.9)	0.139
Steroid dependence	3 (37.5)	11 (52.4)	24 (48.0)	15 (42.9)	0.853
Follow-up (months)	1.71 [1.02, 2.40]	2.93 [2.39, 6.99]	4.31 [2.26, 6.25]	2.22 [1.39, 4.64]	0.270
VEXAS therapy					0.051
No treatment	0 (0.0)	6 (28.6)	11 (21.2)	9 (25.7)	
Steroids	3 (37.5)	5 (23.8)	13 (25.0)	17 (48.6)	
DMARDs	0 (0.0)	4 (19.0)	8 (15.4)	0 (0.0)	
Biologics	5 (62.5)	6 (28.6)	20 (38.5)	9 (25.7)	

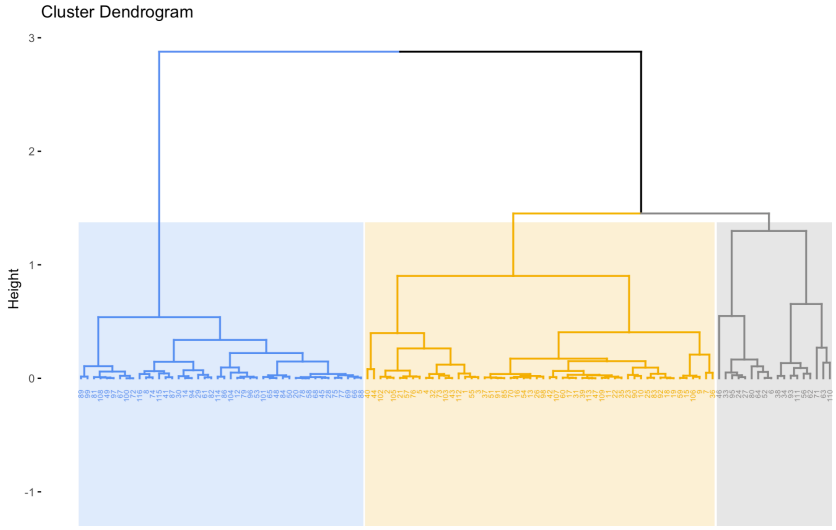
Data are medians with interquartile and number with frequencies.

Figure 1. Unsupervised analysis of VEXAS syndrome patients

(A)

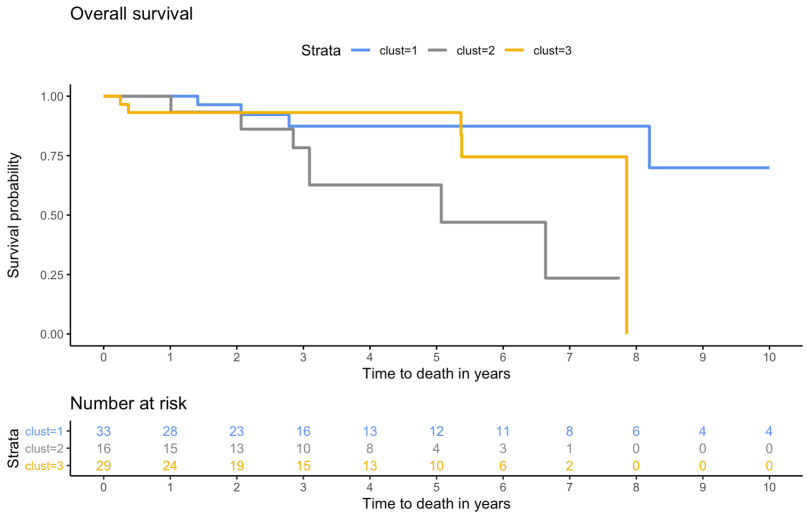


(B)



(A) The Hierarchical Clustering on Principal Components analysis of VEXAS syndrome patients showed 3 clusters (the variables included in the unsupervised analysis were age, male sex, weight loss, fever, chondritis, skin lesions, gastrointestinal, ocular, lung, arterial, kidney, peripheral and central nervous system involvements, venous thrombosis, acute myeloid leukemia, hemoglobin, neutrophils, lymphocytes, C-reactive protein, platelets levels, VGM, positivity of ANCA and antinuclear antibodies, presence of vasculitis, neutrophilic dermatosis, specific localization of myelodysplasia on skin biopsy, presence of MGUS, presence of blasts on bone marrow analysis). (B) Factor map showing the individuals used to generate the dendogram. The first 2 dimensions cumulatively explained 15.2% of the total variance.

(A)



(B)

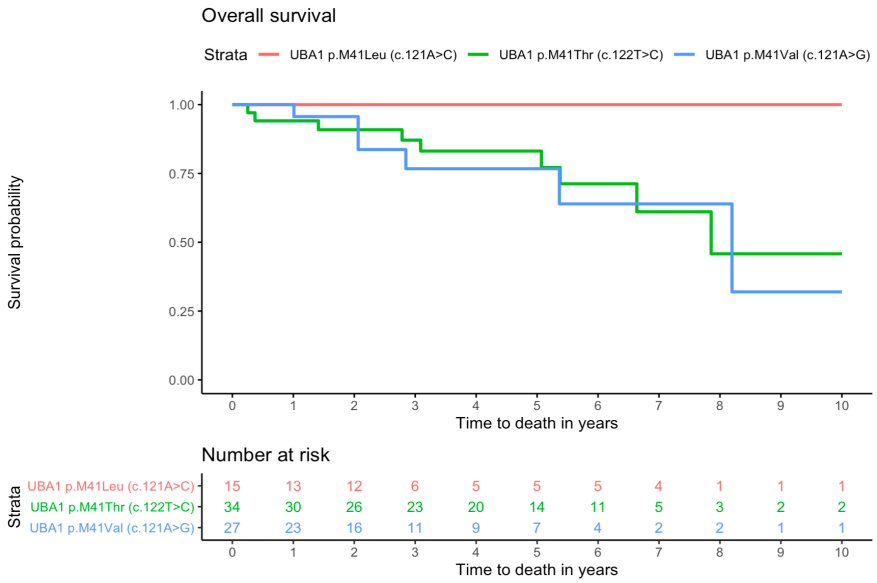


Figure 2. A: Overall survival according to the clusters of VEXAS syndrome (log rank test = 0.03); B: Overall survival according to the type of *UBA1* mutation (log rank p= 0.1).

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