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VEXAS syndrome and cancer: Insights about a possible "Tip of the Iceberg". Ambidirectional data from the international AIDA network registries

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ABSTRACT

Background: VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is an acquired autoinflammatory disorder characterized by severe chronic inflammation and an increased occurrence of hematologic neoplasms. Although chronic inflammation is a well-established risk factor for cancer, the specific contribution of *UBA1* gene mutations to tumorigenesis remains unclear. Therefore, this study aimed to evaluate the overall cancer risk in patients with VEXAS syndrome, including both hematologic and non-hematologic neoplasms.

Methods: The relative risk (RR) of cancer was compared between VEXAS patients and a control cohort comprising individuals with Still's disease, Behçet's disease, and Schnitzler's syndrome. Logistic regression analysis was performed to identify variables potentially associated with cancer development. Patient's data were drawn from the International AutoInflammatory Disease Alliance (AIDA) Network registries for VEXAS syndrome, Still's disease, Behçet's disease, and Schnitzler's syndrome.

Results: Ninety-six VEXAS patients and 2181 controls were enrolled. To minimize selection bias, only subjects aged >60 years were included, yielding 90 and 174 individuals in the exposed and control groups, respectively. The overall RR for cancer in VEXAS patients was 1.93 (95 % Confidence Interval [C.I.] 1.03-3.60, $p = 0.036$). Logistic regression analysis identified associations between cancer development and relapsing polychondritis (RR = 2.67, 95 %C.I. 1.22-10.64, $p = 0.01$), the p.Met41Thr mutation (RR = 3.33, 95 %C.I. 1.29-17.33, $p = 0.02$), elevated serum erythrocyte sedimentation rate (RR = 1.02, 95 %C.I. 1.01-1.05 $p = 0.01$), and lactate dehydrogenase (RR = 1.02, 95 %C.I. 1.01-1.07 $p = 0.04$) levels outside of flares.

Conclusions: VEXAS patients exhibit a significantly increased risk of both hematologic and non-hematologic malignancies compared with controls, particularly among those with RP, p.Met41Thr mutation, and persistent systemic inflammation.

Introduction

VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is an acquired autoinflammatory condition, recently described by Beck et al. [1] as associated with *UBA1* somatic mutations in hematopoietic precursors. Such mutations represent the molecular underpinning of severe systemic inflammation and are frequently associated with hematological disorders, especially myelodysplastic syndrome (MDS) and plasma cell neoplasm [2]. Additionally, more than half of VEXAS patients carry somatic mutations in genes associated with clonal hematopoiesis of indeterminate potential, which is associated with an increased risk of developing MDS and acute myeloid leukemia [2].

Chronic inflammation plays a major role in cancer development and has been estimated to contribute to up to 25 % of all malignancies [3]. Conversely, the NLRP3 inflammasome has been suggested to potentially exert protective effects against carcinogenesis through pyroptosis and other mechanisms [4], highlighting the complex and still unclear relationship between inflammation and cancer. Notably, inactivating mutations in the *UBA1* gene, encoding for the ubiquitin-activating enzyme (E) 1, lead to a decrease in ubiquitination, a type of post-translational protein modification involved in the regulation of various cellular mechanisms, that can ultimately result in systemic inflammation.

Although the correlation between VEXAS syndrome and hematologic malignancies is well described, it is still unclear the association between this disease and solid malignancies. Given its involvement in DNA damage response (DDR) mechanisms, growing evidence suggests a potential pro-oncogenic role of the *UBA1* gene, which was associated with

Table 1
Clinical and demographic data from the exposed group and the disease-specific control groups.

	VEXAS syndrome (n = 90)	Behçet's disease (n = 84)	Still's disease (n = 74)	Schnitzler's syndrome (n = 16)	*p*-value
Sex (n female/male)	5/85	50/34	35/39	7/9	<0.0001
Patient's age at last visit in years, mean ± SD	72.22 ± 11.39	66.73 ± 5.97	67.91 ± 6.63	71.25 ± 6.16	<0.0001
Disease duration at diagnosis in years, median (IQR)	3.2 (4.7)	2.1 (18.6)	0.2 (0.57)	3.25 (3.02)	0.0001
Body mass index, mean±SD	25.06 ± 2.93	25.71 ± 4.15	25.72 ± 5.06	26.57 ± 3.48	0.93
Diabetes	19/90 (21.1 %)	14/84 (16.7 %)	12/74 (16.2 %)	5/16 (31.3 %)	0.22
Smoking habit	20/90 (22.2 %)	19/84 (22.6 %)	15/74 (20.3 %)	4/16 (25 %)	0.34
Regular alcohol consumption	5/90 (5.6 %)	5/84 (5.9 %)	4/74 (5.4 %)	4/16 (25 %)	1
Neoplasms	• Prostate cancer (n = 7) • Bladder cancer (n = 2) • Melanoma (n = 1) • Carcinoma in situ of the skin (n = 1) • Colon cancer (n = 1) • Lung cancer (n = 1) • Ovarian cancer (n = 1) • Non-Hodgkin lymphoma (n = 1) • Multiple myeloma (n = 1) • Chronic lymphocytic leukemia (n = 1) • Myeloproliferative neoplasm (n = 1)	• Breast cancer (n = 2) • Carcinoma in situ of the skin (n = 1) • Bladder cancer (n = 1) • Pancreatic cancer (n = 1) • Myelogenous leukemia (n = 1)	• Breast cancer (n = 2) • Non-Hodgkin lymphoma (n = 2) • Ovarian cancer (n = 1) • Thyroid cancer (n = 1) • Prostate cancer (n = 1) • Carcinoma in situ of the skin (n = 1) • Chronic monocytic leukemia (n = 1)	• Skin cancer (n = 1) • Splenic lymphoma (n = 1) • Multiple myeloma (n = 1)	0.042

The exposed group included 90 patients with VEXAS syndrome, while the control group consisted of 84 patients with Behçet's disease, 74 with Still's disease and 16 with Schnitzler's syndrome, for a total of 174 individuals. The p-value for neoplasms was obtained using exact testing with the mid-P method. Abbreviations: N, number; SD, standard deviation; IQR, interquartile range.

various neoplasms, including lung cancer [5]. Therefore, the purpose of this study is to assess the cancer risk in patients diagnosed with VEXAS syndrome, based on real-world data gathered in the international AutoInflammatory Disease Alliance (AIDA) Network registry for VEXAS syndrome [6].

Materials and methods

Data related to VEXAS patients, including demographic, clinical and laboratory aspects, therapeutic information and malignancies history, were drawn from the international AIDA Network registry dedicated to VEXAS syndrome [6].

A control group was selected including patients affected by different inflammatory diseases such as Still's disease, representative of IL-1 mediated diseases, Behçet's disease, a condition with recognized involvement of adaptive immunity, and Schnitzler's syndrome, a prototype of multifactorial autoinflammatory disease. To minimize the selection bias, only patients aged 60 years or more were included in both study groups. Although the control diseases usually manifest at a younger age [7–10], the threshold of 60 years was also applied to the control group, as approximately 95 % of VEXAS patients fell within this age range. Data for these patients was obtained from the corresponding international AIDA Network registries [11–13]. The follow-up period ranged from the start of symptoms to the last visit collected in the AIDA Network registries (up to October 2025).

The main purpose of the study was to describe the frequency of malignant neoplasms in VEXAS patients and to compare the risk *versus* the control group. The secondary aims were: i) to assess any variable associated with the malignancy risk in the subgroup of VEXAS patients developing cancer; ii) to identify any subgroup of VEXAS patients potentially exposed to a greater cancer risk. The occurrence of malignancies, reported in the AIDA Network registries during the whole follow-up period according to the international classification of diseases, version 10 (ICD-10), accounted for the endpoint of the study. To avoid confirmation bias arising from an initial advantage to the VEXAS group, MDS, monoclonal gammopathy of undetermined significance, and smouldering myeloma were excluded from the neoplasms considered for the endpoint, as these disorders are known to be common in VEXAS syndrome.

Inclusion criteria for the VEXAS cohort required the presence of a pathogenetic or likely pathogenetic *UBA1* gene mutation, along with the onset of a systemic inflammatory condition not otherwise explained. Still's disease patients fulfilled the classification criteria proposed by Yamaguchi et al. [14] and/or Fautrel et al. [15]; Behçet's disease patients fulfilled the International Study Group criteria [16] and/or the International Criteria for Behçet's disease [17]; Schnitzler's syndrome patients fulfilled the Strasbourg criteria [18].

Patients included provided their informed consent to participate; the study protocol was conformed to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Siena, Italy in June 2019 (Ref. N. 14951).

Statistical analysis included descriptive statistics such as sample sizes, percentages, mean, standard deviation (SD), median, interquartile range (IQR), and frequency counts, as required. Episheet tool was used to calculate the relative risk (RR) for cancer development between study groups, along with the corresponding 95 % confidence interval (95 % C. I.), based on the absolute frequency of patients with cancer (cases) and the total number of observations in both patients with VEXAS syndrome (exposed group) and in the control group (unexposed group) [19]. A risk analysis adjusted for several cancer-related risk factors, including sex, patient age, disease duration, smoking habit, body mass index (BMI), regular alcohol consumption, and diabetes, was also performed.

Qualitative data were analyzed using Fisher's Exact test or Chi-squared test based on frequency counts. Quantitative data were analyzed using Student's t-test or Mann-Whitney U test, depending on data distribution assessed through the Shapiro-Wilk test.

Univariate binomial logistic regression was performed to identify variables potentially associated with cancer development in VEXAS patients. The $\beta 0$ and $\beta 1$ estimates were obtained from logistic regression with the exponential of $\beta 0$ corresponding to the odds of cancer development when the variable equals zero. The corresponding RR were also calculated using the inverse-logit function of $\beta 0+\beta 1$, divided by the inverse-logit function of $\beta 0$. Two-tailed statistical analyses were

Table 2
Clinical and demographic data of oncologic and non-oncologic VEXAS patients.

	Oncologic VEXAS patients (n = 18)	Non-oncologic VEXAS patients (n = 78)	*p*-value
Sex (n female/male)	1/17	4/74	1
Disease duration at the last assessment available in years, mean ± SD	5.04 ± 4.58	4.59 ± 3.98	0.85
Disease course (Chronic vs. relapsing-remitting)	9/18 (50 %)	36/78 (46.2 %)	1
Fever during flares (higher vs. lower than 40 °C)	2/12 (16.7 %)	3/53 (5.7 %)	0.49
Skin involvement	15/18 (83.3 %)	62/78 (79.5 %)	1
Ocular involvement	9/18 (50 %)	35/70 (50 %)	1
Arthritis	7/18 (38.9 %)	28/70 (40 %)	1
RP	9/18 (50.0 %)	17/78 (21.8 %)	0.02
Gut involvement	2/18 (11.1 %)	11/69 (15.9 %)	1
Neurological involvement	4/18 (22.2 %)	12/78 (15.4 %)	0.49
Vessel involvement	9/18 (50 %)	35/78 (44.9 %)	0.89
Pulmonary infiltrates	5/18 (27.8 %)	31/70 (44.3 %)	0.39
MDS	9/18 (50 %)	35/78 (44.9 %)	0.89
Vacuoles in bone marrow progenitors	7/14 (50 %)	30/47 (63.8 %)	0.54
Haemoglobin (g/dl) outside flares, mean ±SD	11.69 ± 2.01	11.78 ± 2.02	0.89
Anemia	16/18 (88.9 %)	65/69 (94.2 %)	0.59
Neutropenia	7/18 (38.9 %)	31/78 (39.7 %)	0.52
Lymphopenia	10/18 (55.6 %)	40/78 (51.3 %)	0.94
Monocytopenia	8/18 (44.4 %)	21/78 (26.9 %)	0.24
CRP (mg/dl) outside flares	2.4 (IQR: 14.02)	1.3 (IQR: 5.83)	0.27
ESR (mm/h) outside flares, mean ± SD	74.28 ± 42.36	35.36 ± 32.87	0.01
LDH (U/L) outside flares, mean ± SD	345.25 ± 48.93	215.5 ± 70.37	0.005
Maximum steroid dosage, mean ± SD	26.04 ± 11.56	21.94 ± 13.34	0.42
UBA1 mutation	• M41L (p. Met41Leu) 1/18 (5.6 %) • M41T (p. Met41Thr) 13/18 (72.2 %) • M41V (p. Met41Val) 3/18 (16.7 %) • Non-M41 1/18 (5.6 %)	• M41L (p. Met41Leu) 21/78 (26.9 %) • M41T (p. Met41Thr) 28/78 (35.9 %) • M41V (p. Met41Val) 18/78 (23.1 %) • Non-M41 11/78 (14.1 %)	• 0.17 (M41L) • 0.03 (M41T) • 0.72 (M41V) • 0.68 (Non-M41)

Disease course was defined as relapsing-remitting when distinct inflammatory flares were separated by periods of clinical remission, and as chronic when persistent inflammatory activity was present without remission. Abbreviations: CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LDH, lactate dehydrogenase; MDS, Myelodysplastic syndrome; n, number; RP, relapsing polychondritis SD, standard deviation.

conducted, with type I error set at 0.05 ($p < 0.05$), using RStudio software version 4.4.1.

Results

A total of 96 patients with VEXAS syndrome were enrolled, 90 of whom were at least 60 years old. The control group was sourced among 2181 patients deriving from the international AIDA registry dedicated to Behçet's disease (1346 patients), Still's disease (786 patients), and Schnitzler's syndrome (49 patients), among whom 174 patients (84 with Behçet's disease, 74 with Still's disease and 16 with Schnitzler's syndrome) were at least 60 years. Demographic and clinical data of both groups are summarized in Table 1. Global statistically significant differences reported in this table reflect the inherent clinical characteristics of the included conditions. VEXAS syndrome typically occurs in older male patients and is often diagnosed with delay due to its recent recognition as a distinct clinical entity. The statistical significance observed in relation to the number of neoplasms supports the evidence presented in this study, highlighting the higher frequency of neoplastic disorders in the VEXAS group.

Among the 96 VEXAS patients, 18 (18.8 %) developed malignancies, including prostate cancer (n = 7), bladder cancer (n = 2), melanoma (n = 1), carcinoma in situ of the skin (n = 1), colon cancer (n = 1), lung cancer (n = 1), ovarian cancer (n = 1), and hematological malignancies including non-Hodgkin lymphoma (n = 2), multiple myeloma (n = 1), chronic lymphocytic leukemia (n = 1), and myeloproliferative neoplasm (n = 1). One case (5.6 %) presented with malignancy (non-Hodgkin lymphoma) before the age of 60, and this patient was therefore excluded from the RR calculation. All neoplasms occurred before the VEXAS syndrome diagnosis; demographic and clinical data from these patients are shown in Table 2.

Seventeen (9.8 %) malignancies were identified in the control group as follows: 3 out of 16 (18.8 %) cases in patients with Schnitzler's syndrome, 8 out of 74 (10.8 %) in patients with Still's disease, and 6 out of 84 (7.1 %) in patients with Behçet's disease.

The RR of developing a malignant neoplasm was 1.93 (95 % C.I. 1.03-3.60, $p = 0.036$) in VEXAS patients compared with the control group. Fig. 1 provides the risk of developing cancer in VEXAS syndrome after adjusting for variables potentially representing confounding factors. The increased predisposition to cancer was provided as percentage of risk compared to the control group after adjusting for each confounding variable. **Supplementary Table 1** reports the RR obtained in the VEXAS cohort compared with the control group, stratifying patients according to potential confounding factors. Logistic regression analysis, aimed at identifying associations with cancer development in VEXAS syndrome, found an association between the occurrence of malignancy and a previous diagnosis of relapsing polychondritis (RP) (RR = 2.67, 95 % C.I. 1.22-10.64, $p = 0.01$), the presence of the M41T (p.Met41Thr) mutation (RR = 3.33, 95 % C.I. 1.29-17.33, $p = 0.02$), elevated serum erythrocyte sedimentation rate (ESR) (RR = 1.02, 95 % C.I. 1.01-1.05 $p = 0.01$), and lactate dehydrogenase (LDH) (RR = 1.02, 95 % C.I. 1.01-1.07 $p = 0.04$) levels outside of flares. Results from regression analysis with the corresponding interpretation, and values for non-significantly associated factors are shown in Table 3 and **Supplementary table 2**, respectively.

A further statistical analysis was performed to investigate variables potentially associated with cancer development in oncological VEXAS patients with RP compared with oncological VEXAS patients without RP. This analysis did not yield statistically significant associations, as presented in **Supplementary table 3**.

Discussion

Carcinogenesis is a complex, multistep process that begins with genomic damage caused by spontaneous or induced pro-oncogenic DNA mutations, ultimately leading to genomic instability and loss of proliferative and apoptotic control. Chronic inflammation can promote DNA damage through multiple pathways. In particular, nuclear factor kappa B (NF-κB) has been identified as a key link between intrinsic oncogenic signaling and extrinsic inflammatory stimuli, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) [20].

VEXAS syndrome is an autoinflammatory disorder characterized by persistent and intense inflammation both during and outside disease flares. Loss-of-function mutations in the *UBA1* gene may impair DDR mechanisms, thereby promoting the development of both hematologic and solid malignancies [21–23]. The NF-κB pathway may also upregulate activation-induced cytidine deaminase, an enzyme overexpressed in lymphoid malignancies and various solid tumors [24], as well as in MDS [25], a condition affecting more than half of VEXAS patients [2]. In this

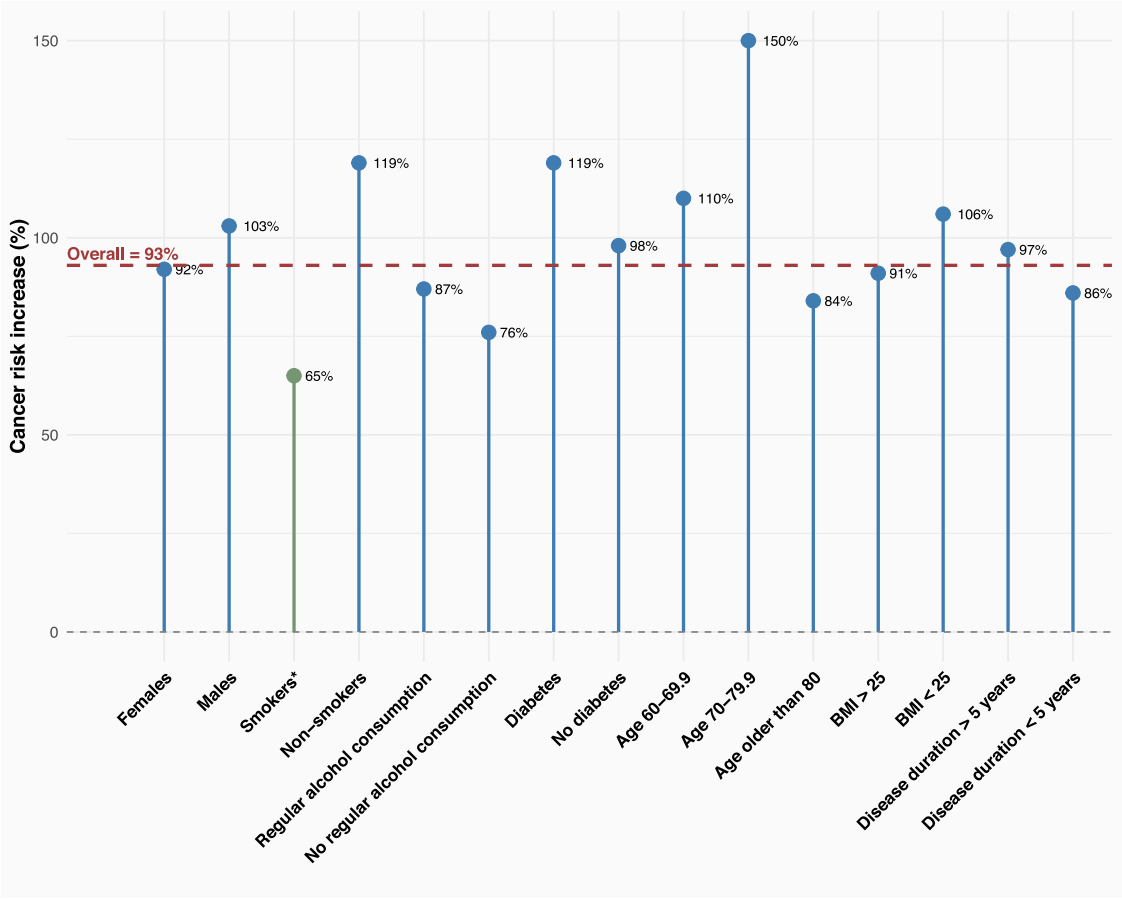

Fig. 1. Lollipop forest plot showing the increased risk of developing cancer in VEXAS patients, expressed as percentage, resulting from the comparison between VEXAS patients and the control group. Percentages of risk were calculated using the following formula: relative risk (RR) increase or decrease (%) = (RR − 1) × 100. The Overall line represents the global risk of cancer when not adjusting for possible confounding variables while the vertical lines represent the percentage of cancer risk increase when adjusting for the following variables specified in the x-axis: sex, smoking habit, alcohol consumption, diabetes, age, body mass index (BMI) and disease duration. *The adjustment for the variable "Smokers" did not reach statistical significance.

context, investigating the risk of cancer development in VEXAS syndrome could clarify how UBA1 dysfunction and chronic inflammation converge in carcinogenesis.

The present study firstly highlights a high frequency of neoplasms among VEXAS patients, comparable to that observed in Schnitzler's syndrome in terms of percentage, but higher than observed in Still's disease or Behçet's disease. Since Schnitzler's syndrome is also an autoinflammatory disorder often linked to hematologic conditions [26], this finding is particularly interesting.

As a whole, the RR of developing malignancies was significantly increased in VEXAS patients compared to the control group, reaching statistical significance both before and after most adjustments, as shown in Fig. 1. The overall cancer risk was estimated to be 93 %, rising to 119 % in patients with diabetes and 150 % in patients aged between 70 and 79.9 years. Interestingly, non-smoking patients exhibited a higher increase in cancer risk (up to 119 %), whereas the additional risk was attenuated in smokers, with an approximately 65 % higher risk that narrowly lost statistical significance. Given the general role of smoking in cancer risk [27], this observation confirms that tobacco use also acts as an effect modifier in VEXAS patients, as it can at least partially mask the impact of the underlying disease on malignancy development.

Chronic systemic inflammation may play a key role in the increased cancer risk observed in VEXAS patients. Notably, prostate cancer accounted for 38.9 % of all malignancies in this cohort, a finding probably influenced by the predominance of males in VEXAS syndrome. However, growing evidence also supports a role for chronic inflammation in the development and progression of prostate cancer [28,29], which may further explain the frequency of prostate neoplasm observed in this study. Supporting this notion, logistic regression analysis revealed a statistically significant association between the occurrence of neoplasms and ESR value, a classic marker of systemic inflammation.

Regarding the role of specific *UBA1* mutations, a statistically significant association was observed for the M41T mutation, which was associated with a 233 % increase in cancer risk. While no association was found for non-M41 variants and other M41 variants, future studies should evaluate whether cancer risk is related to UBA1 haploinsufficiency per se, specific effects of M41 versus non-M41 *UBA1* mutations, or the impact of specific variants.

In this cohort, an increased risk of cancer (up to 167 %) was observed in VEXAS patients with a previous diagnosis of RP. Notably, RP is not generally associated with an increased malignancy risk, apart from its recognized role as a paraneoplastic manifestation, especially for MDS and lymphoma [30,31], and an immune-related adverse event during immune checkpoint inhibitor therapy [32]. An exploratory subgroup analysis was performed on oncologic VEXAS patients to assess statistically significant differences according to the prior diagnosis of RP. As no differences were observed between these subgroups, it was not possible to identify variables capable of defining a higher malignancy risk among VEXAS patients with RP.

Notably, a potential protective effect against cancer has been proposed in the setting of innate immune dysregulation, as reported in familial Mediterranean fever, appearing associated with a reduced cancer RR, particularly when compared with a non-inflammatory condition [33]. Despite these premises, the putative protective role of

Table 3
Variables associated with cancer development in VEXAS patients.

	exp (β0) = Odds	RR	*p-value*	Interpretations
Relapsing polychondritis	Odds = 0.15, 95 % C. I. 0.073-0.297	2.67	0.019	A 167 % higher risk of developing cancer has been found in VEXAS patients with a previous diagnosis of relapsing polychondritis compared to the other VEXAS patients
M41T (p. Met41Thr) mutation	Odds = 0.10, 95 % C. I. 0.036-0.280	3.33	0.023	A 233 % higher risk of developing cancer has been found in patients with M41T (p.Met41Thr) mutation compared to all the other *UBA1* mutations
Increased ESR (mm/h) out of flares	Odds = 0.048 95 % C. I. 0.010-0.228	1.02	0.013	The risk of developing cancer increases by 2 % per unit of ESR
Increased LDH (U/L) out of flares	Odds = 6×10^{-5} 95 % C. I. 5×10^{-9}-0.7	1.02	0.047	The risk of developing cancer increases by 2 % per unit of LDH

Statistically significant associations obtained from univariate binomial logistic regression aimed at identifying variables associated with malignancy in VEXAS patients. The relative risks (RRs) were calculated as the inverse-logit function of (β0+β1) divided by the inverse-logit function of β0, and the corresponding explanations were also provided. Abbreviations; 95 % C.I., 95 % confidence interval; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; RR, relative risk.

inflammation in some autoinflammatory disorders seems to be markedly attenuated in VEXAS syndrome, where persistent inflammation may instead exert a pro-oncogenic influence. In this context, given that most neoplasms arise from somatic mutations [34], a feature shared with VEXAS syndrome, and considering that chronic inflammation is a well-established driver of DNA damage, it is plausible that *UBA1* mutations may occur earlier in life in VEXAS patients, thereby contributing to carcinogenesis via defective DDR mechanisms [21]. Should this hypothesis hold true, the classical inflammatory phenotype of VEXAS would represent the culmination of a long-standing subclinical process that began years before clinical manifestation, ultimately facilitating oncogenesis.

Alternatively, *UBA1* mutations might develop as a secondary phenomenon, emerging as a consequence of a genomic instability induced by the malignancy itself, one of the canonical hallmarks of cancer. Regarding this, *UBA1* screening is typically performed only after the overt onset of VEXAS syndrome; if this latter scenario were accurate, VEXAS syndrome might therefore embody a pro-oncologic status in which the clinical phenotype represents the “tip of the iceberg”. In this context, the increased cancer RR observed in VEXAS patients presenting with RP, a condition frequently described as paraneoplastic, could provide indirect support for this interpretation.

Study limitations include the relatively small number of enrolled VEXAS patients. Similarly, the control group may appear heterogeneous when considering some demographic characteristics. This aspect refers to the later age at onset and the shorter disease duration generally observed in VEXAS syndrome compared with the control group diseases. Nevertheless, potential confounding effects of age, sex, and disease duration were ruled out by specifically adjusting the risk analysis for these variables. In addition, the control group accounted exclusively for patients diagnosed with autoinflammatory diseases rather than individuals from the general population. This choice may have introduced residual confounding, as the cancer risk associated with autoinflammatory conditions is not yet fully defined when compared with the general population.

Variability in cancer screening strategies across different clinical centers and ethnic groups might have influenced malignancy detection rates and should be taken into account when interpreting these results. Lastly, univariate regression analyses were exploratory in nature, and their results should therefore be interpreted accordingly.

Conclusion

In conclusion, VEXAS syndrome represents a condition associated with an increased risk of cancer when compared to other autoinflammatory diseases. This risk appears particularly pronounced in patients with RP, the p.Met41Thr mutation, and elevated ESR and LDH levels. These findings may not merely reflect a heightened susceptibility to malignancies, but could suggest that VEXAS is a pro-oncogenic condition that precedes the clinical inflammatory phenotype, may complicate with neoplasms and therefore culminates in the overt syndrome.

Author contributions

All the authors substantially contributed to the conception or design of the work, the acquisition and interpretation of data and critically revised the paper. All the authors approved the final version and agreed to be responsible for all the aspects of the work. In addition, FG and AV wrote the first draft of the manuscript and performed the preliminary data analysis and interpretation; VC, JS, MF, FC, IC, AHA, EMN, GAGB, JTR, EWS, PS, SR, MS, SB, JHR, VGC, OA, AA, HAMG, AGG, FP, GL, OV, AT, BK, FM, PH, MB, TP, ADP, LD, AT, CC, SB, AM, GRI, ASP, MP, AC, AF, FC, CC, IZ, PT, CG, RV, MP, VR, FS, RT, AMJ, JJAS, AR, MB, AS, AB, VS, EF, BF, CF, LC, AV were involved in the study according to their active role in enrolling patients in the International AIDA Network Registries; AB, is also the bioengineer involved in the technical management of the platform and registries; LC took care of the final revision of the manuscript and accounted for AIDA Registries Coordinator.

Ethics approval and consent to participate

The Ethics Committee of Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to the corresponding author: Luca Cantarini, MD, PhD, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, Department of Medical Sciences, Surgery and Neurosciences, University of Siena. cantariniluca@hotmail.com

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2026.152932.

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(27):2628–38. https://doi.org/10.1056/NEJMoa2026834.

[2] Heiblig M, Patel B, Jamilloux Y. VEXAS syndrome, a new kid on the block of auto-inflammatory diseases: a hematologist's point of view. Best Pract Res Clin Rheumatol 2023;37(1):101861. https://doi.org/10.1016/j.berh.2023.101861.

[3] Liu X, Yin L, Shen S, Hou Y. Inflammation and cancer: paradoxical roles in tumorigenesis and implications in immunotherapies. Genes Dis 2021;10(1):151–64. https://doi.org/10.1016/j.gendis.2021.09.006.

[4] Jalali AM, Mitchell KJ, Pompoco C, Poludasu S, Tran S, Ramana KV. Therapeutic significance of NLRP3 inflammasome in cancer: friend or foe? Int J Mol Sci 2024;25(24):13689. https://doi.org/10.3390/ijms252413689.

[5] Sakuma M, Haferlach T, Walter W. UBA1 dysfunction in VEXAS and cancer. Oncotarget 2024;15:644–58. https://doi.org/10.18632/oncotarget.28646.

[6] Vitale A, Caggiano V, Della Casa F, Hernández-Rodríguez J, Frassi M, Monti S, et al. Development and implementation of the AIDA international registry for patients with VEXAS syndrome. Front Med (Lausanne) 2022;9:926500. https://doi.org/10.3389/fmed.2022.926500.

[7] 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(3):564–74. https://doi.org/10.1111/bjd.20805.

[8] Vitale A, Leone F, Caggiano V, Hinojosa-Azaola A, Martín-Nares E, Guaracha-Basañez GA, et al. Efficacy and safety of conventional disease-modifying antirheumatic drugs in VEXAS syndrome: real-world data from the international AIDA network. Front Pharmacol 2025;16:1539756. https://doi.org/10.3389/fphar.2025.1539756.

[9] Braud A, Lipsker D. Schnitzler syndrome: insights into its pathogenesis, clinical manifestations, and current management. Biomolecules 2024;14(6):646. https://doi.org/10.3390/biom14060646.

[10] Vitale A, Caggiano V, Tufan A, Ragab G, Batu ED, Portincasa P, et al. Risk for cancer development in familial Mediterranean fever and associated predisposing factors: an ambidirectional cohort study from the international AIDA network registries. Front Immunol 2024;15:1397890. https://doi.org/10.3389/fimmu.2024.1397890.

[11] Vitale A, Della Casa F, Lopalco G, Pereira RM, Ruscitti P, Giacomelli R, et al. Development and Implementation of the AIDA international registry for patients with still's disease. Front Med (Lausanne) 2022;9:878797. https://doi.org/10.3389/fmed.2022.878797.

[12] Vitale A, Della Casa F, Ragab G, Almaghlouth IA, Lopalco G, Pereira RM, et al. Autoinflammatory diseases alliance (AIDA) network. development and implementation of the AIDA international registry for patients with Behçet's disease. Intern Emerg Med 2022;17(7):1977–86. https://doi.org/10.1007/s11739-022-03038-1.

[13] Sota J, Vitale A, Więsik-Szewczyk E, Frassi M, Lopalco G, Emmi G, et al. Development and implementation of the AIDA international registry for patients with Schnitzler's syndrome. Front Med (Lausanne) 2022;9:931189. https://doi.org/10.3389/fmed.2022.931189.

[14] Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19(3):424–30.

[15] Fautrel B, Zing E, Golmard JL, Le Moel G, Bissery A, Rioux C, et al. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore) 2002;81(3):194–200. https://doi.org/10.1097/00005792-200205000-00003.

[16] Criteria for diagnosis of Behçet's disease. international study group for Behçet's disease. Lancet 1990;335(8697):1078–80.

[17] International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). The International criteria for Behçet's disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28(3):338–47. https://doi.org/10.1111/jdv.12107.

[18] Simon A, Asli B, Braun-Falco M, De Koning H, Fermand JP, Grattan C, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. Allergy 2013;68(5):562–8. https://doi.org/10.1111/all.12129.

[19] Rothman K. Episheet. Available online at: https://www.rtihs.org/sites/default/files/2022-04/Episheet.xls; 2015.

[20] Mao H, Zhao X, Sun SC. NF-κB in inflammation and cancer. Cell Mol Immunol 2025;22(8):811–39. https://doi.org/10.1038/s41423-025-01310-w.

[21] Moudry P, Lukas C, Macurek L, Hanzlikova H, Hodny Z, Lukas J, et al. Ubiquitin-activating enzyme UBA1 is required for cellular response to DNA damage. Cell Cycle 2012;11(8):1573–82. https://doi.org/10.4161/cc.19978.

[22] Zhang T, Joubert P, Ansari-Pour N, Zhao W, Hoang PH, Lokanga R, et al. Genomic and evolutionary classification of lung cancer in never smokers. Nat Genet 2021;53(9):1348–59. https://doi.org/10.1038/s41588-021-00920-0.

[23] 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(16):3203–15. https://doi.org/10.1182/bloodadvances.2021004976.

[24] Rios LAS, Cloete B, Mowla S. Activation-induced cytidine deaminase: in sickness and in health. J Cancer Res Clin Oncol 2020;146(11):2721–30. https://doi.org/10.1007/s00432-020-03348-x.

[25] Torun ES, Dağlar Aday A, Nalçacı M. Activation-induced cytidine deaminase expression in patients with myelodysplastic syndrome and its relationship with prognosis and treatment. Turk J Med Sci 2021;51(5):2451–60. https://doi.org/10.3906/sag-2101-81.

[26] Sokumbi O, Drage LA, Peters MS. Clinical and histopathologic review of Schnitzler syndrome: the mayo clinic experience (1972-2011). J Am Acad Dermatol 2012;67(6):1289–95. https://doi.org/10.1016/j.jaad.2012.04.027.

[27] Sharma R, Rakshit B. Global burden of cancers attributable to tobacco smoking, 1990-2019: an ecological study. EPMA J 2022;14(1):167–82. https://doi.org/10.1007/s13167-022-00308-y.

[28] Schillaci O, Scimeca M, Trivigno D, Chiaravalloti A, Facchetti S, Anemona L, et al. Prostate cancer and inflammation: a new molecular imaging challenge in the era of personalized medicine. Nucl Med Biol 2019;68-9:66–79. https://doi.org/10.1016/j.nucmedbio.2019.01.003.

[29] Rani A, Dasgupta P, Murphy JJ. Prostate cancer: the role of inflammation and Chemokines. Am J Pathol 2019;189(11):2119–37. https://doi.org/10.1016/j.ajpath.2019.07.007.

[30] Dion J, Costedoat-Chalumeau N, Sène D, Cohen-Bittan J, Leroux G, Dion C, et al. Relapsing polychondritis can be characterized by three different clinical phenotypes: analysis of a recent series of 142 patients. Arthritis Rheumatol 2016;68(12):2992–3001. https://doi.org/10.1002/art.39790.

[31] Yanagi T, Matsumura T, Kamekura R, Sasaki N, Hashino S. Relapsing polychondritis and malignant lymphoma: is polychondritis paraneoplastic? Arch Dermatol 2007;143(1):89–90. https://doi.org/10.1001/archderm.143.1.89.

[32] Mertz P, Costedoat-Chalumeau N, Ferrada MA, Moulis G, Mekinian A, Grayson PC, et al. Relapsing polychondritis: clinical updates and new differential diagnoses. Nat Rev Rheumatol 2024;20(6):347–60. https://doi.org/10.1038/s41584-024-01113-9.

[33] Vitale A, Caggiano V, Tufan A, Ragab G, Batu ED, Portincasa P, et al. Risk for cancer development in familial Mediterranean fever and associated predisposing factors: an ambidirectional cohort study from the international AIDA network registries. Front Immunol 2024;15:1397890. https://doi.org/10.3389/fimmu.2024.1397890.

[34] Luzzatto L. Somatic mutations in cancer development. Environ Health. 2011;10(Suppl 1):S12. https://doi.org/10.1186/1476-069X-10-S1-S12. Suppl 1.