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VEXAS syndrome.

Síndrome VEXAS

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Abstract

VEXAS syndrome is a novel entity, its name is an acronym based upon key features of the syndrome: Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic. It is a monogenic disease of adulthood, clinically observed as an auto-inflammatory disease with rheumatologic and hematologic manifestations. Up to 50% of patients present with an associated hematological malignancy or pre-malignant disorder. There is no standard treatment and outcomes are often fatal, with a median overall survival of 5 years.

KEYWORDS: VEXAS syndrome; Vacuoles; Polychondritis; Vasculitis; Thrombosis; Cytopenias.

Resumen

El síndrome VEXAS es una afección novedosa, su nombre es un acrónimo basado en las características clave del síndrome: vacuolas, enzima E1, ligado al cromosoma X, autoinflamatorio, somático. Es una enfermedad monogénica de la edad adulta, clínicamente observada como una enfermedad autoinflamatoria con manifestaciones reumatológicas y hematológicas. Hasta el 50% de los pacientes tiene una neoplasia hematológica asociada o un trastorno premaligno. No existe un tratamiento estándar y los resultados suelen ser fatales, con mediana de supervivencia general de 5 años.

PALABRAS CLAVE: Síndrome VEXAS; vacuolas; policondritis; vasculitis; trombosis; citopenias.

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BACKGROUND

VEXAS syndrome is a recently described entity, characterized by a highly inflammatory state and a predisposition to hematological malignancy. Is an acronym based upon key features of the syndrome: Vacuoles, E1 enzyme, X-linked, Auto-inflammatory, Somatic. It is a monogenic disease of adulthood caused by a somatic mutation in UBA1 in hematopoietic progenitor cells. E1 enzyme refers to the ubiquitin activating enzyme encoded by UBA1, which is an X-linked gene.[1]

This entity was first described in 2020 in 25 men.[1] VEXAS is a severe and progressive disease with a range of rheumatologic and hematologic conditions. It is characterized by a usually treatment-refractory inflammatory syndrome that develops in late adulthood, with fevers and symptoms that meet clinical criteria for rheumatologic disorders such as relapsing polychondritis, vasculitis, Sweet's syndrome and pulmonary inflammation. Individuals with this disorder also present macrocytic anemia, some with transfusion dependence and a high reported rate of thrombosis. Characteristic vacuoles can be present in myeloid and erythroid precursor cells; and approximately half of the patients have an associated hematological malignancy or pre-malignant disorder, mainly myelodysplastic syndrome, plasma cell dyscrasias, monoclonal B cell lymphocytosis; and an often-fatal outcome.[1,2]

SYSTEMIC MANIFESTATIONS

VEXAS is a progressive disease that affects multiple organs (**Figure 1**). Recurrent fever is the most frequently observed constitutional symptom. Other non-specific manifestations such as fatigue, night sweats and non-intentional weight loss are also commonly present.[3]

In the initial NIH cohort, 64% of patients had evidence of auricular or nasal chondritis. Also, 60% met diagnostic criteria for relapsing polychondritis.[1] Patients with VEXAS and features of relapsing polychondritis more often had fever, periorbital edema, skin involvement and higher inflammatory markers at diagnosis (median erythrocyte sedimentation rate 66.5 mm/h *vs* 11 mm/h).[4] Interestingly, none of the patients within the original cohort presented with tracheobronchial involvement. However, a later series have identified at least 4 cases with airway involvement.[4] On the other hand, the frequency of pulmonary parenchymal abnormalities ranges from 20% to 70% among reported series, and the more frequent radiographic findings are ground glass opacities, cryptogenic organizing pneumonia and bronchiolitis obliterans. Symptoms can be as mild as cough and dyspnea to more severe with mechanical ventilation requirement.[4]

Arthritis has been described in 40% of patients with VEXAS, affecting more commonly the ankles, knees, and wrists compared to the small joints of the hands and feet.[3]

Autoimmune serologies have been noted, with anti–nuclear antigen being seen in 16% of patients and low-level rheumatoid factor and positive anti–citrullinated protein antibodies in 30%. Lupus anticoagulant has been detected in 48% to 54% of patients.[5]

Vasculitis has been described in ~ 50% of cases, specially affecting the skin as histologically confirmed leukocytoclastic vasculitis.[6] Medium-vessel vasculitis has also been reported. In fact, some patients meet criteria for polyarteritis nodosa.[5,6] However, individuals with VEXAS syndrome did not have mesenteric vasculitis or mono-neuritis multiplex compared with those with idiopathic polyarteritis nodosa.[4]

Large and variable-vessel vasculitis appears to be less frequent, with only a few cases reported, including one that fulfilled diagnostic criteria for giant cell arteritis.[7]

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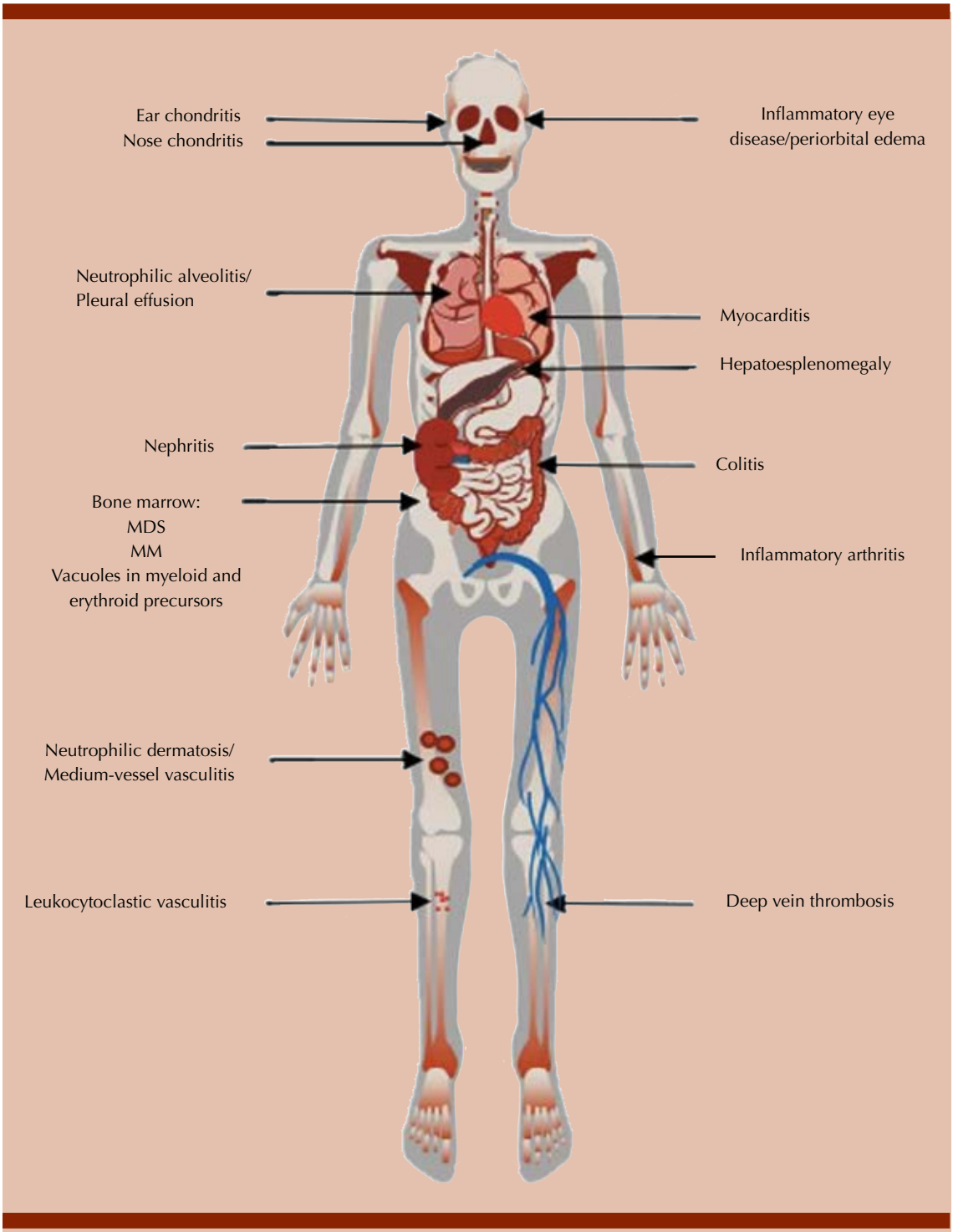

Figure 1. Clinical manifestations of VEXAS syndrome.
MDS: myelodysplastic syndrome; MM: multiple myeloma.

Ocular disease can manifest as scleritis, episcleritis, uveitis, blepharitis, optic perineuritis.[5] Periorbital edema was present in up to 32% patients in the original series,[1] and peri or intraorbital panniculitis has also been reported in another.[8]

Kidney involvement can be observed in approximately 10% of cases. Patients often present with acute kidney injury or nephritis. Histologic findings include vasculitis features, acute tubulointerstitial nephritis, and AA amyloidosis.[9]

Other less frequently affected systems in VEXAS patients are the gastrointestinal and cardiovascular system (myocarditis noted in 2 patients).[10]

HEMATOLOGICAL MANIFESTATIONS

Macrocytic anemia is the predominant cytopenia, followed by thrombocytopenia.[1] In a French multicenter registry cohort consisting of 116 patients, median Hb was 10.1 g/ dL (interquartile range 9-11.5 g/ dL), with a median MCV of 101 fL (interquartile range 94.08-106.75).[11] A simple algorithm using MCV > 100 fL or platelet count < 200 x 10^9/L plus male sex in patients with chondritis, has a 100% sensitivity and 96% specificity to help differentiate between patients with relapsing polychondritis and possible VEXAS and could be considered a basic screening tool.[4]

Patients can also have a history thromboembolic disease.[1] Venous thromboembolism has been described as part of the clinical presentation, with an incidence rate of 10% to 56% in published case series and approximately 40% in all reported cases.

In a series reported by Obiorah et al. (n = 16, thrombotic events in 10), 60% of thrombotic events occurred in the first 2 years from disease onset. D-dimer was elevated in 6 patients tested, and abnormal lupus anticoagulant testing was frequently observed (44%) and may support an antiphospholipid mediated process.[12] Arterial thrombosis appears to be less common in VEXAS than venous thrombosis (< 10%).[6,7]

Myelodysplastic syndrome has been frequently diagnosed in VEXAS patients, with a frequency ranging between 25% and 55%.[1,6,11]

Presence of transfusion-dependent anemia and severe thrombocytopenia (< 50 x 10^3/µL) were associated with myelodysplastic syndrome by WHO criteria in a report of 16 VEXAS patients.[12] On the other hand, approximately 20% of myelodysplastic syndrome cases are associated with systemic and autoimmune diseases, the latter are heterogeneous and related to deregulation of different immune pathways.[13] In a description of 19 male patients with myeloid dysplasia and auto-inflammatory disease, 11 had UBA1 mutations. Six of them had a formal diagnosis of myelodysplastic syndrome according to the 2016 World Health Organization criteria: 5 had refractory cytopenia without excess of blasts and one had a type I myelodysplastic syndrome with excess of blasts. Interestingly, 73% of patients (8/11) had hypercellular bone marrow, and 6 of the 9 patients who underwent bone marrow biopsy presented fibrosis (grade I, n = 5; grade II, n = 1).[14] In another cohort of 85 patients with myelodysplastic syndrome/chronic myelomonocytic leukemia (CMML) and autoimmune diseases, 33 male patients were analyzed for the presence of UBA1 mutations (6 myelodysplastic syndrome with excess of blasts, 21 myelodysplastic syndrome without excess of blasts and 6 CMML). Four (12%) of them had UBA1 mutations, all had myelodysplastic syndrome without excess of blasts. No CMML patient had UBA1 mutation.[15]

Most patients with VEXAS-myelodysplastic syndrome are lower risk according to the Revised International Prognostic Scoring System, with uni- or multi-lineage dysplasia. Additionally, the mutational profile appears to be less com-

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plex with few co-mutations described, such as DNMT3A, MLL, CSF1R, SF3B1, TET2, GNA11, ZRSR2. Whether the UBA1 mutation is the initial clonal event or whether the myelodysplastic syndrome is the result of an inflammatory microenvironment remains to be defined.[12]

Plasma cell dyscrasia has also been reported in patients with VEXAS. In the French multicentre cohort study, 12 patients (10%) had monoclonal gammopathy of unknown significance, all of them also had myelodysplastic syndrome.[11] Additionally, in the series of 16 VEXAS patients previously mentioned, 4 also met diagnostic criteria for plasma cell dyscrasia (2 with multiple myeloma and 2 with monoclonal gammopathy of unknown significance). In all cases, the paraprotein implicated was IgG kappa. It has been hypothesized that a common molecular mechanism associated with somatic mutations in UBA1 may contribute to this association.[12]

PRECURSOR CELL CYTOPLASMIC VACUOLIZATION

Vacuoles in myeloid and erythroid precursors have been reported in all series of VEXAS patients.[1,16] Cytoplasmic vacuoles are predominantly localized in promyelocytes, myelocytes, and blasts in the bone marrow. **Figure 2**

In the original report, electron microscopy showed myeloid cells undergoing cell death that had vacuoles consisting of lipid droplets and disordered cell organelles.[14] However, what vacuoles contain is still not clear. Although this morphologic feature is well established in lymphoid malignancies, it is not frequent in myeloid pathologies.

A recent study identified 24 cases with vacuoles on hematopoietic progenitors among 11,772 bone marrow specimens. In nine, vacuolization was present at onset; two tested positive for UBA1 mutation also showing the typical clinical phenotype of VEXAS. Both these patients had also lower-risk myelodysplastic syndrome and a *DNMT3A* mutation. In the rest of cases, a diagnosis of myelodysplastic syndrome or acute myeloid leukemia was stablished (usually with higher-risk features); the vacuoles appeared during course of disease rather than on onset (9/15 with blast-only pattern), and none carried a UBA1 mutation.[17]

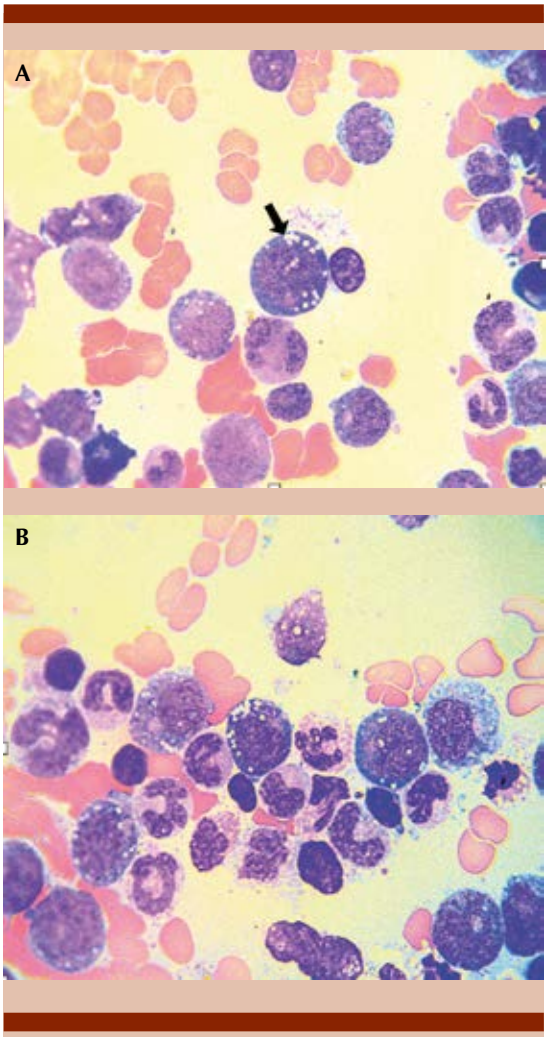

Figure 2. Vacuolization of myeloid precursors. **A.** Vacuoles in proerythroblast (arrow). **B.** Vacuoles in erythroid, granulocytic precursors and a neutrophil.

In conclusion, vacuolization of hematopoietic precursors seems to be typical but not pathognomonic in VEXAS.[14,17] When cytoplasmic vacuoles are identified on morphologic evaluation, the differential diagnosis includes alcohol intoxication, cooper deficiency, zinc toxicity, sepsis and myeloid neoplasms.[18]

GENETIC DIAGNOSIS

The genetic alteration in this syndrome is an acquired mutation of UBA1, an X-linked gene that escapes X inactivation. This gene encodes ubiquitin-activating enzyme 1, that is necessary for the initiation of ubiquitylation, a post-translational modification of proteins used to regulate diverse signaling for protein degradation. UBA1 is expressed in two isoforms: nuclear UBA1a (initiated at p.Met1) and cytoplasmic UBA1b (initiated at p.Met41).[19]

In the first description of this syndrome, all patients had mutations in codon 41 of UBA1.[1] Posterior studies have found additional mutations. Outside of the p.M41 variant, p. Ser56Phe has been described in one patient.[20] A novel variant in the splice motif at the junction of intron 2 and exon 3 (C.118-1G.C), resulting in a UBA1 protein lacking methionine 41 was described in two patients.[16]

Collectively, all VEXAS mutations described to date cause loss-of-function of normal UBA1 and are likely acquired later in life.[20] Since the UBA1 gene is located on the X chromosome, this syndrome is thought to affect only males, the additional allele in women protecting them against the effects of its mutant counterpart.[21] However, a case of VEXAS has been described in a woman with monosomy X, so it can be justified to test women with compatible features.[21]

TREATMENT

Currently, there is no standard treatment for this syndrome. Glucocorticoids are effective, however, almost always require sustained treatment and high doses (>20 milligrams/day) with breakthrough inflammatory flares and drug-associated toxicities.[22]

Disease modifying antirheumatic drugs such as methotrexate; cyclophosphamide, azathioprine and others, have shown a lack of prolonged response.[23]

Given that a significant percentage of patients with VEXAS also have myelodysplastic syndrome, one therapeutic strategy has been to direct management towards the clonal hematologic neoplasia. One study reported genetic, morphologic, and clinical remissions in patients treated with the hypomethylating agent azacytidine. Azacytidine was administered at a dose of 75mg/m2 s.c. QD for 7 days in a 4-week schedule with remission in 2 out of 3 patients, and time-to next line of treatment of 39.7 months in one. Patients with VEXAS syndrome associated with *DNMT3A* mutations displayed a genetic and clinical response, while another patient, not carrying concurrent *DMNT3A* mutations, was unresponsive to the drug.[24]

A retrospective report on the efficacy and safety of azacytidine in 11 VEXAS patients with myelodysplastic syndrome (by WHO 2016 diagnostic criteria) steroid-dependent and/or uncontrolled inflammation, showed a clinical response to azacytidine in 46% (n = 5, major response in 18%) after four cycles of treatment in 4 of 5 patients.[25]

Tocilizumab, an anti-interleukin (IL)-6 receptor antagonist approved for the treatment of inflammatory diseases, may be beneficial in patients with VEXAS- relapsing polychondritis and severe inflammation as shown in small case series reported elsewhere.[1,4,10] In a small single-center pilot study, 2 of 3 patients treated with tocilizumab had clinical response after 4 months of treatment. Two patients had herpes zoster infection as adverse events.[26] It's important

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to mention that, due to the retrospective nature of the report, the follow-up period was short and treatments were not homogeneous.

JAK inhibitors (JAKi) have also been evaluated as therapeutic options for this syndrome.[27] In a retrospective multicenter study of 30 patients treated with JAKi (ruxolitinib [n = 12], tofacitinib [n = 11] and others [n = 7]), 50% had a clinical response (CR) after 1 month of treatment. Biological response (defined as a >50% reduction of C reactive protein level) was observed in 20 patients. After 6 months, 11 remained on treatment, nine of them with complete biological response (normalization of C reactive protein level). The median duration of clinical response was not reached. A subgroup analysis showed higher response rates in patients treated with ruxolitinib compared to those treated with other JAKi (CR at 6 months 87% vs 11%; P 5 .002). Responses were similar in patients with or without myeloid neoplasia; the most frequent adverse events were infections (36.7%) and thromboembolic complications (20%). The better efficacy of ruxolitinib was potentially attributed to its target specificity (JAK1, JAK2, TYK2) and its broader dosing range.[27]

Allogeneic hematopoietic stem cell transplantation (ASCT) appears to be a curative option in suitable individuals. In a small retrospective case series of 6 patients with VEXAS who underwent ASCT (4 patients because of inflammatory symptoms and 2 for myelodysplastic syndrome resistant to multiple treatments), three patients were still in complete remission 32, 38, and 67 months after ASCT and 1 died of infectious complications. The two remaining patients were still alive with a shorter follow-up (3 and 5 months, respectively).[28]

However, the procedure carries an inherent risk of morbidity and mortality that must be judiciously evaluated.[29] ASCT may not be ideal in older or frail patients, as well as those at high risk of infections due to prolonged steroid use or other clinical characteristics.[19] Currently, a phase II clinical trial to evaluate the efficacy of ASCT in patients with VEXAS syndrome is ongoing, with an estimated study competition date by 2025.[30]

More clinical trials will be required to define the subgroup of patients who will benefit the most from this strategy.[28]

CONCLUSIONS

VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a novel entity, characterized by usually severe autoinflammatory features, cytopenias and hematological neoplasms (myelodysplastic syndrome, plasma cell dyscrasia).

Is a complex and heterogeneous syndrome, with many overlapping diseases and a high morbidity associated to progressive disease, transient responses, toxicities or refractoriness to treatment, and worsening cytopenias with or without myelodysplastic syndrome or multiple myeloma.

Diagnosis is made by gene sequencing to demonstrate acquired somatic mutations of the UBA1 gene.

Treatment of this syndrome is complex and multidisciplinary care led by a rheumatologist and a hematologist is often required. As previously mentioned, there is still a lack of effective treatments and the majority of patients affected by this entity shows only transient responses or failure to various lines of treatment including corticosteroids, JAKi, and hypomethylating agents. The role of ASCT in suitable patients as an attempt to eradicate the UBA1 clone needs to be further investigated. The outcome is often fatal, with a median survival of 5 years. More studies are needed for a better comprehension and treatment of the disease.

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