EJCRIM
European Journal of Case Reports in Internal Medicine

FEVER BEYOND INFECTION: VEXAS SYNDROME IN A PATIENT WITH HIV 2

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Received: 28/09/2026
Accepted: 12/10/2026
Published: 23/11/2026

Conflicts of Interests: The Authors declare no conflict of interest.
Patient Consent: Written informed consent for publication was obtained from the patient.
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How to cite this article: Salvado CA, Gorgulho A, Bartilotti F, Rua C, Melo T, Nunes S. Fever beyond infection: VEXAS syndrome in a patient with HIV 2. EJCRIM 2026;13:doi:10.12890/2026_007568

ABSTRACT

Introduction: Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is an adult-onset hematoinflammatory disorder caused by somatic *UBA1* mutations. Its multisystem manifestations may overlap with opportunistic infections and other complications of advanced human immunodeficiency virus (HIV) infection, obscuring diagnosis. We report a case of VEXAS syndrome in a patient with HIV-2 infection.

Case description: A 76-year-old man with newly diagnosed HIV-2 infection (CD4 34 cells/µl) presented with pancytopenia, recurrent fever, purpuric lesions, inflammatory arthritis, and recurrent pulmonary infiltrates. Despite antiretroviral therapy, virological suppression and partial immune recovery (CD4 240 cells/µl), pancytopenia progressively worsened and recurrent inflammatory episodes persisted. Extensive microbiological and autoimmune investigations were unrevealing, although *Pneumocystis jirovecii* pneumonia was documented during the final admission. Bone marrow study showed dyshematopoiesis consistent with myelodysplastic syndrome (MDS). The combination of persistent systemic inflammation, leukocytoclastic vasculitis, arthritis, recurrent pulmonary infiltrates, and MDS prompted testing for VEXAS. Next-generation sequencing detected the *UBA1* p.Met41Thr variant. Treatment with azacitidine was followed by transfusion independence after two cycles and subsequent recovery of blood counts, while corticosteroids were tapered. HIV-2 remained virologically suppressed.

Discussion: This case highlights the diagnostic challenge posed by overlapping manifestations of VEXAS, HIV-2 infection and opportunistic infection. Persistent cytopenias despite virological suppression and immune recovery, with multisystem inflammation and recurrent pulmonary infiltrates not fully explained by infection, should prompt consideration of VEXAS. In patients with pancytopenia—particularly those with MDS—VEXAS should be considered when persistent multisystem inflammation is not fully explained by their coexisting conditions.

KEYWORDS

VEXAS syndrome, human immunodeficiency virus (HIV)-2, myelodysplastic syndrome, *UBA1* mutation

EFIM European Federation of Internal Medicine

Publisher smc media srl

LEARNING POINTS

- Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome may mimic opportunistic infections and other complications of advanced human immunodeficiency virus infection. Persistent cytopenias and systemic inflammation despite virological suppression and immune recovery should raise suspicion for VEXAS syndrome.
- VEXAS syndrome should be considered in patients with unexplained multisystem inflammation, particularly when associated with myelodysplastic syndrome, recurrent pulmonary infiltrates, vasculitis or inflammatory arthritis.
- VEXAS syndrome and opportunistic infections may coexist, potentially complicating the diagnostic evaluation.

INTRODUCTION

Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome is an adult-onset hematoinflammatory disorder caused by somatic mutations in the *UBA1* gene, encoding ubiquitin-activating enzyme 1. First described in 2020, it predominantly affects men in the fifth to seventh decades of life and presents with systemic inflammation, cytopenias, and characteristic vacuolization of myeloid and erythroid precursors[1]. The clinical spectrum is broad, encompassing refractory constitutional symptoms, cutaneous and articular involvement, chondritis, pulmonary infiltrates, and a high risk of myelodysplastic syndromes. Notably, opportunistic infections represent a major cause of morbidity and mortality, even in the absence of pharmacological immunosuppression, due to intrinsic immune dysfunction including impaired natural killer cell function and lymphopenia[1-3].

The coexistence of VEXAS syndrome and human immunodeficiency virus (HIV) infection has been rarely reported in the literature[4]. We present a case of VEXAS syndrome in a patient living with advanced HIV-2 infection, highlighting the unique diagnostic challenges posed by overlapping clinical features between these two conditions.

CASE DESCRIPTION

We present a 76-year-old man with a history of type 2 diabetes mellitus and HIV-2 infection. This was a late presentation, with a CD4 count of 34 cells/µl, a concurrent diagnosis of bilateral lung infiltrates initially interpreted as *Pneumocystis jirovecii* (PJ) pneumonia, purpuric lesions on the lower limbs and pancytopenia. All symptoms were attributable to the advanced HIV infection. PJ polymerase chain reaction on the bronchoalveolar lavage (BAL) was negative, but the patient was already on corticosteroids and trimethoprim-sulfamethoxazole with clinical and radiological improvement, with resolution of the skin lesions. Antiretroviral therapy (ART) was initiated with bictegravir/tenofovir alafenamide/emtricitabine. However, due to nausea-related intolerance, the regimen was switched to dolutegravir/lamivudine.

In the year following the HIV-2 diagnosis, the patient required four hospitalizations. These admissions were primarily prompted by recurrent episodes of recurrent fever (maximum temperature [Tmax] 38.5°C) with no circadian pattern and purpuric lesions on the limbs that were biopsied and revealed leukocytoclastic vasculitis. Concurrently, the patient presented with inflammatory-pattern arthralgia affecting the wrists and ankles, with objective evidence of arthritis on physical examination. Laboratory investigations during these episodes consistently demonstrated elevated inflammatory markers, including C-reactive protein and erythrocyte sedimentation rate, as well as persistent pancytopenia (hemoglobin 6,8g/dl, leukocytes 2.160/µl, platelets 47.000/µl). Notably, despite the persistent cytopenias, the patient demonstrated partial immunologic recovery under antiretroviral therapy, with CD4 counts increasing to 240 cells/µl.

During at least three of these hospitalizations, there was clinical suspicion of respiratory and skin infections based on presenting symptoms and radiologic findings with recurrent pulmonary infiltrates. However, despite thorough microbiological investigations, including blood and urine cultures, BAL and sputum cultures (bacteriology, mycobacteriology and mycology), serologies for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, *Rickettsia conorii*, *Cryptococcus*, *Strongyloides*, and *Human Herpesvirus* 8—an infectious etiology was documented in only one episode. On the last hospitalization, testing for PJ returned positive. At this time, the patient was not on PJ prophylaxis, since the cytopenias were worsening and CD4 counts were >200 cells/µl. Once the infection was documented, treatment with atovaquone was initiated. In all other admissions, no infectious agent was identified. Empiric antibiotic therapy was consistently administered, alongside systemic corticosteroids due to the concurrent vasculitic manifestations and arthralgias.

In parallel to the microbiological investigation, an extensive diagnostic workup was performed to exclude malignancies and autoimmune diseases. This included imaging studies and a comprehensive autoantibody panel, including antinuclear antibodies, complement levels, antiphospholipid antibodies, and antineutrophil cytoplasmic antibodies, all of which returned negative or non-diagnostic results. Given the persistence and progressive worsening of pancytopenia—despite an improving CD4+ T-cell count, which would be unexpected if the cytopenias were primarily HIV-related—a bone marrow study was performed. It demonstrated hypercellular bone marrow with dyshematopoiesis, consistent with a diagnosis of myelodysplastic syndrome (MDS). The bone

marrow aspiration was hypocellular (not representative of bone marrow). Cytogenetic analysis revealed a 45,X,-Y karyotype, indicating loss of the Y chromosome. The MDS was classified as low risk according to the Revised International Prognostic Scoring System (IPSS; R score of 2 points). At that time, the patient was on corticosteroid therapy at a dose of 20 mg daily and required frequent red blood cell transfusion support.

The coexistence of MDS, prior recurrent episodes of fever without an identifiable infectious source, leukocytoclastic vasculitis, recurrent pulmonary radiologic findings, arthralgias and the observed clinical improvement with corticosteroid therapy raised suspicion for VEXAS syndrome. This diagnosis was subsequently confirmed by next-generation sequencing, which identified the *UBA1* p.Met41Thr variant, with a variant allele fraction of 91.5%.

Following diagnostic confirmation, the patient was started on azacitidine, a hypomethylating agent known to improve both inflammatory manifestations associated with VEXAS syndrome and cytopenias related to MDS[3,5]. Following the initiation of azacitidine, the patient achieved transfusion independence after just two cycles, representing a significant milestone in the clinical course. Corticosteroid therapy was subsequently tapered to a maintenance dose of prednisolone 5 mg daily. The patient has since continued regular azacitidine cycles and there was complete recovery of blood counts (hemoglobin 14,3g/dl, leukocytes 2.300/µl, platelets 134.000/µl). Regarding HIV-2 management, antiretroviral therapy has been maintained throughout, with CD4 counts remaining stable between 250 and 300 cells/µl and an undetectable viral load.

DISCUSSION

The diagnosis of VEXAS syndrome in this HIV-2-infected patient presented significant diagnostic challenges due to overlapping clinical and laboratory features between the two conditions. Several key findings contributed to diagnostic uncertainty and delayed recognition of VEXAS syndrome.

In people living with HIV, cytopenias—including pancytopenia—may result from multiple mechanisms (direct viral effects, chronic inflammation, opportunistic infections, drug toxicity, and/or nutritional deficiencies), making initial attribution of the patient's cytopenia to HIV reasonable[6]. Accordingly, after initiating or optimizing ART, an improvement in blood counts may be anticipated, particularly when immunologic recovery is documented. In this case, the persistence (or progression) of pancytopenia despite immunovirological improvement raised concern for an additional, non-HIV-related driver of marrow dysfunction. The patient developed inflammatory arthritis despite virological control on antiretroviral therapy, which is uncommon in HIV-2 infection with undetectable viral load and represents a key diagnostic clue. While rheumatic manifestations occur in 4-9% of HIV-infected patients, arthritis is significantly less common in those with virological suppression on ART[7]. In contrast, arthralgia and arthritis occur in the majority of VEXAS patients, representing a core inflammatory manifestation of the syndrome[2,3,8]. The presence of persistent inflammatory arthritis in a virologically suppressed HIV-2 patient should prompt consideration of an alternative or concurrent autoinflammatory process.

The leukocytoclastic vasculitis observed in this patient is a characteristic feature of VEXAS syndrome but is rare in HIV infection. Histological examination in VEXAS commonly demonstrates neutrophilic dermatosis and leukocytoclastic vasculitis, with cutaneous involvement occurring in more than 80% of cases[9,10]. In contrast, vasculitis in HIV-infected patients is uncommon, occurring in less than 1% of cases, and typically presents in patients with CD4 counts between 200-500 cells/µl rather than in those with severe immunosuppression or virological control[11].

The recurrent pulmonary infiltrates represented a particularly challenging diagnostic dilemma given the patient's CD4 count of 240 cells/µl. At this level of immunosuppression, opportunistic infections remain a significant concern[12]. In HIV-2 infection specifically, patients tend to develop acquired immunodeficiency syndrome (AIDS) at higher CD4 counts compared to HIV-1, with a median CD4 count at AIDS diagnosis of 176 cells/µl in one cohort, making the suspicion of opportunistic infections particularly relevant in this patient[13]. Although multiple previous hospitalizations failed to identify an infectious agent, the isolation of PJ during the final admission further diverted clinical attention toward an infectious etiology and away from an underlying autoinflammatory process. Pulmonary manifestations occur in 47-74% of VEXAS patients, typically presenting as ground-glass opacities, nodular infiltrates, and consolidations that are microbiologically sterile and reversible with corticosteroid therapy[2,14]. The pattern of recurrent sterile pulmonary infiltrates in previous admissions, followed by a documented opportunistic infection, highlights the complexity of distinguishing inflammatory flares of VEXAS from superimposed infections in immunocompromised patients.

This case illustrates the diagnostic complexity when two rare conditions coexist. Recognition of VEXAS syndrome requires a high index of suspicion in older male patients with treatment-refractory systemic inflammation, macrocytic anemia, and multisystem involvement, even when confounding diagnoses, such as HIV infection, are present[2,9].

Genetic testing revealed the *UBA1* p.Met41Thr variant with a remarkably high VAF of 91.5%. Although p.Met41Thr is the most common canonical mutation in VEXAS syndrome, it is not the variant most frequently associated with leukocytoclastic vasculitis—this cutaneous phenotype is more characteristic of the p.Met41Val variant, which correlates with vasculitic lesions and mixed inflammatory infiltrates[10]. Nevertheless, the exceptionally high VAF

observed in this patient carries significant prognostic implications, as recent prospective data demonstrate that elevated baseline VAF independently predicts poor outcomes, including death and transfusion dependence[15]. This case reveals the importance of considering VEXAS syndrome in patients with unexplained systemic inflammation and cytopenias, particularly when standard infectious and autoimmune workups are unrevealing, highlighting the need for increased clinical awareness and genetic testing in complex presentations. It underscores the importance of a multidisciplinary approach, involving haematology, internal medicine, rheumatology and infectious diseases to achieve an accurate diagnosis and individualized management plan in patients with complex overlapping syndromes.

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):2628-2638. doi: 10.1056/NEJMoa2026834.
2. Groarke EM, Turturice B, Patel BA, Quinn KA, Fike A, Grayson PC. VEXAS syndrome: a comprehensive review of pathogenesis, clinical spectrum, and therapeutic strategies. Lancet. 2026;407(10528):637-648. doi: 10.1016/S0140-6736(25)02164-6.
3. Loeza-Uribe MP, Hinojosa-Azaola A, Sánchez-Hernández BE, Crispín JC, Apodaca-Chávez E, Ferrada MA, et al. VEXAS syndrome: Clinical manifestations, diagnosis, and treatment. Reumatol Clin (Engl Ed). 2024;20(1):47-56. doi: 10.1016/j.reumae.2023.12.004.
4. Hagiya A, Siddiqi IN, Wang E, Lu CM. How I diagnose and manage VEXAS syndrome. Am J Clin Pathol. 2024;162(1):28-40. doi: 10.1093/AJCP/AQAE017.
5. Alqatari S, Alqunais AA, Alali SM, Alharbi MA, Hasan M, Al Shubbar MD. VEXAS syndrome: A comprehensive review of current therapeutic strategies and emerging treatments. J Clin Med. 2024;13(22):6970. doi: 10.3390/jcm13226970.
6. Potts BJ, Hoggan MD, Lamperth L, Spivak J. Replication of HIV-1 and HIV-2 in human bone marrow cultures. Virology. 1992;188(2):840–849. doi:10.1016/0042-6822(92)90539-2.
7. Parperis K, Abdulqader Y, Myers R, Bhattarai B, Al-Ani M. Rheumatic diseases in HIV-infected patients in the post-antiretroviral therapy era: a tertiary care center experience. Clin Rheumatol. 2019;38(1):71–76. doi: 10.1007/s10067-018-4089-z.
8. Anderson M, Ercelen D, Richardson A, Kim J, Torene RI, Sirenko M, et al. Clinical manifestations of VEXAS syndrome across a broad spectrum of UBA1 mutation burden. Arthritis Rheumatol. 2025. doi: 10.1002/art.43327.
9. Mekinian AM, Georgin-Lavialle S, Ferrada MA, Savic S, Koster MJ, Kosmider O, et al. American College of Rheumatology Guidance Statement for Diagnosis and Management of VEXAS Developed by the International VEXAS Working Group Expert Panel. Arthritis Rheumatol. 2025. doi: 10.1002/art.43287.
10. Tan IJ, Ferrada MA, Ahmad S, Fike A, Quinn KA, Groarke EM, et al. Skin manifestations of VEXAS syndrome and associated genotypes. JAMA Dermatol. 2024;160(8):822–829. doi: 10.1001/jamadermatol.2024.1657.
11. Patel N, Patel N, Khan T, Patel N, Espinoza LR. HIV infection and clinical spectrum of associated vasculitides. Curr Rheumatol Rep. 2011;13(6):506–512. doi: 10.1007/s11926-011-0214-6.
12. European AIDS Clinical Society. EACS Guidelines Version 12.0 [Internet]. 2023 [cited 2026 Jun 24]. Available from: https://www.eacsociety.org/guidelines/eacs-guidelines/.
13. Martinez-Steele E, Awasana AA, Corrah T, Sabally S, Van Der Sande M, Jaye A, et al. Is HIV-2-induced AIDS different from HIV-1-associated AIDS? Data from a West African clinic. AIDS. 2007;21(3):317–324. doi: 10.1097/QAD.0b013e328011d7ab.
14. Casal Moura M, Baqir M, Tandon YK, Samec MJ, Hines AS, Reichard KK, et al. Pulmonary manifestations in VEXAS syndrome. Respir Med. 2023;213:107245. doi: 10.1016/j.rmed.2023.107245.
15. Kirino Y, Maeda A, Higashitani K, Horita N, Asano T, Migita K, et al. Peripheral blood UBA1 variant burden predicts poor outcomes in VEXAS syndrome: a nationwide prospective study. Ann Rheum Dis. 2026. doi: 10.1016/j.ard.2026.03.003.