Journal for ImmunoTherapy of Cancer

Is immunotherapy safe and effective in patients with VEXAS syndrome?

Chiara Marvisi ,[1,2] Francesco Muratore,[1,2] Vincenza Ylenia Cusenza,[1] Davide Nicoli,[1] Enrico Farnetti,[1] Orsola Bonanno,[1] Lucia Spaggiari,[1] Maria Banzi,[1] Caterina Longo,[1,2] Carlo Salvarani[1,2]

To cite: Marvisi C, Muratore F, Cusenza VY, *et al*. Is immunotherapy safe and effective in patients with VEXAS syndrome? *Journal for ImmunoTherapy of Cancer* 2025;**13**:e012410. doi:10.1136/jitc-2025-012410

Accepted 07 July 2025

Check for updates

© Author(s) (or their employer(s)) 2025. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ Group.

[1]Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy
[2]Università di Modena e Reggio Emilia, Modena, Italy

Correspondence to
Professor Carlo Salvarani;
Carlo.salvarani@ausl.re.it

ABSTRACT

The use of immune checkpoint inhibitors in VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is unknown. Concerns are particularly about their safety, due to their potential capacity to exacerbate inflammatory symptoms. Further, there is a lack of data about their role in controlling the UBA1 clones. In this clinical case, we report a successful use of cemiplimab in a patient with VEXAS syndrome and a concomitant diagnosis of metastatic squamous cell carcinoma.

CLINICAL INSIGHT

Immune checkpoint inhibitors (ICIs) may be safe in VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome and could potentially contribute to controlling UBA1-mutated clones.

INTRODUCTION

VEXAS syndrome is an adult-onset autoinflammatory disease caused by somatic mutations in the UBA1 gene and characterized by cytopenia, macrocytic anemia, bone marrow failure, fever, and systemic inflammation.[1] About 50% of patients present with myelodysplastic syndrome (MDS) at diagnosis. Clones often present clonal hematopoiesis of indeterminate potential mutations, but blood cancers in patients with VEXAS syndrome remain sporadic.[2]

The pathogenesis of VEXAS syndrome still remains unclear due to its recent discovery, the small patient cohorts, and the paucity of experimental models. A higher prevalence of UBA1-mutated cells has been described among hematopoietic stem and myeloid cells, while peripheral T and B lymphocytes remain wild-type. This is likely due to negative selection against mutated lymphoid precursors, potentially causing lymphopenia.[1] However, adaptive immunity dysfunction has been observed with reduced T cell receptor (TCR) diversity and clonal expansions of effector memory CD8+T cells, which exhibit increased cytotoxicity and heightened interferon-γ (IFN-γ) signaling.[3]

The use of T-cell-based treatments, such as ICIs, in VEXAS syndrome remains poorly understood, particularly regarding their potential to exacerbate systemic inflammation. ICIs activate the immune system and can cause immune-related adverse events (irAEs), even in patients without this diagnosis. Conversely, T cells may play a role in VEXAS syndrome progression and in maintaining the survival of UBA1-mutated clones.

METHODS AND RESULTS

A patient in their 70s with a prolonged history of inflammatory manifestations resistant to synthetic and biological immunosuppressants required chronic glucocorticoid (GC) treatment. In July 2022, the p.Met41.Val mutation was identified through Sanger sequencing of exon 3 with a variant allele frequency (VAF) of 55%, leading to a diagnosis of VEXAS syndrome. He started ruxolitinib in November 2022, which provided a moderate GC-sparing effect.

In October 2023, a bone marrow biopsy revealed MDS with low blasts. As transfusion dependence and relapsing inflammatory manifestations emerged, ruxolitinib was discontinued in February 2024. The patient received three cycles of 5-azacytidine, which were stopped in June 2024 following a diagnosis of locally advanced squamous cell carcinoma of the scalp.

Despite the lack of data on the efficacy and safety of ICIs in VEXAS syndrome, cemiplimab, an anti- programmed cell death protein 1 (PD-1) was initiated. The treatment was well tolerated, with only mild diarrhea (irAEs G2), and led to a significant reduction in the neoplastic mass (figure 1), which was maintained at the last available imaging in March 2025.

Journal for ImmunoTherapy of Cancer: first published as 10.1136/jitc-2025-012410 on 31 July 2025. Downloaded from https://jitc.bmj.com on 27 March 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

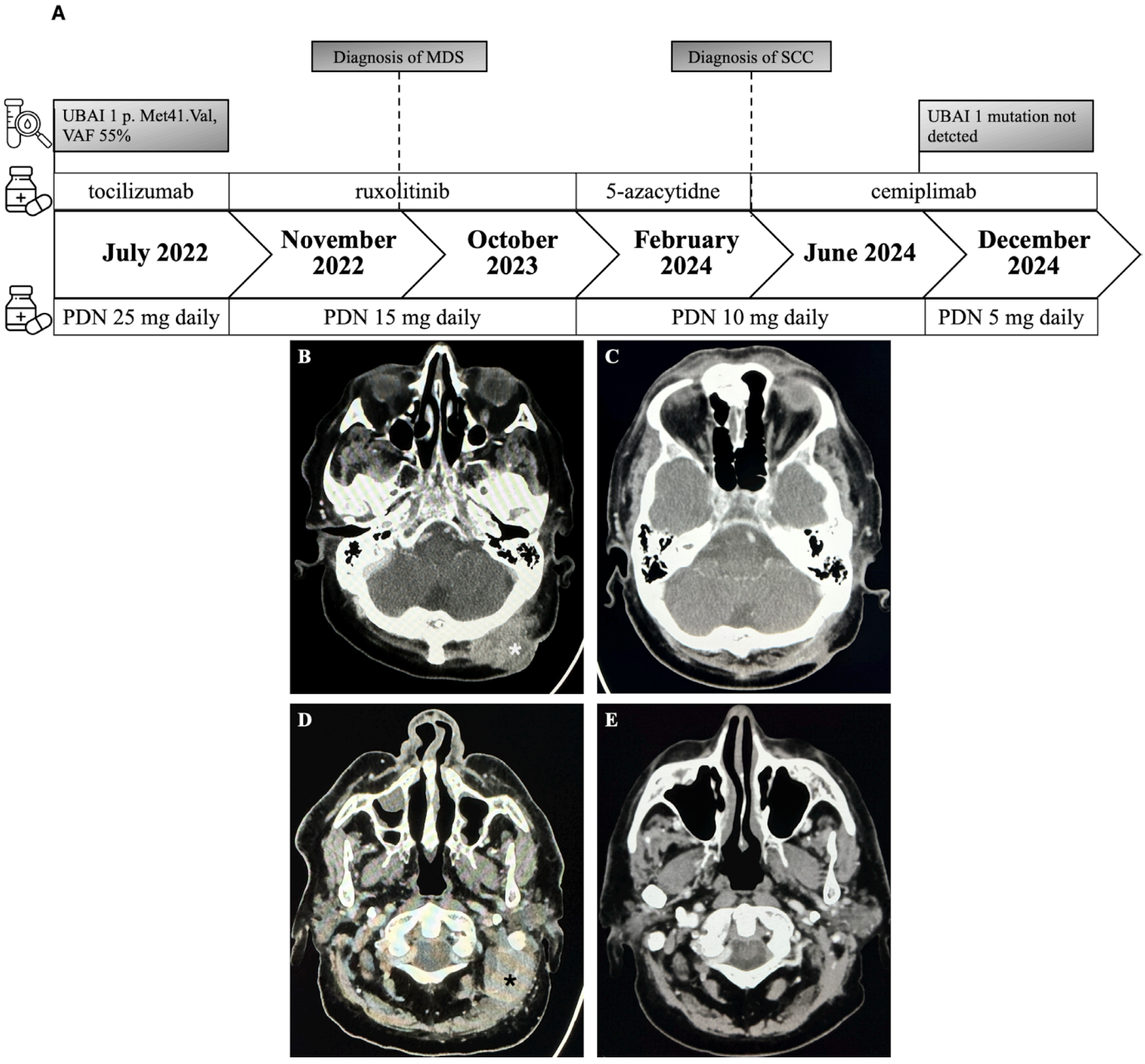

Figure 1 (A) Timeline of the clinical history of the patient. (B and D) CT showing squamous cell carcinoma before (white and black asterisk) and after (C and E) treatment with cemiplimab. MDS, myelodysplastic syndrome; PDN, prednisone; SCC, squamous cell carcinoma; VAF, variant allele frequency.

After a few months of treatment, all VEXAS manifestations resolved, including normalization of acute phase reactants, hemoglobin levels, and lymphocyte counts. A notable steroid-sparing effect was also observed (prednisone was reduced from 15 mg/day to 5 mg/day). In December 2024, after nine infusions of cemiplimab, the UBA1 mutation was reassessed using both Sanger and next-generation sequencing methods, the latter offering higher sensitivity (VAF>5%). Neither method detected any UBA1 mutation.

DISCUSSION

Despite previous prolonged immunosuppression, immunotherapy proved safe and effective in controlling cancer growth in our patient with VEXAS.

Patients with VEXAS syndrome often experience significant immunosuppression and may face an increased risk of developing malignancies beyond hematologic cancers. Although ICIs are known to activate the immune response, potentially worsening VEXAS symptoms, our case report demonstrates their apparent safety in this autoinflammatory condition. We observed no exacerbation of inflammatory symptoms or significant adverse events, suggesting that anti-PD-1 therapy may be safe in clinical practice for inflammatory

Journal for ImmunoTherapy of Cancer: first published as 10.1136/jitc-2025-012410 on 31 July 2025. Downloaded from https://jitc.bmj.com on 27 March 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

conditions like VEXAS syndrome. However, whether all ICIs are safe and whether all patients with VEXAS syndrome can be treated safely with them should be assessed in larger cohorts.

Recent reports suggest that 5-azacytidine effectively controls inflammatory symptoms after at least four cycles and normalizes VAF after 9–21 cycles.[4 5] Although our patient completed only three cycles, genetic remission may have been induced. However, the lack of longitudinal molecular monitoring of the UBA1-mutated clone during and shortly after 5-azacytidine treatment limits our ability to determine whether cemiplimab contributed to achieving clinical remission. Nonetheless, it appears to have played a role in maintaining it.

Recent data from Molteni *et al* shed light on the mechanisms of clonal dominance in VEXAS syndrome. Mutant UBA1 clones present inflammation-resilient progeny on one side, while on the other, UBA1-mutant clones may acquire a resilient state by entering dormancy or undergoing senescence, which may shield mutant cells from inflammation-induced apoptosis and immune clearance.[6] Additionally, immune evasion mechanisms, such as the overexpression of immune checkpoint proteins (eg, PD-1/programmed death-ligand 1 (PD-L1) and cytotoxic T lymphocyte–associated protein 4) on T-cells, lead to T-cell exhaustion and transition toward an immune-evading tumor microenvironment, which may play a role, as described in MDS.[7]

In this context, combined targeted therapies that blunt systemic inflammation and eradicate the resilient mutant clones are more effective than single treatments, as they address both pathogenic components of the disease. Our patient's clinical and molecular remission may suggest that checkpoint inhibition, perhaps in combination with prior hypomethylating therapy, may have disrupted this vicious cycle, enabling re-expansion of wild-type hematopoiesis. Given the complex interplay between clonal hematopoiesis and immune dysregulation in VEXAS syndrome, targeting the interaction between myeloid and adaptive immunity may represent a novel therapeutic avenue. However, this intriguing hypothesis should be evaluated in future in vitro studies and larger patient cohorts.

Acknowledgements This study was partially supported by Italian Ministry of Health – Ricerca Corrente Annual Program 2026.

Contributors CM, FM, VYC, DN, EF, OB, LS, MB, CL and CS contributed to the acquisition and interpretation of data and wrote the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests No, there are no competing interests.

Patient consent for publication Not applicable.

Ethics approval Not necessary for case reports.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Chiara Marvisi http://orcid.org/0000-0001-7027-1410

REFERENCES

1 Beck DB, Ferrada MA, Sikora KA, *et al*. Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease. *N Engl J Med* 2020;383:2628–38.
2 Gutierrez-Rodrigues F, Kusne Y, Fernandez J, *et al*. Spectrum of clonal hematopoiesis in VEXAS syndrome. *Blood* 2023;142:244–59.
3 Wu Z, Gao S, Gao Q, *et al*. Early activation of inflammatory pathways in UBA1-mutated hematopoietic stem and progenitor cells in VEXAS. *Cell Rep Med* 2023;4:101160.
4 Sockel K, Götze K, Ganster C, *et al*. VEXAS syndrome: complete molecular remission after hypomethylating therapy. *Ann Hematol* 2024;103:993–7.
5 Álamo JR, Torres LM, Castaño-Díez S, *et al*. Hypomethylating agents for patients with VEXAS without myelodysplastic syndrome: Clinical outcome and longitudinal follow-up of vacuolization and UBA1 clonal dynamics. *Br J Haematol* 2025;206:565–75.
6 Molteni R, Fiumara M, Campochiaro C, *et al*. Mechanisms of hematopoietic clonal dominance in VEXAS syndrome. *Nat Med* 2025;31:1911–24.
7 Rodriguez-Sevilla JJ, Colla S. T-cell dysfunctions in myelodysplastic syndromes. *Blood* 2024;143:1329–43.

Journal for ImmunoTherapy of Cancer: first published as 10.1136/jitc-2025-012410 on 31 July 2025. Downloaded from https://jitc.bmj.com on 27 March 2026 by guest. Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.