Very long-term remission with azacitidine in VEXAS syndrome

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome is a newly identified monogenic disorder with symptoms including recurrent fever, skin involvement, pulmonary infiltrates, systemic vasculitis, and chondritis.[1] Notably, 25-50% of patients also have myelodysplastic syndrome (MDS). VEXAS syndrome often requires high-dose steroids and is resistant to standard immunomodulatory agents. Emerging therapies such as JAK inhibitors, azacitidine (AZA), and, in severe selected cases, allogeneic stem cell transplantation (alloHSCT) show promise,[2] but optimal management remains unclear. The impact of these treatments on the *UBA1* gene clonal cell fraction (CCF) and associated myeloid malignancy mutations is not well described. We present a VEXAS patient achieving prolonged remission with AZA. Neither the patient nor the public were involved in the design, conduct, reporting, or dissemination plans of this research, which was approved by a formally constituted review board.

A 59-year-old male with Parkinson's disease and hypertension was diagnosed with MDS in 2003, with multilineage dysplasia and no excess blasts (as per the WHO 2016 retrospective reclassification[3]), normal karyotype and a low-risk revised International Prognostic Scoring System (IPSS-R) score of 3. Retrospective molecular analysis of a bone marrow specimen revealed a *UBA1* (p.M41T, CCF 40%) and *TET2* (p.W1233X, variant allelic fraction [VAF] 17%/CCF 34%) mutation, resulting in a low molecular IPSS-R score (-1.3). Moderate cytopenias led to watchful waiting.

One year post diagnosis, the patient developed intermittent purpuric lesions on the lower extremities, accompanied by livedo racemosa. A skin biopsy indicated MDS-related vasculitis with leukocytoclasia. He also experienced symmetric polyarthritis in wrists and proximal interphalangeal joints. C-reactive protein (CRP) was elevated at 30 mg/L, and rheumatoid factor was positive, but anti-cyclic citrullinated peptide antibodies were absent, precluding a

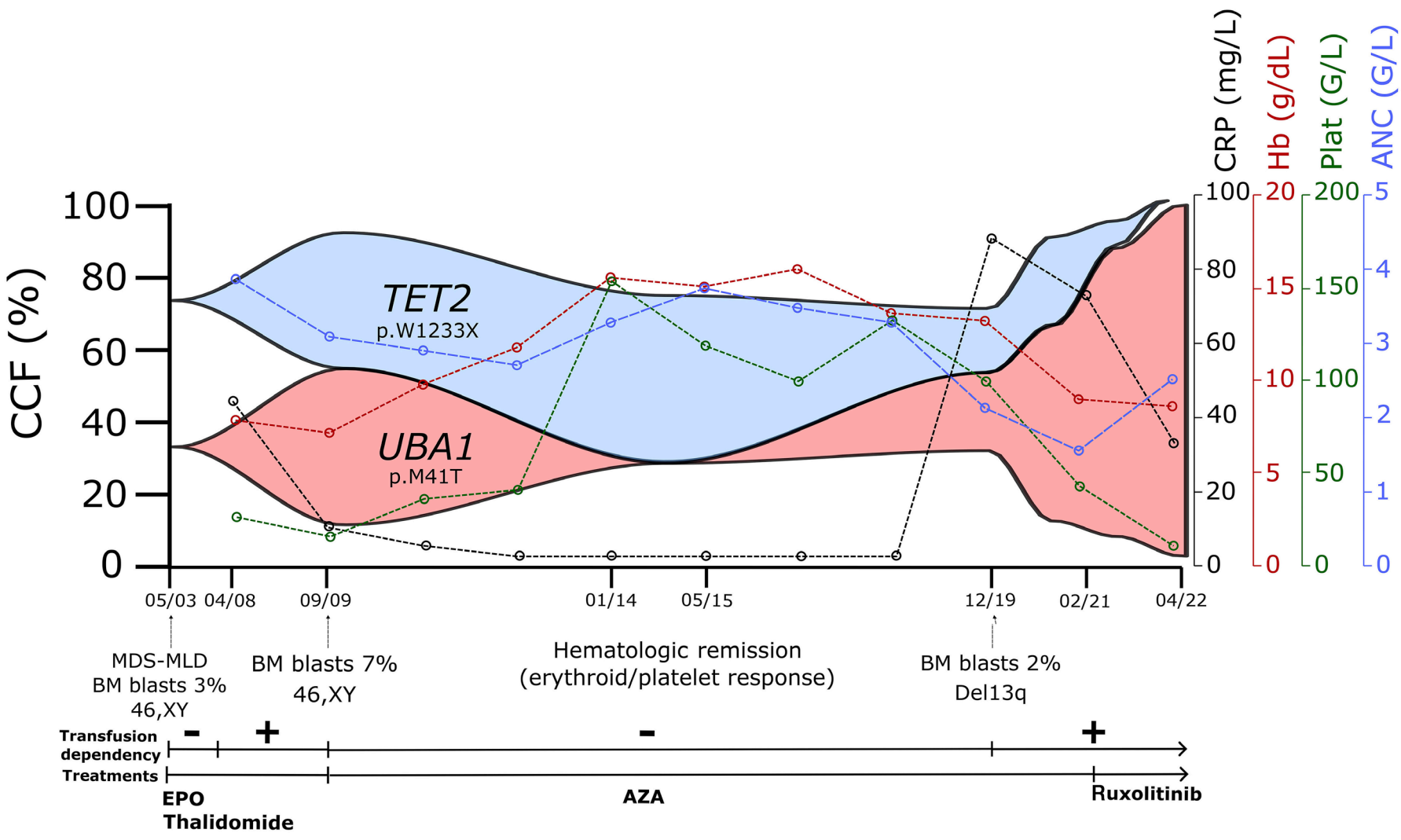

Figure 1. Longitudinal monitoring of clinical course, hematologic parameters, and molecular burden in relation to treatment responses. Timeline showing the association of clonal burden (left axis), hematologic parameters and C-reactive protein (CRP) level (right axis), bone marrow (BM) findings, transfusion dependency and their relation to treatment. Clonal cell fractions (CCF) (representing the proportion of mutated cells) were assessed using next-generation sequencing (sensitivity threshold 1%). ANC: absolute neutrophil count; AZA: azacitidine; EPO: erythropoietin; Hb: hemoglobin; Plat: platelets; MDS-MLD: myelodysplastic syndrome with multilineage dysplasia (according to WHO 2016).

diagnosis of rheumatoid arthritis. Systemic corticosteroids (1 mg/kg) were initiated, partially remitting cutaneous and rheumatologic symptoms, and high-dose steroid dependence developed (at a daily steroid dose of 20 mg). In 2008, cytopenias worsened, requiring red blood cell and platelet transfusions, while treatments with erythropoietin and thalidomide were ineffective. Bone marrow evaluation showed MDS progression with 7% blasts, but a still normal karyotype. AZA (75 mg/m^2/day for 7 days monthly) treatment began in April 2009, leading to rapid and complete remission of cutaneous symptoms, steroid discontinuation, and erythroid and platelet responses (according to IWG 2006 criteria[4]). AZA treatment was sustained for 105 cycles over ten years, with intervals between courses gradually extended from four to six weeks. During this remission period, the *UBA1* clone became undetectable by molecular analysis (with a 1% sensitivity assay), while the *TET2* variant allele frequency (VAF) remained stable (Figure 1).

In December 2019, the patient was admitted with tender erythematous papules and plaques on the lower limbs (Figure 2A), suggestive of Sweet syndrome, accompanied by fever and isolated chondritis of the left ear (Figure 2B). Blood tests showed hemoglobin at 12.4 g/dL, neutrophils at 0.66x10^9/L, monocytes at 0.09x10^9/L, and platelets at 62x10^9/L, with elevated inflammatory markers (CRP 90 mg/L). A skin biopsy revealed an inflammatory infiltrate with CD33$^+$ CD163$^+$ MPO$^+$ immature myeloid cells and few mature neutrophils (Figure 2C). Bone marrow analysis indicated significant dysplasia and vacuolization in progenitors, with only 2% blasts, while karyotype showed the emergence of clonal 13q deletion and molecular analysis increased CCF of mutated *UBA1* (50% and 71% in December 2019 and February 2021, respectively) relative to mutated *TET2* (22% and 10%). Systemic steroids partially controlled skin lesions. Shortening the intervals to four weeks between AZA cycles was ineffective in controlling inflammatory symptoms. Ruxolitinib was initiated as a steroid-sparing agent in December 2021, but the patient did not respond and passed

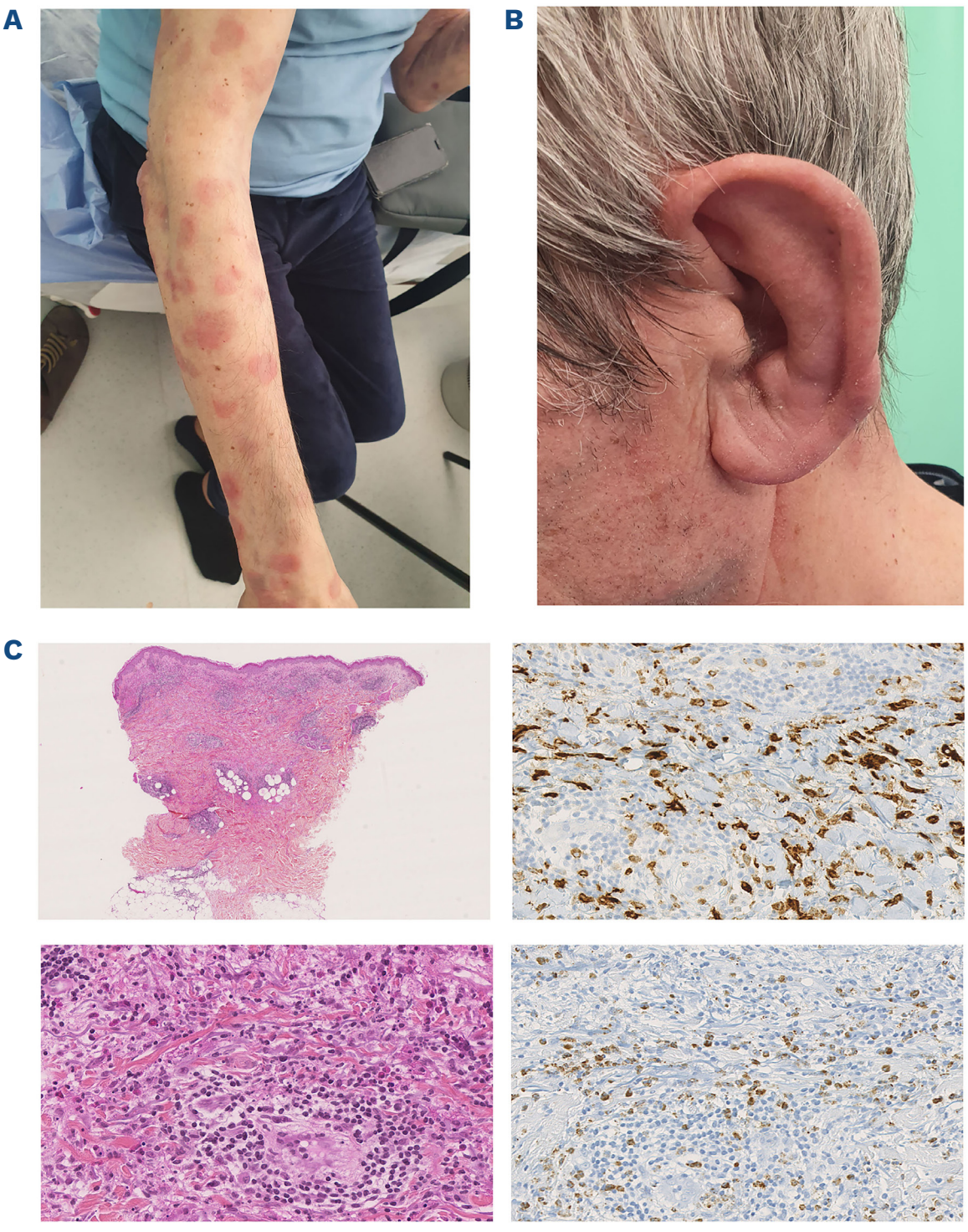

Figure 2. Multisystemic manifestations and histopathological features of VEXAS. (A) Erythematous papules and plaques of the upper right arm. (B) Isolated chondritis of the left ear. (C) Histopathological features of skin biopsy in 2020 comprise a superficial and deep dermal perivascular infiltrate (upper left, HES, x30 magnification) made of lymphocytes, mononucleated histiocytoid cells with incompletely segmented nuclei, few mature neutrophils and eosinophils (lower left, HES, x400 magnification). Histiocytoid cells express CD163 (upper right, x400 magnification) and myeloperoxidase (lower right, x400 magnification), indicating immature non-blastic myeloid cells.

away due to a pulmonary infection in December 2022.

This is to our knowledge the longest clinical and molecular remission (lasting a decade) reported with AZA treatment in a patient with VEXAS syndrome and MDS. The pioneering study by Raaijmakers *et al.* demonstrated significant reductions in *UBA1* clonal burden in 2 out of 3 patients (who received 3, 3, and 8 cycles) treated with AZA,[5] a finding later corroborated by independent studies.[6,7] The efficacy of AZA in controlling both inflammatory and hematologic symptoms was further supported by a French nationwide retrospective study[8] and the prospective Groupe Français des Myélodysplasies (GFM) AZA-SAID trial,[9] where 5 out of 11 (46%) and 9 out of 12 (75%) VEXAS patients, respectively, showed responses to AZA, but with limited follow-up (median 32 and 19 months, respectively).

Although similar response rates (approx. 25-50%) have been reported with JAK inhibitors[10,11] (particularly ruxolitinib[12]) and IL6-inhibitors[11] in retrospective series, these strategies have shown limited impact on controling CCF,[12] primarily acting by targeting inflammatory mediators. Given the lack of established treatment guidelines for VEXAS syndrome, further research is needed to determine whether to prioritize treatment on controlling the cytokine storm (using steroids, JAK inhibitors, or anti-interleukin agents) or on targeting the mutated clone (with AZA or even in some cases alloHSCT) and to determine the optimal scheduling for these approaches.

Our case report suggests that AZA may provide prolonged clinical and deep molecular responses in the treatment of VEXAS supporting its inclusion in the treatment regimen for these patients, particularly those with concurrent MDS. However, larger studies are needed to confirm these findings.

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Contributions

LPZ is the guarantor for this work and had access to the data. LPZ and VJ performed the research. LPZ, VJ and PF wrote the manuscript. All other authors provided clinical or biological care and reviewed the paper.

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Data-sharing statement

Data are available on reasonable request.

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