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CASE REPORT

Brentuximab-induced splinter nail haemorrhages in a patient with Sézary syndrome: A case report

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Sézary syndrome is a systemic variant of cutaneous T-cell lymphoma characterized by erythroderma, lymphadenopathy and circulating atypical lymphocytes (Sézary cells). It may present with nonspecific lesions on multiple digits. We describe an atypical case of brentuximab-induced splinter nail haemorrhages in a patient with Sézary syndrome, associated with a poor prognosis during follow-up. Concomitantly with the appearance of nail lesions, significant lymphocytosis was detected as well as infiltration of bone marrow and nail matrices. The lesions followed a precise sequence, which can be traced back to the monthly application of brentuximab and its direct cytotoxic effect on CD30+ T lymphocytes in the nail matrix. Brentuximab-induced nail lesions might be associated with decreased efficacy of brentuximab in this patient with advanced cutaneous T-cell lymphoma.

KEYWORDS
brentuximab, onychomadesis, Sézary syndrome, splinter haemorrhages

1 | INTRODUCTION

Sézary syndrome is a systemic variant of cutaneous T-cell lymphoma (CTCL) characterized by erythroderma, lymphadenopathy and circulating atypical lymphocytes (Sézary cells).[1,2] This rare form of CTCL accounts for <5% of all cases (affecting exclusively adults). It has a poor prognosis (median survival 32 months from diagnosis), and patients often die of opportunistic infections due to immunosuppression.[1,2]

Clinically, when Sézary syndrome involves the nails, it may present with nonspecific lesions such as subungual hyperkeratosis, yellow nail discolouration, onycholysis, Beau lines (horizontal depressions of the nail plate), paronychia, leukonychia, onychomadesis and twenty-nail dystrophy, which are rarely caused by CD30+ T lymphocyte nail matrix infiltration.[3,4]

We describe an atypical case of brentuximab-induced splinter nail haemorrhages in a patient with Sézary syndrome, associated with a poor prognosis during follow-up. Brentuximab-induced nail lesions might be associated with decreased efficacy of brentuximab in this patient with advanced CTCL.

Nika Filipovic was the principal investigator in this study.

2 | CASE REPORT

A 72-year-old Caucasian female patient was admitted to our hospital due to pruritic erythroderma, axillary lymphadenopathy, violaceous patches and plaques with painless subungual hyperkeratosis, yellow nail discolouration, and hyperkeratosis on her palms and soles.

On admission, the peripheral blood counts revealed a white blood count of 14 520/μL (reference range 4000–11 000/μL) with 55% lymphocytes. Flow cytometry showed an elevated Sézary cell count of 4700 cells/μL. The lactate dehydrogenase level was elevated at 350 U/L (reference range, 135–214 U/L), β_2-microglobulin was also elevated at 3.51 ng/L (reference range, <2.4 ng/L), while no HTLV-1 antibody was detected.

Excisional biopsies of affected skin and an involved axillary lymph node were performed. Histopathological analysis revealed dense, bandlike infiltrates of atypical lymphocytes in the dermis forming large and irregular nests (Figure 1A). The infiltrates were composed predominantly of CD4+ and CD30+ cells (approximately 50%) with loss of CD7+ (leu 9) cells (Figure 1B). Peripheral flow cytometry revealed immunophenotypically a predominance of CD4+ over CD8+ cells (with a ratio of 22:1). Histological and immunohistochemical staining

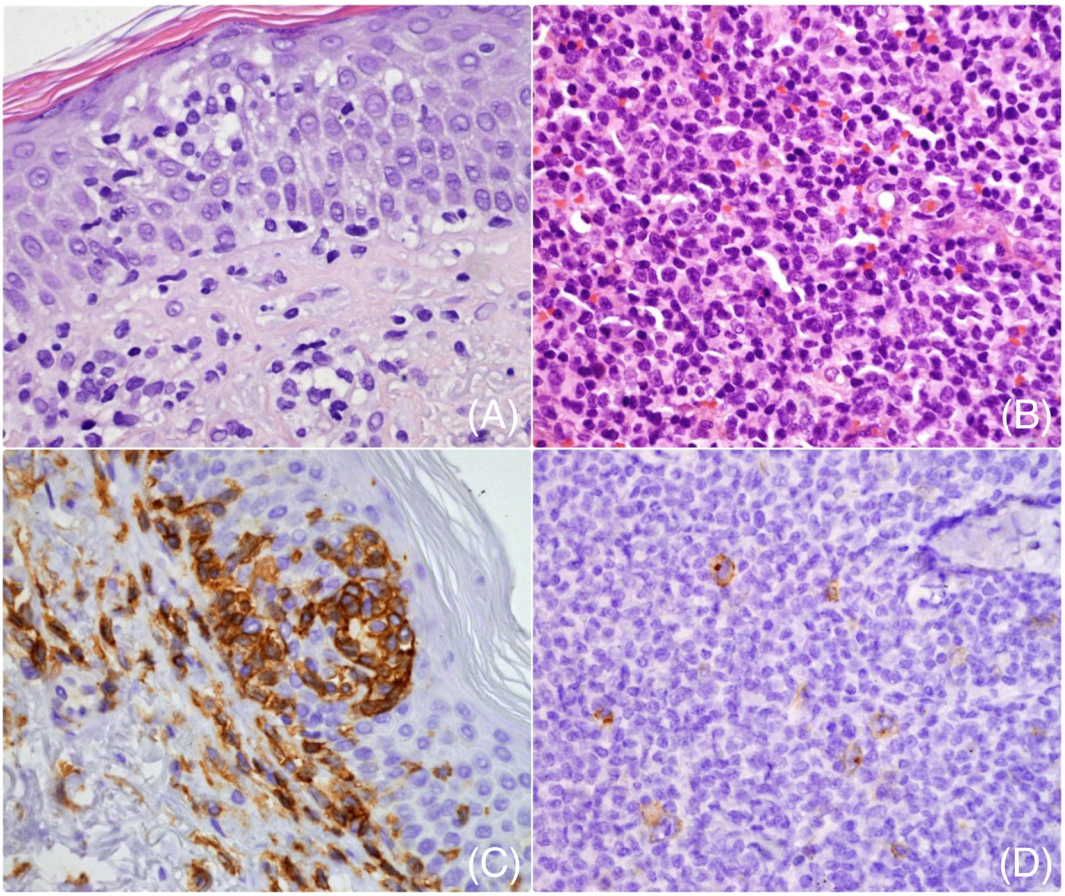

FIGURE 1 Skin (A) and axillary lymph node (B) biopsy specimens showing dense infiltration of neoplastic T cells (haematoxylin–eosin stain, 60×). Immunohistochemical staining of the skin (C) and axillary lymph node (D) shows CD4 and CD30 positivity, respectively (original magnification 60×)

of an axillary lymph node revealed neoplastic cells positive for CD4 and CD30 (Figure 1C,D). The skin, axillary lymph node and blood cells showed clonal T-cell receptor β gene rearrangement. Positron emission tomography–computed tomography scans of the thorax, abdomen and pelvis were performed. Multiple enlarged lymph nodes were found in both axillae (diameter up to 2.4 cm) and groin (diameter up to 1.7 cm). Mediastinal, abdominal and pelvic lymph nodes were within the physiological range (diameter up to 0.8 cm). Consequently, Sézary syndrome was diagnosed in January 2020 in stage IVA2 (T4N3M0B2) and **brentuximab vedotin** therapy was started in April 2020. Onychomycosis, traumatic onychodystrophy, psoriasis, parapsoriasis, atopic dermatitis, pityriasis rubra pilaris and pityriasis lichenoides chronica were all excluded by laboratory and histological findings.

The patient was treated with narrowband UV-B phototherapy with topical steroids and Re-PUVA (retinoid plus 8-methoxypsoralen-UVA) but all of these treatments did not have a significant effect.

The patient then received 15 cycles of 1.96 mg/kg of brentuximab vedotin, a conjugate of an anti-CD30 antibody and monomethylauristatin E, which inhibits the polymerisation of microtubuli. There were 30-day intervals between individual cycles, while the follow-up period was 20 months. The patient was not using any other drugs during this treatment. After 15 cycles, the patient reported bandlike splinter nail haemorrhages, the disruption of the delicate spiral arteries of the nail bed and painful sensations (Figure 2A). Concomitantly with the appearance of these nail lesions, the disease progression to stage IVB (T4N3M1B2) Sézary syndrome was documented. Two weeks before the 15th cycle, significant lymphocytosis and systemic involvement of the spleen and the liver as well as infiltration of the bone marrow and nail matrices were recorded. At this time, the patient's white blood count, lactate dehydrogenase and β_2-microglobulin were significantly elevated at 24 290/μL, 733 U/L and 6.42 ng/L, respectively. The therapy was discontinued after the 16th cycle, which could explain the second bandlike nail lesion seen in Figure 2B.

3 | DISCUSSION

Sézary syndrome is a form of CTCL caused by malignant proliferation of central memory T cells and is characterized by exfoliative erythroderma, lymphadenopathy and neoplastic T cells with hyperconvoluted cerebriform nuclei (Sézary cells). Criteria recommended for the diagnosis of Sézary syndrome include demonstration of an expanded CD4+ T-cell population resulting in a CD4+ to

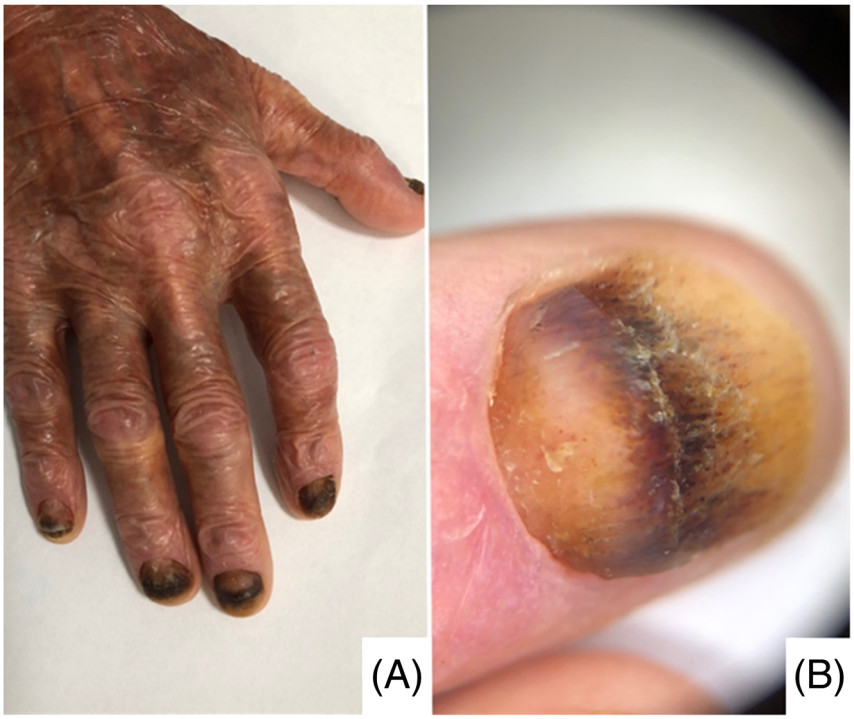

FIGURE 2 Brentuximab-induced nail lesions in a patient with Sézary syndrome. (A) Clinically, all nail plates on both hands and feet were heterogeneously yellow, red and brown pigmented with a complete destruction of the distal half of the nail plate. (B) Prominent sequential splinter nail haemorrhages observed on dermoscopy after 16 cycles of therapy with brentuximab: lesions on the middle of the nail plate mark the 15th, while the lesions seen on the lunula mark the 16th cycle of therapy

CD8+ ratio >10, and/or an aberrant expression of pan-T-cell antigens, and an absolute Sézary cell count of ≥1000 cells/μL.[2] Preferably, the same T-cell clone should be found in the skin, lymph nodes and peripheral blood. Clinically, this syndrome presents with intensely pruritic and thickened erythematous skin of the face (*facies leonina*), ectropion, alopecia, palmoplantar hyperkeratosis and onychodystrophy, which may present with nonspecific lesions such as subungual hyperkeratosis, yellow nail discolouration, onycholysis, Beau lines (horizontal depressions of the nail plate), paronychia, leukonychia, onychomadesis and twenty-nail dystrophy.[5–7]

Our patient presented with pruritic erythroderma with marked exfoliation, characteristic facial features, cervical and axillary lymphadenopathy, violaceous patches and plaques with painless subungual hyperkeratosis, yellow nail discolouration without any signs of haemorrhages, and hyperkeratosis on her palms and soles, indicating CTCL. The diagnosis was further confirmed with immunophenotypic analysis, which showed the same population of expanded CD4+ and CD30+ cells in the skin, lymph nodes and peripheral blood as well as a significantly elevated CD4:CD8 ratio.

Brentuximab vedotin is a chimeric IgG1 antibody against CD30, covalently coupled to the monomethyl auristatin E, which binds tubulin to prevent polymerization, thereby disrupting the microtubule network.[1] Brentuximab vedotin binds CD30 receptor on the surface of malignant CD30+ T cells, after which it is internalized and trafficked to lysosomes where monomethyl auristatin E is released and exerts its antimicrotubule activity within the cell, leading to cell cycle arrest at the G2/M phase.[8] This anti-CD30 antibody–drug conjugate has reduced systemic toxicity by targeting the delivery of antitubulin agent to the specific subpopulation of T cells only after cellular entry. In addition to the direct cytotoxic mechanism of action of monomethyl auristatin E within the cell, brentuximab may also interfere with the nuclear factor-κB signalling pathway, thereby preventing T-cell proliferation.[8]

Furthermore, monomethyl auristatin E may cause additional effects by diffusing out of CD30+ T cells via membrane permeability and exerting cytotoxic effects on neighbouring cells in vitro.[8]

Brentuximab was chosen as a first-line treatment in this case due to its specificity for malignant CD30+ T cells which were predominantly found in our patient with Sézary syndrome.[1] Within the first 2 months of therapy, the patient had a rapid response, the condition of her skin improved and normal blood values were recorded. Two weeks before the 15th cycle of therapy, the disease progressed to IVB (T4N3M1B2) stage, with significant lymphocytosis and systemic involvement of the spleen and the liver as well as the infiltration of bone marrow.

After 15 cycles of therapy, distinct bandlike splinter nail haemorrhages on all digits and the disruption of the delicate spiral arteries of the nail bed were noted, with the patient reporting painful sensations. The nail lesions found on initial examination, prior to the start of therapy with brentuximab, were nonspecific and painless. The appearance of brentuximab-induced nail lesions occurred simultaneously with a significant increase of Sézary cells in peripheral blood as well as in the bone marrow and nail matrices. According to the summary of product characteristics, the half-life of brentuximab in humans is 4–6 days, which could explain the lack of nail lesions between 2 applications of brentuximab.[9]

After the 16th cycle, the patient developed second bandlike haemorrhages on all nail matrices, thus the therapy was discontinued. This was considered as a severe adverse event and a poor prognostic sign which required the change in the treatment protocol.

Longitudinal nail growth provides an accurate insight into the effects of brentuximab on malignant CD30+ T lymphocytes which can be seen in Figure 2B.

In Sézary syndrome, nail involvement usually affects multiple digits, with an unpredictable course. Although the impact of nail alterations on disease prognosis has not been extensively described in the literature, Bishop *et al.*[10] report that nail alterations may be useful in analysing the effectiveness of systemic treatment. Further analyses and larger studies are required to determine whether brentuximab-induced nail haemorrhages have prognostic significance in patients with advanced Sézary syndrome.[10,11]

In very rare cases in which Sézary syndrome presents with nail haemorrhages, the entire nail plate is usually involved, unlike in this case, where lesions followed a precise sequence that can be traced back to the monthly applications of brentuximab and its direct cytotoxic effects on CD30+ T lymphocytes in the nail matrix.[12–14]

This adverse event caused by brentuximab has not yet been reported in the scientific literature, and we hope that these findings will encourage physicians to pay more attention to nail lesions in patients undergoing treatment for Sézary syndrome.

3.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019 a,b).

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COMPETING INTERESTS

The authors declare no conflicts of interests.

AUTHORS' CONTRIBUTIONS

N.F., V.B. and M.D.A. wrote the manuscript and performed literature review, S.G. provided details of the pathohistological analysis and R.L. performed critical revision of the manuscript and assessed brentuximab side effects.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND/OR ANIMALS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and following the guidelines of the 1964 Helsinki declaration and its later amendments.

INFORMED CONSENT

Informed consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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