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A T-cell PTLD in an unused arteriovenous fistula successfully treated with single-agent Brentuximab vedotin first-line therapy

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Disclosure

The authors declare no conflict of interest.

A 58-year-old woman was admitted to our hospital with fever, malaise and weight loss for more than 18 months. She has been treated with antibiotics for pneumonia twice, but fever and fatigue recurred. She received a kidney transplant due to chronic pyelonephritis 20 years ago. Induction therapy was performed with cyclosporine, mycophenolat mofetil and corticosteroids. Therapy with corticosteroids was withdrawn in 2010. She was seronegative for Epstein-barr virus (EBV) and received a kidney from a seronegative donor. The post-transplant course was unremarkable without any episodes of rejection. The physical examination unveiled several enlarged cervical, left-sided supraclavicular and axillary lymph nodes. Her former left-sided arteriovenous (av) fistula was thrombotic since a while, but she reported a sudden enlargement with signs of inflammation. Laboratory findings revealed a stable renal function (estimated glomerular filtration rate 65 mL/min), anaemia and

thrombocytopenia, a slightly elevated C-reactive protein, while leukocytes were within the normal range. LDH was increased (516 U/L, normal range < 214 U/L). EBV DNA was PCR-detectable in the serum; the quantification revealed a copy number of 9,870/mL. A positron emission tomography/computed tomography (PET/CT) detected fluorodeoxyglucose (FDG) enhancement in the mass of the AV fistula and in several enlarged axillary lymph nodes (Fig. 1 A, B). Surgical resection of an aneurysmatic brachial artery with a soft tissue mass (6.5 x 5.5 x 3.0 cm) underwent histological examination. A dense infiltrate consisting of diffusely growing large, occasionally multinucleated, lymphoid blasts, that expressed CD30 and the cytotoxic molecule perforin as well as several blasts with CD15 and CD3 expression led to the diagnosis of a monomorphous T-cell PTLD with features of an anaplastic large T-cell lymphoma (ALCL; Fig 1 C, D). The tumour cells did not express the anaplastic lymphoma kinase and specific markers of a latent EBV infection were undetectable.

A CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone)-like polychemotherapy remains the standard of care for T-cell lymphoma, although often producing disappointing results in this heterogeneous entity[1]. Moreover, regarding $CD20^+$ B-cell PTLD, CHOP-based induction therapy might be effective, but comes with an unacceptably high treatment-related mortality in this particular group of immunocompromised patients[2]. Therefore, a B-cell PTLD-tailored induction protocol was introduced consisting of four initial courses of single-agent anti-CD20 Rituximab immunotherapy followed by another four cycles of a CHOP regimen, achieving excellent long-term survival, largely attributable to reduced toxicity, in Rituximab responders[3]. Given the frail overall condition of our patient at initial presentation, rendering her ineligible for a systemic CHOP-like chemotherapy, we considered here – in analogy to the anti-CD20 Rituximab mono-strategy against B-cell PTLD – an anti-CD30 Brentuximab vedotin (BV) mono-strategy against her T-cell PTLD.

BV is currently approved for the treatment of patients with relapsed/refractory Hodgkin's lymphoma after failure of a high-dose chemotherapy with autologous stem-cell support or two previous lines of polychemotherapy in transplant-ineligible patients, and for patients with systemic ALCL after at least one preceding multi-agent chemotherapy. We found off-label use of BV a particularly appealing option for our patient, since BV is actually an antibody-drug conjugate, designed to deliver relatively high doses of the cytotoxic moiety selectively to their cellular targets while producing limited systemic toxicity. Moreover, BV, unlike Rituximab, does not rely on immune-mediated effector principles (like antibody-dependent cellular cytotoxicity) that may not be fully operational in immunosuppressed recipients of solid organ transplants.

Three courses of BV (1.8 mg/kg bodyweight) were administered every three week. Unfortunately, she developed severe polyneuropathy in her lower extremities, a common side effect of BV therapy, leading to the cessation of BV therapy. Despite no histological evidence of B-cell lymphoproliferation, but due to repetitively positive PCR analyses for EBV DNA in the serum, additional Rituximab therapy (375mg/m^2) was given twice, each dose 10 to 12 days after the first and second cycle of BV, resulting in a negative EBV test after four weeks. Studies about the efficacy of BV monotherapy or even in combination with Rituximab are limited. Very recently, encouraging phase 2 results about the use of single-agent BV in patients with relapsed or refractory $CD30^+$ diffuse large B-cell lymphoma as well as cutaneous T-cell lymphoma and ALCL-related lymphoproliferative disorders were reported [4,5]. To the best of our knowledge, our case represents the first administration of BV monotherapy in the initial treatment of a $CD30^+$ PTLD, which manifested at an unusual site in an unused av fistula. PTLD represent a major complication after solid organ or hematopoietic stem cell transplantation. Approximately 85% of PTLDs are of B-cell origin, while the proportion of T-cell PTLD is only 10-15%. The rate of EBV association is about 50% overall,

with less than 10% in the late cases[3]. Despite the – expected – non-detectability of EBV components in the T-cellular ALCL population, we cannot exclude a co-founding, T-cell proliferation- and –transformation-promoting role of adjacent EBV-positive B-cells. In general, the vast majority of PTLD cases has been found to be $CD30^{+}$ [6], although testing for CD30 immunoreactivity is not mandatory in the approved BV indications. Concomitant use of corticosteroids should be avoided, since it may result in the rapid downregulation of the CD30 target. In the case of our patient, a follow up PET/CT 6 months after the first diagnostic PET (Fig 1 E, F) showed a complete remission. Future follow-up will be based on clinical examination, CT scans and potentially PET[7]. A very recent PET/CT after 2 more years still showed no signs of recurrence, and our patient is in good health.

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Figure legends

Figure 1

PET/ CT detected FDG enhancement in the mass of the AV fistula, and furthermore in several enlarged axillar lymph nodes (A, showing the maximum intensity projection; B, CT showing the mass lesion in the left cubital fossa). Follow up FDG PET/ CT six months later showed no more evidence of significantly increased FDG uptake (E, F).

Histological analysis of the dissected tumour shows a dense infiltrate which consists of sheets of large lymphoid blasts that are occasionally multinucleated (C, haematoxylin and eosin stain x40). All blasts express CD30 (D, immunostains using monoclonal anti-CD30 antibody clone BerH2 x40).

Figure