An atypical case of EBV-positive plasma cell post-transplant lymphoproliferative disorder successfully treated with adoptive cell therapy.

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Post-transplant lymphoproliferative disorder (PTLD) is an uncommon complication of allogeneic haematopoietic stem cell transplantation (HSCT). Incidence ranges from 1-11%, with higher rates seen with mismatched and unrelated donors (1). Plasma-cell PTLD is a rare subtype of monomorphic PTLD, accounting for 4-6% of cases in solid organ transplant (SOT) recipients (2-4); incidence is not characterised in the post-HSCT setting.

Plasma-cell PTLD presents a particular treatment quandary. The mainstay of PTLD therapy comprises reduction of immunosuppression (RI) and rituximab alone or in combination with chemotherapy. In plasma cell PTLD, RI is not associated with long-term survival (4, 5), rituximab is not effective given CD20 negativity, and treatments incorporating chemotherapy have reduced overall survival (OS) compared with non-chemotherapy-based regimens (5). Proteasome inhibitor-based regimens are being increasingly used with improving survival, however prognosis remains poor with median OS 2.4 years (5). Novel approaches to treatment are needed in this space.

We describe herein a particularly unusual case of plasma cell PTLD successfully treated with one such novel approach to treatment – adoptive cell therapy with Epstein Barr Virus (EBV)-specific cytotoxic T lymphocytes (CTLs).

A 24-year-old female underwent fludarabine/melphalan/anti-thymocyte globulin conditioned matched unrelated donor HSCT for EBV-negative Hodgkin lymphoma. EBV serostatus was donor negative/recipient positive. After an uncomplicated transplant admission, she was readmitted on day+45 with rapidly enlarging cervical lymphadenopathy, abdominal pain and melaena. EBV viral load (VL) had risen from undetectable to 4164 IU/mL.

PET scan demonstrated intense FDG-avid uptake in nodes above and below the diaphragm, with extra-nodal uptake in bowel and spleen (Figure 1B). Right cervical lymph node core biopsy revealed effacement by plasma-cell PTLD, with immunohistochemistry demonstrating CD138 and CD20 negativity, CD38 and EBV positivity by Epstein-Barr encoding region in situ hybridization (EBER-ISH), and cytoplasmic kappa light chain (KLC) restriction; biopsy of small and large bowel identified the same population, with no features of graft versus host disease (GVHD). Plasma cell flow cytometry was not performed on nodal and gut tissue. Bone marrow biopsy demonstrated a clonal plasma cell infiltrate accounting for 20% of cellularity, which in contradistinction to node and gut biopsy was CD138 positive by immunohistochemistry and flow cytometry. Inverse EBV seromismatch and early post-transplant presentation suggested recipient-origin PTLD; molecular chimerism by Short Tandem Repeat analysis on nodal tumour tissue confirmed this, with 84% recipient origin in tumour on day+50 post-transplant, while peripheral blood donor chimerism was 100%.

Initial management comprised a single dose of rituximab 375g/m² prior to demonstration of CD20 negativity, and concomitant rapid wean of cyclosporin immunosuppression from 225mg twice daily to cessation at 14 days. No response was achieved, with twice-weekly monitoring of EBV demonstrating
ongoing rise in VL to a peak of 92,648 IU/mL. Worsening abdominal pain requiring total parenteral nutrition ensued alongside a rise in total protein and globulins to 105g/L and 88g/L respectively, and hyperviscosity syndrome developed with headaches and visual impairment. Ophthalmoscopy demonstrated dilated central retinal veins, cotton wool spots and intra-retinal haemorrhages. Serum protein electrophoresis revealed an IgM paraprotein of 67g/L; MYD88L265P mutation was negative. Urgent plasmapheresis was performed with resolution of abdominal pain, headache, and visual impairment. Given the clinical response of abdominal pain to plasmapheresis, this was favoured to be related to evolving PTLD and hyperviscosity rather than emergent gastrointestinal GVHD; endoscopy was not repeated.

The patient was enrolled in a clinical trial of partially HLA-matched third-party donor EBV-specific CTLs and infused with $2 \times 10^7$ CTL/m$^2$ on day+17 following presentation with PTLD (day+62 post-transplant). Clinical and biochemical response occurred within days, with fall in EBV VL, resolution of lymphadenopathy, and reduction in paraprotein. Persisting low-level EBV viremia was noted 12 weeks post-infusion, with 5% residual disease seen on repeat bone marrow biopsy, and restaging PET demonstrating partial response with resolution of nodal disease and ongoing albeit improved bowel activity (Figure 1C). A second CTL infusion (same donor/dose) for residual disease was given on day +86 following presentation with PTLD (day+131 post-transplant). PET complete metabolic response was subsequently achieved (Figure 1D) and EBV VL fell below the detection threshold. At 18 months post-transplant the patient remains in ongoing PET complete metabolic response, with morphologic and immunophenotypic complete remission on bone marrow biopsy, undetectable EBV, and no GVHD. However, evidence of minimal residual disease is noted biochemically, with IgM kappa paraprotein remaining detectable below the level of quantitation. Serial PET-CTs and EBV VL/paraprotein trends relative to CTL infusion are depicted in figures 1 and 2.

This case is particularly unusual in several aspects. In HSCT patients, PTLD typically derives from the donor graft – recipient-derived plasma-cell PTLD is exceedingly rare (6). Furthermore, plasma cell PTLD is nearly always CD138 positive (3, 4, 7), with only one prior published case of CD138 negativity (3). The immunophenotypically distinct CD138-negative gut/nodal disease identified in this case may indicate evolution of a more aggressive subclone; indeed, in de novo myeloma CD138 negative populations are characterised as more immature and proliferative than CD138 positive populations (8). While false negative immunostaining cannot be excluded, this was favoured less likely given CD138 negativity by immunohistochemistry across multiple separately fixed gut and nodal samples with positive staining of control tissue. Finally, while plasma-cell PTLD is commonly associated with paraproteinaemia, typically only modest elevations are seen (2, 4). De novo IgM myeloma accounts for less than 0.5% of cases (9), and only rare cases of IgM secretory plasma-cell PTLD are reported (4, 10). The high-level IgM paraprotein and hyperviscosity syndrome seen in this case is atypical though not undescribed – a previous case of plasma-cell PTLD presenting with IgM hyperviscosity syndrome has been reported in a paediatric liver transplant recipient (10).

With half of plasma-cell PTLD cases expressing EBV (3, 4, 7), adoptive immunotherapy with EBV-CTLs is a promising emerging treatment. EBV-CTLs may be delivered within an unmanipulated donor
lymphocyte infusion (DLI) or as a selectively expanded line of EBV-CTLs of donor, recipient, or third-party origin. In HSCT-recipients EBV-CTLs have been shown to both prevent and successfully treat EBV-PTLD (11-13). Outcomes vary by CTL source, with response rates of 70% for DLI, 70-90% for donor-derived EBV-CTLs, and 50-70% for third-party CTLs (12). Third party ‘off-the-shelf’ CTLs have the benefit of rapid availability and negligible GVHD risk (12). A prospective phase II trial of third-party EBV-CTLs in 31 SOT and 2 HSCT recipients with EBV-PTLD refractory to conventional therapy demonstrated 64% and 52% response rates at 5-weeks and 6-months, with better outcomes seen in best-HLA matched donor CTLs (13). No studies to date have reported outcomes of EBV-CTL therapy by subtype of PTLD. This is to our knowledge the first reported case of successful treatment with EBV-CTLs in the plasma-cell subtype of PTLD, highlighting EBV-CTLs as a promising therapeutic option for future cases.


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