Aids-related plasmablastic lymphoma of the oral cavity associated with an IgH/MYC translocation—treatment with autologous stem-cell transplantation in a patient with severe haemophilia-A

Plasmablastic lymphoma is an AIDS related lymphoma that continues to have a poor prognosis despite significant advances in the management of HIV and lymphoproliferative diseases. In part this has been due to limited insights into the biology of this disease and the molecular mechanisms of oncogenesis. To date molecular abnormalities have not been described in plasmablastic lymphoma, and its aggressive clinical behaviour has been difficult to understand. We describe the first reported cytogenetic abnormality in plasmablastic lymphoma, an IgH/MYC translocation. It is also the first description of autologous stem cell transplantation in a patient with severe haemophilia A.

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Plasmablastic lymphoma (PBL) is a rare and aggressive malignancy that arises in the gingiva of HIV infected patients for which there is little literature to guide therapy. Strategies have included systemic chemotherapy and/or radiotherapy plus highly active antiretroviral therapy (HAART). Despite significant advances in the management of HIV and lymphoma, PBL continues to have a poor outcome with most series describing a median survival of less than 12 months. A better understanding of the biology of the disease is required to develop more effective therapies. The immunophenotype of PBL is consistent with neoplastic transformation of a late B-cell, however, the molecular mechanisms of oncogenesis in this disorder are poorly understood. We describe a case of PBL associated with an IgH/MYC translocation, the first reported cytogenetic abnormality in this disease. It is also the first description of autologous stem cell transplantation (ASCT) in a patient with severe haemophilia A.

A 36-year-old male with severe haemophilia-A (baseline factor VIII <1%) and transfusion acquired HIV, presented with gingival hyperplasia surrounding a left lower molar. Gingival biopsy revealed large plasmablasts with an immunophenotype consistent with PBL (Figure 1). He was HIV treatment naïve with a viral load of 33,200 copies/mL and CD4 lymphocyte count 192 cells/µL, he was also noted to be seropositive for EBV (IgG) and seronegative for CMV. The lymphoma was stage 1A and his age-adjusted IPI was low. In concordance with the diagnosis of PBL, his serum protein electrophoresis and serum free light chain assay did not reveal a monoclonal gammopathy at diagnosis or throughout the course of his disease. He commenced HAART and CHOP-14 with good initial response. Despite excellent virological control, local relapse followed the fifth cycle of CHOP-14. Salvage radiotherapy was minimally efficacious, however, salvage chemotherapy with IVAC6 resulted in a good partial response. Peripheral blood stem cells were collected and he proceeded to ASCT. The conditioning regimen included carmustine (BCNU) 150 mg/m² (day -7 to day -5); etoposide phosphate 68.12 mg/kg (day -4); and cyclophosphamide 100 mg/kg (day -2), following which 2.7x10⁶ CD34+ cells per kg of body weight were infused (day 0). Time to neutrophils ≥ 1.0x10⁹/L and platelets 20x10⁹/L (with no subsequent transfusion support) was 11 days.

Prior to his presentation with PBL he suffered from a moderate deforming haemophilic arthropathy affecting

Figure 1. Morphology, immunophenotype and proliferation index of the original gingival biopsy. (A) Haematoxylin and Eosin stain demonstrating sheets of large neoplastic cells with plasmablastic morphology (see insert). (B) Ki67 staining demonstrates a high proliferative index. The immunophenotype of this lymphoma is consistent with terminally differentiated B-cells staining positive with (C) CD138 and (D) LCA-CD45. There is kappa-restriction (E) with staining for lambda light chains being negative (F). There is some weak staining with (E) CD79a, however these cells do not express (F) CD20. These cells also did not express CD30, CD10, CD43, HHV8-LNA1 or EBV-LMP1 (not shown).

Figure 2. Fluorescence in situ hybridization studies: (A) A bone marrow metaphase spread showing two IGH/MYC fusion signals (arrowed) on the der(8)t(8;14) and der(14)t(8;14) respectively (Probe used: LSI IGH/MYC, CEP 8 tricolor set, dual fusion translocation probe set - Vysis); (B) Interphase FISH performed on a paraffin embedded section of the original gingival biopsy also showing IGH/MYC fusion signals (arrowed) (Probe used: LSI IGH/MYC, CEP 8 tricolor set, dual fusion translocation probe set - Vysis).
his knees and ankles bilaterally. He was fully ambulant and self-sufficient in all his activities of daily living. He was not on prophylactic treatment and suffered from infrequent spontaneous bleeds (approximately 3-4 times a year), which was managed with home-therapy. During therapy for PBL, his haemophilia was managed with 20U/kg recombinant factor-VIII (rFVIII) daily whilst receiving outpatient chemo/radiotherapy and whilst an inpatient he received a continuous infusion of rFVIII to maintain factor levels ≥ 40%. Before procedures and during times of sepsis his infusion was altered to achieve FVIII levels ≥ 100%. Platelet count was maintained ≥ 20 x 10^9/L (nadir during therapy was 21x10^9/L). There were no bleeding problems with strict adherence to these haemostatic goals.

Following his ASCT on maintenance HAART he retained good virological control with viral load of <50 copies/mL and CD4 count 47 cells/µL. The patient chose to discontinue his HAART 4 months following ASCT and within 2 months of HAART cessation had a viral load of >100,000 copies/mL and CD4 count of 7 cells/µL. He remained asymptomatic for a further 4 months but subsequently had a florid systemic relapse with circulating plasmablasts present in peripheral blood. Conventional cytogenetics performed on a bone marrow aspirate sample demonstrated t(8;14)(q24;q32) with FISH demonstrating IgH/MYC fusion (Figure 2A). This was confirmed to be present on the initial diagnostic specimen with IFISH on the paraffin fixed gingival biopsy (Figure 2B). His disease followed an aggressive course and he died 14 months following diagnosis.

PBL is a unique B-cell lymphoma recognized as a distinct nosological entity. The majority of PBL appears to originate from post germinal centre B-cells, similar to the other AIDS-related lymphomas (ARL).

At present four main molecular pathways have been implicated in the development of ARL. These include PAX-5, RHO/TTF, PIM1 and MYC. Whilst there has been considerable research into the molecular histogenesis of the ARL, no genetic aberration has been previously described for PBL. A common mode of lymphomagenesis in the ARL is thought to involve concurrent infection with viruses including HHV-8 and EBV. Indeed EBV onc viral proteins have been demonstrated in mouse models to cooperate with MYC in the development of lymphoma. Whilst, the EBV associated antigen LMP-1 was not demonstrated in this case, it is noteworthy that at least 50% of PBL have been associated with EBV infection with only 5% showing LMP-1 expression. It therefore remains plausible that in the other ARL, EBV infection may play an integral role in the pathogenesis of PBL. The demonstration of an IgH/MYC fusion may account for the rapid proliferation and aggressive clinical course seen in PBL and potentially provides a better understanding of this disease. Whilst it is premature to suggest all PBL is associated with deregulation of MYC, it is important that clinicians and pathologists are aware of this possibility and perform cytogenetic evaluation of tissue samples. Identification of MYC deregulation may in the future lead to more targeted therapies that alter the dismal outcome of this disease.