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Post-transplant lymphoproliferative disorders presenting as gingival overgrowth in patients immunosuppressed with ciclosporin. A report of two cases

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Abstract

Background: Post-transplant lymphoproliferative disorder (PTLD) can occur in patients maintained on immunosuppressive therapy following transplantation. This paper describes two cases of PTLD occurring in gingival tissues, in patients receiving ciclosporin following cardiac transplantation.

Treatment: The lesions were localised to gingival tissues, mimicking ciclosporin-induced gingival overgrowth. They were removed surgically and the ciclosporin dose reduced to help prevent recurrence.

Conclusion: The importance of histopathological examination of all tissue removed during routine gingivectomy procedures for ciclosporin-induced gingival overgrowth is highlighted.

Key words: ciclosporin; gingival overgrowth; non-Hodgkin's lymphoma; post-transplant lymphoproliferative disorder

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The non-Hodgkin's lymphomas (NHL) are neoplastic disorders of lymphocyte growth associated with significant morbidity and mortality. They arise by malignant proliferation of lymphoid cells that become arrested at different stages of differentiation (Raut et al. 2000). In the oral cavity, B-cell lymphomas predominate (Solomides et al. 2002). Oral lymphomas can mimic inflammation (Spatafore et al. 1989) and have a variety of presentations, ranging from ulceration (Raut et al. 2000) to gingival enlargement (Spatafore et al. 1989, Gould & Alpert 1987).

In the UK, nearly 3000 solid organs are transplanted every year and, in total, more than 1 million transplants have been carried out during the last 25 years (UK Transplant website). To prevent rejection, patients receive immunosuppressants. Ciclosporin is a widely used, potent immunosuppressant that acts on T-cell immunity without myelosuppression (Bennett & Norman 1986). A known unwanted effect of ciclosporin is gingival overgrowth (Hassell & Hefti 1991), although the mechanism of ciclosporin-induced gingival overgrowth is poorly understood. Gingival changes are seen in approximately 25% of patients medicated with ciclosporin (Thomason et al. 1996) but this may rise to more than 60% in patients medicated with both ciclosporin and a calcium channel blocker (Thomason et al. 1995). Proposed contributory factors include genetic predisposition, age and sex of the patient and drug pharmacokinetic variables (Boltchi et al. 1999, Seymour et al. 2000, Thomas et al. 2000).

Post-transplant lymphoproliferative disorders (PTLDs) are a newly classified group of lymphoproliferative disorders within the WHO classification of haemopoietic neoplasms (Harris et al. 2001, Oertel & Riess 2002), occurring with long-term use of potent immunosuppressive drugs for prevention of transplant rejection. Latent infection with Epstein–Barr virus (EBV) has been identified as a major causative factor in PTLD, present in approximately 90% of cases. Up to 40% of cases of PTLD arise at extranodal sites (Raut et al. 2000) such as the stomach, intestine, bone, CNS, eyes and skin. This contrasts with NHL in immunocompetent patients, most of which are node based.

Risk factors for PTLD include age and EBV seronegativity at the time of transplant and the type of organ transplanted.

This case report describes two cases of PTLD presenting as gingival overgrowth, detected histologically in tissue removed during routine gingivectomy.

Case Report

Patient 1

This man underwent heart transplantation in 1992, at the age of 60. He had had a number of recurrences of gingival overgrowth since then, which were managed using routine gingivectomy procedures. When he was seen in early 2002 he was maintained on medication of ciclosporin (175 mg), azathioprine (25 mg), prednisolone (5 mg), phenytoin (300 mg) and aspirin (75 mg). In June 2002, he presented to his general dental practitioner complaining of swelling of the gingivae affecting the interdental papilla in the 12–13 region (Fig. 1). He reported that the lesion had been present for approximately 2 weeks and had grown in size fairly rapidly.

This lesion was consistent clinically with ciclosporin-induced gingival overgrowth, and was excised shortly after initial examination. Histology performed on the excised tissue, however, showed diffuse lamina propria infiltration by a monotonous population of large malignant-appearing lymphoid cells (Fig. 2). These were shown by immunohistochemistry to have a mature T-cell phenotype (CD3 positive, TdT negative, B-cell markers negative) and a very high proliferative fraction (90% of nuclei Ki67 positive). The process was classified as PTLD of monomorphic type; morphologically, a peripheral T-cell lymphoma, not otherwise specified, within the WHO system, composed of large cells. There was strong, uniform expression of EBV–EBER RNA sequences by the large cells, as detected by in situ hybridisation (Fig. 3).

Whole-body CT scanning revealed no other suspicious masses, nevertheless immunosuppression was reduced by stopping azathioprine and a gradual reduction in the dose of ciclosporin to achieve trough levels 50% lower than prediagnosis with surveillance cardiac biopsies.

At clinical review the lesion appeared to have been completely excised and there was no sign of recurrence after 1 year.

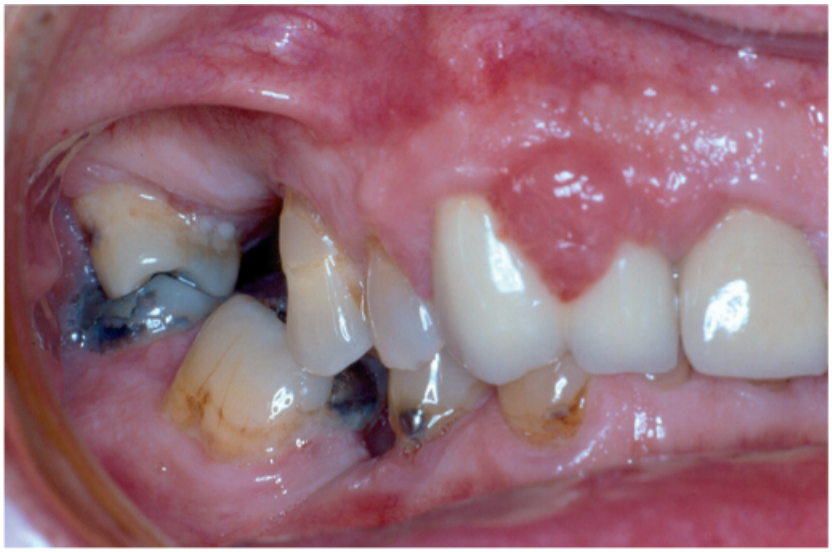

Fig. 1. Lesion resembling gingival overgrowth affecting the interdental papilla in the 12–13 region.

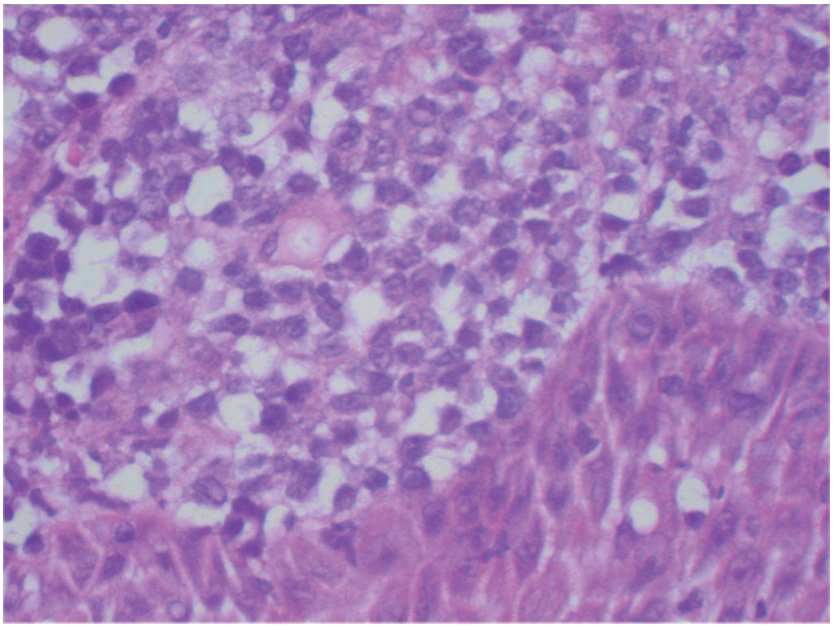

Fig. 2. Patient 1. Gingival lymphoid infiltrate in mucosa, showing heterogenous, large malignant-appearing lymphoid cells. (Base of squamous epithelium seen at lower edge.)

Patient 2

Patient 2 received a heart transplant in August 1997, aged 61, and had subsequently been maintained on a range of medications including immunosuppression with ciclosporin (200 mg), azathioprine (25 mg) and prednisolone (5 mg). The azathioprine was stopped prior to the occurrence of lymphoma for an unrelated reason.

He initially presented for dental assessment in September 2001, complaining of swelling in his upper edentulous maxilla. This swelling did not appear to be associated with the upper denture. The lesion was subsequently excised to facilitate denture wearing. Histology in this case showed areas of diffuse lamina propria infiltration by large malignant-appearing lymphoid cells resembling centroblasts and immunoblasts (Fig. 4). Sheets of atypical, large plasma cells were also present in deeper parts of the tissue. Immuno-

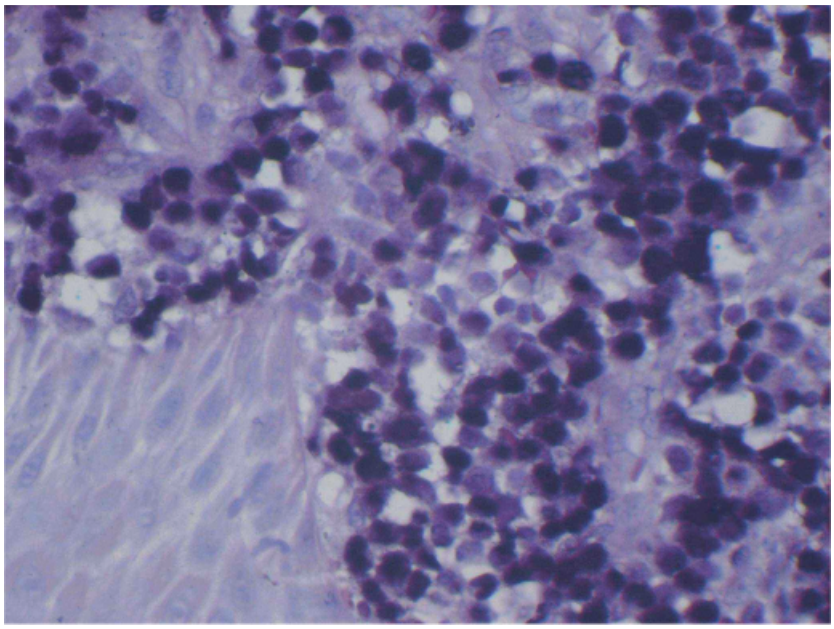

Fig. 3. Patient 1. Gingival lymphoid infiltrate with in situ hybridisation for EBV–EBER showing most nuclei to be EBV positive.

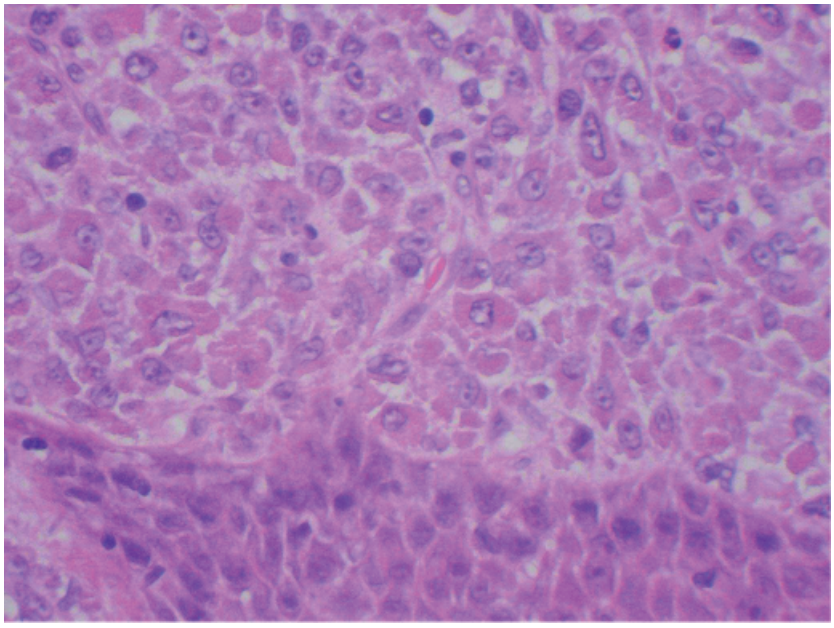

Fig. 4. Patient 2. Gingival lymphoid infiltrate in mucosa, showing monotonous, malignant-appearing lymphoid cells. (Base of squamous epithelium seen at lower edge.)

histochemistry showed the centroblastic and immunoblastic cells to have a B-cell phenotype and a Ki67-positive proliferative fraction of approximately 25%. The plasmablastic cells had a phenotype reflecting their pronounced plasma cell maturation (CD20 negative) and showed kappa immunoglobulin light chain mRNA restriction as evidence of monoclonality. The Ki67-positive proliferative fraction of these cells was only 5%, again in keeping with their marked plasma cell differentiation. Almost all cells, regardless of their precise cytological features, were strongly positive for EBV–EBER RNA, demonstrated by in situ hybridisation. The classification of this lymphoid proliferation was PTLD, monomorphic; morphologically, a diffuse large B-cell lymphoma within the WHO system, showing areas of plasmablastic differentiation.

Subsequent to the detection of this PTLD, the patient's cardiologist successfully reduced his ciclosporin dose without any signs of significant rejection. Whole-body CT scans performed shortly after the initial diagnosis and subsequently for monitoring purposes have shown no other suspicious masses.

At clinical review after diagnosis, the lesion appeared to have been removed completely. However in February 2002 a similar area of gingival overgrowth was again detected. This was biopsied and found to show PTLD, with features only of plasmablastic and plasmacytic differentiation on this occasion, and kappa light chain restriction plus high levels of EBV–EBER expression were found as before, with low proliferative activity. Subsequent to this recurrence, the patient's ciclosporin dose was again reduced, with no signs of transplant rejection.

At review in September 2002, the gingival area appeared completely normal, with no evidence of PTLD recurrence. However, a further recurrence developed subsequently, in January 2003, again with uniform plasmablastic/plasmacytic differentiation and low proliferative activity. There was no evidence of disease elsewhere, but the ciclosporin trough level was reduced further.

Discussion

Lymphoma affecting the oral cavity and gingival tissues may mimic an inflammatory process (Spatafore et al. 1989), making diagnosis based upon clinical appearance alone difficult. Malignant lymphomas are classified according to the origin, immunophenotype, genotype and growth patterns of the neoplastic cells. Studies of the immunohistology of lymphomas arising in the head and neck indicate that B-cell lymphomas predominate in the oral cavity and T-cell lymphomas predominate in the nasal cavity (Gulley et al. 1995, Solomides et al. 2002).

The incidence of lymphoproliferative diseases is significantly increased in patients with congenital or acquired immunodeficiencies. PTLDs form a newly classified group of lymphomas and lymphoma-like diseases within the WHO classification of haemopoietic malignancies. Their frequency is rising with progress in transplant medicine

involving increased use of potent immunosuppressive medication (Oertel & Riess 2002). PTLD may present as isolated or multiple tumour masses (Nalesnik 2002), which can affect any of the body's tissues. The allograft itself is commonly involved following lung, intestine, or pancreas transplants but only rarely following heart transplantation. Heart transplant patients show a high prevalence of PTLD affecting the gastro-intestinal tract and lung (Chen et al. 1993). In heart transplant patients, the estimated incidence of PTLD is 1.5–3% (Oertel & Riess 2002), with the majority of cases arising in the first two post-transplant years (Nalesnik 2002).

Three broad categories of PTLD have been identified (Oertel & Riess 2002): plasmacytic hyperplasia, polymorphic lymphoid proliferations and monomorphic lymphoid proliferations histologically equivalent to NHL. PTLD resembling Hodgkin's disease also occurs. A unifying feature is involvement of latent EBV infection in the development of most cases of all types of these lymphoid proliferations.

We have only been able to find one other case report of PTLD arising in the gingivae of a patient maintained on ciclosporin (Broudy & Sabath 1995). This was an incidental description of a lesion resembling gingival overgrowth in a heart transplant patient. Other authors have reported gingival and bone destruction resulting in crater-like defects (Raut et al. 2000, Maxymiw et al. 1991) in patients taking cyclophosphamide and azathioprine following bone marrow and renal transplantation, respectively. No accompanying lymphoproliferative process was noted.

As can be seen from the cases documented, plus others described elsewhere in the body, PTLD is associated with a number of immunosuppressant agents. To date, no one specific agent has been associated with a significantly greater risk of lymphoma than any others (Trofe et al. 2002). The major risk factors for PTLD are duration of immunosuppression, dosage of immunosuppressive agents, and the number of immunosuppressive agents used either together or sequentially (Legendre & Kreis 1992). It has been observed that administration of multiple immunosuppressants, either simultaneously or sequentially, may seriously impair lymphocyte function and may lead to the development of lymphoma (Penn 1992).

A well-reported, relatively common unwanted effect that can occur with ciclosporin therapy is gingival overgrowth (Seymour et al. 1996, 2000, Boltchi et al. 1999, Thomas et al. 2000). As seen in our patients, the appearance of PTLD may mimic or obscure that of gingival overgrowth in dentate patients and is not substantially dissimilar to that reported in edentulous subjects (Thomason et al. 1994). There is consequently a risk of missed or late diagnosis of PTLD if the possibility of lymphoma is overlooked in assessing apparently uncomplicated, benign gingival overgrowth in patients receiving immunosuppressive drugs.

Despite the common occurrence of EBV in oral secretions, there appears to be a low incidence of EBV associated with intra-oral lymphomas (Gulley et al. 1995) in Western populations. EBV elsewhere shows a strong association with T-cell lymphomas (Solomides et al. 2002). This virus is, however, believed to be the main causative factor in lymphocyte transformation to produce PTLD (Oertel & Riess 2002) being detected in the majority of cases. PTLD cells in both of the cases described in this report exhibited high levels of expression of EBV–EBER RNA.

The treatment strategy for PTLD is still controversial (Oertel & Riess 2002). If technically feasible, complete surgical resection of solitary lesions can result in complete remission. Both of our patients showed no indication of disease elsewhere as assessed by staging CT scans. The gingival tissue is clearly an accessible area, making complete resection a realistic goal. For less easily accessible lesions and for multi-site disease the first line of therapy is usually reduced immunosuppression where possible after histopathological diagnosis. Where the risk of allograft rejection is high, for example following heart transplantation, chemotherapy may be the preferred intervention (Preiksaitis & Keay 2001). Disease confined to one site appears to carry a better prognosis, and patients with localised disease are more likely to achieve complete remission (Choquet et al. 2002) than are those with disseminated disease. More recently, specific therapy with anti CD20 (B-cell) antibody (rituximab) has been utilised successfully in the treatment of this disease with fewer untoward effects than chemotherapy (Garnier et al. 2002).

Conclusion

There is an obvious need for vigilance and monitoring for oral lesions in immunosuppressed patients. In particular, these two cases highlight the importance of histopathology in determining the nature of gingival changes in patients maintained on ciclosporin-containing immunosuppressive regimes, in whom PTLD may mimic this common condition.

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