J Oral Pathol Med (2007) 36: 570–4

doi: 10.1111/j.1600-0714.2007.00557.x
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CASE REPORT

Calcineurin inhibitor-associated oral inflammatory polyps after transplantation

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Calcineurin inhibitors (cyclosporine and tacrolimus) have been used as the mainstay immunosuppressive therapy for solid organ and hematopoietic cell transplantations (HCT) to prevent allograft rejection and for prophylaxis and treatment of the chronic graft-versus-host disease. Adverse effects of these drugs include nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension and gingival hyperplasia. Association of oral non-gingival soft tissue hyperplasia with calcineurin inhibitor therapy has only recently been recognized and is thought to occur infrequently.We present four cases of oral non-gingival inflammatory fibro-vascular hyperplasias attributed to the use of calcineurin inhibitors following solid organ transplantation and HCT. These lesions interfere with function and must be differentiated from other oral lesions, and therefore should be surgically excised.
J Oral Pathol Med (2007) **36:** 570–4

Keywords: calcineurin inhibitor; immunosuppression; oral pathology; solid organ transplantation; stem cell transplantation

Case reports

Case 1

A 14-year-old Caucasian male was referred to the Division of Oral and Maxillofacial Surgery, Children's Hospital, Boston, MA, for evaluation of two tongue lesions. At 11 years of age he was diagnosed with BCR-ABL-positive acute lymphocytic leukemia and underwent a fully matched allogenic hematopoietic cell transplantation (HCT) from a sibling donor 1 year later (Table 1).

Examination revealed exophytic polypoid, multinodular masses on the right and left sides of the tongue each measuring 2.0×1.0 and 0.5×0.5 cm^2. It was unclear if he had oral chronic graft-versus-host disease (cGVHD). The lesions were surgically excised. Two months later, he relapsed and his cyclosporine A (CsA) was weaned over a 2-week period. He died 2 months later from leukemic relapse without recurrence of the oral lesions.

Case 2

An 8-year-old Caucasian male was seen at the Dana-Farber Cancer Institute, Boston, MA, for evaluation of a large tongue mass. He had been diagnosed with BCR-ABL-positive acute lymphocytic leukemia at 6 years of age and underwent a matched unrelated donor HCT (Table 1). He relapsed with disease in the bone marrow 5 months later. At that time CsA was discontinued over a 2- to 3-week period and he was administered imatinib followed by prednisone, 6-mercaptopurine, vincristine and methotrexate and a second remission was achieved. He underwent a second matched unrelated donor HCT 7 months later from the same donor and developed cGVHD of the liver.

Examination revealed a 2.0×1.0 cm^2 ulcerated, slightly tender, exophytic polypoid, multinodular mass on the right lateral side of the tongue (Fig. 1). There was reticulation of the tongue dorsum consistent with early mild oral cGVHD. The lesion was excised and he was continued on CsA. At 6- and 12-month follow-ups there was no recurrence, although he had persistent mild oral cGVHD.

Case 3

A 3-year-old Hispanic male was seen at the Dana-Farber Cancer Institute, Boston, MA, for evaluation of bilateral tongue masses. He had been diagnosed with purine nucleoside phosphorylase deficiency at 14 months of age and underwent matched allogenic HCT from his aunt at 18 months of age (Table 1). Five months following transplantation he had extensive erythematous and ulcerative oral cGVHD of the buccal mucosa and tongue.

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Accepted for publication February 27, 2007

Table 1 Summary of treatments prior to development of oral lesions

	Conditioning regimen	*Graft rejection or cGVHD prophylaxis regimen*	*Medications at time of lesion(s)*	*CNI dose and blood levels (ng/ml)*	*Duration of CNI therapy to onset of lesion(s)*
Case 1	Cy 60 mg/kg × 2 TBI 1400 cGy	CsA, MTX	CsA, lorazepam, ondansetron, magnesium, pentamidine	7 mg/kg/day (CsA) 150–200	75 days
Case 2	1st: Cy 60 mg/kg × 2 TBI 1400 cGy; 2nd: busulfan 1 mg/kg × 8 melphalan 60 mg/m^2 × 3	1st: CsA, prednisone, MTX; 2nd: CsA, prednisone	CsA, amphotericin B, amlodipine, clonidine patch, potassium, magnesium, phosphorus, aluminum hydroxide/ magnesium hydroxide/simethicone, prednisone, pentamidine	5 mg/kg/day (CsA) 120–200	2 months
Case 3	Cy 60 mg/kg × 2 busulfan 1 mg/kg × 8	CsA, discontinued after 2 months due to tremors FK506 substituted	Prednisone, tacrolimus, minoxidil, clonidine patch, trimethoprim/ sulfamethoxazole, acyclovir, penicillin, topical tacrolimus ointment and fluocinonide gel	200 μg in the morning, 100 μg in the evening, every other day (FK506) 5–8 ng/ml	12 months
Case 4	N/A (lung transplantation)	FK506, prednisone	Tacrolimus, prednisone, mycophenylate mofetil, citalopram, nystatin suspension, omeprazole, valganciclovir, trimethoprim/sulfamethoxazole, docusate sodium, hydromorphone	6 mg daily, tapered to 1.5 mg over 1 year (FK506) 5–20 ng/ml	1 month

CNI, calcineurin inhibitor; Cy, cyclophosphamide; TBI, total body irradiation; MTX, methotrexate; FK506, tacrolimus.

Figure 1 Case 2 showing the fleshy nodular mass on the right lateral side of the tongue.

Figure 2 Case 3 showing two fleshy, nodular masses on the tongue, more evident on the right side. Note the smooth, atrophic appearance of the tongue typical for cGVHD.

Examination revealed the presence of two fleshy polypoid, multinodular masses on the right and left dorsum and lateral borders of the tongue measuring 3.0×2.0 and 2.0×2.0 cm^2 respectively (Fig. 2). The tongue was depapillated and atrophic consistent with oral cGVHD. The lesions were surgically excised under general anesthesia and his tacrolimus dose was reduced. Two months later, the lesions recurred and were re-excised. At follow-up 3 years later, he was still on tacrolimus and the lesions had not recurred although he continues to have low-grade oral cGVHD with progressive skin and pulmonary involvement.

Case 4

A 58-year-old female was referred to the Division of Oral and Maxillofacial Surgery, Oral Medicine and Dentistry at Brigham and Women's Hospital, Boston, MA, for evaluation of growths on her upper and lower lips. She had been diagnosed with severe chronic obstructive pulmonary disease at 53 years of age and underwent right lung transplantation 4 years later (Table 1).

On examination, there were two linear, exophytic, slightly tender, sessile polypoid soft tissue masses in the upper right and lower left lip mucosa, each measuring 2.0×0.5 cm^2 (Fig. 3a and b). The patient wore a complete maxillary denture but not a lower denture. Several mandibular teeth had sharp edges. Both lesions

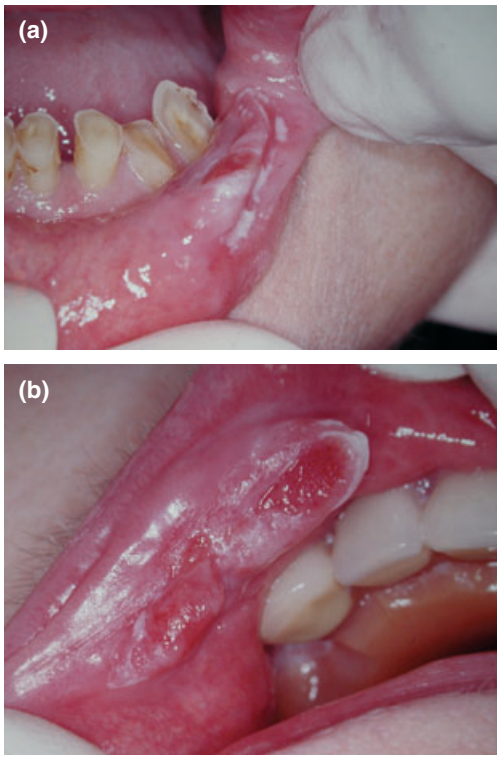

Figure 3 (a) Case 4 showing the linear fleshy mass on the left lower labial mucosa. Trauma from the sharp-edged teeth may have contributed. (b) Case 4 showing the fleshy linear mass on the right upper labial mucosa.

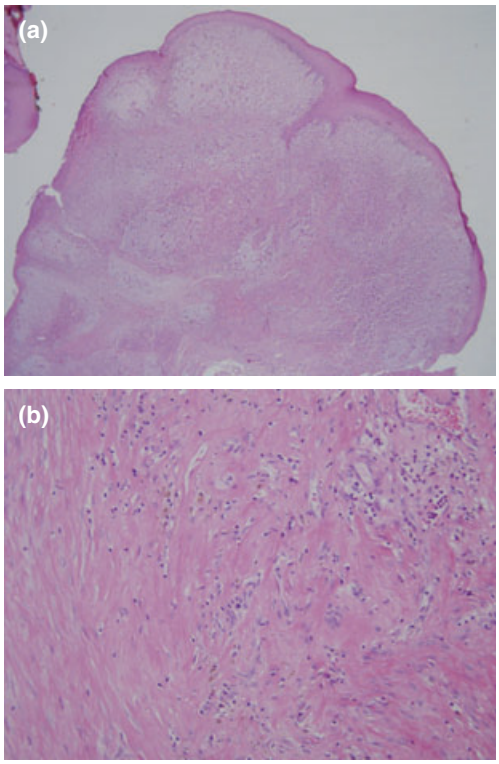

Figure 4 (a) Photomicrograph of the tongue mass from case 2 showing the polypoid nature of the fibrovascular proliferation with overlying ulceration (magnification ×20). (b) Photomicrograph showing the proliferation of edematous fibrous and granulation tissue with scattered chronic inflammatory cells, but without an obvious lobular architecture (magnification ×200).

were surgically excised. The patient died 9 months later from complications related to her transplantation.

Histopathology
All lesions demonstrated essentially identical histopathological findings characterized by masses of granulation and fibrous tissue with varying degrees of collagenization and edema, overlying ulceration, and acute and chronic inflammation (Fig. 4a and b).

Comments

Calcineurin inhibitors are the mainstay of immunosuppressive therapy for solid organ and hematopoietic cell transplantation. CsA is a cyclic polypeptide with potent immunosuppressive activity that acts primarily by inhibiting interleukin-2 (IL-2) gene transcription in $CD4^+$ lymphocytes thereby preventing transmission of signals essential to T- and B-cell maturation and proliferation (1). Tacrolimus is a macrolide immunosuppressant produced by the fungus *Streptomyces tsukubaensis* that is 100 times more potent than CsA (2). The immunosuppressive effect of tacrolimus, similar to CsA, is due to the inhibition of T helper lymphocyte activation. Tacrolimus binding to the FK506-binding protein results in the downregulation of IL-2 and other cytokines critical to T-cell activation (3). Clinical use of CsA is often complicated by several well-documented adverse effects including diabetes and hyperlipidemia, chronic nephrotoxicity, hepatotoxicity, neurotoxicity, hypertension, hirsutism and gingival hyperplasia (4). Hyperlipidemia, hirsutism and gingival hyperplasia occur less frequently with tacrolimus (5).

Gingival overgrowth has been recognized since 1983 as a common adverse effect of CsA (6). The authors note, however, that it is rare to see significant gingival hyperplasia in patients taking CsA for treatment of cGVHD. The development of CsA-associated non-gingival soft tissue hyperplasia has been reported following both HCT and solid organ transplantation (Table 2) (7–12). These soft tissue growths have been described as masses of granulation and fibrous tissue with variable amounts of edema and inflammation and have been referred to as 'pyogenic granuloma' and 'soft tissue overgrowths'. A case reported as herpes simplex virus-induced fibrous hyperplasia appears to represent a CsA-associated fibrovascular hyperplasia with secondary recrudescent HSV infection (12). The case reported by Bhattacharyya et al. may represent acanthosis nigricans as its appearance is entirely different from all other reported cases (13).

Several mechanisms have been proposed to explain the development of these fibro-vascular hyperplasias. Accumulation of connective tissue fibers and/or ground substance may result from increased production of collagen fibers and matrix, reduced activity or production of matrix metalloproteinases, and/or re-

Table 2 Patient characteristics of reported cases of transplantation-associated calcineurin inhibitor-induced inflammatory polyps

Authors	*Age*	*Sex*	*Type of transplant*	*Location*	*Size (cm)*	*Hx of GVHD (+/−)*	*Oral GVHD (+/−)*	*Drug*	*Duration of treatment*	*Treatment*
Gehrke et al. (7)	18	F	Allogenic HCT	Ventro-lateral tongue	N/S	+	+	N/S	N/S	Excision with recurrence
Wandera & Walker (8)	14	F	Allogenic HCT	Lateral tongue bilaterally	3.0 × 3.0 2.0 × 1.0	+	N/S	CsA	3 weeks	Excision
Lee et al. (9)	19	M	Allogenic HCT	Buccal mucosa bilaterally	3.0 × 2.0 2.0 × 1.0	+	+	CsA	6 months	Excision with no recurrence
	45	M	Allogenic HCT	Right buccal mucosa	2.0 × 1.0 1.0 × 1.0	+	+	CsA	< 3 months	Excision with no recurrence
	36	F	Allogenic HCT	Buccal mucosa bilaterally & lower lip	Extensive	+	+	CsA	< 2 months	Excision with no recurrence
Woo et al. (10)	27	F	Allogenic HCT	Buccal mucosa	1.0–1.5	+	+	CsA	3 months	Excision with no recurrence
	31	M	Allogenic HCT	Tongue dorsum	2.0–3.0	+	+	CsA	2 months	Excision with no recurrence
	50	F	Allogenic HCT	Buccal mucosa	0.5	+	+	CsA	1 month	Excision with no recurrence
	29	F	Allogenic HCT	Buccal mucosa	1.0	+	+	CsA	2 months	Excision with no recurrence
	33	F	Allogenic HCT	Lateral tongue bilaterally	0.5–1.0 each	+	+	CsA	1 month	Excision with recurrence
	34	M	Allogenic HCT	Tongue dorsum	3.0 × 4.0	+	+	CsA	1 month	Excision
Al-Zayer et al. (11)	14	F	Renal	Gingiva of anterior maxilla	N/S	N/A	N/A	CsA	N/S	Excision with no recurrence
Tabaee et al. (12)	48	F	Cardiac	Lateral tongue	6.0	N/A	N/A	FK506	12 month	Excision with no recurrence
Al-Mohaya et al. (present study)	14	M	Allogenic HCT	Lateral tongue bilaterally	2.0 × 1.0 0.5 × 0.5	-	-	CsA	2.5 months	Excision with no recurrence
	8	M	Allogenic HCT	Right lateral tongue	2.0 × 1.0	+	+	CsA	2 months	Excision with no recurrence
	3	M	Allogenic HCT	Lateral tongue bilaterally	3.0 × 2.0 2.0 × 2.0	+	+	FK506	12 months	Excision with recurrence
	58	F	Lung	Upper and lower labial mucosa	2.0 × 0.5 2.0 × 0.5	N/A	N/A	FK506	1 month	Excision with no recurrence

HCT, hematopoietic cell transplantation; CsA, cyclosporine; FK506, tacrolimus; N/A, not applicable; N/S = not stated.

duced activity or production of tissue inhibitors of metalloproteinases (14, 15). The alteration of collagen metabolism is thought to be mediated by CsA upregulating the activity of transforming growth factor beta 1 (TGF-β1), a pluripotent cytokine that promotes synthesis of extracellular matrix components and inhibits matrix degradation (16).

Similar to CsA, tacrolimus can increase the production of collagen and increase the activity of tissue inhibitors of metalloproteinases, but to a lesser extent (17). Unlike CsA, tacrolimus is rarely associated with gingival overgrowth and when observed is significantly less severe than is seen with CsA (18). In fact, in patients with severe CsA-associated gingival hyperplasia, substituting CsA with tacrolimus has resulted in dramatic improvement or complete resolution without any increased risk of graft failure or infection (19). Nevertheless, we believe that cases 3 and 4 in the present case series represent tacrolimus-associated non-gingival fibrovascular hyperplasia which has not been previously reported. Their clinical and histopathological presentations were identical to cases 1 and 2 (on CsA only) as well as previously reported cases (Table 2).

Development of these lesions is likely due to a combination of local and systemic inflammatory factors with CsA and/or tacrolimus producing an exaggerated proliferative response of the connective tissue. Local inflammatory factors, such as dental plaque and calculus, may act as a stimulus for this fibrous response in the gingiva. Bite trauma and other local causes of tissue injury may play a role in non-gingival lesions. The patient in case 4 wore upper dentures, and while denture-related soft tissue hyperplasias (epulis fissuratum) are fairly common, these occur in the maxillary and mandibular sulcus/vestibule where the edge or flange of the denture slides over the mucosa. She also had several teeth with sharp edges that may have traumatized the area (Fig. 3a). In cases associated with HCT, cGVHD may be a systemically mediated local inflammatory factor causing tissue proliferation as two of three of the patients reported here had clinically evident oral cGVHD.

While an apparent rare complication of calcineurin inhibitor therapy, these soft tissue fibrovascular lesions must be differentiated from other oral lesions seen in the organ transplantation population, such as granulocytic sarcoma (in HCT), non-Hodgkin's lymphoma, and squamous cell carcinoma, and therefore must be surgically excised and submitted for histopathological diagnosis (20). To prevent recurrence, dose reduction, or in the case of CsA, substitution with tacrolimus, should be considered together with the management of any potential contributing factors.

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