

CLINICAL CASE

Dent. Med. Probl. 2012, 49, 3, 443–449
ISSN 1644-387X

© Copyright by Wrocław Medical University
and Polish Dental Society

DOROTA OLCZAK-KOWALCZYK^{1, A, D, E}, BEATA WOLSKA-KUŚNIERZ^{2, B, F},
EWA KRASUSKA-SŁAWIŃSKA^{3, B, F}, MAJA KLAUDEL-DRESZLER^{2, B}, MACIEJ PRONICKI^{4, A}

Non-Gingival Soft Tissue Growths in Patients with Chronic Graft-Versus-Host-Disease. Report of Two Cases

Zmiany rozrostowe na błonie śluzowej jamy ustnej u pacjentów z przewlekłą chorobą przeszczep przeciwko gospodarzowi – opis dwóch przypadków

¹ Department of Paediatric Dentistry, Medical University of Warsaw, Poland

² Department of Immunology, The Children Memorial Health Institute Warsaw, Poland

³ Specialist Clinics The Children's Memorial Health Institute, Warsaw, Poland

⁴ Department of Pathology, The Children Memorial Health Institute, Warsaw, Poland

A – koncepcja i projekt badania; B – gromadzenie i/lub zestawianie danych; C – opracowanie statystyczne;
D – interpretacja danych; E – przygotowanie tekstu; F – zebranie piśmiennictwa

Abstract

Typical manifestations of oral chronic Graft-Versus-Host Disease (cGVHD) include mucosal atrophy, erythema, erosions, pseudomembranous ulcerations, papular or reticular lichenoid hyperkeratosis and xerostomia. Exophytic lesions of soft tissue are observed less frequently. The cyclosporin A (CyA) may play a significant role in the aetiopathogenesis of the lesions. The authors report the presence of exophytic lesions located on the tongue in two male boys with cGVHD, currently aged 2.5 and 11 years, treated with CyA. Persistent mechanical injuries of the lingual mucosa were the local predisposing factors. Histopathology showed nonspecific inflammatory granulation tissue. Surgical treatment proved to be effective only by elimination of local irritations. Prevention of mechanical injuries to the mucosa of the tongue is mandatory in patients with GVHD since they contribute to the development of proliferative lesions (**Dent. Med. Probl. 2012, 49, 3, 443–449**).

Key words: chronic oral Graft-Versus-Host Disease, exophytic lesions, cyclosporine A, mechanical injury.

Streszczenie

Typowymi zmianami występującymi u pacjentów z przewlekłą chorobą przeszczep przeciw gospodarzowi (cGVHD) są: zanik błony śluzowej, jej zaczerwienienie, nadżerki, owrzodzenia, hiperkeratyczne zmiany lichenoidalne oraz xerostomia. Zdecydowanie rzadziej występują zmiany rozrostowe na języku. W ich etiopatogenezie istotne znaczenie ma prawdopodobnie leczenie CsA. W pracy przedstawiono rozrostowe zmiany egzofityczne języka występujące u dwóch chłopców w wieku 2,5 i 11 lat z cGVHD, przyjmujących CsA. Miejscowym czynnikiem predysponującym do ich wystąpienia mogły być przewlekłe urazy mechaniczne błony śluzowej języka. Zastosowane leczenie chirurgiczne okazało się skuteczne jedynie w przypadku usunięcia miejscowych czynników drażniących. U pacjentów z cGVHD jest konieczne zapobieganie urazom mechanicznym błony śluzowej jamy ustnej, predysponujących do rozwoju zmian rozrostowych (**Dent. Med. Probl. 2012, 49, 3, 443–449**).

Słowa kluczowe: przewlekła choroba przeszczep przeciw gospodarzowi, zmiany egzofityczne, cyklosporyna A, uszkodzenie mechaniczne.

The oral mucous membrane is the second most frequent site (the skin ranks the first in order) for clinical manifestations of systemic chronic graft-versus-host-disease (cGVHD) in patients after haematopoietic stem cell transplantation – HSCT [1]. The prevalence of oral lesions was estimated at 45% in children with cGVHD [2], and at 54–80% in adult patients with the disease [3, 4]. The lesions occur in approximately 90% of cGVHD cases affecting the skin [5].

The lesions are most often located on the buccal mucosa, palate, lips and the dorsal part of the tongue [3]. They may cause discomfort or even pain, which impairs nutrition and may lead to weight loss. The lesions manifest themselves as mucosal atrophy, erythema, erosions, pseudomembranous ulcerations and papular or reticular forms of lichenoid hyperkeratosis [4–9]. Less frequent manifestations include exophytic lesions described as pyogenic granuloma or non-gingival soft tissue growths (NGSTGS). The aetiology is still unclear. The role of the CyA treatment has also been emphasized in the pathogenesis of the lesions [5, 9–13].

Chronic graft-versus-host disease is also typically manifested by an increasingly progressive dysfunction of the major and minor salivary glands resulting in xerostomia [4, 5, 7, 8]. It is occasionally accompanied by mucocoeles localized in the palatal and labial mucosa [9, 14, 15]. Decreased secretion of saliva containing antibacterial factors (e.g. IgA, lysozyme) contributes to the development of dental caries, injury and infectious lesions on the oral mucosa [4, 8, 9]. Susceptibility to viral, fungal and bacterial infections in patients with cGVHD is also due to the progressive atrophy of the lymphatic tissue and long-term immunosuppression [7]. An infection with herpesviridae, particularly with cytomegalovirus (CMV/HHV-5) and Epstein-Barr virus (EBV/HHV-4), may also manifest itself on the oral mucosa as erosions and ulcerations, covered by exudate or pseudomembrane, resembling those in oral cGVHD [16–20]. The EBV infection in a bone marrow recipient has also been described as hairy leukoplakia [21]. It may also result in an uncontrollable proliferation of B lymphocytes and post-transplant lymphoproliferative disease (PTLD) [22, 23]. Organ recipients on immunosuppression affecting proliferative processes of cytotoxic T lymphocytes, may develop an uncontrollable proliferation of EBV-infected B lymphocytes called PTLT [23–25].

EBV was isolated in 90% of PTLT cases [23]. Lymphoproliferative lesions may be systemic or local, e.g. occurring only in the lymph nodes or the oral cavity. Oral PTLT manifestations were described as lesions resembling gingivitis or ulceration [22, 26, 27].

It is generally known that chronic graft-versus-host disease and immunosuppressive therapy are contributory factors in neoplastic diseases, mainly leukaemias and lymphomas, which may occur in the oral cavity [28, 29].

Cases of solid tumours were also reported in the literature (mostly squamous carcinoma, less frequently – malignant melanoma) showing location of the lesions in the oral mucosa, most frequently of the tongue and cheeks, rarely, of the gingivae and lips [28–32].

Oral cGVHD is occasionally diagnosed on the basis of macroscopic examination of lesions and concomitant systemic manifestations.

A biopsy of the oral mucosal lesions most frequently showed abnormal and excessive keratinisation or atrophy of the epithelium, isolated necrotic keratinocytes on the stratum spinosum, hydropic degeneration of the basal stratum, intracellular epithelial oedema, subepithelial infiltration with inflammatory cells (lymphocytes and histiocytes), proliferation of fibroblasts, fibrosis of the lamina propria, and atrophy of the salivary glands [5, 9].

Since there is a high risk of PTLT and a possible neoplasia, it is necessary to perform histopathological differential diagnostics [4, 9, 28–32].

Some authors suggest that histopathology does not provide adequate evidence and should be performed only in cases of inconclusive diagnosis [7].

Reported below are two cases of exophytic lesions on the tongue surface in patients with cGVHD after HSCT.

Case Reports

Case 1

The patient, MS, born in 2003, was given the diagnosis of severe combined immunodeficiency at the age of 12 months. Molecular analysis confirmed the presence of causative mutations in both alleles of the RAG1 gene. The patient was qualified for haematopoietic stem cell transplantation from a matched unrelated donor. He underwent the transplantation procedure at 16 months of age, after a conditioning regimen containing Fludarabine/Treosulfan/ATG. Following the procedure, haematological engraftment and full donor chimerism were achieved. The early posttransplant period was complicated by acute graft-versus-host disease of the skin (grade IV), mucosa, and bowels (grade II/III). A good clinical response was achieved following intense immunosuppression with steroids, CyA, Cell-Cept and ATG. At that time, the mucosal lesions were typical of acute

GVHD with painful desquamation and ulceration. A further evaluation showed mild chronic GVHD, which involved the skin and mucosa as well as keratoconjunctivitis sicca. The condition required the maintenance of immunosuppression, which, subsequently, was gradually reduced and ultimately discontinued 33 months after the transplantation procedure (Fig. 1).

Approximately 11 months after the HSCT, during treatment with prednisone and CyA, a growing exophytic mass was found on the patient's tongue (Fig. 2). The enlarging mass was continuously irritated by biting and required surgical excision. Histopathology showed exuberant reactive granulation with a predominantly granulocytic infiltrate (Fig. 3). Viral cultures were negative, the PAS staining did not disclose fungal infection.



Fig. 1. Pseudomembranous ulcerations limited by erythema and lichenoid lesions on labial mucosa

Ryc. 1. Owrzodzenie rzekomobłoniaste otoczone rumieniem i wykwitami liszajopodobnymi na wardze



Fig. 2. The exophytic masses on the dorsum and lateral part of the tongue and lichenoid lesions on buccal mucosa

Ryc. 2. Wykwity egzofityczne na dolnej i bocznej powierzchni języka i wykwity liszajopodobne na błonie śluzowej policzka

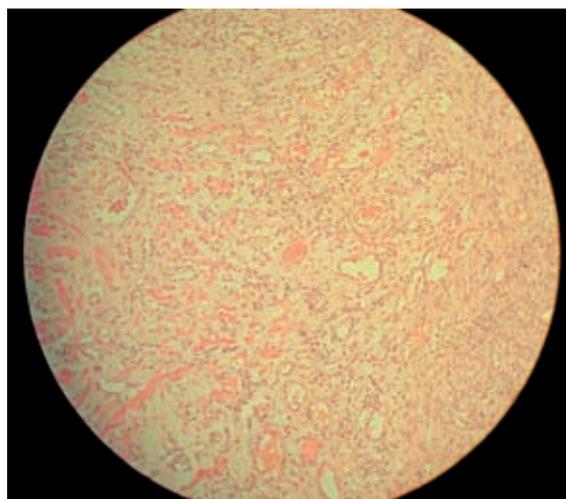


Fig. 3. Histopathology showed exuberant reactive granulation with a predominantly granulocytic infiltrate

Ryc. 3. Badanie histopatologiczne zmiany rozrostowej – tkanka ziarninowa z naciekiem głównie granulocytów

The exophytic mass specimen was also assessed for evidence of viral and fungal infection, using the PCR test. The HPV PCR was inconclusive (\pm). At that stage, a viral infection was also considered as the causative factor in the pathogenesis of the mucosal lesions.

Since the surgical excision of the lesion, there has been no recurrence of exophytic mass formation.

Additionally, at 29 months after the transplantation, a complex treatment of advanced dental caries was performed under general anaesthesia.

The last follow up performed 40 months after HSCT, showed that the patient was in a good clinical condition without any immunosuppressive drugs; however, he still required ophthalmological treatment of exophthalmia. He achieved a complete immune reconstitution with a good specific antibody response after vaccination and had no severe infections.

Case 2

The patient MW, a 13-year-old boy affected with Cernunnos syndrome, which is a rare primary immunodeficiency. The boy suffered from frequent upper and lower respiratory tract infections. He also presented growth retardation (< 3 percentile), significant microcephaly, moderate hepatosplenomegaly and lymphadenopathy. Full blood count showed leukopenia, thrombocytopenia, low serum concentration of IgG and IgA, and a highly elevated IgM level. There was no specific post-vac-

cination response; additionally, there was a progressive B-cell-lymphopenia, accompanied by a dysfunction of T lymphocytes. The final diagnosis was established in 2005, when the patient was 7 years old, after the discovery of causative mutations in the gene named *Cernunnos/XLF*.

Regarding the abnormal bone marrow (a diminished cell count, normal erythropoiesis, impaired granulopoiesis, absent megakaryocytes) and poor prognosis of the newly discovered immunodeficiency, the patient was scheduled for the HSCT from a matched unrelated donor. The procedure was performed in 2006, when the boy was 8 years old. Haematological reconstitution and a complete donor chimerism were achieved. As an early outcome, an acute GVHD of the skin (grade II), and mild hepatitis, presumably of *Cryptosporidium* aetiology were established. A further follow up, five months after the transplantation, showed severe haemorrhagic cystitis of an unknown origin, which required 2 months of intensive treatment and the discontinuation of systemic immunosuppression. Four months later the patient developed acute EBV infection, complicated by fungal *Aspergillus* infection. Over the subsequent months, the boy developed chronic GVHD with progressive sclerodermatous skin lesions, followed by generalized joint involvement. No significant response to immunosuppression with corticosteroids, cyclosporine, mycophenolate mofetil (MMF) and PUVA therapy was achieved. Additionally, twenty months after the HSCT procedure, a complex treatment of advanced dental caries was performed under general anaesthesia. At that time, the patient's joint movement was reduced, with a particular involvement of the mandible. An increasingly progressive chronic GVHD indicated the need for additional treatment with Etanercept, which was started exactly 2 years after the HSCT. The treatment with Etanercept, CyA, MMF and corticosteroids produced a slow but significant remission of skin lesions. The patient, however, developed oral manifestations of cGVHD, i.e. salivary gland hypofunction (xerostomia), erythematoid and hyperkeratotic lesions, ulceration of the buccal, labial and lingual mucosa, and an exophytic mass along the right margin of the tongue (Fig. 4). The lack of teeth 84 and 85, palatal position of tooth 12, lingual inclination of tooth 46 and a deep occlusion, had resulted in persistent biting and irritation of the exophytic lesions in spite of smoothing of sharp tooth edges. The findings were an indication for surgical excision of the exophytic mass.

The surgical excision of the exophytic lesions of the tongue was performed 30 months after the HSCT procedure. Histopathology showed non-specific inflammatory granulation. Biopsy of the

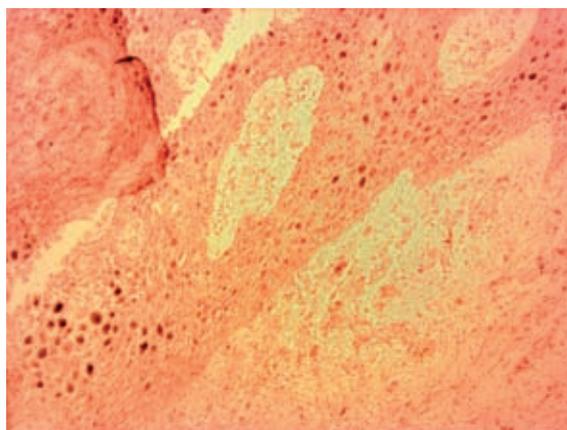
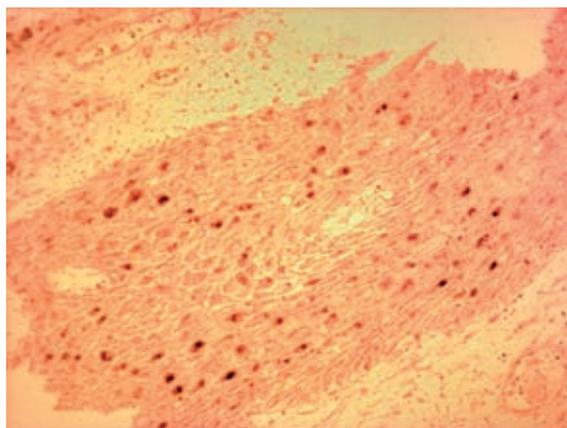
buccal ulceration site revealed similar findings (Fig. 5 and 6). In situ hybridisation for HPV and EBV infection was negative.

Seven weeks after the surgical procedure, oral cGVHD was constantly progressing despite the



Fig. 4. The exophytic mass located along the right margin of the tongue

Ryc. 4. Zmiana rozrostowa wzdłuż prawego brzegu języka



Figs. 5, 6. Biopsy of the buccal ulceration showed reactive granulation with EBV virus in the squamous epithelium cells

Ryc. 5 i 6. Badanie histopatologiczne owrzodzenia błony śluzowej policzka – odczynowa tkanka ziarninowa z wirusem EBV w komórkach nabłonka płaskiego



Fig. 7. Sclerodermatous lesions of the skin. Hair depletion

Ryc. 7. Wykwity twardzinowe skóry, utrata włosów



Fig. 8. The exophytic lesion on the tongue opposite tooth 46

Ryc. 8. Zmiana rozrostowa języka w projekcji zęba 46

systemic immunosuppressive therapy and topical treatment to relieve the oral pain and candidal superinfection. Sclerodermatous lesions reduced the oral space (Fig. 7), which, additionally, resulted in decreased food intake and disrupted the maintenance of oral hygiene. The lichenoid and erythematoid lesions involved the whole surface of the oral mucosa, tongue and lips. Apart from the above, painful ulcerations appeared on the tip and right margin of the tongue, and another exophytic lesion was noted on the tongue opposite tooth 46 (Fig. 8).

On the follow-up, three years after the HSCT procedure, the patient was still on a four-drug-immunosuppressive therapy (described above), including Etanercept (0.4 mg/kg weekly). Due to prophylactic measures, i.e. administration of intravenous immunoglobulins, Aciclovir, antibiot-

ics and antifungal agents, neither serious infectious complications nor reactivation of EBV-infection were noted. The patient achieved a complete donor chimerism and good haematological reconstitution.

Discussion

Exophytic lesions in both patients with oral cGHVD were found on the lateral margins of the tongue, at the sites vulnerable to mechanical injury. In terms of the aetiopathogenesis, not only the role of cGHVD itself and treatment with CyA but also persistently irritated abnormal xerotic oral mucosa should be considered.

The proliferative lesions in the younger patient occurred during the eruption of deciduous lower molar teeth. In this patient, mechanical injuries were caused by sharp cusps of the lateral mandibular teeth as well as teething rings and objects which the boy used to put into the mouth. Those factors were eliminated on eruption of the lower teeth, which had a favourable effect on the efficacy of the surgical treatment. The proliferative lesion in the other patient was found to be progressive. Its recurrence might have resulted from repeated injuries caused by occlusal abnormalities. Active EBV infection was also considered, although not confirmed. A significant role of persistent mechanical injuries to the oral mucosa in the development of proliferative lesions was also demonstrated by histopathological findings. The efficacy of agents used in the topical treatment of oral cGHVD is very low in non-gingival soft tissue growths. Parisi et al. reported only a minimal improvement of the local condition following topical application of steroids and tacrolimus [5]. In patients at risk of neoplastic metaplasia, proliferative lesions in the oral mucosa, particularly those in the area vulnerable to persistent irritation, are an indication for surgical treatment and a histopathological follow-up. It also seems to be contraindicated to administer topical agents that inhibit healing and contribute to the development of opportunistic infections (steroids) or agents stimulating fibroblast proliferation (CyA). In the topical treatment, however, it is vital to eliminate causes of mechanical injuries, to maintain an adequate oral hygiene regimen, to use antibacterial and antifungal agents such as rinses and gels (except for chlorhexidine gluconate in patients with xerostomia), to relieve pain (with topical analgesic rinses or gels), to use aniline dyes, and saliva substitutes in xerostomia. Herbs i.e. mallow flower flax seed are also useful. Topical treatment in children is frequent-

ly difficult due to the noncompliance of patients and their carers. Health education is indispensable with respect to the significance and measures used to maintain a good oral hygiene regimen, and the association between the general health and maintenance of oral health.

Cancer prevention, maintenance of the oral mucosa continuity, and the prevention of infectious lesions are vital in achieving therapeutic success in bone marrow recipients. Erosions and ulcerations of the oral mucosa may be the portal of entry for systemic infections with *Candida* species and gram-negative anaerobic bacteria. They may also be the first clinically detectable manifestation of systemic infection with cytomegalovirus or Epstein-Barr virus. This additionally emphasizes the significance of effective dental care in patients after bone marrow transplantation, as a component of multidisciplinary management.

Pathogenesis of lesions, which are non-gingival soft tissue growths (NGSTGS), in patients with chronic graft-versus-host disease have not been adequately explained. Treatment with cyclosporin A (CyA), stimulating fibroblast proliferation, protein synthesis and collagen production might be of significance [5, 9, 11–14]. Patients treated with CyA were found to have an increased concentration of the keratinocyte growth factor (KGF). Cyclosporin A also increases the synthesis and secretion of transforming growth factor β by T lymphocytes and endothelial cells, stimulating endothelin production and accumulation of extracellular matrix proteins (albumins), which contributes to the development of fibrous connective tissue [33–35]. Apart from that, an increased production of TNF, IFN- γ , IL-4 and IL-6, characteristic of cGVHD, also contributes to an excessive fibroblast proliferation and collagen production [4].

References

- [1] FLOWERS M. E., PARKER P. M., JOHNSTON L. J., MATOS A.V., STORER B., BENSINGER W. I., STORB R., APPELBAUM F. R., FORMAN S. J., BLUME K. G., MARTIN P. J.: Comparison of chronic graft-versus-host disease after transplantation of peripheral blood system cells versus bone marrow in allogeneic recipients: long-term follow-up of a randomized trial. *Blood* 2002, 100, 415–419.
- [2] TREISTER N., WOO S., O'HOLLERAN E., LEHMANN L., PARSONS S., GUANIN E.: Oral chronic Graft-Versus-Host Disease in pediatric patients after hematopoietic stem cell transplantation. *Biol. Blood Transplant.* 2005, 11, 721–731.
- [3] BUSCA A., LOCATELLI F., VAI S., DALL'OMO A.M., CARGIULO A., FALDA M.: Clinical grading of oral chronic graft-versus-host disease in 104 consecutive adult patients. *Haematologica* 2005, 90, 567–569.
- [4] FRANÇA C. M., DOMINGUES-MARTINS M., VOLPE A., FILHO R.S.P., DE ARAÚJO N.S.: Severe oral manifestations of chronic graft-s-host disease. *J. Am. Dent. Assoc.* 2001, 132, 1124–1127.
- [5] PARISI E., SOLLECTIO T. P.: Oral chronic Graft-Versus-Host Disease with non-gingival soft tissue growths: a treatment challenge. *Int. J. Dermatol.* 2003, 2, 1.
- [6] NAIR V., SHARMA A., GHOSH I., ARORA S., KAVITA S., VIBHA D.: Extensive chronic Graft-Versus-Host Disease of skin successfully treated with thalidomide. *JAPI* 2005, 53, 988–990.
- [7] VOSSEN J. M., BREEDEVELD L., BAKKER J. D. J., MERTENS B., VAN WEEL-SIPMAN M. H.: Chronic Graft-Versus-Host Disease and ITS management in children. *Rep. Pract. Oncol. Radiother.* 2002, 7, 345–353.
- [8] IMANGULI M.M., PAVLETIC S. Z., GUADAGNINI P., BRAHIM J. S., ATKINSON J. C.: Chronic graft-versus-host disease of oral mucosa: Review of available therapies. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod.* 2006, 101, 175–183.
- [9] DE LA ROSA-GARCÍA E., BOLOGNA-MOLINA R., VEGA-GONZÁLEZ M. T. J.: Enfermedad de injerto contra huésped. *Med. Oral Patol. Cie. Buccal. Internet* 2006, 11, 486–492.
- [10] KANADA Y., ARAI C., CHIZUKA A., SUGURO M., HAMAKI T., YAMAMOTO R., YAMAUCHI Y., MATSUYAMA T., TAKEZAKO N., SHIRAI Y., MIWA A., IWASAKI K., NASU M., TOGAWA A.: Pyogenic granuloma of the tongue early after allogeneic bone marrow transplantation for multiple myeloma. *Leuk. Lymphoma* 2000, 37, 445–449.
- [11] WOO S. B., ALLEN C. M., ORDEN A., PORTER D., ANTIN J. H.: Non-gingival soft tissue growths after allogeneic marrow transplantation. *Bone Marrow Transpl.* 1996, 17, 1127–1132.
- [12] BARNADAS M. A., BRUNET S., SUREDA A., LOPEZ R., CURELL R., SIERRA J.: Alomar A. Exuberant granulation tissue associated with chronic graft-versus-host disease after transplantation of peripheral blood progenitor cells. *J. Am. Acad. Dermatol.* 1999, 41, 876–879.
- [13] LEE L., MILLER P. A., MAXYMIW W. G., MESSNER H.A., ROTSTEIN L. E.: Intraoral pyogenic granuloma after allogeneic bone marrow transplant: Report of three cases. *Oral Surg. Oral Med. Oral Pathol.* 1994, 78, 607–610.
- [14] GARCÍA F., VILLALTA M. J., PASCUAL-LOPEZ M., ELICES M., DAUDEN E., GARCÍA-DIEZ A., FRAGA J.: Superficial mucocoeles and lichenoid graft-versus-host disease: Report of three cases. *Acta Dermatol. Venereol.* 2002, 82, 453–455.
- [15] DE LA ROSA-GARCÍA E., BOLOGNA-MOLINA R., VEGA-GONZÁLEZ M. T. J., DE JESUS T.: Graft-versus-host disease, an eight case report and literature review. *Med. Oral. Patol. Cie. Buccal. Internet* 2006, 1, E 486–492.
- [16] AMMATUNA P., CAMPISI G., GIOVANELLI L., GIAMBELLUCA D., ALAIMO C., MANCUSO S., MARGIOTTA V.: Presence of Epstein-Barr virus, cytomegalovirus and human papillomavirus in normal oral mucosa of HIV and renal transplant patients. *Oral Dis.* 2001, 7, 34–40.

- [17] SYRJANEN S., LEIMOLA-VIRTANEN R., SCHMIDT-WESTHAUSEN A., REICHART P. A.: Oral ulcers in AIDS patients frequently associated with cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections. *J. Oral Pathol. Med.* 1999, 28, 204–209.
- [18] DOUMAS S., VLADIKAS A., PAPAGIANNI M., KOLOKOTRONIS A.: Human cytomegalovirus-associated oral and maxillo-facial disease. *Clin. Microbiol. Infect.* 2007, 13, 557–559.
- [19] FIRTH N. A., RICH A.M., READE P. C.: Oral mucosal ulceration due to cytomegalovirus infection. Case report and brief review. *Aust. Dent. J.* 1994, 39, 273–275.
- [20] SUN A., CHANG J. G., CHU C. T., LIU B.Y., YUAN J. H., CHIANG C.P.: Preliminary evidence for an association of Epstein-Barr virus with pre-ulcerative oral lesions in patients with recurrent aphthous ulcers or Behcet's disease. *J. Oral Pathol. Med.* 1998, 27, 168–175.
- [21] EPSTEIN J.B., SHERLOCK C. H., WOLBER R. A.: Hairy leukoplakia after bone marrow transplantation. *Oral Surg. Oral Med. Oral Pathol.* 1993, 65, 690–695.
- [22] JOHNSON J., KERECUK L., HARRISON M., TAYLOR J. O., ODELL E.: Epstein-Barr virus-associated lymphoproliferative disease in oral cavity in a renal transplant recipient: A case report. *Pediatr. Transplant.* 2007, 3, 340–344.
- [23] BARRETT J. C.: Post-transplantation lymphoproliferative disease. *Herpes* 2000, 7, 4–8.
- [24] JOHANNESSEN I.: Epstein-Barr virus, post-transplant lymphoproliferative disease and animal models. *Rev. Med. Microbiol.* 2002, 13, 129–140.
- [25] RAZONABLE R. R., PAYA C.: Herpesvirus infections in transplant recipients: current challenges in the clinical management of cytomegalovirus and Epstein-Barr virus infections. *Herpes* 2003, 10, 60–65.
- [26] ROLLAND S. L., SEYMOUR R. A., WILKINS B. S., PARRY G., THOMASON J.M.: Post-transplant lymphoproliferative disorders presenting as gingival overgrowth in patients immunosuppressed with cyclosporin. A report of two cases. *J. Clin. Periodontol.* 2004, 31, 581–585.
- [27] RAUT A., HURYN J., POLLACK A., ZLOTOW I.: Unusual gingival presentation of post-transplantation lymphoproliferative disorder: a case report and review of the literature. *Oral Surg. Oral Pathol. Oral Radiol. Endod.* 2000, 90, 436–41.
- [28] LISHNER M., PATTERSON B., KANDEL R., FYLES G., CURTIS J. E., MEHARCHAND J., MINDEN M. D., MESSNER H. A.: Cutaneous and mucosal neoplasms in bone marrow transplant recipients. *Cancer* 1999, 65, 473–476.
- [29] DEMAROSI F., SOLIGO D., LODI G., MONEGHINI L., SARDELLA A., CARRASSI A.: Squamous cell carcinoma of the oral cavity associated with graft versus host disease: report of a case and review of the literature. *Oral Med. Oral Pathol. Oral Radiol. Endod.* 2005, 100, 63–69.
- [30] OSUBO H., YOKOE H., MIYA T., ATSUTA F., MIURA N., TANZAWA H., SATO K.: Gingival squamous cell carcinoma in a patient with chronic graft-versus-host disease. *Oral Med. Oral Pathol. Oral Radiol. Endod.* 1997, 84, 171–174.
- [31] PARK Y. H., LEE J. H., KIM D. W., CHO S.H.: Secondary tongue cancer in patients with chronic graft-versus-host disease (GVHD) after bone marrow transplantation: report of two cases. *Korean J. Otolaryngol. Head Neck Surg.* 2005, 48, 1047–1050.
- [32] ABDELSAYED R. A., SUMNER T., ALLEN C. M., TREADWEY A., NESS G.M., PENZA S. L.: Oral precancerous and malignant lesions associated with graft-versus-host disease: report of 2 cases. *Oral Med. Oral Pathol. Oral Radiol. Endod.* 2002, 93, 75–80.
- [33] SPOLIDORIO L. C., SPOLIDORIO D. M. P., MASSUCATO E. M. S., NEPPELENBROEK K. H., CAMPANHA N. H., SANCHES M. H.: Oral health in renal transplant recipients administered cyclosporin A or tacrolimus. *Oral Dis.* 2006, 12, 309–314.
- [34] MYRILLAS T., LINDEN G., MARLEY J., IRWIN C.: Cyclosporin A regulates interleukin-1 β and interleukin-6 expression in gingival: Implications for gingival overgrowth. *J. Periodontol.* 1999, 70, 294–300.
- [35] BUDUNELI N., KÜTÜKÇÜLER N., AKSU G., ATILLA G.: Evaluation of transforming growth factor- β 1 level in crevicular fluid of cyclosporine A-treated patients. *J. Periodontol.* 2001, 72, 526–531.

Address for correspondence:

Ewa Krasuska-Sławińska
Specialist Clinics The Children Memorial Health Institute
Aleja Dzieci Polskich 20
04-730 Warszawa
Poland
Tel. +48 22 815 13 15
E-mail: e.krasuska@czd.pl

Received: 30.03.2012

Revised: 30.04.2012

Accepted: 25.07.2012

Praca wpłynęła do Redakcji: 30.03.2012 r.

Po recenzji: 30.04.2012 r.

Zaakceptowano do druku: 25.07.2012 r.