Squamous cell carcinoma and metastases of malignant melanoma during immunosuppression in a patient suffering from pemphigus foliaceus – case report

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Abstract

Pemphigus foliaceus is a rare, superficial form of pemphigus. Due to acantholysis localised in the stratum corneum or within the upper spinous layer of the epidermis, patients suffer mainly from extensive sores, while blisters are rarely found. The antigen in this form of pemphigus is desmoglein 1. The basic therapy consists of corticosteroids and immunosuppression, but in doses lower than in common pemphigus. Long-term suppression increases the risk of non-melanocytic skin carcinomas by 60-100-fold (mainly squamous cell carcinoma). No such relationship was confirmed for malignant melanoma. We present a case of a 59-year-old man treated for pemphigus foliaceus, in whom squamous cell carcinoma of the lower lip developed with multiple metastases to internal organs.

Key words: squamous cell carcinoma, malignant melanoma, pemphigus foliaceus.

Introduction

Pemphigus foliaceus is a rare, superficial form of pemphigus. Due to acantholysis localised in the stratum corneum or within the upper spinous layer of the epidermis, patients suffer mainly from extensive sores, while blisters are rarely found. The antigen in this form of pemphigus is desmoglein 1 [1].

Skin changes are localised mainly on the scalp and on the trunk. Draining, superficial erosions are covered with damp scales and crusts. Erosions are accompanied by rich bacterial growth and an unpleasant smell. Nikolsky's sign is positive. Mucosa are free of changes [1].

The course of pemphigus foliaceus is chronic, with frequently observed aggravations induced by sunlight.

The basic therapy consists of corticosteroids, but in doses lower than in common pemphigus. Other immunosuppressive treatment is also used: azathioprine, cyclophosphamide, methotrexate, chlorambucil. Sulfones and anti-malarial drugs also give positive results [1, 2].

Long-term suppression increases the risk of non-melanocytic skin carcinomas by 60-100-fold (mainly squamous cell carcinoma). No such relationship was confirmed for malignant melanoma [2]. Zwald *et al.* [3] considers the risk of malignant melanoma development in patients subjected to immunosuppression as the same as in the general population. It should be noted that most literature presents mainly patients after organ transplants, while cancerogenesis is very rarely described in the patients subjected to long immunosuppressive treatment due to other causes.

We present a case of a 59-year-old man treated for pemphigus foliaceus, in whom squamous cell carcinoma of the lower lip developed with multiple metastases to internal organs.

Case report

The patient, aged 59 years, was a retired miner. In 1999, malignant melanoma was diagnosed (superficial form) within the lower part of the back and it was removed in the Oncology Institute. No metastases to lymph nodes or internal organs were detected and the patient was subjected to a regular, oncological follow-up (imaging, control of lymph nodes).

The same year, the patient was diagnosed with pemphigus foliaceus. An indirect immunofluorescence test of serum detected pemphigus antibodies (desmoglein type 1),

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at a titre of 80 in the monkey oesophagus and at a titre of 160 in the guinea pig oesophagus. Histopathology confirmed features of pemphigus foliaceus.

A direct immunofluorescence test of the skin around pathological changes showed presence of IgG and complement depositions localised between the epidermal cells.

Physical skin lesions were localised on the whole body and they were most intense on the scalp and on the trunk.

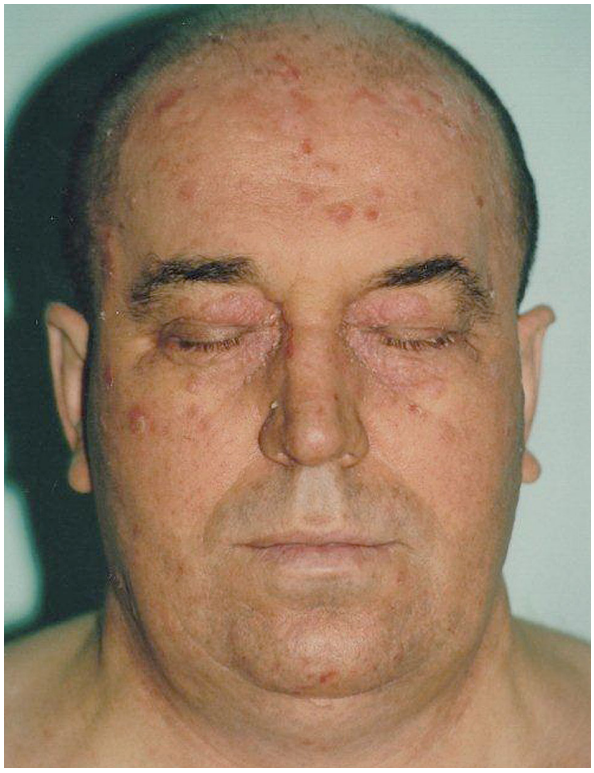

Fig. 1. Patient 59 years old, male. Small erythematous changes on the scalp

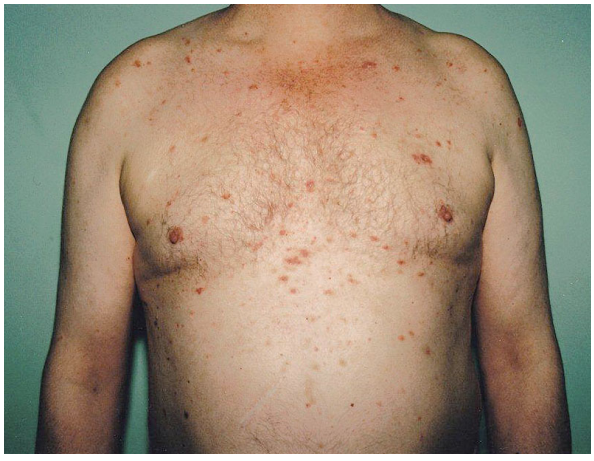

Fig. 2. Patient 59 years old, male. Erythematosus changes on the trunk

They had a form of diffuse erythematous changes, covered with damp scales or a form of accumulating erosions partially covered with crusts. Mucosa were free of any changes. Peripheral lymph nodes were not enlarged.

The oncological consultation excluded any contraindications for immunosuppressive treatment. In 1999, the patient was started with prednisone at a dose of 40 mg. The patient was many times admitted to the Dermatology Clinic and followed up in the outpatient clinic. The treatment included general steroids (prednisone, prednisolone, methylprednisolone), cyclophosphamide for 2 years at a maximal dose of 100 mg, avlosulfon (2 years), erythromycin and antimalarial drugs. During each hospitalization, pemphigus antibody titres were determined, and the titres ranged from 80 to 320 in the monkey oesophagus and from 160 to 640 in the guinea pig oesophagus, which corresponded to active pemphigus foliaceus. Additionally, imaging and laboratory tests were performed with results within the norm. The last hospitalization took place in February 2009.

In February, 2010, computed tomography of the abdomen performed in the Oncology Institute showed the presence of multiple tumour-like structures in the liver, which reflected the metastasis process (malignant melanoma). Chemotherapy included dimethyl-triazeno-imidazole-carboxamide (DTIC) and the treatment was finished after 4 cycles in September 2010 with a recommendation for further oncological follow-up.

In January 2011, a 4-cm, crater-like tumour developed on the lower lip, characterised by erosions within its central part and a hard, wall-like rim (Figs. 1-3). Peripheral lymph nodes were not examined. The skin lesions during the course of pemphigus foliaceus were discrete and they

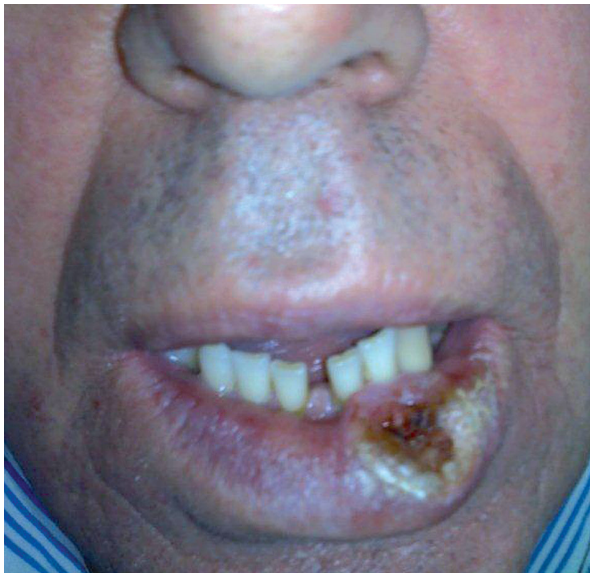

Fig. 3. Patient 59 years old, male. Crater-like tumour on the lower lip, characterised by erosions within its central part and hard, wall-like rim

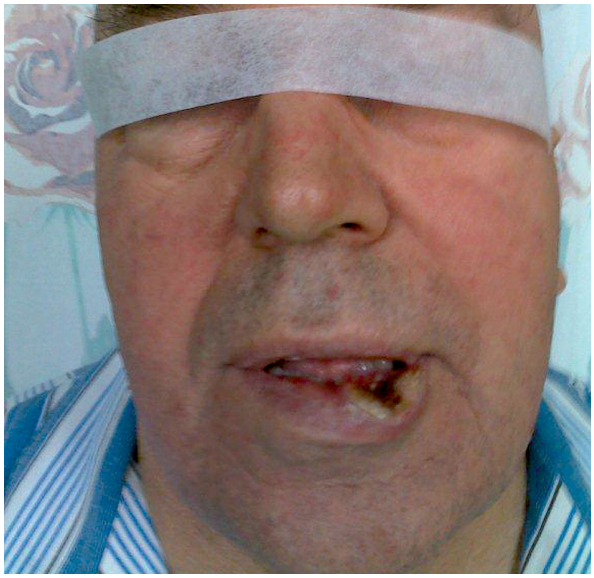

Fig. 4. Patient 59 years old, male. Tumour on the lower lip

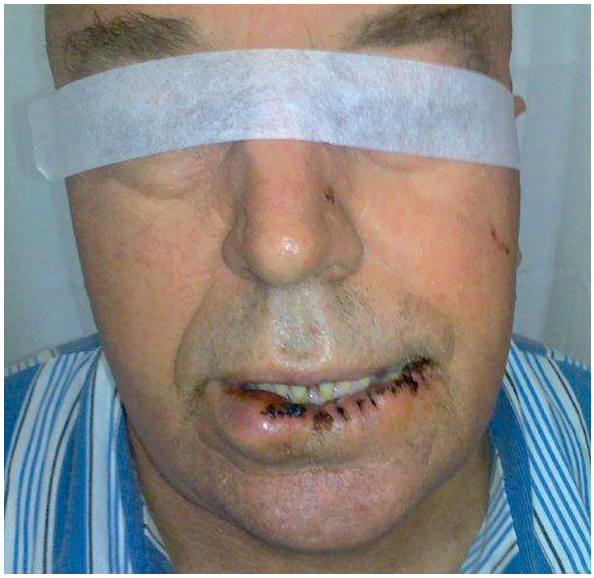

Fig. 5. Patient 59 years old, male. After operation

had a character of small, erythematous changes on the scalp and on the trunk (Figs. 4, 5). The patient took prednisone at a dose of 20 mg/day. The patient, with suspected squamous cell carcinoma, was admitted to the Dermatology Clinic for surgical removal of the lesion.

The tumour was removed under local anaesthesia with a margin of 1 cm and samples for histopathology were taken. Laboratory tests: ESR 10, FBC, electrolytes, liver enzymes, bilirubin level, creatinine level, urea level, glucose, proteins with electrophoresis, iron level, latex reaction, test for the presence of the rheumatoid factor – with no abnormalities. Total cholesterol, triglyceride level, LDL and HDL were increased. Tumour markers CEA, Ca 125, total PSA, CA 19-9 levels were normal. Chest X- ray: no abnormalities. The ultrasonography of the abdomen showed hyperechogenic foci localised within an enlarged liver, corresponding to probable metastases.

Currently, the patient is under the supervision of the Dermatological and Oncological Clinic in order to continue the treatment (prednisone 15 mg/day). The histopathological examination from the tumour of the lower lip, showed squamous cell carcinoma.

Discussion

The literature includes relatively numerous reports on carcinogenesis in patients subjected to immunosuppression following organ transplantation. However, there is scarce information about patients in whom tumours developed or relapsed in the course of treatment of other diseases.

The incidence of epithelial carcinoma following organ transplantation increases 60-100-fold as compared with the healthy population. The role of viral carcinogenesis, sunlight and photosensitizing effects of immunosuppressants is being considered [4].

Mangino and Schena [5] observed reactivation of oncogenic viruses in patients after organ transplantation; it mainly regarded HHV8 (related to Kaposi's sarcoma), human papilloma virus (squamous cell carcinoma [SCC], carcinoma of the vagina, vulva and uterine cervix), and Ebstein-Barr virus (lymphoproliferation). The authors also emphasized the protective effect of sirolimus, which inhibits cellular proliferation and neovascularization by reducing vascular-epithelial growth factor (VEGF) production and VEGF receptor blocking in endothelial cells.

It is estimated that decreased levels of IgG and CD4 lymphocytes due to prolonged steroid therapy achieve the normal values not earlier than after 8 months after discontinuation of treatment.

Nassar *et al.* [6] described a case of a patient on prolonged treatment with triamcinolone, in whom Kaposi's sarcoma developed. The steroid was detected in blood serum for the period of 6 months after treatment discontinuation. In our patient, dissemination from the primary melanoma focus occurred 10 years after immunosuppressive treatment, whereas squamous cell carcinoma developed in the 11th year of therapy.

Stoff *et al.* [7] demonstrated that increased incidence of tumours in patients after kidney transplantation regarded not only epithelial carcinoma, but also malignant melanoma, Kaposi's sarcoma, Merkel cell carcinoma and lymphoproliferative diseases. Ilie *et al.* [8] described a patient with Kaposi's sarcoma that developed during steroid therapy in the course of pemphigus foliaceus.

Saggar *et al.* [9] presented a case of a patient in whom Kaposi's sarcoma was also diagnosed during treatment with prednisone, methotrexate and Dapsone due to pem-

phigus vulgaris. After switching from methotrexate to sirolimus (rapamycin), the pathology started to subside, and the remission of pemphigus vulgaris was observed. Mahomed *et al.* [10] presented a 45-year-old woman treated with prednisone and cyclophosphamide due to pemphigus vulgaris, in whom after 6 years squamous cell carcinoma developed.

Dvoretsky *et al.* [11] described two cases of microinvasive carcinoma of the uterine cervix in patients treated with immunosuppressants due to pemphigus vulgaris. However, it should be noted that these patients also had lesions on genital mucous membranes. Therefore, it is possible that besides immunosuppression, chronic lesions within the uterine cervix mucosa contributed to the development of this carcinoma.

There are also individual reports concerning other diseases, where carcinogenesis could be a complication after immunosuppressive treatment.

Deleuran *et al.* [12] observed increased risk of non-melanocytic skin cancers and skin lymphomas in patients with atopic dermatitis who received prolonged treatment with local steroids. Toyoda *et al.* [13] demonstrated a case of numerous foci of SCC in a patient with deficiency of receptors for interferon γ. This deficiency predisposed patients to *Mycobacterium* infections. The first focus appeared as early as in the first year of life. The patient died at the age of 20 due to disseminated SCC. Long *et al.* [14] evaluated the incidence of non-melanocytic skin cancers in patients with inflammatory bowel disease and rheumatic diseases treated with immunosuppressants. In these groups of patients the risk was approximately 9 times higher than in the healthy population. Han *et al.* [15] studied the effects of ciclosporin on carcinogenesis in mice with immunodeficiency. The incidence of neoplasms (not only skin tumours) was 13 times higher than in immunocompetent animals. Leung *et al.* [16] observed the development of non-melanocytic skin cancers in patients on immunosuppressive treatment, in the course of autoimmunological hepatitis. In 9 of 45 examined patients 20 SCC and basal cell carcinoma (BCC) pathologies developed. Risk factors included beginning of autoimmunological disease at the age over 45 years and patient's age over 54 years.

De novo lesions or dissemination of malignant melanoma due to immunosuppression are rarely reported. In the case of our patient, after 10 years metastases to the liver occurred. Previously the patient was under regular oncological control. Treatment included DTIC, although according to the literature, response to this treatment is observed in approximately 15-30% of cases [1].

Zwald *et al.* [3] demonstrated that melanoma in situ and less than 1 mm thick occurred in post-transplantation patients at the same frequency as in the healthy population, whereas in patients who in the period up to 2 years after transplantation developed a focus of malignant melanoma, the course of disease was more aggressive and the tendency to metastases was greater. Our patient received mainly systemic corticosteroids and cyclophosphamide (2 years). The risk of carcinogenesis is variously evaluated for different therapeutic options.

In vitro studies demonstrated that calcineurin inhibitors stimulate tumour growth via a TGF-β dependent mechanism. Studies on murine models demonstrated that the mTOR kinase (mammalian target of rapamycin) inhibitor rapamycin inhibits angiogenesis and tumour growth. Five years after transplantation in patients who apart from ciclosporin received sirolimus, the proportion of non-melanocytic skin cancers was significantly reduced (3.8% compared with 11% in patients treated only with ciclosporin) [17].

Fekecs *et al.* [18] studied the effects of oxidative stress on carcinogenesis in 116 patients after kidney and pancreas transplantation. In 13.8% of patients non-melanocytic skin cancers developed (SCC, BCC). In order to evaluate oxidative stress, patients' blood samples were examined and the levels of malondialdehyde (MDA), thiol groups, myeloperoxidase, superoxide dismutase and catalase were measured. Malondialdehyde levels in patients with neoplasms were significantly higher than in the healthy controls and tumour-free patients. Thiol groups showed decreased activity in neoplastic patients, whereas antioxidative activity of myeloperoxidase and catalase was significantly higher in tumour-free patients.

Signorell *et al.* [19] observed that calcineurin inhibitors and azathioprine are the main factors in skin carcinogenesis. Concomitant administration of rapamycin exerts a preventive effect.

Molina *et al.* [20] studied the incidence of BCC and SCC in 4,089 patients after heart transplantation. They demonstrated that post-transplantation therapy with azathioprine increased the risk of SCC. No such effects were observed for ciclosporin and tacrolimus. Mycophenolate mofetil had a protective action, whereas the incidence of BCC in this group of patients corresponded to that of the healthy population. Additional risk factors for SCC were age > 45 years, induction therapy and exposure to sunlight.

The studies of Einollahi *et al.* [21] carried out from 1984 to 2008 in Iran showed that 1.14% of patients after kidney transplantation developed neoplasms. Skin cancers made up over half of them. Similarly to other reports, risk factors included age > 45 years and azathioprine use. Kaposi's sarcoma was the most frequently observed neoplasm. Mortality due to skin cancers was 7.8%.

Tjon *et al.* [22] examined the risk of malignancy in 385 patients after liver transplantation. *De novo* lesions occurred in 13% of patients. Ciclosporin and tacrolimus were significant risk factors; patient's age below 50 years was also a risk factor, which was not confirmed by other authors.

Between 1972 and 2009 the incidence of head and neck tumours was evaluated among kidney transplant patients in Croatia. These tumours developed in only 1.7%

of patients, on average 58 months after transplantation. BBC were diagnosed in 88.9%, Merkel cell carcinoma in 1 case, SCC in 1 case, oral Kaposi's sarcoma in 1 case, and laryngeal cancer in 1 patient. The authors also suggest protective effects of sirolimus and limited use of calcineurin inhibitors in this group of patients [23].

Wisgerhof *et al.* [24] observed neoplasms in 13% of kidney transplant patients; 75% of them were skin cancers (BCC and SCC). The authors are of the opinion that concomitant treatment with azathioprine and prednisone may pose a risk. Brewer *et al.* [25] demonstrated that 312 heart transplant patients developed 1,395 new foci of skin cancers, mostly SCC. Risk factors included sunlight, *Herpes simplex* infection, old age and treatment with mycophenolate mofetil following transplantation.

Mackenzie *et al.* [26] described a 46-year-old patient after kidney transplantation, who developed 23 foci of SCC with metastases to myocardium, and 14 foci of BCC. The patient was treated with azathioprine, prednisone and ciclosporin for a period of 4 years.

In the literature there is also some information concerning the prevention of carcinogenesis in patients subjected to immunosuppression. Lapointe *et al.* [27] noted that limited exposure to sunlight and regular dermatological control should become the standard recommendation in patients treated with immunosuppressants. According to Hofbauer *et al.* [2], acitretin is recommended as a method of chemoprevention of epithelial cancers (mainly SCC).

No evidence was found to support the effects of physical activity on carcinogenesis reduction. Whalen *et al.* [28] studied the risk of SCC and BCC occurrence in patients after transplantation of kidneys, liver and pancreas, in relation to the patient's physical activity, type of skin and exposure to sunlight. These cancers developed in 32% of patients, but a protective effect of physical activity was not demonstrated in this group of patients. In the healthy population, however, physical activity decreases the incidence of non-melanocytic skin cancers.

The above literature review supports the fact that carcinogenic effects of immunosuppression have been observed for a long time. In our paper we presented the case of a patient who developed squamous cell carcinoma de novo, and in whom we considered the influence of pemphigus foliaceus treatment on the dissemination of malignant melanoma whose primary focus was removed 10 years earlier.

References

1. Braun-Falco 0, Plewig G, Wolff HH, et al. Pęcherzyca liściasta. In: Dermatologia. Braun-Falco 0, Plewig G, Wolff HH, et al. (eds.) Czelej, Lublin 2002; 635-6.
2. Hofbauer GF, Bouwes Bavinck JN, Euvrard S. Organ transplantation and skin cancer: basic problems and new perspectives. Exp Dermatol 2010; 19: 473-82.
3. Zwald FO, Christenson LJ, Billingsley EM, et al. Melanoma in solid organ transplant recipients. Am J Transplant 2010; 10: 1297-304.
4. Hofbauer GF, Anliker M, Arnold A, et al. Swiss clinical practice guidelines for skin cancer in organ transplant recipients. Swiss Med Wkly 2009; 139: 407-15.
5. Mangino M, Schena FP. Skin cancer in renal transplant recipients. G Ital Nefrol 2010; 27: 75-80.
6. Nassar D, Schartz NE, Bouché C, et al. Kaposi's sarcoma after long-acting steroids: time until remission and drug washout. Dermatology 2010; 220: 159-63.
7. Stoff B, Salisbury C, Parker D, et al. Dermatopathology of skin cancer in solid organ transplant recipients. Transplant Rev (Orlando) 2010; 24: 172-89.
8. Ilie B, Brenner S, Lipitz R, et al. Kaposi's sarcoma after steroid therapy for pemphigus foliaceus. Case report and short review of literature. Dermatologica 1981; 163: 455-9.
9. Saggar S, Zeichner JA, Brown TT, et al. Kaposi's sarcoma resolves after sirolimus therapy in a patient with pemphigus vulgaris. Arch Dermatol 2008; 144: 654-7.
10. Mahomed Y, Mandel MA, Cramer SF, et al. Squamous cell carcinoma arising in pemphigus vulgaris during immunosuppressive therapy. Cancer 1980; 46: 1374-7.
11. Dvoretsky PM, Bonfiglio TA, Patten SF Jr, et al. Pemphigus vulgaris and microinvasive squamous-cell carcinoma of the uterine cervix. Acta Cytol 1985; 29: 403-10.
12. Deleuran M, Zachariae C, Thestrup-Pedersen K. Topical immune modulation and risk of cancer Topical immune modulation and risk of cancer. Ugeskr Laeger 2009; 171: 2468-71.
13. Toyoda H, Ido M, Nakanishi K, et al. Multiple cutaneous squamous cell carcinomas in a patient with interferon gamma receptor 2 (IFN gamma R2) deficiency. J Med Genet 2010; 47: 631-4.
14. Long MD, Kappelman MD, Pipkin CA. Nonmelanoma skin cancer in inflammatory bowel disease: a review. Inflamm Bowel Dis 2010; 4: 127-33.
15. Han W, Ming M, He TC, et al. Immunosuppressive cyclosporin A activates AKT in keratinocytes through PTEN suppression: implications in skin carcinogenesis. J Biol Chem 2010; 285: 11369-77.
16. Leung J, Dowling L, Obadan I, et al. Risk of non-melanoma skin cancer in autoimmune hepatitis. Dig Dis Sci 2010; 55: 3218-23.
17. Alberú J. Clinical insights for cancer outcomes in renal transplant patients. Transplant Proc 2010; 42: 36-40.
18. Fekecs T, Kádár Z, Battyáni Z, et al. Changes in oxidative stress in patients screened for skin cancer after solid-organ transplantation. Transplant Proc 2010; 42: 2336-8.
19. Signorell J, Hunziker T, Martinelli M, et al. Recurrent non-melanoma skin cancer: remission of field cancerization after conversion from calcineurin inhibitor- to proliferation signal inhibitor-based immunosuppression in a cardiac transplant recipient. Transplant Proc 2010; 42: 3871-5.
20. Molina BD, Leiro MG, Pulpón LA, et al. Incidence and risk factors for nonmelanoma skin cancer after heart transplantation. Transplant Proc 2010; 42: 3001-5.
21. Einollahi B, Nemati E, Lessan-Pezeshki M, et al. Skin cancer after renal transplantation: results of a multicenter study in Iran. Ann Transplant 2010; 15: 44-50.
22. Tjon AS, Sint Nicolaas J, Kwekkeboom J, et al. Increased incidence of early de novo cancer in liver graft recipients treated with cyclosporine: an association with C2 monitoring and recipient age. Liver Transpl 2010; 16: 837-46.

23. Basić-Jukić N, Bubić-Filipi L, Prgomet D, et al. Head and neck malignancies in Croatian renal transplant recipients. Bosn J Basic Med Sci 2010; 10: 37-9.
24. Wisgerhof HC, Edelbroek JR, de Fijter JW, et al. Subsequent squamous- and basal-cell carcinomas in kidney-transplant recipients after the first skin cancer: cumulative incidence and risk factors. Transplantation 2010; 89: 1231-8.
25. Brewer JD, Colegio OR, Phillips PK, et al. Incidence of and risk factors for skin cancer after heart transplant. Arch Dermatol 2009; 145: 1391-6.
26. Mackenzie KA, Simcock JW, Lainchbury JG, et al. Myocardial metastasis of cutaneous squamous cell carcinoma in a renal transplant recipient. Transplant Proc 2009; 41: 4414-5.
27. Lapointe AK, Hofbauer G, Anliker M, et al. Swiss clinical practice guidelines for skin cancer in organ transplant recipients. Rev Med Suisse 2010; 6: 854-9.
28. Whalen FM, Jambusaria-Pahlajani A, Speck RM, et al. Effect of physical activity on nonmelanoma skin cancer risk in kidney, liver, and pancreatic transplant patients. Dermatol Surg 2010; 36: 1510-3.