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MERKEL CELL CARCINOMA IN RENAL TRANSPLANT RECIPIENT

Nikolina Bašić-Jukić[1], Ljubica Bubić-Filipi[1], Petar Kes[1], Vladimir Šeparović[2], Josip Šmalcelj[2], Vesna Štitić[3], Tvrtko Hudolin[4], Josip Pasini[4]

[1]Department of Dialysis, Zagreb University Hospital Center, Zagreb; [2]Institute of Oncology, Zagreb University Hospital Center, Zagreb; [3]Department of Pathology, Karlovac General Hospital, Karlovac; [4]Department of Urology, Zagreb University Hospital Center, Zagreb, Croatia

SUMMARY – A 57-year-old male was started on hemodialysis in 1998 because of end-stage renal disease caused by IgA nephropathy. He received an allograft in April 2002 and was treated with cyclosporine, mycophenolate mofetil and steroids. Graft function was optimal, without episodes of acute rejection. A red intradermal painless nodule was observed in the left preauricular region in September 2004. Immunohistochemical staining showed perinuclear expression of cytokeratin 20 and synaptophysin as well as the presence of neuron-specific enolase and chromogranin, characteristic of Merkel cell carcinoma. Radical re-excision with a median margin of 2 cm was necessary. The patient received adjuvant radiotherapy in a total dose of 55 Gy in 20 cycles. Immunosuppressive therapy was reduced. Merkel cell carcinoma is a rare aggressive cancer that may be misdiagnosed as an indolent skin disease. In immunocompromised host it is more likely to occur, at a younger age and probably assuming a more aggressive course than in the general population.

Key words: *Kidney transplantation – postoperative complications; Carcinoma Merkel cell – etiology; Skin neoplasms etiology*

Introduction

Merkel cell carcinoma (MCC) is a rare aggressive skin cancer originally described in 1972 as trabecular cell carcinoma[1]. It is considered to originate from Merkel cells, the neuroendocrine cells present in the basal layer of the epidermis[2]. Tumor appears as an asymptomatic, solitary, small, red-purple, subcutaneous nodule. The exact cause of MCC is unknown, but it has been associated with the exposure to ultraviolet radiation. It tends to occur more often in immunocompromised host[3-5]. Tumor is very aggressive, with a high metastatic potential and high mortality rate. Optimal therapeutic approach has not yet been determined. Guidelines for the treatment of MCC have not yet been established because of the limited number of cases making controlled, randomized studies impossible.

We report on a 57-year-old male patient who developed MCC three years after renal transplantation.

Case Report

A 57-year-old male was started on hemodialysis in 1998 because of end-stage renal disease caused by IgA nephropathy. He received a cadaveric allograft in April 2002 and was treated with cyclosporin A (5 mg/kg/day, adjusted to maintain serum level within the target range), mycophenolate mofetil 2x1000 mg, and steroids (tapered to 0.1 mg/kg/day after 1 year). Graft function was optimal, without episodes of acute rejection. The post-transplantation course was uneventful, except for two episodes of urinary tract infection caused by *Proteus mirabilis* that were successfully treated with antimicrobial therapy.

Correspondence to: *Nikolina Bašić-Jukić, MD, PhD*, Department of Dialysis, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia
E-mail: nina_basic@net.hr

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In September 2004, an intradermal nodule was observed in the left preauricular region. It was a red-purple, painless nodule that measured 12 mm. Tumor excision was performed with 5-mm margins. Immunohistochemical staining showed intradermal tumor with numerous trabecular atypical epithelial cells with large nuclei and numerous mitoses. Tumor cells were cytokeratin positive, S-100 negative, with focal expression of synaptophysin and presence of neuroendocrine markers of neuron-specific enolase and chromogranin (Fig. 1A-D).

Sentinel lymph node scintigraphy showed enhanced signal in the left submandibular area and lower pole of the parotid gland. Radical re-excision with a median margin of 2 cm was performed, along with excision of the sentinel lymph node and lower pole of the parotid gland. Histopathologic findings of the lymph node and parotid gland were negative. The patient received adjuvant radiotherapy in a total dose of 55 Gy in 20 cycles. Immunosuppressive therapy was reduced. He is now receiving cyclosporine 2 mg/kg, mycophenolate mofetil 2x500 mg, and steroids. After two-year follow up, his renal function is stable with creatinine level ranging between 115 and 135 mmol/L, and creatinine clearance 63 mL/min. The patient is under regular follow up by nephrologists and oncologists.

Discussion

In the general population, MCC is an aggressive skin cancer that occurs in older adults. More than 95% of cases are recorded in Caucasians[6]. The tumor is most commonly found on the sun exposed areas of the head and neck, followed by extremities and trunk, suggesting

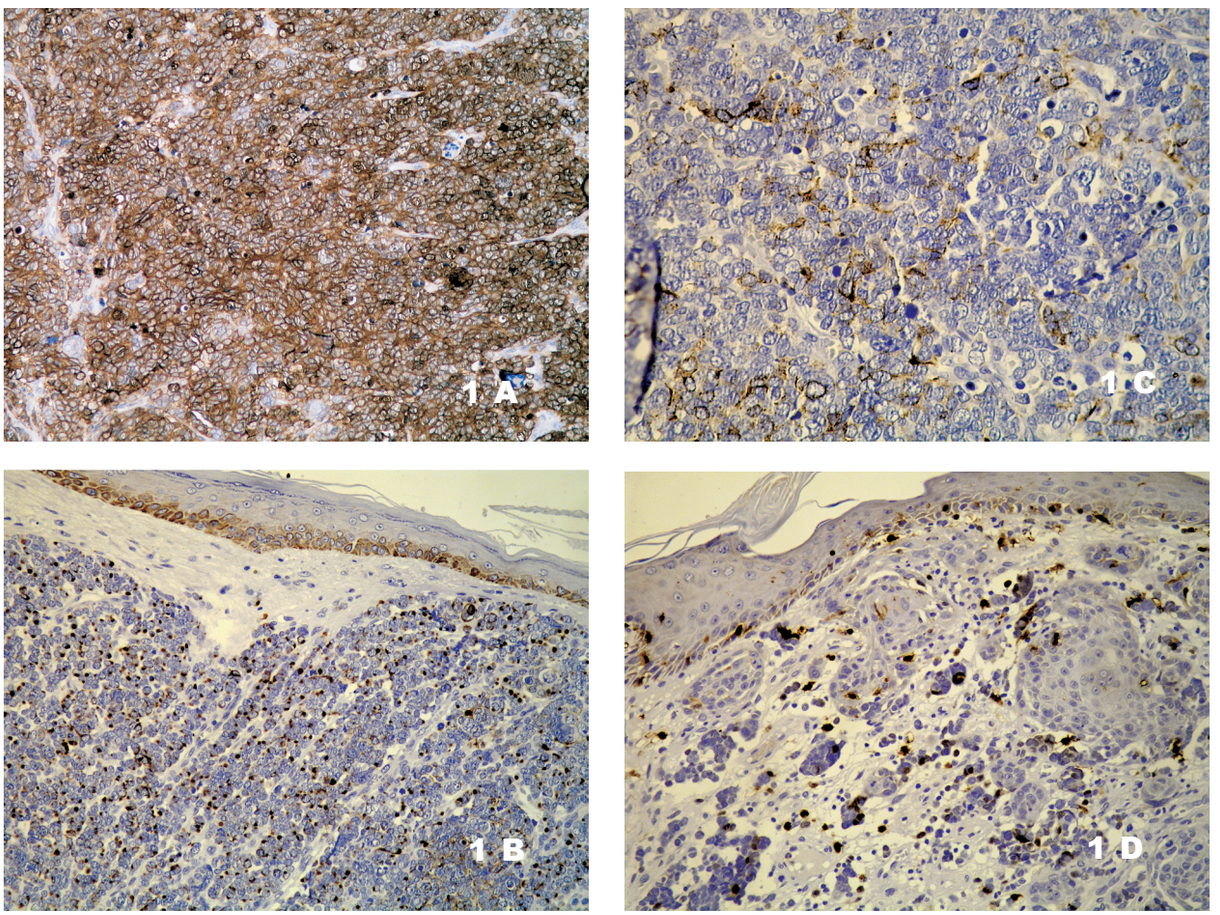

Figure 1. Immunohistochemistry of the skin. Positive staining for neuron-specific enolase (magnification X200) (A), cytokeratin 20 (X200) (B) and synaptophysin (X400) (C); and negative staining for S-100 (X200) (D).

ultraviolet radiation as a possible etiologic factor. However, other factors may be involved in the pathogenesis of the disease, since MCC has been reported to involve genital and oral mucosa[7]. Several lines of evidence suggest that MCC occurs more frequently in immunocompromised patients as compared with the general population. In a literature review, 15% of patients had previously received or were receiving immunosuppressive therapy[8,9]. While in the general population MCC is predominantly a disease of the elderly with only 5% of cases diagnosed before age 50, in transplant recipients 30% of patients are younger than 50[9]. It seems that changes in the immune response to ultraviolet radiation enable development of this malignant tumor.

MCC has a recurrence rate of 30%[8]. It behaves aggressively, with a mortality rate of 56%. Almost 70% of MCC patients have lymph node metastases. In the same time, metastases were found in only 20% of renal transplant recipients who developed melanoma, with a mortality rate of 29%[9]. The presence of lymphatic disease is considered as an adverse prognostic factor[10-12]. The reported 3-year overall survival for MCC is only 31%, with the majority of patients dying from distant metastatic disease[13]. Several cases of spontaneous regression of MCC have been reported[14,15].

There are less than 50 cases of MCC reported to arise after renal transplantation, which is the main reason for the lack of consensus regarding optimal therapeutic approach to MCC in renal transplant recipients. However, its highly aggressive behavior demands radical therapeutic approach that should be determined by the clinical stage at presentation. Wide local excision of the lesion with 2-cm margin should be performed in suspected cases. Local irradiation is recommended to decrease the rate of recurrence, while the tumor is considered to be radiosensitive. In general, the radiation fractionation schemes were 45 to 50 Gy in 10 to 25 fractions over 2 to 5 weeks, depending on the size of the affected area[16]. Positive lymph node scintigraphy demands nodal dissection accompanied by local irradiation[17]. Chemotherapy is used in patients with metastatic disease, and involves use of various combinations of platinum-based chemotherapeutics, cyclophosphamide, doxorubicin, steroids and vincristine[18].

In conclusion, MCC occurs more frequently in renal transplant recipients, who should therefore be regularly screened for the presence of skin changes. The high rate of local recurrence, distant metastases, and high mortality rate require radical therapeutic approach.

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Sažetak

KARCINOM MERKELOVIH STANICA U BOLESNIKA S PRESAĐENIM BUBREGOM

N. Bašić-Jukić, Lj. Bubić-Filipi, P. Kes, V. Šeparović, J. Šmalcelj, V. Štitić, T. Hudolin i *J. Pasini*

Kod muškarca u dobi od 57 godina hemodijaliza je započeta 1998. godine zbog završnog stadija kroničnog zatajenja bubrega uzrokovanog IgA nefropatijom. Bolesnik je primio alograft u travnju 2002. godine te je liječen ciklosporinom, mikofenolatom mofetil i steroidima. Funkcija transplantata je bila optimalna, bez akutnog odbacivanja. U rujnu 2004. zapažen je crveni bezbolni intradermalni čvor u lijevom predaurikularnom području. Imunohistokemijsko bojenje je pokazalo perinuklearnu izraženost citokeratina 20 i sinaptofizina, kao i prisutnost za neuron specifične enolaze i kromogranina, sve znakovito za karcinom Merkelovih stanica. Bila je potrebna ponovna radikalna ekscizija uz medijan granice od 2 cm. Bolesnik je primio dopunsku terapiju u ukupnoj dozi od 55 Gy u 20 ciklusa. Imunosupresivna terapija je smanjena. Karcinom Merkelovih stanica je rijedak agresivni rak koji se može pogrešno dijagnosticirati kao indolentna bolest kože. Kod imunokompromitiranih domaćina on nastaje češće, u mlađoj dobi i vjerojatno poprima agresivniji tijek negoli u općoj populaciji.

Ključne riječi: *Transplantacija bubrega – posoperativne komplikacije; Karcinom Merkelovih stanica – etiologija; Neoplazme kože – etiologija*