Subcutaneous Merkel Cell Carcinoma in a Psoriatic Patient Treated with Methotrexate and TNF-α inhibitors

Subkutanes Merkelzellkarzinom bei einem Psoriasis-Patienten unter der Behandlung mit Methotrexat und TNF-α-Inhibitoren

Authors V. Kucinskiene[1], V. Vilkickaite[1], J. Makstiene[2], S. Silling[3], S. Valiukeviciene[1]

Institutions
[1] Department of Skin and Venereal Diseases, Lithuanian University of Health Sciences, Kaunas, Lithuania
[2] Department of Pathological Anatomy, Lithuanian University of Health Sciences, Kaunas, Lithuania
[3] National Reference Center for Papilloma and Polyoma Viruses, Institute of Virology, University of Cologne, Germany

Bibliography
DOI http://dx.doi.org/10.1055/s-0034-1377833
Akt Dermatol 2014; 40: 404–407

ISSN 0340-2541

Corresponding author
Assoc. Prof. Vesta Kucinskiene
Department of Skin and Venereal Diseases
Lithuanian University of Health Sciences
Eiveniu 2
LT-50009, Kaunas
Lithuania
kvesta@delfi.lt

Abstract

TNF-α inhibitors are used for the treatment of chronic inflammatory diseases and provide a high degree of clinical efficacy in patients with severe psoriasis. Although the effect of blocking agents gives significant improvements in quality of life of psoriatic patients, the use of them might lead to neoplasia not observed before the treatment. We present a case of Merkel cell carcinoma in a patient with a long-standing history of psoriasis and psoriatic arthritis treated with methotrexate and TNF-α inhibitors (etanercept and infliximab).

Case report

A 58-year-old male with 26 years history of psoriasis (**Fig. 1**) and psoriatic arthritis received 10 mg of methotrexate (MTX) weekly for over 19 years; he was also visiting Florida for nine years to get natural sunlight. The patient has never applied psoralen and ultraviolet A (PUVA) therapy. At the age of 58 years, in November 2011 etanercept was started, but 2 months later the skin pustulosis developed and etanercept was changed to infliximab. After 12 months under the treatment with TNF-α inhibitors, the patient noticed a rapidly growing hard subcutaneous nodus on the right arm which was interpreted as lipoma before the start of biological therapy. Physical examination revealed a firm, non-tender red-blue nodus, of approximately 5×6 cm size (**Fig. 2a, b**). The dermatohistopathology revealed the diagnosis of Merkel cell carcinoma (MCC) showing the involvement of dermis and hypodermis with tumour cells which had indistinct cytoplasm and positivity for anti-cytokeratin-20 (anti-CK-20) and neuroendocrine marker synaptophysin (**Fig. 3–5**). Merkel cell polyoma virus (MCPyV) load and DNA integration status was assessed in paraffin embedded carcinoma tissue. Up to one MCPyV copy per cell was detected, but no robust statement concerning the integration status could be made because of the very small sample size (revealed by ß-globin gene PCR). However, a weak tendency of MCPyV DNA integration was observed. A chest CT scan showed two enlarged pathological lymph nodes (~3.0×2.2 cm and 2.1×2.2 cm) with necrosis in the right armpit. There was no evidence of metastasis to the lung. The MRI showed a ~5.0×4.7×2.4 cm tumour in the middle of the right arm in adipose tissue. It infiltrated the skin, but the muscle tissue was not impaired (**Fig. 6**). The MRI confirmed pathological lymph nodes in the right armpit. No changes were observed on the sonography of the internal organs.

The patient underwent a radical tumour excision, lymphadenectomy and local radiotherapy. The patient's treatment of psoriasis with infliximab and methotrexate was stopped. Only topical application of momethasonefuroat as cream was extended. However, the condition of joints and skin deteriorated. It was decided to restart 10 mg weekly of MTX. After nine months a local relapse of MCC in the same arm was confirmed. The abdominal CT scan showed metastases to soft tissues around the pancreas. Adjuvant chemotherapy with etoposide and cisplatine was started (5 courses). The patient lost about 40 kg weight but at the same time psoriatic skin lesions and psoriatic arthritis improved. However, because of common exhaustion and cardiovascular insufficiency the patient did not survive.

Discussion

MCC is more often diagnosed in immunocompromized patients with other malignancies such as B-cell lymphoma [1] and HIV [2] or patients who underwent organ transplantation [3]. In the literature there is an increasing number of cases where MCC arises after therapeutic immunosup-

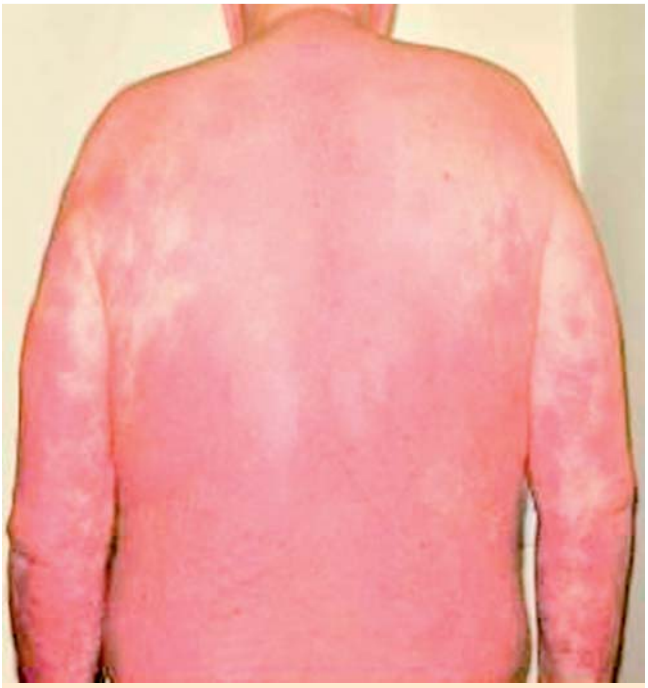
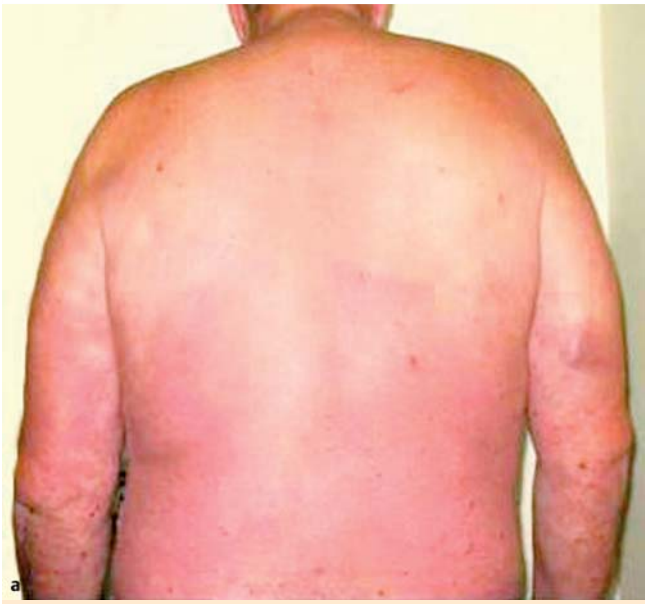


Fig. 1 Red confluent psoriatic patches on the back and arms before the treatment with TNF-α inhibitors.



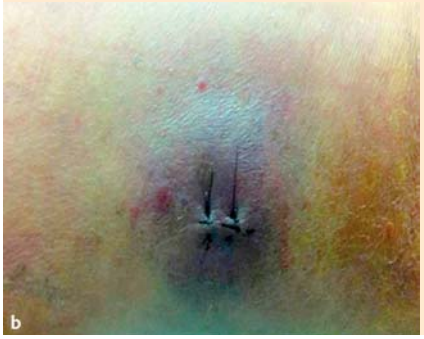


Fig. 2 **a** A firm, non-tender rapidly growing blue nodus, 5×6 cm in diameter, on the right arm which developed during biologic therapy; **b** tumour on the right arm after incisional biopsy.

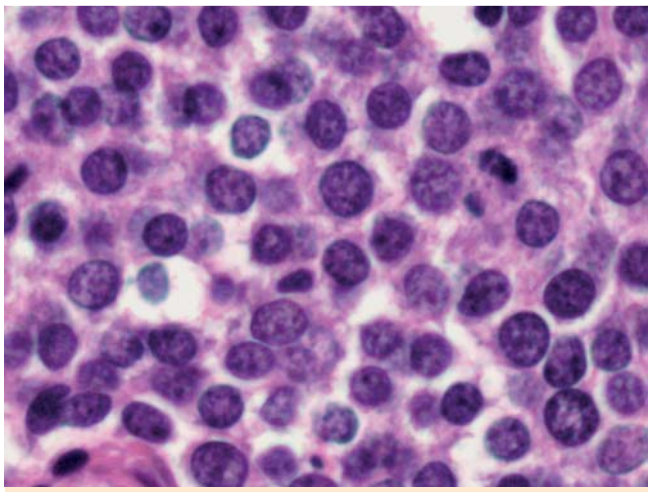


Fig. 3 HE 400×. Deposits of small monomorphic basophilic tumor cells with round nuclei and scanty cytoplasm.

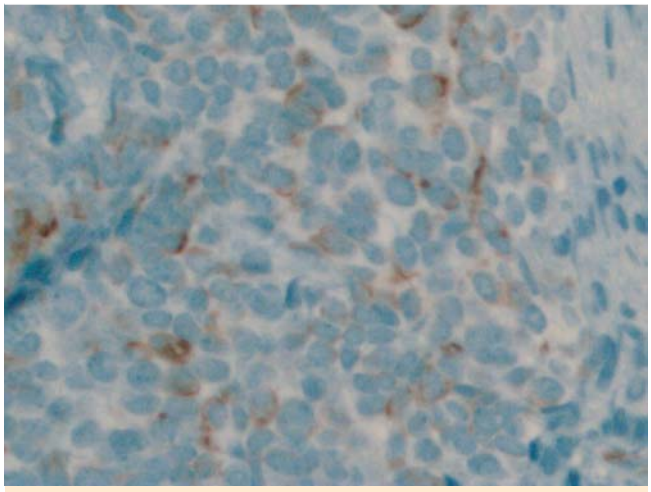


Fig. 4 Section immunostained with anti-CK20 antibody, demonstrating dot-like paranuclear pattern (20×).

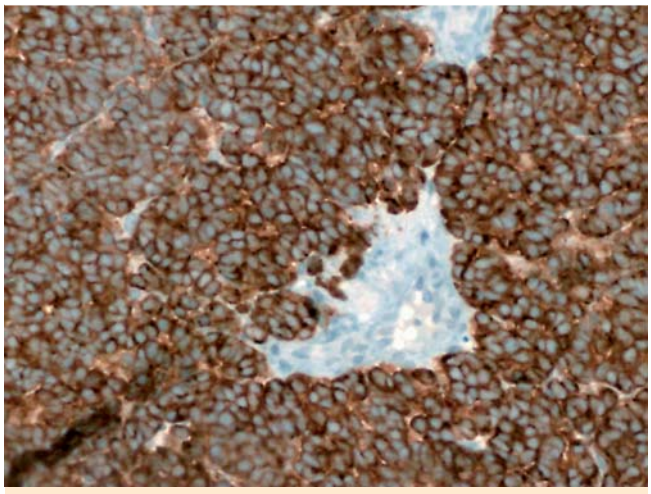


Fig. 5 Positive staining with neuroendocrine marker synaptophysin.

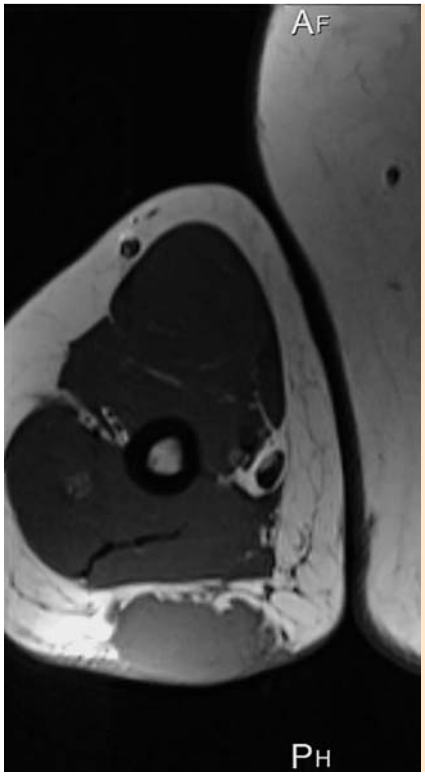


Fig. 6 MRI of the right arm. Tumor infiltration in subcutaneous tissue.

pression [4,5]. Gooptu et al. published three cases of rapidly fatal MCC in patients who were treated with azathioprine for many years [6]. Some authors suggested that the use of any TNF-α inhibitor in combination with MTX may increase the hazard for non-melanoma skin cancer (risk ratio of 1.24 for TNF-α inhibitors without MTX and risk ratio of 1.97 with MTX) [7]. Wirges et al. propose that rituximab may place patients at a higher risk for aggressive MCC [8]. However, the risk of malignancies associated with TNF-α inhibitors are controversial until now. Meta-analyses of randomized controlled trials have not shown the significant increased risk of cancer during treatment with TNF-α inhibitors, but found a higher rate of non-melanoma skin cancer in patients treated with etanercept such as 31.8% in contrast to infliximab with 19.2% [9].

UV radiation exposure is another important etiological factor in the development of MCC. This assumption is based on the fact that the MCC usually appears on body parts exposed to sunlight on the head and neck or dorsal surfaces of extremities [10] and territories with a higher UVB solar index [11,12]. The case we presented mentions that the patient has been visiting Florida for nine years to get natural sunlight and it may have served the development of malignancy too. Lunder et al. prospectively studied 1380 patients with psoriasis who were treated with PUVA. MCC has developed in three cases of these patients [13].

Many studies showed that Merkel cell polyomavirus (MCPyV) has direct causal relations with the development of carcinomas [11, 14–18]. In different MCC tumours, MCPyV DNA sequences were found to be integrated at different sites within the genome [19] and it stimulates the clonal broadening of tumour cells [20]. Extensive retrospective study of German and Australian MCC examined the samples of 174 patients and found that 86% of patients with MCC were infected by MCPyV and 9.7% of them were immunosuppressed [21]. The development of this virus reveals that under normal conditions harmless microflora of the organism may acquire an accurate set of mutations and initiate the development of a MCC if a subject goes to be immunosuppressed [14,22]. The majority of healthy people are thought to get infected with MCPyV in childhood, but in the absence of the predisposing factors this infection is not able to initiate the tumorogenesis [14,23].

In our case we suggest that therapeutic immunosuppression caused by MTX, etanercept and infliximab, has induced the development and rapid progression of MCC. Biologic therapy has significant improvements in quality of life of psoriatic patients but is also related to important side effects especially in a relationship with warning occurrences, such as non-melanoma skin cancer and MCC.

Conflict of interest

The authors declare no conflict of interest.

Zusammenfassung

Subkutanes Merkelzellkarzinom bei einem Psoriasis-Patienten unter der Behandlung mit Methotrexat und TNF-α-Inhibitoren

TNF-α-Inhibitoren werden neben verschiedenen chronisch entzündlichen Krankheiten auch zur Therapie der schweren Psoriasis eingesetzt. Die Therapie führt zu einer deutlichen Verbesserung der Lebensqualität der Psoriasis-Patienten, kann aber unter Umständen eine rasche Progression maligner Tumore begünstigen, die vor der Behandlung nicht diagnostiziert wurden. Wir berichten über einen klinischen Fall des Merkelzellkarzinoms bei einem Patienten mit langjähriger Psoriasis und Psoriasis-Arthritis, der mit Methotrexat und TNF-α-Inhibitoren (Etanercept und Infliximab) behandelt wurde.

Acknowledgment

For helpful assistance with MCPyV genotyping data, we thank Prof. Dr. Cornelia Mauch and her team from University of Cologne, Department of Dermatology and Venereology. Funding for the test was supported by National Reference Center for Papilloma and Polyoma Viruses, BMG Grant No: 1369-401.

References

1 *Howard RA*, *Dores GM*, *Curtis RE* et al. Merkel cell carcinoma and multiple primary cancers. Cancer Epidemiol Biomarkers Prev 2006; 15: 1545
2 *Manganoni MA*, *Farisoglio C*, *Tucci G* et al. Merkel cell carcinoma and HIV infection: a case report and review of the literature. AIDS Patient Care STDS 2007; 21: 447
3 *Koljonen V*, *Kukko H*, *Tukiainen E* et al. Incidence of Merkel cell carcinoma in renal transplant recipients. Nephrol Dial Transplant 2009; 24: 3231
4 *Pathirana D*, *Ormerod AD*, *Saiag P* et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris. JEADV 2009; 23: 5–70
5 *Younger IR*, *Harris DWS*, *Colver GB*. Azatiophrine in dermathology. J Am Acad Dermatol 1991; 25: 281–286
6 *Gooptu C*, *Woollons A*, *Ross J* et al. Merkel cell carcinoma arising after therapeutic immunosuppression. British Journal of Dermatol 1997; 137: 637–641
7 *Krishna SM*, *Kim CN*. Merkel cell carcinoma in a patient treated with adalimumab: case report. Cutis 2011; 87: 81–84

8 *Wirges ML*, *Saporito F*, *Smith J*. Rapid growth of Merkel cell carcinoma after treatment with rituximab. J Drugs Dermatol 2006; 5: 180 – 181
9 *Moulis G*, *Sommet A*, *Bene J* et al. Cancer Risk of Anti-TNF-α at Recommended Doses in Adult Rheumatoid Arthritis: A Meta-Analysis with Intention to Treat and per Protocol Analyses. Plos One 2012; 7: 1 – 7
10 *Morgan MB*, *Smoller BR*, *Somach SC*. Deadly dermatologic diseases: Merkel Cell Carcinoma. Clinicopathologic Atlas and Text 2007; Part I. VIII: 32 – 38
11 *Koljonen V*, *Kluger N*, *Sihto H* et al. Lateral distribution of Merkel cell carcinoma in a nationwide cohort. J Eur Acad Dermatol Venereol 2013; 27: 884 – 888
12 *Agelli M*, *Clegg LX*. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol 2003; 49: 832
13 *Lunder EJ*, *Stern RS*. Merkel-Cell Carcinomas in Patients Treated with Methoxsalen and Ultraviolet A Radiation. N Engl J Med 1998; 339: 1247 – 1248
14 *Chang Y*, *Moore PS*. Merkel Cell Carcinoma: A Virus-Induced Human Cancer. Annu Rev Pathol Mech Dis 2012; 7: 123 – 144
15 *Feng H*, *Shuda M*, *Chang Y* et al. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008; 319: 1096
16 *Kassem A*, *Schöpflin A*, *Diaz C* et al. Frequent detection of Merkel cell polyomavirus in human Merkel cell carcinomas and identification of a unique deletion in the VP1 gene. Cancer Res 2008; 68: 5009
17 *Sharp CP*, *Norja P*, *Anthony I* et al. Reactivation and mutation of newly discovered WU, KI, and Merkel cell carcinoma polyomaviruses in immunosuppressed individuals. J Infect Dis 2009; 199: 398
18 *Carter JJ*, *Paulson KG*, *Wipf GC* et al. Association of Merkel cell polyomavirus-specific antibodies with Merkel cell carcinoma. J Natl Cancer Inst 2009; 101: 1510
19 *Wang TS*, *Byrne PJ* et al. Merkel Cell Carcinoma: Update and Review. Semin Cutan Med Surg 2011; 30: 48 – 56
20 *Sastre-Garau X*, *Peter M*, *Avril MF* et al. Merkel cell carcinoma of the skin: pathological and molecular evidence for a causative role of MCV in oncogenesis. J Pathol 2009; 218: 48
21 *Schrama D*, *Peitsch WK*, *Zapatka M* et al. Merkel cell polyomavirus status is not associated with clinical course of Merkel cell carcinoma. J Invest Dermatol 2011; 131: 1631
22 *Duncavage EJ*, *Le BM*, *Wang D* et al. Merkel cell polyomavirus: a specific marker for Merkel cell carcinoma in histologically similar tumors. Am J Surg Pathol 2009; 33: 1771 – 1777
23 *Chen T*, *Hedman L*, *Matilla PS* et al. Serological evidence of Merkel cell polyomavirus primary infections in childhood. J Clin Virol 2011; 50: 125 – 129