

# Subcutaneous Merkel Cell Carcinoma in a Psoriatic Patient Treated with Methotrexate and TNF- $\alpha$ inhibitors

## Subkutanes Merkelzellkarzinom bei einem Psoriasis-Patienten unter der Behandlung mit Methotrexat und TNF- $\alpha$ -Inhibitoren

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### Bibliography

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### Abstract

TNF- $\alpha$  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- $\alpha$  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- $\alpha$  inhibitors, the patient noticed a rapidly growing hard subcutaneous nodule on the right arm which was interpreted as lipoma before the start of biological therapy. Physical examination revealed a firm, non-tender red-blue nodule, 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  $\beta$ -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.

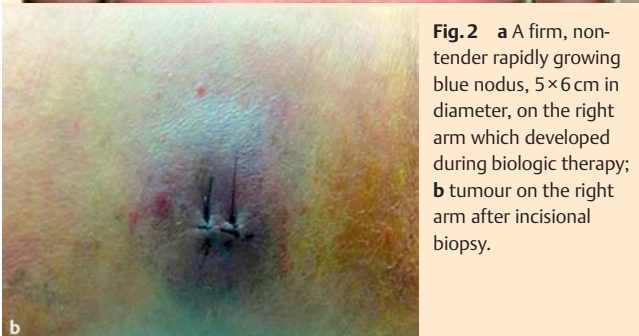
The patient underwent a radical tumour excision, lymphadenectomy and local radiotherapy. The patient's treatment of psoriasis with infliximab and methotrexate was stopped. Only topical application of mometasonefuroate as cream was extended. However, the condition of joints and skin deteriorated. It was 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 cisplatin 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

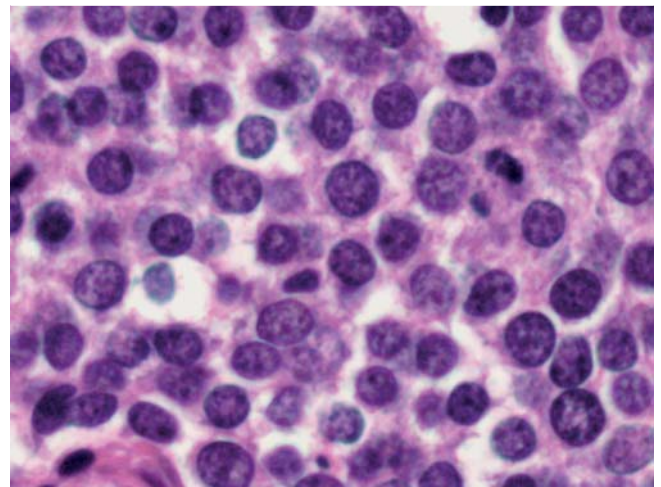
MCC is more often diagnosed in immunocompromized patients with other malignancies such as B-cell lymphoma [1] and HIV [2] or patients who underwent organ transplantation [3]. In the literature there is an increasing number of cases where MCC arises after therapeutic immunosup-



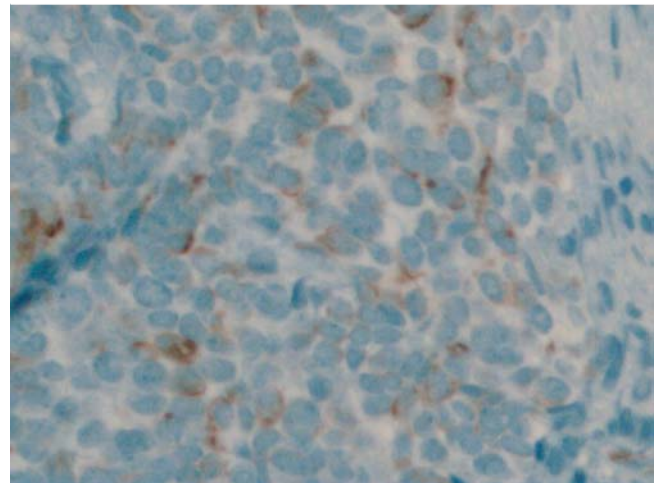
**Fig. 1** Red confluent psoriatic patches on the back and arms before the treatment with TNF- $\alpha$  inhibitors.



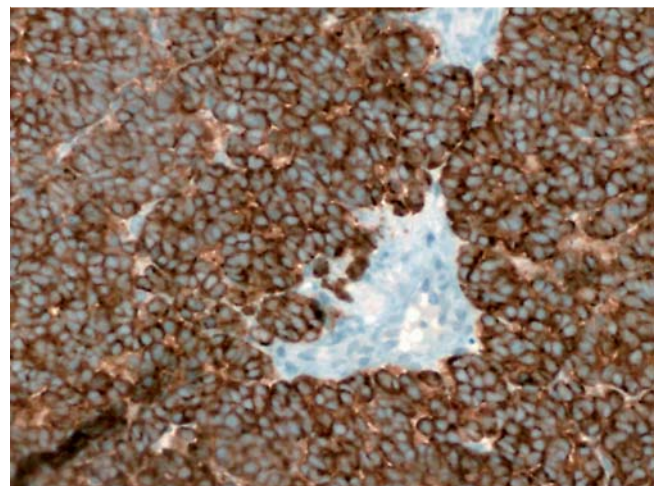
**Fig. 2** **a** A firm, non-tender rapidly growing blue nodus, 5×6 cm in diameter, on the right arm which developed during biologic therapy; **b** tumour on the right arm after incisional biopsy.



**Fig. 3** HE 400 $\times$ . Deposits of small monomorphic basophilic tumor cells with round nuclei and scanty cytoplasm.

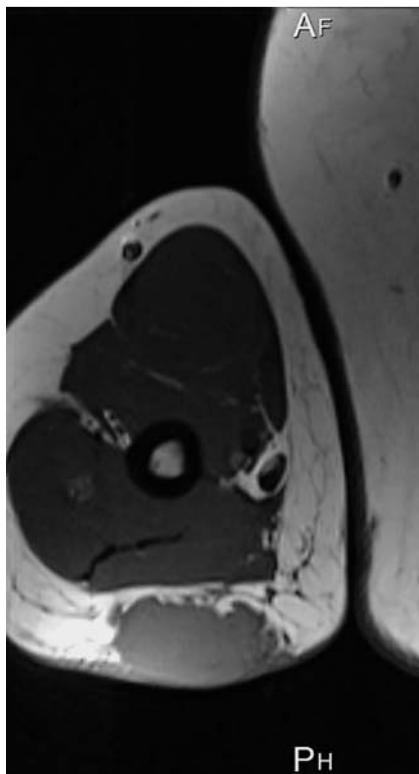


**Fig. 4** Section immunostained with anti-CK20 antibody, demonstrating dot-like paranuclear pattern (20 $\times$ ).



**Fig. 5** Positive staining with neuroendocrine marker synaptophysin.

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**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- $\alpha$  inhibitor in combination with MTX may increase the hazard for non-melanoma skin cancer (risk ratio of 1.24 for TNF- $\alpha$  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- $\alpha$  inhibitors are controversial until now. Meta-analyses of randomized controlled trials have not shown the significant increased risk of cancer during treatment with TNF- $\alpha$  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 de-

velopment 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 tumorigenesis [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- $\alpha$ -Inhibitoren



TNF- $\alpha$ -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- $\alpha$ -Inhibitoren (Etanercept und Infliximab) behandelt wurde.

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