The histopathological diagnosis of spindle cell tumours is often difficult. We present a patient who developed a painful tumour on his head 6 years after renal transplantation. Histologically, the tumour was first interpreted as scar tissue with an unusual fibrohistiocytic component. Cytokeratins, desmin, CD31, CD34 and S100 could not be detected using conventional immunohistochemistry. After two recurrences and intensive immunohistochemical examinations, cytokeratin-positive tumour areas in direct connection with the epidermis were detected. The final diagnosis was therefore spindle cell squamous carcinoma. The patient finally died from brain metastases after experiencing further painful recurrences that were removed surgically. Our case underscores the importance of refined immunohistochemical methods in establishing the diagnosis of spindle cell squamous carcinomas, methods that should be taken into account especially if painful spindle cell tumours arise on sun-exposed skin in immunosuppressed patients.

**Key words:** cytokeratin; immunohistochemistry; immunosuppression; skin; spindle cell tumour.

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**CASE REPORT**

A 52-year-old white male patient with a history of renal insufficiency and renal transplantation in 1992, first presented in 1998 at the Department of Dermatology, University of Heidelberg. Under immunosuppression with cyclosporin A (Sandimmun® 150 mg) and corticosteroids (methylprednisolone 4 mg daily) he had developed multiple actinic keratoses, seborrhoeic keratoses, Bowen’s disease, squamous cell carcinomas and basal cell carcinomas which had been in part removed surgically and in part treated with photodynamic therapy in May 1998. In June 1998 the patient developed a painful nodule on his head at the site of a previously shave-excised actinic keratosis. The skin-coloured and firm nodule measuring 1 cm in diameter was excised. Histological examination revealed a thickened epithelium covering a fibrotic zone composed of irregular collagen bundles. Embedded within the collagen bundles were monomorphic spindle-shaped cells, some of which had large nucleoli. There were only a few mitotic figures. The cells partly surrounded the larger deep cutaneous and subcutaneous vessels. Because of the lack of atypical cells and the cell melanoma, may present histopathologically in a similar pattern: a storiform–pleomorphic lesion with numerous atypical mitoses and giant cells. Immunohistochemistry is a useful tool for distinguishing these four entities: while positivity for cytokeratin strongly suggests an epithelial origin, i.e. a squamous cell carcinoma, the expression of actin and desmin is typical of the muscle-derived leiomyosarcoma. Melanomas mostly express S100 or HMB45 protein, while malignant fibrous histiocytoma, including atypical fibroxanthomas, do not have a “diagnostic” marker and are hence diagnosed by exclusion (5). It has recently been speculated that a high percentage of malignant vimentin-positive spindle cell tumours on sun-exposed skin formerly classified as atypical fibroxanthomas are de-differentiated squamous cell carcinomas with loss of keratin-antigenicity (6).

We present the case of a metastasizing spindle cell neoplasm in a renal transplant recipient that could only be diagnosed as SCSC after refined and repeated immunohistological examination.

Allograft recipients are at increased risk of getting skin cancer. The incidence of cutaneous squamous cell carcinomas is 50–250 times higher in these patients than in the age-matched control population (1). Basal cell carcinoma, actinic keratoses, melanoma, Kaposi’s sarcoma and cutaneous T-cell lymphoma also occur at a higher incidence than in the age-matched control population (2). Furthermore, it has been noted that aggressive squamous cell carcinomas account for a considerable rate of deaths among transplant recipients (3, 4). Differential diagnosis of spindle cell tumours of the skin is often difficult (5). The clinically benign atypical fibroxanthoma and leiomyosarcoma, as well as the clinically unfavourable malignant fibrous histiocytoma, spindle cell squamous carcinoma (SCSC) and spindle

**CLINICAL REPORT**

**Unusual Spindle Cell Squamous Carcinoma in a Renal Transplant Patient**

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predominating fibrocytic reaction, this was not interpreted as neoplasm but as scar tissue. Epithelial changes with altered polarity of the basal layer and nuclear polymorphism, corresponding to an actinic keratosis, were observed at the margins. At the time, no clear criteria of malignancy could be established.

However, the excision site remained painful. Clinically, this was interpreted as scar pain and a consecutive thickening of the scar was interpreted as keloid formation, which was twice confirmed histologically (February and July 1999). Because of continuous growth of a rather firm nodule at the excision site to 4 cm (Fig. 1), a radical excision was performed in November 1999 in order to exclude a malignant tumour. Histologically, the tumour was a malignant spindle cell neoplasm (Fig. 2).

After repeated excisions the margins became tumour-free and the defect was closed with a full-thickness skin graft. One of us raised the working diagnosis of a SCSC. Immunohistochemical analysis was performed as described previously (7) using the ABC method (Amersham), with nickel-enhanced 3,3’-diaminobenzidine being employed for the staining reactions on paraffin embedded sections. For most antibodies, pretreatment using microwave oven heating (10–15 min, 600 W) in standard sodium citrate buffer, pH 6.0, was carried out. For some antibodies, incubation with 0.001% trypsin was necessary. Antibodies against S100 protein rabbit polyclonal (Linaris, Germany), broad spectrum keratin (Kl-1, Immunotech, France) and desmin (D33, Dako, Germany) showed no reactivity in all the tumour specimens from the primary tumour and the recurrent tumours up to July 2000. Vimentin (B9, Camon, Germany) and actin (HHF35, Enzo Diagnostics, USA) showed a strong reaction in the spindle-shaped dermal tumour cells that showed no connection with the epidermis. In sections of one of the recurrent tumour specimens, tumour cells in direct connection with the epidermis showed a positive reaction to keratin antibodies (Fig. 3a). The keratin-positive tumour parts were vimentin-negative and vice versa. The sensitivity of the mAb Kl-1, which does not need retrieval methods according to the manufacturer, could be improved by applying the described antigen retrieval methods. Thus, single keratin-positive tumour cells could be detected in some parts of the tumour (Fig. 3b). Further examination of the type of keratin expressed by the tumour cells revealed positivity for CK 17 (mAb Ks 17.E3, Progen, Germany), broad spectrum mAb against CK 1, 5, 10, 14 (Enzo, New York) and against CK 6 (mAb Ks6.KA12, Progen), while mono-specific antibodies against CK 10 (DE-K10, Progen), CK 19 (Ks 19.1, Progen) and CK 20 (IT-Ks 20.10, Progen) remained negative. Interestingly, mAb CAM 5.2 against CK 8 and 18 (Becton-Dickenson, San Jose, CA) decorated single cells in some parts of the tumour, while the CK 17 positive tumour part directly connected to the epidermis remained unstained.

**Fig. 1.** Ulcerated tumour on the right forehead before surgical removal in November 1999. The ulceration was due to a previous biopsy.

**Fig. 2.** H&E staining on paraffin-embedded sections. (a) Lesion from November 1999: In contrast to previous specimens there were nodal accumulations of epithelioid spindle cells with focal atypical mitoses and prominent nucleoli, strongly suggesting a malignant neoplasm. In some parts, the subcutaneous fatty tissue was diffusely infiltrated by the tumour cells. In addition, there were fibrotic parts resembling keloid tissue, where the tumour cells themselves appeared hidden by the collagen bundles. (b) Higher magnification (×560) reveals atypical pleomorphic cells with prominent nucleoli.
grounds of our immunohistochemical results, the tumour was finally classified as SCSC. Postoperatively, the excision area was irradiated with 30 Gy.

In June 2000 the patient developed a painful induration 1 cm in size at the margin of the skin graft. Because there was a deep penetration of the carcinoma histologically, a wide and radical excision was performed including the periosteum. The excision defect was left to open wound healing. In November 2000, two subcutaneous in-transit metastases were excised. Two months later, new painful nodules developed on the wound margins. Local daily injections of bleomycin (1 mg/ml) into the tumour masses did not provide benefit. In April 2001 an extended excision of the affected scalp skin, including the periosteum and parts of the lamina externa (“scalpectomy”), was performed and the defect was partly closed using a musculocutaneous flap technique. Three months later, new painful nodules that had developed at the wound margins behind the ears were excised. In February 2002 the patient developed brain metastases and died in June 2002 after symptomatic treatment.

**DISCUSSION**

Since Helwig in 1963 (8) described the atypical fibroxanthoma of the skin as cutaneous neoplasm composed of atypical spindled, pleomorphic and polygonal cells with focally xanthomatous appearance and clinically benign course, many studies have focused on the differential diagnosis of spindle cell neoplasms of the skin (5, 6, 9–16). The exact histogenesis of atypical fibroxanthoma is still unclear: morphologic, electron-microscopic and immunohistochemical studies suggest that the tumour cells have mesenchymal properties (10, 12, 17, 18), while other investigators suggest that lesions containing the same features are SCSC (6, 9, 11, 13, 14). Criteria for a keratogenous differentiation are: (a) continuity with an actinic keratosis above the tumour, (b) continuity with more conventional invasive squamous cell carcinoma parts in the upper dermis, (c) dyskeratotic cells within the deeper parts of the lesion, and (d) intercellular bridges between neighbouring neoplastic cells. In our case we found the first and the second criteria.

Cytokeratins are well-established markers for neoplasms of epithelial origin (19). However, rare tumours that are thought to be of mesenchymal origin, such as synovial sarcomas, mesotheliomas and epithelioid sarcomas, have also been found to express cytokeratins (5). Vimentin, on the other hand, although usually confined to tumours of mesenchymal origin, is frequently found in certain epithelial neoplasms. These include the cutaneous mixed tumour, pleomorphic adenomas, adenoid cystic carcinoma, renal cell carcinoma and others (reviewed in 5). Expression of vimentin in epithelial tumours may reflect conversion to an embryonic status or reduced cell-to-cell contact (20, 21). Absence of cytokeratins and presence of vimentin renders the diagnosis of SCSC speculative. This is also the case in the recurrent malignant tumour presented in this study that repeatedly showed this constellation. The clinical course, with multiple local recurrences and in transit metastases, strongly suggested a SCSC. Repeated immunohistochemical investigations of step sections, including antigen retrieval techniques, finally revealed the presence of cytokeratin-positive tumour parts, thus confirming the diagnosis SCSC.

We were interested in identifying the type of cytokeratins expressed by the tumour. We found expression of CK 5/14, CK 6 and CK 17 in the solid tumour parts directly connected to the epidermis, which reflects a “basaloid” or “outer root sheath-like” differentiation (7, 22). The single Kl-1 positive cells that could be found using the antigen-retrieval technique apparently expressed CK 8 and 18, which is a cytokeratin typical for simple epithelia, the basal layer of certain stratified epithelia and for developing squamous epithelia in the embryo (23, 24). Basaloid
skin tumours produce these cytokeratins in some cases. Interestingly, these tumours have also been reported to express vimentin (25, 26). All in all, the cytokeratin pattern indicates the extreme dedifferentiation of our tumour.

Leading clinical symptoms of this tumour, namely pain and tenderness, were underestimated in the beginning. In the course of the disease the patient was able to pinpoint small recurrent satellite tumours that were otherwise clinically barely detectable. Pain as leading symptom for the detection of SCSC or even other forms of squamous cell carcinomas has been reported previously, especially in squamous cell carcinomas of the head and neck. In these tumours, however, perineural infiltration could be demonstrated, giving a good explanation for the tenderness of the lesions (27–29). In our case, perineural infiltration was absent.

In conclusion, SCSC should be taken into account if spindle cell tumours arise on sun-exposed skin in immunosuppressed patients. In order to avoid a fatal outcome, wide and radical excisions should be performed, especially if these tumours recur and are painful.

REFERENCES