Dear Editors,

This case report describes a 75-year-old man diagnosed with an atypical fibroxanthoma (AFX) on the scalp in 2009. The AFX recurred twice locally in May 2016 (Figure 1a) and April 2017, on the last occasion with additional cutaneous retroauricular metastases. The tumors were excised and confirmed histologically as AFX. In August 2017, cerebral magnetic-resonance imaging was performed after the patient developed left hemiparesis with impaired fine motor skills of the left hand, leg and tongue. Three cerebral metastases were found. One was extirpated and analyzed histologically, and was identified as a sarcomatoid tumor with cytokeratin expression. Further molecular-genetic investigations also revealed a TERT C250T mutation (Figure 2). Based on these findings, cerebral metastasis of a pleomorphic dermal sarcoma (PDS) was diagnosed, and the cerebral metastases were stereotactically irradiated. At that time, in January 2018, the patient presented at our department. Further computer-tomographic scans of the neck, chest and abdomen revealed bipulmonary nodules, which were classified as unspecific after consulting our thoracic surgeons. The diagnosis of cerebral metastasis of a PDS led us to re-evaluate the histology from the scalp and to compare it with that of the brain metastasis.

This histological re-evaluation showed that the skin tumor from May 2016 was already a deep-infiltrating pleomorphic tumor with spindle cells and necrotic areas. It was immunohistochemically positive for CD10 and actin; slightly positive for CD99; and negative for desmin, S100, pan-cytokeratin and CD34 (Figure 1). Ki-67 staining revealed increased proliferation activity with 90 % positive cells. The cerebral metastasis also contained pleomorphic cells, which were positive for CD10, focally positive for actin and distinctly positive for cytokeratin. Further molecular-genetic investigations also revealed a TERT C250T mutation (Figure 2). Our patient had no disease recurrence or progression during a follow-up time of 14 months.

Atypical fibroxanthomas and PDSs are rare mesenchymal tissue tumors that are clinically and morphologically very similar. It is debatable whether they are the same entity, of which PDS is the more aggressive form. Both usually occur on chronically sun-exposed skin of the head and neck. Known risk factors are UV exposure and radiation. However, conditions that increase the incidence of epithelial skin cancers (such as immunosuppression, e.g. among organ-transplant recipients) and the rare condition of xeroderma pigmentosum increase the risk [1–3].

Atypical fibroxanthomas are characterized by quite rapidly growing, exophytic ulcerated nodules (size: < 2 cm) and are more common among men (average age: 70). The clinical prognosis is good, although local recurrences occur among 3–20 % of patients [1–5]. PDSs are characterized by rapidly growing nodules that are usually larger than those of AFXs (median size: 2.5 cm, ≤ 6 cm) and have bleeding ulcerations (more rarely plaques). Pleomorphic dermal sarcomas are more common among men than women (ratio 7 : 1) and occur among a slightly older population (average age: 80). Clinically, PDSs are more aggressive than AFXs; local recurrences occur among 10–30% of patients. Patients have a 10 % risk of metastases,

Figure 1 Clinical appearance before surgery at the time of first recurrence in May 2016 (a); MRI (magnetic-resonance imaging) of cerebral metastases in August 2018 (b); histological features of skin tumor (c) stained with hematoxylin-eosin stain (HE), original magnification x 25 (1) and x 200 (2) from May 2016; and cerebral metastasis in original magnification of x 25 (3) and x 200 (4) from August 2017.
especially to the lymph nodes and skin, and rarely to the lungs [1, 3, 4].

Histologically, AFXs and PDSs are composed of atypical, pleomorphic spindle cells that exhibit high mitotic activity with atypical mitotic figures and some giant cells. Atypical fibroxanthomas are generally confined to the dermis, whereas PDSs tend to cross the subcutis to infiltrate fascia or muscle. Areas with necrosis, lymphovascular infiltration or perineural invasion can also occur. The most important differential diagnoses are desmoplastic melanoma, squamous-cell carcinoma and leiomyosarcoma, but benign fibrous histiocytoma and fibroepithelioma of Pinkus should also be considered [3, 6, 7]. Immunohistochemical analyses including S100, cytokeratins and desmin assist with correct diagnosis. Okata-Karigane et al. have also described a case of AFX with infiltration of CD-8 positive lymphocytes and diffuse expression of epithelial membrane antigens [8].

Genetically, AFX and PDS often express a UV signature mutation in the \( p53 \) gene (AFX 65 %, PDS 25 %), but also mutations in \( NOTCH1/2 \) and \( CDKN2A \) (cyclin-dependent kinase inhibitor 2A). Deletions in chromosomes 9p and 13q and high copy-number variations or mutations in \( TERT \) have been found. A mutation in \( TERT \) increases telomerase expression, allowing cells to proliferate continuously without entering apoptosis or senescence. This mutation was first found in melanoma and later in many other human cancers, e.g. in dermatofibrosarcoma protuberans [9–11].

The standard of care for both tumors is micrographically controlled excision with margins of 1–2 cm. The usefulness of the sentinel lymph node biopsy remains unclear. For AFX, a clinical follow-up should be performed every 3–6 months. Because PDS is rare as well as difficult to diagnose and data are scarce, further evidence-based recommendations are lacking. Radiation therapy as an adjuvant treatment has been proposed. Traditional chemotherapy is regarded as largely ineffective.

To our knowledge, this is the first reported case of cerebral metastasis of PDS. Analysis of the \( TERT \) mutation in the primary cancer and brain metastasis showed that the brain metastases originated from the skin tumor.

Conflict of interest
L. Trennheuser: none reported. J.C. Hassel has had a paid consulting role with Merck and Amgen and has received honoraria from Bristol-Myers Squibb, Merck, Novartis, Roche and Pfizer. A. Enk has had a paid consulting role with MSD and Lilly and has received honoraria from Bristol-Myers Squibb, Biotest and Novartis.
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