Review paper

Immunohistochemistry in the differential diagnosis of cutaneous spindle cell neoplasms

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Cutaneous spindle cell neoplasms may cause considerable problems in the diagnosis and proper treatment of affected patients. After exclusion of nonmesenchymal spindle cell lesions, including /spindle cell (sarcomatoid) carcinoma as well as spindle cell and desmoplastic melanoma, the line of differentiation and the dignity must be established. Immunohistochemical stainings are very important in this process, and a number of examples of cutaneous spindle cell neoplasms are described.

Key words: spindle cell neoplasms, sarcomas, dermis, immunohistochemistry.

The diagnosis and differential diagnosis of cutaneous spindle cell neoplasms is often a source of problems for pathologists and dermatopathologists. Especially in elderly patients and in areas of sun-exposed skin nonmesenchymal mimics must be carefully excluded first, and the use of appropriate immunohistochemical markers is of great help. These nonmesenchymal neoplasms include /spindle cell (sarcomatoid) carcinoma (at least focal expression of keratins, p63, epithelial membrane antigen), spindle cell and desmoplastic melanoma (expression of S-100 protein and Sox10), and rare spindle cell B-cell lymphoma (expression of B-cell markers, very high Ki-67 index). After exclusion of a nonmesenchymal neoplasm the line of differentiation and the dignity of a given spindle cell lesion must be determined. Grading of superficially located sarcomas is of limited value only, because most dermal sarcomas have a good prognosis irrespective of morphological grade, important exceptions are epithelioid sarcoma, cutaneous angiosarcoma and rare malignant dermatofibroma, characterized by a poor clinical prognosis. As in deep soft tissues the clinical context is important for the correct diagnosis and simple clinical parameters may play an important role such as age (kaposiform haemangioendothelioma and lipofibromatosis occur in children), anatomic distribution (spindle cell and pleomorphic lipoma occur at the neck, shoulder and upper back; acral fibromyxoma is seen at the fingers and toes and especially in periungual location) and tumour depth (pilar leiomyoma is frequent, whereas leiomyoma in soft tissues is exceedingly rare). Histological features important for the diagnosis of cutaneous spindle cell neoplasms include the architectural arrangement (storiform growth in dermatofibroma and dermatofibrosarcoma protuberans, fascicular growth in myogenic lesions), the interface between tumour and adjacent tissues (well-circumscribed in perineurioma, diffuse infiltrative in dermatofibrosarcoma protuberans), the tumour stroma and the intratumoral vascularity, as well as the mitotic activity and presence or absence of tumour necrosis.

The use of a broad panel of immunohistochemical markers is crucial for the determination of the correct line of differentiation of a given cutaneous spindle cell mesenchymal neoplasm and the following antibodies are helpful:

- myofibroblastic differentiation: variable expression of actin and desmin but lack of expression of h-caldesmon and myogenin,
- smooth-muscle differentiation: expression of actin, desmin and h-caldesmon but lack of expression of myogenin,
- striated muscle differentiation: expression of desmin > actin and of myogenin and MyoD1,
- neural differentiation: expression of S-100 protein, Sox10 and p75,

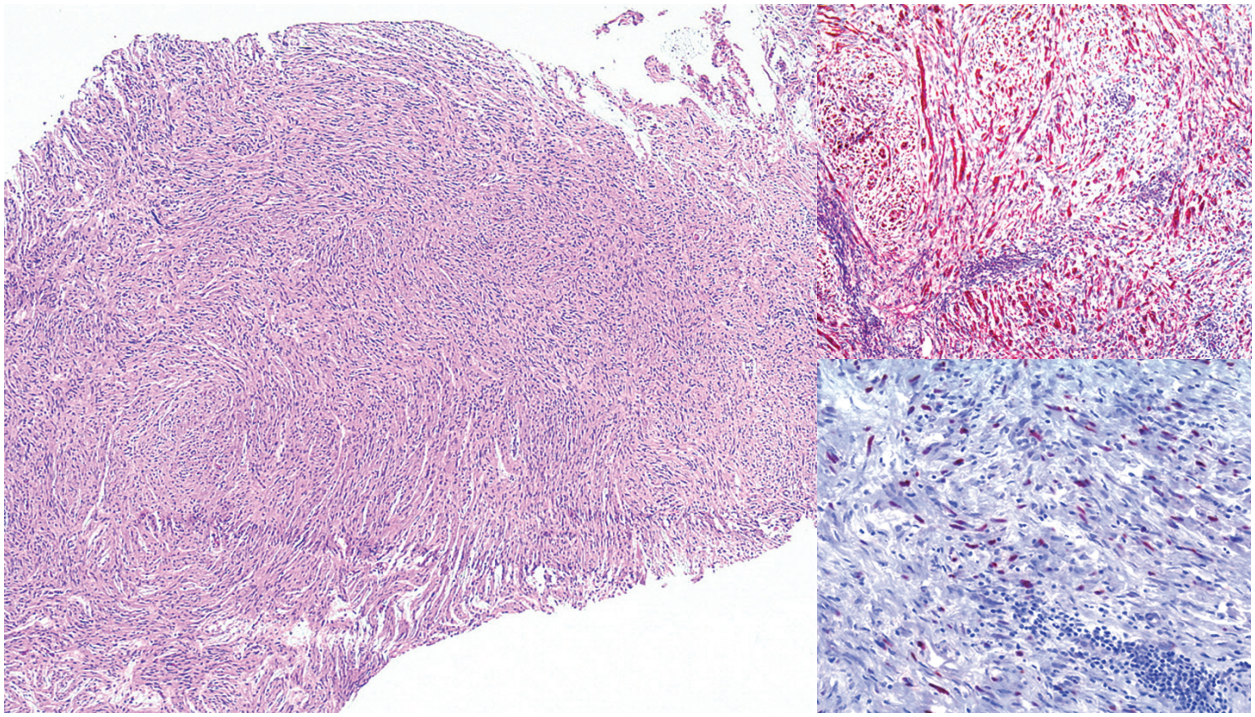

Figure 1. A case of desmoplastic melanoma mimicking neurofibroma arising at the back of a 33-year-old male patient (left). Tumour cells stain positively for S-100 protein (right upper half), and a focal nuclear expression of p53 is noted (right lower half)

- perineurial differentiation: expression of epithelial membrane antigen, claudin-1, glut-1, and variable expression of CD34,
- endothelial differentiation: nuclear expression of ERG and expression of CD31.

In addition, there are several immunohistochemical markers that reflect underlying genetic changes (i.e. CAMTA1 in epithelioid haemangioendothelioma, STAT6 in solitary fibrous tumour), and breakpoint-specific antibodies characterized by a high specificity and sensitivity (SS18-SSX antibody for the diagnosis of synovial sarcoma, NKX2.2 antibody for the diagnosis of Ewing sarcoma).

The following cases emphasize the need of immunohistochemical antibodies:

1. Desmoplastic melanoma: The distinction of desmoplastic melanoma from reactive (hypertrophic scar), benign (neurofibroma) and malignant lesions (spindle cell malignant peripheral nerve sheath tumour) is very important. Desmoplastic melanoma is characterized by homogeneous expression of S-100 protein, Sox10, p75 and focal nuclear expression of p53 (Figure 1), whereas neurofibromas are p53 negative [1]. Spindle cell malignant peripheral nerve sheath tumours are S-100 negative or only focally positive for this marker.

2. Plaque-like dermatofibrosarcoma protuberans: The homogenous expression of CD34 in superficial, plaque-like dermatofibrosarcoma protuberans is of great value in the distinction from its histological mimics (flat dermatofibroma, neurofibroma, dermatomyofibroma). Plaque-like CD34-positive dermal fibroma represents probably a variant of dermatofibrosarcoma protuberans with variable genetic changes [2].

3. Lipofibromatosis-like neural tumour: Lipofibromatosis-like neural tumour, that may occur in purely dermal location [3], represents a member of the growing family of *NTRK*-fused mesenchymal neoplasms characterized by homogeneous coexpression of S-100 protein, CD34 and NTRK1 (Figure 2), whereas Sox10 is negative. These neoplasms of fibroblastic or neural differentiation include low-grade and high-grade neoplasms and targeted treatment with NTRK inhibitors may be useful in clinically aggressive cases.

4. Low-grade fibromyxoid sarcoma: The homogenous expression of MUC4 in rare cases of superficially located low-grade fibromyxoid sarcoma is very important in the differential diagnosis of these aggressive neoplasms from several histological mimics that are all MUC4 negative (Figure 3). The recently described MUC4-positive fibroblastoma is also composed of bland spindled to stellate fibroblastic tumour cells showing a coexpression of MUC4 and ß-catenin [4].

5. Spindle cell lipoma: Spindle cell lipoma represents a well-documented, benign lipogenic neoplasm arising frequently at the neck, the shoulder and the upper back of elderly male patients. The encapsulated lesions are composed of mature lipogenic cells and bland spindled cells staining positively for CD34

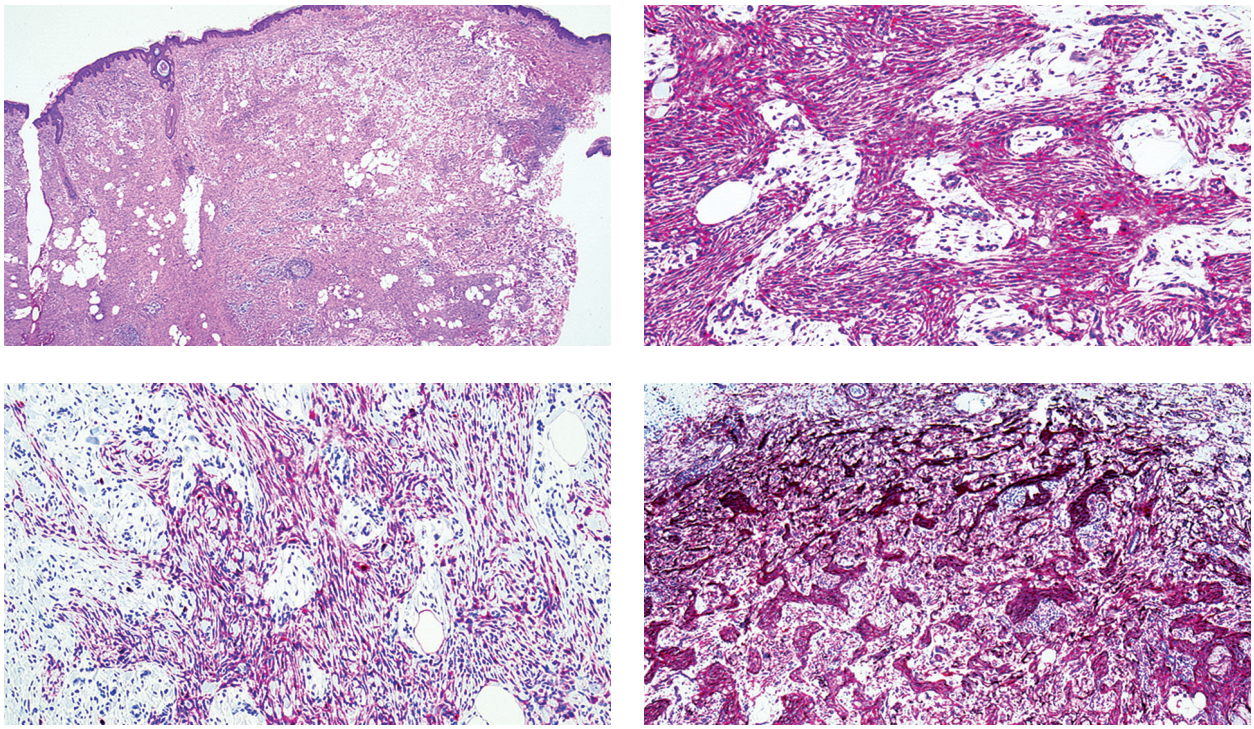

Figure 2. Superficial example of lipofibromatosis-like neural tumour (left upper half). Tumour cells stain positively for S-100 protein (left lower half), NTRK1 (right upper half), and CD34 (right lower half)

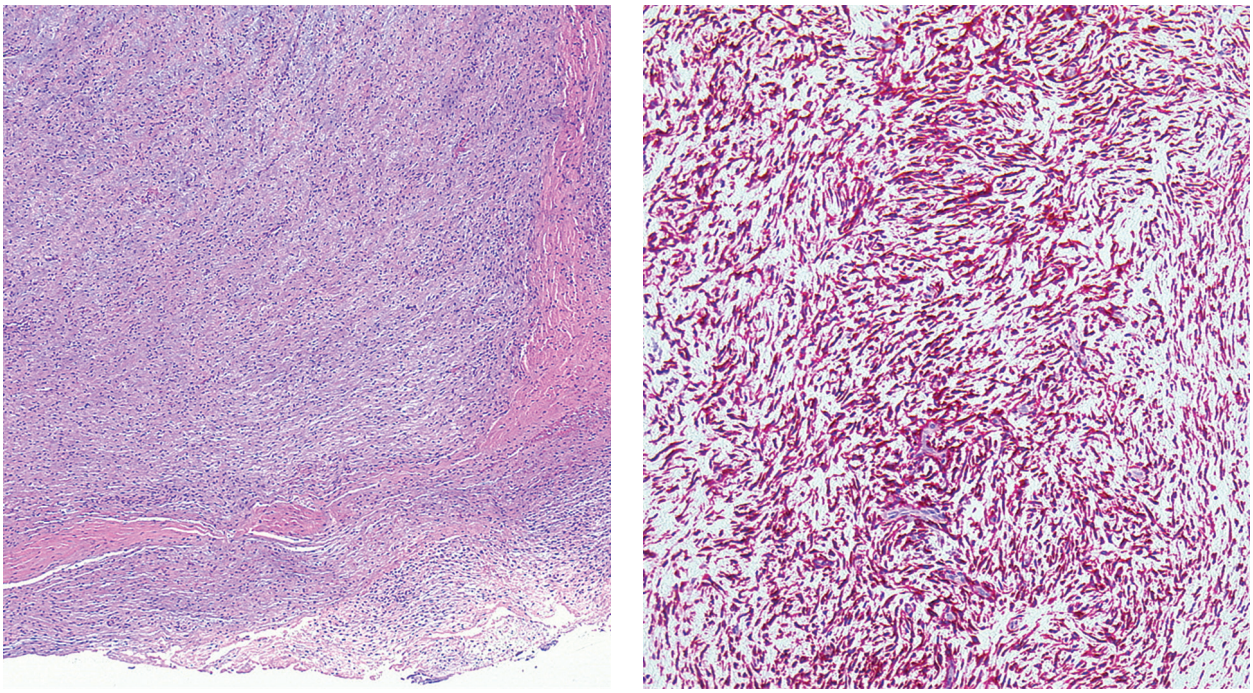

Figure 3. Superficial example of low-grade fibromyxoid sarcoma arising in retroauricular location in a 11-year-old boy (left). Tumour cells stain strongly positive for MUC4 (right)

and show loss of nuclear Rb1 expression. Very rarely, a coexpression of S-100 protein is seen in spindle cell lipoma mimicking a neural neoplasm [5] (Figure 4).

6. Pseudomyogenic haemangioendothelioma: The heterogenous group of haemangioendotheliomas includes pseudomyogenic haemangioendothelioma, a low-grade vascular neoplasm that tends to /be multicentric, and is composed of plump spindled myoid tumour cells [6]. Immunohistochemically, tumour cells stain positively for endothelial markers (ERG, Fli-1, CD31), FOSB reflecting underlying *FOSB* fusions [7] (Figure 5), and pancytokeratin (AE1/3 is positive, MNF116 is nega-

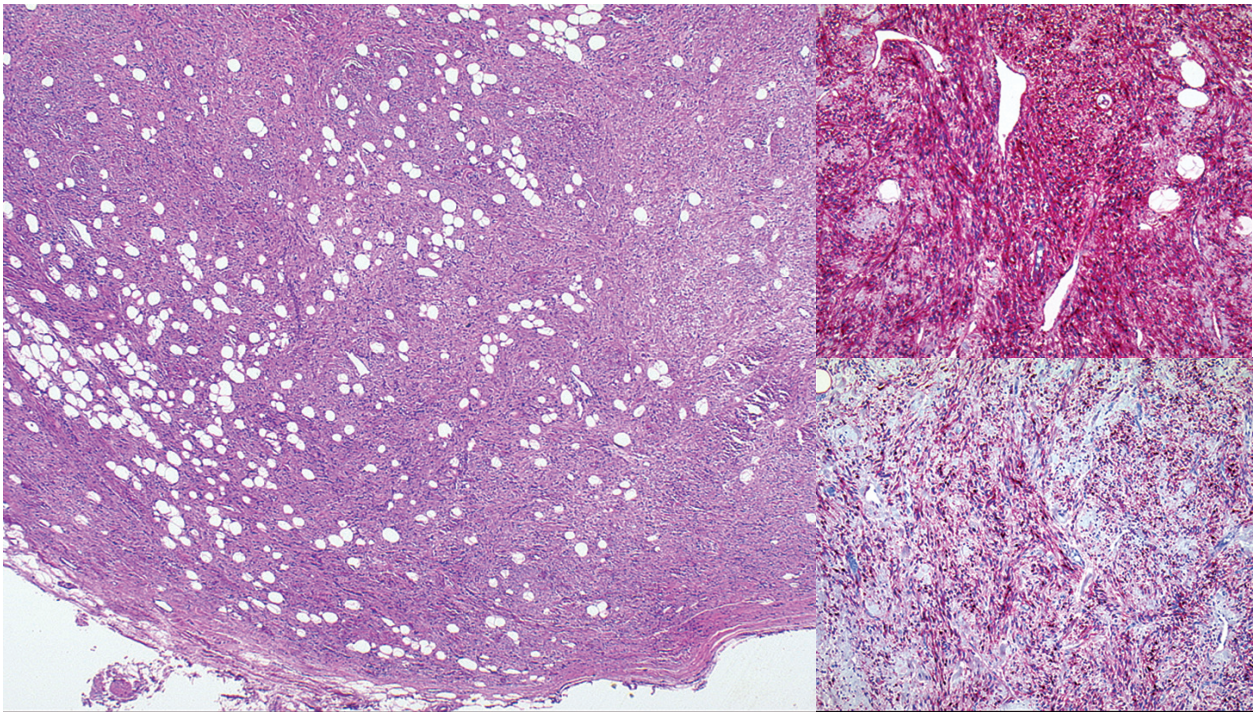

Figure 4. Typical example of spindle cell lipoma arising at the shoulder of a 77-year-old man (left). Tumour cells stain positively for CD34 (right upper half) but show an unexpected coexpression of S-100 protein (right lower half)

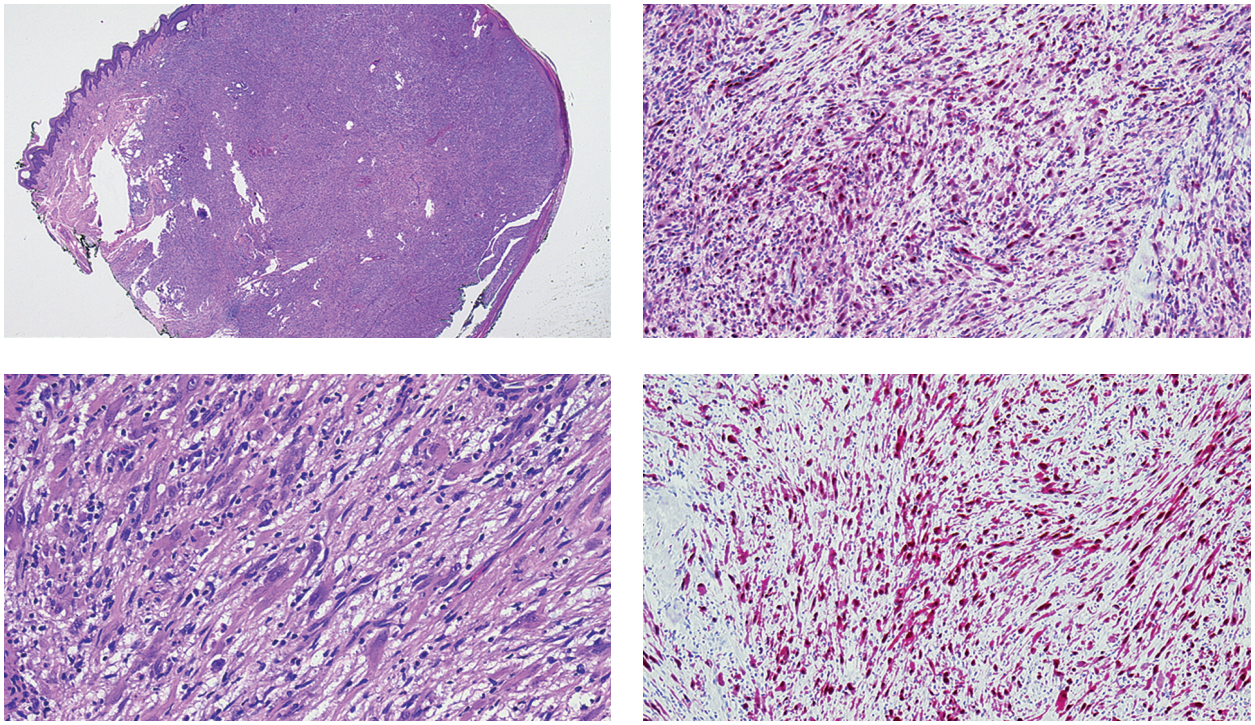

Figure 5. A 17-year-old male patient presented with multiple exophytic dermal lesions arising at the left foot. Histologically, a cellular dermal lesion is seen composed of enlarged myoid, spindled tumour cells (left). Neoplastic cells stain positively for ERG (right upper half) and show nuclear coexpression of FOSB (right lower half)

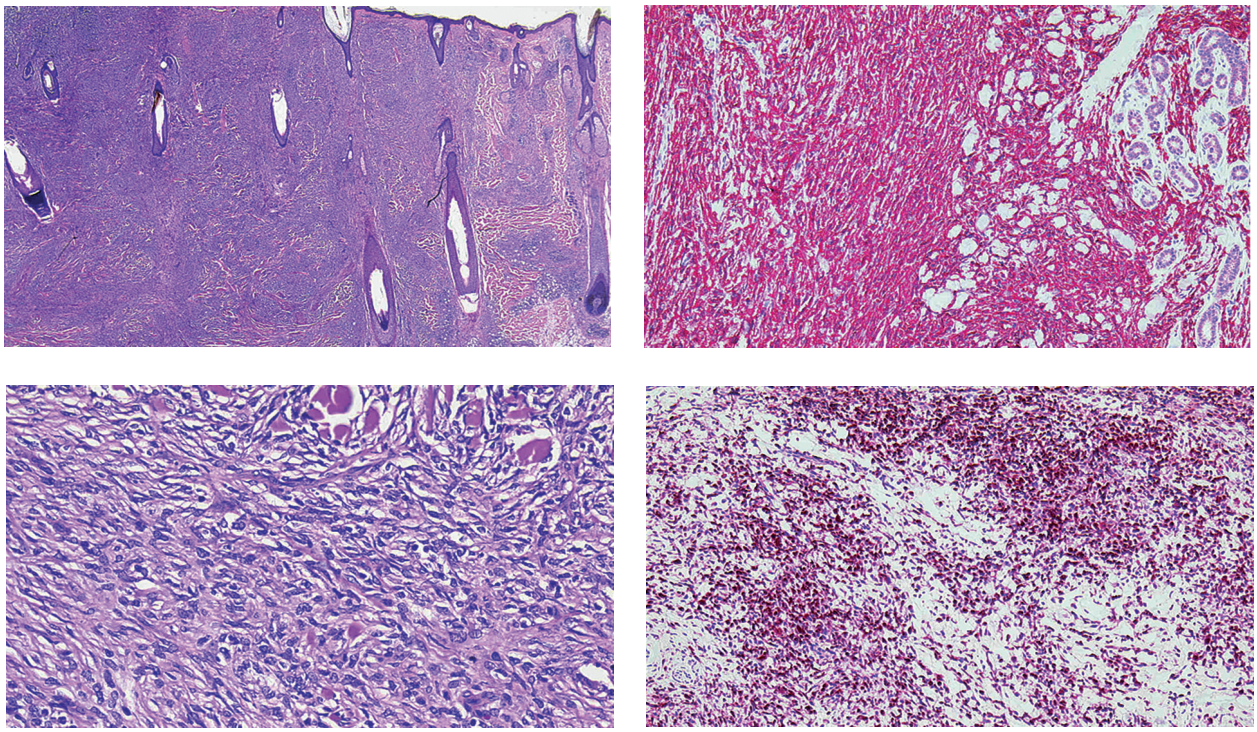

Figure 6. A rare case of spindle cell cutaneous B-cell lymphoma arising at the right cheek of a 56-year-old male patient, composed of atypical, spindled tumour cells (left). Tumour cells stain positively for CD20 (right upper half) and bcl-6 (right lower half)

tive), whereas CD34 and S-100 protein are negative and the nuclear expression of INI1 is preserved.

7. Solid cutaneous angiosarcoma: Rare cases of solid cutaneous angiosarcoma, /which may be composed of epithelioid or spindled tumor cells may cause diagnostic problems. The presence of irregular clefts in the periphery and the strong expression of endothelial markers (ERG, CD31, CD34 +/–) are of diagnostic help.

8. Cutaneous spindle cell B-cell lymphoma: Cutaneous B-cell lymphoma is very rarely mainly composed of atypical, spindled tumour cells mimicking several mesenchymal neoplasms. The presence of scattered atypical lymphoid cells, a very high Ki-67 proliferative index, and a positive staining of tumour cells for lymphatic markers including CD20 and bcl-6 allow the correct diagnosis [8] (Figure 6).

9. Erythema elevatum diutinum: Erythema elevatum diutinum represents a rare dermatosis with evolving morphological features according to the age of the lesions. Late tumour stage of erythema elevatum diutinum is mimicking several mesenchymal spindle cell lesions of fibroblastic, neural or perineurial differentiation. These often multifocal lesions show a proliferation of bland, elongated, fibroblastic cells set in a collagenous stroma with many vessels, and the neutrophilic infiltrate is often hard to see histologically [9]. The presence of leukocytoclasia and focal neutrophilic vasculitis mandatory for the correct diagnosis is highlighted by myeloperoxidase immunohistochemical stainings.

Disclosures

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4. Conflicts of interest: None.

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