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SHORT COMMUNICATION

Increased Expression of S100A6 in Malignant Granular Cell Tumours

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Granular cell tumours (GCT) are rare mesenchymal soft tissue neoplasms that may arise throughout the body. Most tumours are benign and solitary but approximately 2% of tumours are malignant (1). It is difficult to differentiate between benign and malignant GCT. We present a case of malignant GCT with inguinal metastases in which the initial lesions could not be diagnosed as malignant. Interestingly, the S100A6 protein, which is expressed in Schwann cells (2), was seen both in the initial and metastatic tumours.

CASE REPORT

A 61-year-old Japanese woman with a one-year history of subcutaneous tumours on the right thigh (4.0 cm in diameter) and right abdominal wall (1.0 cm in diameter) was referred to our hospital. Magnetic resonance imaging revealed that the lesions were located in the subcutaneous tissue and did not involve deep structures (Fig. 1A). Both lesions were excised. Histopathological staining revealed oval to round cells with abundant eosinophilic granular cytoplasm in both tumours. Partial tumour necrosis, focal pleomorphism, and mitotic figures (1/10 high-power fields) were observed in the thigh tumour (Fig. 1B), but not in the abdominal tumour. The tumour cells in both lesions were immunopositive for the S100 protein, neuron-specific enolase, and CD68, but immunonegative for CD34, keratin AE1/AE3, and human melanoma black-45. The MIB-1 labelling index was 5% in the thigh tumour, compared to 3% in the abdominal tumour. We diagnosed these lesions as GCT and carefully followed up the patient. After 20 months, a right inguinal tumour was noticed, which developed rapidly over 6 months. Physical examination revealed an elastic, hard, and painless mass, 6.5 cm in diameter. The tumour consisted of nests of spindle and oval to round cells with abundant eosinophilic granular cytoplasm, accompanied by necrosis. These cells included vesicular nuclei with large nucleoli, a high nuclear-to-cytoplasmic ratio, and cytologic pleomorphism. Mitotic figures were also occasionally observed (4/10 high-power fields) (Fig. 2A, B). The tumour cells were immunopositive for the S100 protein and CD68. The MIB-1 labelling index was 17%. Cytoplasmic staining of S100A6 and receptor for advanced glycation endproducts, a multiligand receptor that binds a variety of proteins including S100 family proteins, was observed in the abdominal, the thigh and the inguinal tumours (Fig. 2C). Staining for other subtypes of S100 (S100A2, A4, A7, and P) was negative. We resected the right thigh tumour with a wide 2-cm margin and performed right inguinal dissection. Two of the 6 lymph nodes were metastatic. Six months after surgery, computed tomography revealed a right inguinal tumour with vascular invasion and the patient is currently undergoing chemotherapy with doxorubicin and ifosfamide.

DISCUSSION

Because of reciprocal similarity and lack of reliable criteria, distinguishing between benign and malignant GCT is difficult. Fanburg-Smith et al. (1) proposed 6 histopathological criteria to predict malignancy: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (>2/10 high-power fields),

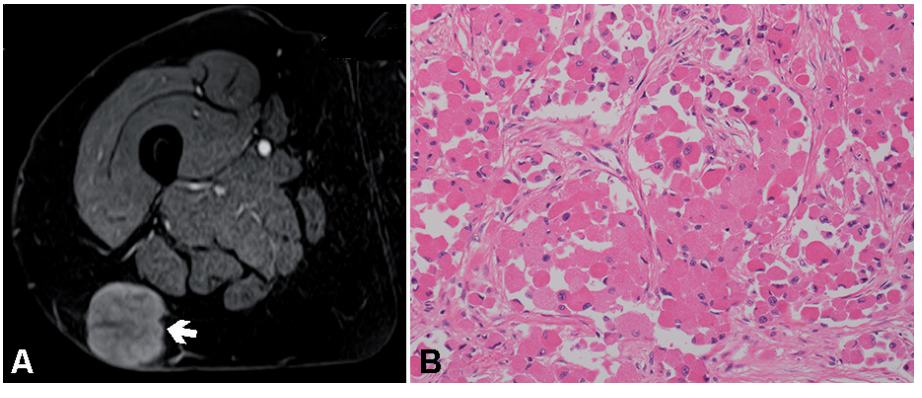

Fig. 1. Magnetic resonance imaging showed subcutaneous tumours on the right thigh (*arrow*) (A). Oval to round cells abundant eosinophilic granular cytoplasm (haematoxylin-eosin staining, ×200) (B).

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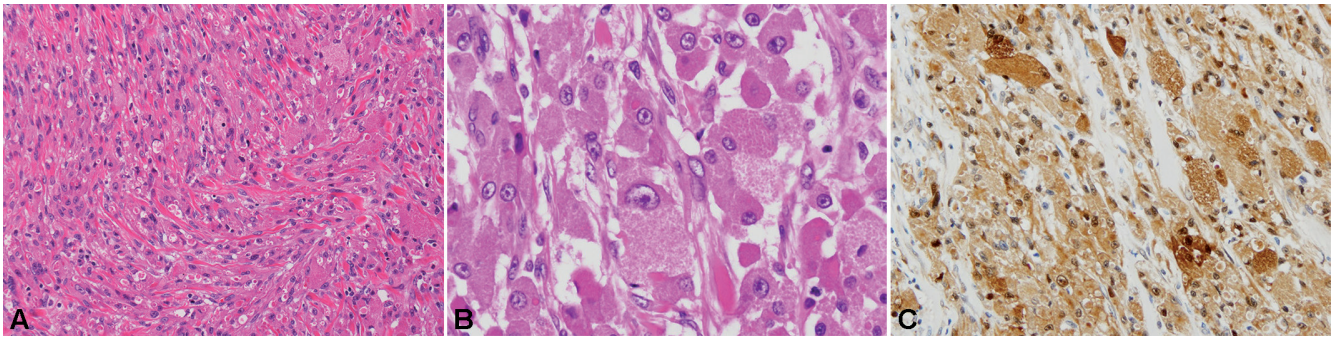

Fig. 2. Spindle cell configuration with nuclear atypia and prominent nuclei (haematoxylin-eosin staining, ×200) (A). Vesicular nuclei with large nucleoli, high nuclear-to-cytoplasmic ratio, pleomorphism, and mitoses (haematoxylin-eosin staining, ×400) (B). Cytoplasmic staining of S100A6 was observed in the inguinal lesion (C).

high nuclear-to-cytoplasmic ratio, and pleomorphism. In addition to histopathological features, the diagnosis of malignancy is also based on the clinical behaviour of the tumour. Metastasis is therefore one of the most important criteria for defining malignancy. Only a few cases of malignant transformation of benign GCT have been reported (3, 4). Chen et al. (4) reported a malignant GCT with breast and axillary lymph node metastases after local recurrences. They suggest that the malignant GCT resulted from transformation of benign GCT. After excising the 2 seemingly benign and atypical initial lesions, we noticed lymph node metastases.

The initial and the metastatic tumours were immunopositive for S100A6. The S100 proteins are a family of acidic, low molecular weight, calcium-binding proteins, which regulate various cellular processes via calcium-dependent interaction with target proteins. The functions of S100A6 have not been fully defined, but the protein may play a role in cell proliferation, cytoskeletal dynamics, and tumourigenesis (5). Increased expression of S100A6 has been reported in various malignancies (6–8). The histogenesis of GCT has been debated for many years, and recent reports emphasize that GCT arises from Schwann cells (3, 4). The S100A6 protein is expressed in numerous cells types, including Schwann cells (9). Fullen et al. (2) reported strong expression of the S100A6 protein in neural tumours, characterised by abundant Schwann cells. These reports and the results of immunohistopathological staining support the hypothesis that GCT is of Schwannian origin. Contrary to our results, Fullen et al. (2) reported that GCTs were negative for S100A6. We are currently unable to explain this discrepancy, but S100A6 expression might reflects the malignant potential of GCT because our patient's initial lesions, which were first considered benign but later metastasised, stained positive for S100A6.

The authors declare no conflicts of interest.

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