Clinical course by compression of the bilateral internal jugular veins by tumors. The patient was diagnosed with superior vena cava syndrome and lung metastasis was diagnosed. The patient had also received chemotherapy consisting of high-dose ifosfamide, cisplatin, doxorubicin, and vincristine, although the therapeutic effect was not significant. Radiation therapy (a total of 60Gy) was administered. After resection and radiation therapy, the tumor recurred 1.5 months later. Histologically, the tumor was diagnosed as a malignant granular cell tumor fulfilling all 6 criteria proposed by Fanburg-Smith et al. Immunohistochemistry revealed diffuse S-100 protein expression but no expression of c-kit or EGFR and Ki-67 index in the malignant area was approximately 40%. This case report demonstrates the potential of benign granular cell tumors for malignant transformation.

Keywords: Tranuscular cell tumor; Malignant transformation; Long clinical course

Introduction

Malignant granular cell tumor is a rare malignant soft tissue neoplasm that occurs at various sites [1-18] and accounts for 1–2% of granular cell tumors [1]. Granular cell tumors are generally divided into 3 categories according to the diagnostic criteria proposed by Fanburg-Smith et al. [1], although these criteria for malignancy are still debated among pathologists. Malignant granular cell tumors have been shown to be of Schwann cell origin [4,5], although it has not yet been clearly determined whether malignant tumors arise de novo or originate from preexisting benign granular cell tumors. Furthermore, no therapeutic strategy against this tumor has yet been established, although some authors have reported that the tumor is resistant to systemic chemotherapy and that surgical resection is the best course of action [17].

We present here a case of malignant granular cell tumor with an unusual clinical course. This tumor contained small areas of benign granular cell tumor at the periphery of the primary malignant tumor, suggesting that it may have undergone malignant transformation from a benign tumor.

Case Report

A 36-year-old man had noticed a mass in the left posterior region of his neck since the age of 24 years, and the mass had been growing gradually until his first admission. He was admitted to our hospital and the tumor was resected after a biopsy that was diagnosed as a malignant tumor. The resected tumor was histologically diagnosed as a malignant granular cell tumor. The surgical margin was positive at the initial surgical treatment, at which time the recurrent tumor was resected and then radiation therapy (a total of 60Gy) was administered. Soon after this treatment, metastasis was diagnosed. The patient had also received chemotherapy consisting of high-dose ifosfamide, cisplatlin, doxorubicin, and vincristine, although the therapeutic effect was only focal and the size of the tumor continued to increase gradually. Clinically, the patient was diagnosed as superior vena cava syndrome by compression of the bilateral internal jugular veins by tumors. The patient died of the disease in May 2011 at the age of 42 years.

Materials and Methods

All of the hematoxylin and eosin-stained slides from the primary and recurrent tumors and the autopsy were available for retrospective review.

Immunohistochemical analysis

Immunohistochemical staining was performed by the streptavidin-biotin method using the following antibodies: anti-β-catenin (BD transduction lab, clone 14), anti-EGFR (Leica Microsystems, UK, clone EGFR.113), anti-CD117 (Dako, Kyoto, Japan, clone rabbit polyclonal), and anti-p53 (Leica Microsystems, UK, clone PAb1801). Antigen retrieval was performed by autoclaving sections in citrate buffer.

Analysis for mutations of the p53 and β-catenin genes

Genomic DNA was extracted from the malignant granular cell tumors collected at autopsy. Exons 4-10 of the p53 gene and exon 3 of the β-catenin gene were examined for mutations by PCR followed by direct sequencing. The primer sequences used in this study have been described previously [19,20].

Results

Pathological findings

The primary tumor was a subcutaneous tumor 75 × 70 × 42 mm in...
The tumor cells were arranged in small nests or short trabecular patterns that occasionally involved peripheral nerve fibers. The tumor cells had eosinophilic granular cytoplasm with vesicular and prominent nucleoli. The tumor cells were tightly packed, and the nuclear to cytoplasmic ratio was high. Nuclear pleomorphism and spindling were also evident. Mitoses were observed at greater than 20/10 high-power fields (HPF), and necrosis was also noted (Figure 1A-C). Lymphocytic infiltration was also observed. Therefore, the tumor was diagnosed as a malignant granular cell tumor. The surgical margin was positive. In addition, small areas of benign granular cell tumor were observed at the periphery of the tumor, adjacent to the extensive malignant area (Figure 1D). These cells were granular, lacked nuclear atypia, had a lower nuclear to cytoplasmic ratio, and were arranged between the collagen fibers. The histology of the recurrent tumor was essentially similar to that of the primary tumor, although the benign granular cell tumor component was not observed.

At autopsy, the neck was quite rigid due to the multiple subcutaneous nodules. Both the left and right internal jugular veins were compressed by the tumor, which was consistent with the clinical diagnosis of superior vena cava syndrome. The tumor had metastasized to bilateral lungs, the liver, the heart, and the lumbar vertebrae in association with its dissemination to the intra-thoracic and intra-abdominal cavities. Lymph node metastasis was also noted. The tumor was composed of polymorphic tumor cells with eosinophilic granular cytoplasm, enlarged nuclei, and prominent nucleoli. Tumor necrosis was also noted. The tumor had proliferated at the serosal side of the sigmoid colon and histologically involved the muscularis propria of the colon. In the lung, in addition to forming masses, the tumor had prominently permeated the lymphatic vessels, resulting in a state of carcinomatous lymphangiosis (Figure 2A). The metastatic lesions were almost entirely composed of highly malignant granular cells (Figure 2B). The tumor cells observed in some metastatic sites showed rather less-pleomorphic histological features, namely, a lower nuclear to cytoplasmic ratio and inconspicuous nucleoli (Figure 2C). Alternatively, more and less malignant-appearing cells were seen admixed in the same metastatic regions. However, the tumor cells observed in the autopsy case were distinct from those observed in the benign granular cell component of the surgically resected specimen.

**Immunohistochemical findings**

The cytoplasmic granules both in malignant and benign areas of the primary tumor stained positive for S-100 protein (Figure 1E). Tumor cells observed at the autopsy was also positive for S-100 protein (Figure 2D). Immunohistochemistry for p53 was totally negative throughout the tumor. Membranous expression of β-catenin with weak cytoplasmic staining was observed; however, no nuclear staining was seen (Figure 2E). The Ki-67 index of the primary tumor was approximately up to 40% at the higher area (Figure 1F), although the tumor cells in benign area at the periphery seldom stained for Ki-67 (Figure 1G). Immunohistochemistry for c-kit was negative. The tumor cells showed no membranous staining for EGFR (Figure 2F).

**Genetic alteration of cancer-related genes**

No mutation of the p53, β-catenin, or EGFR gene was detected.

**Discussion**

Malignant granular cell tumor is often difficult to diagnose due to its rarity. Historically, malignant granular cell tumors have been classified into 2 categories: the "histologically and clinically malignant type" and the "histologically benign, but clinically malignant type" [7]. Fanburg-Smith et al. [1] later proposed 6 histologic criteria for the diagnosis of atypical and malignant granular cell tumors, including necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (> 2 mitoses/10 high-power fields at 200 × magnification), high nuclear-to-cytoplasmic ratio, and pleomorphism. The primary tumor fulfilled all of the 6 above mentioned histologic criteria and was therefore diagnosed as a malignant granular cell tumor. This case could be also classified as a case of "histologically and clinically malignant type" by the former categorization scheme.

It was unusual for this tumor to be classified as a de novo primary malignant tumor considering its slowly growing character for more than 13 years without any treatment. Therefore, the clinical biological behavior of this tumor could be considered as benign, although it...
Granular cell tumor has been reported by Cadotte [8], though the appearance of the sarcomatous regions to a benign appearance in a malignant granular cell tumor were observed adjacent to the highly malignant tumor had undergone malignant transformation, the tumor was classified as atypical granular cell tumor [3]. Therefore, in consideration of the possibility that the transformation has been also reported in a case of benign granular cell tumors have transformed to a malignant granular cell tumor [18]. Malignant transformation has been demonstrated to coexist with malignant granular cell tumor [21]. In this case, the metastatic lesions observed at the autopsy were, with some exceptions, composed almost entirely of highly malignant granular cells with necrosis. The tumor cells observed in some metastatic regions showed histologically rather less pleomorphic features compared with those in the highly malignant area; these tumor cells had lower nuclear-to-cytoplasmic ratios and inconspicuous nucleoli, although occasional binuclear cells were encountered. The less-pleomorphic areas observed in this case could be classified as atypical granular cell tumor, as they still fulfilled 2 of the 6 criteria, namely, vesicular nuclei with large nucleoli and pleomorphism. A case of malignant granular cell tumor in which the metastatic lesion was composed of rather benign-appearing tumor cells has also been reported [4]. Malignant granular cell tumors could therefore be suggested to show a relatively wide range of histology, encompassing apparently malignant features and somewhat benign-appearing features. However, no purely benign-appearing area could be detected at autopsy. These findings may suggest that this is a second case in which a benign tumor transformed into a malignant granular cell tumor during a long clinical course.

In one study, 14 of 25 (56%) malignant tumors had Ki-67 immunostaining in 10–50% of the cell population [1]. In this case, approximately 40% of the tumors were positive for Ki-67 in malignant area, in line with the previous finding. However, positive tumor cells were seldom seen in benign area at the periphery. p53 immunostaining was also reported in more than 50% of the cell population in 17 of 25 (68%) malignant granular cell tumors [1]. Furthermore, p53 expression has been reported in several cases of malignant granular cell tumors [17]. However, no p53-positive cells or p53 mutations were detected in this case. These findings strongly suggest that it is very difficult to diagnose malignant granular cell tumor by immunohistochemical techniques alone.

β-catenin is a multi-functional protein that plays an important role in maintaining cell-cell adhesion as well as a downstream effector of the Wnt-signaling cascade. Expression and mutations of β-catenin in soft tissue sarcomas has also been described [20], though β-catenin expression in granular cell tumors including malignant counterpart has not yet reported so far. Furthermore, possibilities of molecular therapy targeting of Wnt signaling has been demonstrated in a certain type of malignancies [22]. Therefore, expression and mutational status of β-catenin in this tumor was examined. Definite membranous expression of β-catenin was observed without cytoplasmic and nuclear staining, suggesting that activation of Wnt signaling has less importance in this tumor.

The early relapse of the tumor in this case may have been due in part to the positive surgical margins of the initial surgery. Alternatively, the surgery may have activated the tumor growth. At all sites of malignant granular cell tumors, the overall survival is poor. The mortality rate within 3 years has been described to be close to 60% [23]. No treatment for malignant granular cell tumors has yet been well established, and no evidence for the efficacy of chemotherapy against malignant granular cell tumor has been shown to date [17]. This tumor also showed resistance to chemotherapy and radiation therapy. In the hope of identifying molecular therapeutic targets in malignant granular cell tumors, immunohistochemistry for c-kit and EGFR, for which appropriate tyrosine kinase inhibitors are available, was performed. However, the expression statuses of these receptor tyrosine kinases were totally negative, consistent with the findings of the mutation.
analysis. Further information regarding the response of this tumor to various therapeutic agents must be gathered in order to develop an effective therapeutic strategy.

Conclusions

This case report demonstrates the potential of benign granular cell tumors for malignant transformation.

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