G-CSF-Producing Giant Squamous Cell Carcinoma (SCC): Changes in Serum G-CSF in Parallel with SCC Antigen

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Sir,
Squamous cell carcinoma (SCC) can occur anywhere on the skin and in mucous membranes with a squamous epithelium (1). Malignant tumours producing granulocyte colony-stimulating factor (G-CSF) have been reported in lung cancer, thyroid carcinoma, bladder carcinoma and cutaneous angiosarcoma (2). We encountered a case of G-CSF-producing SCC, which was diagnosed by immunohistochemical staining and showed changes in serum G-CSF in parallel with the serum SCC antigen level and the disease course.

CASE REPORT

A 63-year-old Japanese man presented in August 2005 with a 10-year history of a giant tumour on his left upper arm (Fig. 1). The tumour was raised by approximately 3 cm and measured approximately 10 cm in diameter. The tumour surface showed partial necrosis and bled easily. The patient was extremely emaciated with general lassitude and was also afebrile.

A blood cell count revealed anaemia: red blood cells $3.59\times10^6/\mu l$ (normal: $3.65–5.64\times10^6/\mu l$) and haemoglobin 9.4 g/dl (normal: 10.8–16.9 g/dl). The white blood cell count was 20,600/μl, the C-reactive protein level was 3.59 (normal: 0.0–0.5 mg/dl), and the following parameters were elevated: serum G-CSF, 117 pg/ml (normal: 6.1–21.5 pg/ml); serum SCC antigen, 40 (normal: 0.0–1.5 ng/ml). Cultures from the tumour surface were sterile.

A computed tomography (CT) scan of the left upper arm showed attachment of the tumour to the triceps brachii muscle. Although a CT scan of the lung showed no obvious metastatic lesions, it did reveal multiple, large, high-density lesions in the left axillary region, suggesting left axillary lymph node metastasis.

Histological examination showed massive intradermal growth comprising a solid undifferentiated pattern of basophilic atypical cells, which were compatible with SCC (Fig. 2a). Similarly to previous reports, the tumour cells showed positive reactions for G-CSF in immunohistochemical staining with anti-G-CSF monoclonal

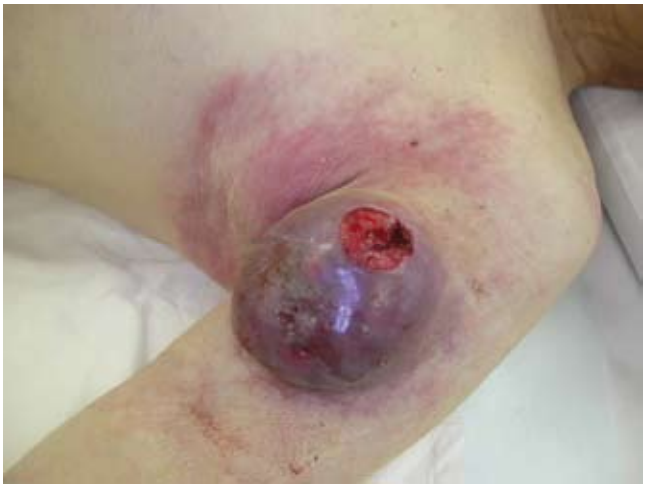

Fig. 1. A huge, dark-reddish dome-shaped tumour was apparent on the left upper arm.

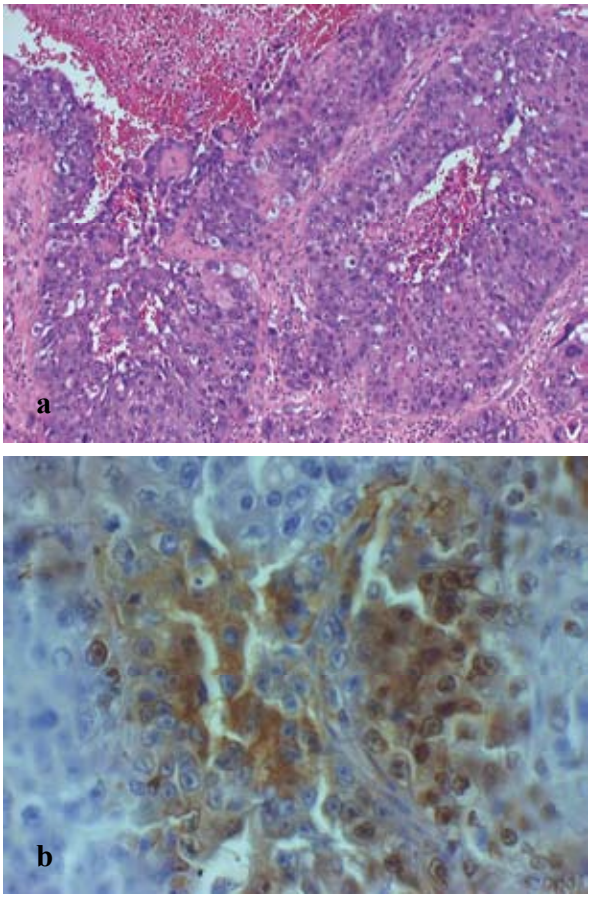

Fig. 2. (a) Basophilic-coloured tumour nest with extravasation of red blood cells (haematoxylin and eosin, original magnification ×40). (b) Immunohistochemical staining with anti-G-CSF monoclonal antibody showed a positive reaction in the cytoplasm of atypical tumour cells (×200).

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antibody (Oncogene Research Products, Cambridge, MA, USA) (Fig. 2b), suggesting G-CSF production by the tumour cells.

We decided to treat the patient with surgical debulking and chemotherapy using pepleomycin sulphate, mitomycin C and docetaxel hydrate, and we also performed electron beam irradiation of 60 Gy on the left upper arm and left axillary region. Despite extensive treatment, metastatic lesions appeared gradually and a CT scan of the chest on January 5th (at the end of the course) showed multi-focal high-density lesions. The patient died of respiratory insufficiency. An autopsy was not permitted.

Serum G-CSF and SCC antigen levels decreased significantly after surgical debulking, but started to increase again in parallel with tumour recurrence and metastasis (Fig. 3). The serum G-CSF level could not be measured in follow-up after August 24th because we were unable to obtain the patient's consent.

DISCUSSION

G-CSF is a 19 kDa polypeptide that participates in neutrophil proliferation and maturation in bone marrow, and is secreted by activated T cells, macrophages, fibroblasts and vascular endothelial cells. Mayumi et al. (3) reported 66 cases of G-CSF-producing tumours occurring in Japan from 1977 to 1990, but the mechanism of G-CSF production in malignant tumours has not been elucidated. Sato et al. (4) found no rearrangement or amplification of the G-CSF gene in the tumour cells of G-CSF-producing bladder carcinoma. Haematopoietic growth factors, including G-CSF, have been reported to stimulate the growth of human colon adenocarcinoma cell lines (5) and small cell lung cancer cell lines *in vitro* (6), and interestingly, Bussolino et al. (7) found that G-CSF can induce migration and proliferation of human endothelial cells. These findings suggest that G-CSF produced by tumour cells may stimulate their proliferation. Reports of G-CSF-producing tumours usually show peripheral granulophilia or leukaemoid reactions, suggesting that tumour-derived G-CSF acts on bone-marrow cell proliferation and differentiation to granulocytes.

Given the previous findings, we concluded that increased serum G-CSF contributed to the leukaemoid reaction in our case, since the serum G-CSF level was markedly increased. The elevation and decrease of the serum G-CSF level and positive immunohistochemical staining for G-CSF in tumour cells suggest that the tumour was a G-CSF-producing squamous cell SCC. In turn, this suggests that G-CSF can act as a tumour marker and a growth factor for proliferation of tumour cells.

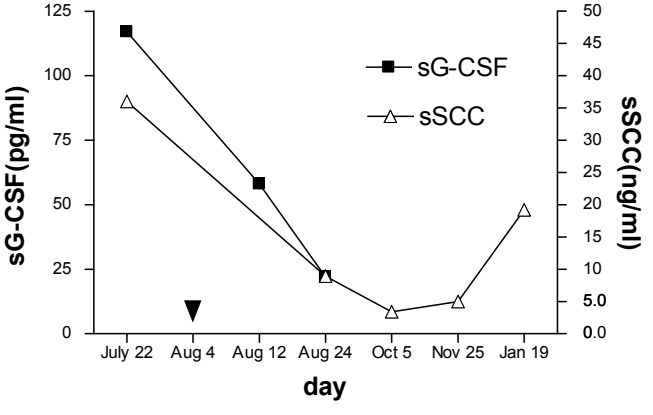

Fig. 3. Serum levels of granulocyte colony-stimulating factor (sG-CSF) and squamous cell carcinoma antigen (sSCC) during the clinical course, showing significant decreases of both markers after treatment. From July 27th to August 1st, the patient received a 1-week course of chemotherapy using pepleomycin sulphate and mitomycin C. On August 4th (arrow head: ▼), surgical debulking of the tumour was performed under general anaesthesia.

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