

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

Takeshi Nara, Hanako Atsuta, Naoto Koizumi, Hideya Takenaka, Norito Katoh and Saburo Kishimoto

Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. E-mail: nararing@koto.kpu-m.ac.jp

Accepted November 2, 2006.

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 $3.59 \times 10^6/\mu\text{l}$ (normal: $3.65\text{--}5.64 \times 10^6/\mu\text{l}$) 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.

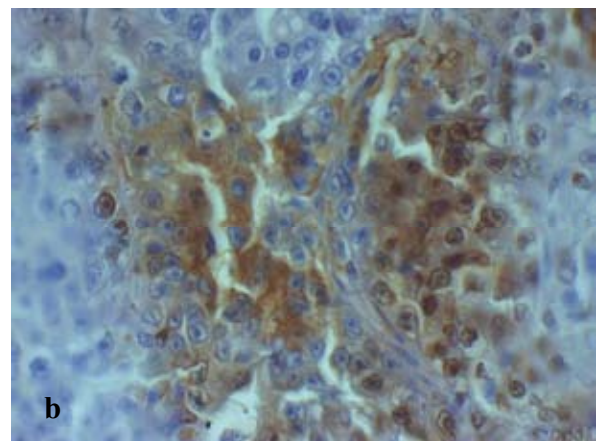
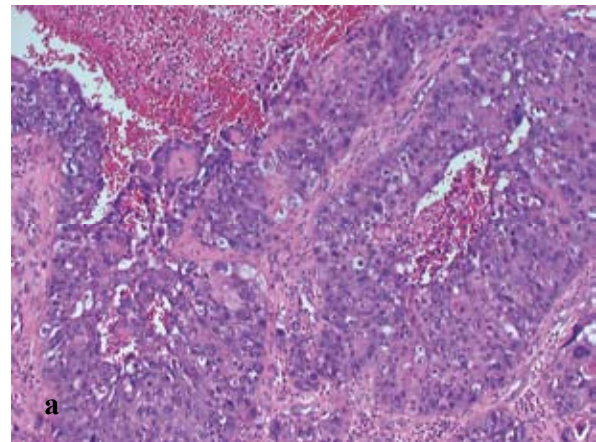


Fig. 2. (a) Basophilic-coloured tumour nest with extravasation of red blood cells (haematoxylin and eosin, original magnification $\times 40$). (b) Immunohistochemical staining with anti-G-CSF monoclonal antibody showed a positive reaction in the cytoplasm of atypical tumour cells ($\times 200$).

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.

REFERENCES

1. Elder DE, Elenitsas R, Johnson BL, Murphy GF, editors. Lever's histopathology of the skin, ninth edition. Philadelphia, PA: Lippincott Williams & Wilkins, 1997: 83.
2. Nara T, Hayakawa A, Ikeuchi A, Katoh N, Kishimoto S. Granulocyte colony-stimulating factor-producing cutaneous angiosarcoma with leukemoid reaction arising on a burn scar. *Br J Dermatol* 2003; 149: 1273–1275.
3. Mayumi E, Okuno T, Ogawa T, Kurata K, Ishioka H, Hamamoto H, et al. Malignant fibrous histiocytoma of soft tissue producing granulocyte colony-stimulating factor. *Intern Med* 2001; 40: 5340–5365.
4. Sato K, Terada K, Sugiyama T, Masuda H, Kakinuma H, Kato T. Granulocyte colony-stimulating factor produced by bladder carcinoma of a patient with leukemoid reaction did not affect proliferation of the tumor cells. *J Urol* 1994; 151: 1687–1690.
5. Berdel WE, Danhauser-Riedl S, Steinhauser G, Winton EF. Various human hematopoietic growth factors (interleukin-3, GM-CSF, G-CSF) stimulate clonal growth of non hematopoietic tumor cells. *Blood* 1989; 73: 80–83.
6. Avalos BR, Gasson JC, Hedvat C, Quan SG, Baldwin GC, Weisbart RH et al. Human granulocyte colony-stimulating factor: Biologic activities and receptor characterization on hematopoietic cells and small cell lung cancer cell lines. *Blood* 1990; 75: 851–857.
7. Bussolino F, Wang JM, Defilippi P, Tririni F, Sanavio F, Edgell F et al. Granulocyte-and granulocyte-macrophage-colony stimulating factors induce human endothelial cells to migrate and proliferate. *Nature* 1989; 337: 471–473.

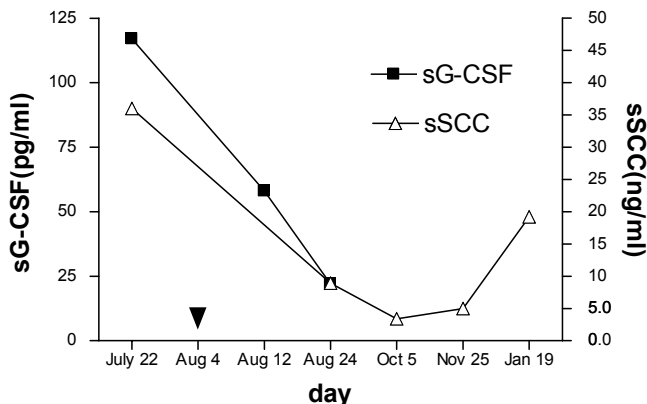


Fig. 3. Serum levels of granulocyte colony-stimulating factor (sG-CSF) and squamous cell carcinoma antigen (sSCC) during the clinical course, showing significant decreases of both markers after treatment. From July 27th to August 1st, the patient received a 1-week course of chemotherapy using pepleomycin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