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Granulocyte colony stimulating factor-producing squamous cell carcinoma of the skin

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## LETTER TO THE EDITOR

**Granulocyte colony stimulating factor-producing  
squamous cell carcinoma of the skin**

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Dear Editor

A 90-year-old woman presented with a bleeding reddish tumor of the vulvar lesion, which had developed over a 10-year period. Physical examinations revealed a 6 × 4.5 cm reddish cauliflower-like tumor on white atrophic areas on her right labium majus (Fig.1). No palpable inguinal lymph nodes were detected. An incisional biopsy disclosed well-differentiated squamous cell carcinoma (SCC). Total body computed tomography (CT) scanning demonstrated no distant metastasis. The results of routine laboratory studies of blood and urine were normal. Serum SCC antigen was elevated to 5.2 ng/ ml (normal: <1.5 ng/ml). A clinical diagnosis of SCC arising from lichen sclerosus et atrophicus was made. Because of her age, the palliative surgery under local anesthesia was performed. Histopathologic examination of the tumor revealed well-differentiated SCC, with tumor nests extending to the deep dermis and subcutaneous tissues

(Fig.2) on the lesion of lichen sclerosus et atrophicus. At this time, serum SCC antigen level was 1.0 ng/ml.

Six months later, local recurrence was found on her left labium majus, which rapidly developed into 8.5 cm-sized ulcerated tumor with occasional bleeding (Fig.3). At this time, white blood cell count (WBC) was 36,740/mm<sup>2</sup> with 89.3% neutrophils and 4.2% lymphocytes. C-reactive protein was 3.53 mg/dl. Serum level of granulocyte colony-stimulating factor (G-CSF) was markedly elevated to 430 pg/ml (normal range <39.0 pg/ml). No infectious signs were detected. Serum SCC antigen level was again elevated to 2.3 ng/ml. A total body CT scanning demonstrated no distant metastasis. She was treated with X-ray radiation of 60Gy on her recurrent site. The size of tumor mass was decreased and WBC count returned to the normal range (4650/mm<sup>2</sup>). SCC antigen decreased to 1.4ng/ml and serum G-CSF level reduced to 38.3pg/ml. Thereafter, she developed multiple lung

metastases and her general condition deteriorated. The WBC count elevated again to 23200/mm<sup>2</sup> (Fig.4). She died 5 months after the radiation therapy.

Marked leukocytosis without clinical evidence of infection is an occasional finding in patients with non-hematological neoplasms. Recently, this phenomenon was shown to be due to tumor-induced hematopoietic growth factors including granulocyte colony-stimulating factor (G-CSF). Despite the presence of various G-CSF producing tumors including carcinoma of the lung, bladder, stomach, thyroid, and buccal mucosa, the cases of squamous cell carcinoma of the skin are very rare<sup>1</sup>.

The diagnostic criteria of a G-CSF producing tumor are (a) severe leukocytosis mainly due to mature granulocytes in the peripheral blood; (b) elevation of serum G-CSF levels; (c) normalization of leukocytosis and serum G-CSF after tumor resection or treatment; and (d) histologic evidence of a G-CSF producing tumor by

immunohistochemistry<sup>2</sup>. We could not obtain the recurrent tumor to prove G-CSF production. However, in our case, the WBC count and G-CSF level was normalized after radiation therapy, but increased again at the time of multiple lung metastases. Our case was diagnosed as G-CSF-producing cutaneous squamous cell carcinoma. Immunohistochemical analysis might be occasionally unsuccessful, because the intracellular retention of the G-CSF protein is very brief.<sup>3,4</sup>

Because no obvious leukocytosis was noticed before the recurrence of the tumor, the tumor might not be G-CSF producing before the recurrence. Horii et al<sup>5</sup> reported a case of G-CSF producing tongue carcinoma. Similar to our case, it was not apparent until the recurrence of the tumor. The biopsy specimen of the recurrent tumor disclosed poorly differentiated SCC, while the surgical specimen before recurrence showed moderately differentiated SCC. Therefore, Horii et al<sup>5</sup> suggested the

tumor might have transformed with the capacity to produce G-CSF at the time of the recurrence.

Another remarkable finding of our case was the rapid tumor progression. This is occasionally observed in G-CSF-producing tumors. Tachibana et al<sup>6</sup> showed that G-CSF producing transitional cell carcinoma of the bladder express G-CSF receptors resulting in autocrine tumor cell proliferation, invasion, and migration. Young et al<sup>7</sup> also demonstrated that G-CSF hampers anticancer immune defenses by the induction of immune suppressor cells. Thus G-CSF might contribute to rapid progression and poor prognosis in our case. Tumor-associated leukocytosis might be induced by G-CSF, which might affect the prognosis of the tumor.



Figure1. A  $6 \times 4.5$  cm-sized reddish cauliflower-like tumor on white atrophic plaque on her right labium majus



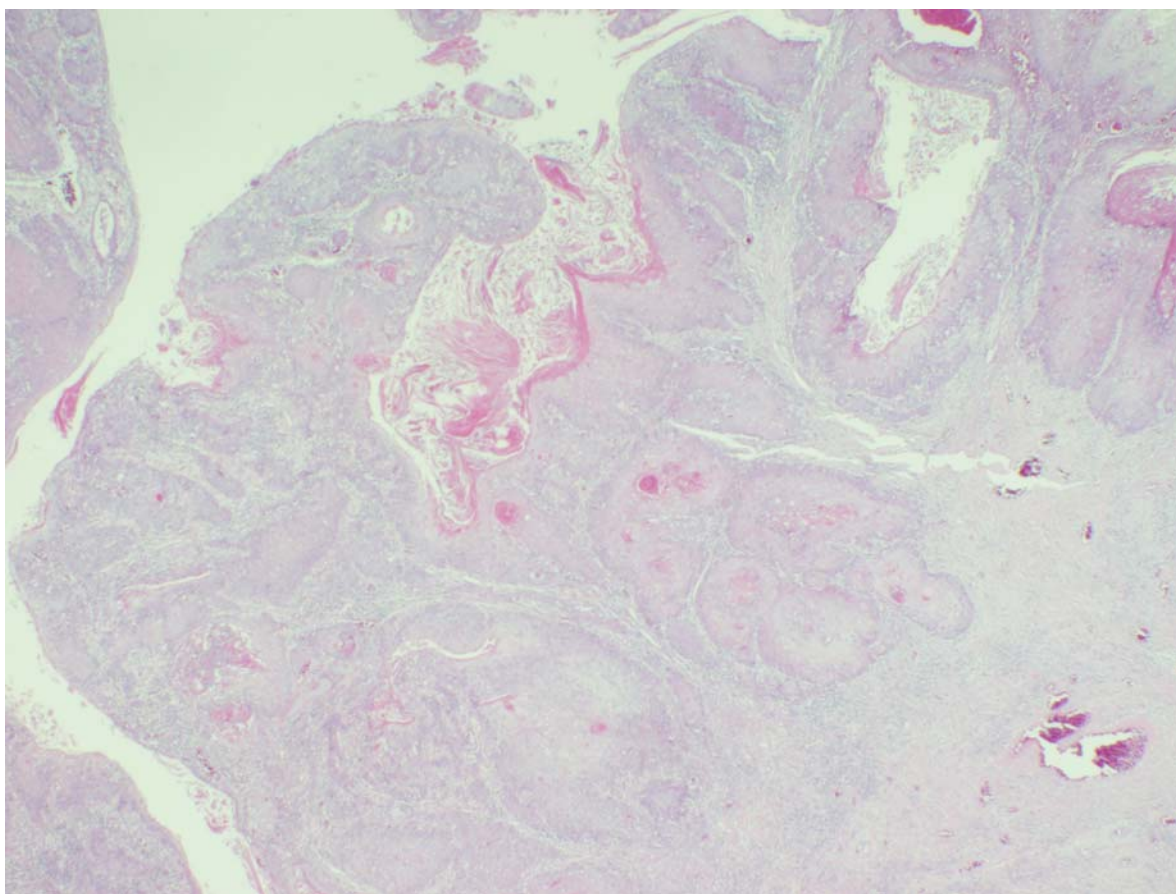


Figure2. Well-differentiated SCC, with tumor nests extending to deep dermis and subcutaneous tissues



Figure3. A 8.5 cm-sized ulcerated tumor on her right labium majus (recurrent site)

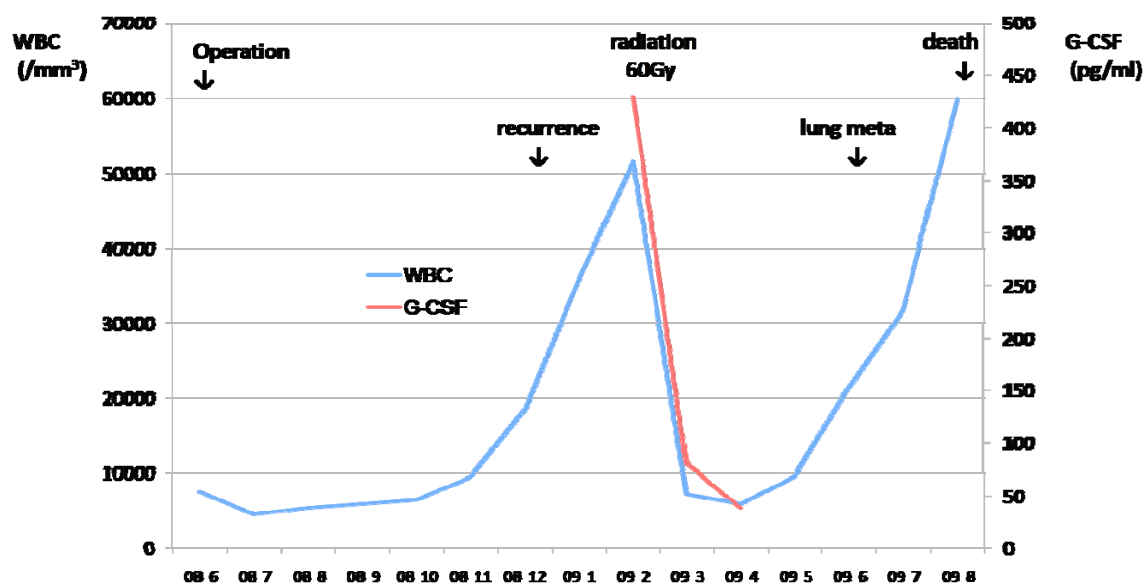


Figure4. Serum G-CSF level and WBC count during the clinical course

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