Granulocyte-colony Stimulating Factor-producing Primary Cutaneous Anaplastic Large Cell Lymphoma with Cerebral Metastasis

Akira Kasuya, Satoshi Hirakawa, Hideo Hashizume and Yoshiki Tokura
Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-Ku, Hamamatsu 431-3192, Japan. E-mail: casuaki@hama-med.ac.jp
Accepted February 15, 2012.

Tumours producing granulocyte-colony stimulating factor (G-CSF) have been documented in various tissues, with remarkable neutrophilia as an unexplained laboratory finding before the diagnosis (1). G-CSF-producing malignant lymphomas are rare; there have been only 2 documented cases of Hodgkin's lymphoma and 1 of gastric anaplastic large cell lymphoma (ALCL) (2, 3). We report here a case of G-CSF-producing primary cutaneous ALCL with cerebral metastasis. To the best of our knowledge, this is the first reported case of G-CSF-producing primary cutaneous lymphoma.

CASE REPORT

A 78-year-old Japanese man was admitted to our hospital for further evaluation and treatment of a 2-year history of lobulated tumours on his forehead. Two months before admission, the tumours enlarged with ulceration and necrosis on the surface (Fig. 1). No swollen superficial lymph node was palpable. Concomitantly with the tumour growth, the patient had intermittent high fever and leukocytosis (38,300/μl) with prominent neutrophilia (87%). The following values were elevated: C-reactive protein, 5.0 mg/dl (normal, 0.0–0.5 mg/dl); serum soluble interleukin-2 receptor, 4,270 U/ml (145–519 U/ml); and serum G-CSF 847 pg/ml (<39.0 pg/ml). The patient's serum was negative for anti-human T-lymphotropic virus type 1 (HTLV-1) antibodies. Peripheral blood smear showed no atypical cell. Repeated blood culture was negative for any bacteria. No visceral lesions were detected by 18F-positron emission tomography (PET) or computed tomography (CT) scan.

Skin biopsy revealed massive infiltration of atypical large cells in the dermis and subcutaneous fat (Fig. 2A). The atypical cells were positive for CD30 (Fig. 2B) and negative for CD3, CD20, CD79a, and anaplastic lymphoma kinase. PCR analysis confirmed clonal gene rearrangement of the T-cell antigen receptor Cβ1 chain. When deparaffinized sections were immunohistochemically stained with anti-G-CSF rabbit polyclonal antibody (Abcam, Cambridge, UK), positive immunoreactivity was found in neoplastic cells and intercellular spaces (Fig. 2C). On the other hand, tumour cells in 2 cases of typical primary cutaneous ALCL as control were negative (Fig. 2D). There was no influx of granulocytes in the tumour of our case. This may be explained by the fact that G-CSF does not have chemotactic effect (4).

A biopsy specimen from the tumour was measured for the concentration of G-CSF (Special Reference Laboratories, Tokyo, Japan). The G-CSF level was 20,600 pg/g tissue weight, which was much higher than the serum level (847 pg/ml). These findings suggested that the neoplastic cells produced G-CSF. We diagnosed the tumour as G-CSF-producing primary cutaneous ALCL.

After radiation therapy (45 Gy/15 Fr), the tumour disappeared, and leukocyte count and serum G-CSF level decreased to 5,400/μl and 107 pg/ml, respectively. One month later, however, he complained of visual field defect. Brain magnetic resonance image revealed a hypophysal tumour, suggesting metastasis of ALCL. Additional radiation therapy to the tumour, 30 Gy/15 Fr, resulted in a partial reduction in its size.

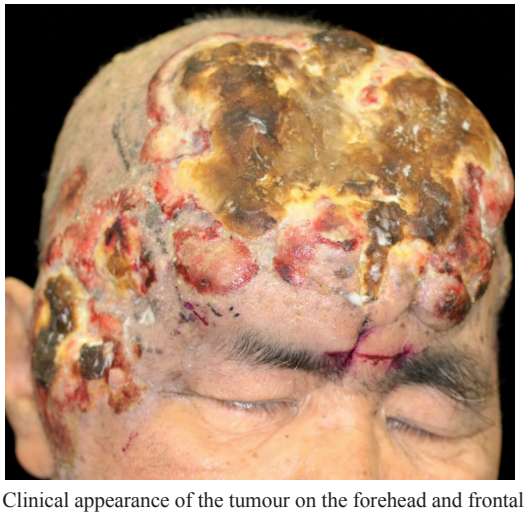

Fig. 1. Clinical appearance of the tumour on the forehead and frontal scalp.

DISCUSSION

G-CSF-producing tumours are rare, but clinically important, because its symptoms, neutrophilia and intermittent fever, mimic bacterial sepsis. In the case described here, negative results in repeated blood culture

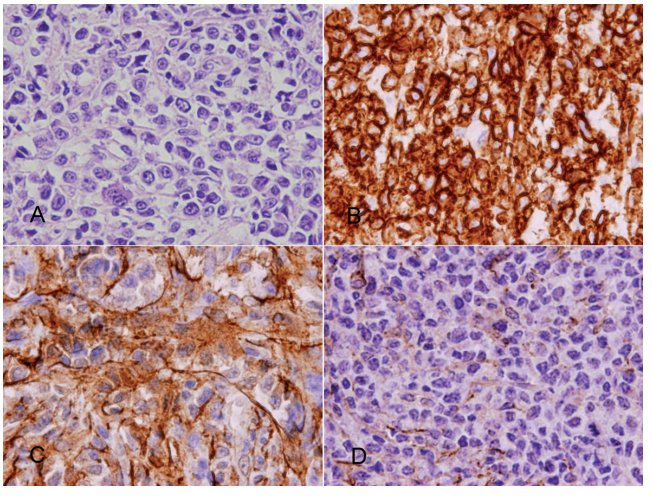

Fig. 2. Histopathology and immunohistochemistry of the tumour (original magnification ×400). (A) Massive infiltration of atypical cells in dermis (haematoxylin-eosin stain). (B) Tumour cells positive for CD30. (C) Tumour cells and interstitial tissue positive for granulocyte-colony stimulating factor. (D) Representative primary cutaneous anaplastic large cell lymphoma as control.

and failures to find visceral abscess in imaging studies made us think of G-CSF-producing tumour.

The diagnostic criteria for G-CSF-producing tumours were proposed (5). In our case, the diagnosis was made based on the following findings: (*i*) leukocytosis predominant with granulocytosis; (*ii*) elevated serum G-CSF; (*iii*) reductions in blood neutrophil number and serum G-CSF level after successful treatment; and (*iv*) demonstration of intratumour G-CSF production by immunohistochemistry and tissue G-CSF measurement.

Primary cutaneous ALCL usually has a good prognosis, and cases with a fatal outcome have rarely been reported (6). However, aggressive cerebral metastasis was found in our case. Rapid progression and multiple metastasis are frequently documented (7). In a case of G-CSF-producing squamous cell carcinoma, the presence of G-CSF receptors on the tumour cell was demonstrated by immunohistochemistry (1), suggesting that autocrine expansion of the tumour cell with G-CSF contributes to the poor prognosis. Overexpressed G-CSF might activate the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway through the receptor, leading to unusual enlargement and cerebral metastasis, as in the present case.

The authors declare no conflicts of interest.

REFERENCES

1. Toyoda M, Chikamatsu K, Sakakura K, Fukuda Y, Takahashi K, Miyashita M, et al. A case of squamous cell carcinoma of the head and neck producing granulocyte-colony stimulating factor with marked leukocytosis. Auris Nasus Larynx 2007; 34: 267–271.
2. Shimizu K, Iida M, Takahashi S. Hodgkin's disease producing granulocyte colony stimulating factor. Am J Hematol 2001; 68: 134.
3. Sugimoto M, Kajimura M, Hanai H, Shirai N, Tanioka F, Kaneko E. G-CSF-producing gastric anaplastic large cell lymphoma complicating esophageal cancer. Dig Dis Sci 1999; 44: 2035–2038.
4. Wengner A, Pitchford S, Furze R, Rankin S. The coordinated action of G-CSF and ELR CXC chemokines in neutrophil mobilization during acute inflammation. Blood 2008; 111: 42–49.
5. Asano S, Urabe A, Okabe T, Sato N, Kondo Y. Demonstration of granulopoietic factor(s) in the plasma of nude mice transplanted with a human lung cancer and in the tumor tissue. Blood 1977; 49: 845–852.
6. Tokura Y, Sugita K, Yagi H, Shimauchi T, Kabashima K, Takigawa M. Primary cutaneous anaplastic large cell lymphoma with fatal leukemic outcome in association with CLA and CCR4-negative conversion. J Am Acad Dermatol 2007; 57: S92–96.
7. Takahashi H, Yasuda A, Ochi N, Sakamoto M, Takayama S, Wakasugi T, et al. Granulocyte-colony stimulating factor producing rectal cancer. World J Surg Oncol 2008, 6: 70.