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CASE REPORT

Dedifferentiated liposarcoma can induce a leukemoid reaction

Po-Chun Shih [a,b], Kai-Yuan Lin [c,g], Chien-Feng Li [d], Kuen-Huang Chen [e], Cheng Liu [a,f], Cheng Yang [a], Yu-Shan Lin [a], Kuo-Feng Huang [a,*]

[a] *Division of Plastic Surgery, Department of Surgery, Chi Mei Medical Center, Tainan, Taiwan*
[b] *Division of Plastic Surgery, Department of Surgery, Changhua Christian Hospital, Changhua, Taiwan*
[c] *Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan*
[d] *Department of Pathology, Chi Mei Medical Center, Tainan, Taiwan*
[e] *Division of Musculoskeletal Radiology, Department of Medical Imaging, Chi Mei Medical Center, Tainan, Taiwan*
[f] *Department of Cosmetic Science and Institute of Cosmetic Science, Chia Nan University of Pharmacy and Science, Tainan, Taiwan*
[g] *Department of Biotechnology, Chia Nan University of Pharmacy and Science, Tainan, Taiwan*

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Summary Liposarcoma is one of the most common malignant soft tissue neoplasms in adults; however, few reports of liposarcoma had been described the expression of leukocytosis and granulocyte-colony stimulating factor (G-CSF). In this report, we present the rare case of a patient who had de-differentiated liposarcoma and elevated G-CSF levels that resulted in a leukemoid reaction. The patient was a 65-year-old man who had been lame for one month due to right thigh swelling. His body temperature was slightly elevated at 38°C and leukocytosis with an elevated white blood cell (WBC) count (41500/μL) was noted. The findings of computed tomography of the lower extremities indicated the presence of a malignancy. Therefore, an incision biopsy was performed. Based on the finding of magnetic resonance imaging (MRI) and the biopsy pathology report, we diagnosed the patient with liposarcoma. Moreover, the preoperative serum G-CSF level was elevated (261.8 pg/mL). An *en bloc* excision including the entire biopsy pathway was performed 5 days after admission. After *en bloc* excision of the tumor, WBC count, C-reactive protein (CRP) level, and G-CSF expression decreased. The final

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* Corresponding author. Division of Plastic Surgery, Department of Surgery, Chi Mei Medical Center, 901 Zhonghua Road, Yongkang District, Tainan City 710, Taiwan.
E-mail address: huangkuofeng@gmail.com (K.-F. Huang).

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pathologic report confirmed the diagnosis of de-differentiated liposarcoma. No local recurrence or distant metastasis was detected in the follow-up image study, and the patient has remained asymptomatic 2 years after surgery. The case described here is a rare type of liposarcoma that produces G-CSF, which in turn, induces leukocytosis. Liposarcoma with elevated G-CSF levels resulting in a leukemoid reaction may indicate a poorly differentiated cell type and may be associated with a poor prognosis; however, *en bloc* excision of the tumor remains the primary treatment for this type of tumor. Moreover, the WBC count and G-CSF serum level can be as the tools monitoring the tumor recurrence.

1. Introduction

Liposarcoma, first described in 1857 by Virchow,[1] is one of the most common malignant soft tissue neoplasms in adults. It usually occurs in the extremities and retroperitoneum and is currently classified into five main histologic variants: well-differentiated, dedifferentiated, myxoid, round cell, and pleomorphic.[2] Dedifferentiated liposarcoma, first described by Evans[3] in 1979, has the characteristics of a well-differentiated liposarcoma as well as a nonlipogenic dedifferentiated sarcoma-like component, and is most frequently noted in retroperitoneal lesions.[4] Leukocytosis, which refers to the elevation of the white blood cell (WBC) count above the normal level, is a sign of inflammation and most commonly results from infection. Leukemoid reaction is defined as the presence of leukocytosis involving a WBC count of $> 50 \times 10^9$/L, along with a significant increase in early neutrophil precursors.[5] Granulocyte-colony-stimulating factor (G-CSF), a growth factor that stimulates the bone marrow to produce granulocytes and stem cells, plays a role in the development of leukocytosis and leukemoid reaction; however, only a few types of malignancy are associated with G-CSF.[6–8] Here, we present an unusual case of dedifferentiated liposarcoma with leukemoid reaction due to the elevation of serum G-CSF.

2. Case report

A 65-year-old man without any systemic disease or trauma history presented to our emergency department with difficulty in walking for 1 month due to swelling in his right thigh. Physical examination revealed local heat of the right thigh without surrounding erythema, and a slightly elevated body temperature (38°C). The patient had an elevated WBC count (41.5×10^9/L) with 92.7% segmental neutrophils (Seg), and a C-reactive protein level of 85.6 mg/L were found. Computed tomography of the lower extremities indicated the presence of a malignancy (Fig. 1), and an incision biopsy was then performed. Magnetic resonance imaging was performed 2 days after admission, revealing a large multilobulated tumor, with the superior portion manifesting with a signal intensity similar to that of fat tissue. Thus, we diagnosed the patient with liposarcoma (Fig. 2). The findings of the biopsy pathology report obtained 2 days after admission confirmed the presence of liposarcoma. The patient's WBC count had a left shift to 68.8×10^9/L, with 93.5% Seg and 5% band neutrophils. To distinguish between leukemoid reaction and chronic myelogenous leukemia, leukocyte alkaline phosphatase staining was performed, yielding a score of 387 (a score < 100 indicates the presence of chronic myelogenous leukemia). These findings were consistent with a leukemoid reaction. An elevated G-CSF serum level (261.8 pg/mL) was also noted. *En bloc* excision of the tumor that included the entire biopsy pathway was performed 5 days after admission (Fig. 3). During surgery, a frozen section procedure indicated tumor-free margins.

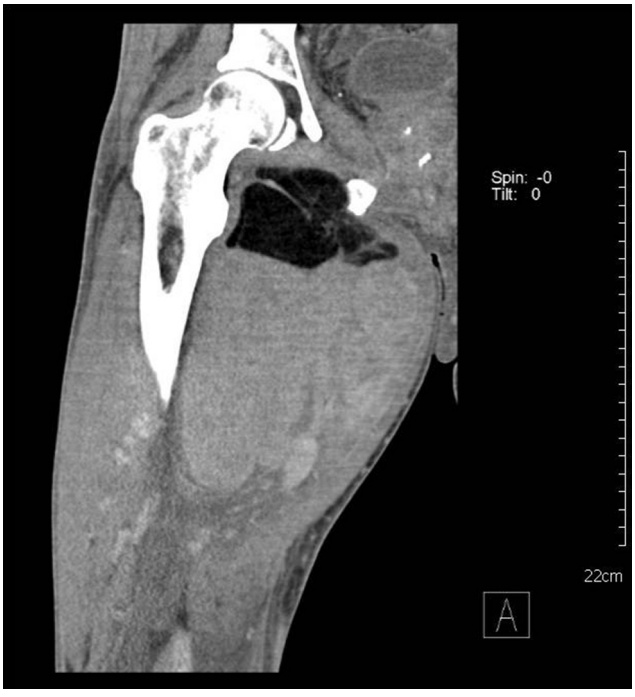

Figure 1 Computed tomography findings. Precontrast computed tomography scan of the right hip and upper thigh showing a large multilobular soft tissue mass, measuring approximately 13 cm × 13 cm × 20 cm. This mass extended from the right pelvic floor to the middle third of the right thigh and involved the entire medial compartment. Obvious fat tissue was noted in the superior portion of the mass, indicative of a malignant soft tissue sarcoma.

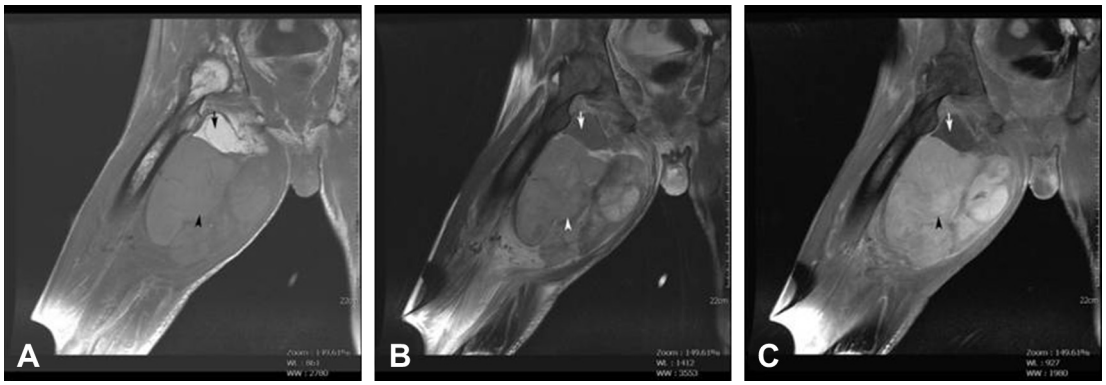

Figure 2 Magnetic resonance imaging findings. (A) Coronal T1 weighted imaging, (B) fat-suppressed T2 weighted imaging, and (C) fat-suppressed Gd-enhanced T1 weighted imaging revealed a large multi-lobulated soft tissue mass in the right upper thigh. The superior portion of the lesion indicated a signal intensity similar to that of fat tissue (arrows) without contrast enhancement. The inferior portion of the mass (arrowheads) manifested as an unspecified soft tissue mass with a low to intermittent T1 signal, a mild high T2 signal and a moderate degree of heterogeneous contrast enhancement. The tumor abutted on the medial surface of the right femur without focal bone destruction or intramedullary extension. The femoral neurovascular bundle was displaced laterally and anteriorly by the mass. The preoperative magnetic resonance imaging diagnosis was liposarcoma.

2.1. Outcome

After *en bloc* excision of the tumor, the patient's WBC count, C-reactive protein, and G-CSF decreased (Table 1 and Fig. 4). Pathological examination showed the presence of a well-differentiated lipoma-like component and a nonadipogenic component with sheets of pleomorphic spindle cells. Based on these findings, the patient was diagnosed with dedifferentiated liposarcoma (Figs. 5 and 6). Leukocytosis was resolved 5 days after surgery, with a WBC count of 8.5×10^9/L and Seg at 65.6%. In addition, G-CSF serum levels decreased to 98.7 (pg/mL) 8 days after surgery, and the patient was discharged 2 weeks after admission. No local recurrence or distant metastasis was detected during the follow-up MRI study (Fig. 7), and thus no further chemotherapy or radiation therapy was required. At the time of this case report, 2 years after surgery, the patient was asymptomatic with a WBC count of 6.1×10^9/L, Seg level of 66%, and undetectable serum G-CSF levels.

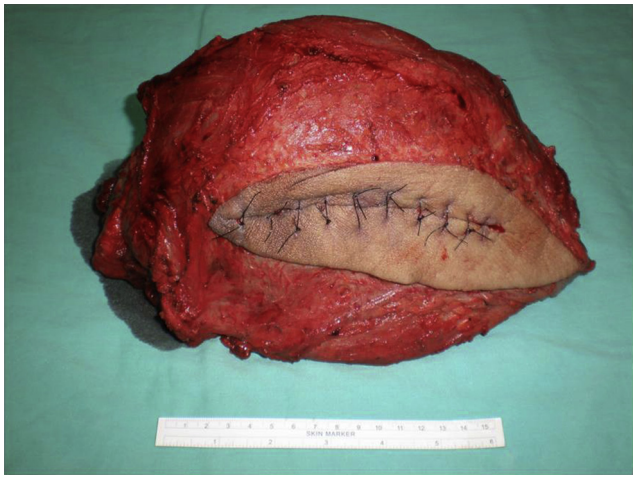

Figure 3 *En bloc* excision of the tumor including the entire biopsy pathway.

3. Discussion

Previous studies have indicated that almost 50% of the liposarcomas are located in the lower extremities, whereas 33.5% are located in the retroperitoneum.[9] In a previous study of 910 patients with liposarcoma from a single institution, the percentage of liposarcoma within each histologic subtype was as follows: well-differentiated (46%), dedifferentiated (18%), myxoid (18%), round cell (10%), and pleomorphic (8%).[9] Dedifferentiated liposarcoma,[3] has the characteristics of a well-differentiated liposarcoma with a high-grade nonlipogenic dedifferentiated sarcoma-like component that usually resembles malignant fibrous histiocytoma or fibrosarcoma.[10] Dedifferentiated liposarcoma was most frequently noted in retroperitoneal lesions, followed by the extremities.[11]

Some solid tumors may cause a leukemoid reaction by producing cytokines, such as G-CSF or granulocyte—macrophage colony-stimulating factor, which is also known as a paraneoplastic leukemoid reaction, that were usually presented at an advanced stage of the disease, and illustrated by poorly differentiated adenocarcinomas, such as lung, gastrointestinal cancers,[6–8] more than the tumors in extremities. We reviewed the presented literature in PubMed and found eight cases with paraneoplastic leukemoid reaction or leukocytosis resulting from the skin and soft tissue tumor in the lower extremities (Table 2).[12–19] Including the current case in this report, the tumor sites were as follows: four cases in the thigh, two cases in the foot, two case in the knee, and one case in the buttock. The pathologic type of these cases was liposarcoma in two cases, squamous cell carcinoma in two cases, angiosarcoma in one case, MFH in two cases, spindle cell sarcoma in one case, and melanoma in one case. Six of the eight presented case reports described the elevation of G-CSF or granulocyte—macrophage colony-stimulating

Table 1 Blood data summary.

Days from operation	−5	−3	−1	1	5	8	35	2 years
WBC ($\times 10^3/\mu L$)	41.5	68.8	N/A	20.3	8.5	N/A	7.1	6.1
Seg (%)	92.7	93.5	N/A	95	65.6	N/A	67.8	66
CRP (mg/L)	85.6	155.8	N/A	109	16.7	N/A	N/A	N/A
G-CSF (pg/mL)	N/A	N/A	261.8	N/A	N/A	98.7	N/A	0

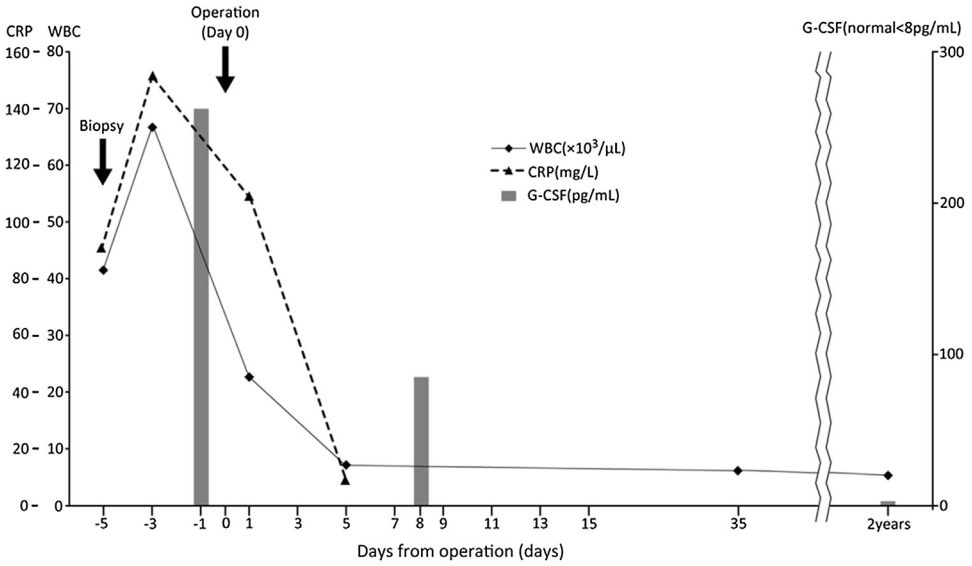

Figure 4 Changes in white blood cell (WBC) count, C-reactive protein (CRP) level, and granulocyte-colony stimulating factor (G-CSF) serum levels over time.

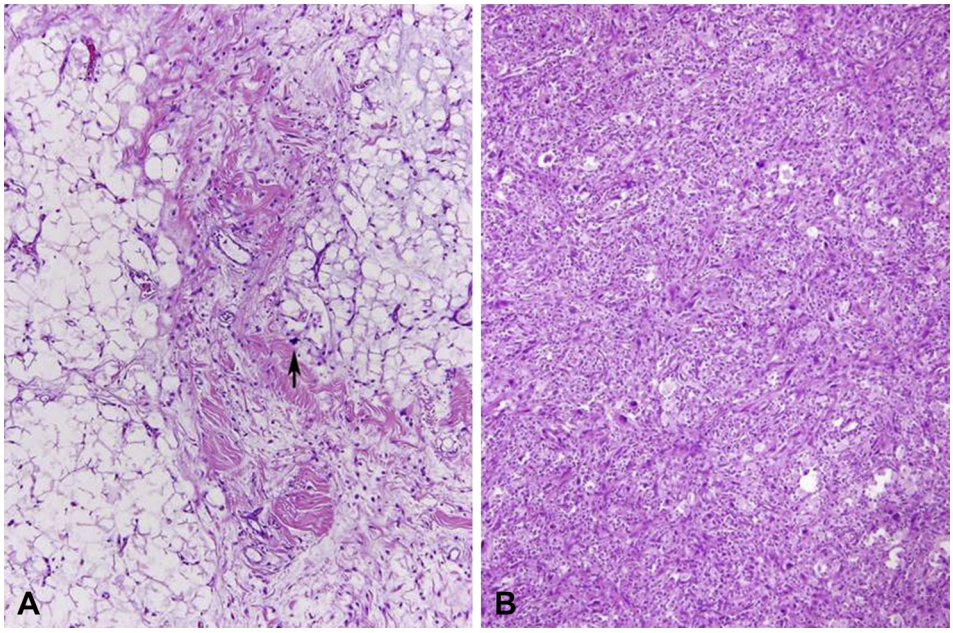

Figure 5 Hematoxylin and eosin (HE) staining of the resected tumor. (A) HE stain, 100×; mixture of well-differentiated lipoma-like component with occasional bizarre-shaped stromal cells (arrow) in variable-sized adipocytes. (B) HE stain, 100×; focally, the tumor transformed into a non-adipogenic pleomorphic tumor with bizarre-shaped spindle cells in a storiform pattern.

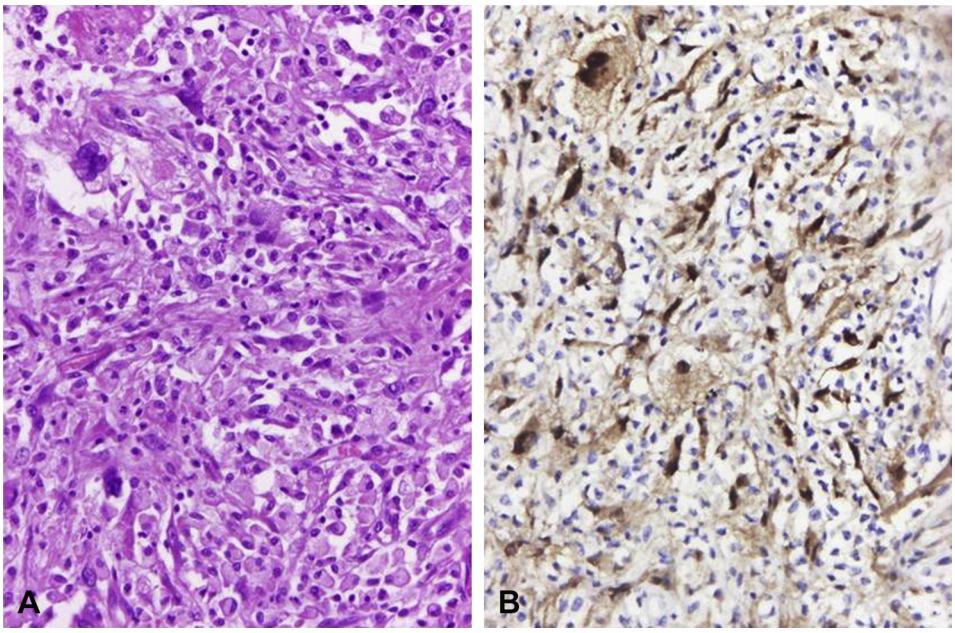

Figure 6 Hematoxylin and eosin and Cdk4 staining of the resected tumor. (A) Hematoxylin and eosin stain, 400×; pleomorphic tumor cells admixed with densely packed inflammatory elements. (B) Cdk4 stain, 400×; immunohistochemically, these pleomorphic tumor cells are positive for Cdk4.

factor. The presented liposarcoma case in the thigh demonstrated that the liposarcoma cell line (NDDLS-1) produces interleukin-6 (IL-6) and G-CSF and induces leukocytosis.[12]

Most tumors that produce G-CSF are believed to be poorly differentiated and invasive,[20,21] and G-CSF is known to stimulate tumor cell growth and migration.[22] Only seven cases of liposarcoma with elevated serum G-CSF levels resulting in leukocytosis or leukemoid reaction have been reported (Table 3).[11,23–28] Including the current case, the mean age of these patients was 67 years (range, 50—84 years, 5 men and 3 women). The tumor sites were as follows: retroperitoneum in four cases, mesenterium in one case, upper arm in one case, and thigh in two cases. The pathologic subtype of these liposarcoma cases was dedifferentiated liposarcoma in six cases and pleomorphic

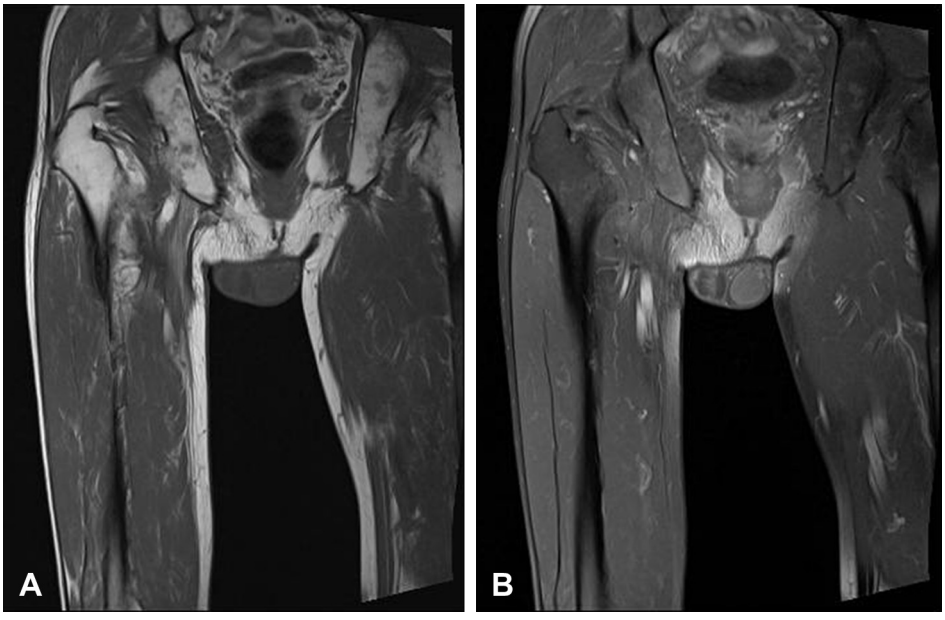

Figure 7 Magnetic resonance imaging at the 2-year postoperative follow-up. (A) Coronal T1-weighted imaging, and (B) fat-suppressed Gd-enhanced T1-weighted imaging revealed mild muscle atrophy at the medial aspect of the right thigh without evidence of local tumor recurrence.

Table 2 Malignant soft tissue tumor cases with leukemoid reaction or leukocytosis in the lower extremities.

Reference	Year	Age (y)	Sex	Tumor site	Tumor type	Max. WBC count	Elevation of G-CSF	Prognosis
Asirwatham JE. et al.	1978	47	Male	Thigh	Malignant fibrous histiocytoma	38,000/μL	Not described	21 years after surgery, still alive
McKee LC. et al.	1985	59	Not reported	Foot	Squamous cell carcinoma	79,000/μL	Not described	Died
Kato N. et al.	1999	58	Male	Foot	Squamous cell carcinoma	57,110/μL	Yes	Died
Mayumi E. et al.	2001	80	Female	Thigh	Malignant fibrous histiocytoma	84,300/μL	Yes	Died 50 days after admission
Nara T. et al.	2003	46	Male	Buttock	Angiosarcoma	113,000/μL	Yes	Died 55 days after admission
Simon CC. et al.	2007	65	Female	Knee	Melanoma	105,000/μl	Yes	12 months after surgery, still alive
Snyder MC. et al.	2010	41	Female	Knee	Spindle cell sarcoma	126,700/μL	GM-CSF elevation	12 months after surgery, still alive with tumor recurrence
Takashi A. et al.	2011	84	Male	Thigh	Dedifferentiated liposarcoma	89,150/μL	Yes	Died after 4 months
Current case		65	Male	Thigh	Dedifferentiated liposarcoma	68,800/μL	Yes	2 years after surgery, still alive

G-CSF = granulocyte-colony stimulating factor; GM-CSF = granulocyte—macrophage colony-stimulating factor; WBC = white blood cell.

liposarcoma in two cases. However, to our knowledge, no reports have described a case of well-differentiated liposarcoma with elevated serum G-CSF levels resulting in leukocytosis, which suggests that there may be an association between leukocytosis due to elevated G-CSF levels and poorly differentiated tumors.

Two major factors influence the prognosis of liposarcoma: the tumor histologic subtype,[29] and tumor site.[30] In a study of primary liposarcoma, the dedifferentiated type had the worst prognosis with a 5-year disease specific survival rate of 44%, compared with the well-differentiated type (93%), myxoid type (92%), round cell type (74%), and pleomorphic type (59%).[9] Additionally, retroperitoneal liposarcomas have a worse prognosis than those located in the extremities.[30] Retroperitoneal liposarcoma may have a deeper location and influence surrounding organs, thus making the *en bloc* excision difficult and more likely to leave unclear margins. Our patient had a dedifferentiated type of tumor, which is a tumor site associated with a better prognosis. He only received surgical treatment without any other adjuvant therapy and was still alive 2 years after surgery. Compared with the other seven reports,[11,23–28] our patient has survived the longest. Although the association between prognosis and the presence of liposarcoma with leukemoid reaction remains

Table 3 Liposarcoma cases with leukocytosis and increased granulocyte-colony stimulating factor expression.

Reference	Year	Age (y)	Sex	Tumor site	Pathologic type	Treatment	Prognosis
Matsumoto M. et al.	1976	57	Female	Retroperitoneal	Pleomorphic	N/A	Died
Hisaoka M. et al.	1997	69	Male	Retroperitoneal	Pleomorphic	Surgery	Died after 5 months
Nakamura A. et al.	1998	77	Female	Mesenterium	Dedifferentiated	Surgery	7 months after surgery, still alive
Nasser SM. et al.	2001	63	Male	Retroperitoneal	Dedifferentiated	Surgery	22 months after surgery, still alive
des Guetz G. et al.	2004	50	Female	Retroperitoneal	Dedifferentiated	C/T + Surgery	Not reported
Sakamoto A. et al.	2007	72	Male	Upper arm	Dedifferentiated	Surgery	Died after 3 months
Takashi A. et al.	2011	84	Male	Thigh	Dedifferentiated	Surgery + RT	Died after 4 months
Current case		65	Male	Thigh	Dedifferentiated	Surgery	2 years after surgery, still alive

CT = chemotherapy; RT = radiation therapy.

unclear, *en bloc* excision of the tumor is still the primary treatment.

In conclusion, in the present report we described a rare case of dedifferentiated liposarcoma with elevated G-CSF serum levels that resulted in a leukemoid reaction, which may indicate a poorly differentiated cell type and a poor prognosis. Moreover, the WBC count and G-CSF serum level can used be as tools for monitoring tumor recurrence.

References

1. Virchow R. Ein Fall von bösartigen zum Theil in der Form des Neurons auftretenden Fettgeschwulsten. *Arch A Pathol Anat Phys*. 1857;11:281—288 [In German].
2. Dalal KM, Antonescu CR, Singer S. Diagnosis and management of lipomatous tumors. *J Surg Oncol*. 2008;97:298—313.
3. Evans HL. Liposarcoma: a study of 55 cases with a reassessment of its classification. *Am J Surg Pathol*. 1979;3:507—523.
4. Singer S, Antonescu CR, Riedel E, Brennan MF. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. *Ann Surg*. 2003;238:358—370. discussion 370—371.
5. Hoffman R. *Hematology: basic principles and practice*. 4th ed. Edinburgh: Elsevier Churchill Livingstone; 2005.
6. Endo K, Kohnoe S, Okamura T, et al. Gastric adenosquamous carcinoma producing granulocyte-colony stimulating factor. *Gastric Cancer*. 2005;8:173—177.
7. Shijubo N, Inoue Y, Hirasawa M, et al. Granulocyte colony-stimulating factor-producing large cell undifferentiated carcinoma of the lung. *Intern Med*. 1992;31:277—280.
8. Hasegawa S, Suda T, Negi K, Hattori Y. Lung large cell carcinoma producing granulocyte-colony-stimulating factor. *Ann Thorac Surg*. 2007;83:308—310.
9. Dalal KM, Kattan MW, Antonescu CR, Brennan MF, Singer S. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity, or trunk. *Ann Surg*. 2006;244:381—391.
10. Henricks WH, Chu YC, Goldblum JR, Weiss SW. Dedifferentiated liposarcoma: a clinicopathological analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. *Am J Surg Pathol*. 1997;21:271—281.
11. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. *World Health Organization, International Agency for Research on Cancer. WHO Classification of Tumours of Soft Tissue and Bone*. 4th ed. Lyon: International Agency for Research on Cancer; 2013.
12. Ariizumi T, Ogose A, Kawashima H, et al. Establishment and characterization of a novel dedifferentiated liposarcoma cell line, NDDLS-1. *Pathol Int*. 2011;61:461—468.
13. McKee Jr LC. Excess leukocytosis (leukemoid reactions) associated with malignant diseases. *South Med J*. 1985;78:1475—1482.
14. Kato N, Yasukawa K, Onozuka T, Kimura K. Paraneoplastic syndromes of leukocytosis, thrombocytosis, and hypercalcemia associated with squamous cell carcinoma. *J Dermatol*. 1999;26:352—358.
15. Mayumi E, Okuno T, Ogawa T, et al. Malignant fibrous histiocytoma of soft tissue producing granulocyte colony-stimulating factor. *Intern Med*. 2001;40:536—540.
16. Simon CC, de Rooij PD, Berghout A. A mass in the popliteal fossa and leucocytosis caused by a paraneoplastic leukemoid reaction. *Ned Tijdschr Geneeskd*. 2007;151:2469—2474 [Article in Dutch].
17. Nara T, Hayakawa A, Ikeuchi A, Katoh N, Kishimoto S. Granulocyte colony-stimulating factor-producing cutaneous angiosarcoma with leukaemoid reaction arising on a burn scar. *Br J Dermatol*. 2003;149:1273—1275.
18. Snyder MC, Lauter CB. Eosinophilic and neutrophilic leukemoid reaction in a woman with spindle cell sarcoma: a case report. *J Med Case Rep*. 2010;4:335.
19. Asirwatham JE, Pickren JW. Inflammatory fibrous histiocytoma: case report. *Cancer*. 1978;41:1467—1471.
20. Yamano T, Morii E, Ikeda J, Aosaza K. Granulocyte colony-stimulating factor production and rapid progression of gastric cancer after histological change in the tumor. *Jpn J Clin Oncol*. 2007;37:793—796.
21. Sohda T, Shiga H, Nakane H, Watanabe H, Takeshita M, Sakisaka S. Cholangiocellular carcinoma that produced both granulocyte-colony-stimulating factor and parathyroid hormone-related protein. *Int J Clin Oncol*. 2006;11:246—249.
22. Bussolino F, Wang JM, Defilippi P, et al. Granulocyte- and granulocyte-macrophage-colony stimulating factors induce human endothelial cells to migrate and proliferate. *Nature*. 1989;337:471—473.
23. Matsumoto M, Yazawa Y, Kanzaki M. An autopsy case of liposarcoma with granulocytic leukemoid reaction. *Acta Pathol Jpn*. 1976;26:399—408.
24. Nakamura A, Tanaka S, Takayama H, et al. A mesenteric liposarcoma with production of granulocyte colony-stimulating factor. *Intern Med*. 1998;37:884—890.
25. Hisaoka M, Tsuji S, Hashimoto H, Aoki T, Uriu K. Dedifferentiated liposarcoma with an inflammatory malignant fibrous histiocytoma-like component presenting a leukemoid reaction. *Pathol Int*. 1997;47:642—646.
26. Nasser SM, Choudry UH, Nielsen GP, Ott MJ. A leukemoid reaction in a patient with a dedifferentiated liposarcoma. *Surgery*. 2001;129:765—767.
27. des Guetz G, Mariani P, Freneaux P, Pouillart P. Paraneoplastic syndromes in cancer: Case 2. Leucocytosis associated with liposarcoma recurrence: original presentation of liposarcoma recurrence. *J Clin Oncol*. 2004;22:2242—2243.
28. Sakamoto A, Matono H, Yoshida T, et al. Dedifferentiated liposarcoma with leukocytosis. A case report of G-CSF-producing soft-tissue tumors, possible association with undifferentiated liposarcoma lineage. *World J Surg Oncol*. 2007;5:131.
29. Wong CK, Edwards AT, Rees BI. Liposarcoma: a review of current diagnosis and management. *Br J Hosp Med*. 1997;58:589—591.
30. Linehan DC, Lewis JJ, Leung D, Brennan MF. Influence of biologic factors and anatomic site in completely resected liposarcoma. *J Clin Oncol*. 2000;18:1637—1643.