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Cutaneous Intravascular B-cell Lymphoma Mimicking Thrombophlebitis

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Intravascular lymphoma is an uncommon disease in the skin and central nervous system. Here, we present a 75-year-old woman who suffered from severe pain, swelling and erythema bilaterally over her thighs with intermittent fever for over 10 days. Skin biopsy showed medium-sized neoplastic cells with atypical nuclei and arranged in a discohesive pattern with aggregation in vascular lumens. Under the impression of lymphoma, immunohistochemical staining was performed and revealed positive staining for CD45 and CD20 in the tumor cells. Therefore, intravascular B-cell lymphoma was confirmed. The patient had relatively normal brain, chest, and abdominal radiography. Blood smears and bone marrow aspirates showed no abnormal cells. The patient was given one cycle of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone chemotherapy. After one cycle of chemotherapy, the erythema disappeared and the fever subsided. To date, no tumor relapse has been seen after seven months of follow up.

Key words: B-cell, cutaneous tumor, erythematous plaque, intravascular lymphoma, thrombophlebitis.

INTRODUCTION

Intravascular lymphoma (IVL) is defined as malignant lymphocytes confined within the lumen of blood vessels[1]. Tumor cells in most IVL cases are of B-cell origin and have been recognized as a subtype of diffuse large B-cell lymphoma[2,3]. In addition to the skin and central nervous system, lung, liver, kidney and spleen are often involved by IVL[4-8]. Intravascular lymphoma is an extremely rare subtype of diffuse large B-cell lymphoma characterized by extranodal proliferation of neoplastic lymphoid cells within the lumen of small vessels[9]. Because IVL clinically mimics thrombophlebitis, the diagnosis of IVL should be based on histological and immunohistochemical findings[10].

CASE REPORT

A 75-year-old woman was hospitalized when intermittent fever occurred following a two-week history of erythematous plaques and swelling with a painful sensation bilaterally over her thighs (Fig. 1A). She had a history of type II diabetic mellitus, under regular medication, for more than 10 years. Before admission, the patient had received antibiotics at clinics for possible thrombophlebitis, but in vain. Physical examination revealed no regional lymph node enlargement. Brain, chest and abdominal radiographs were noncontributory. Laboratory tests revealed only a mild normocytic anemia (Hgb: 10.2). There were no abnormal cells in her blood smears or bone marrow aspirate. Bilateral biopsies of the skin of her thighs were performed under localized anesthesia. The biopsy specimens revealed a monotonous arrangement of medium-sized tumor cells (compared with red blood cells) with scanty cytoplasm, irregular nuclear contour, and prominent nucleoli present in the vascular lumen (Figure 1B). Immunohistochemical staining demonstrated CD45 and CD20 positive neoplastic cells situated in the CD34-outlined vessel lumens (Figure 1C and 1D). These findings confirmed the diagnosis of cutaneous intravascular B-cell lymphoma. The patient was then given one cycle of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (CHOP) chemotherapy treatment. After one cycle of chemotherapy, the erythema disappeared and her fever subsided. To date, no tumor relapse has been seen after seven months of follow up.

DISCUSSION

In 1959, Pfleger and Tappeiner first reported a case of an intravascular neoplasm, which was named “angioendotheliomatosis proliferans systematisata,” presuming the neoplastic cells to be derived from endothelial cells[4].

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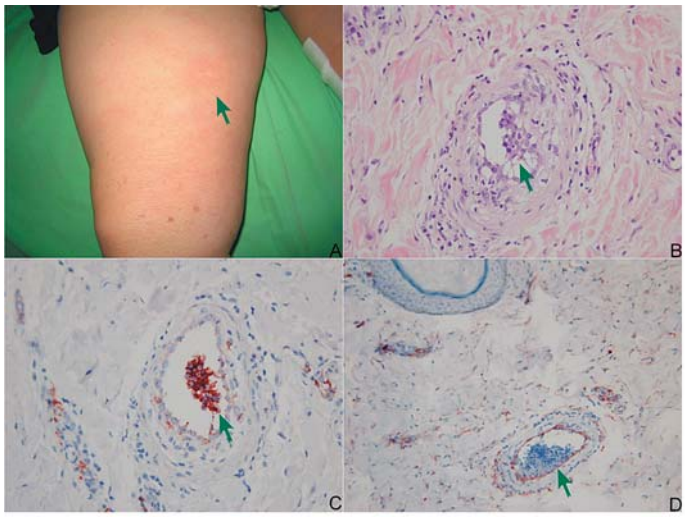

Fig. 1 (A) Closer view of the erythematous plaques and mild swelling over the thigh (arrowhead). (B) Medium-sized neoplastic cells aggregated within vessel lumens (arrowhead, H&E, ×400). (C) The neoplastic cells were positive for the expression of CD20. (arrowhead, H&E, × 400). (D). CD34 expression outlining the vascular endothelium. (arrowhead, H&E, ×400).

However, the development of immunohistochemical studies has proved that these tumors belonged to the B or T lymphoid series[11-13]. IVL predominantly affects elderly patients and more than half of all cases have B-cell symptoms[3]. Lymphoma cells had been reported to disseminate to the heart, lungs, pancreas, liver, kidneys, adrenal glands, genital tract, bone marrow and lymph nodes[14-16]. The overall prognosis of IVL is poor, but early intensive treatment of the localized lesion can improve the survival rate[4].

The neoplastic cells of IVL predominantly exist within the vessels and are not found extravascularly. The detailed mechanisms of this have not been well studied [17,18]. It has been proposed that unrecognized surface receptors on the vascular endothelium or neoplastic cells have a homing effect and maintain the intravascularization of the tumor cells[19,20]. Unlike other malignant lymphomas, IVL rarely involves the bone marrow and lymph nodes[19,21]. However, bone marrow examination is still required for differentiation from other hematological diseases[22].

The skin and brain are the organs most commonly involved in IVL and symptoms depended on tumor location. The cutaneous lesions of IVL often reveal erythematous tender plaques and telangiectasias. In our case, the patient presented with intermittent fever and dermatologic symptoms such as a moderate degree of bilateral swelling over her lower legs. Thrombophlebitis was initially diagnosed based on these skin symptoms and the patient's long-term history of diabetic mellitus. Skin biopsy was performed because of the extremely different treatments and prognoses of these two diseases.

Microscopically, neoplastic lymphoid cells of median size with vesicular nuclei were mainly located in the lumina of small vessels. The tumor cells were positive when stained for CD19, CD20, CD22, and CD79a. Endothelial markers such as Factor VIII and CD34 can outline the vascular lumens, but are absent in the neoplastic cells[2]. In this case, the confirmation of IVL depended on the presence of the CD20-expressing neoplastic cells with pleomorphic nuclei and occasional mitoses situated within the CD34-outlined vessel lumens.

We reviewed 66 cases of IVL reported in the English-language literature from 2000 to 2005 (Table 1). IVBL (90.9%) showed a predilection for elderly female subjects, with a mean age at presentation of 60 years, while IVTL (9.1%) revealed a male predominance, with a mean presentation age of 53 years. In IVBL, more than one third of cases have skin and/or brain involvement, while half of the IVTL cases revealed lung involvement. In these reported cases, less than one fifth of the IVL cases were free of visceral organ involvement. Most IVL cases in these studies were treated with chemotherapy alone, using CHOP regimens, but the prognoses were generally poor. More than half of IVL patients died of multiple organ failure within one year from the development of symptoms. Nearly one third of cases were alive more than three years with chemotherapy treatment. Of 14 IVBL cases with more than a three-year survival time, four cases had only skin lesions without visceral involvement and the other cases presented with involvement of one visceral organ. Similarly, both cases of IVTL with three-year survival only had skin lesions or involvement of one visceral organ. In general, IVL is an aggressive hematological neoplasm and regularly involves visceral organs. Although chemotherapy remains the main treatment, the prognosis of IVL is poor, and may be related to the number of visceral organ involved.

In summary, the woman in this case presented with erythema of her skin and intermittent fever, along with long-term diabetes mellitus. Various examinations revealed no remarkable changes in her bone marrow, viscera, or brain. The differential diagnosis between IVL and thrombophlebitis was difficult when based only on clinical, radiological, and laboratory examinations. In conclusion, skin biopsy is necessary to discriminate between thrombophlebitis and IVL, especially with the coexistence of vascular dysfunctional, intermittent fever, and localized skin lesions.

Table 1 Comparison of the epidemiology, clinical features, treatment and prognosis of 60 IVBL cases and six IVTL cases

	Intravascular B cell lymphoma	Intravascular T cell lymphoma
Clinical feature		
No of patients	60	6
Sex (Male/Female)	Female predominant (26/31, 3 cases unknown)	Male predominant (5/1)
Median age	60.1 years (13-82 years)	52.7 years (23-74 years)
Skin lesion	21/60 (35.0%)	1/6 (16.7%)
Brain involvement	23/60 (38.3%)	1/6 (16.7%)
Visceral involvement		
Lung	15/60 (25.0%)	3/6(50.0%)
Liver	13/60 (21.7%)	1/6 (16.7%)
Kidney	7/60 (11.7%)	2/6 (33.3%)
Spleen	11/60 (18.3%)	1/6 (16.7%)
No visceral involvement	5/60(8.3%)	1/6 (16.7%)
Bone marrow involvement	16/44 (31.8%, 16 cases unknown)	1/5 (20.0%, 1 case unknown)
Treatment		
Chemotherapy	37/48 (77.8%)	4/6 (66.7%)
Radiotherapy	0	0
Chemotherapy+radiotherapy	2/48 (4.1%)	0
Unknown	12/60	0
No treatment	9/48 (18.8%)	2/6 (33.3%)
Survival time		
More than 3 years	14/50 (28.0%)	2/6 (33.3%)
1 to 3 years	9/50 (18.0%)	0
Less than 1 year	27/50 (54.0%)	4/6 (66.7%)
Lost to follow up	10/60	0

C/T, chemotherapy; R/T, radiotherapy.

REFERENCES

1. Weichert G, Martinka M, Rivers FK. Intravascular lymphoma presenting as telangectasias: response to Rituximab and combination chemotherapy. J Cutan Med Surg 2003;7:460-463.
2. Jaffe ES, Harris NL, Stein H, Vardiman JW. WHO classification of tumors of Hematopoietic and lymphoid tissues. Lyon;IARC pressed. 2001:177.
3. Ferreri AJ, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A, Zucca E, Rossi G, Armando LG, Pavlovsky MA, Gerrts ML, Candoni A, Lestani M, Asioli S, Milani M, Piris MA, Pileri S, Facchetti F, Cavalli F, Ponzoni M. Intravascular lymphoma: clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasia on the "cutaneous variant". Br J Hematol 2004;127:173-183.
4. Pflegar L, Tappeiner. Zur kenntnis der systemisisierten endotheliomatosem der cutanen blutgefasse. Hautarzt 1959;10:359-363.
5. Bogomolski-Yahalom V, Lossos LS, Okun E, Sherman Y, Lossos A, Polliack A. Intravascular lymphomatosis- an indolent or aggressive entity. Leuk Lymphoma 1997;29:585-593.
6. Kitagawa M, Matsubara O, Song SY, Kurashima C, Okeda R, Kasuga T. Neoplastic angioendotheliosis. Immunohistochemical and electron microscopic findings in three cases. Cancer 1985;56:1134-1143.
7. Parrens M, Dubus P, Agape P, Rizcallah E, Marit G, De Mascarel A, Merlio JP. Intrasinusoidal bone marrow infiltration revealing intravascular lymphomatosis. Leuk Lymphoma 2000;37:219-223.
8. Rose C, Staumont D, Jouet JP. Successful autologous bone marrow transplantation in intravascular lymphomatosis. Br J Hematol. 1999;105:313-320.
9. DiGiuseppe JA, Nelson WG, Seifter EJ, Boitnott JK, Mann RB. Intravascular lymphomatosis: a clinicopathologic study of 10 cases and assessment of response to chemotherapy. J Clin Oncol. 1994;12:2573-2579.
10. Eros N, Karolyi Z, Kovacs A, Takacs I, Radvanyi G, Kelenyi G. Intravascular B-cell lymphoma. J Am Acad Dermatol. 2002;47:S260-262.
11. Willemze R, Kruyswijk MRJ, De Brulin CD, Meijer CJLM, van Berkel W. Angiotrophic (intravascular) large cell lymphoma of the skin previously classified as malignant angioendotheliomatosis. Br J Dermatol. 1987;116:393-399.
12. Chakravarty K, Goyal M, Scott DGI, McCann BG. Malignant "angioendotheliomatosis" –(intravascular lymphomatosis) an unusual cutaneous lymphoma in rheumatoid arthritis. Br J Rheumatol 1993;32:932-934.
13. Snowden JA, Angel CA, Winfield DA, Pringle JH, West KP. Angiotropic lymphoma: report of a case with histiocytic features. J Clin Pathol 1997; 50:67-70.
14. Beal MF, Fisher CM. Neoplastic angioendotheliomatosis. J Neurol Sci 1982;53:359-375.
15. Carrol TJ, Schelper RL, Goeken JA, Kemp JD. Neoplastic angioendotheliomatosis: immunopathologica and morphologic evidence for intravascular malignant lymphomatosis. Am J Clin Pathol 1986;85:169-175.
16. Daniel SE, Rudge P, Scaravilli F. Malignant angioendotheliomatosis involving the nervous system: support for a lymphoid origin of the neoplastic cells. J Neurol Neurosurg Psychiatry 1987;50:1173-1177.
17. Lukes RJ, Collins RD. Tumors of the hematopoietic system. Washington, DC: Armed Forces Institute of Pathology, 1992:220.
18. Warnke R, Weiss L, Chan J, Cleary M, Dorfman R. Tumors of the lymph node and spleen. Washiington, DC: Armed Forces Institute of Pathology, 1994:184-187.

19. Demirer T, Dail DH, Aboulafa DM. Four varied cases of intravascular lymphomatosis and a literature review. Cancer 1994;73:1738-1745.
20. Jalkanen S, Aho R, Kallajoki M, Ekfors T, Nortamo P, Gahmberg C, Duijvestijn A, Kalimo H. Lymphocytes homing receptors and adhesion molecules in intravascular malignant lymphomatosis. Int J Cancer 1989;44: 777-782.
21. Chapin JE, Davis LE, Kornfeld M, Mandler RN. Neurologic manifestations of intravascular lymphomatosis. Acta Neurol Scand 1995;91:494-499.
22. Tucker TJ, Bardales RH, Miranda RN. Intravascular lymphomatosis with bone marrow involvementL a case report and review of the literature. Arch Pathol Lab Med 1999;123:952-956.