

Hodgkin's lymphoma associated with myelofibrosis: A case report

RONG FU, HONG YU, YU-HONG WU, HUI LIU and ZONG-HONG SHAO

Department of Hematology, Tianjin Medical University General Hospital, Tianjin 300052, P.R. China

Received August 27, 2014; Accepted May 20, 2015

DOI: 10.3892/ol.2015.3438

Abstract. In the present study, the case of a patient with nodular sclerosing Hodgkin's lymphoma (NSHL) presenting with diffuse fibrosis of the bone marrow (BM) was reported. A 30-year-old male complained of fever for 1 year, as well as lumbago, lymph node swelling and night sweats for 3 months. A biopsy of the lymph nodes established a diagnosis of NSHL. Aspiration of BM was a dry tap, and the BM biopsy demonstrated marked myelofibrosis with increased proliferation of reticulin fiber. Multiple skeletal lesions were detected in the patient's vertebra, pelvis, sternum and bilateral femur by magnetic resonance imaging and computed tomography. Following numerous courses of chemotherapy and radiotherapy, remission of the lymphoma was achieved. Subsequently, the BM aspiration became possible, and BM biopsy demonstrated a reduction in fibrosis.

Introduction

Hodgkin's lymphoma (HL) accounts for ~30% of all lymphomas, presenting with generalized lymphadenopathy, hematological abnormalities and B symptoms (including fever, weight loss and night sweats) (1). Due to the development of highly active chemotherapy and radiotherapy strategies, patients with HL have an excellent prognosis following front-line therapy, and the 5-year progression-free survival rate can be as high as 75-80% (2). Myelofibrosis is a chronic myeloproliferative neoplasm characterized by clonal proliferation of myeloid hematopoietic cells and intramedullary fibrosis (3). Clinical manifestations of myelofibrosis include cytopenias, profound splenomegaly, bone pain, night sweats, weight loss, and fatigue (4). Secondary MF (SMF) is often observed in a number of hematological malignancies, including acute megakaryoblastic leukemia (5), chronic myeloid leukemia (6) and hairy cell leukemia (7); however, SMF is rare in lymphoid neoplasms. The present study reported a case of reversible

MF associated with Hodgkin's lymphoma (HL), which was resolved following remission of lymphoma. Subsequent to a thorough review of the literature using the PubMed database (<http://www.ncbi.nlm.nih.gov/pubmed>), 7 reported cases of SMF accompanied by HL were identified (Table I); however, no HL cases with SMF have been previously reported in China. Previously reported lymphomas associated with MF were of various histological types, including T-cell lymphoma (8-12), B-cell lymphoma (13) and HL (14-17).

Case report

A 30-year-old male presented to the Tianjin Medical University General Hospital (Tianjin, China) on October 10, 2012 with fever that had persisted for 1 year, night sweats and lumbago that had persisted for 3 months, and weight loss of 25 kg within 1 year. At the time of admission, the patient exhibited a high temperature of 40.2°C, a mild degree of pallor and palpable surface lymph nodes. Marked cervical, supraclavicular, axillary and inguinal lymphadenopathy had developed, with rubbery lymph nodes reaching 2-3 cm in size. The patient presented mild hepatomegaly and tender pain in the section of the lumbar vertebrae; however, no splenomegaly, adenopathy or skin eruptions were observed. A complete blood cell count revealed a normal white blood cell count (10.2×10^9 cells/l; normal, $4-10 \times 10^9$ /l), 88% neutrophilic granulocytes and 10% lymphocytes, normocytic normochromic anemia (hemoglobin level, 81 g/l; normal, 120-160 g/l) and an increased platelet count (410×10^9 /l; normal, $100-300 \times 10^9$ /l). No teardrop-shaped red blood cells or erythroblasts were detected in the peripheral blood. The prothrombin time and activated partial thromboplastin time were found to be 12.1 sec and 37.1 sec (normal, 20-40 sec), respectively, while the fibrinogen level was 511 mg/dl (normal, 1.8-40 mg/dl) and the D-dimer level was 497 μ g/l (normal, 0-500 μ g/l). Blood chemistry studies demonstrated elevated levels of lactate dehydrogenase (253 U/l; normal, 94-250 U/l) and β_2 -microglobulin (1.41 mg/l; normal, 0.1-0.3 mg/l). The serum albumin level was 30 g/l (normal, 35-55 g/l), and the hepatic and renal functions were normal. Direct and indirect Coombs tests were negative, while hypergammaglobulinemia and monoclonal gammopathy were not detected and blood sample cultures failed to reveal any pathogens. The patient was serologically negative for Epstein-Barr virus, hepatitis virus, cytomegalovirus, parvovirus B19, toxoplasmosis, coccidiomycosis, brucellosis and human immunodeficiency virus. In addition, the erythrocyte sedimentation rate was 64 mm/h (normal, 0-15 mm/h), while

Correspondence to: Miss Rong Fu or Mr. Zong-Hong Shao, Department of Haematology, Tianjin Medical University General Hospital, 154 Anshan Street, Heping, Tianjin 300052, P.R. China
E-mail: florai@sina.com
E-mail: shaozonghong@sina.com

Key words: Hodgkin's lymphoma, myelofibrosis

Table I. Hematological and clinical features of patients with HL with myelofibrosis.

Case (Ref.)	Age/sex	WBC (x10 ⁹ /l)	Hb (g/l)	Platelet (x10 ⁹ /l)	Lymph node	Liver	Spleen	Bone marrow/invasion	Histologic type	Treatment	Survival time
1 (7)	12/F	2.3	115	41	Yes	No	No	Fibrosis/Yes	LPHL	MOPP	3 months
2 (7)	50/M	11.1	141	630	Yes	No	Yes	Fibrosis/No	NSHL	BOPP	10 years
3 (7)	31/F	1.8	46	100	Yes	Yes	Yes	Fibrosis/Yes	MCHL	COPP	20 months
4 (7)	20/F	2.15	77	100	No	No	No	Fibrosis/No	LPHL	MOPP	9 years
5 (8)	37/M	2.5	41	50	Yes	Yes	Yes	Fibrosis/No	NSHL	MOPP/BCVPP	11 years
6 (9)	31/M	6.0	118	250	Yes	Yes	Yes	Fibrosis/Yes	NSHL	BCVPP	4 years
7 (10)	35/M	0.8	88	122	Yes	Yes	Yes	Fibrosis/Yes	LDHL	MOPP/ABVD/HDAC	2 years

HL, Hodgkin's lymphoma; WBC, white blood cell count; Hb, hemoglobin; F, female; M, male; LPHL, lymphocyte-predominant HL; NSHL, nodular sclerosis HL; MCHL, mixed cellularity HL; LDHL, lymphocyte-depleted HL; MOPP, mechlorethamine, vincristine, procarbazine and prednisone; BOPP, carmustine, oncovin, procarbazine and prednisone; COPP, cyclophosphamide, oncovin, procarbazine and prednisone; BCVPP, carmustine, cyclophosphamide, vinblastine, bleomycin, procarbazine, prednisone; ABVD, adriamycin, bleomycin, procarbazine, prednisone; HDAC, high-dose cytosine arabinoside.

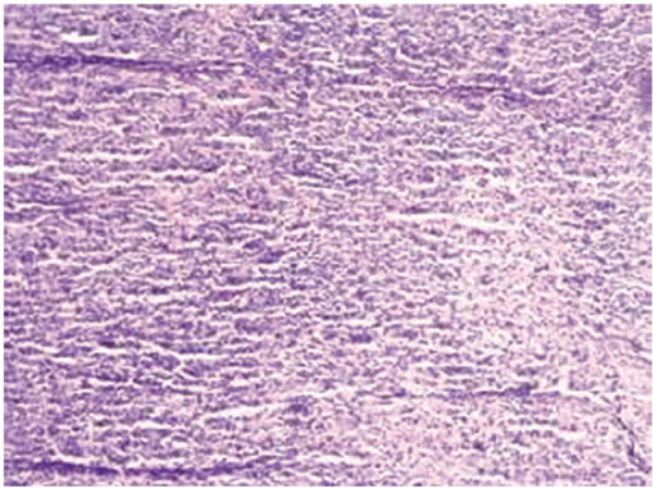


Figure 1. Microscopic view of the lymph node biopsy specimen, diagnosed with nodular sclerosing Hodgkin's lymphoma (magnification, x40; stain, hematoxylin and eosin).

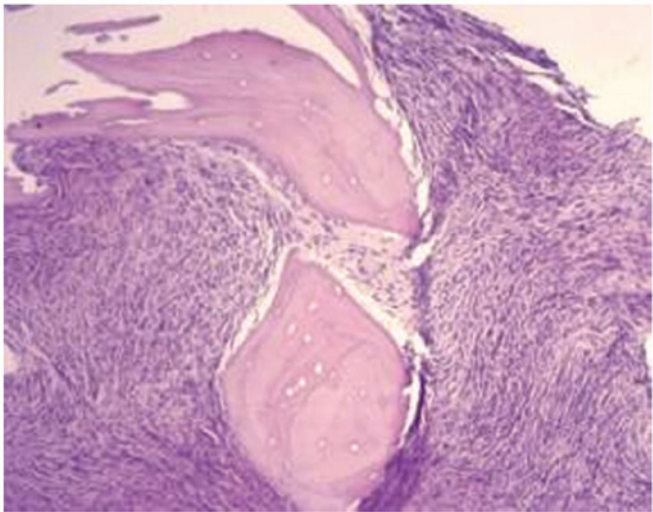


Figure 2. Microscopic view of the bone marrow biopsy specimen, diagnosed with myelofibrosis. Increased proliferation of fibroblasts and reticulin fiber is observed (magnification, x40; stain, hematoxylin and eosin).

immune screening, including autoantibody and complement, was negative. Finally, the CD4/CD8 ratio (1.01%; normal, 0.8-2.5%) was within the normal range.

A systemic computed tomography (CT) scan demonstrated multiple swellings of the bilateral cervical, supraclavicular, mediastinal, axillary, para-aortic, inguinal and mesenteric lymph nodes, an enlarged liver and no splenomegaly. A cranium CT scan demonstrated no lesions. A single-photon emission computed tomography bone scan revealed numerous areas of increased tracer uptake, indicating skeleton invasion. Fluorodeoxyglucose positron emission tomography was not performed at this time.

Biopsy of the cervical lymph node demonstrated disappearance of the normal architecture and neoplastic cells. Immunohistochemical staining demonstrated that the cells were positive for CD30, as well as for CD20 and CD3 in scattered cells, and negative for CD15. These findings were

compatible with a diagnosis of NSHL (Fig. 1). Bone marrow (BM) aspirations of the sternum and iliac bone were dry taps, and biopsy of the BM from the iliac bone demonstrated diffuse MF, showing proliferation of fibroblasts and reticulin fiber, without an increase in megakaryocytes and without lymphomatous infiltration (Fig. 2).

Based on the aforementioned findings, the patient was diagnosed with an NSHL variant with MF. The lymphoma was classified as clinical stage IV (18). Subsequently, the patient underwent 4 courses of chemotherapy with ABVD (doxorubicin, 120 mg, days 1 and 15; bleomycin, 15 mg, days 1 and 15; vinblastine, 3 mg, days 1 and 15; and dacarbazine, 600 mg, days 1 and 15) achieving a partial response. The patient showed resolution of B symptoms with anemia improvement, and reduction in the size of the lymph nodes and liver. Aspiration of BM became possible and a BM biopsy demonstrated a hypocellular marrow without evidence of lymphoma and a reduction in fibrosis. Flow cytometric analyses of BM lymphocytes revealed that they were positive for CD7, CD3, CD5 and CD38, and negative for CD20, CD22, CD23, CD10, CD9, ZAP70 and CD79a. In addition, chromosome analysis of BM cells demonstrated a normal karyotype (46XY). A JAK2 mutation, V617F, was detected and immunoglobulin gene rearrangement was negative. However, small lymph nodes (1-2 cm in diameter) remained in the neck and supraclavicular after 4 courses of chemotherapy. Therefore, the patient was treated with 2 courses of BEACOPP (bleomycin, 15 mg, day 8; etoposide, 200 mg, days 1-3; doxorubicin, 80 mg, day 1; cyclophosphamide, 1,200 mg, day 1; vincristine, 4 mg, day 8; procarbazine, 700 mg, days 1 and 15; and prednisone, 80 mg, days 1-14) combined with local radiotherapy (2 Gy, days 1-20). Residual lesions were not observed on CT scans, and a BM biopsy demonstrated recovery of hematopoiesis and a disappearance of fibrosis. The patient was followed-up until relapse occurred after 2 years, and he was subsequently subjected to stem cell transplantation. Written informed consent was obtained from the patient prior to publication of this study.

Discussion

Primary or idiopathic MF is a myeloproliferative disorder characterized by myeloid metaplasia, evident splenomegaly, pancytopenia and a leukoerythroblastic peripheral blood smear. SMF occurs in a variety of systemic diseases, including tuberculosis, metastatic carcinoma, osteopetrosis and toxic marrow injury following irradiation or chemical exposure (19,20). SMF is also observed in a variety of hematological malignancies, including acute megakaryoblastic leukemia, chronic myeloid leukemia and hairy cell leukemia. However, SMF is uncommon in malignant lymphoma and reported cases of MF associated with HL are extremely rare.

In the present study, at the time of NSHL diagnosis, the patient's BM aspiration was a dry tap. A BM biopsy specimen demonstrated MF representing the proliferation of fibroblasts and reticulin fiber. No apparent increase in megakaryocytes was observed. Infiltration by lymphoma cells was not confirmed in the BM biopsy specimen or in the BM aspiration smear, when it became available. The fibrosis was reversible following successful chemotherapy for HL.

To the best of our knowledge, only 7 previous reports of MF associated with HL exist (Table I) (8-11). The patient ages were variable (median, 31 years; range, 12-50 years) and no significant difference in incidence based on gender was identified (male, 4; female, 3). The patients, with the exception of 1 case, exhibited pancytopenia without BM invasion by the lymphoma cells; in addition, 5 patients experienced bicytopenia and 3 patients had BM invasion by lymphoma cells. Furthermore, 6 of the 7 patients presented lymph node swelling, 5 demonstrated splenomegaly and 4 had hepatomegaly. The histological type of HL was reported to be of the nodular sclerosis subtype in 3 cases, lymphocyte-depleted in 2 cases, and of mixed cellularity or lymphocyte-predominant in one case each. All the patients were treated with chemotherapy, but survival times differed widely. Patients without marrow involvement presented a relatively good prognosis (survival, 9-11 years). However, marrow involvement was common, and those patients had an extremely poor prognosis (survival, 3 months to 4 years).

No specific association is known between MF and lymphoma, despite a few reported cases of MF complicated by concomitant or subsequent lymphoma (21). However, lymphoma is a recognized cause of MF, although it is uncommon. Gisselbrecht *et al* (22) reported that there were no patients with MF in a series of 1,883 patients with diffuse aggressive NHL. In addition, the pathogenesis of the fibrotic change in the BM of HL patients is unknown. Fibroblasts have been reported to be stimulated by certain cytokines, such as transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) (23). These cytokines are known to play an important role in the development of stromal proliferation. PDGF induces the proliferation of fibroblasts, while TGF- β induces the synthesis and accumulation of extracellular matrix proteins, including fibronectin and type I and III collagens (24). Megakaryocytes and monocytes have been reported to be sources of these cytokines. In cases of lymphoma with SMF, PDGF is expressed in monocytes (25). T cells are not known to secrete PDGF, which causes MF in myeloproliferative diseases; however, T cells secrete TGF, which can cause fibrosis. Plasma TGF- β levels were found to be elevated in cases of MF associated with peripheral T-cell (8), cytotoxic T-cell (12) and splenic marginal zone lymphomas (13). In addition, there is evidence that the nodular sclerosis of certain cases of Hodgkin's disease is due to the increased TGF levels (26,27).

In the present case, the patient developed MF and lymphoma simultaneously, and these regressed completely following chemotherapy. In conclusion, the disease status of MF was similar with that of HL, suggesting that HL plays an important role in the pathogenesis of MF. Certain cytokines are hypothesized to stimulate the growth of fibroblasts and synthesis of collagen in BM fibroblasts. Further studies and additional case reports will be required to clarify the pathogenesis of SMF and improve our understanding of the immunological dysregulation associated with lymphoma.

Acknowledgements

This study was supported by a grant from the Tianjin Cancer major special project (no. 12ZCDZSY18000).

References

1. Younes A: Novel treatment strategies for patients with relapsed classical Hodgkin lymphoma. *Hematology* 2009: 507-519, 2009.
2. Eichenauer DA, Böll B and Diehl V: Pharmacotherapy of Hodgkin lymphoma: standard approaches and future perspectives. *Expert Opin Pharmacother* 15: 1139-1151, 2014.
3. Tefferi A: Pathogenesis of myelofibrosis with myeloid metaplasia. *J Clin Oncol* 23: 8520-8530, 2005.
4. Tefferi A: Primary myelofibrosis: 2014 update on diagnosis, risk-stratification, and management. *Am J Hematol* 89: 915-925, 2014.
5. Niino D, Tsuchiya T, Tomonaga M, Miyazaki Y and Ohshima K: Clinicopathological features of acute megakaryoblastic leukaemia: Relationship between fibrosis and platelet-derived growth factor. *Pathol Int* 63: 141-149, 2013.
6. Aljinovic N, Bogusz AM, Kantarci S, Buck TP and Dewar R: An unusual case of Philadelphia chromosome-positive chronic myelogenous leukemia with trisomy 19 presenting with megakaryoblastosis and myelofibrosis. *Arch Pathol Lab Med* 137: 1147-1151, 2013.
7. Araki H, Matsunaga T, Murase K, Kuroda H, Kuribayashi K, Terui T and Niitsu Y: Successful induction and complete improvement of myelofibrosis and erythema nosodum with cladribine in a case of hairy cell leukemia. *Gan To Kagaku Ryoho* 31: 965-969, 2004 (In Japanese).
8. Okabe S, Miyazawa K, Lguchi T, Sumi M, Takaku T, Ito Y, Kimura Y, Serizawa H, Mukai K and Ohyashiki K: Peripheral T-cell lymphoma together with myelofibrosis with elevated plasma transforming growth factor- β 1. *Leuk Lymphoma* 46: 599-602, 2005.
9. Kikukawa M, Umahara T, Kikawada M, Kanaya K, Sakurai H, Shin K, Mori M and Iwamoto T: Peripheral T-cell lymphoma presenting as myelofibrosis with the expression of basic fibroblast growth factor. *Geriatr Gerontol Int* 9: 395-398, 2009.
10. Matsui K, Adachi M, Tominaga T, Shinohara S and Kamei T: Angioimmunoblastic T cell lymphoma associated with reversible myelofibrosis. *Int Med* 47: 1921-1924, 2008.
11. Rao SA, Gottesman SR, Nguyen MC and Braverman AS: T cell lymphoma associated with myelofibrosis. *Leuk Lymphoma* 44: 715-718, 2003.
12. Abe Y, Ohshima K, Shiratsuchi M, Honda K, Nishimura J, Nawata H and Muta K: Cytotoxic T-cell lymphoma presenting as secondary myelofibrosis with high levels of PDGF and TGF- β . *Eur J Haematol* 66: 210-212, 2001.
13. Matsunaga T, Takemoto N, Miyajima N, Okuda T, Nagashima H, Sato T, Terui T, Sasaki H, Ohmi N, *et al*: Splenic marginal zone lymphoma presenting as myelofibrosis associated with bone marrow involvement of lymphoma cells which secrete a large amount of TGF- β . *Ann Hematol* 83: 322-325, 2004.
14. Meadows LM, Rosse WR, Moore JO, Crawford J, Laszlo J and Kaufman RE: Hodgkin's disease presenting as myelofibrosis. *Cancer* 64: 1720-1726, 1989.
15. Carroll WL, Berberich FR and Glader BE: Pancytopenia with myelofibrosis. An unusual presentation of childhood Hodgkin's disease. *Clin Pediatr (Phila)* 25: 106-108, 1986.
16. Vukelja SJ, Krishnan J, Ward FT and Redmond J III: Synchronous Hodgkin's disease and myelofibrosis terminating with granulocytic sarcoma and acute megakaryocytic leukemia. *South Med J* 83: 1317-1320, 1990.
17. Viola MV, Kovi J and Nukhopadhyay M: Reversal of myelofibrosis in Hodgkin disease. *JAMA* 223: 1145-1146, 1973.
18. Izumi T and Ozawa K: Clinical staging classification of non-Hodgkin's lymphoma. *Nihon Rinsho* 58: 598-601, 2000 (In Japanese).
19. Viallard JF, Parrens M, Boiron JM, Texier J, Mercie P and Pellegrin JL: Reversible myelofibrosis induced by tuberculosis. *Clin Infect Dis* 34: 1641-1643, 2002.
20. Atasever T, Vural G, Yenidunya S, Ataoğlu O, Atavci S and Unlü M: Tc-99m MIBI bone marrow uptake in bone marrow fibrosis secondary to metastatic breast carcinoma. *Clin Nucl Med* 22: 655-656, 1997.
21. Gabali AM, Jazaerly T, Chang CC, Cleveland R and Kass L: Simultaneous hepatosplenic T-cell lymphoma and myelofibrosis. *Avicenna J Med* 4: 34-36, 2014.
22. Gisselbrecht C, Gaulard P, Lepage E, Coiffier B, Brière J, Haioun C, Cazals-Hatem D, Bosly A, Xerri L, Tilly H, *et al*: Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). *Blood* 92: 76-82, 1998.
23. Tefferi A: Myelofibrosis with myeloid metaplasia. *N Engl J Med* 342: 1255-1265, 2000.
24. Charni Chaabane S, Coomans de Brachène A, Essaghir A, Velghe A, Lo Re S, Stockis J, Lucas S, Khachigian LM, Huaux F and Demoulin JB: PDGF-D expression is down-regulated by TGF β in fibroblasts. *PLoS One* 9: e108656, 2014.
25. Wang JC, Chang TH, Goldberg A, Novetsky AD, Lichter S and Lipton J: Quantitative analysis of growth factor production in the mechanism of fibrosis in agnogenic myeloid metaplasia. *Exp Hematol* 34: 1617-1623, 2006.
26. Kadin ME, Agnarsson BA, Ellingsworth LR and Newcom SR: Immunohistochemical evidence of a role for transforming growth factor beta in the pathogenesis of nodular sclerosing Hodgkin's disease. *Am J Pathol* 136: 1209-1214, 1990.
27. Newcom SR and Tagra KK: High molecular weight transforming growth factor beta is excreted in the urine in active nodular sclerosing Hodgkin's disease. *Cancer Res* 52: 6768-6773, 1992.