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CASE REPORT

Follicular Lymphoma with Prominent Sclerosis ("Sclerosing Variant of Follicular Lymphoma") Exhibiting a Mesenteric Bulky Mass Resembling Inflammatory Pseudotumor. Report of Three Cases

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We present three cases of follicular lymphoma (FL) exhibiting prominent sclerosis (sclerosing variant of follicular lymphoma), resembling inflammatory pseudotumor (IPT) of the lymph node, arising from mesenteric lymph node. Clinically all three cases represented bulky masses of the mesenteric lymph node. Histologically, the lesions were characterized by neoplastic lymphoid follicles separated by stromal collagenization and sclerotic process, with cellular infiltrate extending into the adjacent adipose tissue. The lesions contained variable cellular spindle cell proliferation and inflammatory infiltrate including numerous reactive T cells and histiocytes. Small capillary proliferation with vascular change was also noted. Immunohistochemical study demonstrated the myofibroblastic nature of the spindle cells. Moreover, neoplastic follicles were composed of intermediate to medium-sized lymphocytes, somewhat resembling reactive lymphoid aggregates. The overall histomorphological findings of the three lesions were similar to those of IPT of the lymph node. However, CD10, Bcl-2 and Bcl-6 immunostaining demonstrated the neoplastic nature of the lymphoid follicles and the lesions were diagnosed as FL grade 1. The present three cases indicate that the sclerosing variant of grade 1 FL should be added to the differential diagnosis from IPT of the lymph node. (Pathology Oncology Research Vol 13, No 1, 74–77)

Key words: follicular lymphoma, sclerosis, mesenterium, inflammatory pseudotumor, immunohistochemistry

Introduction

Inflammatory pseudotumor (IPT) is a term that has been used to describe an inflammatory/fibrosing tumoral process which may involve a variety of organ systems, including lung, spleen, liver, skin and soft tissues.[1,2] Morphologically, the lesions may mimic a neoplasm, but their clinical behavior has been that of a benign self-limited condition.[1,2] In 1988, IPT of the lymph node was first described by Perrone et al in seven patients who presented with lymphadenopathy and symptoms suggestive of lymphoid malignancy, such as fever, fatigue and night sweats.[3] Histologically, IPT of the lymph node is characterized by marked inflammatory response admixed with a prominent myofibroblastic proliferation leading to subtotal effacement of the nodal architecture, often with extension of the disease process beyond the capsule into perinodal fat.[3-7] In the late stage of disease, the process is characterized by almost complete replacement of the lymph node by diffuse sclerosis with scant inflammatory elements and residual lymphoid tissue, and a total loss of the lymph node architecture.[6,7]

Some degree of sclerosis is common in follicular lymphoma (FL), particularly in those involving in retroperitoneum and groin. When sclerosis is prominent, the term

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Table 1. **Summary of clinical findings**

	Age/ gender	*Clinical presentation*	*Site of lymphoma*	*Tumor size (cm)*	*Therapy and outcome*
1	45/M	fever, diarrhea	mesenteric lymph node	>10	tumor biopsy, CHOP, 12 months alive, well
2	69/F	abdominal pain	mesenteric lymph node, small intestine	>10	tumor biopsy, THP-COP, under treatment
3	76/F	abdominal discomfort	mesenteric lymph node	7.5	tumor resection, THP-COP, 2 months alive, well

M, male; F, female; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; THP+COP, pirarubicin, cyclophosphamide, vincristine, prednisone

"sclerosing variant of FL" has previously been applied.[8-11] We report here three cases of "sclerosing variant of FL" exhibiting a large mesenteric mass that resembled histological findings of IPT of the lymph node.

Materials and Methods

Three cases were collected from a series treated by one of the authors (M.K.) between 2002 and 2005. Medical records of the cases were extensively reviewed.

The tissue specimens were fixed in formalin solution, routinely processed and embedded in paraffin. For light microscopic examination, the sections were stained with hematoxylin-eosin (HE).

Immunohistochemistry was performed on paraffin sections using a Ventana automated (BenchMark^{T}M) stainer according to the manufacturer's directions. A panel of antibodies were used against human immunoglobulin light chain (kappa and lambda) (Novocastra, Newcastle, UK), CD3 (PS-1; MBL Co. Nagoya, Japan), CD5 (4C7; Novocastra), CD10 (56C6; Novocastra), CD20 (L26; Dako, Glostrup, Denmark), CD23 (1B12; Novocastra), CD68 (PG-M1; Dako), cyclin D1 (5D4, MBL Co.), Bcl-2 (1242, Dako), Bcl-6 (polyclonal; Dako), anti-follicular dendritic cell (FDC) antibody (CNA.42; Dako), vimentin (V9; Nichirei Co., Tokyo, Japan), muscle-specific actin (HHF-35; Nichirei Co.) and human herpes virus type-8 (HHV-8) (137B1; Novocastra). Replacement of the primary antibodies by normal rabbit or mouse serum was used as negative control.

In situ hybridization (ISH) with Epstein-Barr virus (EBV)-encoded small RNA (EBER) oligonucleotides was performed to test the presence of EBV small RNA in formalin-fixed paraffin-embedded sections, also using a Ventana automated (BenchMark^{TM}) stainer.

Results

Clinical findings

The main clinical findings are shown in the *Table 1*. All three patients exhibited bulky mass of the mesenteric lymph node.

Histological findings

There were essentially similar histopathological findings in all three cases. Under low-power magnification, the normal lymph node structure was completely effaced, and lymphoid aggregates exhibiting variable shapes and sizes were separated by stromal collagenization, variable cellular spindle cell proliferation and an inflammatory cell infiltrate (*Fig. 1*). A portion of the lymphoid aggregates contained small blood vessels in all cases[12] (*Fig. 2*). The cellular infiltrate and sclerotic process extended into the adjacent adipose tissue.

With higher magnification, the lymphoid aggregates consisted of mainly intermediate to medium-sized cells (centrocytes) with a few large lymphoid cells (centroblasts) (*Fig. 3a*). Few mitoses and benign macrophages were detected. Immunohistochemical study demonstrated that the tumor cells were CD10+ (*Fig. 3b*), Bcl-6+/-, CD20+, CD5-, CD23- Bcl-2+ (*Fig. 3c*) and cyclin D1-. Well-preserved follicular dendritic cell networks were easily detected with anti-CD23 or CAN.42 in all of the patients. Numerous CD5+ T cells were admixed with tumor cells (*Fig. 4*). Based on the WHO classification,[8] the three cases were diagnosed as FL grade 1.

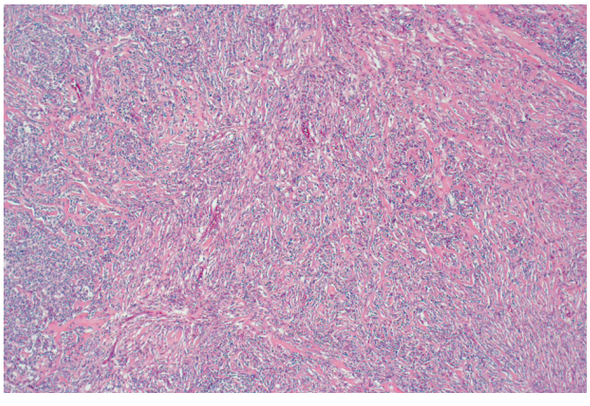

Figure 1. *Lymphoid aggregates separated by stromal collagenization, variable cellular spindle cell proliferation and an inflammatory cell infiltrate. Numerous small capillaries are also seen (case 3, HE x10).*

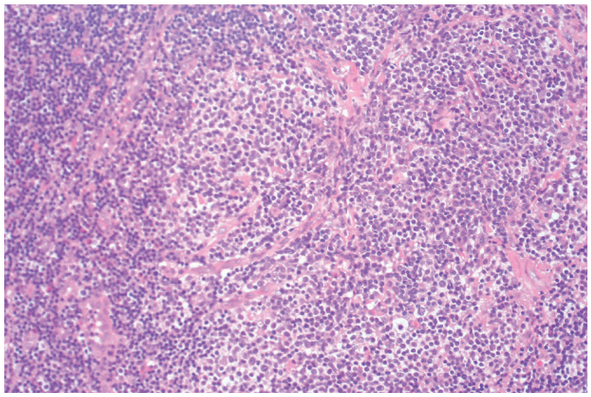

Figure 2. *A portion of the lymphoid aggregates contained small blood vessels (case 1, HE x50).*

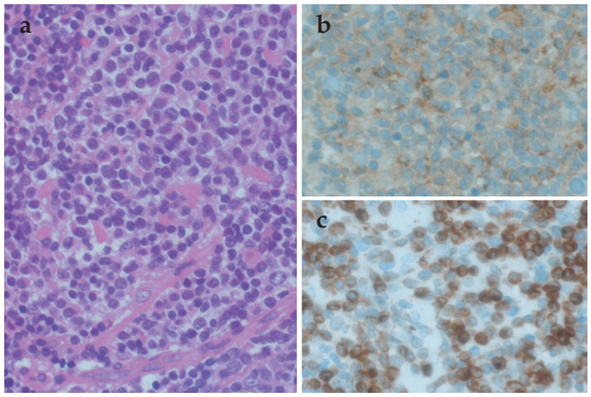

Figure 3. (a) *Lymphoid follicles were mainly composed of intermediate to medium-sized lymphocytes with indented nuclei (HE x100). These lymphocytes were* ***(b)*** *CD10+ and* ***(c)*** *Bcl-2+ (case 1, x100).*

The spindle cells had relatively long attenuated cytoplasmic processes and round to oval nuclei without prominent nucleoli (*Fig. 5a*). There was a variable degree of vascular proliferation, usually small capillary-type vessels, and vascular changes with fibrous obliteration were also observed.

The spindle cells were stained strongly for vimentin, but desmin was not apparent. Some cells also expressed muscle-specific actin (*Fig. 5b*). CD68 staining demonstrated a population of histiocytes and also highlighted some of the spindle cells.

There were no HHV-8- or EBER-positive cells found.

Discussion

In FL exhibiting prominent sclerosis (sclerosing variant of FL), sclerosis can take the form of broad collagenous bands subdividing the lymphoma into irregular nodules and extending into the perinodal soft tissue, or fine compartmentalization around clusters of lymphoma cells.[8,10,11] In these three cases, neoplastic lymphoid follicles were separated by stromal collagenization and sclerotic process, and the cellular infiltrate extended into the adjacent adipose tissue. However, the lesions contained variable cellular spindle cell proliferation and inflammatory infiltrate including numerous reactive T cells and histiocytes. Immunohistochemical study demonstrated the myofibroblastic nature of the spindle cells. Small capillary proliferation with vascular change was also noted. Moreover, neoplastic follicles were composed of intermediate to medium-sized lymphocytes, somewhat resembling reactive lymphoid aggregates.

The overall histological findings also appear to resemble the late stage of the IPT of lymph node, which is characterized by complete replacement of the lymph node by diffuse sclerosis with scant inflammatory element and residual lymphoid tissue, and a total loss of the lymph node architecture.[3-7] However, CD10, Bcl-2 and Bcl-6 immunostaining demonstrated the neoplastic nature of the lymphoid follicles.

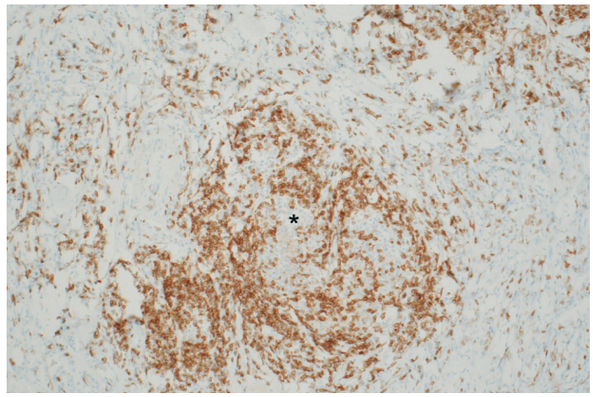

Figure 4. *Numerous T cells infiltrating the lesion. Note two neoplastic follicles (asterisks) (case 3, CD5 x25).*

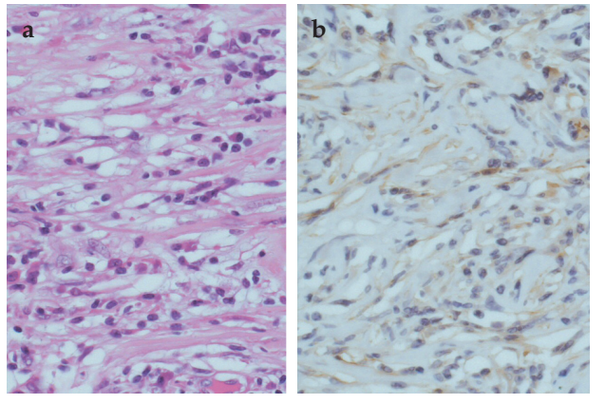

Figure 5 (a) *The lesion contained spindle cells, lymphocytes and histiocytes (case 3, HE x100).* ***(b)*** *Numerous spindle cells showing muscle-specific actin positivity (case 3, x100)*

Interestingly, a portion of lymphoid follicles were penetrated by hyalinized small vessels in all three cases. The histological findings are similar to those of hyaline vascular follicles of Castleman's disease of hyaline-vascular type. The unusual morphological variant of FL mimicking Castleman's disease of the hyaline-vascular type is very rare.[8-13] This type of neoplastic follicles may be frequently observed in the "sclerosing variant of FL". However, further study is needed to clarify this issue.

McCurley et al[14] reported that extracellular fibrotic material is composed predominantly of fibronectin, in addition to type I, III, and IV collagen, probably produced by fibroblasts and myofibroblasts. Our immunohistochemical study demonstrated the myofibroblastic nature of the spindle cells in the lesions, confirming their observation.

In the lymph node, the differential diagnosis of IPT including histiocytic necrotizing lymphadenitis, Castleman's disease, Hodgkin's disease, peripheral T-cell lymphoma of angioimmunoblastic type and various mesenchymal tumors have been well described.[3-7] Clinically, both "sclerosing variant of FL" and IPT of the lymph node occasionally exhibited a bulky mass.[3-7,10,11] IPT of the lymph node may also affect intraabdominal lymph nodes.[3-6] The present three cases indicate that the sclerosing variant of FL, particularly of grade 1, should be added to the differential diagnosis of IPT of the lymph node.

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