Malignant Lymphoma of the Uterus

Report of Seven Cases with Immunohistochemical Study

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Background. **Uterine lymphoma is a rare disease; therefore, information regarding histologic type, immunophenotype of tumor cells, and etiologic factors are limited.**

Methods. **Seven patients with uterine lymphoma, three from the corpus and four from the cervix, were collected by a nationwide study in Japan. Selection of cases was preferentially made from the "Annual of Pathologic Autopsy Cases in Japan."**

Results. **All cases with cervical lymphoma presented with vaginal bleeding. Abdominal pain or backache was observed in patients with corpus lymphoma. The age ranges of patients with corpus and cervical lymphomas were 46–78 years of age (mean, 63 years) and 30–71 years of age (mean, 53 years), respectively. Information about clinical staging was available for six patients; two patients with Stage I, three patients with Stage II, and one patient with Stage III. A definite diagnosis of uterine lymphoma was made by biopsy in all cases. Total hysterectomy, with or without bilateral salpingo-oophorectomy, was carried out in three patients, and tumor resection was carried out in one patient. Adjuvant therapy was given in six cases. Follow-up showed that five patients died due to tumor within 1 year of treatment. Histologically, all cases were non-Hodgkin lymphoma showing a diffuse pattern of proliferation. All but one were diffuse large cell type. Immunohistochemistry revealed the tumor cells in all cases were of B-cell nature. Expression of HLA-DR antigen was evaluable in four cases, of these three showed an increased expression on the vascular endothelium.**

Conclusions. **Uterine lymphoma comprises exclusively B-cell type. *Cancer* 1993; 72:1959–64.**

Key words: malignant lymphoma, uterus, immunohistochemistry, B-lymphocytes, HLA-DR.

Malignant lymphoma of the female genital tract is a rare disease. Its frequency in Western countries was reported to be 0.008% among primary cervical tumors[1] and 2% among extranodal lymphomas in women[2] The frequency (1.6%) among Japanese female patients with extranodal lymphoma was close to that in North America. Because of the differences in clinical and pathologic findings between cases with uterine and ovarian lymphomas, they have been reported separately. Among the uterine lymphomas, the cervix and vagina were more prevalent sites than the corpus (85% of Japanese[4] and 78% of North American cases[6]). The rarity of uterine lymphoma made a study of a large series of cases difficult,[6,11] and single or a few cases with uterine lymphoma have been reported sporadically.[7–10,12–15] Therefore, information on uterine lymphoma including its histologic type, immunophenotype of tumor cells, and etiologic factors are relatively limited.

An etiologically important role of chronic inflammation of the autoimmune or nonautoimmune nature for development of extranodal B-cell lymphoma, such as thyroid, salivary, gastrointestinal, and pleural lymphoma, has been suggested.[16–17] Recently, the presence of lymphocytic mastopathy in patients with breast lymphoma was confirmed by histologic findings together with immunohistochemical corroboration showing positive reactivity of duct epithelium for anti-HLA-DR antibody.

In this article, the histologic and immunohistologic

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findings such as immunophenotype of uterine lymphoma cells and reactivity for HLA-DR were described in seven cases collected by nationwide study in Japan.

Patients and Methods

Malignant lymphomas of the uterus were collected from a histologic review of 1766 cases with malignant lymphoma and related diseases diagnosed at Osaka University and its associated hospitals from 1964–1988 (Cases 3, 6, and 7) and a review of "Annual of Pathologic Autopsy Cases in Japan" (Cases 1, 2, 4, and 5). Adequate clinical and follow-up data were available for all patients. Staging of patients was in accordance with the criteria established at the Ann Arbor Conference. All patients were staged clinically by a thorough physical examination, chest radiograph, blood count, and routine clinical chemistry together with the findings at laparotomy. In addition, findings by the computed tomography, echogram, drip intravenous pyelography, and barium enema were available for staging in seven, four, one, and one patient, respectively. No patient had bone marrow biopsies before treatment. All patients died, and autopsy was performed in four. Histologic specimens obtained by operation and/or autopsy were fixed in 10% formalin or Bouin solution and routinely processed for paraffin embedding. Histologic sections were cut at 4 μm thickness and stained with hematoxylin and eosin. Tumors were histologically classified according to the Working Formulation.[19] Immunohistochemical studies were made on paraffin-embedded specimens in all cases. The following staining procedures was used for immunoperoxidase procedures (ABC method): sections were incubated with normal horse serum for 30 minutes and incubated overnight at 4°C with mouse-antihuman monoclonal antibodies Mx-PanB (CD20) (Kyowa Medex, Tokyo, Japan), MB1, MT1 (Bioscience, Emmenbrucke, Switzerland) diluted at 1:50, UCHL-1 (CD45RO) (Dakopatts, Copenhagen, Denmark) diluted at 1:100. Subsequent reactions were carried out by using the Vectastain Kit Lot No. PK-4001 (Vector, Burlingame, CA). The peroxidase reaction completed in phosphate buffered saline (pH 7.4) containing 0.005% hydrogen peroxide and 0.03% 3',3-diaminobenzidine tetrachloride. Antibodies Mx-PanB and MB-1 are directed for human B-lymphocytes and UCHL-1 and MT-1 for T-lymphocytes. The expression of HLA-DR antigen by the uterine lymphoma tissue was examined by using anti-HLA-DR antibody (Dakopatts) as a primary antibody. Four cases of uterine lymphoma were available for the examination. As a control, cervical tissues from ten cases with cervical cancer and uterine leiomyoma were examined.

Results

Clinical findings are summarized in Tables 1 and 2. Site of tumors were in the uterine corpus in three patients and the cervix in four patients. All cases with cervical lymphoma presented with genital bleeding. Patients with corpus lymphoma presented with abdominal pain and backache. Physical examination revealed abdominal tumors in all cases of corpus lymphoma. Swelling of the cervix with or without erosion was a constant finding in all cases with cervical lymphoma. Superficial lymphadenopathy was found in the axillary region in one case with corpus lymphoma (Case 2) and in the inguinal region in one patient with cervical lymphoma (Case 5). Hepatosplenomegaly was not present in any patient. Total hysterectomy with or without bilateral salpingo-oophorectomy was carried out in three cases, and one was treated by tumor resection. Autopsy was performed in four cases (Cases 1, 2, 4, and 5). Macroscopic findings of tumors at surgery or autopsy were diffuse thickening of wall in one case of corpus and one case of cervical lymphoma, and tumor formation with a size ranging from 4×4 to 15×10 cm in the remaining cases. Adjuvant therapy was carried out in six cases (combined chemotherapy and radiation therapy in one, chemotherapy in two, and radiation therapy in three). Follow-up showed that five patients died due to tumor within 1 year.

Histologically, all cases were non-Hodgkin lymphoma (NHL) showing a diffuse pattern of proliferation (Fig. 1). All but one of them were large cell type. Cervical and/or corpus tissues free from tumor infiltration were available only in three cases; among them, lymph follicle formation was observed in one case (Case 1) of cervical lymphoma. Immunohistochemically, the tumor cells in five cases were positive for CD20 with or without positive reaction for MB1, thus judged to be B-cell type. One case (Case 2) was $CD20^+$, $MB1^+$, $MT1^+$, $CD45RO^-$. Because occasional reactivity of activated B-lymphocytes for MT1 is well-known, we judged this case also to be B-cell type. Tumor cells in one case (Case 4) did not show positive reactions for any antibodies against B-lymphocytes and T-lymphocytes. In this case, histologic specimens were obtained after chemotherapy, thus showing a degenerative change. Varying numbers of T-lymphocytes ($CD45RO^+$ and/or $MT1^+$) with small lymphocytic morphology infiltrated in and around the tumors.

When positive staining of large lymphoid cells in the specimens were used as positive internal control for HLA-DR staining, three of seven cases with uterine lymphoma were excluded because of absence of positively stained cells. In three (Cases 3, 6, and 7) of the remaining four cases with uterine lymphoma, numer-

Table 1. Pretreatment Characteristics in Seven Patients with Uterine Lymphoma

Patient no.	Age (yr)	Site of primary tumor	Presenting symptoms	Physical findings	Histologic type of tumor	Stage of disease	
						Ann Arbor	FIGO
1	46	Corpus	Abdominal pain, weight loss	Abdominal tumor	DIB	II	III
2	78	Corpus	Lumbago	Abomdinal tumor	DLNC	III	IVb
3	64	Corpus	Genital bleeding	Abdominal tumor	DIB	I	II
4	71	Cervix	Genital bleeding	Anterior vaginal wall tumor	Diffuse lymphoma*	NA	NA
5	30	Cervix	Genital bleeding	Inguinal lymph node swelling	DLNC	II	II
6	41	Cervix	Genital bleeding	Cervical erosion	DLC	II	VIa
7	71	Cervix	Genital bleeding	Swelling of cervix	DMix	I	I

FIGO: International Federation of Obstetrics and Gynecology; DIB: diffuse immunoblastic; DLNC: diffuse large, predominantly noncleaved cell; DLC: diffuse large, predominantly cleaved cell type; NA: enough data not available.

* Type not specified due to degenerative change by chemotherapy.

ous blood vessels were strongly stained by anti-HLA-DR antibody. In one (Case 7) of these cases, subendothelial lymphocyte infiltration was occasionally found (Fig. 2). The blood vessels in the cervix of two cases with cervical cancer and two with uterine myoma were frequently stained to a faint to moderate degree by the anti-HLA-DR antibody.

Discussion

Fox and More proposed the criteria necessary for the diagnosis of true primary uterine lymphoma,[14] which was roughly identical with clinical Stage I disease by the Ann Arbor system. By this criteria, all of the current cases with Stage I uterine cervical and corpus lymphoma could be accepted as primary uterine lymphoma. Three cases were Stage II, and one did not have enough information for staging. The study made by Harris et al.[6] was outstanding in its higher frequency (78%) of Stage I disease. Meanwhile, only 1 of 10 cases with uterine lymphoma reported by Castaldo et al.[11] was Stage I. Four of the current cases were collected through review of "Annual of Pathologic Autopsy Cases in Japan," which resulted in a high frequency of cases with advanced diseases resulting in the poor survival rate. Among the cases selected for the current study, the pathology registry cases were older and had more advanced disease than the other cases. The prognosis of uterine lymphoma was reported to be relatively favorable when the disease was in early stage and treated properly.[5,6] Several studies reported a poor prognosis of cervical lymphoma; two of five cases reported by Castaldo et al. died within 1 year[11] and four of six patients reviewed by Komaki et al. who died of disease lived less than 1 year.[7]

Table 2. Treatment and Outcome in Seven Patients

Case	Surgery	Radiation therapy (Gy)	Chemotherapy	Follow-up (months)
1	Probe laparotomy	No	No	3, DT
2	ND	No	Prednisolone, 60 mg	1, DT
3	Total hysterectomy–bilateral salpingo-oophorectomy	No	Cyclophosphamide, 500 mg Doxorubicin, 60 mg Vincristine, 2 mg Bleomycin, 15 mg Prednisolone, 60 mg	12, D
4	ND	1.5	Mitomycin C (peritoneal injection), 100 mg	2, DT
5	Total hysterectomy	39.6	No	20, DT
6	Total hysterectomy–bilateral salpingo-oophorectomy	30.0	No	8, DT
7	Resection of tumor	36.0	No	24, DID

ND: not done; DT: died of tumor; D: died of unknown cause; DID: died of intercurrent disease.

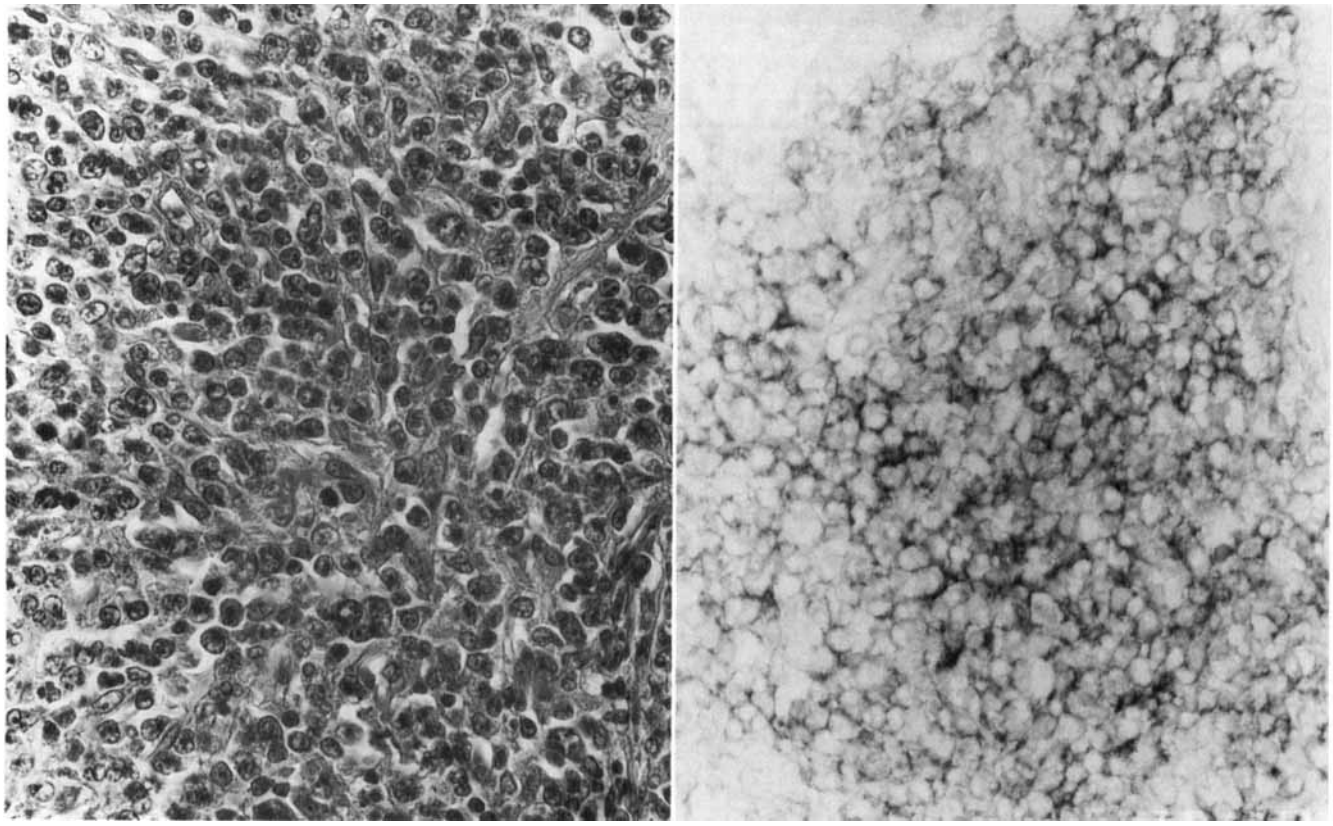

Figure 1. (Left) Non-Hodgkin's lymphoma of diffuse large, predominantly non-cleaved cell type in the uterine cervix. H&E, ×160. (Right) Tumor cells were positively stained by L26. Avidin-biotin-complex (ABC) method, ×160.

The current study comprised three cases with corpus and four with cervical lymphomas. This preponderance of cervix to corpus lymphoma was in agreement with previous study from North America[6] and Japan.[4] Vaginal bleeding was the commonest symptom in the current and previously reported cases of uterine lymphoma,[6,7,11] although the abdominal pain or backache was the main symptom in the two of our cases of corpus lymphoma. Abdominal or pelvic masses with or without perineal discomfort were the presenting symptoms in three patients with corpus lymphoma reported by Chorlton et al.[5] Fox and More reported a case of corpus lymphoma presented with abdominal pain and vaginal bleeding.[14] Generally, patients with the cervical lymphoma were younger (median age, 44 years) at onset of disease than those with corpus lymphoma (median age, 52 years)[7,11,14,20,21] in the series reported by Harris et al.[6] By colposcopy, cervical lymphoma showed diffuse enlargement of the cervix with or without erosion or polypoid mass.[6,11–13]

Histologically, all cases in the current series were NHL of diffuse type mainly of the large cell morphology, which was similar to the previous studies of uterine lymphoma.[6,7] Harris et al. suggested that the tumor cells in their cases of uterine and vaginal lymphomas were B-lymphocytic origin on purely morphologic grounds.[6] Since then, results of immunohistochemical studies on a small number of cases with uterine lymphoma were reported to reveal the B-cell nature of the proliferating cells.[4,8,15] All six of the current cases with preserved reactivities to antibodies were B-cell in nature, further confirming exclusively B-cell nature of the uterine lymphoma.

In one of the current cases with cervical lymphoma, formation of lymph follicles was observed, suggesting the presence of preceding inflammation in the cervix. Recently, long-standing inflammation frequently with lymph follicle formation was supposed to be pathognomonic for the development of several types of extranodal lymphoma.[16,17] Weseley et al. suggested an etiologically important role of lymph follicle formation for lymphoma development in the uterine cervix.[22] These findings prompted us to evaluate a presence or absence of findings suggestive of preceding inflammatory change in the remaining eight cases, but the current study failed to find lymph follicle formation.

Bottazzo et al. proposed that aberrant expression of HLA-DR on the thyroid epithelial cells allowed them to

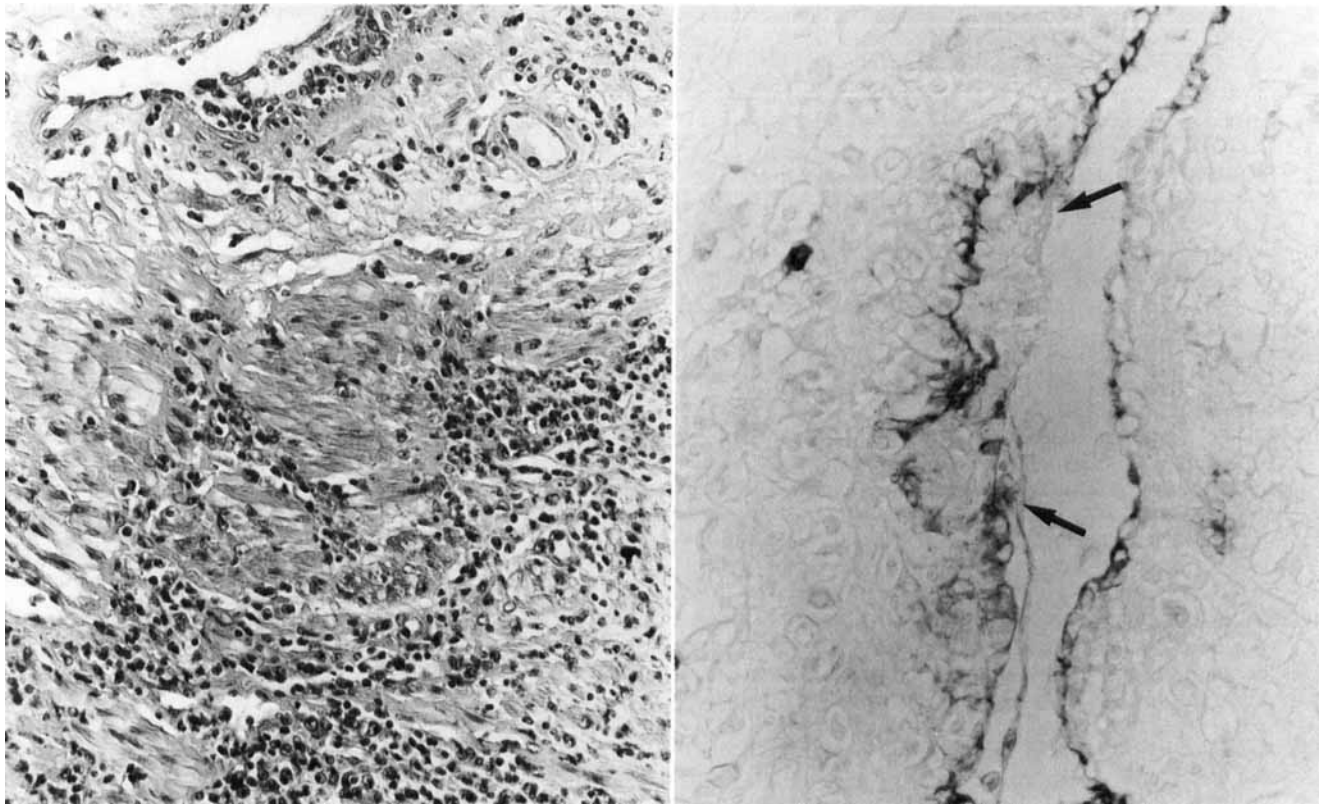

Figure 2. (Left) Subendothelial lymphocyte infiltration in the blood vessels (upper field). In the lower field, diffuse proliferation of lymphoma cells was observed. H&E, ×60. (Right) Cytoplasm of endothelial cells was positively stained by anti-HLA-DR antibody. The area of subendothelial lymphocyte infiltration was indicated by arrows. ABC method, ×330.

function as antigen-presenting cells, thus triggering the generation of Hashimoto thyroiditis.[23] Hashimoto thyroiditis is well known as a risk factor for the development of thyroid lymphoma.[16] In patients with breast lymphoma, presence of lymphocytic mastopathy, a recently proposed disease of putative autoimmune nature,[24] was shown by histologic change and expression of HLA-DR on the epithelial cells of the mammary duct.[18] Expression of HLA-DR antigen could be tested in the current four cases. Although glandular and ductal epithelium did not show positive reaction in any case, a markedly increased expression of HLA-DR antigen on the vascular endothelium in three of four cases with cervical or carpus lymphoma compared with those in patients with cervical cancer and uterine leiomyoma was distinct.

It has been shown that endothelial cells normally do not express Class II major histocompatibility antigens (HLA) but could be induced to do so by interferon-gamma released by activated T-lymphocytes.[25,26] After Class II MHC induction, the endothelial cells can serve as antigen presenting cells to lymphocytes.[27] These processes were considered as a prime immune event responsible for rejection of transplants. In one of three cases with an increased expression of HLA-DR in the endothelium, infiltration of small lymphoid cells beneath the endothelium accompanying with edema and fibrin deposits was found. This appearance mimicked endothelitis in hepatic allografts.[28] The meaning of HLA-DR expression in the endothelial cells of cervical lymphoma, however, is not known at present. None of the investigations used in our study suggested the presence of underlying autoimmune process in uterine lymphoma.

References

1. Carr I, Hill AS, Hancock B, Neal FE. Malignant lymphoma of the cervix uteri: histology and ultrastructure. *J Clin Pathol* 1976; 29:680–6.
2. Freeman C, Berg JW, Cutler S. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972; 29:252–60.
3. Aozasa K, Tsujimoto M, Sakurai M, Honda M, Yamashita K, Hanada M, et al. Non-Hodgkin's lymphomas in Osaka, Japan. *Eur J Cancer Clin Oncol* 1985; 21:487–92.
4. Murotsuki A, Yazaki A, Hayakawa S, Yamashita T, Takahashi K. A case of primary malignant lymphoma of the cervix uteri. *Cancer Clin* 1989; 35:1716–20 (in Japanese).

5. Chorlton I, Karnei RF Jr., King FM, Norris HJ. Primary malignant reticuloendothelial disease involving the vagina, cervix, and corpus uteri. *Obstet Gynecol* 1974; 44:735–48.
6. Harris NL, Scully RE. Malignant lymphoma and granulocytic sarcoma of the uterus and vagina: a clinicopathologic analysis of 27 cases. *Cancer* 1984; 53:2530–45.
7. Komaki R, Cox JD, Hansen RM, Gunn WG, Greenberg M. Malignant lymphoma of the uterine cervix. *Cancer* 1984; 54:1699–704.
8. Matsuyama T, Tsukamoto N, Kaku T, Matsukawa K, Hirakawa T. Primary malignant lymphoma of the uterine corpus and cervix. Report of a case with immunohistochemical analysis. *Acta Cytol* 1989; 23:228–32.
9. Maeda T, Kumagai H, Mori H. Malignant lymphoma presenting as initial symptom in the uterus: case report. *Br J Obstet Gynecol* 1988; 95:1195–7.
10. Cunningham D, Gilchrist NL, Lee FD, Haxton M, Heppleston A, Forrest GJ, et al. T-cell lymphoblastic lymphoma of the uterus complicated by chlamydia trochomatis pneumonia. *Post Grad Med J* 1986; 62:55–7.
11. Castaldo TW, Ballon SC, Lagasse LD, Petrilli ES. Reticuloendothelial neoplasia of the female genital tract. *Obstet Gynecol* 1979; 54:167–70.
12. Retikas DG. Hodgkin's sarcoma of the cervix: report of a case. *Obstet Gynecol* 1960; 80:1104–7.
13. Johnson CE, Soule EH. Malignant lymphoma as a gynecologic problem: report of five cases including one primary lymphosarcoma of the cervix uteri. *Obstet Gynecol* 1957; 9:149–57.
14. Fox H, More JRS. Primary malignant lymphoma of the uterus. *J Clin Pathol* 1965; 18:723–8.
15. Nishikawa T, Kasajima T, Takeo Y, Ando A, Masuda A, Kawakami M. Two cases of primary lymphoma of uterus- An immunohistochemical study. *Jpn J Reticuloendothel Soc* 1991; 31:87–94 (in Japanese).
16. Holm FM, Blomgren H, Lowhagen H. Cancer risks in patients with chronic lymphocytic thyroiditis. *N Engl J Med* 1985; 312:601–4.
17. Aozasa K, Ueda T, Kurata A, Kim CW, Inoue M, Matsuura N, et al. Prognostic value of histology and clinical factors in fifty-six patients with gastrointestinal lymphomas. *Cancer* 1988; 61:309–15.
18. Aozasa K, Ohsawa M, Saeki K, Horiuchi K, Kawano K, Taguchi T. Malignant lymphoma of the breast: its immunologic type and association with lymphocytic mastopathy. *Am J Clin Pathol* 1992; 97:699–704.
19. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphomas: summary and description of a Working Formulation for clinical usage. *Cancer* 1982; 49:2112–35.
20. Anderson GG. Hodgkin's disease of the uterine cervix: report of a case. *Obstet Gynecol* 1967; 29:170–2.
21. Retikas DG. Hodgkin's sarcoma of the cervix: report of a case. *Obstet Gynecol* 1960; 80:1104–7.
22. Weseley AC, Berrigan MW. Reticulum cell sarcoma of the vagina. *Obstet Gynecol* 1958; 11:192–5.
23. Bottazzo GF, Pujol-Borrell R, Hanafusa T, Feldman M. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. *Lancet* 1983; 2:1115–8.
24. Schwartz IS, Strauchen JA. Lymphocytic mastopathy: an autoimmune disease of the breast? *Am J Clin Pathol* 1990; 93:725–30.
25. Collins T, Korman AJ, Wake CT, Boss JM, Kappes DJ, Fiers W, et al. Immune IFN activates multiple class II major histocompatibility complex genes and the associated invariant chain gene in human endthelial cells and dermal fibroblasts. *Proc Natl Acad Sci U S A* 1984; 81:4917–21.
26. Pober JS, Gimbrone MA Jr., Collins T, Cotran R, Clayberger C, Reiss CS, et al. Interactions of T lymphocytes with human vascular endothelial cells: role of endothelial cells surface antigens. *Immunobiology* 1984; 168:483–94.
27. Markus BH, Colson YL, Fung JJ, Zeevi A, Duquesnoy RJ. HLA antigen expression on cultured human arterial endothelial cells. *Tissue Antigen* 1988; 32:241–53.
28. Ludwig J, Batts KP, Ploch M, Rakela J, Perkins JD, Wiesner RH. Endotheliitis in hepatic allografts. Symposium on liver transplantation-Part V. *Mayo Clin Proc* 1989; 64:545–54.