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Case Study

Intravascular Large B-Cell Lymphoma Coexisting with an Ovarian Carcinoma

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We report an incidental case of intravascular large B-cell lymphoma (IVLBCL) coexisting with an ovarian carcinoma in a 76-year-old woman. She visited our hospital with difficulty in defecation. Magnetic resonance imaging and computerized tomography scan revealed a solid and cystic mass probably arising from the left ovary. Gross examination of the tumor obtained by an exploratory surgery showed a solid area in a simple cyst. The ovarian tumor was diagnosed as a high-grade serous carcinoma (HGSC). Early in the post-operative course, this patient developed fever of unknown origin with central nervous system manifestations. Magnetic resonance imaging of the brain showed multiple space-occupying lesions. When we reviewed the histological sections, atypical lymphocytes were found in the lumina of small vessels of almost the entire ovary. These cells were positive for CD20 and CD79a by immunohistochemistry. A diagnosis of IVLBCL coexisting with HGSC was finally made. Although radiation therapy for brain lesions was performed and rituximab was administered, she died two months after the operation. To the best of our knowledge, this is the first case of IVLBCL incidentally identified in HGSC through microscopic examination. This case serves to create awareness of the rare event where IVLBCL may involve the ovary of patients who also have carcinoma in the organ. 〔*J Clin Exp Hematop 56(1):59-63, 2016*〕

Keywords: intravascular large B-cell lymphoma, high-grade serous carcinoma, ovary, composite neoplasm

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) has been defined as a rare subtype of extranodal diffuse large B-cell lymphoma characterized by the selective growth of neoplastic cells within blood vessels.[1] The organs most commonly affected in the Western variant are the central nervous system (CNS) and skin, while patients with the Asian variant more often present with hemophagocytic syndromes.[2] The diagnosis of IVLBCL is often difficult because of its nonspecific clinical manifestations, and many cases were diagnosed only at autopsy due to its aggressive clinical course. IVLBCL can essentially involve the vessels of any organ, but ovarian involvement has rarely been reported. Histopathologic diagnosis of IVLBCL is difficult in case when the lesion is present in the stroma of more readily recognizable neoplasms such as carcinoma. The purpose of this report is to inform that composite IVLBCL and carcinoma can occur in organs in which development of lymphoma is rare.

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CASE REPORT

A 76-year-old Japanese woman (gravida-3, para-3) visited our hospital with difficulty in defecation. She had no specific family history or medical history of related problems. Gynecological examination revealed a large cystic mass with a solid component measuring 13 x 11 x 8 cm in the pelvic lesion (Fig. 1a). Magnetic resonance imaging and computerized tomography scan showed peritoneal dissemination with swelling of the iliac and para-aortic lymph nodes. There was no evidence of hepatosplenomegaly. Clinical diagnosis of ovarian cancer was given. Laboratory findings were as follows: hemoglobin, 10.0 g/dL (normal range, 11.3-15.2); serum lactate dehydrogenase, 611 U/L (116-230); C-reactive protein, 0.3 mg/dL (< 0.3) and CA125, 536 U/ml. The serum level of soluble interleukin-2 receptor was not

measured. The peripheral blood contained no atypical lymphoid cells. According to a diagnosis of unclassifiable carcinoma by a uterine cervical biopsy, a left adnexectomy was performed. The resected left ovarian tumor, which measured 13 x 11 x 8 cm, was composed of a simple cyst and a solid component with hemorrhage and necrosis (Fig. 1b). Histological examination showed characteristic features of high-grade serous carcinoma (HGSC), consisting of solid nests of atypical columnar epithelial cells with papillary, glandular and cribriform patterns. The tumor cells had significant nuclear atypia and numerous mitoses. Immunohistochemistry showed that the cells were diffusely positive for WT-1 (Novocastra, Newcastle, UK) and complete loss of p53 (Novocastra) expression (null type). Additionally, the MIB-1 (Invitrogen, Camarillo, USA) index was calculated to be 71.8%.

Six days after the operation, the patient had fever with difficulties in communication and speech. Asymmetric brain

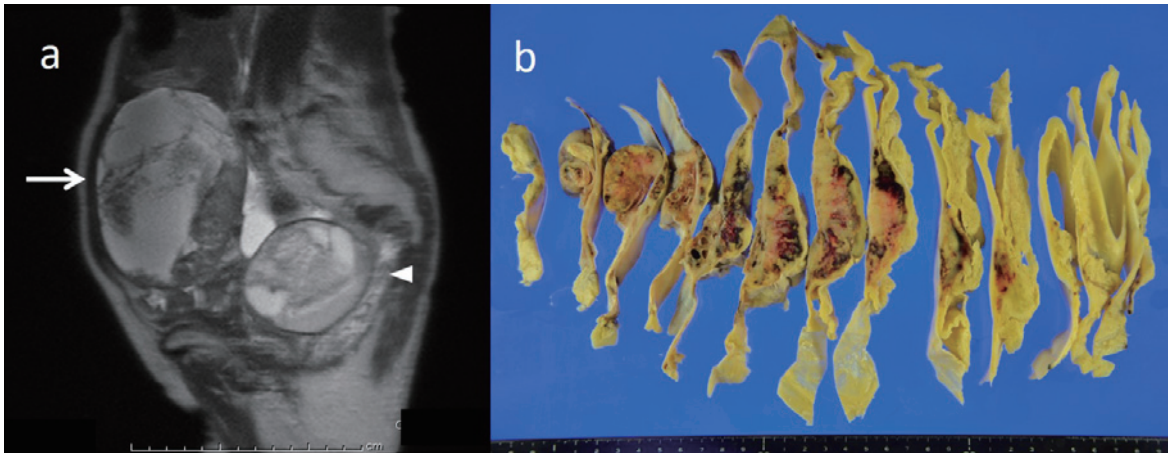

Fig. 1. Radiological image and macroscopic appearance of the ovarian tumor. (***1a***) Magnetic resonance imaging T2WI sagittal image of the pelvic area. Cystic lesion with solid components are evident (*arrow*). Other solid components in the Douglas' pouch are suspicious for peritoneal dissemination (*arrowhead*). (***1b***) Sequential sectional appearance of the solid and cystic lesions which were resected and fixed. The solid lesion is associated with hemorrhage and necrosis.

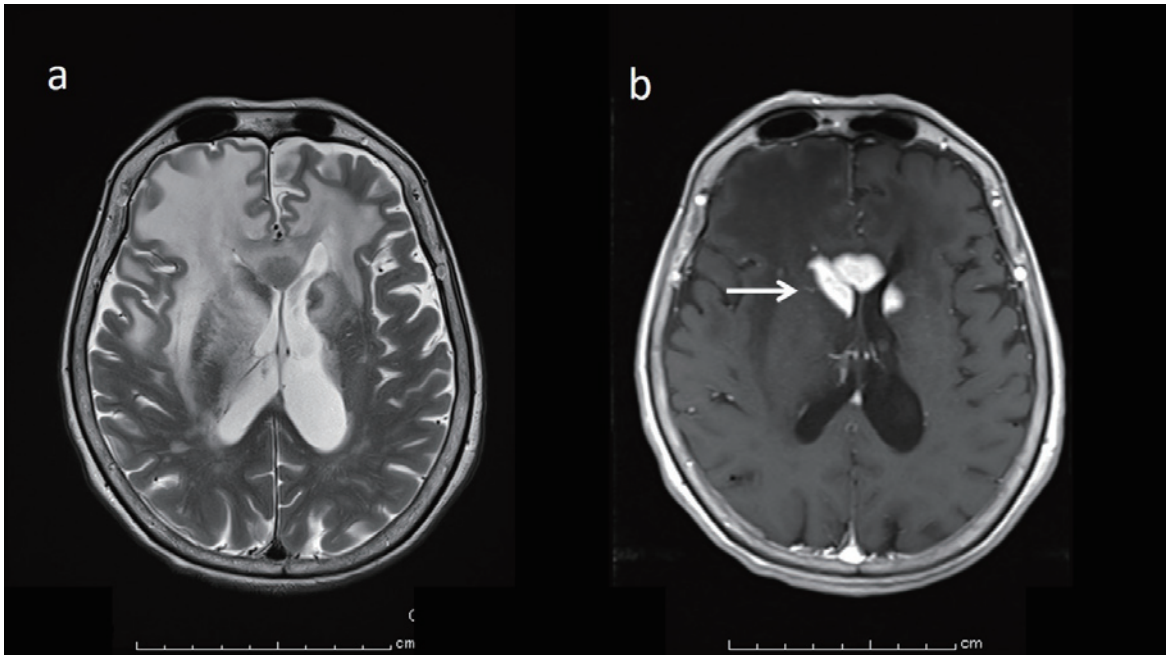

Fig. 2. Radiological images of the brain. (***2a***) Magnetic resonance imaging T2WI sagittal image of the brain. Asymmetric brain edema is noted in the frontal lobe. (***2b***) Gadolinium-enhanced T1 weighted magnetic resonance image shows the lesions with contrast enhancement in the head of the caudate nucleus and genu of corpus callosum (*arrow*).

edema and masses in the head of the caudate nucleus, genu of corpus callosum, hypothalamus, and areas around the fourth ventricle were revealed by magnetic resonance imaging (Fig. 2). Because these findings were indicative of malignant lymphoma or metastatic tumor, we reviewed the histological sections of both biopsy and resected tissues. As a result, there were aggregates of large lymphoid cells in the background of numerous inflammatory cells, such as small lymphocytes and plasma cells in the stroma of HGSC of resected tissues. The large cells had hyperchromatic nuclei with distinct nucleoli and scant amount of cytoplasm. Moreover, many of these cells were found in the lumina of capillary-sized vessels (Figs. 3 & 4). No such features were seen in the biopsy tissue. Immunohistochemical study revealed that the cells were diffusely positive for CD20 (Dako, Glostrup, Denmark), CD79a (Dako), CD5 (Novocastra), Bcl-2 (Dako) and HLA-DR (Dako), and focally positive for MUM1 (Dako). The cells were negative for AE1/AE3 (Invitrogen), CD3 (Dako), CD10 (Novocastra), Bcl-6 (Novocastra), cyclin D1 (Nichirei, Tokyo, Japan), κ-light chain (Novocastra) and λ-light chain (Novocastra). The MIB-1 index was 71.1%. Epstein-Barr virus was not detected by *in situ* hybridization using an oligonucleotide probe specific for Epstein-Barr virus-encoded small non-polyadenylated RNAs (Leica, Newcastle, UK).

Based on these finding a pathological diagnosis of

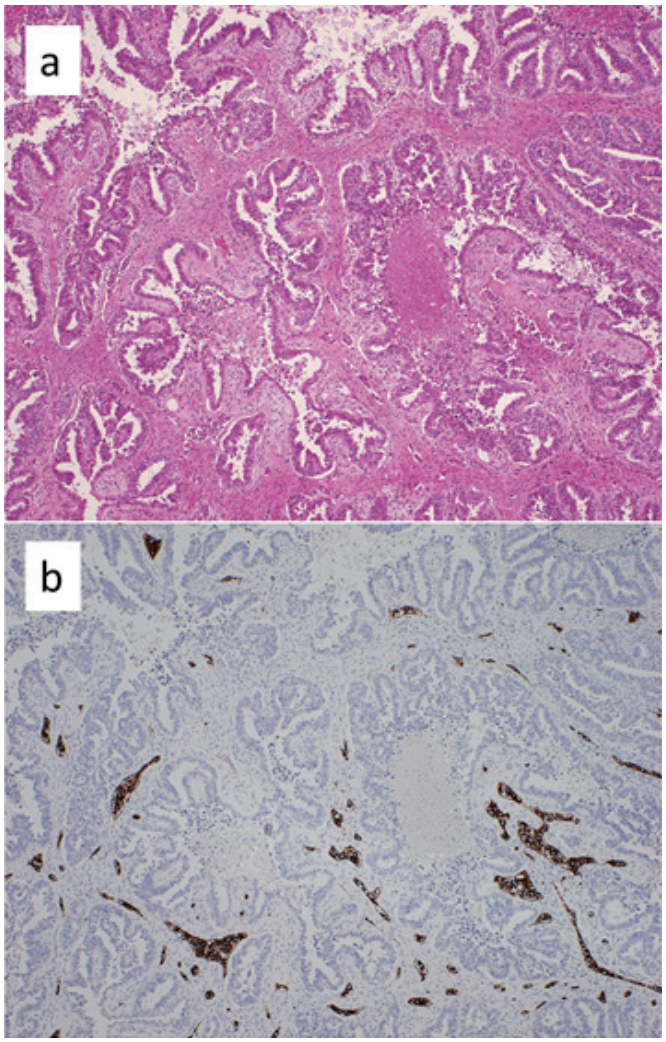

Fig. 3. Low-power view of high-grade serous carcinoma and intravascular large B-cell lymphoma. (***3a***) Atypical columnar epithelial cells with papillary and glandular patterns are readily seen, but intravascular large B-cell lymphoma is difficult to be recognized. H&E stain. (***3b***) Ovoid and arboroid nests of CD20-positive cells are present in the stroma of high-grade serous carcinoma. Immunoperoxidase stain with hematoxylin counterstain.

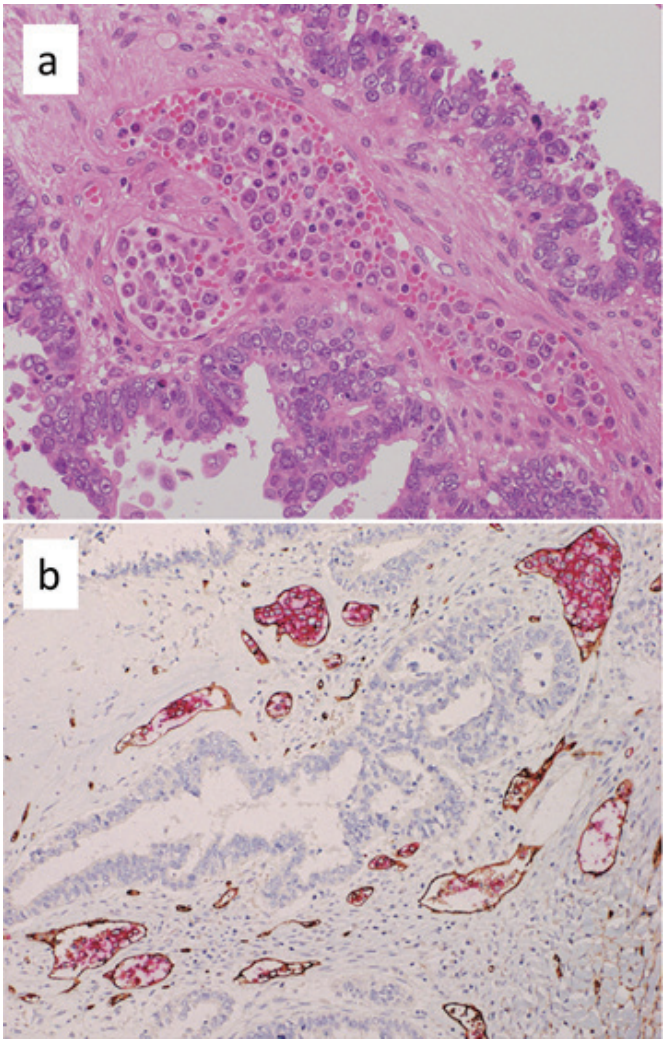

Fig. 4. High-power view of high-grade serous carcinoma and intravascular large B-cell lymphoma. (***4a***) Large lymphoid cells are present in the vessels of the carcinomatous stroma. Erythrocytes are admixed, but an erythrophagocytic feature is not found. H&E stain. (***4b***) Intravascular localization of the lymphoid cells is evident by a double immunostain (CD20, *red color*; CD34, *brown color*). The lymphoma cells positive for CD20 are surrounded by CD34-positive vascular endothelial cells.

composite neoplasm consisting of IVLBCL and HGSC was finally made. Brain and bone marrow biopsies, and positron emission tomography could not be performed due to poor performance status of the patient. She regained consciousness by radiation as well as chemotherapy consisting of rituximab and prednisolone. However she died two months postoperatively and autopsy was not conducted.

DISCUSSION

In patients with disseminated lymphoma, ovarian involvement is relatively common with frequencies ranging from 7 to 26% at autopsy.[1] However, little has been reported about primary ovarian lymphoma, probably because it is difficult to be clinically recognized at an early stage due to its asymptomatic nature.[3] The differential diagnosis of ovarian lymphoma includes chronic inflammatory infiltrates, granulosa-cell tumor, dysgerminoma, small cell carcinoma, metastatic carcinoma and carcinosarcoma.[4] Although immunohistochemistry is effective in many instances, it may not be helpful in differentiating lymphoma in the stroma of carcinoma from inflammatory infiltrates as a stromal reaction to the carcinoma. In our case, both intravascular and extravascular lymphoid proliferations were seen in the stroma of HGSC. Neoplastic, but not inflammatory, nature of the proliferation was highly suspicious on the morphological basis, as intravascular proliferation was unusual in the inflammatory process and the diagnosis of B-cell lymphoma was immunohistochemically confirmed.

IVLBCL is a very rare and aggressive extranodal lymphoma with nonspecific symptoms at presentation and a poor prognosis, with the exception of the disease limited to the skin.[5] Median survival rate of the patients with IVLBCL has been reported to be 13 months.[6] By definition of the WHO classification,[7] proliferation of lymphoma cells outside the vessels in IVLBCL is rare and described as 'minimal'. If extravascular proliferation is still minimal at the late stage, however, it is unlikely that the lymphoma cells are life-threatening and prognosis of patients with IVLBCL is poor. Ponzoni *et al*. reported that a focal intraparenchymal spread may occur together with the classic intravascular pattern.[5] Hence, we finally characterized our case to be one of IVLBCLs, although there was an extravascular proliferating area measuring 2-3 mm in diameter with an intravascular lesion. It is unlikely to characterize our case to be an Asian variant of IVL, because we could not confirm hemophagocytic features.

For brain lesion in our case in the absence of histologic confirmation, the differential diagnosis includes i) secondary ovarian involvement of primary CNS diffuse large B-cell lymphoma, in which IVLBCL is excluded, ii) brain metastasis of HGSC, and iii) brain involvement of IVLBCL. The lymphoma cells in our case were positive for HLA-DR, but the molecule is often negative in primary CNS or testicular lymphoma.[2,8] Brain metastasis of ovarian carcinoma is rare and the well-known sites of involvement are cerebellar, frontal, parietal, and occipital regions.[9] In addition, there was no evidence of liver or lung metastasis in our case. In the case

Table 1. Reported cases of IVLBCL diagnosed by resections of the ovary and/or uterus

Case	Reference	Age	Clinical findings	Preoperative diagnosis	Location	Stromal invasion of IVLBCL	Therapy	Follow-up
1	Yamada, *et al*.	42	Fatigue, weight loss, genital bleeding, sIL-2R 1,260 U/mL	Huge myoma uteri	Uterus, adnexa	ND	ATH, R-CHOP	NED, 10 mo
2	Sur, *et al*.	63	Genital bleeding	Undiff. tumor*	Uterus, adnexa	ND	ATH+BSO, R-CHOP	NED, 14 mo
3	Lannoo, *et al*.	63	Fever, weight loss, enlarged uteri, FDG-PET(+)	B-cell lymphoma*	Uterus, adnexa, PLN and other organs	(+)	ATH+BSO, R-CHOP, further treatment	DOD
4	Fujiwara, *et al*.	62	Fever, uterine mass, sIL-2R 2,250 U/mL	Undiff. tumor*	Uterus, adnexa, PLN/PAN	(+)	ATH+BSO, R-CHOP	NED, 25 mo
5	Yamamoto, *et al*.	71	Fever, genital bleeding, sIL-2R 10,400 U/mL	B-cell lymphoma*	Uterus, adnexa	(+)	ATH+BSO, R-CHOP	NED, 51 mo
6	This case	76	Fever, CNS manifestations	Ovarian cancer	Ovarian cancer	(+)	LSO, RT+rituximab	DOD

ATH, abdominal total hysterectomy; BSO, bilateral salpingo-oophorectomy; CNS, central nervous system; CT, chemotherapy; DOD, dead of disease; FDG-PET, fluorodeoxyglucose-positron emission tomography; IVLBCL, intravascular large B-cell lymphoma; LSO, left salpingo-oophorectomy; mo, months; ND, not described; NED, no evidence of disease; PAN, para-aortic lymph nodes; PLN, pelvic lymph nodes; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RT, radiation therapy; sIL-2R, soluble interleukin-2 receptor; Undiff. tumor, undifferentiated malignant tumor; ※diagnosis by endometrial curettage

of CNS involvement of IVLBCL, multiple cerebral infarctions due to small vessel occlusion by the tumor cells are common. However, there are some reports about IVLBCL with CNS mass lesions implying extravascular involvement.[10] Because there are no specific radiological findings in the CNS involvement of IVLBCL, a careful differential diagnosis is required. Collectively, from these findings, it is speculated that the brain lesion was due to CNS involvement of IVLBCL. Patients with IVLBCL having CNS involvement is associated with worse performance status because rituximab is unable to prevent CNS involvement.[5]

In the literature, there are five reported cases of IVLBCL with the diagnoses made by resections of the ovary and/or uterus (Table 1).[11-15] Lymphoma was not included in the differential diagnosis before surgery in three of the cases, though they had clinical manifestations of lymphoma, such as fever of unknown origin and general fatigue. Three cases in which IVLBCL was limited to the ovary and/or uterus had no evidence of disease at the time of reporting, as chemotherapy was effective. This indicates that an early recognition of lymphoma cells may contribute to better prognosis.

In summary, we described an incidental case of IVLBCL coexisting with an ovarian carcinoma. Our case serves to create awareness of the rare event where IVLBCL may involve the ovary of patients who also have carcinoma in the organ.

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DISCLOSURE STATEMENT

The authors declare that they have no conflict of interests regarding the publication of this paper.

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