Primary Cardiac Lymphoma

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***Objective*: To report a rare autopsy case of primary cardiac lymphoma with microscopical involvements of extracardiac organs in an immunocompetent man.**
***Methods*: An autopsy case of primary cardiac lymphoma in a 70-year-old man was examined grossly, microscopically and immunohistochemically. In addition, *in situ* hybridization for Epstain-Barr virus was performed.**
***Results*: Clinically, a tumor was at first found only in the heart by various imaging techniques but tumor involvements were noted in chest and abdominal organs as the disease progressed. He died of cardiac failure six months after the first presentation. An autopsy revealed a tumor formation only in the right atrium and right ventricle of the heart. Histological and immunohistochemical studies showed that the cardiac tumor was diffuse large B cell lymphoma of non-germinal center B-cell like type. In addition to the heart, the tumor cells were found to microscopically involve lungs and peritoneal and retroperitoneal fat tissue of several organs. Epstein-Barr virus protein and DNA were negative by immunohistochemistry and *in situ* hybridization.**
***Conclusions*: It was suggested that primary cardiac lymphoma may involve extracardiac organs as the disease progresses and that it may occur in immunocompetent persons.**

Key words: heart, malignant lymphoma, autopsy, immunohistochemistry, histopathology

INTRODUCTION

Primary cardiac lymphoma (PCL) is exceeding rare. It is defined in a strict sense as a non-Hodgkin lymphoma involving only the heart and pericardium [1]. It occurs almost in immunosupressed patients, but it very infrequently develops in immunocompetent patients [2]. The author here reports on an autopsy case of PCL with microscopical involvements of extracardiac organs in a 70-year-old immunocompetent man.

CASE REPORT

A 70-year-old man presented loss of appetite, nausea and vomiting, and admitted to our clinic for scrutiny. Various imaging techniques including ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI) showed pericardial effusion and a tumor around the right ventricle. Gallium-scintigraphy showed signals only in the heart. A blood laboratory test showed elevated serum lactic dehydrogenase (LDH) (215 IU/L). Laboratory data showed no immunosuppresion, and an antibody to human immunodeficiency virus (HIV) was negative. A cytological test of pericardial effusion showed atypical lymphocytes suggestive of malignancy (Fig. 1A), and the patient underwent chemotherapy (seven courses of CVP; cyclophosphamide, vincristine, predonisone: and one course of CHOP-B; cycrophosphamide, vincristine, adriamycin, predonisone, bleomycin) under the diagnosis of PCL. Bone marrow biopsy showed no atypical lymphocytes. The patient then showed complete remission three months after the admission. Tests of electrocardiogram showed occasional atrioventricular block and flatter. However, his condition deteriorated three months after the remission. Blood laboratory data showed elevated LDH (7871 IU/L), leukocytosis without atypical lymphocytes, and increased C-reactive protein. Gallium-scintigraphy showed signals in the chest and abdominal organs in addition to the heart. He showed a downhill course and died six months after the initial presentation. There was no lymph node swelling, splenomegaly or leukemic state during the clinical course.

An autopsy showed a heart tumor measuring 30× 50 mm in the right atrium and right ventricle (Fig. 1B). The heart weighed 420 g. Pericardial effusion (55 ml) was noted. No coronary atherosclerosis was recognized. Other gross findings included left pleural effusion (800 ml), bullae of bilateral lungs, pulmonary congestion and edema, cortical tumor (1 cm) of the right adrenal gland, emaciation, prostatic hyperplasia, atrophy of systemic organs, and pleural plaques. No lymph node swelling or splenomegaly was noted. No tumor formations were recognized in the organs other than the heart. The cause of death was thought to be cardiac and respiratory failure.

Microscopically, the heart tumor consisted of diffuse monotonous proliferation of atypical large lymphocytes with hyperchromatic nuclei (Figs. 1C and 1D). Many mitotic figures were recognized (Fig. 1D). Immunohistochemically, the tumor cells were negative for terminal deoxynucleotidyl transferase (TdT, Dako, Glostrup, Denmark, polyclonal), CD3 (Dako, clone PC3/188A) (T cell marker), CD5 (Dako, clone CD5/54/F6), CD10 (Dako, clone SS2/36), cyclin D1 (Novocastra, Newcastle upon Tyne, UK, clone DCS-6),

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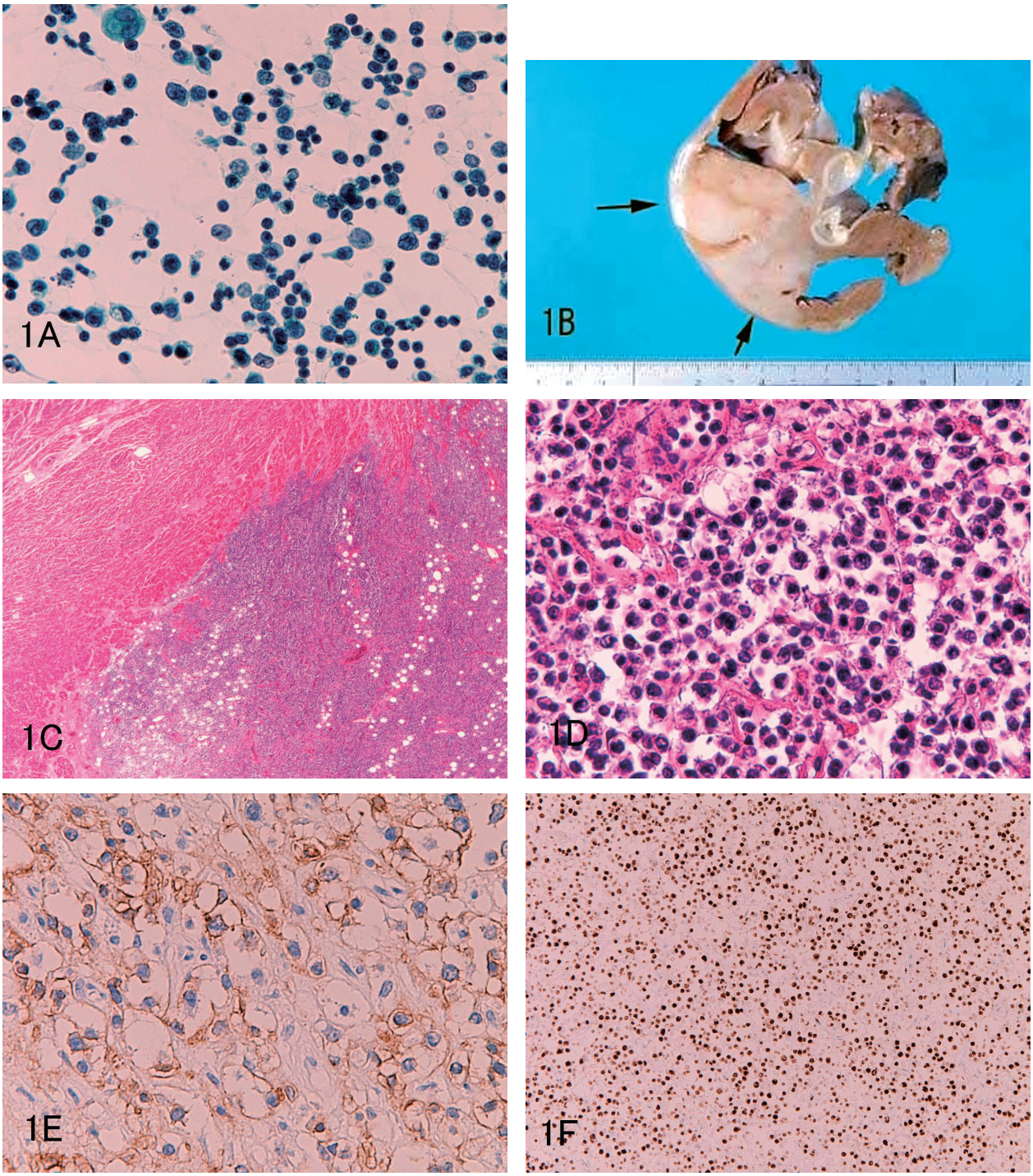

Fig. 1 **A**: Cytology of pericardial effusion. Many atypical lymphocytes are seen. Papanicolaou, ×400. **B**: Horizontal cut surface of the heart. A tumor (arrows) measuring 5×3 cm is noted in the right atrium and ventricle. **C**: Low power view of the periphery of the tumor (right). HE, ×40. **D**: High power view of the tumor. Tumor cells are atypical lymphocytes regarded as lymphoma cells. HE, ×400. **E**: The tumor cells are positive for CD20. Immunostain for CD20, ×400. **F**: Ki-67 labeling of the lymphoma cells is approximately 80%. Immunostain for Ki-67, ×200.

cytokeratins using various antibodies (AE1/3: Dako, clone AE1+AE3, MNF116: Dako, clone MNF116, Wide: Dako, polyclonal), epithelial membrane antigen (Dako, clone E29), S-100 protein (Dako, polyclonal), CD68 (Dako, clone KP-1), CD30 (Dako, clone Ber-H2), CD15 (Dako, clone C3D-1), vimentin (Dako, clone V9), CD45RO (Dako, clone UCHL-1) (T cell marker), bcl-6 (Santa Cruz Biotechnology, Santa Cruz, USA, polyclonal), and MUM1 (Dako, clone MUM1p). In contrast, tumor cells were positive for CD45 (leukocyte common antigen, Dako, clone 2B11+PD7/26), CD20 (Dako, clone L26) (B cell marker) (Fig. 1E), CD79-alpha (Dako, clone JCB117) (B cell marker), bcl-2 (Dako, clone 124) (bcl-2 oncoprotein) and lamda chain (Dako, polyclonal). Ki-67 (Dako, clone MIB-1) labeling was 80% (Fig. 1F). The tumor cells were negative for Epstein-Barr virus (EBV) encoded latent membrane protein 1 (LMP-1) (Dako, clone CS1-4), and also negative for EBV DNA as detected by in situ hybridization (Dako, in situ hybridization kit). The cardiac tumor

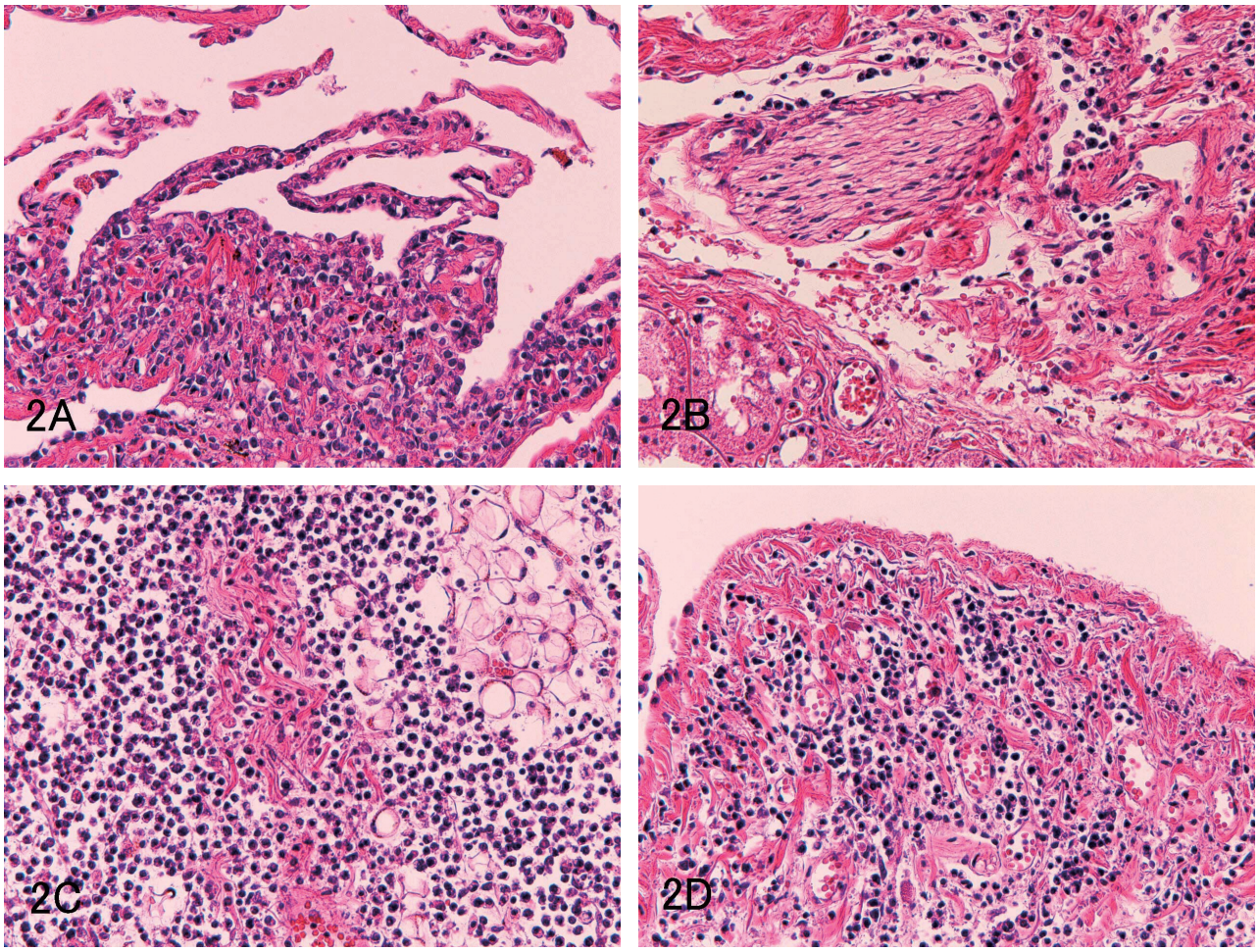

Fig. 2 Microscopical foci of lymphoma cells are present in the extracardiac organs such as lung (**A**), kidneys (**B**), retroperitoneum (**C**) and urinary bladder (**D**). HE, ×300

was diagnosed as non-Hodgkin diffuse large B cell lymphoma according to the WHO criteria [3]. In addition, negative immunoreactions for CD10, bcl-6 and MUM1 showed that the lymphoma was non-germinal center B-cell type [4].

The lymphoma cells with identical histology and immunohistochemiical findings to the heart tumor were seen to involve microscopically the alveolar walls of lungs (Fig. 2A), peritoneal fat tissue around the liver, pancreas and large intestine, retroperitoneal fat tissue around the kidneys (Fig. 2B), renal pelvic fat tissue (Fig. 2C), and urinary bladder mucosa (Fig. 2D). The pleura was not involved by lymphoma cells. Systemic lymph nodes, bone marrow and spleen were free of lymphoma cells. There were no intravascular involvements of lymphoma cells such as sinusoids of the liver and spleen. The adrenal tumor was cortical adenoma.

DISCUSSION

PCL is an exceeding rare tumor with poor prognosis. Most of PCL occur in the right atrium or right ventricle [1, 2, 5, 6] as in the present case. Review of Chalabreysse *et al*. in 2002 [2] showed 35 reported cases in the literature. Recent review by Ikeda *et al*. in 2004 [6] showed 39 case reports of PCL in the English and Japanese literature during 1995-2002. Clinically, our case was diagnosed by imaging modalities and cytology. PCL was previously diagnosed largely at autopsy, but recent advance of myocardial biopsy and effusion cytology made it possible that patients with PCL were correctly diagnosed antemortem [5]. The present case was also diagnosed as PCL by imaging techniques and cytology, and the patient could receive chemotherapy. However, the prognosis of our patient was very poor.

The reason why PCL develops mainly in the right side of the heart is obscure. Ikeda *et al*. [6] who reviewed 39 cases of PCL described that the locations of PCL were as follows: right side of the heart, 33 cases; left side of the heart, 2 cases, both right and left sides of the heart, 3 cases; only pericardium, 1 case. The present case of PCL involved right atrium and right ventricle. Such preferential site of the origin of PCL is now entirely unknown [1]. Similar situation is present in much more common cardiac myxoma, which occurs largely in the left atrium.

Many kinds of malignant tumors occur in the heart, though the incidence is very low. They include angiosarcoma, undifferentiated sarcoma, malignant fibrous histiocytoma, leiomyosarcoma, osteosarcoma, fibrosarcoma, myxosarcoma, rhabdomyosarcoma, synovial sarcoma, liposarcoma, malignant schwannoma, malignant mesenchymoma, malignant rhabdoid tumor, Kaposi's sarcoma, malignant hemangioperi-

cytoma, PCL, granulocytic sarcoma, malignant mesothelioma, and metastatic malignant tumors [1]. Differential diagnosis of PCL from other malignant cardiac tumors is relatively easy. Granulocytic sarcoma should be differentiated from PCL. The present case is PCL on hematoxylin-eosin stained sections as well as by immunohistochemistry.

In general, PCL is defined in a strict sense as a lymphoma confined within the pericardial sac [1]. Another definition is that PCL is a lymphoma primary to the heart if the bulk of tumor is within the pericardium or if there are cardiac symptoms from lymphomatous cardiac infiltration at the time of initial diagnosis [1, 7]. The present case showed a tumor only in the heart, though microscopic involvements of lymphoma cells were recognized in several organs at autopsy. No lymph node or bone marrow involvements were recognized at autopsy. In addition, Gallium-scintigraphy showed signals only in the heart in the initial stage and in chest and abdominal organs in addition to the heart in the terminal stage. These findings suggest that the present case at first is PCL in a strict sense. It is also suggested that PCL may show microscopical metastases to the visceral organs as the disease progresses.

The histology of the present case was diffuse large B cell lymphoma. Most of the reported cases of PCL are diffuse large B cell lymphoma, though a minority of them are of immunoblastic, lymphoblastic, diffuse medium cell, diffuse small cell, and Burkitt types [6]. Most of PCL are of B cell type, while a few cases of T cell type were reported [6]. Recently, diffuse large B cell lymphoma has been classified at least into germinal center B cell-like (GCB) and non-GCB according to the immunohistochemistry of CD10, bcl-6 and MUM1 [4]. In general, non-GCB shows poorer prognosis than GCB [4]. The present case was non-GCB lymphoma which may reflect the poor prognosis of the present case.

PCL usually occurs in immunosuppressed patients such as HIV-infected patients [1, 6]. PCL in immunocompetent patients are extremely rare [2]. It is well known that patients with immunosuppression may develop several cancers including lymphoma. The present PCL occurred in an immunocompetent man. Although the reason for this is unclear, it may be possible that subclinical immunosuppressive state might be present in the present elderly man as suggested previously [2, 6].

EBV may be involved in the pathogenesis of several types of malignant lymphomas including Burkitt lymphoma and pyothrax-associated lymphoma [8]. In addition, immunocompromised patients may be infected by EBV. However, the present case was negative for EBV-related protein and EBV DNA, suggesting that EBV was not involved in the pathogenesis of the present case. Review of the literature shows no association between EBV and PCL [6].

In summary, the author reported an autopsy case of PCL with microscopical metastases to the visceral organs in a 70-year-old immunocompetent patient. It is suggested that PCL occurs in immunocompetent persons, and that PCL may show microscopical metastases to the extracardiac visceral organs as the disease progresses.

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