

Diffuse Large B-Cell Lymphoma Associated with Chronic Inflammation Manifested as a Soft Tissue Mass: Incidental Discovery on Histological Examination

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Received: November 9, 2010

Accepted: December 6, 2010

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We report an extraordinary case of diffuse large B-cell lymphoma arising in a cystic necrotic mass in a 35-year-old man who presented with a soft tissue mass at the site of previous surgery. A benign mass was surgically removed 17 years ago, after which a cystic lesion gradually developed at the same site. The resected mass appeared as a thick-walled cyst filled with brown necrotic and hemorrhagic material. On microscopic examination, the cyst wall was primarily necrotic tissue with some aggregates of large atypical lymphoid cells. These atypical cells were diffusely positive for CD20 and showed a high proliferation index, Epstein-Barr virus positivity, and clonal rearrangement of the immunoglobulin gene. His present condition was diagnosed as Epstein-Barr virus-associated diffuse large B-cell lymphoma arising from chronic inflammation. It is important to be aware of the clinical manifestations and histological features of this rare disease in light of diagnosis and treatment.

Key Words: Lymphoma, large B-cell, diffuse; Inflammation; Epstein-Barr virus infections

Diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation (CI) is a new category in the 2008 World Health Organization (WHO) classification of hematopoietic and lymphoid tissues tumors.¹ DLBCL is a lymphoid neoplasm that arises due to long-standing CI and is associated with the Epstein-Barr virus (EBV). In addition to pyothorax-associated lymphoma (PAL), which is a prototype of this new category, several cases of DLBCL arising in patients with diverse CI status such as that found in chronic osteomyelitis,² metallic implants,³ surgical mesh implants,⁴ or chronic skin ulcers² have been reported. It is important to be aware of the clinical manifestations and histological features of this rare disease for diagnosis and treatment. In this study, we report a rare case of DLBCL arising in a cystic necrotic mass at the site of previous surgery and present a review of the relevant literature. To the best of our knowledge, this is the first case report describing DLBCL associated with CI in Korea.

CASE REPORT

A 35-year-old man was referred to the hospital to resect a huge cystic mass on his lower back. The mass had recently enlarged, measuring 20 × 14 cm, and was painful. He had a probable lipoma at the same site 17 years ago, which was surgically excised. He was otherwise healthy. A physical examination performed at the current admission revealed a huge subcutaneous mass protruding from the lower back, but the overlying skin was intact (Fig. 1A). Magnetic resonance imaging revealed a cystic mass of high signal intensity with hemorrhagic portions (Fig. 1B). The clinical and radiological test findings indicated a benign lesion such as an epidermoid cyst. On macroscopic examination, the mass consisted of two thick-walled cystic portions filled with brown, necrotic, and hemorrhagic material (Fig. 1C). Portions of yellow adipose tissue and whitish fibrotic tissue were observed between the two cystic lesions (Fig. 1D). A microscopic examination of the mass revealed mostly necrosis with a few aggregates of large atypical lymphoid cells. (Fig. 2A-C). A immunohistochemical study revealed that the cells were posi-

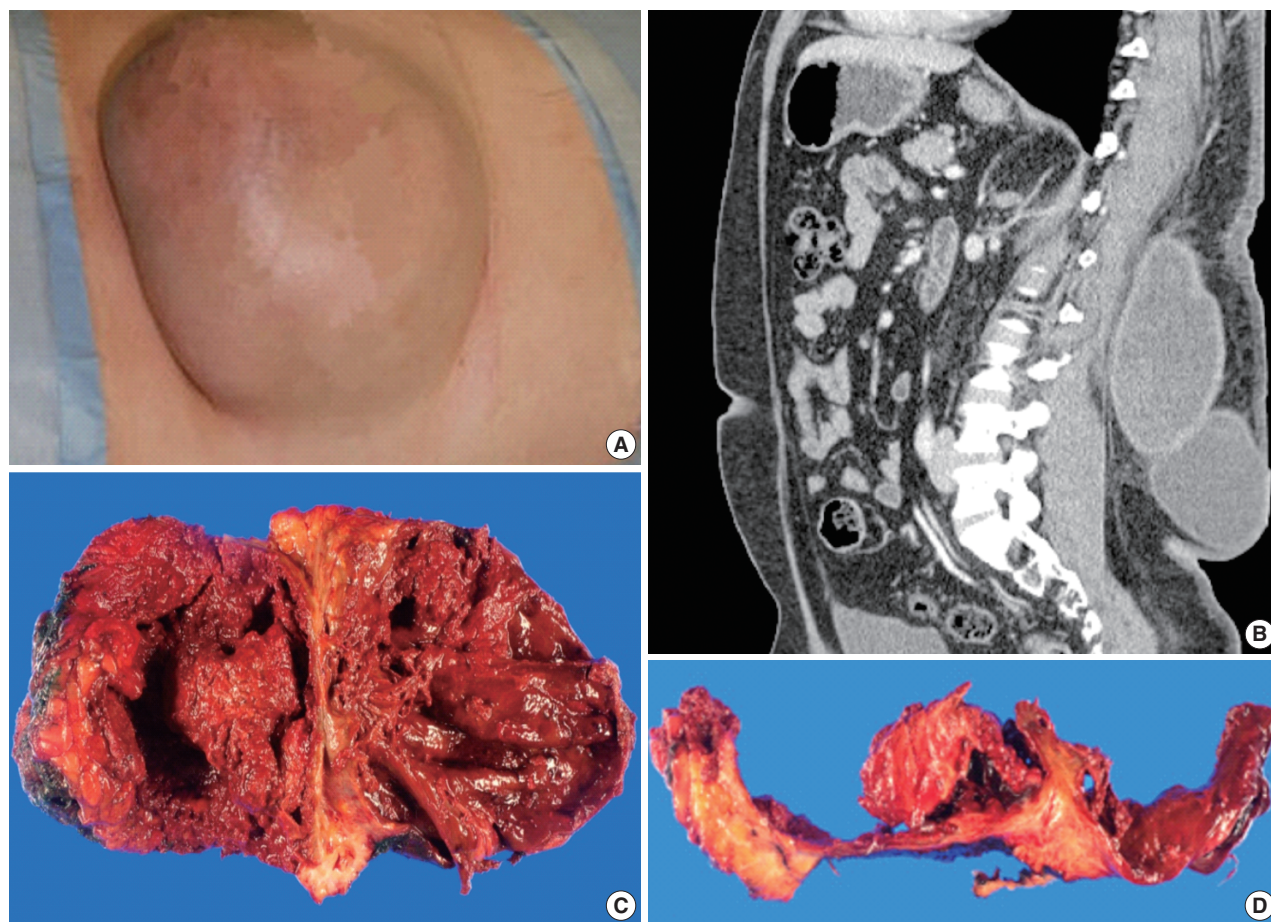


Fig. 1. (A) Protruding subcutaneous mass on the back. (B) Magnetic resonance imaging reveals a high signal intensity cystic mass on the subcutaneous tissue of the lower back. (C) Grossly, two cystic masses are filled with necrotic and hemorrhagic material. (D) The cut surface of the resected tumor shows a thickened fibrous capsule.

tive for CD20 (Fig. 2E), CD79a, and PAX-5 (Fig. 2F); focally positive for Bcl-6 but negative for CD3, MUM-1, and CD10. More than 90% of the tumor cells were positive for Ki-67 (Fig. 2G). *In situ* hybridization revealed that the lymphocytes were diffusely positive for EBV (Fig. 2H) but negative for human herpes virus-8. A clonal immunoglobulin gene rearrangement was shown by polymerase chain reaction. Therefore, we diagnosed this condition as EBV-associated DLBCL associated with CI. After the surgery, the EBV copy number in the whole blood was determined, but it was less than the detectable limit (< 3.8 copies/ μ L whole blood). The results of a bone marrow examination were negative. No systemic involvement was observed on further evaluation. The patient received five courses of chemotherapy (R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

DISCUSSION

In addition to PAL, cases of DLBCL associated with chronic osteomyelitis,² metallic implants,³ or chronic skin ulcers² have been reported. These conditions share the following common features: they arise in an enclosed area or environment, have clinical or histological evidence of long-standing or slow-growing lesions with CI, show morphological features of DLBCL, and are associated with EBV.^{1,3} The WHO classification of hematopoietic and lymphoid tumors has adopted "DLBCL associated CI" as a distinct entity in its 2008 revision.¹

This report describes an unusual case of DLBCL associated with long-standing CI that was diagnosed incidentally. Although the lesion merely consisted of microscopic aggregates, the atypical lymphoid cells expressed B-cell markers uniformly and showed a high proliferation index, EBV positivity, and clonal rearrangement of the immunoglobulin gene. These findings are

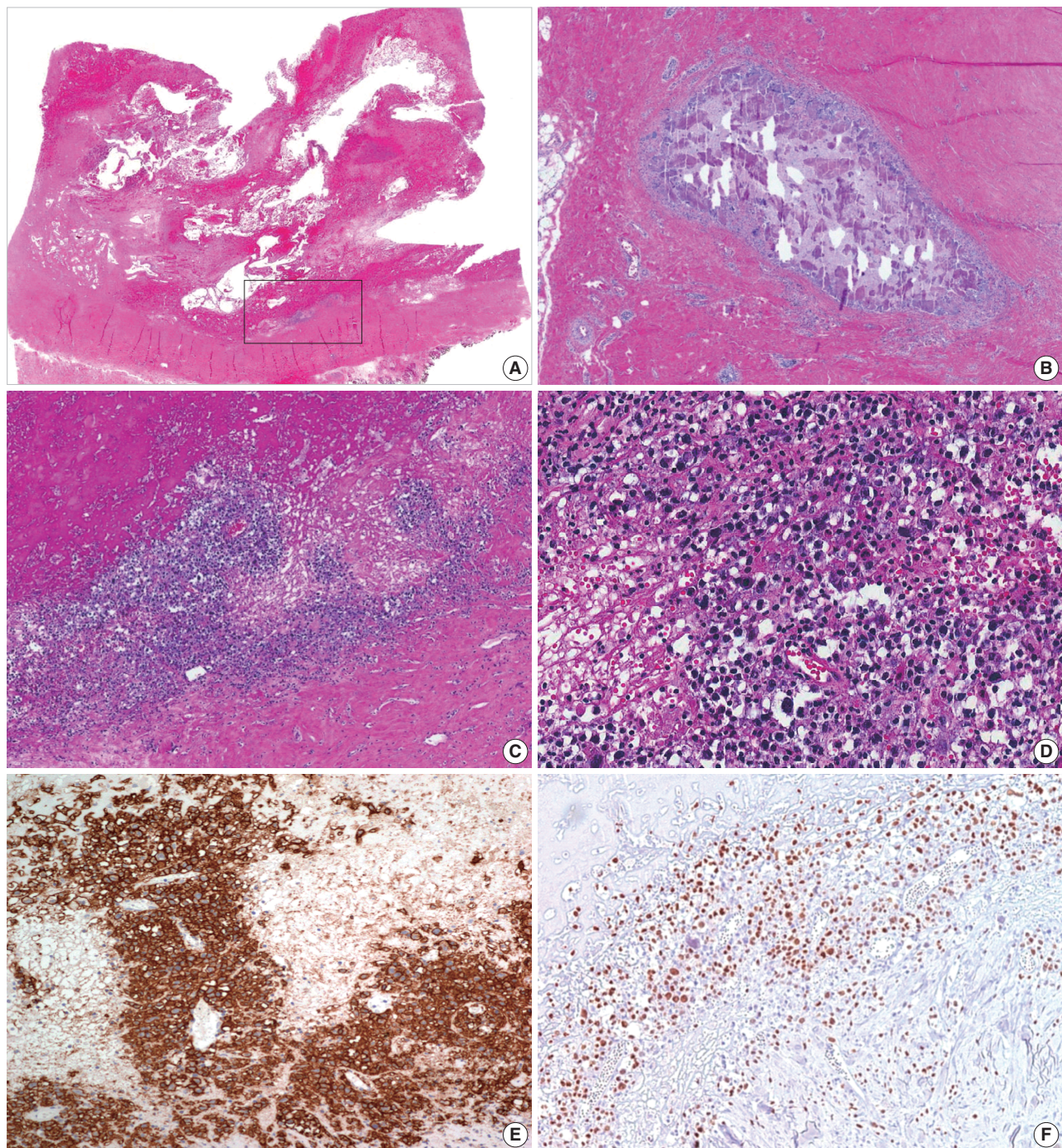


Fig. 2. Microscopic findings of the resected tumor. (A) Scanning magnification shows the thickened fibrous capsule (bottom) and inner hemorrhagic and necrotic material (top). (B) The magnification of the inset from (A) shows the foreign body granuloma. (C, D) Atypical large lymphoid cells are marked and are admixed with necrotic material and apoptotic bodies. (E) The large lymphoid cells are positive for CD20 (F) and PAX5. (Continued to the next page)

sufficient for diagnosing DLBCL. It is important to be aware of this rare disease, because the aggregates of atypical lymphoid cells may be easily neglected on the microscopic examination, particularly when the patient shows no systemic symptoms, as in this case. Localized immunodepression induced by CI or im-

munosuppressive cytokines may have favored the clonal proliferation of EBV-infected B-cells. We observed multiple foreign body granuloma foci with basophilic material and cholesterol clefts in the lesion (Fig. 2B), leading to the suspicion that the remnant foreign material from the previous surgery may have

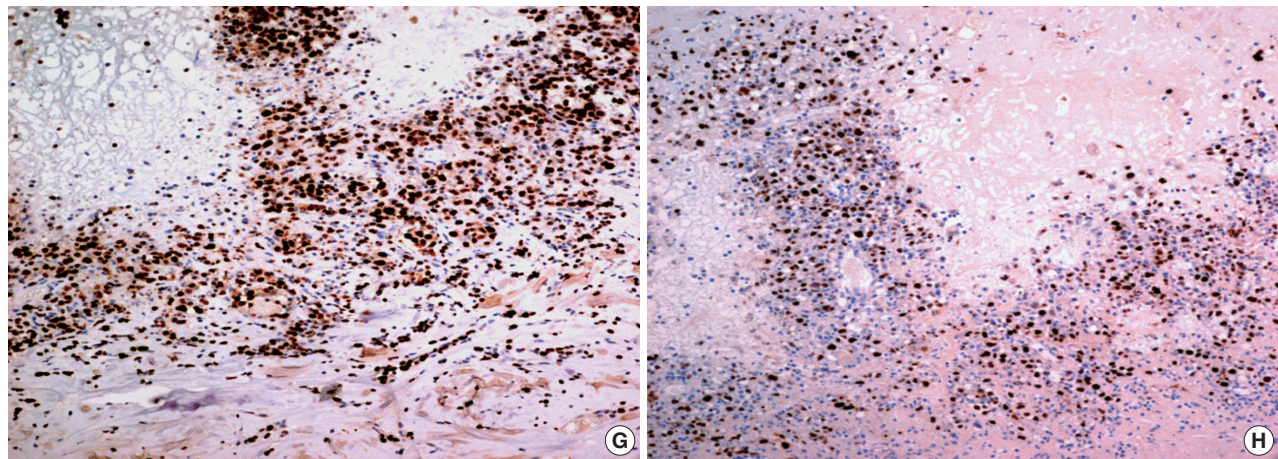


Fig. 2. (Continued from the previous page) (G) More than 90% of the tumor cells are positive for Ki-67. (H) The tumor cells are positive for Epstein-Barr virus based on *in situ* hybridization.

Table 1. Diffuse large B-cell lymphoma (DLBCL) associated with chronic inflammation and a foreign body

Author	Age (yr)/Sex	Foreign body	Interval (yr)	Histology	Tumor site	EBV	Treatment	Follow up
McDonald (1981) ⁵	48/M	Orthopedic metallic implant	17	Histiocytic lymphoma	Tibia soft tissue	NA	RT and CT	Alive well at 2 years
Dodion <i>et al.</i> (1982) ⁶	49/M	Orthopedic metallic implant	1	DLBCL	Thigh	NA	RT and CT	Died at 7 months
Albat <i>et al.</i> (1994) ⁷	66/F	Prosthetic mitral valve	8	Large cell lymphoma	Left atrial wall	NA		Alive at 6 months without recurrence
Radhi <i>et al.</i> (1998) ⁸	25/M	Orthopedic metallic implant	8	DLBCL	Ankle soft tissue	NA	CT	Alive at 6 months without recurrence
Ito and Shimizu (1999) ⁹	63/F	Orthopedic metallic implant	4	DLBCL	Thigh soft tissue	NA	CT and RT	NA
	80/F	Orthopedic metallic implant	8	DLBCL	Ischium	NA	RT	Local recurrence and died of unrelated cause at 1 year
Ganapathi <i>et al.</i> (2001) ¹⁰	85/F	Orthopedic metallic implant	12	DLBCL	Femur	NA	RT	Died soon
Syed <i>et al.</i> (2002) ¹¹	75/F	Orthopedic metallic implant	8	DLBCL	Acetabulum	NA	RT	Died of unrelated cause at 1 year
Dürreman <i>et al.</i> (2005) ¹²	65/F	Dacron mitral valve	9	Centroblastic lymphoma	Atrial endocardium	NA	CT	NED of recurrence
Cheuk <i>et al.</i> (2005) ³	78/M	Orthopedic metallic implant	32	DLBCL	Femur	+	RT	Died from secondary digestive lymphoma at 10 months
O'Shea <i>et al.</i> (2006) ¹³	75/F	Orthopedic metallic implant	13	Immunoblastic lymphoma	Femur	NA	RT and CT	NED at 2 years
Afrapoli <i>et al.</i> (2007) ¹⁴	79/M	Dacron vascular graft	6	B-cell lymphoma	Ascending aorta	NA	NA	Died of disease at 20 weeks
Fujimoto <i>et al.</i> (2008) ⁴	81/M	Surgical mesh	20	DLBCL	Thoracic wall	+	ND	NA
Bagwan <i>et al.</i> (2009) ¹⁵	50/M	Porcine aortic valve	3	DLBCL	Aortic valve	+	CT	Died of disease at 4 months
Miller <i>et al.</i> (2010) ¹⁶	48/M	Mechanical aortic valve	24	DLBCL	Ascending aorta	+	ND	Died at 6 months
	80/F	Bioprosthetic aortic valve	8	DLBCL	Aortic valve	+	ND	NE of lymphoma at autopsy
	79/F	Synthetic tube graft of aorta	5	DLBCL	Ascending aorta	+	ND	Alive without recurrence at 6 months
Loong <i>et al.</i> (2010) ¹⁸	78/M	Orthopedic prosthesis	16	DLBCL	Knee	+	RT	Died from other disease
Present study	35/M	Gauze (?)	17	DLBCL	Back soft tissue	+	CT	NE of lymphoma at 18 months

EBV, Epstein-Barr virus; M, male; NA, not available; RT, radiotherapy; CT, chemotherapy; F, female; NED, no evidence of disease; NE, no evidence; ND, not done.

caused the CI in this patient and facilitated the occurrence of DLBCL. Several cases of DLBCL associated with CI caused by foreign bodies have been reported (Table 1).⁴⁻¹⁶ Of the 17 cases reported, 10 were associated with orthopedic metallic implants,^{3,5,6,8-11,13} five with prosthetic cardiac valves,^{7,12,15,16} two with synthetic aortic grafts,^{16,17} and one with surgical mesh.⁴ The interval between the implant and onset of lymphoma varies from 14 months to 32 years (median, 8 years). EBV positivity was marked in seven cases.^{4,12,15,16}

Recently, Loong *et al.*¹⁸ reported four cases of DLBCL associated with CI in patients with a splenic cyst, hydrocele, atrial mass, or a knee joint prosthesis. They argued that these cases were distinct from the typical cases of DLBCL associated with CI, as they were discovered incidentally. Moreover, they raised the query of whether the standard treatment for localized extranodal DLBCL is optimal for these incidental DLBCLs, even if the tumor volume is microscopic, or whether the tumor be completely removed along with the diseased organ or pathological lesion.¹⁸ The similarity between our case and the cases of Loong *et al.*¹⁸ lies in the aspect of incidental discovery of DLBCL in a cystic mass lesion with CI. According to the current standard treatment for localized extranodal DLBCL, our patient is now on chemotherapy despite complete excision of the cystic mass and no systemic involvement. Some reports have stated that the optimal treatment for PAL is radiation therapy and not primary chemotherapy or open window thoracotomy prior to and during chemotherapy.¹⁹ However, no standard treatment for DLBCL associated with CI has been established. Elderly patients with PAL may have poor pulmonary function due to a history of tuberculosis or chronic pyothorax, so their prognoses are unfavorable. However, the factors described above may play a role distinguishing therapeutic approaches between incidentally found microscopic DLBCL associated with CI and PAL.

In conclusion, we report a rare case of incidentally found DLBCL associated with CI, which was probably caused by a foreign body such as gauze left at the site of previous surgery. When CI is limited within a closed space for an extended duration, it can induce DLBCL via EBV infection. Further research is required to determine the standard treatment for such incidentally found DLBCL associated with CI.

REFERENCES

1. Chan JK, Aozasa K, Gaulard P. Diffuse large B-cell lymphoma associated with chronic inflammation. In: Swerdlow SH, Campo E, Harris NL, *et al.*, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: IARC Press, 2008; 245-6.
2. Copie-Bergman C, Niedobitek G, Mangham DC, *et al.* Epstein-Barr virus in B-cell lymphomas associated with chronic suppurative inflammation. *J Pathol* 1997; 183: 287-92.
3. Cheuk W, Chan AC, Chan JK, Lau GT, Chan VN, Yiu HH. Metallic implant-associated lymphoma: a distinct subgroup of large B-cell lymphoma related to pyothorax-associated lymphoma? *Am J Surg Pathol* 2005; 29: 832-6.
4. Fujimoto M, Haga H, Okamoto M, *et al.* EBV-associated diffuse large B-cell lymphoma arising in the chest wall with surgical mesh implant. *Pathol Int* 2008; 58: 668-71.
5. McDonald I. Malignant lymphoma associated with internal fixation of a fractured tibia. *Cancer* 1981; 48: 1009-11.
6. Dodion P, Putz P, Amiri-Lamraski MH, Efira A, de Martelaere E, Heimann R. Immunoblastic lymphoma at the site of an infected vitallium bone plate. *Histopathology* 1982; 6: 807-13.
7. Albat B, Messner-Pellenc P, Thévenet A. Surgical treatment for primary lymphoma of the heart simulating prosthetic mitral valve thrombosis. *J Thorac Cardiovasc Surg* 1994; 108: 188-9.
8. Radhi JM, Ibrahim K, al-Tweigeri T. Soft tissue malignant lymphoma at sites of previous surgery. *J Clin Pathol* 1998; 51: 629-32.
9. Ito H, Shimizu A. Malignant lymphoma at the site of a total hip replacement. *Orthopedics* 1999; 22: 82-4.
10. Ganapathi M, Lake DN, Griffiths AP. Periprosthetic high-grade B-cell lymphoma complicating an infected revision total hip arthroplasty. *J Arthroplasty* 2001; 16: 229-32.
11. Syed AA, Agarwal M, Fenelon G, Toner M. Osseous malignant non-Hodgkin's B-cell lymphoma associated with total hip replacement. *Leuk Lymphoma* 2002; 43: 2213-6.
12. Dürreleiman NM, El-Hamamsy I, Demaria RG, Carrier M, Perrault LP, Albat B. Cardiac lymphoma following mitral valve replacement. *Ann Thorac Surg* 2005; 79: 1040-2.
13. O'Shea K, Kearns SR, Blaney A, Murray P, Smyth HA, McElwain JP. Periprosthetic malignancy as a mode of failure in total hip arthroplasty. *J Arthroplasty* 2006; 21: 926-30.
14. Afrapoli AH, Brunet AP, Marnette JM. Heart lymphoma 6 years after a prosthetic ascending aorta replacement: related or unrelated? *Minerva Chir* 2007; 62: 43-5.
15. Bagwan IN, Desai S, Wotherspoon A, Sheppard MN. Unusual presentation of primary cardiac lymphoma. *Interact Cardiovasc Thorac Surg* 2009; 9: 127-9.
16. Miller DV, Firchau DJ, McClure RF, Kurtin PJ, Feldman AL. Epstein-Barr virus-associated diffuse large B-cell lymphoma arising on cardiac prostheses. *Am J Surg Pathol* 2010; 34: 377-84.
17. Tresnasari K, Takakuwa T, Ham ME, Rahadiani N, Nakajima H, Aoi

- zasa K. Telomere dysfunction and inactivation of the p16(INK4a)/Rb pathway in pyothorax-associated lymphoma. *Cancer Sci* 2007; 98: 978-84.
18. Loong F, Chan AC, Ho BC, *et al.* Diffuse large B-cell lymphoma associated with chronic inflammation as an incidental finding and new clinical scenarios. *Mod Pathol* 2010; 23: 493-501.
19. Yoshitomi A, Chida K, Suda T, *et al.* Pyothorax associated lymphoma treated by chemotherapy after thoracostomy. *Nihon Kokyuki Gakkai Zasshi* 1999; 37: 619-22.