



## Case Report

# Non-Hodgkin Lymphoma Mimics Infected Total Knee Arthroplasty

## 非何傑金氏淋巴瘤模仿全膝關節置換感染

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## ABSTRACT

Lymphoma associated with total knee arthroplasty is a rare condition. We report a case of non-Hodgkin lymphoma mimicking an infected total knee arthroplasty. A 73-year-old woman who received left total knee replacement presented with fever and a discharging sinus over her left knee 12 weeks after surgery. The diagnosis of prosthetic joint infection was made and a two-stage revision arthroplasty planned. After implant removal and insertion of an antibiotic spacer in the first-stage operation, culture results of all intraoperative specimens were negative but the pathology report showed diffuse large B-cell lymphoma. She then received chemotherapy and a second-stage reconstruction operation. The wound healed uneventfully and she regained independent mobility.

## 中文摘要

與全膝關節置換相關的淋巴瘤是罕見病症。我們報告一宗非何傑金氏淋巴瘤模仿全膝關節置換感染的病例。一名73歲的女性患者在接受左膝全膝關節置換術12週後出現人工關節感染的病徵。臨床診斷為全膝關節置換感染，我們安排病人進行兩個階段全膝關節翻修置換術。我們為她進行第一階段清創手術後，膝關節組織樣本的病理報告顯示為淋巴瘤。在接受了化療及第二階段全膝關節翻修置換術後，她的傷口順利癒合並能夠獨立步行。

## Introduction

Non-Hodgkin lymphoma is a cancer of the lymphatic system resulting from uncontrolled proliferation of lymphocytes. It typically presents with lymphadenopathy of the neck, arm, and groin. It might occasionally affect the skeletal system, giving rise to a palpable mass, bone pain, and pathological fracture. Lymphoma associated with total knee arthroplasty is rare and poses a diagnostic challenge to orthopaedic surgeons. A case of non-Hodgkin lymphoma mimicking infected total knee arthroplasty and a review of the literature are presented here.

## Case Report

A 73-year-old woman presented with bilateral mechanical knee pain ongoing for 10 years. She enjoyed good health in the past. Her knee pain deteriorated progressively and she had become

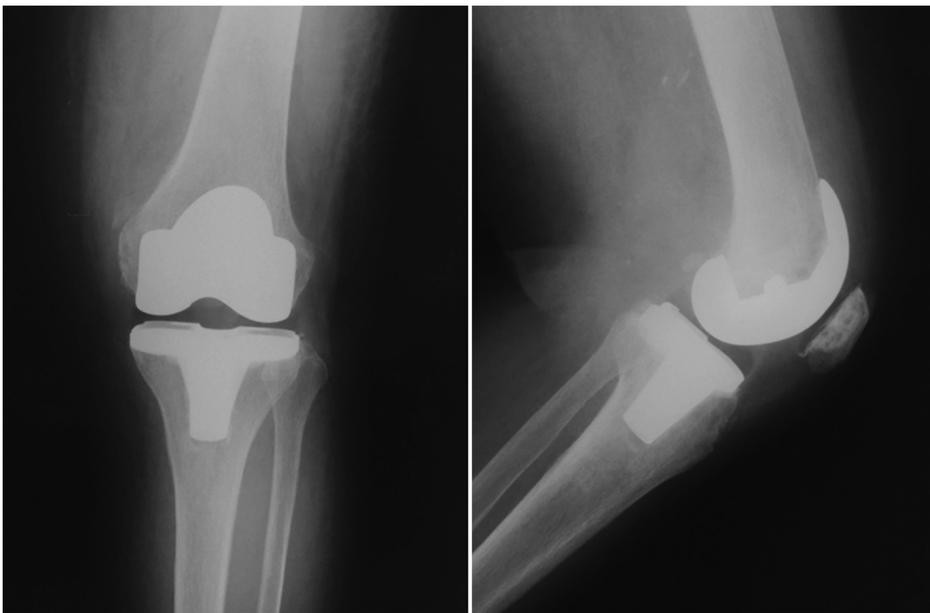
wheelchair-bound for the previous 6 months. There was no history of trauma or septic arthritis. Plain radiographs showed tri-compartmental osteoarthritis of her knees without any bone lesion (Figure 1). Preoperative chest radiography and blood tests including complete blood count, erythrocyte sedimentation rate, C-reactive protein, serum alkaline phosphatase, and serum calcium were normal. Right total knee replacement was performed in June 2011 using a cemented implant (NexGen Complete Knee Solution Legacy Knee; Zimmer, Warsaw, IN, USA). A subsequent left total knee replacement was performed in November 2011 using the same implant. Both operations were uneventful. Upon follow-up in January 2012, she had good recovery from her operations and was able to walk with a frame independently for 30 minutes.

She developed fever and left knee pain in February 2012. She did not have night sweats, weight loss or fatigue. Physical examination revealed left knee effusion and a 1-cm discharging sinus at the distal wound edge. There was no enlarged lymph nodes or hepatosplenomegaly. Radiographs did not reveal any bone erosion or implant loosening (Figure 2). Blood tests showed an elevated white cell count ( $1.39 \times 10^{10}/L$ ), erythrocyte

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**Figure 1.** Plain radiograph of the patient's left knee on initial presentation, showing features of osteoarthritis without bone lesion.

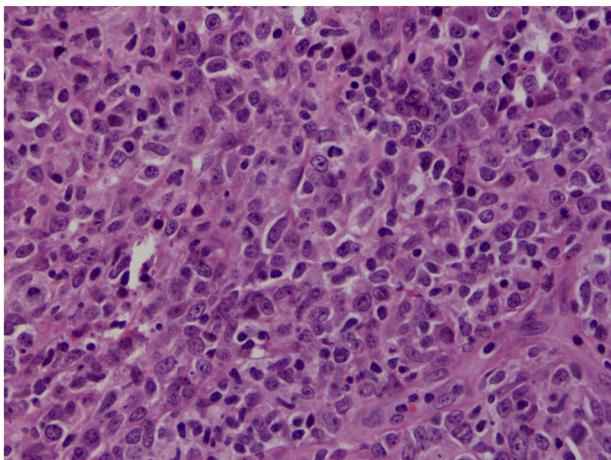


**Figure 2.** Plain radiograph of the patient's left knee when she presented with fever and a discharging sinus. The implant was well fixed without bone erosion.

sedimentation rate (97 mm/h), and C-reactive protein (167 mg/L). Serum calcium and alkaline phosphatase were normal. Bacterial culture of the left knee discharge was negative. Based on the Musculoskeletal Infection Society criteria, the presence of sinus tract communicating with the prosthesis was suggestive of infected knee prosthesis despite a negative culture result. Open debridement with removal of all the implants and insertion of a cement spacer was performed in February 2012. The synovium was inflamed with 10 mL of turbid fluid collected inside the joint. The knee implants were well fixed. There was no bone erosion or soft tissue mass. Intraoperative frozen sections of the synovium and femoral and tibial membranes showed chronic inflammatory cell infiltration with 5–10 polymorphs per high-power field. The bacterial and acid-fast bacilli cultures for the synovium and femoral and tibial membranes were negative. Formal

pathological reports of the femoral membrane revealed diffuse infiltration of large and small lymphoid cells (Figure 3). The lymphoid cells were positive for CD20 (B-cell marker) in immunohistochemical studies. Molecular studies using polymerase chain reaction showed a clonal proliferative pattern for immunoglobulin heavy chain *Fr2/JH* gene which was suggestive of B-cell lymphoma.

The diagnosis of diffuse large B-cell lymphoma was made and she was referred to a haematologist with a positron emission tomography/computed tomography scan showing hypermetabolic lesions at the diaphragm and the left knee. She was put on eight courses of chemotherapy consisting of rituximab, cyclophosphamide, etoposide, vincristine, and prednisone for 5 months. After discussion with the haematologist, a second-stage reconstruction operation was performed in May 2012 using stemmed implants



**Figure 3.** Histology of femoral membrane revealed atypical large-sized lymphoid cells, which possessed coarse chromatin and prominent nucleoli. They were admixed with small lymphoid cells and other inflammatory cells.

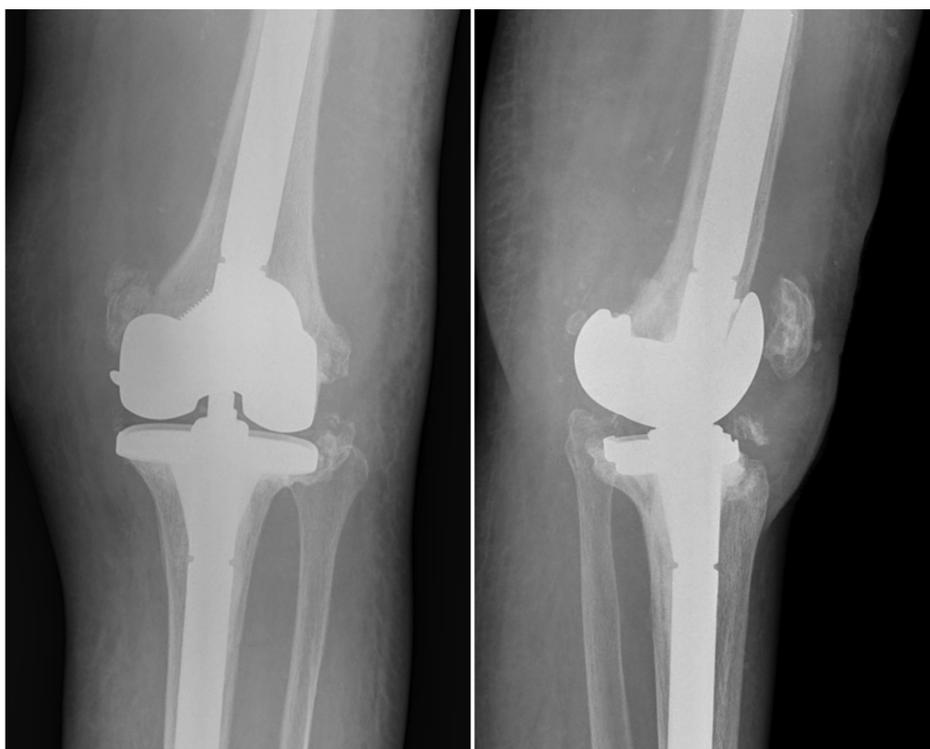
(NexGen Legacy Constrained Condylar Knee; Figure 4). The wound healed uneventfully and she was able to walk with a quadripod independently for 15 minutes 3 months after operation.

### Discussion

In 2013, non-Hodgkin lymphoma comprised 3% of all cancers in Hong Kong.<sup>1</sup> The aetiology of lymphoma is unknown; association with Epstein–Barr virus, human immunodeficiency virus, and human herpes virus-6 has been reported in certain subtypes of lymphoma.<sup>2</sup> Metallic orthopaedic implants have been implicated to induce lymphoma.<sup>3</sup> Cobalt and chromium wear particles are demonstrated to be carcinogenic in animal models.<sup>4</sup> Elevated levels of these metals have been found in human tissue near the implants,

in regional lymph nodes, bone marrow, liver, and spleen.<sup>5</sup> A longitudinal study from the Finnish Cancer Registry involving 31,651 patients, however, failed to demonstrate a causal relationship between hip replacement and lymphoma.<sup>6</sup> Since the time frame between tumour presentation and knee replacement was so short in our case, knee surgery and the presence of an implant was unlikely to have been the cause of lymphoma, and the lymphoma might have been present before the operation. The operation might have accelerated the local tumour growth, with opening of the medullary canal and postoperative hyperaemia. The insertion of an intramedullary femoral guide might also have caused tumour emboli and accelerate systemic spread.

The incidence of non-Hodgkin lymphoma peaks in the 5<sup>th</sup> decade with a slight male predominance.<sup>7</sup> Non-Hodgkin lymphoma of the skeletal system most often involves the femur, pelvis, and vertebrae.<sup>8</sup> Common presentations are bone pain unrelieved by rest, palpable lump, pathological fracture, and B symptoms consisting of fever, night sweat, weight loss, and fatigue.<sup>8,9</sup> Blood tests might reveal anaemia with elevated alkaline phosphatase, calcium level, and erythrocyte sedimentation rate.<sup>8,9</sup> Radiological findings are nonspecific with lytic, blastic, and mixed lesions reported.<sup>8</sup> Periprosthetic lymphoma presenting after total knee arthroplasty is exceedingly rare. Only three cases have been reported in the literature (Table 1). The patient described by Cheuk et al<sup>3</sup> developed knee pain and osteolysis around the femoral implant 16 years after total knee arthroplasty. Revision operation was performed with incidental finding of diffuse large B-cell lymphoma in the remaining materials submitted for histological examination. Chaudhry et al<sup>10</sup> described a patient who presented with bone pain and osteolysis 3 years after total knee arthroplasty. Radiographs showed osteolysis around the tibial tray. Bone scan revealed a metabolically active lesion in the proximal tibia. The patient underwent open biopsy with histological finding of diffuse large B-cell lymphoma. The patient reported by Eskander et al<sup>11</sup> developed persistent knee effusion and ecchymosis 6 months after total knee arthroplasty. The



**Figure 4.** Plain radiograph of the patient's left knee after second-stage reconstruction operation.

**Table 1**  
Clinical features of cases of periprosthetic lymphoma presenting after total knee arthroplasty

Reference	Sex/age (yr)	Presentation	Radiograph	Histology
Cheuk et al <sup>3</sup>	Male/78	Right knee pain at 16 yr after total knee arthroplasty	Osteolysis over lateral femoral condyle	Diffuse Large B-cell lymphoma
Chaudhry et al <sup>10</sup>	Male/76	Focal right knee pain at 3 yr after total knee arthroplasty	Osteolysis over medial side of proximal tibia	Diffuse large B-cell lymphoma
Eskander et al <sup>11</sup>	Female/70	Persistent left knee effusion and ecchymosis 6 mo after total knee arthroplasty	Not available	Diffuse large B-cell lymphoma

patient had no fever and inflammatory markers were normal. Open drainage for suspected haematoma collection and biopsies of soft tissue were performed. The pathology report came back as diffuse large B-cell lymphoma. We believe that our present patient is the fourth reported case in the literature. None of the previous cases were clinically compatible with infection with fever, wound break down, discharging sinus, and elevated inflammatory markers in the early postoperative period. This posed a major diagnostic difficulty to orthopaedic surgeons. The confusion led to unnecessary removal of a well-fixed implant.

Diagnosis of non-Hodgkin lymphoma is established by the histological morphology and immunophenotyping of biopsy tissue. Intraoperative frozen section may identify malignant lymphoid cells to direct operative management. Artifacts caused by the frozen section technique could, however, distort the cellular details and disrupt the architectural relationship of lymphoid tissue, making diagnosis difficult.<sup>12</sup> Given the limitation of frozen sections, close cooperation between surgeon and pathologist is required to achieve a meaningful frozen report.<sup>12</sup> While the surgeon should convey all the relevant information including clinical history, location of biopsy, and suspected diagnosis to the pathologist, the pathologist should have a high index of suspicion to look for histological features of lymphoma in frozen sections for infected prosthesis, even for cases that are clinically compatible with infection.

The management of non-Hodgkin lymphoma is determined by the histological subtype and disease staging. Diffuse large B-cell lymphoma constitutes one-third of all non-Hodgkin lymphoma and is the commonest histological subtype affecting the skeletal system.<sup>2,9</sup> Diffuse large B-cell lymphoma grows and spreads rapidly, causing death in 1–2 years if left untreated. Response to therapy is, however, good. The standard treatment approach is chemotherapy. Local irradiation can be added for localised disease. The prognosis depends on the disease staging and patient performance status with a 3-year survival rate of 60–90%.<sup>2</sup>

In conclusion, we presented a case of diffuse large B-cell lymphoma manifested as infected total knee arthroplasty. With the marked increase of joint replacement surgery performed nowadays, together with a better awareness of the long-term complications and improvement in follow-up, we might expect more cases of periprosthetic lymphoma presenting after total knee arthroplasty in the future. Non-Hodgkin lymphoma should be put into the list of differential diagnoses for patients presenting with

wound complications after total knee arthroplasty. A high index of suspicion for possibility of neoplasm is required in frozen section diagnosis for suspected infected prosthesis, even for cases that are clinically compatible with infection.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

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**References**

- Hong Kong Cancer Registry. Hospital Authority Hong Kong; 2015.
- Ansell SM. Non-Hodgkin lymphoma: diagnosis and treatment. *Mayo Clin Proc* 2015;**90**:1152–63.
- Cheuk W, Chan AC, Chan JK, et al. 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.
- McKee GK. Carcinogenic properties of wear particles from prosthesis made in cobalt-chromium alloy. *Lancet* 1971;**1**:750.
- Case CP, Langkamer VG, James C, et al. Widespread dissemination of metal debris from implants. *J Bone Joint Surg Br* 1994;**76**:701–12.
- Paavolainen P, Pukkala E, Pulkkinen P, et al. Cancer incidence in Finnish hip replacement patients from 1980 to 1995: a nationwide cohort study involving 31,651 patients. *J Arthroplasty* 1999;**14**:272–80.
- Müller AM, Ihorst G, Mertelsmann R, et al. Epidemiology of non-Hodgkin's lymphoma (NHL): trends, geographic distribution, and etiology. *Ann Hematol* 2005;**84**:1–12.
- Clayton F, Butler JJ, Ayala AG, et al. Non-Hodgkin's lymphoma in bone. Pathologic and radiologic features with clinical correlates. *Cancer* 1987;**60**:2494–501.
- Ventre MB, Ferreri AJ, Gospodarowicz M, et al. Clinical features, management, and prognosis of an international series of 161 patients with limited-stage diffuse large B-cell lymphoma of the bone (the IELSG-14 study). *The Oncologist* 2014;**19**:291–8.
- Chaudhry MS, Mather H, Marks A, et al. Diffuse large B cell lymphoma complicating total knee arthroplasty: case report and literature review of the association of diffuse large B cell lymphoma with joint replacement. *Acta Haematol* 2011;**126**:141–6.
- Eskander MS, McPhee E, Eskander JP, et al. A left knee wound complication by non-Hodgkins lymphoma in bilateral total knee arthroplasties. *Arch Orthop Trauma Surg* 2008;**128**:1387–90.
- Jaafar H. Intra-operative frozen section consultation: concepts, applications and limitations. *Malays J Med Sci* 2006;**13**:4–12.