Epstein-barr Virus Associated Extranodal Natural Killer T Cell Lymphoma of Nasal Type Mimicking Pyogenic Osteomyelitis of the Proximal Humerus

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Extranodal natural killer (NK) cell lymphoma/leukemia, nasal type, is rare but highly aggressive. These neoplasms are found to be associated with infection of the Epstein-barr virus (EBV). We report a male patient who suffered from EBV associated NK/T cell lymphoma of the proximal humerus but presented as pyogenic osteomyelitis with the clinical signs and symptoms of fever, local erythema, elevated erythrocyte sedimentation rate and C-reactive protein. The patient was treated using antibiotic therapy but the clinical course did not improve until the initiation of systemic chemotherapy. The patient developed tumor recurrence and died due to pneumonia and respiratory failure 10 months after the initial diagnosis. The purpose of this case report was to emphasize the unusual presentation of a neoplasm mimicking osteomyelitis. (Chang Gung Med J 2008;31:314-9)

Key words: natural killer cell lymphoma, proximal humerus, shoulder, osteomyelitis

Natural Killer (NK) cell neoplasms including extranodal NK/T cell lymphoma, nasal type, and aggressive NK cell leukemia are rare but highly aggressive. These neoplasms have been found to be associated with infection of Epstein-barr virus (EBV). Previous case reports have mentioned that patients with extranodal NK/T cell lymphoma of the nasal type die within 6 months following the diagnosis. Neoplasms of the musculoskeletal system may be confused with other diseases such as infection. The involvement of these neoplasms in the shoulder and proximal humerus has not been reported in the literature. Here, we present a case of proximal humerus EBV associated NK/T cell lymphoma in a male patient who was initially treated for pyogenic osteomyelitis.

**CASE REPORT**

A 38-year-old man sustained left shoulder injury during housekeeping 7 months prior to this presentation. He received medication and subacromial injection at another hospital without improvement. Pain, erythema, limited range of motion of the left shoulder, intermittent fever up to 39°C and night sweating gradually developed as well as weight loss of 10 kg during the 2 months prior to this admission. His medical history was unremarkable. Physical examination at presentation showed severe tenderness and erythema over his left deltoid and axillary region. Forward elevation of the left shoulder was limited to 20 degrees. No neck lymphadenopathy was noted. Abnormal laboratory examination results included elevated liver function (Alanine transaminase: 276...
u/L), alkaline phosphatase was 389 u/L, C-reactive protein was 119.1 mg/L and erythrocyte sedimentation rate was 91 mm/hr. The complete blood count showed leukocytosis at 11800/cmm and left shift of the white blood cells. Radiographs of the left shoulder showed mild osteopenia and equivocal permeative changes. After admission to the medical department, a whole-body bone scintigraphy with technecium-99m displayed increased uptake on the left humerus head. Magnetic resonance imaging (MRI) (Fig. 1) showed heterogenous lesions involving the proximal humerus and deltoid muscle with small amount of fluid accumulation compatible with pyogenic osteomyelitis with abscess formation. With the MRI diagnosis of pyogenic infection, empiric antibiotic therapy was performed after blood culture. After orthopedic consultation, echo-guided aspiration of the left shoulder was performed and no growth of any organism was obtained. While parental antibiotic including oxacillin and amikin were given for 2 weeks, the patient displayed persistent spiking fever, slurred speech and unsteady gait.

Due to failure of antibiotics treatment with persistent fever, the patient underwent surgical debridement. Diffuse grayish fragile tissue was noted in the subacromial space following a delto-pectoral approach. The fragile tissues were debrided and sent for pathologic diagnosis. Tissue culture was sterile. Pathological examination of the proximal humerus showed infiltration of malignant cells with large-sized vesicules, round to irregular and prominent nuclei and prominent cytoplasm, which was consistent with non-Hodgkin’s lymphoma (Fig. 2). Immunocytochemical stains showed that the tumor cells were positive for T200, CD3 cytoplasmic staining and CD56 but negative for CD20 (Fig. 3), which confirmed the diagnosis as NK/T cell lymphoma.

Staging studies revealed negative results in lesions at the nasal cavity, abdomen and chest. Bone marrow examination through the right posterior iliac bone was negative for lymphoma involvement. Lumbar puncture study was positive for malignant cells, which was compatible with meningeal involvement. Epstein-barr DNA immunoassay showed positive findings for both the plasma and white blood cell EBV polymerase chain reactions. After a complete survey, the definite diagnosis was extranodal NK/T cell lymphoma of the nasal type, Stage IV B.

The patient underwent whole brain radiotherapy at a total dose of 1500 cGy. Systemic chemotherapy regimens including cyclophosphamide, Adriamycin and Etoposide, as well as intrathecal (Ara-C) chemotherapy were given. The fever and consciousness improved gradually, the repeated magnetic reso-

![Fig. 1](image1.jpg) T1 weighted MRI study showed heterogenous signals at the proximal humerus and deltoid muscle with small amount of fluid accumulation.

![Fig. 2](image2.jpg) Biopsy of the proximal humerus revealed infiltration of malignant cells bearing large-sized vesiculaes, round to irregular and prominent nuclei and prominent cytoplasm, a picture consistent with malignant lymphoma.
nance imaging study 2 months after the surgery showed a regressive change of the left proximal humerus and shoulder (Fig. 4). The patient was discharged after 42 days of hospitalization and was lost to follow-up for a period of 3 months. The patient was readmitted due to tumor recurrence and bone marrow dissemination. He acquired pneumonia 4 months after the second admission and died due to respiratory failure 10 months after the initial diagnosis.

**DISCUSSION**

EBV infection has been noted to be strongly associated with extranodal NK/T cell lymphoma in Asia and South America.\(^1\)\(^-\)\(^3\) Although malignant lymphoma of the bone mimicking osteomyelitis has been previously documented as case reports,\(^4\) few reports notified the cases with primary extranodal NK/T cell lymphoma, nasal and nasal type, of the shoulder girdle and the proximal humerus. To our knowledge, this is the first report in the literature in which primary EBV associated nasal type NK/T cell lymphoma occurred at the proximal humerus.

Primary bone lymphoma constitutes less than 5% of the primary bone tumors and 5% of the extranodal non-Hodgkin’s lymphomas.\(^5\) The presentation age ranged from the second to seventh decades, with a peak occurring at the ages between 45 and 75 years.\(^6\) The most common sites of involvement include the femur and the pelvis. NK cell lymphoma constituted 6.5% of all lymphomas. The World Health Organization (WHO) and the revised European-American Classification of lymphoid neoplasm (REAL) defines three categories of NK cell neoplasm: extranodal NK/T-cell lymphoma, aggressive NK cell leukemia and blastic NK cell lymphoma.\(^2\)\(^,\)\(^7\) Extranodal NK/T cell lymphomas, according to their anatomy, can be further divided into nasal and nasal type. The former often presents with nasal obstruction and is most commonly found in Asian patients. The nasal type occurs outside the nasal cavity and includes variable presentations depending upon the site of involvement such as skin, gastrointestinal tract, spleen, testis, and often presents as a mass lesion.\(^8\)
NK/T cell lymphoma is a very aggressive neoplasm. There has been no prospective clinical study on the extranodal NK/T cell lymphoma and the retrospective data was only limited to the nasal forms due to extremely limited number of cases. Systemic presentations may include fever, pancytopenia, hepatosplenomegaly, hemophagocytosis and multiorgan failure. The involvement of bone presents diagnostic difficulties. However, a delay in diagnosis and treatment usually leads to fatal outcomes. Certain neoplasms such as lymphomas are marked by a reactive lymphocyte invasion similar to that seen in infections. Sterile abscesses can result from a neoplastic process. Therefore even in cases of obvious symptoms of bony infections, lymphomas in the musculoskeletal tissues should be considered especially when the symptoms are aggravated after treatment and no growth of organisms was obtained from the abscesses.

Primary bone lymphoma has a wide spectrum of radiographic findings from a near-normal-appearance bone to a lytic destructive pattern. For radiographic osteomyelitis involvement of the shaft of long tubular bones in patients older than 40 years, alternative diagnosis such as bone lymphoma should be considered. Despite this variability, MRI may be used because it is highly sensitive to soft tissue lesions. MRI findings of the nasal NK/T cell lymphomas were intermediated signal intensity on T1 and T2 weighted images and included bone marrow replacement, soft tissue involvement and cortical erosion. However, MRI features alone cannot reliably distinguish this tumor from other tumors and nonneoplastic conditions, including Wegner's granulomatosis, sarcoidosis, cocaine abuse and infections such as leprosy, syphilis, tuberculosis. There has been little data about the MRI findings of the metaphyseal lesion in patients with extranodal NK/T cell lymphoma of the nasal type. Our patient’s MRI findings of heterogenous signals with abscess accumulation, before and after treatment, may become imaging references in this rare disease.

A definitive diagnosis requires adequate viable tissues for morphological, immunocytochemical and molecular analyses. Typically, the cells bear CD56 on the surface, with or without CD3. CD20 is usually absent. Most patients with NK/T cell lymphoma had relatively short median survival rates. Patients died within 6 months of diagnosis due to pneumonia or septic shock in spite of radiotherapy or chemotherapy. Our patient survived for 10 months after the initial diagnosis.

When we treated our patient, the initial misdiagnosis of musculoskeletal infection was made due to the presentations of shoulder injury, subacromial injection, fever, local erythema and elevated erythrocyte sedimentation rate, C-reactive protein, which were apparent pictures of musculoskeletal infection. Persistent fever and infective symptoms unresponsive to antibiotic treatment indicated an unusual underlying pathology. The accurate diagnosis was delayed 2 months after the onset of symptoms. In conclusion, infections and tumors can mimic one and the other clinically or radiographically. We must pay attention to such a rare neoplasm when we treat bone infections.

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REFERENCES
模仿骨髓炎的近端肱骨結節外自然殺手細胞淋巴癌鼻腔型之病例報告

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結環外自然殺手淋巴癌鼻腔型是一種高侵犯性罕見疾病。我們報告一位病患肩外伤、肩峰下注射病史，因肩部紅腫，發燒而就診。上升的 C 反應蛋白球和紅血球沈降速率數值及影像學檢查，皆為骨髓肌肉感染之臨床表現，但最終病理報告結報外自然殺手淋巴癌鼻腔型。本文強調在臨床治療上明顯為骨髓感染病例之同時，應特別注意是否有其它複雜且罕見的腫瘤存在之可能。(長庚醫誌 2008;31:314-9)

關鍵詞：殺手細胞淋巴癌，近端肱骨，肩關節，骨髓炎

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