CASE REPORT

Primary Breast Natural Killer/T-cell lymphoma with Cutaneous Involvement: A Case Report

Hao Wu, MM; Sheng-Yu Jin, MD

ABSTRACT

Objective • Extranodal natural killer/T-cell lymphoma comprises less than 1% of all non-Hodgkin lymphomas. It is rare in Western countries but is common in East Asia and Central and South America. The pathological features are angiocentricity /angioinvasion and significant tissue necrosis.

Case Presentation • A 72-year-old woman was diagnosed with primary breast extranodal natural killer/T-cell lymphoma. The patient presented with a painless right breast tumor and had uneven internal echo and strip blood flow signal on breast ultrasonography. After right breast tumor resection, the pathological diagnosis was extranodal natural killer/T-cell lymphoma. Despite receiving CHOP chemotherapy, the patient died of lymphoma and multiple organ dysfunction syndrome 27 months after diagnosis.

Conclusion • Extranodal natural killer/T-cell lymphoma with breast tissue as the primary site is very rare. The disease is prone to misdiagnosis and missed diagnosis, and diagnosis by ultrasound is difficult, so pathological examination after biopsy is particularly important. (*Altern Ther Health Med.* 2023;29(8):252-254).

Hao Wu, MM; Attending Doctor, Department of Rehabilitation, Shaoxing People's Hospital, Shaoxing, China; **Sheng-Yu Jin**, MD; Chief Physician, Department of Hematology, Yanbian University Hospital, Yanji, China.

Corresponding author: Sheng-Yu Jin, MD
E-mail: jinsy11@163.com

INTRODUCTION

Primary breast lymphoma is a rare form of breast tumor that accounts for 0.4% to 0.5% of all breast cancers. Extranodal natural killer/T-cell lymphoma (NKTCL) has obvious geographical and ethnic distributions; it is rare in Western countries and is most common in East Asia and Central and South America.[4-7] Extranodal NKTCL is a rare subtype of NKTCL that comprises less than 1% of all non-Hodgkin lymphomas. Extranodal NKTCL occurs almost exclusively outside the lymph nodes.[1] Approximately 80% of cases of Extranodal NKTCL occur in the nasal cavity, nasopharynx, oropharynx and Waldeyer ring.[1] These lymphomas are collectively referred to as nasal NKTCLs.[2] Approximately 20% of cases of Extranodal NKTCL occur in non-nasal areas, including the skin, testes, gastrointestinal tract, trachea and muscle. These lymphomas are called non-nasal NKTCLs.[2]

The pathological features of Extranodal NKTCL are angiocentricity /angioinvasion and tissue necrosis. Infection with Epstein-Barr virus (EBV) is closely related to the pathogenesis, development, and prognosis of NKTCL. EBV-encoded proteins can interfere with the cell cycle and can arrest cells in the G1 phase, causing proliferation of EBV-infected tumor cells. Patients with higher titer of EBV is one of the risk factor of NKTCL.[3] There are few reports about primary breast extranodal NKTCL, and the post-treatment effects on extranodal NKTCL are often unsatisfactory with unacceptable relapse rates.[1]

We report a case of primary breast extranodal NKTCL. The patient presented with a painless right breast tumor and had uneven internal echo and strip blood flow signal on breast ultrasonography. After resection of the right breast tumor, the pathological diagnosis was extranodal NKTCL. Extranodal NKTCL with breast tissue as the primary site is very rare. Here we describe the characteristics of the disease and present a literature review of Extranodal NKTCL.

CASE PRESENTATION

A 72-year-old woman was admitted for treatment of a painless tumor in her right breast. The patient had no fever, no night sweats, and no weight loss of more than 10% within the previous six months. Color Doppler ultrasonography of the breast showed hyperplasia of the lymphoid tissue beside the right papilla. To further clarify the cause of the disease, the right breast tumor was excised and a biopsy was taken. Hematoxylin and eosin staining of the biopsy showed extranodal NKTCL of the right breast (Figure 1).

Figure 1. Extranasal Natural Killer/T-Cell Lymphoma in a Biopsy of the Right Breast Hematoxylin and eosin staining of breast biopsy tissue. **A**, original magnification ×100. **B**, original magnification ×200. Lymphoid tissue with hyperplasia can be seen. The cells are medium in size, the cytoplasm is lightly stained, the nuclei are not uniform, and small nucleoli are visible. The mitotic figures are easily visible.

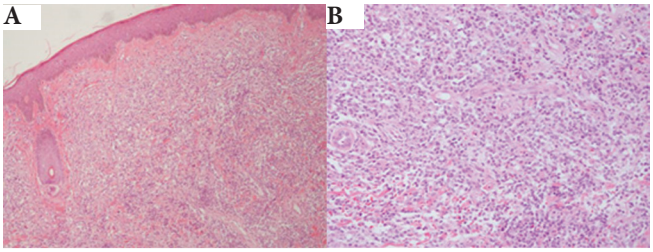


Figure 2. Immunohistochemical Staining and In Situ Hybridization Staining Results. Immunohistochemical staining of breast tissue for (**A**) CD56 (diffuse positive staining) (original magnification ×200) and (**B**) Ki-67 (proliferation index, 70%) (original magnification ×200). Epstein-Barr encoding region in situ hybridization staining (**C, D**) was positive. C, original magnification ×100. D, original magnification ×200.

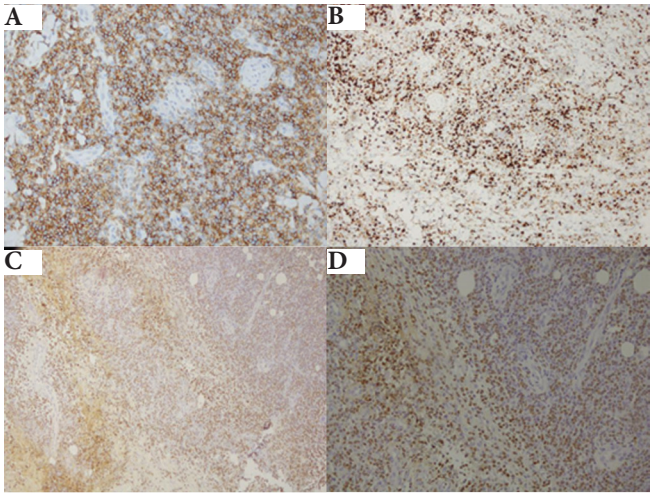
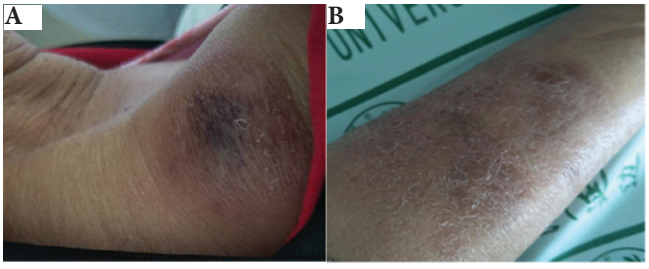


Figure 3. The picture of lesion**.** Tumor development at the 10th month after diagnosis, multiple, asymptomatic, deep-seated, erythematous nodules with central necrotic crusts on the (**A**) left shoulder and (**B**) left calf.



Immunohistochemistry analysis showed that tumor cells were present. The tumor cells were negative for CD4, CD10, CD20, CD21, CD30, anaplastic lymphoma kinase, myeloperoxidase, paired box 5, and terminal deoxynucleotidyl transferase. The tumor cells were positive for CD3, CD7, CD38 (partial), CD56 (diffuse), and granzyme-B. The tumor tissue had a Ki-67 proliferation index of 70%. In situ hybridization showed positivity for the Epstein-Barr encoding region. Figure 2 shows the results of immunohistochemical staining of CD56 and Ki-67 and in situ hybridization staining of the Epstein-Barr encoding region.

An EBV test was negative. Chest and abdominal computed tomography showed enlarged lymph nodes on the right side of the axilla. The Ann Arbor classification was stage IIEA.

The patient and her family chose to refuse treatment and wait and observe because of her older age and current poor condition. In the 10th month after diagnosis, the patient had tumors in the left shoulder (approximately 4×2 cm), left abdomen (approximately 3×3 cm), and left calf (approximately 5×5 cm) (Figure 3). The skin temperature near to the tumors was slightly higher than normal, and a mass was present in the nasal cavity that was accompanied by symptoms of nasal obstruction. Pathological examination after biopsy was diagnosed NKTCL. At this time, the patient received five cycles of CHOP chemotherapy (750 mg/m^2 cyclophosphamide on day 1, 40 mg/m^2 doxorubicin on day 1, 1.4mg/m^2 vincristine on day 1, and 100 mg prednisone on days 1 to 5). Nasal radiotherapy was performed with intensity-modulated radiotherapy twice every 4 weeks. After treatment, the patient's nasal congestion improved, her skin masses were smaller, and her general condition was acceptable. At the 15th month after diagnosis, new masses appeared in her right leg, right shoulder, and left breast, and the patient received four cycles of CHOP chemotherapy and intensity-modulated radiation treatment of the right leg and right shoulder. The masses did not continue to increase in size after treatment and were slightly smaller than before. At the 20th month after diagnosis, the patient was readmitted to the hospital for examination. The diameter of the mass in the left breast was approximately 5 cm, and the diameter of the mass in the right shoulder was approximately 4.5 cm. The boundaries were clear, and the skin surface temperature near to the tumors was high. The mass in the right calf had disappeared. Two new tumors were found on the right calf, each with a diameter of approximately 1 cm. Their borders were clear, and the skin temperature local to the tumors was high.

We performed tissue biopsies to clarify the nature of the right calf skin masses. Pathological examination of the biopsies from the right calf showed non-Hodgkin NKTCL. Immunohistochemistry analysis showed the tumor cells were negative for CD4, CD10, CD20, CD21, CD30, anaplastic lymphoma kinase, myeloperoxidase, paired box 5, and terminal deoxynucleotidyl transferase. The tumor cells were positive for CD3, CD7, CD38 (partial), CD56 (diffuse), and granzyme B. The tumor tissue had a Ki-67 proliferation index of 70%. In situ hybridization showed positivity for the Epstein-Barr encoding region.

In the right front rib area, an area of skin of approximately 10 cm in diameter was red and swollen, and the skin temperature was high. There were 6 new tumors next to this skin area, each with a diameter of approximately 1.5 cm. The patient began to have symptoms of poor breathing. Chest computed tomography revealed inflammation of the lungs and the presence of nodules at the tracheal bifurcation. A consultation of doctors from pneumology department advised that the nodules may be a part of the primary tumor, and they could cause respiratory obstruction, leading to dyspnea and even suffocation. However, the patient was weak, and multiple organ failure was gradually occurring. The patient's condition was not suitable for invasive examination (such as by fiberoptic bronchoscopy) and further chemotherapy; only temporary symptomatic treatment was suitable. Despite receiving further CHOP chemotherapy, the patient died of lymphoma and multiple organ dysfunction syndrome 27 months after diagnosis.

DISCUSSION

The primary tumor site of this case of extranodal NKTCL was in the breast tissue, which is not a common location compared with the more common nonnasal sites such as the skin and gastrointestinal tract. Based on the past medical history, physical examination, and other information, we initially considered diagnoses of breast dysplasia, fibroadenoma, intraductal papilloma, breast cancer, and other common breast diseases. Because extranasal NKTCL is rare and because it is rare to find the primary tumor site in the breast, extranasal NKTCL is prone to misdiagnosis and missed diagnosis, and diagnosis by ultrasound is difficult, so pathological examination after biopsy is particularly important. Several months later, the patient presented, in turn, with skin masses, a nasal mass, and a tracheal mass. Pathological examination of the skin and nasal mass biopsies identified non-Hodgkin NKTCL. We did not actively treat the patient at first because of the patient's unwillingness, older age, and poor general health.

We found 1 case report on primary breast NKTCL in the literature.[8] Primary breast NKTCL has a poor prognosis and often rapidly progresses. Extranodal NKTCL prognosis correlates with age at diagnosis, higher local tumor invasion, clinical stage, treatment response, natural killer/T-cell International Prognostic Index, serum lactate dehydrogenase concentration, and EBV DNA level in the circulation.[9] A retrospective multicenter study have shown that only some patients responded well to treatment, whereas others were treated with long-term high-intensity chemotherapy, and most patients died of tumor invasion.[10] Combination chemotherapy and radiotherapy were effective. Two studies have shown that radiotherapy alone is effective in 75% of patients with nasal type of extranodal NKTCL, but the systemic recurrence rate is as high as 25% to 40%.[11,12] Combined chemotherapy and radiotherapy, either concurrently or sequentially, is the most widely accepted approach for treatment of patients with stage I/II nasal type of extranodal NKTCL.[13] Conventional anthracycline-containing chemotherapy regimens are ineffective because of the expression of the multidrug resistance P-glycoprotein in NKTCL tumor cells.[2,14] Current effective regimens comprise L-asparaginase and other drugs not affected by P-glycoprotein.[15] Patients with relapse who are sensitive to chemotherapy may choose to receive autologous hematopoietic stem cell transplantation; allogeneic hematopoietic stem cell transplantation is recommended if a suitable donor is available. In relapsed or refractory cases, blockade of programmed cell death protein 1 has recently shown promising results with high response rates.[1] Due to the patient's financial status, the above treatments were not performed.

CONCLUSION

Extranodal NKTCL with breast tissue as the primary site is very rare. The disease is prone to misdiagnosis and missed diagnosis, and diagnosis by ultrasound is difficult, so pathological examination after biopsy is particularly important. Primary breast Extranodal NKTCL progresses rapidly and invades the skin, trachea, and other tissues or organs. It is easy to relapse after treatment, and the prognosis is poor.

CONSENT

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

HW and SJ designed the study and performed the experiments, HW collected the data, SJ analyzed the data, and HW and SJ prepared the manuscript. All authors read and approved the final manuscript.

FUNDING

This study did not receive any funding in any form.

REFERENCES

1. Tse E, Kwong YL. NK/T-cell lymphomas. *Best Pract Res Clin Haematol*. 2019;32(3):253-261. doi:10.1016/j.beha.2019.06.005
2. Tse E, Kwong YL. How I treat NK/T-cell lymphomas. *Blood*. 2013;121(25):4997-5005. doi:10.1182/blood-2013-01-453233
3. Chim CS, Ma SY, Au WY, et al. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. *Blood*. 2004;103(1):216-221. doi:10.1182/blood-2003-05-1401
4. Pathologists LSGJ; Lymphoma Study Group of Japanese Pathologists. The world health organization classification of malignant lymphomas in japan: incidence of recently recognized entities. *Pathol Int*. 2000;50(9):696-702. doi:10.1046/j.1440-1827.2000.01108.x
5. Oshimi K, Kawa K, Nakamura S, et al; NK-cell Tumor Study Group. NK-cell neoplasms in Japan. *Hematology*. 2005;10(3):237-245. doi:10.1080/10245330400026162
6. Kim TM, Heo DS. Extranodal NK / T-cell lymphoma, nasal type: new staging system and treatment strategies. *Cancer Sci*. 2009;100(12):2242-2248. doi:10.1111/j.1349-7006.2009.01319.x
7. Aoki R, Karube K, Sugita Y, et al. Distribution of malignant lymphoma in Japan: analysis of 2260 cases, 2001-2006. *Pathol Int*. 2008;58(3):174-182. doi:10.1111/j.1440-1827.2007.02207.x
8. Fréling E, Granel-Brocard F, Serrier C, Ortonne N, Barbaud A, Schmutz JL. [Extranodal NK/T-cell lymphoma, nasal-type, revealed by cutaneous breast involvement]. *Ann Dermatol Venereol*. 2015;142(2):104-111. doi:10.1016/j.annder.2014.11.007
9. Suzuki R, Takeuchi K, Ohshima K, Nakamura S. Extranodal NK/T-cell lymphoma: diagnosis and treatment cues. *Hematol Oncol*. 2008;26(2):66-72. doi:10.1002/hon.847
10. Lee J, Suh C, Park YH, et al. Extranodal natural killer T-cell lymphoma, nasal-type: a prognostic model from a retrospective multicenter study. *J Clin Oncol*. 2006;24(4):612-618. doi:10.1200/JCO.2005.04.1384
11. Kim SJ, Kim WS. Treatment of localized extranodal NK/T cell lymphoma, nasal type. *Int J Hematol*. 2010;92(5):690-696. doi:10.1007/s12185-010-0720-8
12. Wang ZY, Li YX, Wang WH, et al. Primary radiotherapy showed favorable outcome in treating extranodal nasal-type NK/T-cell lymphoma in children and adolescents. *Blood*. 2009;114(23):4771-4776. doi:10.1182/blood-2009-07-235853
13. Vargo JA, Patel A, Glaser SM, et al. The impact of the omission or inadequate dosing of radiotherapy in extranodal natural killer T-cell lymphoma, nasal type, in the United States. *Cancer*. 2017;123(16):3176-3185. doi:10.1002/cncr.30697
14. Yamaguchi M, Kita K, Miwa H, et al. Frequent expression of P-glycoprotein/MDR1 by nasal T-cell lymphoma cells. *Cancer*. 1995;76(11):2351-2356. doi:10.1002/1097-0142(19951201)76:11<2351::AID-CNCR2820761125>3.0.CO;2-1
15. Tse E, Au-Yeung R, Kwong YL. Recent advances in the diagnosis and treatment of natural killer/T-cell lymphomas. *Expert Rev Hematol*. 2019;12(11):927-935. doi:10.1080/17474086.2019.1660640