Mediastinal Single Nodal Relapse of a Nasal Nk/T cell Lymphoma

Kyoung Hoon Rhee, M.D., Seok Chan Hong, M.D., Jeong Min An, M.D., Jooryung Huh, M.D., Ryu Jin Sook, M.D., Jin Seong Lee, M.D. and Cheolwon Suh, M.D.

Departments of Internal Medicine, Pathology, Nuclear Medicine and Radiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

A nasal NK/T cell lymphoma is a very aggressive form of lymphoma. Patterns of relapse after treatment have not been systematically evaluated, and mediastinal nodal relapse at a primary site has never been documented. We describe here a 40-year-old man who presented with a nasal obstruction caused by a protruding mass that was identified as a nasal NK/T cell lymphoma. The initial work-up, including chest and abdominopelvic computed tomography (CT) and positron emission tomography (PET), showed no regional or distant metastasis. A CT scan performed following three cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) showed that the mass had nearly disappeared. Radiation therapy undertaken following chemotherapy was given to the primary site. However, PET performed following radiotherapy revealed a single mediastinal lymphadenopathy, with no evidence of residual tumor in the nasal cavity. A biopsy using video-assisted thoracoscopic surgery (VATS) showed the presence of a recurrent NK/T cell lymphoma with an immunophenotype identical to that of the primary nasal lymphoma. An additional three cycles of CHOP chemotherapy were administered, and the patient remains alive, with no evidence of disease 30 months after the initial relapse. These findings indicate that early detection with PET and prompt surgical excision with the use of VATS can lead to successful treatment of a relapsed nasal NK/T cell lymphoma.

Key Words: Nasal NK/T-cell lymphoma, Relapse, Mediastinal node, Positron Emission Tomography, Video-Assisted Thoracic Surgery

INTRODUCTION

Natural killer (NK)/T-cell lymphoma is the most common subtype of primary nasal lymphoma. Nasal NK/T cell lymphoma is a very aggressive form of lymphoma, with over 50% of the tumors showing involvement of the adjacent alveolar bones, hard palate, orbits, nasopharynx, and an association with an extensive soft-tissue mass. Relapse patterns of nasal NK/T cell lymphoma after treatment have not been systematically evaluated, and mediastinal nodal relapse at a controlled primary site has not been previously reported. Here we report a case of mediastinal single nodal relapse of a NK/T cell lymphoma, detected by positron emission tomography (PET) and confirmed pathologically, which was removed completely with surgery using video-assisted thoracoscopic surgery (VATS).

CASE REPORT

A previously healthy 40-year-old Korean male was admitted...
to Asan Medical Center, Seoul, Korea, in December 2003 with symptoms of nasal obstruction and fever. A radiological examination of the paranasal sinus disclosed a soft tissue mass in the left middle meatus and associated obstructive sinusitis in the left maxillary sinus (Figure 1). A rhinoscopic examination revealed an irregular, and partly ulcerated protruding mass occupying the nasal cavity. A punch biopsy showed the presence of extensively necrotic tissue with a few viable foci of sheets of atypical medium- to large-sized lymphocytes with irregularly shaped nuclei. Individual necrosis and apoptosis were frequent. The tumor cells were positive by immunostaining for CD3, CD 56, cytotoxic granule marker TIA-1, and UCHL-1 (CD45RO), but negative for CD20, CD79a, CD4, and CD8. In situ hybridization showed the presence of Epstein-Barr virus in the majority of the tumor cell nuclei. The patient was diagnosed with an extranodal CD 56+ nasal NK/T cell lymphoma.

To evaluate the disease status, computed tomography (CT), bone marrow aspiration and biopsy, and PET were performed. CT showed no abnormal findings in other areas. Fluorine-18 fluorodeoxyglucose (FDG) PET showed a focal hypermetabolic lesion with a 4.8 maximal standardized uptake value (SUV) in the left nasal cavity, but no abnormally hypermetabolic lesions in the chest or abdomen (Figure 2, Figure 3A). All of these findings were consistent with a stage IEB nasal NK/T cell lymphoma.

Hematological levels were hemoglobin 12.8 g/dL, hematocrit 36.9%, platelet count 172 x 10^3/mm^3, and white blood cell count 4,200/mm^3 (66% neutrophils, 29% lymphocytes, 5% monocytes, and 0.5% eosinophils). A bone marrow biopsy showed no malignant cell infiltration. All blood chemistry findings were normal, except for a slightly elevated lactate dehydrogenase (LDH) level, and regional lymph node status.

The patient was treated with three cycles of chemotherapy, consisting of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), followed by 28 fractions of local radiation therapy to the primary site, with a total dose of 5,040 cGy.

In April 2004, about one month after completion of the radiation therapy, FDG PET-CT revealed a newly developed focal hypermetabolic lesion with a maximal SUV of 3.6 in the aorto-pulmonic nodal station. There were no abnormal findings at other sites, except for post-radiation sinusitis and thyroiditis (Figure 3B). A biopsy using VATS was performed, and the lymph node was removed completely. Microscopically, the node showed numerous histiocytes and epithelioid granulomas and scattered medium-sized CD56-positive lymphocytes in the paracortex; the nuclei of these cells were positive for Epstein-Barr virus. The tissue specimen of the mediastinal lymph node showed histology similar to that of the nasal mass (Figure 4A-D).

The patient was treated with an additional three cycles of CHOP chemotherapy. A follow-up chest CT and PET showed no evidence of residual tumor. Thirty-five months after the initial diagnosis and thirty months after the initial relapse, the patient is still alive, without any evidence of further relapse.

**DISCUSSION**

An extranodal NK/T cell lymphoma is characterized by extensive mucosal ulceration and angioinvasive or angiodestructive lymphomatous infiltration. These tumors have an immunophenotype of NK/T cell neoplasms, including expression of cytoplasmic CD 3 epsilon and CD56, and many are positive for EBV. These NK cell lymphomas show a geographic predilection, in that they are more common in Asian regions such as Hong Kong, Japan, and Korea, and in Latin American countries including Mexico, Peru, and Guatemala.

"Nasal" NK/T cell lymphomas are classified as lesions confined within the nasal cavity and nasopharynx, whereas "nasal-type" NK/T cell lymphomas are lesions involving sites outside the nasal cavity/nasopharynx, such as the oral cavity, palate, larynx, tonsil, skin, soft tissues, and the visceral organs. The prognosis for patients with primary non-Hodgkin’s lymphoma of the nasal cavity is poor, and the rates of distant metastasis and local relapse are high. The 5-year overall survival and disease-free survival rates for 102 patients with stage IIE nasal NK/T cell lymphoma have been recently reported to be 71.7% and 60.9%, respectively.

Outcomes of 262 extranodal NK/T cell lymphomas were recently used to develop a prognostic model of these tumors, with new prognostic factors including B symptoms, stage, lactate dehydrogenase (LDH) level, and regional lymph node status. According to this model, our patient, who had B symptoms and an elevated LDH level, is in group 3 (two risk factors).

Because of the low incidence and geographic occurrence of these tumors, a systematic evaluation of the treatment for nasal NK/T cell lymphomas has not been fully performed. Therefore, the optimal therapy for nasal NK/T-cell lymphoma has not yet been established. Although a prospective randomized trial about optimal treatment has not been performed, several retrospective studies have shown radiotherapy to be superior to chemotherapy alone for stage I/II disease. Some studies report that the addition of chemotherapy to radiotherapy does not appear to confer any survival benefit in early stage patients. Consequently radiotherapy, either as the initial treatment or as part of the chemotherapy regimen, is presently the mainstay of a treatment program for early stage NK/T cell lymphoma. The patient in this case was treated with three cycles of chemotherapy, followed by in-field radiation therapy as initial treatment program.
Figure 1. Computed tomography of the paranasal sinus showing a soft tissue density mass in the left middle meatus and associated obstructive sinusitis in the left maxillary sinus.

Figure 2. FDG PET of the nasal cavity at the initial diagnosis. There was a focal hypermetabolic lesion in the left nasal cavity at the initial diagnosis.

Figure 3. FDG PET of the mediastium at the initial diagnosis (A) and at relapse (B). (A) There was no abnormal hypermetabolic lesion in the chest and abdomen at the initial diagnosis. (B) There was increased metabolic activity at the mediastinal lymph node of the AP window (maximal SUV=3.6). Diffuse increased uptake was observed in both thyroid glands, indicative of thyroiditis.

Secondary lymph node involvement is rarely encountered until late in the course of disease. In the patient described here, we diagnosed mediastinal relapse promptly using PET, a highly sensitive diagnostic tool for various cancers that can detect increased glucolytic activity of neoplasms. PET is usually performed to diagnose and stage tumors and to monitor response to therapy. Although CT is frequently performed for patients with lymphoma, it is less sensitive for small tumor foci. Following treatment of a lymphoma, CT can reveal residual masses or enlarged lymph nodes, which may or may not
The pathological and immunohistochemical features of the mediastinal lymph node were identical with those of the nasal mass.

Various techniques can be used to perform diagnostic mediastinal biopsies, the most widely used being the use of percutaneous fine-needle aspiration, cervical mediastinoscopy, parasternal mediastinotomy, open biopsy through a thoracotomy, and more recently VATS. VATS is currently indicated not only for diagnostic procedures, but also for its versatility, permitting other surgical treatments at the same time. Mediastinoscopy is still the most widely used procedure for mediastinal lymph node biopsy, but access to the aortopulmonary window may be difficult and is limited by the aorta and left main bronchus. However, VATS makes it possible to reach all lymph node stations, including the posterior subcarinal, paraesophageal, and prevertebral stations.
The potentially aggressive behavior of relapsed NK/T-cell lymphomas makes early and correct pathological diagnosis and prompt treatment important. The patient described here developed a single mediastinal nodal relapse one month after initial treatment of the nasal NK/T cell lymphoma, and was diagnosed and treated using PET and VATS. This patient is still alive 35 months after the initial diagnosis and 30 months after the initial relapse without any evidence of further relapse.

REFERENCES

1) Cheung MM, Chan JK, Lau WH, Foo W, Chan PT, Ng CS, Ngan RK. Primary non-Hodgkin’s lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. J Clin Oncol 16:70-77, 1998
2) Ooi GC, Chim CS, Liang R, Tsang KW, Kwong YL. Nasal T-cell/natural killer cell lymphoma: CT and MR imaging features of a new clinicopathologic entity. AJR Am J Roentgenol 174:1141-1145, 2000
3) Chan JK, Jaffe ES, Ralfkiaer E. Extranodal NK/T cell lymphoma, nasal type. In: Jaffe ES, Harris NL, Stein H, eds. Pathology and genetics—tumors of hematopoietic and lymphoid tissue. p. 204-207, Lyon, IARC Press, 2001
4) Jaffe ES, Chan JK, Su IJ, Frizzera G, Mori S, Feller AC, Ho FC. Report of the Workshop on Nasal and Related Extranodal Angiocentric T/Natural Killer Cell Lymphomas: definitions, differential diagnosis and epidemiology. Am J Surg Pathol 20:103-111, 1996
5) Ferry JA, Skar J, Zukerberg LR, Harris NL. Nasal lymphoma: a clinicopathologic study with immunophenotypic and genotypic analysis. Am J Surg Pathol 15:268-279, 1991
6) Liang R, Todd D, Chan TK, Chiu E, Lie A, Kwong YL, Choy D, Ho FC. Treatment outcome and prognostic factors for primary nasal lymphoma. J Clin Oncol 13:666-670, 1995
7) Kim GE, Cho JH, Yang WI, Chung EJ, Suh CO, Park KR, Hong WP, Park HY, Hahn JS, Roh JK, Kim BS. Angiocentric lymphoma of the head and neck: patterns of systemic failure after radiation treatment. J Clin Oncol 18:54-63, 2000
8) Chim CS, Ma SY, Au WY, Choy C, Lie AK, Liang R, Yau CG, Kwong YL. Primary nasal natural killer cell lymphoma: long-term treatment outcome and relationship with the International Prognostic Index. Blood 103:216-221, 2004
9) Ko YH, Cho EY, Kim JE, Lee SS, Huh JR, Chang HK, Yang WI, Kim CW, Kim SW, Ree HJ. NK and NK-like T-cell lymphoma in extranasal sites: a comparative clinicopathological study according to site and EBV status. Histopathology 44:480-488, 2004
10) Yao B, Li YX, Fang H, Jin J, Liu XF, Yu ZH. Prognostic factors of primary non–Hodgkin’s lymphoma of the nasal cavity: a report of 129 cases. Ai Zhong 25:465-470, 2006
11) Lee J, Suh C, Park YH, Ko YH, Bang SM, Lee JH, Lee DH, Huh J, Oh SY, Kwon KH, Kim HJ, Lee SI, Kim JH, Park J, Oh SJ, Kim K, Jang C, Park K, Kim WS. Extranodal natural killer T-cell lymphoma, nasal type: a diagnostic model from a retrospective multicenter study. J Clin Oncol 24:612-618, 2006
12) Sobrevilla-Calvo P, Meneses A, Alfaro P, Bares JP, Amador J, Reynoso EE. Radiotherapy compared to chemotherapy as initial treatment of angiocentric centrofacial lymphoma (polymorphic reticulosis). Acta Oncol 32:69-72, 1993
13) Li YX, Yao B, Jin J, Wang WH, Liu YP, Song YW, Wang SL, Liu XF, Zhou LQ, He XH, Lu N, Yu ZH. Radiotherapy as primary treatment for stage IE and IIE nasal natural killer/T-cell lymphoma. J Clin Oncol 24:181-189, 2006
14) Kim K, Chie EK, Kim CW, Kim IH, Park CI. Treatment outcome of angiocentric T-cell and NK/T-cell lymphoma, nasal type: radiotherapy versus chemoradiotherapy. J Clin Oncol 35:1-5, 2005
15) Ng WK, Lee CY, Li AS, Cheung LK. Nodal presentation of nasal type NK/T-cell lymphoma: report of two cases with fine needle aspiration cytology findings. Acta Cytol 47:1063-1068, 2003
16) Gutte H, Hojgaard L, Kjaer A. Early clinical experience and impact of 18F-FDG PET. Nucl Med Commun 26:989-994, 2005
17) Brix G, Nosske D, Gatting G, Minkov V, Reske SN. A survey of PET activity in Germany during 1999. Eur J Nucl Med Mol Imaging 29:1091-1097, 2002
18) Radford JA, Cowan RA, Flanagan M, Dunn G, Crowther D, Johnson RJ, Eddleston B. The significance of residual mediastinal abnormality on the chest radiograph following treatment for Hodgkins disease. J Clin Oncol 6:940-946, 1988
19) Surbone A, Longo DL, DeVita VT Jr, Ihde DC, Duffey PL, Jaffe ES, Solomon D, Hubbard SM, Young RC. Residual abdominal masses in aggressive non-Hodgkin’s lymphoma after combination chemotherapy: significance and management. J Clin Oncol 6:1822-1837, 1988
20) Massone PP, Lequagliel C, Magnani B, Ferro F, Cataldo I. The real impact and usefulness of video-assisted thoracoscopic surgery in the diagnosis and therapy of clinical lymphadenopathies of the mediastinum. Ann Surg Oncol 10:1197-1202, 2003