Primary pulmonary NK/T-cell lymphoma: A case report and literature review

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Abstract. Extranodal natural killer (NK)/T-cell lymphoma (ENKTL) is an aggressive disease with poor prognosis. The lung is a relatively rare site of involvement. The current study presents a case of primary pulmonary ENKTL with fever and dyspnea, mimicking pneumonia and initially treated with empirical antibiotics. The patient demonstrated rapid deterioration and died shortly following diagnosis. To the best of our knowledge, large-scale investigations referring to primary pulmonary ENKTL are not available. As a result, the exact incidence and clinical features of primary pulmonary ENKTL are unknown. In the current report, a literature review is presented to discuss the clinical characteristics, diagnosis, treatment, and prognosis factors of this malignant disease.

Introduction

ENKTL has several unusual characteristics, including being predominantly involved in the nasal cavity and nasopharynx, and closely associated with Epstein-Barr virus (EBV) infection. Primary extranasal sites of involvement are mainly the skin, soft tissue, gastrointestinal tract and testis (1). There are no differences in ethnicity, gender, age or immunophenotypic profile between the nasal and extranasal cases; however, the latter exhibit a more aggressive clinical outcome (2). In cases of extranasal ENKTL, the lung is a relatively rare site of involvement. To the best of our knowledge, there is no large-scale investigation referring to primary pulmonary ENKTL.

Case report

A 34-year-old female was admitted to the respiratory intensive care unit of The First Affiliated Hospital of Zhengzhou University (Zhengzhou, Henan, China) on 8 November, 2016 with chief complaints of fever for one month and progressive dyspnea for 6 days. At first, the patient had an intermittent fever ≤39˚C. She was subsequently admitted to a local hospital and initially received empirical antibiotic treatment (cefoxitin) for more than a week, but her clinical condition deteriorated. As the patient showed no response to empirical antibiotic therapy, a computed tomography (CT) of the chest was performed for proper diagnosis. The chest CT showed multiple massive infiltrates in both lungs with cervical, mediastinal and axillary lymphadenopathy. The patient was therefore referred to The First Affiliated Hospital of Zhengzhou University for further study. She was a farmer and non-smoker. There was no relevant personal or familial medical history. The patient was immunocompetent and human immunodeficiency virus-negative.

Physical examination. On admission, the patient's vital signs included blood pressure, 137/97 mmHg; pulse rate, 100 beats/min; respiratory rate, 25 breaths/min; and body temperature, 38.4˚C. Her face had an acutely ill-looking appearance. On chest auscultation, bilateral moist rales were found in both lung fields. Physical examination confirmed cervical and axillary lymph node enlargement.

Laboratory assessments. Laboratory assessments were conducted and revealed in Table I.

On admission, a repeat chest CT revealed progressive multiple nodules in both lungs with ground-glass opacities, measuring ≤27x22.5 mm in diameter, as shown in Fig. 1. CT also revealed bilateral pleural effusion and cervical, mediastinal and axillary lymphadenopathy. These findings suggested an advanced lung cancer or severe pneumonia. The patient was then treated with broad-spectrum antibiotic therapy (imipenem, moxifloxacin and voriconazole) for 6 days. Despite enhanced antibiotic therapy, the patient showed aggravated dyspnea and her clinical condition continued to deteriorate. A CT-guided transthoracic needle biopsy of the right lung was therefore undertaken. The surgical specimen was fixed in 4% formalin, embedded in paraffin and stained with hematoxylin and eosin. Histologically, the small to medium-sized cells presented angiodestructive growth patterns with an inflammatory response and necrosis. Immunohistochemical (IHC) staining was positive for CD43, CD3, TIA-1, GranzymeB, CD30 and 70%Ki-67; and negative for CD20, CD79α,

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thyroid transcription factor 1, CD56, SYN and cytokeratin (AE1/AE3). The antibodies of IHC were purchased from ZSGB-BIO(Beijing, China). The IHC staining was performed according to the manufacturer's instructions. The cells were labeled for EBV-encoded RNA (EBER) *in situ* hybridization, as shown in Fig. 2. These findings were consistent with NK/T-cell lymphoma, although there was no previous ENKTL history and no evidence of lymphoma involvement in the extrapulmonary site. Thus, the patient was diagnosed with primary pulmonary ENKTL. Unfortunately, the patient refused to undergo chemotherapy and showed rapid deterioration. She died three days after hospital discharge as a result of disease progression with respiratory failure. This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University, and written informed consent was obtained from this patient.

Table I. Laboratory assessments.

Variables	Results	Reference range
White blood cell count	$3.0x10^9$/l	$4-10x10^9$/l
Absolute neutrophil count	$1.8x10^9$/l	$2-7.7x10^9$/l
Hemoglobin	115 g/l	110-160 g/l
Platelet count	$214x10^9$/l	$100-300x10^9$/l
Alanine aminotransferase	63 U/l	0-40 U/l
Aspartate aminotransferase	130 U/l	0-40 U/l
Albumin	26 g/l	35-55 g/l
Globulin	28.6 g/l	20-35 g/l
Serum total bilirubin	5.77 μmol/l	0-25 μmol/l
Direct bilirubin	2.15 μmol/l	0-10 μmol/l
Indirect bilirubin	3.6 μmol/l	0-14 μmol/l
Lactate dehydrogenase	1184 IU/l	75-240 IU/l
β2-microglobulin	5.38 mg/l	0.9-2.3 mg/l
Urea nitrogen	2.85 mmol/l	1.8-7.5 mmol/l
Serum creatinine	42 μmol/l	30-110 μmol/l
C-reactive protein	10.44 mg/l	0-10 mg/l
Erythrocyte sedimentation rate	3.7 mm/h	0-20 mm/h
Procalcitonin	0.095 ng/ml	0-0.1 ng/ml
pH	7.46	7.35-7.45
PCO_2	32.8 mmHg	35-45 mmHg
PO_2	61.3 mmHg	80-100 mmHg
HCO_3 concentration	21.1 mmol/l	22-26 mmol/l
SaO_2 concentration	92.6%	91.9-99%
CEA	1.86 ng/ml	0-5 ng/ml
AFP	2.29 ng/ml	0-10 ng/ml
CA125	36.25 U/ml	0-35 U/ml
CA19-9	105 U/ml	0-35 U/ml
CA15-3	21.78 U/ml	0-35 U/ml
Cyfra21-1	6.48 ng/ml	0-3.3 ng/ml
CA72-4	0.67 U/ml	0-10 U/ml
NSE	30.39 ng/ml	0-20 ng/ml
G test	Negative	Negative
GM test	Negative	Negative
T-SPOT	Negative	Negative

Discussion

There are few studies in the literature on the clinicopathological characteristics, therapy and prognostic factors of primary pulmonary ENKTL. The similar cases of pulmonary ENKTL in the latest literature have been listed here (3-14). Due to the rarity of this disease, nonspecific clinical symptoms and limited availability of biopsy tissues, the diagnosis of primary pulmonary ENKTL is notably difficult. Patients are frequently presumed to present with pneumonia and initially treated with empirical antibiotics. Therefore, CT-guided needle biopsy or bronchoscopic examination should be considered when clinical symptoms show deterioration in spite of adequate antibiotic therapy. It should also be differentiated from tuberculosis, pneumomycosis and lung cancer. A delay in diagnosis may result in a fatal outcome, so an early correct diagnosis is crucial to determine prognosis. In the previous reports, the patients most presented with fever (90%), cough (70%), and dyspnea (45%). Fever was the most common initial clinical symptom. It was different from primary pulmonary MALT lymphoma, which most frequently presented with dry cough (41%) and dyspnoea (35%). We presumed that the possible reason was EBV infection and aggressive nature of ENKTL.

ENKTL is an aggressive disease with poor prognosis. Primary pulmonary ENKTL is associated with shorter survival rate and poorer therapy response irrespective of the stage, compared with nasal disease. The aggressive clinical behavior of primary extranasal disease is similar to that of advanced stage nasal disease (2). Furthermore, survival does not differ between primary pulmonary ENKTL and any other subset of primary pulmonary lymphoma (15). There is still no consensus on the optimal therapy for primary pulmonary ENKTL (16,17). Cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP/CHOP-like) chemotherapy has generally been used for the treatment of primary pulmonary ENKTL, but with unsatisfactory results; p-glycoprotein may be responsible for the multiple drug resistance. However, chemotherapy remains the main treatment for primary extranasal ENKTL; more effective treatment strategies are therefore required for this disease. Recent large-scale studies demonstrated that the outcome of ENKTL was noticeably improved with the advent of asparaginase/gemcitabine-based regimens including SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide) and DDGP(dexamethasone, cisplatin, gemcitabline and pegaspargase) (18,19). It has been identified that asparaginase/gemcitabine-based regimens are superior to CHOP/CHOP-like chemotherapy in ENKTL patients and asparaginase/gemcitabine-based regimens have been recommended for patients with advanced-stage or relapsed/refractory ENKTL (20). In the previous reports, the patients who received asparagine/gemcitabine-based chemotherapy survived for 24 and 3 months, respectively (11,13). Therefore, we propose that asparaginase-basedchemotherapy may be the optimal treatment strategy for primary pulmonary ENKTL. However, there remains no prognostic model for primary pulmonary ENKTL. In the published lieratures, we identified only one risk factor(female) out of various clinical parameters that was prognostic for overall survival by univariate analysis.

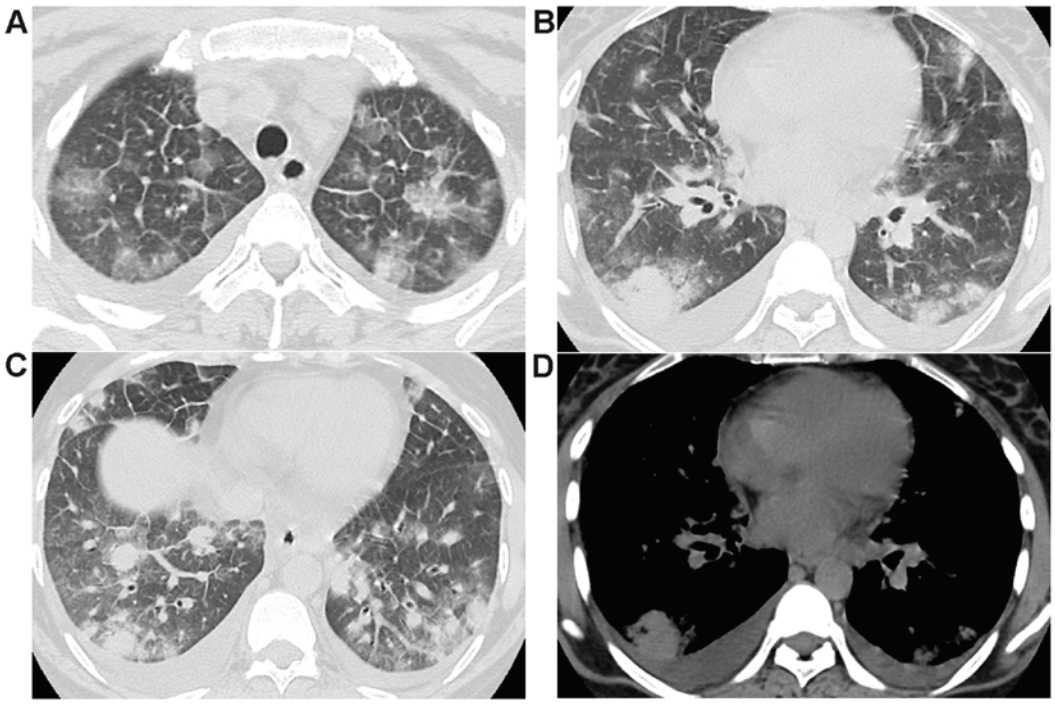

Figure 1. Chest CT revealed multiple bilateral pulmonary nodules with ground-glass opacities and pleural effusion.

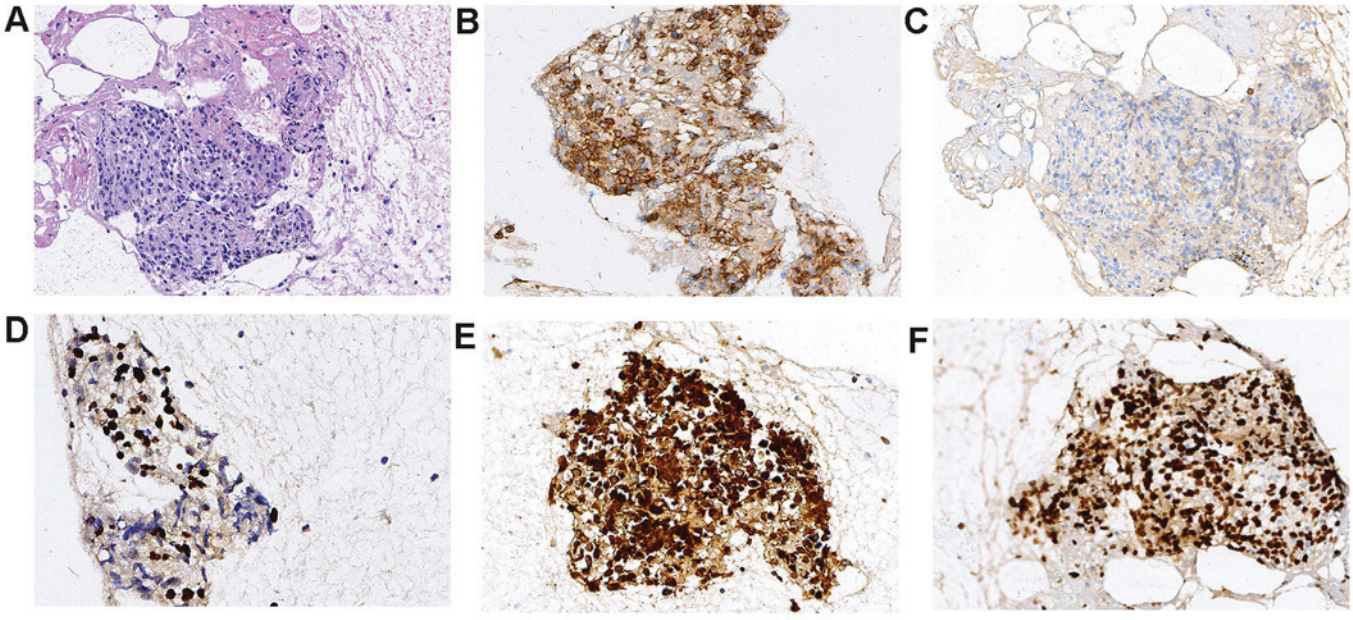

Figure 2. Pathologic findings of CT-guided transthoracic needle biopsy. (A) Histologically, the small to medium-sized tumor cells presented angiodestructive growth patterns with inflammatory response and necrosis (H&E, magnification, x400); (B) immunohistochemical staining was positive for CD3 (magnification, x400); (C) immunohistochemical staining was negative for CD20 (magnification, x400); (D) *in situ* hybridization for Epstein-Barr virus encoded RNA was positive (magnification, x400); (E) immunohistochemical staining was positive for Granzyme B (magnification, x400); (F) immunohistochemical staining was positive for 70% Ki-67 (magnification, x400).

There were also limitations in this study: i) EBV-DNA level is very important to ENKTL, but we did not test the plasma EBV-DNA level; ii) given the patient found the ineffective treatment and supposed to suffer from the potential lymphoma in other hospital, we did not conduct a needle biopsy for confirmation as early as possible. It may result in a delay in diagnosis and unfavourable prognosis. An earlier needle biopsy and asparaginase-basedchemotherapy would have been better for the patient.

In conclusion, primary pulmonary ENKTL is extremely rare with dismal survival, the diagnosis should be considered when patients present with fever, lung mass and non-responsive to antibiotics. Correct diagnosis with early effective treatment may have benefit for prognosis. Further prospective

multicenter studies should be conducted to define the best therapeutic strategies and prognostic factors.

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Authors' contributions

YQ made contributions to the conception and design of the study, and wrote the manuscript. JH and DH performed data collection. DZ performed histological examination. The final version of the manuscript has been read and approved by all authors.

Ethics approval and consent to participate

This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University, and written informed consent was obtained from the patient.

Consent for publication

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

Competing of interests

Authors declare no competing of interest.

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