Cutaneous Intravascular Natural Killer–Cell Lymphoma
A Case Report and Review of the Literature

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ABSTRACT

Objectives: To our knowledge, since 2003, there have been 11 reported cases of intravascular natural killer (NK)–cell lymphoma (IVNKL). Herein we describe the 12th case.

Methods: H&E and Envision immunohistochemical stains as well as in situ hybridization were used to study this disease in combination with review of the literature.

Results: Half of the cases reported to date are from China and Taipei. The clinical manifestation of IVNKL is erythema in the limbs and trunk, although patients’ conditions have varied notably from each other. One-year survival rate is about 40%.

Conclusions: IVNKL should be distinguished from extranodal NK/T-cell lymphoma (nasal type) and aggressive NK-cell leukemia. These three diseases have a similar phenotype and are all related to Epstein-Barr virus infection. However, the pathogenesis of similarities and differences needs further study. In particular, IVNKL is quite unusual. The treatment of IVNKL is difficult, and the prognosis is poor. Currently, IVNKL is not included in the World Health Organization classification subtypes and has been classified into NK/T-cell lymphoma (nasal type). However, in view of the unique characteristics of this disease, we propose that the diagnosis be independent, since this will facilitate further study of this disease.

Intravascular lymphoma is a rare and aggressive variant of extranodal non-Hodgkin lymphoma, characterized by the proliferation of neoplastic lymphocytes within blood vessels. About 90% of reported cases of intravascular lymphoma are large B-cell lymphomas, and only 10% to 15% of intravascular lymphomas are of T-cell lineage. To date, 11 cases of intravascular natural killer (NK)–cell lymphoma (IVNKL) have been reported. The first case was reported by Santucci et al in 2003. The next seven cases were reported in the English literature. Another three cases were reported from China in 2011 and 2012. Our case is the 12th worldwide. We have reviewed the 12 cases, and the clinical characteristics and prognosis have been analyzed.

Case History

A 38-year-old woman sought care because of a 9-month history of increasing numbers of erythematous, plaque-like, firm, subcutaneous lesions involving the skin of the chest and back and an intermittent fever (temperature up to 39.5°C). The lesions were not painful or pruritic, skin temperature was slightly increased, and the skin felt hard but without edema. There was no peripheral adenopathy and no mass in her nose. All laboratory studies were normal. WBCs were 4.09 × 10^9/L. Bone marrow biopsy specimens and aspirate revealed no evidence of tumor. The liver and spleen were of normal size, and no abnormalities were observed in any other systems by computed tomography scan.
**Materials and Methods**

A biopsy of the chest skin was performed. The tissue was fixed in 4% formalin and paraffin embedded, and 3- to 4-µm-thick sections were cut. These were stained with H&E as well as Envision (Fuzhou, China) immunohistochemical stains.

The following antibodies were purchased from Maixin Biotechnology Development Company (Fuzhou, China): CD20, Pax-5, CD3, CD56, Granzyme B (GrB), CD2, CD5, CD7, CD4, CD8, Ki-67, and CD34. In situ hybridization studies were performed on paraffin-embedded sections using a probe synthesized in the pathology department at Aarhus University (Aarhus, Denmark), which allows for the testing of two kinds of Epstein-Barr virus (EBV)–encoded messenger RNAs (EBER1 and EBER2). In situ hybridization was performed according to a published method. The lymph node from the infectious mononucleosis case was used as a positive control.
Results

The histologic study revealed many distended vessels filled with atypical large lymphoid cells in the dermis and subcutaneous tissue [Image 2]. The tumor cells were all confined to the vessels and had large, irregular hyperchromatic nuclei with an ample eosinophilic cytoplasm. Many mitotic figures and necrosis were observed. Immunohistochemical studies showed that tumor cells were CD3+, CD56+, GrB+, CD4−, CD5−, CD8−, CD20−, CD30−, Pax-5−, and TdT−. More than 90% of the tumor cells were Ki-67+. In situ hybridization for EBER was positive. The immunohistochemical tests and EBER in situ hybridization suggested IVNKL (Image 2) [Image 3], [Image 4], [Image 5], [Image 6], [Image 7], [Image 8], and [Image 9]. Following five courses of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), the erythema was reduced and the patient became afebrile. Seven months after initial diagnosis, reexamination of the patient revealed clinical findings worrisome for central nervous system involvement. The patient refused intrathecal chemotherapy, and 13 months after initial diagnosis, the patient succumbed to disease.

Discussion

Since 2003, 11 cases of IVNKL have been reported worldwide. The current case is the 12th. The clinical characteristics and follow-up of each case are shown in Table 1. Among the 12 cases, four (33.3%) were reported in China, two (16.7%) in Taiwan, two (16.0%) in the United States, one (8.0%) in Austria, one (8.0%) in Japan, one (8.0%) in Korea, and one (8.0%) in Italy. China and Taiwan accounted for six (50%) of 12 of the reported cases, which was consistent with the distribution characteristics of extranodal NK/T-cell lymphoma, nasal type (ENKTCL), which has a high incidence in China. Of the 12 patients, eight were female and four were male. The maximum age was 71 years, and the minimum age was 4 years. The clinical course lasted from 2 months to 3 years, and more than half of the patients had fever. The clinical manifestation was erythema in the limbs and trunks. The patients’ conditions varied notably from each other. Multisystem involvement (brain, bone marrow, spleen, and kidney) occurred in most patients (eight of 12). The other four patients developed only a rash. Four of 12 patients showed nervous system involvement.

In the 12 published cases in which the morphology of IVNKL was described, the venules, capillaries, and arterioles at the dermal and subcutaneous levels were involved. Tumor cells were all confined within the vessels. Fibrin thrombi mixed with atypical lymphoid cells were occasionally found in some cases. The size of the tumor cell was medium to large and was similar in morphology to lymphoblastoid cells. The cytoplasm was pale or eosinophilic. Nuclei were round, ovoid, or irregular. The chromatin was coarse and the nucleolus was visible in some cases. Scattered mitotic figures and necrosis usually were found. In all 12 cases, IVNKL, CD3, CD56, and Ki-67 were always positive; CD3ε, GrB, EBER, TIA-1, CD2, CD7, CD30, CD43, CD45, and CD45RO were positive in partial cases. CD20, CD4, CD8, CD5, CD7, CD79a, Pax-5, and TdT were consistently negative in all the cases reported. The immunophenotype of our case was identical to that of ENKTCL—that is, CD3, CD56, perforin, GrB, and EBER were positive, while CD5, CD4, and CD8 were negative. After a follow-up of 2 to 17 months, seven of 12 patients had died, with a 1-year survival rate of less than 40%.
We believe that IVNKL should be distinguished from the ENKTCL. Patients with IVNKL had no nasal symptoms, and no nasal abnormalities were found. ENKTCL can also occur in the skin but presents with multiple nodules with ulceration. In ENKTCL, tumor cells were distributed in tissues and showed vascular invasion. IVNKL tumor cells were confined to the endovascular system, a feature that is different from ENKTCL. IVNKL should also be distinguished from aggressive NK-cell leukemia. A rash is typically prominent in IVNKL without obvious abnormalities in the peripheral blood, although bone marrow abnormalities might be present in some patients. In aggressive NK-cell leukemia, tumor cells are diffusely scattered in the extravascular tissue rather than deposited in blood vessels. The features of IVNKL and aggressive NK-cell leukemia may overlap during the course of disease, which may represent different disease states. Because of the similar phenotype of ENKTCL, IVNKL, and aggressive NK-cell leukemia, as well as the common association with EBV infection, their pathogenic similarities and differences need further study.

For example, why are all tumor cells distributed intravascularly in IVNKL? The lack of adhesion molecule (CD29 and CD57) expression by tumor cells in intravascular large B-cell lymphoma is thought to explain why these tumor cells do not infiltrate extravascular sites. Whether similar mechanisms exist...
in IVNKL is not yet known. The high prevalence of EBER positivity in IVNKL suggests that EBV infection is somehow involved in the pathogenesis of this rare lymphoma. Because these are rare cases, the origin of intravascular NK-cell lymphoma has not been studied in depth. Only two of the 12 cases had T-cell receptor gene rearrangement analysis performed, which confirmed NK-cell origin.

IVNKL treatment is ineffective, and the disease has a poor prognosis. The CHOP regimen, combined with other chemotherapy drugs and radiation therapy or stem cell transplantation therapy, may be efficacious for a limited time in some patients. Most deaths occurred within a few months (seven of 12 [58.3%]), and only five (41.7%) of 12 had even temporary remission. The poor prognosis may be due to multiorgan, multisystem involvement. Currently, IVNKL is not classified in the World Health Organization classification subtypes and is linked with ENKTCL. However, in view of the unique characteristics of this disease, we propose that the diagnosis should be independent, which will help further study of this disease.

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References


