Pathol. Oncol. Res. (2012) 18:519–522
DOI 10.1007/s12253-011-9360-4

CASE REPORT

Primary Uterine NK-Cell Lymphoma, Nasal-Type: A Unique Malignancy of a Prominent Cell Type of the Endometrium

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Received: 17 December 2010 / Accepted: 5 January 2011 / Published online: 28 January 2011

Abstract Natural killer (NK) cells host in the human endometrium with dedicated role in reproductive physiology. Interestingly, malignant transformation of these specialized cells has not been presented thus far. Here we report a primary endometrial NK-cell lymphoma of a 48 year-old patient presenting with irregular bleeding. The endometrial curetting showed a dense lymphomatous infiltrate demonstrating highly infiltrative aggressive features with characteristic angiocentric, partially angiodestructive growth pattern and accompanying focal necroses. The lymphoma cells displayed a CD3ε/CD56/TIA-1/granzyme-B-positive and CD5/CD4/CD8/TCRγδ-negative immunophenotype, proved to be positive for Epstein-Barr virus by EBER in situ hybridization, and revealed no clonal T-cell receptor gene rearrangement. The diagnosis of uterine extranodal NK-cell lymphoma, nasal-type was made. Clinically, the disease was limited to the uterus at diagnosis, but progressed rapidly, and the patient died within 5 months due disseminated lymphoma, irrespective of intensive chemotherapy. Genuine NK-cell lymphomas occurring in the uterus as primary site seem to be rare making the therapeutic decisions extremely complicated.

Keywords Aggressive lymphoma · Uterine NK-cells · Angiogenesis · EBV · Dissemination

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Introduction

Natural killer (NK) cell neoplasms are classified as lymphomas with nodal and extranodal presentation as well as the more aggressive NK-cell leukemia [1]. NK-cell malignancies are rare in Caucasians, but are more prevalent in Asians and in the native American population of Central- and South-American countries. Extranodal NK/T-cell lymphomas (ENKTL) represent lymphoid neoplasms that characteristically involve the upper aerodigestive tract as the prototypic site. Most frequently developing in the nasal cavity. Accordingly, the terminology of nasal and nasal-type lymphoma is broadly used in the clinical practice. A currently proposed staging system [2] classifies ENKTLs as upper aerodigestive (UAD) and non-UAD. The non-UAD primary ENKTLs usually arise from the skin, lung, gastrointestinal tract or testis. Histologically, they all typically show significant necrosis due to their characteristic angioinvasive/angiodestructive growth pattern [3, 4]. There are accumulating data about special biological factors influencing the outcome [5, 6].

Here we report a case of primary uterine ENKTL diagnosed from endometrial curetting which showed all the highly characteristic features of an aggressive NK-cell lymphoma.

Clinical History

A 48 year-old woman, without relevant previous anamnesis, presented with irregular bleeding. Ultrasonography indentified a 12 cm intrauterine mass, and a fractionated curettaging was performed. The obtained tissue sample composed of several solid fragments of 10–15 mm in diameter which was fixed in neutral buffered formalin (10%) and routinely processed. Histopathological evaluation revealed lymphomatous infiltrate dissecting the endometrial glands (Fig. 1a) intermixed with well demarcated large areas of coagulative necrosis containing apoptotic nuclear debris (Fig. 1b). The tumor cells demonstrated a prominent angioinfiltrative growth pattern with concentric arrangement around small arteries (Fig. 1c). The atypical lymphoma cells were densely packed, showed an abundant cytoplasm and enlarged nuclei with activated chromatin and several large nucleoli. Mitotic figures were frequently seen (Fig. 1d).

The tumor cells revealed an immunophenotype consistent with activated NK-cells. Cytoplasmic CD3ε and membranous CD56 coexpression (Fig. 2a, b) was demonstrated with negativity for CD4, CD5, CD8, CD16, CD20, CD79α, CD30, CD246, TCRβ (βF1), and TCRγδ. Cytotoxic proteins TIA-1 and granzyme-B (Fig. 2c) as well as granzyme M displayed strong cytoplasmic granular staining pattern EBV LMP-1 and HHV8 LNA proteins were negative. EBER in situ hybridization demonstrated homogenous tumor cell positivity providing evidence for of EBV infection (Fig. 2d). Polymerase chain reaction using the Biomed 2 consensus primers for T-cell receptor-γ chain (TCRγ) rearrangement showed no clonal rearrangement. The angiocentric growth pattern was further evaluated by IHC for the endothelial components. CD31 highlighted the vascular network frequently infiltrated and partly occluded by tumor cells, which was accompanied by tissue necroses in the adjacent areas. Anti-cytokeratin immunostaining (clone AE1/AE3), on the other hand, presented dissected endometrial glands which were partially displaced, compressed or distorted but not infiltrated by the invasive process. On the basis of morphological, immunophenotypical and molecular characteristics, the diagnosis of extranodal (uterine) NK-cell lymphoma, nasal-type was made.

Computer tomography and ultrasound examinations revealed involvement of the uterus and bilateral adnexa, furthermore, paraaortic lymph node enlargements were described. No supradiaphragmatic manifestation could be stated and a detailed imaging of the head and neck region including the nasal cavity proved also to be negative. Bone marrow trephine biopsy was free of the disease. Based on the primarily pelvic localization, a radical histerectomy was performed which was followed by high-dose chemotherapy. The histological examination of the hysterectomy material resulted in the same diagnosis. Irrespective of chemotherapy, the disease progressed rapidly affecting the retroperitoneal tissues, liver, and lung as it was detected by follow-up radiological imaging. Despite intensified chemotherapy, no

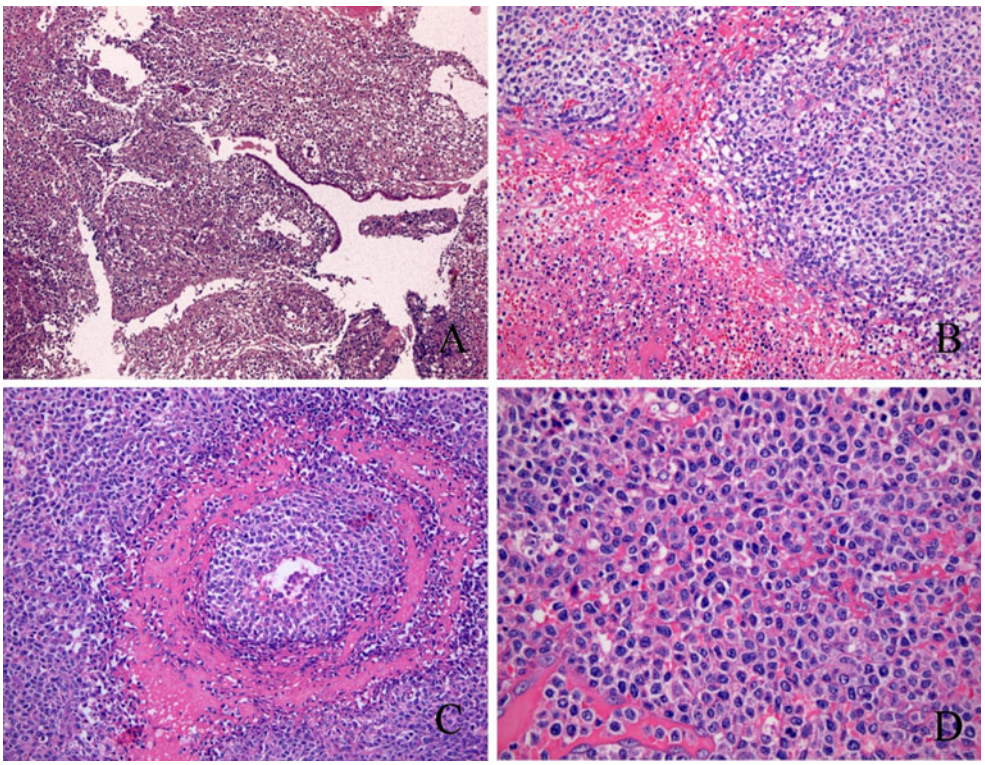

Fig. 1 Histomorphological features of endometrial lymphomatous infiltrate. **a** Dense lymphomatous infiltrate partially covered by intact columnar epithelium in the primary sample obtained by fractionated curettaging (HE, ×50 magnification). **b** The lymphomatous proliferation was interrupted by coagulative necrotic areas, and **c** frequently showed an angiocentric growth pattern (HE, ×200 magnification). **d** Atypical cytomorphological features of tumor cells are shown with irregular nuclei and clear cytoplasm (HE, ×400 magnification)

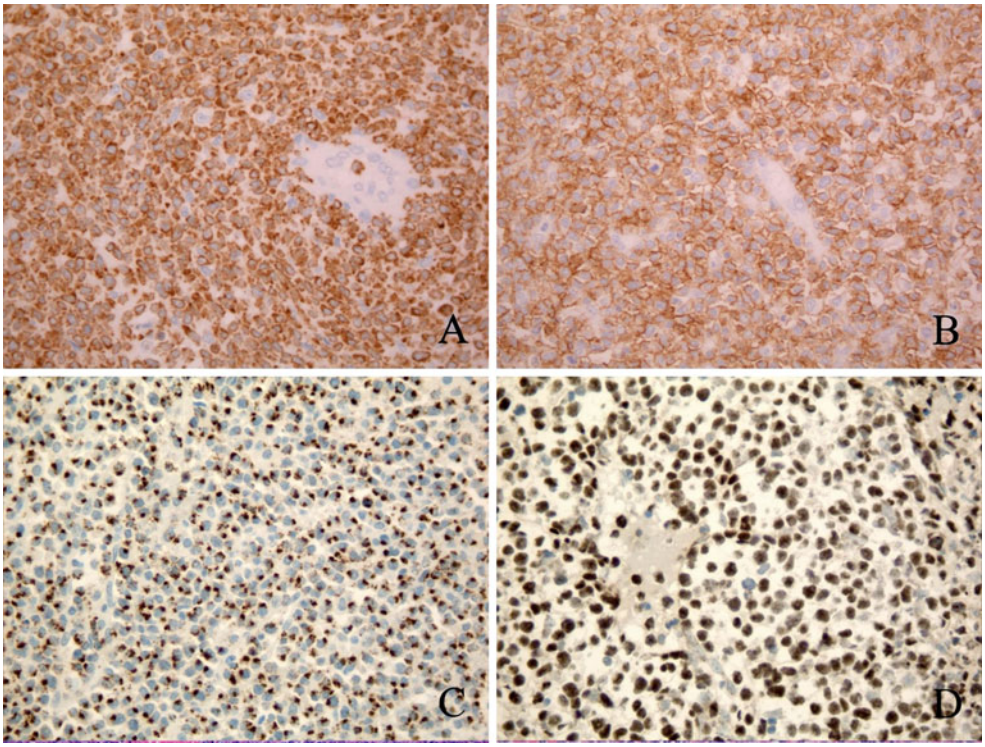

Fig. 2 Phenotypic characteristics of tumor cells. **a** The lymphoma cells showed cytoplasmic CD3ε **b**, **c** membranous CD56 and cytoplasmic granular TIA-1 positivity by immunohistochemistry (×400 magnification). **d** In situ hybridization for EBER sequences clearly supported EBV infection of the lymphoma cells (×400 magnification)

significant therapeutic response was achieved, and the patient died within 5 months after diagnosis. Postmortem examination demonstrated widespread NK-cell lymphoma with abdominal nodal and extranodal dissemination in all major parenchymal organs.

Discussion

Primary lymphomas of the uterus were reported at a frequency of only 2% of all extranodal lymphomas in women. The overwhelming majority of these cases represent aggressive B-cell lymphomas. Thus far, only a few cases of T- or NK/T-cell neoplasms have been reported [7–9]. As a common feature, these lymphomas were highly aggressive, and conventional prognostic factors failed to predict their outcome [10]. In the presented case, a genuine NK-cell lymphoma was identified in endometrial curetting sample. The diagnosis was based on the characteristic morphological features of an aggressive lymphoma with angiodestructive growth pattern showing the immunoprofile of activated NK-cells—coexpression of cytoplasmic CD3ε and membranous CD56 with cytotoxic granular proteins, positivity for latent EBV infection, lack of expression T-cell receptor and co-receptor proteins as well as lack of T-cell receptor rearrangement.

NK-cells of the endometrium (so-called endometrial granulocytes) have special physiological role [11]. CD56+ lymphocytes become abundant in the human uterus during every menstrual cycle, in parallel with final oocyte maturation, initialized by the pituitary-derived luteinizing hormone. The rapid increase of CD56+ cells is thought to be due to proliferation of the resident population, accompanied by recruitment of CD56+ lymphocytes from the circulation which proliferate and differentiate to become the predominant lymphoid cell type of the post-ovulatory uterus [12, 13]. These distinct, tissue-specific NK-cells either die prior to menses or increase in number during early pregnancy [14].

In mouse models, pregnancy-associated uterine NK (uNK) cells are, further to immunological processes, implicated in the regulation of midgestation structural changes to major arteries supplying the placenta. Emerging data indicate that interactions between lymphocytes and endothelial cells within the uterine microenvironment are mediated by classical molecules associated with lymphocyte trafficking in response to inflammation [14, 15]. The uNK cells produce angiogenic growth factors and are potential regulators of decidual angiogenesis in early pregnancy. According to these data it was proposed that the endometrium functions as an ‘inducible tertiary lymphoid tissue’ that supports the recruitment and expansion of CD56+/CD16- uNK cells and induces transcriptional up-regulation of an angiogenic machinery in response to local hormonal factors, cytokines and hypoxia. Increased numbers of phenotypically unusual CD56+/CD16- uNK cells have been also associated with recurrent reproductive failure [15]. The link between the normal NK-cell function and angiogenesis may help to

understand some of the important characteristics occurring in NK-cell lymphomas of uterine or in other localization, including angiocentric/angioinvasive growth pattern, high vascularization, and fast hematogenic dissemination. The vascular endothelial damage, on the other hand, may result in occlusion which explains the extensive coagulative necrosis, another characteristic feature of NK/T-cell lymphomas [1].

It seems to be established that uterine NK cells form a dynamic lymphoid pool in each menstruation cycle. One could expect that these cells may frequently undergo genetic and regulatory errors leading to malignant transformation. For this reason it is difficult to understand, why uterine NK-cells transform to malignant lymphoma with such a low frequency. As one possible explanation, the relatively short duration of a menstrual cycle and the regular shed of the endometrium may prevent the expansion and malignant transformation of uNK cells.

Although most extranodal lymphomas have good prognosis, aggressive behavior can be predicted in extranodal NK/T-cell lymphomas which were reported to have a median survival of only 0.28 years [3]. For comparison, in the presented uterine NK-cell lymphoma case the rapid progression ended in death after 5 months (0.42 year). Unfortunately, treatment experience is mostly limited to the upper aerodigestive tract disease. Extranodal NK-cell lymphomas of other sites are extremely rare and very limited data for optimal treatment strategies are currently available.

In conclusion, here we report a uterine NK/T-cell lymphoma, nasal type of a 48 year-old woman diagnosed from endometrial curetting sample and presented as a rapidly disseminating fatal disease. The tumor cells revealed pheno- and genotype of genuine NK-cell lymphoma.

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