Diagnostic and therapeutic difficulties in nasal-type NK/T-cell lymphoma – a case report

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Abstract

Extranodal NK/T-cell lymphoma, nasal type occurs more frequently in Asia and Central America and is undoubtedly associated with Epstein-Barr virus. The skin is the second most common site of involvement after the nasal cavity and nasopharynx. Clinically papulonodular lesions are observed on the trunk, limbs or face, within which decay often occurs. The characteristic histological features concern an angiocentric and angiodestructive growth pattern. In most cases the lymphoma cells have the immunophenotype of NK cells: CD2(+), CD45RO(+), CD43(+), CD56(+), TCR$\alpha\beta$(–) and TCR$\gamma\delta$(–). Surface antigen CD3 is usually absent, although its cytoplasmic form (cCD3) is detected. The clinical course of this disease is very aggressive, and although successful treatment has not been developed yet, a first-line treatment, recommended in the early stages of the disease, is radiotherapy. Chemotherapy is recommended for advanced forms of NK/T-cell lymphoma, but usually results in short remissions.

In this paper we describe the clinical course of extranodal NK/T-cell lymphoma, primary extranasal. The patient presented with growing cheek oedema with signs of infiltration involving swelling of both eyelids, leading to their necrosis. Moreover, in the extremities there were single lesions of erythematous infiltrated type present. Diagnosis of extranodular NK/T-cell lymphoma nasal type was the result of histopathological examination of the skin. Despite an initially good response to chemotherapy, the patient died after the second treatment cycle due to staphylococcal sepsis.

Key words: nasal-type lymphoma, NK/T lymphoma, radiotherapy.

Introduction

Natural killer (NK) cell lymphomas are a relatively rare and heterogeneous group of proliferative diseases of the lymphatic system. According to the classification of the World Health Organization and the European Organization for the Research and Treatment of Cancer (WHO-EORTC) of 2005 these lymphomas are analysed together with T-cell lymphomas (tab. 1). Invasion of the skin may be a primary or a secondary symptom of the disease. In both cases, the clinical course of the disease, which is aggressive, and the response to applied treatment are very similar. Therefore it seems to be groundless to specify "primary" and "secondary" cutaneous form [1]. However, studies conducted in a large group of patients with an extranodal NK/T-cell lymphoma revealed that the lymphoma with extranasal primary location shows more negative clinical signs compared to nasal-type NK/T-cell lymphoma. Mean survival time for patients with nasal-type lymphoma is shorter, and the response to radiotherapy in the early stage of the disease is worse [2].

Natural killer cells are large granular lymphocytes with sCD3(–), CD16(+) and CD56(+/–) phenotype. CD56 antigen is an isoform of the neural cell adhesion molecule (NCAM). In the majority of cases, NK cells differ from T-lymphocytes by lacking the T-cell receptor (TCR), although it is known that an insignificant percentage (5%) of NK cells have this receptor [3].

Extranodal NK/T-cell lymphomas may be primarily located in the skin, the respiratory system, the digestive system, the central nervous system, the testicles, the kidneys and in the skeletal muscles, where in many cases they imitate the inflammation process. NK/T-cell lymphoma of the nose tends to primarily invade the nasal cavity and the paranasal sinuses. It develops in the median line of the face, and secondarily it infiltrates the skin and other tissues. In contrast, extranasal NK/T-cell lym-

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Tab. 1. WHO-EORTC classification of cutaneous T-cell lymphomas

Mature T-cell and NK-cell neoplasms
Mycosis fungoides
Pagetoid reticulosis (localized disease)
Follicular, syringotropic, granulomatous variants
Granulomatous slack skin
Sezary syndrome
CD30+ T-cell lymphoproliferative disorders of the skin
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous peripheral T-cell lymphoma
PTL, unspecified
Subtypes of PTL (provisional)
Primary cutaneous aggressive epidermotropic CD8-positive T-cell lymphoma
Cutaneous γ/δ-positive T-cell lymphoma
Primary cutaneous CD4-positive small/medium-sized pleomorphic T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Hydroa vacciniforme-like lymphoma (variant)
Adult T-cell leukaemia/lymphoma
Mature B-cell neoplasms
Cutaneous marginal zone B-cell lymphoma (MALT-type)
Cutaneous follicle centre lymphoma
Cutaneous diffuse large B-cell lymphoma
Intravascular large B-cell lymphoma
Immature haematopoietic malignancies
Blastic NK-cell lymphoma / CD4+/CD56+ haematodermic neoplasm

phoma primarily originates from the skin, and secondarily infiltrates structures of the nose and sinuses. Clinically, in both types of NK/T-cell lymphomas nodular and nodous eruptions can be observed, which may be accompanied by erythema and oedema of the eyelids and destruction of the palate; the histological picture is also similar, but the angiocentric and angiodestructive infiltration type draws attention [4]. It is believed that NK/T-cell lymphomas are connected with Epstein-Barr virus infection.

The clinical course of nasal-type NK/T-cell lymphoma is very aggressive, and successful treatment mainly depends on the stage of the disease. Despite the fact that the optimal method of treatment has not been unambiguously established so far, radiotherapy is recommended as the first line treatment in early stages of the disease [5]. Chemotherapy, which is reserved for advanced forms of NK/T-cell lymphomas, usually leads to only short remissions. Resistance to applied chemotherapy is also observed, which significantly worsens prognosis in patients [6].

Case report

A 43-year-old female patient was admitted to the Department of Dermatology, Venereology and Allergology of the Medical University of Gdańsk in order to diagnose infiltrative lesions in facial tissues, which initially suggested suspicion of anaplastic lymphoma. Six months before hospitalization the patient had her tooth extracted – periapical inflammation was suspected at this time. Despite completed dental treatment, oedema of the cheek gradually increased. Actinomycosis was suspected in the patient, but bacteriological swabs did not confirm this diagnosis. The general condition of the patient systematically worsened. The patient reported weakness and subfebrile body temperature. Within increasing oedema of the cheek, an extensive infiltration formed. At admission of the patient to the Department, the oedema also included both eyelids, which made eye opening impossible. Within infiltration, foci of the skin necrosis were noticeable (fig. 1). Single lesions of erythematous and infiltrative nature with superficial lysis were present on the skin of the left arm, the left shank, and the superior and anterior surface of the left thigh (fig. 2). Laboratory evaluation revealed anaemia (Hgb 9.6 g/dl) and lymphopenia (0.45 G/l). In addition, an elevated level of transaminases was determined (AST 372 U/l, ALT 122 U/l), as well as increased concentration of creatine kinase (1669 U/l), lowered level of albumins (27 g/l) and abnormalities in the coagulation system (D-dimers 5301, fibrinogen 0). Gasometry was normal. Levels of antigranulocyte antibodies PRG3 and MPO were normal (the evaluation was performed in order to rule out Wegener's granulomatosis). The histopathological image of the dermis visualized focal infiltrations made of partially necrotic atypical lymphocytes of medium and large size (fig. 3). Immunohistochemical evaluation revealed the following phenotype of the neoplastic cells: CD3(+), CD56(–), granzyme B(+), CD4(–), CD5(–), CD43(+) and Ki67(+) in 90% of the cells. Based on this evaluation, nasal-type NK/T-cell lymphoma was diagnosed. The negative result for EBV and CD56 did not rule out this diagnosis, because according to the histopathologist, due to extensive necrosis of the neoplastic tissues, performing some histochemical reactions was impossible.

Due to the extent and intensity of the neoplastic lesions, the decision was made to use polychemotherapy according to the CHOP regimen (cyclophosphamide,

doxorubicin vincristine and prednisone). After the first cycle of treatment, lesions located on the face and extremities became significantly absorbed. After the second cycle of chemotherapy, the patient died due to staphylococcal sepsis.

Discussion

Primary extranodal NK/T-cell lymphomas are rare, but they are more common in Asia and Central and Latin America than they are e.g. in Europe.

Both types of NK/T-cell lymphomas lead to ulcerative and destructive lesions due to extensive necrosis occurring in the tumour. Lesions within the course of NK/T-cell lymphoma most often occur in the structures of the median line of the face (the nasal cavity and the palate) – NK/T-cell lymphoma of the nose; they also may primarily involve the skin or develop in the testicles, the digestive system and soft tissues – nasal-type NK/T-cell lymphoma.

Neoplastic lymphoma cells usually reveal presence of the Epstein-Barr virus (EBV) genome, but it occurs much more often in patients with NK/T-cell lymphoma of the nose than in patients with nasal-type NK/T-cell lymphoma. In connection with the aforementioned observations, EBV infection was assumed to play a pathogenetic role in development of these lymphomas. Based on the number of EBV-DNA copies in the serum, attempts were even made to monitor the course of the disease and predict the prognosis. However, further studies excluded that concentration of EBV-DNA in blood serum may have any prognostic value [7].

The histological image of NK/T-cell lymphoma mainly shows angiocentric proliferation with a significant area of segmental necrosis and destruction of the vessels, as well as polymorphic nature of the neoplastic cells, among which large cells with hyperchromatic or vesicular nuclei are dominant. However, the appearance of the neoplastic cells is significantly diverse and different in many cases. Sometimes small- and medium-size lymphocytes with fine signs of atypia are dominant. Infiltration containing plasma cells, eosinophils and histiocytes is less typical [8].

Lymphoma cells reveal NK cell immunophenotype: CD2(+), CD45RO(+), CD43(+), CD56(+), TCR$\alpha\beta$(–) and

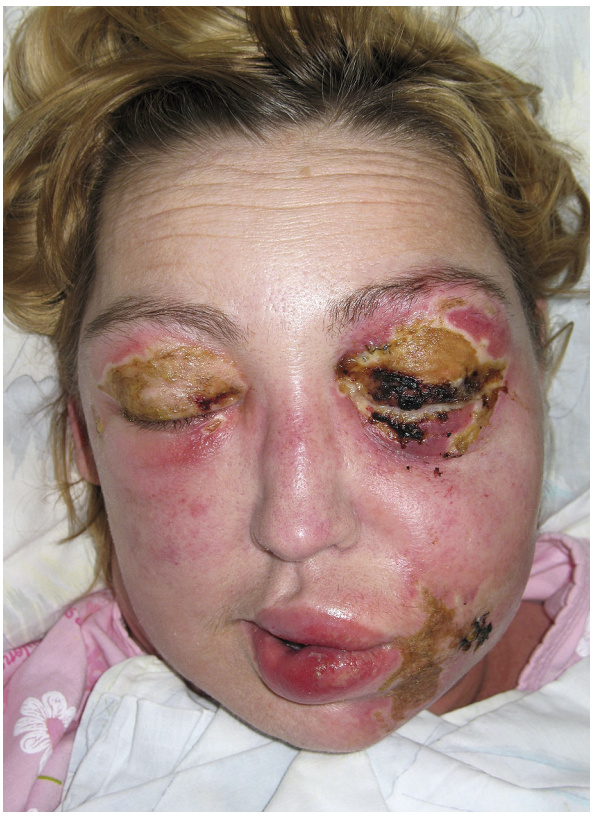

Fig. 1. Massive neoplastic infiltration of the left cheek and both eyelids; noticeable foci of superficial necrosis of the skin in the female patient with nasal-type NK/T-cell lymphoma

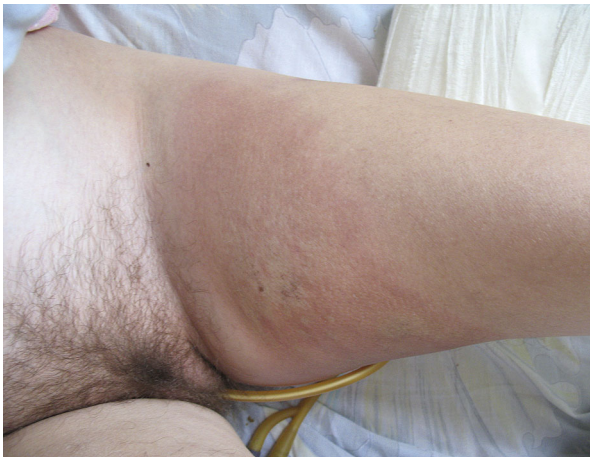

Fig. 2. Erythematous and infiltrative lesion on the skin of the left thigh in the female patient with nasal-type NK/T-cell lymphoma

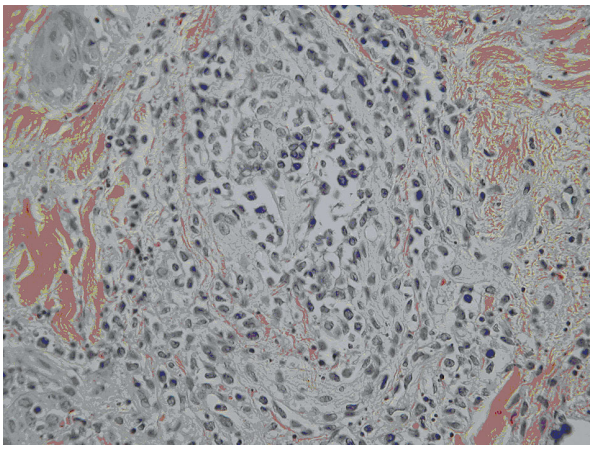

Fig. 3. Nasal-type NK/T-cell lymphoma – infiltration of the dermis by atypical lymphocytes of various size with numerous accompanying inflammatory cells

TCRγδ(–), in the majority of cases. Superficial antigen CD3 is usually absent, but its cytoplasmic form (cCD3) is detected [8]. These lymphomas may also, but more rarely, present the phenotype of cytotoxic T lymphocytes, but expression of CD56 is not detected in these cases [1].

Stage of the disease is important from a prognostic point of view. Usually, the course of the disease is aggressive and in the majority of cases, NK/T-cell lymphoma is characterized by high mortality. Only 30-60% achieve long-term survival without symptoms of recurrence among patients in the early stage of NK/T-cell lymphoma of the nose [9]. Mean survival time in patients with nasal-type extranodal NK/T-cell lymphoma, who reveal only skin lesions, is lower than 12 months [10]. Radiotherapy provides good effects in treatment of early stages of NK/T-cell lymphoma of the nose, when these lesions are established in the upper respiratory tract and they do not infiltrate surrounding bones or skin [5]. Complete remission occurs in approximately 60-70% of patients, but only half of them achieve permanent recovery after applied treatment [11]. In more advanced stages of the disease (Ann Arbor I/II with local infiltration of the bones or skin and III/IV) multicomponent chemotherapy is used, which frequently fails to provide the expected effect. When selecting the treatment regimen, use of e.g. iphosphamide, methotrexate, etoposide and/or prednisolone should be considered, but anthracyclines should be avoided, because extranodal NK/T-cell lymphomas are resistant to them.

Factors which worsen prognosis include extradermal location of the lesions [12], infiltration of the bones [5], high proliferation index Ki-67 [13] and expression of the lymphocyte antigens in the skin [14]. Complications may occur such as haemophagocytic syndrome in some cases, [15] or more rarely sepsis, which may rapidly lead to death of the patient.

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