Primary cutaneous lymphomas - diagnostic problems

Primary cutaneous lymphomas comprise a group of heterogeneous lymphomas, initially developing in the skin. The diagnosis, especially of the early stages of the disease creates diagnostic dilemma for both dermatologists and pathologists. In this paper the authors presented clinical picture and problems concerning diagnosis of individual diseases.

INTRODUCTION

Primary cutaneous lymphomas (PCL) are a group of heterogeneous malignancies which originate from the lymphatic system. The incidence is 1/100 thousand cases per year. In the 1980s, mycosis fungoides (MF), sporadically Sézary syndrome (SS) and rarer B lymphomas were mainly recognized by dermatologists in this group of diseases [1]. Currently, the development of molecular diagnostic methods and the improved histological technique with immunophenotyping allowed for more frequent identification of other rare diseases in this group. An increase in the incidence of these primarily cutaneous lymphatic hyperplasia is another undeniable fact. Despite advances in pharmacology, PCL is still a diagnostic and therapeutic problem.
Of course, the confirmation of hyperplasia by the pathomorphologist is the basis for making the diagnosis of PCL and implementation of therapy [2]. However, the clinical picture is equally important, because even a negative histological result should prompt the doctor to maintain the so-called oncological alertness. Many years of observations show that the initial histological picture of PCL may not be characteristic. The diagnoses we receive at the initial stages of this hyperplasia include: psoriasiform pattern or lichen planus pattern. Often, biopsies are performed repeatedly from various skin lesions, such as erythema, infiltrates or tumours. It is worth remembering that for about 2 weeks before collecting the material for histological examination we should not apply any steroid preparations to the skin. Specimens should not be taken from skin lesions in the seborrheic areas, because they statistically more often give a negative histopathological result.

DIFFERENTIATION

Skin lesions that should prompt a doctor to diagnose or observe for PCL include:

- eczema resistant to classic anti-histamine or local glucocorticoid therapy,
- erythematous plaques with foci slightly peeling on the surface, often located on the lateral parts of the torso, thighs, inner surfaces of the upper limbs (plaque parapsoriasis),
- recurrent scabies without the presence of Sarcoptes scabiei in the microscopic or dermatoscopic examination,
- long-term atopic dermatitis in the form of erythroderma resistant to treatment,
- lichen ruber pilaris resistant to treatment,
- poikilodermic foci located in the armpits, groins and on the buttocks (poikilodermic parapsoriasis).

Sporadically, vitiligo-like foci may be the first skin lesions, also in children. In mycosis fungoides a significant increase in serum IgE is common, unfortunately some physicians misunderstand this result and make the diagnosis of atopic dermatitis. Similarly, the presence of healthy skin areas in erythroderma is usually associated with lichen ruber pilaris. However, a very similar clinical picture may be observed in Sézary syndrome. Special attention should be paid to patients diagnosed with multifocal and plaque parapsoriasis, as many studies confirm that the condition is de facto the initial stage of mycosis fungoides [3]. Suddenly appearing, persistent itching resistant to therapy is a symptom which should also alarm a doctor. Patients who have been histologically diagnosed with lymphomatoid papulosis (LyP), regardless of its subtype, require close monitoring. Although this lymphoma is prone to spontaneous resolution and does not require aggressive treatment, it can precede or coexist with Hodgkin’s disease, mycosis fungoides or systemic large cell anaplastic lymphoma. Coexistence of LyP and chronic lymphocytic and myeloid leukaemia has also been reported.

Skin lesions in PCL depend on the type of lymphoma. In the most common form, mycosis fungoides, we observe light pink or dark red erythema of various size, with slight peeling on the surface not always accompanied by itching. Then, there are infiltrative foci, often developing inside previously formed erythema (dark red colour predominates), poikilodermic foci (erythema with discoloration, decolouration or telangiectasia), eczema-like nodules and foci of various sizes or psoriatic-like lesions. Soft infiltrative plaque foci may occur on the scalp, leading to alopecia, which may be accompanied by similar, single lesions located on the upper parts of the torso. Such a picture is often found in the folliculotropic form of mycosis fungoides which is diagnosed based on the result of histological examination. Also, any case of generalized dermatitis of the unknown aetiology should prompt the doctor to exclude PCL. On the other hand, the presence of tumours, often dark red or dark brown with a tendency to form ulcers, is a rare diagnostic problem because at this stage lymphomas usually have a characteristic histological and immunophenotypic picture. Rare skin lesions observed in MF include seeded cysts, macular lesions, pustules, blisters, vesicles and anetodermic lesions.

AETIOLOGY

The aetiology of PCL remains unknown. However, more and more proponents suggest that the clonal expansion of T-helper lymphocytes in primary cutaneo-
us T-cell lymphomas is due to chronic antigenic stimulation. Medications (hydrochlorothiazide) or infections may play a role in the development of the most common lymphoma, mycosis fungoides. An increased incidence of T-cell receptor (TCR) monoclonal rearrangements has been described, as well as a more advanced stage of the disease diagnosed in the group of patients with MF treated for hypertension with hydrochlorothiazide compared to those not receiving this drug [3]. 28.8% of patients who discontinued the therapy with hydrochlorothiazide showed complete or partial remission of skin lesions in the course of MF. However, there is still debate as to whether hydrochlorothiazide is a medicine that promotes the development of lymphoma or whether the lesions should be classified as pseudo-lymphoma.

A role of human T-lymphotropic virus type 1 (HTLV-1) is also well documented in the development of lymphoma/T-cell leukaemia in adults [7]. It is also believed that the state of immunosuppression, e.g. after bone marrow transplantation, may predispose to the development of CTCL. Rare reports on the familial susceptibility to MF, as well as finding specific deletions in HLA class II antigens may suggest, at least in some cases, the genetic background of the disease [5,6]. A role of Borrelia burgdorferi infection is also emphasized in low-grade B-cell lymphoma. The impact of environmental factors (occupational exposure, smoking, pesticides, sun exposure, halogenated aromatic hydrocarbons, e.g. benzene) has not been sufficiently documented [8].

CURRENT CLASSIFICATION

The WHO-EORTC classification, which was modified in 2005 and 2008 and is currently in force, distinguished MF from Sézary syndrome requiring aggressive treatment from the beginning. Thus the view that SS is the erythrodermic form of mycosis fungoides is in fact out of date. According to the International Society for Cutaneous Lymphomas (ISCL), the diagnosis of SS should be based on the determination of an absolute Sézary cell count of at least 1000/mm³ in peripheral blood, or an increase in the population size of CD4+ lymphocytes (CD4+/CD8+ ratio > 10) alternatively, the loss of one or part of the T lymphocyte antigens (CD2, CD3, CD4, CD5) [9], as well as the presence of erythroder-
plies – the skin lesions, i.e. blue-red nodules and tumours are located mainly on the limbs, but eruptions can also occur apart from the limbs. As in all primary cutaneous lymphomas, the diagnosis is made based on the histopathological picture and immunophenotyping.

DIAGNOSTICS

As 10% or more of the skin surface covered by the same eruptions, e.g. infiltrates, changes the stage of the disease, a clinical examination is very important to make diagnosis of lymphomas, including a precise description of skin lesions and their extent. On the other hand, the presence of ulceration in MF along with other eruptions is an unfavourable prognostic factor. At the stage of tumour, a diameter of the largest tumour, size and number of eruptions should be given.

The evaluation of the lymph nodes is another important diagnostic component; suspicious nodes are hard, 1.5 cm or more in diameter, irregular, not shifted in relation to the ground.

The diagnosis of a lymphoma variant is based on a biopsy with immunophenotyping. We should collect several specimens at the same time, if possible, avoiding seborrheic areas. Approximately 2-4 weeks before the collection of specimens, general medications, e.g. immunosuppressants ought to be discontinued, and steroid preparations should not be applied to the skin.

During the course of the disease, a biopsy of the lesions should be repeated (possible transformation into a more aggressive lymphoma). Other necessary diagnostic methods which should be repeated every few months (depending on the stage of the disease and response to therapy) include immunophenotyping with the use of flow cytometry from peripheral blood, imaging examinations: ultrasound of the abdomen and lymph nodes, a plain X-ray of the chest, and in special cases computed tomography or magnetic resonance imaging (MRI). The exception to this rule is the early (stage I) of MF, in which peripheral blood immunophenotyping or MRI is not recommended. Routine complete blood count, platelet counts and microscopic smear should be done in all patients; in addition, hepatic enzyme activity, LDH, beta-2-microglobulin concentration and other parameters, depending on the patient’s condition.

The expression of T and B cell markers is important in the diagnosis of primary cutaneous lymphomas. It is assessed both in immunophenotyping of the biopsy specimen and in the blood. The examination evaluates the expression of T cell antigens (CD2, CD3,
CD4, CD5, CD7, CD8, CD26, CD45 RO, CD30) and B cells antigens (CD19, CD20). The loss of CD7 and CD26 antigens indicates a more aggressive course of MF and SS [13].

**SUMMARY**

Before choosing the therapy, we must determine the stage of the disease. Although in the most common forms of CTCL prognosis is good, long-term remissions or recovery are rare. Therefore, effective palliative care is the main goal of the management [12]. A method that gives effective remission with the least toxicity is the gold standard.

**References:**


**Adres do korespondencji:**

Joanna Maj
Katedra i Klinika Dermatologii, Wenerologii i Alergologii
ul. Chałubińskiego 1, 50-368 Wrocław
Poland/Polska