Mycosis fungoides – case report and short overview of the literature

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Here we present a case report of a patient with mycosis fungoides (MF). A short overview of the currently used clinical algorithm and diagnostic methods is presented. The authors also provide a comparison of other T-cell skin lymphomas. The currently recommended disease staging is given.

Key words: mycosis fungoides, diagnosis, classification.

Introduction

Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL) and accounts for approximately 50% of all CTCL. The disease has a slowly progressive clinical course. Typically, MF starts as an indolent disease progressing from patch stage through confluent plaques to the development of skin tumours. Finally it evolves to a systemic form of the disease. In the majority of patients such progression takes years, and in some even decades. The incidence is correlated with patient's age. There is recognized male predisposition, as the disease was found be about 2 times more common in them compared to women [1]. Moreover, nowadays, population-based studies have shown increasing incidence of MF [2]. The cause of MF remains unknown. However, it has been proposed that chronic lymphocyte stimulation contributes to the development of MF. That is why the pathogenetic role of various chemicals as well as viruses (namely, HTLV-1 and HHV-8) and bacterial colonization of the skin have been investigated – unfortunately so far without success in identifying any agent as the cause [3-6].

The diagnosis of MF is based on the medical history of lesions, clinical findings and confirmation by histopathological examination of the skin biopsy. However, in some cases multiple skin biopsies might be required. Sometimes a second expert opinion with a "second-look diagnosis" is crucial, and review by an experienced pathologist is necessary to confirm the diagnosis. The recommended diagnostic schemes require histological examination extended by immunohistochemistry for immunophenotyping of neoplastic cells. Recently there was introduced preferable T-cell receptor gene analysis which should be carried out in all patients on tissue samples. After decades of discussion on standard procedures that should be used in cases of MF, lately there was introduced the WHO-EORTC classification based on a combination of clinical and histological including immunophenotypical features/criteria (Table I) [1].

Case report

A 60-year-old male patient was admitted to hospital with skin lesions on the lumbar area, abdomen, and right groin. Physical examination performed at admission revealed patch and plaque lesions (Fig. 1 and 2); the patient had found them about 3 months ago. No other pathology or lymph node enlargement was found. Basic laboratory analysis of blood samples done at admission revealed no abnormality. The patient's history revealed that

Table I. WHO-EORTC classification of cutaneous lymphomas with primary cutaneous manifestations [adopted from 1]

Cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
MF variants and subtypes
Folliculotropic MF
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukaemia/lymphoma
Primary cutaneous CD30+ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)
Cutaneous γ/δ T-cell lymphoma (provisional)
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)
Cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle centre lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other intravascular large B-cell lymphoma
Precursor haematological neoplasm
CD4+/CD56+ haematodermic neoplasm (blastic NK-cell lymphoma)

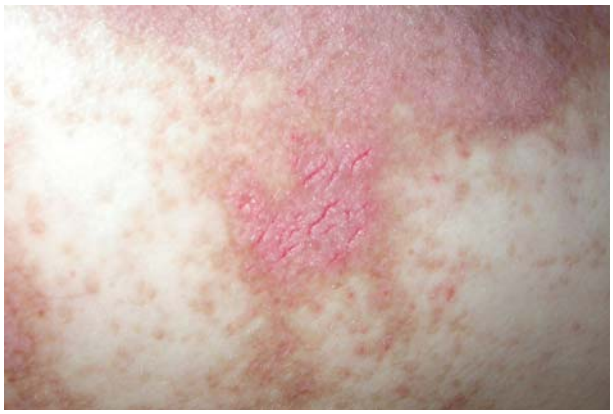

Fig. 1. Gross finding on the skin of the patient with mycosis fungoides. Patch lesions with excoriation

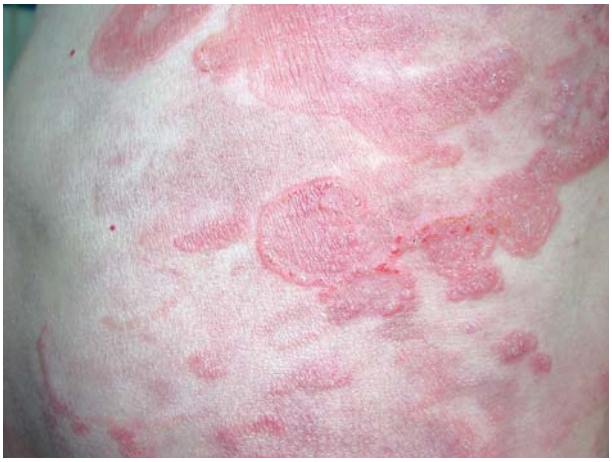

Fig. 2. Example of macroscopic presentation of skin lesion in patient with mycosis fungoides. Typical plaques on the abdomen

the first skin lesions were noticed some years ago. Such lesions were described as polycyclic, deep pink or erythematous patches, which appeared on the arms and abdomen and were accompanied by severe itching. The patient was using skin locally administered steroids and after such therapy transient improvement was achieved. Also, it was noticed that the lesions would usually spontaneously disappear in the summer period. Skin abnormalities consistent with patch lesions first appeared 6 years ago. Medical history revealed that the patient suffered only from childhood diseases, but not any dermatological ones. He was employed for 20 years in a chemical factory and worked with epoxide resins. At present he is being continuously treated for hypertension. No other symptoms or any

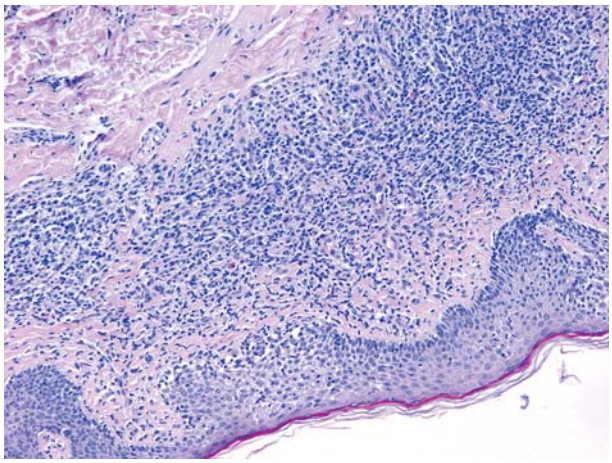

Fig. 3. Skin biopsy with very intensive lymphocytic cells infiltrate. They are found in the dermis as well as single cells within the epidermis. HE, primary magnification 20×

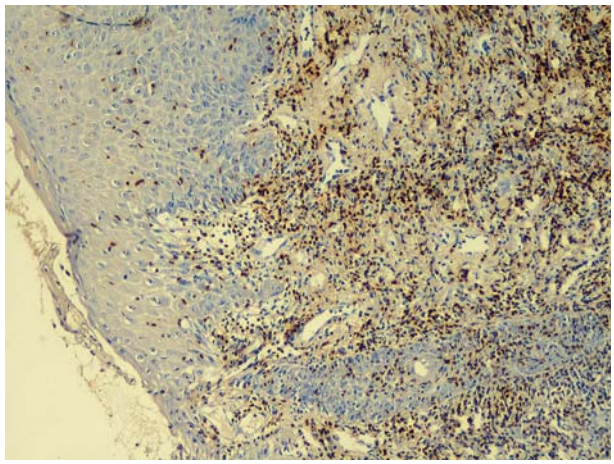

Fig. 4. Infiltrating skin cells almost exclusively of T lymphocyte infiltrate. Immunohistochemistry for CD3 antigen, ABC method with DAB as chromogen. Primary magnification 20×

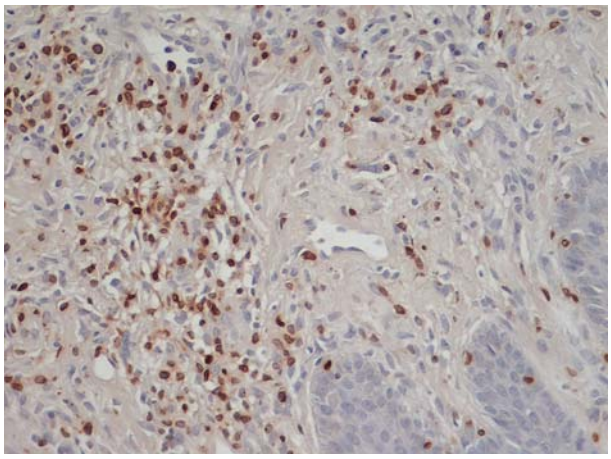

Fig. 5. The cells are mainly CD4 positive. Immunohistochemistry, ABC method with DAB as chromogen. Primary magnification 20×

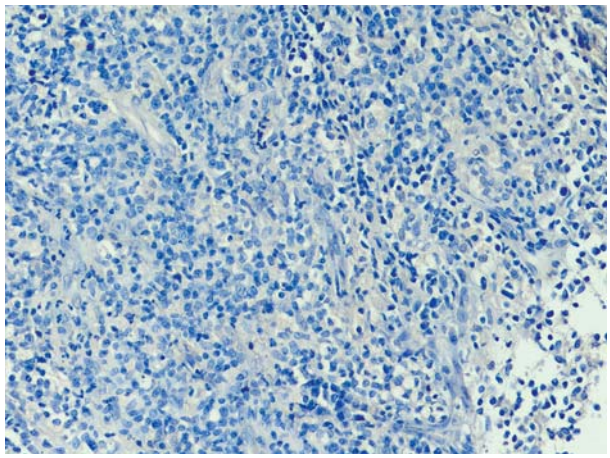

Fig. 6. In the skin lesion there were almost no B lymphocytes. Immunohistochemistry for CD20 antigen, ABC method with DAB as chromogen. Primary magnification 20×

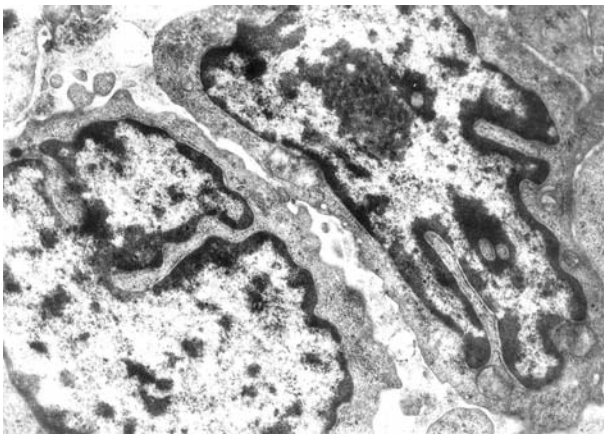

Fig. 7. Two lymphocytes from skin infiltrate in patient with mycosis fungoides. The nuclear membrane is rather convoluted. The chromatin is condensed mainly beneath the nuclear membrane. The cytoplasm forms a rather thin rim. Electron micrograph. Primary magnification 12 000×

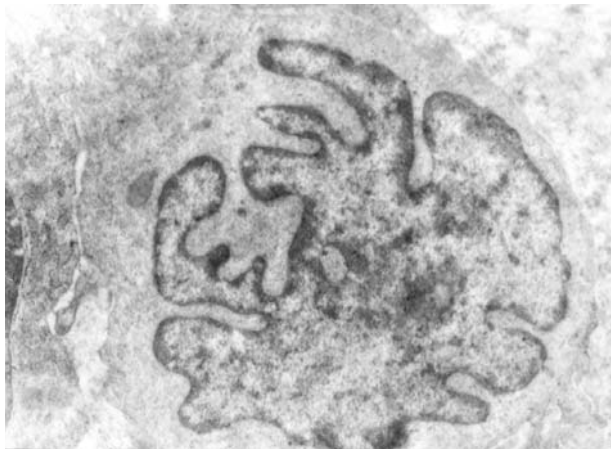

Fig. 8. The so-called cerebriform nucleus of the neoplastic cell in mycosis fungoides. Electron micrograph. Primary magnification 12 000×

malfunction of body organs were found. The family history for the occurrence of neoplastic diseases was negative.

After clinical discussion, a skin sample involving part of an erythematous patch was taken for further histological studies. After routine processing, in the haematoxylin and eosin staining a very intensive infiltrate of mononuclear cells was seen. It was found mainly in the subepithelial area. However, focally mononuclear cells with lymphocyte appearance were found within the basal layer of epidermis (Fig. 3). Immunohistochemical studies were done. The cells were found to be T cells with CD3+ and CD4+ phenotype (Fig. 4 and 5). There were also scattered single CD3+ CD8+ T cells. In the infiltrate only a few cells were of B lymphocyte phenotype (Fig. 6). Under higher magnification the lymphocytes were found to be larger than normal lymphocytes and they had hyperconvoluted nuclei known as cerebriform. This last feature was even more clearly visible in samples processed for electron microscopy (Fig. 7 and 8). The histological features as well as clinical data were consistent with a diagnosis of MF. After diagnosis proper treatment was introduced. The patient is still in clinical observation.

Mycosis fungoides overview and diagnostic recommendations

Mycosis fungoides is characterized by an indolent course. The disease usually has a long-term progression that might last for years from the first patch lesions through the infiltrative stage and might end with tumours. In some cases, such progression takes even decades. The beginning of the disease and its first stage could be related to diagnostic difficulties as the skin lesions present in a non-characteristic way. Namely they might mimic other diseases such as psoriasis, parapsoriasis en plaque, eczema, and atopic dermatitis. In all aforementioned conditions one can observe patch lesions on patients' skin. There were even published reports that parapsoriasis en plaque could precede MF development. In the classical case of MF, the first skin lesions are found on the buttocks and sun-protected body parts. In the second stage, the infiltrative changes are seen within patch lesions and outside of them in normally appearing skin. The lesions start to expand peripherally or forming round or oval foci. In the last tumour stage there are simultaneously patch, plaque and tumour lesions with ulceration. The average time of transition from stage I to III is around 12 years. Characteristically, skin lesions are accompanied by intensive itching [7]. In advanced stages the disease might involve lymph nodes and internal organs as well. If there are present isolated tumours which were not preceded by a patch or plaque, other types of T-cell lymphomas should be taken into consideration [1]. Besides the classical MF there have also been described several other clinical and histological variants. Some of them, such as bullosus, hyper- and hypopigmented variants, have a similar clinical course as the classical variant and are placed in one group. On the other hand, folliculotropic MF, pagetoid reticulosis and granulomatous slack skin are characterized by distinct clinical course and dissimilar histological presentation, which is why they are discussed as separate entities [8].

According to present recommendations of the WHO-EORTC classification, the diagnosis of skin lymphomas includes immunohistochemical studies as well as molecular techniques.

Histopathological diagnosis

In the tissue samples of the early patch stage, the features of light microscopic study include superficial or band-like infiltration composed mainly of lymphocytes and histiocytes. Sporadically there are observed small and medium-sized atypical cells with characteristic hyperchromatic nuclei with nuclear membrane invaginations. Such nuclei are known as cerebriform. Such cells, in the early stage of disease, are limited to the epidermis. They are found generally as single cells, mainly in the basal layer [9]. In typical cases of the infiltrative stage, the epidermotropism is more extensive. For this stage there have been described characteristic Pautrier's microabscesses. They are intra-epidermal accumulations of atypical lymphocytes, found mainly within the granular layer or just beneath it. Unfortunately they could be found only in limited cases [10]. Then with the disease progression, in the tumour stage, the skin infiltrate becomes more dispersed and epidermotropism disappears. However, the number of neoplastic cells increases, and cells become larger. All cells from small to large ones contain cerebriform nuclei. And in blastic cells even nucleoli are visible [11]. Classically, a band-like infiltrate involving the papillary dermis is found. These consist of small, medium and some large mononuclear cells with hyperchromatic, cerebriform nuclei without spongiosis.

Immunohistochemical studies

Using classical immunophenotyping, the malignant cells are described as CD3+, CD4+, CD7– (neg.), CD8– (neg.), and CD45RO+ with CD4 : CD8 ratio 10 : 1. In rare cases there have also been described MF patients with lymphocytes of CD4– (neg.) and CD8+. A very helpful feature in MF diagnosis is presence of lymphocytes with loss of

Table II. T cells/lymphocytes phenotype in T-cell lymphoma [adopted from 1]

DISEASE	CELL PHENOTYPE
mycosis fungoides	CD3+, CD4+, CD45RO+, CD8–, CD30– CD3+, CD4–, CD8+ (rarely), CD2–, CD3–, CD5–, CD7– (loss of pan-T antigens)
mycosis fungoides folliculotropic variant	CD3+, CD4+, CD45RO+, CD8-, CD30+/–
pagetoid reticulosis	CD3+, CD4+, CD8– CD3+, CD4–, CD8+ CD30+/–
granulomatous slack skin	CD3+, CD4+, CD8-
Sézary syndrome	CD3+, CD4+, CD8–, CD30– CD7–, CD26–
T-cell leukaemia	CD3+, CD4+, CD8–, CD25+
primary cutaneous large CD30+ cell skin lymphoma	CD4+, CD8-,CD2+/–, CD3+/–, CD5+/–, CD30+
lymphomatoid papulosis	type A and C: CD4+, CD8-CD2+/–, CD3+/–, CD5+/– CD30+ type B: CD3+, CD4+, CD8–, CD30–
subcutaneous panniculitis-like T-cell lymphoma (SPTL)	CD3+, CD4+, CD8–, CD30+, CD56+ (rarely)
NK/T-cell lymphoma, nasal type	CD3–, CD2+, CD56+

pan-T antigens, e.g. CD2– (neg.), CD3– (neg.), CD5– (neg.) and CD7– (neg.). It is especially well visible in cerebriform cells. In some cases there is observed transformation into large T-cell lymphoma with CD30 positive cells [12-16]. A detailed description of T-cell CD profiles in MF and other lymphomas is presented in Table II [1]. Neoplastic cells circulating in blood in Sézary syndrome are missing surface molecules such as CD7 and CD26. If in the skin infiltrates the major population consists of cells CD3+, CD4–, and CD8+, the differential diagnosis with actinic reticuloid should be taken into consideration [17-19]. As in some cases the transformation into anaplastic lymphoma is observed, it should be taken into consideration that in large cell anaplastic skin lymphoma neoplastic cells are also CD4+. Additionally, there is presence or loss of some surface antigens such as CD2, CD5 and CD3. This is accompanied by strong expression of cytotoxic proteins, namely: granzyme B, TIA-1, and perforins [20, 21]. In this group in 5% of cases, tumour cells might have the phenotype of CD8+ cells. To confirm the diagnosis of anaplastic lymphoma at least 75% expression of CD30 is required [22]. However, in contrast to systemic CD30 positive lymphoma, in skin lymphomas positive expression of CLA (cutaneous lymphocyte antigen) is found. Additionally, in the latter group no epithelial membrane antigen (EMA) or anaplastic lymphoma kinase (ALK) is observed. Some authors have also pointed out that large cells similar to those found in Hodgkin disease, in skin lymphomas are missing CD15 (which is a marker for Reed-Sternberg cells). Yet, some recently published data proved that in rare cases in large cells CD56 expression could be found. But so far, no influence of such co-expression on prognosis has been found [23-26].

Molecular studies

Development of molecular diagnostic procedures allowed for adaptation of polymerase-chain reaction (PCR) use in diagnosis of T-cell lymphomas. This technique makes use of the fact that T cells have on their surface receptors called TCR. They are responsible for the ability of T cells to recognize different antigens. The genes for proteins involved in formation of TCR are located on chromosome 7 ($\alpha\gamma$ chains) and chromosome 14 ($\beta\delta$ chains). In a healthy patient at the molecular level rearrangement of different regions of TCR occurs. In lymphomas it was proved that the cells are a monoclonal proliferation of one cell lineage, so all cells express the same TCR gene rearrangement, which is the diagnostic finding in the majority of skin lymphomas. The diagnosis of monoclonality is extremely useful in early stages of lymphomas and in clinically questionable cases, as even with a low number of cells monoclonality can be confirmed.

Ultrastructural studies

Sézary cells (mycosis cells, Lutzner cells) are atypical lymphocytes with distinctive nuclei. In those cells the nuclear membrane is convoluted in

Table III. ISCL/EORTC revision to the classification of mycosis fungoides and Sézary syndrome [for details see 28]

TNMB STAGES	
Skin	
T_1	Limited patches*, papules, and/or plaques† covering < 10% of the skin surface. May further stratify into T_{1a} (patch only) vs. T_{1b} (plaque ± patch).
T_2	Patches, papules or plaques covering ≥ 10% of the skin surface. May further stratify into T_{2a} (patch only) vs. T_{2b} (plaque ± patch).
T_3	One or more tumours‡ (≥1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node	
N_0	No clinically abnormal peripheral lymph nodes§; biopsy not required
N_1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative#
N_{1b}	Clone positive#
N_2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN_3
N_{2a}	Clone negative#
N_{2b}	Clone positive#
N_3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal peripheral lymph nodes; no histological confirmation
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation¶ and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells‖
B_{10a}	Clone negative#
B0b	Clone positive#
B_1	Low blood tumour burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but the criteria of B2 are not met
B_{1a}	Clone negative#
B_{1b}	Clone positive#
B_2	High blood tumour burden: ≥ 1000 μl Sézary cells‖ with positive clone#

**For skin, patch indicates any size skin lesion without significant elevation or induration. Presence/absence of hypo- or hyperpigmentation, scale, crusting, and/or poikiloderma should be noted.*
†For skin, plaque indicates any size skin lesion that is elevated or indurated. Presence or absence of scale, crusting, and/or poikiloderma should be noted. Histological features such as folliculotropism or large-cell transformation (> 25% large cells), CD30+ or CD30–, and clinical features such as ulceration are important to document.
‡For skin, tumour indicates at least one 1 cm diameter solid or nodular lesion with evidence of depth and/or vertical growth. Note total number of lesions, total volume of lesions, largest size lesion, and region of body involved. Also note if histological evidence of large-cell transformation has occurred. Phenotyping for CD30 is encouraged.
§For node, abnormal peripheral lymph node(s) indicates any palpable peripheral node that on physical examination is firm, irregular, clustered, fixed or 1.5 cm or larger in diameter. Node groups examined on physical examination include cervical, supraclavicular, epitrochlear, axillary, and inguinal. Central nodes, which are not generally amenable to pathological assessment, are not currently considered in the nodal classification unless used to establish N3 histopathologically.
¶For viscera, spleen and liver may be diagnosed by imaging criteria.
‖For blood, Sézary cells are defined as lymphocytes with hyperconvoluted cerebriform nuclei. If Sézary cells are not able to be used to determine tumour burden for B2, then one of the following modified ISCL criteria along with a positive clonal rearrangement of the TCR may be used instead: (1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of 10 or more, (2) expanded CD4+ cells with abnormal immunophenotype including loss of CD7 or CD26.
#A T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene.

a complicated way, giving an impression of so-called cerebriform nuclei. Cells typical for T-cell lymphoma with cerebriform nuclei have been found in skin samples as well as in peripheral blood. Their name comes from one of the scientists who described them. In 1938 Sézary and Bouvrain published a leukaemic case of MF with giant atypical cells. Nowadays, this type of disease is known as Sézary syndrome. In 1968 Lutzner and Jordan studied Sézary cells with the electron microscope and described their ultrastructure [27]. Using the parameter of their diameter they selected three types of such cells, namely: small cells with diameter below 12 microns, large cells with diameter above 12 microns, and very large cells with diameter greater than 15 microns. The nucleus of such cells usually occupies up to 80% of the cell area. It has

Table IV. ISCL/EORTC revision to the staging of mycosis fungoides and Sézary syndrome [recommendation presented in 28]

	T	N	M	B
IA	1	0	0	0.1
IB	2	0	0	0.1
II	1.2	1.2	0	0.1
IIB	3	0-2	0	0.1
III	4	0-2	0	0.1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA1	1-4	0-2	0	2
IVA2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

a distinct shape, from fairly convoluted to cerebriform. The chromatin is condensed and localized in accumulations beneath the nuclear membrane. Sometimes nucleoli are visible, too. The cell cytoplasm is usually visible as a thin rim around the nucleus. In the cell cytoplasm there can be observed mitochondria placed close to the endoplasmic reticulum, some polysomes and wavy filaments. Although electron microscopy is a very detailed diagnostic technique, due to the rather complicated procedure and high costs it is used rarely now.

Diagnostic algorithm

Diagnosis and treatment of primary skin lymphomas is an interdisciplinary issue. For proper patient management it should include a team composed of a dermatologist, pathologist, oncologist, radiologist, and haematologists. The therapeutic approach in skin lymphomas is based on histological diagnosis and disease stage evaluated according to TNMB classification. A detailed description of currently used classifications is presented in Tables III and IV [28].

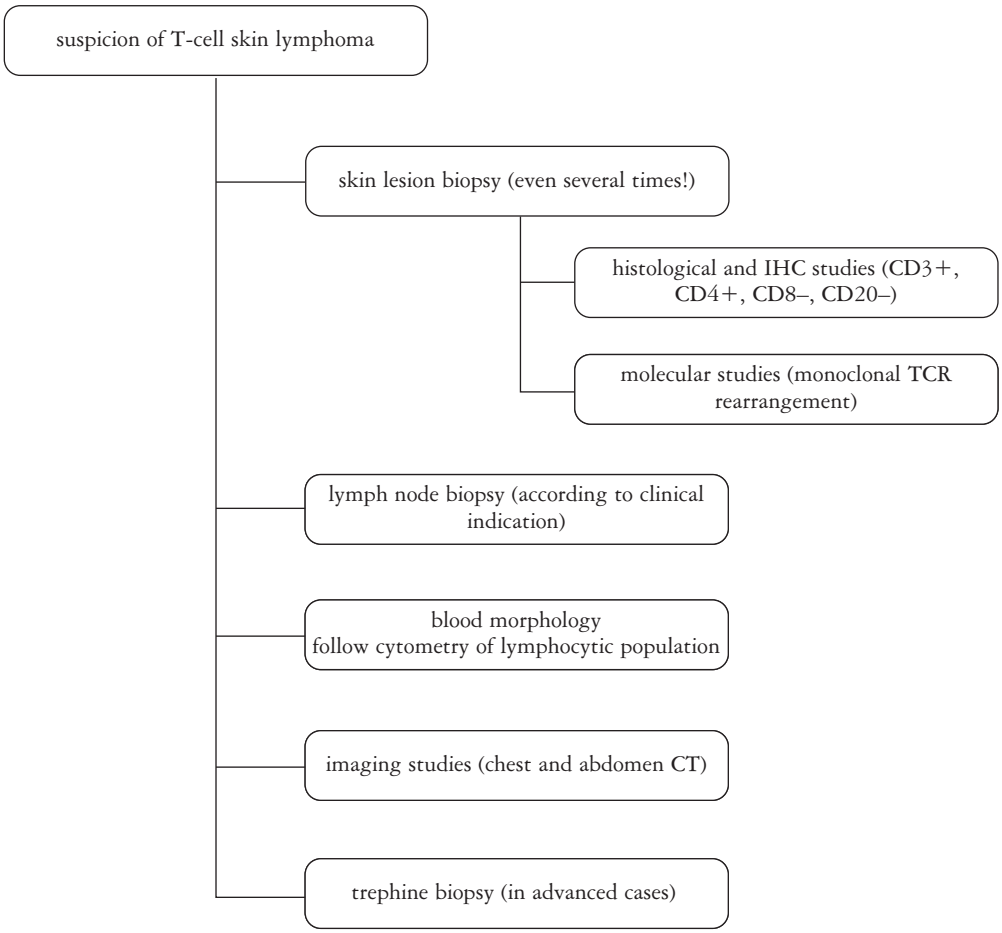

Fig. 9. Schematic presentation of clinical management of patients in diagnosis of mycosis fungoides

Concluding this short review, we would like to make readers aware of the possible diagnosis of MF, which in some cases might cause certain clinical and

pathological diagnostic problems. For better cooperation between clinicians and pathologists, in Fig. 9 we propose a scheme that could be helpful in management of a MF case.

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