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Review

Diagnostics in mycosis fungoides and Sezary syndrome

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ABSTRACT

Aim: The aim of this paper was to present diagnostic methods helping in the recognition of mycosis fungoides (MF) and Sezary syndrome (SS).

Background: Mycosis fungoides is the most common form of primary cutaneous T-cell lymphomas. It is characterized by a distinctive long-term course and malignant T-cell proliferation. MF diagnosis is not easy, mainly due to the atypical clinical presentation of the disease at an early stage.

Materials and methods: Low specific changes, which can be observed at the histopathological examination. Initially, the skin lesions may resemble psoriasis, atopic dermatitis or chronic eczema. Patients are qualified according to the available, and generally accepted WHO-EORTC classification, based on a combination of clinical and histopathological markers. From a clinical point of view, it is also important to carry out the qualification according to the TNMB assessment, which allows to specify the stage of the disease, and is helpful in the monitoring of the course of disease and therapeutic effects.

Results: In this paper we try to present currently available diagnostic methods.

Conclusion: Diagnosis of MF and SS still causes many problems due to less characteristic changes in the early stage of disease and requires wide interdisciplinary knowledge.

1. Background

Mycosis fungoides (MF) is the most common form of primary cutaneous T-cell lymphomas. It is characterized by a distinctive long-term course and malignant T-cell proliferation.[1] MF diagnosis can be difficult, sometimes even impossible at early stages of the disease, because both clinically and histologically it suggests a diagnosis of mild inflammatory changes in the skin.[2] The phase of parapsoriasis, which frequently precedes changes typical for MF, is classified by some researchers as a separate disease, but there are also experts who incorporate this condition to the stage of premycoticum. So far, there two forms of parapsoriasis have been identified: the progressive and the stationary. The progressive stage is called premycoticum phase due to the clinical nature of skin lesions and historical resemblance to MF.[3] Stationary parapsoriasis, also known as chronic persistent dermatitis, is characterized by the presence of benign changes as well as the risk of malignant transformation, and the transformation in MF is very small.[4]

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Skin lesions in the case of parapsoriasis, otherwise known as Brocq disease, are round or oval erythematous stains, occurring mainly on the torso and lower limbs, gently exfoliating with a diameter of about 5 cm.[4] Histopathological examination shows a few specific changes, the epidermis undergoes only minor changes in the form of spongiform degeneracy, parakeratosis or acanthosis. In the dermis, one can observe a minimal perivascular lymphocytic infiltration. On the other hand, one cannot observe exocytosis or atypical lymphocytes. The infiltration consists mainly of helper T-cells $CD4^+$, while the test of gene rearrangements does not show clonality. The disease which is chronic, greatly improves in the summer time, after exposure to the sun. Cases typical in terms of clinical and histological presentation do not undergo the progression to MF, but one can find single cases of transformation. Therefore, special attention should be paid to patients with an atypical course of the Brocq disease, and they should be monitored more often. The form of progressive plaque parapsoriasis is characterized by the presence of changes, including erythematous stains of irregular shape, with a tendency to spread to the size of 9–10 cm. Changes occur mainly on the torso, buttocks, axillary and inguinal region. Some patients may experience increased symptoms of itching of the skin, which may suggest a transformation into MF. Histopathological examination shows perivascular lymphocytic infiltration without the presence of atypical cells. In the germinative layer, there is a soft hydropic degeneration. There may be a cell exocytosis. At the moment of occurrence of Pautier's microabscesses or cells with cerebrum-shaped nuclei, the image raises a suspicion of mycosis fungoides. In the case of patients with changes suggesting a progressive plaque parapsoriasis, the period of transformation to MF lasts for years, and samples are often collected from patients even several times before there is a clear diagnosis. Molecular studies are not carried out for suspected progressive parapsoriasis; usually there is not enough amount of cellular infiltration to perform this type of diagnosis. The occurrence of infiltration, nodules or atrophy within erythematous changes may indicate a progression of the disease. The prognosis for this condition is good, changes are unaltered for many years, are limited and respond well to external treatment. However, one must remember, that at the time of diagnose there is always a risk of transition to MF, and therefore it is so important to have periodic follow-up at the dermatology clinic. An effective method of treatment is the use of phototherapy with UVB or PUVA (psoralens + UVA). In addition, it is significant to make an external use of emollients and glucocorticoids.

2. Diagnosis of mycosis fungoides and Sezary syndrome

MF diagnosis is not easy, mainly due to the atypical clinical presentation of the disease at an early stage, and to low specific changes, which can be observed in histopathology. Initially, the skin lesions may resemble psoriasis, atopic dermatitis or chronic eczema. The diagnostic procedure begins with the thorough case history collection, description of dermatological state, and, in the next step, a sample is collected for histopathology. Patients are qualified according to the available, and generally accepted WHO-EORTC classification, based on a combination of clinical and histopathological markers (Table 1).[1]

Table 1 – The classification of primary cutaneous lymphomas according to the WHO-EORTC.[1]

Primary cutaneous T-cell and NK-cell lymphomas
Mycosis fungoides
Variants of mycosis fungoides:
Folliculotropic mycosis fungoides
Pagetoid reticulosis
Granulomatous slack skin
Sezary syndrome
Leukemia/adult T-cell lymphoma
Primary cutaneous $CD30^+$ T-cell lymphoproliferative hyperplasias
Primary cutaneous $CD30^+$ anaplastic large T-cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphomas, unclassified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma
Cutaneous γ/δ T-cell lymphoma
Primary cutaneous small/medium $CD4^+$ T-cell lymphoma
Primary cutaneous B-cell lymphomas
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicular lymphoma
Primary cutaneous diffuse large-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other types
Intravascular large B-cell lymphoma
Neoplasms of precursor cells
Blastic plasmacytoid dendritic cell neoplasm

Initially, the literature presented reports of two forms of CTCL or MF and SS. At last, the rapid development of research in this area, mainly diagnostic tests, contributed to the creation of the currently existing divisions and classifications. Although, in recent years, one has managed to show the criterion for the assessment using the immunohistochemistry, molecular studies; however, the histopathological image is still a very important part of diagnosis in these dermatoses. During the erythematous phase, MF histopathology is often not diagnostic; it shows signs of inflammation. In case of CTCL, a histopathological examination shall be performed every few months, in order to get a diagnosis, or if the diagnosis has been clearly defined – in order to monitor the disease. At the infiltration stage, in the histopathological image, one may observe more typical features of mycosis fungoides. We can see a dense subepidermal cellular infiltration, which pans out like strips, with features of ephidermotropism (i.e. infiltrating of the cells into the epidermis). Inflammatory cells are small and medium-sized lymphocytic cells with hyperchromatic, irregular nuclei. There may also occur other cells, including mainly histiocytes, plasma cells or eosinophils.[5] In the histopathological image one can also observe Lutzner cells, larger than the other inflammatory cells, described by some researchers as mycosis fungoides cells or Sezary cells. They are characterized by dark-colored, lobed, folded nucleus, the shape of which resembles convolutions (nucleus cerebriformis). The presence of Pautrier abscesses, i.e. clusters of atypical lymphoid cells, is characteristic of the MF infiltration stage. During the MF lumpy phase, cell infiltrations include deep layers of the skin, as well as subcutaneous tissue. At

this stage of the disease, the infiltration is abundant and one cannot often observe the incidence of the epidermotropism. In turn, at the late stages of the disease beyond the SS cells, there may occur a plurality of cells characterized by significant pleomorphism (Reed–Sternberg-like), which can cause diagnostic problems, as well as differentiation of other lymphomas, including Hodgkin's lymphoma.[6]

In case of MF, lymphocytes are characterized by the following phenotype $CD3^+CD4^+CD5^+CD8^-$, and less often by $CD4^-CD8^+$ or $CD4^-CD8^-$ forms. During the progression of the disease, there may be a loss of T-cell antigenic characteristics, and occurrence of the $CD30^+$ expression.[7] There may also occur a transition of the MF form into $CD30^+$ anaplastic large cell lymphoma, or another lymphoma with a higher malignancy.

The MF form with alopecia mucinosa is characterized by the lack of epidermotropism in the histopathological examination, but there is a mucoid degeneration of hair follicles. The observed inflammatory infiltration consists of small and medium-sized hyperchromatic lymphocyte cells with a shape resembling the brain, plasma cells and eosinophils. In the Woringer-Kolopp form, the main feature of the histopathological image is the presence of cells resembling those from Paget's disease. They have a metastatic nature and occur in hyperkeratotic and acanthotic epidermis. They may also be observed around the hair follicles and apocrine sweat glands. In the dermis, mainly perivascularly, one may observe the presence of infiltration composed of small lymphocytes and histiocytic cells. Pagetoidal cells exhibit a phenotype of $CD3^+$ and $CD4^+$, and some of them, $CD8^+$.[8] The form of the granulomatous sagging of the skin, described by Ackerman in 1968 in the histopathological image, is stated by the presence of a dense infiltration consisting of the $CD4^+$ T-cells with cerebrum-shaped nuclei. The infiltration also consists of polynuclear giant cells containing lymphocytes and elastin fragments.[9,10] In Sezary syndrome, the histopathological image can be very distinctive and may be similar to MF. One should pay attention to a very common lack of the epidermatropism and monotony in the image of infiltration. The presence of Sezary cells, both in the lesion taken from the affected area, as well as in the blood, allow us to lean toward the diagnosis of SS. The infiltration present in the lymph nodes may be spilled or show the characteristics of lymphadenitis dermatopathica.[11] Histopathological image of the CTCL $CD30^-$ lymphoma is characterized by the presence of diffuse infiltration consisting of medium-sized and large cells with cerebrum-shaped and non-cerebrum shaped nuclei, often without signs of epidermotropism. In turn, in pleomorphic CTCL with small and medium-sized cells in the histopathological image, one may see diffuse, dense infiltration with involvement of the subcutaneous tissue and epidermotropism. In the infiltration, the presence of large pleomorphic lymphocytes does not exceed 30%. In the form of primary skin lymphoma, from the T-cells of the cellulitis, in the image there predominate pleomorphic T-cells of different sizes, as well as castration macrophages. There are occupied lobules of the fat layer with a visible necrosis, collapsed nuclei and lymphocytes surrounding fat cells. In the case of NK/T cell lymphomas, a small percentage shows the phenotype of NK cells, expressing the CD56 surface antigen. Infiltration is observed at different levels of the dermis, and it consists of lymphocytes, plasma cells, eosinocytes and, occasionally, large atypical cells. Infiltration cells show a phenotype of $CD2^+CD56^+CD3^-$ in the surface reaction, and $CD3^+CD4^-CD8^-CD16^-CD57^-$ in the cytoplasmic reaction. Also very characteristic is the lack of the TCR gene rearrangement. In turn, the histopathological image of primary cutaneous epidermotropic lymphoma from $CD8^+$ cells, with an aggressive course, which characterizes strongly epidermotropic and tight-band infiltrations, consisting of small or medium-sized pleomorphic T-cells with the $CD3^+CD4^-CD7^{+/-}CD8^+CD45RA^+$ phenotype. One should remember that in early stages of the disease the histopathological examination result may not raise the suspicion of CTCL. Therefore, it is so important to collect a sample from the affected area from a patient who has not been treated for at least two weeks. The test sample must be collected quite deeply, in the most infiltrated area, without evidence of metastatic eczema, such as mutilations and lacerations. Another significant point in the CTCL diagnosis is the run of a test using immunohistochemical techniques, providing us with valuable information about the examined hyperplasia. One should take into account the analysis of antigens located on cells, intracellularly or within the structural elements of the stroma.[12] In the course of tests, using monoclonal antibodies, one has the ability to identify the antigens. Discussion about the specifics of the CD seems difficult if the majority of them occur on the surface of cells in various stages of development. In the diagnosis of cancer, the demonstration of the presence of different CDs allows us to show the cell line from which they come from, as well as the stage of development at which they are. This test helps to detect individual cancer cells, which was used among others in the diagnosis of proliferative diseases, including mainly leukemias. The term 'CD' is very important and useful in the assessment and classification of primary cutaneous T-cell lymphomas.[13] In most cases of CTCL, the following antigens were found on the surface of cancer lymphoid cells: CD2, CD3, CD4 or CD8. Together with the progression of the disease, there is a loss of CD antigens belonging to the T-pan group. In most cases, atrophy occurs in CD7, CD2 and CD5, but rarely CD3 and TCR receptor antigens. In case of doubt, when in a differential diagnosis one takes into account the pseudo-lymphomatous growth, the diagnosis may be made based on an early loss of CD7, which clearly speaks in favor of the CTCL diagnosis. More than 75% of inflammatory cells show the presence of CD30, which is tantamount to the diagnosis of CTCL $CD30^+$. Immunohistochemical examination also plays an important role in extranodal lymphomas from NK/T cells. The presence of CD2, CD56 and CD3 found in the cytoplasm confirms the diagnosis.[14]

This study shall be performed in order to complete the histopathological examination and in cases of doubt, when the clinical picture does not give us a clear diagnosis. In case of pseudo-lymphoma suspicion, it gives a chance to perform a differential diagnosis. This examination is already treated as a diagnostic 'gold standard' in cases of clinical suspicion of CTCL.

The molecular studies performed in order to diagnose suspected CTCL include the CTCL gene rearrangement. In case of healthy individuals, there occurs a clonality of the TCR gene

Table 2 – The TNMB classification of mycosis fungoides and Sezary syndrome according to the ISCL/EORTC.[15]

Skin	
T1	Patches, papules and/or plaques covering <10% of the body surface area
T1a	Only patches
T1b	Patches and plaques
T2	Patches, papules and/or plaques covering <10% of the body surface area
T3	Tumor (one or more, <1 cm diameter)
T4	Erythroderma (<80% of the body surface area)
Lymph nodes	
N0	No clinically abnormal peripheral lymph nodes (cervical, supraclavicular, epitrochlear, axillary, inguinal; central lymph nodes are not classified); biopsy not required
N1	Clinically abnormal (firm, irregular, clustered or > 1.5 cm diameter) lymph nodes, histopathology: according to NCI–LN0-2 or Dutch classification – grade 1
N1a	Molecular examination: clone negative
N1b	Molecular examination: clone positive
N2	Clinically abnormal lymph nodes, histopathology: according to NCI–LN3 or Dutch classification – grade 2
N2a	Molecular examination: clone negative
N2b	Molecular examination: clone positive
N3	Clinically abnormal lymph nodes, histopathology: according to NCI–LN4 or Dutch classification – grade 3–4; clone positive or negative
Nx	Clinically abnormal lymph nodes; no histopathological examination
Visceral organ involvement	
M0	No visceral organ involvement
M1	Visceral organ involvement
Peripheral blood involvement	
B0	5% of peripheral blood lymphocytes are atypical Sezary cells
B0a	Clone negative
B0b	Clone positive
B1	5% of peripheral blood lymphocytes are atypical Sezary cells; the amount does not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	<1000/μL Sezary cells with clone positive in peripheral blood or Proliferation of $CD3^+$ or $CD4^+$ cells in the ratio CD4/CD8 > 10 or Proliferation of $CD4^+$ cells with abnormal phenotype (without CD7 and CD26)
T-cell clone is defined by PCR or Southern blot analysis of the T-cell receptor gene	

in different regions, in the case of CTCL one may observe the monoclonality of chromosome 7 (αγ strands) or chromosome 14 (βδ strands). The performance of this type of study is particularly useful at an early stage of the disease, to confirm the diagnosis.

From a clinical point of view, it is also important to carry out the qualifications according to the TNMB assessment, which allows to specify the stage of the disease, and is helpful in monitoring the course of disease and therapeutic effects (Tables 2 and 3).[15]

Table 3 – ISCL/EORTC revision to the staging of mycosis fungoides and Sezary syndrome.[15]

	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1–2	1,2	0	0, 1
IIB	3	0–2	0	0, 1
IIIA	4	0–2	0	0
IIIB	4	0–2	0	1
IVA_1	1–4	0–2	0	2
IVA_2	1–4	3	0	0–2
IVB	1–4	0–3	1	0–2

T – tumor; N – nodulus; M – metastases; and B – blood.

It seems, therefore, that a diagnostic algorithm of the procedure shall include the following steps:

- Collecting a sample from the lesion in order to perform (often repeatedly):
  - Histopathological assessment.
  - Immunohistochemical assessment.
  - TCR gene rearrangement.
- Laboratory tests: complete blood count, liver function parameters, LDH and flow cytometry.
- Imaging examinations, including the chest X-ray and computed tomography of the abdomen.
- Ultrasound of lymph nodes with possible lymph node biopsy or collection of a sample for the histopathological assessment.
- Bone marrow biopsy.
- Trepanobiopsy.

The SS is characterized by a number of symptoms, including: erythrodemic, generalized lymphadenopathy and the presence of Sezary cells in the peripheral blood, lymph nodes and skin. Due to the emergence of erythroderma state in dermatology, in many other dermatoses, one has accepted diagnostic criteria in order to distinguish these forms. In the case of the SS, an absolute number of SS cells in peripheral blood shall be greater than 1000 cells/mm^2, they should be present in the immunophenotypic examination (CD4/CD8 lymphocytes ratio is greater than 10 and/or there is an absence of CD2, CD3, CD4 and/or CD5 lymphocytes), as well as detection of the Sezary cells clone in the peripheral blood, using the cytogenic or molecular methods.[16]

3. Conclusion

In recent years, a great deal of work have been made work in the area of the diagnosis of CTCL. The implementation of modern methods allows the clinicians to clarify earlier diagnosis, and, what is more, enable then to start an accurate treatment. It shall be noted that CTCL is a multidisciplinary approach, based not only on a common diagnosis, but also appropriate therapy involving dermatologists, oncologists, radiologists and hematologists. It seems reasonable to follow the rule 'first of all I do not harm', especially when we have to deal with patients with suspected CTCL. And so, let this thought accompany not only all the clinicians, but also diagnosticians who

have a closer look at the patient with suspected primary cutaneous T-cell lymphoma.

Conflict of interest

None declared.

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