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Primary cutaneous lymphomas: the analysis of cases treated in the Department of Dermatology University Hospital in Krakow

Pierwotne chłoniaki skóry – analiza przypadków leczonych w Oddziale Klinicznym Dermatologii Szpitala Uniwersyteckiego w Krakowie

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Introduction: Primary cutaneous lymphomas are lymphoproliferative skin infiltrates of T-, B- or NK-cells, classified according to the World Health Organization - European Organization of the Research and Treatment of Cancer (WHO-EORTC) criteria. They are the second most common group of extranodal non-Hodgkin lymphomas, that present in the skin with no evidence of systemic involvement at the time of diagnosis.

Aims: The aim of the study was the analysis of clinical profile of cutaneous lymphomas in the tertiary referral center in Poland.

Material and Methods: We analyzed case records of 63 patients (26 women, 37 men aged 19 - 86) referred to the Department of Dermatology, University Hospital in Cracow for the diagnosis and treatment of cutaneous lymphoma.

Results: After analysis of clinical and histological data, the final diagnoses were: mycosis fungoides (42 patients), primary cutaneous CD30+ lymphoproliferative disorder (7), Sezary syndrome (3), parapsoriasis (3), primary cutaneous B-cell lymphoma (1), acute myeloid leukemia (1), Hodgkin lymphoma coexistent with mycosis fungoides (1), generalized allergic contact dermatitis (2) and erythema elevatum diutinum (1). We excluded 2 patients due to incomplete data. The most common location of skin lesions was the lower limb (52.46%) and most common clinical presentation was raised erythematous lesion (26.23%). Pruritus was present in 45.9% of the patients and 39.3% had extracutaneous symptoms, with lymphadenopathy as the most common symptom. 37.7% of patients presented with mild eosinophilia and another 37.7% with mild monocytosis. Prior to referral to our center, general practitioners misdiagnosed the lymphomas commonly as: atopic and contact dermatitis, borreliosis, drug-induced exanthema.

Conclusions: The diagnosis of cutaneous lymphoma is often delayed due to their indolent, often recurring

Wprowadzenie: Pierwotne chłoniaki skóry stanowią grupę nowotworów charakteryzujących się rozrostem limfocytów T, B oraz komórek NK w skórze. Klasyfikowane według kryteriów Światowej Organizacji Zdrowia i Europejskiej Organizacji Badań i Leczenia Raka (WHO-EORTC), są drugą co do częstości grupą chłoniaków pozawęzłowych. Chłoniaki definiuje się jako pierwotnie skórne, jeśli chwili rozpoznania proces chorobowy jest ograniczony wyłącznie do skóry.

Cele: Celem pracy była analiza obrazów klinicznych pierwotnych chłoniaków skórnych u pacjentów hospitalizowanych w polskim ośrodku referencyjnym trzeciego stopnia.

Materiały i metodyka: Dokonaliśmy analizy historii chorób 63 pacjentów (26 kobiet, 37 mężczyzn w wieku 19-86 lat), którzy zostali skierowani do Oddziału Klinicznego Dermatologii Szpitala Uniwersyteckiego w Krakowie, celem diagnostyki pierwotnego chłoniaka skóry.

Wyniki: Po analizie danych klinicznych i wyników badań histopatologicznych pacjentów, ostatecznymi rozpoznaniami były: ziarniniak grzybiasty (42 pacjentów), pierwotnie skórna choroba limfoproliferacyjna z komórek T CD30+ (7), zespół Sezary-'ego (3), przyłuszczyca (3), pierwotny chłoniak B-komórkowy (1), ostra białaczka szpikowa (1), chłoniak Hodgkina współistniejący z ziarniniakiem grzybiastym (1), uogólnione alergiczne kontaktowe zapalenie skóry (2), rumień wyniosły i długotrwały (1). 2 pacjentów wykluczono z badania ze względu na niekompletne dane kliniczne. Najczęstszą lokalizacją zmian skórnych była kończyna dolna (52,46%) z wykwitami o charakterze rumieniowym, uniesionymi ponad poziom skóry (26,23%). Świąd skóry był obecny u 45,9% pacjentów, a 39,3% miało objawy pozaskórne (najczęściej limfadenopatię). W badaniach laboratoryjnych w 37,7% przypadków zaobserwowano łagodną eozynofilię, w kolejnych 37,7% niewielką monocytozę. Przed przyjęciem do

course, non-specific symptoms and uncommon appearance. The cooperation of a clinician and pathologist is essential in the diagnostic process.

Kliniki rozpoznawano u pacjentów poza chłoniakiem skóry najczęściej: atopowe, kontaktowe zapalenie skóry, boreliozę, osutkę polekową. Wnioski: Rozpoznanie pierwotnego chłoniaka skóry może być opóźnione ze względu na często indolentny, nawrotowy przebieg, niespecyficzne objawy, mogące imitować częściej występujące choroby skóry. Ścisła współpraca klinicysty i histopatologa jest niezbędna w procesie diagnostycznym.

Introduction

Primary cutaneous lymphomas (PCLs) are a heterogenous group of non-Hodgkin lymphomas that present in the skin with no evidence of extracutaneous manifestations of the disease at the time of diagnosis. PCLs are lymphoproliferative skin infiltrates of T-, B- or NK-cells and have commonly a chronic course [1-3]. They form the second largest group of extranodal non-Hodgkin lymphomas after lymphomas of the gastro-intestinal tract. The annual incidence of primary cutaneous lymphomas is 1:100000/year, with approximately 75-80% of cutaneous T-cell lymphomas (CTCLs) and 20-25% of cutaneous B-cell lymphomas (CBCLs). NK-cell lymhpomas are rare [1]. The pathogenesis of primary cutaneous lymphomas is complex. Cutaneous lymphomas are classified according to WHO-EORTC classification criteria (Tab. I, Tab. II). The diagnosis of PCLs is often difficult and should be made after the analysis of clinical, histological and immunophenotypic data; however, clinical manifestation is the most important criterion in decision-making process [1,4-6].

Mycosis fungoides (MF) is the most common subtype of primary skin lymphoma, characterized by a monoclonal proliferation of epidermotropic CD4+ and CD45RO+ T-cells with commonly aberrant expression of mature T-cell antigens [7]. The incidence of MF in United States is 3.6-4.6 cases/1000000/year which has increased over time [7-9]. It commonly affects males more than females in the fourth to sixth decade [10-13]. Typically, the natural history of MF is indolent with long-lasting cutaneous lesions. The median duration from onset of symptoms to diagnosis is 4 to 6 years [7,14]. Histologically, classic mycosis fungoides is characterized by epidermotropism, tagging of atypical T cells along the dermo-epidermal junction and Pautrier microabscesses. The subtypes of MF mentioned in WHO criteria include: folliculotropic MF, pagetoid reticulosis, granulomatous slack skin. The diagnosis of early mycosis fungoides is challenging due to subtle histological features that may be present and that diagnostic T-cell clones are found only in approximately half of the skin biopsies in the early phase of the disease. Clinical presentation remains the most important part of the diagnostic process and if suspicion of lymphoma remains high, the biopsies should be repeated [15]. Mycosis fungoides is classified into 4 stages, according to the morphology of skin lesions: premycotic, patch, plaque and tumor stage. The morphology and extracutaneous involvement is included in staging I-IV. The TNM classification is presented in table III [9,10]. Management includes a combination of topical and systemic therapy [14,16,17].

Primary cutaneous CD30+ lymphoproliferative disorders (CD30CLPD) represent the second largest group of cutaneous lymphomas (approximately 25-30%). This group is divided into primary cutaneous ana-plastic large-cell lymphoma (PCALCL) and lymphomatoid papulosis (LyP). PCALCL is an indolent lymphoma commonly manifesting as a solitary lesion or localized group of nodules and tumors (usually ulcerated, over 1 cm in diameter). Regional lymph node involvement is observed in 10% of the patients. It has favourable prognosis, with more than 90% of patients having a 10-year disease-related survival [18,19]. The diagnosis is made after analysis of clinical history and histopathology of the lesion. Histologically, a minimum of 75% cells should express CD30+ and anaplastic lymphoma kinase should be negative [20,21,25]. Lymphomatoid papulosis has an indolent course with a disease-related survival of 100% at 5 years. LyP is characterized by multifocal, papulonodular eruptions often resolving without treatment [24,25]. Nevertheless, 5%-20% of patients have a risk of developing systemic anaplastic large-cell lymphoma, mycosis fungoides or Hodgkin's disease and should be monitored regularly [20,22,23].

Sézary syndrome (SS) accounts for 3% of cutaneous T-cell lymphomas. Its course is aggressive with a 5-year survival rate of 24% [24,25]. The classic features of this disorder include: erythroderma, diffuse lymphadenopathy and the presence of atypical T lymphocytes (>1000/mm^3) in peripheral blood, skin and lymph nodes. There are single cases describing nonerythrodermic variants of SS, such as papular forms [15,26]. KIR3DL2 (CD158k) receptor, a specific marker of atypical T lymphocytes, is a tool used in identifying Sezary cells. Its level is highly correlated with the clinical course of the disease [27]. The clinical and histological

Table I
WHO-EORTC T and NK-cell cutaneous lymphomas classification.
Klasyfikacja WHO-EORTC chłoniaków skórnych z komórek T i NK [1].

T and NK-cell lymphomas	Frequency (%)	5-Year Survival Rate (%)
Indolent clinical behavior		
Mycosis fungoides	44	88
Mycosis fungoides variants and subtypes		
— Folliculotropic mycosis fungoides	4	80
— Pagetoid reticulosis	< 1	100
— Granulomatous slack skin	< 1	100
Primary cutaneous CD30+ lymphoproliferative disorder		
— Primary cutaneous anaplastic large cell lymphoma	8	95
— Lymphomatoid papulosis	12	100
Subcutaneous panniculitis-like T-cell lymphoma (provisional)	1	82
Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (provisional)	2	75
Aggressive clinical behavior		
Sézary syndrome	3	24
Adult T-cell leukemia/lymphoma	NR	NR
Extranodal NK/T-cell lymphoma, nasal type	NR	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified	2	16
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (provisional)	< 1	18
Cutaneous gamma/delta-positive T-cell lymphoma (provisional)	< 1	NR
Precursor Hematologic Neoplasm (not a T-cell lymphoma)		
CD4+/CD56+ hematodermic neoplasm (blastic NK-cell lymphoma)	NR	NR

Table II
WHO-EORTC B-cell cutaneous lymphomas classification [1].
Klasyfikacja WHO-EORTC chłoniaków skórnych z komórek B.

WHO-EORTC Classification (B-cell lymphomas)[1]
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type

Table III

Staging according to the International Society for Cutaneous Lymphomas (ISCL), the European Organization of Research and Treatment of Cancer (EORTC) and 2010 Tumour-Nodes-Metastasis- Blood (TNMB) classification.
System klasyfikacji według Międzynarodowego Towarzystwa Chłoniaków Skóry (ISCL), Europejskiej Organizacji Badań i Leczenia Raka (EORTC) oraz klasyfikacji TNMB (guz-węzły-przerzuty-krew).
MF - mycosis fungoides, NCI – National Cancer Institute, NCI-VA – National Cancer Institute – Veterans Affairs, Clone negative, positive – for T-cell receptor gene

	Cutaneous lesions
- **T1**	Limited patches, papules and/or plaques covering < 10% of the skin surface
	T1a Patch only (< 10% of the skin surface), T1b Plaque and patch (< 10% of the skin surface)
- **T2**	Patches, papules or plaques covering ≥ 10% of the skin surface
	T2a Patch only (≥ 10% of the skin surface), T2b Plaque and patch (≥ 10% of the skin surface)
- **T3**	≥ 1 tumour (≥ 1 cm diameter)
- **T4**	Erythema covering ≥ 80% of body surface area
	Lymph nodes:
- **N0**	No clinically abnormal peripheral lymph nodes; biopsy not required
- **N1**	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN 0–2
	N1a Clone negative (for T-cell receptor gene), N1b Clone positive
- **N2**	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN 3
	N2aClone negative, N2b Clone positive
- **N3**	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN4; clone positive or negative
- **Nx**	Clinically abnormal peripheral lymph nodes; not confirmed histologically
	Central nodes are not currently considered in the nodal classification.
	Histopathologic staging of lymph nodes
	ISCL/EORTC (TNMB), Dutch system: grades 1-4, NCI-VA: LN0-4
- **N1**	Grade 1: dermatopathic lymphadenopathy (DL),
	LN0: no atypical lymphocytes
	LN1: occasional and isolated atypical lymphocytes (not arranged in clusters)
	LN2: many atypical lymphocytes or in 3–6 cell clusters
- **N2**	Grade 2: DL; early involvement by MF (presence of cerebriform nuclei > 7.5 µm)
	LN3:
	aggregates of atypical lymphocytes; nodal architecture preserved
- **N3**	Grade 3: partial effacement of LN architecture; many atypical cerebriform mononuclear cells
	Grade 4: complete effacement
	LN4: partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells
	Visceral involvement
- **M0**	No visceral organ involvement
- **M1**	Visceral involvement (imaging studies are sufficient for viscera, spleen and liver, otherwise histopathological exam should be performed)
	Peripheral blood involvement
- **B0**	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B0a	Clone negative, B0b Clone positive
- **B1**	Low blood-tumour burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells. Does not meet the criteria of B2.
	B1a Clone negative, B1b Clone positive
- **B2**	High blood-tumour burden: ≥ 1,000/µl Sézary cells (lymphocytes with hyper-convoluted cerebriform nuclei cells) with positive clone
	If the level of Sézary cells cannot be determined, one of the following modified ISCL criteria may be used: 1) expanded CD4+ or CD3+ cells with CD4/CD8 ratio of ≥ 10; 2) expanded CD4+ cells with abnormal immunophenotype, including loss of CD7 or CD26.

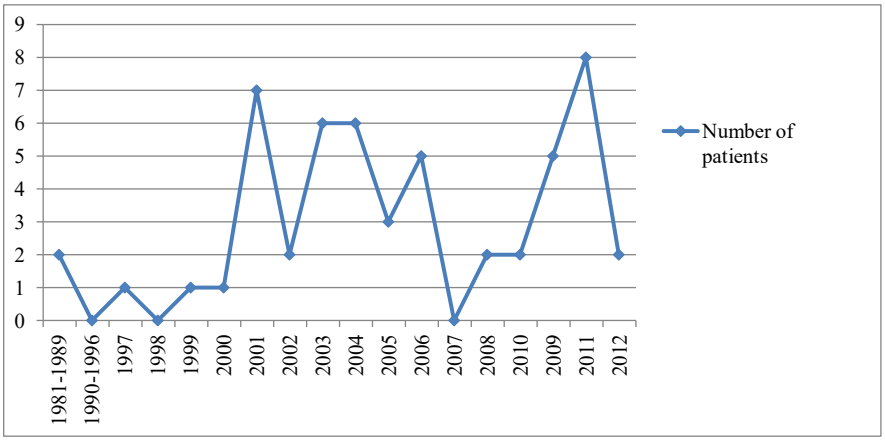

Figure 1
Year of first admission to the clinic.
Data pierwszej hospitalizacji pacjenta.

features of late-onset atopic dermatitis, red man syndrome and early Sezary syndrome may be similar. In up to 40 % of biopsies in patients with Sezary syndrome, the histologic features are nonspecific. Identification of microRNAs specific for T-cell cutaneous lymphoma may be helpful in distinguishing them from inflammatory diseases [15]. There are no curative therapies, treatment is considered palliative, long-term remissions are rarely described. The standard treatment methods include: topical agents, phototherapy, radiotherapy, chemiotherapy, extracorporeal photopheresis, IFN-gamma and other systemic agents [16,17].

Materials and Methods

We analysed case records of 63 patients: 26 women and 37 men aged 19-86 y.o. (median 60.5, mean 58.1, SD 15.68) hospitalized in the Department of Dermatology, University Hospital in Krakow between 2002 and 2012. We investigated the electronic database and selected patients admitted to Clinic with initial diagnosis of primary cutaneous lymphoma. After further analysis of medical records we excluded 2 patients due to lack of complete patients' data.

Results

All the patients were consulted by hematologist in order to exclude secondary skin involvement. Among 61 patients, 53 patients had a final histopathological confirmation of the primary cutaneous lymphoma (Fig. 1). In this group, 42 patients had final diagnosis (based on clinical and histological examination) of mycosis fungoides, 7 with primary cutaneous CD30+ lymphoproliferative disorder, 3 with Sezary syndrome and 1 with primary cutaneous B-cell lymphoma. 3 patients were diagnosed with parapsoriasis, 2 with generalised allergic contact dermatitis, 1 with erythema elevatum diutinum, 1 with acute myeloid leukemia (AML), 1 with Hodgkin lymphoma (HL) coexistent with mycosis fungoides. None of the patients diagnosed with primarily cutaneous lymphomas had features of extracutaneous disease at the time of diagnosis.

Clinical characteristics of the lesions

Initial lesions in all patients with suspected primary cutaneous lymphoma (61 patients) were primarily localized: on the lower limb (most commonly on the thigh, followed by the inguinal area and lower leg) in 32 (52.46%) patients, on the upper limb (usually affecting both arm and forearm) in 30 (49.18%) patients. 25 (40.98%) primary lesions were located on the trunk (60% of patients had lesions both on the dorsal and ventral side). 13 (21.31%) patients had initial lesion localized on the head (10 on the face, 1 on the scalp and 3 involving the ear). 7 (11.48%) patients had primary skin lesion on the buttocks and 1 (1.64%) in the sacral area. 3 patients (4.92%) had lesion located on the neck (Fig. 2).

The morphology of the presenting lesions also varied among our patients. 26.23% of patients presented with erythematous infiltration, 24.59% with exfoliating plaques, 19.67% with erythema and 3.28% with erythematous swelling. 14.75% of

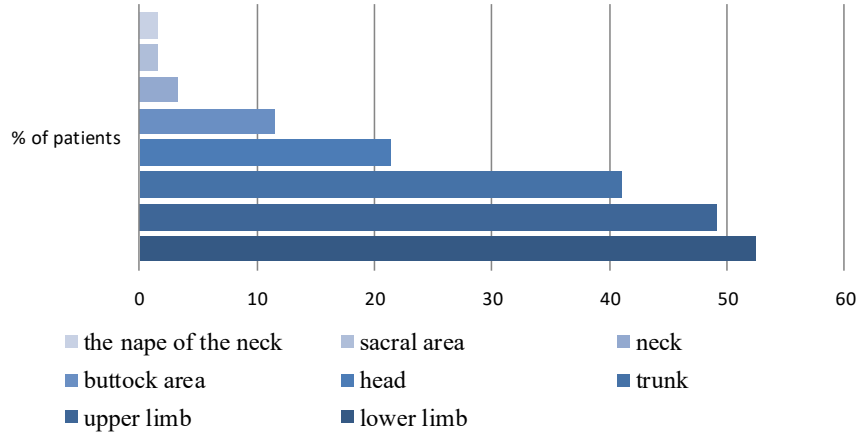

Figure 2
Locations of the skin lesions in all patients.
Lokalizacja zmian skórnych u wszystkich badanych pacjentów.

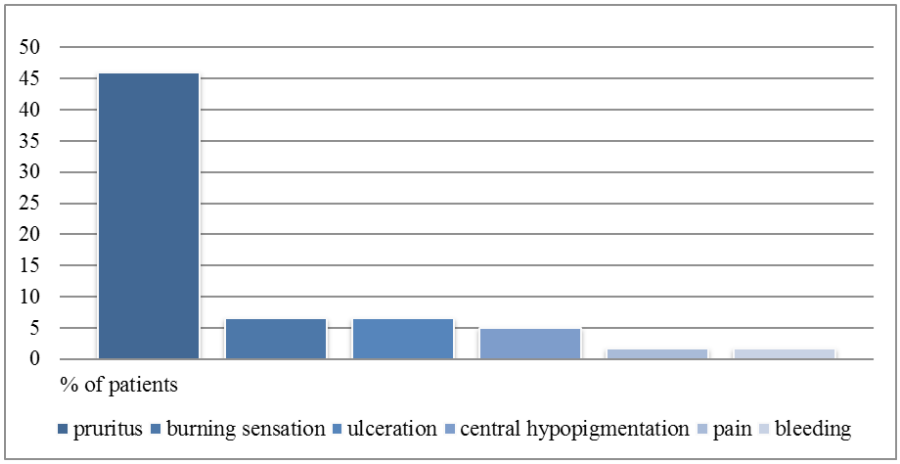

Figure 3
Additional features of skin lesions in all patients.
Cechy dodatkowe zmian skórnych u wszystkich badanych pacjentów.

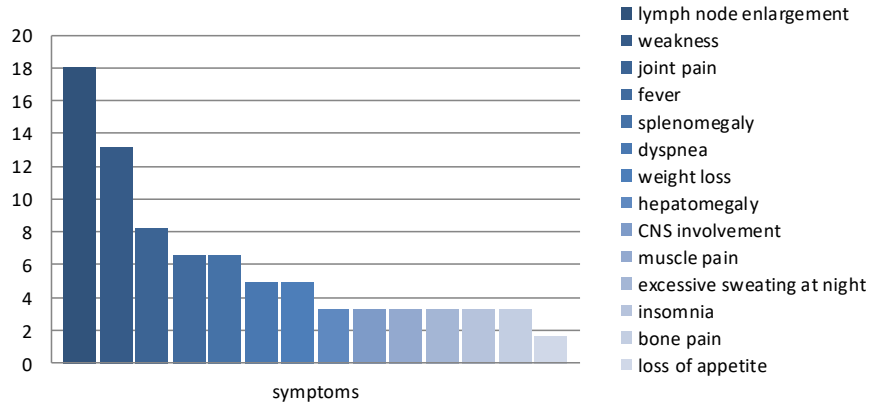

Figure 4
The percentage of patients presenting with a particular symptom.
Odsetek pacjentów prezentujących dany objaw.

patients presented with papules, 8.2% with infiltrated lesions, 3.28% with erythematous patches and 1.64% had erythroderma with exfoliation. 4 patients presented with ulcers and 3 with centrally hypopigmented lesions. 28 (45.9%) of patients reported pruritus, 4 (6,56%) reported burning and 1 (1.64%) reported pain (Fig 3). 39.3% of patients had generalized symptoms with lymphadenopathy being the most prevalent (Fig. 4). The most common laboratory abnormalities included eosinophilia and monocytosis (both with 37.7%) (Tab. IV). ESR was elevated in 26.2% of patients. 32.8% of patients were ex-smokers, 21.31% of patients had a history of allergies and 21.31% had history of another neoplasm.

Mycosis fungoides characteristics

19 women and 23 men had a final diagnosis of mycosis fungoides. The mean age of patients was: 58.14 y.o. (median 60.5). Initial previous diagnoses (made by primary care physicians – PCPs and less commonly

Table IV
The most common findings in blood test results – number of patients (%).
Najczęściej spotykane zmiany w wynikach krwi – odsetek pacjentów (%).

Findings No (%)	
eosinophilia	23 (37,7%)
monocytosis	23 (37,7%)
granulocytopenia	20 (32.8%)
low hematocrit	15 (24,6%)
lymphocytopenia	14 (23%)

by dermatologists before admission of the patient to Clinic) included: parapsoriasis (6 patients), allergic contact dermatitis (5), drug exanthema (2), atopic dermatitis (2), diffuse eczema (2), disseminated granuloma annulare (2), borreliosis, sarcoidosis, systemic lupus, infectious etiology, Sezary syndrome, photodermatosis and lymphomatoid papulosis. Mean time from first skin lesion appearance to first visit was 4 years 7 months. 42.86% of patients were overweight or obese, 38.1% of patients were ex- or present smokers, 11.9% admitted to drinking alcohol often. 7.14% had additional diagnosis of psoriasis, 4.76% had history of tuberculosis and 4.76% megaloblastic anemia. 19.05% had a previous history of cancer (2 with basal cell carcinoma, 1 with history of basal cell carcinoma and spinocellular carcinoma, 1: hepatocellular cancer, brain tumor, thymoma, breast cancer, pancreatic tumor).

At the time of diagnosis 66.67% of patients were stage I, 2.38% stage IIA, 16.67% – IIB, 2.38% – IIIA, 11.9% – IVB. 35.71% were in patch stage, 45.24% in plaque stage, 19.05% in tumor stage. 3 patients had the folliculotropic variant of MF.

69.04% had skin lesions localized in more than one area of the body. The most common site was upper limb (in 61.9%) (Fig. 5) with most prevalent skin manifestation being erythematous infiltration (28.57%) (Fig. 6). Additional features of the lesions and general symptoms are presented in Fig. 7. The most common findings in blood tests were: eosinophilia and monocytosis (both 42.86%) (Fig. 8). ESR was elevated in 33.33% of patients and 7.14% had an elevated CRP value.

Sezary syndrome

3 male patients had final diagnosis of Sezary syndrome, all of whom were between 60 and 69 years old at the time of diagnosis. In all patients we observed erythroderma. Associated medical conditions included psoriasis in 1 patient and history of prostate cancer in another. 2 patients with Sezary syndrome had lymphopenia, 1 had leukopenia and 1 had eosinophilia and monocytosis and 1 patient presented with an elevated CRP level.

Primary cutaneous CD30+ lymphoproliferative disorder (CD30CLPD)

7 patients (4 men, 3 women) had histopathologic confirmation of CD30CLPD - 6 (85.71%) with the diagnosis of lymphomatoid papulosis and 1 (14.29%) with unspec-

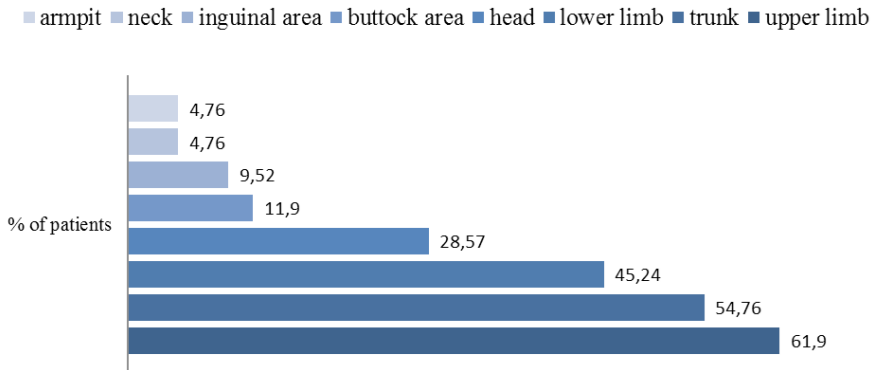

Figure 5
Location of the skin lesions in mycosis fungoides.
Lokalizacja zmian skórnych u pacjentów z ziarniniakiem grzybiastym.

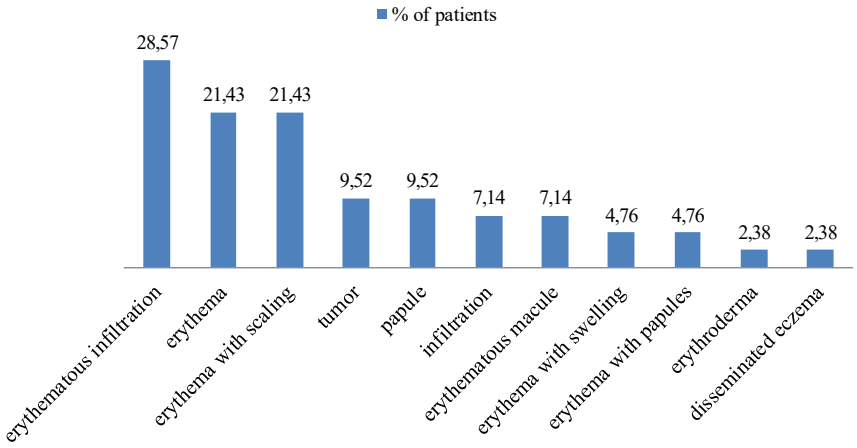

Figure 6
Types of skin lesions in patients with mycosis fungoides.
Morfologia zmian skórnych u pacjentów z ziarniniakiem grzybiastym.

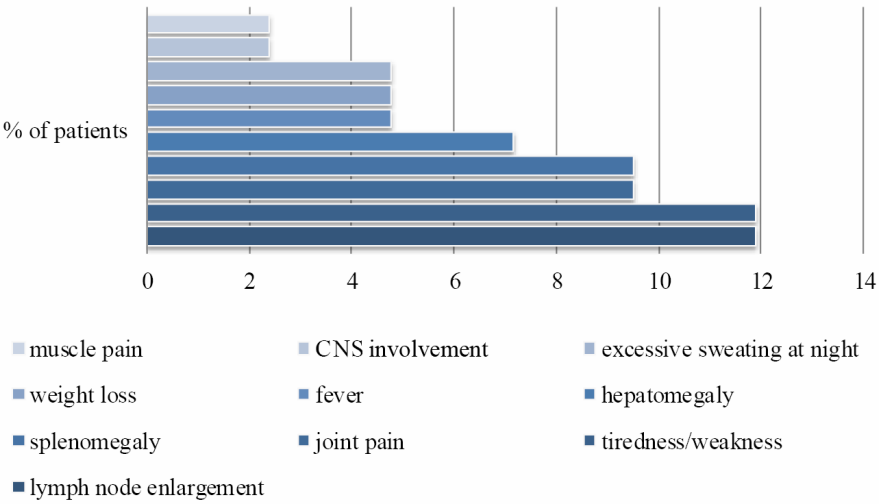

Figure 7
General symptoms presented by patients with mycosis fungoides.
Objawy ogólne u pacjentów z ziarniniakiem grzybiastym.

ified CD30+ lymhpoproliferative disorder. Preliminary diagnoses made according to clinical manifestation of the disease were: parapsoriasis (in 2 patients), atopic dermatitis (1), MF (1). Average time to diagnosis was 4 years and 2 months. Four patients had primary lesions involving more than one area of the body. In 6 patients disease manifested on the lower limb (lesions were equally common on the thigh and on the lower leg), 3 patients on the upper limb (in 2 on the arm and forearm, in one solely on the arm) and two on the trunk and in the sacral area. Pruritus was present in 2 patients, lymphadenopathy in one patient. The morphology of skin lesions is shown in Fig. 9 – papules were most prevalent (42.86%). Among all patients with CD30CLPD 3 had monocytosis, 2 had eosinophilia, 2 had granulocytosis, CRP was in reference range in all patients.

Primary B-cell lymphoma

One female patient, aged 86 was diagnosed with cutaneous B-cell lymphoma, leg type. She had a 6-month history of raised, erythematous skin lesions located on a thigh and lower leg with concurrent macrocytic anaemia, mild thrombocytopenia, lymphadenopathy and leg edema. The patient had history of meningioma and renal cell carcinoma.

Parapsoriasis

3 patients had parapsoriasis (2 females, 1 male, median age 42.67). One patient had a 20 – year history of skin lesions before presenting to their primary care physician (PCP), while the other two patients presented 2 and 4 months after onset. The diagnosis of vasculitis and borreliosis was considered by the PCP prior to referral. Associated symptoms included weakness, joint pain, burning and pruritus. In one patient the primary lesions were located on the trunk and upper limb. The second patient had lesions on the lower limb and the third had lesion on the face. The morphology varied from tumors and erythema, erythematous patches with scale and an erythematous patch with an erosion. The CRP was in the reference range for all patients. Two patients had mild neutropenia, two had eosinophilia and one had mild lymphocytosis and monocytosis. Two patients had history of allergy.

Hodgkin lymphoma (HL) and acute myeloid leukemia (AML)

One male patient developed cutaneous manifestation of Hodgkin lymphoma (nodular sclerosis variant) coexistent with mycosis fungoides. Skin lesions were described as erythematous, scaly lesions, with central hypopigmentation and raised erythematous lesions from one to few cm in diameter, located on the forehead and arm. The patient developed central nervous system involvement and had lymph node enlargement 15 years after his first skin manifestation. The lesions clinically resembled primary cutaneous lymphoma, but previous histologic diagnoses were nonspecific and included: eczema, early discoid lupus erythematosus, mucinosis follicularis, localized pagetoid reticulosis and suspicion of mycosis fungoides. The diagnosis of Hodgkin lymphoma coexistent with MF was based on clinical presentation, histology of skin lesion and lymph nodes.

One male patient had cutaneous manifestation of acute myeloid leukemia (AML). The patient presented with lymphadenopathy and raised erythematous lesion on dorsal part of the trunk.

Discussion

In our study 98.11% of patients with primary skin lymphoma had cutaneous T-cell lymphoma – the percentage is higher than in the previous studies (CTCLs accounted for 71%) [8]. Only one patient (1.89%) developed cutaneous B-cell lymphoma – leg type (CBCLs accounted for 29% in previous studies) [8,29]. In previous studies males had a statistically higher incidence ratio than females [M/F IRR] = 1.72. In our study M/F IRR was lower: 1.3. We found male predominance for all T-cell cutaneous lymphomas:

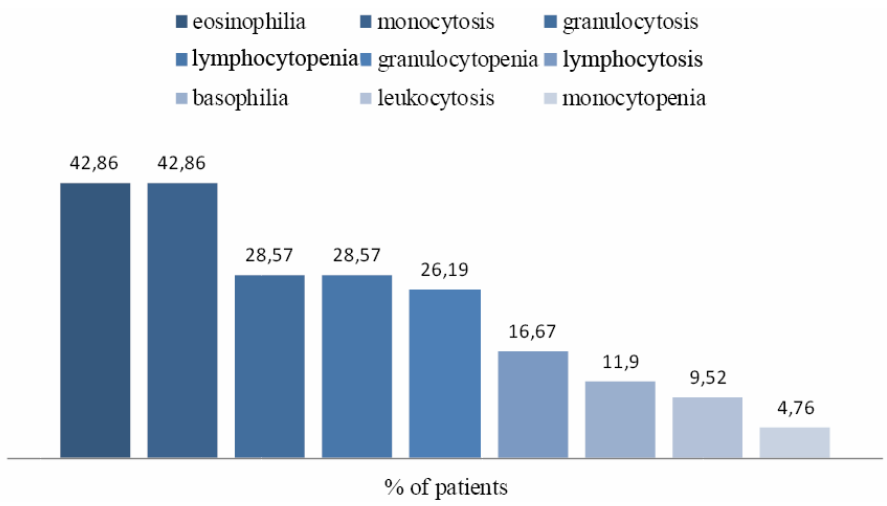

Figure 8
The most common findings in blood test results in patients with mycosis fungoides.
Najczęstsze odchylenia w badaniach laboratoryjnych u pacjentów z ziarniniakiem grzybiastym.

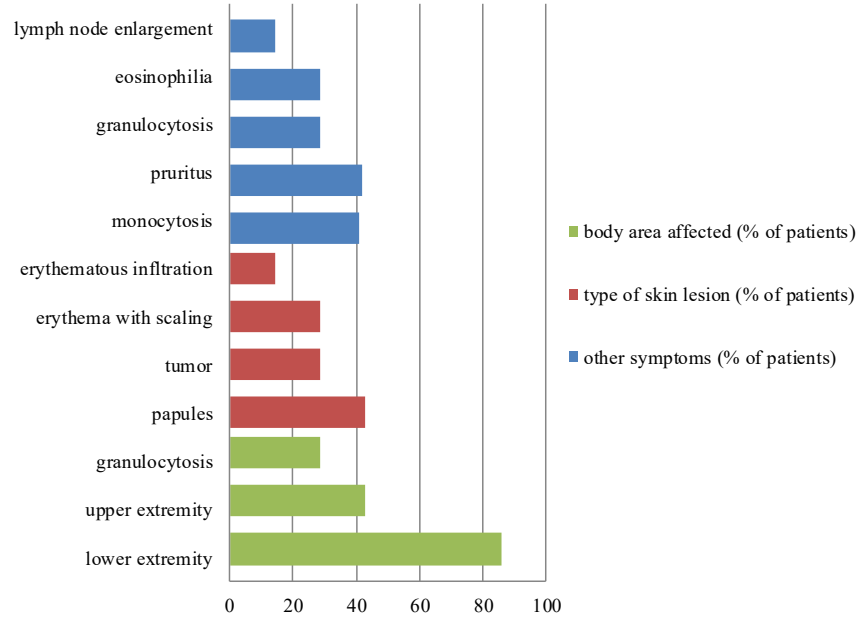

Figure 9
Clinical characteristics of primary cutaneous CD30+ lymphoproliferative disorder.
Obraz kliniczny zmian oraz najczęstsze objawy występujące u pacjentów z pierwotnie skórną chorobą limfoproliferacyjną z komórek T CD30+.

M/F IRR 1.21, for CD30CLPD 1.33, all the patients with Sezary syndrome were males which supports previous studies [8]. The great majority of the patients with primary cutaneous lymphoma (79.24%) had mycosis fungoides – the incidence is higher than in previous studies (where MF accounts for nearly 50% of CTCLs) [2,8,12], followed by CD30CLPD (13.2%) and Sezary syndrome (5,66%).

Mycosis fungoides

79.25% of our patients had the diagnosis of mycosis fungoides, with male to female ratio 1.21 : 1. The result confirms previous studies, where male predilection to mycosis fungoides was observed, but the ratio was higher: Al Ghamdi et al. - 2:1, Shaikh and Rahman 2.6:1 [28,29]. Average time to diagnosis was 4 years and 9 months, which is also similar to the other studies [7,14]. Median age of patients with MF was 60.5 y.o., which confirms the results of previous studies [7,8,14]. According to previous observations MF clinically resembles atopic dermatitis, nonspecific chronic dermatitis, eczema, parapsoriasis [30,31]. In our study the most common diagnoses before histopathologic evaluation were: allergic contact dermatitis, large-plaque parapsoriasis (7.14% each), drug exanthema, atopic dermatitis, diffuse eczema, disseminated granuloma annulare (4.76%). Typically, MF is characterized by erythematous macules, scaly papules, patches, plaques, tumors or erythroderma. The morphology can vary from arciform, annular, serpinginous or polycyclic configurations with colours ranging from orange, red or with livid or brown-red components. Lesions have a tendency to spontaneously regress from the center of lesion [32]. 3 patients had lesions with central hypopigmentation. The largest group of skin lesions observed in our study were: erythematous raised lesions (26.23%), exfoliating erythematous lesions (24.59%), erythema (19.67%+ 3.28% erythema with swelling), papules (14.75% - on erythematous base, tumor (11.48%). The most common locations of MF were the: upper limb (61.9%), followed by trunk (54.76%), which partially confirms previous data, where the trunk with buttocks area, thighs were main targets of mycosis fungoides. Factors responsible for development of MF remain unknown. Previous observations indicate that employment in particular sectors of industry may be a risk factor [33]. The correlation between smoking status and MF has not been confirmed. We observed 38.1% of the MF patients were smokers or ex-smokers and 42.86% of patients were overweight or obese. The percentages are similar to what is observed in the general population [34].

Sezary syndrome

Patients with SS were men 60-69 years old which is similar to other studies, where M/F ratio was 2:1 and Sezary syndrome typically presented in adults over 60 years of age [19,35]. 2 of 3 patients reported itch, 2 developed erythroderma with desquamation. In all patients lesions evolved into generalized erythema. 1 patient was a smoker, 1 had elevated CRP value, and 1 had a history of cancer (prostatic). The sample size of patients with Sezary syndrome in this study is insufficient to take these factors into further consideration.

Primary cutaneous CD30+ lymphoproliferative disorder

We found a M:F ratio of 1.33:1 M:F which is similar to previous studies [36]. The peak incidence has been reported to be in the fifth decade and in our study that mean age at diagnosis was 53.71. Lymphomatoid papulosis may occur in children and individuals older than 50 years – in our study 3 patients were more than 50 y.o. [37,38]. LyP is a chronic, recurrent process with an eruption of red papules, nodules (with hemorrhage, necrosis, crusting) that spontaneously regress taking on a brownish-red color (they may leave areas of increased pigmentation and scars) [37-39]. In our study the most common skin manifestations were papules and tumors. The general symptoms present were: pruritus in two patients, lymphadenopathy in one patient. The presence of systemic symptoms raises the suspicion of an associated systemic lymphoma and requires further evaluation of the disease [40,41]. In our study no associated lymphoma was found. Lymphomatoid papulososis was misdiagnosed as: parapsoriasis (2 patients), atopic dermatitis (1) and MF (1). Previous data show that clinically primary cutaneous CD30+ lymphoproliferative disorders resemble mycosis fungoides, but in contrary to MF lesions they may spontaneously disappear [35]. MF and LyP can coexist in 10-20% of cases [42]. In our group lesions had predilection to the lower limb (6 patients), and the upper limb (3) which correlated with previous studies of lymphomatoid papulosis which showed a predilection for the extremities [42].

Parapsoriasis

In our study 3 patients with suspected MF had parapsoriasis - after clinical and his-

tological evaluation. Parapsoriasis is a group of uncommon dermatoses occurring mainly in adults [43]. In our group the mean age was 42.67. Parapsoriasis is characterized by erythematous, scaly patches of variable size (large- and small plaque parapsoriasis) [1]. 2 patients had patches while 1 had a tumor as a primary lesion. In our group 1 patient was diagnosed with large plaque parapsoriasis. Parapsoriasis has a chronic course and large plaque parapsoriasis is regarded as a premalignant condition with a risk of progression to MF and thus warrants regular observation [44-47].

Acute myeloid leukemia and Hodgkin lymphoma

One patient had acute myeloid leukemia manifesting primarily on the skin. The clinical presentation suggested mycosis fungoides. Previous studies show that the most common cutaneous manifestations of leukemia are: reddish/violaceous papules, plaques, nodules, generalized erythematous maculopapular eruptions [48] - our patient had raised erythematous lesions.

Cutaneous Hodgkin's disease is an extremely rare condition - it usually occurs late in the course of the major disease [49] - our patient had skin manifestations 15 years after the appearance of CNS metastases and lymph node enlargement. Skin involvement is correlated with poor prognosis of HL [50]. 17-53% of patients with HL have pruritus, hyperpigmentation, urticaria, erythroderma or acquired ichthyosis [51,52]. Our patient had features of ichthyosis. Some lesions represented raised erythematous lesions. Frequently in cutaneous HL, the clinical manifestations are single or multiple nodules with ulceration involving the skin of the chest [36,52]. Our patient had involvement of the head and arm. During remission of Hodgkin disease induced by systemic treatment, skin biopsy of remaining erythematous lesion revealed mycosis fungoides.

Conclusions

The possible limitation of the study may be the lack of data concerning the treatment methods used in this particular group of patients. Our study aimed to present the diversity of symptoms reported by the patients with cutaneous lymphomas. Primary cutaneous lymphomas are rare conditions of the skin that may imitate various skin disorders. The indolent, often recurring course, nonspecific symptoms and uncommon appearance require cooperation of a clinician and pathologist in the process of diagnosis of the disease. The subtypes of cutaneous skin lymphomas have similar clinical presentation, demanding precise observation of the patient and analysis of all conditions. There is a strong need of further studies in order to discover factors responsible for the development of this skin condition. At present little is known about etiology of primary cutaneous skin lymphomas with few studies suggesting the triggering role of environmental factors, bacterial and viral infections.

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