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OPIS PRZYPADKU
CASE REPORT

Pediatric lymphomatoid papulosis – a case report and management considerations

Lymphomatoid papulosis w populacji pediatrycznej – opis przypadku i rozważania terapeutyczne

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ABSTRACT

Lymphomatoid papulosis (LyP) is a rare cutaneous disorder, most commonly observed in adults, and its occurrence in the pediatric population is exceedingly rare. We present the case of an 6-year-old male patient who exhibited clinical and histopathological features consistent with LyP. The patient presented with multiple erythematous papules on the trunk and extremities, which were accompanied by mild pruritus. The lesions intermittently appeared, disappeared, and changed in morphology. No lymphadenopathy or systemic symptoms were noted. The histopathological examination revealed a dense infiltrate of atypical lymphocytes with cerebriform nuclei in the dermis. Immunohistochemical analysis confirmed CD30 expression in the infiltrating cells, supporting the diagnosis of LyP.

Topical corticosteroids were administered to alleviate pruritus and inflammation, although only minimal symptomatic relief was achieved. The beneficial effects of narrowband ultraviolet B (UVB) 311 phototherapy were observed for a duration of four months. Nevertheless, following the cessation of treatment, the reappearance of both the nodular lesions and smaller papular lesions was observed. Consequently, a therapeutic regimen consisting of the administration of methotrexate at a dosage of 10 mg once per week was initiated.

The treatment of LyP varies depending on the severity of the lesions and the patient's symptoms, treatment decisions need to be carefully weighed due to the relatively benign nature of the disease.

The diagnosis of LyP in pediatric patients is challenging because of its rarity and potential confusion with malignant lymphomas. Histopathology and immunohistochemistry play a pivotal role in distinguishing LyP from more aggressive entities.

KEYWORDS

lymphomatoid papulosis, CD30-positive lymphoproliferative disorder, phototherapy, immunohistochemistry, methotrexate

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STRESZCZENIE

Lymphomatoid papulosis (LyP) jest rzadką chorobą skóry, najczęściej obserwowaną u dorosłych, a jej występowanie w populacji pediatrycznej jest niezwykle rzadkie. W pracy przedstawiono przypadek 6-letniego dziecka płci męskiej, u którego stwierdzono cechy kliniczne i histopatologiczne zgodne z rozpoznaniem LyP. Na skórze pacjenta obserwowano liczne rumieniowe grudki zlokalizowane na tułowiu i kończynach, a towarzyszył im łagodny świąd. Zmiany chorobowe pojawiały się nawrotowo, następnie ustępowały i zmieniały morfologię. W badaniu przedmiotowym nie stwierdzono limfadenopatii ani objawów ogólnoustrojowych. W badaniu histopatologicznym w skórze właściwej stwierdzono gęsty naciek limfocytów atypowych z hiperchromatycznymi i nieregularnymi jądrami komórkowymi. Analiza immunohistochemiczna potwierdziła ekspresję CD30 w naciekających komórkach, co potwierdza rozpoznanie LyP.
W celu złagodzenia świądu i stanu zapalnego podawano miejscowo glikokortykosteroidy, chociaż uzyskano jedynie minimalne złagodzenie objawów. Korzystne efekty fototerapii wąskopasmowej UVB 311 obserwowano przez cztery miesiące. Niemniej jednak po zaprzestaniu leczenia zaobserwowano ponowne pojawienie się zarówno zmian guzkowych, jak i mniejszych zmian grudkowych. W związku z tym rozpoczęto schemat terapeutyczny polegający na podawaniu metotreksatu w dawce 10 mg raz na tydzień.
Leczenie LyP różni się zależnie od ciężkości zmian i objawów u pacjenta. Decyzje dotyczące leczenia należy dokładnie rozważyć ze względu na stosunkowo łagodny charakter choroby.
Rozpoznanie LyP u dzieci i młodzieży stanowi wyzwanie ze względu na rzadkość występowania choroby i możliwość błędnego rozpoznania tej jednostki chorobowej z chłoniakami złośliwymi. Histopatologia i immunohistochemia odgrywają kluczową rolę w odróżnianiu LyP od bardziej agresywnych jednostek chorobowych.

SŁOWA KLUCZOWE

lymphomatoid papulosis, choroby limfoproliferacyjne z komórek CD30+, fototerapia, immunohistochemia, metotreksat

CASE RAPORT

A male child aged 6 years was sent to our facility for additional medical intervention. The patient exhibited a medical condition characterized by the occurrence of papulonecrotic papules and nodules in various regions of the body. These skin lesions cleared spontaneously over a period of 4 months, resulting in the formation of atrophic scarring and dyspigmentation. During the physical examination, several raised dome-shaped nodules and papules with a reddish hue and a shiny, smooth surface were observed on multiple regions of the body, encompassing the trunk, upper and lower limbs, neck, and genital area, accompanied by a limited number of brownish macules. A few components of these lesions exhibited necrosis, ulceration, and the existence of black crusts at the core, accompanied by white scales on the outside layer. The observation of atrophic scars with diverse sizes and colors suggested the manifestation of prior lesions (Figure 1 and Figure 2). No involvement of the palms, soles or mucous membranes was noted. The patient's medical background encompassed a history of asthma, allergic rhinitis, as well as previous procedures of surgical repair of an atrial septal defect (ASD II). There was an absence of any documented instances of nocturnal sweating, elevated body temperature, or itching. The individual's immunizations were current. Upon conducting a physical examination, it was observed that the youngster exhibited a state of good health, with no signs of visceromegaly or lymphadenopathy.

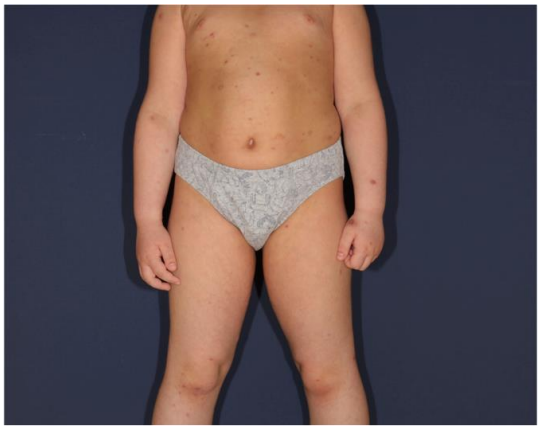

Fig. 1. Lymphomatoid papulosis type presenting as multiple reddish papules noted on patient's extremities and trunk.

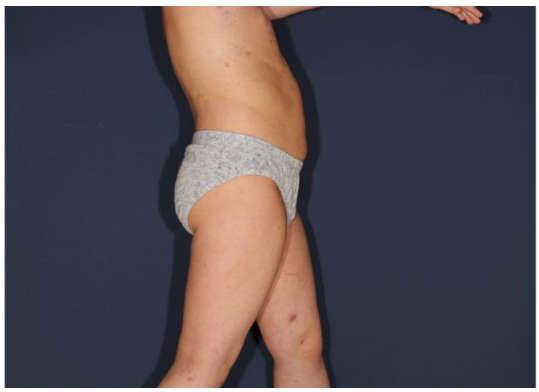

Fig. 2. Right flank and lateral thighs showing distribution of papules with residual atrophic scarring.

Consequently, the original diagnosis of this illness was *pityriasis lichenoides et varioliformis acuta* (PLEVA). The prescribed treatment for the patient consisted of an antibiotic, specifically azithromycin, administered orally at a dosage of 250 mg once daily for a duration of one week. Additionally, a corticosteroid cream was prescribed to be applied twice daily for a period of two weeks. However, there was no observed improvement during the follow-up after two weeks. There were no additional atypical findings in the laboratory results, including serology tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, the QuantiFERON test, RF, immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement component 3 (C3), complement component 4 (C4), anti-nuclear antibodies (ANAs), and the extractable nuclear antigen test (ENA Screen), results were within normal ranges. Additionally, a histopathological and immunohistochemical study was conducted. A 4-mm punch biopsy specimen of lesioned skin revealed the presence of necrotic keratinocytes within the epidermis, as well as a concentrated infiltration of lymphohistiocytic cells in the mid-dermal and deep dermal layers surrounding the blood vessels and within the interstitial spaces. The cells exhibited an immunophenotype distinguished by the expression of CD3 and CD30. In contrast, the lymphocytes exhibited a lack of expression for CD8, activin receptor-like kinase 1 (ALK-1), and CD15. The diagnosis of LyP was made.

The effectiveness of narrowband ultraviolet B (UVB) phototherapy was observed for a period of four months. Nevertheless, upon discontinuation, both the nodular lesions and smaller papular lesions reappeared. We did not decide to use psoralen with ultraviolet A (PUVA) therapy on the patient because oral psoralen is generally not preferred in children younger than 12 years of age due to the potential side effects, including nausea, vomiting, cataracts and ocular toxicity, in addition to phototoxic reactions. As a result, a treatment plan involving the administration of methotrexate 10 mg once a week was commenced.

This combined approach led to amelioration of the pruritus symptoms and the achievement of disease remission. At present, the patient is under frequent observation at our department, exhibiting a stable clinical condition and no indications of malignant progression, as observed over a period of 4 months since the original presentation.

There were no more ulcerative nodules observed. Nonetheless, throughout the subsequent follow-up period, tiny papules emerged and healed spontaneously.

DISCUSSION

Epidemiology

LyP is a chronic papulonodular dermatitis that exhibits a tendency for recurrence. This particular disease typically exhibits a benign progression, despite its classification as one of the CD30-positive cutaneous lymphoproliferative disorders and malignancies. It is characterized by malignant histopathologic characteristics, including the presence of large atypical CD30 lymphoid cells [1].

The prevalence of LyP is estimated to be between 1.2 and 1.9 cases per 1,000,000 individuals, with a higher occurrence observed among males. In two retrospective studies of 118 and 180 patients, respectively, men were slightly more commonly affected than women (69.49% vs. 56.7 %) [2,3]. The occurrence of this condition is possible at any stage of life, but it is relatively uncommon during childhood, its peak incidence is in the 4th and 5th decade [4]. The specific cause of lymphoproliferation, which triggers an abnormal increase in lymphocytes, remains unknown. The pathogenesis of lymphomas is commonly hypothesized to involve the persistent stimulation of a single lymphocyte or lymphocyte clone by a persistent antigen, such as a viral antigen. This continuous stimulation can lead to the accumulation of mutations and subsequent uncontrolled proliferation, ultimately resulting in the development of a neoplasm [5,6]. Several researchers have suggested potential viral origins such as human T-lymphotropic virus type 1 (HTLV-1), herpesvirus, and endogenous retroviruses [7,8]. However, comprehensive research has thus far been unable to substantiate this correlation [9,10,11,12]. The increase in the size of lesions could potentially be linked to genetic mutations affecting the growth inhibitory function of the transforming growth factor-b type I receptor in CD30-positive tumor cells [13]. Additional factors that have been linked in the proliferation of cells include environmental stimuli like as radiation, as well as pharmaceutical agents including fingolimod, infliximab, adalimumab, and efalizumab [14,15,16,17,18,19,20]. Research studies have explored the phenomenon of spontaneous regression in LyP and have focused on the interaction between CD30 and its ligand. These studies have observed that healing lesions exhibit a noteworthy upregulation of ligand expression in comparison to non-healing lesions [21].

LyP is distinguished by a diverse range of clinical manifestations, comprising erythema, papules, pustules, vesicles, plaques, nodules, and ulcers.

The primary feature of LyP is the presence of papules and nodules on the skin. These lesions are usually

raised, dome-shaped, with a red or reddish-brown hue and can vary in size from a few millimeters to several centimeters [3,4,22,23,24]. These papules can occur individually, in clusters, or across the body. As the lesions progress, they have the potential to evolve into larger nodules and plaques, generally with a maximum diameter not exceeding 1–2 cm [25]. LyP predominantly manifests on the extremities and trunk, segmental or localized presentation, which may include acral and facial involvement, observed in rare cases [22,23,24]. There have been a limited number of studies documenting instances of oral or vaginal involvement [4,22]. Roughly 40–55% of patients report pruritus [4]. In addition to the abovementioned classical form, there are less prevalent morphological forms of LyP, such as vesicular, plaque-type eczematoid, and ulcerative presentations [25,26,27]. LyP is generally considered a benign disorder, with a relapsing--remitting course. Most cases exhibit self-healing skin lesions without systemic involvement [28]. Nevertheless, a small proportion of cases can progress to more aggressive lymphomas.

Histopathology is a crucial diagnostic tool in evaluating skin lesions and confirming the diagnosis of LyP. One of the defining features of LyP is the presence of an atypical lymphocytic infiltrate in the dermis.

The 2016 World Health Organization classification of cutaneous lymphomas distinguishes LyP types A through E based on histological criteria, which encompass the infiltration pattern, tumor cell shape, and phenotype [29]. LyP is characterized by five well--established histopathologic subgroups, namely A, B, C, D, and E. These subtypes differ in terms of the major cell type and tropism [30,31].

From the histopathological perspective, it is important to distinguish LyP from many benign illnesses that may exhibit CD30-positive lymphoid cells, such as atopic dermatitis, viral infections, scabies, mycobacterial infection, and medication responses. Additionally, it is crucial to separate LyP from malignant disorders, including mycosis fungoides.

Immunohistochemistry (IHC) is a diagnostic technique used to identify specific proteins in tissue sections using antibodies that bind to these proteins. In the case of LyP, the pattern of staining, intensity, and distribution of these markers in tissue samples helps pathologists confirm the presence of CD30-positive lymphocytes and differentiate LyP from more aggressive lymphomas.

The immunophenotype of the proliferating cells in LyP is commonly characterized by the presence of CD3+, CD4+, CD25+, CD30+, (Ki-1), CD45RO+ markers, and the expression of human leukocyte antigen – DR isotype (HLA-DR) [32,33,34,35,36,37]. Histopathological evaluation of skin biopsies in suspected cases of LyP is essential to confirm the diagnosis. Nonetheless, it is important to note that the histological features of LyP can sometimes overlap with other cutaneous lymphoproliferative disorders or inflammatory conditions. Therefore, a combination of clinical presentation, immunohistochemistry, and histopathology is typically necessary for an accurate diagnosis.

Diagnosis

The clinical identification of LyP is a significant obstacle, often resulting in prolonged periods of unrecognized presence [22]. The mean duration from the appearance of lesions to the conclusive diagnosis is reported to be 45–75 months [3]. The diagnosis usually requires clinicopathological correlation, and the spontaneous remission of LyP lesions plays a crucial role within this framework. Skin biopsies can require repetition in cases where lesions do not exhibit regression or when they grow in size. The recommended laboratory tests include, but are not limited to, complete blood count with differential, serum creatinine, liver profile, lactate dehydrogenase, flow cytometry, and, if clinically indicated, human T-cell lymphotropic virus type 1 evaluation. When palpable lymphadenopathy is present, it is advisable to utilize computed tomography imaging.

Common differential diagnoses for LyP presenting with papular lesions may include reactions to insect bites, persistent nodules resulting from scabies, and, in the case of face lesions, eosinophilic granuloma. Papulonecrotic lesions can often be misdiagnosed for PLEVA, also known as Mucha-Habermann disease, which is characterized by the sudden onset of erythematous papules that evolve into pustules and then form superficial ulcers with a “cigarette-paper” appearance. LyP and PLEVA share a similar appearance of papules on the skin, making clinical differentiation challenging. Histopathological examination can reveal atypical lymphocytes in both LyP and PLEVA lesions, but CD30 expression is a key feature of LyP [4,29]. The differential diagnosis of plaque-type eczematoid LyP includes various forms of localized dermatitis [36], whereas ulcerative LyP, may make one think of pyoderma gangrenosum. Other conditions that might be considered in the differential diagnosis of LyP are: cutaneous T-cell lymphoma (CTCL), anaplastic large cell lymphoma (ALCL), and cutaneous Langerhans cell histiocytosis. Mycosis fungoides represents a significant differential diagnosis for types A and B. Tumor-stage mycosis fungoides can have a notable resemblance to LyP, characterized by an abundance of CD30-positive blasts. Patients who have previously experienced mycosis fungoides or mycosis fungoides-like lesions in other areas should only be diagnosed with LyP if the clinical presentation and progression of the disease align with diagnostic patterns. Otherwise, the diagnosis should be tumor--stage mycosis fungoides with CD30 expression [37].

LyP patients run the risk of developing additional hematological conditions, most commonly mycosis fungoides, erythrodermic T-cell lymphoma, Hodgkin disease, or large-cell CD30+ lymphoma. The development of LyP may occur before, after, or concurrently with a hematological malignancy. After five years of evolution, this risk ranges from 2% to 15%, although it rises with the severity of the illness. Significant risk factors for the development of a second hemopathy include advanced age and, in particular, the presence of a T-cell clone in the papulosis lesions [2,38].

The average time period between the diagnosis of LyP and the development of a secondary lymphoma is estimated to be around 3 to 4 years. Risk factors associated with the development of secondary lymphomas include being male (with a male-to-female ratio more than 2:1), having childhood-onset LyP, and having histologic categories B and C [3,39].

Treatment

The treatment of LyP in children is a complex and individualized process, as pediatric cases of LyP are rare and there is limited specific guidance. The treatment approach for children with LyP is generally similar to that for adults, focusing on managing the symptoms and minimizing the impact of the disease on the child's quality of life.

In many cases, LyP lesions exhibit a relapsing--remitting pattern and tend to resolve spontaneously over time. A watchful waiting approach may be appropriate for mild cases that do not cause significant discomfort or impairment. Topical corticosteroids can be used to manage the itching, inflammation, and discomfort associated with LyP lesions. They can help reduce the inflammatory response and provide symptomatic relief. They can be applied directly to the affected skin areas. Emollients or moisturizers can be applied to the skin to prevent dryness and soothe irritated areas. They can be used in conjunction with other treatments to maintain skin health. Narrowband UVB phototherapy has been used to treat LyP lesions in both adults and children. UVB therapy can help reduce inflammation and promote the healing of skin lesions. The duration of phototherapy treatment varies based on the patient's response and the clinical situation. Phototherapy is generally well-tolerated, but potential side effects can include temporary skin redness, irritation, and increased sensitivity to sunlight. Although the outcomes of UVB phototherapy in children are inconsistent, general treatment may be necessary to prevent scarring of the lesions [4]. De Souza et al. [40] conducted a study with a cohort of eight pediatric patients who underwent treatment with UVB nb 311. The duration of follow-up for these patients ranged from one to thirteen years. Four cases were reported to have a complete response (CR), two cases had a partial response (PR), and two cases showed no response.

The use of PUVA therapy to treat LyP has been advocated for more than 30 years. In a study conducted by Kempf [41], a total of 19 patients were subjected to PUVA treatment. The results showed a CR rate of 27% and a PR rate of 68%. Thomsen and Wantzin [42] documented a cohort of six patients who had positive responses to PUVA therapy. However, as anticipated, these individuals experienced recurrence following the cessation of treatment.

In cases where LyP lesions are more extensive, symptomatic, or resistant to other treatments, systemic therapies may be considered. Methotrexate is an immunosuppressive medication that is sometimes used as a treatment option for certain cases of LyP that are severe, symptomatic, or resistant to other therapies. The decision to use methotrexate in the treatment of LyP is based on careful assessment of the patient's condition and the overall risk-benefit profile. The dosage and frequency of administration are tailored to the patient's individual needs and response to treatment. The duration of methotrexate treatment varies based on the patient's response and the clinical situation. Used orally, subcutaneously, or intramuscularly, methotrexate is the systemic treatment of choice for LyP, regardless of the histological type. Methotrexate has demonstrated efficacy in treating a considerable number of individuals diagnosed with LyP. Thomsen and Wantzin [42] documented a cohort of nine patients who exhibited positive responses to methotrexate treatment, administered at a dosage range of 2.5–25 mg per week for a duration of 5–18 months. Nevertheless, it is noteworthy that a recurrence of symptoms was observed in all the patients except for one upon discontinuation of the treatment. In a study conducted by Everett [43] a total of eight instances were examined, wherein the patients were administered methotrexate at a dosage ranging from 2.5 to 15 mg per week for a duration of 6 to 12 months. Subsequently, these patients were monitored for a period of 4 to 9 years. The findings revealed that half of the patients experienced recurrences, requiring the need for retreatment with methotrexate. Vonderheid et al. [44] documented a cohort of 45 patients who achieved sustained control on methotrexate therapy. The patients were treated for a median duration of 39 months, with a range of 2–205 months. A positive response to methotrexate was observed within a period of 4 weeks, and a majority of 39 patients (87%) exhibited long-term control. Less than one-third of the patients were able to stop treatment after achieving complete and sustained remission, according to a recent article on a Dutch cutaneous lymphoma group regarding their experience using methotrexate in LyP, which showed 90% of good to very good results [3,45].

Newland et al. [46] reported 25 patients with LyP who were treated with oral methotrexate 20–30 mg per week for at least six months and then for two to six months during the withdrawal period; 22 patients had a partial or complete response. Only 6 successfully stopped the drug and maintained a response for six months.

Champagne and Walsh [47] observed favorable outcomes in six cases that underwent treatment with mycophenolate mofetil at a dosage of 2–2.5 g, administered twice daily. Additionally, four patients were treated with mycophenolic sodium at a dosage of 1440–1800 mg, divided into two daily doses. The patients achieved remission after a treatment duration of 5–6 weeks, despite previous unsuccessful attempts with methotrexate.

Biologic therapies that target specific immune pathways, such as monoclonal antibodies like alemtuzumab or brentuximab vedotin, have been used in some cases of LyP that are resistant to other treatments. Brentuximab is a monoclonal antibody that specifically targets CD30. The molecule impairs the process of microtubule polymerization and induces cell cycle arrest at the G2/M phase, ultimately resulting in cellular demise. Brentuximab could potentially play a significant role in the therapeutic management of severe or refractory LyP. Duvic et al. [48] described a cohort of nine patients diagnosed with LyP who had a positive response to brentuximab therapy during a treatment duration ranging from 3 to 9 weeks. Out of the whole sample, five participants exhibited a CR, while four participants demonstrated a PR. The observed median response time of 26 weeks was found to be comparatively lower than the response duration observed in previous trials including individuals with *mycosis fungoides*. In a study conducted by Wieser et al. [3] a total of 21 patients were administered brentuximab. Among these patients, ten individuals (47.6%) achieved a CR following one to two infusions. Nonetheless, it is noteworthy that seven of these patients eventually experienced a recurrence. In that study, a total of four patients exhibited a PR, while seven patients demonstrated a non-response.

It is important to note that the treatment approach for LyP should prioritize the patient's well-being and quality of life; treatment decisions for LyP should be made on a case-by-case basis, taking into account factors such as the patient's age, overall health, the extent of skin involvement, and the presence of symptoms. Additionally, as LyP can exhibit a relapsing-remitting course, treatment plans may need to be adjusted over time. Some patients may benefit from combining different treatment modalities to achieve better control of symptoms and disease progression.

Author's contribution

Study design – M. Dec, H. Arasiewicz
Manuscript preparation – M. Dec, H. Arasiewicz
Literature research – M. Dec, H. Arasiewicz
Final approval of the version to be published – M. Dec, H. Arasiewicz

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