Unilateral lower extremity lymphedema as a first symptom of primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT)

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Abstract
Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT), is a rare and aggressive variant of extranodal lymphoma. We report the case of a 64-year-old woman with unilateral lymphedema of the lower limb as the first and only symptom of PCDLBCL-LT for six months. Violaceous nodules were the second symptom and they progressively developed on the edematous calf. Initially, they were diagnosed as warty overgrowths, which are common skin changes in the course of chronic lymphedema. The lack of improvement in the violaceous nodules after compression therapy prompted to perform a skin biopsy. Histopathological evaluation revealed the presence of PCDLBCL-LT. In this article, we want to highlight the challenges of making a diagnosis of PCDLBCL-LT. To our knowledge, no other study has reported on lymphedema as an initial symptom of PCDLBCL-LT.

Key words: lymphedema; primary cutaneous diffuse large B-cell lymphoma; leg type (PCDLBCL-LT); violaceous nodules; warty overgrowths; methotrexate-associated lymphoproliferative disorder (MTX-LPD)

Introduction
Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is a rare medical condition. It accounts for 15% of all primary cutaneous B-cell lymphomas (CBCL) and 4% of all primary cutaneous lymphomas (PCL). It usually affects elderly women in the 7th decade of life with a strong predilection for the lower limbs. However, in some cases (15–20%) it may affect other parts of the body [1, 2]. Compared to other primary cutaneous lymphomas (PCL) subtypes, PCDLBCL-LT is a more aggressive variant that manifests with rapidly growing red or violaceous nodules. It is characterized by a poor prognosis with a 5-year survival rate of 40–50% [1, 3, 4]. Regarding histological features, large B-lymphocytes with numerous mitotic figures and a diffuse growth pattern are seen, as well as a strong expression of B-cell lymphoma 2 (Bcl-2), CD-20, B-cell lymphoma 6 (Bcl-6) and multiple myeloma oncogene-1 (MUM-1) of those cells. In about 10% of cases, MUM-1 can be negative while CD-10 is usually negative [5].

Case report
A 64-year old woman with a 28-year history of rheumatoid arthritis (RA) treated for 27 years with methotrexate (MTX) and low doses of glucocorticoids,
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and after a colostomy performed 4 years earlier due to perforation of the diverticulum ulcer, was referred to the department of angiography due to lymphedema of the right lower limb. Lymphedema was first noticed ten months earlier and gradually progressed. Doppler ultrasound examination ruled out deep vein thrombosis (DVT). After 4 months of lymphedema, compression therapy was applied with slight effect. Finally, six months after the appearance of the first signs of edema a number of papular changes developed on the affected leg. Skin lesions were consulted dermatologically and treated with topical ointments without a positive effect. Later, the papules developed into hard, bluish nodules.

The physical examination at the time of admission to the hospital revealed a lymphedema of the right lower limb accompanied by numerous violaceous nodules on the edematous skin (Fig. 1). The nodules were also present on the left knee. There were no clinical signs of systemic disease, such as weakness, emaciation, enlarged lymph nodes, or low-grade fever. The violaceous nodules were not painful. Laboratory parameters showed a moderately elevated concentration of C-reactive protein — 17 mg/L (normal value: 0–5 mg/L) and a significantly elevated concentration of lactate dehydrogenase — 1078 U/L (normal value: 0–248 U/L). Other laboratory parameters were within normal limits. Based on the medical history and clinical symptoms, skin cancer was suspected and diagnostic tests were scheduled.

First, contrast-enhanced computed tomography (CT) of the chest, abdomen, pelvis, and lower extremities was performed. The skin lesions visible in the CT of the right leg can be described as nodular thickening of the skin and subcutaneous tissue, covering the entire circumference of the limb without features of pathological contrast enhancement (Fig. 2). The CT showed no other abnormalities, such as enlarged lymph nodes, which may explain the presence of lymphedema in the lower limb.

Histopathology revealed a highly atypical population of large malignant lymphoid cells with immunoblast and centroblast morphology and an inconsistent growth pattern. Cancer cells have invaded the dermis in a destructive way. The subcutaneous tissue was also involved. Immunohistochemical staining revealed the presence of large lymphoid cells positive for CD-20, CD79a, Bcl-2, and p63 and negative for CD-10, TdT, MUM-1. The proliferation rate assessed by Ki-67 staining was close to 100%. Mitotic figures were numerous (approximately 30/10 HPFs). The final diagnosis of PCLBCL-LT was made based on histopathological findings (Fig. 3).
In order to start the treatment as early as possible, the patient was referred to the department of hematology, where a PET-CT examination was performed and chemotherapy was started using the R-CHOP protocol. During this time, the nodules spread to the forearms, but they disappeared shortly after starting treatment. MTX was discontinued from RA treatment immediately after diagnosis.

Discussion

Primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) is an extranodal variant of non-Hodgkin lymphoma. The clinical presentation is most often manifested as rapidly growing tumors, plaques or violaceous nodules within one or both lower extremities [1, 4, 6]. However, skin manifestations of PCDLBCL-LT are clinically heterogeneous and may sometimes take unusual forms, e.g. verrucous plaque-like lesions, multiple nodules with widespread garland-like patches, bluish-reddish multicolored rainbow patterns or even annular patches with erythematous, well-defined borders that resemble erythema chronicum migrans [7–10]. Moreover, in many cases of PCDLBCL-LT, the appearance of skin lesions may suggest a benign nature and contribute to the delay in making the correct diagnosis [7–10]. Considering the wide spectrum of the clinical picture of PCDLBCL-LT and its rarity, it is worth highlighting the challenges in the diagnosis of patients with this disease entity.

The violaceous nodules on the calf of our patient developed 6 months after the appearance of the first symptoms of lymphedema. Therefore, they were initially thought to be warty overgrowths, which are common skin lesions in chronic lymphedema. There are many synonyms for warty overgrowths in the literature, including verrucous papillomatosis, papillomatosis cutis lymphostatica, lymphostatic verrucosis, lymphatic papillomatosis, lymphedematous keratoderma, verrucous elephantiasis and elephantiasis nostras verruciformis [11]. According to the International Society of Lymphology, warty overgrowths correspond
to stage III lymphedema [12]. They occur after a rather long course of lymphedema and disappear or decrease after compression therapy. Nevertheless, we would like to point out the similarity between these two skin abnormalities and the importance of properly performed diagnostics, including an early skin biopsy. Figure 4 presents photos of warty overgrowths in the course of lymphedema, which may imitate skin lesions in the course of PCDLBCL-LT. In other reports, it was pointed out that skin lesions in the course of PCDLBCL-LT may also mimic such diseases as cellulitis, sporotrichosis [13], DVT, lymphangiosarcoma (which was also initially taken into account in the differential diagnosis in our patient) or even erythema migrans, which is often observed in Lyme disease [10]. Taking all this into account, the initial diagnosis of PCDLBCL-LT can be difficult and often may be preceded by numerous misdiagnoses.

Unilateral lower extremity lymphedema as the first and initially the only symptom of PCDLBCL-LT in our patient additionally hindered the diagnosis. Malignancy and its treatment is the most common cause of secondary lymphedema in developed countries [14, 15].
However, malignant lymphedema is usually accompanied by other symptoms of systemic involvement. Lymphedema in the course of lymphoma is a result of obstruction of lymphatic vessels by cancer cells. A retrospective study of 4676 patients with lymphedema showed that 11 of them had lymphoedema caused or aggravated by lymphoma, including 1 case of upper limb edema, 9 cases of lower limb edema and 1 case of systemic edema. However, in patients from this study, apart from lymphoedema, clinical symptoms such as weakness, emaciation, pain or lymphadenopathy were also observed [16]. In our patient, lymphedema and skin lesions were the only symptoms of PCDLBCL-LT. Hawkins et al. [17] presented ten cases of unilateral leg edema as the only symptom of lymphoma. However, our case refers to primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT). Hawkins et al. [17] presented ten cases of unilateral leg edema as the only symptom of lymphoma. However, our case refers to primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT). On the contrary, there are several reports that PCDLBCL-LT may be a rare complication of long-standing lymphedema [18]. Thirteen such cases were described in the literature [19]. The time between the occurrence of lymphedema and the development of PCDLBCL-LT skin lesions ranged from 40 years to only 1 year [19, 20]. In general, long-standing congenital or acquired lymphedema is a well-known risk factor for many other malignancies, including lymphangiosarcoma, squamous cell carcinoma, malignant melanoma, and Kaposi’s sarcoma [18]. Impaired lymph drainage may result in an area prone to cancer, including lymphoma. Considering that lymphedema was the first symptom in our patient, it cannot be ruled out that PCDLBCL-LT may be a complication of lymphatic system insufficiency also in our case. However, the absence of another
cause of lymphedema in our patient and the short time between the onset of lymphedema and the appearance of skin lesions rather preclude such a sequence of events.

It is also worth noting that our patient used MTX as a treatment for rheumatoid arthritis for 27 years. There are reports about lymphoproliferative disorder (LPD) which occasionally develop in rheumatoid arthritis as induced by MTX (MTX-associated LPD; MTX-LPD) [21–24]. As in our patient, approximately half of MTX-LPD cases occur at primary extranodal sites, including the skin [21]. It has also been reported that discontinuation of MTX treatment results in spontaneous remission in many patients with MTX-LPD, without additional treatment [21, 25, 26]. In our patient, immediately after establishing the diagnosis, MTX was discontinued, however, taking into account the extent of skin lesions in our patient, it was decided to start chemotherapy.

The optimal management for PCDLBCL-LT includes immunotherapy, consisting of R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone) as the first-line treatment and radiotherapy as a therapeutic option. A large study showed that the use of the R-CHOP regimen resulted in an increase in the 5-year survival rate from 46% to 66% [27]. Early initiation of treatment reduces the risk of extracutaneous dissemination, and thus increases the chances of complete remission [27]. According to the literature, the time from onset of symptoms to diagnosis and treatment of primary cutaneous lymphomas ranges from 1 to 24 months, with a median of 7 months [16].

In conclusion, PCDLBCL-LT may cause many diagnostic difficulties, therefore, increased clinical awareness of physicians of all specialties is required that this neoplasm should be considered in the differential diagnosis in patients with unilateral lower extremity lymphedema. Delay in proper diagnosis has a significant impact on prognosis.

Conflict of interest

None.

References


