An uncommon case of chronic leg ulcers in an 80-year-old woman

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SUMMARY

Ulcers of the lower extremities, particularly in individuals older than 65, are a common cause for visits to the dermatologist, primary-care physician, or vascular surgeon. There are many different causes of leg ulcers, among which vascular causes are the most frequent. Less commonly, other pathological processes result in leg ulcers. Unfortunately some of them are malignant. Large B-cell lymphoma, leg type, is a malignant lymphoma of intermediate behavior, occurring mostly on the legs in elderly patients. Usually it presents as erythematous or bluish-red nodules or tumors, but ulcerations are not uncommon. When faced with unusual and non-healing ulcers, the physician should also have in mind rarer but more lethal causes.

KEY WORDS

leg ulcer, primary cutaneous B-cell lymphoma, primary cutaneous diffuse large B-cell lymphoma leg type

Introduction

Chronic leg ulcers are a common disease of the elderly population mainly connected with vascular problems. Chronic venous insufficiency (CVI) is the most frequent cause for chronic leg ulcers (70–80% patients). The second most important cause for chronic leg ulcers is arterial disease, either isolated (5–10%) or in combination with CVI (10–15%). Other causes such as infection, connective tissue diseases, vasculitis, and tumors are less common. In any case, it is necessary to exclude all rare causes in patients with non-healing ulcers, an uncommon history, and an uncommon clinical picture (1).

Case report

An 81-year-old woman was admitted to the Dermatology Department because of painful non-healing chronic leg ulcers. Three months before admission, she noticed edema and painful erythematous patches on the skin of the lower right leg. Systemic antibiotics had been administered twice in order to treat cellulitis as the suspected primary cause, but there was no improvement. Her medical history included arterial hypertension and herpes zoster, and she had suffered a cerebral stroke 5 years prior and undergone a hysterectomy 10 years prior to admission.

The examination upon admission to our department revealed erythematous patches with diameters up to 1.5 cm, and four small ulcers with diameters of 0.5 to 1 cm around the right ankle and on the lower right leg. Later, erythematous patches spread to the entire lower right leg and ulcers became more numerous (Fig. 1). We noted 14 ulcers around the right ankle with diameters

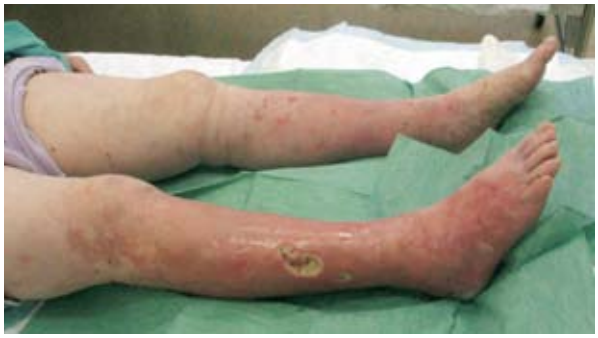

Figure 1. Erythema, edema, infiltration, and ulcers on the lower right leg.

of 1.5 to 2.5 cm coated with fibrin, but also three new erythematous patches 1 to 2 cm in diameter on the lower left leg (Fig. 2). Both legs and feet were edematous. There were no varicose veins on the legs, capillary refill was normal, and arterial pulses were palpable. Nevertheless, we also excluded any vascular etiology with color ultrasound examination of the leg veins, arterial brachial index (ABI), and partial oxygen pressure measurement on both legs.

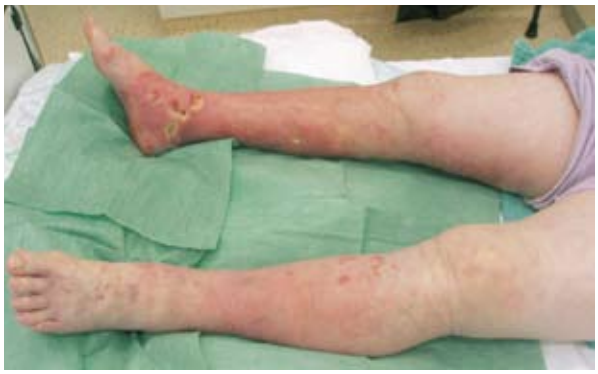

Figure 2. Multiple ulcers around right ankle. Erythematous patches on the lower left leg.

Bacteriological cultures from the ulcers showed the presence of *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Staphylococcus aureus*. Among other routine laboratory results, only CRP (32 mg/L) and the erythrocyte sedimentation rate (38 mm/H) were slightly elevated. We also assayed for antinuclear antibody (ANA), ANCA antibodies, and C3 and C4 complement components. All results were within normal ranges. We concluded that infectious and systemic tissue diseases were not likely to be the cause of the skin ulcers.

Upon detailed clinical examination, an unusually thick infiltration was noticed around some ulcers. Punch biopsies were taken from the affected skin of the lower right leg and routine histology and immunohistochemical examinations were done.

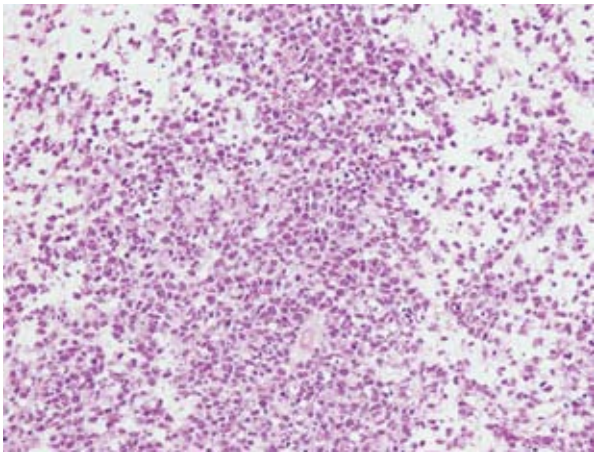

Figure 3. Histopathology revealed a dense diffuse infiltrate of round lymphoid cells with numerous mitoses and apoptoses.

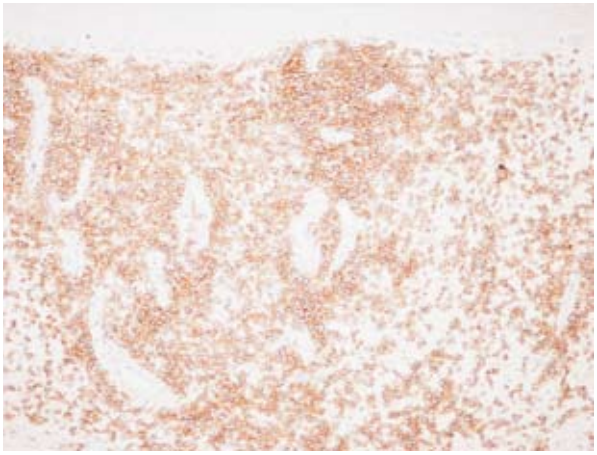

Figure 4. Immunohistochemistry: the great majority of lymphoid cells showed positive staining for B-cell marker CD 20.

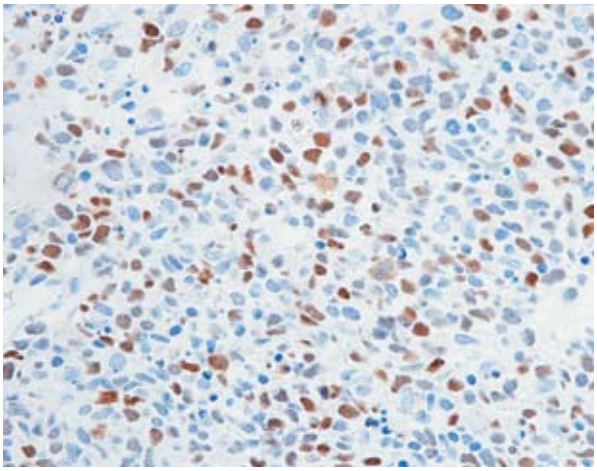

Figure 5. Immunohistochemistry: many cells expressed Bcl-6.

Histopathology revealed a dense diffuse infiltrate composed mostly of round lymphoid cells with numerous mitoses and apoptotic cells (Fig. 3). The infiltrate involved the entire dermis and superficial layer of subcutaneous fat. There was no significant epidermotropism. With immunohistochemical techniques the great majority of cells expressed B-cell marker CD20 (Fig. 4) and many expressed Bcl-6 (Fig. 5). Bcl-2 protein was also positive. The proliferation marker Ki-67 stained a large proportion of the cells. CD10, CD5, cyclin D1, CD30, lysozyme, CD68, CD1a, CD34, CD3, and myeloperoxidase were negative. Results were in accordance with cutaneous diffuse large B-cell lymphoma, leg type.

A bone marrow biopsy, ultrasound sonography of the superficial lymph nodes and abdomen, standard X-ray examination of the chest, and detailed clinical examination by an otorhinolaryngologist were performed. The results revealed no pathologic findings. The diagnosis of primary cutaneous diffuse large B-cell lymphoma, leg type was confirmed.

The patient was immediately transferred to the oncology department, where therapy with Rituximab was started. She received three of four planned pulses of chemotherapy but died 3 months later.

Discussion

Lymphomas are tumors of the lymph nodes and lymphatic system. Extranodal lymphomas are tumors that occur in organs or tissues outside of the lymphatic system. When lymphomas occur in the skin with no evidence of extracutaneous disease at the time of diagnosis, they are called "primary" cutaneous lymphomas (2). There are many different types of primary cutaneous lymphomas, but they can be broadly divided into two categories: cutaneous T-cell lymphomas and B-cell lymphomas. Primary B-cell–type cutaneous lymphomas comprise approximately 20% of cutaneous lymphomas (3).

Cutaneous B-cell lymphomas occur when there is a malignant proliferation of lymphocytes of the B-cell type. Mutation occurring at different points in B-cell development leads to different forms of lymphoma. The primary cutaneous B-cell lymphomas included in the WHO-EORTC classification of cutaneous lymphomas published in 2005 are: primary cutaneous follicle center lymphoma, primary cutaneous marginal zone B-cell lymphoma, primary cutaneous diffuse large B-cell lymphoma, leg type, and primary cutaneous diffuse large B-cell lymphoma, and other intravascular large B-cell lymphoma (4). Cutaneous B-cell lymphomas represent distinct clinical and histopathological subtypes of extranodal lymphomas. They occur far more frequently than is generally believed (5). Primary cutaneous diffuse large B-cell lymphoma, leg type occurs mainly in elderly females and presents as erythematous, brownish or bluish-red nodules or tumors usually on one or both lower legs. Ulcerations are not uncommon (3, 6). Lesions with similar histopathological and phenotypic features can arise at cutaneous sites other than the legs (large B-cell lymphoma, leg type, occurs in approximately 60% of cases on the leg(s) only) (7).

In our patient, we did not note nodules or tumors, but rather erythematous patches and later ulcerations. These clinical features led her physicians to investigate more frequent reasons for leg ulcers first.

Histopathologically, these lymphomas show a diffuse monotonous population of centroblasts and immunoblasts. A precise immunohistological classification is often not possible. It has been proposed that most cases of large B-cell lymphoma of the leg represent large-cell lymphomas originating from the lymphocytes of the germinal center. Immunohistology shows monotypic surface immunoglobulins and cytoplasmic immunoglobulin (6). In our case, the neoplastic cells were positive for CD20, bcl-6, and bcl-2, and so this and the clinicopathological pattern suggested the diagnosis of primary cutaneous large B-cell lymphoma, leg type (Figs. 4, 5).

Several therapeutic options can be considered in the treatment of patients with primary cutaneous B-cell lymphomas. The choice of any particular modality of treatment depends on several factors, including the type of lymphoma, the number of lesions, and the age and general condition of the patient (6). First and second-line therapies for primary cutaneous B-cell lymphomas are local radiotherapy, systemic multiagent chemotherapy, systemic Rituximab, chlorambucil, surgical excision, radiochemotherapy, and antibiotic treatment. Investigational therapies include intralesional interferon, intralesional Rituximab, and adenovirus-mediated interferon gene transfer. Frequently, combination therapies are used for large B-cell lymphoma of large cells in the entire dermis and subcutis. Only some localized small tumors may be treated using radiotherapy. Anthracycline-based chemotherapy is used for most skin tumors or when tumors have spread to other parts of the body. Some cases have shown response to the anti-CD20 antibody Rituximab. Death usually occurs with disseminated disease (8).

Primary cutaneous large B-cell lymphoma, leg type, is more aggressive than large B-cell

lymphoma of the head and neck, often disseminates to extracutaneous sites, and has a more unfavorable prognosis, with a 5-year survival rate of 58% (9). We did not find any extracutaneous signs of tumor at the time of the diagnosis. Unfortunately, our patient died 3 months later.

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