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Case Report

An elderly man with multiple indolent nodules: primary cutaneous large B-cell lymphoma

老年男性患者多發性無痛結節：皮膚大 B 細胞性淋巴瘤

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Primary cutaneous large B-cell lymphoma of the leg characteristically affects elderly, with female predominance. It presents as indolent tumour nodules on one or both lower limbs. The prognosis is worse comparing with other primary cutaneous B-cell lymphoma. Complete staging including bone marrow trephine biopsy and various imaging techniques are mandatory to distinguish primary and secondary cutaneous lymphoma. This is a report of an 83-year-old man presenting with typical features, clinically and histologically, compatible with diffuse large B-cell lymphoma of the leg. Primary or secondary could not be distinguished since full staging was not performed in this patient who had a recent haemorrhagic stroke. Palliative radiotherapy is planned by the oncologist because of poor general condition.

腿部原發性皮膚大 B 細胞性淋巴瘤患者多為老年人，女性較多。首發表現為一側或雙側下肢無痛結節。與其他原發性皮膚 B 細胞性淋巴瘤相比，預後較差。全面的分期檢查包括骨髓環鑽活檢。須有多種影像學檢查才能區分原發抑或繼發性淋巴瘤，此例患者男，83 歲，臨床及組織學表現為大 B 細胞性淋巴瘤。由於患有新近中風，故未能接受全面的分期檢查，以確定為原發抑或繼發性淋巴瘤。 由於患者基本狀較差，腫瘤科醫生計畫採用姑息性放射治療。

Keywords: cutaneous large B-cell lymphoma of the leg, elderly, indolent

關鍵詞：腿部皮膚大 B 細胞性淋巴瘤，老年人，無痛

Introduction

Cutaneous B-cell lymphoma (CBCL) is uncommon and accounts for only one-third of the primary cutaneous lymphoma.[1] Most CBCLs run an indolent course and have a good prognosis with a 5-year survival rate of >90%.[2] Primary cutaneous large B-cell lymphoma of the leg (PCLBCL-leg) is considered as a separate entity by EORTC (European Organization for Research and Treatment of Cancer). Comparing to other CBCL, it has a poorer prognosis with a 5-year survival rate of about 58%.[2] Tumour cells of PCLBCL-leg express bcl-2. An elderly gentleman with clinical and histological features of diffuse large B-cell lymphoma of the leg was reported.

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Case report

An 83-year-old gentleman presented with six months history of asymptomatic nodular lesions on his left leg. There was no history of preceding trauma. He had recently suffered from haemorrhagic stroke about two months before presenting to us. The stroke resulted in right hemiplegia and dysphasia and was managed conservatively. He had hypertension.

Clinical examination revealed multiple dusky brown nodules on left leg (Figures 1 & 2). They were non-tender. There were no palpable lymph nodes. The liver, spleen and kidneys were not palpable. The clinical differential diagnoses included cutaneous malignancies such as cutaneous lymphoma, Kaposi's sarcoma and granulomatous dermatoses of infective aetiology.

Skin biopsy of a nodule was performed and showed dense lymphoid infiltrate in the dermis forming nodular pattern focally. The lymphoid infiltrate was comprised of aggregates of large lymphoid cells with irregular nuclei, prominent nucleoli and amphophilic cytoplasm. Moderate amount of dispersed small lymphocytes were found among these large cells. Immuno-histochemically, the large pleomorphic lymphoid cells expressed B-cell marker (L-26) and T-cells were found in the background. CD21 (follicular dendritic cell marker) did not highlight the follicular area. Special stain for fungal organism showed negative result. The histological features were compatible with malignant lymphoma of diffuse large B-cell type. Tissue culture for acid fast bacilli and deep fungi were negative.

Initial investigations including liver function test and lactate dehydrogenase level were normal. Complete blood count showed mild anaemia (Hb 12.4 g/dl) (normal: 13.2-16.7 g/dl). The renal function was mildly impaired with creatinine of 177 µmol/L (normal: 62-106 µmol/L) and elevated uric acid level of 0.6 mmol/L (normal: 0.22-0.48 mmol/L). Serum Ig G level was raised at 20.77 g/L (normal: 7-16 g/L), IgA and IgM levels were normal. There was no paraprotein band detected by serum protein electrophoresis. Full staging workup was not performed because of his frail general condition.

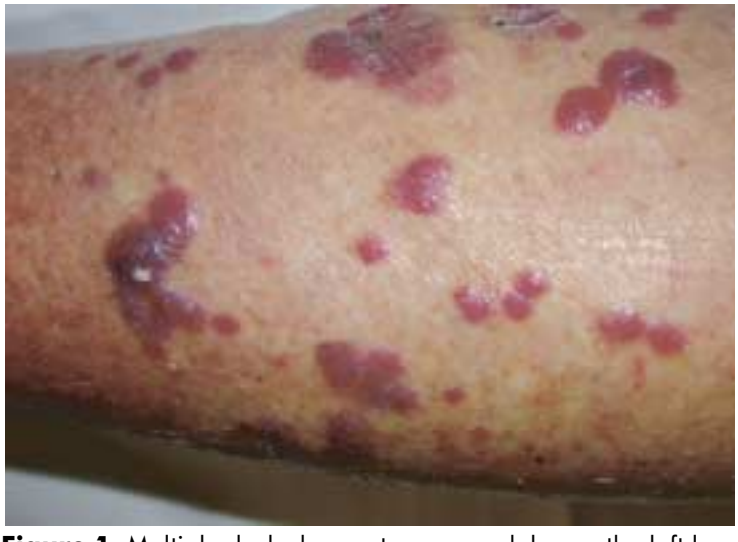

Figure 1. Multiple dusky brown tumour nodules on the left leg.

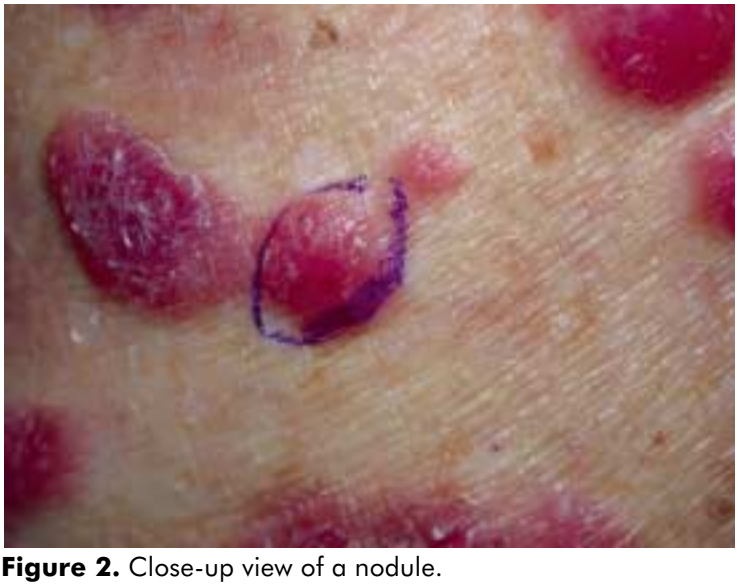

Figure 2. Close-up view of a nodule.

The clinicopathological diagnosis of our patient was diffuse large B-cell lymphoma of the leg. Primary or secondary in origin could not be distinguished in our case because complete staging was not done.

Discussion

The classification of lymphoma has undergone evolution in recent years.[3-5] In the last decade, the well-known classification systems include the REAL (Revised European American Classification of Lymphoma) proposed in 1994, EORTC in 1997 and the new WHO (World Health Organization) classification. The WHO classification is based on the principle of REAL. It recognises disease entities based on a combination of morphology, immunophenotype, genetics and clinical features.[3] No single feature is regarded as a diagnostic gold standard.

According to the new WHO classification, primary cutaneous lymphoma is defined as cutaneous disease in the absence of extracutaneous manifestation at the time of diagnosis (except in the case of mycosis fungoides and Sezary syndrome) following comprehensive staging that includes bone marrow trephine biopsy.[3] EORTC requires a 6-month extracutaneous disease-free period after initial diagnosis. Less than one-third of primary cutaneous lymphoma is of B-cell origin.[1] PCLBCL-leg is categorised by EORTC as a separate subgroup of primary CBCL.

PCLBCL-leg predominantly affects elderly female (M:F = 1:3-4).[2] It presents as solitary or multiple reddish brown or violaceous tumours which usually affects one lower leg. Sometimes both lower limbs can be affected. Regional lymph nodes and extracutaneous involvement may occur.[6] It can mimic chronic venous leg ulcer.[7] Relapses occur in 50% of cases.

The histological feature of diffuse large B-cell lymphoma is characterised by diffuse monomorphous dermal and/or subcutaneous proliferation of large atypical lymphocytes resembling immunoblasts or centroblasts.[8] These cells have large vesicular nuclei with prominent nucleoli and abundant indistinct or basophilic cytoplasm. Diffuse is defined by the absence of follicular pattern histologically and lack of $CD21^+$ follicular dendritic cells immunohistochemically.[3] bcl-2 protein (apoptosis inhibitor) is expressed in PCLBCL-leg but commonly absent in follicular centre cell lymphoma of trunk and head.[6]

Proper staging with bone marrow trephine biopsy and various imaging techniques such as ultra-sonography and computerised tomography is mandatory to differentiate primary and secondary cutaneous lymphoma. There is no controlled clinical trials in the treatment of CBCL.[8] Surgical excision is only effective in solitary lesion or limited disease. Radiotherapy is the first line treatment of choice since CBCL is highly sensitive to radio-therapy. It is used in localized disease. One study suggested that by inclusion of at least two centimeter of healthy skin into the irradiation field and a total dose of at least 30 Gy resulted in lower recurrence.[7] Perilesional injection of interferon-α 2a was reported effective in treating CBCL.[9] Polychemotherapy is reserved for widespread skin disease or extracutaneous involvement. CHOP (cyclophosphamide, adriamycin, vincristine and prednisolone) or COP was employed in treating primary CBCL.[10] The overall objective response rate was 98%, with an 89% complete remission rate and a 33% relapse rate. This study concluded that CHOP was preferable to COP because of reduction in relapse rate.

Rituximab is an anti-CD20 chimeric mouse-human monoclonal antibody.[1,7,11,12] CD20 is a non-glycosylated phosphoprotein which is a transmembrane protein expressed on all mature B-cells and 90% B-cell lymphoma. It acts as or controls a calcium channel and involves in B-cell proliferation and differentiation.[1,7,11] In vitro, rituximab induces

complement-mediated cytotoxicity of B-cells. It inhibits proliferation and directly induces apoptosis in some B-cell lines. In vivo, it causes a transient depletion of B-cells which regenerate over a period of six to twelve months.[1,7]

It has been used in the treatment of systemic B-cell lymphoma. It is administered as intravenous infusion of 375 mg/m^2 weekly over 4 weeks (cumulative dose of 1500 mg/m^2 per course). The side effects occur within the first two hours of infusion, usually with the first dose. They include dyspnoea, bronchospasm, hypoxia, fever, chills and rigor, urticaria, and angioedema.[2,7] Severe reaction may be related to high initial tumour load and is due to cytokine release. Premedication with antihistamine and analgesic is recommended. Other reported adverse effects are hypotension, anaemia, thrombocytopenia and leucopenia.[2,7]

Rituximab has been reported in the management of primary CBCL. Intravenous infusion[1,7] and intralesional injection[11,12] have been used but the response is not consistent in the reports. Intralesional injection was given two to three times per week.[11,12] Undiluted stem solution (10 mg/ml) was used. One study introduced a 3-week treatment free interval.[11] Inflammatory response was reported at the injected lesion.

PCLBCL-leg has a poorer prognosis with a 5-year survival rate of around 58% (n=18).[2] On the contrary, primary cutaneous follicular centre cell lymphoma of head and trunk (PCFCCL) has good prognosis with a 5-year survival rate of more than 90%. A recent European multicentre study further confirmed PCLBCL-leg has poorer prognosis comparing with PCFCCL. The 5-year survival rate was 52% vs 94% respectively.[13]

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