Large B-cell Lymphoma of the Leg in a Patient with Multiple Malignant Tumours

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A patient who had primary gastric B-cell non-Hodgkin’s lymphoma, invasive ductal breast cancer and a basocellular carcinoma of the forehead in her medical history was studied. Three years after polychemotherapy and irradiation of the breast cancer, a rapidly enlarging, ulcerated violaceous tumour developed on the patient’s left leg. The tumour was identified by the histopathological, immunohistochemical and immunoglobulin gene rearrangement analyses as a cutaneous large B-cell lymphoma. No signs of extracutaneous involvement were detectable. Despite surgical excision, interferon-α2b treatment and chlorambucil + prednisone chemotherapy, a relapse occurred in the previously affected site, whereafter the patient received radiotherapy. She was lost to follow-up, and died approximately 14 months after the surgical intervention without autopsy. We discuss the clinical and histologic features and outcome of the large B-cell lymphoma of the leg, its coincidence with other diseases, and the uncommon occurrence of primary multiple malignant tumours. Key words: basocellular carcinoma; breast cancer; cutaneous B-cell lymphoma; gastric B-cell lymphoma; primary multiple malignant tumours.

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Large B-cell lymphoma of the leg is a recently recognized distinct type of the primary cutaneous B-cell non-Hodgkin’s lymphomas with an unfavourable prognosis. The disease predominantly affects elderly women in the form of a rapidly growing red or violaceous nodule or tumour on one or both legs. The lesions may be solitary or multiple, the latter with a less favourable prognosis. This cutaneous lymphoma often involves the regional lymph nodes but the other extracutaneous manifestations are also common. Despite early radiotherapy or polychemotherapy, relapses occur in about 50% of cases. The estimated 2-year survival rate is 77%; the 5-year survival rate only 58% (1).
hilar lymph nodes and residual post-tuberculotic lesions in the right subclavicular region, but there were no signs of thoracic lymphadenopathy.

Histological examination of the skin biopsy specimen revealed dense lymphocytic infiltrate throughout the dermis with mild epidermotropism composed of centroblasts and immunoblasts with cerebriform nuclei and nucleoli (Fig. 2a). Nuclear polymorphism and numerous mitoses were observed. The immunohistochemical analysis identified the tumour as a CD45 and CD20 positive large B-cell lymphoma (Fig. 2b). Intensity of the MIB-1 (Ki-67) reaction was 80–90%. The p-53 and bcl-2 expression were both positive, while the Epstein-Barr virus latent membrane protein reaction (LMP-1) and bcl-6 expression were negative. Polymerase chain reaction study showed clonal rearrangement of the immunoglobulin heavy chain gene. This rearrangement was not detectable in the previous biopsy of the gastric B-cell lymphoma, which suggested that there were two different tumour clones. The histological examination of the right axillar lymph nodes and bone marrow aspiration did not reveal lymphoid infiltration.

The cutaneous tumour was excised and skin transplantation was performed. Owing to the poor prognosis of the disease the patient was treated with a low dose of interferon-α2b until complete adherence of the skin graft; then she received Knospe chemotherapy (chlorambucil + prednisone). A few months later a relapse occurred in the previously affected site of the leg (Fig. 1b). The patient did not respond well to the intralesional interferon treatment, so she was transmitted to another institute for radiotherapy. She was lost to follow-up.

**Fig. 1.** Violaceous, ulcerated tumour on the left leg (a) and its recurrence after excision, interferon treatment and chemotherapy (b).

**Fig. 2.** Lymphoid infiltration in the entire dermis (haematoxylin-eosin) (a), which was composed of CD20 positive large B-cells (anti-CD20) (b).
and died approximately 14 months after the surgical excision.

**DISCUSSION**

Large B-cell lymphoma of the leg is a relatively uncommon form of primary cutaneous B-cell lymphoma with an intermediate behaviour. This entity is referred to as centroblastic-immunoblastic lymphoma by the Kiel classification, and diffuse large B-cell lymphoma by the Revised European-American Classification of Lymphoid Neoplasms (REAL classification). Based on the evaluation of a large number of patients it was later defined by the European Organization for Research and Treatment of Cancer (EORTC) classification as a distinct disease group with intermediate prognosis (2). The observations revealed that in patients with leg involvement the prevalence of extra-cutaneous dissemination was higher and the lymphoma had a worse prognosis than in patients with head, neck or trunk lesions (1, 3, 4). Other characteristic features of the disease are onset at an older age and female predominance. It is observed principally in people older than 70 years, and the male:female ratio is 1:3–4. The histopathological and immunohistochemical features of the tumour are the CD19+ CD20+ CD22+ CD79a+ centroblasts, large centrocytes and immunoblasts throughout the entire dermis. The lymphoid infiltrate sometimes involves the subcutis, but the epidermotropism is uncommon. The bcl-2 expression is present in 100% of cases, unlike cases of follicle centre cell lymphomas of the head and trunk. The tumour cells express monotypic surface immunoglobulins. The immunoglobulin gene rearrangement is monoclonal, but the t(14;18) translocation and ICAM-1 and LFA-1 expression are negative (5–7).

The prognosis is better if the patient has a solitary lesion, if there is a centrocyte predominance and a tendency to spontaneous regression. The prognosis is more unfavourable in patients over 70 years of age, in cases with multiple (>5) lesions and elevated levels of lactate dehydrogenase (8). The presence of round cells ( centroblasts, immunoblasts), the bcl-2 expression and the absence of ICAM-1 and LFA-1 expression on the neoplastic cells are correlated with the worse prognosis (1, 5, 8, 9).

Irradiation and polychemotherapy are the recommended first-line treatments of this disease. Successful treatment with interferon and anti-CD20 monoclonal antibody (rituximab) has been described recently (10, 11).

Our patient suffered from a relatively uncommon type of cutaneous B-cell lymphoma, and had multiple malignant tumours in her medical history. Multiple primary malignant tumours were first described by Billroth in the 1800s and the criteria for this entity were created by Warren & Gates in 1932 (12). Primary multiple malignant tumours are neoplasms that are malignant, independent and non-metastatic. The second tumour could develop simultaneously, synchronously (within 6 months) and metachronously (6 months after the first neoplasm) (13). Development of multiple tumours is most commonly seen in the head and neck region (“field cancerisation”), in the female genital region and in the breast (14). The risk of a second malignancy is 3–5% (5–20% in the head and neck region), while the risk of the third and fourth is 2–5% and 0.06%, respectively (15).

Development of second malignant tumours following chemotherapy or radiotherapy of Hodgkin’s and non-Hodgkin’s lymphomas is well known, especially among the long-term survivors. These malignancies are mainly solid tumours (rectal, stomach, bladder, kidney, lung and breast carcinomas) or acute leukaemias (16). It has been suggested that the exposure to potentially carcinogenic and mutagenic therapies such as alkylating agents or ionizing radiation might be causally associated with the development of these second malignant tumours. The tumours may develop due to direct DNA damage, oncogene activation, cytogenetic alteration or disturbance of the DNA repair mechanisms. The suppressed state of the immune system due to the immunosuppressive therapy or to the cellular and humoral immunodeficiency caused by the first malignancy itself further increases the risk of secondary cancers.

In our case the gastric lymphoma and breast cancer were synchronous neoplasms because of a 5 months interval between their occurrence. These tumours were malignant, independent and non-metastatic. Development of the basocellular carcinoma (third neoplasm) in the fifth month of the breast cancer treatment might be a coincidence, as this is the most common skin cancer on the photo-damaged skin in the elderly. The large B-cell lymphoma of the leg (fourth neoplasm) occurred 3 years after the polychemotherapy and radiotherapy, so it could be considered as a treatment-related secondary neoplasm. We presume that the gastric B-cell lymphoma and the large B-cell lymphoma of the leg are two different tumours, because approximately 3.5 years elapsed between their onset, so the cutaneous lymphoma is more a metachron tumour than a metastasis. To our knowledge, metastasizing to the skin is not a characteristic feature of gastric non-Hodgkin’s lymphomas. Moreover, the large B-cell lymphoma of the leg is a distinct entity. Monoclonal immunoglobulin heavy chain gene rearrangement could have been proved only in the cutaneous lymphoma and it failed in the case of the gastric tumour, so we assumed that the tumour clones might be different ones besides the possible methodological problems.

Large B-cell lymphoma of the leg has been described in association with rheumatoid polyarthritises (17), chronic lymphoedema (1, 18) and malignant melanoma (19). In
a unique case described by Vermeer et al. (1), a large B-cell lymphoma of the leg developed 12 years after a large B-cell lymphoma of the hard palate, while in another recently described case a primary cutaneous large B-cell lymphoma of the leg relapsed as a cutaneous intravascular large B-cell lymphoma (20). Our case is the first report of a patient suffering from large B-cell lymphoma of the leg associated with multiple malignant tumours.

REFERENCES


