Allogeneic Haematopoietic Stem Cell Transplantation in a Patient with Cutaneous γ/δ-T-cell Lymphoma

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Reported cases of subcutaneous panniculitis-like T-cell lymphoma (SPTL) show different clinical courses depending on the immunophenotype of the tumour cells. They can either express α and β or γ and δ polypeptide chains in the T-cell receptor (TCR). These differences caused the World Health Organization’s European Organization for Research and Treatment of Cancer (WHO-EORTC) to classify this type of lymphoma into an α/β-TCR subtype (SPTL-AB) solely constituting the group of panniculitis-like T-cell lymphoma, and a γ/δ-TCR subtype (CGD-TCL), which was regrouped into the broad category of peripheral T-cell lymphoma, not otherwise specified (1).

Clinically, CGD-TCL appears as indurated red plaques and nodes with predominance to the trunk and the extremities often leading to diagnostic confusion with differential diagnosis such as lupus panniculitis, cellulitis or other erythematous skin diseases. Ulcerations have rarely been reported.

CASE REPORT

A 51-year-old woman presented with a 10-month history of partly ulcerating painful subcutaneous nodules and plaques with predominance of the trunk and the extremities (Fig. 1 a, b). She did not report any B-symptoms. The patient’s medical history revealed chronic seronegative rheumatoid polyarthritis, myocardial infarction at the age of 45 years, arterial hypertension, lung emphysema, allergic rhinoconjunctivitis and substituted cardial infarction at the age of 45 years, arterial hypertension, revealed chronic seronegative rheumatoid polyarthritis, myo-

normal 4,600–9,500), neutrophils: 1,610/µl, (1,800–7,200), without elevated lymphocyte count (1,470, (1,000–4,050)).

A representative histological specimen showed a superficial and deep angiocentric infiltrate of medium- to large-sized pleomorphic lymphocytes with focal “fat-cell-rimming” as well as necrosis of the dermis and subcutis (Fig. 1c). Immunohistochemical staining revealed a CD4-, CD8- and CD56-negative infiltrate, whereas granzyme B, and especially Ki67 showed high positivity (Fig. 1d). Beta-F1 staining was negative in 80% of the tumour cells. Furthermore, we found a positive TCR-γ-rearrangement in the monoclonal lymphocytes, while TCR-δ-rearrangement was lacking. In situ hybridization for Epstein Barr virus (EBER) was negative in the tumour material. A γ/δ-T-cell lymphoma was diagnosed with regard to the histological appearance and the immune profile (Table S1; available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1460) according to the EORTC classification of T-cell lymphomas (2).

Staging included computed tomography scan of the chest and abdomen, sonography of the lymph nodes, bone marrow smear, bone marrow biopsy, and peripheral blood smear, all showing no signs of lymph node, organ or bone marrow involvement. The resulting tumour-node-metastasis (TNM)-classification before treatment according to the EORTC was T3N0M0 at first presentation (1).

Our patient underwent combined topical psoralen and ultraviolet A (PUVA)-therapy, as well as treatment with methotrexate and systemic corticosteroids, all with no response. After establishment of the diagnosis of CGD-TCL, monotherapy was started with 800 mg/m² body surface gemcitabine over 2 cycles, followed by a monochemotherapy with 100 mg/m² body surface bendamustine over 2 cycles, then by a short course systemic corticosteroids, all with no response. After establishment of the diagnosis of CGD-TCL, monotherapy was started with 800 mg/m² body surface gemcitabine over 2 cycles, followed by a monochemotherapy with 100 mg/m² body surface bendamustine over 3 cycles. Both led to no clinical improvement.

With regard to the limited prognosis of the CGD-TCL, the relatively young age, with regard to the type of her disease, and the patient’s otherwise reasonable medical status (Eastern Cooperative Oncology Group (ECOG) performance status: 1) we took allogeneic stem cell transplantation (SCT) into consideration. The tumour stage before transplantation was T3N0M0 according to the EORTC. A non-related HLA-identical donor could be identified. Pre-transplant myeloablative conditioning included 175 mg fludarabine, 200 mg busulfan and 5,800 mg cyclophosphamide. For immunoprophylaxis, cyclosporine (according to serum level, starting with 2 mg/kg body weight in intravenously) and a short course of methotrexate, 15 mg/m² body surface, were used. We avoided performing in vivo T-cell depletion or administering a T-cell depleted graft in order to permit a possible T-cell mediated graft-vs.-lymphoma reaction. The patient received peripherally collected hematopoietic progenitor cells at a concentration of 9.6 × 10⁶/kg body weight CD34-positive cells.

Fig. 1. (a) Deep lymphocytic infiltrate and (b) highly positive Ki67-staining. (c, d) Red patches, plaques and partly ulcerating nodules on initial presentation, and (e, f) completely regressive skin lesions with remaining ulcerations on the right ankle 18 months after allogeneic hematopoietic stem cell transplantation.
Complete remission of symptoms of disease, with regression of plaques and nodes as well as the continuous healing of ulcerations, was noted after allogeneic SCT (Fig. 1 e, f). The patient developed acute and subsequently secondary chronic cutaneous graft vs. host disease (GvHD) that could be controlled by systemic immunosuppressive treatment with cyclosporine 35 mg daily and prednisone 10 mg daily. Other complications comprised viral infections. BK-virus (human polyomavirus 1)-induced cystitis and an ocular herpes simplex infection were observed during the early post-transplant course and were treated successfully by virostatic therapy. After a follow-up of 21 months the patient is in complete remission with no signs of disease recurrence. She has severe chronic GvHD with skin and lung involvement, which is currently under good control with moderate inflammatory activity. Scoring of chronic GvHD was performed by National Institute of Health (NIH) criteria (3). Pulmonary GvHD was ascertained 8 months after SCT by pulmonary function test and radiology. Severe impairment of forced expiratory volume (FEV1) to 15% of normal values was found, as defined by bronchiolitis obliterans (BO). By the use of anti-obstructive treatment and increased immunosuppression the course of BO remained stable. The patient was last seen in January 2012.

DISCUSSION

CGD-TCL is associated with an often fatal prognosis (5-year overall survival: 11%). In our case, no B-symptoms (fever, weight loss and night sweats) or organ involvement were present. Nevertheless, cutaneous involvement was progressing steadily, with poorly healing ulcerating nodes, and was refractory to any treatment.

To date, there is no established therapy for CGD-TCL and treatment guidelines are mostly based on anecdotal reports (4). Most treatments consisted of multi-agent doxorubicin-based chemotherapies (mostly CHOP) as first- or second-line treatment, as well as prednisone and autologous or allogeneic SCT in case of progressive disease. Narrow-band ultraviolet radiation (NB-UVB) and low-dose methotrexate have been shown to be a useful treatment in the patch/plaque lesions of primary CGD-TCL, especially in elderly people (5). Bexarotene has been used alone, in combination with or as maintenance therapy after, CHOP/CHOP-like regimen in the treatment of SPTL-AB and CGD-TCL (6). Hathaway et al. (7) reported a case of a patient with CGD-TCL with partial remission under denileukin diftitox and complete response after its combination with bexarotene.

Willemze et al. (2) reported one case of CGD-TCL with complete remission after allogeneic SCT. In a meta-analysis Go & Wester (8) report that after treatment with high-dose chemotherapy and stem cell transplantation for refractory or recurrent disease, a complete remission was achieved in 92% of all cases, with a median response duration of 14 months. A distinction between SPTL-AB and CGD-TCL was lacking in this meta-analysis, which was published prior to the new EORTC classification. Yuan et al. (9) reported one case with relapse of disease in a patient with CGD-TCL after allogeneic SCT and complete remission after withdrawal of immunosuppressive treatment (cyclosporine). This underlines the possibility of a graft-vs.-T-cell lymphoma effect, which has been described for non-T-cell lymphomas and leukaemia (2, 10). Table SII (available from http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1460) summarizes the previously published cases.

Selecting the best timing for allogeneic haematopoietic stem cell transplantation in patients with T-cell lymphomas is often difficult. Radical therapies are rarely accepted by both patient and practitioner as long as the symptoms of disease do not appear life-threatening. Yet a good physical condition is essential for a favourable post-transplant outcome. Early recognition of possible candidates for allogeneic SCT and individualized, toxicity-reduced conditioning regimens, combined with modern concepts of immunoprophylaxis, could contribute to minimize transplant-related mortality.

The authors declare no conflicts of interest.

REFERENCES