

Secondary acute leukaemia (s-ALL) is a destructive complication in patients who have been previously treated for other cancer. Secondary acute lymphoblastic leukaemia is rarely reported whereas secondary acute myeloid leukaemia is much more common. Chromosomal 11q23 abnormality, frequently detected in therapy-related acute myeloid leukaemia, is the most common cytogenetic alteration in secondary ALL too. However, s-ALL cases without 11q23 abnormality have rarely been described. Furthermore, there are only a few published medical reports describing occurrence of acute lymphoblastic leukaemia in multiple myeloma (MM) patients. We would like to present our experience with a patient with MM, who developed ALL without 11q23 abnormality, nine years after alkylating-agent containing treatment. The course of the disease was complicated by thrombosis that obstructed the possibility of effective treatment. In conclusion, it should be kept in mind that the development of a more aggressive neoplasm related to chemotherapy treatment as well as the inherent genetic instability of normal and abnormal lymphoid progenitors may affect overall survival of an indolent lymphoma patient.

Key words: multiple myeloma, secondary acute leukaemia, chemotherapy.

Secondary acute lymphoblastic leukaemia in a multiple myeloma patient

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Introduction

Secondary acute leukaemia (s-ALL) is a destructive complication in patients who have been previously treated for other cancer. Secondary acute lymphoblastic leukaemia is rarely reported whereas secondary acute myeloid leukaemia is much more common. Chromosomal 11q23 abnormality, frequently detected in therapy-related acute myeloid leukaemia, is the most common cytogenetic alteration in secondary acute lymphoblastic leukaemia too. However, s-ALL cases without 11q23 abnormality have rarely been described. Furthermore, there are only a few published medical reports describing occurrence of acute lymphoblastic leukaemia in multiple myeloma (MM) patients. We would like to present our experience with a patient with MM, who developed ALL without 11q23 abnormality, nine years after alkylating-agent containing treatment.

A 56-year-old woman who presented with fatigue and bone pain of the lumbar-sacral area was admitted to our hospital in July 2000. Serum immunoelectrophoresis showed increased monoclonal IgG (1.9 G/dl), and normal creatinine level. The bone marrow (BM) aspiration revealed 11.2% plasma cells and 51% infiltration by malignant plasma in trephine biopsy. Skeletal survey showed many lytic lesions of the skull and lumbar-sacral area. A diagnosis of MM was made. The patient was treated with seven cycles of the VCMP (vincristine, cyclophosphamide, melphalan, and prednisone) regimen. The evaluation of the response after treatment was partial remission. Due to the progression of MM the patient was treated with nine cycles of melphalan, prednisolone (dexamethasone) and thalidomide (MPT), from January 2004 to April 2005. The patient achieved partial remission. From May 2005 the patient was treated with thalidomide in monotherapy.

On September 2009 the patient was admitted to the Haematology Department due to complaints of oedema of the right lower limb and dyspnoea. The physical examination revealed enlargement of the spleen 10 cm below the costal margin, tachypnoea and pleural friction rub. The complete blood count showed white blood cell count (WBC) 30.77 G/l, haemoglobin (HGB) 8.6 g/dl, platelet count (PLT) 80 000/ml and 5% blastic cells in the peripheral smear. The BM was infiltrated by 37.8% blasts, immunophenotyped as B-cell lymphoblasts by flow cytometry (CD19+, CD20+, CD22+, HLA-DR+ CD10+) and negative antigen of myeloid and T-cell lineage. Results were consistent with acute lymphocytic leukaemia B common. Cytogenetics revealed normal karyotype (46,XX [20/20]) with negative fluorescence in situ hybridization (FISH) examination for mixed lineage leukaemia gene MLL rearrangement and BCR/ABL fusion gene. The serum immunoelectrophoresis showed the IgG monoclonal protein with level 0.36 g/dl. Doppler examination of the right lower limb confirmed deep venous thrombosis and CT pulmonary angiography revealed multiple filling defects of principal branches of the pulmonary arteries, due to pulmonary embolism. The vascular complications were treated with low molecular

heparin in therapeutic doses. In view of all these conditions and the poor overall prognosis the patient was managed conservatively with steroids alone. After ten days of treatment the patient died due to acute cardio-pulmonary failure.

Therapy-related acute leukaemia is a heterogeneous disease that may occur especially after treatment containing an alkylating agent/radiotherapy and/or topoisomerase II inhibitor [1]. The alkylating agent-related subgroup is characterized by having a mean latency period of 5 to 7 years and antecedent myelodysplasia with chromosomal aberration typical for this state [2]. These alkylating agent-related acute leukaemias are mostly classified as acute myeloid leukaemia (AML) [3]. On the other hand, DNA topoisomerase II inhibitors cause secondary leukaemias with relatively short latent periods (1–5 years) without antecedent myelodysplasia. The most common characteristic chromosomal aberrations are translocations involving 11q23, the *MLL* gene locus. Most of the leukaemias are diagnosed as AML [4]. Therapy-related acute lymphoblastic leukaemia, which represents approximately 12% of all therapy-related acute leukaemias and 1.2% to 4% of adult ALLs [5, 6], is seen much less frequently than therapy-related AML. The most common chromosomal abnormalities in s-ALL affect the *MLL* gene (11q23); others are extremely rare but have been reported previously. In patients with multiple myeloma, the risk of developing secondary AML has been calculated to be 3–5% at 3 and 10–15% at 10 years after treatment with alkylating agent therapy. On the other hand, secondary acute lymphoblastic leukaemia is rare, occurring in about 0.5–1‰ of treated patients [7].

Ueda *et al.* (2009) reported the case of a multiple myeloma patient, treated with an alkylating agent, that terminated in acute lymphoblastic leukaemia with gene *MLL* aberration one year after autologous transplantation. The authors performed IgH gene rearrangement studies on genomic DNA extracted from the BM aspirates at the time of diagnosis of MM and that of ALL, which showed different monoclonal bands on DNA extracted from both samples [8]. Based on this, they concluded that previous MM and s-ALL were derived from different lymphoid clones. The authors postulated that *MLL* modification may lead to ALL in the multi-step tumorigenesis process [9]. However, that kind instability in a lymphoid progenitor of MM cells *in vivo* or *in vitro* has not yet been confirmed. Furthermore, the development of s-ALL without *MLL* gene aberration, 3 years after tandem autologous stem cell transplantation due to MM, was previously described by Lau *et al.* (2005). The presented patient was treated with the VAD regimen (vincristine, doxorubicin, dexamethasone) as induction therapy, and with alkylating agents (cyclophosphamide and melphalan as a mobilization and a conditioning treatment respectively). The authors confirmed that two separate monoclonal B-cell populations were involved in the pathogenesis of these two lymphoid malignancies at two different time points [10]. Recently, Chen *et al.* (2010) described 6 adults with secondary treatment related ALL without 11q23 abnormalities following various treatment regimens for primary malignancies (2 MM patients included). They also reviewed 48 s-ALL cases, with complete chromosomal karyotyping, reported in the literature from 1992 to 2007 (13 patients with haematological malignancy, num-

ber of MM not specified). In the 48 cases, an 11q23 abnormality involving the *MLL* gene locus was the predominant chromosomal aberration (67%), and 8% had a normal karyotype. The two described cases of MM patients previously treated with anthracycline agents revealed s-ALL 78 and 60 months after diagnosis of primary malignancy and had no 11q23 abnormalities. The authors showed that s-ALL cases with an 11q23 abnormality compared to cases without an 11q23 abnormality had a longer latency period (median, 36 vs. 19 months) and a different primary malignancy spectrum [11].

Our patient had a normal karyotype and received only an alkylating agent in MM treatment. The latency period was 102 months from diagnosis of MM and was comparable with the mean latency time described in the literature for s-ALL related to alkylating agents. The vascular incident that complicated the course of disease obstructed the possibility of aggressive and more effective treatment. In our clinical practice we have to remember that s-ALL may complicate the course of other indolent haematological malignancies. The development of a more aggressive neoplasm could be related to applied chemotherapy as well as the inherent genetic instability of normal and abnormal lymphoid progenitors.

The authors declare no conflict of interest.

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