Extramedullary relapse of acute myelogenous leukaemia due to chronic GVHD as a complication of allogeneic HSCT

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Abstract

We report a 41-year-old man with AML and unfavourable complex chromosome abnormalities who was treated with alloHSCT in first complete remission. Two years after transplant due to limited chronic GVHD this patient presented painful oedema around the left wrist. Histology of the soft tissue tumour, found in CT scanning of this wrist, revealed isolated extramedullary (EM) leukaemia relapse. He was treated with surgery, local radiotherapy and systemic chemotherapy. This case suggests that the anti-leukaemic effect of GVHD in EM sites might not be effective. Moreover, there is a possibility that GVHD predisposes to isolated EM relapses of leukaemia.

Key words: AML, alloHSCT, GVHD, isolated extramedullary relapse.

Introduction

Extramedullary (EM) recurrences with or without bone marrow involvement are reported in up to a half of leukaemic relapses after allogeneic haematopoietic stem cell transplantation (alloHSCT). Graft versus host disease (GVHD) which triggers a graft-versus-leukaemia (GVL) reaction is known to be associated with decreased incidence of leukaemic relapses [1]. But it seems that the anti-leukaemic effect of GVHD and GVL in EM sites might not be so uniformly effective as that in the marrow. Moreover, it is possible that GVHD may predispose to EM relapse of acute myelogenous leukaemia (AML) [1, 2]. We present a case of a patient with AML relapse as a tumour in the subcutaneous tissue around the left wrist and without evidence of bone marrow infiltration due to chronic GVHD two years after alloHSCT.

Case report

A 41-year-old man in good clinical condition with no relevant past medical history was diagnosed with high risk AML M0 on March 2005 based on cytochemical, cytoenzymatic (100% of blasts myeloperoxidase negative), immunophenotyping (CD34+, HLADR+, D13+, CD33+, CD117+) and karyotype analysis (complex chromosomal abnormalities: 66~72,XY,der

(2)t(2;?)(q?37;?), +4, der (5)t (5;?)(q?33;?)x2,+6,+21, inc[cp3]/46XY [17]).

Complete haematological and cytogenetic remission was confirmed following two induction courses of chemotherapy: DAC-7 (daunorubicin 45 mg/m^2 daily, days 1-3 and cytarabine 200 mg/m^2 daily, days 1-7) and CLAG-M (cladribine 5 mg/m^2 daily, days 1-5, cytarabine 2.0 g/m^2 daily, days 1-5, mitoxantrone 10 mg/m^2 daily, days 1-3, and G-CSF 300 µg s.c. daily to ANC > 0.5 g/l). Then, two cycles of consolidation: HAM (cytarabine 1.5 g/m^2 daily, days 1-3 and mitoxantrone 10 mg/m^2 daily, days 3-5) and HDAraC (6 doses of cytarabine 3.0 g/m^2 daily, days 1, 3, 5) were administered.

Thereafter, this patient received alloHSCT from his HLA-matched sister in October 2005. The conditioning regimen consisted of intravenous busulfan (3.2 mg/kg daily on days -8, -7, -6, -5) and cyclophosphamide (60 mg/kg/day *i.v.* on days -4 and -3). He received 6.7×10^6 of non-T-cell-depleted peripheral blood stem cells.

As GVHD prophylaxis cyclosporine A (CsA) 3 mg/kg/day *i.v.* from day -1 with a target level of 200-400 ng/ml in whole blood and methotrexate 15 mg/m^2 on day +1 and 10 mg/m^2 on day +3, +6 and +11 were applied. He received palifermin 60 µg/kg once daily *i.v.* for three consecutive days before and after conditioning therapy (total 6 doses) for oral mucositis prophylaxis. We did not observe any symptoms of acute GVHD or other early transplant complications. The dose of CsA was slowly tapered from day +100 until +140 when limited chronic GVHD developed (xerostomia, moderate abnormalities of liver tests). We stopped to withdraw CsA and effectively added steroids 0.5 mg/kg daily for 2 months. Then immunosuppressive therapy was slowly tapered and completely discontinued two years following HSCT. The monitoring of chimerism (short tandem repeats) and disease status was performed every three months. This patient remained in complete haematological and cytogenetic remission with a 100% donor-cell population until October 2007 (two years after transplant) and then he presented with painful oedema around the left wrist. X-ray imaging (Figure 1A) and CT scanning (Figure 1B) of this wrist and bone scintigraphy were performed. In CT scanning, a distal radius pathological fracture without periosteal reaction and a tumour in the soft tissue with diameter 49 × 66 × 43 mm were found.

His bone marrow was still in complete haematological and cytogenetic remission with complete donor chimerism. Cerebrospinal fluid analysis did not reveal leukaemic cells.

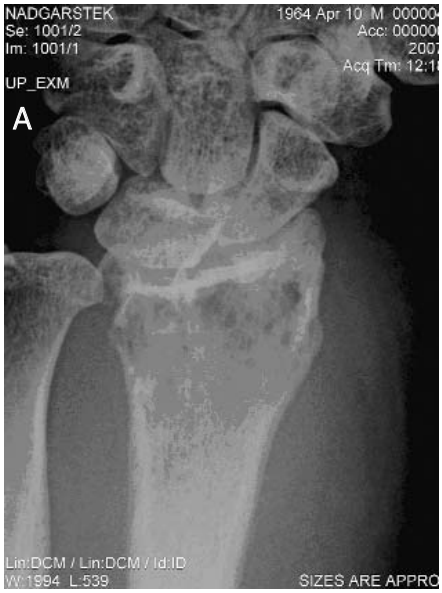
He was operated on to completely excise the tumour from his distal radius (Figure 1C). Histological (Figure 1D-F) and cytogenetic (Figure 1G) evaluation of this tumour showed diffuse blast cell infiltration with complex chromosomal abnormalities: 43~46,XY,-15,+1~2mar [cp4]/46,XY [4] (different than at diagnosis). Analysis of tumour cells chimerism showed 100% of recipient cell population. Tuberculosis was excluded and isolated EM of AML after alloHSCT was diagnosed in this patient.

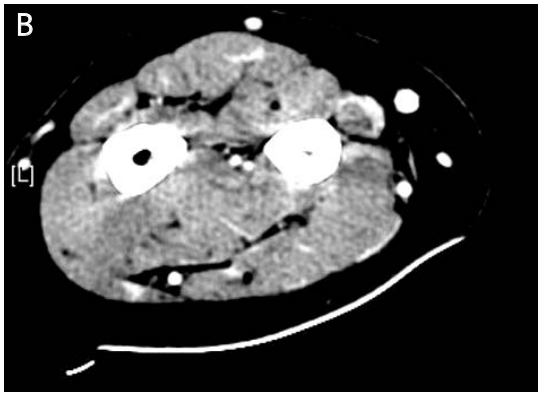
After surgical intervention he was treated with local radiotherapy and HDAraC (6 doses of cytarabine 3.0 g/m^2 daily, days 1, 3, 5). At the present time, 8 months from diagnosis of EM relapse, he is alive, still with complete donor chimerism in bone marrow, planning to receive the next course of systemic chemotherapy.

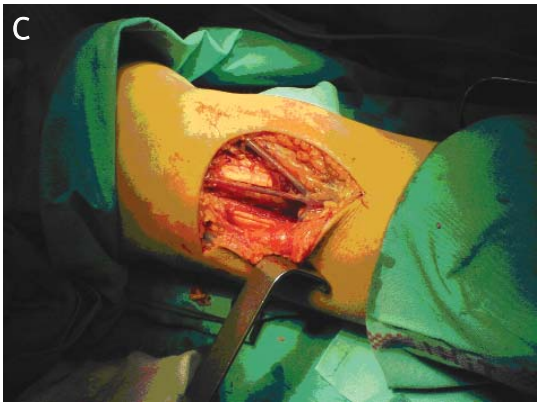
Discussion

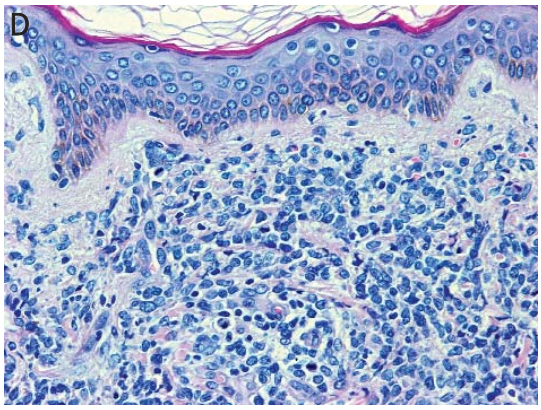
Cunningham has recently summarized the published reports of leukaemia EM relapses after transplant [1]. She focused on elucidation of the pathogenesis and predisposing factors for EM relapses of AML and emphasized that these relapses occur usually as a first sign of relapse, without simultaneous marrow involvement, in soft tissue (skin and subcutaneous tissue), late – within 2 years after transplant – mostly in cases classified as M3, M4 or M5 (FAB typing) and with abnormal karyotypes [1]. These characteristics perfectly matched our patient beside FAB classification (M0 in our case). Extramedullary relapse after alloHSCT may be more common than previously thought and have a better prognosis, with longer post-relapse overall survival than marrow-only relapse [2]. The main problem in such cases is optimal therapy, which has not been established yet. It seems that excision of the tumour and local radiotherapy in combination with systemic chemotherapy as were applied in our patient or second alloSCT could be most effective [1-3]. The effectiveness of donor lymphocyte infusion (DLI) in AML EM following alloSCT is still not known but it appears to be less effective than cytotoxic therapy [4]. Moreover, it was observed that isolated EM relapses seem to be more common after chemotherapy and DLI applied because of AML relapse following alloHSCT [5]. Other therapeutic agents for treatment of myeloid sarcomas containing FLT3 mutations could be inhibitors of FLT3 [6]. Monoclonal antibodies such as gemtuzumab ozogamicin were also effectively used in the case of multiple sites of AML EM relapse [7].

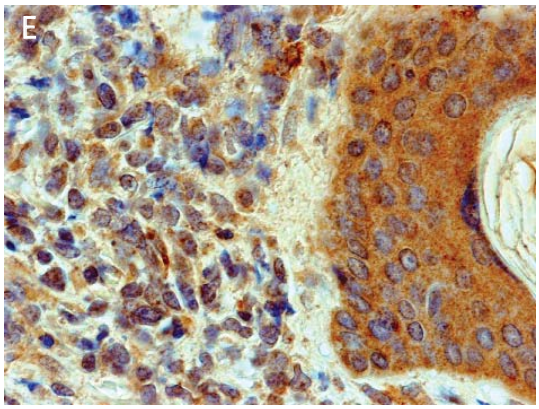
In our case even chronic GVHD which triggers the GVL effect did not prevent relapse. It seems that GVL is not so effective in myeloid as in lymphoid malignancies and the strongest effect occurs in bone marrow excluding EM sites [2, 4, 8]. Moreover, it was found that the presence of chronic GVHD

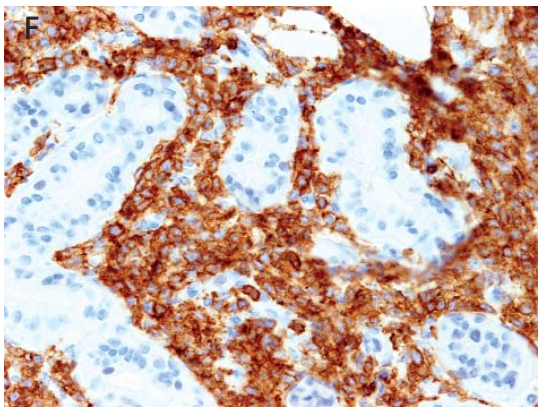












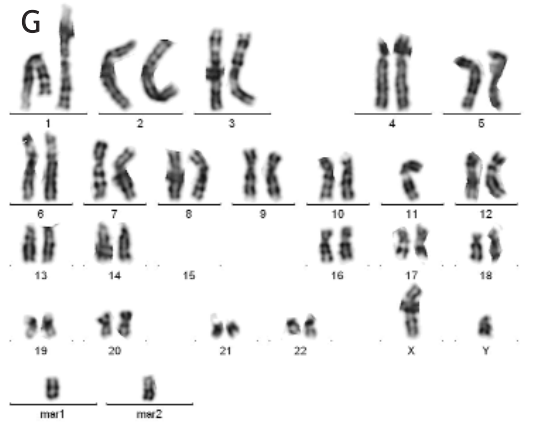


Figure 1. A – X-ray of the left wrist – fine osteolytic focuses with cortical fractures of distal radius; subchondral bone remodelling of radius articular part; Sudeck type spotted atrophy of scafoid and lunate bones. B – CT scan of the left wrist – fracture of distal radial diaphysis with palmar dislocation; osteolytic bone destruction close to the fracture area with tumour in the soft tissue with diameter 49 × 66 × 43 mm. C – Surgery of the left wrist and forearm – solid tumour from distal radius with elevation and destruction of periosteum with surrounding soft tissue compression; no evidence of distal radial diaphyseal fracture; cortical surface of radius with fine erosions. D – Histology of tumour – blast cells without differentiating features diffusely infiltrate skin and adipose tissue. There are numerous mitotic figures. H & E stain, 200 ×. E – Immunohistochemical stains of tumour cells – weak myeloperoxidase positivity. En Vision stain, 400 ×. F – Immunohistochemical stains of tumour cells – CD34 expression. En Vision stain, 200 ×. G – Karyotype of tumour cells (described in the text)

and a longer interval between transplant and relapse were independently associated with an increased risk of EM compared to marrow-only relapse [9]. There is a possibility of immunological escape of recurrent leukaemia cells from the activated T-lymphocytes in EM sites [10]. It seems that T-cell alloreactivity more precisely controls the haematopoietic targets compared to non-haematopoietic cells. Minor histocompatibility antigens (mHA), expressed also on tumour cells, are targets for GVL. One hypothesis is that mHA-specific cytotoxic T-cells destroy host haematopoietic cells – both normal and malignant – but not non-haematopoietic cells after HLA-matched alloHSCT [11]. Cunningham in her article showed that acute or chronic GVHD was noted in 70% of cases with acute leukaemia and EM relapse [1]. Of course, detailed examination of the influence of acute and chronic GVHD on medullary or EM relapse rate of AML needs additional studies. The accumulation of detailed cases is also needed to establish the optimal therapy for EM relapse of AML after alloHSCT to cure such cases and prolong overall survival.

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