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CASE REPORT

Severe radiotoxicity in an allogeneic transplant recipient with a heterozygous *ATM* mutation

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Abstract

Patients receiving radiotherapy often experience toxicity of the skin and mucous membranes. While radiotherapy is a mainstay of myeloablative conditioning for allogeneic hematopoietic stem cell transplantation (ASCT), no risk factors for radiotoxicity have been identified in this setting. Here, we report on a patient with excessive radiation-induced toxicity after ASCT who carried a heterozygous mutation in the *Ataxia telangiectasia mutated* (*ATM*) gene. This is the first case to suggest a genetic basis for increased radiotoxicity after myeloablative ASCT.

Key words *ataxia telangiectasia mutated*; hematopoietic stem cell transplantation; radiotoxicity; radiosensitivity; risk factor

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In May 2011, an otherwise healthy 30-yr-old female was diagnosed with pro-B acute lymphoblastic leukemia (ALL). Initially, two cycles of induction therapy according to the 07/2003 German Multicenter ALL-protocol (GMALL) were administered (1). The patient experienced multiple complications including sepsis, hepatotoxicity grade II, hematotoxicity grade IV, and atypical pneumonia, ultimately requiring premature termination of the second induction cycle. After recovery, one cycle of consolidation therapy was administered. The patient subsequently developed grade IV mucositis and fever of unknown origin. With supportive care, she again recovered quickly. Bone marrow examination revealed complete remission (CR) on day +11 and absence of minimal residual disease (MRD) on day +71. However, due to diagnosis of pro-B ALL (high risk), allogeneic hematopoietic stem cell transplantation (ASCT) in first CR was recommended according to the GMALL guidelines and the patient was admitted to our center in October 2011. For conditioning, the patient received 6 × 2 Gray total body irradiation (TBI, days −7, −6, −5) and 1 × 60 mg/kg VP16 (day −4). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A (target serum level of 200 μg/L) and methotrexate (15 mg/m^2 on day 1 and 10 mg/m^2 on days 3, 6, and 11). Following conditioning, the patient received a non-T-cell-depleted stem cell allograft from her HLA-identical sister. Already, on day −1, increasing erythema mainly on hands and trunk was noted (Fig. 1A). In the following days, skin changes progressed, covering approximately 35% of the body surface and forming bullae and erosions (Fig. 1B). The patient also experienced grade IV mucositis and reported diarrhea beginning on day 0. Due to the temporal association with TBI, radiation-induced damage was deemed a possible cause of these symptoms. Our differential diagnosis included medication-associated toxicity, but no causative agent could be identified. Studies for infectious causes of colitis turned out negative. We treated the dermatitis with rich cream and later added topical steroids and linimentum aquosum, leading to gradual improvement of skin symptoms (Fig. 1C).

On day +20, a new episode of diarrhea and fever was noted. Upper endoscopy showed gastric erythema. Histological analysis revealed CD3-positive lymphoid infiltrates in the duodenum consistent with GVHD. Administration of high-dose methylprednisolone led to rapid improvement of abdominal symptoms. However, diarrhea returned few days later. Repeated upper endoscopy turned out macroscopically unremarkable, and duodenal biopsies now only revealed histiocytic and granulocytic infiltrates not indicative of

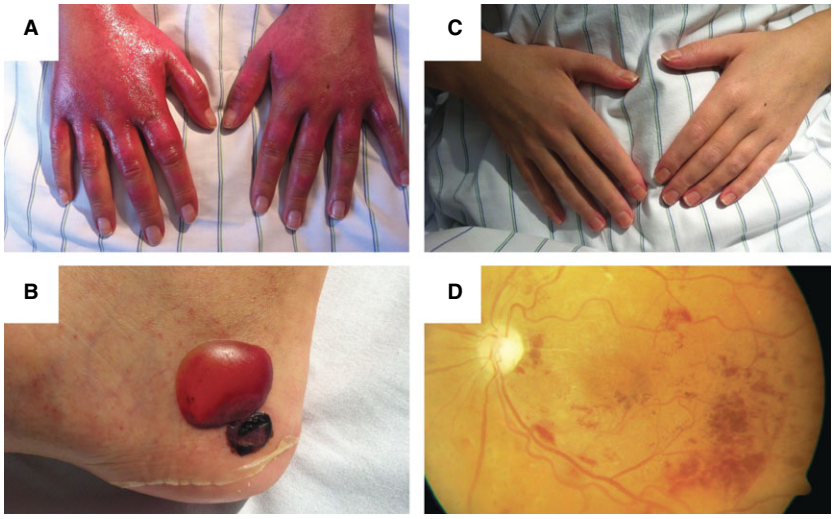

Figure 1 Extensive toxicity after radiation-based conditioning for allogeneic hematopoietic stem cell transplantation. Dermatitis developed shortly after radiation, mainly affecting hands and trunk (A). Dermatitis later progressed with the formation of erosions and bullae (B). Under supportive care, symptoms gradually improved (C). Fundoscopy revealed retinal hemorrhages and cotton wool spots (D).

persistent GVHD. Thus, with studies for infectious causes also remaining negative, we deemed radiation a likely contributor to prolonged gastrointestinal inflammation. On days +18 and +39, neutrophil and platelet engraftment were achieved and bone marrow examination on day +28 indicated sustained CR. Thirty days post-transplantation, the patient reported gradual deterioration of visual acuity. Fundoscopy revealed bilateral microangiopathy with intraretinal hemorrhages, cotton wool spots, and macular edema consistent with radiation-induced retinopathy. In light of the exceptional degree of radiation-induced toxicity, sequencing of the *ATM* locus on chromosome 11q22-q23 was performed. Analysis of buccal mucosa cells as well as of preserved peripheral blood acquired prior to transplantation revealed the heterozygous nonsense mutation c.4396C/T, which leads to the ATM truncation p.R1466. This mutation has so far only been described as a somatic mutation in colorectal cancer (2). After discharge on day +44, ophthalmological treatment continued with intravitreal administration of bevacizumab and ranibizumab (Fig. 1D). Eight months after transplantation, the patient suffered from vitreous hemorrhage that was treated with retinal laser coagulation. Visual acuity stabilized at a low level afterward. The patient is alive and in MRD-negative CR at a follow-up of 24 months. She is currently being treated for chronic GVHD of the skin and connective tissues by extracorporeal photophoresis.

Several aspects concerning radiotoxicity in patients undergoing ASCT need to be discussed in light of this case. While currently no pretransplantation risk assessment of individual radiosensitivity is routinely performed, mutations in *ATM* may be a useful predictive factor. *ATM* codes for a protein kinase playing a major role in DNA repair and apoptosis (3). It is homozygously mutated in patients suffering from ataxia telangiectasia, a hereditary neurodegenerative disease leading to immunodeficiency, increased radiotoxicity, and a predisposition for cancer, in particular for lymphoproliferative malignancies (4, 5). There is evidence that patients harboring a heterozygous mutation are intermediate in their radiosensitivity as well as cancer predisposition (6, 7). In the general population, heterozygous mutations of *ATM* are estimated to occur at a rate of 1% (5). Given the association between *ATM* mutations and the development of lymphoid cancers, pretransplant screening for *ATM* mutations might be effective in patients with lymphoproliferative diseases. A broader genetic screening for radiosensitivity is difficult as the genetic background is heterogeneous and conclusive data guiding an efficient screening approach are lacking (8). Thus, functional assays rather than sequencing methods have been proposed (9).

Patients with ALL and leukemic *ATM* gene deletion were shown to have better survival after chemotherapy (10), possibly due to ATM protein deficiency rendering leukemia cells more susceptible to cytotoxic therapy. Whether *ATM* mutations affect overall survival in the context of ASCT due to increased toxicity on the one hand and possibly reduced relapse risk on the other hand is unknown. It is therefore an important question, whether risk stratification should be different for patients harboring an *ATM* mutation and how conditioning should be performed in case of ASCT. Finally, it is unknown whether increased radiation-associated inflammation leads to a higher incidence of GVHD.

In summary, we report on a female patient with ALL and a heterozygous *ATM* mutation who experienced severe radiation-associated toxicity after conditioning for ASCT. This is the first case to suggest a genetic basis for increased radiotoxicity in a patient undergoing ASCT, although other factors

contributing to the patient's symptoms cannot definitely be ruled out. It raises the question whether *ATM* screening should be considered in patients undergoing evaluation for ASCT, particularly in those with lymphoid malignancies and excessive toxicity during prior therapies. Whether such patients should undergo distinct risk stratification and how conditioning should be performed remains to be investigated.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

BNO and THT wrote the paper. PGH, DB, UP, and RA provided images and critically revised the manuscript.

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