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Fatal Outcome Despite Full Lympho-Hematopoietic Reconstitution After Allogeneic Stem Cell Transplantation in Atypical Ataxia Telangiectasia

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Abstract Allogeneic hematopoietic stem cell transplantation (HSCT) has not been a therapeutic option in ataxia telangiectasia (AT) due to overwhelming toxicity of conditioning in the context of the global DNA repair deficiency. Furthermore HSCT is unable to cure neurological involvement of AT. We report on a Turkish child with a Hyper IgM phenotype disorder, in which clinical aspects of AT were absent and thus, AT not diagnosed. He was transplanted with a reduced toxicity, but full intensity conditioning regimen comprising treosulfan, fludarabine and ATG. The peritransplant period was uneventful and the patient was discharged at day +57. 8 months after HSCT, the patient developed hepatopathy with monoclonal gammopathy of unclear significance and died due to hepatic failure and encephalopathy at the age of 32 months. Post mortem high throughput sequencing revealed a mutation in the ATM gene.

Keywords Stem cell transplantation · primary immunodeficiency · ataxia telangiectasia · liver disease

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For decades allogeneic hematopoietic stem cell transplantation (alloHSCT) has not been a therapeutic option in ataxia telangiectasia (AT), based on the observation of overwhelming toxicity of pretransplant conditioning in the context of global DNA repair deficiency; furthermore, HSCT is unable to cure neurological involvement of AT and to correct the inherent susceptibility to cancer [1]. We report on a Turkish child of consanguineous parents with recurrent severe respiratory infections and hepatosplenomegaly. A Hyper-IgM phenotype was seen (IgM max. 3420 mg/dl; IgG, IgA absent), but CD40 and CD40L expression proved normal. Stimulated lymphocytes showed increased radiosensitivity and AFP levels were mildly elevated; thus Hyper IgM syndrome with an unknown radiosensitive underlying immunodeficiency was suspected. Due to a clinical progredient course (hepatosplenomegaly, effusions, increasing susceptibility to viral infections) the patient was transferred to our transplant unit. The spleen was partially removed, showing hypoplastic white and hyperplastic red pulp on histologic examination. As the patient was privileged to have four related HLA-identical healthy donors we quickly proceeded to related bone marrow transplantation ($6{,}8\times10^6$ TNC/kg, 9×10^6 CD34+ cells/kg) at the age of 22 months. We chose a reduced toxicity, but full intensity conditioning regimen comprising 3×12 g/m^2 treosulfan, 5×30 mg/m^2 fludarabine, and 3×20 mg/kg ATG-Fresenius, as recently reported to be effective in children with primary immunodeficiency [2]. Cyclosporine and mycophenolate mofetil were taken for GvHD prophylaxis.

After an uneventful peritransplant period he achieved prompt neutrophil (day+21) and platelet (day+17)

engraftment. GvHD (GvHD III, skin 2, liver 2, gut 0) developed on day +25 (macular rash and elevated liver enzymes, bilirubin), but was fully controlled after initiation of a prednisolone therapy. He did not suffer from severe infections and full donor chimerism (>99%) was demonstrated on day +47. The patient could be discharged at day+57 and subsequent flow cytometry analysis revealed immune reconstitution (day +64: WBC 3700/μl, CD3 1865 cells/μl, CD20 40 cells/μl). Immunoglobulin G levels were within normal ranges (494 mg/dl).

At the age of 30 months, we observed increasing IgG levels. The B cell count increased dramatically within weeks (day +187: 91 cells/μl; day +208: 857 cells/μl) and neutrophils declined (+267: 375 cells/μl). Serum protein electrophoresis revealed monoclonal gammopathy with predominant free kappa light chains (see Table I). Liver enzymes were elevated. Whole body imaging studies and bone marrow examination did not reveal any pathological findings. In particular, we found no plasma cell increase in bone marrow morphology. After detection of increasing EBV levels in peripheral blood (max. 79500 K/ml) we strongly suspected post-transplant-lymphoproliferative-disorder (PTLD) and steroids, rituximab (5×375 mg/m²/d) and cyclophosphamide (1×150 mg/m²/d) were administered. Unfortunately, despite this treatment the patient progressed to hepatic encephalopathy due to fulminant hepatic failure, and died at the age of 32 months. Histology of the liver showed a major destruction of hepatic parenchyma. Immunohistochemistry (see Fig. 1) only showed a sparse infiltration of CD3 T lymphocytes with very few CD20 B lymphocytes suggestive of virus-associated hepatitis.

In search for the underlying molecular defect leading to immunodeficiency with features of Hyper IgM syndrome, array-based sequence capture revealed a novel homozygous mutation in exon 11 (1316 T>C/439 L>P) of the ATM gene, known to be mutated in ataxia telangiectasia [3]. In a cohort of 100 AT patients 9% present with a total IgG deficiency and normal or elevated IgM levels suggestive of a class-switch-recombination defect [4]. In consistence with other published cases [5–7], mildly elevated AFP values (22 months: 98 μg/l; reference 6–23 months: <87 μg/l, >23 months: <6,2 μg/l) and increased

Table I Monoclonal gammopathy with predominant free kappa light chains revealed by serum protein electrophoresis

	Day +267 value	Reference range
IgG	3648 mg/dl	453–916
IgA	52 mg/dl	20–100
IgM	170 mg/dl	19–146
Kappa κ light chains	1120 mg/dl	200–440
Lambda λ light chains	139 mg/dl	110–240
K: λ ratio	8:1	2:1

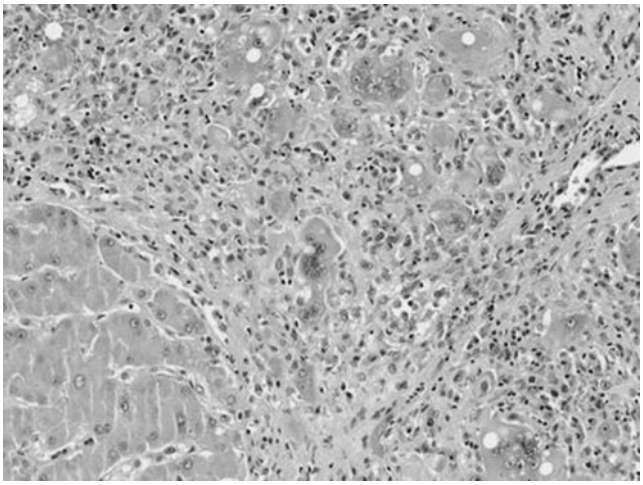

Fig. 1 Liver histology: Fulminant liver necrosis with formation of giant cells and sparse lymphocytic infiltration (predominantly CD3+ T lymphocytes as revealed by immunohistochemistry). Hepatocytes are only focally preserved. Most likely a viral etiology has to be assumed

radiosensitivity (see Fig. 2), this child represents a case of Hyper IgM phenotype in an AT patient. Typical clinical features (ataxia, telangiectasia) were absent.

The precise cause of death in this patient remains enigmatic. Post-mortem hepatic histology did not reveal prominent lymphocytic infiltrations and EBV could not be

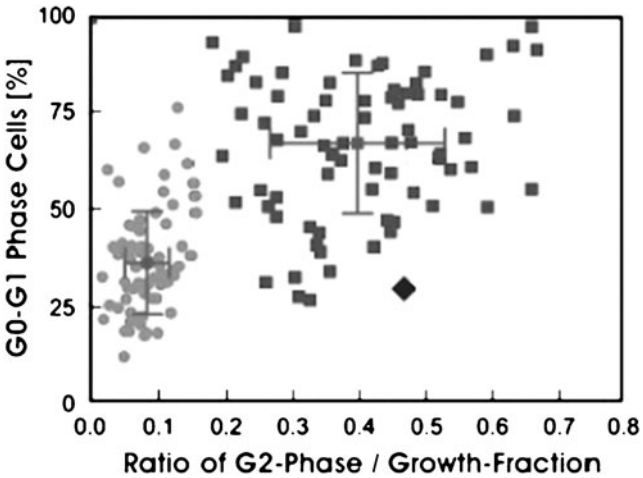

Fig. 2 Radiosensitivity assay (Professor Schindler, Insitute of Human Genetics, University of Würzburg): Resting lymphocytes of the patient were exposed to 1.5 Gy of ionizing irradiation and cultured for 72 h after PHA stimulation. Subsequent double-staining with Hoechst 33258/ethidium bromide (EB) and flow cytometry resulted in a density plot of cell cycle distribution (not shown). The G2 phase cluster, representing cells in a cell cycle arrest, is related to overall growth fraction (abscissa). The ordinate depicts the resting (G0/G1) cell fraction representing non-activated lymphocytes. The patient's culture (*diamond*) shows an increased radiosensitivity (ratio of G2 phase), indicating that the cells were not able to repair radiation-induced DNA damage, comparable to other AT patients (*squares*). Dots indicate normal healthy controls

demonstrated by immunohistochemistry. Molecular studies were not performed as they were assumed to be positive, as EBV was detectable in the peripheral blood. On the other side we observed monoclonal gammopathy with a predominance of kappa light chains, which often occurs in patients with PTLD, but also other systemic disorders (leukemia, lymphoproliferative diseases, connective tissue disorders). There are reports of EBV negative PTLD in solid organ transplants [8]; additionally, a retrospective analysis of patients with primary immunodeficiencies undergoing SCT revealed that lymphoproliferative disorders, predominantly PTLD, constituted the majority of malignancies occurring after transplantation [9]. However, histological examination did not reveal any signs of lymphoproliferation.

VOD (veno occlusive disease) is caused by conditioning regime-related hepatic toxicity. Patients suffer from jaundice, ascites and tender hepatomegaly after HSCT (mostly day +1–+40). In severe cases refractory thrombocytopenia and fluid retention in other compartments are seen. All these features were not primarily observed in our case. Classical radiological and histological findings of VOD (e.g. concentric or eccentric non-thrombotic narrowing of the lumen of small intrahepatic veins) were also not detected.

Unfortunately little is known about hepatic involvement in AT patients. Case reports show in post mortem biopsies a "variety of pathological patterns from hepatitis with periportal fibrosis to cirrhosis" [10]. In two children with AT hepatic veno-occlusive disease was observed, in one of them following chemotherapy due to T cell leukemia [10]. In ATM deficient mice it was shown that hepatocytes have an impaired survival upon genotoxic insults and an impaired ability to regenerate.

In summary, AT must be highlighted as a main differential diagnosis in addition to severe combined disorders in patients with an immunological Hyper IgM phenotype and radiosensitivity, especially in infants and young children, as typical AT features may develop often years later. Reports have shown fatal treatment due to missing diagnosis of AT [5–7]. To our knowledge this is the first published case of alloHSCT in an AT patient in the last three to four decades. In 2004, bone marrow transplantation in ATM deficient mice showed immune reconstitution and prevented the development of lymphoma [11]. As shown, the regimen with treosulfan, fludarabin and ATG shows less toxic complications and might represent an option for patients presenting with radiosensitive severe combined immunodeficiency (SCID) requiring urgent stem cell transplantation. However, it is obvious that alloHSCT should not generally be recommended in AT patients. The risk of toxic effects remains high in these patients, and though hepatic failure was not a result of early conditioning-regime associated toxicity, we cannot rule out that the outcome is linked to it. Moreover, neurologic manifestation of AT will not be cured. The final cause of death in our patient remains obscure and this outcome certainly deters us from recommending alloHSCT in AT patients.

Conflict of Interest The authors declare no conflict of interest.

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