Three cases of renal relapse after allogeneic hematopoietic stem cell transplantation for childhood akute lymphoblastic leukemia

Isolated renal relapse after allogeneic hematopoietic stem cell transplantation (alloHSCT) in children with acute lymphoblastic leukemia (ALL) is a rare condition. Generally, in ALL, the sites most frequently affected by extramedullary relapse are the central nervous system (CNS) and the testicles. Here we report on three young boys with relapsed B-precursor ALL, who underwent alloHSCT from HLA-identical siblings and suffered a histopathologically proven isolated unilateral renal relapse (two patients) or a combined renal and testicular relapse (one patient) 6, 10 and 12 months post alloHSCT. In all patients at the time of relapse bone marrow showed complete remission with complete donor hematopoiesis. They all received total body irradiation with partial shielding of the kidneys as part of their conditioning therapy, such that renal shielding could be an explanation for the observed accumulation of renal relapses. Moreover, during the past few years so called *immune privilege* has been postulated for frequent relapse sites such as the CNS, the testicles and the anterior chamber of the eye. Impaired accessability of these organs by cytotoxic T-cells (CTLs) with a reduced graft-versus-leukemia (GvL) effect after alloHSCT is based on a number of different molecular and cellular mechanisms. Similar mechanisms have been shown to be effective in the tubulointerstitial space of the kidney, rendering the kidney a potentially immune privileged site. Due to these observations we advocate sufficient treatment of the kidneys during conditioning therapy.

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Extramedullary relapse (EM relapse) of hematological malignancies following allogeneic hematopoietic stem cell transplantation (alloHSCT) is seldom reported in children but is common in adult patients with rates of EM involvement documented in 45-50% of cases.[1] In adult patient cohorts isolated or combined EM relapse after allo HSCT is associated with a better outcome than medullary relapse.[1,2] Also, EM versus medullary relapse seem to be favoured by chronic graft versus host disease (GvHD) and a long time interval between transplantation and relapse.[2] Yet, there are only few reports assessing frequency and course of EM relapse after HSCT in childhood acute lymphoblastic leukemia (ALL).

Among all children with relapsed ALL enrolled into an Europe-wide treatment protocol (ALL-REZ BFM study) since 1990, a homogenous population of 396 children was transplanted during 2nd or 3rd complete remission (CR). After HSCT an overall relapse rate of 32,6 % (n= 129) was observed. Only 10 patients (7,8%) with relapsed disease suffered from combined and 21 patients (16,3%) from isolated EM relapse (Stackelberg v., A; unpublished results).

Most isolated EM relapses after alloHSCT for ALL occur in the central nervous system (CNS) and the testicles, while relapses to other localisations are exceedingly rare. There are single reports on relapses affecting abdominal lymph nodes, bones, thoracic wall, mediastinum, orbit/ upper eyelid, retro-orbital tissue, iris, heart and breast.[3-11] To our knowledge, only one case of renal ALL recurrence after bone marrow transplantation (BMT) has been published by Nakayama in 1992.[12] Except for this single report, data are sparse. In the Center for International Blood and Marrow Transplant Research (CIBMTR) not a single case of post transplant renal relapse has been documented among a total of 3375 patients transplanted for ALL at < 21 years of age ‡. Here we delineate the clinical course of three children enrolled and treated according to the ALL-REZ BFM study who suffered an isolated relapse in the kidney 6, 10 and 12 months after matched sibling alloHSCT.

‡The data presented here are preliminary and were obtained from the Statistical Center of the Center for International Blood and Marrow Transplant Research. The analysis has not been reviewed or approved by the Advisory or Scientific Committees of the CIBMTR.

Case Reports

Patient I

Patient I was diagnosed with cALL at the age of 6 years. Due to a poor prednisone response he was treated according to the high-risk arm of the ALL-BFM 95 protocol and achieved complete remission (CR). As the initial therapy was performed at another center, abdominal sonography at the time of diagnosis is not available. 40 months after initial diagnosis he presented with an isolated epidural relapse involving the lumbosacral junction. After incomplete tumor resection the patient received four courses of postoperative chemotherapy and 18 Gray (Gy) fractionated radiation of the relapse site. This was followed in CR by alloHSCT from an HLA-identical sibling. The pretransplant conditioning regimen consisted of total body irradiation (TBI) (6×2 Gy) and etoposide/VP 16 (60 mg/kg). TBI was performed with partial shielding of the lungs and kidneys (pulmonary and renal dose = 8 Gy). For GvHD prophylaxis the patient received cyclosporine A (CSA) until day +108. Following engraftment on day +14, he consistently presented with 1% mixed chimaerism in the peripheral blood (PB) and < 1% recipient hematopoiesis in the bone marrow (BM) 3 and 12 months post HSCT. During and shortly after engraftment he suffered from acute GvHD grade 1 of the skin. The patient showed no signs of chronic GvHD.

12 months after HSCT he presented with abdominal pain. A palpable mass in the left flank was noted corresponding to a lymphoma to the left kidney with a size of 388 cm^3 on ultrasound. The initial CT scan of the kidney is shown in Figure 1. A biopsy was taken and lymphoblastic infiltration of the kidney corresponding to the known ALL was documented by histopathological and immunohistochemical examination. At the time of extramedullary relapse, no blasts were noted either in PB and BM both morphologically as well as by flow cytometry. After the 1st course of reinduction therapy according to the ALL-REZ BFM 99 pilot protocol, a reduction of the renal mass was seen by MRI. During aplasia following the 2nd course of chemotherapy the patient unfortunately developed a systemic infection and died in multiorgan failure.

Patient II

Patient II was diagnosed with B-precursor ALL at the age of 3 years and was treated according to CoALL-06-97 high risk (PB leukocyte count > 25/nL) protocol. Sonographically there was no renal enlargement as a sign for kidney involvement at the time of diagnosis. After 7 months of maintainance therapy, he suffered an early medullary relapse. Relapse therapy consisted of

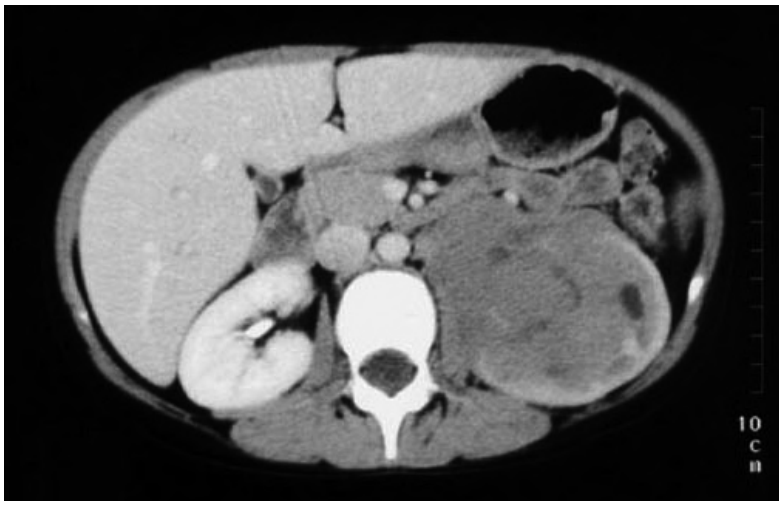

Figure 1. CT scan of the abdomen of patient I showing leukemic infiltration of the left kidney 12 months after alloHSCT.

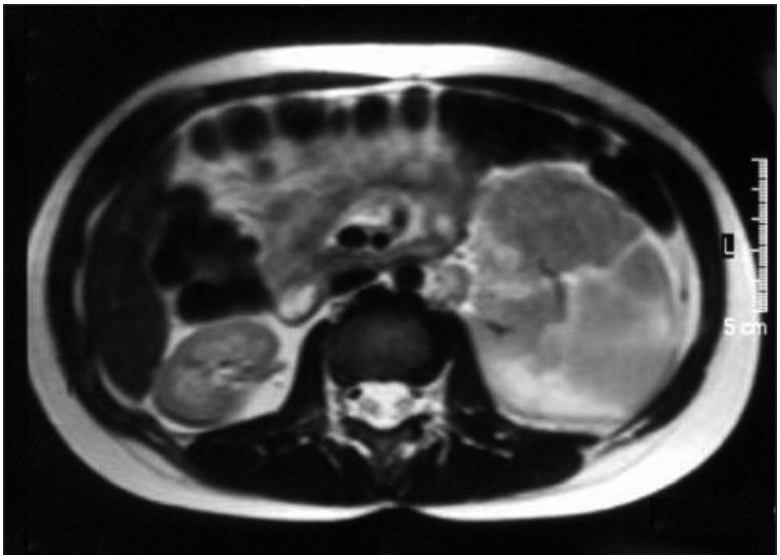

Figure 2. MRI scan of the abdomen of patient II showing leukemic infiltration of the left kidney 10 months after alloHSCT.

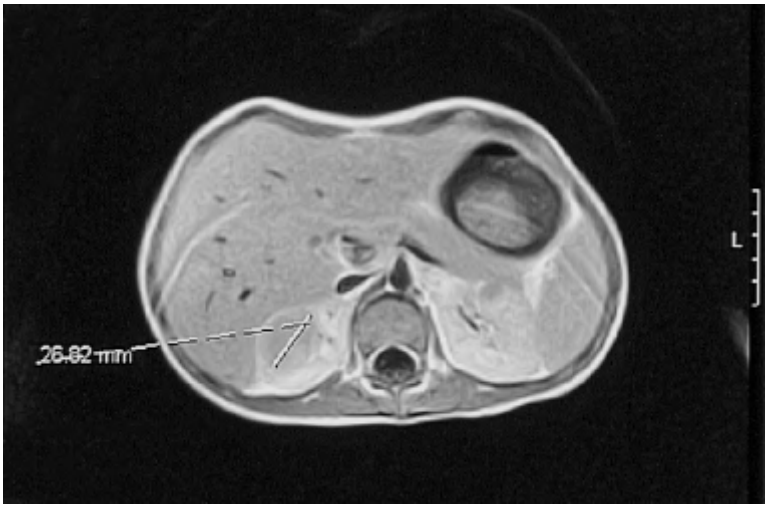

Figure 3. MRI scan of the abdomen of patient III showing leukemic infiltration of the right kidney 5 months after second alloHSCT.

chemotherapy according to ALL-REZ BFM 96 protocol (S3 arm) and consecutive alloHSCT from an HLA-identical sibling. TBI (6×2 Gy) with selective partial shielding of the lungs and kidneys as described above and etoposide/VP16 (60 mg/kg) were applied for conditioning. GvHD prophylaxis consisted of methotrexate 10 mg/mÇ on days +1, +3 and +6 and CSA until day +173. He engrafted on day +21 with concomitant grade 1 acute GvHD of the skin. Chimaerism analysis performed weekly by PCR amplification[13,14] consistently showed complete donor hematopoiesis in PB and on day +34 also in BM. During follow up no signs of chronic GvHD were documented.

Ten months after HSCT the patient presented with pain in the left flank. Ultrasound showed a mass within the left kidney suggestive of a lymphoma with a size of 235 cm^3. The corresponding MRI is shown in Figure 2. Histopathological and immunological typing of the biopsy material revealed a pathological population of B cells consistent with the known B-precursor ALL. At the time of extramedullary relapse donor chimaerism was complete both in PB and in BM and morphologically as well as immunologically the BM showed CR. Reinduction chemotherapy was performed according to the ALL-REZ BFM 99 pilot protocol. After 3 cycles of chemotherapy the lymphoma was no longer detectable by ultrasound. In view of potentially active minimal residual disease, complementary immunotherapy consisting of 3 cycles of simultaneous dendritic cell vaccination (DCV) and low dose donor leukocyte infusion (DLI) from the younger sibling donor was applied in monthly intervals. For dendritic cell vaccination peripheral blood monocytes were differentiated to dendritic cells *in vitro* and incubated with patient's tumor cell lysate in order to stimulate an antigen specific T-cell response after infusion *in vivo*. After the last vaccination after a total of 6 months free of detectable disease since the relapse the lymphoma in the left kidney recurred together with an additional lymphoma in the right kidney. After 2 nd reinduction with daunorubicine and cyclophosphamide remission was sustained by fractionated maintainance chemotherapy with VP16, trophosphamide, amsacrine and dexamethasone for 7 months when the patient suffered a CNS relapse with blasts detected in the cerebrospinal fluid and the anterior chamber of the eye as well as intraabdominal spreading of the lymphoma. Intrathecal triple chemotherapy, orbital radiation and dexamethasone could again induce remission. Subsequently, a 2 nd immunomodulatory course with alternating cycles of DCV/DLI and lymphokine activated killer cells was initiated. One month after the last block of immunotherapy the renal lymphoma progressed bilaterally and the patient finally developed a 2nd marrow relapse. CR was achieved again with additional chemotherapy consisting of daunorubicine, vincristine, PEG-Asparaginase and dexamethasone. Given the frequent relapses despite immunotherapy, in order to increase alloreactivity the patient then underwent 2 nd alloHSCT from a matched unrelated donor 33 months after 1st alloHSCT. Engraftment and the early post transplant course were uneventful. Unfortunately, 5 months after the 2nd HSCT a new isolated extramedullary relapse progressing from an abdominal lymph node was diagnosed. Medullary involvement was noted 2 months later and the patient died from disease progression 8 months post 2nd transplantation.

Patient III

Patient III was diagnosed with cALL at the age of 5 years. The initial sonography showed a normal size and structure of both kidneys. After initial treatment according to the high risk arm (PB leukocyte count > 25/nL) of the CoALL 06/97 protocol he suffered an early combined relapse affecting the testicles and the bone marrow with the TEL/AML 1 translocation as marker for minimal residual disease (MRD). Because of persisting evidence of blasts in BM during ensuing chemotherapy according to the ALL-REZ BFM 2002 protocol, the patient underwent alloHSCT from an HLA-identical sister. The conditioning regimen consisted of TBI (6×2 Gy) with partial shielding of the lungs and kidneys as described above, local irradiation of the testicles (total dose 18 Gy) and VP 16 (60 mg/kg). After HSCT, mixed chimaerism with 1-5% autologous cells was documented repeatedly without evidence of blasts neither in PB nor BM. TEL/AML 1 was detectable in BM on day +46 post alloHSCT. After early cessation of the immunosuppressive therapy with CSA on day +51, complete donor chimaerism was reestablished in BM (by day +71) and PB (by day + 104). On day +71 TEL/AML 1 was also negative in BM.

11 months after HSCT the patient presented with pain in the right hip and diaphysis of the femur. Ultrasonography and MRI showed an effusion of the hip joint and several lesions in the pelvic bones suggestive of leukemic infiltrations which was subsequently proven by cytological analysis of the effusion aspirate. The BM showed 13% blast cell infiltration. Further chemotherapy according to ALL-REZ BFM could again induce remission. The patient then underwent 2nd alloHSCT from another HLA-identical sister as the former matched sibling donor was no longer available due to pregnancy. Busulfan (4×4 mg/kg) and cyclophosphamide (2×60 mg/kg) were used for myeloablation. Grade 1 acute GvHD of the skin resolved after intensification of immunosuppressive therapy with CSA. On day +106 TEL/AML 1 became detectable again in BM. Chimaerism analysis showed complete donor hematopoiesis in PB and BM with no evidence of blasts both morphologically as well as by flow cytometry.

During an episode of systemic bacterial infection with Pseudomonas aeruginosa 6 months after HSCT an abdominal ultrasonography accidentally revealed a tumor of the right kidney with a volume of 24 cm^3 highly suspicious of leukemic infiltration. The MRI of the right kidney is shown in Figure 3. The differential diagnosis of a bacterial infiltration could be excluded by normal urinalysis and persistence of the tumor after clinical and laboratory recovery from infection. In addition, a swelling of the left testicle was observed. The ultrasonographical findings were consistent with leukemic infiltration of both testicles, which lead to bilateral orchidectomy. Pathological examination confirmed the diagnosis of ALL infiltration. Considering the preexisting impairment of renal function after two HSCTs, nephrectomy as well as therapeutical irradiation of the affected kidney could not be performed without taking the risk of severe renal insufficiency. Alternating cycles of chemotherapy and DLI led to no significant change in size of the lymphoma. Despite intensifying chemotherapy, 10 and 13 month after the renal relapse leukemic infiltration of the proximal tibia and fibula as well as of the right femur with a big extraossary component occurred. Given the patient's increasing toxicity-related morbidity the situation is now regarded as palliative. BM examinations 5, 6, 7, 8, 10, 12, and 14 months after HSCT showed CR morphologically, by flow cytometry and by complete donor chimaerism. TEL/AML was inconstantly detectable in BM. Monthly chimaerism analysis in PB still shows complete donor chimaerism 24 months after 2nd alloHSCT.

Discussion

An update of the experience of the Europe-wide treatment protocol ALL-REZ BFM showed that isolated extramedullary relapse occurred in 21 of 396 children who received alloHSCT as relapse treatment (Stackelberg v., A; unpublished data). We here report on three of these patients, who underwent alloHSCT from an HLA-identical sibling at our center and subsequently suffered a renal relapse. The occurrence of three cases of renal relapse was striking and gives reason to discuss possible underlying mechanisms.

Interestingly, all of our patients received TBI and etoposide as conditioning regimen (patient III prior to his 1st HSCT). The total TBI dose of 12 Gy was delivered in 6 fractions of 2 Gy twice daily over three consecutive days. TBI was performed in anterior-posterior technique with partial shielding of the kidneys by customized dorsal shielding blocks resulting in a total dose of 8 Gy to the kidneys as adopted by our centre in 1998 in order to prevent radiogenic nephropathy and to reduce the cumulative renal damage resulting from radiation and post transplant immunosuppression with CSA. The literature provides only little and contradictory data concerning the necessity and efficacy of renal shielding during TBI. Borg et al. reported on one case of radiation nephritis in 59 adults 24 months after TBI for BMT with a dose of 12 Gy at 2 Gy fractions,[15] whereas Lawton et al. documented a rate of post BMT nephritis of 14% in adults 30 months after TBI with a 12 Gy renal dose.[16] They describe a significant decrease in post BMT nephropathy in adults with increasing shielding of the kidney and therefore recommend renal shielding when doses higher than 10 Gy are applied. In a comparable study including adults and children Miralbell et al. found that renal dysfunction is significantly related to the delivered TBI dose and recommend renal shielding if doses greater than 12 Gy are applied.[17] Also Igaki *et al.* report a reduction of the renal dysfunction rate two years post BMT from 21,5% to 0% by constraining the renal dose from 12 to 10 Gy in a cohort of 109 leukemia patients between 5 and 54 years of age.[18] On the contrary, in a recent prospective study including 71 adult patients that received TBI for various hematologic malignancies, Miralbell et. al found a higher rate of early post BMT renal dysfunction in patients with partial shielding of the kidneys to 10 Gy compared with the full TBI dose of 12 Gy.[19] There are no data about the incidence and prevention of radiation nephropathy in a pure pediatric patient population. Given the available data, the necessity of renal shielding to 8 Gy has to be put into question and even a dose reduction to 10 Gy has to be considered controversially. Between 1989 and 1997 28 ALL patients at our center received TBI (12 Gy) without renal shielding prior to alloHSCT. Among the 8 post transplant relapses in this patient group there was no case of renal relapse. Of the 30 ALL patients transplanted after initiation of the renal shielding in 1998, with reduced radiation dose to the kidneys (8 Gy), 9 patients suffered a relapse among which we observed the three reported renal relapses (33,3 % of overall relapses). Thus, renal shielding could be an explanation for the observed accumulation of renal relapses in our cohort. Due to this observation we abandoned the technique of renal shielding in patients with ALL at our center in January 2004. Among the eight ALL patients which received TBI without renal shielding since then, one bone marrow relapse was observed so far. Differences in post BMT renal function between both groups have not been evaluated systematically.

Furthermore, the selective involvement of extramedullary sites in the three reported cases seems remarkable. The presence of GvHD has been shown to favour EM relapse over medullary relapse.[2] In our patients only mild acute and no signs of chronic GvHD were observed prior to nor at the time of EM relapse. They all received standard GvHD prophylaxis with CSA +/- MTX. However, in two patient cohorts analyzed at our center that either received intensified GvHD prophylaxis with addition of a CD25 murine monoclonal antibody after alloHSCT from a matched unrelated donor or a cord blood transplantation that is expected to be associated with a lower risk for GvHD no cases of EM relapse of ALL or AML among the documented relapses[20, 21]have been observed.

Patient I died from therapy-related toxicity before the efficacy of the used therapeutic strategy on the further course of the disease could be assessed. In Patient II marrow remission could be sustained for 21 months by a combination of chemotherapy and immunotherapy. The extramedullary disease initially responded well to systemic chemotherapy. But despite ensuing immunotherapy the remission was of short duration. The 2nd relapse after 1st HSCT affected both kidneys. The leukaemia then reoccurred in other extramedullary sites such as the CNS and the anterior chamber of the eye before affecting the BM. In patient III the disease progresses with involvement of further extramedullary sites despite chemotherapy and DLI still sparing the marrow.

Efficacy of HSCT is attributed to the cytotoxicity of the conditioning regimen and to the GVL-effect of immunoreactive donor cells. Cytotoxicity is limited by the blasts' spontaneous and therapy-dependent resistance to chemo- and radiotherapy. The observed selective involvement of extramedullary sites preceeding marrow relapse for 21 months in patient II and sparing the marrow in patient III for now 24 months suggests either a high affinity of the blasts to extramedullary sites due to specific biological features such as receptors or adhesion molecules. Supporting this hypothesis, it has been shown that high expression of CXCR4, a chemokine receptor important for extravasation and trafficking of lymphocytes, on blast cells predicts extramedullary organ involvement in childhood ALL.[22]

Another explanation would be a common predisposition of the affected organs to leukemic invasion in terms of immune privilege leading to a reduced GVL-effect as well as a reduced efficacy of GVL-enhancing immunotherapy in the affected extramedullary sites as compared to the lymphohematopoietic system including BM.

So called *sanctuary sites*, that are protected from systemic chemotherapy by biological blood barriers (CNS) or distinct growth conditions (lower temperature, testicles) are well described phenomenons. In analogy to the *sanctuary sites for chemotherapy sanctuary sites for the GVL-effect* or *immune privileged sites* that are not sufficiently accessible to cytotoxic T-lymphocytes (CTLs) have been discussed in the context of extramedullary relapse.[23,24] This hypothesis is supported by a growing number of reports of EM relapse after successfully applied DLI for hematological relapse of AML, ALL and myeloma.[25,29] Schäfer et al. described two cases of ALL-EM relapse in the breast and pleural fluid after HSCT where no donor lymphocytes could be detected at the relapse site by chimaerism analysis.[8] Berthou *et al.* report on a 3 year old boy who received DLI for early BM relapse of ALL after HSCT from his HLA-identical brother.[28] The E2A/PBX1 fusion transcript used as molecular marker was still detectable in BM in 3rd CR after relapse chemotherapy.

The signal disappeared 6 months after application of DLI. After another six months bilateral kidney tumors developed, containing E2A/PBX1 transcript positive lymphocytes. Concomitantly, E2A/PBX1 transcript was found in PB and BM despite normal cytological analysis. Sato et al. reported on a boy with ALL who presented with acute renal failure due to leukemic infiltration at onset and who suffered repeated extramedullary relapses to the CNS, testicles and pancreas despite chemotherapy and haploidentical BMT.[30]

The term *immune privileged site* was originally used in the field of transplant immunology to describe sites, where allo-transplants are protected from the effect of antigen-specific immune effectors. Various structures of the eye (cornea, anterior chamber, subretinal space, vitreous corpus), the CNS, the testicles, the ovaries, the adrenal cortex, a pregnant uterus and hair follicles are considered to be immune privileged in that sense.[31] Several of the mentioned sites (anterior chamber of the eye, CNS, testis) were as well affected in our patients II and III.

Among the best investigated mechanisms leading to peripheral immunological tolerance are the sequestration of CD8+ cells by tissue barriers, low density expression of MHC class I and II- molecules and an increased CD95-ligand (fas-ligand) induced apoptosis of CTLs.[32] Furthermore, anergy induction and active suppression of antigen-reactive T-cells have been shown to be involved in creating immunological tolerance.[31] The status of immune privilege has also been proposed for the tubulointerstitium of the kidney given its low density of MHC-I, CD95-ligand mediated apoptosis of infiltrating CTLs and the tubular basement membrane acting as tissue barrier.[33-36] Other reports suggest that in the kidneys additional mechanisms distinct from CD95 signalling play a role in creating immunological tolerance.[37] Our cases may provide further evidence of reduced CTL-mediated immune effects in the kidney.

Further data will be needed to give treatment recommendations or to assess strategies to prevent extramedullary relapse after HSCT. However, the potential immune privilege of the kidneys may be another reason to advocate sufficient treatment of the kidneys during conditioning therapy.

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