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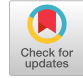
Research Paper

Intestinal Adenovirus Shedding Before Allogeneic Stem Cell Transplantation Is a Risk Factor for Invasive Infection Post-transplant



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ABSTRACT

Human adenoviruses (HAdV) are a major cause of morbidity and mortality in pediatric human stem cell transplant (HSCT) recipients. Our previous studies identified the gastrointestinal tract as a site of HAdV persistence, but the role of intestinal virus shedding pre-transplant for the risk of ensuing invasive infection has not been entirely elucidated. Molecular HAdV monitoring of serial stool samples using RQ-PCR was performed in 304 children undergoing allogeneic HSCT. Analysis of stool and peripheral blood specimens was performed pre-transplant and at short intervals until day 100 post-HSCT. The virus was detected in the stool of 129 patients (42%), and 42 tested positive already before HSCT. The patients displaying HAdV shedding pre-transplant showed a significantly earlier increase of intestinal HAdV levels above the critical threshold associated with high risk of invasive infection ($p < 0.01$). In this subset of patients, the occurrence of invasive infection characterized by viremia was significantly higher than in patients without HAdV shedding before HSCT (33% vs 7%; $p < 0.0001$). The data demonstrate that intestinal HAdV shedding before HSCT confers a greatly increased risk for invasive infection and disseminated disease post-transplant, and highlights the need for timely HAdV monitoring and pre-emptive therapeutic considerations in HSCT recipients.

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1. Introduction

Human adenovirus (HAdV) infections are associated with life-threatening complications in immunocompromised individuals including particularly children undergoing human allogeneic stem cell transplantation (HSCT) (Feghoul et al., 2015; Lion et al., 2010; Mynarek et al., 2014; van Tol et al., 2005). In this setting, viral reactivation is reportedly more prevalent than de-novo infection (Veltrop-Duits et al., 2011). Primary infections in immunocompetent individuals occur most commonly in early childhood, often without any clinical symptoms, but HAdV can subsequently persist in tonsillar and adenoidal lymphocytes as well as in the gastrointestinal (GI) tract (Roy et al., 2011; Garnett et al., 2002). The role of the GI-tract as a sanctuary for HAdV persistence has been discussed for decades, because shedding of the virus into stool was found in immunocompetent individuals even without any evidence of disease (Adrian et al., 1988). In HSCT recipients, increasing HAdV loads in serial stool specimens have been documented during the post-transplant period prior to invasive infection, supporting the notion of intestinal virus persistence and reactivation (Feghoul et al., 2015; Lion et al., 2010; Jeulin et al., 2011). Our recent study in immunocompetent pediatric patients revealed HAdV persistence in mucosal lymphoid cells in the GI-tract, with particularly high prevalence in the ileum, whereas in HSCT recipients with HAdV reactivation post-transplant, an enormous virus density has been documented in intestinal epithelial cells (Kosulin et al., 2016a). These observations revealed that intestinal lymphocytes apparently serve as a major site of HAdV persistence, but epithelial cells in the GI-tract are exploited for massive virus production (Kosulin et al., 2016a). The highly productive virus replication in epithelial cells explains the rapidly expanding virus numbers in stool specimens of HSCT recipients prior to the onset of viremia and disseminated disease (Feghoul et al., 2015; Lion et al., 2010; Mynarek et al., 2014; Berciaud et al., 2012).

According to the current ECIL (European Conference of Infections in Leukemia) guidelines, peripheral blood (PB) samples are recommended as the primary material for HAdV screening in HSCT recipients (Matthes-Martin et al., 2012). There is, however, increasing evidence reported by different centers that rapidly increasing HAdV DNA copy numbers exceeding defined threshold levels in serial stool samples herald invasive infection days to weeks before the virus becomes

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detectable in PB (Feghoul et al., 2015; Lion et al., 2010; Mynarek et al., 2014; Jeulin et al., 2011). The monitoring of HAdV DNA copy numbers in stool could therefore serve as a basis for timely initiation of pre-emptive therapy, in attempts to prevent invasive infection. Disseminated HAdV-mediated disease is associated with dismal outcome, partly because delayed onset of therapy by current treatment options often fails to control adenovirus-related complications (Feuchtinger et al., 2006; Lion, 2014). Since HAdV persistence in the GI-tract of immunocompetent children and post-transplant reactivation of the virus in pediatric patients were shown to occur at similar frequencies (Kosulin et al., 2016a), we hypothesized that detection of HAdV shedding into stool before HSCT may provide an early marker for the risk of viremia and HAdV-related disease post-transplant. To address this notion, the present study involving a large cohort of pediatric HSCT recipients was performed.

2. Material and Methods

2.1. Patients

The samples studied included serial stool and peripheral blood specimens from 304 consecutive patients (Table 1) who underwent allogeneic HSCT at the St. Anna Children's Hospital, Vienna, Austria, between 2000 and 2015. The samples were collected as part of the routine HAdV screening starting before conditioning, and subsequently at seven-day intervals until day +100 post-transplant. Only patients with available stool samples before HSCT were included. Since the present study was based exclusively on the analysis of results obtained by routine diagnostic testing, for which written informed consent had been obtained from each patient and/or the parents, additional approval by the ethics committee was not required to ensure that the study is carried out in agreement with the Helsinki-Declaration. Patients with HAdV viremia received antiviral therapy with cidofovir, sometimes in combination with ribavirin, in the presence of HAdV species C. In cases of failed response to antivirals and absence of HAdV-specific T-cells, adoptive T-cell transfer with donor-derived HAdV-specific T cells was offered (Lion et al., 2010; Lion, 2014).

Table 1
Patient and transplant characteristics ($n = 304$).

Median age (years)	9.3 (range:0.2–28.0)	%
Underlying disease		
Acute leukemia	134	44
Chronic myeloid leukemia	23	8
Myelodysplastic syndrome	23	8
Lymphoma	19	6
Solid tumor	19	6
Severe aplastic anemia	13	4
Hemoglobinopathy	14	4.6
Fanconi's anemia	9	3
Immunodeficiency	41	13.5
Metabolic disorders	8	2.6
Idiopathic hypereosinophilia	1	0.3
Donor		
Matched sibling donor	92	30
Matched family donor	3	1
Mismatched family donor	35	12
Unrelated donor	174	57
Graft		
Bone marrow	219	72
Unmanipulated peripheral stem cells cells SC	63	20.7
T cell-depleted peripheral stem cells	17	5.6
Cord blood	5	1.7
GvHD		
aGvHD ≥ grade 2	63	21
aGvHD < grade 2	241	79
Lymphocyte reconstitution		
$CD3^+ > 300$ cells/μl	175	58
$CD3^+ < 300$ cells/μl	129	42

2.2. Isolation of Viral DNA

The QIAamp DNA Mini Kit (Qiagen) was employed for isolation of DNA from peripheral blood (PB). Extraction of DNA from stool specimens was performed by the QIAamp DNA Stool Mini Kit (Qiagen) according to the manufacturer's recommendations.

2.3. RQ-PCR Analysis

A broad-spectrum real-time quantitative (RQ)-PCR assay including 50 cycles of amplification was employed for HAdV-screening using the ABI 7500 Sequence Detectors (Thermo Fisher Scientific, Waltham, MA, USA), as described previously (Ebner et al., 2005; Kosulin et al., 2016b). Specimens that tested positive for HAdV by the broad-spectrum RQ-PCR screening assay were analyzed by PCR tests specifically identifying individual HAdV species (Lion et al., 2003). The detection limit of these tests is 10 virus DNA copies per PCR reaction, and specimens displaying ≥ 5x10E2 DNA copies/g stool by the assay employed were regarded as positive. Similarly, adenoviremia was defined as HAdV detectable in peripheral blood at levels ≥ 5x10E2 DNA copies/ml. In contrast to blood specimens where the virus concentration is indicated as copy number per ml blood, in stool it is denoted as virus copy number per gram of the sample because the presence of high levels of free lytic viruses cannot be excluded.

2.4. Statistics

Fisher's exact test or exact chi-square test were used to analyze the correlation between adenoviremia until day 100 after HSCT and HAdV positivity in stool before and after HSCT, considering other treatment- and patient-related characteristics including donor type, graft source, graft-versus-host disease (GvHD) of all grades, and T-cell reconstitution. Multivariate analysis was done using logistic regression with Firth correction. Odds ratios (OR) with the respective 95% confidence intervals (CI) are indicated in addition to *p*-values in univariate and multivariate analysis. Odds ratios are not defined in the absence of adenoviremia in one group. In this instance, only the lower limit of the 95% CI for the OR is indicated. In 262 of 304 patients, a single transplantation was performed, while two or three consecutive transplantations were done in 37 of 304 and 8 of 304 patients, respectively. The variables were assessed considering the first transplantations only (Table 2). All indicated *p*-values are two sided, and values ≤ 0.05 were considered significant.

3. Results

3.1. Onset of HAdV Shedding Into Stool and Post-transplant Kinetics of Intestinal Virus Levels

Pan-adenoviral RQ-PCR screening of serial stool specimens revealed positive results in 129 of 304 (42%) pediatric HSCT patients analyzed. Intestinal shedding of the virus was detected already prior to transplantation in 42 individuals, corresponding to 14% of the entire cohort ($n = 304$), while 87 patients revealed first HAdV positive test results in stool only after transplantation. In the majority of patients within the latter subset ($n = 74$), HAdV was detected within 56 days post-transplant, including 32 patients with first virus detection within 14 days, 23 between 15 and 28 days, 10 between 29 and 42 days, and 9 between 43 and 56 days after transplantation, respectively (Fig. 1A). Only 13 patients showed first HAdV positivity in stool beyond day 56 post-transplant.

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