Pre-Transplant Screening for Latent Adenovirus in Donors and Recipients

Gabriella Piatti[*, 1,2]

[1] *Department of Surgical and Diagnostic Sciences, Section of Microbiology, University of Genoa, Italy*
[2] *Division of Microbiology, San Martino Hospital, Genoa, Italy*

Abstract: Human adenoviruses are frequent cause of slight self-limiting infections in immune competent subjects, while causing life-threatening and disseminated diseases in immunocompromised patients, particularly in the subjects affected by acquired immunodeficiency syndrome and in bone marrow and organ transplant recipients. Here, infections interest lungs, liver, encephalon, heart, kidney and gastro enteric tract. To date, human adenoviruses comprise 51 serotypes grouped into seven species, among which species C especially possesses the capability to persist in infected tissues. From numerous works, it emerges that in the recipient, because of loss of immune-competence, both primary infection, *via* the graft or from the environment, and reactivated endogenous viruses can be responsible for transplantation related adenovirus disease. The transplants management should include the evaluation of anti-adenovirus pre-transplant screening similar to that concerning cytomegalovirus. The serological screening on cytomegalovirus immunity is currently performed to prevent viral reactivation from grafts and recipient, the viral spread and dissemination to different organs and apparatus, and potentially lethal outcome.

Keywords: Adenovirus, antibodies, latency, reactivation, real-time polymerase chain reaction, screening, serostatus, transplantation.

INTRODUCTION

Human adenovirus (HAdV) infections, frequent in children since they are naïve hosts, are common in all age groups of the population, and are generally asymptomatic or slight self-limiting in the immune competent subjects, where they present variable symptomatology and different localizations, *i.e.*, ocular, cardiac, respiratory and gastro-intestinal. Despite their usual weak pathogenicity, HAdVs can cause severe affections, requiring hospitalization, such as acute respiratory diseases (ARDs) and intestinal lymphoid hyperplasia up to intussusception. In immunocompromised patients, particularly in the subjects suffering from acquired immunodeficiency syndrome (AIDS) and in allogenic hematopoietic stem cells (HSC) and solid organ transplant recipients, HAdV often cause life-threatening and disseminated infections, named transplantation related adenovirus disease [1]. In these subjects, adenoviruses are responsible for a broad range of evident infections, affecting bloodstream, lungs, liver, encephalon, heart, kidney, bladder and gastro enteric tract, singly or together.

To date, 51 distinct HAdV serotypes and numerous "types" are identified and grouped within seven species (A-G) defined through genomic criteria. Specific anti-adenovirus neutralizing antibodies recognize single species, while those recognizing the exon protein capsid are common to all species [2]. Different adenoviral serotypes possess different biological and pathogenetic properties, such as the oncogenic potential, detectable on *in vitro* and *in vivo* rodent's models, the spectrum of virus-host interactions and associated diseases. Since 1958, human adenoviruses are known to establish persistent and latent infections, both in lymphatic tissue and in solid organs, like kidney and liver [3]. Adenoviruses belonging to species C (adenovirus type 1, 2, 5, 6) are the most ascertained to remain in infected organisms and the most commonly encountered in affected patients, especially in children under five. It is likely that the

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* Address correspondence to this author at the Department of Surgical and Diagnostic Sciences, Section of Microbiology, University of Genoa, Italy; Tel: 39-320 4207437; 39-010 3537658; E-mail: piatti@unige.it

various features and presentations of HAdV, which depend on the infecting serotype, would occur both in immune-competent and in immunocompromised hosts [4, 5].

In the last thirty years, the number of transplanted subjects and people suffering from AIDS enormously increased and so the importance of HAdV and other latent viruses. Among these, the most relevant are those belonging to herpes family, *i.e.*, Cytomegalovirus (CMV), Epstein-Barr (EBV), Herpes Simplex (HSV), Human Herpesvirus 6 (HHV6) and Varicella-Zoster (VZV) viruses [1]. Nevertheless, the pre-transplant protocols, which include the serological screening in donors and recipients for all Herpes viruses, do not include that for Human Adenoviruses.

Many investigations on transplantation related adenovirus disease have looked at several clinical variables, such as age of recipient and donor, kind of transplant, *i.e.*, bone marrow or solid organs, preparatory regimen and primary disease, to summarize the common characteristics of the infection. Nowadays, it is known that the rate of adenovirus infection, the severity of disease and the incidence of mortality broadly vary, mostly depending on age of patients and kind of graft. The highest prevalence is in fact among the pediatric population transplanted with hematopoietic stem cells, while the lowest one is among adults transplanted with solid organs. In this second cluster of patients, the adenoviral infection usually occurs in the graft, often leading to transplant failure and organ loss [5 - 7].

However, as effectively asserted by Chakrabarti, not enough is understood regarding the specific contribution of primary infection, which can take place *via* the graft or environment, and the precise contribution of the reactivation of endogenous viruses [8 - 10]. For this reason, specific strategies to provide a correct prevention are quite missing.

KNOWLEDGE ON CMV DISEASE TRANSPLANT RELATED, AND MANAGEMENT

As previously mentioned, serological assays towards the Herpes virus family is included in pre-transplant protocols, and the relative data became more and more numerous and useful over time. Particularly, those results concerning the cytomegalovirus serostatus, collected in homogenous groups of patients, allowed to achieve a deep knowledge of the different pathways of CMV disease. The consequent preventive strategies have had a significant impact in reducing mortality over the past two decades. Another example of usefulness of serology preventive emerges from the results about EBV. The relative data, in fact, led to the discovery of the Epstein-Barr virus-associated post-transplantation lymphoproliferative disease and to the awareness of the risk associated with the transplantation procedure [9, 11].

In 2010, thanks to the analysis of CMV serostatus, George and colleagues stated that the highest risk of cytomegalovirus infection in adults was due to hematopoietic stem cell transplantation (SCT) whose recipient was positive. The lowest risk was related to CMV naïve condition of both donor and recipient, and the intermediate one was related to the negative recipient, even in the case of positive donor [12]. These finding highlighted the negligible importance of primary infections and the dramatic role of endogenous reactivations in adults for the onset of CMV infections related to stem cells transplant.

Kulberg-Lindh and colleagues, to study in children the viral opportunistic infections SCT related, retrospectively analyzed serum samples by quantitative Real-time polymerase chain reaction (RT-PCR) detection of CMV, EBV, HHV6 and HAdV DNA during the first 6-12 months after the transplant, investigated the specific serostatus prior to transplant and clinical variables. Data on DNAemia, which occurs in 47% for CMV, in 45% for EBV, in 28% for HHV6 and in 28% for HAdV, and increased to high levels in the three lethal infectious outcomes, allowed distinguishing significant infections. The serum positivity for CMV immunoglobulin G in either recipient or donor, other than the total body irradiation procedure and the anti-thymocyte globulin conditioning, indicated those patients who needed to be closely followed and treated with preventive therapy [13]. Hiwarkar and colleagues, analyzing the impact of viral reactivation in pediatric SCT recipients, reported that CMV and HAdV reactivation was the major risk factor for mortality following transplant [14]. However, the authors considered the pre-transplant CMV and EBV seropositivity in donors and recipients as the first choice of investigation. On the contrary, they assessed the presence of adenoviruses through the use of RT-PCR assay on recipient's naso-pharyngeal aspirate and stool. The evaluation of HAdV presence was thus restricted to pre-existing viruses from very recent or acute phases of infection, in a few tracts of organism and only in recipients, wasting any detection of adenovirus during latency, in any tract of body and in donors.

KNOWLEDGE ON TRANSPLANTATION RELATED ADENOVIRUS DISEASE, MANAGEMENT AND LIMITS

Currently, the pre-hematopoietic cell transplant protocol does not include the evaluation of anti-adenovirus

serostatus, since it is considered not useful because of the existence of many different serotypes and because of the little knowledge about the diagnostic efficiency of cross-reactive immunity. On the other hand, the authors of protocol affirm that cellular immune responses, cross-reactive across various serotypes, likely provide a long-term protection against the adenoviral reactivation and make serious adenovirus infections in adults uncommon [15]. These considerations led to a stratification of the risk of adenoviral disease that only concerns a generic evaluation of kind of graft and preparatory regimen, and that misses the possibility to discover subjects at specific risk of HAdV reactivation.

The management of HAdV infections related to SCT currently implies great efforts and very high coasts to monitor HAdV viremia early after transplant, like suggested in the scheme by Sive and colleagues. The scheme proposes weekly PCR on blood, and stools or nasopharyngeal samples in the case of symptoms, until day 100 [16]. This protocol is not a definitive strategy against HAdV infection, but is actually useful to early detect the disease, allowing both preventive treatment and immediate therapy, possibly preventing disease severity. The protocol fits as well with the routine weekly PCR screening for CMV and EBV [17].

Nevertheless, it is evident that the use of RT-PCR, nowadays the most suitable molecular technique for early monitoring of viral presence, can just allow the tailoring of immune-suppression [6, 18]. Unlike the treatment for CMV, no established therapy against adenovirus infections does exist and the therapeutic options are currently not satisfying. In fact, the clearance of HAdV and a definitive cure require adequate immune reconstitution after HSCT, despite the preemptive and therapeutic treatment with Cidofovir, characterized by relevant toxicity [6, 8, 19].

In 2011, Veltrop-Duits and colleagues evaluated the pre-existing HAdV serostatus in children recipients, to predict viral reactivations after hematopoietic SCT, and the presence of viral DNA in graft material, measured by PCR, to investigate as well the possible HAdV transmission from donor to recipient [20]. High pre-transplant titers of serotype specific neutralizing antibodies against HAdV appeared to predispose to infections with the same serotype after transplant, instead of protecting from it. These results, explainable by the decreased or disappeared immunity due to the preparatory regimen, contradict the statements in the pre-hematopoietic cell transplant protocol [15] about the long-term protection against HAdV reactivation. These data also suggest that reactivated endogenous viruses rather than primary infections would be the major pathway of adenoviral infection, like mentioned for CMV disease in the work by George [12]. A significant risk for adenoviral reactivation and dissemination also emerged from data about HAdV DNA presence, detected prior to SCT in feces or nasopharyngeal aspirates of pediatric recipients [18, 21]. In a previous investigation, instead, positive donor's serostatus appeared as very important risk for HAdV infection in recipients, thus suggesting the contagious with the graft [22].

Discrepancies between different studies show how complex the problem of transplant related adenovirus infection and the need to get more information. Moreover, in the opinion of Sive and other authors, also the true incidence and the clinical significance of HAdV DNA presence in the blood, as well as the viremic titer, remain unclear because of the wide variation in the study populations and in the methodology [16, 23].

Clinicians usually perform serological tests to obtain indirect diagnosis of viral infections, but the presence of specific antibodies is especially the evidence of specific protection against acute self-limiting viral infections, such as flu and hepatitis A. Among cohorts of people where immune-competence does persist, such as children affected by cystic fibrosis and military recruits, they turned out to be protected against HAdV infection by the presence of specific neutralizing antibodies [20]. Data on serostatus are of scarce utility if the antibodies production gets weak, such as after transplant when the frequent use of blood transfusions and intravenous immunoglobulin also limit the significance [13]. Differently, when performed prior to transplant, the seropositivity towards persistent and latent viruses should represent evidence for their possible presence and for possible reactivation, which could occur after immunosuppression.

INTERPRETATION OF ANTI-CMV SEROLOGICAL ASSAY AND CLINICAL USE

As already mentioned, several authors consider HAdV serostatus of recipients and donors of limited value because most individuals was in contact with one or more serotypes, while diagnostic tests usually detect generic HAdV antibodies, not type-specific [15, 20, 22, 24]. At the same, however, the immunological plurality of viral strains could also diminish the utility of serological screening for the transplant related CMV disease. In fact, the cytomegalovirus serostatus is commonly valuated with commercial enzyme-linked immunosorbent assay (ELISA) kits, which use entire CMV-infected cells as antigens and do not allow distinguishing between antibodies against different strains. A not routine, strain-specific seroepidemiology towards the conserved CMV antigen domain 2 (AD2) epitope of glycoprotein B (gB) and towards the not conserved glycoprotein H (gH) allowed observing the protection from CMV reinfection in

renal transplant in patients CMV-gH antibody matched, but not in those CMV-gH antibodies mismatched [25]. The mismatching of gH serotypes was associated with CMV disease after renal transplantation and with low level of neutralizing antibodies against gB AD2. This finding described the strain-dependent immune responses, the consequent absence of protection towards different CMV strains and explained the why of viral transmission during pregnancy in mothers routinely CMV seropositive [26, 27]. The strain-specific analysis, performable at the aim of epidemiologic investigations, makes possible to recognize the relevant burden of reactivation and reinfection in the pathogenesis of transplant related CMV disease. Nevertheless, the simple routine serological screening, despite its limit, is currently performed in patients prior to transplant, resulting in the basic discovery of risk for CMV reactivation.

INTERPRETATION OF ANTI-HADV SEROLOGICAL ASSAY AND LIMITS OF CLINICAL USE

Nowadays, the genomic investigations replace the neutralization assays in the definition of HAdV types and are performed in the contest of epidemic infectious events or specific investigations [28]. The serological typing characterization of adenovirus is still useful for detecting type-specific neutralizing anti-HAdV antibodies. These assays, although represent a diagnostic effort, could be at least addressed to discovery species C, which most frequently shows the biological behavior of latency, to evaluate the dynamics of viral diffusion and to clarify basic pathogenic aspects. However, more important and feasible, any data obtained from the performance of routine cross-reacting antibodies assay should be hopeful to recognize the recipients at risk for endogenous reactivation.

As already highlighted, the persistent lack of effective therapies against HAdV makes the reconstitution of antiviral immunity of paramount importance, leading to the need of adoptive therapy. Specific cytotoxic lymphocytes can be utilized as a passive immunization for prophylaxis in high-risk allogenic hematopoietic SCT and solid organ recipients, and for the treatment in the case of infection, when any necessity would be in advance recognized. In fact, even if the new generation of virus-specific lymphocytes has increased the feasibility of their use, this therapy remains demanding in terms of cost and time [29, 30]. Moreover, it was also demonstrated that human CD4+ T cells stimulated by conserved adenovirus hexon peptides from a single species recognize cells infected with HAdV serotypes belonging to different one [31]. The cross-reactivity, while for the gene therapy may limit the utility of switching to HAdV-based vectors derived from not common adenoviral serotypes, instead may benefits the utilization of HAdV-specific T cells in transplant recipients and makes the early individuation of recipients at risk, and a careful evaluation of any reciprocal donor-recipient serostatus, necessary. Since the generation of antigen-specific T cells from naïve T cell donors is still difficult, laborious and time-consuming, allogeneic third party T-cell donors offers an alternative option for recipients with virus seronegative donors or receiving cord blood in HSCT and cadaveric graft in SO transplantation [32]. The efficient treatment of high-risk patients requires the rapid recruitment of suitable T-cell donors, selected from the allogeneic cell registry alloCELL (www.alloCELL.org) established at Hannover Medical School (MHH). Here, donor seropositivity provides an opportunity to transfer virus-specific lymphocytes to mediate immune protection in the immunosuppressed recipient. In this context, a recent work evaluated CMV-, EBV- and ADV-specific serostatus as preliminary assay to screen and monitor the relevant T-cell immunity and showed antigen-specific T cells to be present in 73% of ADV-seropositive donors [33].

JC POLYOMAVIRUS: SIGNIFICANCE OF SERO-STATUS IN THE MANAGEMENT OF A PERSISTENT VIRUS

In the field of viral persistence, it is nowadays ascertained that the persistent infection caused by JC polyomavirus (JCV) and its reactivation are prerequisites for the onset of the progressive multifocal leukoencephalopathy (PML), observed in immunocompromised subjects [34]. Gorelik and colleagues described a JCV-specific higher-affinity ELISA performed for retrospectively assessing the JCV serostatus before the immunosuppressive therapy in multiple sclerosis patients, and to achieve a PML risk stratification. The authors detected anti-JCV antibodies in 100% of serum samples collected prior to PML diagnosis [35]. They also detected JCV DNA in urine to identify infected individuals and to establish the positive reference sera. Moreover, JCV as well shows important genomic and phenotypic plurality of strains. Particularly, a set of mutations, deletions and duplication verifying in noncoding control region (NCCR) sequence of JCV genome was found as modifying the archetype polyomavirus JC and allowing neurovirulence, *i.e.*, the virus entrance into human central nervous system, a preliminary condition for PML onset [36]. This feature does not make vain a possible application of serology for the prevention of PML. On the contrary, it led to a project aimed to restrict the identification of high-risk subjects to those bearing JCV DNA rearrangement [37]. The diseases caused by the reactivation of JCV and HAdV due to immunosuppressive therapies, or due to any immunodeficiency status, share the lack of effective therapies and the great necessity to identify subjects at risk. The management of

immunosuppressive protocols and pre-transplant screening cannot include the evaluation of anti-polyomavirus serostatus, since commercial routine assays to perform standardized measures are not nowadays available. Serological assays detecting HAdV-antibodies, instead, are suitable in microbiology laboratories for achieving diagnosis for acute and symptomatic infections in immune competent subjects [2, 38].

CONCLUSION

In the case of immunodeficiency planned for conditioning regimens or for therapeutic protocols, any effort have to be supported to avoid as much as possible primary infections with latent and persistent viruses and microorganisms, and their reactivation, or to be at least strictly aware of the underlying risk resulting from the treatment. The same authors who propose the PCR-based surveillance of HAdV infection are not sure whether this method is of benefit for the patients. However, they consider direct molecular assay as an opportunity they recommend not to waste [16, 23]. The management of immunosuppressive therapies performed without using every available tool to avoid or reduce the risk of consequent infections, diseases and death, could be an extreme responsibility.

To conclude, the pre-transplant screening should include the evaluation of latent HAdV infections, performing serological tests in donor and recipient, similar to the screening aimed at preventing cytomegalovirus infections. It is important to remind that the serological CMV screening is performed in spite of the existence of established and effective therapies. This screening currently represents a necessary condition, even if not sufficient, to prevent and to manage the onset of CMV infection in immunocompromised patients [11, 12]. It allows the protective matching of donors and recipients, avoiding organ transplantation from a seropositive donor to a seronegative recipient, the discovery of subjects at risk to carefully survey, the consequent preemptive therapy and active or passive immunization to prevent post-transplant CMV infections.

Improving the pre-transplant screening with serostatus towards HAdV obviously would not exclude the use of molecular assay for early surveillance, which most clinicians believe as the best method to manage the consequences of graft related immunodeficiency. Indeed, in some setting, molecular assays are not only performed on blood, to discover disseminate infections, but also on accessible tracts [18, 21]. This procedure can be useful especially in the contest of solid organ transplantation, where HAdV infections firstly involve the graft and are not early revealed by blood PCR surveillance. Moreover, prior to transplant, the detection of HAdV DNA on accessible tracts of recipients, along with that on graft's tissue, could be performed to preliminarily know the risk of reactivation and to avoid or minimize the risk of primary infection. The HAdV serological screening would not imply any procedural waste or danger or significant increase of the coasts, representing just a complementary test.

The epidemiological data emerging from a pre-transplant HAdV serological screening could be useful for enhancing the knowledge of adenoviral pathogenesis, nowadays incomplete on several aspects. As already mentioned, the most unclear and important query concerns the true responsibility by the primary infection *via* the graft and by the reactivation of pre-existing viruses in the onset of the infection in the immune-compromised host [9]. The interesting association joining the graft *versus* host disease (GvHD) and CMV reactivation is recently found for HAdV as well [39, 40]. On the contrary, in children with severe steroid-refractory acute GvHD treated with mesenchymal stromal cells, HAdV but not CMV infection was associated with decreased survival [41]. Therefore, the knowledge on connections between HAdV and not infectious complications of transplant procedures, such as allograft rejection and loss, and GvHD, could benefit from acquisition of new serological data [5, 7].

The specific associations between adenovirus species or individual types and single diseases is also not clear [2, 4]. New serological data can add information on the most frequent serotypes, the relative neutralizing antibodies and their possible cross-protective activity, on serotypes connected with graft's complications, with different localizations and with high case fatality.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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