different ribosomal proteins has been characterized; Diamond-Blackfan anemia is associated with haploinsufficiency in multiple different ribosomal proteins (but not RPSA) and results in bone marrow failure as well as multiple developmental defects. However, in these patients, there is no evidence of splenic abnormalities, and the current study found no evidence of hematologic abnormalities (or developmental abnormalities) in the patients harboring the RPSA mutations.

REVIEWER COMMENTS. The importance of this study is that many of these cases developed invasive bacterial infection early in childhood, most often involving Streptococcus pneumoniae (61%) with a high mortality rate (45%) (Mahaoudi N, et al. J Pediatr. 2011;158[1]:142–148, 148.e1). Thus, isolated congenital asplenia has overlapping features with recently defined TLR defects (eg, MyD88, IRAK4 deficiency) in that both are associated with childhood invasive bacterial infections that have a high mortality rate. Consequently, any child with invasive bacterial infection should be evaluated for absence of a spleen (presence of Howell-Jolly bodies, directed imaging studies) as well as studied for other congenital immune defects associated with this clinical presentation. In view of the autosomal dominant transmission of some cases of isolated congenital asplenia, family members of an affected patient should also be evaluated for possible asplenia.

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HIV AND INFECTIOUS DISEASES

Chronic Progressive HIV-1 Infection Is Associated With Elevated Levels of Myeloid-Derived Suppressor Cells


PURPOSE OF THE STUDY. Myeloid-derived suppressor cells (MDSC) consist of a heterogeneous population of progenitor cells and immature myeloid cells that are potent suppressors of T-cell function in many tumor models. The purpose of this study was to evaluate the possibility that MDSC play a role in HIV-induced immunosuppression.

STUDY POPULATION. Ninety-seven patients participated in this study: 16 healthy controls; 20 HIV-infected individuals with suppressed viral loads; 49 HIV-infected treatment-naïve individuals; 2 individuals with hepatitis C co-infection; 4 HIV-infected individuals failing to respond to treatment; and 8 individuals with lung cancer as positive controls.

METHODS. Flow cytometry analysis was performed on freshly isolated peripheral blood mononuclear cells. MDSC were defined as CD11b+CD14−CD33+CD15+. CD4+CD25+, FoxP3+ regulatory T cells were also analyzed. Mixed lymphocyte reactions and proliferation assays were used to measure suppressor function.

RESULTS. Subjects with progressive or chronic uncontrolled HIV infection had significantly higher levels of MDSC than healthy controls. Subjects with lung cancer, as expected, had elevated MDSC. In HIV-infected individuals, percent MDSC correlated positively with elevated viral load (>50 000/mL) and low CD4 count (<250/mm3). In addition, effective antiretroviral therapy was associated with normalization of MDSC number; individuals with elevated MDSC before antiviral therapy had significant reductions in MDSC after initiation of therapy. MDSC number was correlated with generation of CD4+CD25+FoxP3+ regulatory T cells. Finally, MDSC directly impaired the proliferative capacity of T cells of healthy donors and HIV controllers.

CONCLUSIONS. Uncontrolled HIV infection is associated with elevated levels of MDSC. These cells potentially contribute to the impaired T-cell responses characteristic of progressive HIV disease.

REVIEWER COMMENTS. The variety of hematopoietic cells seems endless, and as new cell types are defined, they routinely seem to be affected by HIV infection. MDSC are a case in point. The relevance of these cells in tumor biology has recently been better defined. It has long been known that chronic inflammation creates a tumor-inducing environment. It is now speculated that infiltrating MDSC inhibits effective immunologic control of evolving malignant cells. The current study suggests that MDSC may contribute to the immunopathogenesis of HIV. Are these cells contributing to the immunologic suppression associated with HIV, or are they a regulatory response to HIV-associated persistent immune activation? As described in an accompanying Editorial Comment (Macatangay BJ, et al. AIDS. 2012;26[12]:1567–1569), dampening the effects of MDSC could be important in purging latent HIV reservoirs in approaches aimed at curing HIV disease. However, understanding the immunoregulatory networks involved in HIV pathogenesis is likely critical for the design of effective HIV immune-based therapies.

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Vaccine-Induced Plasma IgA Specific for the C1 Region of the HIV-1 Envelope Blocks Binding and Effector Function of IgG


PURPOSE OF THE STUDY. A recently completed Phase III vaccine trial demonstrated a 32% estimated efficacy. An
earlier analysis suggested that envelope (Env)-specific antibody responses were associated with a lower risk of infection. Of particular interest, anti-HIV Env immunoglobulin A (IgA) antibodies correlated with increased infection risk. The purpose of this study was to evaluate potential mechanisms of this phenomenon.

STUDY POPULATION. Phase III controlled evaluation of the RV144 HIV vaccine to prevent HIV infection was conducted in Thailand. The current study represents a sub-study in which all participants provided written consent to have plasma and cellular samples stored and subsequently tested.

METHODS. The levels and affinities of IgA and immunoglobulin G (IgG) antibodies for HIV Env proteins were measured. The ability of patient IgA as well as patient-derived IgA monoclonal antibodies to inhibit natural killer cell–mediated, antibody-dependent cell-mediated cytoxicity (ADCC) was measured.

RESULTS. The Env-specific IgA/IgG ratio directly correlated with infection risk, suggesting that the presence of IgA antibody directly inhibited ADCC function. Furthermore, IgA monoclonal antibodies derived from vaccines inhibited binding and blocked ADCC function. The phenomenon of interference of IgG function by IgA antibodies has been reported previously in other settings.

CONCLUSIONS. Postvaccination polyclonal antibody responses vary among individuals. Those generating an excess of Env-specific IgA seem to be at increased risk for infection secondary to reduced ADCC effector function of natural killer cells.

REVIEWER COMMENTS. HIV has evolved multiple mechanisms to evade immune detection and elimination. These include impairment of neutralizing antibody generation, emergence of escape mutants, and Env glycosylation and conformational shielding. The vaccine studied in this article resulted in “blocking IgA antibodies” in a number of recipients and thus adds another level of complexity to vaccine design.

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Innate Immune Function and Mortality in Critically Ill Children With Influenza: A Multicenter Study

PURPOSE OF THE STUDY. The influenza virus can inhibit leukocyte function in vitro and in vivo, and is associated with severe secondary bacterial infections. Immunoparalysis is the state marked by reduction in the ability to produce tumor necrosis factor (TNF)-α in response to lipopolysaccharide (LPS). This study sought to test the hypothesis that mortality from influenza in critically ill children and young adults is associated with both hypercytokinemia and innate immune suppression.

STUDY POPULATION. Patients <18 years old, who were admitted to 1 of the 15 PICUs that belong to the Pediatric Acute Lung Injury and Sepsis Investigators network, with community-acquired influenza infection, from December 2008 to November 2009 were included. A control group of outpatient children who presented for elective phlebotomy was also evaluated.

METHODS. Serum samples were assayed for 31 cytokine levels and ex vivo LPS-stimulated TNF-α production capacity by using a standardized stimulation protocol. Levels were drawn within 72 hours of ICU admission.

RESULTS. Fifty-two subjects and 21 controls were sampled. There were 8 deaths among the subjects. Nonsurvivors had significantly lower counts of neutrophils, monocytes, and lymphocytes, and more frequent secondary bacterial infection than survivors. Six mediators [granulocyte macrophage colony–stimulating factor, interleukin-6, interleukin-8, interferon-inducible protein-10, monocyte chemotactic protein-1, and macrophage inflammatory protein-1α] were significantly higher among nonsurvivors compared with survivors and controls. ICU patients had significantly lower TNF-α production in response to LPS compared with controls. Nonsurvivors also had lower TNF-α production compared with survivors. Lower TNF-α production was also associated with more days in the ICU. The most common influenza subtype was 2009 H1N1, which was associated with lower TNF-α production compared with other influenza strains. Staphylococcus aureus, the most common bacterial co-infection, was associated with lower TNF-α production compared with other bacterial co-infection or no co-infection.

CONCLUSIONS. Children with critical influenza can have marked innate immune suppression, which can co-exist with high serum cytokine levels. Severe innate immune suppression is highly associated with mortality and S. aureus co-infection.

REVIEWER COMMENTS. This is the first multicenter evaluation of the relationships between innate immune function, serum cytokines/chemokines, and outcomes in children with critical illness resulting from influenza. Despite elevated levels of proinflammatory cytokines/chemokines, innate immune function was suppressed. The hypercytokinemia echoes studies of adult influenza nonsurvivors. The study shows the feasibility of large-scale immune monitoring among multiple centers. Of note, the subjects were sampled at only 1 time point.
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