Enterovirus D68: a new threat to hematology patients?

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In this issue of Blood, Waghmare et al report 8 patients with hematologic malignancies retrospectively diagnosed with enterovirus D68 (EV-D68) infections.1

Enterovirus D68 is not a new virus, as it was identified in 1962, and small numbers of cases have been regularly reported to the US Centers for Disease Control and Prevention (CDC). However, during the summer of 2014, outbreaks of severe respiratory disease, especially in children and teenagers with a history of asthma, occurred in Missouri and Illinois.2,3 EV-D68 was identified in a majority of these cases, and during the rest of 2014, more than 1100 cases with documented EV-D68 infections were diagnosed all over the United States and reported to the CDC, including a small number of fatal infections. It has been suggested that the diagnosed cases are only “the tip of the iceberg,” with a large number of undiagnosed mild infections occurring as well. Therefore, the proportion of severe infections is difficult to assess. Outbreaks with EV-D68 have also been documented in other countries, including Norway4 and the Netherlands.5 The latter report also included 3 cases occurring in solid organ transplant recipients.

For decades, viral infections have been recognized as threats to hematology patients, especially to hematopoietic stem cell transplant recipients. In the study by Waghmare et al, 6 patients were stem cell transplant recipients. Similarly to what is commonly seen with other respiratory viruses, the clinical manifestations varied greatly from mild upper respiratory symptoms to respiratory failure, with 2 of 8 patients requiring mechanical ventilation. All 8 diagnosed infections occurred in adults, and most patients had lymphopenia, a well-known risk factor for more severe disease in infections caused by other respiratory viruses such as respiratory syncytial virus and influenza virus.6-8 Obviously, these observations are too limited to allow assessment of the pathogenic potential of EV-D68 in hematology and stem cell transplant patients, but if EV-D68 infections become more prevalent in the community, as recent epidemiology suggests, we will most likely get more information regarding the clinical importance of infections with this virus during the next couple of years.

With the development of molecular virology techniques, the number of “new” viruses is steadily increasing, and investigators need to address the impact of these new viruses in immunocompromised patients. The authors employed an interesting strategy by analyzing samples from patients with respiratory symptoms who had either tested negative for respiratory viruses by multiplex polymerase chain reaction (PCR) or tested positive for rhinoviruses. The latter group is interesting, because 10% of patients who tested positive for rhinovirus were in fact, after sequencing, proven to have EV-D68, showing that the rhinovirus primers used in the original multiplex PCR had limited specificity. This report illustrates a couple of important points. First, it shows the importance of having repositories of saved specimens allowing reanalysis when new technology becomes available. Second, this might explain some of the uncertainties about whether and how frequently rhinovirus causes severe lower respiratory tract disease, including respiratory failure.9,10 Third, as discussed by the authors, there is no way to guarantee, even with negative diagnostic test results in patients with respiratory symptoms, that such patients are not contagious and cannot contribute to nosocomial spread of viral infections in hematology and stem cell transplant units. It is therefore important to include EV-D68 in the diagnostic strategy used in highly immunocompromised patients with upper or lower respiratory symptoms despite the fact that there is no available antiviral therapy for infections caused by EV-D68.

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REFERENCES


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Comment on Mei et al, page 1739

Thucydides and longer-lived plasma cells

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In this issue of Blood, Mei and colleagues characterize the population of CD19⁻ plasma cells in human bone marrow and provide evidence that this plasma-cell subset substantially contributes to long-lived protection against infections and vaccination.¹

During the Peloponnesian War, the plague killed nearly one-third of the Athenian population. In his writings, The History of the Peloponnesian War (late fifth century BC), the Greek philosopher and historian Thucydides observed that “the same man was never attacked twice—never at least fatally.” This was an astute observation, and probably the first to recognize that after an individual was exposed to a pathogen, he or she could be protected from disease on subsequent exposures without suffering the effects of infection. Although he did not realize it at the time, Thucydides was describing the process by which the mammalian immune system elicits long-lived serological memory that can often persist for a lifetime.² In the ~2400 years since, we have learned a lot about the cellular and molecular processes underlying this phenomenon. For instance, we know that plasma cells (PCs) are largely responsible for serological memory.²⁻⁵ PCs are generated in germinal centers (GCs) from naive precursors that are activated after exposure to T-cell-dependent antigens. GC B cells undergo affinity-based selection and, depending on which and when signals are received, differentiate into plasmablasts, exit the physical structure of the GC, and start heading to the bone marrow (BM). In the BM, plasmablasts begin a new life as long-lived PCs, lodged in a survival niche, comfortably surrounded by supportive cell types that enable them to do their job: secrete copious quantities of high-affinity, antibody (Ab)-specific immunoglobulin that rapidly disarms invading pathogens before the host is aware it has been infected.³⁻⁵ Remarkably, it has been estimated that the half-life of neutralizing Abs ranges from 10 to >10,000 years, depending on the pathogen.² So, if those survivors from the fifth century BC were alive today, they might still be immune to the plague!

Although this summary gives the impression that all is known about PC biology, this is far from reality. Indeed, many caveats exist in this simplified version of events. For instance, not all PCs home to the BM; they can remain in their tissue of origin, such as spleen, lymph nodes, tonsils, or gut.⁴⁻⁷ Numerous PC subsets have been identified on the basis of their expression of different immunoglobulin isotypes and homing receptors that allow trafficking to distinct sites and endow these subsets with specific functions.⁴⁻⁸ Not all PCs are long-lived; both short-lived and long-lived PCs have been identified.⁴⁻⁸ And despite the terminology, PCs are not intrinsically long-lived: they rely on a microenvironment provided by hematopoietic and nonhematopoietic cells that produce survival factors (eg, BAFF [B cell–activating factor], APRIL [a proliferation-inducing ligand], interleukin-6) critical for their long-term persistence.²⁻⁵,⁸⁻¹² Lastly, our immune tissues can only support the survival of a finite number of PCs; thus, continual exposure to new pathogens generates new PCs that have to compete for limited survival niches.³⁻⁵ In the classic setting of Darwin’s survival of the fittest, only those PCs capable of maintaining access to such niches will remain for protracted periods of time, whereas “weaker” PCs will be “bumped” from survival niches and undergo apoptosis.⁸⁻¹² One inference from this scenario is that the half-lives of all immunoglobulins should be approximately similar; however, this is clearly not the case because half-lives can differ by orders of magnitude.²

Thus, many questions remain about the nature and dynamics of PC generation and survival. Importantly, PCs not only are the linchpin of long-lived protective immunity against pathogens and, by extension, underlie the success of vaccination but also contribute to human diseases such as autoimmunity (eg, systemic lupus erythematosus, rheumatoid arthritis), malignancies (eg, multiple myeloma, PC leukemia), and primary immunodeficiency in which they are not produced in sufficient quantities, rendering affected individuals susceptible to pathogen infection. For these reasons, it is necessary to elucidate the “unknowns” of PC biology.

Human PCs are typically identified by a CD38hiCD27hiCD20⁻ phenotype, with expression of other markers varying depending on the tissue harvested.⁶⁻⁷ Mei and colleagues have now investigated the subset of CD19⁻ PCs.¹ These cells were largely restricted to the BM and preferentially expressed intracellular immunoglobulin G (IgG). In contrast, CD19⁻ PCs are detected in blood, tonsils, and spleen, as well as in BM, and most express IgA or IgG.¹⁻⁷ CD19⁻ BMPCs exhibited a unique transcriptome, with elevated expression of prosurvival genes, as well as features associated with a state of advanced maturation and terminal differentiation. Consistent with these findings, CD19⁻ BMPCs were nonproliferating cells with greater survival capacity than CD19⁺ BMPCs, at least during in vitro culture. However, CD19⁻ PCs did not appear to be simply derived from CD19⁺ PCs...
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