

Editorial

Varicella zoster virus: The potentially useful virus

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Varicella zoster virus (VZV), a double-stranded DNA virus, is a highly contagious human neurotropic virus that belongs to the alpha group of herpes viruses [1-4]. Primary VZV infection (chickenpox) occurs in childhood then the virus becomes latent in the nerve ganglia [1,5-7]. Reactivation of the virus may occur decades later and cause herpes zoster (HZ) which is manifested by a typical painful skin eruption that has characteristic dermatomal distribution [1,5]. Reactivation of VZV is usually predisposed to: old age; comorbid medical conditions such as diabetes mellitus, chronic obstructive airway disease, and end-stage renal disease; and immunosuppression due to malignancy, autoimmune disorders, immunosuppressive therapies, trauma, cytotoxic chemotherapy, hematopoietic stem cell transplantation (HSCT), and solid organ transplantation (SOT) [1,5-7].

VZV infections can cause not only transient pancytopenia but also aplastic anemia that may require allogeneic HSCT [8-12]. Additionally, VZV infections have been reported to be associated with increased risk of developing lymphoid malignancies and solid tumors [13-17]. On the contrary, there is growing evidence showing certain beneficial effects of the virus in immunocompromised individuals and these effects may be translated into prolongation of overall survival (OS) [18,19]. In a single center, case-controlled, retrospective study that included 16 episodes of VZV infections occurring in 14 patients with various types of hematologic malignancies (HMs) and bone marrow (BM) failure syndromes, Al-Anazi KA et al., reported an increase in white blood cell count, hemoglobin (Hb) level, and platelet count starting approximately 6 weeks following VZV infections and this stimulation of the 3 hematopoietic cell lines in the BM that followed VZV infections was maintained for periods longer than 3 years following the infection [18]. In another single center retrospective study that included a large number of patients with multiple myeloma subjected to high-dose melphalan followed by autologous HSCT after control of their

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primary disease, Kamber C et al., reported that approximately one third of these patients developed VZV infections either before or after HSCT [19]. Despite encountering VZV infections in patients with worse expected prognosis, the OS in patients who developed VZV infection was superior to that in patients who never developed the infection [19]. Recently, Al-Anazi KA et al., reported BM biopsy-proven reversal of pure red cell aplasia manifested by a gradual increase in Hb level starting 6 weeks following a localized HZ infection till the Hb level plateaued above 14g/dL fourteen months following the viral infection [4]. Additionally, several studies have demonstrated that VZV infection may trigger chronic graft versus host disease (GVHD) following allogeneic HSCT [20-22]. GVHD is associated with graft versus cancer effects and, provided GVHD is of low-grade, it can be associated with improvement in OS in patients with acute leukemia or lymphoma [23-25].

Although viruses can cause infectious complications that may be associated with significant morbidity and mortality and evolution of certain cancers, they may provide hope to effectively treat several serious medical illnesses by being utilized as: vaccines; anticancer agents in the setting of oncolytic virus therapy; as well as vectors in induced pluripotent stem cells, gene therapy for several hereditary and acquired disorders, and chimeric antigen receptor (CAR) T-cell therapy [26-33]. VZV is the only virus consistently reported to have an inverse association with glioma suggesting a protective effect of VZV infection against the tumor [34,35]. Studies have shown that: the protective effect of prior VZV infection against glioma is stronger for high-grade tumor; this protective effect may be mediated by the VZV-specific T-lymphocytes; VZV exhibits an extrinsic oncolytic potential in malig-

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nant glioma cultures; and human mesenchymal stem cells (MSCs) are suitable for delivering VZV to the sites of tumor growth [34,36,37]. However, efficacy of oncolytic virotherapy in malignant glioma has several difficulties that need to be overcome [35].

VZV pathogenesis, latency, and reactivation are difficult to study due to the fact that VZV is an exclusively human pathogen [38-40]. Numerous efforts have been made to develop adequate animal models of VZV infection but these models remain limited because all aspects of VZV infection, latency and reactivation, and understanding VZV pathology will remain not only difficult but also incomplete without a suitable model [38,40]. Despite the rare reports of breakthrough VZV infections that may become disseminated and life-threatening particularly in immunocompromised hosts, VZV vaccines including the live-attenuated ones have been shown to be generally safe and effective in: recipients of SOT as well as HSCT; patients with HMs and solid tumors; patients with diabetes mellitus, autoimmune disorders and renal disease; elderly individuals on corticosteroid maintenance therapy; and patients with history of HZ infection [41-55].

VZV infections are associated with specific alterations in the BM microenvironment induced by stress-related hematopoiesis [56-58]. Studies have shown that the following stromal and immune cells are involved in the pathogenesis of VZV: (1) MSCs, the masters of hematopoiesis, which have antimicrobial and anticancer effects [59-62]; (2) dendritic cells, the essential cells for initiating antiviral immune response, which are found to transmit VZV to T-cells in order for the virus to disrupt the function of immune cells [63,64]; (3) natural killer cells, which play important roles in controlling VZV infection and eliminating malignant cells, may themselves become manipulated by the virus for its advantage [65,66]; (4) T-lymphocytes, including CD4, CD8 effector cells and memory T cells, that are involved in T cell immunity encountered following primary VZV infection and in maintenance of latency [67]; and (5) mononuclear cells, which once infected with VZV, disseminate the virus to distal organs to produce clinical disease [68]. Additionally, the following cellular proteins are involved in the pathogenesis of VZV infections: open reading frames, glycoproteins, promyelocytic leukemia protein, chaperons and small ubiquitin-like modifier proteins [69-73]. Extracellular vesicles, exosomes, and micro-RNAs are also implicated in VZV infections [74-76]. Studies have also shown that several cytokines, chemokines and ligands are involved in VZV infections and that certain complications of VZV infections such as: postherpetic neuralgia, vasculopathy, myelopathy, encephalopathy, and acute retinal necrosis have specific cytokine profiles [77-81]. A number of signaling pathways; such as Janus kinase/signal transducer and activator of transcription proteins (JAK/STAT), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and PI3K/Akt pathways; have been found to be activated in VZV infections [82-85].

Apparently, VZV behaves differently from other herpes viruses. Additionally, it has the following peculiar features: (1) having the smallest genome; (2) losing almost all the genes that are not essential for its survival; (3) being highly fusogenic and cell-associated; (4) having no inhibitors of autophagy; (5) being an exclusively human pathogen; (6) having a species-specific cytokine profile; (7) having an inverse relationship with glioma; (8) association with GVHD in recipients with allogeneic HSCT; and (9) having BM stimulatory effects as well as several antitumor actions in patients with HMs and BM failure syndromes [1-4,18-22,34,35,86,87].

The reported beneficial effects may develop through several direct or indirect immunological mechanisms. Hence, these beneficial effects merit thorough investigations and should encourage scientists and researchers to give this potentially useful virus the attention it deserves. The antitumor effects as well as the stimulatory effect exerted by the virus on the 3 cell lines in the BM can be explained by one or more of the suggested mechanisms or may be due to a new mechanism yet to be elucidated. The virus itself, modified or engineered versions of the virus, or specific materials obtained from the serum of patients infected with VZV may ultimately become novel therapeutic modalities in the management of these immunocompromised patients.

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