EXAMPLE ASSIGNMENT #1: Grand Rounds Review. Attend one of the City-Wide Infectious Disease Conferences held every Wednesday at Noon in the auditorium behind the elevators on the ground floor of the DeBakey Building, Baylor College of Medicine (BCM DeBakey Rm M112). (This building is the white building next to the new Baylor Graduate School Building and across the street from the Jones Library). Usually three cases are presented as unknowns, a differential diagnosis is made, and the outcome and ramifications of the case are discussed. Alternatively, you may attend another seminar or grand rounds on an immunologic topic and write a thorough summary of that presentation. Your job is to investigate the immunologic aspects of the disease and incorporate them into your interpretation and description of the case. Choose ONE of the cases presented. The case must have an immunologic implication. Provide a hardcopy of any handouts or notes made with your assignment, preferably with the markings you made while analyzing it. Below is an example. Note: there are alternate formats that would also satisfy the goals of the assignment; complete the assignment that best answers the questions outlined in your syllabus.

An average Essay Assignment is depicted below. This example would have earned approximately 7.5 out of a possible 10 points. Increasing details related to immunological mechanisms, and use of stronger primary references would have increased the overall score.
The case presented is a complication of a varicella zoster virus infecting the central nervous system. An eleven-year old Pakistani male developed severe headaches with vomiting and fever that persisted for ten days. Three days into the illness, his primary care physician diagnosed a stomach virus. No treatment was indicated. He became afebrile on day four. On day five the vomiting subsided, but the headaches continued to increase in intensity and severity. He developed an itchy skin rash on day seven. Upon entry to the emergency room, the patient was described as “awake, alert and in acute distress.” He has a history of migraines, and contracted chicken pox at nine months of age. He has no known drug allergies. He lives with his parents and seventeen-year old sister, all of whom have non-contributory medical history. The family moved from Pakistan seven years ago.

After the patient was admitted to the hospital his vitals were as follows:


His throat was clear with no exudates. His neck was easily moveable with no signs of meningismus. Both the Kernig and Brudzinski signs were negative. His right axilla and scapular area contained small clusters of vesicles and crusted lesions which followed a dermatomal distribution. The remaining physical exam was normal.

The initial work-up included a CT scan without contrast and a lumbar puncture. The CT scan was normal, and the lumbar puncture showed the following:

WBC: 1059 (95% lymphocytes)            RBC: 76            Glucose: 49            Protein: 76

Gram stain: no organisms

The blood and cerebrospinal fluid were cultured and neither showed any growth. The patient was negative for HIV and TB. The skin lesions were negative for VZV, and the CSF was positive for VZV by polymerase chain reaction (PCR). VZV IgG and IgM were both elevated. The patient completed a 10-day course of acyclovir in the hospital.

This is a very unusual complication of a varicella zoster virus infection. Varicella zoster virus (VZV) is one of eight herpes viruses known to infect humans. It is a linear, double-stranded, enveloped DNA virus. It is primarily transmitted through respiratory droplets but can be transmitted by direct contact with infected skin lesions. Usually, the first exposure to VZV causes the acute disease, varicella, also known as chickenpox. The infected cells show degenerating enlargement and syncytia formation. The primary infection begins in the mucosa of the respiratory tract then spreads via the circulatory and lymphatic systems to the reticuloendothelial system. This secondary viremia results in the formation of vesicular lesions. A latent infection of dorsal root or cranial nerve ganglia can occur. Due to an
immuneocompromised host, the virus can exit the latent phase and cause a recurrent infection. The virus migrates to the skin where lesions develop in the affected dermatome. This recurrent infection is known as Shingles. Very uncommonly, the virus spreads to other cells beyond the given dermatomal distribution via circulating antibodies.\(^1\) As seen in this patient, VZV meningitis occurred. The case presented was treated with acyclovir, which proved to be an effective treatment.

The immune responses to varicella zoster infections include the induction of interferon, the antibody response, and cell-mediated immunity. Various types of interferons are produced as an early response mechanism to a viral pathogen. Interferon-α and interferon-β are produced by leukocytes, fibroblasts, and other virally infected cells. These interferons have multiple functions, including: activating genes that interfere with viral replication; stimulating the production of MHC class I molecules; increasing the concentration of proteasome proteins within an infected cell; and activating natural-killer cells. Both the MHC class I and proteasome protein molecules increase the ability of the infected cell to degrade viral peptides and present the peptides to T cells. Through the actions of interferon-α and β, activated natural-killer cells are able to decrease viral production by eliminating host cells through antibody-dependent cell-mediated cytotoxicity. Interferon-γ is produced by T cells and activates natural killer cells and macrophages. The humoral response to VZV causes an increase in the production of antibodies to the viral antigens, specifically surface proteins.\(^3\) IgG has shown to be the most active isotype against viruses, which explains the elevated IgG seen in the patient. Furthermore, since the patient’s infection was a secondary response presenting after a latent infection, there was a shift in the antibody response. The production of IgM shifted to the synthesis of IgG, also known as class switching. This explains both the elevated IgM and IgG levels seen in the patient.\(^4\) These elevated antibody levels, as well as elevated protein levels, are a common finding in patients with VZV meningitis.\(^5\)

Interferon and antibody production both aid in viral elimination, but cell-mediated immunity significantly contributes to both the symptoms and the resolution of the infection. The cellular response results in the production of specific CD4+ and CD8+ T cells, which are required for effective viral elimination. The CD4+ T cells are directly involved in generating an antibody response by mediating the class switching. CD4+ T cells are also responsible for producing cytokines which stimulate the inflammatory response at virally-infected areas. This response presented in the patient as a vesicular rash located in the region of the virally-infected dermatome. The CD8+ T cells have a cytotoxic function, killing host cells through recognition of MHC class I molecules.\(^3\)

In immunocompromised patients or in severe cases of VZV, acyclovir is indicated. Acyclovir has limited water solubility and has poor oral bioavailability, thus requiring intravenous administration.\(^6\) Although the patient’s immune response appeared competent and was not significantly compromised by other infections, the progression of the VZV infection to meningitis required acyclovir administration. Varicella zoster immune globulin (VZIG) is currently being used prophylactically for varicella zoster infections, but the therapeutic advantages are currently under investigation. VZIG is made from the plasma of blood donors who have been identified to have high antibody titers to VZV. It contains between 10% and 18% globulins, primarily being IgG.\(^7\) With further research, this treatment, in conjunction with acyclovir, could potentially reduce the time course of VZV meningitis. A live, attenuated
vaccine, Varivax, is now widely available to prevent varicella infections. Zostavax is a more concentrated form of the Varivax vaccine that is designed to produce an immune response in older adults whose immunity to VZV has waned.\(^8\)

This case was a very rare complication of a varicella zoster infection. Although the immune response generated by the patient did occur, it did not seem effective in eliminating the virus. After completing the treatment regimen of acyclovir, the patient fully recovered from the VZV meningitis.

References:


