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CLINICAL VIGNETTE

Prevention of Varicella Zoster Virus Complications after Stem Cell Transplant: Insights from a Case Series

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Case Descriptions

Patient 1

A 37-year-old man with a history of relapsed Hodgkin's lymphoma status post autologous stem cell transplant (SCT), allogenic SCT, and CAR T-cell therapy presented to the hospital with one week of abdominal pain. He was diagnosed with Hodgkin's lymphoma 9 years prior to presentation following an excisional lymph node biopsy demonstrating Reed-Sternberg cells. His disease course has been complicated by several relapses treated with multiple varying chemotherapy regimens, chronic graft versus host disease affecting skin, gastrointestinal tract, and liver, and dermatomal shingles. Prior treatments include autologous SCT, allogenic SCT, and CAR T-cell therapy. Four months prior to presentation, he received his second Shingrix vaccine and discontinued prophylactic acyclovir that he had been taking in the four years following his allogenic SCT. He had received his third cycle of pembrolizumab ten days prior to presentation and presented with one week of epigastric pain with anorexia.

He was admitted for evaluation of his abdominal pain, with initial testing notable for normal liver function tests (LFTs) and lipase. CT abdomen noted mild soft tissue stranding in the porta hepatis but was otherwise unremarkable, and an upper endoscopy with biopsies was negative for gastrointestinal graft versus host disease. A temporary celiac plexus block was performed on hospital day 4 but provided only a few hours of pain relief. On hospital day 5, he developed a vesicular rash initially forming in small clusters on his abdomen but progressing to involve his entire face, chest, abdomen, back, and extremities, which prompted immediate initiation of IV acyclovir (Figure 1). An unroofed vesicle swab returned positive for Varicella Zoster (VZV) PCR. Repeat LFTs at this time were notable for a new transaminitis with AST 67 and ALT 191. After completing one week of IV acyclovir his lesions crusted over, and he was discharged on oral valacyclovir.

Patient 2

A 66-year-old man with a history of acute lymphoblastic leukemia status post allogenic SCT presented with vomiting and abdominal pain. Eighteen months ago, he received hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, cytarabine) chemotherapy and imatinib, which resulted in a clinical remission. About 11 months ago, he underwent an uncomplicated SCT. Four months ago, he developed graft versus host disease of his skin, gastrointestinal tract, and liver. Increased immunosuppression was instituted. Three days prior to admission, he developed abdominal pain, vomiting, and a worsening maculopapular rash, which prompted presentation to the hospital.

The patient was admitted and treated for presumed gastroenteritis. Initial infectious work-up was negative. His baseline LFTs swiftly rose from near normal values to AST 9744, ALT 6875, alkaline phosphatase 825, and total bilirubin 7.9. His rash became vesicular, so a VZV PCR was sent, and a dose of acyclovir was administered. The patient had a rapid decline, developing disseminated intravascular coagulation, renal failure requiring dialysis, lactic acidosis, and subsequently expired. Post-mortem, his serum VZV returned positive and limited autopsy revealed intranuclear inclusions in the epidermis (Figure 2) and hepatocytes (Figure 3) with immunofluorescence positive for VZV, confirming the diagnosis of disseminated VZV leading to fulminant liver failure as the cause of death.

Discussion

Post-transplant VZV reactivation is a well-known complication of patients undergoing SCT with a recent study showing recurrence rate of 20.7% within 2 years without antiviral prophylaxis.[1] In one retrospective analysis, approximately 11% of zoster cases were disseminated,[2] which confers a greater mortality risk if there is visceral involvement. These cases show the broad spectrum of severity in visceral involvement ranging from a mild transaminitis to acute liver failure precipitating death. The diagnosis can be challenging, as patients can present

with abdominal pain for days to weeks prior to the onset of rash, which occurred in both of our patients.[3]

For VZV-seropositive patients undergoing allogenic transplant, the 2009 American Society for Blood and Marrow Transplantation guidelines recommend antiviral prophylaxis for one year following transplant, with optional prophylaxis for autologous transplants. The duration of prophylaxis is extended for those requiring immunosuppression for conditions such as graft versus host disease, though appropriate discontinuation criteria are poorly defined. These recommendations, along with the 2013 Infectious Diseases Society of America guidelines, advise against the use of live attenuated VZV vaccine (Zostavax) in SCT patients, due to risk of infection from its high viral loads.[4,5]

In 2017, the FDA approved a new conjugated subunit vaccine (Shingrix) for use in immunocompetent adults.[6,7] The FDA did not specifically comment on its application in immunocompromised adults, but this vaccine has been shown to be safe and effective in reducing VZV recurrence in SCT patients when given peri-transplant.[8,9] Of note, the prevention of primary VZV infection relies on a humoral immune response, while secondary reactivation prevention is more dependent on a cell-mediated response.[10] The Shingrix vaccine has proven robust humoral and cell-mediated responses, but its efficacy in preventing reactivation relies more heavily on the patient mounting a cell-mediated response.[7]

Our first patient received the Shingrix vaccine series, yet still developed disseminated VZV four months after stopping acyclovir prophylaxis, implying that he was unable to mount an adequate cell-mediated response to the vaccine. His last allogeneic transplant was four years prior to the vaccine and is an unlikely cause of this impairment. Immune reconstitution is gradual after SCT and may vary due to multiple factors, though in many cases, immunizations may begin at 6-12 months following transplant.[11,12] However, our patient received three rounds of lymphodepletion (fludarabine and bendamustine) in preparation for CAR T-cell infusion eleven months prior to his first dose of the vaccine. The use of fludarabine is associated with an increased risk for zoster infections.[13,14] Some authors have suggested that patients be placed on prophylactic acyclovir prior to conditioning chemotherapy.[15] Complete T-cell reconstitution after lymphodepletion therapy may take up to 1-2 years,[16] and it is likely that his therapy impaired his ability to mount a cell-mediated response to Shingrix. His prior use of prednisone for chronic GVHD, which was discontinued approximately 18 months prior to receiving Shingrix, was unlikely to contribute as prior studies demonstrated good immunogenicity to live zoster vaccine among patients on glucocorticoids.[17]

Despite our first patient's development of herpes zoster, his course was relatively uncomplicated with only a mild transaminitis. It is possible that Shingrix protected him from the complications that led to the death of our second patient. In a prior study, Shingrix was effective in reducing non-post herpetic neuralgia complications, including ophthalmologic disease, neurologic disease, and herpes zoster vasculitis.[18] The influenza vaccine has similarly shown a high efficacy in reducing the number of severe cases, even though the patients studied had positive influenza swabs and therefore were not fully protected by the vaccine.[19]

The development of disseminated zoster in a patient with a SCT who discontinued antiviral prophylaxis after receiving the Shingrix vaccine series highlights the importance of updating SCT antiviral prophylaxis and immunization guidelines in light of new vaccine development. There are currently no studies examining the efficacy of Shingrix after lymphodepletion and CAR T-cell therapy, as both treatments are relatively new. Some effects of CAR T-cell therapy, such as the risk of cytokine release syndrome[20] and risk of infection in the first 90 days following therapy,[21] have been studied on larger scales. Reports of delayed infectious complications following CAR T-cell therapy are limited.[22] As CAR T-cell therapy is used in the treatment of more patients, data about the long-term infectious risk, whether conferred by re-engineered T-cells or conditioning chemotherapy regimens, is needed. Until updated guidelines emerge, caution should be exercised when discontinuing VZV prophylaxis, particularly in the setting of further immunosuppressive therapy following SCT.

Conclusions

Abdominal pain with an extensive negative evaluation in a patient who underwent a SCT warrants high suspicion for prodromal pain related to a varicella infection. Preventing recurrent VZV with the new zoster subunit vaccine (Shingrix) requires a robust T-cell response, which may be impaired in immunocompromised patients. Guidelines for Shingrix are unavailable given its recent approval, and caution should be exercised when discontinuing acyclovir in patients after SCT with further immunosuppressive therapy.

FIGURES

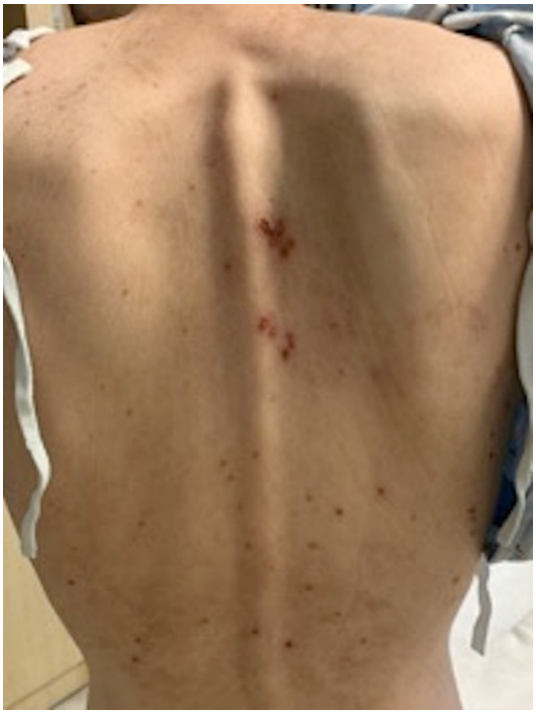

Figure 1. Rash. Back of Patient 1 depicted following development of vesicular rash across multiple dermatomes characteristic of disseminated zoster.

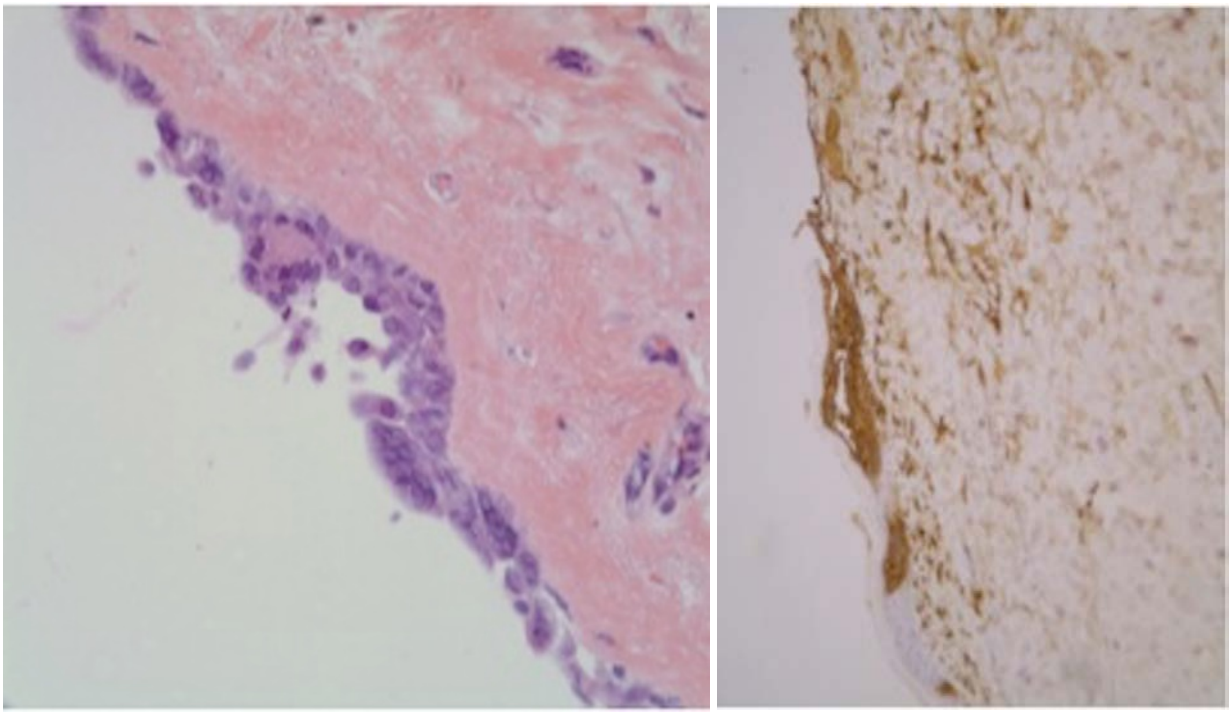

Figure 2. Skin Pathology. *Left:* **I**ntraepidermal blistering with acantholysis as well as nuclear inclusions with dark purple border and eosinophilic center suggestive of VZV. *Right:* Positive immunohistochemistry for VZV, confirms the diagnosis.

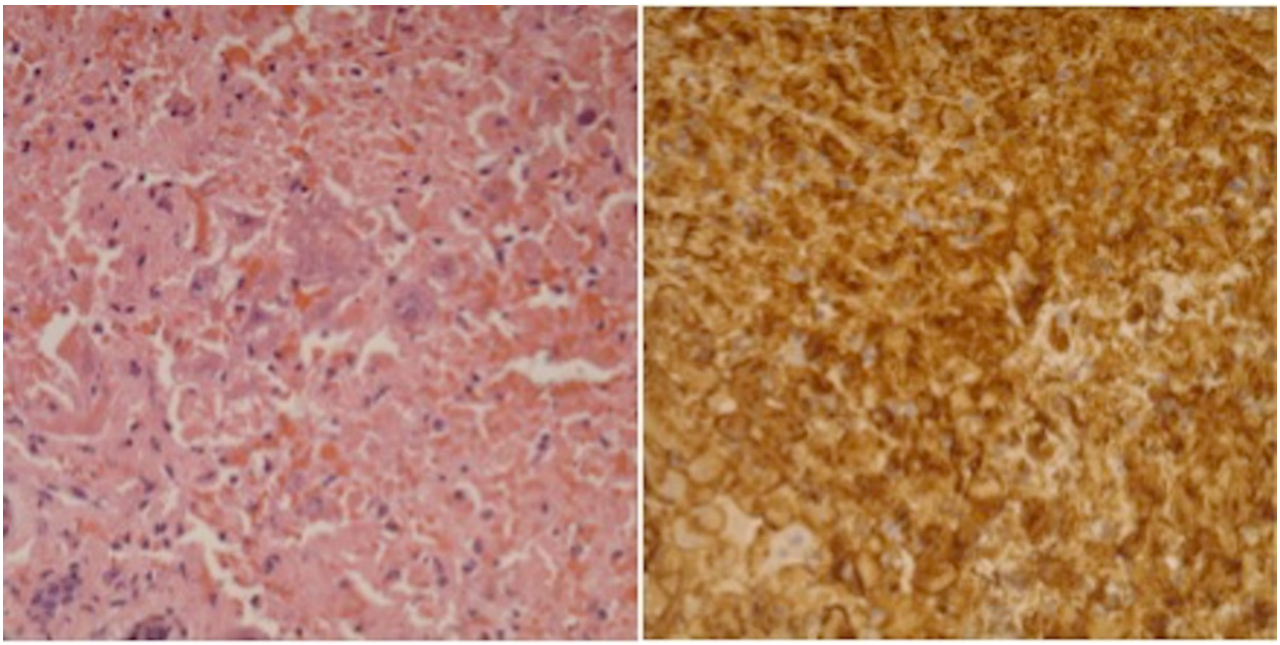

Figure 3. Liver pathology. *Left:* The liver is congested with diffuse damage. Nuclei exhibit dark purple nuclear border and central glassy appearance suggestive of VZV intranuclear inclusions.. *Right:* Immunohistochemistry extensively positive for VZV in hepatocytes.

REFERENCES

1. **Blennow O, Fjaertoft G, Winiarski J, Ljungman P, Mattsson J, Remberger M**. Varicella-zoster reactivation after allogeneic stem cell transplantation without routine prophylaxis--the incidence remains high. *Biol Blood Marrow Transplant*. 2014 Oct;20(10):1646-9. doi: 10.1016/j.bbmt.2014.06.002. Epub 2014 Jun 7. PubMed PMID: 24914821.
2. **Kim DH, Messner H, Minden M, Gupta V, Kuruvilla J, Wright J, Lipton J**. Factors influencing varicella zoster virus infection after allogeneic peripheral blood stem cell transplantation: low-dose acyclovir prophylaxis and pre-transplant diagnosis of lymphoproliferative disorders. *Transpl Infect Dis*. 2008 Apr;10(2):90-8. Epub 2007 Jul 1. PubMed PMID: 17605742.
3. **Verdonck LF, Cornelissen JJ, Dekker AW, Rozenberg-Arska M**. Acute abdominal pain as a presenting symptom of varicella-zoster virus infection in recipients of bone marrow transplants. *Clin Infect Dis*. 1993 Jan;16(1):190-1. PubMed PMID: 8448313.
4. **Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I; Infectious Diseases Society of America**. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014 Feb;58(3):e44-100. doi: 10.1093/cid/cit684. Epub 2013 Dec 4. Erratum in: *Clin Infect Dis*. 2014 Jul 1;59(1):144. PubMed PMID: 24311479.
5. **Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, Wingard JR, Young JA, Boeckh MJ; Center for International Blood and Marrow Research; National Marrow Donor program; European Blood and MarrowTransplant Group; American Society of Blood and Marrow Transplantation; Canadian Blood and Marrow Transplant Group; Infectious Diseases Society of America; Society for Healthcare Epidemiology of America; Association of Medical Microbiology and Infectious Disease Canada; Centers for Disease Control and Prevention**. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. *Biol Blood Marrow Transplant*. 2009 Oct;15(10):1143-238. doi: 10.1016/j.bbmt.2009.06.019. Erratum in: *Biol Blood Marrow Transplant*. 2010 Feb;16(2):294. Boeckh, Michael A [corrected to Boeckh, Michael J]. PubMed PMID: 19747629; PubMed Central PMCID: PMC3103296.
6. Shingrix (Zoster Vaccine recombinant, adjuvanted) [package insert]. Research Triangle Park, NC: GlaxoSmithKline Biologicals; 2017.
7. **Cunningham AL, Heineman TC, Lal H, Godeaux O, Chlibek R, Hwang SJ, McElhaney JE, Vesikari T, Andrews C, Choi WS, Esen M, Ikematsu H, Choma MK, Pauksens K, Ravault S, Salaun B, Schwarz TF, Smetana J, Abeele CV, Van den Steen P, Vastiau I, Weckx LY, Levin MJ; ZOE-50/70 Study Group**. Immune Responses to a Recombinant Glycoprotein E Herpes Zoster Vaccine in Adults Aged 50 Years or Older. *J Infect Dis*. 2018 May 5;217(11):1750-1760. doi: 10.1093/infdis/jiy095. PubMed PMID: 29529222; PubMed Central PMCID: PMC5946839.
8. **Stadtmauer EA, Sullivan KM, Marty FM, Dadwal SS, Papanicolaou GA, Shea TC, Mossad SB, Andreadis C,**

Young JA, Buadi FK, El Idrissi M, Heineman TC, Berkowitz EM. A phase 1/2 study of an adjuvanted varicella-zoster virus subunit vaccine in autologous hematopoietic cell transplant recipients. *Blood*. 2014 Nov 6;124(19):2921-9. doi: 10.1182/blood-2014-04-573048. Epub 2014 Sep 18. PubMed PMID: 25237196; PubMed Central PMCID: PMC4327150.

9. **Winston DJ, Mullane KM, Cornely OA, Boeckh MJ, Brown JW, Pergam SA, Trociukas I, Žák P, Craig MD, Papanicolaou GA, Velez JD, Panse J, Hurtado K, Fernsler DA, Stek JE, Pang L, Su SC, Zhao Y, Chan ISF, Kaplan SS, Parrino J, Lee I, Popmihajlov Z, Annunziato PW, Arvin A; V212 Protocol 001 Trial Team**. Inactivated varicella zoster vaccine in autologous haemopoietic stem-cell transplant recipients: an international, multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2018 May 26;391(10135): 2116-2127. doi: 10.1016/S0140-6736(18)30631-7. Epub 2018 May 24. PubMed PMID: 29856344.
10. **Arvin AM**. Humoral and cellular immunity to varicella-zoster virus: an overview. *J Infect Dis*. 2008 Mar 1;197 Suppl 2:S58-60. doi: 10.1086/522123. Review. PubMed PMID: 18419410.
11. **Carson K, Mehta J, Singhal S**. Chapter 35 – Reimmunization after stem cell transplantation. In: Treleaven J. Barrett AJ, eds. *Hematopoietic Stem Cell Transplantation in Clinical Practice*. Edinburgh: Churchill Livingstone; 2009:363-368.
12. **Ottinger HD, Beelen DW, Scheulen B, Schaefer UW, Grosse-Wilde H**. Improved immune reconstitution after allotransplantation of peripheral blood stem cells instead of bone marrow. *Blood*. 1996 Oct 1;88(7):2775-9. PubMed PMID: 8839875.
13. **Goenaga Vázquez Y, Cabanillas F, Concepción JR, Díaz Miranda OL**. Incidence and Risk Factors for Developing Herpes Zoster Among a Cohort of Patients Diagnosed With Lymphoma at a Community Cancer Center. *Clin Lymphoma Myeloma Leuk*. 2019 Mar;19(3):e153-e158. doi: 10.1016/j.clml.2018.12.001. Epub 2018 Dec 19. PubMed PMID: 30655095.
14. **Byrd JC, McGrail LH, Hospenthal DR, Howard RS, Dow NA, Diehl LF**. Herpes virus infections occur frequently following treatment with fludarabine: results of a prospective natural history study. *Br J Haematol*. 1999 May;105(2):445-7. PubMed PMID: 10233419.
15. **Brudno JN, Kochenderfer JN**. Toxicities of chimeric antigen receptor T cells: recognition and management. *Blood*. 2016 Jun 30;127(26):3321-30. doi: 10.1182/blood-2016-04-703751. Epub 2016 May 20. Review. PubMed PMID: 27207799; PubMed Central PMCID: PMC4929924.
16. **Williams KM, Hakim FT, Gress RE**. T cell immune reconstitution following lymphodepletion. *Semin Immunol*. 2007 Oct;19(5):318-30. Epub 2007 Nov 19. Review. PubMed PMID: 18023361; PubMed Central PMCID: PMC2180244.
17. **Russell AF, Parrino J, Fisher CL Jr, Spieler W, Stek JE, Coll KE, Su SC, Xu J, Li X, Schlienger K, Silber JL**. Safety, tolerability, and immunogenicity of zoster vaccine in subjects on chronic/maintenance corticosteroids. *Vaccine*. 2015 Jun 17;33(27):3129-34. doi: 10.1016/j.vaccine.2015.04.090. Epub 2015 May 8. PubMed PMID: 25964168.
18. **Castilla J, Godoy P, Domínguez A, Martínez-Baz I, Astray J, Martín V, Delgado-Rodríguez M, Baricot M, Soldevila N, Mayoral JM, Quintana JM, Galán JC, Castro A, González-Candelas F, Garín O, Saez M, Tamames S, Pumarola T; CIBERESP Cases and Controls in Influenza Working Group Spain**. Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza. *Clin Infect Dis*. 2013 Jul;57(2):167-75. doi: 10.1093/cid/cit194. Epub 2013 Mar 26. PubMed PMID: 23532475.
19. **Kovac M, Lal H, Cunningham AL, Levin MJ, Johnson RW, Campora L, Volpi A, Heineman TC; ZOE-50/70 Study Group**. Complications of herpes zoster in immunocompetent older adults: Incidence in vaccine and placebo groups in two large phase 3 trials. *Vaccine*. 2018 Mar 14;36(12):1537-1541. doi: 10.1016/j.vaccine.2018.02.029. Epub 2018 Feb 17. PubMed PMID: 29463421.
20. **Kroschinsky F, Stölzel F, von Bonin S, Beutel G, Kochanek M, Kiehl M, Schellongowski P; Intensive Care in Hematological and Oncological Patients (iCHOP) Collaborative Group**. New drugs, new toxicities: severe side effects of modern targeted and immunotherapy of cancer and their management. *Crit Care*. 2017 Apr 14;21(1):89. doi: 10.1186/s13054-017-1678-1. Review. PubMed PMID: 28407743; PubMed Central PMCID: PMC5391608.
21. **Hill JA, Li D, Hay KA, Green ML, Cherian S, Chen X, Riddell SR, Maloney DG, Boeckh M, Turtle CJ**. Infectious complications of CD19-targeted chimeric antigen receptor-modified T-cell immunotherapy. *Blood*. 2018 Jan 4;131(1):121-130. doi: 10.1182/blood-2017-07-793760. Epub 2017 Oct 16. PubMed PMID: 29038338; PubMed Central PMCID: PMC5755046.
22. **Zahid U, Shaukat AA, Hassan N, Anwer F**. Coccidioidomycosis, immunoglobulin deficiency: safety challenges with CAR T cells therapy for relapsed lymphoma. *Immunotherapy*. 2017 Oct;9(13):1061-1066. doi: 10.2217/imt-2017-0070. PubMed PMID: 29032736; PubMed Central PMCID: PMC6040055.