Cytokine storm: A detrimental overreaction

When it comes to responses by the body, the immune response is usually a good thing. Your body recognizes an invading pathogen that does not belong there: bacteria, a virus, and other substances. In response to these pathogens, the immune system must react in a regulated manner and then shut off when it has solved the problem. But sometimes this goes awry, creating an overactive reaction that does not turn off and can end up harming the body it is trying to protect.

One of these immune system overreactions has become fairly common in the last few months. After one year of dealing with the COVID-19 pandemic and being bombarded with new information about this disease daily, you may have encountered a term you had never heard before: cytokine storm. Cytokines are molecules released by the immune cells of the body that act as the signals of the immune system[1]. They perform critical functions during the immune response, such as regulating the immune cells of the body. They can tell certain cells to divide, to create other molecules, or can even signal them to turn off while also controlling other aspects of the body such as blood vessel dilation.

Cytokines are critical in modulating the immune response, making sure there is an appropriate level of activity. Cytokine release syndrome, also called a cytokine storm, occurs when there is an excessive production of cytokines, which then circulate throughout the body affecting different organs[2,3]. They then rile up other immune system cells, leading to hyperactivation of the immune system which may damage the body, including the lungs, the brain, and other organs.

This damage is reflected as a variety of symptoms in patients suffering a cytokine storm. One of the most common manifestations is a high fever due to the high levels of inflammation throughout the body[3]. Pulmonary (lungs), renal (kidney), neurological (brain), and hepatic (liver) function may also be affected (Figure 1). Treatments are focused on trying to maintain normal functioning of these along with suppressing the overactive immune system. For example, neutralizing the circulating antibodies or dampening the function of immune cells are usually used as treatments to subdue a cytokine storm[3].

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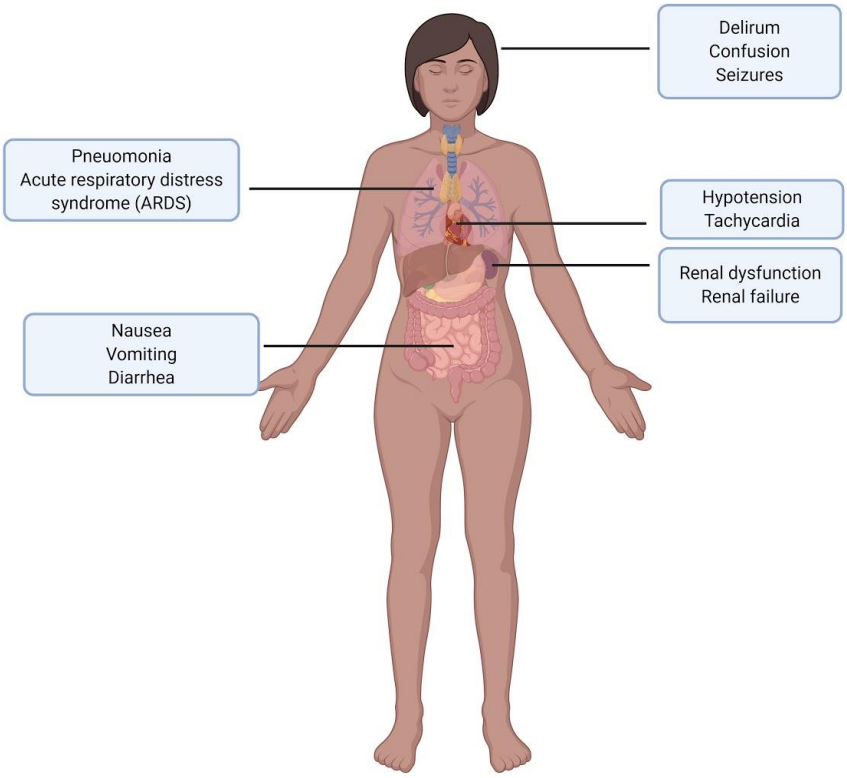

Figure 1. Symptoms associated with different organs in response to a cytokine storm (Adapted from Fajgenbaum & June, 2020).

Cytokine storms can occur in response to viral infection. For example, cytokine storms have been increasingly observed with SARS-CoV-2 infection, the virus that causes COVID-19. When COVID-19 cases started increasing, scientists and doctors were puzzled by a confusing observation: people were succumbing later in the progression of the disease or even after recovery[4]. Even when people were surviving the initial consequences of the infection, they found that the overactive immune response was leading to severe illness, organ failure, and sometimes death. In these cases, it was not the virus that led to this damage, but rather the exaggerated response of the body against the virus.

In these patients, doctors found high levels of cytokines such as interleukin 6 (IL-6), a pro-inflammatory cytokine that has been identified as a common driver of cytokine storms[5]. Cytokines from this family, called the interleukins, and from another family, interferons, are critical components of these storms[2].

In some ways, a cytokine storm can be likened to an autoimmune disease in which there is a faulty immune response. In autoimmune conditions such as autoimmune encephalitis (AE), the immune system mistakenly attacks the body by generating antibodies against important proteins. Similarly, a cytokine storm creates an overabundance of cytokines that can negatively affect bodily functions, although in a more general manner than the targeted antibodies created in AE.

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Unfortunately, people with autoimmune diseases are more susceptible to cytokine storms. Some studies suggest that autoimmune disorders themselves might be a trigger for cytokine storms. For example, studies show that IL-6, the same cytokine increased in COVID-19 patients with cytokine storms, is also increased in autoimmune disorders, including AE[6]. One study in patients with lupus suggests that people with autoimmune conditions could also be at higher risk of developing a cytokine storm in response to COVID-19[7].

Although there are no research studies linking cytokine storms specifically to AE, there have been case studies, in which one patient is observed, that suggest a potential relationship. In one of these case studies, researchers found that one patient diagnosed with COVID-19 had developed antibodies against the NMDA receptor, which led to a diagnosis of NMDA-receptor encephalitis. The patient also had increased levels of IL-6, which suggested that a cytokine storm was occurring[8]. Further research is needed to delve into the complex interaction between AE, COVID-19, and the development of cytokine storms.

References

1. Steinke, J., & Borish, L. (2006). Cytokines and chemokines. *Journal of Allergy and Clinical Immunology*, *117*(2). https://doi.org/10.1016/j.jaci.2005.07.001
2. Tisoncik, J. R., Korth, M. J., Simmons, C. P., Farrar, J., Martin, T. R., & Katze, M. G. (2012). Into the Eye of the Cytokine Storm. *Microbiology and Molecular Biology Reviews*, *76*(1), 16–32. https://doi.org/10.1128/mmbr.05015-11
3. Fajgenbaum, D. C., & June, C. H. (2020). Cytokine Storm. *New England Journal of Medicine*, *383*(23), 2255–2273. https://doi.org/10.1056/nejmra2026131
4. Ye, Q., Wang, B., & Mao, J. (2020). The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. *Journal of Infection*, *80*(6), 607–613. https://doi.org/10.1016/j.jinf.2020.03.037
5. Ragab, D., Eldin, H. S., Taeimah, M., Khattab, R., & Salem, R. (2020). The COVID-19 Cytokine Storm; What We Know So Far. *Frontiers in Immunology*, *11*. https://doi.org/10.3389/fimmu.2020.01446
6. Lee, W.-J., Lee, S.-T., Moon, J., Sunwoo, J.-S., Byun, J.-I., Lim, J.-A., … Chu, K. (2016). Tocilizumab in Autoimmune Encephalitis Refractory to Rituximab: An Institutional Cohort Study. *Neurotherapeutics*, *13*(4), 824–832. https://doi.org/10.1007/s13311-016-0442-6
7. Sawalha, A. H., Zhao, M., Coit, P., & Lu, Q. (2020). Epigenetic dysregulation of ACE2 and interferon-regulated genes might suggest increased COVID-19 susceptibility and severity in lupus patients. *Clinical Immunology*, *215*, 108410. https://doi.org/10.1016/j.clim.2020.108410
8. Panariello, A., Bassetti, R., Radice, A., Rossotti, R., Puoti, M., Corradin, M., … Percudani, M. (2020). Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: A case report. *Brain, Behavior, and Immunity*, *87*, 179–181. https://doi.org/10.1016/j.bbi.2020.05.054

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