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Hidradenitis Suppurativa Found Associated With Cytokine Storm

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory disease that generates multiple cytokines. Here, we present an example of the cytokines forming a cytokine storm and its effects on the patient.
Case Presentation: We report the case of a 55-year-old man who had severe but stable HS. Serum samples were collected from the patient and extraordinarily elevated cytokine concentrations were identified in the patient's serum.
Conclusion: Cytokine storms may be a condition associated with HS posing additional risk to patient survival.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory disease that causes painful, foul-smelling, and movement-restricting lesions in intertriginous regions. One of the primary therapies for HS and one of the two FDA-approved treatments for severe HS is adalimumab (Humira), a tumor necrosis factor (TNF-α) antagonist,[1,2] TNF-α plays a role in the inflammatory cascade, which can lead to a cytokine storm, excessive or uncontrollable release of proinflammatory cytokines.[3,4] Due to their high mortality rate, cytokine storms have garnered significant attention, as seen in events such as the avian influenza outbreak of 2005 and the COVID-19 pandemic.[4]

Both autoimmune disorders and pathogen-induced triggers can induce cytokine storms and HS can be considered an intersection of both.[2,3,5] HS, while not caused by a specific infection, is propagated by the presence of bacteria in and on the skin, agitating the immune system. The linkage between HS and autoimmune diseases, such as systemic lupus erythematosus and inflammatory bowel disease, has been observed.[5,6] Identification of cytokine storm patterns in HS will lead to a better understanding of the disease.

CASE

A 55-year-old male Caucasian man visited the clinic for HS treatment. The patient had Hurley stage 3, with the presence of dermal tunnels. The patient reported having no history of smoking, but was obese with a BMI of 39.5, noted as smoking and obesity are factors linked to HS severity.[5] The patient was not taking any pain medication and his HS was stable at the time of serum collection.

Serum cytokine levels for the patient and 3 HS-free healthy controls were measured in quadruplicate using a QAH-NEU cytokine array (RayBiotech).

DISCUSSION

Multiple cytokines were heavily upregulated in the serum of the HS patient (Table 1). Notable HS treatment target TNF-α was found to be upregulated in the patient compared to the healthy controls 7.47-fold. Also, among these were several proinflammatory cytokines. Interleukin 1β (Il-1β) was the most upregulated with over 400-fold expression and is associated with inflammasome activity. It can amplify the cascade and induce the activation of other cytokines such as IL-6, IL-8, and MCP-1, which were upregulated in the patient 25-fold, 21.6-fold, and 2.54-fold, respectively.[4] Elevated IL-1β and IL-6 are known to be correlated with more severe inflammation and worse disease outcomes.[6] IL-6 is also associated with restricting the development of T-regs, immune cells responsible for suppressing immune response and maintaining self-tolerance.[7] Both IL-6 and IL-8 play a major role in the attraction of neutrophils to inflammation sites.[1]

TABLE 1.

Cytokines Measured in HS Patients and Average of Healthy Controls as Well as the Fold Change Between the Two Groups

Symbol	Name	Concentration in pg/mL		Fold Change
		HS	HC	
IL-1β	Interleukin 1 beta	8216	20.00	410.80
IL-1α	Interleukin 1 alpha	202	1.33	151.50
IL-4	Interleukin 4	5393	38.33	140.69
LIF	Leukemia inhibitory factor	213	2.00	106.50
β-NGF	Beta-nerve growth factor	278	2.67	104.25
VEGF	Vascular endothelial growth factor	3541	41.33	85.67
CNTF	Ciliary neurotropic factor	79084	1214.67	65.11
TGFβ1	transforming growth factor-beta	148495	2997.67	49.54
Eotaxin-3	C-C motif chemokine ligand 26	28910	619.33	46.68
IFNγ	Interferon gamma	1320	39.33	33.56
GDNF	Glial cell derived neurotropic factor	1046	40.33	25.93
IL-6	Interleukin 6	766	30.67	24.98
IL-8	Interleukin 8	1232	57.00	21.61
MMP-2	Matrix metalloproteinase-2	3138	170.33	18.42
Fas	Fas receptor	608	34.33	17.71
TARC	C-C motif chemokine 17	13907	916.67	15.17
IL-10	Interleukin 10	53	4.00	13.25
GM-CSF	Granulocyte-macrophage colony-stimulating factor	1174	92.33	12.71
TNFα	Tumor necrosis factor	13781	1844.67	7.47
EGF	Epidermal growth factor	11	4.00	2.75
MCP-1	Chemokine ligand 2	296	116.67	2.54
IL-18	Interleukin 18	59	34.67	1.70
MIP-1β	Macrophage inflammatory protein-1β	13	8.00	1.63
Eotaxin	C-C motif chemokine ligand 11	72	47.33	1.52
MMP-3	Matrix metalloproteinase-3	9138	7264.33	1.26
Eotaxin-2	C-C motif chemokine ligand 24	163	153.33	1.06
RANTES	Chemokine ligand 5	1371	1376.33	1.00
TIMP-1	TIMP metallopeptidase inhibitor 1	1006	1102.33	0.91
BDNF	Brain-derived neurotrophic factor	1104	2582.33	0.43

Interleukin 1α (IL-1α), interleukin 4 (IL-4), β-nerve growth factor (NGF), and leukemia inhibitory factor (LIF) were all heavily upregulated, with over 100-fold expression. IL-1α binds to the same receptor, IL-1R1, as IL-1β.[8] IL-4 is linked to the immune response, causing helper T cells to release more cytokines but also serves an anti-inflammatory role.[7] NGF plays a role in the survival and differentiation of neurons but has also been found highly upregulated at sites of inflammation, possibly promoted by IL-1β, TNFα, and IL-6.[9] While LIF is of the same family as IL-6, recent studies showed that LIF could act in opposition to IL-6 and be an indicator of increased immune tolerance and reduced IL-6 activity.[10]

Interferon-γ (IFNγ) was also found 33.6-fold upregulated. IFNγ is a proinflammatory cytokine and is involved in the activation of macrophages.[3] IL-18 was also elevated (1.7-fold), which can cause an increased presence of IFNγ.[3]

Interestingly, IL-10 was also upregulated (13.25-fold) despite being an anti-inflammatory interleukin. Production of IL-10 following the onset of a cytokine storm is an example of the body mounting an anti-inflammatory response to overstimulation of the immune response, but prolonged periods in this state of "immunoparalysis" can still be hazardous.[4] This could indicate that the patient was recovering from a cytokine storm or was in the process of reducing inflammation.

Regardless, circulating cytokine levels have short half-lives, so to identify the remnants of a cytokine storm is a great opportunity to further our understanding of HS. Linkage of cytokine storms to HS can also open the investigation of shared treatments, giving HS patients access to a plethora of cytokine storm-related therapies.

DISCLOSURES

The authors have no conflicts to disclose.

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