these pathologies and/or genetic syndromal PG being more frequent than we think.

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Should we look beyond the interferon signature in chilblain-like lesions associated with COVID-19?

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The appearance of chilblain-like lesions (CLL) ('COVID toes') during the COVID-19 pandemic has been associated with a type I interferon (IFN) response that is present in asymptomatic and mild cases,[1] but not in severe disease.[2] The link between IFN signalling and CLL is supported by the occurrence of chilblains in inherited type I interferonopathies.[3] Type I IFNs typically participate in the innate immune response to viral pathogens and are powerful inflammatory molecules expressed by both immune and nonimmune cells. The accumulation of double-stranded nucleic acids in the nucleus results in cytotoxic sensing by Toll-like receptors, retinoic acid-inducible gene receptors and NOD-like receptors that initiate a signalling pathway resulting in expression of IFN regulatory factors -7 and -3, inducing IFN-β and IFN-α, respectively. The IFN-α response is greater in infancy and childhood, but decreases with age,[4] which may explain why CLL are more prevalent in younger individuals.

While there are many reports of CLL in association with the COVID-19 outbreak, Frumholtz *et al.*[5] are the first to study the pathophysiology of these cutaneous lesions using transcriptomics, and to include comparisons with a number of control groups (healthy individuals, those with a history of seasonal chilblains, and those without chilblains who tested positive for COVID-19). Analysis of blood markers – in addition to histological comparisons – revealed a systemic and local immune response characterized by a type I IFN signature and IgA antineutrophil cytoplasmic antibodies, in addition to endothelial dysfunction. Viral particles of SARS-CoV-2 have previously been detected in the cytoplasm of skin endothelial cells, supporting an association between the virus and CLL.[6] In cases of severe COVID-19 disease, SARS-CoV-2 particles were also detected in endothelium of other organs in association with endothelialitis resulting in the hypothesis that stabilization of endothelium maybe beneficial for vulnerable patients.[7]

However, while transcriptomic analysis supports the role of IFN signalling in endothelial dysfunction in both CLL and seasonal chilblains, other contributing factors should be considered. Interestingly, it has been proposed that mast cell hyperactivation could contribute to COVID-19 progression and to cutaneous manifestations. Ricke *et al.*[8] suggest that viral-driven vascular ischaemia and mast cell-derived histamine are primary initiating factors in COVID-19-related cutaneous lesions. As SARS-CoV-2 is predicted to bind and activate the cyclooxygenase-2 promoter,[9] a subsequent increase in prostaglandin E2 expression could facilitate hyperactivation of mast cells. However, this theory remains to be explored.

Another interesting consideration is the role of sex hormone differences. The angiotensin-converting enzymes 1 and 2 provide entry of the SARS-CoV-2 virus into endothelial cells and in male patients, there is a preference for downstream activation of the angiotensin (AT)1R, compared with AT2R, which is more predominant in female patients.[10] AT2R activation results in increased nitric oxide (NO), vasodilation and anti-inflammatory effects; in contrast, AT1R activation results in decreased NO, vasoconstriction and inflammation,[11] potentially contributing to the prevalence of CLL in men.

Still, there is no proven direct causality between COVID-19 and CLL and a recent epidemiological analysis suggests that changes in behaviour during the pandemic may have resulted in increased diagnosis of chilblains.[12] Thus, while this article contributes important insights into the pathophysiology of CLL, further exploration of the wider tissue inflammatory response, and the influence of age and sex could be explored to better understand the impact of COVID-19 and guide treatments for associated cutaneous effects.

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Understanding the paradoxical proinflammatory effects of an immunosuppressant

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Glucocorticoids are frequently used as immunosuppressive treatment in skin disease and asthma. Glucocorticoids bind to a protein called the glucocorticoid receptor in the cytoplasm of cells, which then translocates to the nucleus and binds DNA, activating transcription.[1] From an epidermal standpoint glucocorticoid treatment can accelerate epidermal barrier formation,[2,3] suggesting a still not fully understood link between innate immunity and epidermal barrier function. There is also a paradoxical side-effect of glucocorticoid treatment, in that it can induce a rosacea-like disease.[4] Why is it that treatment with an immunosuppressive drug can induce an immune response in the skin? This is the question that Wang *et al*. address in this issue of the *BJD*.[5]

Dexamethasone is an inhaled steroid used to treat asthma. In the lung, there is increased expression of the proinflammatory cytokine CCL20 and its cognate receptor CCR6 in response to dexamethasone treatment.[6] Interestingly, increased CCL20 has been observed in a mouse model of rosacea,[7] leading to the possibility that glucocorticoids increase CCL20 expression. Sure enough, treatment with the glucocorticoid dexamethasone in cultured keratinocytes and mouse epidermis led to the upregulation of CCL20, but – interestingly – also reduced expression of another classical proinflammatory cytokine, interleukin (IL)-1β. Furthermore, differentiating keratinocytes, which produce more of the key epidermal barrier proteins keratin 10 and filaggrin, produced increased levels of CCL20, even in the absence of an immune insult, suggesting that CCL20 induction in response to glucocorticoids is more specifically related to epidermal barrier function.

Tumour necrosis factor (TNF)-α is a key inducer of immune response in the skin. Glucocorticoids reduced TNF-α-mediated proinflammatory cytokine expression via the reduction of p38 mitogen-activated protein kinase (MAPK).[8] p38 MAPK controlled CCL20 expression in response to TNF-α, independently of classical proinflammatory pathways. The glucocorticoid receptor bound to regions of DNA upstream of CCL20 to enhance gene expression but not to similar regions of other proinflammatory cytokines, further strengthening the concept of a specific CCL20-mediated response to glucocorticoids.

These data reinforce the importance of CCL20 in an epidermal barrier and proinflammatory response, distinct from the typical proinflammatory response. However, an open question is whether the increase in CCL20 represents part of the T helper 17 cytokine signature typically seen in psoriasis,[9] or is this a more specific glucocorticoid-related response? Could CCL20 function be suppressed to reduce the proinflammatory side-effects of glucocorticoids? While there are no specific CCL20 inhibitors, there are small-molecule inhibitors of the cognate receptor CCR6,[10] which suggests that there may be promise in being able to dissect therapeutically the barrier restorative properties of glucocorticoids from their paradoxical proinflammatory side-effects.