Our arsenals for fighting off bacteria are so powerful, and involve so many different defense mechanisms, that we are in more danger from them than the invaders. We live in the midst of explosive devices; we are mined.

--Lewis Thomas, MD
The Lives of a Cell

Although the late Dr. Thomas was actually referring to bacterial sepsis, his statement could easily have applied to the cytokine "storm" of HIV infection and Kaposi's sarcoma (KS). This cytokine dysregulation, nicely described in the article by the UCLA group, is one of the major culprits responsible for the proliferation of KS in HIV-infected patients. The abnormally high cytokine levels are produced not only by HIV infection and opportunistic and nonopportunistic infections but also by the KS cells themselves.
The paracrine and autocrine effects of these cytokines can lead to both the development of KS lesions and the proliferation of preexisting lesions. The tremendous synergy between cytokines and the HIV tat protein provides a possible insight into why AIDS-related KS (AIDS/KS) is much more virulent than the classic Mediterranean form of KS in older men, in which HIV tat protein would not be expected to play any role.

Two Important Clinical Scenarios
Two important clinical scenarios, in particular, need to be kept in mind, given the prominent role that cytokine dysregulation plays in the pathogenesis of KS. The first scenario is that of corticosteroid therapy, which has been associated with the induction of KS and with the exacerbation of preexisting KS in HIV-infected persons [1,2], as well as in non-AIDS patients, such as those receiving steroids for organ transplantation, autoimmune disorders, or lymphoproliferative diseases [3]. Steroid use is not uncommon in HIV-infected patients, who have a variety of disorders, including immune thrombocytopenic purpura and Pneumocystis carinii pneumonia. Kaposi's sarcoma lesions may regress upon reduction or withdrawal of steroids [1-3]. The laboratory correlate of these clinical observations is the in vitro stimulation of AIDS/KS cells by dexamethasone [4]. Furthermore, simultaneous exposure to dexamethasone and oncostatin-M (Onco-M), a major cytokine involved in the pathogenesis of KS, produces a dramatic synergistic effect on the proliferation of AIDS/KS cells, suggesting an interaction between glucocorticoid and growth factor intracellular pathways in these cells [4].
The second scenario is that of opportunistic infections, which also have been associated with the induction of KS and with the exacerbation of preexisting KS similar to that described above with corticosteroid therapy. As the authors note, high levels of tumor necrosis factor-alpha (TNF- alpha), interleukin-1 beta (IL-1 beta), and interleukin-6 (IL-6), which have been demonstrated in the setting of opportunistic infections, may account for the above-mentioned effects on KS. High levels of IL-6 have been found in patients with KS and may precede the development of the disease in HIV-infected men [5]. Finally, the recent demonstration of sequences of the KS-associated herpes virus (KSHV) in KS lesions is truly a seminal observation [6]. This striking association has quelled much of the previous controversy regarding the roles of cytomegalovirus, Epstein-Barr virus, human papilloma virus, mycoplasma, and inhaled nitrites in the pathogenesis of KS. As aptly stated by the authors, the exact role of KSHV in the pathogenesis of KS will require further research--an extraordinary tale that we will eagerly follow as it unfolds.

Plausible Model of Pathogenesis
The authors' model of the pathogenesis of KS is plausible. In brief, they suggest the following steps
in pathogenesis:

1. transformation of normal mesenchymal cells to a "pre-KS" cell by KSHV;
2. proliferation and differentiation of the KS tumor stimulated by the cytokine dysregulation brought on by HIV infection, opportunistic and nonopportunistic infections, and the KS cells themselves;
3. further proliferation of the KS tumor induced by the synergy between cytokines and the HIV tat protein and, in certain clinical settings, by the synergy between cytokines and exogenous steroids; and
4. transformation of KS into a more malignant phenotype as HIV induces greater immunosuppression and as tumors enlarge.

This model of a progressively aggressive tumor may explain why KS is contributing more and more to both morbidity and mortality in HIV-infected individuals as they live for progressively longer [7]. New treatments based on the pathogenesis of KS, as the authors note, are a direct consequence of this model; these treatments involve inhibition of KSHV, inhibition of cytokine production or blockade of cytokine receptors, inhibition of angiogenesis, and blockade of intracellular signal transduction.

References:

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