Loss of Endothelial Surface Expression of E-Selectin—A Third LAD Syndrome?

To the Editor:

The recent report by DeLisser et al[1] is very interesting, proposing a third syndrome of human neutrophil adhesion cascade defect. A child with severe recurrent infections and low expression of E-selectin on blood vessel endothelium caused by increase cleavage of E-selectin is described. In contrast to the other 2 known syndromes, this patient missed 2 of the main hallmarks of the syndromes: leukocytosis and persistent periodontitis.[2,3] An experimental model resembling this report is the E-selectin knockout mice.[4] In this model no leukocytosis is observed, but in sharp contrast to the reported patient, the mice do not suffer from severe infections. The clinical picture of the patient is reminiscent of the severe form of leukocyte adhesion deficiency I (LAD I). On the other hand, LAD II involving the selectin system has a milder course.[3]

In the mouse model, it was shown that P-selectin can compensate for the lack of E-selectin, and only when both selectins are blocked does a marked defect in neutrophil adhesion to the endothelium occur.[4] With this in mind, how can the discrepancy between the clinical picture and the laboratory findings be explained? One possible explanation not addressed in the report is persistent and prolonged activation of neutrophils due to the continuous high blood level of soluble E-selectin. This high level, which persisted when the child was free of infection, could cause neutrophil activation.[5] This activation may induce increased apoptosis of neutrophils leading to the observed neutropenia. To clarify this situation, several additional studies could be performed. The expression of activated epitopes of the CD18 molecule can be looked at on unstimulated circulating neutrophils.[6] Kinetic studies investigating the half-life of the neutrophils may help to understand the cause of the neutrophenia. Such studies were previously very informative in LAD I and LAD II.[7]

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Response

The issue of peridontal disease is an important one. Our patient has had chronic peridontitis, the severity of which has been mild, possibly as a result of the long courses of antibiotics for her infections. We do not disagree with Dr Etzioni that mechanisms other than the mere absence of E-selectin from the endothelium may be responsible for this patient's clinical syndrome, given mouse data which suggest that in certain models of inflammation, P-selectin may be able to compensate for the chronic absence of E-selectin. We, in fact, indicated this in our discussion and suggested that the increased levels of soluble (s)E-selectin may also be a factor in this patient that contributes to leukocyte dysfunction. We are grateful to Dr Etzioni for indicating another mechanism by which sE-selectin might be playing a role in this patient's clinical picture and his suggestions for further studies. With respect to studies of mice with targeted deletions of the selectins, we would note, as we indicated in our report, that there is also evidence which suggests that P-selectin and E-selectin may have some distinct, nonoverlapping functions,[1,2] and as others have done, would urge caution in extrapolating data from murine knockout studies to humans.[3,4]

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