Table 1. Anti-VZV IgM and IgG Antibody Levels in Patients with Zoster and Varicella Compared to Control Subjects.

	IgG Mean (U/ml) ± SE	IgM Percent of positive
Control	1090.63 ± 166.87 (n = 8)	0% (n = 9)
Zoster	4585.30 ± 774.91 (n = 17)	22% (n = 18)
Varicella	974.50 ± 183.05 (n = 10)	80% (n = 10)

DISCUSSION

Immune activation, as reflected by marked increase of T cell antigens, cytokines, cytokine receptors, or adhesion molecules, has been shown in a wide variety of virus infections[8-13] and immune-mediated diseases.[14-20] In our current study of primary and recurrent infections of VZV, we found significant increases in sCD4, sCD8, and sCD25. Since these antigens are markers of T cell subsets (CD4 for helper, CD8 for cytotoxic, and CD25 for activated T cells), their increase in patients' sera indicates activation of T cells in VZV disease. The increase of sCD4 in zoster as well as varicella patients suggests activation of helper T cells in both primary and recurrent infections of VZV. The sCD8 increase was seen in varicella patients only, which implies activation of cytotoxic T cell activation in primary VZV infections. sCD25 was increased in zoster and varicella patients, which also suggests activation of helper T lymphocytes because CD25 is expressed mainly by activated helper T cells. These findings clearly demonstrate that primary VZV infection leads to activation of helper T cells, a phase that continues well into the secondary zoster phase. VZV infection, however, induces immunosuppression as indicated by a significant increase of sCD8 in varicella infection. Immune suppression may result from either increased cytotoxic cells (or) associated cytotoxic factors or decreased helper cells (or) associated helper factors. Immune suppression is indicated in VZV infections.

In addition to T cell-derived immune activation antigens, we also measured anti-VZV IgM and IgG antibodies. This was done to assess the helper/cytotoxic function of T cells in patients with VZV infection. The IgG antibody increase in zoster infection, but not in varicella infection, is likely due to hyperactivity of helper cells that persists into the recurrent phase when IgM antibodies become less prevalent. Thus, the immune activation profile, to some degree at least, parallels the antibody responses, which indirectly correspond with the viral phases of the infection. In our study, IgM was positive in 22% of zoster patients, whereas, according to Kangro et al.,[24] IgM is positive in 98% of zoster patients using IgM antibody-capture radioimmunoassay (MACRIA). The differences between the sample size (n = 18 in our study vs. n = 233 in their study) and the method used (EIA vs. MACRIA) may have contributed to this discrepancy. Direct measurements of various immune factors, in particular T cell-derived cytokines in vivo, will be necessary to understand the basis of antibody responses in VZV infections.

Increases of sCD4, sCD8, and sCD25 in VZV infections are consistent with reports of immune activation in other virus infections and immune-mediated diseases. Heightened levels of sCD4 have been found in human immunodeficiency virus (HIV),[10] dengue virus infection,[12] lymphoma and leukemia,[23] rheumatoid arthritis,[15] protozoan infection,[25] and Kawasaki disease.[20] Elevated levels of sCD8 and IL-2R are generally found in organ-specific autoimmune disease,[14,16] including those involving the nervous system.[18,19] Furthermore, the cytokine profile determines the nature of the specific immune response elicited in a disease, and thus the measurement of circulating cytokines is of considerable clinical significance. For example, a specific increase of interleukin-12 (IL-12) and interferon-gamma (IFN-γ) but not other cytokines points to a pathogenic role of Th1 cells in autism,[18] a disorder of the brain and development with suspected viral etiology. Since VZV is a neurotropic virus, it would be extremely important to analyze cytokine profiles in zoster and varicella infections. The identification of cytokine(s) should help elucidate the basis of T cell activation, as reported herein, for the pathogenesis of VZV-induced disease in man. Depending upon the primary or secondary nature of infection, we found evidence for activation of both helper and cytotoxic T cells, which may contribute to the severe complications of VZV infection.