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# VARICELLA ZOSTER VIRUS-SPECIFIC CELLULAR IMMUNITY IN IMMUNOCOMPETENT AND IMMUNOCOMPROMISED PATIENTS WITH ACUTE HERPES ZOSTER SHOWS DISTINCT ALTERATIONS OF PHENOTYPE AND FUNCTIONALITY

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Objectives: Varicella zoster virus (VZV) establishes lifelong persistence and may frequently reactivate in immunocompromised patients such as hemodialysis patients (HD) and transplant recipients (Tx). To assess correlates of protection and to identify immunologic parameters associated with acute VZV-reactivation, T-cell immunity and IgG responses towards VZV were characterised in 59 immunocompetent and immunocompromised patients with acute herpes zoster and compared with those of 98 patients and controls without VZV reactivation (11 healthy controls, 37 HD and 50 Tx patients).
Methods: VZV-specific CD4 T cells were analyzed after whole blood stimulation with VZV-lysate using intracellular staining for IFNg, IL-2, and TNFa. CD127, CTLA-4 and PD-1 were chosen as markers for functional anergy. Stimulation with VZV-free control-lysates and the superantigen *Staphylococcus* Enterotoxin-B (SEB) served as negative and positive controls, respectively. IgG titers were assessed using standard ELISA.
Results: VZV-seropositive non-symptomatic immunocompetent controls had median frequencies of VZV-specific CD4 T cells of 0.15% (0.03-0.29%). The VZV-specific T-cell profile showed multifunctional characteristics, marked by a predominant expression of all three cytokines (median 54.0%, IQR 9.8%; IFNg-single positive cells: median 5.2%, IQR 4.0%), but low expression of the inhibitory receptors CTLA-4 (MFI 1081±654) and PD-1 (MFI 215±94). Moreover, nearly all cells were positive for CD127 (96.0±6.2%). Non-symptomatic immunocompromised patients had similar T-cell properties showing only slightly lower median frequencies (p=0.02) and percentages of multifunctional (IFNg, IL-2, and TNFa positive) VZV-specific cells (p=0.12). In contrast, elevated IgG titers (median 7102 IU/L, IQR 2912 IU/L) as well as frequencies of VZV-specific CD4 T-cells (median 0.40%, IQR 0.64%) were found in both immunocompetent and immunocompromised patients with acute herpes zoster. The cytokine-profile of VZV-specific T cells was shifted towards IFNg-single positive cells (27.0±21.4%). Furthermore, these T-cells showed a significant increase in CTLA-4 and PD-1 expression, and a concomitant decrease in CD127 expression, whereas there was no effect on polyclonally stimulated T-cells. Interestingly, VZV-specific T cells analysed >3 months after acute reactivation reverted back to the phenotype observed in non-symptomatic individuals.
Conclusions: VZV-specific CD4 T cells in patients with acute herpes zoster are elevated in frequencies and bear typical features of anergic cells such as increased expression of CTLA-4 and PD-1, decreased expression of CD127, and restricted functionality, marked by an increased percentage of IFNg-single positive cells. This dynamic phenotype may be applied for monitoring infectious complications in patients at risk.