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KSHV activation, human and viral IL-6 production, and other cytokine dysregulation: Association with the symptomatology of KSHV-associated multicentric Castleman's disease

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Background

KSHV-associated multicentric Castleman's disease (MCD) is a frequently fatal lymphoproliferative disorder characterized by inflammatory flares of fever, cytopenias, hypoalbuminemia, hyponatremia, and splenomegaly. Most cases occur in HIV-infected patients. KHSV viral interleukin-6 (vIL-6), human IL-6 (hIL-6), and possibly other proinflammatory cellular cytokines are believed to contribute to the pathophysiology of MCD flares.

Methods

We identified MCD patients with clinical flares. KSHV viral load (VL) in peripheral blood mononuclear cells, vIL-6, and the cellular cytokines IL-6, IL-1b, IL-8, IL-10, IL-12p70, interferon gamma, and tumor necrosis factor alpha were measured during flares and remissions to identify parameters best characterizing flares. The assay for vIL-6 was modified from Aoki Y. et al., Blood, 97, 2526, 2001; the cutoff of detection was 1560 pg/ml. Factors statistically associated with flares ($p<0.01$) were explored in relationship to common disease manifestations with multiple linear regression models.

Results

20 patients (18 male, 2 female) were studied during 33 flares (range 1-3 per patient) and, in 18 patients, remission with therapy. Median (range) values of key parameters during flares included hemoglobin 9.9 mg/dL (6.8-14.4); platelet count 97 K/μL (6-377); sodium 133 mEq/L (127-143); albumin 2.7 mg/dL (1.2-3.9); spleen size 14.5 cm (9-28); temperature 38°C (36.1-40.5); CD4 count 240 cells/μL (24-1319); HIV VL <50 copies/mL (<50-64100). Flares were associated with elevated KSHV VL (median 23448 copies/mL; range 0-3913043; $p<0.0001$ compared with remission), vIL-6 (2575 pg/mL; <1560-20497; $p=0.0039$), hIL-6 (24.2 pg/mL; 1.4-171.5; $p=0.0034$), hIL-10 (783.9 pg/mL; 2.8-26021; $p=0.0027$), and hIL-1b (1.3 pg/mL; 0-11.3; $p=0.0074$). In two of the 33 flares vIL-6 was elevated but hIL-6 was not; in 14 hIL-6 was elevated but vIL6 was undetectable; and in 15 both were elevated. Neither was initially elevated in 2 flares, but hIL-6 later became elevated in both. Disease manifestations did not differ among flares with differing vIL-6/hIL-6 profiles. In multiple regression analysis, elevated KSHV VL was the strongest predictor of level of hemoglobin ($p<0.0001$), sodium ($p<0.0001$), albumin ($p<0.0001$), and spleen size ($p=0.0002$); hIL-6 the strongest predictor of thrombocytes ($p=0.0011$), and KSHV and hIL-6 together the strongest predictors of body temperature ($p<0.0001$). For hemoglobin, but not other parameters, vIL-6 and hIL-6 in combination were stronger predictors than either independently ($p=0.0002$), though less strong than KSHV VL alone.

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Conclusions

KSHV activity, vIL-6 production, and associated human hIL-6 dysregulation are key determinants of the clinical manifestations of MCD. vIL-6 and hIL-6 each appear sufficient to induce flares without the other. hIL-10 and hIL-1ß are also elevated in MCD flares, but their contribution to symptomatology remains to be determined.

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