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Serum levels of vascular cell adhesion molecule 1 in the early post-treatment defervescence phase of falciparum malaria

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Abstract Elevated plasma or serum levels of vascular cell adhesion molecule 1 (VCAM-1) have been reported in the febrile phase of falciparum malaria. However, little is known about serum VCAM-1 levels in the early post-treatment defervescence phase. Serum VCAM-1, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and creatinine levels were determined in six Japanese patients with uncomplicated falciparum malaria during the acute febrile phase and the early post-treatment defervescence phase. The serum VCAM-1 values recorded for patients during the early post-treatment defervescence phase were significantly lower than those noted during the febrile phase (P < 0.05), but no significant difference in serum creatinine values was identified. TNF-α and IL-1β levels were below the limit of detection in the serum of all patients during both the febrile phase and the early post-treatment defervescence phase. The serum levels of VCAM-1 were not related to parasitemia.

Introduction

Falciparum malaria is a distinctive acute systemic febrile disease caused by Plasmodium falciparum infection. Because of its high morbidity and mortality, this parasitic disease is a major clinical and public health problem in endemic areas in tropical and subtropical countries, and it is now becoming an important problem as an infectious disease imported into nonendemic developed countries from endemic areas.

Vascular cell adhesion molecule 1 (VCAM-1), a member of the immunoglobulin superfamily, binds cells that express the very late antigen 4 (α1β1) and α4β7, such as lymphocytes (Elices et al. 1990), eosinophils (Bochner et al. 1991; Walsh et al. 1991), basophils (Bochner et al. 1991), and monocytes (Rice et al. 1990). VCAM-1 is found on cytokine-activated endothelial cells (Osborn et al. 1989) as well as on epithelial cells, macrophages, and dendritic cells (Rice et al. 1991). Elevated levels of serum VCAM-1 have recently been detected during the febrile phase of falciparum malaria (Boehme et al. 1994), but little is known about serum levels of VCAM-1 during the early post-treatment defervescence phase.

In the present study we measured serum levels of VCAM-1 together with tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in patients during the febrile phase and the early post-treatment defervescence phase of falciparum malaria, and we discuss herein the correlations between the levels of VCAM-1 and these cytokines.

Patients and methods

Patients

Serum samples obtained from six Japanese patients with acute-phase falciparum malaria (three men and three women, mean age ± SD 50.2 ± 14.4 years, range 28–66 years) were tested for levels of VCAM-1, TNF-α, IL-1β, and creatinine during the febrile and the early post-treatment defervescence phases. None of the patients had cerebral malaria. The interval between the onset of illness and the time of sampling was 2–7 days (mean 3.8 days) during the febrile phase and 4–7 days (mean 5.1 days) during the early post-treatment defervescence phase. Parasitemia resulting from the presence of trophozoites and schizonts of P. falciparum in the patients was <0.1–10.8% and 0 during the febrile and early post-treatment defervescence phases, respectively. All patients had contracted the disease outside Japan and were diagnosed by confirmation of the presence of P. falciparum in their blood. All patients received a standard regimen consisting of sulfadoxine pyrimethamine, mefloquine, or quinine dihydrochloride, and good clinical and parasitologically therapeutic effects were obtained. Patients showed no evidence of malignant disease, collagen disease, vascular disease, or infectious disease other than falciparum malaria. The serum samples were stored at −30 °C until assayed.

This study was approved by the Clinical Research Committee of the Tokyo Metropolitan Bokutoh General Hospital.
Assays

Serum VCAM-1 and TNF-α were measured with sandwich enzyme-linked immunosorbent assay kits (VCAM-1: R&D Systems Europe, UK; TNF-α: Japan Immunoresearch Laboratories, Japan). Serum IL-1β was measured by the immunoradiometric assay method (BioSource Europe, Switzerland). Serum creatinine levels were also determined by a creatinase enzyme method (Iatron, Japan).

Statistical analysis

Statistical analysis was performed using Student’s t-test for assessment of the differences between values recorded during the febrile and the early post-treatment defervescence phases for the same patients. A level of \( P < 0.05 \) was considered statistically significant.

Results

Serum VCAM-1 levels

The results are shown in Fig. 1. The serum VCAM-1 levels were significantly lower during the early post-treatment defervescence phase than during the febrile phase in all of the patients \( (P < 0.05) \).

![Graph showing serum levels of VCAM-1](image)

**Fig. 1** Serum levels of VCAM-1 as determined during the acute febrile phase and the early post-treatment defervescence phase in patients with uncomplicated falciparum malaria

Serum TNF-α, IL-1β, and creatinine levels

Serum TNF-α and IL-1β levels were below the limit of detection during the febrile phase as well as the early post-treatment defervescence phase in all patients. No significant difference in serum creatinine levels was identified between the febrile phase and the early post-treatment defervescence phase \( (P > 0.1) \).

Discussion

Although only small numbers were involved, we report herein that the elevated serum VCAM-1 levels recorded during the febrile phase decreased during the early post-treatment defervescence phase and that this decrease in serum VCAM-1 levels should reflect the efficacy of the therapy against malaria. Although one study has shown that patients with renal failure have higher serum VCAM-1 levels than do controls (Gearing et al. 1992), the absence of any significant difference between the febrile phase and the early post-treatment defervescence phase with regard to serum creatinine levels in the present study suggests that the elevated serum VCAM-1 levels could not be attributable to delayed clearance from the kidney. Serum or plasma levels of VCAM-1 have been reported to be elevated in a variety of infectious diseases (Gearing and Newman 1993), malignant diseases (Gearing and Newman 1993), collagen diseases (Gearing and Newman 1993), and vascular diseases (Gearing and Newman 1993; Hwang et al. 1997), but to our knowledge, none of the patients in our study suffered from any disease known to cause increased levels of adhesion molecules other than falciparum malaria.

VCAM-1 has been demonstrated in vitro in supernatants of TNF-α- and IL-1β-stimulated endothelial cells (Pigot et al. 1992), and another report has shown that plasma levels of TNF-α are higher in fatal cases of falciparum malaria than in nonfatal cases (Kwiatkowski et al. 1990). In our study, serum TNF-α and IL-1β levels were below the limit of detection in both the febrile phase and the early post-treatment defervescence phase in all patients. These findings may indicate that the elevations in serum VCAM-1 did not reflect the serum levels of those cytokines during the febrile phase of falciparum malaria in our patients, but more studies are needed on the mechanism underlying elevation of serum levels of VCAM-1 in falciparum malaria. Since TNF is accepted as a primary mediator associated with the severity of malaria (Kwiatkowski et al. 1990), the observation that serum TNF-α levels were not elevated in our patients may indicate that their condition was not serious.

It is well known that both infected and uninfected red blood cells are sequestered in patients with falciparum malaria, and the pathogenesis of falciparum malaria is due largely to this sequestration. Postmortem brain tissue from patients who had died from cerebral malaria expressed multiple cell adhesion molecules, including E-selectin and VCAM-1, on cerebral microvascular