Diagnosing latent tuberculosis with interferon-gamma release assays in patients with concurrent malaria in Tanzania

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Introduction

Interferon-gamma (IFN-γ) release assays (IGRAs) are based on the principle that T-cells of individuals who have acquired TB infection respond to re-stimulation with *Mycobacterium tuberculosis*-specific antigens by secreting interferon gamma (IFN-γ). The chemokine Interferon-gamma inducible protein 10 (IP-10) is an alternative biomarker to IFN-γ. Assays measuring IFN-γ or IP-10 can be used to diagnose latent tuberculosis infection; however, a wide range of immunosuppressive conditions are known to interfere with IGRA test performance, such as HIV infection, helminth infection, glucocorticoid treatment, severe disease in children, cigarette smoking, etc.

The aim of this study in Tanzania was to assess the influence of acute *Plasmodium falciparum* malaria on the performance of the commercially available IGRA test QuantiFERON TB GOLD® In Tube Test (QFT) and an in-house IP-10 release assay.

Methods

Study participants included adult patients (>15 years) with confirmed uncomplicated *P. falciparum* malaria at Muheza District Hospital in north-eastern Tanzania, who also took part in a larger clinical trial of malaria treatment efficacy and safety in patients co-infected with HIV and receiving antiretrovirals (*ClinicalTrials.gov* ID NCT00885287).

A total of 241 adults were included: 96 patients with malaria only, 88 with malaria and HIV, and 57 patients with HIV infection only. Patients with malaria were treated with a standard dose of artemether-lumefantrine (Coartem ®) and were followed up for 42 days. A total of 167 patients completed 42 days of follow-up and had no malaria reinfection.

QFT testing was performed on day 0 (before initiation of malaria treatment) and again on day 7 and 42. IFN-γ and IP-10 levels were measured in QFT supernatants. Malaria parasites and CD4 cells were likewise counted on day 0, 7 and 42.

Results

Before initiation of malaria treatment, patients with malaria had significantly elevated IFN-γ and IP-10 levels in the unstimulated samples and reduced levels in mitogen-stimulated samples, compared to the non-malaria patients. Measured IFN-γ and IP-10 were associated with malaria parasite density levels. We also observed that CD4 cells were lower in malaria patients with high parasite densities (Figure 1) .These alterations in cytokine and CD4 cell levels all reverted after malaria treatment, i.e. by day 42.

Prior to malaria treatment, 10% of malaria patients in the high parasite density group had indeterminate QFT test results versus only 2% in both the low and intermediate parasite density groups, respectively (p=0.04). 25% of patients had indeterminate IP-10 results in the high parasite density group compared to 5% and 3% in the low and intermediate parasite level groups, respectively (p<0.001). 42 days after malaria treatment the proportion of patients with indeterminate IP-10 test results had declined significantly, e.g. from 16% to 4% (p=0.03) in HIV-negative malaria patients. Changes in QFT test results classified as indeterminate were only modest, probably related to better validated cut-off values in the QFT test.

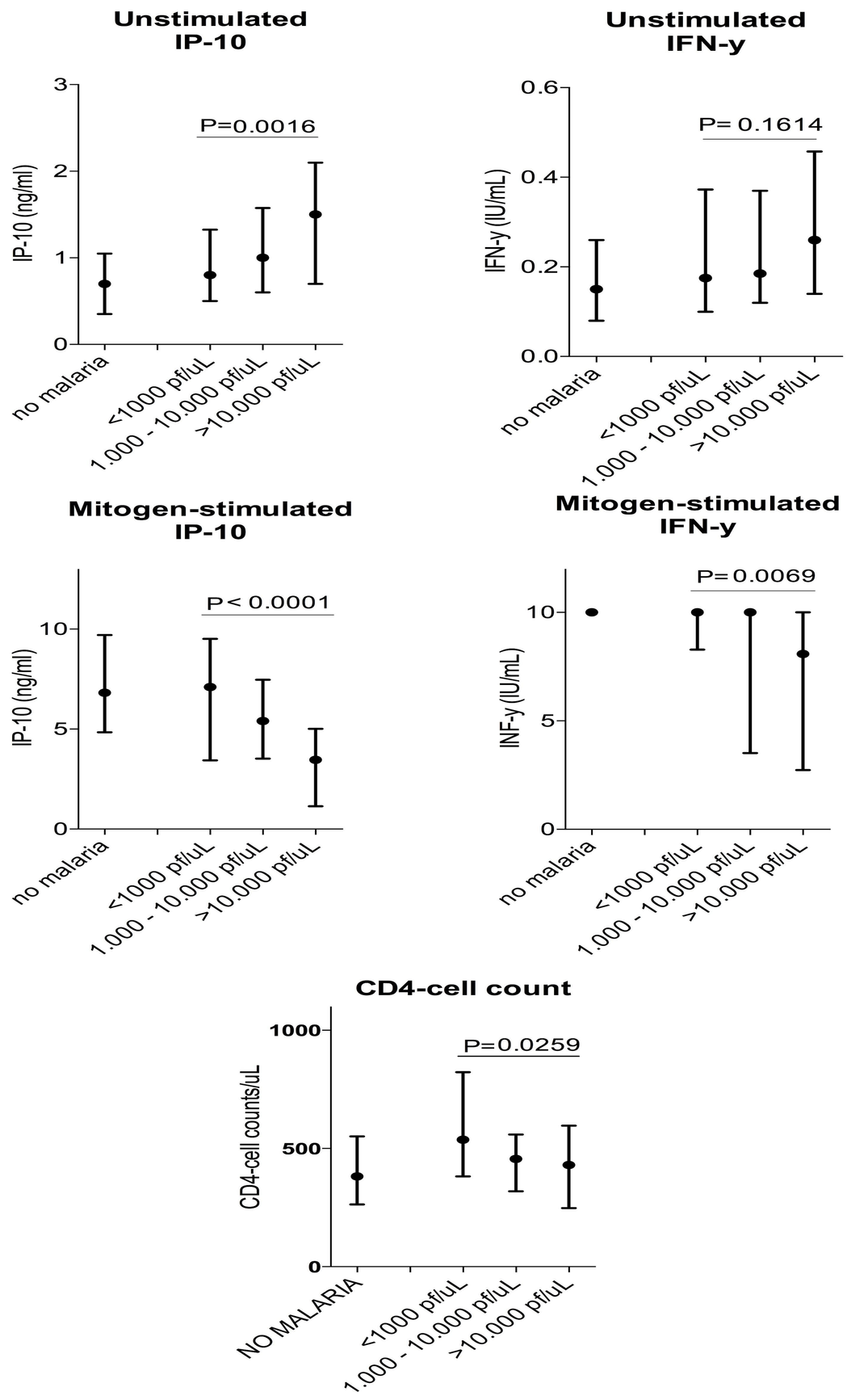

Figure 1: Measured levels of IFN-γ, IP-10 and CD4 cells by parasite density level prior to malaria treatment.

Conclusions

We found concurrent malaria to interfere with IGRA testing through impairment of INF-γ and IP-10 responses. Clinicians who suspect latent tuberculosis in a patient should therefore be cautious when interpreting IGRA test results in patients with acute or recent malaria, and should consider to postpone IGRA testing.

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