

## Concurrent Hyperreactive Malarial Splenomegaly and Quartan Malarial Nephropathy – *Plasmodium malariae* Revisited

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Chronic immunological complications of malaria include hyperreactive malarial splenomegaly (HMS) and quartan malarial nephropathy. HMS represents an abnormal immunological response to recurrent malarial infections as a result of defective T suppressor cell regulation.<sup>1,2</sup> On the other hand, quartan malarial nephropathy, which usually presents in childhood with nephrotic syndrome, is not responsive to antimalarial therapy, and thus may progress to end-stage renal failure.<sup>1,2</sup> We presented a patient with HMS, who developed recrudescence of malaria, and quartan nephropathy after splenectomy.

### Case report

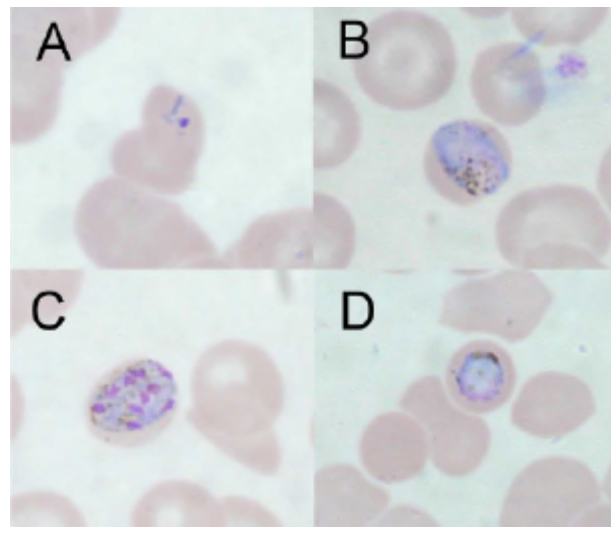
A 66-year-old woman presented with pancytopenia and hepatosplenomegaly. She moved to Hong Kong in 1949 but revisited her rural hometown in mainland China annually thereafter. Complete blood picture showed thrombocytopenia ( $110 \times 10^9/L$ ) and leukopenia ( $2.7 \times 10^9/L$ ). Physical examination showed hepatomegaly (3 cm below right costal margin) and splenomegaly (10 cm below the left costal margin). Serum biochemistry showed normal transaminase and creatinine levels. Serum protein electrophoresis showed a polyclonal increase of IgM measuring 604 mg/dL (normal: <307). Serum rheumatoid factor measured 553 IU/ml (normal < 42). Bone marrow examination was unremarkable. Percutaneous liver biopsy showed no evidence of schistosomiasis. Serology for viral hepatitis (A, B and C) was negative. To exclude possibility of lymphoproliferative disease, splenectomy was performed, which yielded a spleen measuring 1.2 kilogram and  $22 \times 15 \times 7$  cm in dimension. Histology showed normal white pulp but congested red pulp with polyclonal plasma cells.

Four weeks after splenectomy, she developed recurrent febrile episodes, ankle edema and progressive hepatomegaly (progressing from 3 cm prior to splenectomy to 8cm below right costal margin). Despite repeated negative sepsis work-up, careful review of the peripheral blood film showed low level parasitaemia of *Plasmodium malariae* (Figure 1). Serum albumin/globulin then measured 26/91 g/L but was 36/48 g/L prior to splenectomy. 24-hour urine collection showed proteinuria of 3.4g. Renal biopsy demonstrated IgM nephropathy with segmental increase in mesangial matrix and in the glomeruli, and granular mesangial deposits of IgM and C3 (Figure 2). Electron microscopy showed mesangial expansion with many small mesangial electron dense deposits. After treatment with chloroquine the fever subsided and hepatomegaly reduced to six cm three months after therapy. However, patient retired to mainland China and was lost to follow-up.

### Discussion

The identity of *P. malariae* was based on the followings. Firstly, in contrast to red cells infected by *P. vivax* and *P. ovale*, where the parasitized red cells are larger than

the uninfected normal ones, the infected red cells in this case in fact appeared smaller than the normal red cells. Secondly, the band form trophozoite (Figure 1B) is the most characteristic of *P. malariae*, and is not seen in other species. Thirdly, in the routine Giemsa staining, there are no stippling of the infected red cells which are characteristic of other *Plasmodium* species such as



**Figure 1.** *Plasmodium malariae* in peripheral blood smear of the patient. A, an early trophozoite; B, a band form trophozoite; C, a schizont with 10 merozoites; D, macrogametocyte with eccentric chromatin.

**Figure 2.** A. glomerulus showing segmental mild increase in mesangial cells. (H&E, original magnification  $\times 200$ ); B. The silver stain highlights mild segmental increase in mesangial matrix in the same glomerulus. (Methenamine silver, original magnification  $\times 200$ ); C. Immunofluorescence study showing a mesangial pattern of IgM deposits. (IgM, original magnification  $\times 200$ ); D. Electron microscopy showing many small electron dense deposits in the mesangial area. (scale bar = 2  $\mu$ m).

Schuffner's dots in infection with *P. vivax* or *P. ovale*, and Maurer's clefts in *P. falciparum*. Lastly but not the least, the level of parasitaemia is also much lower than the other species.<sup>3</sup>

On the other hand, the diagnosis of HMS in this patient was based on the presence of *P. malariae* parasitaemia, gross splenomegaly, elevated serum IgM, clinical response to antimalarial treatment, and of course exclusion of other causes of splenomegaly.<sup>4</sup> The presence of hepatosplenomegaly in our patient indicated a chronic malarial infection that might have lasted for decades,<sup>2</sup> though the exact time of first infection remained unknown. Moreover, as she made frequent visits to the endemic rural homeland,<sup>5</sup> parasitaemia due to recurrent malarial infections could not be excluded.

Splenectomy, frequently performed in the past,<sup>6</sup> is obsolete<sup>1</sup> as it results in compensatory hepatomegaly, and recrudescence of clinical malaria.<sup>7</sup> Indeed, our patient demonstrated compensatory hepatomegaly, and the recrudescence of quartan malaria as recurrent febrile

episodes after splenectomy.

Renal biopsy in our patient showed a mild mesangial proliferative glomerulonephritis with granular mesangial deposits of IgM and C3. While this is compatible with quartan malarial nephropathy,<sup>8-12</sup> the findings are by no means specific. Without knowledge of malarial infection in this patient, the diagnosis of the glomerulonephritis would have been IgM nephropathy. Therefore, the diagnosis of quartan nephropathy in this case could only be made in the presence of malarial infection. Moreover, as the proteinuria developed after splenectomy and recrudescence of clinical malaria, this suggested that immune deposition in the glomeruli was part of an immune response to the infection, further supporting malarial nephropathy in animal models, in which nephrotic syndrome developed in splenectomised but not intact aotus monkeys infected with *P. malariae*.<sup>11</sup>

The demonstration of plasmodium parasitemia at the time of recrudescence of malaria was crucial to the diagnoses of HMS prior to, and quartan malarial nephropathy after splenectomy. While HMS may be caused by all *Plasmodium* species, nephropathy manifesting with nephrotic syndrome, as seen in our patient, is only caused by *P. malariae*.

In summary, our patient had chronic *P. malariae* infection complicated by HMS, recrudescence of malaria, and development of quartan malarial nephropathy after splenectomy. HMS, manifesting as chronic hepatosplenomegaly, might occur in endemic areas. Awareness of, and an early diagnosis, might have saved the patient from splenectomy, and subsequent recrudescence of malaria and possibly development of malarial nephropathy.

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