Plasmodium infection unmasked by corticosteroid therapy

CKM Ng, AYK Mak, TS Au, TC Au, ST Lai, JY Lai

In the past four years, we have encountered three patients in whom malaria parasites were found incidentally in their blood when they were receiving corticosteroid therapy. Although there is little direct evidence that corticosteroid therapy can activate human malaria, animal studies have successfully demonstrated the recrudescence effect of immunosuppression on malaria infection.

HKMJ 1997;3:328-30

Key words: Malaria; Plasmodium malariae; Corticosteroids; Thrombocytopenia

Case reports

Case 1. A 78-year-old man was given prednisolone and azathioprine for pemphigus vulgaris. He developed steroid-induced diabetes mellitus. A low-grade temperature developed and septic workup confirmed a *Klebsiella* spp. urinary tract infection and *Pseudomonas* spp. pneumonia. Courses of cefuroxime and tobramycin were given. The azathioprine was stopped and the prednisolone was reduced to 30 mg/day. Isolated thrombocytopenia with a platelet count of 25 x 10^9/L (normal range, 150-450 x 10^9/L) was noted 10 weeks after the commencement of prednisolone therapy. Ten days later, his blood film showed *Plasmodium malariae* 4+ (>4000 parasites/μL); he was afebrile. Chloroquine followed by primaquine was prescribed and his blood film was clear of the parasites in 10 days. The prednisolone was continued because of his skin condition, but the patient also had a methicillin-resistant *Staphylococcus aureus* chest infection and died six weeks later. The patient gave no history of blood transfusion and the only time he had been out of Hong Kong was 10 years ago, when he visited Beijing.

Department of Medicine, Princess Margaret Hospital, Lai King Hill, Kowloon, Hong Kong
CKM Ng, FHKCP, FHKAM (Medicine)
ST Lai, FRCP, FHKAM (Medicine)
JY Lai, FRCP, FHKAM (Medicine)
Department of Medicine, Tuen Mun Hospital, Tsing Chung Koon Road, New Territories, Hong Kong
AYK Mak, MRCP, FRCS (Edin)
TC Au, FRCP, FHKAM (Medicine)
Skin Clinic, Social Hygiene Service Headquarters, Department of Health, Hong Kong
TS Au, MRCP

Correspondence to: Dr CKM Ng

Case 2. A 65-year-old woman presented with generalised oedema secondary to nephrotic syndrome. A renal biopsy showed mesangial proliferative glomerulonephritis. She was treated for this with prednisolone, at 40 mg/day. Two weeks after the initiation of corticosteroid treatment, she started to develop thrombocytopenia and had a platelet count of 92 x 10^9/L. After further haematological monitoring, *P. malariae* 3+ (400-4000 parasites/μL) were found incidentally in her blood film; she was afebrile. Chloroquine was administered, but she developed sudden cardiac arrest three days afterwards. This patient gave no history of travel to any malarial endemic region.

Case 3. A 45-year-old woman was admitted in October 1995 because of a two-month history of petechiae over both lower limbs. She complained of spontaneous gum bleeding, easy bruising, and menorrhagia for the past two years. She had no organomegaly and investigations showed hypochromic, microcytic anaemia due to iron deficiency with haemoglobin of 7.0 g/dL (normal range, 12.0-15.0 g/dL), white cell count of 4.9 x 10^9/L (normal range, 0-5 x 10^9/L), and platelet count of 2 x 10^9/L. Anti-nuclear factor and anti-platelet antibody were negative. A bone marrow trephine biopsy was carried out after a platelet transfusion had been given. It showed a moderate to marked increase in the number of megakaryocytes. Idiopathic thrombocytopenic purpura was diagnosed and prednisolone, at 60 mg/day was started with iron replacement therapy. The platelet count returned to normal after one week.

Three weeks after treatment began, she developed a fever (39°C), chills, rigor, severe myalgia, and arthralgia. Examination showed a 2 cm liver edge and

a spleen tip. Her blood tests showed features of haemolysis [reticulocyte count 18% (normal range, 10-75 x 10^6/L), bilirubin 105 μmol/L (normal range, 2-18 μmol/L), lactate dehydrogenase 783 U/L (normal range, 50-150 U/L), and haptoglobin 0.16 g/L (normal range, 0.50-2.20 g/L)]. Her platelet count dropped to 33 x 10^9/L and the blood film revealed *P. falciparum* 4+ (>4000 parasites/μL). She was treated with quinine and tetracycline and had an uneventful recovery. She had lived in the countryside in Thailand for two years, from 1992 to early 1994, and returned to Hong Kong in January 1994. She did not take any chemoprophylaxis during her stay in Thailand. She developed malaria three weeks after the platelet transfusion. On tracing the donor, we located an Indian native who had a raised antibody titre (1:1280) by the falciparum-spot immunofluorescence test. He had no prior history of malaria and had been resident in Hong Kong for 10 months. Active malarial infection was not confirmed apart from the raised antibody titre. He was subsequently closely monitored.

Discussion

Plasmodium infection is well known for its immunosuppressive effect on the host. Likewise, immunosuppression affects the clinical course of malaria. Carriers are asymptomatic because they have acquired immunity. Corticosteroid administration tilts the balance and lowers immunity to the parasite, leading to its recrudescence.

There are two such clinical reports. In one, a Nepalese soldier who had lived in Assam, India, for 15 years, was treated with the standard four-drug regimen for pulmonary tuberculosis and given prednisolone, 30 mg daily. Recrudescence of *P. falciparum* occurred on day 30 of the treatment.[1] A case of *P. vivax* infection was reported in an 18-year-old Pakistani male who was treated with immunosuppressants for Ewing's sarcoma of the left ilium. He had had episodes of malaria in childhood. His platelet count dropped to 43 x 10^9/L and normalised after chloroquine treatment.[2]

Several animal studies have successfully demonstrated the effect of immunosuppression on malaria infection. The administration of cyclophosphamide to mice infected with *P. berghei* blocks antibody synthesis and increases parasitaemia.[3] These mice also lose their acquired immunity to *P. berghei* during the second half of pregnancy, when there is a natural increase in corticosteroid secretion.[4] The relative immunosuppressive state created by pregnancy is thought to be the cause of the recrudescence.[5] Another study has shown the depressed proliferative response of spleen cell cultures, taken from mice immune to *P. berghei*, to parasitised reticulocytes when corticosterone is added.[6] In a recent study in the Baltimore Zoo (Maryland, US), parasite recrudescence was demonstrated in African black-footed penguins (*Spheniscus demersus*) after corticosteroid administration. Nine adult penguins were placed in a mosquito-free environment in winter. Subclinical avian malaria infections were diagnosed by Giemsa-stained thin blood smears and subinoculation of penguin blood into one-day-old ducklings. All nine penguins showed no evidence of *Plasmodium* spp. infection. After being given dexamethasone, four non-symptomatic penguins were found to be infected with *P. relictum* by the blood inoculation method.[7] However, there is little direct evidence that corticosteroids can activate malaria in humans.

Thrombocytopenia, especially severe cases, is commonly found in non-immune subjects but this does not occur in residents of holoendemic areas.[8] Inyang et al studied platelet recovery, survival, and the sialic acid content of the platelet membrane in Wistar rats infected with *P. berghei*. The extent of reduction in sialic acid was directly related to the degree of parasitaemia. They concluded that shortened platelet survival and decreased total platelet sialic acid content might account for the reported thrombocytopenia.[9]

Conclusion

Plasmodium infection was diagnosed in three patients who received corticosteroid therapy. The level of parasitaemia was high when the diagnosis was made. Human malaria is probably also activated or aggravated by the immunosuppression caused by corticosteroids. A typical fever pattern was not observed and the only common feature was thrombocytopenia, which occurred a few days before the malaria parasites appeared in the blood film. Malaria should be considered in patients who develop thrombocytopenia during corticosteroid treatment, especially those with a history of travel to endemic areas or who have had a blood transfusion. It has been suggested that patients who are receiving corticosteroids or other immunosuppressive drugs and who live in malaria endemic areas be given routine malaria prophylaxis.[10]

References

1. Livesey JR, Henderson A. Chloroquine-resistant malignant subtertian malaria unmasked by system(at)ic steroid therapy. J R Army Med Corps 1983;129(3):174-5.

2. Richard A, Gordon P, David P, Philips RH. Opportunistic malaria. Lancet 1980;10:1037-8.
3. Endardjo S, Boonpucknavig S, Boonpucknavig V, Bhamarapravati N. Immunopathological studies of *P. berghei*—infected mice: effect of cyclophosphamide. J Trop Med Hyg 1978;81:25-31.
4. Van Zon AA, Eling WM, Hermsen CC, Van de Wiel TJ, Duives ME. Malarial immunity in pregnant mice, in relation to total and unbound plasma corticosterone. Bull Soc Pathol Exot 1983;76(5):493-502.
5. Van Zon AA, Eling WM, Hermsen CC. Pregnancy-induced recrudescences strengthen malarial immunity in mice infected with *Plasmodium berghei*. Parasitology 1985;91(Pt 1):9-17.
6. Van Zon AA, Termaat RM, Schetters TP, Eling WM. *Plasmodium berghei*: reduction of the mouse's specific lymphoproliferative response in relation to corticosterone and pregnancy. Exp Parasitol 1986;62(1):71-8.
7. Cranfield MR, Graczyk TK, Beall FB, Ialeggio DM, Shaw ML, Skjoldager ML. Subclinical avian malaria infections in African black-footed penguins (*Spheniscus demersus*) and induction of parasite recrudescence. J Wild Dis 1994;30(3):372-6.
8. Essien EM. Platelets and platelet disorders in Africa. Bailliere's Clin Haematol 1992;5(2):441-56.
9. Inyang AL, Okpako D, Essien EM. Decrease in platelet survival and total platelet sialic acid concentration in rats infected with Pla*smodium berghei*. Afr J Med Med Sci 1995;24(1):41-6.
10. Greenwood BM, Whittle HC. Immunology of medicine in the tropics. London: Edward Arnold, 1981.