"Collateral" effect of artemether in an atypical kidney involvement by *Plasmodium falciparum* malaria: A case report

Carmelina Calitri[1], Silvia Garazzino[1], Roberta Camilla[2], Licia Peruzzi[2], Alessandro Amore[2] & Pier-Angelo Tovo[1]

[1]*Department of Paediatrics, Infectious Diseases Unit, University of Turin, Regina Margherita Children Hospital, Turin;* [2]*Nephrology, Dialysis and Transplantation Unit, Regina Margherita Children Hospital, Turin, Italy*

Key words   Child; glomerulonephritis; malaria*; Plasmodium falciparum*

Malaria was the first parasitic infection clearly recognized as responsible for renal disease in tropical areas. Renal manifestations are mainly associated with two parasites: (i) *Plasmodium malariae*, which usually gives rise to an immune-complex mediated mesangiocapillary glomerulonephritis (GN) several weeks after the onset of symptoms; and (ii) *Plasmodium falciparum*, which can cause different types of renal alterations, ranging from asymptomatic disorders to acute renal failure[1–2]. Here we describe an unusual pattern of GN in an Ivorian girl with *P. falciparum* infection, and its unexpected response to artemether therapy.

Case report

An Ivorian 13-yr old girl was admitted to a peripheral hospital for a 15-day history of fever, asthenia, and a weight loss of about 7 kg in the past four months. She had arrived in Italy one month before; at 10-yr of age she had uncomplicated malaria. Clinical examination revealed mild splenomegaly and macroscopic haematuria with laboratory findings, severe anaemia (Hb = 7.2 g/dl), elevation of C-reactive protein (17.6 mg/dl, normal value (n.v.) <0.5) and erythrocyte sedimentation rate (112 mm/h, n.v. <20). As malaria testing was found positive for *P. falciparum* parasitaemia (4%), she was given oral atovaquone-proguanil for three days with resolution of parasitaemia. However, the girl developed a progressive impairment of renal function (creatinine level up to 1.49 mg/dl, n.v. 0.4–1.1, and proteinuria/creatinuria ratio 1.2, n.v. <0.2) with persistence of fever and increased inflammatory indices. She was thus referred to our Department for further investigations: serum creatinine increased up to 2.1 mg/dl and proteinuria/creatinuria ratio up to 2.5; estimated glomerular filtration rate (eGFR) went down to 30 ml/min/1.73 m^2 (according to the Schwartz's formula). She had hypergamma-globulinemia (IgG 1933 mg/dl), decreased albumin (down to 2.69 mg/dl, n.v. 3.92–5.18), but no alteration in lipid profile and in complement components. No hyper-tension or evident peripheral edema was noted. Abdomen ultrasound imaging revealed kidneys' enlargement (12 cm the right and 11.3 cm the left), increased parenchymal echogenicity and lump profile.

Malarial parasitaemia was repeated in many occasions and was persistently negative; however, considering the previous malaria as the sole identified agent responsible for renal impairment (other infectious agents, lymphoproliferative disorders and iatrogenic causes of renal damage were sorted out), the patient was empirically retreated with oral artemether plus mefloquine. This was discontinued after Day 1 for intolerance (nausea and vomiting), and artemether was thus administered for 7 days: the patient had rapid improvement of clinical conditions, normalization of body temperature, and no further deterioration in renal function, but decrease in creatinine levels (1.7 mg/dl) and macroscopic haematuria were noticed. On the ultrasound-guided biopsy performed to clarify renal disease, the unexpected pattern of rapidly progressive GN was observed instead of the chronic membranous GN typically associated with *P. falciparum* infection. Florid "crescents" were found in 10 out of 34 glomeruli (30%), with fibrotic evolution in five glomeruli and massive extracapillary proliferation. Inflammatory cells infiltrated the Bowman's capsule, immunoglobulins G and C3 deposits were evident along the basement membrane and in subepithelial spaces; haematic dross and cellular cylinders were detected in tubular lumens. Given the poor prognosis associated with this histological pattern, the girl started a massive immunosuppressive therapy (10 mg/kg iv methylprednisolone for three doses, shifted to 1 mg/kg/day oral prednisone, and 2 mg/kg/day cyclophosphamide for eight weeks) associated with eight plasmapheresis. After three weeks, renal function was considerably improved, and at last check 18-months later, the girl maintained a normal renal function, with serum creatinine 0.8 mg/dl, no evident proteinuria or haematuria, and a proteinuria/creatinuria ratio of 0.18.

J Vector Borne Dis 51, June 2014

DISCUSSION

Renal impairment is listed among the severe complications of *P. falciparum* infection[3]: it usually turns up in the context of high parasitaemia (> 5%), and it is mostly related to acute tubular necrosis (ATN)[1, 4–5]. *Plasmodium falciparum* can occasionally trigger a nephritic or nephrosic syndrome commonly reversible in 2–6 weeks after parasitic eradication[2]. These clinical manifestations are usually sustained by membranous GN histological pattern, defined by mesangial proliferation and basement membrane thickening at microscope, subendothelial and mesangial electron-dense deposits made up by IgM, IgG3 and C3 at electron microscopy, suggesting deposition of circulating immune complexes[1–2, 5]. Hypo complementemia due to complement cascade activation is common, as well as hypergammaglobulinemia due to polyclonal B lymphocyte expansion. Therefore, malaria nephropathy is interpreted as an immune-mediated disease resulting from immune-complex deposition, activation of locally marginated mononuclear cells, and release of inflammation mediators (cytokines, reactive oxygen intermediates–ROI and nitric oxide–NO) leading to endothelial damage[1–2, 5]. In our patient, the long exposure to malarial parasites might have elicited a massive immune response leading to rapidly progressive GN. It's the first time that this histological pattern is described in association with *P. falciparum* infection. Rapidly progressive GN gives rapid loss of renal function, with a 50% eGFR decline within three months after onset of symptoms: if untreated, it quickly evolves to end-stage renal disease in 50% of the patients[6].

The girl needed an aggressive immunosuppressive therapy to have renal function recovered. However, her clinical improvement started with the 7-day course of artemether therapy, with creatinine levels and macroscopic haematuria decrease, results already maintained after artemether suspension. Artemether might have had a "collateral" but significant role in reducing the massive immune response which led to the rapidly progressive GN pattern. Several investigations underlined the possible immunomodulatory effects of artemisinin and its derivatives, such as a Treg proliferation by Foxp3 up-regulation and suppression of Th17 pathway that can diminish immune reactivity and tissue inflammation[7]. These effects are potentiated by suppression of NO synthesis and Tumour Necrosis Factor (TNF) down-regulation[7–8], usually involved in endothelial cells activation and damage of malarial disease[8]. Artemisinin derivates can also inhibit the binding of Vascular Endothelial Growth Factor (VEGF) to its receptors and down regulate VEGF receptor expression, with inhibition of the angiogenesis implicated primarily in cerebral malarial dysfunctions[8–9].

In conclusion, renal impairment by *P. falciparum* infection may be related to an immune-mediated disease configuring as rapidly progressive GN. The use of artemisinin derivates can combine an efficient parasitic eradication to an oxidative stress down-regulation and effective modulation of massive immune responses to parasites.

REFERENCES

1. Barsoum RS. Malarial nephropathies. *Nephrol Dial Transplant* 1998; *13*(6): 1588–97.
2. Elsheikha HM, Sheashaa HA. Epidemiology, pathophysiology, management and outcome of renal dysfunction associated with plasmodia infection. *Parasitol Res* 2007; *101*(5): 1183–90.
3. *Guidelines for the treatment of malaria.* II edn. Available from: *http://www.who.int/malaria/publications/atoz/9789241547925/ en/index.html* (Accessed on April 29, 2012).
4. Ehrich JHH, Eke FU. Malaria-induced renal damage: Facts and myths. *Pediatr Nephrol* 2007; *22*(5): 626–37.
5. Das BS. Renal failure in malaria. *J Vector Borne Dis* 2008; *45*(2): 83–97.
6. Hoschek JC, Dreyer P, Dahal S, Walker PD. Rapidly progressive renal failure in childhood. *Am J Kidney Dis* 2002; *40*(6): 1342–7.
7. Li T, Chen H, Wei N, Mei X, Zhang S, Liu D, *et al*. Anti-inflammatory and immunomodulatory mechanisms of artemisinin on contact hypersensitivity. *Int Immunopharmacol* 2012; *12*(1): 144–50.
8. Golenser J, Waknine JH, Krugliak M, Hunt NH, Grau GE. Current perspectives on the mechanism of action of artemisinins. *Int J Parasitol* 2006; *36*(14): 1427–41.
9. Chen HH, Zhou HJ, Wang WQ, Wu GD. Antimalarial dihydroartemisinin also inhibits angiogenesis. *Cancer Chemother Pharmacol* 2004; *53*(5): 423–32.

Correspondence to: Dr Carmelina Calitri, Department of Paediatrics, Infectious Diseases Unit, University of Turin, Regina Margherita Children Hospital, Turin, Italy.
E-mail: carmelina_calitri@libero.it