Case Report

A nephrotic syndrome of tropical origin: case report and short review of the aetiology

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We present a case of nephrotic syndrome in a 38-year-old man of Ivorian origin. In the search of the cause of his illness an infection with *Plasmodium malariae* (*P. malariae*) was diagnosed by serology and by microscopy of a Giemsa thin blood smear which revealed rare gametocytes of *P. malariae.* Proteinuria significantly diminished within three months after antimalarial treatment. Antibodies against *Schistosoma* were detected as well. Examination of kidney biopsy revealed a discrete mesangioproliferative glomerulonephritis. This case highlights that a thorough history-taking may be essential and that infectious diseases should be included in the differential diagnostic thinking process when a nephrotic syndrome is diagnosed.

Keywords: Imported malaria, Nephrotic syndrome, Eosinophilia, Travel history

Case Report

A 38-year-old African man, born in Ivory Coast, consulted the emergency services in Liège, Belgium with a one month history of swollen legs. He gained about 8 kg in body weight and felt generally ill with a loss of appetite and intermittent nausea without vomiting. There was no fever, no night sweats, no urinary complaints and no diarrhoea either. He did not feel short of breath; there were no neurological complaints. Generally there were no pain complaints, though he mentioned a continuous body discomfort.

His travel history was as follows: he migrated to Belgium in 2005 for political reasons. Between 2005 and the time of his current illness at the end of 2013, he returned three times to his country of origin, each time for about two months. He never took any drug prophylaxis for malaria, despite the fact that Ivory Coast is known as a hyperendemic malarial region; neither did he protect himself against mosquitoes by using bed nets or skin repellents. He swam in the local natural lake several times during his stays abroad.

In his personal medical history, we mentioned schizophrenia for which he was followed up regularly by a psychiatrist and put on Paliperidone, an antipsychotic drug. There had not been any recent changes in his medication. He did not take other drugs as such. However, he smoked Marihuana on a daily basis as well as ordinary cigarettes. He consumed alcohol with moderation. The patient was single at the time of clinical presentation and his family history was without significance.

On clinical examination we noticed a black non febrile African man in moderate general condition with a body weight of 81 kg, a pulse rate of 88 beats per minute and a blood pressure of 130/80 mm Hg. The blood oxygen saturation was correct. There were no clinical signs of cardiac failure. Auscultation of lungs and heart was normal; organomegaly was absent on abdominal palpation. However, there was severe oedema especially at the lower extremities and infra-orbital (anasarca). As a consequence, peripheral arteries were not palpable.

Laboratory examination showed only slight inflammation (C-reactive Protein at 7.7 mg/l) without alteration of blood nuclear cells apart from an eosinophilia (absolute eosinophil count of 840/mm^3). Exploration of the origin of the oedema revealed a urinary protein/creatinine ratio of 6704 mg/g. There was equally severe hypo-albuminaemia (14.8 g/l), as well as a marked hypercholesteroleaemia (total cholesterol at 457 mg/dl). Hence, we established the diagnosis of nephrotic syndrome. There was no anaemia. Kidney function was preserved at admission (serum creatinine at 1.19 mg/dl, estimated glomerular filtration rate [CKD-Epi equation] at 77 ml/min/1.73 m^2). Auto-immune antibodies returned negative as well as infectious serology on HIV, Hepatitis B and

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C. However, in the search of the origin of his nephrotic syndrome and taken into account the hypereosinophilia as well as the patients' origine, we searched for antibodies against *Schistosoma, Plasmodium, Strongyloides, filaria, Toxoplasma* and *Toxocara.* Serology for *P. malariae* was strongly positive: 1/10 240, versus 1/640 for *P. falciparum*. Furthermore, serology for *Schistosoma spp.* was positive as well. Some rare schizonts and gametocytes of *P. malariae* were found in the thin film. The rapid test 'Palutop+4' was positive for 'pan-malaria' antigen (common pLDH antigen).

A kidney biopsy was performed and revealed moderate proliferative glomerulonephritis mainly involving the mesangium with endocapillary but no extracapillary proliferation. Immunofixation for c1q, IgM and c3d was positive at the level of the glomerular basal membrane and the mesangium. PCR for *P. falciparum* was equally performed on this biopsy but turned out negative. Complementary investigations did not reveal major pathology (an ultrasound of the kidneys did not show dilated ureters and an X-ray of the chest was non-contributive) apart from an angioscan of the chest showing small peripheral pulmonary embolisms.

We treated this patient for malaria due to *P. malariae* and for presumptive schistosomiasis. For the former condition he received Chloroquine 25 mg base/kg spread over three subsequent days; the latter was treated by a single dose of Praziquantel (40 mg/kg). Concomitantly, symptomatic treatment for his nephrotic syndrome was initiated with high doses of diuretics (Bumetanide 5 mg daily) and chlorthalidone (25 mg daily), together with an antiproteinuric treatment (Perindopril 5 mg daily). Furthermore, we started low molecular weight heparines for his pulmonary embolism. Our patient did not receive corticosteroids. Three months after the antimalarial treatment, his proteinuria diminished with a urinary protein/creatinine ratio decreasing from nearly 7 g/g to 2 g/g. We consider this significant improvement under symptomatic treatment, Chloroquine and Praziquantel, as a strong argument for a nephrotic syndrome of infectious origin.

Discussion

Malaria is known as one of the most important infectious diseases worldwide with a considerable mortality of at least 1 million deaths yearly. The disease is transmitted by night biting *Anopheles* mosquitoes. The parasite involved is usually *P. falciparum*, causing an acute febrile illness with development of life-threatening complications such as kidney failure, severe anaemia and cerebral malaria. Acute respiratory distress syndrome and concomitant septicaemia with Gram-negative bacteria are not uncommon. In this case however, another malaria parasite was involved, known as *P. malariae.* Like *Plasmodium ovale* (*P. ovale*) and *Plasmodium vivax* (*P. vivax*) this parasite may cause febrile attacks even years after exposure.[1] The golden standard for the diagnosis of all five types of malaria (*P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*) remains the thick and thin blood film which allow for species and stage identification and for determination of the level of parasitaemia. Delayed attacks by both *P. ovale* and *P. vivax* are explained by the existence of hypnozoites, a minority of parasites that remain in the liver instead of inducing a blood stage as the majority of them do. Hence, these dormant bacilli remain viable for many years, capable of causing late attacks. In the case of *P. malariae* on the other hand, scientists assume a low-level parasitaemia existing for several years, quite below the level of detection on a thick film with the possibility of a recurrence even more than 15 years after primary infection.[2] We found a high anti-*P. malariae* antibody titer and detected rare schizonts of *P. malariae* by microscopy strongly suggesting that this parasite was involved in the pathogenesis of this patient's nephrotic syndrome. We presumed that the anti-*P. falciparum* antibody titer was a mere cross-reaction. Full immunity against malarial infection does not exist. People living in hyper- or holo-endemic regions will obtain – given constant exposure through mosquito-borne infection – some degree of immunity; they will however loose this 'semi-immune' status after they have left the endemic area for at least six months.

It is hypothesized that a chronic immune complex glomerulonephritis is the mechanism which causes nephrotic syndrome in *P. malariae* infection (*P. malariae* induced glomerular damage). This 'Quartan Malarial Nephropathy' was first described in children by Gilles and Hendrickse, et al in 1960.[3] This study shows a possible aetiological role of Quartan Malarial Nephropathy in 81% of cases. In general, literature on *P. malariae* induced nephrotic syndrome is scarce, especially in adults. According to more recent literature it seems that its incidence has declined,[4] possibly following improved antimalarial treatment within better organized primary health-care services. Confounding factors, such as drepanocytosis and HIV infection, common co-morbidities on the African continent, make it difficult to attribute the real risk of plasmodial infection to nephrotic syndrome. However, in our case, suspicion of *P. malariae* induced nephrotic syndrome is very high, envisaging the serological and microscopic evidence of the infection and the patient's travel history: serology for *P. malariae* was strongly positive and schizonts as well as gametocytes were seen in the thin film. Moreover, a partial therapeutic response on the level of proteinuria

was seen, three months after Chloroquine had been given to treat malarial infection. It emphasizes the importance of taking a detailed travel history from any migrant (and in theory even from travellers, albeit much more unlikely) arriving in a non-endemic country who presents with a condition as in our patient. Furthermore, medical doctors should not reject a possible diagnosis of malaria-induced nephrotic syndrome even when the potential exposure has taken place more than 10 years ago.

Our case equally holds suspicion of an infection with *Schistosoma*. This worm, belonging to the class of trematodes, is transmitted via exposure to water in which snails are present as an intermediate host; many lakes and slow-flowing rivers in Africa, South-America and to a lesser extent Asia, harbour the parasite. If worm load is high, many medical problems may arise. Two species are prevalent in Africa: *Schistosoma haematobium* (*S. haematobium*) and *Schistosoma mansoni* (*S. mansoni*). Both can be responsible for kidney and bladder damage. In the case of *S. haematobium* immune mechanisms directed towards the eggs of the worm, cause damage such as fleshy polyps and ulcerations, usually in the bladder wall. This could result in haematuria and, in severe infections, even proteinuria may occur. Furthermore, ureteral obstruction may give rise to hydro-ureter and hydronephrosis. *S. haematobium* is therefore responsible for parasite-induced bladder cancer, once very common and well described in Egypt. Extensive control programs have reduced the prevalence of bladder cancer dramatically. *S. mansoni* is known to be related to glomerulonephritis due to a deposit of immune complexes in the kidneys. A nephrotic syndrome can occur, possible accompanied by hypertension. Hence, schistosomiasis can be a cause of chronic kidney failure.[5] Admitted, we do not at all have certainty whether active infection with *Schistosoma* explained even part of the kidney problems in our patient. The presence of the antibodies could have been the result of a former exposure, not related to his current pathology. However, we decided we reached our decision threshold to treat our patient with Praziquantel as this drug has no major side effects and as its efficacy is excellent.

When people from malaria endemic regions arrive as immigrants in a different part of the world, awareness that tropical diseases may be involved in a patient presenting with a nephrotic syndrome, is of uttermost importance. This entails that a detailed travel history should be taken, going back several years, as this case clearly illustrates.

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