Case report

Massive Epistaxis due to Profound Malaria-Induced Thrombocytopenia in a 16 Years Old Adolescent: A case report at the Yaounde Gynaeco-Obstetric and Pediatric Hospital, Cameroon

Épistaxis massive secondaire à une thrombopénie d'origine paludéenne chez un adolescent de 16 ans : à propos d'un cas observé à l'hôpital gynéco obstétrique et pédiatrique de Yaoundé

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ABSTRACT
We report the case of a 16 years old adolescent male admitted in the pediatric unit of the Yaounde Gynaeco-Obstetric and Pediatric Hospital for severe malaria with convulsions. On the second day of admission he developed with abundant epistaxis which led to severe anemia. After investigations, malaria induced-thrombocytopenia was retained as cause of the epistaxis. Management included quinine infusions for the malaria, and transfusions with fresh whole blood, direct nasal compressions with gauze pledgets. The outcome was favorable and the patient was discharged on the 11th day of admission day.
KEY WORDS: Epistaxis, thrombocytopenia, malaria, *Plasmodium falciparum*

RÉSUMÉ
Il s'agit du cas d'un adolescent de 16 ans de sexe masculin admis dans le service de pédiatrie de l'Hôpital Gynéco-Obstétrique et Pédiatrique pour paludisme grave avec convulsions. Au deuxième jour de l'admission, il a présenté une épistaxis abondante qui a entrainé une anémie sévère. Après investigations la thrombopénie induite par le paludisme a été retenu. La prise en charge a consisté en un traitement antipaludique avec la quinine en perfusion, transfusions sanguines avec du sang frais total, et des compressions nasales antérieures.
L'évolution a été favorable et le patient est sorti au bout de 11 jours d'admission.
MOTS CLÉS : Épistaxis, thrombopénie, paludisme, *Plasmodium falciparum*

INTRODUCTION

Malaria continues to be a major global health problem, with over 40% of the world's population – more than 2400 million people – exposed to varying degrees of malaria risk in some 100 countries(1) .It constitutes an important cause of death and illness in children and adults in tropical countries, with mortality currently estimated at over a million people per year (2).
In Cameroon, malaria remains the main cause of morbidity and mortality in children below five years of age and in pregnant women, and is responsible for 35 to 40 % of deaths in health facilities(3). This high mortality is due to the severe forms of the disease, whose criteria have been well elaborated (2,4,5). Abnormal bleeding (bleeding gums, epistaxis, petechiae and sub conjunctival hemorrhages etc) is one of the criteria of severity (2,4,5)and could occur in up to 10% of adult patients with severe malaria (1,6).Thrombocytopenia has been incriminated as one of the causes, usually without coagulation abnormalities(1,6). Although not considered a criteria of severity by the World Health Organisation, it is a frequent complication of both *Plasmodium vivax* and *Plasmodium falciparum* malaria (7)**.** The frequency of thrombocytopenia (platelet count below 150,000/mm3) in malarial infection ranges from 24-94% in published reports, despite the low occurrence of severe bleeding even in the case of severe malaria (7).
We present a case of severe malaria with convulsions, and in which massive epistaxis due to profound thrombocytopenia occurred during the course of hospitalization in a male adolescent admitted and managed at the Yaounde Gynaeco-Obstetric and Pediatric Hospital.

CASE REPORT

A male adolescent M.H. was admitted in the pediatric ward of the Yaounde Gynaeco-Obstetric and Pediatric Hospital on the 8th of July 2013 for generalized convulsions and fever. Onset 6 days before admission with fever, headaches and two convulsive episodes, and was taken to a health center where two quinine drips were administered without any
improvement. Two more episodes of convulsions (each lasting 3minutes) followed and he was then brought to our hospital.

In the past history, he had never convulsed before, and there was no family history of convulsions. Also, there was no notion of epilepsy in the family. He had no past history of abnormal bleeding, had never been hospitalized before and was not sleeping under a insecticide treated net.

On admission he was conscious with a weight: 56kg, temperature 38.5°C, blood pressure 100/60mmHg, heart rate 96/minute and a respiratory rate of 24/minute. The conjunctivae were well colored. Heart and lungs were normal. The abdomen was soft, with no liver or spleen enlargement. Neurological assessment was normal. The ear-nose-throat examination was normal. The diagnosis of severe malaria was made (with convulsions as criteria of severity) and meningitis as a differential.

A lumbar tap was done and analysis of the cerebrospinal fluid (CSF) showed 2 leucocytes/mm^3, and no germs on Gram coloration, culture was sterile; the blood count showed leucocytes at 12, 000 /mm^3 with 57% lymphocytes, hemoglobin (Hb) at 8.2 g/dl and platelets at 15, 000/mm^3 ; thick blood smear: 129 trophozoites of *Plasmodium falciparum* /mm^3 . Severe malaria was retained as diagnosis. We administered as treatment quinine base 8mg/kg/8hours in 10% glucose drips, paracetamol 1g every 8 hours slow intravenous, phenobarbital injectable 10mg/kg body weight loading dose and 5mg/kg to be given after 24hours and every 24hours. On the 2nd day of admission, he started having bilateral massive epistaxis. This persisted despite manual nasal compression and head-forward tilting. Blood coagulation and vascular disorders were suspected. His blood pressure was 100/60mmHg.

A full blood count showed Hb :5.8g/dl, platelets 15, 000/mm3 ; the blood smear confirmed thrombocytopenia, and there were no abnormal blood cells. Prothrombin time was normal at 77%; activated partial thromboplastin time (aPTT) was normal at 37seconds.

With the persistence of the bleeding and ensuing hemodynamic instability

500 ml of fresh whole blood was transfused. The nasal cavity mucosae was examined by an Ear-Nose-Throat specialist and a Kiesselbach's plexus watershed area could not be ruled out equivocally, as this was done in active and persistent bleeding. However anterior compression with intranasal lidocaine-naphazoline gauze pledgets was done.

Despite this local treatment and transfusion with fresh blood, the bleeding persisted abundantly although intermittently into the 3rd day. A second blood count showed a Hb of 5.7 g/dl and a platelet level at 36, 000/mm3. A second transfusion with fresh blood was done, accompanied with another nasal compression. Antibiotic coverage with ceftriaxone was instituted, since the nasal pledgets were left in place permanently. On the 4th day a control blood smear for malaria parasites was negative, and the nose bleeding had reduced to only spotting.

By the 5th day the bleeding stopped and he became afebrile. The quinine drips were stopped and switched to dihydroartemisinin+piperaquine phosphate tablets. The nasal pledgets were removed at the 9th day and no bleeding was noted.

A control blood count on the 9th day showed a Hb level at 7.8 g/dl and platelets at 818 000/mm3. He was finally discharged on the 11th day, on iron supplements. He was assessed 1 week later and a control blood count showed a Hb level at 8.5g/dl and 230,000/mm^3.

DISCUSSION

The case presented is that of a patient with severe malaria in which the criteria of severity was initially convulsions. In the course of hospitalization, abnormal bleeding (epistaxis), added a second criteria. These are amongst the criteria for severity elaborated by the World Health Organization (2,4),and the Cameroon's Ministry of Public Health **[5]**.

Abnormal bleeding could occur in 5% of patients with severe malaria (8) and in 10% of adult patients with severe malaria(6)

When the epistaxis started we hypothesized as possible etiologies, coagulation disorders, and bleeding from a fragile Kiesselbach's plexus (also known as Little's area). Hypertension (he had headaches on admission), was ruled out as the blood pressure taken on two occasions was normal. The coagulation workup was normal and the blood count still confirmed severe thrombocytopenia at 15000/mm^3, which had been noted on the previous blood count done on admission. However on admission there was neither epistaxis nor any other bleeding sites anywhere in the body. Also there was no past personal or family history of bleeding tendencies. Given the abundance of the bleeding the nasal mucosa was explored to exclude a fragile Kiesselbach's plexus since the bleeding was anterior**.**

There are two important areas in the nose that play a role in epistaxis :

- the Kiesselbach's plexus also known as Little's area (which is responsible for anterior bleeding), located on the anterior nasal septum, and formed by the anastomosis of four arteries - superior labial artery, anterior ethmoidal artery, greater palatine artery and the spheno palatine artery ;

-Woodruff 's plexus (responsible for posterior bleeding), located over the posterior middle turbinate, and is primarily made up of anastomosis of branches of the

internal maxillary artery, namely, the posterior nasal, spheno-palatine, and ascending pharyngeal arteries. (9,10)

Although the ENT examination did not reveal active mucosal bleeding nor prominent blood vessels, it was equivocal as to the presence of scabs, ulcerations, or erosions, since the patient was still at the active phase of bleeding.

We retained severe thrombocytopenia as the most likely cause of the bleeding, since this was confirmed on two different blood counts, and all other causes (coagulation disorders, hypertension, vascular) ruled out.

This was severe thrombocytopenia as classified by Ansari et al (11) **:** mild thrombocytopenia: <150,000 but >50,000/l, Moderate thrombocytopenia: <50,000 but ≥20,000/l, severe thrombocytopenia: <20,000/l.

The relevance of thrombocytopenia in the individual patient is variable and depends on the clinical presentation. Because platelets play an essential role in preserving vessel wall integrity, thrombocytopenia is associated with a defect of primary hemostasis. Clinically significant spontaneous bleeding does not usually occur until the platelet count is less than 10-20,000/l (12).

We retained that the cause of this thrombocytopenia was malaria as the blood smear had confirmed the presence of trophozoites of *Plasmodium falciparum.*

There have been reports of malaria- associated thrombocytopenia for *Plasmodium falciparum* (11**,**13)and *Plasmodium vivax* (14,15), and in both plasmodium strains (16,17,18,19)**.**

The mechanisms involved in the pathogenesis of malaria-induced thrombocytopenia are multifactorial, and include:

- Coagulation disorders with disseminated intravascular coagulation (DIC) (7).
- Splenomegaly: platelets may be sequestered in the spleen during the acute infection, or the macrophage-colony stimulating factor which increases during malaria might be associated with thrombocytopenia, suggesting the possible role of macrophages in the destruction of platelets [7].
- Bone marrow alterations: there is likelihood of dysmegakaryopoiesis (7); or platelets might be invaded by the malaria parasites (17,20).
- Antibody-mediated platelet destruction: there is evidence that platelet-associated immunoglobulins are increased in malaria and might be associated with thrombocytopenia. Specific immunoglobulins bind to platelet-bound malaria antigen through the Fab portion of the immunoglobulin molecule (7,21).
- Oxidative stress: free radicals may play an important role in the platelet destruction in malarial infection (7,21).
- Platelet aggregation: platelets from patients with acute malaria are highly sensitive to adenosine diphosphate (ADP). ADP release following haemolysis could contribute to platelet aggregation (7).
- Platelet phagocytosis in malaria has been shown to be associated to thrombocytopenia and correlates with TNF-α, a cytokine normally attributed to severity in malaria (14)

Quinine-induced thrombocytopenia due to quinine-dependent platelet-reactive antibodies has been reported in some patients taking quinine to prevent nocturnal leg cramps (22).This was not a possible etiology in our patient as he was on quinine up to the 5th day, and the platelet count had risen from the initial 15000/mm^3 on day 1 to 83,000/mm^3 on day 5.

However, there are none or very rare literature reports of quinine-induced thrombocytopenia in malaria (17,23)**.**

There is no conclusive evidence or recommendation on how to manage patients with malaria-induced thrombocytopenia. Platelet transfusion has been widely used but with no confirmed efficacy. The indication of prophylactic platelet transfusion when platelet counts are under 10,000/mm3 probably applies only when the bone marrow is compromised and is not able to release enough platelets, but this does not seem to be the case in malaria (7).The World Health Organization just recommends transfusion of fresh blood or platelets as required with no other precisions(1,24)**.** In our patient we transfused whole fresh blood due to the unavailability of platelets in our milieu.

A control blood count on the 9^{th} day showed thrombocytosis. The platelet count returned to normal one week later after discharge. This thrombocytosis was certainly reactive thrombocytosis. Reactive thrombocytosis is due to increased megakaryopoiesis and thrombopoiesis from bone marrow recovery. Thrombopoietic growth factors have been implicated as the cause of reactive thrombocytosis in various infections. Although the exact mechanism is unknown, reactive thrombocytosis may result from persistent overproduction of one or more thrombopoietic factors that act on megakaryocytes or their precursors . Many cytokines such as interleukin (IL)-6, IL-1, IL-8 and tumor necrosis factor (TNF), (which are part of an acute-phase response during infections) have been shown to stimulate in-vivo and in-vitro megakaryocytopoiesis, or production of platelets. However, the principal regulator of megakaryocytopoiesis is hepatic thrombopoietin (TPO), also called megakaryocyte growth and development factor(25,26)**.**

CONCLUSION

Abnormal bleeding could occur in about 5 -10% of patients with severe malaria. Thrombocytopenia is a frequent finding in *Plasmodium falciparum* and *vivax* malaria, usually without other coagulation abnormalities. In a few cases it could be severe as to cause massive bleeding from any site in the body, thus worsening the outcome. Management consists of local control of the bleeding, ruling out other causes of the bleeding, and adequately treating the malaria infection. Transfusion of platelet concentrates if available or of fresh whole blood improves outcome as illustrated in our case.

CONFLICT OF INTEREST

None

All the authors read and approved the final manuscript.

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