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Case Report

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Abstract

Background

Malaria’s treatment improved throughout the last decades mainly focused on eradicating the plasmodium. Nevertheless, its severe form is still a threat to over half the world’s population leaving opportunities to evaluate new approaches in managing the cytokine storm often associated with these cases.

Case Presentation

A previously healthy 60 years-old male was hospitalized due to a prolonged high fever after a recent visit to the Equatorial Guinea. The *Plasmodium Falciparum* Malaria diagnosis was made and soon after hospital admission his clinical condition rapidly deteriorated with hemodynamic instability, need of mechanical ventilation and acute kidney injury. Continuous renal replacement therapy (CRRT) was initiated using the Oxiris® filter, an endotoxin and cytokines adsorption membrane currently used in our center in septic shock especially when due to gran negative bacteria. In the present case, the rational for its prescription was based on the similarity of sepsis and malaria cytokine storm in severe cases. A remarkable clinical improvement started within 24 hours after CRRT, followed by a clear decreasing in blood inflammatory mediators after 72 hours of its initiation (lactate: from 71 to 20 mg/dL; procalcitonin: from 73.9 to 33ng/L, interleukin-6: from 590 to 106 pg/mL). Seven days after admission, the patient acquired a ventilator-associated pneumonia, and targeted antimicrobial treatment was started. Because of multiple complications related to long in-hospital stay, patient remained hospitalized for five months before being discharged. He recovered renal function and no longer needed renal replacement therapy after discharge.

Conclusions

There are no previous or ongoing trials regarding the use of endotoxins and cytokines adsorbing membranes in the setting of severe malaria. The prompt clinical and laboratory improvement after the initiation of blood purification suggests cytokine adsorptive filters may have a beneficial impact in those cases.

Background

Malaria incidence is still high in some endemic regions, especially in Sub-Saharan Africa where the *Plasmodium falciparum* (*Plasmodium f.*) is responsible for most infections. (1) The clinical spectrum ranges from asymptomatic forms to severe malaria, which may include severe anemia, metabolic acidosis, cerebral malaria, and acute kidney injury (AKI). (2) Despite appropriate treatment, mortality rates can be as high as 18.5% in these severe cases. (3) Moreover, 40% of patients present multiple organ dysfunction and AKI. (4)

The kidney injury induced by the *Plasmodium* species is mainly caused by immunocomplex deposition, endothelial dysfunction, and inflammation mediated by cytokines activation, notably tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 and IL-17. (4, 5) Up-regulation of inflammatory mediators, such as IL-6 and procalcitonin (PCT), are also associated with more severe presentations in *Plasmodium f.* infection, (6, 7) cardiac involvement (up to 26% of the cases), (7) and a higher parasite burden. (6, 7, 8)

While the standard treatment targets the *Plasmodium* parasites, the cytokine cascade and the Multiorgan failure syndrome when present, contribute to a worse prognosis. (8, 9) Encouraging results have been obtained with the use of endotoxin and cytokines adsorption membranes used during extracorporeal blood purification procedures in septic shock induced by gram-negative bacterial infections. Fast-decrease in lactatemia, less need for vasopressors and better survival rates than predicted by Simplified Acute Physiology Score (SAPS) II are among its observed beneficial effects. (10, 11)

Oxiris® (Baxter™, IL, USA) is a biocompatible heparin coated hemodialysis filter that allows continuous renal replacement therapy (CRRT) and non-selective removal of blood inflammatory mediators, namely IL-6, IL-8 and TNF-α, and *Lipopolysaccharide* (LPS) gram-negative endotoxin. (12) The Oxiris® membrane has a three-layer structure: an AN69 base membrane which provides efficient renal support by diffusion and convection, a polyethylenimine surface treatment which adsorbs the molecules that are negatively charged like LPS-endotoxin, and a heparin coating that remains actively inhibiting thrombin, reducing the chance of the dialysis system
coagulation. Based on the cytokine removal property, this filter has been already studied in other settings, such as cardiovascular shock (13), cardiac surgeries (14) and in COVID19 (15, 16) but has never been described, to our knowledge, as a complementary treatment for acute cytokine storm and AKI in malaria patients.

In this case-report we describe a critically ill patient with severe malaria and AKI, treated with CRRT using Oxiris® filter as an adjuvant therapy.

Case Presentation

A 60 years-old male, without comorbidities, was admitted to the emergency department due to acute disorientation with agitation and sudoresis. He arrived in Brazil from Equatorial Guinea 12 days before and was in his fifth day of amoxicillin-clavulanate treatment prescribed empirically in the outpatient setting for a suspected bacterial infection. At admission, he had axillary temperature of 39º C, arterial blood pressure of 85 x 55 mmHg, oxygen saturation on ambient air of 97%. At physical examination he showed a pale mucosa and hypohydration, without further changes. An arterial blood gas sample collected in the emergency room was within the normal range except for a lactate of 133mg/dL. Due to his epidemiological exposure, malaria was suspected and guided further laboratory analysis (Table 1). A peripheral blood smear and an antigen-based test were performed and returned positive for *Plasmodium f.* with high parasitemia (classified as 4+/4+, indicating more than 100.000 parasites per mm³) (Fig. 1). He was transferred to the intensive care unit (ICU) and the treatment with Artesunate plus Clindamycin was immediately started in addition to cautious venous hydration, close hemodynamic and fluid balance monitoring.
<table>
<thead>
<tr>
<th></th>
<th>Emergency Room admission</th>
<th>Pre CRRT with Oxiris</th>
<th>24h</th>
<th>48h</th>
<th>72h – End of CRRT with Oxiris</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
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<td>—</td>
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<td>384</td>
<td>325.2</td>
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<td>127.1</td>
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<td>57,200</td>
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<td>155</td>
<td>153</td>
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<td>—</td>
<td>2.7</td>
<td>2.1</td>
<td>3.7</td>
<td>3.2</td>
<td>3.5</td>
<td>4</td>
<td>—</td>
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<td>570</td>
<td>180</td>
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<td>2950</td>
<td>1400</td>
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<td>2910</td>
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<td>10.7</td>
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<td>7.5</td>
<td>7.6</td>
<td>7.4</td>
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<td>25,300</td>
<td>25,700</td>
<td>15,800</td>
<td>15,600</td>
<td>17,100</td>
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<td>133,000</td>
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<td>123/99</td>
<td>184/107</td>
<td>140/126</td>
<td>135/110</td>
<td>100/93</td>
<td>70/75</td>
<td>49/56</td>
<td>173/144</td>
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<td>139/55</td>
<td>38/3.8</td>
<td>123/30</td>
<td>105/40</td>
<td>125/82</td>
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<td>75/62</td>
<td>59/75</td>
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<td>4.3/1.5</td>
<td>2.6/1.3</td>
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<td>1.2</td>
<td>0.89</td>
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<td>0.73</td>
<td>1.19</td>
<td>0.73</td>
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<td>91</td>
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<td>81</td>
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<td>71</td>
<td>81</td>
<td>54</td>
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<td>Lactate (mg/dL)</td>
<td>133</td>
<td>71</td>
<td>63</td>
<td>32</td>
<td>20</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>6</td>
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<td>C Reactive Protein (mg/dL)</td>
<td>23.7</td>
<td>23.7</td>
<td>23.2</td>
<td>32.2</td>
<td>23.6</td>
<td>18.2</td>
<td>8.8</td>
<td>5.4</td>
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<tr>
<td>Procalcitonin (ng/mL)</td>
<td>—</td>
<td>73.9</td>
<td>—</td>
<td>—</td>
<td>33</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Interleukin – 6 (pg/mL)</td>
<td>—</td>
<td>590</td>
<td>—</td>
<td>—</td>
<td>106</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Cardiac index monitored thru EV1000 monitor, result shown after first calibration in the morning, following Operators Manual available at https://edwardsprod.blob.core.windows.net/media/Br/devices/monitoring/hemodynamic%20monitoring/ev1000-manual-nov-2016-hpi.pdf

AST- Aspartate aminotransferase; ALT- Alanine aminotransferase; ALP- alkaline phosphatase; GGT- Gamma Glutamyl transferase.
Twelve hours after ICU admission, patient’s condition deteriorated, and he presented severe hemodynamic instability, increased serum lactate, acute pulmonary edema, and AKI. He was sedated and put on mechanical ventilation, with need of increasing doses of norepinephrine and vasopressin for keeping his blood pressure and tissue perfusion. A transthoracic echocardiogram (ECHO) showed diffuse hypokinesia and a moderate dysfunction of the left ventricle. The ejection fraction could not be predicted at this point. Due to clinical severity, after excluding hemophagocytic syndrome, we opted to initiate CRRT using an Oxiris® filter. Baseline IL-6 and PCT were measured and are depicted in Table 1.

Seventy-two hours after CRRT initiation with Oxiris® filter, serum lactate levels decreased to normal values, norepinephrine and vasopressin doses were drastically reduced, cardiac function by ECHO improved. A new dosage of PCT and IL-6 showed a great reduction (Table 1) and the parasitemia dropped to 0.5+/4+. No acute side effect of the therapy was observed. On the 6th day of ICU a ventilator-associated pneumonia by Pseudomonas aeruginosa was diagnosed and targeted treatment was started. The patient presented multiple hospital-associated complications and was discharged five months after admission. At discharge the patient was no longer dialysis dependent, and the serum creatinine was in the normal range (1.27 mg/dL). He is currently at home and following rehabilitation programs.

Discussion

Malaria is still a life-threatening condition for over half of the world’s population (1, 17) with a high mortality rate despite an appropriate treatment. (3, 17) Although the number of malaria related deaths has declined over the past few years, new treatments are needed especially considering the emergence of resistance to current front-line therapy. (18)

Severe malaria and bacterial sepsis are similar regarding the pathogenic of multi-organ dysfunction, and have similar cytokines imbalance. (3–5, 7, 19) Therefore, medical management and life support are similar, such as early start in antipathogen drugs (antibiotics or antimalarials), hemodynamic management and need for supportive therapies, such ventilatory support and renal replacement therapy. (20, 21)

Malaria's specific treatment targets the parasite and aims its eradication. Despite recent studies focusing on adjunctive therapy aiming to reduce oxidative cell injury, such as vitamin C and E and N-Acetylcysteine, no benefit has been shown so far. (22, 23, 24) On the other hand, bacterial sepsis treatments targeting reduction of the exaggerated immune response such as adsorptive membrane for endotoxin and proinflammatory cytokines has shown promising outcomes in other settings (10–12) suggesting those might have a beneficial impact in severe malaria.

The new frontier for cytokine storm producing diseases is the management of the inflammatory state that sometimes overlaps the original pathogen aggression. (25) Cytokine adsorbing membranes are gaining space, being used in an increasing range of clinical situations, and are being studied in several others. (10, 13–15) Recently, the U.S. Food and Drug Administration has granted emergency use authorization for the Oxiris® filter to treat critically ill patients who have confirmed COVID-19 infection, (16) widening the horizon for the membrane usage, and leaving space for similar diseases to take advantage of this technology.

Because of its action mechanism and cytokines removal during CRRT, (11, 13) its use as an adjunctive therapy in severe malaria makes biological sense, and leaded the medical team to the prescription decision in the current case. As far as we know this is the first case-report to describe the use of a special cytokine and endotoxin adsorbing hemodialysis membrane in the treatment of severe malaria.

Conclusion

The use of cytokines adsorptive membrane Oxiris® has shown to be safe and potentially beneficial in a patient with severe malaria, though further studies are needed to evaluate the safety and its cost-effectiveness.

List Of Abbreviations

CRRT - Continuous renal replacement therapy
AKI - Acute kidney injury
TNF-α - Tumor necrosis factor alfa
IL - Interleukin
PCT - Procalcitonin
SAPS - Simplified Acute Physiology Score
LPS - Lipopolysaccharide
ICU - Intensive care unit
ECHO - Transthoracic echocardiogram
AST- Aspartate aminotransferase
ALT- Alanine aminotransferase
ALP- Alkaline phosphatase
GGT- Gamma Glutamyl transferase.

**Declarations**

**Consent to participate**

The patient agreed to consent for participation by signing our institutional consent form.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors' contributions**

Material preparation and data collection were performed by all authors. The first draft of the manuscript was written by Flavia Zuchen and Elizabeth Maccariello. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**References**


**Figures**

![Figure 1](image_url)

*Figure 1*

*Plasmodium falciparum* parasites are found in its ring form (star), trophozoite (arrow) and gametocyte (triangle). Peripheral blood smear, stained by Giemsa, 400x.