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Case Series

Case series of paediatric patients of acute acalculous cholecystitis associated with severe malaria in endemic region over past 3 years at single center

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ABSTRACT

Although acute acalculous cholecystitis (AAC) is a rare occurrence in all age groups; its incidence in paediatric patients is 50-60%. Yet ACC in children with malarial parasitic infection is extremely rare with only 12 cases reported as per English literature. We report 7 children with severe malaria developing ACC in a single institute in India over past 3 years. They were managed conservatively under strict observation and recovered completely without any surgical intervention. At a mean follow up of 1.5 years they are asymptomatic with a normal ultrasound imaging.

Keywords: AAC, Malaria, *Falciparum*, Paediatric

INTRODUCTION

AAC is responsible for only 2-15% cases of acute cholecystitis across all age groups.[1,2] It is mainly limited to critically ill, trauma, burns or septic patients. Its association with malaria is uncommon. As symptoms of pain in abdomen are present in majority cases of malaria not all patients undergo ultrasound examination; which may be the cause for its underreporting. ACC can have a very high complication, morbidity, and mortality rates.[1,3] Timely diagnosis and determination of the underlying etiology is crucial. Although the standard of treatment for AAC is urgent cholecystectomy or percutaneous cholecystostomy in adults, non-operative management with appropriate antibiotic therapy should be considered for paediatric patients with infectious ACC especially when associated with malaria. We report 7 such children with high grade fever; diagnosed of malaria (6: *falciparum*; 1 with combined *vivax* and dengue) developing ACC. All were managed conservatively with analgesia, rehydration, intravenous anti-malarial and antibiotics followed by enteral antibiotics. They were kept under strict clinical and imaging observation and recovered without any surgical intervention. At a mean follow up of 1 year they are asymptomatic with a normal ultrasound imaging.

CASE SERIES

We are reporting a series of 7 paediatric patients developing ACC secondary to and associated with severe malaria over past 3 years at a single centre (Table 1). Their age ranged from 9 months to 9 years. Three of them were boys and four were girls. All of them were symptomatic with high grade fever, vomiting, pain in abdomen and 3 children of them also had drowsiness and irritability. All of these 3 had normal computed tomography of brains, and hypotension requiring fluid resuscitation. Only 2 of altered sensorial patients required dopamine support initially. Of these 1 also had acute renal failure for which he needed peritoneal dialysis for 5 days later the renal output improved. All patients came positive for *Plasmodium falciparum* infection except one who had *Plasmodium vivax* along with Dengue NS1 antigen positive. Covid swab of all these patients were negative on two occasions 4 days apart. All of them had a

drop in platelet counts; of these only three required platelet transfusion. Liver enzymes were marginally raised in 4 patients and creatinine was deranged in one patient. Four patients required ICU care ranging from 2-8 days. On ultrasound all patients showed features of ACC with gall bladder thickness >3.5 mm in all. All of these patients were managed conservatively with fluid resuscitation, analgesia and anti-malarial and antibiotics. Details of same are as in Table 1. All of them were kept nil by mouth with nasogastric tube aspiration until pain in abdomen settled and naso-gastric output decreased and was clear which took nearly 2-6 days. Apart from clinical monitoring repeated blood investigations and ultrasound on 3rd day of antibiotics. Thereafter if there was no worsening, we did not repeat investigations as children improved. All patients recovered well with conservative management not requiring any surgical intervention. All were discharged in 5-15 days post admission. On a mean follow up of 1 year all of these children are asymptomatic with repeat ultrasounds showing a normal gall bladder.

Table 1: Characteristics of 7 pediatric patients of ACC with malaria.

Variables	Case 1	Case2	Case3	Case4	Case5	Case6	Case7
Age/sex	5 years/M	8 years/F	9 months/F	7 years/F	2 years/M	3 years/M	9 years/M
Symptoms	High grade Fever/ vomiting/ pain in abdomen	High grade fever/ vomiting/ severe pain in Rt HC/ drowsy	High grade fever/ vomiting/ pain in abdomen	High grade fever/ vomiting /pain in Rt upper abdomen	High grade fever/ vomiting /pain in Rt upper abd	High grade fever/vomiting/pain in abdomen/ disoriented/ edema	High grade fever/ vomiting/ pain in abdomen/ irritable
Clinical findings	Febrile, icteric, petechia +, No H megaly, no S megaly, rt HC tenderness+	Febrile, No HS megaly Rt HC tenderness +, severe dehydration, Improved ith fluid rescucitation Received platelet transfusion for blood-stained nasogastric aspiration	Febrile, No HS megaly post admission on day 2 not tolerating oral feeds Rt HC tenderness +	Febrile no HS megaly, Rt HC tenderness	Febrile no HS megaly, Rt HC tenderness	Febrile/ anasarca/ no urine output since 24 hours/ petechiae/rt HC severe tenderness/Abdominal distension -Patient in ARF received dialysis with fluids, platelet transfusion/ -Output improved since 5th day	Febrile, no H megaly, mild spleenomegaly Rt HC tenderness +, hypotension, fluid replacement with dopamine support, On day 2 of admission altered blood in naso-gastric tube platelets dropped, platelet transfusion given,
***Plasmodium* species/ others**	*Falciparum*	*Falciparum*	*Falciparum*	*Falciparum*	*Falciparum*	*Falciparum*	*Vivax* + dengue
Hb	11.2	9.2	11.8	9.7	8.4	8.4	11.2 on admission dropped to 10.2
WBC	5400	6700	7200	10300	5600	11600	5400
Platelets	80000	52000	120000-dropped to 100000	70000	84000	48000	69000
AST/ALT	112/128	98/normal	normal	normal	normal	98/92	198/206
Bilirubin T/D	2/0.5	1.2/0.2	Normal	Normal	Normal	1.6/0.4	Normal
Urea/ creatinine	Normal	Normal	Normal	Normal	Normal	Creat 3.8 post dialysis 1.2 and 0.9 at discharge	Normal

Continued.

Variables	Case 1	Case2	Case3	Case4	Case5	Case6	Case7
ICU	Yes 4 days	Yes 2 days	no	no	no	Yes 8 days	Yes 5 days
USG	ACC GB 4 mm thickness, mild ascites	ACC GB 4.5 mm pericholecystic free fluid, mild ascites	ACC GB 3.5 mm, mild free fluid	ACC GB 3.7 mm, mild free fluid	ACC GB 4.2 mm pericholecystic free fluid, mild ascites	ACC GB 4.5 mm pericholecystic free fluid, moderate address, mild HS megaly,	ACC GB 3.5 mm thickness, pero-cholecystic collection mild hepatomegaly Mild spleeno-megaly
Other investigation	G6PD	G6PD	G6PD	G6PD	G6PD	CT brain normal Xray chest b/l moderate effusion G6PD	CT brain normal Xray chest mild rt pleural effusion G6PD
Anti-malarial	Inj. Artesunate 7 days	Inj. Artesunate 7 days	Inj. Artesunate 7 days	Inj. Artesunate 7 days	Inj. Artesunate 7 days	Inj. Artesunate 7 days	Inj. Artesunate 7 days
Antibiotics	Injection clindamycin 7 days Inj. taxim Inj. Metro-nidazole f/b oral anti-malarial and antibiotics	Injection clindamycin 7 days Inj. taxim Inj. Metro-nidazole f/b oral anti-malarial and antibiotics	Injection clindamycin 7 days Inj. taxim Inj. Metro-nidazole f/b oral anti-malarial and antibiotics	Injection clindamycin 7 days Inj. taxim Inj. Metro-nidazole f/b oral anti-malarial and antibiotics	Injection clindamycin 7 days Inj. taxim Inj. Metro-nidazole f/b oral anti-malarial and antibiotics	Injection clindamycin 7 days Inj. taxim Inj. Metro-nidazole f/b oral anti-malarial and antibiotics	Injection clindamycin 7 days Inj. taxim Inj. Metro-nidazole f/b oral anti-malarial and antibiotics
Surgery	No	No	No	No	No	No	No
Days of hospital stay (Days)	12	10	12	6	5	15	12
On follow up	At 2 years no complaints USG abdomen N	At 1.8 years no complaints USG normal	At 1.2 years no complaints USG normal	At 1 years no complaints USG normal 5 years	years no complaint USG normal	At 10 months no complaints USG normal	At 6 months no complaints USG normal

Rt- right, HC- hypochondrium, Hmegaly-hepatomegaly, Smegaly-sleenomegaly, HS megaly-Hepatosplenomegaly.

Patients received tab. primaquine for 14 days after above medications.

DISCUSSION

As per WHO malaria report 2020, India is the only high endemic country which has reported a decline of 17.6% in 2019 as compared to 2018. India has sustained API less than one since year 2012. The percentage drop in the malaria cases was 71.8% and deaths were 73.9% from 2000 to 2019. It is still a potentially life-threatening disease cause by malarial parasites transmitted by female Anopheles mosquitoes. Of various complications associated with it; the ACC is an uncommonly reported occurrence. On reviewing literature only isolated case reports are found especially in paediatric age group. Only 12 such paediatric cases are reported till date.[4]

Unlike in adults where calculous cholecystitis is predominant in pediatric age group acalculous cholecystitis is commoner contributing to 50-60% cholecystitis.[5] First reported case of ACC associated with malaria was in 1999. As per English literature we found only 12 such cases reported in paediatric age group.

Including our cases, all are from *Plasmodium* endemic areas, with an age range from 9 months to 9 years. These patients presented the usual malaria symptoms (fever,

chills, drowsiness, headache) associated with specific digestive symptoms (abdominal pain, diarrhea, vomiting) and more characteristic symptoms or signs related to cholestatic syndrome (tenderness in the right hypochondrium, Murphy's sign-painful palpation of the subcostal region during inspiration-jaundice and dark urine).[6-9]

All patients underwent an ultrasound which showed findings of ACC (gall bladder wall thickening ≥ 3 mm, wall edema, distension >5 cm, biliary sludge or pericholecystic fluid). (3,10). All were treated with antimalarials, broad spectrum antibiotics, showing improvement in 2-7 days without surgery.

Different hypotheses have been proposed to explain the physiopathology of AAC due to malaria. In cases of severe malaria, both resetting and cytoadherence that cause microvascular obstruction and ischemia in multiple organs have been documented. These phenomena have been related to different complications, such as ischemic injury of brain parenchyma in cerebral malaria and acute tubular necrosis causing acute kidney injury (as found in one of our patients). AAC could also be secondary to microcirculatory obstruction in the gallbladder vessels. A third proposed mechanism is the release of pro-inflammatory cytokines (TNF, IL-6, IL-8, IL-12 or IL-18) during malaria infection that can contribute to gallbladder inflammation.[11]

Cholecystectomy can be done open or laparoscopically and is indicated for acalculous cholecystitis as definitive treatment in adult patients (who are able to tolerate surgery). However, the procedure is associated with risks including bile leak or peritonitis, in addition to the risks related to general anesthesia. After cholecystectomy, as many as 47% of patients report symptoms of gastritis and diarrhea.[1,12] While percutaneous cholecystostomy is less invasive, complications including hemorrhage and peritonitis have been reported in as many as 13% of cases. While these risks may seem slight, they are much more severe and prevalent than the side effects of antibiotic treatment. The epidemiology and etiology of paediatric AAC is quite different from adults. Therefore, even the therapeutic management of AAC in children is different and, in particular, the frequency of the surgical approach is generally much lower than in adults.[13] Most AAC children who finally required surgical management were affected with vasculitis or systemic bacterial infections or, interestingly, were patients who did not receive a final diagnosis, as the cause of AAC remained unknown.

The current therapeutic management of AAC in children with severe malaria is mostly conservative, but hospital admission should be recommended in order to monitor the clinical and sonographic evolution in any individual case as is evident from the 12 cases reported earlier and the 7 cases from our series. Regardless of the clinical condition, supportive therapy (analgesia, rehydration) is necessary; oral feeding was suspended until the resolution of symptoms and inflammation. Evacuation of gastric contents via nasogastric tube may be appropriate in some cases. Consequently, use anti-malarial and intravenous fluid replacement is paramount. Due to the frequent implication of infections in the development of AAC, antibiotic therapy should almost always be recommended and we used combination of a third-generation cephalosporin and metronidazole unless there is a different indication from the clinical situation and/or microbiological results.[14,15]

As is evident from our case series ACC with severe malaria can be conservatively managed on antibiotics without need for any surgical intervention. However, vigilance and monitoring are important with respect to progressive symptoms clinical findings and laboratory and imaging is important to avoid missing a timely intervention. Apart from clinical monitoring we repeated blood investigations and ultrasound on 3rd day of antibiotics. Thereafter if there was no worsening, we did not repeat investigations as the children improved. On an average f/u of 1 year none of these children show any recurrence of symptoms and imaging is clear with no signs of GB inflammation or stones or sludge.

Unfortunately, specific guidelines for ACC in paediatric patients are not available, and hence more of such cases and their successful management need to be reported to establish the most appropriate management.

CONCLUSION

ACC as a complication of malaria is rare, yet could be underreported. Conservative management with antibiotics is therapeutic without any surgical intervention and is found to be sufficient. However strict vigilance and monitoring is a must.

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