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REVIEW

Splenic infarction and malaria

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Background: Splenic infarction is a well recognised complication of malaria that has been infrequently reported in the literature.

Methods: A review was performed to describe the spectrum of characteristics associated with this complication.

Results: Most patients presented with fever, left upper quadrant pain and/or splenomegaly, but no specific symptoms or signs appear to predict underlying infarction. The majority of cases reported were associated with autochthonous *Plasmodium vivax* infections, whereas cases reported in travellers were mostly due to *P. falciparum* acquired in Africa.

Conclusion: Identification of infarction may allow specific recommendations for management, and associated complications such as splenic rupture should be excluded. Outcome is generally favourable and conservative management is the preferred option.

Keywords: Malaria, *Plasmodium falciparum*, *Plasmodium vivax*, Splenic infarction, Traveller

Introduction

Although the estimated incidence and mortality rates decreased globally between 2000 and 2010,[1] malaria currently remains a significant health problem. According to the WHO, an estimated 219 million cases of malaria occurred worldwide in 2010, and approximately 660 000 people died from the infection. Most fatal cases were due to *Plasmodium falciparum* and occurred in children under 5 years of age in sub-Saharan Africa.[2]

The spleen plays an important role in host defence against *Plasmodium* sp. infection. Splenic involvement in malaria may lead to asymptomatic splenic enlargement but also to severe complications including splenic rupture, splenic infarction, hyper-reactive malarial splenomegaly, hypersplenism and splenic torsion.[3,4]

In non-endemic areas, recognition and management of complicated malaria may pose a challenge for clinicians. Although splenic infarction is a well recognised and potentially life-threatening complication of malaria, it has been rarely reported in the literature. A literature review was performed to describe the spectrum of characteristics associated with this complication.

Methods

A literature search was performed in PubMed for all published articles until March 2014 using the terms 'malaria' and 'splenic infarction' or 'malaria' and 'spleen' and 'infarct' or '*Plasmodium*' and 'splenic infarction' or '*Plasmodium*' and 'spleen' and 'infarct'. No language, age or gender restrictions were imposed.

Results

A search of the literature using the terms specified above identified 42 cases of malaria associated with splenic infarction. Data on two cases of *P. falciparum* malaria with splenic infarcts diagnosed at a referral hospital in Madrid, Spain, were also included (unpublished data). With the 2 previously unpublished cases described in this report, there were a total of 44 cases, of which 31 were case reports and the remaining 13 were patients identified from a retrospective series reporting CT findings.[4–28] In total, 14 cases were due to infection with *P. falciparum*, 24 were due to *P. vivax*, 5 were mixed infections (*P. falciparum*/*P. vivax*) and 1 case was associated with *P. ovale* infection. No cases of splenic infarction associated with *P. malariae* or *P. knowlesi* infection were identified. The age range of patients was 3–65 years and seven cases occurred in children <18 years of age (data not available for all reports). Most cases were diagnosed in endemic countries (autochthonous cases, n=32), whereas 12 cases of splenic infarction were associated with imported malaria infections in travellers. The majority of cases presented with fever and left upper

quadrant pain/splenomegaly. Only four patients referred left shoulder pain. For the retrospective series on CT findings, 13/34 patients (38%) had areas of focal low attenuation (multifocal, wedge-shaped, low-attenuated regions were frequently observed in the periphery of the spleen suggesting splenic infarction).[5] Data were not available on the exact number of patients with multiple infarcts, but overall, in the majority of reported cases multiple infarctions were more frequently observed than single splenic infarcts. Splenic infarction was identified at the time malaria was diagnosed in a proportion of cases, but infarction was also detected during treatment and after treatment was completed (up to 20–25 days after the episode of malaria) (information on when infarction was diagnosed was not available for some of the cases).[6,7] Most cases were managed conservatively and the outcome was favourable. Of note, four cases had both splenic infarctions and splenic rupture,[6,8,27] in another case splenic infarction and haemorrhage were identified,[20] and in a further case a mixed infection with *P. falciparum* and *Leishmania* sp. was described.[11]

Additional data on the cases reported in the literature are summarised in Table 1.[4–28]

Discussion

Splenic infarction is a well recognised complication associated with *Plasmodium* sp. infection in humans that has, however, been infrequently reported in the literature. Splenic rupture has been more frequently reported complicating malaria infection (>200 cases, including cases identified in a recent review on malaria and splenic rupture).[29] Although this review includes, to the authors' knowledge, the largest number of reported cases to date, only 42 cases of splenic infarction were identified following a literature search, and 2 additional cases were included.

Taking these figures into consideration and after reviewing the reported characteristics of infarction of the spleen in malaria, it appears that this complication is most probably underdiagnosed for several reasons, especially in malaria-endemic areas. The majority of cases identified presented with left upper quadrant pain and/or splenomegaly, but these symptoms/signs are frequently associated with malaria and do not necessarily appear due to major complications in this organ. In some cases there were few reported symptoms associated with infarction. In resource-poor settings of some endemic areas, patients are less likely to undergo additional tests such as abdominal ultrasound and CT that would help confirm the diagnosis of splenic infarction, especially if they experience minor symptoms, and this complication could go unnoticed as most patients appear to have a favourable outcome with conservative management. In the retrospective review of patients with *P. vivax* undergoing CT from South Korea (the largest series to date), 38% (13/34) had imaging findings suggestive of splenic infarction.[5] In non-malaria-endemic areas, where a proportion of cases of malaria and infarction have been diagnosed (12/44; 27%), access to imaging studies is usually more readily available. Although no specific symptoms or findings on examination appear to help predict which patients may have an underlying splenic infarction, persistent splenomegaly with associated pain, especially if severe, and/or left shoulder pain (Kehr's sign) may assist in identification of patients needing further studies to aid diagnosis.

The majority of reported cases of malaria with splenic infarction were associated with autochthonous *P. vivax* infections, whereas cases in travellers were mostly due to *P. falciparum* acquired in Africa. Over one-quarter of the infarctions described in the literature were in travellers, which also reflects the probable degree of underdiagnosis and under-reporting of this complication considering that most of the malaria burden worldwide occurs in endemic areas. Autochthonous cases have been reported either from India (n=17) and South Korea (n=15), but no autochthonous cases of malaria with splenic infarction have been reported from Africa or the Americas. Despite the significant morbidity and mortality associated with malaria infection in childhood, only seven cases of splenic infarction have been reported in children. In addition, some cases may be associated with splenic rupture and therefore may not have been identified during the literature search: two of the cases with splenic infarction were identified in a report reviewing 55 cases of splenic rupture due to malaria.[6,8,27,30]

Severe/complicated malaria is generally associated with *P. falciparum* infection (although *P. vivax* has been more frequently associated with enlargement of the spleen, rupture and infarction).[21,31] In falciparum malaria, high levels of parasitaemia and microvascular sequestration of parasitised red blood cells may contribute to the pathophysiology of splenic infarction, and these predisposing factors are not characteristic features of malaria due to *P. vivax*.[4] However, based on published reports, splenic infarction appears to be more frequently associated with *P. vivax* monoinfection (24/44; 54%), suggesting other mechanisms are probably involved (such as acute splenic enlargement).[31] If published data on splenic infarction are considered, parasitaemia does not appear to correlate with the occurrence of infarction (ranging from ≤0.001% to 25%; see Table 1), but due to the paucity of cases and incomplete data only preliminary observations may be made. Higher parasitaemias are generally associated with an increased risk of complicated and severe malaria. Thus, even though the large proportion of cases of splenic infarction diagnosed in returning travellers in non-endemic areas (around 27%) may partly be due to under-reporting in endemic areas, other factors may be involved. Conventional travellers and other non-immune patients may present with higher parasitaemias and do not usually have a chronically enlarged spleen, and may therefore be especially at risk for this complication, both with *P. falciparum* and *P. vivax* infections. This should alert physicians managing these patients in non-endemic areas.

Many cases were reported from malaria-endemic areas and the possible role of other factors that may have contributed to the development of splenic infarction, such as underlying haemoglobinopathies, could not be ascertained as this was not investigated in most cases. Although the presence of old infarcts could not be excluded, in the majority of cases, including the retrospective series of CT findings in patients with *P. vivax* infection, diagnosis of infarction was temporally associated with the episode of malaria (in the retrospective series patients underwent CT owing to gastrointestinal symptoms and one of the exclusion criteria was more than a 3-day interval between peripheral blood film and CT).

The issue arises as to the importance and possible benefits of diagnosing all splenic infarctions in patients with malaria, especially as conservative management appears to be sufficient in most cases. Definite conclusions may not be drawn based on the paucity of cases reported, the possibility of underdiagnosis

Table 1. Splenic infarction and malaria: cases reported in the literature

Reference	No. of cases	Place of acquisition	Age (years)	Im-T vs Au	Symptoms/signs	*Plasmodium* species	Parasitaemia (as reported in original publication)	Time splenic infarct diagnosed	No. of lesions (single vs multiple)	Management and outcome	Additional comments
Christoforov et al., 1976[7]	1	Senegal	28	Im-T	Fever, LUQ and left shoulder pain	Pf	NA	Confirmed at splenectomy Day 25	Multiple	Splenectomy/ favourable	Laparoscopy+scintigraphy performed Day 23 owing to persistent LUQ pain; infarcts confirmed following splenectomy Day 25
Ramos García et al., 1985[8]	1	Ethiopia	23	Im-T	Fever, LUQ pain, hepatosplenomegaly	Pv	NA	Day 7 (splenectomy)	Single	Splenectomy/ favourable	Laparotomy performed due to increased pain Day 7. Haemoperitoneum due to splenic infarct with rupture
Coche et al., 1990[9]	1	DR Congo (Zaire)	30	Im-T	LUQ pain, splenomegaly	Pf	NA	Day 8	Single	Conservative/ favourable	
Salord et al., 1991[10]	1	NA	NA	Im-T	NA	Pf	NA	NA	Single	Conservative	Review of 21 cases of severe malaria admitted to ICU 1985–1990; 20 had acquired infection while travelling in Africa, 1 in Thailand
Singh and Kumar, 1991[11]	1	India	36	Au	Fever, recurrent acute pain left flank, hepatosplenomegaly	Pf	NA		Multiple	Conservative/ favourable	Presented with intermittent undiagnosed pyrexia of 3 months duration. Mixed infection Pf–kala azar. US findings suggestive of repeated infarcts
Hovette et al., 1994[12]	1	French Guiana	28	Im-T	Fever, LUQ and left shoulder pain, splenomegaly	Pf/Pv	Pf: 35 000/ml, Pv: 500/ml	Day 7	Single	Conservative/ favourable	
Sur et al., 1997[13]	1	India	11	Au	Fever, LUQ pain, splenomegaly	Pf	NA	Day 6	Single	Conservative/ favourable	
Agarwal et al., 1997[14]	2	India	7 3	Au Au	Fever, LUQ pain, splenomegaly in both	Pf Pf	NA	After unspecified number of days of chloroquine Rx	Multiple Single	Conservative/ favourable in both	Persistent splenomegaly 1 month after Rx in both
Oga et al., 2001[15]	1	Mali	47	Im-T	Fever	Pf	25%	Post-mortem	Single	Conservative/ deceased	Infarction detected at autopsy. Also diagnosed with metastatic papillary carcinoma of thyroid
Bonnard et al., 2005[16]	1	Guinea-Conakry	36	Im-T	Fever, LUQ pain, splenomegaly	Pf	0.5%	Day 4	Multiple	Conservative/ favourable	At diagnosis LUQ pain but US ruled out splenic infarction
Kim et al., 2007[17]	1	South Korea	34	Au	Fever, LUQ and left shoulder pain, splenomegaly	Pv	1.875×10^9/l	Day 6	Multiple	Conservative/ favourable	
Prasad and Singh, 2007[18]	1	India	57	Au	Fever, LUQ pain, hepatosplenomegaly	Pf/Pv	Blood film negative Day 1 (patient taking chloroquine), ICT positive for Pf and PV	Day 1	Multiple	Conservative/ favourable	Findings on US confirmed by CT
Choudhury et al., 2008[6]	1	India	8	Au	LUQ and periumbilical pain, splenomegaly, low grade fever for 2 days	Pf/Pv	No parasitaemia on Day 20	Day 20	Single	Conservative/ favourable	Infarct with rupture. Treated for malaria 20 days before the episode
Cho et al., 2008[19]	1	South Korea	38	Au	Fever, LUQ pain, splenomegaly	Pv	2440×10^9/l	Day 1	Multiple	Conservative/ favourable	Periodic fever+LUQ pain for 3 weeks prior to diagnosis
Balfe and Reynolds, 2008[20]	1	Southern Africa	25	Im-T	Fever, LUQ pain	Pf	NA	Day 2	Single	Conservative/ favourable	Infarction+haemorrhage, 'layering' of free peritoneal blood suggesting several haemorrhagic events in previous days
Kumar et al., 2008[21]	2	India	41	Au	Fever, LUQ pain, jaundice, splenomegaly	Pv	NA	Day 1	Multiple	Conservative/ favourable	
			65	Au	Fever, LUQ pain, splenomegaly	Pv/Pf	Pv (++++), Pf (+)	Day 2	Multiple	in both	

Continued

Table 1. *Continued*

Reference	No. of cases	Place of acquisition	Age (years)	Im-T vs Au	Symptoms/signs	*Plasmodium* species	Parasitaemia (as reported in original publication)	Time splenic infarct diagnosed	No. of lesions (single vs multiple)	Management and outcome	Additional comments
Gupta et al., 2010[22]	4	India	55 22 18 42	Au Au Au Au	Fever, LUQ pain, splenomegaly in all cases	Pv Pv Pf Pf/Pv	12 800/mm^3 4600/mm^3 1.2 lacs/mm^3 92 000/mm^3	Day 3 Day 1 Day 1 Day 1	Multiple Multiple Multiple Multiple	Conservative/ favourable in all cases	
Cinquetti et al., 2010[23]	1	Ivory Coast	34	Im-T	Fever, LUQ pain, splenomegaly	Po	0.001%	Day 6	Multiple	Conservative/ favourable	Infection probably acquired in Ivory Coast although the patient had also travelled to Senegal 6 years before the episode
Kim et al., 2010[5]	13	South Korea	48.1 (mean age of patients in series)	Au	NA	Pv	NA	NA	NA	Conservative	Retrospective series describing CT findings in cases with Pv: 13/34 (38.2%) with areas of focal low attenuation (multifocal wedge-shaped, low-attenuated regions frequently observed in periphery of spleen)
Sonkar et al., 2011[24]	1	India	28	Au	Fever, LUQ pain, splenomegaly	Pv	NA	Day 1	Multiple	Conservative/ favourable	
Thabah et al., 2013[25]	1	India	40	Au	Fever, LUQ pain, splenomegaly	Pv	NA	Day 1	Single	Conservative/ favourable	Infarct Dx by US on Day 1 and confirmed by CT on Day 3 but pain present 4 days before diagnosis/Rx started
Aggarwal et al., 2013[4]	1	India	16	Au	Fever, LUQ pain, splenomegaly	Pv	NA	Day 1	Multiple	Conservative/ favourable	
Tamaria and Agarwal, 2013[26]	1	India	6	Au	Fever, LUQ pain, splenomegaly	Pv	NA	Day 1	Single	Conservative/ favourable	
Zainoun et al., 2014[27]	1	Congo	48	Im-T	Fever, LUQ and left shoulder pain, splenomegaly	Pf	1%	Day 1	Multiple	Conservative/ favourable	Infarction and rupture diagnosed by CT
Aggarwal et al., 2014[28]	1	India	11	Au	Fever, LUQ pain, splenomegaly	Pv	NA	Day 6	Multiple	Conservative	Findings on US confirmed by CT
Current report (unpublished data)	2	Liberia	37	Im-T	LUQ pain, splenomegaly	Pf	0%	Day 7	Multiple	Conservative/ favourable in both	Malaria diagnosed in Liberia, patient referred pain on Day 4 of treatment
		Cameroon	39	Im-T	Fever, LUQ pain, Splenomegaly	Pf	4%	Day 4 of Rx (US), Day 11 by CT	Multiple		One lesion identified by US on Day 4. CT on Day 11 of Rx: multiple splenic infarcts and partial splenic rupture

Au: autochthonous; Dx: diagnosis; ICT: rapid immunochromatographic test; Im-T: imported, traveller; lac: unit in the Indian numbering system (=100 000); LUQ: left upper quadrant; NA: not available; Pf: *Plasmodium falciparum*; Po: *P. ovale*; Pv: *P. vivax*; Rx: treatment; US: ultrasound.

of this complication and therefore that the complete clinical spectrum of splenic infarction in malaria remains unknown. However, several aspects should be considered. Identification of infarction may allow specific recommendations for the individual such as relative rest (to avoid trauma and further damage to the spleen) and would determine further follow-up with additional imaging studies. In this respect, CT has been reported to be more sensitive than ultrasound, especially during the acute stage of splenic infarction. On CT, images for splenic infarction, splenic rupture and subcapsular haematomas are distinctively different .[17,32] Associated complications, such as splenic rupture or splenic abscess, should be excluded, especially as these may require different management. There are benefits associated with spleen conservation due to its role in intravascular infections and this should generally be the preferred option in cases of splenic infarction, which should therefore be correctly identified.[21] In this context, the possibility that large splenic infarctions may lead to a degree of residual hyposplenism should be considered. This would be relevant for patients who may be at risk for future severe malaria, and for those in whom vaccination against common bacterial infections (such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* and *Salmonella enterica* serovar Typhi) could be recommended. Finally, although splenic infarction is known to occur in association with malaria, in selected cases exclusion of other causes of infarction, such as underlying coagulation defects (protein C and S deficiencies or presence of Factor V Leiden), sickle cell disease or underlying malignancies, should be considered.

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