Autopsy discoveries of death from malaria

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ABSTRACT

Malaria inflicts a huge health care burden in terms of mortality and morbidity worldwide. There has been evidence in the literature where many unexpected/unexplained deaths turned out to be related to malaria on autopsy. The aim of this study is to review autopsy diagnosed malaria related deaths in the literature with due stress to its biologic and forensic aspects. A meticulous literature search was performed for “sudden malaria death”, “malaria death postmortem diagnosis” and “unexplained death malaria” across PubMed, SCOPUS, Cochrane Database of Systematic Reviews, Allied and Complementary Medicine, British Nursing Index, CINAHL, EMBASE, Ovid-MEDLINE and Google Scholar. All the literature was thoroughly reviewed and analyzed with reference to the type of study, location, travel history, age, gender, circumstance of death, method of diagnosis, species involved, chemoprophylaxis usage and take home message from the particular study. Plasmodium falciparum was responsible in most of the cases. The symptoms mimicked influenza in most of the case reports. Travel to endemic areas was common to most of the victims. The travelers were from all over the world including USA, France, Switzerland, Spain, Portugal, Germany and Asia (China and Japan). Vascular congestion with the presence of malarial pigment laden RBCs in capillaries of various organs was the major histopathology finding. Such lesions were found in the brains of all subjects (100%), liver of 78% of the cases, spleen in 67%, lungs in 56% and myocardium in 43% of the cases. Peripheral smear and rapid diagnostic test was of great aid to the autopsy in many cases. PCR was used for diagnosis as well as exclusion of possibility of co-infection with other species in case of Plasmodium knowlesi related death. The postmortem and histopathology findings in this case were similar to P. falciparum except for the fact that brain sections were negative for intracellular adhesion molecule-1. Chemoprophylaxis was not taken by the victims except for two in whom history of chloroquine based chemoprophylaxis was mentioned. Given the worldwide prevalence of the disease, increasing international travel and rapidly developing drug resistance, malaria will continue to be an important disease and should be considered in all cases of unexpected deaths particularly in malaria endemic regions or in presence of travel history to endemic regions.

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1. Introduction

Malaria is a major public health problem in developing countries and is the top ranked priority tropical disease of the World Health Organization. There are approximately 500 million clinical attacks of malaria worldwide annually. Among them, 2–3 million cases are severe and about a million people die a year (about 3000 deaths every day) [1–4]. In majority of the cases, malaria is well diagnosed in ante-mortem settings and there have been only few reported cases in the literature where malaria has been diagnosed as the cause of death posthumously [5–14]. This necessitates forensic pathologists from including malaria in the differential diagnosis for unexpected deaths [15]. Since it is not a common cause of unexpected death and can potentially masquerade a variety of disorders, it can easily be missed if this possibility is not considered while performing autopsy especially in malaria endemic regions or when there is a travel history to endemic regions. Moreover, in highly endemic regions where asymptomatic parasitemia is common, clinical diagnosis may be easily missed and confirmation of the diagnosis of malaria as the cause of unexpected death often has to rely on postmortem findings. This study has been undertaken with an objective to closely appraise the autopsy diagnosed malaria related deaths in the literature with particular emphasis to the biologic and forensic aspects of such deaths.

2. Methodology

2.1. Data collection

A rigorous electronic search was performed across PubMed, SCOPUS, Cochrane Database of Systematic Reviews, Allied and Complementary Medicine, British Nursing Index, CINAHL, EMBASE, Ovid-MEDLINE and Google Scholar. The keywords “sudden malaria death”, “malaria death postmortem diagnosis” and “unexplained death malaria” were used to search the literature. All the entries were thoroughly reviewed and included in the review process if they met the following criteria:

1. The study contained data related to unexpected/unexplained death in which postmortem examination confirmed malaria as the cause of death by histopathologic, microbiologic and/or rapid diagnostic tests.
2. No diagnosis present before death and not under any treatment for malaria.
3. Other possible causes of death excluded by extensive post-mortem examination.
4. The studies were in English language and published in peer reviewed journals in the last 50 years (1960–61 through 2010–11).

A total of 10 studies (seven case reports and three case series) met the criteria of the study and were reviewed [5–14]. Literature obtained by this method was back-referenced and hand-searched.

2.2. Data organization

The data from the different studies [6–14] were tabulated (Table 1) and analyzed with reference to the following: type of study, location, travel history, age, gender, circumstance of death, method of diagnosis, species involved, chemoprophylaxis usage and take home message from the particular study. One of the case reports that was later cited in another case series publication was not included in the tabulation [5,14].

3. Results

3.1. Data appraisal

3.1.1. Epidemiology

Among the nine studies that were included in the review process, eight of them were reported after the year 2000 and only one was reported before 2000. Six of them were case reports and three were case series. The age of the victims ranged from 22 years to 70 years and most of them were males. Travel to endemic areas was common to most of the victims. The travelers were from all over the world including USA, France, Switzerland, Spain, Portugal, Germany and Asia (China and Japan). Plasmodium falciparum was the organism responsible in all the cases but in one case Plasmodium knowlesi related death was identified by PCR technique and documented [13].

3.1.2. Circumstance of death

The circumstance of death was highly variable ranging from found dead at railway station to sudden death in the hospital, domicile, workplace, hotel and ship. While there was a history of fever and other clinical manifestations for several days in some individuals, others were either found dead with no information on symptoms prior to death or died within hours of onset of symptoms. The symptoms mimicked influenza in most of the case reports. Fever, myalgia and sudden collapse were the presentation in the case caused by P. knowlesi [13]. In the case series from Cote d’Ivoire which involved 12 patients [12], the initial symptoms were abrupt onset of hyperthermia accompanied by chill, disorders of consciousness resulting in agitation (75%) and coma (25%). In the case report from Germany, the victims had nausea and bloody diarrhea but no fever [9]. Chemoprophylaxis was rarely mentioned in the case studies. In two cases, chloroquine-based chemoprophylaxis had been given, but the dosage was not stated [6,12]. The time from onset of symptoms to death was also highly labile ranging from 2 days at the minimum to 11 days at the most.

3.1.3. Postmortem examination

Vascular congestion with the presence of malarial pigment laden RBCs in capillaries of various organs was the major histopathology finding (Table 2). Such lesions were found in the brains of all subjects (100%), liver of 78% of the cases, spleen in 67%, lungs in 56% and myocardium in 43% of the cases. Gross findings in the brain showed petechiae and perivascular edema. Microscopically,
Table 1
Case reports and series discussing malaria related unexpected deaths diagnosed on postmortem examination.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study (no. of patients)</th>
<th>Case(s) location</th>
<th>Travel history (destination)</th>
<th>Average age (years)</th>
<th>Gender</th>
<th>Method of diagnosis</th>
<th>Circumstance description</th>
<th>Chemoprophylaxis</th>
<th>Take home message</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al. [18]</td>
<td>Case report (1)</td>
<td>Germany</td>
<td>Yes (Kenya)</td>
<td>35</td>
<td>M</td>
<td>Histopathologic findings; Giemsa stained preparations; malaria immunofluorescence test</td>
<td>Time interval from travel return to death: 20 days Symptoms/presumed diagnosis: influenza</td>
<td>No</td>
<td>Malaria suspicion in cases of unexplained death. Blood should always be taken for appropriate investigations in addition to histopathological examination</td>
<td>P. falciparum</td>
</tr>
<tr>
<td>Ette et al. [12]</td>
<td>Case series (12)</td>
<td>Cote d'Ivoire</td>
<td>No</td>
<td>44</td>
<td>M (10)</td>
<td>Histopathologic findings</td>
<td>Time interval from travel return to death: not available Symptoms/presumed diagnosis: the symptom common to all was hyperthermia accompanied by chills and altered level of consciousness</td>
<td>Yes (1)</td>
<td>Significance of malaria prophylaxis.</td>
<td>P. falciparum</td>
</tr>
<tr>
<td>Wichman et al. [9]</td>
<td>Case series (2)</td>
<td>Germany</td>
<td>Yes (Burkina Faso)</td>
<td>48 (M)</td>
<td>M</td>
<td>Histopathologic findings; peripheral smears</td>
<td>Time interval from travel return to death: 7 days Symptoms/presumed diagnosis: nausea and bloody diarrhea, but no fever</td>
<td>No</td>
<td>Malaria suspicion in cases of unexplained death.</td>
<td>P. falciparum</td>
</tr>
<tr>
<td>Chappuis et al. [11]</td>
<td>Case report (1)</td>
<td>Switzerland</td>
<td>Yes (Madagascar)</td>
<td>43</td>
<td>M</td>
<td>Histopathologic findings; peripheral blood films; ICT malaria P.f/P.v test</td>
<td>Time interval from travel return to death: 7 days Symptoms/presumed diagnosis: fever and flu-like symptoms</td>
<td>No</td>
<td>Malaria suspicion in cases of unexplained death.</td>
<td>P. falciparum</td>
</tr>
<tr>
<td>Stoppacher and Adam [7]</td>
<td>Case report (1)</td>
<td>USA</td>
<td>Yes (Africa)</td>
<td>24</td>
<td>F</td>
<td>Histopathologic findings; Blood smear; immunoassay</td>
<td>Time interval from travel return to death: 18 days Symptoms/presumed diagnosis: Flu-like symptoms including dry cough, nausea, vomiting, and diarrhea. Also found to have urinary tract infection and treated with amoxicillin</td>
<td>No</td>
<td>Malaria suspicion in cases of unexplained death.</td>
<td>P. falciparum</td>
</tr>
<tr>
<td>Muehlethaler et al. [10]</td>
<td>Case report (1)</td>
<td>Switzerland</td>
<td>Yes (Kenya)</td>
<td>34</td>
<td>M</td>
<td>Histopathologic findings; Giemsa stain; rapid diagnostic test</td>
<td>Time interval from travel return to death: 14 days Symptoms/presumed diagnosis: abrupt onset of fever, chills, malaise, and muscle aches; treated for influenza</td>
<td>No</td>
<td>Significance of malaria prophylaxis. Malaria suspicion in cases of unexplained death.</td>
<td>P. falciparum</td>
</tr>
<tr>
<td>Rastogi et al. [14]</td>
<td>Case series (5)</td>
<td>India</td>
<td>No (South India)</td>
<td>Not specified (all elderly)</td>
<td>M (5)</td>
<td>Histopathologic findings</td>
<td>Time interval from travel return to death: not applicable Symptoms/presumed diagnosis: not available Three found dead in or around railway station, 1 found dead in room and 1 in public place</td>
<td>Not mentioned</td>
<td>Malaria incidence increasing due to resistance of drugs and insecticides</td>
<td>Undetermined</td>
</tr>
<tr>
<td>Alunni-Perret et al. [6]</td>
<td>Case report (1)</td>
<td>France</td>
<td>Yes (Cameroon)</td>
<td>38</td>
<td>M</td>
<td>Histopathologic findings; QFBC preparation; rapid diagnostic test</td>
<td>Time interval from travel return to death: 4 days Symptoms/presumed diagnosis: flu like symptoms</td>
<td>Yes</td>
<td>Malaria suspicion in cases of unexplained death.</td>
<td>P. falciparum</td>
</tr>
<tr>
<td>Cox-Singh et al. [13]</td>
<td>Case report (1)</td>
<td>Malaysia</td>
<td>No</td>
<td>40</td>
<td>M</td>
<td>Histopathology; nested-PCR for species confirmation</td>
<td>Time interval from travel return to death: 10 days Symptoms/presumed diagnosis: Abrupt onset of fever and body ache and presented in a state of collapse.</td>
<td>Not mentioned</td>
<td>Need to develop P. knowlesi specific diagnosis and management guidelines are urgent.</td>
<td>P. knowlesi</td>
</tr>
</tbody>
</table>
there were thrombi composed of parasitized and/or pigmented RBCs residing within the cerebral capillaries. Similarly, malarial pigment deposits were also observed in the liver sinusoids and Kupffer cells in 78% of the cases. These deposits were distributed inside the venous sinuses of the spleen in 67% of the cases. In addition, alveolitis, pulmonary congestion and hemorrhage and malarial pigment in lungs were noticed in 56% of the cases. Malarial pigment deposits were found in the interstitial tissue of the myocardium in 43% of the cases. One case even had pericardial vessel congestion and focal inflammatory infiltrate suggestive of pericardial involvement. In other organs, capillary congestion resulting in foci of punctate hemorrhages was noted. Periperal smear stained with Giemsa stain was used for parasite visualization in 19% of the cases. In one case report this was aided by malarial antibody using immunofluorescence technique which was weakly positive at 1:40 titre. In three case reports rapid diagnostic test was used as diagnostic tool. *P. knowlesi* involvement was diagnosed using nested PCR where dengue hemorrhagic fever was a close differential for that case. Toxicological analysis of viscera was performed in most of the cases in order to rule out other causes that could have led/contributed to death. Heroin overdose was suspected as a cause of death in one case report which was ruled out by toxicological analysis. Ten percentage of the cases however did not mention anything about chemical analysis.

### 4. Discussion

Malaria remains the most important parasitic disease worldwide. The case fatality rate of strictly defined cerebral malaria in endemic areas remains of the order of 20% in adults and 15% in children [16]. Until proven otherwise, malaria must be suspected in all febrile people returning from malaria endemic areas; therefore a detailed travel history is mandatory. As we have observed in this literature review of autopsy diagnosed malaria deaths that the manifestation of malaria particularly in the non-immune traveler varies so widely that any symptom with a positive travel history should be interpreted with caution and hence should never be treated otherwise until the possibility of malaria is excluded from a detailed clinical and laboratory examination. Surveillance data of European travelers showed that diarrhea is experienced in up to 14% of those with *P. falciparum* malaria infection [17]. Since diarrhea is one of the major causes for post-travel consultations [18], it can easily be misinterpreted as trivial travelers’ diarrhea by both patients and physicians. Similarly, the classic clinical presentation of malaria consists of fever accompanied by other symptoms such as headache, malaise, nausea, muscular pain, and this clinical picture can easily be mistaken for influenza, especially during winter when influenza is highly prevalent [8]. The other major confront in malaria related deaths is that microbiological analyses are not routinely completed following forensic autopsies since cardiopulmonary etiology is almost always given due importance and malaria is hardly taken into consideration by forensic pathologists in the differential diagnosis for sudden unexpected death. However, the literature review vividly stresses on the fact that fatal undiagnosed cases of malaria are not uncommon, especially when death occurs in the endemic areas or in relation to travel to an endemic area and is fairly easy to let pass when the possible clinical diversity of malaria manifestations are not mastered by forensic pathologists at the time of the postmortem investigations.

Human cerebral malaria caused by *P. falciparum* is the malignant form of malaria responsible for sudden deconditioning and death. In the present literature review, more than 95% of the sudden unexpected malaria deaths were due to *P. falciparum*. However, one case report has outlined *P. knowlesi* related fatal malaria diagnosed posthumously, thereby revitalizing the previously entertained prospect that *P. knowlesi* may emerge as a human pathogen beyond its current zoonotic manifestations [19]. Macroscopic findings during autopsy were often nonspecific in most of the cases. Histopathology confirmed sequestration of erythrocytes and malarial pigment in macrophages in most organs. The microscopic lesions in brain involving the presence of microthrombi made of malarial pigment infected erythrocytes on the cerebral capillary walls in all the case reports indicate cerebral malaria contributing partly or entirely in the death. ARDS and myocardial dysfunction may be potential contributors to malaria deaths as observed in some cases.

Microscopy of cadaveric blood smears revealed remnants of intraerythrocytic parasites in most of the case reports. Presence of this postmortem finding in sudden unexpected death due to malaria varies considerably in the literature from 25% in one study [9] to as high as 80% in another [10]. One of the possible reasons for this disparity may be delay in timing of autopsy as microbiological analyses may be compromised or impossible due to autolysis in some cases. Rapid diagnostic tests were used as a tool for diagnosis as well as species differentiation in two case reports [6,11]. They

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Liver involvement</th>
<th>Spleen involvement</th>
<th>Kidneys involvement</th>
<th>Myocardial involvement</th>
<th>Thrombi in brain</th>
<th>Pulmonary congestion/atelectasis</th>
<th>Toxicological analysis</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albert et al. [18]</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td>+</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Ette et al. [12]</td>
<td>+(100%)</td>
<td>+(100%)</td>
<td>+(50%)</td>
<td>+(33%)</td>
<td>+</td>
<td>+(423%)</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Chappuis et al. [11]</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td></td>
<td>−</td>
<td>Not mentioned</td>
<td>Microscopy; rapid diagnostic test</td>
</tr>
<tr>
<td>Stoppacher and Adam [7]</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>+</td>
<td>NM</td>
<td>Not mentioned</td>
<td>Negative</td>
</tr>
<tr>
<td>Wichman et al. [9]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Muehlethaler et al. [10]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>−</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Rastogi et al. [14]</td>
<td>+(100%)</td>
<td>+(100%)</td>
<td>+(100%)</td>
<td>+(80%)</td>
<td>+(100%)</td>
<td>+(100%)</td>
<td>−</td>
<td></td>
</tr>
<tr>
<td>Aluni-Perret et al. [6]</td>
<td>+</td>
<td>NM</td>
<td>NM</td>
<td>NM</td>
<td>+</td>
<td>NM</td>
<td>Negative</td>
<td>Microscopy; rapid diagnostic test</td>
</tr>
<tr>
<td>Cox-Singh et al. [13]</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
<td>−</td>
<td>Microscopy; PCR</td>
</tr>
</tbody>
</table>

*The term “involvement” refers to microscopic changes noticed in various organs in terms of congestion, microthrombi in the capillaries, inflammation, malarial pigment deposition and/or parasitized RBCs in the capillaries.*
may be very helpful to perform rapid diagnosis as well as speciation in situations where no skilled blood smear examiner is available. However, the possibility of false positive and false negative results with these tests should not be over sighted. PCR was used for diagnosis as well as exclusion of possibility of co-infection with other species in the case of *P. knowlesi* related death. The postmortem and histopathology findings in this case were similar to *P. falciparum* except for the fact that brain sections were negative for intracellular adhesion molecule-1 [13].

Chemoprophylaxis was not taken by the victims except for two in whom history of chloroquine based chemoprophylaxis was mentioned but no information on dosage or method of use was detailed. Among these individuals, there was no difference in clinical presentation or onset of symptoms to the time of death than in non-prophylaxis individuals. This may mean either the travel zone that the victims went to, had prevalence of chloroquine resistant species or the dosage, duration and/or consistency of use were not questionable. It is a well known fact that chemoprophylaxis may not confer a full protection against malaria and hence the importance of effective, accessible and appropriate pre-travel health advice should never be underestimated given such grave consequences of the disease.

Finally, the analysis of objectives behind the case reports in the literature clearly disclose the importance of malaria as the first cause of unexplained death in the context of travel to endemic areas or sudden unexpected death in endemic regions itself. This was the “take home message” in 77% of the studies. One of the autopsy studies done in 1994–1995 had shown that 50% cases of malaria were initially misdiagnosed as hepatic failure [20]. Hence the diagnosis of malaria knows no bounds in alive as well as dead persons in endemic areas and among travelers visiting these areas. Similarly, the significance of chemoprophylaxis was highlighted in two studies as the most important “take home message” of the study. However, the fact that there were two unexpected deaths secondary to malaria despite being on chemoprophylaxis points towards the importance of pre-travel advice including but not limited to pharmacologic prophylaxis to prevent from any disastrous consequence of travel to tropical areas.

5. Conclusion

Given the worldwide prevalence of the disease, increasing international travel, and rapidly developing drug resistance, malaria will continue to be an important disease and should be considered in all cases of unexpected deaths particularly in endemic regions or in presence of travel history to endemic regions. Clinicians as well as forensic pathologists should be aware of the fact that malaria can virtually masquerade any disease and hence these symptoms in relation to travel should be given due significance in antemortem as well as postmortem diagnosis of malaria.

References