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Unsuspected imported malaria in a case of sudden infant death

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Abstract

Here we describe the case of a 4-mo-old female who died suddenly without any apparent cause that was initially mistaken as a case of sudden infant death syndrome. Histologic observation of brain sections revealed blue-black bodies in erythrocytes of the blood vessels, suggestive of specific stages of the hematic schizogonic cycle. Further examinations revealed hemozoin and hemosiderin deposits in the parenchyma of all organs, leading to the diagnosis of malaria by *Plasmodium falciparum* (*P. falciparum*). The death occurred in Italy, the native country of the infant, two weeks after a Christmas holiday spent in Pakistan, the parents' birthplace, which has a high malarial endemicity. As this case demonstrates, the diagnosis of malaria should always be considered as a differential diagnosis in subjects, including infants, that die unexpectedly after returning from *P. falciparum* endemic areas.

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Key words: Parasitemia; *Plasmodium falciparum*; Protozoa; Sudden infant death; Unsuspected imported malaria

Core tip: This report describes the case of a 4-mo-old baby whose sudden death was initially attributed to sudden infant death syndrome. Histologic examination of organ specimens unexpectedly revealed blue-black bodies in erythrocytes, suggestive of specific stages of the hematic schizogonic cycle, and hemozoin and hemosiderin deposits in the parenchyma of all organs. These observations led to the diagnosis of death from malaria by *Plasmodium falciparum*. In support of this diagnosis, the baby had recently returned from a stay in Pakistan, a region with high malarial endemicity.

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INTRODUCTION

Malaria is an infection caused by the protozoa *Plasmodium* with high morbidity and mortality in endemic areas, including Asia and Africa^[1-3]. The virulence of the malarial agents is a consequence of a number of features, the most important of which is the tendency for parasitized erythrocytes, with the consequent occlusion of the capillaries and blockade of circulation^[4,5]. The clinical syndromes associated with *Plasmodium* infections range from asymptomatic parasitemia to high fever, chills, convulsions, coma and death^[6,7]. In infants, in particular, the typical signs of malaria (*e.g.*, febrile illness), are generally absent, and include only sudden behavioral changes like irritability, lethargy, drowsiness^[1,6]. Thus, infants are at increased risk for a rapid disease progression due to the undiagnosed infection. In the absence of a timely diagnosis, erythrocyte parasitemia may reach critical values

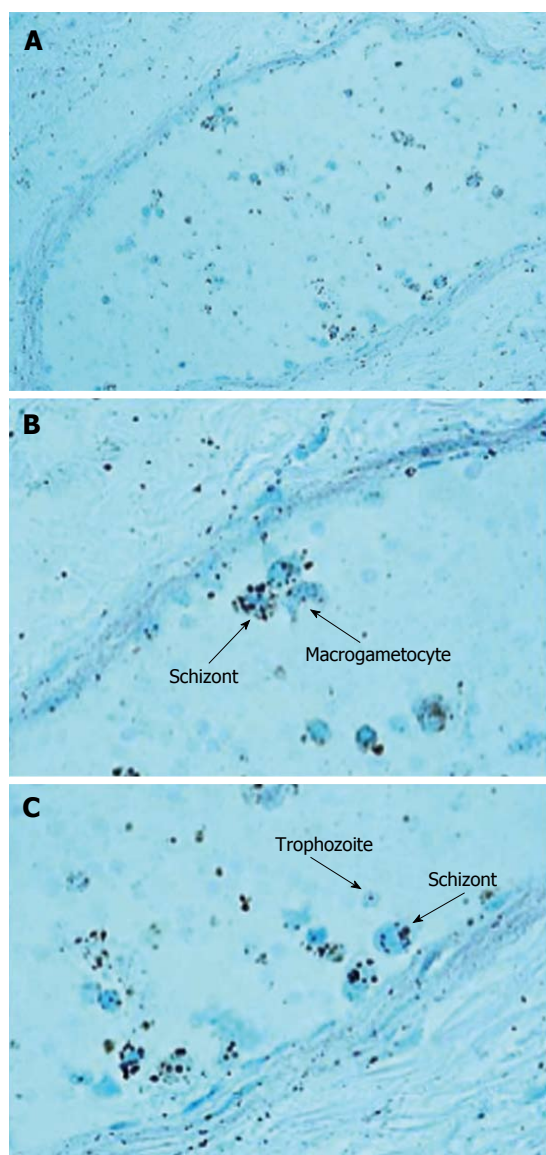


Figure 1 Different stages of the hematic schizogonic cycle of malarial parasite (schizont, trophozoite and crescent-shape macrogametocyte) in a splenic vessel. Giemsa stain, magnification A: 20 ×; B: 100 ×; C: 100 ×.

and cause massive hemolysis and multiple organ dysfunction, resulting in death. The World Health Organization estimates that in malaria-endemic areas, infants become vulnerable to *Plasmodium* at around three months of age, when immunity acquired from the mother starts to wane^[2]. Here, we report a case of an unsuspected and postponed malaria diagnosis in a 4-mo-old female, who died suddenly in Italy, her native country, two weeks after a Christmas holiday spent in her parent's birthplace, Pakistan, which has high malarial endemicity.

CASE REPORT

The case of a 4-mo-old female who died suddenly during sleep without any apparent cause was sent as a suspected case of sudden infant death syndrome to the "Lino Rossi" Research Center of the Milan University, according

to Italian law: 31/2006 "Regulations for Diagnostic Post Mortem Investigation in Victims of the Sudden Infant Death Syndrome (SIDS) and Unexpected Fetal Death".

The parents brought their daughter to northern Pakistan, their region of origin, in occasion of the Christmas holiday for around 50 d (from November 20, 2013 to January 10, 2014). During this stay, the baby was in good health. Approximately 15 d before the end of the visit, the parents noticed signs of a mosquito bite on the baby's face. On the tenth days after their return to Italy, although showing no signs of fever, the baby did not eat and showed a lack of responsiveness. For this reason, the parents brought her directly to the nearest hospital, where she arrived with no signs of heartbeat or breathing. Despite the attempts of resuscitation, physicians confirmed the absence of vital signs and death.

The autopsy examination did not show a clear cause of death, and excluded important disease processes and/or congenital malformations. An in-depth study of the autonomic nervous system, performed according to the above-mentioned Italian law in case of sudden infant death, did not detect any alteration, particularly of the brainstem vital centers. However, examination of hematoxylin/eosin-stained brain sections highlighted the presence of small blue-black bodies within erythrocytes in capillaries, indicative of infection from malarial parasites. The examination was then extended to samples of all organs. Histologic sections were processed with Giemsa staining to determine the intensity and distribution of the parasite in the different stages of the hematic schizogonic cycle in the capillaries of each organ. It was possible to recognize trophozoites, schizonts, merozoites and crescent-shape macrogametocytes, which are a distorted form of gametocyte specific to *Plasmodium falciparum* that allow differentiation from other types of malarial infection (Figures 1-3). The Perls method for iron was also used to distinguish the intra- and extra-erythrocyte hemozoin and hemosiderin, the malaria pigments arising from rupture of mature schizonts (Figures 4 and 5). Pigmented phagocytic cells were frequently found dispersed in all organs. The final diagnosis was imported acute malignant malaria from *Plasmodium falciparum*.

DISCUSSION

Malaria disease begins with the injection of sporozoites from an infected female *Anopheles* mosquito into the skin of a human host. The sporozoites primarily reach the liver and then develop within the hepatocytes through schizogonic divisions. This leads to the formation of numerous merozoites that, immediately after release in the bloodstream, parasitize red blood cells, thus initiating the intra-erythrocytic cycle, which is responsible for the initiation of clinical malaria^[8,9]. *Plasmodium* parasites therefore have two obligatory intracellular development phases, first in hepatocytes and subsequently in erythrocytes. We believe that in this case, the severe congestion of parasitized erythrocytes observed in microvessels of

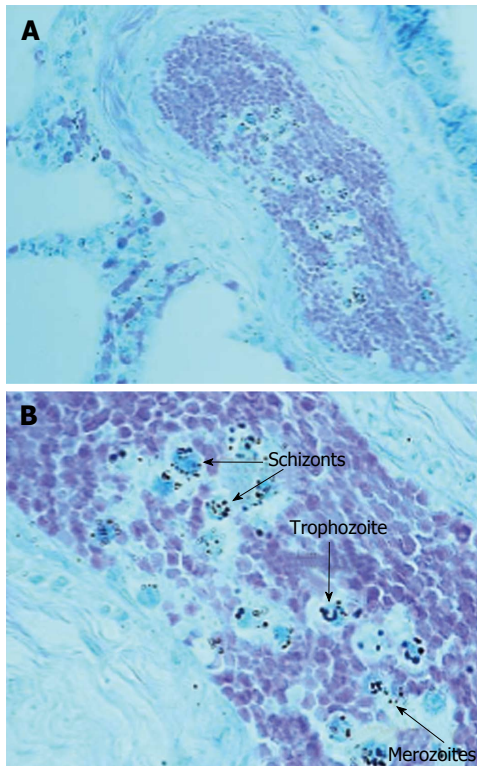


Figure 2 Malarial parasites in a pulmonary vessel. Giemsa stain showing merozoite, schizont and trophozoite stages; magnification A: 20 ×; B: 40 ×.

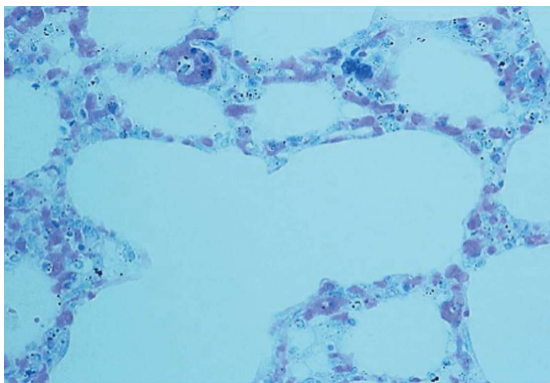


Figure 3 Numerous schizonts in the capillaries of pulmonary alveolar septa. Giemsa stain, 20 × magnification.

all organs, and especially in the brain, played a crucial role in the pathogenic mechanism of the sudden death.

The baby returned from a trip in Pakistan, a region where malaria continues to be a serious public health problem. Despite a well-established malaria control program, 500000 malaria infections and 50000 malaria-attributable deaths occur each year in Pakistan^[10,11]. Although polymerase chain reaction has been introduced to detect *Plasmodium*-positive samples, the Giemsa staining method remains, for simplicity and low cost, the gold standard for the diagnosis of *Plasmodium* infections^[12-14]. This report highlights that a diagnosis of malaria must be considered as an important differential diagnosis in subjects who have recently stayed in malarial endemic regions, with or without specific clinical symptoms. Even if the

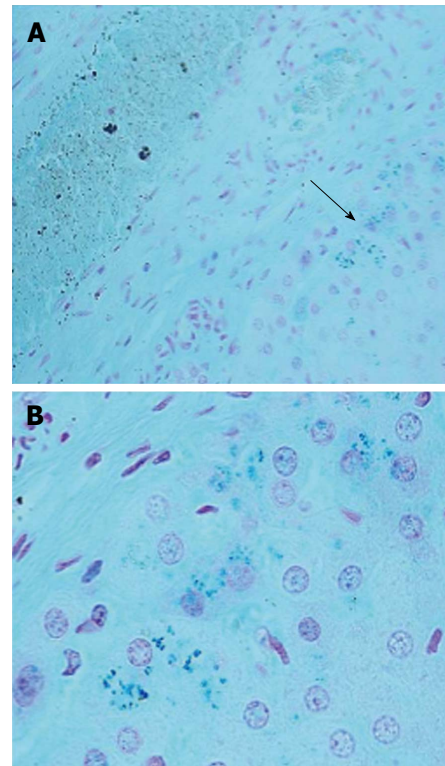


Figure 4 Malarial pigment grain accumulation in the splenic reticuloendothelial system. Perls stain showing hemozoin and hemosiderin; magnification A: 40 ×; B: 100 ×.

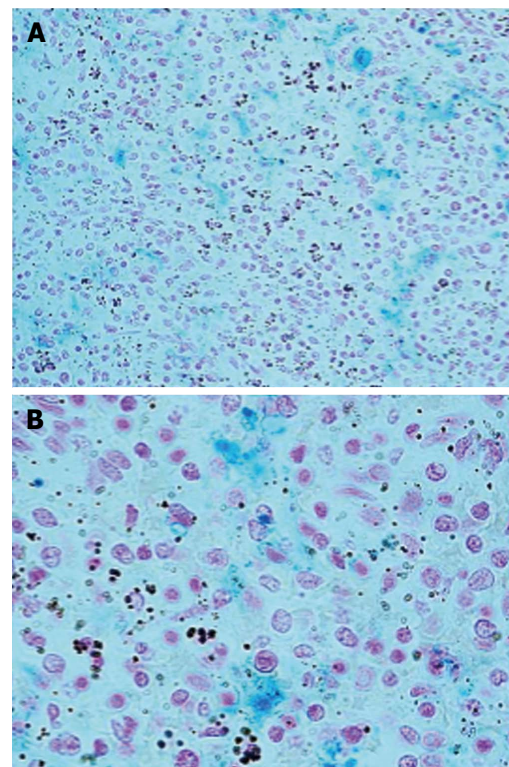


Figure 5 Malarial pigment grain accumulation in the splenic reticuloendothelial system. Perls staining method for iron showing hemozoin and hemosiderin; magnification A: 20 ×; B: 100 ×.

malaria is an infrequently encountered infection in non-

endemic areas, particularly in Europe^[15], a high degree of suspicion is needed. Furthermore, proper questioning by a doctor is fundamental in the diagnosis of imported malaria, especially when the clinical signs are non-specific and sometimes misleading. This should be applied also in cases of infants who die suddenly in the first months of life, which often occur during sleep and are classified as SIDS.

COMMENTS

Case characteristics

The paper describes a case of a 4-mo-old female who died suddenly without any apparent cause, which was initially mistaken as a sudden infant death syndrome (SIDS) case.

Clinical diagnosis

Clinical diagnosis was SIDS and other death cause were not considered.

Pathological diagnosis

Acute malignant malaria from *Plasmodium falciparum*.

Treatment

Despite the attempts of resuscitation, physicians established the non-resumption of vital signs and death.

Term explanation

SIDS is defined as the sudden death of an infant under one year of age that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and a review of the clinical history.

Experiences and lessons

This case with a post-mortem diagnosis of malaria is important from a medico-legal point of view because of the potential responsibility of the physician treating a patient of any age who has returned from endemic areas.

Peer review

The manuscript is a case report of interest in the area of health, as it can lead to greater awareness among those responsible for the area, to the attention of individuals and newborns who travel from endemic areas in malaria to non-endemic areas.

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Statistical data

Write as mean \pm SD or mean \pm SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as *v* (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Use SI units. For example: body mass, *m* (B) = 78 kg; blood pressure, *p* (B) = 16.2/12.3 kPa; incubation time, *t* (incubation) = 96 h; blood glucose concentration, *c* (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, *p* (CEA) = 8.6 24.5 μ g/L; CO₂ volume fraction, 50 mL/L CO₂, not 5% CO₂; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, etc. Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.

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