

Three New Cases of Leishmaniasis: Implications for the Singapore Medical Community

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Abstract

Although visceral and cutaneous leishmaniasis are important clinical and public health problems worldwide, these diseases are not endemic in Singapore and the medical profession here has little opportunity to diagnose and manage these conditions. We report our experience with two patients with culture-proven visceral leishmaniasis and one with histologically-proven cutaneous leishmaniasis. The patients with kala-azar were migrant workers from countries in which the disease is endemic. The patient with proven cutaneous leishmaniasis (and another who was diagnosed to have the condition clinically) had entered the jungles of an endemic area. With increasing travel on the part of Singaporeans along less well-trodden paths to exotic destinations as well as the burgeoning traffic of migrant workers from less developed countries, doctors in Singapore will continue to see diseases such as leishmaniasis.

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Introduction

Visceral and cutaneous leishmaniasis are diseases of major importance worldwide.¹ Visceral leishmaniasis (kala-azar) is endemic in China north of the Yangtze, in central Asia and in East Africa.² It occurs sporadically in the Mediterranean. Major epidemics of visceral leishmaniasis have been recorded in Sudan and Bangladesh.^{2,3} Cutaneous leishmaniasis is of two forms—the “old-world” form, the classic Oriental sore, which is endemic in much of China, Asia Minor, the Mediterranean, India and Africa; and the “new-world” form, which is widespread in Latin America.⁴ The first patient with culture-positive visceral Leishmaniasis diagnosed and treated in Singapore has only just been reported.⁴ We report here three other cases of leishmaniasis seen recently at the Communicable Disease Centre (CDC) over the past few months. All were proven by culture or biopsy or both. We discuss these cases (and one other diagnosed clinically) and their implications for doctors in Singapore.

Case Reports

Case 1

A 27-year-old Bangladeshi man, who had been in Singapore for four months, was admitted to the CDC on 16 December 1996 for the problem of fever

of ten days' duration. He claimed to have had no health problems while in Bangladesh and had been well while working in Singapore until the onset of fever. The fever was associated with chills but no rigors. He had some abdominal pain and had been vomiting in the three days prior to admission. There was no diarrhoea.

Clinical examination was unremarkable, with no organomegaly, and with stable vital parameters. The initial impression was that of gastroenteritis.

His blood results are tabulated in Table I.

The next day he complained of abdominal pain and his blood pressure was 85/40. He was given intravenous (iv) fluids, with improvement in his blood pressure. A possible diagnosis of dengue with shock was entertained and he was maintained on iv fluids.

He continued, however, to have high spiking temperatures up to 40°C, though he never appeared toxic. The history was retaken with some difficulty as there was a language barrier. He stayed in a container at the work site with six other people. They cooked their own meals. There were many rats in and around their container. He was started on doxycycline for possible murine typhus.

The twice-daily temperature peaks continued. He was switched to a combination of ceftriaxone and metronidazole on the suspicion that he had a liver abscess, but

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TABLE I: BLOOD RESULTS OF CASE 1

	16/12/96	17/12/96	24/12/96	28/12/96	11/1/97
Hb (g/dL)	12.8	13.6	10.9	10	8.8
MCV (fl)	81				78
WCC ($\times 10^9/L$)	5.1	4.2	5.5	4.0	2.8
Polys (%)		50	53	43	37
Lymp (%)		33	38	40	43
Mono (%)		15	7	15	18
Eos (%)		2	1	1	2
Bas (%)		0	0	0	1
Plt ($\times 10^9/L$)	136	117	169	181	67
Urea (mmol/L)	3.7				
Na ⁺ (mmol/L)	130			132	
K ⁺ (mmol/L)	5.1				
Cl ⁻ (mmol/L)	99				
Cr (umol/L)	104			88	
Prot (g/L)			72	69	
Alb (g/L)			32	32	
Bil (umol/L)			7	6	
ALP (U/L)			693	521	
ALT (U/L)			94	29	
AST (U/L)			109	31	
GGT (U/L)			285	264	
WWF		neg		neg	

MCV: mean corpuscular volume, fl: femtolitres, poly: polymorphs, lymp: lymphocytes, mono: monocytes, eos: eosinophils, bas: basophils, Na⁺: sodium, K⁺: potassium, Cl⁻: chloride, Cr: creatinine, Prot: protein, Alb: albumin, ALP: serum alkaline phosphatase (reference range: 32 to 103), ALT: alanine transaminase (reference range 7 to 36), AST: aspartate transaminase (reference range 15 to 33), GGT: gamma glutamyl transferase (reference range 9 to 41), WWF: Widal Weil-Felix, neg: negative

subsequent ultrasound of the hepatobiliary system showed no focal hepatic lesions.

The chest X-ray was normal. Urine microscopy showed 1 to 2 white cells per high powered field, and urine culture was negative. Six sets of blood cultures were negative. Six sets of blood films were negative for malarial parasites. Serological tests for the following infections were negative—*Entamoeba*, *Brucella*, cytomegalovirus (CMV), dengue, Epstein-Barr virus (EBV), *Leptospira*, *Toxoplasma* and syphilis. Although his haemoglobin (Hb) fell, rectal examination showed no melena and stools were repeatedly negative for occult blood. Haemoglobin electrophoresis, however, revealed a Hb E band. Stools were negative for *Salmonella*, *Shigella*, *Campylobacter* and *Vibrio*.

After two weeks in the ward, the patient looked weaker and became more easily tired. His spleen could now be felt 2cm from the left subcostal margin. A computed tomographic (CT) scan of the abdomen showed a homogeneously enlarged spleen with no intra-abdominal lymphadenopathy. A bone marrow aspiration and biopsy was performed. The biopsy was considered inadequate but the marrow aspirate was reported to show haemophagocytic histiocytes, consistent with a haemophagocytic syndrome of

unknown cause. A haematologist was consulted and the bone marrow biopsy was repeated. This revealed Leishman-Donovan bodies (Fig. 1). Another marrow aspiration was done and marrow was cultured for *Leishmania* in Novy-MacNeal-Nicolle (NNN) media. The patient was started on intravenous pentamidine (4 mg/kg/day for 14 days). His temperature settled in four days and he made an uneventful recovery. Marrow culture for *Leishmania* was positive after ten days' incubation.

Case 2

A 27-year-old Bangladeshi man presented to a general hospital with left hypochondria1 pain of five days' duration. He understood and spoke even less English than the patient in Case 1 above and very little history could be obtained from him. He had come to Singapore ten months before and was working in the construction industry.

He was thin but appeared comfortable and non-toxic. The blood pressure was 105/60 and pulse rate was 80/min. He was febrile, with temperature peaks reaching 39°C. The liver could be felt 2 cm below the right subcos-

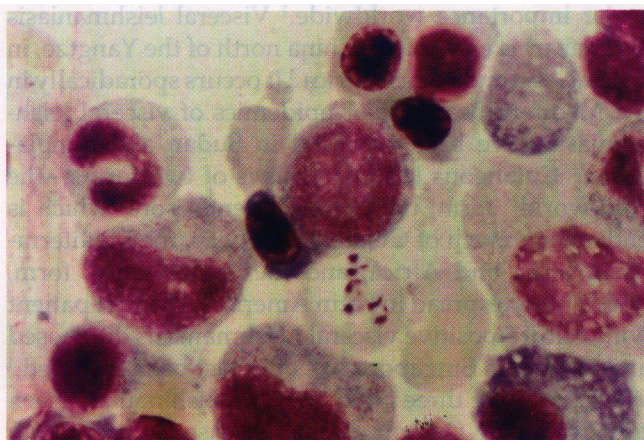


Fig. 1(a).

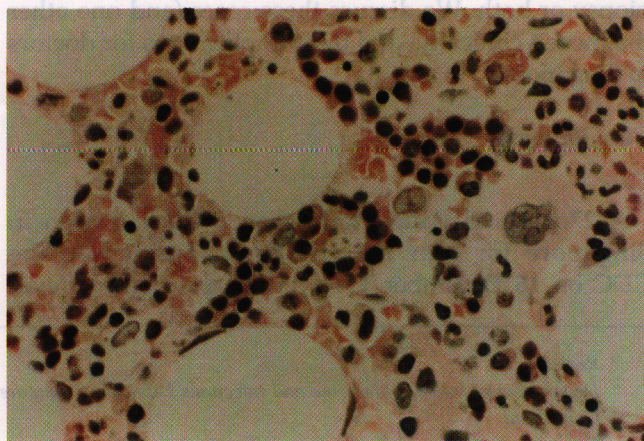


Fig. 1(b).

Fig 1. Marrow aspirate (a) and trephine biopsy (b) of case 1 showing Leishman donovan bodies

tal margin and the spleen could be felt 10 cm below the left subcostal margin.

The Hb was 8.6 g/dL, white cell count (WCC) 1.41×10^9 /L and platelet count (Plt) 86×10^9 /L. Serum Na⁺ was 126 mmol/L and creatinine was 93 μ mol/L. Total protein (Prot) was 70 g/L, albumin (Alb) 24 g/L, bilirubin (Bil) 10 μ mol/L, alkaline phosphatase (ALP) 268 U/L, alanine transaminase (ALT) 87 U/L, aspartate transaminase (AST) 144 U/L and gamma-glutamyl transferase (GGT) 119 U/L. The prothrombin time (PT) was 14.7 s (control 12.9 s), activated partial thromboplastin time (APTT) 29.5 s (control 23.6 s). Blood film was negative for malarial parasites. A bone marrow was performed because of concern about a haematologic malignancy. This showed Leishman-Donovan bodies and the patient was transferred to the CDC.

The patient was started on iv pentamidine (4mg/kg/day). A repeat marrow aspiration was performed and marrow was sent for culture using NNN media—this was positive for *Leishmania* after three weeks of incubation.

The fever settled after four days of starting pentamidine and the patient went on to complete 14 days of treatment. The Hb remained at 8.6 g/dL, but the WCC had risen to 3.1×10^9 /L and Plt to 264×10^9 /L.

Case 3

A 35-year-old Gurkha was referred to the outpatient clinic at CDC for the complaint of a rash in the left groin of eight months' duration. He had resided in Belize for 20 months and had returned to Singapore two months before. He had received 20 intra-lesional stibogluconate injections in the left thigh over a two-month period while in Belize.

The skin lesion was described as being pruritic but not painful. He was well otherwise and denied all other symptoms. On examination there was an erythematous, indurated lesion, 3 to 4 cm in diameter, in the anterior aspect of the left thigh about four fingerbreadths from the inguinal ligament. Three enlarged inguinal nodes, each about 1 cm in diameter, could be felt in the left groin.

The Hb was 14.9 g/dL and the WCC was 8.7×10^9 /L (Poly 64%, Lymp 24%, Mono 7%, Eos 4% and Bas 1%). Blood film was negative for malarial parasites. Total protein was 75 g/L, Alb 42 g/L, Bi19 μ mol/L, ALP 106 U/L, ALT 43 U/L and AST 37 U/L.

As he refused a skin biopsy, he was treated empirically for cutaneous leishmaniasis with ketoconazole 600 mg once a day for four weeks. The skin lesion remained unchanged. He was again offered a skin biopsy and this time he agreed to undergo the procedure. The biopsy showed epidermal hyperplasia with an infiltrate of mononuclear cells. Multiple epithelioid granulomas were

present in the dermis, with numerous dot-like organisms consistent with *Leishmania* in the cytoplasm of histiocytes.

He was started on iv stibogluconate at a dose of 20 mg/kg/day. In the course of his daily injections, he experienced headache and myalgia which were relieved with paracetamol. His skin lesions healed after 28 injections. A review of this patient at the clinic three months after completion of treatment revealed no disease relapse.

Discussion

Although leishmaniasis occurs in widely dispersed areas of the globe,⁷ it is not endemic in many parts of the developed world and its importance as a clinical problem has, until recently, been underappreciated. The description of a systemic illness, "viscerotropic" leishmaniasis,⁵ in American soldiers who had served in Operation Desert Storm, as well as the reports and reviews of visceral leishmaniasis in individuals infected with the human immunodeficiency virus⁶⁻⁸ have focused attention on a condition that has been classified as exotica⁹ in developed countries.

Visceral leishmaniasis is not endemic in Singapore. It is a disease of such rarity that even though kala-azar is frequently mentioned as a cause of splenomegaly in medical textbooks, it is taboo to suggest the condition as a possible cause of an enlarged spleen in local examinations. We have had the opportunity to see and manage a few cases of leishmaniasis in Singapore and therefore would like to raise a few issues pertinent to the condition in the local context.

These cases indicate that patients with visceral leishmaniasis may be encountered in Singapore. The condition presents as a prolonged fever associated with hepatosplenomegaly with the commonest laboratory abnormalities being anaemia, leukopaenia and hypergammaglobulinaemia. Such a combination of physical signs and laboratory abnormalities should raise the possibility of kala-azar, especially if it occurs in an immigrant from an endemic area or in a local who has been to an endemic area. Singapore has a large number of immigrant workers, and many are employed in the construction industry. A sizeable proportion of these workers are from the Indian sub-continent, where *Leishmania* species are endemic. Hence, it is likely that more cases of visceral leishmaniasis will be seen in Singapore.

Leishmaniasis has been reported to reactivate when the host is immunosuppressed.¹⁰ Individuals who have entered an endemic area and sustained a subclinical infection may come down with the full-blown disease years later when an immunocompromised state develops.¹⁰ Indeed, there are numerous reports of *Leishmania spp* acting as an opportunistic pathogen in different types of immunocompromised hosts, including HIV-infected individuals, patients on steroids, and recipients

of organ transplants.¹²⁻¹⁴ The diagnosis can prove difficult if the condition is not suspected, or if the epidemiologic exposure is remote and therefore considered irrelevant.

The cases of cutaneous leishmaniasis that we have seen are of the “new-world” variety. Apart from Case 3 above, another member of the Gurkha contingent that had trained in Belize also had probable cutaneous leishmaniasis. This other patient developed a non-tender ulcer over the left scapula two weeks after he had entered the jungles of Belize. The diagnosis of cutaneous leishmaniasis was made clinically by the doctor in Belize and he was given two injections of intra-lesional stibogluconate. The edge of the ulcer was biopsied when he presented to the CDC immediately after his return and sent in NNN media to the Parasitology laboratory. The culture was negative and this was attributed to an overgrowth of *Staphylococcus aureus*. It is possible that the intra-lesional injections he had received contributed to the negative result. Interestingly, the 187 patients with “new world” cutaneous leishmaniasis in the series of Hepburn et al¹⁵ of the Royal Infirmary of Edinburgh were military men who had trained in Belize. In Belize, cutaneous leishmaniasis, most commonly caused by *Leishmania mexicana*, is a zoonosis and is mainly restricted to those entering tropical forests.¹⁶

The agents of visceral leishmaniasis are transmitted by *Phlebotomus* sandflies and those of cutaneous leishmaniasis are transmitted by *Lutzomyia* sandflies.¹ The presence of a vector-borne disease in our midst raises the spectre of local transmission. Although several species of sandflies can be found in Singapore, none is of the species that act as vectors of leishmaniasis (K M Lee, personal communication).

Leishmaniasis is not the only disease, endemic in a less developed area of the world, that has found its way across international boundaries to more developed parts. Transfusion-associated Chagas’ disease has been reported in a non-endemic area of North America, attributed to the use of blood from donors who originated in countries endemic for the disease.¹⁷ An outbreak of typhoid fever at a hotel in Sullivan County, New York, was thought to have been caused by contamination of orange juice prepared by an itinerant service worker from Central America.¹⁸ Similarly, an outbreak of cysticercosis among orthodox Jews living in New York City was reported after food was contaminated with *Taenia solium* eggs by immigrant cooks infected with pork tapeworm.¹⁹ As the world becomes a global village, doctors in more advanced and developed countries such as Singapore will encounter diseases once only rarely seen in developed, urban settings. The immigration of people from endemic to non-endemic areas is only one cause of this phenomenon. Increased travel to exotic destinations for adventurous holidays, and increased

engagement in religious, social, military and para-military activities in these less developed areas will also expose people to diseases once thought to excite only the tropical medicine and parasitology enthusiast. As the international human traffic increases, doctors in Singapore need to be cosmopolitan in their approach to patients and their complaints.

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