Original papers

New world mucosal and cutaneous leishmaniasis: an emerging health problem among British travellers

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Summary

Background: Mucosal leishmaniasis (ML) is an important complication of new world cutaneous leishmaniasis (CL) caused by species of the *Leishmania Viannia* subgenus. Previous reports of ML among travellers to Latin America are few.
Aims: To determine the annual number of cases of CL due to *L. Viannia* species diagnosed at this institution and to correlate this with changing patterns of travel. Secondly, to document the clinical presentation, diagnosis, treatment and outcome of ML at this institution.
Design: Retrospective observational study.
Methods: Data were collected from a clinical database, laboratory records, patient case notes and an international passenger survey.
Results: Between 1995 and 2003, the annual number of cases of CL (total 79) steadily increased from 4 per year to 18 per year; the estimated number of travellers from the UK to Latin America increased

3.5-fold. Six cases of ML were diagnosed among British travellers in 1995 (1), 1997 (1) and 2002 (4). These infections were acquired in Bolivia (3), Colombia (2) and Belize (1). Nasopharyngeal symptoms developed 0–15 months after returning to the UK. Four patients had concurrent CL at diagnosis. Diagnosis of ML was delayed up to 6 months from the onset of symptoms. Mucosal biopsies from all 6 patients were PCR-positive for *L.* (*Viannia*) DNA; microscopy and culture were less sensitive. ML relapsed in one patient following treatment.
Discussion: Increasing travel to Latin America from the UK was associated with an increasing number of diagnoses of *L. Viannia* CL. ML is likely to emerge as a more frequently imported infection among such travellers. Familiarity with these diseases is important for prompt diagnosis and optimal management.

Introduction

Leishmaniasis results from infection with protozoan parasites of the genus *Leishmania,* which are transmitted by species of phlebotomine sand flies.

Humans and a wide range of vertebrates serve as reservoirs of infection.[1,2] Three dominant clinical forms of disease are recognized: cutaneous,

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mucosal and visceral leishmaniasis.[1,2] Old World and New World cutaneous leishmaniasis (CL) encompass a diversity of clinical manifestations and severity, and result from replication of Leishmania species within the macrophages of the dermis. Typically, lesions become clinically apparent within a few weeks of infection, usually evolving from papules to nodules, which then ulcerate centrally to leave a raised indurated border.[1,2]

The particular importance of New World CL is that certain species belonging to the Leishmania Viannia subgenus endemic in Central and South America (Leishmania V. braziliensis, guyanensis and panamensis) have a greater tendency to disseminate systemically from the skin, compared to other species.[1,3] These species are endemic in many countries, extending from southern Mexico to the north of Argentina. Systemic dissemination of these parasites may lead to secondary mucosal disease, a dreaded complication that may present concurrently with CL, or months or years later. Mucosal leishmaniasis (ML) is caused by parasites infecting and replicating within macrophages of the naso-oropharyngeal mucosa, setting up a destructive inflammatory process. Systemic antileishmanial drugs are often used to treat CL caused by L. Viannia species, not only to promote healing of the primary lesion but also to reduce the risk of developing ML.[1,4]

Advanced ML is a destructive, disfiguring disease. Mucosal lesions are thought to be immune-mediated, rather than resulting from any direct toxic effects of the parasite. However, the biological mechanisms of immune evasion that permit initial parasite dissemination and the later establishment of mucosal immune-mediated disease are not understood. Nasal disease may cause septal perforation and destruction of the anterior nares. In the pharynx, there may be loss of the uvula, gluing of the soft palate to the posterior pharyngeal wall and pharyngeal narrowing due to tonsillar fibrosis. Laryngeal disease can cause hoarseness, aspiration and suffocation.[1,2] Treatment success rates decline with disease progression, and so early diagnosis is vital to optimize the chances of clinical cure.

Since cases of CL and ML are infrequently diagnosed in non-endemic countries, these infections are often not considered in individuals with unusual skin lesions or inflammatory processes of the upper respiratory tract. Moreover, the potential significance of a history, however remote, of travel to Latin America is often overlooked. At the Hospital for Tropical Diseases (HTD), London, we have observed an increasing number of cases of New World CL and ML in recent years. We speculated that this may be the result of increasing travel from the UK to destinations in Central and South America. This raises concerns that New World CL and ML may emerge as increasingly frequent imported infections. In this study we documented the number of cases of L. (V.) CL and ML diagnosed at HTD over a 9-year period, and correlated this with the annual number of travellers to Central and South America from the UK. We also describe six cases of ML diagnosed and treated at HTD, highlighting key lessons learned about this uncommon imported infection.

Methods

A retrospective observational study identified cases of New World CL and ML diagnosed and treated at HTD between 1995 and 2003. All referred patients in whom CL was suspected were clinically evaluated, and those with suspected ML were also examined by an otorhinolaryngologist. Formalin-fixed biopsies of lesions were examined histologically. Giemsa-stained impression smears from fresh tissue biopsies were examined for the presence of amastigotes and cultured on modified Novy-McNeal-Nicolle medium for promastigotes. Polymerase chain reaction (PCR) was also used to detect Leishmania DNA in fresh tissue biopsies and cultures.[5] PCR has been in routine use at HTD since 1995 both for the diagnosis of leishmaniasis and identification of L. (V.) subgenus infections. However, identification to species level was not done.

Cases of CL and ML diagnosed between January 1995 and December 2003 were identified from laboratory records cross-checked with a clinical database. Cases were defined as patients from whom cutaneous or mucosal biopsies were PCR-positive for L. Viannia subgenus DNA. All cases were diagnosed and treated at HTD, and all had lesions that were clinically and histologically consistent with CL or ML. The age and sex of all CL cases was recorded, and the clinical case notes of patients with ML were reviewed in detail. Data regarding overseas travel by UK residents were obtained from the Office for National Statistics as part of the International Passenger Survey (IPS).[6] The IPS is a survey of incoming and departing passengers conducted throughout the year at all major seaports and airports in the UK. The data provides country and region-specific estimates of the number of overseas journeys made by UK residents each year.
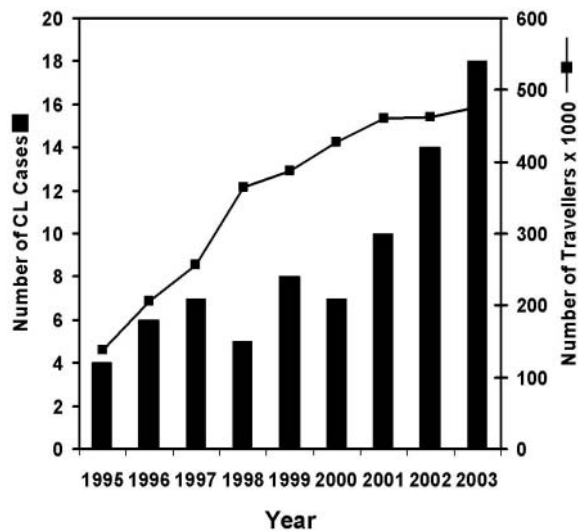
Figure 1. Graph showing the annual number of cases of new world cutaneous leishmaniasis (CL) due to parasites belonging to the *Leishmania Viannia* subgenus (bars) diagnosed and treated at the Hospital for Tropical Diseases, London, 1995–2003 (*n* = 79). The number of estimated travellers from the UK to South and Central America during the same period is also shown (line). The number of travellers in 2003 is an estimate based upon data available for the first 9 months of the year.

Results

Seventy-nine cases of *L. Viannia* CL were identified. Their median age was 26 years (range 17–81 years); 54 were male and 25 female. Most were civilian travellers, a few were military personnel, and all were UK residents. The number of CL cases diagnosed each year increased between 1995 and 2003, with 3.2-fold more cases presenting in the two-year period 2002–2003 compared to 1995–1996 (Figure 1). There has been no change in referral patterns to HTD during this period to account for this observation.

The estimated number of individuals travelling from the UK to Central and South America between 1995 and 2003 showed a similar marked increase during the same period, with 3.5-fold more travellers in 2003 compared to 1995 (Figure 1). There was a positive correlation between the annual number of CL cases and the annual number of travellers (*r* = 0.72, Spearman's). Data specifying the country where CL was thought most likely to have been acquired were not available for all patients. However, we have previously reported among a sub-set of these patients that the countries where infection was most commonly acquired were Bolivia and Belize, and that other countries included Colombia, Brazil, Guatemala, Peru and Ecuador.[7]

Of the CL cases, four (5.1%) also had concurrent diagnoses of ML, and two further cases of ML without CL were also diagnosed. All six cases of ML had travelled to forested areas in Latin America where leishmaniasis is endemic. Although only two cases presented between 1995–2001, four cases presented in 2002 alone. Of the latter, three were thought to have acquired their disease in Bolivia. All cases were unlinked and details of each are summarized in Table 1.

Patient 1. On returning from South America, Patient 1 presented to her general practitioner with a one-month history of a non-healing leg ulcer and nasal symptoms. Urgent investigation was arranged at HTD. She had a large ulcer on her right lower leg (Figure 2a) and a smaller punched-out ulcer on her left upper arm. Otorhinolaryngeal examination revealed diffuse, marked inflammation of the nasal mucosa overlying the turbinates and nasal septum, and numerous pale inflammatory papules on her pharyngeal mucosa (Figure 2b). Parasitological diagnoses of CL and ML were established. On the second day of treatment with intravenous sodium stibogluconate, she developed marked pharyngeal inflammation with a membranous exudate, which resolved over the following week without respiratory compromise. The skin lesions responded slowly to treatment with intravenous sodium stibogluconate and eventually healed.

Patient 2. Four weeks after returning to the UK from South America, Patient 2 developed a swelling in the right groin and his general practitioner found right inguinal lymphadenopathy associated with a small ulcerative skin lesion on his right buttock. He was investigated at a regional centre of infectious diseases where the lesion was suspected as being due to CL, sporotrichosis or tuberculosis. Biopsies were reviewed by a tropical histopathologist and showed a pattern of granulomatous inflammation that was most consistent with CL, but no organisms were identifiable. However, samples were not tested by PCR for *Leishmania* parasite DNA.

As the lesion was self-healing after 3 months, a decision was made not to give empiric anti-leishmanial treatment and he was discharged from follow up. However, 9 months later, the patient developed nasal congestion, which persisted for a further 6 months until crusting lesions developed on the exterior of his nose (Figure 3a). Otorhinolaryngeal examination revealed a granular and oedematous nasal mucosa (Figure 3b) and a polypoid lesion extending from the lateral nasal wall across to the nasal septum. Computerized tomography (CT) revealed a polyp in the maxillary antrum and mucosal thickening over the turbinates. Muco-

Table 1 Characteristics of British travellers with imported mucosal leishmaniasis (ML)

Patient	Age/sex	Year	Country[a]	ML symptoms	Concurrent CL[b]	Symptom delay (months)[c]	Treatment delay (months)[d]	Microscopy	Culture	PCR	Treatment[e]	Response	Duration follow-up (months)
1	19 F	2002	Bolivia	Nasal obstruction, rhinorrhoea, pharyngitis	Yes	0	1	−	+	+	SSG 39 days	Cured	18
2	38 M	2002	Bolivia	Nasal obstruction	No	15	6	−	−	+	SSG 41 days	Cured	18
3	26 M	2002	Bolivia	Asymptomatic	Yes	4	0.5	−	+	+	1. SSG 21 days 2. AmB 3. AmB	ML recurrence ML recurrence Cured	18
4	17 F	2002	Belize	Rhinorrhoea	Yes	3	2	−	−	+	SSG 28 days	Cured	24
5	24 M	1997	Colombia	Hoarse voice, odynophagia	No	3	6	+	+	+	SSG 24 days	Cured	48
6	30 M	1995	Colombia	Nasal obstruction, rhinorrhoea	Yes	6	1	+	+	+	1. SSG 30 days 2. AmB	CL recurrence Cured	>48

[a]Most patients travelled to several countries in Latin America. The country is stated where the patient had the greatest likelihood of exposure to leishmaniasis based on history of forest exposure. [b]CL, cutaneous leishmaniasis. [c]Symptom delay, time between leaving leishmaniasis-endemic area and developing symptoms of ML. [d]Treatment delay, time between onset of symptoms of ML and the start of antileishmanial treatment. [e]SSG, intravenous sodium stibogluconate (20 mg/kg); AmB, intravenous liposomal amphotericin (Ambisome).
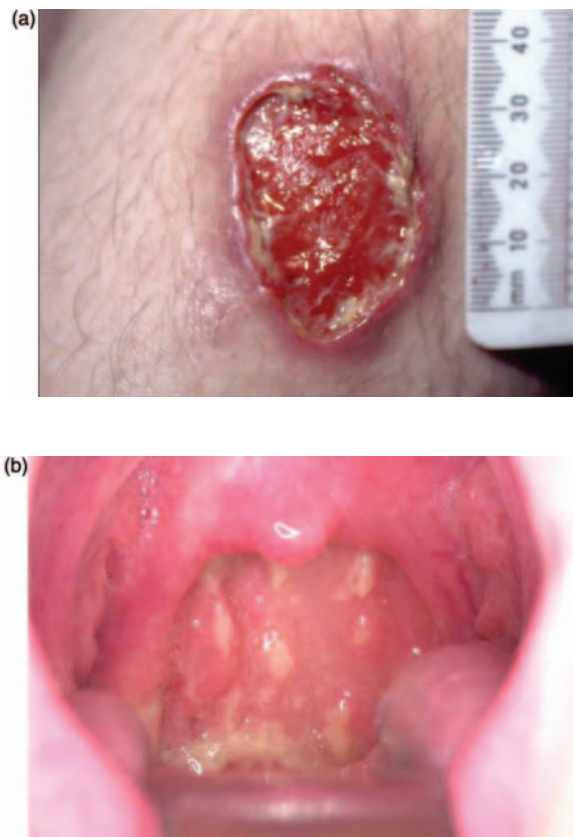
Figure 2. **a** Leg ulcer due to cutaneous leishmaniasis and **b** pharyngeal lesions due to mucosal leishmaniasis in Patient 1.

Figure 3. **a** Lesions on the exterior nasal skin and **b** granulomatous lesions of the nasal septum due to mucosal leishmaniasis in Patient 2.

sal biopsies analysed at HTD established a diagnosis of ML. The patient was treated with sodium stibogluconate until all the lesions had fully healed.

Patient 3. Two weeks after leaving South America, Patient 3 developed a single centrally ulcerated skin lesion 4.5 cm in diameter on the right nasal ala, extending onto the cheek. At HTD, a diagnosis of CL was established parasitologically but no abnormality of the nasal mucosa was found on otorhinolaryngeal examination. During treatment with sodium stibogluconate, a marked inflammatory exacerbation was observed during the first week extending over the whole right cheek. After 21 days treatment the lesion had completely re-epithelialized, and two weeks later microscopy and PCR examinations of slit skin smears were negative for *Leishmania spp.* parasites.

Six weeks after completing treatment, inflammation recurred at the site of the original lesion together with inflammation and oedema of the right inferior turbinate. *L. (V.)* parasites were detected in biopsies of the nasal mucosa, confirming relapse of CL and the development of ML. Re-treatment with intravenous amphotericin caused marked nephrotoxicity, and treatment was switched to lipo-
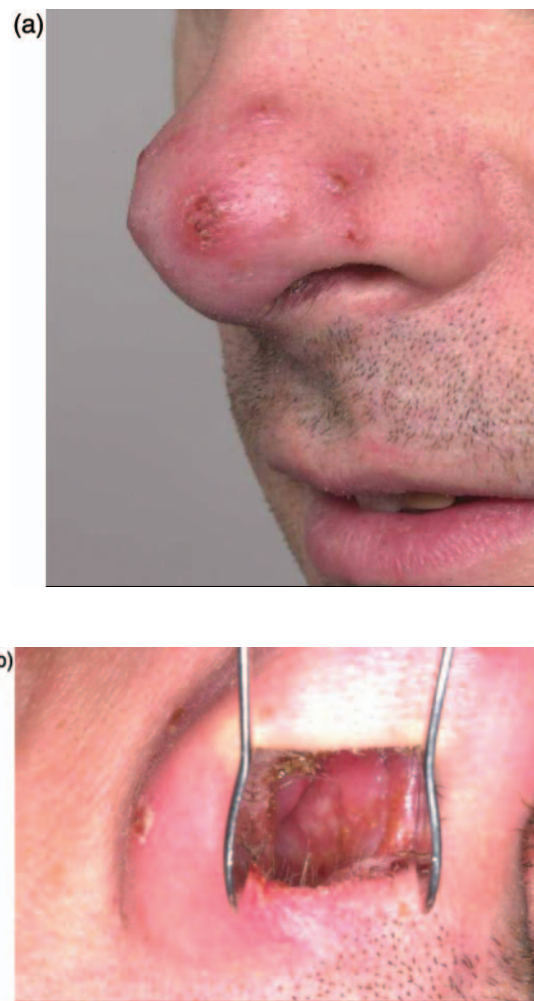
somal amphotericin (Ambisome) 3 mg/kg/day for a further 10 days. The skin and mucosal lesions healed fully but a further parasitologically confirmed relapse of ML occurred 6 months later. This responded to a further course of 18 doses of Ambisome 3 mg/kg administered on alternate days.

Patient 4. One month after returning to the UK from Central America, this patient developed a swelling at the tip of her nose. The skin was erythematous and indurated, but not ulcerated. Having been treated at her local hospital for suspected bacterial skin sepsis, she was later referred to HTD for investigation. By this time she complained of mild nasal discharge and otorhinolaryngeal examination revealed erythema of the right inferior turbinate. After establishing a parasitological diagnosis of CL and ML, treatment with intravenous sodium stibogluconate resulted in a satisfactory response.

Patient 5. While in South America, Patient 5 developed two subcutaneous lesions in the epitrochlear region of his left arm but no associated skin lesion. On returning to the UK the lesions were biopsied at his local hospital and histology revealed lymph-node tissue, in which the architecture was almost completely replaced by coalescing epithelioid granulomata, scattered Langhan's giant cells and extensive caseation. No acid–alcohol fast bacilli, fungi or amastigotes were seen. A chest radiograph was normal, but a mantoux text was strongly positive. Empiric treatment for suspected tuberculosis was commenced, but subsequent cultures for mycobacteria were sterile. After several months of antituberculosis treatment, he developed a persistent hoarse voice and odynophagia, and a new cutaneous lesion developed on his left arm distal to the site of the previous lymph node biopsy. He was referred to HTD and otorhinolaryngeal examination revealed inflammation of the arytenoid folds at the posterior commissure, an inflamed right vocal cord and a granulomatous appearance in the subglottis. Analysis of skin and mucosal biopsies established a diagnosis of CL and ML. The patient was treated with sodium stibogluconate until he developed severe myalgia. Oral steroids were co-prescribed with the initial antileishmanial treatment in view of vocal cord involvement. He made a full recovery, and 6 months later the patient's voice had returned to normal.

Patient 6. Two months after returning to the UK from South America, Patient 6 developed a persistent non-healing skin lesion over the upper abdomen. When he developed upper respiratory tract symptoms 4 months later, he was referred to HTD. He had two non-healing ulcers on the abdomen and scalp, bilateral post-auricular lymphadenopathy and multiple shallow ulcers on the soft palate and uvula. ENT examination also revealed lymphoid hyperplasia extending from the post-nasal space to the piriform fossa. A skin biopsy from the edge of an ulcer showed non-specific granulomatous inflammation. Lymph node and mucosal biopsies revealed caseating granulomatous inflammation that was most consistent with tuberculosis. However, a diagnosis of ML was established by culture and PCR, and the patient was treated with intravenous sodium stibogluconate. This resulted in complete healing of the ML and marked improvement of the CL. Four months later a clinical relapse of the CL developed, but with negative parasitology. Retreatment with sodium stibogluconate was unsuccessful. Amphotericin resulted in serious toxicity and liposomal amphotericin (Ambisome) treatment eventually led to long-term cure.

Discussion

Previous reports of ML among travellers returning from Latin America to non-endemic countries are few.[8–12] In a report of 96 US military personnel with leishmaniasis, only one had ML.[13] This is the largest series of ML among travellers reported in the English literature to date. The risk of ML among travellers to Latin America should clearly not be disregarded. All these patients were 'backpackers' who had travelled for two or more weeks through forested areas where transmission generally occurs. The steadily increasing annual number of diagnoses of CL caused by *L. Viannia* species at this institution was not associated with any change in local referral patterns. Instead this trend mirrored the increase in visits made by UK residents to Central and South America, and the ongoing expansion of tourism in this region. Since ML most commonly arises as a complication of *L. Viannia* CL, it seems likely that cases of ML will similarly increase, as perhaps is reflected by the cluster of four unlinked cases presenting in 2002.

Although the total number of travellers to Latin America has increased, it is not possible to determine the proportion that actually visited areas of leishmaniasis transmission and that were therefore at risk of acquiring the disease. Indeed, another possible factor which may explain the increase in imported CL and ML may be that travellers are more frequently visiting 'hot spots' of leishmaniasis transmission. Three of the ML cases diagnosed in 2002 were acquired in the Bolivian tropical rainforest. In a recent report of CL among Israeli travellers, 11 out of 12 cases were similarly acquired in Bolivia[14] where *L. V. braziliensis* is known to be endemic.[15,16] The conjunction between the Tuchi and Beni Rivers in the Bolivian Amazon Basin is an attractive area increasingly visited by travellers.[14] These cases perhaps reflect increased travel to this area rather than the development of a more 'virulent' strain. Detailed travel data collected prospectively from patients with newly diagnosed CL and ML may be able to more precisely identify such sites of transmission and risk factors for these diseases. Such data might provide a useful source of pre-travel health advice regarding 'high risk' areas and activities and effective means of avoiding sand-fly bites. Furthermore, speciation and typing of cultured *Leishmania* isolates from future patients may yield insights into the epidemiology of these diseases.

Only one patient in this series had symptoms of ML on returning to the UK and the rest developed symptoms up to 15 months later (Table 1). Delays in the diagnosis and treatment of CL may well

have contributed to the progression to ML in some. Furthermore, the delay between onset of symptoms of ML and starting appropriate treatment was 6 months in two patients (Table 1). A low index of suspicion by clinicians may have contributed to these delays. Increased medical awareness of the risk of CL and ML among travellers to Latin America may reduce delays in diagnosis and thereby optimize chances of cure. Fortunately, disease was mild in all patients with none having destructive mucosal lesions and all were ultimately clinically cured.

The risk of *L. Viannia* CL progressing to ML in travellers from non-endemic countries is undefined. Among indigenous people in rural Bolivia with untreated CL, progression to ML was estimated to occur in 5–20% of patients.[16] Among our cohort of CL patients, 5% had concurrent ML but it is not possible to estimate the numbers of cases of ML that were averted through treatment of CL. The factors that affect progression to ML among untreated patients are not clear but are likely to relate to the infecting species, the extent of CL disease, host immune function and genetic predisposition. *L. V. braziliensis* is the species most strongly associated with ML.[2] Those who develop ML are more likely to have had multiple CL lesions sited above the waist.[17,18] The more proximal CL lesions are to the head, the shorter the distance parasite-laden macrophages have to travel through lymphatic channels to reach the systemic circulation. Indeed, three of our patients had CL affecting the face. All our patients were young, healthy travellers with no evidence of impaired immunity. However, in an endemic area of Bolivia, it is reported that healthy migrants to the area who develop CL have a 2.3-fold greater risk of developing ML compared to the indigenous population.[19] In this respect, travellers from non-endemic countries may similarly be more susceptible to ML.

CL due to *L. (V.) braziliensis* is reported to have high rates of spontaneous healing, with the great majority doing so during the first year.[20] However, self-healing of CL does not preclude progression to ML. Indeed, two of our patients did not have active CL at the time of diagnosis, and ML may develop years or even decades after CL lesions have healed.[21] Patient 2 provides an important illustration of the fact that even if CL heals spontaneously, treatment should nevertheless be considered for *L. (V.)* infections in view of a persisting risk of developing ML. Moreover, it is imperative that patients with confirmed or possible new world CL are warned about the potential significance of persistent nasopharyngeal or laryngeal symptoms. Patient 2 was not warned of this, and when he subsequently developed nasal symptoms, he did not seek medical attention for over 6 months, potentially compromising his chances of cure.

Diagnosis of CL and ML rests upon demonstration of the presence of the parasite in infected tissues; serology is unhelpful except in some patients with advanced ML. Amastigotes may be seen within macrophages in giemsa-stained biopsies and culture of promastigotes may increase sensitivity further. However, diagnosis of ML may be hampered by difficulties in obtaining sufficient biopsy material and parasite numbers are too low to detect by these means in a proportion of CL and ML lesions. At HTD, we have found that use of PCR has greatly facilitated diagnosis and in this series PCR had greater sensitivity than routine microscopy and culture of mucosal samples (Table 1), as has been demonstrated in settings with endemic leishmaniasis.[22] We therefore strongly advocate use of PCR in diagnosis and speciation.

Although ML develops in only a minority of patients with CL, treatment of ML is difficult, requiring prolonged parenteral treatment with drugs that are associated with frequent adverse effects. Moreover, cure rates for ML are lower than for CL and decline substantially as the disease progresses.[1,23] Thus, prevention of ML by optimal treatment of CL lesions is important. ML is best managed jointly by physicians and otorhinolaryngologists with experience of ML. First line treatment is with parenteral pentavalent antimonials (20 mg/kg/day) for 28 days,[1,23] although two of our patients were treated longer than this because of slow clinical response.

Two patients developed local inflammatory reactions during initial treatment. This may reflect a post-treatment exacerbation of host immune response to local antigen release mediated by a local pro-inflammatory cytokines. Such paradoxical reactions to treatment are commonly observed during treatment of tuberculosis.[24] Extreme care must be taken when treating patients with laryngeal ML, as reactive oedema upon starting treatment can precipitate suffocation.[21] Thus, Patient 5 also received prednisolone prophylactically.

ML relapsed twice in Patient 3 and CL relapsed once in Patient 6. Some isolates of *L. Viannia* parasites have diminished susceptibility to sodium stibogluconate, increasing the risk of treatment failures.[7] Re-treatment regimens may be associated with additional drug toxicity and require prolonged in-patient stays, as described. This further emphasizes the importance of early diagnosis and treatment of CL and ML, which result from increased awareness and knowledge of these diseases in the medical community.

Acknowledgements

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