Diagnostic dilemma of primary mucosal leishmaniasis

Mubarak S. Al-Qahtani, MBBS, *Nadeem W. Malik,* FRCS (Edin), FRCS (Glas), *Salim Jamil,* MD, PhD, *Taj E. Mekki,* MD, ABIM.

ABSTRACT

تسبب طفيليات اللشمانيا داء الليشمانيات، وهذا الداء منتشر بشكل واسع في أكثر من 88 بلداً. وقد أدى إلى ما يربو على 80,000 حالة وفاة سنوياً. يكون لداء اللشمانيات عدة أنواع وهي: ليشمانيا حشوية، أو جلدية، أو مخاطية جلدية. وتحدث الليشمانيا المخاطية بشكل ثانوي بعد الليشمانيا الجلدية أو الحشوية. ومع ذلك يمكن أن يحدث داء الليشمانيات المخاطية الأولي دون حدوث اللشمانيا الجلدية أو الحشوية بشكل مترافق معه أو سابق له، وهذا أمر نادر جداً، كما أن تشخيصها قد يشكل تحدياً صعباً قبل الوصول للتشخيص الصحيح. ويكون من الصعب تمييزه عن الحالات الحبيبية مثل السل، وساركويد، والجذام، والالتهابات الفطرية، وحبيبة فيغينر، والأورام. نستعرض في هذا المقال حالة مصابة بداء الليشمانيات المخاطية الأولي هنا في المملكة العربية السعودية.

Leishmaniasis is caused by *Leishmania* protozoa. It is widely present in more than 88 countries worldwide, resulting in up to 80,000 deaths annually. Leishmaniasis occurs as visceral, cutaneous, or mucocutaneous variants. Mucosal involvement can occur secondarily to the cutaneous or visceral varieties. However, primary mucosal leishmaniasis (PML) occurs without any present or past cutaneous and or visceral disease. It is extremely rare, and its diagnosis may present a serious challenge. It may be difficult to differentiate it from granulomatous conditions like tuberculosis, sarcoidosis, leprosy, fungal infections, Wegener's granuloma, and neoplasms. Here, we present a case of PML in Saudi Arabia.

Saudi Med J 2012; Vol. 33 (11): 1234-1238

From the Departments of Otolaryngology, Head and Neck Surgery (Al-Qahtani, Malik), Pathology (Jamil), and Department of Medicine (Mekki), Armed Forces Hospital Southern Region, Khamis Mushayt, Kingdom of Saudi Arabia.

Received 29th May 2012. Accepted 26th August 2012.

Address correspondence and reprint request to: Dr. Nadeem W. Malik, Department of Otolaryngology, Head and Neck Surgery, Armed Forces Hospital Southern Region, Khamis Mushayt, PO Box 101, Kingdom of Saudi Arabia. Tel. +966 (7) 2500001 Ext. 22529. Fax. +966 (7) 2500001 Ext. 22534. E-mail: nwmalik@hotmail.com

The word Leishmaniasis originates from William Leishman and Charles Donovan. In 1903 they published their findings describing the parasite causing the disease.[1] This was named *Leishmania Donovani (L. Donovani)* after them. Leishmaniasis-like conditions were mentioned as early as the 7th century BC and later, but by different names. Avicenna wrote in detail in the 10th century AD about cutaneous leishmaniasis, which he called Balkh sore.[1] Leishmaniasis has a wide distribution and is a major endemic disease in Central and South American countries. Except Australia and Antarctic, cases have been reported worldwide. It is reported as endemic in as many as 88 countries.[2] The global incidence may be as high as 1-2 million new cases annually, with up to 70,000 to 80,000 deaths per year.[3] The is on the increase due to more people travelling to and from endemic areas. A traveller may become infected after less than a week's stay in such areas.[4] Leishmaniasis may affect the skin, mucosal membranes, and viscera. It is caused by protozoan parasites *Leishmania*. The vertebrates (including humans) become infected by the bite of a female sand fly already infected with *Leishmania* parasite. Three clinical varieties are described: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and muco-cutaneous leishmaniasis (MCL). These are caused by more than 20 different species of the parasite. The species of parasite causing these clinical varieties may differ in the New and Old World. The New World includes some parts of Mexico, Central America, and South America. While the Old World includes parts of Asia, the Middle East, Africa, and southern Europe. In the Old World, visceral leishmaniasis is mainly caused by *L. donovani* and *Leishmania infantum* (*L. infantum*). Cutaneous leishmaniasis is caused by 5 species of *Leishmania*: L. *infantum*, *Leishmania tropica* (*L. tropica*), *Leishmania major* (*L. major*), *Leishmania aethiopica* (*L. aethiopica*), and *L. donovani*. Mucosal lesions of leishmaniasis are rare in the Old World, but may be caused by any one of those species. Lesions of the buccal mucosa or larynx may be caused by *L. infantum*, *L. major*, and *L. tropica* in elderly people. In the New World, visceral leishmaniasis is caused by *L. Infantum*; cutaneous leishmaniasis by

multiple species of both the *Leishmania* and Viannia subgenera; and mucocutaneous leishmaniasis mainly by *Leishmania braziliensis* and *Leishmania panamensis* (subgenus Viannia).

Mucosal involvement is rare and usually secondary to cutaneous or visceral disease. It may present with or after a variable duration of CL or VL. Primary mucosal leishmaniasis (PML) is a disease of the mucous membranes, usually nose and upper aerodigestive tract; it is neither preceded nor accompanied by CL or VL. True PML is very rare and may provide many diagnostic difficulties. Histology and serology used usually for diagnosis of leishmaniasis may be of limited benefit in PML. Here, we describe a case of PML in Saudi Arabia, and the diagnostic difficulties faced in the management of this rare condition.

Case Report. A 75-year-old male patient presented with hoarseness and weak voice for one year. There were no other ears, nose, throat, head & neck, or medical complaints. He was not a smoker and gave no history of weight loss. External head and neck examinations were normal. Flexible nasopharyngolaryngoscopy showed no abnormality in the nasal cavities and pharynx. Both vocal cords had normal structure and movement. There was a smooth reddish purple mass in the right subglottis, immediately below the right vocal cord. Under anesthesia, direct laryngoscopy was performed and the findings were confirmed by macro and microscopic examination. The mass was biopsied; the biopsy forceps could penetrate only the superficial part of the mass. The deeper part was firm, and cartilaginous involvement was suspected. Multiple small biopsies were taken but the deeper firm part of the mass could not be biopsied, hence leaving a residual mass at the end of the procedure.

At post-operative review, his voice had improved. Endoscopic examination showed a residual smooth reddish purple mass. Histology was reported as chronic non-specific inflammation with non-caseating granulomas. X-rays chest had shown fibrotic changes in the apical region of the right lung. Medical consultation was carried out with the suspicion of tuberculosis in mind. The Mantoux test was performed, but was negative. Sputum samples were also negative for acid-fast bacillus (AFB). The possibility of other conditions causing non-caseating granulomas was also considered. Serum calcium, angiotensin-converting enzyme (ACE) levels, Brucella titre, perinuclear anti-neutrophil cytoplasmic antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, hepatitis c virus, and human immunodeficiency virus investigations were carried out, but all were in normal ranges. His case was discussed with the rheumatologist, chest physician, and pathologist, and it was decided not to start any specific treatment. However close follow-up of the patient was continued. After 3 months, he complained of worsening hoarseness. In addition, he also complained of deafness in the right ear. Otoscopy showed right serous otitis media. Flexible nasolaryngoscopy showed a right subglottic mass, larger than described earlier. In view of the previous inconclusive histology, worsening hoarseness, serous otitis media, and increasing size of the subglottic mass, it was decided to repeat endoscopy and biopsies under general anesthesia.

Computed tomography (CT) was carried out prior to surgery showing opaque right maxillary sinus, thickening in the post-nasal space, and a smooth right subglottic mass. At surgery, the right middle ear effusion was drained and a ventilation tube was inserted. The right maxillary sinus was opened endoscopically and smooth hypertrophic mucosa was found. Similar findings were present in the post-nasal space. Microscopic direct examination of the larynx showed a similar but larger subglottic mass with the same characteristics. Multiple biopsies were carried out from the right maxillary sinus, post-nasal space, and right subglottis. All the tissues were sent for histopathology, culture, and microscopic examination.

Unfortunately, the histology report was similar with non-caseating granulomas. Culture and microscopy (AFB and fungi) were negative even after 6 weeks. In view of the clinical and radiological progression of disease, the chest consultant decided to start the patient on empirical anti-tuberculosis treatment. The patient completed the course without any significant improvement. Regular periodic follow-up was continued. Two years had passed since the initial presentation of the patient. The hoarseness was worse with bilateral nasal obstruction. Flexible nasopharyngolaryngoscopy again showed smooth mass in the post-nasal space and right subglottic mass, but was larger. The CT scan was repeated showing opaque left maxillary sinus, smooth thickenings and masses in the post-nasal space, right tonsil, right subglottis, and lower trachea (**Figure 1**). Again, direct macroscopic and microscopic examination was performed under general anesthesia. Multiple biopsies were taken from the trachea, subglottis, right tonsil, right post-nasal space, and both maxillary sinuses. Histology showed similar findings of chronic inflammation and non-caseating granuloma. However, in addition, Leishman-Donovan bodies (LD bodies, amastigote intracellular stage of

Leishmania parasites) were identified in the tissues, especially from the post-nasal space (**Figure 2**). He was admitted, and a detailed history and examination were carried out with the diagnosis of leishmaniasis in mind. He resided in Khamis Mushayt (a town in the south-west of Saudi Arabia at an altitude of nearly 2,000 meters) with no history of desert travel or family history of leishmaniasis. There was no history or evidence of existing or past cutaneous lesions. There was also no evidence of hepatosplenomegaly on clinical and radiological assessment. *Leishmania* antibody titre was 1:256 (titre of 1:128 and above is significant). With no clinical or radiological evidence of visceral involvement and a not very high antibody titre, it was decided not to do bone marrow aspiration.

He was diagnosed as a case of PML because there was no evidence of (past or present) cutaneous disease and visceral involvement. His leishmaniasis was limited to the mucosa of the post-nasal space, maxillary sinuses, larynx, and trachea. Treatment with intra-venous Pentostam (GSK, sodium stibogluconate) 20mg/kg/day was started. At the start of treatment he was reviewed, and flexible nasolaryngoscopy was carried out to record the findings (**Figure 3**). Treatment was continued for 10 days, during which he was admitted to hospital. He was reviewed again after 2 months, and there were no hoarseness and no nasal complaints. Flexible nasolaryngoscopy was repeated, and the masses in post-nasal space and subglottis had regressed completely (**Figure 4**). He is still under follow-up for any recurrence.

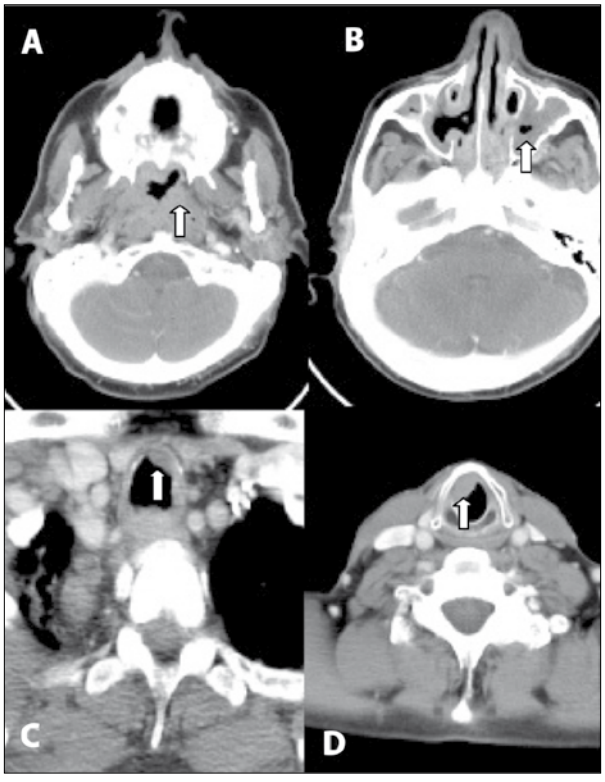

Figure 1 - Computed tomography images with contrast showing **A)** post-nasal mass. **B)** Mucosal thickening in the left maxillary sinus. **C)** Mass in trachea. **D)** Right subglottic mass.

Discussion. Clinically, leishmaniasis is described as VL, CL, and MCL. Mucosal involvement is rare, but may occur as secondary involvement in CL and VL. This is more common with the New World than with the Old World *Leishmania* species. The reported incidence is around 1-10%, being much less in the Old World species. The mucosal lesions may appear at the time of CL, or more often 1-5 years after healing of the

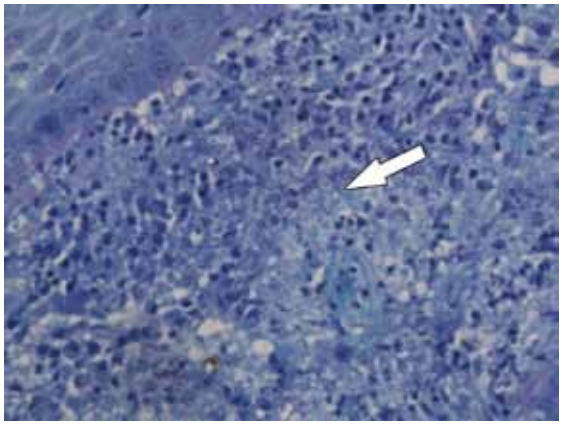

Figure 2 - Giemsa stained slide with pointer showing Leishman-Donovan bodies. (X40)

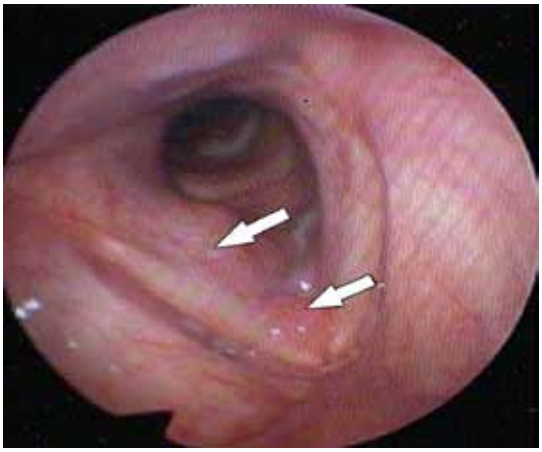

Figure 3 - Mass involving the right subglottis extending to the anterior commissure (white arrow). Photo taken at start of treatment.

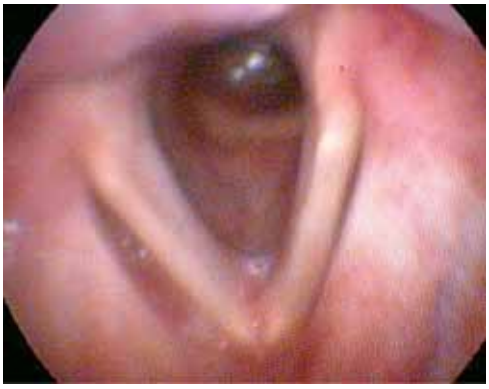

Figure 4 - Photo showing resolution of the mass, taken 2 months after the end of treatment.

cutaneous lesions.[3] Mucosal involvement may occur in any part of the nasal cavity, oral cavity, pharynx, and larynx in this frequency. This involvement may be in the form of ulceration, mass, or granular inflammation; these are usually painless.[5]

The spread is via lymphatics, blood vessels, and direct contact. The preference for the nose and upper aerodigestive tract mucosa is due to lower temperature, which affects the macrophages ability to destroy the parasite.[6] Primary mucosal leishmaniasis (not preceded or accompanied by CL or VL) is very rare, with the true incidence still not known. Why these patients have only PML and no cutaneous lesions is not clear. Patients with PML, especially in areas where the incidence of leishmaniasis is low, present a diagnostic challenge, as it may not be considered in the differential diagnosis. Early diagnosis and treatment are important to minimize irreversible damage and fatality. Neoplasms, fungal infections, tuberculosis, sarcoidosis, syphilis, leprosy, mid-line granulomas, and Wegener's granuloma may present similarly making diagnosis more difficult.

It took us more than 2 years to reach the correct diagnosis. The patient had extensive investigations without any diagnosis. He had CT scans twice and a full course of anti TB treatment. He had general anesthesia 3 times with biopsies and extensive surgeries before LD bodies were seen in the biopsies. It was a diagnosis that we had not considered. Our initial suspicion was of malignancy, but histology showed granulomas. With radiological evidence of possible previous TB, he was treated for it on clinical grounds. When he continued to deteriorate, we looked for other diseases causing granulomas. However, we failed to reach a diagnosis until LD bodies were seen. The *Leishmania* antibody titre was 1:256 (titre 1:128 and above is significant); although not very high it still provided support to the diagnosis of PML. This case highlights the difficulties that may be faced in diagnosing a rare condition not suspected. The first step towards correct diagnosis is to consider its possibility hence the differential diagnosis. Histology and serology are the most common methods for the diagnosis of leishmaniasis. The visualization of parasites in the infected tissues (LD bodies) is probably the most widely used confirmation of leishmaniasis. This tissue sample may be obtained in the form of smear from the cutaneous/mucosal lesion, or biopsy from the suspected tissue. This may not be diagnostically helpful in all cases as it may not be possible to obtain sufficient tissue or the parasites may be too few to be detected. If the parasite is not visualized, histology may show nonspecific chronic inflammation with or without granuloma. This may lead the clinician to consider other possibilities.

Enzyme-linked immunosorbent assays (ELISA) may be beneficial if the antibody titre is raised. Unfortunately, this is mainly in visceral leishmaniasis; the titre in cutaneous and mucosal disease may be within the normal range. Therefore, in PML, serological tests in the form of ELISA may not prove to be of any diagnostic benefit. A skin test similar to Mantoux test is available, and may also be used for diagnostic support. In the Montenegro test, antigenic material from the parasite is applied intradermally on the anterior surface of the forearm and a read 48 hours later. Nodules with an induration exceeding 5 mm may be considered positive.[7] However, again it may be negative especially in PML, and may not assist in its diagnosis. From this, it is clear that diagnosing PML may prove to be a challenge as the commonly available and used tools may not provide any direction. However, recent advances in specific molecular genetics technology has provided an extremely sensitive test to detect *Leishmania* parasite infection. In polymerase chain reaction (PCR), the DNA of *Leishmania* parasite is detected and used for confirmation. Previously, available PCR tests required around one week, but now rapid test kits are available that require only one hour. This is especially effective with low parasite burden,[8] such as in PML. The PCR test has successfully detected the parasite even in normal tissues of infected individuals. This test is, however, not widely available yet. A comparison of this PCR assay demonstrated it to be significantly more sensitive (97%) than expert microscopy (76%).[9] Unfortunately, we could not perform PCR assay, as it is not presently available in our institute.

Once diagnosed, treatment should be started at the earliest. The main stay of treatment is medical; surgery has a role limited to diagnostic biopsy, and correction of any deformity. Varieties of pharmacotherapies are available to treat different *Leishmania* infection. However, mucosal leishmaniasis is usually treated with pentavalent antimonials (sodium stibogluconate) and lipid formulation of amphotericin B. Sodium stibogluconate (SSG) is still the drug of choice for mucosal leishmaniasis in many countries.[10] It is available as 100 mg/ml/vials, and usually used in doses of 20mg/kg/day intravenously for 20 to 28 days for mucosal leishmaniasis. There are published trials showing SSG at a dosage of 20 mg/kg/day for 10 days appears to have been therapeutically equivalent and less toxic than the standard 20-day course.[11] The SSG directly inhibits DNA topoisomerase I leading to inhibition of both DNA replication and transcription. However, due to development of resistance it is being replaced by liposomal formulation of amphotericin B. This variety of amphotericin is taken up well by the reticuloendothelial system targeting the cells that host the parasite, and has decreased nephrotoxicity. The usual dosage is 2-3mg/kg/day for around 20 days in mucosal leishmaniasis.

In conclusion, because of the absence of cutaneous and visceral involvement, PML may become a diagnostic challenge. Histology and antibody titre (ELISA) may not assist in diagnosis. However, PCR assay if available may be of great assistance in the diagnosis of such PML cases.

References

1. Bari A. Chronology of cutaneous leishmaniasis: An overview of the history of the disease. ***Journal of Pakistan Association of Dermatologists*** 2006; 16: 24-27.
2. Sharma U, Singh S. Insect vectors of Leishmania: distribution, physiology and their control. ***J Vector Borne Dis*** 2008; 45: 255-272.
3. Murray HW, Berman JD, Davies CR, Saravia NG. Advances in Leishmaniasis. ***Lancet*** 2005; 366: 1561-1577.
4. Scope A, Trau H, Bakon M, Yarom N, Nasereddin A, Schwartz E. Imported mucosal Leishmaniasis in a traveler. ***Clin Infect Dis*** 2003; 37: E83-E87.
5. Aliaga L, Cobo F, Mediavilla JD, Bravo J, Osuna A, Amador JM, et al. Localized mucosal Leishmaniasis due to Leishmania (Leishmania) infantum: clinical and microbiologic findings in 31 patients. ***Medicine*** 2003; 82: 147-158.
6. Scott P. Impaired macrophage leishmanicidal activity at cutaneous temperature. ***Parasite Immunol*** 1985; 7: 277-288.
7. Manzur A, Bari A. Sensitivity of leishmanin skin test in patients of acute cutaneous leishmaniasis. ***Dermatology Online Journal*** 2006; 12: 2.
8. Ovalle BC, Porras de Quintana L, Muvdi AS, Rios PM. Polymerase chain reaction with two molecular targets in mucosal Leishmaniasis' diagnosis: a validation study. ***Mem Inst Oswaldo Cruz*** 2007; 102: 549-554.
9. Hochberg L, Aronson N, Neafie R, McEvoy P, Gilmore L, Fishbain J, et al. A comparison of diagnostic methods for Old World cutaneous Leishmaniasis [Abstract P-429]. Program and Abstracts of the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy. 2004 Oct 30-Nov 2; Washington (DC). American Society for Microbiology; 2004. 453.
10. Amato VS, Tuon FF, Campos A, Bacha HA, Nicodemo AC, Amato Neto V, et al. Treatment of Mucosal Leishmaniasis with a Lipid Formulation of Amphotericin B. ***Clin Infect Dis*** 2007; 44: 311-312.
11. Wortmann G, Miller RS, Oster C, Jackson J, Aronson N. A randomized, double-blind study of the efficacy of a 10- or 20-day course of sodium stibogluconate for treatment of cutaneous leishmaniasis in United States military personnel. ***Clin Infect Dis*** 2002; 35: 261-267.

Related Articles

Cakan HS, Iscan MY, Oz V, Aslan M, Karayel TM, Cakir I, et al. Coping with visceral leishmaniasis in Turkey. ***Saudi Med J*** 2009; 30: 1480-1482.

Al-Mendalawi MD, Al-Nahhas SA. Serodiagnosis of cutaneous leishmaniasis in the Syrian Arab Republic. ***Saudi Med J*** 2009; 30: 1365.

Arya SC, Agarwal N. Concern regarding the differential diagnosis of leishmaniasis. ***Saudi Med J*** 2009; 30: 722.