The Journal of Laryngology and Otology
December 1994, Vol. **108**, pp. 1086–1088

Laryngeal leishmaniasis

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Abstract

A patient suffering from persistent hoarseness was eventually shown to have laryngeal leishmaniasis. The incubation period for the disease must have been at least 16 years, following infection in Southern Europe. Mucosal leishmaniasis is rare in the Eastern hemisphere, and laryngeal leishmaniasis has not previously been reported in the UK. Previous Mediterranean cases have run a similar chronic course and have caused diagnostic difficulty, in particular being mistaken for malignancy. Treatment with aminosidine was ineffective, but the patient responded to liposomal amphotericin.

Key words: Larynx; Leishmaniasis; Amphotericin B

Introduction

Mucosal involvement is uncommon as a complication of Old World leishmaniasis. We report the case of a woman with laryngeal leishmaniasis acquired in Europe who failed to respond to treatment with aminosidine but did respond to liposomal amphotericin.

Case report

A 64-year-old British woman first noticed hoarseness of her voice in December 1991. She had a complicated past medical history which included asthma since the age of 32 years. She had been maintained on inhaled and oral steroids for most of this period. Since her early fifties, she had had diabetes mellitus, treated with insulin. She was also hypertensive. She had travelled to Mediterranean countries including the south of France, Italy and the former Yugoslavia, but since 1975 she had not left England, and she had never travelled outside Europe.

Her hoarseness worsened steadily. Initial investigations included indirect laryngoscopy, then direct laryngoscopy and bronchoscopy, which were all normal. In September 1992, further laryngoscopy and laryngeal biopsy were performed. Histology demonstrated leishmaniasis and she was referred to the Hospital for Tropical Diseases for further management.

Physical examination revealed a cushingoid woman with a hoarse voice and inspiratory stridor. She was afebrile. Her liver was enlarged, palpable 10 cm below the costal margin but her spleen was not palpable and there were no enlarged lymph nodes.

Investigations revealed a normal full blood count and bone marrow aspirate. Abdominal ultrasound confirmed hepatomegaly but the spleen was of normal size. Leishmanial indirect fluorescent antibody test (IFAT) was negative but the direct agglutination test was positive at a titre of 1 in 6400. An electrocardiogram showed partial left bundle branch block with lateral ST depression and T-wave inversion. A chest X-ray showed no significant abnormality.

Direct laryngoscopy showed generalized oedema throughout the larynx. Granulations and ulceration were seen on the true folds and false folds, throughout the subglottis, and extending into the trachea (Figure 1). Vocal fold mobility was normal. Laryngeal biopsy demonstrated amastigotes of *Leishmania sp.* on impression smears but there was no growth on culture.

In view of the conduction abnormality on ECG, and the presence of other risk factors for ischaemic heart disease, she was not given sodium stibogluconate. Initial treatment was with aminosidine, 14 mg/kg daily by intravenous infusion, with an increase in her regular oral steroid dose, at the initiation of treatment, in view of her stridor and the risk of respiratory obstruction. After 17 days of treatment there was no clinical change. Repeat direct laryngoscopy showed no significant difference macroscopically, and impression smears from a second laryngeal biopsy were again positive for amastigotes of *Leishmania sp.*

Her therapy was changed to liposomal amphotericin (AmBisome, Vestar Inc., San Dimas, California, USA) at an initial dose of 1 mg/kg by intravenous infusion, increased the following day to 3 mg/kg. She noticed an improvement in her voice after six days, and a laryngoscopy after 14 days of treatment showed considerable improvement, although impression smears remained positive until the 24th day after commencing liposomal amphotericin. She received a total of 32 days of treatment with amphotericin, after which there was a noticeable improvement in her voice. No adverse effects were observed: her blood count and electrolytes remained stable.

At follow-up six weeks after finishing the treatment, her voice had improved further, although she remained dysphonic. Laryngoscopy showed complete resolution of the granulations and ulceration that had been noted previously in the supraglottic larynx and glottis. Histology showed no amastigotes and impression smears and culture were also negative for *Leishmania sp.*

Discussion

The leishmaniases are a group of infectious diseases caused by protozoa of the genus *Leishmania*. Transmission is by the bite of the sandfly (*Phlebotomus* in the Old World; *Lutzomyia* in the New World). Classically they are divided into three clinical syndromes: (i) visceral leishmaniasis (Kala-azar), a systemic illness with weight loss, fever, hepatosplenomegaly and hypersplenism; (ii) cutaneous leishmaniasis, characterized by chronic skin

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Accepted for publication: 28 May 1994.

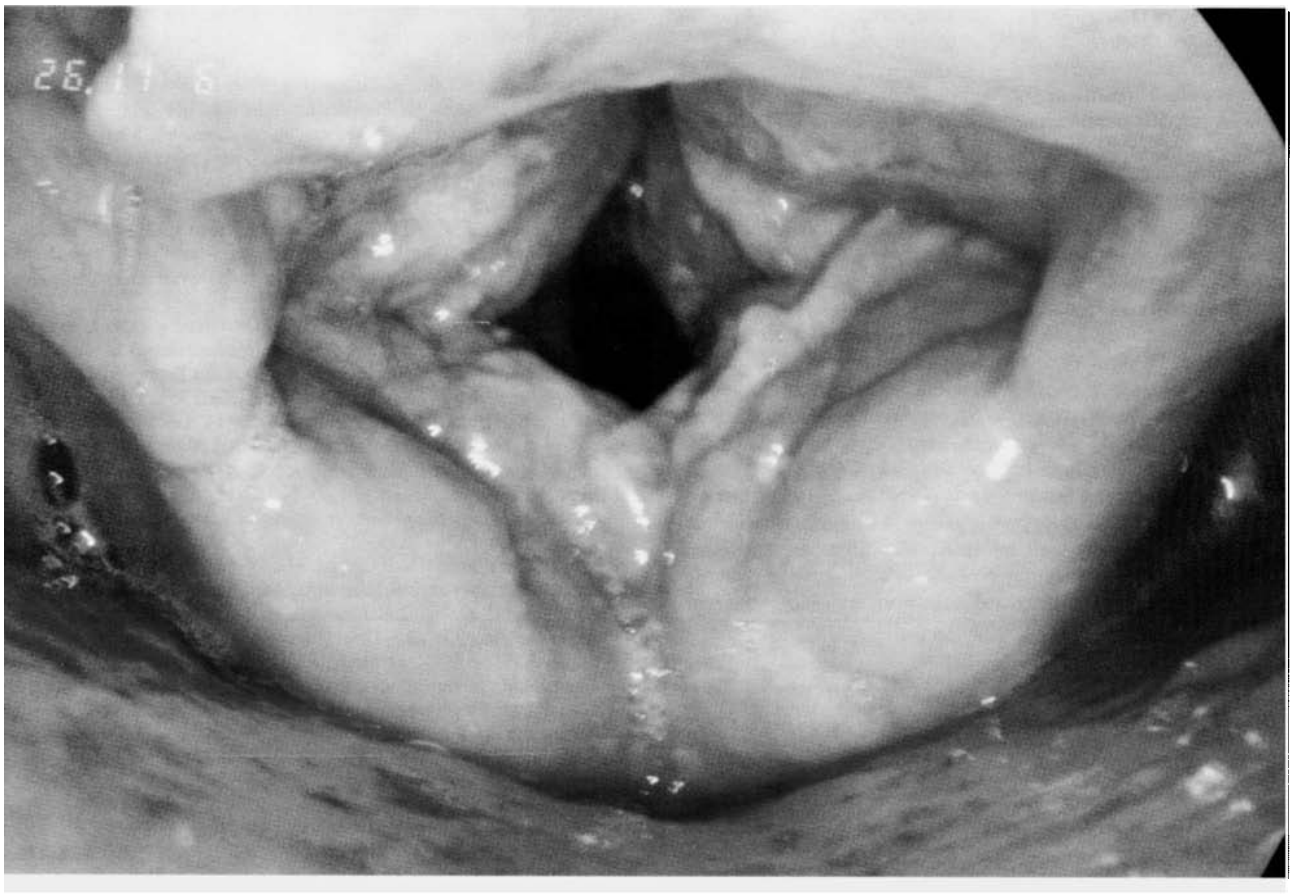

FIG. 1
Findings at direct laryngoscopy.

ulcers; and (iii) mucosal leishmaniasis, which causes nodular infiltration of the mucosa of the nose, mouth, nasopharynx and upper respiratory tract.

Mucosal leishmaniasis is common in South America as a sequel to a healed or healing cutaneous infection with *Leishmania braziliensis*, but is very uncommon with any of the species in the Eastern hemisphere. It is recognized as an occasional complication of visceral leishmaniasis due to *Leishmania donovani* in the Sudan and East Africa, and of post-Kala-azar dermal leishmaniasis in India. Isolated mucosal leishmaniasis is, however, very unusual in the Old World, and laryngeal leishmaniasis is extremely rare: it has not been previously reported in the UK. There are 15 cases of isolated laryngeal leishmaniasis in the literature from the Mediterranean and East Africa, of which five are from Italy (D'Anna and Jemma, 1964; Pototschnig, 1964; Garcovitch *et al.*, 1976; Ferlito *et al.*, 1986), five from France (Ranque *et al.*, 1962; Pazat *et al.*, 1968; Lanotte *et al.*, 1980; Dupond *et al.*, 1984; Ravisse *et al.*, 1984), three from the Sudan (Abdalla *et al.*, 1975), one from Morocco (Meyruey *et al.*, 1974) and one reported from North America but almost certainly acquired in the Mediterranean (Zinneman *et al.*, 1961). A common theme running through these reports is the difficulty in making the correct diagnosis: several patients were thought to have cancer, and two received radiotherapy before the correct diagnosis was made (Garcovitch *et al.*, 1976; Ravisse *et al.*, 1984).

There has been much speculation from the authors of these reports as to whether the mucosal disease observed represents the primary site of inoculation of the parasite or secondary localization of the parasite from a dormant site elsewhere. Although our patient had unexplained hepatomegaly, she showed none of the clinical or laboratory features of visceral leishmaniasis. One might hypothesize that the long-term oral steroids taken by our patient could have contributed to the unusual presentation: in support of this idea, the patient reported by Pazat *et al.* (1968) had also been taking oral steroids chronically, and two other patients (Dupond *et al.*, 1984; Ferlito *et al.*, 1986) had a heavy alcohol intake which may have modified their immune response to the parasite.

The long incubation period in our patient – at least 16 years between the last possible exposure and the development of symptoms – is surprising. Most of the cases of European mucosal disease described have been in individuals resident in endemic areas of the Mediterranean in whom it is difficult to estimate the likely incubation period. Pazat *et al.* (1968) reported a case in which the patient had moved into a non-endemic part of France nine years prior to developing symptoms, but had made a brief visit to an endemic area one month prior to becoming symptomatic and therefore could have been infected during that time. However, in two other Mediterranean cases an incubation period of six years has been documented (Zinneman *et al.*, 1961; Pototschnig, 1964). In South American mucosal leishmaniasis, latent periods of up to 24 years between the initial cutaneous lesion and secondary mucosal disease have been reported (Walton *et al.*, 1973).

The progress of the disease may be very protracted: Ravisse *et al.* (1984) reported laryngeal leishmaniasis in a patient born in Algeria who was symptomatic for 23 years before the diagnosis was made. Early in the course of the illness, he had received a course of radiotherapy, despite the lack of a histological diagnosis. One might speculate that previously damaged mucosa acted as a focus for the later development of leishmaniasis.

We were unable to culture *Leishmania spp.* from our patient's larynx for speciation, but *Leishmania infantum* would be the most likely on geographical grounds. The causative organism was identified in only two of the reported cases of European mucosal leishmaniasis: in a case described by Ferlito *et al.* (1986) *L. donovani* (*sensu latu* and thus embracing *L. infantum*) was identified using immunoperoxidase techniques, and Bor-

https://doi.org/10.1017/S0022215100128968 Published online by Cambridge University Press

zoni *et al.* (1991) identified *L. infantum* from a case of lingual and palatine disease using electrophoretic analysis of 14 isoenzymes.

The standard treatment for South American mucosal leishmaniasis is with pentavalent antimonials such as sodium stibogluconate. Cardiac arrhythmias are a potential complication of these compounds and therefore we were reluctant to use them in our patient. Aminosidine (paromomycin) has been shown to be more effective as a single agent than sodium stibogluconate in visceral leishmaniasis in Kenya (Chunge *et al.*, 1990), and we had previously used it successfully in complicated cases of visceral leishmaniasis in London (Scott *et al.*, 1990). Unfortunately in the case described here there was no effect on the mucosal disease after 17 days of treatment. Amphotericin B has been used with success in visceral leishmaniasis (Mishra *et al.*, 1992) and in mucosal leishmaniasis in South America (Crofts, 1976) but its use is limited by toxicity, intolerance or drug resistance. Liposomal amphotericin B had, by the end of 1992, been used successfully in visceral leishmaniasis (Croft *et al.*, 1991), but we were and are unaware of its previous use in mucosal disease. In our patient it was very well tolerated with no adverse effects. Although it is expensive, it may be a useful alternative in patients with mucosal disease unresponsive to conventional treatment with sodium stibogluconate.

Acknowledgements

We wish to thank Dr Luigi Gradoni for his help in obtaining Italian literature on leishmaniasis, and Dr Flavia Bustreo and Dr Jean Paul Guthmann for their help with the translation.

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