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ARTIGO DE REVISÃO

MUCOSAL LEISHMANIASIS DUE TO *LEISHMANIA (VIANNIA) BRAZILIENSIS* L(V)b IN TRÊS BRAÇOS, BAHIA-BRAZIL

Philip Davis Marsden

Brazilian mucosal leshmaniasis is briefly reviewed, emphasis being given to recent advances clinical management. Patients continue to occupy much hospital bed space and in some cases are notoriously difficult to treat. Indefinite follow up is recommended. Many aspects of the aetiology remain mysterious although Leishmania (Viannia) braziliensis *is the most common organism isolated. Perspectives for a more effective treatment, oral and cheap, are still remote.*

Key-words: Mucosal leishmaniasis. Leishmania (Viannia) braziliensis. *Clinical management. Três Braços, Brazil.*

HISTORY AND CLINICAL FEATURES

The first good clinical description of mucosal leishmaniasis in Brazil was by Antonio Carini who was born and died in Italy but worked in Brazil for 35 years[4]. He accompanied the large Italian migration that occurred to Southern Brazil after the abolition of slavery. Clearing of the forest in São Paulo State gave rise to much cutaneous leishmaniasis often resulting in late mucosal involvement. It is probable that these lesions were caused by the leishmanial species we now know as *Leishmania (Viannia) braziliensis* L(V)b. Carini describes a single case history of a São Paulo man of 45 years of age who had scars and active lesions of cutaneous leishmaniasis on his legs. His palate showed an inflammatory infiltrate and the uvula had been destroyed. The left nostril was blocked by granuloma. Histology of biopsy material showed scanty amastigotes.

Later in the same year Peru Escomel[8] gave a more complete account of mucosal leishmaniasis or *Espundia*, an alternative local name. Further accounts from other Latin American countries followed culminating in the monumental monograph of Pessoa and Barreto "American Tegumentary Leishmaniasis"[22]. We have worked for 20 years at one of the few surviving stands of littoral forest in the State of Bahia on the mucocutaneous leishmaniasis prevalent there. Taxonomic identification has revealed we are working in a virtual monotransmission of L(V)b[7]. The clinical features of mucosal disease in this setting have been recently described. Where references are not given here they are present in the original review[16].

Recently there have been suggestions that other species of *Leishmania* can be involved in the causation of mucosal leishmaniasis in Latin America, including *Leishmania (Viannia) panamensis, Leishmania (Viannia) peruana* and *Leishmania (Viannia) guyanensis*, depending on the area. Rarely Leishmania species of the Mexicana complex have been identified. The distribution of the various species causing cutaneous leishmaniasis in New World has been reviwed[11]. Mucosal leishmaniasis is more prevalent in males over 40 years of age. The author prefers the simple name mucosal leishmaniasis to mucocutaneous leishmaniasis because 20% of our patients in the endemic area of Três Braços, Bahia, have mucosal disease without any evidence of a skin lesion. Probably the leishmanial granuloma resulting from the inoculation of L(V)b promastigotes was so transient without leaving a scar. The great majority of patients do exibit a scar of previous cutaneous leishmaniasis (Figure 1). This is sugestive, being the result of a relatively deep chronic skin ulcer (Figure 2). It is depressed hypopigmented and puckered. Commonly seen on the limbs it must be distinguished from the scar of a deep burn. About one in ten of mucosal patients in our area has an active skin lesion at the time of initial consultation as did Carini's case.

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Figure 1 - Showing positive leishmanin skin test on the numbered arm and the puckered scar of old skin leishmaniasis on the other.

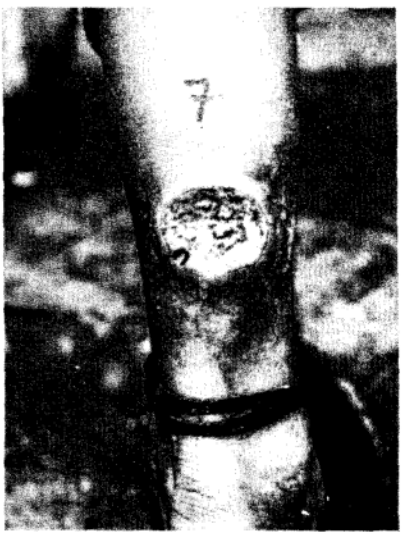

Figure 2 - Typical L(V)b skin ulcer deep, destructive, and on the lower limb. The punch biopsy site at seven o'clock is clearly visible.

Since the review[16] we have developed further ideas about the genesis of mucosal disease. It seems probable to us that metastasis of amastigote laden macrophages occurs early in the skin granuloma development. We have seen a number of patients where regional lymphadenopathy occurred before skin ulceration and in such lymph glands amastigotes of L(V)b have been recovered[24]. This implies that early effective treatment of skin granuloma due to L(V)b may avoid mucosal disease later. We have never recovered L(V)b from the circulating blood of patients with active skin lesions but have recently isolated this parasite repeatedly from the liver of a chronically infected marmoset[27]. Probably its occurence in the circulating blood is transitory and parasite laden cells are captured by phagocytic capillary beds such as occurs in the nasal septum. Since the external nares receive cool air and low skin temperature favours leishmanial development, it is perhaps not surprising that the cartilaginous nasal septum is the usual initial site of leishmanial multiplication and granuloma formation. Histologically such granuloma can be seen invading the cartilage which is a non-immunogenic tissue. Its fragility leads to rapid perforation. Fortunately the skin of the external septum is often retained and the leishmanial lesion is restricted to the cartilaginous septum. The osseous septum can be the site of secondary infection and may be lost in advanced cases. Granuloma on the nasal floor may extend through to the palate or separate palatal granulomata may develop. Isolated palatal disease is rare. Both hard and soft palates can be the site of active granuloma formation with irregularities resembling a cobbled street (Figure 3). As in Carini's case, the uvula may be lost.

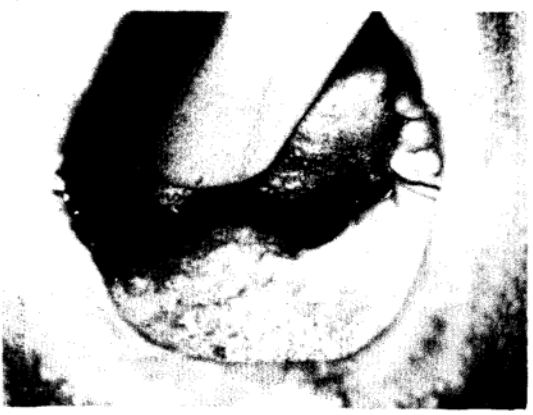

Figure 3 - Palatal granuloma of mucosal leishmaniasis.

The next extension is to the fauces and the wall of the oropharynx. From there extension to the nasopharynx and hypopharynx occurs. Finally the larynx and upper trachea may be inflammed with impairment of vocal cord movement due to

involvement of the muscles and cartilages of the larynx. The epiglottis is frequently oedematous, hyperaemic and the site of active granuloma. This process results in the valuable sign of a hoarse weak voice. We have described lone laryngeal leishmaniasis. The author knows of single cases of tracheal and even oesophageal granulomas in diffuse cutaneous leishmaniasis (unpublished).

A few patients with advanced mucosal disease have refused treatment and choose to die at home. In such patients laryngeal and pharyngeal oedema results in airway obstruction and difficulty in swallowing. Demise is usually the result of suffocation or aspiration pneumonia from infected secretions. Severe disease of this type may require emergency tracheostomy especially at the begining of treatment when tissue reaction may occur.

The differential diagnosis of nasal leishmaniasis is extensive and trauma, cocaine sniffing, treponematoses, leprosy, sarcoidosis, rhinosporidiosis, histoplasmosis and lethal midline granuloma must be considered. Bucal leishmaniasis can be confused with South American blastomycosis as suggested by Carini. A chest x-ray is a diagnostic short cut since usually mucosal blastomycosis is associated with upper or mid zone nodular pulmonary infiltrations.

The initial skin lesion of L(V)b is rapidly ulcerating and has a marked raised border (Figure 2). It is located on the limbs since these are more exposed to the bite of infected phlebotomines, but trunk and facial lesions are also seen. One third of our patients in field clinics have multiple skin lesions due either to repeated phlebotomine bites at the time of exposure or metastatic spread. The latter possibility can be sometimes suspected by the later development of proximal lesions. These skin ulcers are chronic lasting often months in spite of treatment. Our work suggests that extensive longstanding ulcers above the belt line favours mucosal metastasis probably due to the facility of parasite migration by the lymphatic system to the circulation. The frequent correlation of late mucosal metastasis with inadequate treatment of the initial skin lesion has also been noted[16]. Therefore all patients with L(V)b skin granuloma must be urged to complete recommended treatment schedules. They should be told that if they develop sysmptoms of mucosal disease such as epistaxis, nasal blockage, buccal ulceration or hoarse voice they must seek medical help. A curious feature of the mucosal metastasis is latency. The parasite may remain for decades in the mucosa of the nose before initiating granuloma. Predisposing factors to this activation are not clear but could include local trauma or immunosupression. Recently reports of disseminated skin leishmaniasis associated with the acquired immunodeficiency syndrome have appeared. As mentioned in the previous review[16], a mechanism promoting mucosal granuloma in leishmaniasis could be an exaggerated hypersensitivity reaction to an unknown antigen present in L(V)b. The exaggerated skin hypersensitivity favours such an interpretation. Analagous speculations have occurred to explain Idiopathic Midline Destructive Disease (IMDD)[9 26]. Many such patients had a favourable response to radiation therapy[9]. In the presence of a strong cellular immune response such therapy of persistent mucosal disease could be considered with antimicrobial and antimonial therapy. We currently have two such patients who have relapsed despite all therapeutic options and have maintained a strong leishmanin response for over 20 years. With such a long observation period one notes that relapses take longer and the disease seems less severe with time but a definitive therapeutic solution is desirable. Perhaps we should try radiation therapy as these patients always improve with glucantime but relapse later.

DIAGNOSIS

L(V)b is the most difficult of the leishmanial species to isolate and classify because it is present in both skin and mucosal granulomas in such small numbers[23]. The rapid cellular immune response and widespread necrosis contrast strangely with the sparse parasitaemia in the tissues. From mucosal L(V)b granulomas parasite isolation is especially difficult. We have rarely achieved more than 50% success. One problem is bacterial contamination of cultures as even cleaned nasal area remains rich in bacteria and fungi. The hamster has proved useful in this respect since triturated biopsy material

inoculated into the hind feet of this animal frequently results in isolation. Growth of L(V)b is slow however and ideally the animal should be kept for a year: the inoculation site needled and cultures being seeded monthey. Often the skin granuloma in the hamster is almost imperceptible. For this reason while Giemsa stained of aspirates of the granuloma and multiple cultures are routinely examined for parasites hamster inoculation has more eventual success. This result comes too late to help the clinician to decide on patient's management. Recently monoclonal fluorescent antibody techniques have defined amastigotes in mucosal biopsies[29]. L(V)b specific monoclonal antibody for this technique is still not available. This would simplify diagnosis considerably. While biopsy evaluation aids diagnosis it has proved difficult to develop histological prognostic criteria since the tissue response is irregular in L(V)b and does not form a continuous spectrum as in leprosy[23]. Because of the difficulties in parasite isolation, indirect immunological tests are important. The leishmanin skin test is the most widely used and reliable skin test in parasitic disease (Figure 1). We have devoted much research to establishing its specificity and sensitivity. The recent thesis of EM Netto[19] cites a sensitivity for the leishmanin skin test of 82% and a specificity of 98% in Três Braços. Equivalent figures for specific serology in the same area were 89% and 84%. This thesis also shows, as we previously reported, strong delayed hypersensitivity skin reaction in mucosal leshmaniasis when reliable antigens are used. Such an antigen is promissed by the World Health Organization. Antigens are usually crude extracts of *Leishmania mexicana* promastigotes for this species grows much better in culture. Skin reactions are only group specific and not species specific. A negative skin reaction in a patient with advanced mucosal disease is a bad prognostic sign. It probably reflects associated malnutrition with consequent immunosupression.

Netto[19] analyses in detail leishmanial serology using indirect immunofluorescence and ELISA technique. The former is perhaps less sensitive but our clinicians have found such titred serological results to be of great help in evaluating prognosis in treated mucosal leishmaniasis. These cross react with Chagas' disease and visceral leishmaniasis but these are not present in our field station at Três Braços, Bahia. While we would not initiate treatment on the basis of positive serology alone it would stimulate us to search carefully for evidence of a recurrence of mucosal leishmaniasis.

PROGNOSIS

The complications of mucosal leishmaniasis have been previously discussed[16]. The degree of deformity is very variable, ranging from simple nasal septal perforation to varying degrees of destruction of the centre of the face (Figure 4).

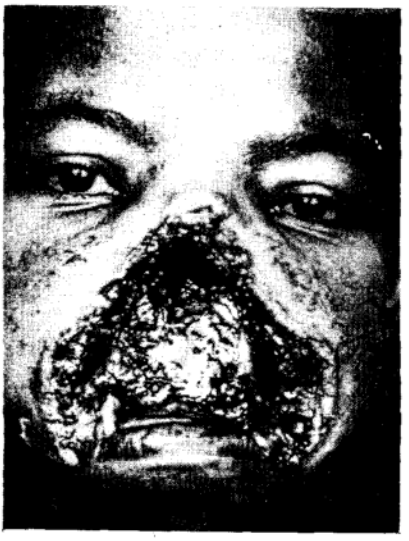

Figure 4 - Extensive destruction from mucosal leishmaniasis.

Secondary infection may be so marked as to require initial antibiotic treatment, especially to prevent cavernous sinus thrombosis. Myiasis must be eliminated otherwise maggots can invade the base of brain. Lymphoedema of the face due to lymphatic obstruction is a rare complication (Figure 5). Recently we have seen two patients in whom mucosal disease arrested spontaneously without specific therapy[17]. Normally disease progress is slow but inevitable without treatment resulting in increasing deformity and eventually death. We have recently published the results of a long term study showing that mucosal disease develops in less

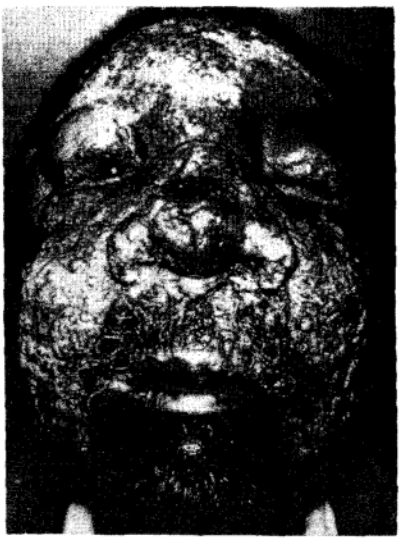

Figure 5 - The rare lymphoedema in acute mucosal leishmaniasis.

than 5 % of patients who have had cutaneous disease in our area[20]. Figures for relapse of mucosal disease after treatment are also given. As our work shows, it is mandatory for groups working in endemic areas to know what types of leishmaniasis are present and their relative prevalence.

TREATMENT

Not only is L(V)b the most difficult leishmanial parasite to isolate but it is also the most difficult to treat. Infection, especially of the mucosa, often relapses years after antimony treatment. Patients should have a yearly clinical follow up examination indefinitely.

As has been discussed elsewhere[1 15] pentavalent antimonials remain the first line treatment of leishmaniasis. Two are available. Glucantime (N-methylglucamine antimoniate) is a French drug used in Latin America in a 5cc ampoule each cubic centimetre theoretically containing 85mg of pentavalent antimony base (Sb^V). Pentostam is English and manufactured in 100cc bottles containing 100mg Sb^V. Standartisation is a problem and variations in osmolarity and efficacy have been noted with both drugs. With time polymerisation of the complex molecules containing the heavy metal occurs and whether such polymers are therapeutically active is unknown. Neither drug company seems interested not even in the deterioration to trivalent antimonial which is responsible for many more side effects. All recent comparative therapeutic trials of drugs with pentavalent antimonials in the literature are useless if the batch is not detailed, efficacy established, and deterioration minimised. Currently we store one batch lot of glucantime of known efficacy at 4°C, in the dark, and assess osmolarity and pH every two months to control deterioration. Only this glucantime is used in our therapeutic trials.

The problems with antimonial therapy are such that we have investigated many alternatives. Currently we are working with aminosidine (an aminoglycoside) which gave promising results in Kala azar in Kenya[5]. We have hopes that this might be an alternative to glucantime therapy although such treatment still requires a relatively long course of injections.

Another therapeutic alternative is liposome linked amphotericin B and we have a hospital study underway in mucosal leishamaniasis using ambisome one of the three available preparations. These new drugs for leishmaniasis have been recently reviewed[21]. Unfortunately promising compounds are all parenteral use and therefore unsuitable for field use except under special clinic conditions. We have had relapses in mucosal leishmaniasis both with aminosidine and ambisome.

As pointed out elsewhere cutaneous L(V)b infectious are so frequent in our study area that a local treatment centre is essential[15]. Our waiting list for hospital beds of patients with mucosal disease excludes such patients from an in-patient service. We have two fied clinics where we are treating L(V)b infections. Trained field personnel weigh the patient and calculate the daily dose of Sb^V base per kilogram body weight. Recently we have switched from 20mg/Sb^V/kg body weight to 10mg Sb^V/kg for twenty days for simple skin ulcers due to L(V)b as a well conducted double blind trial by Haman has shown little difference a clinical response and side effects are less with the lower dose. The key is twenty days of continuous treatment. Similar schedules for 10 days were significantly inferior[12].

The problems of field treatment with glucantime have been discussed elsewhere[15]. Currently the greatest practical contribuition that can be made to our attempts to control L(V)b transmission in Três

Braços, Bahia, is a supply of boilable plastic 10cc syringes. We train people to give their own injections in remote farms because they can't walk miles to the clinic every day. They boil up their glass syringe and needle in a kettle before application by intramuscular injection in daily sequence using, in turn, both lateral buttocks, both thighs, and both biceps. Injection is often painful and volumes large. Local muscle massage should be applied by the patient for 5 minutes and he should rest for one hour before walking home. The glass syringe is often broken so plastic is preferable but beyond our financial means. Because of practical difficulties like these we know that compliance with the drug schedules prescribed is often faulty[12]. Recently, when we had no antimonial in our field clinics for many months because ministry supplies failed, we confirmed once again that cutaneous leishmaniasis due to L(V)b heals spontaneously[6].

Mucosal disease however is different for, apart from two cases[17], we have never seen healing without treatment, only slow relentless progression. Hence our field recommendation is 20mg Sb^V/kilo per day for 30 days, followed by clinical review for evidence of activity and continuation until one week after complete clinical healing. Many patients with mucosal disease will respond in 30 days particularly if the lesions are not advanced. The maximum continuous antimony schedule at this dose level we have given to a patient with mucosal disease was 86 days: and he relapsed[18].

The side effects of glucantime are considerable, cumulative and dose dependent. We have only seen one patient who had an anaphylactic reaction on first injection so we no longer give a test dose. Both glucantime and pentostam are best given by slow intravenous injection (over 3 minutes) without diluent as it is diluted with 5 litres of blood almost immediately. Only if local thrombosis occurs, which is virtually unknown in our practice, should diluent be used. A single daily bolus dose has been shown to be the most effective. Really the mechanism of action of the drug is still unknown but in the first 4 days an extravascular compartment is saturated which must be operative in antiamastigote action. Nasal mucosal concentrations and dynamics are unknown[12].

Side effects are dose related and usually in the second week the patient complains of muscular pain; arthralgia and sometimes anorexia. With mucosal disease therapy a weekly blood urea and creatinine, electrocardiogram and liver enzymes estimations are desirable. Like all heavy metals antimony, even in its less toxic pentavalent form, can affect the target organs as the heart, kidney, liver and brain in this order of frequency. The single dose toxic limit for man is about 30mg Sb^V per kilogram body weight[15]. The indications for stopping treatment have been described[1,15]. In our experience significant electrocardiographic changes and renal dysfunction are the most frequent reasons. We have recently tried Bryceson's suggestion[2] for mucosal disease treatment of 20mg Sb^V/kg body weight *twice* a day. This proved too toxic particularly in the most affected age groups of adults over 40 years where cardiac and renal reserves are naturally deteriorating.

If antimony therapy does not serve to resolve mucosal granuloma the recommended alternative drugs are amphotericin B or pentamidine both difficult to administer[1,15]. Amphotericin B is much used in deep systemic mycoses and many readers will have experience of its administration in a continuous drip infusion over four hours. Starting with a dose of 0.25mg/kilogram this is raised during the first week of alternate day administration to 1mg/kg. The major side effects apart from venous thrombosis and the inevitable nausea are on the kidney and renal function which must be carefully monitored. We like to give a total dose of 2.5 grams of drug for an adult of 60 kilos. We have achieved what appears to be clinical cure of mucosal leishmaniasis with less than 1 gram in some patients. Few of our patients have relapsed after amphotericin B therapy.

We have treated a few patients with pentamidine because it is not easily available in Brazil but in our small trial there were some relapses and there have since been more[25]. It does not appear therefore to be a strong alternative to amphotericin. Pentamidine isethionate, a dry white powder is dissolved in 5cc of distilled water and given in a single daily intramuscular injection of 4mg/kg body weight. Various treatment schedules are possible from 8 injections on alternate days to 6 weeks of 3 injections per week. Intravenous injection is dangerous due to hypotension and hypoglycemia, although AIDS patients with Pneumocystis frequently receive it by

slow intravenous drip. Intramuscular injection is painful and can cause sterile abcess and muscular massage after injection is essential. The chief complication of pentamidine therapy is pancreatic damage with diabetes so a weekly blood sugar is desirable. Despite much research there is no satisfactory oral treatment for L(V)v infection.

Control of mucosal granulomata of L(V)b with subsequent healing, fibrosis, and a fall in the leishmanial serological titre to negative for a year opens the way for plastic surgical reconstruction but only feeble efforts have been made to date. This is because these patients have no money wich is why antimonials (the mainstay of 19th Century medicine) are still in use. Fortunately mucosal leishmaniasis is mainly a disease of old men who don't mind so much if they have a deformed nose or mouth but take the case of the 15 year old boy who I have followed since a child. He is cured and is a bus conductor (Figure 6). All he needs is a tinted prothesis fitted in place of his nasal septum. You don't notice it because it's in shadow on his face and he takes it out at night like false teeth. Then he can do his job with more confidence and get a girl friend!

Certainly much can be done for deformative healed mucosal leishmaniasis with simple aids like straw hats, dark glasses etc. These restore the patient's confidence to move among the community especially the men who can often make a good psychological adjustment. Severe damage such as is shown in Figure 4 is a different matter. Many expensive operation may be necessary to build a nose[13].

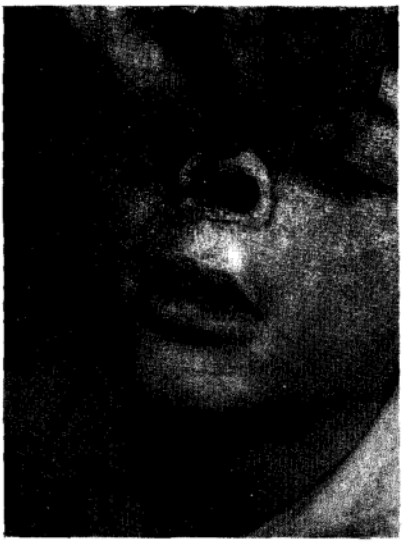

Figure 6 - Loss of cartilaginous and skin septum. A suitable case for prothesis.

CONCLUSION

L(V)b transmission continues unchecked in our study area for the Ministry of Health has no answer to this problem apart from individual therapy[28]. Recently we have reported a large epidemic[10] compared to our previous experience[14]. The genesis of these epidemics is unknown despite years of study. The population seeks our field clinics for medical help. If vaccination were feasible how would we identify the group at risk in this epidemiological situation? Surely the first task is to do a geographical biopsy as Burkitt did with his lymphoma[3]. Mucosal leishmaniasis is a pathogenic condition. Distribute such photos to all field hospitals in Brazil and we might have an idea of the size of the problem.

RESUMO

Neste trabalho, é feita uma breve revisão da leishmaniose mucosa existente no Brasil enfatizando os recentes avanços no tratamento clínico. Os pacientes frequentemente ocupam os leitos hospitalares e alguns casos são notoriamente difíceis de tratar. Recomenda-se um acompanhamento por tempo indefinido. Embora a Leishmania (Viannia) braziliensis *seja o microorganismo mais comumente isolado, muitos aspectos da etiologia permanecem obscuros. As perpectivas de um tratamento oral e barato são ainda remotas.*

Palavras-chaves: Leishmaniose mucosa. Leishmania (Viannia) braziliensis. *Tratamento clínico. Três* Braços, Brasil.

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