Personal Experience with Diagnostic and Therapeutic Aspects of Human *Leishmania (Viannia) braziliensis* in Três Braços

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Diagnostic and therapeutic aspects of human infection with Leishmania (Viannia) braziliensis *found in the littoral forest of the State of Bahia are reviewed. There is pressing need for alternative cheap oral drug therapy.*

Key words: human *Leishmania (Viannia) braziliensis* infection - State of Bahia - diagnosis therapy

Our group in Brasilia has always had close contact with the group in Salvador because our funding came from a common grant administered by Cornell University from the NIH. Aluízio Prata determined that kala azar work would remain in Jacobina under Salvador control and that Air Barreto, Cesar Cuba Cuba and I should open a field area of mucocutaneous leishmaniasis - a condition for which at that time (1973) no prognosis was possible.

From the outset we were interested in better therapy to escape from the tyranny of glucantime. We have tested over 20 alternative compounds without success. Still today we have a hospital group in Brasília studying candidate drugs under carefully controlled conditions and a field group involved in community care with an emphasis on management of cutaneous and mucosal leishmaniasis and its epidemiology. We have two field clinics: a treatment clinic by the side of the road BR-101 joining Salvador to Rio de Janeiro which receives a new patient with leishmaniasis daily and the original clinic at Três Braços mainly involved in long term follow up and epidemiology. Data will be quoted from both clinics and from the base hospitals in Salvador and Brasília.

DIAGNOSIS

Três Braços (three arms) is so called because here three rivers join which eventually, as the Rio Preto, discharge into the great Bahia de Todos os Santos at Valença. The rivers also deliniate three municipalities: Cravolândia, Ubaira and Wenscesiau Guimarães. Ecologically these parts of this small community of a few thousand souls are very different. In the village of Três Braços, the Cravolândia area, the site of the leishmaniasis clinic, has a paved road and piped water; on the Ubaira side of the river there are no such facilities. Our group was viewed with suspicion for years, specially me who must be an "estrangeiro" who wanted to buy a farm. This suspicion was dispelled by our field medical service. Today with the second clinic at the side of a main road we are serving a wide area.

We established in those early years a high prevalence of mucosal leishmaniasis because they rarely improve permanently (Barreto et al. 1981), dogs as an important reservoir (Barreto et al. 1984) and *Lutzomyia whitmani* as the probable vector (Vexenat et al. 1986). The endemic areas were outside the village and after much walking in the virtually constant rain we established 15 study farms. Here among 276 families of 1956 subjects the incidence was 8/1,000, prevalence (1984) 160/1,000 and 2.7% of mucosal disease, the rest being cutaneous (Jones et al. 1987). It is some indication of our difficulties that our first paper appeared in 1981 after six years work in the area. Recently we have described another series of ten farms in a neighbouring area where the incidence in an epidemic rose ten fold above the cited figure for Três Braços (França et al. 1991). We have published a five year follow up study of treated patients (Netto et al. 1990) and are working on the ten year follow up to establish prognostic data.

The first priority was to establish the *Leishmania* subspecies in transmission in the area. This was the doctorate thesis of Cesar Cuba Cuba (Cuba et al. 1985) and we have now examined several hundred isolates (Rosa et al. 1988). We have a virtual monotransmission of *Leishmania (Viannia) braziliensis* (Lvb). This has proved convenient for establishing the diagnostic features of this infection.

Usually the patients have a single ulcer below the knee but other exposed sites can be affected. The ulceration is rapid and deep with a typically infiltrated edge. Multiple lesions occur in one

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third of patients. Parasites are difficult to find either in aspirates of the ulcer border stained with Giemsa or Haematoxylin and Eosin histological sections, yet necrosis is marked. Pathological analysis has not helped much in formulating prognosis as the great majority of patients occupy the mid spectral position. Multiple cultures and hamster inoculation from aspirates or triturated biopsy material result in promastigote recovery in up to 70% of cutaneous cases and 50% of mucosal patients. Because of the difficulty of parasite isolation compatible histology, a positive leishmanian skin test and positive IFA or Elisa serology are valuable in establishing the diagnosis. Actually an experienced clinician is usually correct in his initial impression but for scientific work naturally the strongest diagnostic evidence must be assembled.

Mucosal leishmaniasis is a notorious treatment problem. Metastasis occurs early from the skin lesion, sometimes before the skin granuloma is evident, and 10% of our patients with mucosal disease have no scar of previous skin ulceration. In contrast to Sudanese mucosal leishmaniasis, Três Braços disease almost invariably begins on the cartilaginous nasal septum. Its clinical onset is measured months, years or decades after skin infection and we have never succeeded in recovering the parasite from normal mucosa in infected patients. 15% of one mucosal series had active cutaneous and mucosal disease simultaneously.

One third of Três Braços patients with mucosal disease have multiple mucosal surface involvement and this is the dangerous group, especially when the larynx is affected. 5% of these patients die either from suffocation due to laryngeal closure or aspiration pneumonia of infected secretions. The whole question of mucosal leishmaniasis with a research review of our work is published (Marsden 1986).

Parasite recovery is even more difficult in mucosal disease due to culture contamination and the difficulty of obtaining adequate biopsy fragments. Such patients are often exquisitely sensitive to leishmanin. Serological titres are high and after successful treatment fall within a year, a useful indicator. No graft procedure should be undertaken less than a year after serological conversion.

TREATMENT

This aspect has been much discussed at this meeting but not in relation to mucosal disease. Skin ulceration due to Lvb usually responds well to glucantime. This has to be given in our field clinics because both Salvador and Brasília hospitals have waiting lists of mucosal patients needing admission. Marchán Haman (1989) made an important contribution when he showed in a double blind trial that skin ulcer closure was just as rapid with 10 mg Sb^v as 20 mg Sb^v kilo/body wt if drug was given in a single daily dose continuously for 20 days. This means our trained drug applicators in peripheral farms can use 10 rather than 20cc syringes. Adequate early glucantime therapy is an important factor limiting mucosal recurrence and our observations on risk factors for mucosal leishmaniasis (Llaños-Cuentas et al. 1984) have recently been confirmed in Peru. A complicating factor which is difficult to control in drug trials in the field is spontaneous healing of cutaneous ulcers which occurs even with Lvb (Costa et al. 1990). It must occur with *Leishmania (Viannia) guyanensis*. Glucantime was not available in the area for a year and a large series of such spontaneous healers were noted.

In mucosal disease spontaneous healing is virtually unknown (Marsden et al. 1991) but, curiously, refractory patients occur, (and I have some I have followed for twenty years). Gradually they improve with time after all that chemotherapy to the point of leading relatively normal lives. The initial treatment recommendation is irrefutable. Effective glucantime in a single dose of 20 mg Sb^v/kilo/day for 30 days and then review the status of the affected mucosal surfaces. Persistent granuloma or erythema are indications for not stoping the glucantime but continuing until biopsy confirmation and then to the limit of tolerance. This time can reach 80-90 days in a young patient with good renal and cardiac reserve. Unfortunately, too many mucosal patients are over 40 years of age. There is good evidence that intermittent therapy with poorly active drugs creates drug resistance (Olliario & Bryceson 1993).

It is important to nourish a patient who has with difficulty in swallowing before commencing treatment. The drug should be given slowly, intravenously and without dilutent. The patient should rest for one hour after the injection. He is best treated at home if field treatment is the only possibility or living with the group in the health post. Laryngeal aperture narrowing is a danger sign and accompanied by a hoarse voice. Such patients should only be treated in hospital because of oedema early in the course of treatment (a Herxhiemerlike effect) may necessitate emergency tracheostomy (Costa et al. 1986).

If glucantime fails then the second line drugs amphotericin B or pentamidine are indicated in this order. Mucosal disease response to amphotericin B is usually very satisfactory and permanent cure achieved with a two gram total dose. Hospitalization is necessary because of side effects. Dr Sampaio (Sampaio et al. 1988) has had successes too with pentamidine, be it the isethionate or the methylsulphonate. These are dangerous drugs intravenously due to hypoglycemia

and hypertension. I prefer multisited intramuscular injection with local massage to prevent sterile abscess formation.

A number of new possibilities are available but none of them oral. We have already had a mucosal relapse with aminosidine but this aminoglycoside could have a place. We are currently trying Vestar's Ambisome - a liposome-linked amphotericin preparation - but hardly an answer for field clinic work in view of the application difficulties and cost (Olliario & Bryceson 1993). We have had relapse with this drug also.

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