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# RELATO DE CASO

## DIABETES MELLITUS ASSOCIATED WITH PENTAMIDINE ISETHIONATE IN DIFFUSE CUTANEOUS LEISHMANIASIS

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*The authors report a case of a male patient from Bacabal, MA with diffuse cutaneous leishmaniasis (DCL), for at least nine years, with 168 lesions on his body. These were tumour-like nodules with some ulceration. He used pentavalent antimonial (glucantime®) and an association of gamma interferon plus glucantime with improvement of the lesions but relapsed later. Recently, pentamidine isethionate (pentacarinat®) was given a dosage of 4mg/kg/weight/day on alternate days for 20 applications. After 3 months a similar course of 10 application was given 2 times. Later he developed diabetic signs with weight loss of 10kg, polydypsia, polyuria and xerostomia. The lower limbs lesions showed signs of activity. Blood glucose levels normalised and remain like this at moment. Attention is drawn to the fact that pentamidine isethionate should be used as a therapy option with care, obeyng rigorous laboratory controls including a glucose tolerance test.*

*Key-words: Diffuse cutaneous leishmaniasis. Pentamidine isethionate. Diabetes mellitus. Maranhão State.*

Diffuse cutaneous leishmaniasis (DCL) is a rare form of cutaneous leishmaniasis in which cellular immunity to leishmania antigens is absent and which shows a poor response to antileishmanial agents. According to Silva[12], who originally described the disease in Brazil, initial lesions are macular, papular or nodular containing abundant parasites. Regional lymphadenopathy and mucosal lesions are uncommon and visceral lesions unreported[5].

The disease begins as a nodule, to spread locally and distally to the rest of the skin. Although the Montenegro skin test is negative, indicating a lack of cellular immunity to leishmania antigens, DCL patients do respond to unrelated skin test antigens such as PPD and candidin[3,5].

Bryceson[4] used various treatment regimens of drug in 24 DCL patients, pentamidine mesylate (4mg/kg/daily) resulted in improvement in all 24 patients, but relapsed. Pentostam (10mg/sbV/kg for 5-30 days) resulted in initial improvement. One of 6 patients was cured with primaquine 30mg per day for 2 months, and did not relapse over 14 months. This case probably shows that the rare case of diffuse disease with only one lesion may self heal. Amphotericin B (1mg/kg/for about 2 months) was used in 4 patients. In Peru, pentostam (20mg/sbV/day for 60 days) resulted in improvement but not cure[7].

In Brazil, the drug of choice for the treatment of mucocutaneous and DCL is the pentavalent antimonial (glucantime®)[10,13]. If relapse occurs, second line therapy with amphotericin B or pentamidine are indicated. Pentamidine isethionate is not available, being imported from England (pentacarinat®). The Brazilian Ministry of Health furnishes this drug for special cases such as DCL

Bryceson 1970[3] and Bouchard and cols 1982[1], reported that pentamidine may cause diabetes mellitus. Recently, our team attended a patient with DCL who developed diabetes mellitus after pentamidine isethionate, that we would like to report .

### CASE REPORT

RNPS, 31 years old, man, landworker, from the state of Maranhão, northeast of Brazil, had DCL caused by *Leishmania amazonensis*, for at least nine years. During the last three years, he was submitted to various therapy schedules (glucantime®, amphotericin B, glucantime® plus gamma-interferon),

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showing improvement but with subsequent relapses.

Before the administration of pentamidine isethionate in September 1991 a clinical-laboratorial evaluation was performed. At that occasion the patient had active lesions with small nodules and erythematous tubercules associated with scars on his face, chest and abdomen. A total of 168 active lesions were found plaques and erythematous tubercules with ulcerations covered with crusts were observed on his hands and feet. Red and white blood cells counts, urea, creatinine, alkaline phosphatase, AST, ALAT were without alterations. The blood glucose level was 77mg/dl.

Pentamidine isethionate was administered in a dose of 4mg/kg on alternate days for 20 IM applications. When glucose alteration appeared (123mg/dl), the drug was dismissed temporarily. After 3 months, pentamidine was reintroduced in the same dose regimen for 10 applications. At the end of these series glucose blood level was 100mg/dl. Another regimen of the drug was done three months later, and the same evolution occurred. The total dose was 8.4g of pentamidine isethionate. In this period glucose blood levels varied between 80 to 100mg/dl in the last three regimens. The patient was discharged with improvement, but still showing crusts on the lower limbs and scars throughout the body. The Montenegro skin test remained negative.

He returned to the hospital a month after discharge (October 1992), with weight loss of, 10kg, polydypsia, polyuria, xerostomia, weakness and relapse of the lesions of the lower limbs (ulcerations with crusts and secondary infection). The glucose blood level was 420mg/dl, glucose and ketonic bodies were present on the urinalysis. He needed insulin control for 22 days, when glucose levels became normal, persisting some active lesions on his legs. He later improved after therapy with aminosidine.

## DISCUSSION

Bryceson[2,3] treated 33 patients with diffuse cutaneous leishmaniasis (DCL) with a variety of agents. Pentamidine mesylate gave the best results, with initial improvement in all patients and long term cure in seven. He concluded that pentamidine given weekly or biweekly was the best available therapy for this disease although its toxic effects limited the dosage and frequency of injections. The side effects included collapse (presumably due to the drug entering a vein), profound weakness, anorexia, nausea, vomiting, abdominal pain, glycosuria, altered glucose tolerance test and diabetes.

Although clinical experience appears to be lacking, several authors recommended pentamidine for the treatment of cases of visceral leishmaniasis and mucocutaneous leishmaniasis that have been unresponsive to antimonial agents[6,9]. Jha[8] has reported to have sucessfully treated 81 of 82 cases of pentavalent antimony-resistant kalazar with pentamidine mesylate in North Bihar, India.

There is a suggestion that the dimethanesulfonate salt (mesylate) of pentamidine may be more diabetogenic than isethionate[2,4,6,8]. The mechanism of the diabetogenic effect of pentamidine is considered to be similar to that of streptozocin, causing an early citolytic release of insulin and hypoglicemia, followed by insulin deprivation and diabetes mellitus because of a toxic effect on the ß-cells of the pancreas. Approximately 5% of the treated patients will develop glucose intolerance or insulin-dependent diabetes during pentamidine therapy, some having antecedent hypoglicemia[1,11].

Only this patient out of five cases of DCL in Maranhão treated with isethionate of pentamidine developed diabetes mellitus, being the first report of DCL in Brazil, treated with this drug that developed diabetes mellitus, without previous renal damage. Fortunately insulin independent, but control of glucose on the blood, are being done every three months.

## RESUMO

*Os autores relatam o caso de um paciente procedente de Bacabal, MA, portador de leishmaniose cutânea difusa (LCD) há 9 anos, apresentando um total de 168 lesões distribuídas pelo corpo, de caráter nódulo tumoral e algumas ulceradas, tendo sido submetido a tratamentos anteriores à base de antimonial pentavalente (glucantime®) e associação interferom gamma+glucantime® com melhora e posterior recidiva das lesões. Recentemente quando da utilização do medicamento isotianato de*

*pentamidina (pentacarinat®) na dose de 4mg/kg/peso/dia, aplicados IM em dias alternados em 3 séries de 20, 10, 10 aplicações com intervalos entre as séries de 3 meses. Na evolução do tratamento desenvolveu um quadro de perda de peso 10kg, polidpsia, poliúria, xerostomia, lesões de membros inferiores com sinais de atividade. Glicemia em jejum 420mg/dl, presença de glicose e corpos cetônicos na urina. Instituída insulinoterapia houve melhora do quadro e retorno dos níveis glicêmicos permanecendo estável até o presente momento. Alerta-se os clínicos que devido a disponibilidade da pentamidina como opção terapêutica, a mesma deve ser usada com critérios, obedecendo rigoroso controle laboratorial incluindo os níveis glicêmicos dos pacientes.*

*Palavras-chaves: Leishmaniose cutânea difusa. Isotionato de pentamidina. Diabetes mellitus. Estado do Maranhão.*

## REFERENCES

1. Bouchard P, Sai P, Reach G, Cambarrere I, Fanavel D, Assan R. Diabetes mellitus following pentamidine induced hypoglycemia in human. Diabetes 31: 40-45, 1982.
2. Bryceson AD. Pentamidine induced diabetes mellitus. East African Medical Journal 45:110-117, 1968.
3. Bryceson AD. Diffuse cutaneous leishmaniasis in Ethiopia. II.Treatment Transactions of the Royal Society of Tropical Medicine and Hygiene 64:369-379, 1970
4. Bryceson AD, Woodstock L. The cumulative effect of pentamidine dimethanosulfonate on the blood sugar. East African Medical Journal 46:170-173, 1969 .
5. Convit J, Pinardi ME, Rondon AJ. Diffuse cutaneous leishmaniasis: a disease due to an immunological defect on the host.Transactions of the Royal Society of Tropical Medicine and Hygiene 66:603- 610, 1972.
6. Costa JML. O uso clínico das pentamidinas com especial referência nas leishmanioses. Acta Amazonica 23:163 -172,1993 .
7. Frank EC, Wignall FS, Cruz ME, Rosales E, Tovar AA, Lucas CM, Llanos-Cuentas EA, Berman JD. Efficacy and toxicity of sodium stibogluconate for mucosal leishmaniasis. Annals of Internal Medicine 113: 934-940, 1990.
8. Jha TK. Evaluation of diamidine compound (pentamidine isethionate) in the treatment of resistent cases of Kalazar occurring in North Bihar, India. Transactions of the Royal Society of Tropical Medicine and Hygiene 77:167-170, 1983.
9. Jha TK, Sharma VW. Pentamidine induced diabetes mellitus. Transactions of the Royal Society of Tropical Medicine and Hygiene 78:252-253, 1984.
10. Marsden PD. Mucosal leishmaniasis ("Espundia" Escomel, 1911). Transactions of the Royal Society of Tropical Medicine and Hygiene 80:859-876,1986.
11. Sands M, Kron MAS, Brown RB. Pentamidine: A Review. Reviews of Infectious Diseases 7:625-634, 1985.
12. Silva F. Forma raríssima de leishmaniose tegumentar. Leishmaniose dérmica não ulcerada em nódulos e extensas placas infiltradas e hiperpigmentadas. II Reunião de Dermatossifilógraficos Brasileiros, Rio de Janeiro 1:97-103, 1945.
13. Vieira JB, Lacerda MM, Marsden PD. National reporting of leishmaniasis the Brazilian experience. Parasitology Today 6:3339-3340,1990.