An Unusual Case of Drug Induced Diabetes Mellitus

¹ Dr. Dhruba Lal Singh

² Dr. Kiran Manandhar

³ Dr. Prajwol Joshi

A 38 year old male with Kala-azar (Visceral Leishmaniasis) was treated initially with sodium stibogluconate to which he didn't respond. He was next treated with Pentamidine, 10 wks after which he presented to the Bir Hospital Emergency with the features of Diabetic Ketoacidosis and had to be managed with insulin.

Keywords: Kala-azar, Pentamidine, Sodium stibogluconate, Resistant, Hyperglycaemia.

INTRODUCTION

Drug induced diabetes mellitus is one of the known causes of secondary diabetes mellitus. Commonly mentioned drugs in this category include the thiazide diuretics, glucocorticoids, phenytoin sodium, diazoxide, and adrenergic drugs. Some of these drugs exacerbate the already existing diabetes while others cause it through various mechanisms -- some by peripheral resistance, while others do my inhibiting insulin release. Usually, the state of hyperglycaemia reverts to normality in most of these cases as they don't cause a permanent damage to the beta cells in the pancreas. Though hyperglycaemia is an adverse effect of pentamidine, it is hardly mentioned as a cause of secondary diabetes mellitus in any text book. Hence we report a case of pentamidine induced diabetes mellitus requiring insulin therapy in an antimony resistant kala-azar.

CASE REPORT

38 yrs old Mr. x from Udayapur, a service holder by profession was residing in Rolpa (Hills) for last 5 yrs. In may '92 he was posted to Mahottari (Terai). Nine months after he came to Mahottari, i.e. in Feb. '93 he had a sore throat, and the next month, i.e. in March '93 he developed fever with rigor which was last for 2 days and was given symptomatic treatment. The next month, i.e. April '93, he started having left sided abdominal pain along with fever. A local practitioner was consulted, who found him to have a massive splenomegaly, and empirically diagnosed him as a case of kala-azar, and was given inj. sodium stibogluconate 8 ml IM o.d. for 7 days. Not getting any better, he went to another physician who gave him same drug 8 ml IM od. for 10 days. His fever didn't get any better, hence he went to Patna where bone marrow test done revealed LD bodies. ELISA also gave a positive

1 FRCP (edn), Consultant Physician & Head of Dept. of Medicine, Bir Hospital, Kathmandu

2 MBBS, MD, Registrar, Bir Hospital.

3 MBBS, Medical Officer, Bir Hospital.

test at that time. He next decided to come to Kathmandu for further treatment, and was admitted to Bir Hospital at May 93. On admission, he was febrile, slight icterus and pallor. Liver was moderately enlarged while massive splenomegaly was present. No other significant finding was detected on examination. Past history of illness was unremarkable. A year back he was tested for Diabetes Mellitus on his own (without any symptoms, as he says) and was tested negative. Personal history revealed him to be smoker for the last 10-11 yrs. and he used to take alcohol quite frequently for last 10 yrs.

Investigations on admission showed:

Total blood count: 5000/cmm with N : 38% L : 60% M : 1% E : 1%
Hb: 6.2 gm/dl ESR: 70 mm in 1st hr.
Blood sugar (R) : 92 mg/dl Blood urea: 19 mg/dl
Serum creatinine: 1.6 mg/dl LFT: WNL
Serum Na+ : 135 meq/l. Serum K+ : 3.7 meq/l.
Total serum protein: 8.3 gm/dl
Serum albumin: 3.0 gm/dl
Chest XR : NAD USG Abdomen:
Hepatosplenomegaly.
Aldehyde test: positive. Bone marrow aspiration: positive for LD bodies.

As Mr. x was already treated unsuccessfully with sod. stibogluconate, treatment was started with inj. pentamidine i/mg (120 mg) IM alternate days for 15 doses. Response was seen within 8 (eight) days and he made a good recovery. The only treatment related symptoms he had were transient sweating and thirst immediately after the injection with every shot. This according to him was relieved by taking some water to drink. Since his general condition remained satisfactory and he didn't have significant complaints, he was discharged. Liver was 4 cm. palpable at the MCL and spleen was 6 cm palpable during discharge.

His general condition was satisfactory over the ensuing weeks, and was starting to put on some weight. On 30th July, he felt a bit weak. The weakness went on increasing over the ensuing days. From the same day onwards

he started having excessive thirst and urination. From 11th Aug he started having repeated bouts of vomiting and was brought to the Bir hospital again. He was found to be markedly dehydrated on admission.

Investigations this time revealed:

Total blood count: 7000/cmm with N : 57%
L : 43% Hb: 7.0 gm/dl
Blood sugar: 425 mg/dl
Blood Urea : 60 mg/dl
Serum Na+ : 139 meq/l.
K+ : 3.7 meq/l.
Urine sugar: ++++
Urine for Ketone bodies: positive.

Rehydration was done. Hyperglycaemia and ketosis was controlled with insulin drip. He responded to the treatment and was maintained on Mixtard insulin. An attempt to wean away his insulin was unsuccessful. He still needed his insulin till his last follow-up visit 4 months after beginning the insulin.

DISCUSSION

Antimony sodium has been the drug of choice for kala-azar for a long time, and is still the drug of first choice though the strains resistant to it are emerging rapidly. Due to the same problem the optimal dose of antimony sodium has been modified time and again.

Though the latest recommendation of WHO is 20mg/kg/d to a max of 850mg/d, certain studies done in various places show the effective dose for kala-azar to be higher.^{1,2} These recent studies have shown that the 850mg restriction should be removed as the dose of 20mg/kg/d without an upper limit is more efficacious and not more toxic than the regimens with the lower daily doses. The specific upper limit of 850mg was chosen simply because this is the amount of stibogluconate in two 5ml ampoules (85mg/ml) of Glucantime. CDC in the United States has also recommended recently to remove the upper limit of 850 mg from the dosage regimen to make treatment more efficacious.

In our country various regimens are used, but almost all of them tend to limit the dose below 800mg as usual. This dose as has been just mentioned seems to be inadequate because of the emerging Primary drug resistance. Development of secondary antimonial resistance too is feared with an inadequate dosage. This fact is brought in discussion here because we too are using the conventional doses so far.

With the emerging resistance of kala-azar to the conventional dose of antimony sodium, the emerging trend in our country seems to be to use the alternative drug pentamidine which is more effective. Once forgotten in many developed countries, pentamidine once again is of interest because of its use in PCP (Pneumocystis Carinii Pneumonia) especially in AIDS cases.

The efficacy of pentamidine unfortunately is at the cost of its toxicity and the price. The toxicity ranges from transient palpitation, flushing, sweating to more dangerous hypotension, azotemia, or cardiac arrhythmias. Both, hypoglycaemia and hyperglycaemia also come in the range of adverse reaction though the former is much more common than the later. Pentamidine is supposed to damage beta cells of Islets of Langerhans in pancreas causing an initial hypoglycaemia due to insulin release followed by hyperglycaemia due to insulin deficiency later on. The features suggestive of early hypoglycaemia is a noted phenomenon by many of those treating the patients in our country too, but the feature of hyperglycaemia doesn't seem to be noted -- one of the reasons might be because it comes later and our patients usually fail to come for a follow-up.

A study from Patna reports the incidence of hyperglycaemia to be as high as 10% (4% reversible and 6% irreversible). Another report mentions of 5 cases of hyperglycaemia requiring insulin therapy.¹ The case we are reporting we think is the first of such cases reported in our country. Though the expected hypoglycaemia prior to the hyperglycaemia could not be documented in

this case, the transient sweating experienced by the patient during each shot of pentamidine might have been due to the early hypoglycaemia. While the 'putting on weight' by the patient before presenting in DKA might have been the evidence hyperinsulinaemic state of ongoing beta cell destruction causing the release of more insulin.

The first reporting of the association of DM with pentamidine was done by Bryceson and Woodstock more than 20 yrs ago⁴ Being highly tissue-protein bound, tissue deposition of pentamidine persists for many months enabling an ongoing cytotoxicity to the pancreatic islet cells. It has been claimed that DM with pentamidine can occur as late as two to 150 days after therapy.

CONCLUSION

In view of the severity of adverse effects of pentamidine, it seems that we should have a proper policy regarding the use of drugs in kala-azar. This holds true for the use of antimony sodium too, the optimum dose of which in the present context is to be defined and proper dose should be used for a proper duration before labelling a case to be 'Drug Resistant'.

Early reports on the alternative drugs like Aminosidine have already been published.^{5,6} This means we should have our eyes on these drugs in the search of more efficacious and less toxic drugs to our patients in future!

ACKNOWLEDGEMENTS

We acknowledge the helps provided by C.N. Chunge, college of Health Science, University of Nairobi and C.P. Thakur, Patna Medical College for providing the reports of their studies on kala-azar. We also acknowledge the Health Learning Material Project, Maharajgunj for providing the Medline search, and Prime Computers Dharma Path for helping with the computer facility.

REFERENCES

1. Anabwani GM, Ngira JA, Dimiti G, Bryceson ADM, 1983. Comparison of two dosage schedule of sod. stibogluconate *Lancet* i: 210-213.
2. Thakur CP, Kumar M, Kumar P, Mishra BN, Pandey AK, 1988. Rationalisation of regimens of treatment of kala-azar ... *BMJ* 296: 1557-1561.
3. Singh NK, Agrawal SK, Jha TK, 1989. Persistent hyperglycaemia requiring insulin therapy following the use of pentamidine in the treatment of kala-azar, 1989. *J.Assoc-Phy-India.* 37: 154-6.
4. Bryceson A, Woodstock L: The cumulative effect of pentamidine on blood sugar. *East Afr. Med. J.* 1969, 46: 170-73.
5. Chungu CN, Owate J, Pamba HO, Donno L: Treatment of v.l. in Kenya by aminosidine alone or combined with sod. stibogluconate. *Trans-R-Soc-Trop-Med-Hyg.* 1990; 84; 221-225.
6. Thakur CP et al: Treatment of v.l. with aminosidine-antimonial combinations, a pilot study in Bihar. *Trans-R-Soc-Tro-Med-Hyg.* 1992; 86; 615-16.