Hirata's disease (insulin autoimmune syndrome) following envenomation by a common krait

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Hirata's disease (insulin autoimmune syndrome) following envenomation by a common krait

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Abstract

Snakebite envenomation is known to cause local as well as systemic haematological, myotoxic and neurological effects. Adverse effects on the endocrine system following envenomation are rarely reported. Hirata's disease, also known as insulin autoimmune syndrome (IAS) is a rare disorder that causes hypoglycaemia due to excessive production of insulin autoantibodies. This report describes a rare case of IAS which developed in a snakebite victim following envenomation by a common krait and antivenom treatment. The patient was initially treated with dextrose and corticosteroids, although plasmapheresis was required to reduce the concentration of insulin antibodies and normalise the patient's glucose level. The patient then made an uneventful recovery without permanent sequelae. This report demonstrates the impacts of envenomation by a common krait on developing Hirata's disease and creates awareness among clinicians who treat snakebite envenomation.

Introduction

Snakebite envenomation (SBE) is a high priority neglected tropical disease that predominantly affects rural communities in India, as well as other parts of Asia, Africa, Central and South America [1]. SBE frequently results in local swelling, pain, and more serious systemic effects such as haemotoxic, myotoxic and neurotoxic complications. Generally, viperid envenomings present with haematological abnormalities and local tissue destruction while elapid bites primarily cause neurotoxic effects. Nevertheless, overlap does occur, and health care providers should be cautious in their assessment [2]. In addition, rare envenomation effects such as priapism, splenic rupture, pituitary failure and pseudoaneurysm may develop shortly after envenomation or subsequent to discharge and create challenges for healthcare providers [3-5]. Insulin autoimmune syndrome (IAS) or Hirata's disease, is a rare form of autoimmune hypoglycaemia which may have an insidious onset and is often difficult to diagnose [6]. It is characterised by the production of antibodies to endogenously released insulin. These antibodies initially sequester the insulin molecules and prevent their binding to the insulin receptor which manifests as hyperglycaemia. However, afterwards the antibodies release the insulin which results in hypoglycaemia [7]. Multiple triggers may induce the production of auto-insulin antibodies including medications such as methimazole and alpha-lipoic acid, as well as viral infections, and haematologic conditions such as multiple myeloma [6]. Hypoglycaemic effects typically occur post-prandially and high insulin concentrations are often reported. Here, we report a unique case of Hirata's disease which

developed in a victim 10 days after envenoming by a common krait (*Bungarus caeruleus*), one of the Indian 'Big Four' venomous snakes.

Case report

A 54-year-old female agricultural worker with an unremarkable medical history from a rural village in Tamil Nadu, South India was bitten by a common krait (*Bungarus caeruleus*) on her left foot. The identity of the offending snake was confirmed by a herpetologist by analysing the dead snake specimen which was brought to the hospital. She developed ptosis, frothing and excessive salivation. She was treated in a local primary care centre with intravenous administration of 20 vials (i.e., 200 mL) of polyvalent antivenom raised against the Indian 'Big Four' venomous snakes (Russell's viper, cobra, krait and saw scaled viper) (Bharat Serum and Vaccines Limited, India) without any adverse reactions. She was subsequently discharged four days later. Six days after discharge she began to experience dizziness, palpitations, light-headedness, and diaphoresis. She returned to the same hospital several times, where she was found to be hypoglycaemic. Her condition deteriorated and on one occasion she presented with loss-of-consciousness and was discovered to have a blood glucose of 35 mg/dL. Therefore, she was admitted in a secondary care hospital, where intravenous infusion of dextrose returned her to baseline mental status. She reported that her symptoms did not occur in the immediate post-prandial period but developed few hours after eating. The patient was started on high-dose corticosteroids empirically to treat suspected adrenal insufficiency with transient improvement in her symptoms. After discontinuation of the corticosteroids the hypoglycaemia has returned. Therefore, she was referred to a tertiary care hospital.

Here, insulinoma was suspected and additional assessments were performed. An abdominal ultrasound scan was unremarkable except for mild hepatomegaly which was deemed non-contributory for this condition. A contrast enhanced computed tomography (CT) scan (triple phase) of the upper abdomen did not reveal any masses or adrenal haemorrhage. A chest CT as well as an MRI scan of the sella turnica were also normal. The patient denied any history of diabetes mellitus, hypertension, allergic or autoimmune conditions and indicated she had no prior exposure to any exogenously administered insulin. No other medication was in use as reported by the patient. Hence, she was then referred to our hospital (21 days after the bite incident) as the previous clinicians suspected that this could be directly related to her snakebite incident.

On examination, the patient appeared well-nourished, conscious, alert, and oriented with stable haemodynamics and was maintaining adequate oxygen saturation in the room air. There was no pallor, oedema, hyperpigmentation, or outward signs of thyroid abnormalities. Her renal, thyroid, and hepatic laboratory tests as well as electrolytes and hemogram were all within normal limits. Her glycosylated haemoglobin (A1c) was 5.0%, well within the normal range (4 - 5.6%). An extended 75-gram oral glucose tolerance test (OGTT) was performed and resulted with a basal value of 78 mg/dL, a peak at 1 hour of 138 mg/dL and a four-hour level of 33 mg/dL which was the nadir. A 48-hour fasting test was performed and the patient failed to develop hypoglycaemia. However, she developed spontaneous hypoglycaemia with 40 mg/dL after eating with a measured insulin of >700 μIU/mL (normal 4 - 24 μIU/mL). The C-peptide was 1.2 ng/mL, and proinsulin of 2.7 pmol/L, both were within the normal ranges. Her fasting serum cortisol at 8 am on two consecutive days was 14.53 and 15.17 μg/dL (normal 3.7-19.4 μg/dL), respectively. Her thyroid panel tests were unremarkable with a thyroid stimulating hormone (TSH) of 2.5 μIU/mL (normal 0.4-4.2 μIU/mL), a free thyroxin (T4) of 0.92 ng/dL (normal 0.6-1.1 ng/dL), and a free triiodothyronine (T3) of 2.8 pg/mL (normal 1.7-3.7 pg/mL). Additionally, her growth hormone resulted as 5.21 ng/mL (normal up to 8 ng/mL) and her prolactin as 12.2 ng/mL (normal 2.0 - 29.0 ng/ml). Due to the elevated total insulin level and a normal anti-insulin antibody test was ordered and found it be significantly elevated with >200 U/mL (normal <0.4 U/mL). Tests were also performed for anti-thyroid and anti-nuclear antibodies as well as rheumatoid factor and all resulted negative.

As noted above, the patient was started on corticosteroids and dextrose but developed hypoglycaemia upon weaning them. Due to the failure of these interventions, along with the above laboratory results, a decision was made to treat the patient with three sessions (each session for three hours) of plasmapheresis (on 26th day from the bite incident). Subsequently, the dextrose infusions were discontinued, and the patient remained euglycemic. An insulin antibody test performed seven days after the treatment revealed that the level of insulin antibodies had decreased from >200 U/mL to 20 U/mL. After treatment the patient made an uneventful recovery without further episodes of hypoglycaemia over one year. Initially, she was monitored every week for three months, then bi-weekly for another three months and afterwards monthly for six months.

Discussion

This paper reviewed the details of a case of IAS which developed 10 days after an envenomation by a common krait in South India. The patient developed signs and symptoms typical for a common krait envenomation including ptosis and was successfully treated with polyvalent antivenom and discharged from the hospital four days after the bite. Ten days after envenomation, the patient developed episodes of hypoglycaemia, one of which resulted in loss of consciousness. Laboratory investigations were significant for post-prandial hypoglycaemia, an elevated circulating insulin level with a normal C-peptide, and the presence of insulin autoantibodies.

IAS was first reported by Hirata and colleagues in the early 1970's and has been documented in various papers since that time. Although the initial classification of the syndrome excluded exogenously administered insulin as a source of antigen, some classifications do not differentiate between the two [8, 9]. IAS does not fit within the standard definitions of the four major types of hypersensitivity reactions. In 1995, Hirata et al. suggested a new concept for a type VII reaction, however, widespread use of this designation is not evident [10]. A recent review described classifications of IAS using several different criteria. Some authors include IAS as an independent autoimmune condition while others consider it as a component of other immune disorders. An additional classification includes whether the syndrome was induced by medications or caused by an alternative mechanism [7].

Most IAS case reports have originated from Japan with a smaller number reported in China, Korea, and India. In a study of endogenous hyperinsulinemic hyperglycaemia in Japan from 2017-2018, the rate of IAS was 0.017 per 100,000 [11]. Another study reported that there were 380 published cases of IAS worldwide from 1970 through 2007 [12]. A study of patients in China revealed 73 cases of IAS over a 30-year span and 6% of 84 patients in a Korean report described the patients as having an autoimmune cause for their hypoglycaemic episodes [13, 14]. In India, only one prior case report of IAS was discovered [15]. In 2009, a study revealed limited prevalence of IAS in Western countries and only 58 cases had been reported in non-Asian patients [16].

Patients that present with IAS typically display hypoglycaemia, an elevated insulin level and detectable insulin antibodies. These antibodies, most often IgG, are thought to bind circulating insulin and prevent it from acting as a ligand for its receptor. The antibodies are thought to possess a high capacity but low affinity for the insulin molecule. This may lead to an initial episode of mild hyperglycaemia immediately after eating, however, as the low affinity binding sites release the insulin peptides, hence they are free to bind their receptors causing hypoglycaemia [7]. The underlying mechanism for the development of these autoantibodies has not been fully elucidated, however it is likely that when a genetically susceptible individual is exposed to specific external triggers, the syndrome may develop. Many of the cases have been reported in patients with certain HLA genotypes. Specifically, the HLA-DRB1*0406 allele has been strongly associated with IAS [17]. An additional type of autoimmune-related hypoglycaemia can occur in Flier's disease or type B insulin resistance in which antibodies are directed against the insulin receptor itself [6].

The development of IAS in a genetically predisposed patient often follows exposure to a precipitating trigger. Commonly recognized triggers include medications, viruses, and certain haematological conditions. Medications which are reducing agents and/or possess sulfhydryl groups have been implicated in IAS, the most common being methimazole and alpha-lipoic acid [18, 19]. In

addition to these two agents, limited reports indicate that certain antibiotics, antihypertensives, antiplatelet drugs, and proton pump inhibitors may play a role as well [7]. It is theorised that the reduction of the intramolecular disulphide bond between insulin A and B chains by these agents increases the antigenicity of the monomer molecules with subsequent production of autoantibodies [6, 20]. Potential viral causes of IAS include hepatitis C, measles, mumps, rubella, Coxsackie B, and varicella but these tend to produce IgM type antibodies [6, 21]. It is important to note that while these precipitating events have been described, it is likely that there are many that remain unrecognised.

This patient presented with variable blood glucose levels during the course of her OGTT investigation with a nadir of 33 mg/dL but no hyperglycaemia was detected. Her basal glucose was 78 mg/dL at the start of her OGTT. In a healthy patient, the OGTT test typically produces an increase in glucose around 30 minutes after ingestion with a gradual decrease to euglycemia within several hours. The patient in this study developed an initial increase for an extended period (peaking at 1 hour) but then overcorrected and became hypoglycaemic within four hours. During a normal response to hypoglycaemia, the neuroendocrine system stimulates the release of epinephrine and cortisol from the adrenal gland, glucagon from the pancreas and somatostatin from the pituitary [22]. As the OGTT did not provide enough information to diagnose this patient, additional testing was performed as noted above. Interestingly, the circulating insulin was highly elevated despite low blood glucose and a normal C-peptide. The combination of these findings may suggest that the SBE did not stimulate the pancreas to produce more insulin but may have triggered the development of insulin antibodies.

The mechanism leading to the production on insulin antibodies remains to be identified. Snake venom contain many biomolecules that may have antigenic potential. If the venom of common krait contained a molecule with a portion of its structure similar enough to that of endogenous insulin, it might be able to induce antibodies towards its epitope(s). Alternatively, venoms could contain disulphide reducing agents leading to monomer formation (as previously discussed). Indeed a previous study revealed the existence of such compounds in nature; a toxin isolated from *Escherichia coli*, thioredoxin, was able to reduce the disulphide bonds in insulin [23]. However, literature search failed to reveal evidence for venom components known to act as reducing agents that might disrupt the A and B chains of insulin. An additional consideration may be the use of antivenom to treat the initial envenomation. These products are developed via injection of venom into horses and then extracting the antibodies. While purification processes reduce the number of undesired proteins, contamination does occur in antivenom preparations. It is possible that these foreign molecules may have triggered a response which induced the development of autoantibodies. Further research on antivenom composition, purity and contaminants may demonstrate if antivenom could be a potential cause for IAS. Lastly the literature would indicate that genetic disposition, especially the presence of the HLA-DRB1*0406 allele, is associated with the development of IAS. A test for this allele was not performed in this patient.

Although IAS is typically self-limiting and drug-induced cases may resolve with discontinuation of the offending agent, various treatments have been provided in the past [9]. According to case reports, treatment of IAS has consisted of dextrose infusions, corticosteroids, somatostatin, diazoxide, azathioprine, rituximab, metformin, dietary modifications, and in severe cases, plasmapheresis [7]. In this patient, initial treatments with dextrose and corticosteroids returned the patient to euglycemia, however, the hypoglycaemia came back once these treatments were weaned. The subsequent use of plasmapheresis was rapidly effective in decreasing the autoantibody level and reversing the patient's condition. Hence, we recommend its use early as a treatment once the diagnosis has been established specifically in patients with krait envenomation. However, facilities for plasmapheresis may be limited in low- and middle-income countries. In such circumstances, the use of alternative options such as dietary modifications should be explored. This condition may also be specific only to krait envenomation, and therefore, thorough investigation is needed prior to tackling this issue with plasmapheresis in victims who are bitten by other snake species.

This case report is one of the few studies that describe IAS in India and the only one to our knowledge that has been reported after SBE. While we cannot be certain that the IAS was caused by the SBE, there are a number of potential molecules within the venom or antivenom which might have

triggered the syndrome in a genetically susceptible individual. Providers caring for patients who have experienced a recent SBE should be aware of the possibility for the development of IAS if unexplained hypoglycaemia should develop. This report aims to highlight a novel and rare complication of SBE and paves a robust management regime for patients who have suffered envenomation and develop symptoms associated with IAS. The key is to reduce the effect of IAS action through administration of drugs that decrease carbohydrate digestion and adsorption or those that limit insulin release e.g., acarbose, diazoxide, octreotide. Most importantly immediate implementation of plasmapheresis should be performed to reduce the level of insulin antibodies.

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References

1. Longbottom J, Shearer FM, Devine M, Alcoba G, Chappuis F, Weiss DJ, et al. Vulnerability to snakebite envenoming: a global mapping of hotspots. The Lancet (British edition). 2018;392(10148):673-84. doi: 10.1016/s0140-6736(18)31224-8.

2. Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA. Snakebite envenoming. Nat Rev Dis Primers. 2017;3:17063. Epub 2017/09/15. doi: 10.1038/nrdp.2017.63.

3. Senthilkumaran S, Williams HF, Patel K, Trim SA, Thirumalaikolundusubramanian P, Vaiyapuri S. Priapism following a juvenile Russell's viper bite: An unusual case report. PLoS Negl Trop Dis. 2021;15(3):e0009242. Epub 2021/03/26. doi: 10.1371/journal.pntd.0009242.

4. Bhattacharya S, Nagendra L, Tyagi P. Snakebite Envenomation and Endocrine Dysfunction. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc. Copyright © 2000-2022, MDText.com, Inc.; 2000.

5. Valenta J, Stach Z, Vagenknechtová E, Hoskovec D. Splenic Rupture and Massive Hemoperitoneum Due to Coagulopathy after Atheris Viper Snakebite. Prague Med Rep. 2021;122(3):216-21. Epub 2021/10/05. doi: 10.14712/23362936.2021.19.

6. Censi S, Mian C, Betterle C. Insulin autoimmune syndrome: from diagnosis to clinical management. Ann Transl Med. 2018;6(17):335. Epub 2018/10/12. doi: 10.21037/atm.2018.07.32.

7. Cappellani D, Macchia E, Falorni A, Marchetti P. Insulin Autoimmune Syndrome (Hirata Disease): A Comprehensive Review Fifty Years After Its First Description. Diabetes Metab Syndr Obes. 2020;13:963-78. doi: 10.2147/DMSO.S219438.

8. Su CT, Lin YC. Hyperinsulinemic hypoglycemia associated with insulin antibodies caused by exogenous insulin analog. Endocrinol Diabetes Metab Case Rep. 2016;2016. Epub 2016/12/10. doi: 10.1530/edm-16-0079.

9. Chen F, Yang J, Liu Y, Wang W, Zhu L, Wang W, et al. Insulin autoimmune syndrome: Three case reports. Medicine (Baltimore). 2018;97(51):e13486. Epub 2018/12/24. doi: 10.1097/md.0000000000013486.

10. Uchigata Y, Hirata Y, Omori Y. A novel concept of type VII hypersensitivity introduced by insulin autoimmune syndrome (Hirata's disease). Autoimmunity. 1995;20(3):207-8. Epub 1995/01/01. doi: 10.3109/08916939508993352.

11. Yamada Y, Kitayama K, Oyachi M, Higuchi S, Kawakita R, Kanamori Y, et al. Nationwide survey of endogenous hyperinsulinemic hypoglycemia in Japan (2017-2018): Congenital hyperinsulinism, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome and insulin autoimmune syndrome (Hirata's disease). J Diabetes Investig. 2020;11(3):554-63. Epub 2019/11/20. doi: 10.1111/jdi.13180.

12. Uchigata Y, Hirata Y, Iwamoto Y. Drug-induced insulin autoimmune syndrome. Diabetes Res Clin Pract. 2009;83(1):e19-20. Epub 2008/12/17. doi: 10.1016/j.diabres.2008.10.015.

13. Wang YL, Yao PW, Zhang XT, Luo ZZ, Wu PQ, Xiao F. Insulin Autoimmune Syndrome: 73 Cases of Clinical Analysis. Chin Med J (Engl). 2015;128(17):2408-9. Epub 2015/09/01. doi: 10.4103/0366-6999.163376.

14. Woo CY, Jeong JY, Jang JE, Leem J, Jung CH, Koh EH, et al. Clinical features and causes of endogenous hyperinsulinemic hypoglycemia in Korea. Diabetes Metab J. 2015;39(2):126-31. Epub 2015/04/30. doi: 10.4093/dmj.2015.39.2.126.

15. Gopal K, Priya G, Gupta N, Praveen EP, Khadgawat R. A case of autoimmune hypoglycemia outside Japan: Rare, but in the era of expanding drug-list, important to suspect. Indian J Endocrinol Metab. 2013;17(6):1117-9. Epub 2014/01/02. doi: 10.4103/2230-8210.122644.

16. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. Medicine (Baltimore). 2009;88(3):141-53. Epub 2009/05/15. doi: 10.1097/MD.0b013e3181a5b42e.

17. Uchigata Y, Kuwata S, Tokunaga K, Eguchi Y, Takayama-Hasumi S, Miyamoto M, et al. Strong association of insulin autoimmune syndrome with HLA-DR4. Lancet. 1992;339(8790):393-4. Epub 1992/02/15. doi: 10.1016/0140-6736(92)90080-m.

18. Cappellani D, Sardella C, Campopiano MC, Falorni A, Marchetti P, Macchia E. Spontaneously remitting insulin autoimmune syndrome in a patient taking alpha-lipoic acid. Endocrinol Diabetes Metab Case Rep. 2018;2018. Epub 2018/12/12. doi: 10.1530/edm-18-0122.

19. Hirata Y. Methimazole and insulin autoimmune syndrome with hypoglycemia. Lancet. 1983;2(8357):1037-8. Epub 1983/10/29. doi: 10.1016/s0140-6736(83)91031-0.

20. Matsushita S, Takahashi K, Motoki M, Komoriya K, Ikagawa S, Nishimura Y. Allele specificity of structural requirement for peptides bound to HLA-DRB1*0405 and -DRB1*0406 complexes: implication for the HLA-associated susceptibility to methimazole-induced insulin autoimmune syndrome. J Exp Med. 1994;180(3):873-83. Epub 1994/09/01. doi: 10.1084/jem.180.3.873.

21. Bodansky HJ, Grant PJ, Dean BM, McNally J, Bottazzo GF, Hambling MH, et al. Islet-cell antibodies and insulin autoantibodies in association with common viral infections. Lancet. 1986;2(8520):1351-3. Epub 1986/12/13. doi: 10.1016/s0140-6736(86)92003-9.

22. Cryer PE. Hierarchy of physiological responses to hypoglycemia: relevance to clinical hypoglycemia in type I (insulin dependent) diabetes mellitus. Horm Metab Res. 1997;29(3):92-6. Epub 1997/03/01. doi: 10.1055/s-2007-978997.

23. Holmgren A. Thioredoxin catalyzes the reduction of insulin disulfides by dithiothreitol and dihydrolipoamide. J Biol Chem. 1979;254(19):9627-32. Epub 1979/10/10.