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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

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

47

48 Case report

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

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

75 On examination, the patient appeared well-nourished, conscious, alert, and oriented with stable
76 haemodynamics and was maintaining adequate oxygen saturation in the room air. There was no pallor,
77 oedema, hyperpigmentation, or outward signs of thyroid abnormalities. Her renal, thyroid, and hepatic
78 laboratory tests as well as electrolytes and hemogram were all within normal limits. Her glycosylated
79 haemoglobin (A1c) was 5.0%, well within the normal range (4 - 5.6%). An extended 75-gram oral
80 glucose tolerance test (OGTT) was performed and resulted with a basal value of 78 mg/dL, a peak at 1
81 hour of 138 mg/dL and a four-hour level of 33 mg/dL which was the nadir. A 48-hour fasting test was
82 performed and the patient failed to develop hypoglycaemia. However, she developed spontaneous
83 hypoglycaemia with 40 mg/dL after eating with a measured insulin of >700 μ U/mL (normal 4 - 24
84 μ U/mL). The C-peptide was 1.2 ng/mL, and proinsulin of 2.7 pmol/L, both were within the normal
85 ranges. Her fasting serum cortisol at 8 am on two consecutive days was 14.53 and 15.17 μ g/dL (normal
86 3.7-19.4 μ g/dL), respectively. Her thyroid panel tests were unremarkable with a thyroid stimulating
87 hormone (TSH) of 2.5 μ IU/mL (normal 0.4-4.2 μ IU/mL), a free thyroxine (T4) of 0.92 ng/dL (normal 0.6-
88 1.1 ng/dL), and a free triiodothyronine (T3) of 2.8 pg/mL (normal 1.7-3.7 pg/mL). Additionally, her growth
89 hormone resulted as 5.21 ng/mL (normal up to 8 ng/mL) and her prolactin as 12.2 ng/mL (normal 2.0 -
90 29.0 ng/ml). Due to the elevated total insulin level and a normal anti-insulin antibody test was ordered
91 and found it be significantly elevated with >200 U/mL (normal <0.4 U/mL). Tests were also performed
92 for anti-thyroid and anti-nuclear antibodies as well as rheumatoid factor and all resulted negative.

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

102 Discussion

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

110 IAS was first reported by Hirata and colleagues in the early 1970's and has been documented in
111 various papers since that time. Although the initial classification of the syndrome excluded exogenously
112 administered insulin as a source of antigen, some classifications do not differentiate between the two
113 [8, 9]. IAS does not fit within the standard definitions of the four major types of hypersensitivity reactions.
114 In 1995, Hirata et al. suggested a new concept for a type VII reaction, however, widespread use of this
115 designation is not evident [10]. A recent review described classifications of IAS using several different
116 criteria. Some authors include IAS as an independent autoimmune condition while others consider it as
117 a component of other immune disorders. An additional classification includes whether the syndrome
118 was induced by medications or caused by an alternative mechanism [7].

119 Most IAS case reports have originated from Japan with a smaller number reported in China,
120 Korea, and India. In a study of endogenous hyperinsulinemic hyperglycaemia in Japan from 2017-2018,
121 the rate of IAS was 0.017 per 100,000 [11]. Another study reported that there were 380 published cases
122 of IAS worldwide from 1970 through 2007 [12]. A study of patients in China revealed 73 cases of IAS
123 over a 30-year span and 6% of 84 patients in a Korean report described the patients as having an
124 autoimmune cause for their hypoglycaemic episodes [13, 14]. In India, only one prior case report of IAS
125 was discovered [15]. In 2009, a study revealed limited prevalence of IAS in Western countries and only
126 58 cases had been reported in non-Asian patients [16].

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

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

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

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

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

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

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

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

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