CASE REPORT

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# Hirata's Disease: A Case Report

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**Abstract**

Insulin Autoimmune Syndrome (IAS), also known as Hirata's disease, is a rare endocrine disorder characterized by recurrent hypoglycemia due to endogenous hyperinsulinemia and the presence of insulin autoantibodies (IAAs). We report a case of IAS successfully treated with corticosteroid therapy. Notably, the definitive diagnosis was established only during the second hospitalization, after multiple recurrent hypoglycemic episodes. The delayed diagnosis reflects the nonspecific presentation and the low initial suspicion for autoimmune hypoglycemia. In the first admission, although insulinoma had been excluded, the patient was discharged without a confirmed diagnosis. This case highlights the importance of early insulin autoantibody testing in patients with unexplained endogenous hyperinsulinemic hypoglycemia to prevent diagnostic delay and unnecessary investigations. Initial evaluation prioritized exclusion of insulinoma, the most common cause of endogenous hyperinsulinemic hypoglycemia, before autoimmune testing was pursued.

*Key words: Insulin Autoimmune Syndrome, Hirata's disease, hypoglycemia*

## INTRODUCTION

Endogenous hyperinsulinemic hypoglycemia (EHH) is a condition characterized by low blood glucose levels resulting from excessive endogenous insulin secretion. The diagnosis of clinically significant hypoglycemia relies on Whipple's triad, which includes: (1) Symptoms consistent with hypoglycemia; (2) Documented low plasma glucose concentration; and (3) Relief of symptoms after glucose administration. Once Whipple's triad is fulfilled, biochemical evaluation is required to determine the underlying etiology. Endogenous hyperinsulinemic hypoglycemia is established when plasma insulin exceeds 3 μIU/mL, plasma C-peptide is greater than 0.6 ng/mL, and plasma glucose is less than 3.0 mmol/L.[1] Severe hypoglycemia due to EHH can significantly impair quality of life and may be life-threatening. The main causes of EHH include insulinoma, Insulin Autoimmune Syndrome (IAS), and type B insulin resistance syndrome (TBIRS), among which insulinoma is the most common etiology.[2] IAS, also known as Hirata's disease, was first described by Yukimasa Hirata and colleagues in Japan in 1970.[3] IAS represents an exceptionally uncommon condition in the general population. In Japan, the estimated incidence is approximately 0.017 cases per 100,000 population per year.[4] In China, despite its very large population, only a few dozen cases have been reported over several decades (84 cases within 30 years).[5] With increasing awareness, more cases have been found in Western countries.[4]

Due to its rarity and overlapping features with insulinoma, IAS is often misdiagnosed or diagnosed at a late stage. In Vietnam, Vu Bich Nga et al., reported a case of delayed diagnosis of IAS, initially mistaken for insulinoma.[6] Such diagnostic errors emphasize the need to raise awareness of this rare disorder. Herein, we present a case of IAS in a patient with recurrent hypoglycemia, emphasizing the importance of early recognition of endocrine causes to prevent diagnostic delay and guide appropriate management.

## CASE

We report the case of a 64-year-old retired male who presented with repeated episodes of hypoglycemia. During the attacks, he typically experienced marked hunger, tremors of the extremities, and palpitations.

The patient had suffered from recurrent hypoglycemia since 2019 and was initially evaluated at another medical facility. A prolonged 72-hour fasting test was conducted but failed to reproduce a hypoglycemic event. Assessment at that time focused on excluding insulinoma. Given the rarity of insulin autoimmune syndrome and its overlapping clinical features with insulinoma, autoimmune causes were not prioritized. He was subsequently referred to our tertiary endocrine center for further evaluation. He had no past history of hepatic or renal disease. A detailed medication history revealed no exposure to sulfhydryl–

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**Table 1.** Biochemical findings during hypoglycemic episode

| Test | Value | Reference range |
|---|---|---|
| ***Glucose (mmol/L)*** | 2.05 | 3.9 – 5.6 |
| ***Insulin (µIU /mL)*** | 4128.6 | 2.6 – 24.9 |
| ***C peptide (ng/mL)*** | 8.69 | 0.78 – 5.19 |
| ***IAA (%)*** | 80.2 | <7 |
| ***HbA1c (%)*** | 5.5 | 4-6.2 |
| ***Cortisol 8h (nmol/L)*** | 255 | 166-507 |
| ***GOT (U/l)*** | 37 | 11-34 |
| ***GPT (U/l)*** | 43 | <45 |
| ***Creatinin (µmol /L)*** | 73 | 64-100 |

**Table 2.** HLA typing results

| Locus | Alleles |
|---|---|
| ***HLA-DRB1**** | 04:05/04:06 |
| ***HLA-DQA1**** | 03:01/03:01 |
| ***HLA-DQB1**** | 03:02/04:02 |

containing medications, including methimazole, captopril or alpha-lipoic acid. Drug-induced IAS has been reported in association with medications such as carbimazole.[7] The patient had never received insulin therapy or oral hypoglycemic agents, particularly sulfonylureas. Although biochemical screening for sulfonylurea exposure was not available, detailed medication history did not suggest exogenous hypoglycemic agent use. Screening for associated autoimmune disorders was performed with negative results, including antinuclear antibodies (ANA), anti-double-stranded DNA antibodies, rheumatoid factor (RF) and thyroid function tests, all within normal limits.

On admission, he was fully conscious and interactive, and no abnormal findings were noted on physical examination. His hypoglycemic events generally developed in the post-absorptive period, with a frequency of three to four episodes per day, occurring consistently over the last six years.

Biochemical testing during a symptomatic episode demonstrated a plasma glucose level of 2.05 mmol/L, a C-peptide concentration of 8.69 ng/mL (reference 0.78–5.19), and a markedly elevated insulin level of 4128.6 µIU/mL (reference 2.6–24.9), confirming endogenous hyperinsulinemic hypoglycemia (Table 1). Urine ketones were negative during the hypoglycemic episode, consistent with suppressed ketogenesis in the setting of hyperinsulinemia. Further evaluation to exclude alternative causes of hypoglycemia showed that morning serum cortisol was within normal limits, making adrenal insufficiency unlikely. Abdominal computed tomography did not reveal any pancreatic mass. Magnetic resonance imaging could not be performed due to cervical spine fixation hardware. In accordance with the common diagnostic approach prioritizing exclusion of insulinoma – the most frequent cause of EHH, imaging was undertaken before autoimmune testing. Subsequent immunological analysis revealed a striking elevation of insulin autoantibodies (IAA 80.2%, normal <7%). Taken together, the presence of endogenous hyperinsulinemia, the absence of pancreatic neoplasm on imaging, and the high titer of IAA supported the diagnosis of Insulin Autoimmune Syndrome (Hirata's disease).

To further investigate a potential genetic predisposition, high-resolution HLA class II typing was performed using PCR–sequence-specific oligonucleotide (PCR-SSO) methods. The analysis revealed the presence of HLA-DRB1*04:06, along with HLA-DQA1*03:01 and HLA-DQB1*03:02/04:02 alleles, which have been previously reported to be associated with Insulin Autoimmune Syndrome (Table 2).

Therapeutically, the patient was first managed with an alpha-glucosidase inhibitor (50 mg three times daily before meals), but no clinical improvement was observed. Corticosteroid therapy with methylprednisolone was subsequently initiated at 32 mg daily and gradually tapered by 4 mg each month, leading to a marked reduction in the frequency and severity of hypoglycemic episodes. At one-year follow-up, the patient remained in good clinical condition with stable glycemic control while continuing on a low maintenance dose of methylprednisolone at 4 mg daily. Insulin autoantibody titers were not serially monitored during follow-up. However, the sustained clinical improvement after initiation of corticosteroid therapy supported an immune-mediated mechanism. Given the prolonged six-year history of recurrent hypoglycemia prior to treatment, spontaneous remission appeared unlikely in this case. The patient was maintained on a low dose of methylprednisolone and was closely monitored for potential steroid-related adverse effects, with no significant complications observed during follow-up.

## DISCUSSION

Insulin Autoimmune Syndrome (IAS), also known as Hirata's disease, is a rare but clinically significant cause of endogenous hyperinsulinemic hypoglycemia. Although insulinoma remains the most common etiology of endogenous hyperinsulinism, IAS should be considered after pancreatic tumors have been excluded. This case is notable for its prolonged clinical course, atypical diagnostic features, and delayed diagnosis, highlighting the challenges of recognizing IAS in routine clinical practice.

Our patient experienced recurrent hypoglycemic episodes for approximately six years before a definitive diagnosis was established. Although insulinoma had been excluded during the first hospitalization, the absence of a confirmed alternative diagnosis resulted in delayed identification of the underlying cause. This prolonged diagnostic process reflects a common pitfall in clinical practice, in which

IAS may be overlooked after structural pancreatic disease has been ruled out and autoimmune etiologies are not adequately considered. Similar diagnostic delays have been reported previously. In a Southeast Asian case series, several patients with Insulin Autoimmune Syndrome were initially investigated for insulinoma before insulin autoantibodies were identified, underscoring the need to consider IAS after pancreatic tumors have been excluded.[8]

The pathophysiology of IAS involves sequestration of endogenous insulin by circulating autoantibodies after meals, followed by unregulated delayed insulin release, leading to late postprandial hypoglycemia.[4] In this case, a previously performed 72-hour fasting test failed to provoke hypoglycemia, a finding that is uncharacteristic of insulinoma and more consistent with IAS. As reported in the literature, hypoglycemia associated with IAS tends to occur predominantly in the postprandial or late post-absorptive period rather than during prolonged fasting. IAS is characterized by circulating insulin autoantibodies that bind endogenous insulin and cause its unpredictable release. This leads to disproportionately elevated measured insulin levels relative to C-peptide, often resulting in a high insulin-to-C-peptide ratio, which helps distinguish IAS from insulinoma. In our patient, the markedly elevated insulin level compared with the moderately increased C-peptide supported this mechanism.

Type B insulin resistance syndrome (TBIRS) should also be considered in antibody-mediated insulin disorders. However, TBIRS is typically characterized by severe insulin resistance and hyperglycemia due to anti-insulin receptor antibodies. In contrast, our patient presented with recurrent hypoglycemia without features of severe insulin resistance, findings more consistent with IAS.

Measurement of insulin autoantibodies (IAA) played a decisive role in establishing the diagnosis in this patient. The markedly elevated IAA level, together with biochemical evidence of endogenous hyperinsulinemia and the absence of a pancreatic mass on imaging, was sufficient to confirm IAS and avoid unnecessary invasive investigations.

The management of IAS differs fundamentally from that of insulinoma because the underlying mechanism is immune-mediated rather than tumor-related. Initial treatment strategies typically include dietary modification and agents aimed at reducing postprandial glucose excursions. In our patient, therapy with an alpha-glucosidase inhibitor was ineffective. In contrast, corticosteroid treatment resulted in rapid and sustained improvement in glycemic control. Glucocorticoids are thought to suppress autoantibody production and reduce insulin variability, thereby alleviating hypoglycemic episodes. In a case series of Hirata syndrome by Mudagall et al., corticosteroid therapy was also shown to improve hypoglycemic episodes.[8]

Although IAS is often described as self-limiting, with spontaneous resolution reported in 80-82% of cases, our patient had experienced recurrent hypoglycemia for six years prior to diagnosis, making spontaneous remission unlikely. The marked clinical improvement and sustained control achieved with a low maintenance dose of methylprednisolone suggest that corticosteroid therapy can be an appropriate option in prolonged and symptomatic cases. Similar clinical characteristics and favorable responses to corticosteroid therapy have been reported in recent case series, including the study by Mudagall et al., which further supports the role of immunomodulatory treatment in selected patients with Hirata syndrome.[8]

Genetic susceptibility plays an important role in the pathogenesis of Insulin Autoimmune Syndrome (IAS), with established associations between IAS and specific HLA class II alleles, particularly HLA-DRB1*04:06 and HLA-DRB1*04:03, which are prevalent in East Asian populations.[4,9] In the present case, high-resolution HLA typing identified HLA-DRB1*04:05/04:06, HLA-DQA1*03:01/03:01 and HLA-DQB1*03:02/04:02. The presence of HLA-DRB1*04:06, together with HLA-DQA1*03:01 and HLA-DQA1*03:02, is consistent with the HLA class II allele combination previously associated with IAS. Although HLA typing is not routinely required for the diagnosis of IAS, these findings provided additional supportive evidence for an immune-mediated mechanism and helped strengthen the diagnosis in the context of a prolonged and atypical clinical course.

IAS has been reported more frequently in East Asian populations, particularly in Japan and China, whereas published cases from Vietnam remain scarce.[4,5] Recent reports from Southeast Asia, including a case series by Mudagall et al., have also highlighted the clinical heterogeneity of IAS and the need for increased clinical awareness in the region.[8] This case contributes to the limited regional data and demonstrates clinical features and treatment responses consistent with previous reports. These findings underscore the importance of increasing clinical awareness and considering early IAA testing in patients with unexplained endogenous hyperinsulinemic hypoglycemia after insulinoma has been excluded, in order to prevent diagnostic delay and unnecessary investigations.

## CONCLUSION

Insulin Autoimmune Syndrome is a rare but important cause of endogenous hyperinsulinemic hypoglycemia that may be easily overlooked. This case underscores the need to consider autoimmune causes and to measure insulin autoantibodies early in patients with unexplained hypoglycemia after insulinoma has been excluded. Timely diagnosis allows appropriate treatment, with corticosteroids providing effective and sustained glycemic control.

**Ethical Consideration**

Patient's consent was obtained before submission of the manuscript.

**Statement of Authorship**

All authors certified fulfillment of the ICMJE authorship criteria.

**CRediT Author Statement**

**QTL:** Writing – review and editing; **TTN, LTV, NBL, LTTN:** Investigation; **NHTP, MVN:** Visualization.

**Data Availability Statement**

The data supporting the findings of this case report are included within the article. Additional data are not publicly available due to patient confidentiality.

**Author Disclosure**

The authors declared no conflict of interest.

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