


## CASE REPORT

# Hypoglycemia secondary to insulinoma masking the onset of type 1 diabetes in an adolescent

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## Abstract

Type 1 diabetes and insulinoma can co-occur in pediatric patients and may present with episodes of hypo- and hyperglycemia, significant glycemic variability, and weight gain. Surgical resection leads to development of fulminant diabetes.

## KEYWORDS

autoantibodies, diabetes mellitus, hypoglycemia, insulinoma, type 1 diabetes

## 1 | INTRODUCTION

We report the co-occurrence of insulinoma and type 1 diabetes (T1D) in the youngest known patient—the presence of opposing pathologies obscured typical clinical presentations. Development of fulminant T1D was anticipated with insulinoma resection, and as such, T1D-related surgical complications were prevented. Longitudinal assessment and data re-evaluation are critical.

Insulinomas are well-differentiated pancreatic neuroendocrine tumors (NET) and are rare causes

of hypoglycemia, especially in children.<sup>1</sup> Type 1 diabetes (T1D) has been associated with a prodrome of hypoglycemia, attributable to delayed insulin secretion.<sup>2,3</sup> Natural history studies have elucidated three stages of T1D that begin with pancreatic autoantibody positivity in the setting of euglycemia.<sup>4</sup> Progression to stage 2 occurs when there is evidence of dysglycemia in the absence of symptomatology. Stage 3 represents symptomatic hyperglycemia. Patients progress with variable speed, dictated by the interaction of genetics and environment.<sup>4</sup>

Sriya Subramani has since relocated to Seattle Children's Hospital to continue her training.

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We describe the case of an adolescent male who presented with acute altered mental status secondary to hyperinsulinemic hypoglycemia. Evaluation revealed both stage 2 T1D and an insulinoma. This case is the youngest described co-occurrence of T1D and insulinoma and highlights the importance of thorough data evaluation to ensure that antagonist processes do not mask the complete diagnosis. This case also demonstrates beta-cell destruction and inflammation adjacent to neuroendocrine proliferation, which may have implications for the prevention and treatment of T1D.

## 2 | CASE HISTORY/ EXAMINATION

A 17-year-old previously healthy male presented to the emergency department due to acute altered mental status. Initial laboratories demonstrated a low blood glucose (BG) of 1.8 mmol/L (reference range 3.6–7.7 mmol/L), and he received 1 ml/kg intravenous 50% dextrose solution (D50W). Repeat BG twelve minutes later was 5.4 mmol/L. BG continued to rise for three hours, peaking at 12.1 mmol/L. Mental status improved after dextrose administration.

His past medical history is pertinent for attention deficit hyperactivity disorder for which he took dextroamphetamine-amphetamine. Family history is relevant for autoimmune thyroid disease in his mother and father. Initial workup included thyroid studies and urine drug screen. Thyroid-stimulating hormone (TSH) was normal. Urine drug screen returned presumptive positive for tetrahydrocannabinol (THC), and he endorsed using marijuana 48 hours prior to presentation. A sulfonylurea screen drawn at presentation was negative.

## 3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATIONS, AND INITIAL TREATMENT

He was admitted and made nil per os (NPO). BGs were monitored every 1–2 h (Figure 1). His BG dropped to 2.1 mmol/L ten hours into the fast. A critical sample was obtained which was notable for a total insulin level of 158.35 pmol/L (reference range 18.06–172.93 pmol/L) and c-peptide level of 1.09 nmol/L (0.36–1.46 nmol/L), both inappropriately elevated relative to his low BG. Beta-hydroxybutyrate was suppressed. Adrenocorticotrophic hormone (ACTH), cortisol, growth hormone, and the remainder of critical sample laboratories were appropriate for clinical context (Table 1). He received a second dose

of 1 ml/kg D50W, and dextrose-containing fluids were titrated to maintain euglycemia overnight. After initiation of a general diet, BGs were assessed every two hours and ranged from 2.9–9.1 mmol/L.

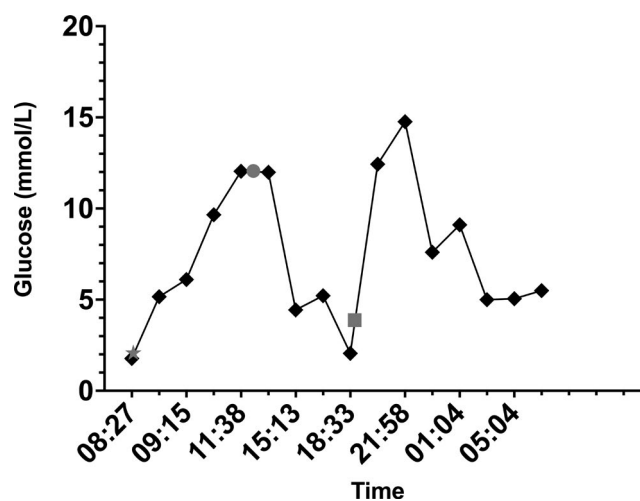
Pancreatic autoantibodies (insulin, IgG Islet Cell, Islet Antigen 2, Glutamic Acid Decarboxylase) were obtained due to suspicion of insulin autoimmune syndrome or T1D, given the evidence of reactive hyperglycemia, generous post-prandial blood glucoses, and family history of autoimmune thyroid disease.<sup>5</sup> All pancreatic antibody levels returned positive, and he was given a diagnosis of stage 1 type 1 diabetes. Abdominal ultrasound was obtained to assess for presence of a pancreatic mass and was read as normal.

Glucagon administration, self-monitoring of blood glucose (SMBG) teaching, and nutrition education were completed, and he was discharged after three days.

## 4 | OUTCOME AND FOLLOW-UP

He subsequently enrolled in TrialNet Pathway to Prevention and tested positive for five pancreatic autoantibodies (islet cell antibody—ICA, glutamic acid decarboxylase antibody 65kd—GAD65, islet cell autoantibody 512—ICA512, micronized insulin autoantibody—mIAA, and zinc transporter 8—ZnT8).<sup>6</sup> See Table 2 for a summary of all islet antibodies obtained over the clinical course.

He was instructed to continue SMBG three times per day, which demonstrated modest hyperglycemia with hypoglycemia predominance (Table 3). Approximately three



**FIGURE 1** This figure demonstrates the evolution in response to stimuli during his hospitalization and shows hypoglycemia with fasting as well as reactive hyperglycemia. Star signifies when patient was given D50. Circle signifies start of NPO. Square signifies second D50 administration with start of D10 infusion

**TABLE 1** Inclusive list of all laboratory tests sent as part of the critical sample (when plasma glucose was 2.0 mmol/L) and their corresponding reference ranges

Laboratory test	Patient's value	Reference range
ACTH	5.06 pmol/L	1.32–12.10 pmol/L
Anion Gap	15 mmol/L	<17 mmol/L
Acylcarnitine profile	Normal profile	Normal profile
Ammonia	19 umol/L	21–50 umol/L
Bicarbonate	23 mmol/L	22–29 mmol/L
Beta-hydroxybutyrate	0.3 mmol/L†	0.0–0.3 mmol/L
C-peptide	1.09 nmol/L*	0.36–1.46 nmol/L
Cortisol	311.74 nmol/L	74.49– 507.62 nmol/L (random timed)
Free fatty acids	0.8 mmol/L†	*No reference for <18yo
Growth Hormone	5.69 ug/L	0.08–10.80 ug/L
Insulin	158.35 pmol/L*	0.56–172.93 pmol/L
Lactate	0.6 mmol/L	0.5–2.2 mmol/L
Plasma amino acids	Normal profile	Normal profile

Values denoted with an asterisk are inappropriately elevated relative to the clinical context (ie, hypoglycemia), and the values denoted with a † are relatively low for the clinical context. All other values are within normal limits.

**TABLE 2** Islet autoantibody status

Islet antibody	Date obtained	Patient's value	Reference range	Interpretation
Insulin antibody*	5/14/2020	0.7 U/ml	0–0.4 U/L	Positive
mIAA (micronized insulin) †	6/3/2020	0.038	≤0.010	Positive
mIAA †	7/24/2020	0.054	≤0.010	Positive
Insulin antibody‡	3/19/2021	28.6	0–0.4 U/L	Positive
Islet cell antibody (IgG)*	5/14/2020	1:16	<1:4	Positive
Islet cell antibody†	6/3/2020	160	<10	Positive
Islet cell antibody†	7/24/2020	320	<10	Positive
Islet cell antibody (IgG) ‡	3/19/2021	<1:4	<1:4	Negative
Glutamic acid decarboxylase*	5/14/2020	>250 IU/ml	0.0–5.0 IU/ml	Positive
Glutamic acid decarboxylase†	6/3/2020	663	≤20	Positive
Glutamic acid decarboxylase†	7/24/2020	760	≤20	Positive
Glutamic acid decarboxylase‡	3/19/2021	>250 IU/ml	0.0–5.0 IU/ml	Positive
Islet antigen 2*	5/14/2020	>120 U/ml	0.0–7.4 U/ml	Positive
ICA512/IA–2H†	6/3/2020	382	≤5	Positive
ICA512/IA–2H†	7/24/2020	385	≤5	Positive
Islet antigen 2‡	3/19/2021	>120 U/ml	0.0–7.4 U/ml	Positive
ZnT8†	6/3/2020	0.3310	≤0.020	Positive
ZnT8†	7/24/2020	0.3630	≤0.020	Positive
ZnT8‡	3/19/2021	>500	0–15 KU/ml	Positive

All 4 antibodies sent during the initial inpatient admission were positive and are denoted with \*. The second and third sets were obtained as part of TrialNet and are denoted with †. ‡ denotes testing sent 4 months after surgical resection of mass and initiation of insulin therapy. The only antibody that became negative after surgical resection was Islet Cell IgG.

months after hospital discharge, the patient underwent an oral glucose tolerance test (OGTT) (Figure 2), which demonstrated a 1-h BG of 12.0 mmol/L and a 2-h BG of 11.1 mmol/L, indicative of significant impairment in glucose tolerance (stage 2 T1D) and imminent risk to progress to clinically evident T1D.<sup>7</sup>

Over the next month, the patient had significant weight gain. He discontinued SMBG, so a continuous glucose monitor (CGM) was placed. CGM demonstrated patterns of prolonged fasting hypoglycemia juxtaposed with hyperglycemia (Figure 3). HbA1c increased from 28 mmol/mol (4.7%) at presentation to 37 mmol/mol (5.5%) (reference 29–42 mmol/mol). Abdominal magnetic resonance imaging (MRI) was obtained due to suspicion that the patient's dysglycemia was not solely attributable to the beta-cell dysfunction that can be noted in stage 2 T1D.<sup>2,3,8</sup> MRI demonstrated a 1.9 × 1.3 cm solid lesion in the tail of the pancreas (Figure 4A–D). Compared to the normal pancreatic parenchyma, the lesion showed low signal intensity (dark) on T1W images and high signal intensity (bright) on T2W images. After IV contrast enhancement using gadolinium, there was decreased contrast differentiation between the lesion and the normal parenchyma in both arterial and venous phases.

He subsequently underwent endoscopic fine-needle biopsy. Cytopathology confirmed the presence of a somatostatin-receptor 2a (SSTR2a) positive, well-differentiated NET (KI-67 proliferation index 13.6%) lesion. Serum chromogranin A, pancreastatin, and gastrin levels were normal. Serotonin was slightly elevated (1.61  $\mu\text{mol/L}$ , reference 0.28–1.14  $\mu\text{mol/L}$ ). Pre-biopsy laboratories demonstrated fasting hyperglycemia (17.7  $\text{mmol/L}$ ) with elevated fasting insulin (341.0  $\text{pmol/L}$ ) and c-peptide levels (1.39  $\text{nmol/L}$ ) without evidence of ketosis.

He underwent T1D education, as it was anticipated that he would develop insulinopenia after removal of his endogenous insulin source. The patient developed persistent hyperglycemia and ketonuria without acidosis within five hours of surgical resection. C-peptide level was inappropriately low (0.33  $\text{nmol/L}$ ) with hyperglycemia (17.0  $\text{mmol/L}$ ). Insulin therapy was initiated, and he was discharged on a total daily insulin dose of 0.6 U/kg/day. One-month post-resection, his HbA1c was 50  $\text{mmol/mol}$  (6.7%) on 0.7 U/kg/day. Non-tumorous peripancreatic tissue demonstrated classic histologic findings of T1D, including inflammatory infiltration around the residual islets (Figure 5A–J).<sup>9</sup> Quantitative evaluation of 50 islets revealed that 11/50 (22%) showed insulinitis, 50/50 (100%) expressed glucagon, and 6/50 (12%) expressed insulin.

Genetic testing was completed via the Detect Hereditary Pancreatic Cancer Program, which includes *MEN1*, *NF1*, *VHL*, *TSC1*, and *TSC2*. Testing returned negative except a heterozygous variant of unknown significance in *RECQL4* c.2069 C>T. Human leukocyte antigen (HLA) genotyping demonstrated the presence of one high-risk T1D class 2 haplotype, DR4, in the context of six total risk-associated class 2 alleles (five unique alleles, with two copies of the *DQA1\*03:01* allele). There were no protective *DRB1*, *DQB1*, or *DPB1* alleles present.<sup>10–12</sup> (Supplemental Table 1).

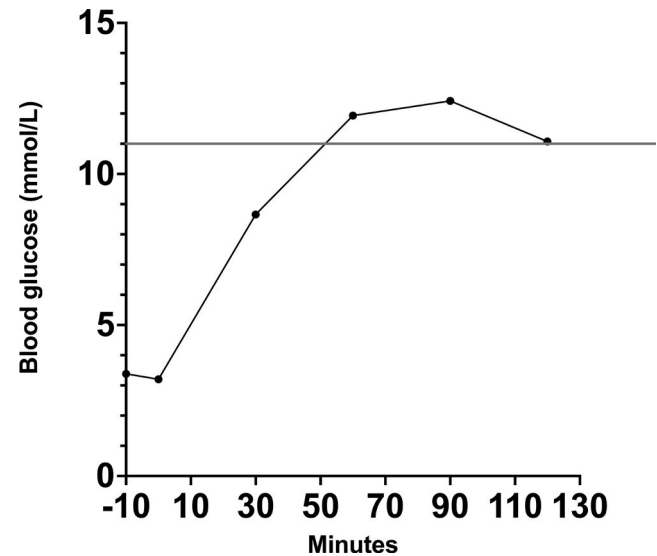
**TABLE 3** SMBG readings from hospital discharge (May 2020) to second clinic follow-up (September 2020)

Average BG (mmol/L)	4.7 $\text{mmol/L}$
Coefficient of variation	36%
Percent of BG below 3.0 $\text{mmol/L}$	10%
Percent of BG between 3.0–3.9 $\text{mmol/L}$	31%
Percent of BG between 10–13.9 $\text{mmol/L}$	2%
Percent of BG above 13.9 $\text{mg/dl}$	0%

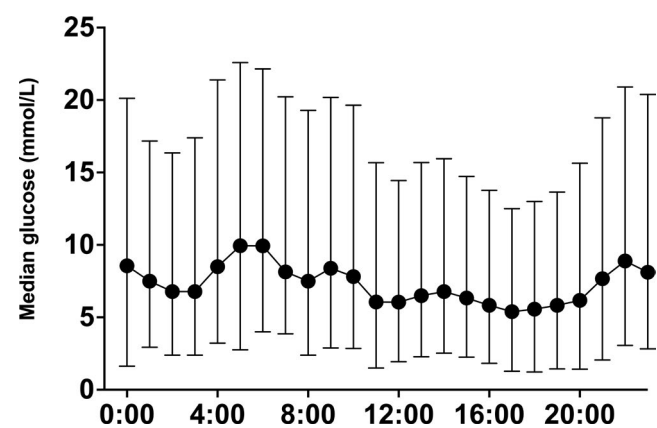
This reflects a total of 94 SMBG readings. Adherence to SMBG declined over time, initially testing 4–5 times per day but then only testing with symptoms. Only one blood glucose value was obtained between the beginning of August 2020 and the middle of September 2020, which was 5.3  $\text{mmol/L}$ . Subsequently, the decision to begin CGM monitoring was made.

## 5 | DISCUSSION

This previously healthy 17-year-old male met the criteria for Whipple's triad [signs/symptoms of hypoglycemia, low plasma glucose, resolution of signs/symptoms of hypoglycemia after hypoglycemia correction].<sup>13</sup> The differential diagnosis for hypoglycemia in an adolescent is broad and falls into many overarching categories including metabolic



**FIGURE 2** Oral glucose tolerance test. The patient demonstrated significant glucose intolerance to 75 g glucola OGTT. The 2-hour blood glucose value of 11.1  $\text{mmol/L}$  was at the 2-h diagnostic cut point for diabetes mellitus and is depicted by the horizontal line



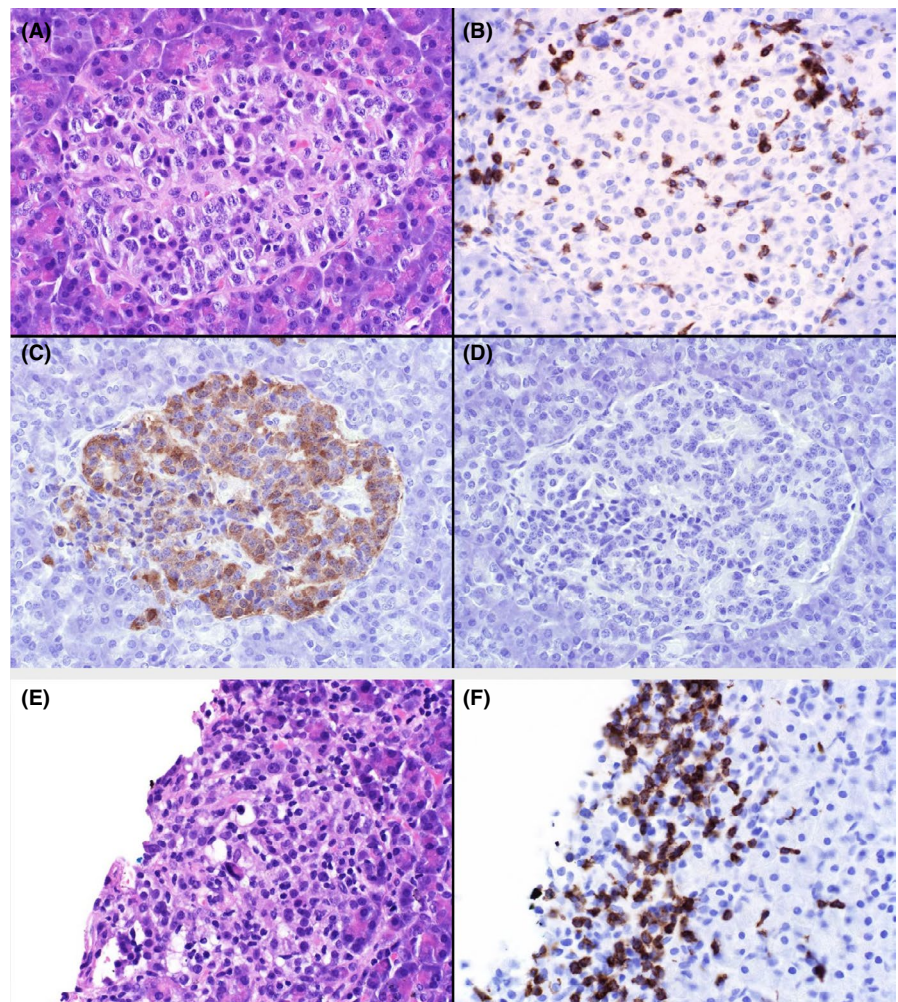
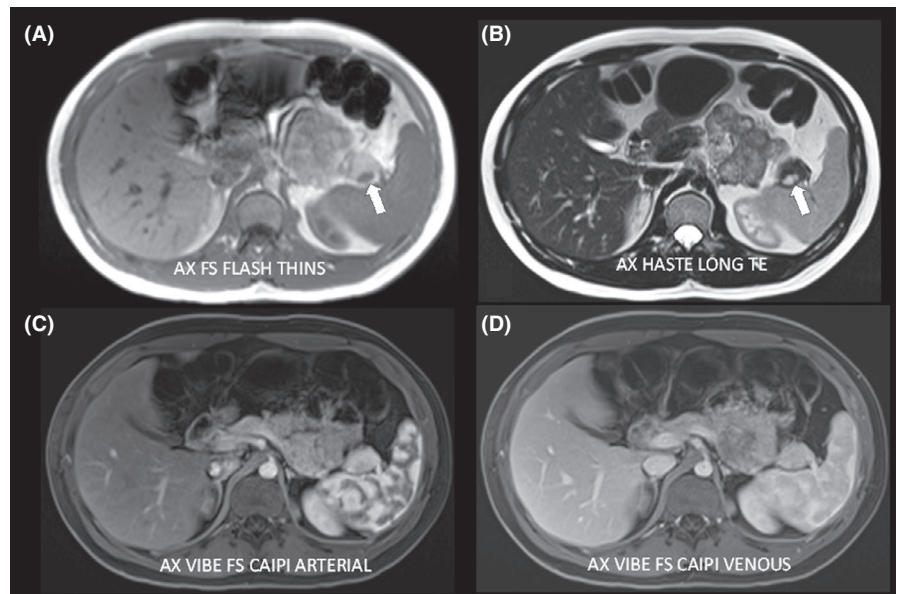
**FIGURE 3** Preoperative CGM values. Curve represents glucose frequency distribution by time. Median values with the IQR are plotted on graph. The patient's average CGM reading for the 42 days prior to surgery was 7.9  $\text{mmol/L}$  with a predicted HbA1c of 50  $\text{mmol/mol}$  (6.7%). 19.9% of CGM glucoses were less than 3.3  $\text{mmol/L}$ , with 5% time less than 3.0  $\text{mmol/L}$ . 26% of values were above 10  $\text{mmol/L}$ , with almost 10% of values above 13.9  $\text{mmol/L}$ . This is an aggregate of 11,087 CGM data points

disorders, drugs, critical illness, hormone deficiency, and endogenous hyperinsulinism.<sup>14</sup>

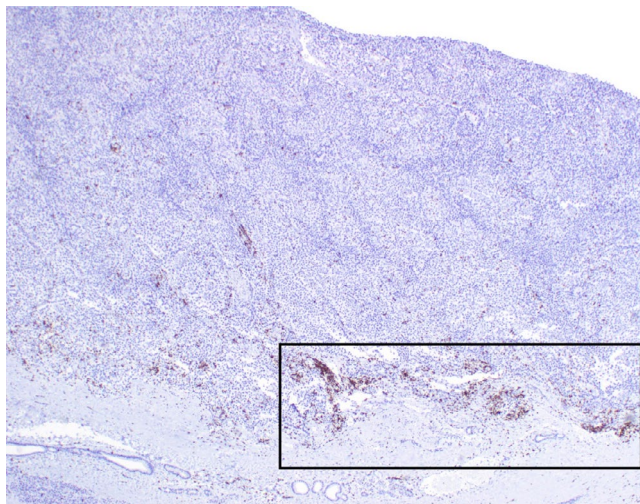
The patient's insulin secretagogue screen returned negative, and while his urine drug screen returned presumptive

positive for THC, there is no literature to suggest that THC induces hypoglycemia. Exogenous insulin administration can induce hypoglycemia; however, the insulin and c-peptide levels both returned relatively elevated.

**FIGURE 4** A-D Non-contrast axial MRI of the pancreas (A & B) showed a pancreatic tail mass (arrow). It showed low signal intensity on T1W (FLASH sequence) image (A) and high signal intensity on T2W (HASTE) (B) compared to normal parenchyma. After intravenous gadolinium, the lesion showed less conspicuity in both arterial (C) and venous (D) phases



**FIGURE 5** A-F Panels A-D represent a peritumoral islet with insulinitis. Panel A is the H&E stain. Panel B is a CD3 immunostain demonstrating approximately 60 infiltrating T cells. Panels C & D are glucagon and insulin stains, respectively. Panels E (H & E) and F (CD3 immunostain) demonstrate significant insulinitis



**FIGURE 6** Demonstration of inflammation within the insulinoma. CD3-stained image demonstrating T cells lightly dispersed throughout the tumor with accentuation at the edge of the tumor

Critical illness and hormone deficiency secondary to inborn errors of metabolism or congenital defects were unlikely based on the patient's previous well-appearing clinical picture and initial laboratory findings. It is important to note that this patient does not fit a clinical picture consistent with adrenal insufficiency, as the only known reports of patients with stage 3 T1D presenting with hypoglycemia are those with concurrent primary adrenal insufficiency.<sup>15,16</sup>

The evaluation led to the diagnosis of hyperinsulinism, which can occur via a multitude of etiologies including insulinoma, insulin autoimmune syndrome, and functional beta-cell disorders (including early-stage T1D).<sup>2,3,5</sup> It was important to assess for insulin antibodies that might be present in insulin autoimmune syndrome, and given the family history and presence of reactive hyperglycemia, it was prudent to obtain multiple islet autoantibodies simultaneously in the event the insulin antibody was positive. After determining that the hypoglycemia was more profound than expected with a T1D prodrome, it was necessary to obtain more sensitive imaging to screen for insulinoma as this was not detected on initial ultrasound, specifically noted to have low sensitivity for pancreatic mass.<sup>17</sup> The discovery of multiple pancreatic autoantibodies, in conjunction with his OGTT and CGM data, led to two antagonistic diagnoses that each somewhat masked the other.

NET are exceedingly rare in the pediatric population, with an estimated incidence of 2.8 per 1,000,000.<sup>18</sup> T1D is much more common, with an incidence of approximately 22 per 100,000 in the United States.<sup>19</sup> Insulinoma masking the diagnosis of T1D has only been documented twice previously, in a 71-year-old woman and

a 49-year-old man, making our patient the youngest described.<sup>20</sup> Pancreatic NET is observed with increasing frequency in genetic syndromes including multiple endocrine neoplasia type 1, von Hippel-Lindau syndrome, neurofibromatosis type 1, and tuberous sclerosis but so far our patient has tested negative for these associated conditions.<sup>21</sup>

Beta-cell destruction adjacent to neuroendocrine proliferation may suggest that the T1D antigen is expressed on the native beta cells only and not the insulin-producing NET cells. Our patient's rising blood glucoses pre-operatively could represent the natural history of T1D or provide evidence that there was autoimmune attack on the tumor. Inflammation and cancer are intimately linked, but there is anecdotal evidence that insulinomas do not demonstrate T-cell infiltration.<sup>20,22</sup> However, CD3+ T cells were noted to have infiltrated the adjacent insulinoma (Figure 6). Determination of the antigenic target of the islet T cells and the tumoral T cells may play a role in understanding more of the pathogenesis of T1D.

## 6 | CONCLUSION

This case highlights the utility of investigating multiple pancreatic autoantibodies in a pediatric patient with hyperinsulinemic hypoglycemia as this prevented us from erroneously diagnosing him with insulin autoimmune syndrome if only insulin antibody had been ordered and returned positive. Instead, this led to the diagnosis of dual processes that each needed to be addressed. Diabetes education was able to be initiated pre-operatively and awareness of impending hyperglycemia prevented development of ketoacidosis, which may have been difficult to distinguish from a post-operative complication. Co-existence of proliferative and destructive processes in a patient at high genetic risk to develop T1D may lead to further understanding of the pathogenesis of T1D. To conclude, the possibility of co-existing T1D and insulinoma, although exceedingly rare, should be considered when early-stage T1D is predominated by hypoglycemia with weight gain as it will significantly impact management of both processes.

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### CONFLICT OF INTEREST

The authors have no conflicts of interests relevant to this article to disclose.

### AUTHOR CONTRIBUTIONS

Sriya Subramani wrote the initial draft of the manuscript. Catherina T. Pinnaro conceptualized the case report, assisted in drafting the initial manuscript, revised the manuscript critically for important intellectual content, and created the majority of the figures. Andrew M. Bellizzi completed the pancreatic staining, created the related figures, and revised the manuscript for important intellectual content. Nicholas Borcharding provided critical clinical insight into the pathology of neuroendocrine tumors and adjacent islet cells and revised the manuscript for important intellectual content related to neuroendocrine tumors. Michael J. Tansey and Andrew W. Norris were responsible for revising the manuscript critically and for important intellectual content. Joseph Dillon and James Howe provided clinic expertise on neuroendocrine tumors and revised the manuscript. Simon C. Kao provided critical clinical and radiologic expertise, helped prepare the images for submission, and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

### ETHICS APPROVAL

Verbal consent and written informed consent for publication were obtained from the patient and his parents.

### CONSENT

Written informed consent was obtained from the patient and his parents.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are contained within the article, tables, and supplemental table.

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### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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