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ARTICLE

Clinicopathological Features of Pediatric Insulinoma: A Single-Centre Study

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Abstract

Aims/Background Insulinoma is an extremely rare condition in pediatric patients. This study aims to examine the pathological and clinical characteristics of pediatric insulinoma.

Methods A retrospective, single-center study was conducted involving five pediatric patients diagnosed with insulinoma. The study involved evaluating the postoperative status of the patients during follow-up and analyzing their clinical manifestations, diagnostic work-up, pathological findings, and therapeutic approaches.

Results The study cohort comprised four males and one female, aged between 4 and 9 years. Common symptoms included dizziness and fatigue. The insulinomas were located in various parts of the pancreas: two in the head, one in the neck, one in the body, and one in the tail. After undergoing subtotal pancreatectomy, four patients experienced no side effects during a follow-up period of 41 to 153 months. One patient, who underwent an incomplete pancreatic resection, required ongoing postoperative treatment with 150 mg Creon due to pancreatic enzyme deficiency. Postoperative pathological results indicated that all cases were low-grade neuroendocrine tumours, classified as grade 1 (G1) or grade 2 (G2). Two cases exhibited capsule invasion, and one case showed microvascular invasion. Despite these invasions, no recurrences or metastases have been observed to date.

Conclusion Surgical resection is a viable treatment option for pediatric insulinoma, yielding a favorable prognosis. The presence of capsular and microvascular invasions does not seem to affect the overall prognosis in these cases.

Key words: children; insulinoma; pathology; outcome

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Introduction

Childhood pancreatic tumours, including pancreatic cancer, pancreatic neuroendocrine tumours, solid pseudopapillary neoplasms, and pancreatoblastoma, are significant entities in the realm of pediatric oncology (de Herder and Hofland, 2000). Among these, insulinomas, which are functional tumours arising from pancreatic islet beta cells, are the most prevalent hormone-producing neuroendocrine neoplasms (NENs) of the pancreas (Melikyan et al, 2023). Individuals harbouring these tumours often present with hypoglycemic symptoms due to excessive insulin secretion. Typical clinical manifestations include neuroglycopenic symptoms such as confusion, somnolence, seizures, visual disturbances, weakness, palpitations, sweating, and tremors. With an estimated incidence rate of 4 per million people per year (O'Hanlon et al, 2001), insulinomas commonly develop in the sixth decade

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of life but can affect individuals of any age. They are rare in children and young adults, with less than 1% of cases occurring in individuals under 30 years of age (Garnier et al, 2021). Pediatric insulinomas are extremely rare compared to adult cases, with most of the cases primarily documented in case studies, underscoring the need for comprehensive research to elucidate their characteristics. Herein, we present a series of five pediatric insulinoma cases, providing valuable insights into this uncommon condition.

Methods

This study was approved by the Ethics Committee of Children's Hospital of Fudan University (No. (2024)76). Five cases of insulinoma recorded over the period spanning from 2010 to 2022 were retrieved from the hospital's pathological archives, with diagnoses independently verified by two pathologists. The diagnosis of insulinoma is primarily made based on Whipple's triad: (1) symptoms are attributed to hypoglycemia; (2) low plasma glucose is detected during symptom manifestation, and (3) symptoms are relieved upon the normalization of low glucose levels (Palani et al, 2023). Each of the patients also presented with a mass within the pancreas. Formalin-fixed paraffin-embedded tissue sections (3 mm thick) were used for both hematoxylin and eosin (HE) staining and immunohistochemical (IHC) staining. Postoperative pathological examination of HE-stained tissue sections revealed well-differentiated neuroendocrine cells arranged in various patterns, such as trabecular, acinar, or solid nests. IHC staining was performed using a Roche Ventana BenchMark XT automated stainer (Ventana Medical Systems, batch number: 716192, Tucson, AZ, USA), to identify specific biomarkers. Markers such as insulin, chromogranin A (CgA), and synaptophysin (Syn) were subjected to IHC staining for diagnostic purposes. Kiel67 (Ki67) staining was conducted to assess tumour proliferation. The antibodies used in the IHC staining experiment included: insulin (RM1019, 1:10,000 dilution; Abcam, Cambridge, UK), CgA (2N5Q4, 1:100 dilution; Roche, Basel, Switzerland), Syn (SY38, 1:5000 dilution; Abcam, Cambridge, UK), and Ki67 (RM360, 1:200 dilution; Roche, Basel, Switzerland). Clinical and pathological details were gleaned from the archives, encompassing gender, age, clinical presentations, tumour characteristics (size and location), serum glucose levels (before and after surgery), radiological findings, histopathological features, treatment strategies, post-surgery medication status of the patients, and patient outcomes. All data were collected and stored in a database. Statistical analysis was conducted using IBM SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).

During the initial two years following surgery, all five patients were regularly monitored during outpatient visits scheduled every three months. These visits entailed comprehensive radiological scans and physical examinations specifically tailored for pediatric patients. Additionally, continuous tracking of blood glucose levels was conducted for these individuals. To ensure comprehensive follow-up and obtain updates on the health status of the patients, we had proactively reached out to those who missed their scheduled appointments or had been followed up for

more than two years through phone calls, letters, and emails. Furthermore, collaboration with nearby hospitals was forged to gather relevant medical information and test results for comprehensive analysis of the current subjects.

Results

Clinical Features

The key clinicopathological characteristics of the patients are summarized in Table 1. In this sample, there was one female and four males. The age of insulinoma onset ranged from 4 to 9 years (median: 7 years, average: 6.6 years). Dizziness was the most common among the symptoms reported, with 4 out of 5 cases proclaiming having been affected. Additionally, one patient presented with seizures as the initial symptom. The duration between symptom onset and definitive diagnosis varied, ranging from 1.5 months to 2 years, with an average duration of approximately 10 months. The lowest recorded serum glucose concentrations ranged from 0.5 to 3.9 mmol/L, while the highest insulin concentrations measured were between 69.3 and 1736 pmol/L. After surgery, the patient's blood glucose levels have stabilized within the range of 4.3 to 5.2 mmol/L. Two cases of insulinoma were located at the head of the pancreas, and each at the neck, body, and tail of the pancreas, respectively. The tumour removal methods applied to the patients included tumour enucleation, partial resection, and subtotal resection. Following a subtotal pancreatic resection, a pediatric patient was given continued postoperative Creon (150 mg orally, three times daily), due to pancreatic enzyme deficiency as a consequence of the surgical intervention. Throughout a follow-up period spanning 41 to 153 months, all patients underwent surgical resection, with all but one experiencing uneventful recoveries. Imaging analysis revealed no abnormalities indicative of pituitary/adrenal gland cancer or parathyroid adenoma. Furthermore, there were no signs of hereditary disorders, including multiple endocrine neoplasia type 1 (MEN1), and neither of the patients' parents had such disorders.

Pathological Examination

Gross Examination

Three of the insulinomas presented as solitary, spherical tumours with well-defined borders, with cut surfaces exhibiting a range of stain colours from greyish-white to yellowish-tan. However, two of the tumours displayed indistinct borders. Fig. 1 depicts the gross examination of one of the cases. The maximum diameters of the tumours ranged from 0.8 to 3 cm, with an average diameter of 1.76 cm.

Histological Examination

The histological features of the patient's tumour specimens are summarized in Table 2. The predominant histological pattern observed in the majority of insulinomas (3/5) was trabecular pattern; for the remaining insulinomas, one showed a solid pattern while the other a tubuloacinar pattern. Three instances showed evidence of intense hyalinized sclerosis; specifically, one case exhibited microvascular invasion, while capsule invasion was observed in two cases. Numerous sinusoids were

Table 1. Clinicopathological characteristics of the patients with pediatric insulinomas.

	Patient number				
	1	2	3	4	5
Gender	Female	Male	Male	Male	Male
Age (years)	9	7	9	4	4
Chief complaints	Dizziness	Dizziness	Dizziness	Seizure	Dizziness
Lowest serum glucose concentration (mmol/L)	1.8	3.9	0.5	1.5	2.2
Highest insulin concentration (pmol/L)	129	1736	69.3	94.2	219.2
Blood glucose concentration after surgery (mmol/L)	5.2	4.3	5.0	4.9	5.2
Location of insulinoma	Head	Tail	Neck	Body	Head
Surgical method	Tumour enucleation	Partial resection	Tumour enucleation	Partial resection	Subtotal resection
Tumour maximum diameter (cm)	3	1.5	2	1.5	0.8
Medication given after surgery	No	No	No	No	Creon 150 mg, orally, t.i.d.

Table 2. Pathological features of pediatric insulinomas.

	Patient number				
	1	2	3	4	5
Histopathological pattern	Solid & trabecular	Tubuloacinar	Trabecular	Solid	Trabecular
Intense hyalinized sclerosis	Yes	No	Yes	Yes	No
Microvascular invasion	No	No	Yes	No	No
Capsule invasion	No	Yes	Yes	No	No
Sinusoids	Abundant	Abundant	Abundant	Abundant	Abundant
Pancreatic invasion	No	No	No	No	No
Nuclear pleomorphism	No	Moderate	Mild	No	No
Mitotic figures/10 HPF	0	3	2	1	0
Ki67 proliferation index	2%	15%	10%	3%	1%
Grade	G1	G2	G2	G1	G1

HPF, high-power field; Ki67, Kiel67; G1, grade 1; G2, grade 2.

also evident in each instance. None of the cases demonstrated pancreatic invasion. Nuclear pleomorphism was present in two cases. The mitotic count ranged from 0 to 3 per high-power field (HPF), and the Ki67 proliferation index ranged from 1% to 15%. All tumours reported in this study were low-grade, classified as grades G1–G2.

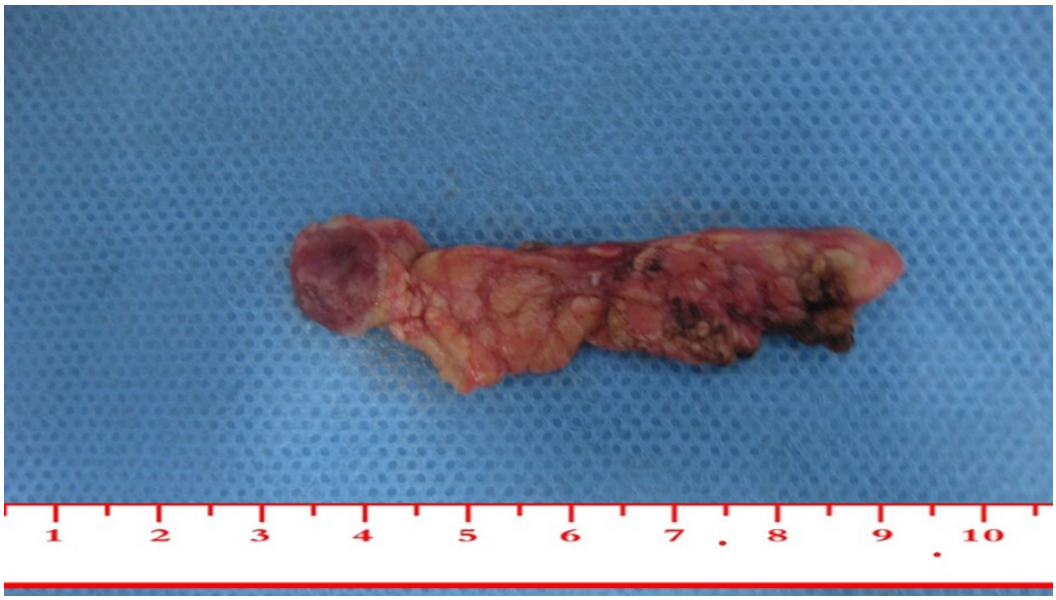

Fig. 1. Macroscopic appearance of insulinoma. The tumour appeared solitary, round, and well-demarcated, exhibiting tan cut surfaces. The diameter of the tumour was 0.8 cm.

As depicted in Fig. 2, the hematoxylin and eosin (HE) images in Fig. 2A and B illustrate the histological morphology of patient 1, demonstrating a combination of partially solid and trabecular patterns. Fig. 2C and D depict the histological morphology of patient 2, tubuloacinar patterns are observed, with evidence of capsule invasion indicated by the red arrow in Fig. 2C,E and F, corresponding to patient 3, reveal trabecular patterns, with capsule invasion denoted by the red arrow in Fig. 2E, and microvascular invasion by the red arrow in Fig. 2F. Fig. 2G shows the histological pattern of patient 4, depicting solid formations. Meanwhile, Fig. 2H displays the histological morphology of patient 5, featuring trabecular patterns. Insulin and chromogranin A (CgA) staining, as shown in Fig. 2I and J, respectively, exhibit strong positivity. Coarse clumping of the chromatin pattern, termed “salt and pepper”, was noted in all cases, with necrosis notably absent.

Imaging

A transabdominal ultrasound was performed on all five patients. Additionally, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans were conducted in five cases. The results of various imaging techniques utilized for the evaluation of pancreatic lesions in this patient cohort are depicted in Fig. 3. Insulinomas were detected at the head of the pancreas for two cases, and each at the neck, body, and tail of the pancreas. Among the cases, one presented with a

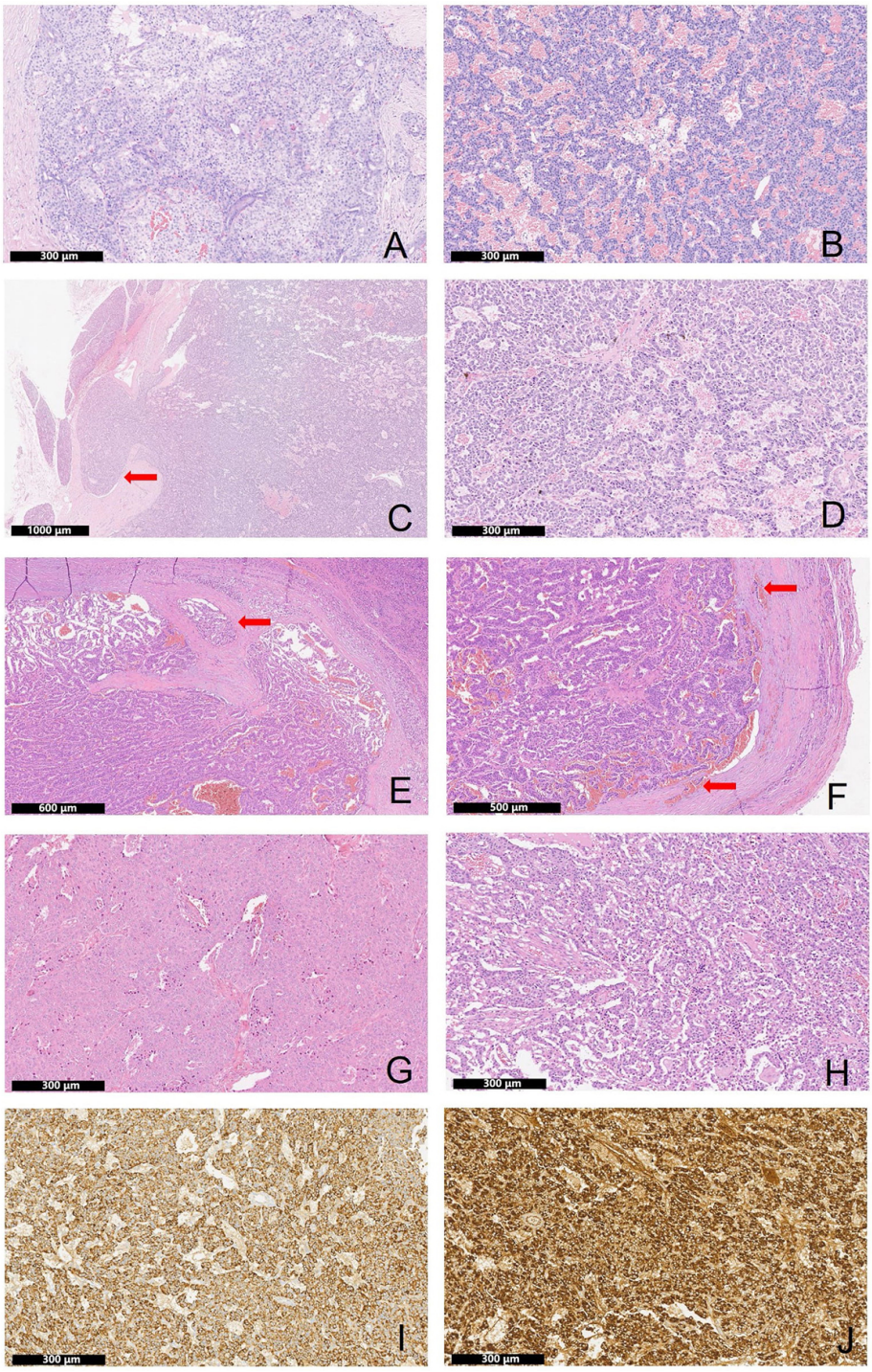

Fig. 2. Histopathology of insulinomas. (A,B) Hematoxylin and eosin (HE)-stained sections of patient 1 exhibiting a histological pattern characterized by solid and trabecular areas. (C,D) HE-stained sections of patient 2 displayed a histological pattern of tubuloacinar architecture, with capsule invasion indicated by the red arrow in (C). (E,F) HE-stained sections of patient 3 demonstrating a trabecular histological pattern, with capsule invasion indicated by the red arrow in (E) and microvascular invasion by the red arrow in (F). (G) HE-stained section of patient 4 exhibiting a solid histological pattern. (H) HE-stained section of patient 5 displaying a trabecular histological pattern. (I,J) Positive immunohistochemical staining of insulin (I) and chromogranin A (CgA) (J) indicates the presence of insulin-secreting cells within the tumour.

pseudoaneurysm in the body of the pancreas, which was caused by splenic artery dilation.

Treatment and Prognosis

Various surgical techniques were employed to treat the patients, including pancreaticoduodenectomy, distal pancreatectomy, and tumour enucleation. Following surgery, all patients were followed up for a duration ranging from 3 to 12 years, during which none of them experienced recurrence.

Discussion

Insulinoma, gastrinoma, and vasoactive intestinal peptide tumours are among pancreatic islet cell tumours. The annual morbidity rate for insulinoma is approximately 4 per million per year, with a median age of onset around 47 years. Pediatric cases of insulinoma are exceedingly rare (Garnier et al, 2021). Most insulinomas are sporadic in nature, with about 10% of insulinomas occurring associated with MEN1 syndrome (Liang et al, 2018). Notably, children with insulinoma are more likely to harbour *MEN1* mutations compared to their adult counterparts (Murray et al, 2024).

Insulinoma is generally characterized as a solitary benign tumour, with only 5.8% of affected cases showing potential for malignancy. Islet cell carcinoma represents the most prevalent pancreatic islet cell tumour in teenagers and young adults (15–39 years old) (Waters et al, 2019).

One of the common presentations of insulinoma is fasting hypoglycemia. This is the most typical clinical manifestation of insulinoma, occurring in 73% of the affected cases. It is characterized by isolated episodes of neuroglycopenic signs, which may or may not be accompanied by autonomic or sympathoadrenal signs (Grosfeld et al, 1990). Nevertheless, in certain individuals, postprandial hypoglycemia or even one of its features are probably the only signs of hypoglycemia (Moszczyńska et al, 2024). Instead of increased glucose utilization, the main cause of hypoglycemia in people with insulinomas is decreased hepatic glucose production (Güemes et al, 2020). A few of the neuroglycopenic signs of insulinoma included disorientation, changes in vision, and strange conduct. Palpitations, diaphoresis, and tremulousness are examples of sympathetic-adrenal signs. Hypo glycemia-related amnesia is also a frequent occurrence among those with insulinoma (Pratò et al, 2022). Typically, the related signs would have been present for a median of fewer than 1.5 years before a proper evaluation of the condition or diagnosis. Some individuals, nevertheless, would have very likely been experiencing symptoms for decades before a confirmed diagnosis was made (Kurakawa et al, 2021). Up to 20% of individuals may receive an incorrect diagnosis, such as a neurologic or mental condition, before a standard differential diagnosis is performed until insulinoma is identified. Seizures are commonly mistaken for the clinical presentations of insulinoma. In addition, patients with insulinoma may face an 18% increase in weight (Karanth et al, 2022).

Noninvasive imaging techniques applicable to examining insulinoma include spiral computed tomography (CT), magnetic resonance imaging (MRI), transab-

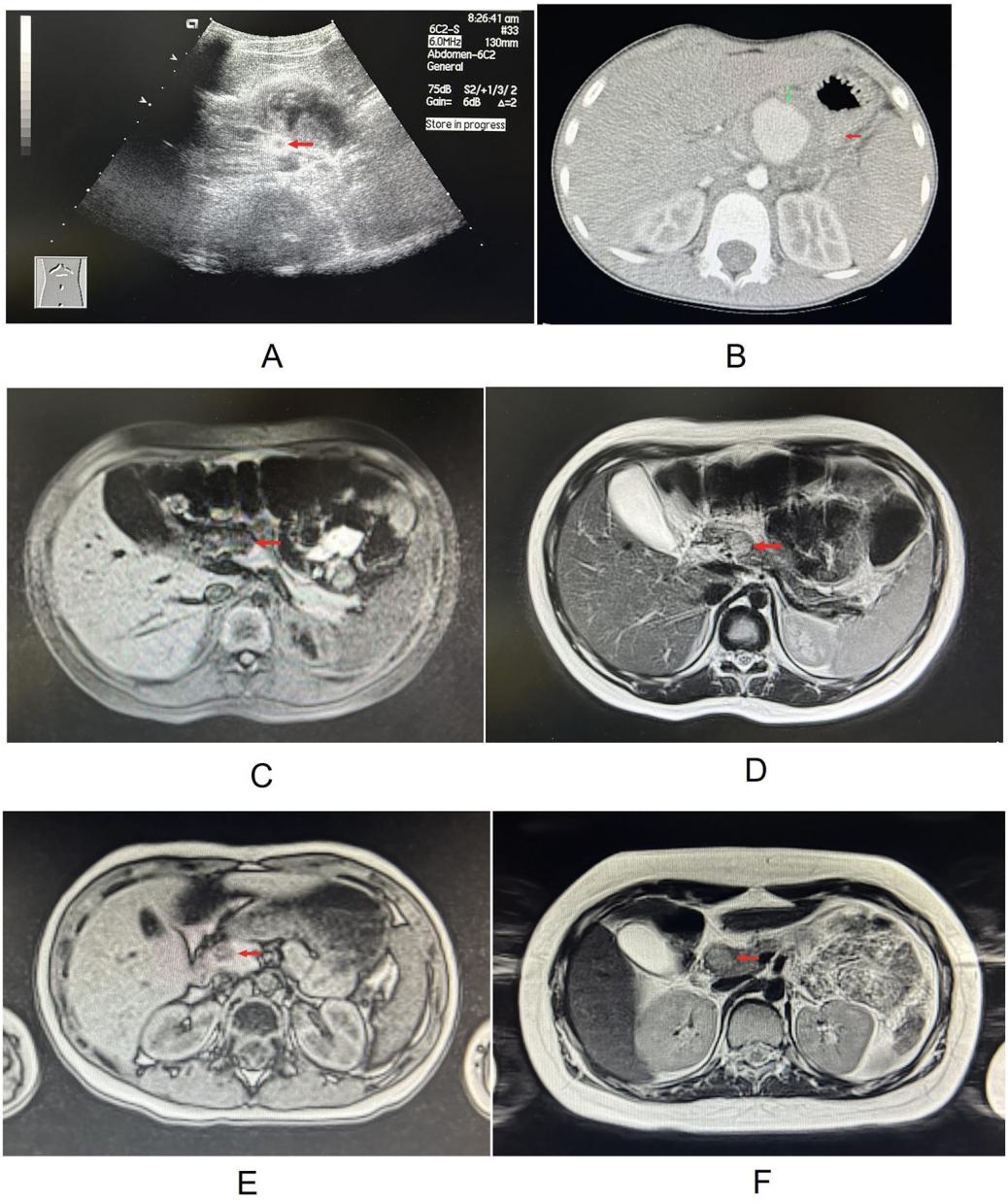

Fig. 3. Radiographic features of insulinoma in pediatric patients. (A) Ultrasound scan of the pancreas (patient 3): The red arrow indicates the insulinoma located at the neck of the pancreas. (B) Computed tomography (CT) scan of the pancreas (patient 2): The green arrow highlights a 6 cm pseudoaneurysm caused by splenic artery dilation at the body of the pancreas. Additionally, the red arrow denotes the presence of an insulinoma at the tail of the pancreas. (C) Magnetic resonance imaging (MRI) T1-Weighted Imaging Sequence 1(T1W1) result (patient 4): The red arrow indicates a 1.5 cm round-shaped lesion with reduced enhancement at the body of the pancreas. (D) MRI T2-Weighted Imaging Sequence 1 (T2W1) result (patient 4): The image shows a highly enhanced, round-shaped lesion measuring 1.5 cm at the body of the pancreas, as indicated by the red arrow. (E) MRI T1W1 result (patient 5): The red arrow indicates a 0.8 cm round-shaped lesion with reduced enhancement at the head of the pancreas. (F) MRI T2W1 result (patient 1): The image shows a highly enhanced, round-shaped lesion measuring 3 cm at the head of the pancreas, as indicated by the red arrow.

dominal ultrasonography, ^{111}In-pentetreotide imaging, and fluorine-18-L-dihydroxyphenylalanine positron emission tomography (18F-DOPA PET) (Shah et al, 2021). Given the majority of insulinomas are intrapancreatic, benign, and solitary, a localizing investigation that includes the following modalities can be performed: CT, intraoperative ultrasound, gadolinium-enhanced MRI, and octreotide scanning (Imperiale et al, 2022). During diagnosis, the site of sporadic insulinomas must be confirmed, and additional tumours, either preoperatively or intraoperatively, must be identified using palpation and intraoperative ultrasound in order to exclude the possibility of numerous lesions, even though they are typically solitary (El Sayed et al, 2021). Whether a tumour is enucleated or requires a more conventional resection depends on its size and location with respect to the pancreatic duct and/or common bile duct. Previous research has indicated that the majority of insulinomas are seen on the body's margins or at the tail of the pancreas (Melikyan et al, 2023).

In clinical settings, rapid blood glucose decline is typically regarded as a symptom of insulinoma. To diagnose insulinoma and ascertain whether it is associated with MEN1, a thorough systemic investigation is required. Additional IHC tests to detect Ki67, CgA, or insulin may be necessary to lend credence to the pathologic diagnosis of insulinoma. Most pediatric insulinomas are low-grade, and high-grade tumours have rarely been reported (Giannis et al, 2020). The reported ubiquity of low-grade insulinoma resonates with our findings in this report. We observed that among the five pediatric cases of insulinoma in this study, two exhibited capsule invasion, and one exhibited microvascular invasion. However, none of these five patients have experienced recurrence or metastasis to date, suggesting that these factors may not have a definitive impact on prognosis.

Pediatric insulinomas are extremely rare, and detailed studies on their clinical and pathological features remain scarce. This research represents the first report on the clinicopathological characteristics of multiple pediatric insulinoma cases in China, providing valuable insights into the clinical presentation, diagnosis, and potential prognostic factors of this uncommon condition.

For most affected individuals, surgical resection of insulinoma is the best option. Robotic-assisted surgery has been reported to show positive outcomes in a number of pediatric patients recently, with decreased risk for injury and bleeding being the prominent benefits (Yin et al, 2024). For small insulinomas (less than 2 cm) that do not border the pancreatic duct, enucleation should be considered (Xu et al, 2021). However, an ordinary resection would be a better therapeutic option for insulinomas larger than 2 cm, those that border the pancreatic duct, and those that lack a distinct plane separating the tumour capsule from the pancreatic parenchyma. A more conventional resection should be done if the lesion is bigger (>2 cm), contacts the pancreatic duct or common bile, or lacks a distinct plane separating the tumour capsule from the pancreatic duct (Schulte Am Esch et al, 2021).

Malignant insulinomas account for 10% of the total cases and entail liver metastases or local lymph node involvement. Individuals with malignant insulinoma ought to be treated with peripancreatic lymph node dissection. If this technique is proved to be safe, removal of the main tumour and any accessible metastases is advised in cases where liver metastases are present (Sada et al, 2021). Tumour

debulking is associated with extended survival and reduced hypoglycemic symptoms. If a tumour is determined to be incurable, medications can be appropriately used to control hypoglycemia and slow down the disease progression rate (Kulke et al, 2010). These recommended treatment methods may bring up the cure rates of insulinoma up to nearly 100% (Xiao et al, 2024).

Actreotide and lanreotide, two analogues of somatostatin (SST), are used to treat various kinds of hyperinsulinemic hypoglycemia (HH) in adults and children. Octreotide use in neonates should be done so with caution due to an increased risk of developing Neonatal Necrotizing Enterocolitis (NEC) (Haris et al, 2020). Following surgical resection of insulinoma, patients who do not harbour *MEN1* mutations generally have a favourable prognosis and a low chance of recurrence (Kim et al, 2024). However, an important consideration is the potential rise in blood sugar levels due to the post-operative decrease in insulin production. Separately, chemotherapy and radiation therapy are typically employed as treatments for high-grade insulinomas. Types of treatment for insulinomas vary with the age of the affected individuals. For instance, different management strategies are applied to children under 15 years of age since pediatric insulinomas are predominantly low-grade (Damaskos et al, 2023).

Differential Diagnosis

Congenital Hyperplasia of Pancreas Islet

Similar to insulinoma, congenital hyperplasia of the pancreas islet is characterized by elevated serum insulin levels and increased islet cell proliferation. However, hyperplasia of the pancreas islet cannot be detected through imaging or during surgery, and the proliferation of islet cells is only observable under the microscope.

Pancreatoblastoma

Pediatric patients with pancreatoblastoma under 8 years old often have elevated serum alpha-fetoprotein (AFP) levels. Histologically, HE staining could reveal the characteristic squamous bodies in pancreatoblastoma, while IHC staining enables the positive detection of cytokeratin (CK), Syn, and CgA, but not insulin, in pancreatoblastoma.

Solid Pseudopapillary Neoplasm of Pancreas

Solid pseudopapillary neoplasm of the pancreas is more prevalent in women, typically developing in those at an average age between 25 and 35 years. Among juniors, it is predominantly observed in adolescents aged 9 to 17. The affected patients commonly present with symptoms such as anorexia, weight loss, and abdominal pain, while their serum tumour markers usually remain within normal ranges. Contrary to insulinoma, hypoglycemic symptoms are absent in the solid pseudopapillary neoplasm of the pancreas. IHC staining of this type of mass demonstrates nuclear positivity for beta-catenin.

Conclusion

Insulinomas in children are exceedingly rare, typically presenting as low-grade neuroendocrine tumours with favourable clinical outcomes. In our report, we discuss five cases of insulinoma in young children, emphasizing the distinctive features observed in pediatric patients. Although the causes of hypoglycemia in children are diverse, insulinoma accounts for a small fraction of cases. Identifying insulinoma, particularly in cases of childhood hyperinsulinemia, including congenital hyperinsulinemia, is essential to avoid misdiagnosis. An accurate pathological diagnosis is crucial in directing healthcare professionals toward suitable management strategies and forecasting patient prognosis.

Learning Points

- Insulinomas in children are exceedingly rare.
- They predominantly manifest as low-grade neuroendocrine tumours with favourable clinical outcomes.
- Although hypoglycemia in children is multifactorial, insulinoma, being one of the cases, accounts for only a small fraction of the hypoglycemia cases.
- Recognizing insulinoma, particularly in cases of childhood hyperinsulinemia like congenital hyperinsulinemia, is crucial to avoid misdiagnosis.
- Accurate pathological diagnosis is crucial for guiding healthcare professionals in selecting suitable management strategies and forecasting prognosis.

Availability of Data and Materials

All data included in this study are available upon request by contact with the corresponding author.

Author Contributions

YYM designed the research study. FT performed the research. FT, JZ, DD and JYF analyzed the data. FT wrote the first draft. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Informed consent was obtained from all patients for this study. The study strictly adhered to the Declaration of Helsinki and obtained the approval of the Ethics Committee of Children's Hospital of Fudan University (No. (2024)76).

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Conflict of Interest

The authors declare no conflict of interest.

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