CASE REPORT

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Insulinoma diagnosed as drug-refractory epilepsy in an adolescent boy: a case report

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Abstract

Solitary insulinoma is a rare pancreatic tumor in all age groups with an estimated incidence of 1 in 250 000 persons a year. It is even rarely in childhood and mostly shows benign behavior. Cases with uncertain or malignant biology are extremely rare with less than 30 cases described in the literature. Here we report a case of pediatric insulinoma, the first in our department files in the past 20 years, with rapid clinical course following a clinical misdiagnosis as juvenile myoclonic epilepsy, which was complicated with low glucose level (20 mg/dL) and neuroglycopenia. Our case underlines some unusual features of a pediatric insulinomas presented without past medical and family history, after surgery complicated with mental retardation and recurrent epileptiform episodes. Despite the small tumor size, low Ki67 index/mitotic rate and benign immunophenotype marked by positivity for pro-insulin but negativity for β-HCG, the diagnosis was concluded as insulinoma of uncertain biological behavior due to vascular tumor invasion in agreement with the 2003 *WHO Classification for Pancreatic Endocrine Neoplasms*. Besides these features, perineural invasion can differentiate insulinomas of uncertain outcome from benign insulin producing tumors. Pediatric insulinomas may present misleading symptoms of epilepsy in neglected cases coming from poor socioeconomic background. Chronic insufficient blood glucose level might contribute to mental retardation and epilepsiform myoconvulsions to be prevented. Differentiation between insulinoma with benign and uncertain behavior is difficult where histological pattern and tumor immunophenotype are less important than the critical morphological parameters. Life long follow-up including regular control of blood glucose and abdominal status of patients are essential for proper assessment of clinical outcome of pediatric insulinoma.

Keywords: pediatric insulinoma, vascular invasion, uncertain biological behavior, epilepsy.

Introduction

Insulinoma is a rare pancreatic tumor with unpredictable clinical course. Its incidence is higher in adults than in children representing 1–2% of all pancreatic neoplasms [1]. Because hypoglycemia is an important cause of neural damage and cerebral dysfunctions in childhood, the initial diagnosis of hyperinsulinemic hypoglycemia can masked by neurological symptoms leading to a potential misdiagnosis [2, 3]. In accordance with the *WHO Classification of Pancreatic Endocrine Tumors*, insulinoma is defined as well-differentiated neoplasm with benign or uncertain behavior [1]. Based on histopathology and immunophenotype the prognostication of insulinoma is difficult. Moreover, in order to prevent tumor recurrence and metastatic growth or the neurological symptoms due to neuroglycopenia, each case requires a personalized diagnostic and therapeutically approach.

Patient and Methods

A 16-year-old boy was presented to the Pediatric Emergency Department of Emergency County Hospital, Tîrgu Mureş, Romania, with seizures associated with a mental confusion in March 7, 2008. His disease was diagnosed as malnutrition associated hypoglycemia with low blood glucose level (25 mg/dL), which was normalized after intravenous glucose administration. His familiar history was remarkable for symptoms of neuroglycopenia characteristic of malnourished children living in poor socioeconomic conditions as a support of the clinical diagnosis.

Two months later (May 22), he was presented with unusual mental behavior, which was followed by myoclonia and generalized tonic-clonic seizures (GTCS). The blood glucose level was minimally higher than before (28 mg/dL). Having been hospitalized in the Pediatric Neuropsychiatry Department, his clinical examination was focused on the neurological symptoms. Alterations in resting EEG were interpreted as juvenile myoclonic epilepsy (JME). As a confirmation, Carbamazepine treatment (800 mg/day) resulted in the temporary resolutions of his symptoms. During the period under treatment, he presented more generalized seizures, being interpreted as drug-refractory epilepsy. Due to the poor family conditions, he was placed under foster care. In August 4, 2008, he presented intermittent cranial hypertension syndrome followed by

seizure-like episodes, associated with a falling glucose level (20 mg/dL). Intravenous glucose quickly improved his symptoms and he was transferred to the Diabetology unit of the 2nd Pediatric Department.

Physical examination clarified a height-weight hypotrophy (40 kg/148 cm), soft abdomen without palpable masses and organomegaly. Neurological examination detected mild mental retardation but without focal neurological deficit. Basic hematological and biochemical investigations were within normal limits, apart from the low blood glucose (25 mg/dL) and low-to-normal calcium (8.24 mg/dL).

Inappropriate insulin secretion was confirmed in the plasma as 23.8 μU/mL (reference values: 2.6–24.9 μU/ml). Blood glucose/serum insulin ratio was 1.19. During hospitalization 24 hours, multiple glucose level curve showed several values below 50 mg/dL associated with low glycated hemoglobin (2.53%). Urinary sample was negative for ketones. Abdominal ultrasonography was reported normal.

Taking into consideration the clinical findings and case history and excluding other causes of hyperinsulinemic hypoglycemia such as exogenous insulin administration and accidental ingestion of oral anti-diabetics, the case was finally interpreted as insulinoma.

Because multiple endocrine neoplasia type 1 (MEN1) syndrome can be associated with insulinoma in 5–10% of the cases [9], prolactin, thyroid-stimulating hormone, free thyroxin and free triiodothyronine (fT3 and fT4) were also determined but shoed showed normal values. Computed tomography (CT) revealed normal conditions in the brain but a round, encapsulated intra-pancreatic discreet hypodense solitary tumor of 23 mm diameter in the pancreas tail. Peripancreatic fatty tissue and lymph nodes and the adjacent tissues were not involved.

After diagnosis, a high-caloric diet was started and surgery was performed three weeks later by enucleating the solitary insulinoma of the pancreatic tail, which was routinely fixed in 4% formaldehyde and embedded in paraffin wax for histopathology examination.

The excised tumor mass was well-circumscribed, softer than the surrounding pancreatic parenchyma and had a yellow-brownish cut surface without necrotic and cystic changes, measuring 16 mm in diameter (Figure 1).

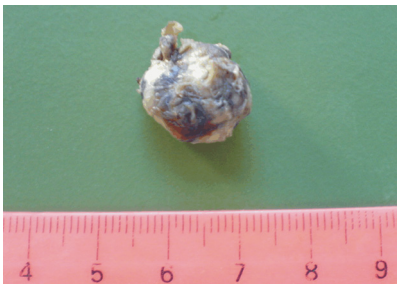

Figure 1 – ***Excised insulinoma: well-defined tumor measuring 16 mm diameter.***

Results

Histopathological examination in HE stained paraffin sections confirmed the endocrine origin of the tumor. Round and monomorphic tumor cells without nuclear pleomorphism showed solid and trabecular pattern surrounded by an incomplete capsule (Figure 2). The tumor stroma deposited amyloid occupying ~10% of the tumor volume as visualized by Congo red staining.

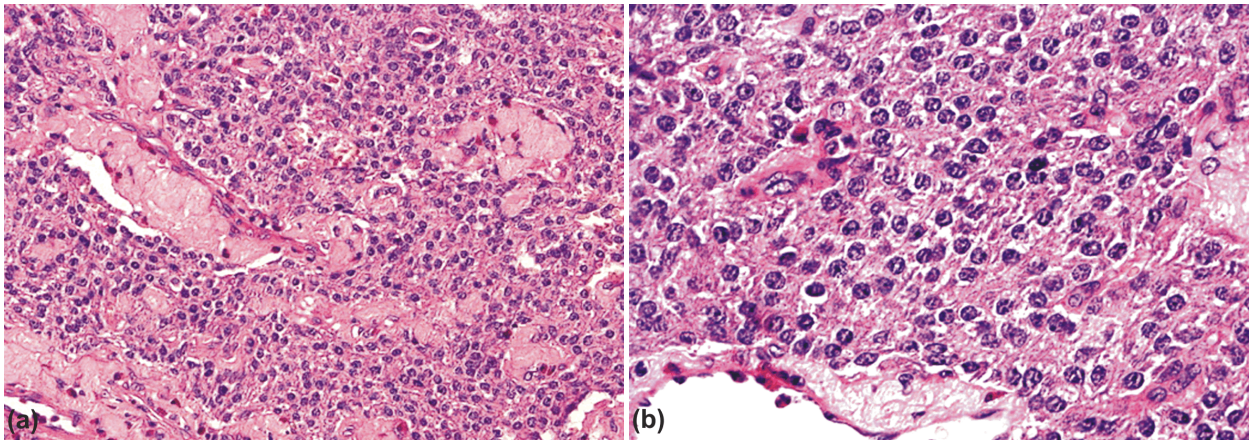

Figure 2 – ***(a) HE stained insulinoma of compact trabecular pattern with monotonous endocrine tumor cells (ob. 10×); (b) HE stained insulinoma seen at higher power (ob. 20×).***

The endocrine origin of the tumor was confirmed using immunostaining for Chromogranin A (1:100, clone SP12), NSE (1:600, clone BBS/NC/VI-H14), Synaptophysin (1:50, clone SY38). In addition, 75% of the tumor cells were positive for pro-insulin (1:600, clone 1G4,) and negative for β-hCG (1:600, clone CGO4). To assess the proliferation index and to visualize incidental angioinvasion, additional immunohistochemical markers, Ki67 protein (1:200, clone SP6) and CD34 (1:200, Clone BI-3C5) were used. UltraVision LP Large Volume Detection System HRP Polymer was used for antibody detection. All immuno-reagents were obtained from LabVision–Thermo (Kalamazoo, MI, USA), except that for NSE (Dako, Glostrup, Denmark).

Our case showed characteristic features a differentiated insulinoma including amyloid deposition (Figure 3a) strong and granular pro-insulin immunoreaction associated to the neurosecretory granules in tumor cell cytoplasm (Figure 3b) and low frequency (~2%) of nuclear Ki67 positivity (Figure 3c) and mitotic rate <2%/10 HPF.

To predict clinical behavior, several histopathological criteria were considered: tumor size, local, perineural and intravascular invasion, structural atypia, necrosis, mitotic and Ki67 index, tumor cells immunophenotype. Despite the small tumor size, low Ki67 index and mitotic rate, and the benign immunophenotype of the tumor cells (positivity for pro-insulin and negativity for β-HCG),

the diagnosis was concluded as insulinoma of uncertain biological behavior based on the vascular tumor invasion (Figure 3d) in agreement with the 2003 *WHO Classification for Pancreatic Endocrine Neoplasms* [1].

During the next three years, the patient was asymptomatic, free of recurrence or metastasis. In May 2011, he was brought to the Neurological Emergency Department with a history of relapsing epileptiform convulsions and pneumonia. Abdominal CT scan did not reveal tumor recurrence or metastasis. Since then he has not attended any routine control examination.

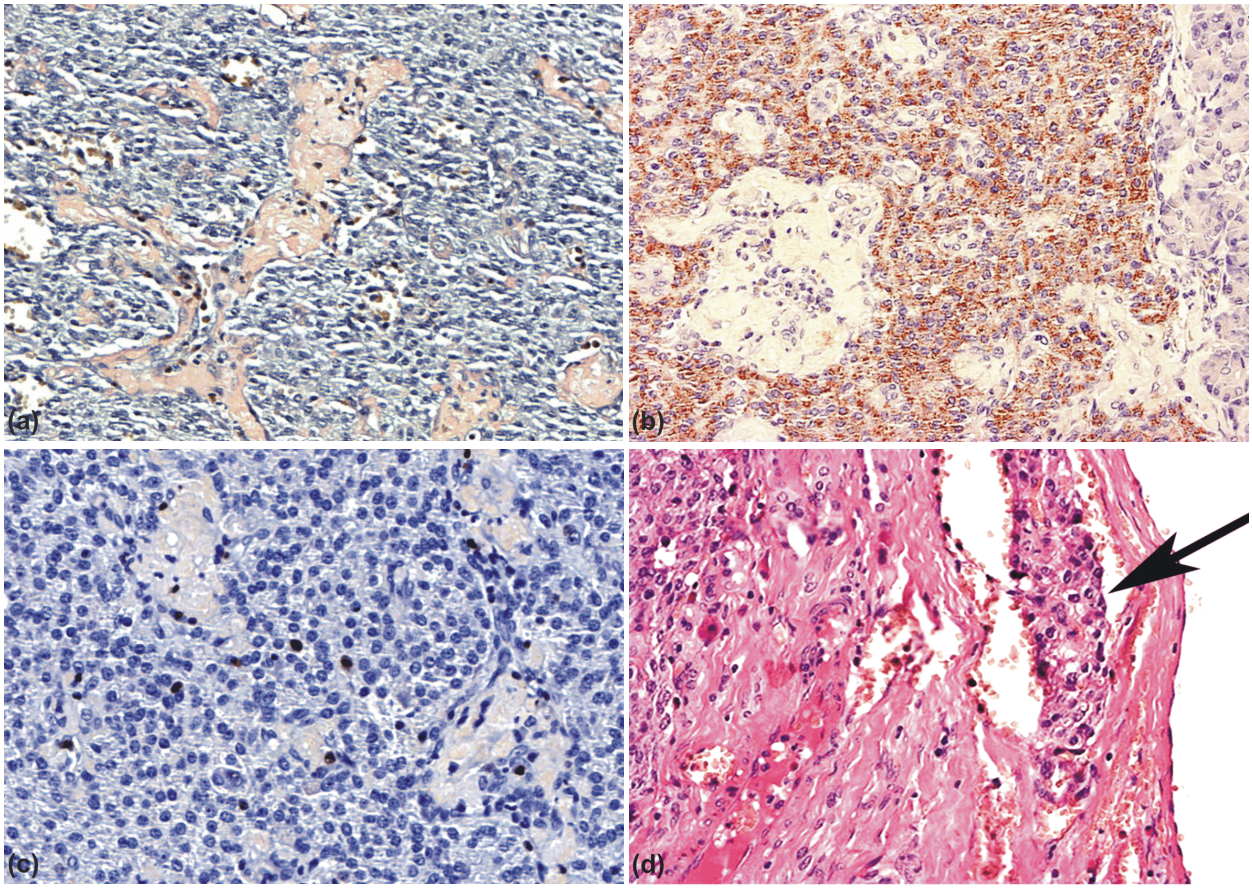

Figure 3 – ***(a) Stromal amyloid deposition showing Congo red staining (ob. 10×); (b) 50% of the tumor cells with perinuclear immunoreactivity to proinsulin antibody (DAB-brown, ob. 10×); (c) Tumor cells with low frequency of nuclear Ki67 immunoreactivity (DAB-brown, ob. 10×); (d) Intravascular invasion of the tumor (arrow) (HE staining, ob. 10×).***

Discussion

Hyperinsulinemic hypoglycemia in newborn and infancy is a well-documented phenomenon and may be transient or persistent. It is known, that most common cause of transient hypoglycemia in childhood is exogenous insulin administration and ingestion of oral antidiabetics [4].

The persistent form is caused by nesidioblastosis of the pancreas, a diffuse pancreatic endocrine abnormality involving all endocrine cell types or by insulin secreting islet cell adenoma (insulinoma)/carcinoma, a very rare tumor in infants and children [5]. The clinical diagnosis of hyperinsulinemia is based on the estimation of the blood glucose/serum insulin ratio as the most important diagnostic factor [6]. A ratio of <2.6 detected at least four consecutive occasions are required for confirming the diagnosis. Up to now, there is no aid available for the etiological differentiation of adenoma from nesidioblastosis [7].

In a study covering a 60 years period at Mayo Clinic, only 4.9% of symptomatic insulinomas occurred in children aged >10 years [8]. The first complete clinico-pathological report proving that hyperinsulinism results from single or multiple pancreatic adenoma and nesidioblastosis were published 50 years ago [9, 10].

The clinical course of insulinoma in children generally characterized by short disease history, lack of overweight and the occurrence of convulsions as the leading symptoms of hypoglycemia [6, 9, 11, 12]. The median interval from the onset of symptoms to the diagnosis of insulinoma is ~2 years [13, 14]. In our case, the negative past medical history could not be assessed due to the poor socio-economic circumstances of the family. Mental confusion and drug-refractory seizures resulting from neuroglycopenia and increased catecholamine release are not characteristic for JME, but fit well to the hypoglycemic events. However, in the literature varying degrees of EEG changes have been mentioned in combination with epileptic activity in patients with insulinoma [2, 13, 15].

In young children, hypoglycemia may manifest as behavioral abnormalities, seizures or coma. In our case, the absence of a personal history due to mild mental retardation and missing of the parents at patient examination caused confusion in interpreting the clinical symptoms.

At the time of surgery the majority of insulinomas of any age groups are solitary, equally distributed throughout

the pancreas and usually <2 cm in diameter [15]. Tumors larger than 3 cm raise concern for malignancy [16]. Sporadic forms are usually solitary, while multiple endocrine neoplasia type 1 (MEN1) associated tumors are usually multiple [11]. In contrast to adult insulinomas, childhood insulinomas including our case are most commonly found in the pancreas tail [17].

The histomorphology of insulinoma may vary. In the stroma, amyloid deposition is considered to be a common feature, which has been demonstrated in more than 50% of tumors [16]. Though amyloid deposition is proportional with the tumor size, it lacks prognostic significance [16].

Insulinoma expresses β-cell markers and stains immunohistochemically for general endocrine markers including synaptophysin and chromogranin, and may also demonstrate varying degree of multi-hormone expression involving gastrin, VIP, ACTH, ADH and calcitonin [18]. In insulinomas, usually express less insulin than normal β-cells and about half of them also show a diffuse labeling for proinsulin [19]. Signs of cellular dedifferentiation including partial loss of chromogranin A and/or reduced insulin immunoreactivity may be associated with poor prognosis. Also, the expression of the β subunit of hCG has been demonstrated in 50–75% of malignant insulinomas but only in <10% of benign tumors [19].

Differentiating benign from malignant tumors of the endocrine pancreas is difficult and can be based on the critical tumor size of <2 cm and the absence of lymph node and/or distant metastases. In adults, 90% of all endocrine pancreatic tumors are insulinomas and of these, only 7% to 10% are malignant. In children, the prevalence of malignant form of insulinoma represent an even smaller proportion [6]. In general, malignancy is associated with a shorter history and more pronounced hypoglycemia [5, 20, 21]. Though our presented insulinoma was measured by CT as 23 mm in diameter, it fell below the 2 cm cut-off value for declaring malignancy under the *WHO* classification (16 mm) after histological processing.

The most important criteria for malignancy are the presence of tumor infiltration or metastases, vascular invasion and the degree of cell proliferation as determined by Ki67 or PCNA expression and ploidy [18]. About half of the pancreatic endocrine tumors exhibit an aneuploid DNA pattern. This does not allow a distinction between benign and malignant tumors but seems to correlate with clinical aggressiveness in the malignant group [18].

Because pediatric insulinoma is very rare, the lack of experience in the diagnostic and therapeutic management of the disease is the major issue for clinicians [5]. Insulinoma in most cases can be successfully treated [3]. The first surgical cure of an islet cell adenoma was published by Howland G *et al.* in 1929 [22]. Surgical resection, involving either enucleation or subtotal pancreatectomy, is considered for all cases of solitary insulinoma because they are usually benign and the complete resection rate is 60%. Tumor enucleation is desirable for preservation of pancreatic function [23].

Conclusions

It is widely accepted, that ambiguously defined tumors should be considered as borderline processes. In our case, vascular invasion was the feature that determined the borderline prognostic classification. Repeated hypoglycemic episodes can arise complicated with retardation of mental development, pyramidal syndromes and recurrent epileptiform episodes. All these masked the right conclusion in our case leading to the initial misdiagnosis. Failure to raise the chance of hypoglycemia behind neurological symptoms in childhood and to recognize initial episodes of hypoglycemia may lead to repeated hypoglycemic attacks with potentially severe neurological consequences.

Declarations

All authors contributed to the compilation and critical revision of the manuscript. The authors disclose no conflict of interest.

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