THEMATIC REVIEW

Insulinomatosis: new aspects

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Abstract

Endogenous hyperinsulinemic hypoglycemia (EHH) is a rare condition with an incidence of approximately 4–6 per million person-years and comprises a group of disorders causing hyperinsulinemic hypoglycemia without exogenous administration of insulin or its secretagogues. In adults, most cases (approximately 90%) are secondary to a single insulinoma. Other causes include insulinoma in the context of multiple endocrine neoplasia type 1 (approximately 5% of cases) and non-insulinoma pancreatogenous hypoglycemia syndrome, which is estimated to account for 0.5–5% of all cases. Recently, an entity called insulinomatosis has been described as a novel cause of EHH in adults. The characteristic feature of insulinomatosis is the synchronous or metachronous occurrence of multiple pancreatic neuroendocrine tumors expressing exclusively insulin. While most cases arise sporadically, there is recent evidence that autosomal dominant inheritance of mutations in the v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA) gene can cause a familial form of insulinomatosis. In these families, EHH is paradoxically associated with the occurrence of diabetes mellitus within the same family. This review summarizes the current clinical, biochemical, imaging and genetic knowledge of this disease.

Introduction

Endogenous hyperinsulinemic hypoglycemia (EHH) is a rare condition with an incidence of approximately 4–6 per million person-years (Grant 2005). A key diagnostic feature of EHH is the Whipple triad, which includes symptoms consistent with hypoglycemia, documentation of a low glucose concentration and relief of the symptoms after ingestion of carbohydrates (Cryer et al. 2009). Symptoms of hypoglycemia include those of the autonomous nerve system, such as sweating, weakness, tachycardia and hunger, as well as those of neuroglycopenia including a panoply of neurological symptoms including irritability, cognitive deficits and transient focal neurological deficits which may progress to seizures and coma (Valente et al. 2018). Thus, patients with EHH often present first to neurologists or even psychiatrists. An additional nonspecific, but helpful detail in the clinical history, is a significant increase in weight over recent years in more than 50% of patients (Jabri & Bayard 2004, Valente et al. 2018).

In adults, most cases (approximately 90%) of EHH are secondary to a single insulinoma, a well-differentiated insulin-producing pancreatic neuroendocrine tumor.
In about 5% of cases, EHH is secondary to an insulinoma developing in the context of multiple endocrine neoplasia type 1 (MEN1; Anlauf et al. (2009)). A rare cause of EHH in adults is non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) which is estimated to account for 0.5–5% of all EHH cases (Jabri & Bayard 2004). NIPHS represents a heterogenous group of disorders characterized by post-prandial hypoglycemia and beta cell hypertrophy (also known as nesidioblastosis) and includes both idiopathic forms and cases secondary to previous bariatric surgery (Klöppel et al. 2008). Recently, a novel cause of EHH in adults known as insulinomatosis has been described. Insulinomatosis is characterized by multiple insulinomas (predominantly micro-insulinomas) scattered throughout the entire pancreas in the absence of extra-pancreatic clinical manifestations. While the exact prevalence of insulinomatosis is unknown, in a large series of patients with adult-onset EHH, insulinomatosis accounted for 5% of all cases (Anlauf et al. 2009).

While insulinomas represent the most common cause of EHH in adults, most cases of EHH in children fall within the category of familial hyperinsulinism. This entity comprises cases with either congenital or childhood-onset hyperinsulinism and is secondary, in approximately 60% of probands, to pathogenic mutations in at least 14 different genes (Gillis 1993).

The differential diagnosis of EHH should include exogenous administration of insulin secretagogues or insulin (factitious hypoglycemia) as well as the insulin autoimmune syndrome (also known as Hirata’s disease) (Service 1999). The clinical, biochemical and imaging characteristics of the different diagnoses are summarized in Table 1.

In a patient with symptoms consistent with hypoglycemia and documented hypoglycemia, additional biochemical assessment including insulin, C-peptide and, if possible, pro-insulin and beta-hydroxy-butyrate have to be performed in the emergency department or by performing a provocative test, the so-called prolonged fasting test (Cryer et al. 2009). This test consists of a maximum 72 h supervised fast in an inpatient setting with regular assessment of glucose, insulin and C-peptide levels and, in case of symptomatic hypoglycemia (usually neuroglycopenic symptoms), it is considered positive in the presence of inappropriate insulin and C-peptide levels with concomitant hypoglycemia. In case of suspicion of factitious hypoglycemia, assessment of oral hypoglycemic agents (sulfonylurea, meglitinides) and their metabolites is recommended (Cryer et al. 2009). In addition, the normal response of the counter-regulatory hormones should be documented, namely cortisol, growth hormone and glucagon (Cryer et al. 2009).

**Morphological assessment in case of EHH**

Once the biochemical diagnosis of EHH is established, morphological investigations are recommended (Falconi et al. 2016). Usually, conventional imaging is performed via free access

### Table 1  Differential diagnosis of endogenous hyperinsulinemic hypoglycemia (EHH) in adults.

<table>
<thead>
<tr>
<th>Occurrence of symptoms</th>
<th>Glucose (mmol/L)</th>
<th>C-peptide (nmol/L)</th>
<th>Insulin (pmol/L)</th>
<th>Additional parameters</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting hypoglycemia</td>
<td>&lt;3</td>
<td>&gt;0.2</td>
<td>&gt;20.8</td>
<td>Weight gain, single lesion on imaging.</td>
<td>Insulinoma</td>
</tr>
<tr>
<td>Fasting hypoglycemia</td>
<td>&lt;3</td>
<td>&gt;0.2</td>
<td>&gt;20.8</td>
<td>Weight gain, known MEN1 mutation and/or additional endocrine diseases like primary hyperparathyroidism and/or pituitary adenoma and/or adrenal adenomas.</td>
<td>Insulinoma(s) in the context of MEN1</td>
</tr>
<tr>
<td>Fasting or postprandial hypoglycemia</td>
<td>&lt;3</td>
<td>&gt;0.2</td>
<td>&gt;20.8</td>
<td>Weight gain, no focal lesion on conventional imaging, focal or generalized increased uptake on molecular imaging possible. Often recurrent disease after surgery. Definitive diagnosis only on histology. Patients may have a history of bariatric surgery.</td>
<td>NIHPS</td>
</tr>
<tr>
<td>Fasting hypoglycemia</td>
<td>&lt;3</td>
<td>&gt;0.2</td>
<td>&gt;20.8</td>
<td>Weight gain, one or &gt;1 lesions on imaging. Often recurrent disease after surgery. Definitive diagnosis only on histology.</td>
<td>Insulinomatosis</td>
</tr>
<tr>
<td>Mainly postprandial</td>
<td>&lt;3</td>
<td>&gt;0.2</td>
<td>&gt;20.8</td>
<td>Anti-insulin antibodies detectable. Negative imaging.</td>
<td>Insulin autoimmune syndrome</td>
</tr>
<tr>
<td>Mainly fasting</td>
<td>&lt;3</td>
<td>&gt;0.2</td>
<td>&gt;20.8</td>
<td>Insulin secretagogues (sulfonylureas and meglitinides) detectable. Negative imaging.</td>
<td>Exogenous administration of oral hypoglycemic agents</td>
</tr>
</tbody>
</table>

MEN1, multiple endocrine neoplasia type 1; NIHPS, non-insulinoma pancreatogenous hypoglycemia syndrome.
first, that is, contrast-enhanced magnetic resonance imaging (ceMRI) or contrast-enhanced computed tomography (ceCT) scan (Falconi et al. 2016). There is no clear evidence whether ceMRI outperforms ceCT (Falconi et al. 2016, Antwi et al. 2021). It is noteworthy that the inferior limit of detection of conventional imaging is approximately 0.5–1cm (Falconi et al. 2016, Antwi et al. 2021). If a lesion consistent with a neuroendocrine tumor is found on conventional imaging, surgery for insulinoma can be performed, including enucleation or more extensive surgery such as Whipple procedure or distal pancreatectomy depending on the size, location of the tumour and relationship to the pancreatic duct (Antwi et al. 2018, 2021). However, in approximately 20–30% of cases, the lesions cannot be localized and, in this case, additional investigations are recommended including endoscopic ultrasonography (EUS) or selective intra-arterial calcium stimulation with venous sampling (Falconi et al. 2016). Both are invasive procedures, whereas, in particular, the calcium stimulation test requires the selective cannulation of the different feeding arteries of the pancreas and the hepatic vein (Wiesli et al. 2004a). Although both tests have a high sensitivity and specificity, the EUS is operator-dependent and the results of the calcium stimulation test indicate only the arterial catchment area of the lesion and not the lesion itself (Falconi et al. 2016, Wiesli et al. 2004b). This is a drawback in the rare situation of e ectopic insulinoma (Wild et al. 2008).

Molecular imaging is an elegant method to localize hidden pancreatic insulinomas. Insulin-secreting neuroendocrine tumors, including benign insulinomas as well as insulinomas in the context of MEN1 and probably insulinomatosis, do rarely overexpress somatostatin receptors subtype 2 (sst2) in contrast to other neuroendocrine tumors and, therefore, molecular imaging using ⁶⁸Ga-DOTATOC or DOTATE is not always successful (Reubi 2003). However, ⁶⁸Ga-DOTATOC or DOTATE PET/CT is meanwhile widely available and used for localizing insulin-secreting pancreatic neuroendocrine tumors with positive results in 50–60% of the cases (Falconi et al. 2016). In addition, there is evidence for a successful localization of the biggest lesion in a patient with possible insulinomatosis on histology using ⁶⁸Ga-DOTATATE PET/CT (Babic et al. 2016). Benign insulinomas overexpress GLP-1 receptors (Reubi 2003) and recent results of prospective trials indicate that the positron emitter ⁶⁸Ga linked to the GLP-1 analog exendin is a very sensitive method for non-invasive localization of insulinomas (Antwi et al. 2018).

Personal experience indicates that the larger lesions in the case of insulinomatosis can also be visualized using this technique. However, lesions below the detection limit of PET imaging (<0.3–0.5 cm) cannot be identified. While imaging may allow the diagnosis of multifocal neuroendocrine tumors, it would not be possible to differentiate insulinomatosis from MEN1-related insulinomas on the basis of conventional or functional imaging. Family history, additional endocrine disorders (mainly primary hyperparathyroidism and pituitary tumors) and genetic testing can be helpful to diagnose EHH in the context of MEN1; however, for insulinomatosis, only the histological examination of the surgical sample will establish the diagnosis.

Clinical features of insulinomatosis

Approximately 22 cases of sporadic insulinomatosis and 3 kindreds with familial insulinomatosis have been described to date (Tragl & Mayr 1977, Anlauf et al. 2009, Iacovazzo et al. 2018, Snith et al. 2020, Anoshkin et al. 2021, Mintziras et al. 2021, Fottner et al. 2022, Tartaglia et al. 2022). Among the patients with sporadic insulinomatosis, 17/22 are females (77.3%). All patients presented the first symptoms of the disease as adults, with a mean age at diagnosis of 42.6 years (range 17–64). The diagnosis was confirmed histologically in all cases. Overall, 11/22 patients had either persistent or recurrent EHH following the initial surgery and at least eight patients required more than one pancreatic resection. At the last follow-up, 16/22 patients were reported to be in clinical remission. It should be noted that, in two cases, insulin levels at the time of hypoglycemia were undetectable and the diagnosis was confirmed by measuring pro-insulin levels, which were inappropriately raised.

In the 3 families with familial insulinomatosis, 12 subjects were diagnosed with insulinomatosis (10 females; mean age at diagnosis 40.9 years, range 18–65). Eight patients underwent pancreatic surgery, and five required more than one operation. The remaining patients were managed with dietary changes and medical treatment with either diazoxide and/or somatostatin analogs. At the last follow-up, three out of eight patients who had undergone surgical treatment were reported to be in clinical remission. Importantly, at least 21 subjects in these families were diagnosed with diabetes mellitus (14 males; mean age at diagnosis for those with available data was 37.7 years, range 11–65). BMI was reported to be normal and there were no clinical features of insulin resistance in...
these patients. Hyperglycemia was mild to moderate and was managed with diet and/or oral hypoglycemic agents.

The clinical features of patients with available clinical and biochemical data are summarized in Table 2.

### Histological features of insulinomatosis

The characteristic histological features of insulinomatosis are shown in Fig. 1 and consist of multiple insulin-expressing pancreatic neuroendocrine tumors, including predominantly micro-adenomas (<5 mm) and scattered macro-tumors (>5 mm), which develop both synchronously and metachronously (Anlauf et al. 2009). Over 100 micro-adenomas can be identified in patients with extensively sampled pancreatic resection specimens. The expression of insulin in all lesions discriminates insulinomatosis from other forms of micro-adenomatosis: in MEN1 patients, micro-adenomas express a range of different hormones, including predominantly glucagon and pancreatic polypeptide while in patients with Von Hippel-Lindau syndrome, micro-adenomas are typically negative for pancreatic hormones (Périgny et al. 2009). Glucagon-cell adenomatosis represents another condition of pancreatic micro-adenomatosis which can arise as a consequence of inactivating mutations in the glucagon receptor gene leading to glucagon resistance and hyperglucagonemia in the absence of glucagonoma syndrome (Zhou et al. 2009, Miller et al. 2015). While in glucagon cell adenomatosis the multiple glucagon-producing micro-adenomas are accompanied by islet cell hyperplasia, hyperplastic islets are not a feature of insulinomatosis. Furthermore, insulinomatosis differs from nesidioblastosis, as the latter is a non-neoplastic condition characterized by islets with hypertrophic beta cells without tumor formation (Klöppel et al. 2008). Interestingly, no cases of lymph node or distant metastases have been reported to date in patients with insulinomatosis, while MEN1-related pancreatic neuroendocrine tumors have the potential for metastatic spread which occurs in approximately 20–30% of patients.

### Genetic background of insulinomatosis

While most patients with insulinomatosis present with sporadic disease, rare instances of familial insulinomatosis with autosomal dominant inheritance patterns have been described. Recently, two different missense mutations in the MAFA gene have been identified in three unrelated families: Ser64Phe (Lacovazzo et al. 2018) and Thr57Arg (Fottner et al. 2022). MAFA belongs to the family of large MAF transcription factors and is expressed in islet β cells. It is required for postnatal β cell function and acts as a transactivator of insulin and several genes involved in glucose-stimulated insulin secretion (Zhang et al. 2005, Artner et al. 2010).

Both missense mutations (Ser64Phe and Thr57Arg) resulted in the development of an adult-onset dual phenotype of either insulinomatosis (more likely in female carriers) and interestingly also MODY-like diabetes mellitus (more likely in male carriers) (Lacovazzo et al. 2018, Fottner et al. 2022). Four cases of congenital eye disease (including glaucoma and/or congenital cataracts) were reported in one family, including two homozygous mutation carriers (Lacovazzo et al. 2018). The disease presents with high penetrance (Lacovazzo et al. 2018, Fottner et al. 2022). Importantly, both mutations are located in highly conserved residues within the transactivation domain (Lacovazzo et al. 2018, Fottner et al. 2022). Functionally, the Ser64Phe mutation impairs the phosphorylation cascade of MAFA with impairment of transactivation activity and degradation (Lacovazzo et al. 2018). The Thr57Arg mutation is expected to have a similar effect on MAFA phosphorylation since it affects one of the residues which are phosphorylated by GSK3 and are relevant in determining the stability and transactivation activity of MAFA (Benkhelifa et al. 2001, Guo et al. 2009).

The two phenotypes of MAFA mutations, namely insulinomatosis and MODY-like diabetes mellitus, possibly dependent on gender, are intriguing and the underlying mechanisms remain to be established. Interestingly, the same Ser64Phe mutation causes diabetes mellitus selectively in male mice, while female carriers are hypoglycemic with improved glucose clearance (Walker et al. 2021). The potential effects of sex hormones were investigated in this animal model: ovariectomy at three weeks resulted in glucose intolerance in wildtype mice by four weeks of age, while glucose sensitivity was unaffected in mutant mice, suggesting that the effect of the S64F mutation was dominant over the effects of estrogen deficiency. Furthermore, testosterone levels in four- and five-week-old male mice were expectedly low and similar to those observed in age-matched females, suggesting that the effects of androgens on the development of the sexual dimorphic phenotype would be negligible and that the diabetic phenotype might precede the onset of puberty in males. Overall, these data suggest that additional...
genetic or environmental factors other than exposure to sex hormones are implicated in the sexual dimorphism observed in MAFa mutation carriers.

While all described instances of familial insulinomatosis are a consequence of an MAFa mutation, the genetic background of sporadic insulinomatosis, which comprises the majority of reported cases of the disease, is still unknown. An in-frame single histidine deletion in the MAFa gene has been reported in a patient with sporadic insulinomatosis (Mintziras et al. 2021). However, this appears to represent a common polymorphism as deletions or duplications involving the

Table 2  Clinical features of the published patients with insulinomatosis with available clinical and biochemical data.

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>Biochemistry at diagnosis (fasting test)</th>
<th>Treatment</th>
<th>TNM staging (UICC 8th edition)</th>
<th>Tumor grading</th>
<th>Persistent or recurrent disease after initial surgery</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fa1</td>
<td>M</td>
<td>30</td>
<td>Glu 2.1, Ins 316.7, C-pep 1.7</td>
<td>Enucleation ×2, diazoxide + verapamil</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Fa2</td>
<td>M</td>
<td>38</td>
<td>Glu 2.3, Ins 84, C-pep 0.8</td>
<td>Verapamil</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Fa1</td>
<td>F</td>
<td>48</td>
<td>Glu 2.7, Ins 105.7</td>
<td>Partial pancreatectomy, diazoxide</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Fa1</td>
<td>F</td>
<td>44</td>
<td>Glu 2.5, Ins 77.8</td>
<td>Octreotide + verapamil + dexamethasone</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Fa1</td>
<td>F</td>
<td>53</td>
<td>Glu 2.3, Ins 84, C-pep 0.8</td>
<td>Partial pancreatectomy, diazoxide</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Fa2</td>
<td>F</td>
<td>28</td>
<td>Glu &lt;1.1, Ins 1111.2</td>
<td>Enucleation, partial pancreatectomy, diazoxide</td>
<td>n/a</td>
<td>G1</td>
<td>Yes</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Fa2</td>
<td>F</td>
<td>65</td>
<td>Glu 2.4, Ins 18.8</td>
<td>Diazoxide</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Fa3</td>
<td>F</td>
<td>38</td>
<td>Glu 0.9, Ins n/a, C-pep n/a</td>
<td>Partial pancreatectomy ×2</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Fottner et al. (2022)</td>
</tr>
<tr>
<td>Fa3</td>
<td>F</td>
<td>53</td>
<td>Glu 1.9, Ins 97.2, C-pep 1</td>
<td>Partial pancreatectomy</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>No</td>
<td>Fottner et al. (2022)</td>
</tr>
<tr>
<td>Sp1</td>
<td>F</td>
<td>17</td>
<td>Glu 1.9, Ins 104, C-pep 1</td>
<td>Enucleation ×2, diazoxide + dexamethasone</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Sp2</td>
<td>F</td>
<td>48</td>
<td>Glu 2.3, Ins 137.5, C-pep 0.8</td>
<td>Enucleation, partial pancreatectomy, diazoxide</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Sp3</td>
<td>F</td>
<td>64</td>
<td>Ins undetectable, pro-Ins 20.4, C-pep 0.1</td>
<td>Partial pancreatectomy ×2</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Iacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Sp4</td>
<td>F</td>
<td>47</td>
<td>Glu 1.6, Ins 305.6, C-pep 1.8</td>
<td>Partial pancreatectomy</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>No</td>
<td>Lacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Sp5</td>
<td>F</td>
<td>51</td>
<td>Glu 1.6, Ins 29.4, C-pep 0.2</td>
<td>Distal pancreatectomy</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>No</td>
<td>Lacovazzo et al. (2018)</td>
</tr>
<tr>
<td>Sp6</td>
<td>F</td>
<td>40</td>
<td>Glu 1.6, Ins 305.6, pro-Ins 122, C-pep 1.8</td>
<td>Enucleation ×2, total pancreatectomy, diazoxide, everolimus</td>
<td>pT2(m) N0</td>
<td>G2</td>
<td>Yes</td>
<td>Snaith et al. (2020)</td>
</tr>
<tr>
<td>Sp7</td>
<td>F</td>
<td>48</td>
<td>Glu 2, Ins 13.9, pro-Ins 21.9, C-pep 0.08</td>
<td>Enucleation, distal pancreatectomy</td>
<td>pT2(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Mintziras et al. (2021)</td>
</tr>
<tr>
<td>Sp8</td>
<td>F</td>
<td>41</td>
<td>Glu 2.4, Ins 25.7, C-pep 0.4</td>
<td>Distal pancreatectomy, octreotide</td>
<td>pT1(m) N0</td>
<td>G1</td>
<td>Yes</td>
<td>Tartaglia et al. (2022)</td>
</tr>
</tbody>
</table>

C-pep, C-peptide (nmol/L); F, female; Fa, familiar case; Glu, glucose (mmol/L); Ins, insulin (pmol/L); M, male, n/a, not available/applicable; pro-Ins, pro-insulin (pmol/L); Sp, sporadic case.
histidine repeats in this region of the gene are extremely common in the general population. Next-generation sequencing of a panel of cancer-related genes in a case of sporadic insulinomatosis highlighted the presence of somatic copy number variants affecting several tested genes, including FOXL2, IRS2, CEBPA and ATRX (Anoshkin et al. 2021). It is, however, uncertain how these would contribute to the pathogenesis of the disease.

Treatment of insulinomatosis

Due to the multicentric nature of the disease, treatment of EHH in the context of insulinomatosis is challenging. In the original case series, six out of 14 patients (43%) had persistent or recurrent disease following surgical treatment (either enucleation, distal pancreatectomy or Whipple procedure) (Anlauf et al. 2009). It should be noted, however, that some patients achieved disease remission following either initial or repeat surgery (typically distal pancreatectomy). In the two families carrying the Ser64Phe MAFA mutation, six patients underwent surgery, with persistent or recurrent EHH in all cases (Iacovazzo et al. 2018). Four of the six patients required more than one operation, including two subjects who developed insulin-dependent diabetes mellitus following the completion of total pancreatectomy. In the third family, two patients were diagnosed with insulinomatosis, including one patient with persistent EHH following distal pancreatectomy who eventually required a new surgical resection to achieve disease remission (Fottner et al. 2022). One case of sporadic insulinomatosis with persistent EHH despite total pancreatectomy has been recently described, suggesting the presence of microscopic remnants of pancreatic tissue causing persistent hyperinsulinism (Snaith et al. 2020). Responsiveness to medical treatment, including diazoxide or somatostatin analogs, is largely anecdotal.

Figure 1
Histopathology of sporadic insulinomatosis. (A) HE, 50× and (B) Insulin staining, 50×: Two insulin producing micro-tumors, staining for insulin. (C) Third micro-tumor staining for insulin, below normal islets. (D) Glucagon staining negative in the micro-tumor, but positive in normal α-cells at the periphery of normal islets. Long arrowheads, neuroendocrine tumors; short arrowheads, normal islets.
considering the rarity of the disease. Poor results with persistent hypoglycemia were reported in patients with familial insulinomatosis (Iacovazzo et al. 2018). However, a case of complete remission of an insulinoma has been recently described in a patient with sporadic insulinomatosis following treatment with octreotide long-acting release (Tartaglia et al. 2022). Dietary changes with frequent consumption of complex carbohydrates have been shown, in our experience, to help alleviate the symptoms of hypoglycemia in patients with persistent episodes of hypoglycemia.

**Conclusion**

EHH is a rare and heterogeneous clinical entity. Insulinomatosis is a recently described cause of EHH in adults and is characterized by the occurrence of multiple insulinomas scattered throughout the pancreas. While most patients present with sporadic disease, in some cases, the disease can present in a familial setting with an autosomal dominant inheritance pattern. In these families, insulinomatosis occurs more frequently in female carriers while male carriers develop MODY-like diabetes mellitus with high penetrance. This dual phenotype has been recently shown to result from missense mutations in the MAFA gene, encoding a key β cell transcription factor, while the genetic background of sporadic insulinomatosis is still largely unknown. Clinically, biochemically and with regard to localization using conventional or molecular imaging, insulinomatosis cannot be differentiated from single insulinomas or other rare causes of EHH, including insulinoma in the context of MEN-1 or NIPHS. Only the histological assessment by an experienced pathologist can establish the diagnosis.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Endocrine-Related Cancer
E Christ, D Lacovazzo et al.


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