Aggressive multimodal therapy of sporadic malignant insulinoma can improve survival: A retrospective 35-year study of 12 patients

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Abstract

Aim. – Sporadic malignant insulinoma (SMI) is a rare disease, and the consequent paucity of data in the literature and the development of aggressive treatments for liver metastases have led us to retrospectively analyze a series of 12 cases of SMI.

Methods. – Every patient presenting with SMI, according to the WHO 2004 histopathology criteria, between 1970 and June 2005 in Marseille was included in the study. Patients with multiple endocrine neoplasia type 1 (MEN-1) and tumours of uncertain malignant potential were excluded.

Results. – The ratio of male/female was 4/8, and mean age at diagnosis was 52.5 years. A 48-h fasting test in 10 patients was conclusive in nine, after a mean duration of 12 h 45 min. SMI size ranged from 7–120 mm (mean 30.3 mm). Six patients had liver metastases and one had isolated lymph-node invasion. Surgery was performed in 12 patients. Five persisting diseases (mean follow-up of 1.8 years) required other treatments (chemoembolization, radiofrequency thermoablation [RFTA], liver transplantation); one patient relapsed 8.5 years after surgery; six were still in complete remission (mean follow-up of 5.8 years), and one patient had died by the time of the 24-month follow-up.

Conclusion. – Aggressive sequential multimodal therapy can prolong the survival of patients with SMI even in the presence of liver metastases.

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Résumé

Une stratégie multimodale de traitement agressif des insulinomes malins sporadiques peut améliorer la survie : étude descriptive rétrospective de 12 cas.

Introduction. – Les insulinomes malins sporadiques sont une pathologie rare. Le manque d’informations sur cette pathologie dans la littérature et le développement de traitements agressifs sur les métastases hépatiques nous ont conduit à analyser de façon rétrospective une série de 12 cas d’insulinome malin sporadique.

Patients et Méthodes. – Tous les patients d’une métropole régionale présentant un insulinome malin selon les critères de l’OMS de 2004, hors néoplasie endocrinienne multiple de type 1 et tumeurs à risque d’évoluer vers la malignité, avec confirmation anatomopathologique entre 1970 et juin 2005 ont été inclus.

Abbreviations: SMI, sporadic malignant insulinoma; RFTA, radiofrequency thermoablation.

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**Résultats.** – Le sex-ratio était de 4H/8F avec un âge moyen au diagnostic de 52,5 ans. L’épreuve de jeûne a pu être effectuée chez dix patients et a été interrompue chez neuf d’entre eux après une durée moyenne de 12 heures 45 minutes. La taille moyenne des tumeurs réséquées était de 7 à 120 mm (moyenne 30,3 mm). Les 12 patients ont été opérés. Six patients avaient une ou des métastases hépatiques et une patiente avait un envahissement ganglionnaire adjacent au pancréas. Après la chirurgie, six patients avaient une maladie persistante (suivi moyen de 1,8 ans) appelant d’autres traitements (chimioembolisation, radiofréquence, transplantation hépatique, analogues de la somatostatine...), un patient a récidivé 8,5 ans après la chirurgie, six patients sont en rémission complète (suivi moyen de 5,8 ans). Seulement une patiente est décédée après 24 mois de traitement.

**Conclusion.** – Cette étude rétrospective illustre la grande variabilité du pronostic des insulinomes malins sporadiques. Leur habituel bas grade de malignité et leur évolution lente conduit à permettre des traitements agressifs sur les métastases hépatiques. La prise en charge de ces patients demande une collaboration multidisciplinaire pour pouvoir améliorer leur survie.

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**Keywords:** Sporadic malignant insulinoma; Islet cell tumour; Insulinoma; Tumour; Hyperinsulinism

**Mots clés :** Insulinome malin sporadique ; Tumeur endocrine pancréatique sécrétante ; Insulinome ; Hyperinsulinisme

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1. **Introduction**

Sporadic malignant insulinoma (SMI) is a rare disease, representing 2.6–16% of functioning islet cell tumours, according to criteria used to define the condition [1–5]. The Mayo Clinic’s 60-year experience, reported by Service et al. [6], includes one of the largest published series of SMI cases. Thirteen patients exhibiting malignant insulinoma, confirmed by the presence of hepatic metastases, were diagnosed among the 224 patients referred to this institution with functional islet cell tumours (5.8%). Another survey on 1085 insulin-secreting islet tumours in Japan identified a 13.6% rate of malignancy with a 6% rate of metastasis [7].

These malignant tumours are potentially curable in cases where complete surgical resection is possible [8]. Follow-up of such patients has been reported in two retrospective series [1,9]. Despite the progressive improvement in therapeutic methods over time at our institution, the standard policy had been an aggressive sequential multimodal approach to better control the tumour mass or hypoglycaemic symptoms. To evaluate the efficacy of such a strategy, we retrospectively analyzed a series of 12 patients collected over a 35-year period of time. The aims of this study were to:

- evaluate the overall prognosis;
- review the efficacy of various therapeutic options in this rare clinical situation;
- and delineate the best therapeutic strategy so far.

2. **Subjects and methods**

This retrospective analysis of SMI was based on a survey of every case seen at the University Hospitals (Assistance publique des hôpitaux de Marseille) and Cancer Institute (Institut Paoli-Calmettes) in Marseille over the past 35 years (from 1970 to June 2005). As the database of every department was retrospectively reviewed (Endocrinology and Nutrition, Endocrine Surgery, Oncology, Pathology), we assumed that this approach—involving so many of the city’s main medical institutions—would result in an exhaustive collection. Patients with multiple endocrine neoplasia type 1 (MEN-1), or with clinical or biological signs evocative of MEN-1 (hyperparathyroidism, pituitary secretion, adrenal secretion, cutaneous lesions), were excluded. We also excluded four patients with tumours of uncertain malignant potential [10]. Altogether, 12 patients were selected with SMI, as defined by WHO 2004 histopathology criteria [10]. We considered as malignant a tumour with liver and/or lymph-node metastases in conjunction with histological characteristics. Insulinomas that are not overtly malignant were classified as low-grade carcinomas when two or more of the following features were present: extrapancreatic soft-tissue invasion; vascular and/or perineural invasion; necrosis; high mitotic rate. Insulinomas presenting with only one of these characteristics, and a high nuclear grade and a diameter greater than 2 cm, were considered borderline tumours and were, therefore, excluded. In all cases, the diagnosis of overt malignant insulinoma was confirmed after surgical resection of the pancreatic tumour by histological analysis. Medical charts as well as surgical and pathological files of the patients were also analyzed to determine the investigations used for diagnosis, preoperative localization of tumour tissue, evaluation of pancreatic tumour size, local and extrapancreatic distributions, and curative and palliative therapeutic approaches and outcomes.

3. **Results**

The clinical characteristics of the 12 patients with SMI are presented in Table 1. The male/female ratio was 4/8, and the mean age at diagnosis was 52.5 years (range 28–68). Some patients had a prolonged symptomatic phase with manifestations of neuroglycopenia preceding the diagnosis of hyperinsulinism (more than four years in five patients). The 48-h fasting test performed in 10/12 patients was conclusive in nine cases (clinical manifestations and hypoglycaemia after a mean duration of 12 h 45 min). In one patient (#9), who had no overt clinical manifestations, the plasma glucose at the end of the 48-h fasting test was 0.21 g/L. In another patient (#6), the 48-h fasting test was considered unnecessary and dangerous because of profound and permanent spontaneous hypoglycaemia. For a further patient (#2), data were not available. During these investigations, the Turner index was abnormal in 8/10 patients. In one patient with a normal index, but a discrepancy between insulin...
Table 1
Clinical characteristics of 12 patients with malignant insulinoma

<table>
<thead>
<tr>
<th>Patients</th>
<th>Gender (M/F)</th>
<th>Age (years)</th>
<th>Symptom duration (months)</th>
<th>Clinical symptoms</th>
<th>Fasting test cessation (h)</th>
<th>Turner index</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>F</td>
<td>49</td>
<td>60</td>
<td>AS</td>
<td>6 h 30</td>
<td>633</td>
<td>39</td>
</tr>
<tr>
<td>#2</td>
<td>F</td>
<td>57</td>
<td>12</td>
<td>Confusion</td>
<td>NA</td>
<td>NA</td>
<td>24</td>
</tr>
<tr>
<td>#3</td>
<td>M</td>
<td>50</td>
<td>18</td>
<td>Tremor</td>
<td>6 h 45</td>
<td>1217</td>
<td>104</td>
</tr>
<tr>
<td>#4</td>
<td>F</td>
<td>51</td>
<td>9</td>
<td>AS</td>
<td>12 h</td>
<td>260</td>
<td>16</td>
</tr>
<tr>
<td>#5</td>
<td>M</td>
<td>49</td>
<td>72</td>
<td>Epilepsy</td>
<td>6 h</td>
<td>113</td>
<td>41</td>
</tr>
<tr>
<td>#6</td>
<td>F</td>
<td>28</td>
<td>6</td>
<td>Coma</td>
<td>NA</td>
<td>NA</td>
<td>32</td>
</tr>
<tr>
<td>#7</td>
<td>F</td>
<td>71</td>
<td>48</td>
<td>Confusion</td>
<td>5 h</td>
<td>230</td>
<td>74</td>
</tr>
<tr>
<td>#8</td>
<td>M</td>
<td>57</td>
<td>5</td>
<td>Epilepsy</td>
<td>26 h 15</td>
<td>890</td>
<td>20</td>
</tr>
<tr>
<td>#9</td>
<td>F</td>
<td>53</td>
<td>72</td>
<td>Epilepsy</td>
<td>48 h</td>
<td>310</td>
<td>22</td>
</tr>
<tr>
<td>#10</td>
<td>F</td>
<td>46</td>
<td>24</td>
<td>Confusion</td>
<td>6 h 45</td>
<td>175</td>
<td>171</td>
</tr>
<tr>
<td>#11</td>
<td>M</td>
<td>48</td>
<td>3</td>
<td>Confusion</td>
<td>2 h 30</td>
<td>800</td>
<td>13</td>
</tr>
<tr>
<td>#12</td>
<td>F</td>
<td>67</td>
<td>6</td>
<td>Coma</td>
<td>9 h</td>
<td>92</td>
<td>77</td>
</tr>
</tbody>
</table>

AS: autonomic signs; NA: not available.

and C-peptide levels, the explanation was the secretion of large amounts of proinsulin by the tumour. In six patients, a panel of other secretions specific to endocrine tumours was measured. Increased plasma levels of these secretions were observed in four patients (especially plasma chromogranin A, found to be increased in three cases).

Localization and measurement of the tumours, and correlations with pre- and perioperative findings, are presented in Table 2. Sporadic malignant insulinoma size ranged from 7–120 mm (mean 30.3 mm). Small tumours (less than 20 mm) were observed in four patients, and multiple pancreatic tumours in three cases. During the 35-year study period, imaging strategies changed. Among the earlier cases, selective angiography was performed (patients #1 and #12; one positive, one false-negative, respectively). More recently, computed tomography (CT) and endoscopic ultrasound (EUS) were used as first-line investigations, with a sensitivity of 54.5% (6/11) and 88.8% (8/9), respectively. There was a reasonable correlation between tumour size as evaluated by EUS and pathological findings (Table 2). An OctreoScan was informative in three of the six tests performed. Other investigations included magnetic resonance imaging (MRI) and positron emission tomography (PET), but these were too rarely performed to be included in an analysis.

Liver metastases were observed in six patients (three known before surgery, one discovered during surgery, one diagnosed during a second operation after relapse of hypoglycaemic attacks and one after a relapse 8.5 years after surgery). In other patients, invasion of peripancreatic tissue and/or lymph nodes was noted. Fig. 1 shows the patients’ outcomes. Pancreatic surgery was carried out in every patient: one subtotal pancreatectomy; four Whipple’s pancreatoduodenectomy with regional lymphadenectomy; five left pancreatectomy with splenectomy and/or liver metastatic resection; and one tumour enucleation with cancer-free surgical margins. For the oldest patient, no surgical report was available. Five patients were not cured after surgery. No patient had extrahepatic metastases.

Every patient with remaining tumour tissue after surgery was subjected to an aggressive multimodal strategy aimed to either reduce or remove malignant insulin-secreting tissue and/or control hyperinsulinaemia. One patient (#2, the oldest case in the series) was treated by a palliative treatment comprising...
Fig. 1. Outcome and survival of 12 patients with malignant insulinoma.

4. Discussion

This retrospective series was an exhaustive register of aggressive multimodal therapy in a single referral centre over the past 35 years to control either tumour mass and/or hypoglycaemic symptoms, the standing policy of our institution despite the introduction of newer methods. Two opposing situations can be distinguished, according to the presence or absence of overt liver metastases.

Patients without metastases had a good outcome after resection of pancreatic tumours and local invasion of surrounding tissues or organs. The prognosis is similar to that observed in tumours of uncertain malignant potential. Long-term survival in these patients has already been noted in previous series [1,12,13]. However, these patients need to be followed-up in case of either local relapse or metastasis, even after years of being in remission [14]. In such patients, malignancy is difficult to diagnose. Risk factors (extrapancreatic soft-tissue invasion, vascular and/or perineural invasion, necrosis, high mitotic rate) are listed in different orders by the authors. Soft-tissue and vascular invasion were the most important for Rindi et al. [11], while the most predictive were necrosis and rate of mitosis for Hochwald et al. [13].

In patients with liver metastases, aggressive multimodal therapy improved both survival and quality of life. Several active strategies need to be considered to prolong survival and/or prevent hypoglycaemic episodes. Our long-term retrospective study demonstrates that efforts to control either tumour mass or hypoglycaemic symptoms by various approaches can lead to long-term survival in many patients, although the rarity of islet cell cancer does not allow specific analysis of the respective efficacy of the various approaches found in the literature. Also, most of the studies dedicated to the subject lumped together various types of endocrine tumours [12,13].

Liver metastases can be treated by either surgical resection (non-anatomical enucleation, segmentectomy, right or left hep-
atectomy) or non-surgical therapy. The efficacy and safety of concurrent resection of pancreatic islet cell cancer and hepatic metastases have been analyzed by Sarmiento et al. [15] in a series of 23 endocrine tumours. They noted no perioperative deaths, although major surgical complications were seen in 18% of the patients. The overall and symptom-free survival at five years was 71 and 24%, respectively, confirming the 79% five-year survival rate observed in the 17-patient series reported by Carty et al. [16]. Other authors have also reported that an aggressive strategy against liver metastases will prolong survival [17,18]. Surgical resection of liver metastases is indicated except in cases where less than 90% of the tumour is treatable [19].

In association with surgery or instead of it, image-guided radiofrequency thermoablation (RFTA) may be considered. RFTA of metastases is a non-invasive palliative treatment that decreases tumour volume while keeping healthy tissues relatively intact. It can be performed percutaneously or laparoscopically, and is suitable for the smallest metastatic lesions (<3 cm) [20]. Gillams et al. reported on their experience of 25 endocrine liver metastases treated by this approach [21]. Their complication rate was 12%, a complete response was obtained in 32% and the hormone-related symptoms were controlled in 74% of cases.

Transarterial chemoembolization is another treatment option. Streptozotocin-based combinations, including 5-fluorouracil and doxorubicin, can induce partial remission in 40–60% of pancreatic endocrine tumours with liver metastases [22]. However, Kress et al. [23] have reported their experience of 26 attempts and rather poor results: regression of the tumour burden in two cases; stabilization in 14; evolution in five; and technical failure in five. They concluded that better results were obtained when the tumour burden was low (<50%) and lipiodol uptake was high (>50%). In the Starke et al. series of 10 malignant insulinomas with hepatic metastatic disease [8], repeated transarterial chemoembolization and chemoperfusion using high-dose streptozotocin (3–4 g per session) was systematically applied, with the result that four patients died after a median survival of 1.8 years, while six survived (median survival: 3.7 years). As expected, the better survival rates were associated with resection of the primary tumour and intention-to-treat metastatic cure [12,18].

Finally, hepatectomy and orthotopic liver transplantation are options to be considered in patients with intractable hepatic metastases without systemic dissemination and with a relatively stable clinical condition. Other important selection criteria are well-differentiated tumours and a low proliferation rate [24]. One 28-year-old patient (#6) in the present series, who did not improve with successive surgical and medical treatments, did finally benefit from a liver transplant from her living sister. In fact, a few small series of liver transplants in cases of intractable metastases of endocrine tumours in the literature [25,26] show that, in some cases, liver transplantation is not just palliative, but curative [20]. Patient #6 illustrates how the sequential progression in successive attempts to control tumour mass can finally lead to liver transplantation.

Palliative medical treatment aimed at inhibition of insulin secretion by tumour tissue is another possible option. Diazoxide has been used in the past, but long-acting somatostatin analogues (octreotide and lanreotide) are more comfortable for the patient. These treatments are able to transiently control hormone-related symptoms in 30–70% of patients, depending on the type of receptor (sst2A or sst5) in the tumour [27]. Vezzosi et al. [28] have shown that this response is more accurately predicted by a short test with subcutaneous octreotide than by OctreoScan scintigraphy. However, despite inhibition of the hormonal response, there is little or no effect on tumour growth, although it is worth noting that, with time, every patient escapes from somatostatin analogue therapy in terms of both symptoms and tumour growth [review in 28]. Finally, as the use of alpha-interferon [29] and radiopeptide therapy for malignant insulinomas have been anecdotal, it is not possible to precisely define their place in any therapeutic strategy [30].

In conclusion, this long-term retrospective study confirms that aggressive sequential, multimodal therapy may considerably improve survival and quality of life of patients with SMI, even in the presence of liver metastases.

As stated in the guidelines established by the UKNET work for Neuroendocrine Tumours [22], surgery should be offered as the first-line treatment for all patients with pancreatic tumour, and for liver metastases in patients who have potentially resectable liver metastases (at least 90% of the tumour can be removed). In other cases, palliative treatments—the sequence of which depends on the number, localization and dissemination of liver metastases—should be used to prolong survival and control insulin-related symptoms. At present, liver transplantation is considered only in rare circumstances because of organ shortage and the risk of relapse, although long-term symptom-free survival has been observed in some patients as a result of this intervention.

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