SESSINE I
TUMORI NEUROENDOCRINI DEL TRATTO GASTRO-ENTERO-PANCREATICO

- Il ruolo dell’anatomo-patologo S. Pizzolitto
Cosa chiedere al Patologo?

“LA DIAGNOSI”
Dicembre 2012: Imaging
Spleno-pancreasectomia distale
Dicembre 2012: Pathology

Multipli focolai microadenomatosi di 1-5 mm “nesidioblastosi?”

Macro-tumori ≥5 mm
Sinaptofisina
Sinaptofisina
1. β-cell and islet hyperplasia
2. Multicentric insulinoma
3. Metastasized insulinoma
4. MEN-1 with the development of multiple insulinomas
5. Adult nesidioblastosis
6. Insulinomatosis
The immunohistochemical determination of insulin expression by tumor cells is not absolutely necessary for diagnosis, but it provides verification of hormonal production, it may identify specific cell types. In patients without MEN1 but with multiple insulinomas or multiple recurrences, insulinomatosis should be suspected [140].
# Insulinomatosis

**A Multicentric Insulinoma Disease that Frequently Causes Early Recurrent Hyperinsulinemic Hypoglycemia**

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<table>
<thead>
<tr>
<th>Insulinoma</th>
<th>Patients</th>
<th>No. Insulinomas (Total/Mean per Patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary/sporadic</td>
<td>253 (90%)</td>
<td>≥ 5 mm: 253/1, &lt; 5 mm: 0/0</td>
</tr>
<tr>
<td>MEN1 associated</td>
<td>13 (4.6%)</td>
<td>≥ 5 mm: 20/1.5, &lt; 5 mm: 21/1.6</td>
</tr>
<tr>
<td>NF1 associated</td>
<td>1 (0.4%)</td>
<td>≥ 5 mm: 1/1, &lt; 5 mm: 0/0</td>
</tr>
<tr>
<td>Insulinomatosis</td>
<td>14 (5%)</td>
<td>≥ 5 mm: 53/3.8, &lt; 5 mm: 285/20.4</td>
</tr>
</tbody>
</table>

Incidences of patients (281) with solitary and multiple insulinomas.
Insulinomatomatosis
no MEN-1

IMECCs: insulin-expressing monohormonal endocrine cell clusters
Insulinomatosis is a monohormonal disease that affects the entire β-cell population.
Insulinomatose
(disease that affects the entire β-cell population)

- Multifocal multicentric beta-cell disease
- Hyperplasia-neoplasia sequence (precursor lesions)
- IMEECs: insulin-expressing monohormonal endocrine cell clusters < 1 mm in size
- Insulin microadenomas (< 0.5 cm)
- Metachronous development of insulin macrotumors (> 0.5 cm)
- No hereditary background
- Female/Male ratio 10/4 and younger patients
- Recurrent hypoglycemia

Anlauf M, Bauersfeld J, et al. AJSP 2009
Kaplan-Maier analysis of disease recurrences
Insulinomatosis
n=17 (5.4%)
Age: 46+/−16

Nesidioblastosis
n=22 (6.9%)
Age: 44+/−20

Normal Pancreas
n=5 (1.6%)
Age: 56+/−22

NF1-associated Insulinomas
n=1 (0.3%)
Age: 36

MEN1-associated Insulinomas
n=15 (4.8%)
Age: 38+/−14

Sporadic Insulinomas
n=255 (81.0%)
Age: 51+/−17

n = 305 patients

Courtesy of Gunter Kloppel
Microadenomatosis of the Endocrine Pancreas in Patients With and Without the Multiple Endocrine Neoplasia Type 1 Syndrome

Martin Anlauf, MD,* Regina Schlenger, MD,*† Aurel Perren, MD,*‡ Christian A. Koch, MD,§ Henning Dralle, MD,⊥ A. Wolfram T. Knoefel, MD,¶ Eberhard Weihe, MD,# Phil Nolte, MD,∗ and Anne Couvelard, MD,† † Paul Komminoth, MD,‡ ‡ and Günter Klöppel, MD.*

(Am J Surg Pathol 2006;30:560-6)
Endocr Pathol. 2014 Apr 10. [Epub ahead of print]

Hyperplasia to Neoplasia Sequence of Duodenal and Pancreatic Neuroendocrine Diseases and Pseudohyperplasia of the PP-cells in the Pancreas.

Klöppel G¹, Anlauf M, Perren A, Sipos B.

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Abstract

Hyperplastic changes of the neuroendocrine cell system may have the potential to evolve into neoplastic diseases. This is particularly the case in the setting of genetically determined and hereditary neuroendocrine tumor syndromes such as MEN1. The review discusses the MEN1-associated hyperplasia-neoplasia sequence in the development of gastrinomas in the duodenum and glucagon-producing tumors in the pancreas. It also presents other newly described diseases (e.g., glucagon cell adenomatosis and insulinomatosis) in which the tumors are (or most likely) also preceded by islet cell hyperplasia. Finally, the pseudohyperplasia of PP-rich islets in the pancreatic head is defined as a physiologic condition clearly differing from other hyperplastic-neoplastic neuroendocrine diseases.
Glucagon Cell Adenomatosis: A Newly Recognized Disease of the Endocrine Pancreas

Tobias Henopp,* Martin Anlauf,* Anja Schmitt, Regina Schlenger, Attila Zalatnai, Anne Couvelard, Philippe Ruszniewski, Klaus-Peter Schaps, Yvonne M. H. Jonkers, Ernst-Jan M. Speel, Natalia S. Pellegata, Philipp U. Heitz, Paul Komminoth, Aurel Perren,‡ and Günter Klöppel‡

Nesidioblastosis in adults

ORIGINAL ARTICLE

Persistent Hyperinsulinemic Hypoglycemia in 15 Adults With Diffuse Nesidioblastosis
Diagnostic Criteria, Incidence, and Characterization of β-Cell Changes

Martin Anlauf, MD,* Daniel Wieben,* Aurel Perren, MD,† Bence Sipos, MD,* Paul Komminoth, MD,† Andreas Raffel, MD,‡ Marie L. Kruse, MD,§ Christian Fottner, MD,‖ Wolfram T. Knoefel, MD,‡ Heiner Mönig, MD,§ Philipp U. Heitz, MD,† and Günter Klöppel, MD*

More islets as well as enlarged islets (above 300 μm)
• Lobular arrangement of islets cells
• β-cells with enlarged nuclei and clear cytoplasm
NESIDIOBLASTOSIS

β-cells hypertrophy, hyperplasia and hyperfunction

Major criteria

- Macroscopic, microscopic, and immunohistochemical exclusion of an insulinoma
- Multiple β-cells with enlarged and hyperchromatic nucleus and abundant clear cytoplasm in the majority of the islets
- Islets with normal spatial distribution and regular hormone expression patterns of the various cell types
- No proliferative activity of the Ki-67 antigen (Mib-1) of endocrine cells
Diffuse nesidioblastosis as a cause of hyperinsulinemic hypoglycemia in adults: A diagnostic and therapeutic challenge

Andreas Raffel, MD, Markus Krausch M, Martin Anlauf, MD, Daniel Wieben, Stefan Braunstein, MD, Günter Klöppel, MD, Hans-Dietrich Röher, MD, and Wolfram Trudo Knoefel, MD. Düsseldorf, Germany

(Surgery 2007;141:179-84.)
The extent of pancreatic resection is controversial. Some studies have shown that selective arterial calcium stimulation test may be useful to guide the extent of resection [14] but a study by Witteles et al. has shown that resection of 60-89% of pancreas (i.e., **distal or subtotal pancreatectomy**) is possibly the most appropriate surgery for nesidioblastosis because the risk of diabetes mellitus is below 10% with 70% success rate in achieving normoglycemia [2].
Diffuse nesidioblastosis with hypoglycemia mimicking an insulinoma: a case report

Chiara Ferrario¹, Delphine Stoll¹, Ariane Boubaker², Maurice Matter², Pu Yan¹ and Jardena J Puder¹

[13]. Conservative therapy is sometimes suggested. Diazoxide, octreotide and verapamil could be effective and safe alternative conservative therapies when surgery has failed or is considered to be too risky [8,10]. Patients’ information should include the necessity for multiple diagnostic procedures and the postoperative risks for pancreatic exocrine insufficiency and diabetes. In the
Pancreatic Nesidioblastosis in Adults

Nesidioblastosis Arising from Heterotopic Pancreas and Presenting with Hypertension: A Clinical, Immunohistochemical and Ultrastructural Study

A. RISALITI¹, S. PIZZOLITTO²


SUMMARY: A rare case of nesidioblastosis in an adult arising from heterotopic pancreas and presenting with hypertension is reported. To our knowledge it is the first case to be described in literature. The pathogenic mechanisms to explain hypertension are not clear. The stimulating action of glucagon on the adrenal gland or on peripheral beta receptors could be considered as hypothetical factors.

KEY-WORDS: Nesidioblastosis. — Heterotopic pancreas. — Hypertension. — Adult.
APUDOMAS TODAY-'70s

TRIBUTE

TO BENIAMINO ANTOCI
IN CONCLUSIONE:
MA LA DIAGNOSI NELLO SPECIFICO CASO?

1. La diagnosi più “attraente” potrebbe essere quella di insulinomatosi non MEN-1
2. Tuttavia dovrebbe essere ricercata la mono-ormonalità per insulina con anticorpi specifici nelle IMEECs (Insulin-expressing Monohormonal Endocrine Cell Clusters)
3. Tenuto conto dell’ancora breve follow up della PHH il razionale della terapia conservativa adottato sembra prudente e giustificato.
C’era un tempo in cui i dottori curavano tutti con i salassi.
Poi e’ venuto un periodo intermedio, con numerose strade, ma obbligate.
Adesso le strade sono infinite: solo i Medici molto bravi sanno scegliere quella buona, in collaborazione fra di loro.

(Piero Ottone, 2000)