Malattie rare in Endocrinologia

Dalla teoria alla pratica

Dott.ssa Daniela Agrimi
Casi Clinici/Oncogenetica

- **Malattie rare** (prevalenza nella popolazione generale < 0.05 %, UE)
- **Malattie genetiche ed eredo-familiari**

- **Test genetico presintomatico e prognostico** sul probando
Fabiana

S.F. 15 aa
Visita endocrinologica: amenorrea primaria

Anamnesi fisiologica: primogenita, nata a termine, II° liceo scientifico, rendimento scolastico buono; pratica sport saltuariamente

Anamnesi patologica remota: a 10 aa tonsillectomia, sin dall’infanzia eccesso ponderale

Dati clinici:
165 cm 83 Kg BMI 30.49 B3 P4
Adiposità ginoide, lieve iperisutismo (mento ++)
Fabiana
3° inferiore lobo dx: nodulo ipoeocogeno, 8 x 6.6 x 11 mm

III livello latero-cervicale dx: linfonodo oblungo, 9 x 5 x 15 mm

CT (eluato): 2000 pg/ml

CT (eluato): 9.92 pg/ml
<table>
<thead>
<tr>
<th>ESAMI di LABORATORIO</th>
<th>ESAMI STRUMENTALI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEA</td>
<td>Ecografia addome superiore</td>
</tr>
<tr>
<td>Ca</td>
<td>Ecografia addome inferiore</td>
</tr>
<tr>
<td>Ca++</td>
<td>Rx torace</td>
</tr>
<tr>
<td>Calciuria (24 h)</td>
<td>Visita cardiologica, ECG</td>
</tr>
<tr>
<td>PTH-intatto</td>
<td>RMN regione sellare e parasellare</td>
</tr>
<tr>
<td>Metanefrine plasmatiche</td>
<td></td>
</tr>
<tr>
<td>Metanefrine urinarie (24 h)</td>
<td></td>
</tr>
<tr>
<td>Catecolamine plasmatiche</td>
<td></td>
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<tr>
<td>Catecolamine urinarie (24 h)</td>
<td></td>
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**CALCITONINA (CT): 38 pg/ml (v.n. 0.1-9.9)**
Tiroide sede, a carico del lobo destro, di carcinoma midollare (1 cm) e di duplice microcarcinoma midollare (cm 0.3 e cm 0.1) e a carico del lobo sinistro di microcarcinoma midollare (cm 0.3). Lieve iperplasia bilaterale delle cellule C. Linfonodi, in numero di 5, esenti da neoplasia.
Mutazione germinale nel gene RET c.1901G>T (p.Cys634Tyr)

Metodica: sequenziamento del DNA, PCR
La MEN 2 (prevalenza 1/35.000) è classificata in 3 sottotipi:

- MEN 2A (70-80 %)
- FMTC (10-20 %)
- MEN 2B (5 %)

Il MTC compare tipicamente nella infanzia nella MEN 2B, nei giovani adulti (5-25 aa) nella MEN 2A e in età media nella FMTC

### Table 2. Percent of Clinical Features by MEN 2 Subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Medullary Thyroid Carcinoma</th>
<th>Pheochromocytoma</th>
<th>Parathyroid Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN 2A</td>
<td>95%</td>
<td>50%</td>
<td>20%-30%</td>
</tr>
<tr>
<td>FMTC</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>100%</td>
<td>50%</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Prevention of Primary Manifestations

Prophylactic thyroidectomy is the primary preventive measure for individuals with an identified germline RET mutation [Cohen & Moley 2003, American Thyroid Association Guidelines Task Force 2009].

Prophylactic thyroidectomy is safe for all age groups; however, the timing of the surgery is controversial [Moley et al 1998]. According to the consensus statement from the American Thyroid Association Guidelines Task Force, the age at which prophylactic thyroidectomy is performed can be guided by the codon position of the RET mutation (Table 4, Genotype-Phenotype Correlations) [American Thyroid Association Guidelines Task Force 2009]. However, these guidelines continue to be modified as more data become available.
Table 4. Risk for Aggressive MTC Based on Genotype and Recommended Interventions

<table>
<thead>
<tr>
<th>ATA Risk Level</th>
<th>Mutations</th>
<th>Age of Prophylactic Surgery</th>
<th>Age to Begin Screening For PHEO</th>
<th>Age to Begin Screening For HPT</th>
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Multiple Endocrine Neoplasia Type 2
Synonyms: MEN 2, MEN 2 Syndrome. Includes: Familial Medullary Thyroid Carcinoma (FMTC), Multiple Endocrine Neoplasia Type 2A (MEN 2A, Sipple Syndrome), Multiple Endocrine Neoplasia Type 2B (MEN 2B, Mucosal Neuroma Syndrome)

Jessica Molina, MS, CGC and Charis Eng, MD, PhD, FACP.

*Author Information
Initial Posting: September 27, 1999; Last Update: January 10, 2013.
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<th>ATA&lt;sup&gt;1&lt;/sup&gt; Risk Level</th>
<th>Mutations&lt;sup&gt;2, 3&lt;/sup&gt;</th>
<th>Age of Prophylactic Surgery</th>
<th>Age to Begin Screening For PHEO</th>
<th>Age to Begin Screening For HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level C</td>
<td>p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr</td>
<td>&lt;5 yrs</td>
<td>8 yrs</td>
<td>8 yrs</td>
</tr>
</tbody>
</table>

<sup>1</sup> ATA: American Thyroid Association

<sup>2</sup> p.Cys634Arg/Gly/Phe/Ser/Trp/Tyr: Mutations in the RET gene

<sup>3</sup> RET: Recessive Inherited Mutation

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- Jessica Moline, MS, CGC and Charis Eng, MD, PhD, FACP.

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## CLASSE di RISCHIO B

<table>
<thead>
<tr>
<th>ATA Risk Level</th>
<th>Mutations 2, 3</th>
<th>Age of Prophylactic Surgery</th>
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### Multiple Endocrine Neoplasia Type 2
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Initial Posting: September 27, 1999; Last Update: January 15, 2013.
<table>
<thead>
<tr>
<th>Level A</th>
<th>Mutations</th>
<th>Age of Prophylactic Surgery</th>
<th>Age to Begin Screening For PHEO</th>
<th>Age to Begin Screening For HPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Arg321Gly</td>
<td>May delay beyond age 5 yrs if criteria met</td>
<td>20 yrs</td>
<td>20 yrs</td>
<td></td>
</tr>
<tr>
<td>p.Glu768Asp</td>
<td>p.Arg912Pro</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Criteria: normal annual basal and or stimulated serum calcitonin; normal annual neck ultrasound examination; family history of less aggressive MTC.
M.C. 41 aa
Coniugato, 1 figlio; infermiere

09/2008

Per comparsa di febbre, dolore toracico e dispnea viene ricovero in Medicina Interna, con diagnosi di "Pleurite acuta sinistra con polmonite e pericardite satellite"
In corrispondenza del mediastino anterio-superiore si evidenzia neoformazione di 6 x 7 cm, disomogenea per la presenza di calcificazioni intra-lesionali, riferibile a timoma.
In corrispondenza del corpo del pancreas, sul versante anteriore, area focale nodulare di tenue iperenhancement in fase arteriosa di 15 mm circa, compatibile con possibile tumore neuroendocrino.
La FAMIGLIA MEN1
MEN 1

Ca: 11.7 mg/dl (8.5-10.5 mg/dl)

Ecografia tiroidea: struttura ecografica del parenchima omogenea se si accettua la presenza di un nodulo isoecogeno al 3° superiore del lobo destro 1 x 1 cm, non processi occupanti spazio in sede paratiroidea
Scintigrafia tiroidea: areola ipercaptante al polo inferiore del lobo tiroideo dx, sospetta per paratiroide iperfunzionante; probabile presenza di un’altra areola al polo superiore dello lobo stesso.

Ecografia addome: nella norma, pancreas non visualizzabile.
07/2004

Ca ↑ P ↓ PTH ↑

Ecografia tiroidea: al 3° superiore nodulo del lobo destro di 21 x 17 mm, solido ed ipoecogeno, al 3° inferiore è presente una formazione ipoecogena di 22 x 11 mm (paratiroide?)

Scintigrafia paratiroidi: adenoma paratiroideo al di sotto del lobo tiroidea di destra

Ecografia addome: neoformazione pancreatica
07/2004

**TAC addome:** presenza di **nodulo a livello della testa pancreaticca di 1.5 cm** con patologica impregnazione.

**RMN regione sellare e para sellare:** nella norma

**Diagnosi:** **Neoplasia endocrina multipla MEN1** (adenoma della paratiroide dx, neoformazione pancreaticca e del lobo destro della tiroide).

Opportuna **emitiroidecotomia destra e paratiroidectomia dx.**
Multiple Endocrine Neoplasia tipo 1 (MEN1) is a rare autosomal dominant hereditary cancer syndrome presented mostly by tumours of the parathyroids, endocrine pancreas and anterior pituitary, and characterised by a very high penetrance and an equal sex distribution. It occurs in approximately one in 30,000 individuals. Two different forms, sporadic and familial, have been described. The sporadic form presents with two of the three principal MEN1-related endocrine tumours (parathyroid adenomas, enteropancreatic tumours and pituitary tumours) within a single patient, while the familial form consists of a MEN1 case with at least one first degree relative showing one of the endocrine characterising tumours. Other endocrine and non-endocrine lesions, such as adrenal cortical tumours, carcinoids of the bronchi, gastrointestinal tract and thymus, lipomas, angiofibromas, collagenomas have been described. The responsible gene, MEN1, maps on chromosome 11q13 and encodes a 610 aminoacid nuclear protein, menin, with no sequence homology to other known human proteins. MEN1 syndrome is caused by inactivating mutations of the MEN1 tumour suppressor gene. This gene is probably involved in the regulation of several cell functions such as DNA replication and repair and transcriptional machinery. The combination of clinical and genetic investigations, together with the improving of molecular genetics knowledge of the syndrome, helps in the clinical management of patients. Treatment consists of surgery and/or drug therapy, often in association with radiotherapy or chemotherapy. Currently, DNA testing allows the early identification of germline mutations in asymptomatic gene carriers, to whom routine surveillance (regular biochemical and/or radiological screenings to detect the development of MEN1-associated tumours and lesions) is recommended.
Terapia chirurgica

Intervento di **Cervicotomia e Sternotomia** presso reparto di Chirurgia Toracica

- Carcinoma neuroendocrino moderatamente differenziato (Ki 67 25%) in sede timica con coinvolgimento dei margini, invasione vascolare e localizzazioni linfonodali.
- Lesioni neuroendocrina del pancreas non tipizzata
- Iperparatiroidismo primitivo in paziente affetto da MEN 1
The prevalence of thymic NET is ~3% of the total number of NETs at all sites. In the last SEER database, a reported incidence of thymic NETs is 0.02/100,000 population per year [4]. They constitute ~5% of all thymic tumors. Both bronchial and thymic NETs may be part of multiple endocrine neoplasia type 1 syndrome (MEN-1, 5%-15%). The median age at diagnosis for bronchial NETs is 64 years and for thymic NETs 59 years. This review is restricted to typical/atypical NETs and thymic NETs.
Most thymic NET cases are completely asymptomatic and imaging performance for other reasons generally incidentally discovers thymic NETs. Not infrequently distant metastases are present at the time of diagnosis. Clinical symptoms usually occur at a later stage of the disease, such as chest discomfort, superior vena cava syndrome, dyspnea and cough. Thymic NETs are frequently associated with hormonal hyper-secretion such as ACTH secretion giving rise to Cushing’s syndrome and growth hormone releasing hormone (GHRH) hyper-secretion with ectopic acromegaly [10]. The tumor seems to have a predilection for men (man to female ratio 3:1).
predilection for men (man to female ratio 3:1). A characteristic feature of these tumors is the presence of nests of tumor cells that are detached from the surrounding stroma and contain areas of necrosis. The tumors often show architectural features of neuroendocrine differentiation with positive immunohistochemistry for chromogranin A, synaptophysin and CD56. They can be divided into low, intermediate and high-grade tumors. Low-grade tumors present <10 mitoses/10 high power field (HPF), intermediate tumors 10-20 mitoses/HPF and high grade tumors < 20 mitoses/10 HPF. The tumors may be
The prognosis for patients with primary thymic NETs remains poor. This is due to the aggressive nature of tumor with a high incidence of recurrence following surgery. Low-grade thymic NETs present a 5-year survival of 50% and a 10-year survival of 9%, whereas high-grade thymic NETs have a 5-year survival of nearly 0% [10].
emission tomography (PET) scanning (III, B) [11, 12]. For more aggressive bronchial NETs such as LCNEC and SCLC, fluoro deoxy glucose (FDG) PET is more informative than somatostatin receptor scintigraphy (III, B) [13, 14]. For thymic NETs contrast enhanced CT or magnetic resonance imaging (MRI) is recommended to detect tumor metastases. Somatostatin receptor scintigraphy may be used for these tumors as well as PET scanning with $^{68}$Gallium-DOTATATE (III, B). Bronchial NETs sometimes present with AC syndrome related to the secretion of
Scintigrafia OCTREOSCAN
• **Sternotomia esplorativa**, biopsia del pericardio e della pleura parietale sinistra

• Timo di 44 g e di 12 x 7 x 2 cm con un addensamento di 4,5 cm di asse maggiore

• **Focolai di carcinoma neuroendocrino**, con modificazioni architetturali e citocariologiche riferibili a terapia, in timo parzialmente fibrotico e minime localizzazioni pleuriche e pericardiche.
• **Immunofenotipo della popolazione neoplastica**: positivo per cromogranina, sinaptofisina e CD56. La frazione di proliferazione (Ki-67) è pari al 5%.
Ricca cellularità costituita da elementi cellulari di tipo plasmocitoide con polimorfismo nucleare, isolati o riuniti aggregati abbastanza coesi a struttura cordonale. (THY4)
01/2013

- Tiroide comprendente **multipli nodi di carcinoma neuroendocrino**.
  Immunoistochimica con anticorpi anti TTF1 e calcitonina, negativa. Confronto con esame istologico relativo alla lesione mediastinica si propende per una **localizzazione in sede tiroidea del carcinoma neuroendocrino precedentemente diagnosticato in sede mediastinica**.
Nelle neoplasie eredo-familiari qual la finalità del counseling genetico nella definizione di rischio di malattia nei componenti il nucleo familiare e/o nella valutazione prenatale?