多發性神經內分泌瘤
--案例分享及討論

內分泌暨新陳代謝科
李晏榮 醫師

Basic profile

- A 58-year-old man
- Married
- Past medical Hx:

  --**HTN** and **Dyslipidemia** for around one year

  --**Diabetes** diagnosed recently before admission
- Personal history: no smoking/ quit drinking for over 30 yrs/no betel nut
- Family Hx: nil
- Admission date: 2016/05/12

Case Summary

- Chief complaint:

  -- progressive bilateral four limbs weakness three months before admission

- Associated S/S:

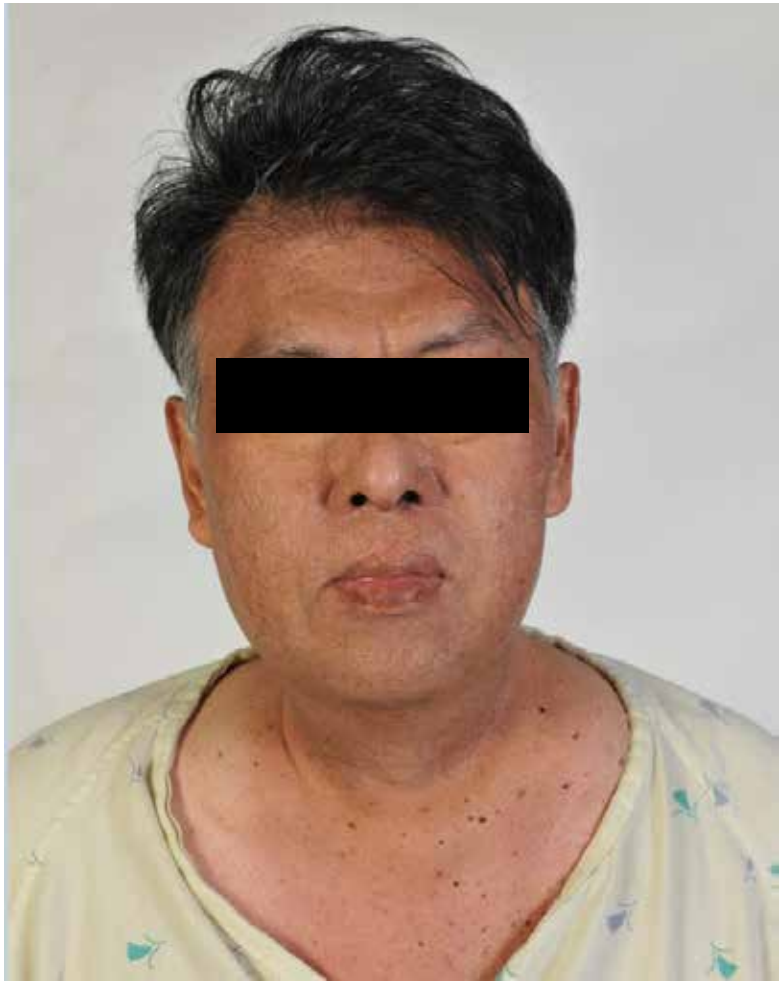
  -- could not stand up after squatting down

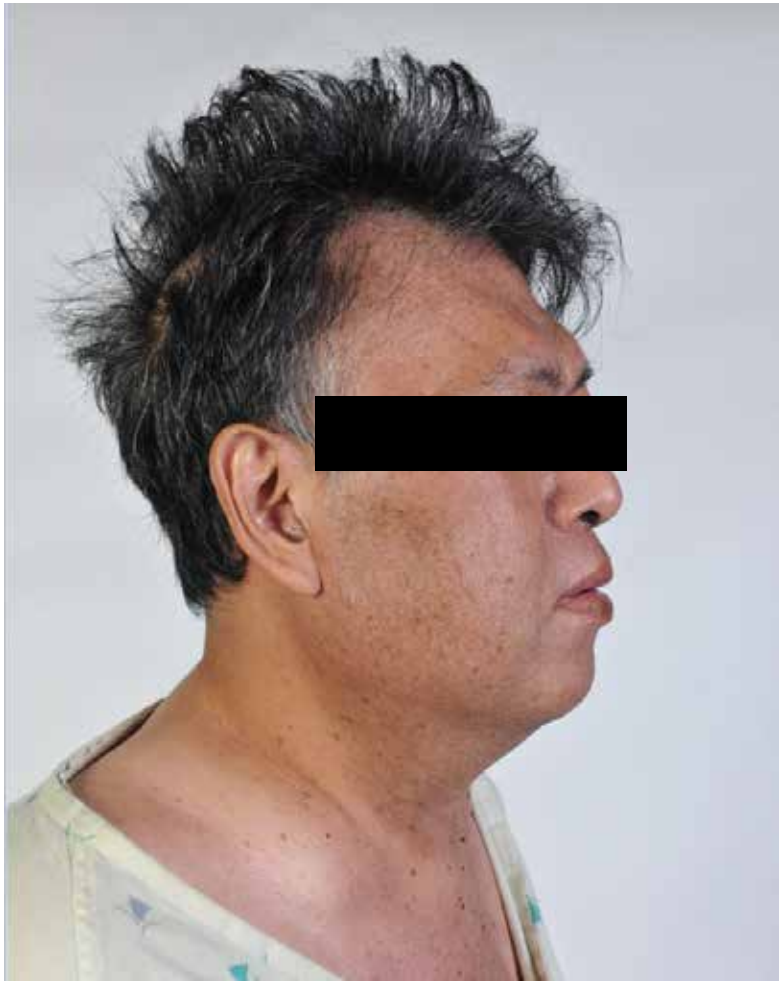
  -- hard to twist towel while washing his face

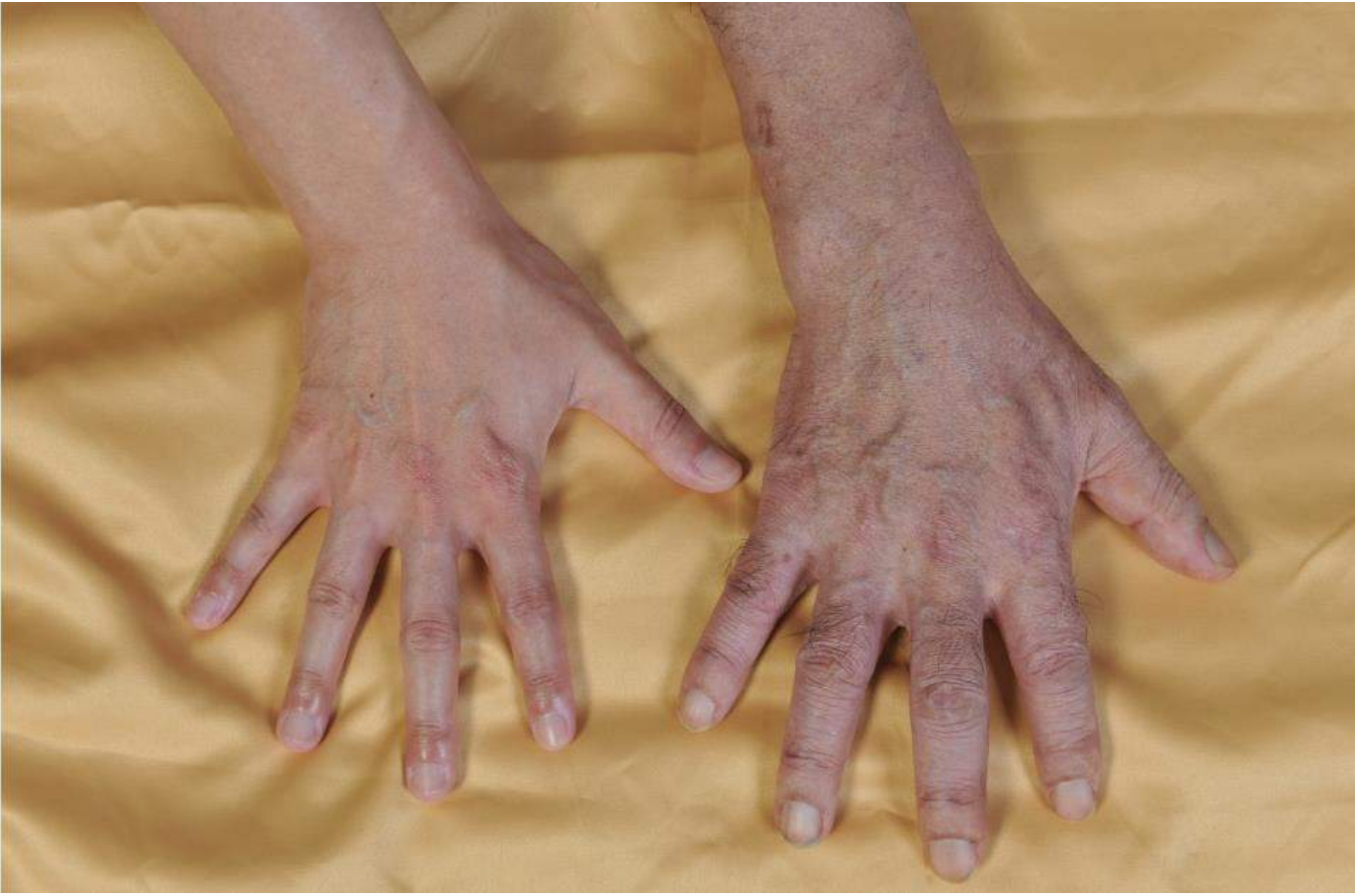
  -- unsteady walking with crutch

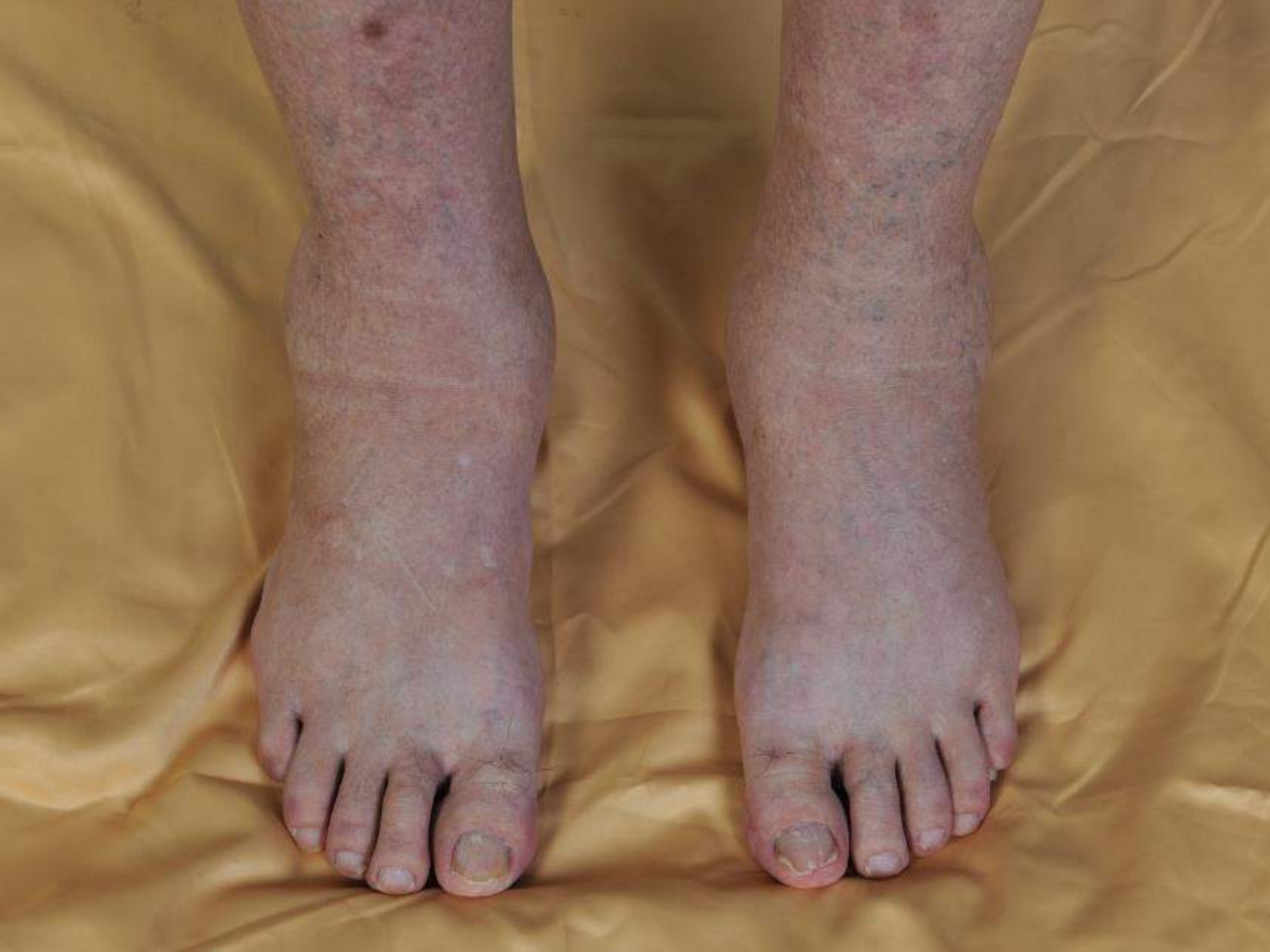
  -- erectile dysfunction

  -- ↓ BW (4kg within 2 months) with decreased appetite but general edema









Clinical course

2016/05/12 :
-- admitted to neurologic ward
→NCV/EMG/brain MRI/lumbar puncture→polyneuropathy
→posterior pituitary tumor??
→IGF-1: 292(81~225)
→24-UFC:8224.6(20.9 ~ 292.3)
ACTH: 76.90(≦46)
Cortisol: 20.79(8am:5~23)
K: 3.2

2016/05/28:
--75g OGTT: nadir GH 2.5(<1)
→acromegaly

Nosocomial pneumonia

2016/05/09
Neuro OPD
→suspected demyelinating polyneuropathy
→arrange admission

2016/05/25 :
-- consult meta
--high ACTH under hypercortisolism
→8mg overnight high dose dexamethasone suppression test
→**Cortisol:76.41(pituitary origin<5)
→arrange chest/abdomen CT
→pancreatic body 4.7 cm with multiple liver metastases

Q1:What is your impression and differential diagnosis?

A1:

-- Impression:

Suspected sporadic MEN-1 with EAS P-NET and acromegaly

- ✓Suspected ectopic ACTH syndrome (EAS) due to pancreatic neuroendocrine tumor (P-NET)
- ✓Suspected acromegaly

-- Ddx: EAS and ectopic acromegaly due to ACTH and GHRH producing P-NET

INTERNAL MEDICINE

□ CASE REPORT □

Metastatic Pancreatic Neuroendocrine Tumor that Progressed to Ectopic Adrenocorticotropic Hormone (ACTH) Syndrome with Growth Hormone-releasing Hormone (GHRH) Production

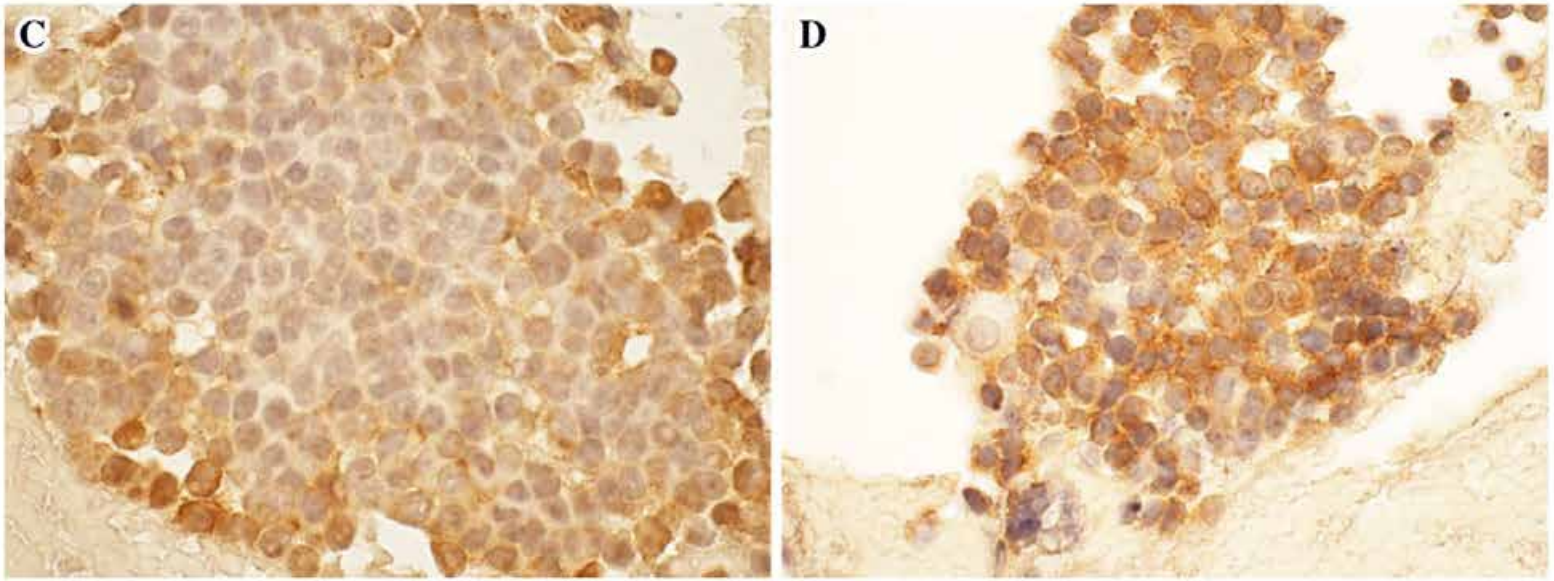
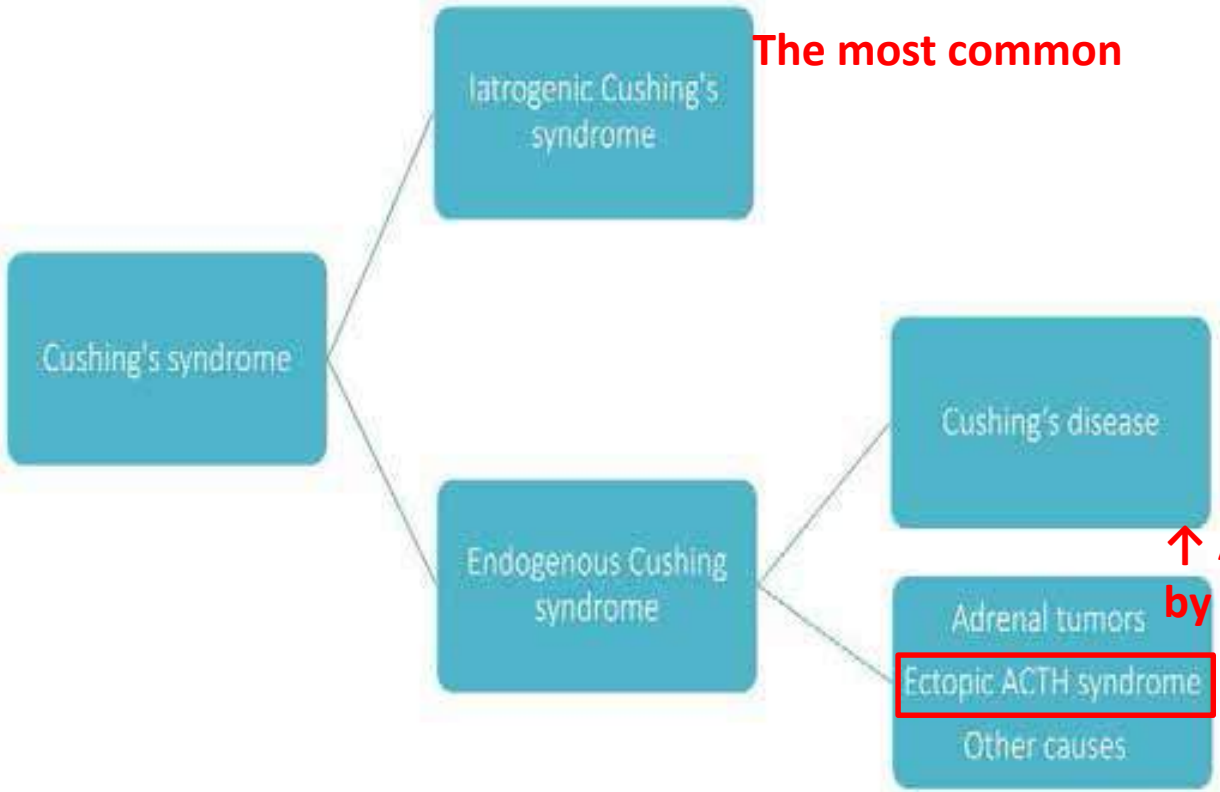


Figure 2. Pathological examination of the pancreatic tumor. A) Well-differentiated neuroendocrine tumor (Hematoxylin and Eosin staining). B) The percentage of Ki67 positive cells was 11.5%. C) Positive immunostaining for ACTH. D) Positive immunostaining for GHRH. ACTH: adrenocorticotropic hormone, GHRH: growth hormone-releasing hormone

Cushing's syndrome

- **Definition:**

  --symptoms and signs directly from **chronic** exposure to **excess glucocorticoid**



The most common

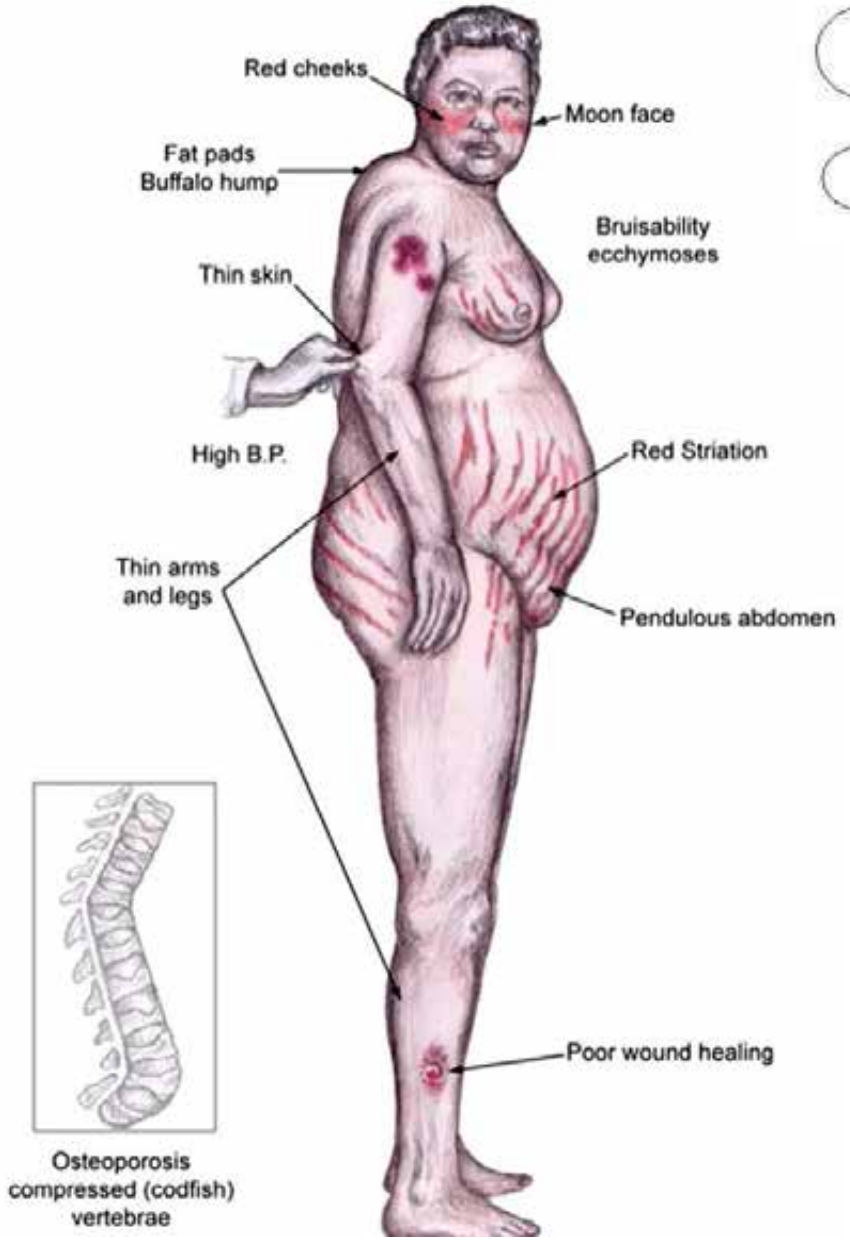
↑ ACTH by nonpituitary tumors 2~3 per 10 millions

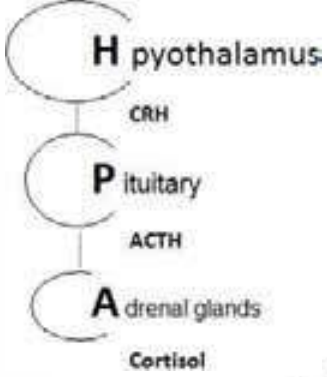
J Clin Endocrinol Metab. 2001 Jan. 86 (1):117-23.

Causes of Cushing's syndrome

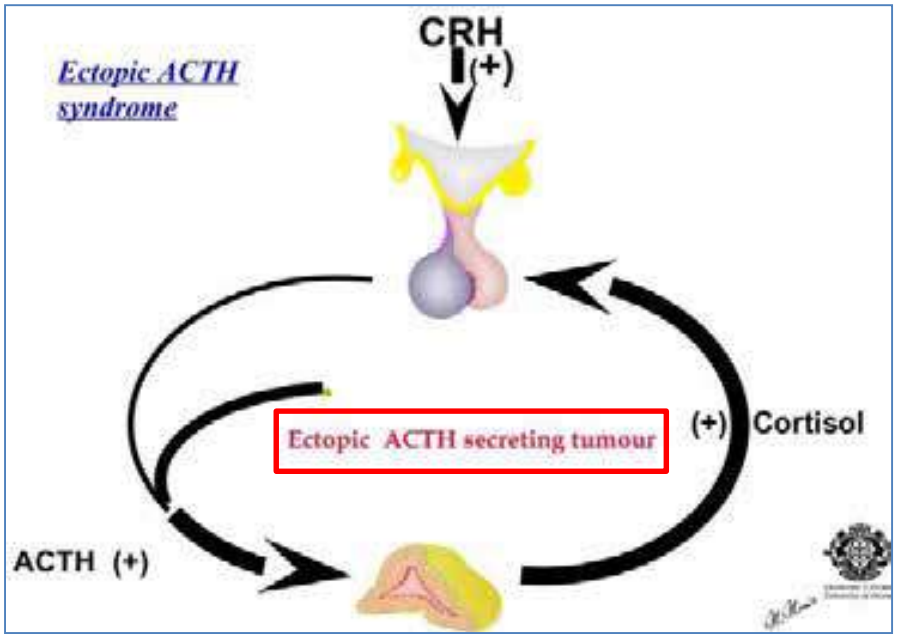
Diagnosis	Patient (%)
• ACTH-dependent	
Pituitary-dependent Cushing's syndrome (Cushing disease)	65
Ectopic ACTH syndrome (*i.e.* bronchial, thymic, pancreatic carcinoids, medullary thyroid carcinoma, *etc.*)	7
Ectopic CRH syndrome	<1
• ACTH-independent	
Adrenal adenoma	18
Adrenal carcinoma	6
PPNAD (including the Carney complex)	1
AIMAH (aberrant expression of ectopic and eutopic membrane receptors: gastric inhibitory polypeptide, catecholamines, or LH/human chorionic gonadotropin, vasopressin, and serotonin)	3

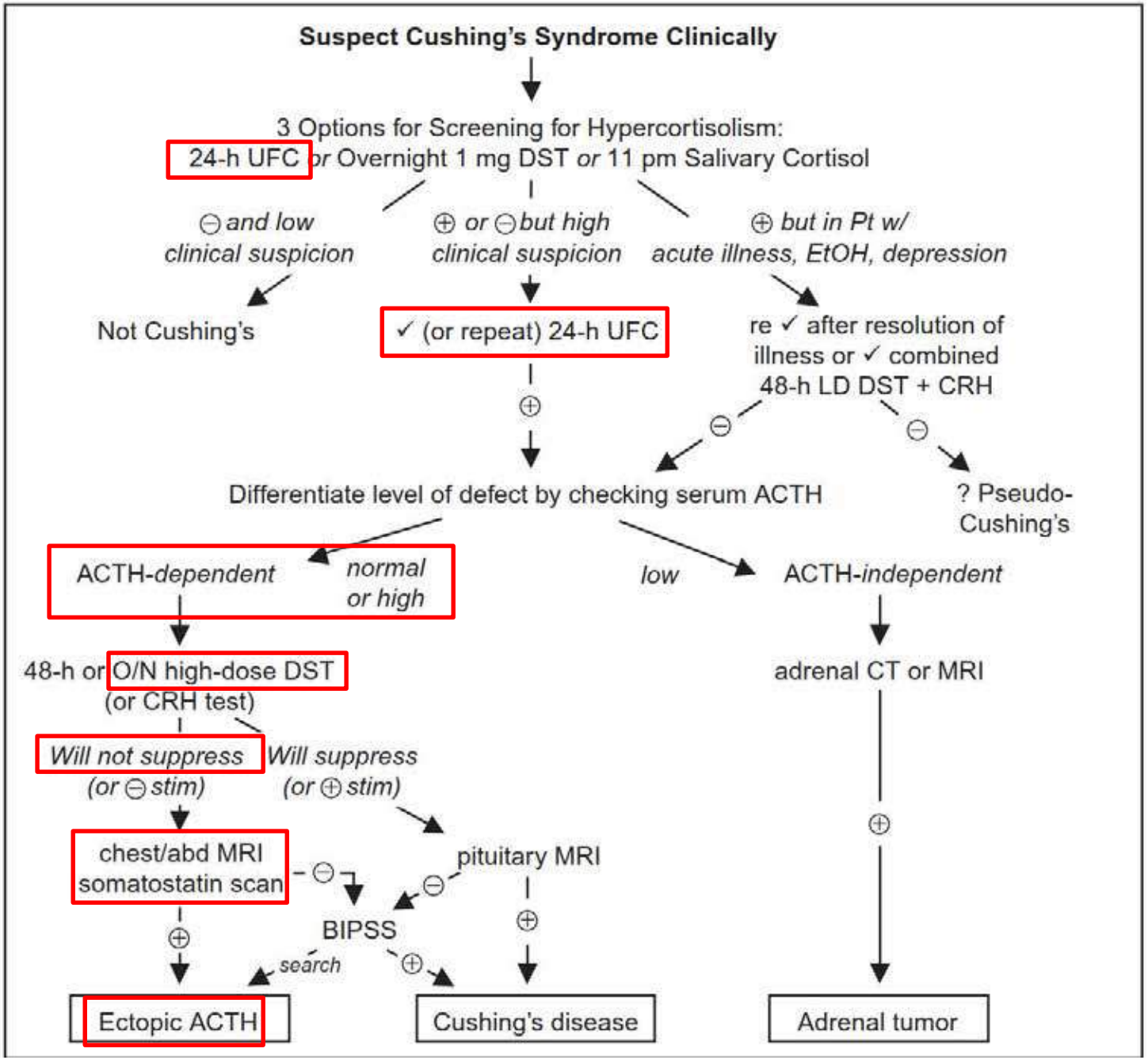
J Clin Endocrinol Metab. 94: 3121–3131, 2009


Red cheeks
Moon face
Fat pads
Buffalo hump
Bruisability
ecchymoses
Thin skin
High B.P.
Red Striation
Thin arms
and legs
Pendulous abdomen
Poor wound healing
Osteoporosis
compressed (codfish)
vertebrae


H pyothalamus
CRH
P ituitary
ACTH
A drenal glands
Cortisol

CRH
(+)
(-)
ACTH (+)
(-)
Cortisol

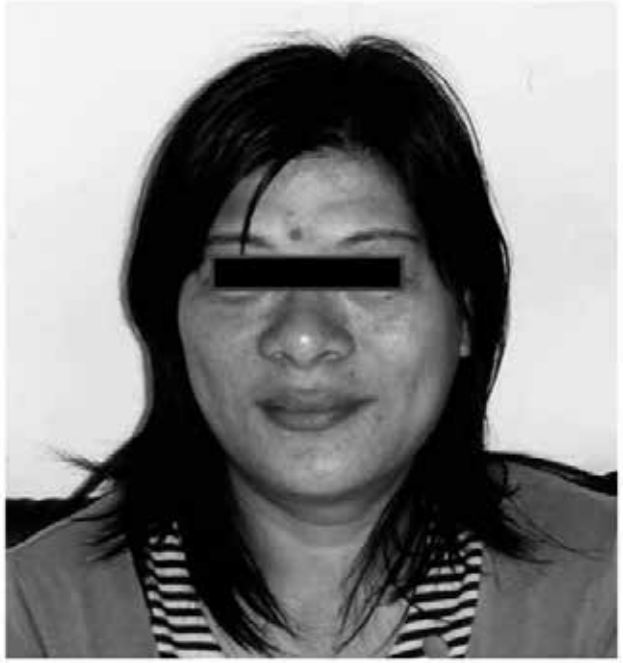

Ectopic ACTH
syndrome
CRH
(+)
Ectopic ACTH secreting tumour
(+)
Cortisol
ACTH (+)



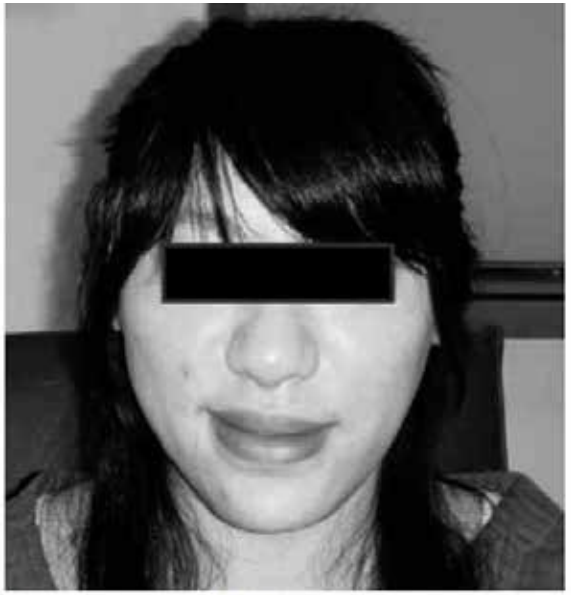
Endo Metab Clin North Am 2005;34:385

J Clin Endocrinol Metab 2008;93: 1526 –1540

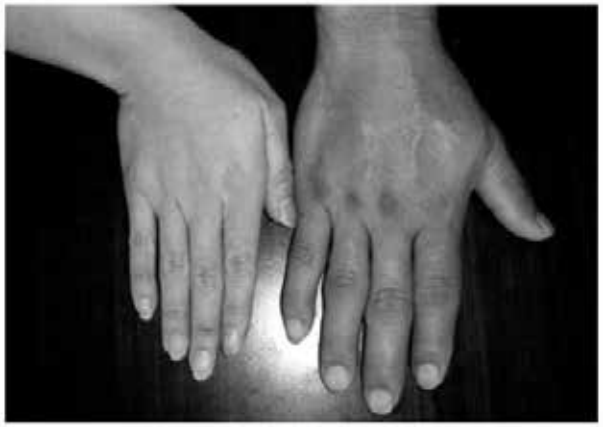
Acromegaly



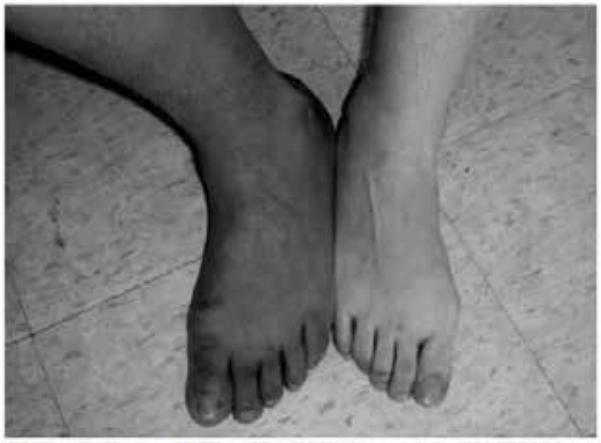
圖一：皮膚粗厚，頭顱皮膚明顯增厚，鼻樑變寬，額部皮膚皺褶肥厚，鼻額竇增大。



圖二：顏面部表現尤為特別，唇變肥厚，鼻唇溝皮褶隆起，鼻樑變寬，下頜增大前突，眉弓和顴骨過長，鼻額竇增大。



圖三：手粗大、肥厚，無法做精細動作。（左為正常對照）。



圖四：腳粗大、肥厚，所穿鞋變小。（右為正常對照）。

J Intern Med Taiwan 2011; 22: 9-18

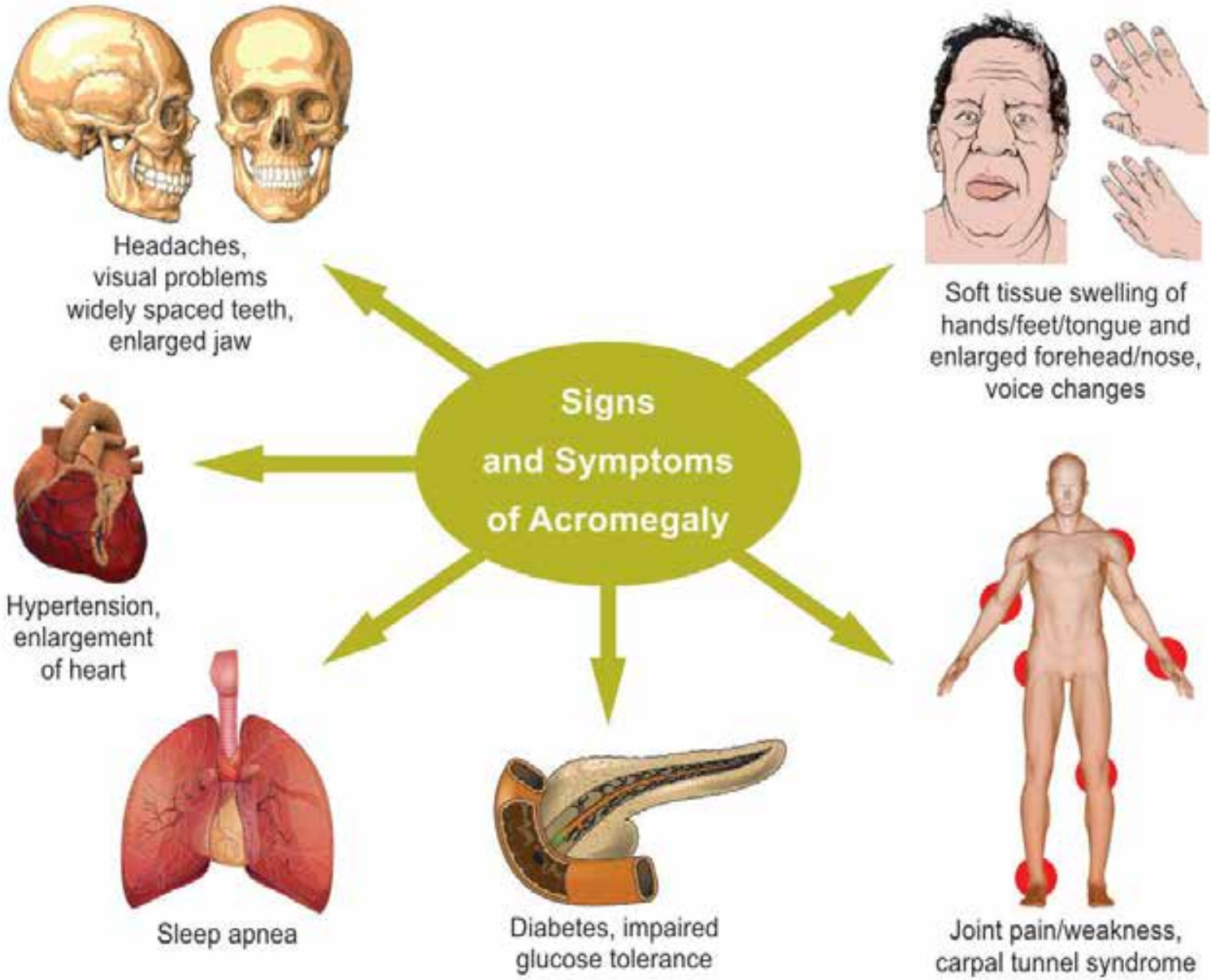


Figure 4. Common signs and symptoms of acromegaly

Causes of Acromegaly

- GH-secreting pituitary tumors

  -- **benign adenoma (most common)**

  -- carcinoma

- GHRH-secreting tumors

- Ectopic GH-secreting tumor

- Exogenous sources of GH

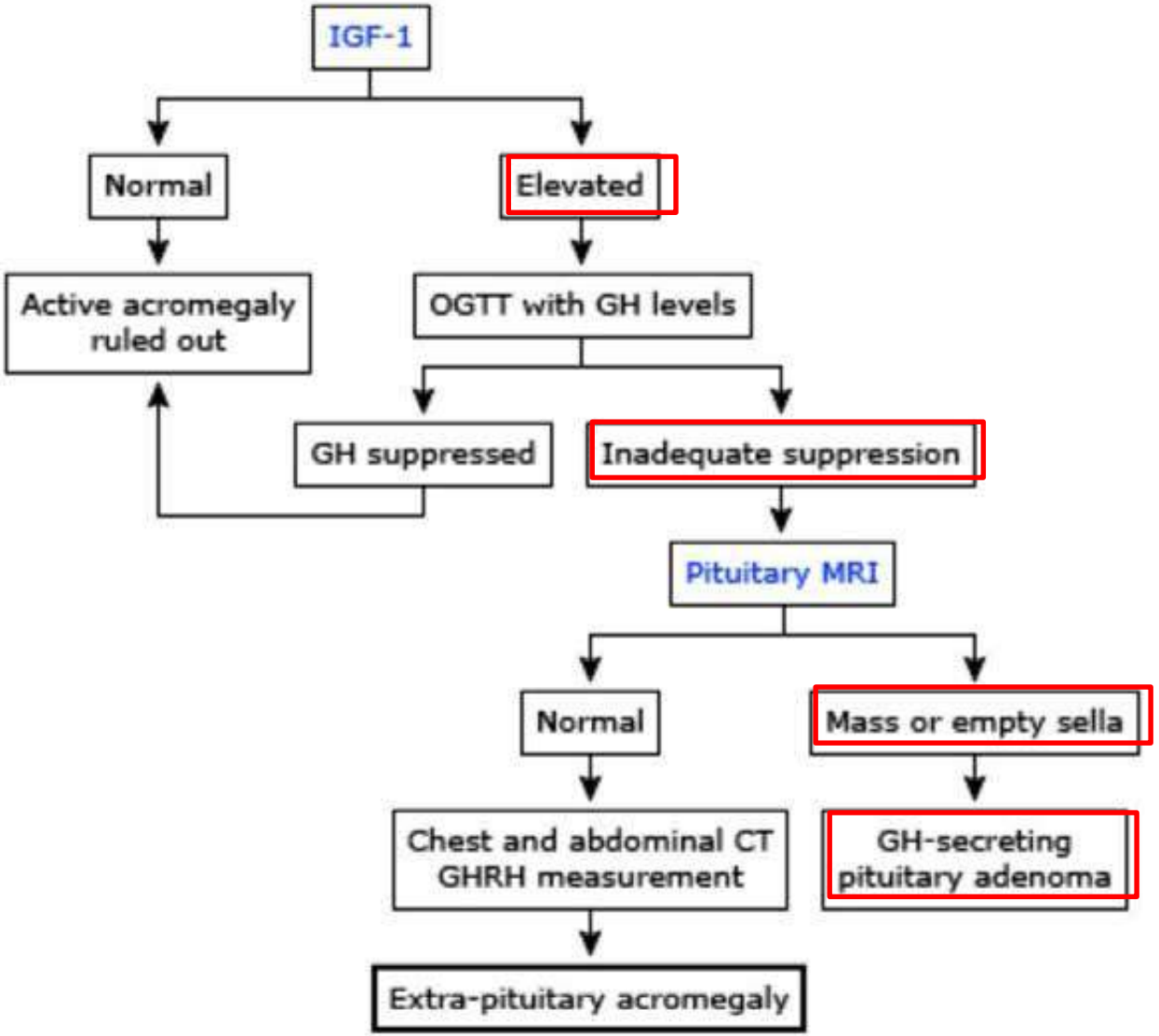
- Genetic causes

  -- MEN 1

  -- McCune Albright syndrome

  -- Carney's complex

Algorithm for the diagnosis of acromegaly



Melmed S, Anterior pituitary. In: Current Practice of Medicine, Korenman S (Ed), 1996.

Definition of MEN1

- A rare disorder with classically characterized
  -- parathyroid gland tumor
  -- anterior pituitary tumor
  -- pancreatic islet cells tumor

- Diagnosis
  -- two or more primary MEN1 tumors
  -- one MEN1-associated tumor with family Hx

J Clin Endocrinol Metab. 2012;97(9):2990.

Q2:What is the next examination should you arrange for this patient after abdominal CT and pituitary MRI?

- **A2:**

  -- Biopsy for pancreatic tumor or metastatic lesions of liver

Clinical course

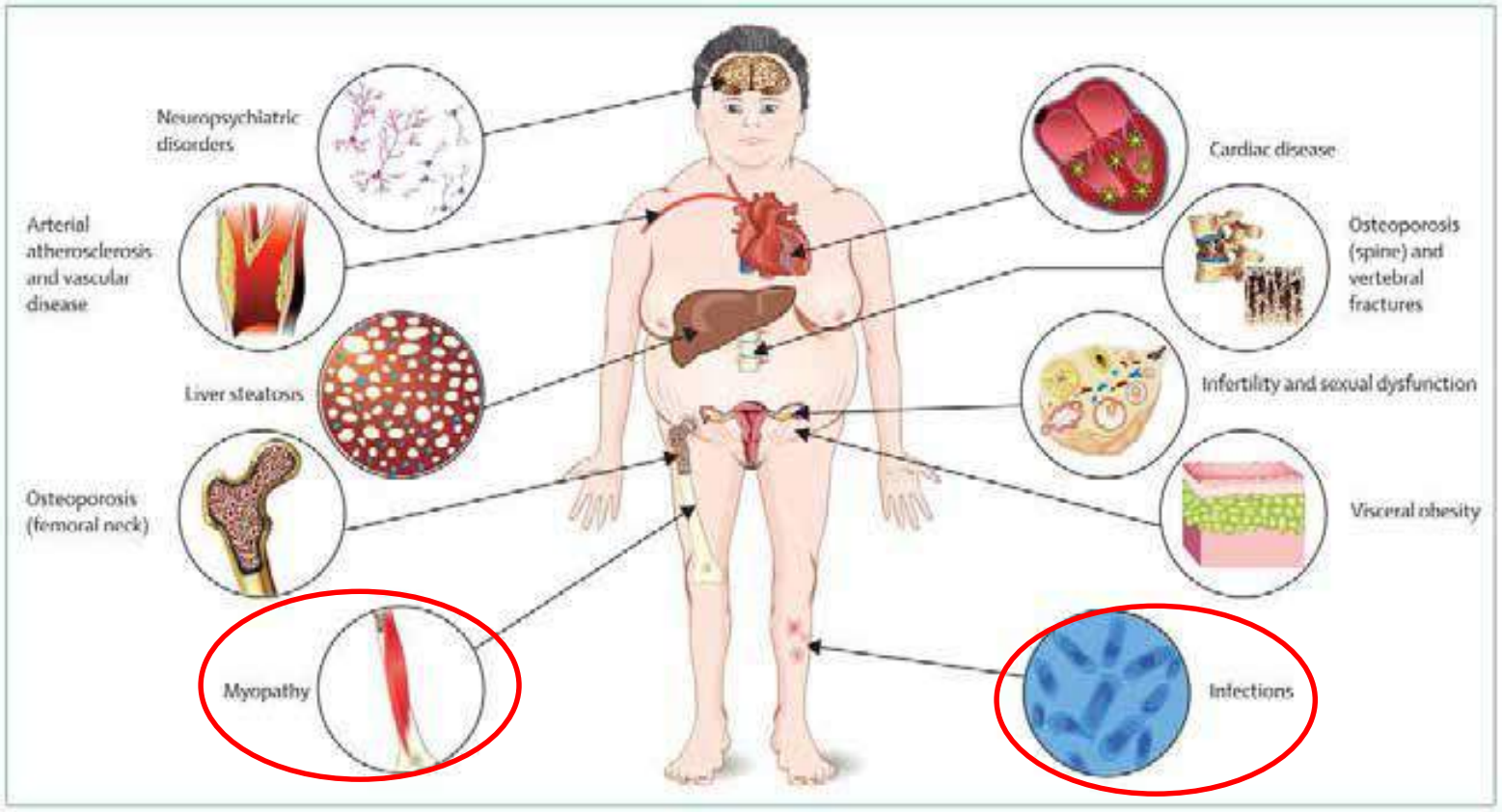
2016/06/08:
--Liver, needle biopsy
→ACTH secreting grade 1 neuroendocrine tumor, metastatic (IHC: no GH; GHRH not available in Taiwan)

2016/06/02:
-- ectopic ACTH syndrome and acromegaly were impressed
→Octreotide LAR 30mg 1pc IM

2016/06/17:
-- MRI of Sella Turcica ((C+-)
→1.348cm left pituitary macroadenoma with central sellar floor erosion→ **Origin of acromegaly !?**
--Tentative Dx: **Suspected sporadic MEN-1 with EAS P-NET and acromegaly**

Q3:What is the major complications of hypercortisolism? How to treat his severe hypercortisolism?

- **A3-1: Complication of excess glucocorticoid**



Lancet Diabetes Endocrinol. 2016 Jul;4(7):611-29.

Treatment of severe hypercortisolism due to EAS

- Steroidogenesis inhibitor
- Glucocorticoid receptor antagonist
- **Bilateral adrenalectomy**

SPECIAL FEATURE

Clinical Practice Guideline

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, and Antoine Tabarin

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Objective: The objective is to formulate clinical practice guidelines for treating Cushing's syndrome.

Participants: Participants include an Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer. The European Society for Endocrinology co-sponsored the guideline.

Evidence: The Task Force used the Grading of Recommendations, Assessment, Development, and Evaluation system to describe the strength of recommendations and the quality of evidence. The Task Force commissioned three systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: The Task Force achieved consensus through one group meeting, several conference calls, and numerous e-mail communications. Committees and members of The Endocrine

Table 1. Medical Treatment of CS

Drug	Pros		
Steroidogenesis inhibitors			
Ketoconazole[b]	Quick onset of action		
Metyrapone[b]	Quick onset of action		d;
Mitotane[c]	Adrenolytic, approved for adrenal cancer		0
Etomidate	Intravenous, quick onset of action		
Pituitary-directed			
Cabergoline		Adverse effects: asthenia, GI, dizziness	1–7 mg/wk
Pasireotide[d]		Most successful when UFC <2-fold normal; sc administration; adverse effects: diarrhea, nausea, cholelithiasis, hyperglycemia, transient ↑ LFTs; ↑ QTc	600–900 μg twice daily
Glucocorticoid receptor-directed			
Mifepristone[e]		Difficult to titrate (no biomarker); abortifacient; adverse effects: fatigue, nausea, vomiting, arthralgias, headache, hypertension, hypokalemia, edema, endometrial thickening	300–1200 mg/d

Abbreviations: GI, gastrointestinal; DDI, drug-drug interactions; HT, hypertension; CNS, central nervous system; WBC, white blood cell count; LFTs, liver function tests; CBG, corticosteroid binding globulin; ICU, intensive care unit; QTc, corrected QT interval.

[a] Except as noted, the lowest dose may be used initially, unless the patient has severe hypercortisolism (UFC more than five times normal), in which case the starting dose may be doubled.

[b] Ketoconazole and metyrapone are approved by the European Medicines Agency for the treatment of CS.

[c] Mitotane has FDA approval for treatment of adrenal cancer.

Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93:1526–1540. (17)

Clinical course

2016/06/02:
-- ectopic ACTH syndrome and acromegaly were impressed
→Octreotide LAR 30mg 1pc IM

2016/06/08:
--Liver, needle biopsy
→ACTH secreting grade 1 neuroendocrine tumor, metastatic

2016/06/17:
-- MRI of Sella Turcica ((C+-)
→1.348cm left pituitary macroadenoma with central sellar floor erosion→ **Origin of acromegaly??**
--Tentative Dx: **Suspected sporadic MEN-1 with EAS P-NET and acromegaly**

Plan:
--bilateral adrenectomy for hypercortisolism
--TSS for pituitary macroadenoma
--primary tumor resection with liver transplant if no extra-hepatic metastasis??

Prevalence and clinical features of the ectopic ACTH syndrome in patients with gastroenteropancreatic and thoracic neuroendocrine tumors

K Kamp[1], R A Alwani[1], E Korpershoek[2], G J H Franssen[3], W W de Herder[1] and R A Feelders[1]

[1]Sector of Endocrinology, Department of Internal Medicine, [2]Department of Pathology and [3]Department of Surgery, ENETS Center of Excellence, Erasmus Medical Center, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

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European Journal of Endocrinology

Abstract

Objective: Several series report on the relative contribution of ectopic ACTH syndrome (EAS) in the spectrum of Cushing's syndrome. However, prevalence of EAS in patients with thoracic or gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is currently unknown.

Design: We assessed, in a tertiary referral center, the prevalence of EAS in a large cohort of thoracic and GEP-NET patients including clinical, biochemical, and radiological features; management; and treatment outcome.

Methods: In total, 918 patients with thoracic or GEP-NETs were studied (1993–2012). Multiple endocrine neoplasia type 1 and small cell lung carcinoma patients were excluded. Differentiation between synchronous, metachronous, and cyclic occurrence of EAS was made.

Results: Out of the 918 patients with thoracic and GEP-NETs (469 males and 449 females; median age 58.7 years (range: 17.3–87.3)), 29 patients (3.2%) had EAS (ten males and 19 females; median age 48.1 years (range: 24.7–77.9)). EAS occurred synchronously in 23 patients (79%), metachronously in four patients (14%), and cyclical in two patients (7%) respectively. NETs causing EAS included lung/bronchus ($n=9$), pancreatic ($n=9$), and thymic ($n=4$). In four patients, the cause of EAS was unknown ($n=4$). Median overall survival (OS) of non-EAS thoracic and GEP-NET patients was 61.2 months (range: 0.6–249.4). Median OS of EAS patients was 41.4 months (range: 2.2–250.9). After comparison, only the first 5-year survival was significantly shorter ($P=0.013$) in EAS patients.

Conclusion: Prevalence of EAS in this large cohort of patients with thoracic and GEP-NETs was 3.2%. EAS was mostly caused by thoracic and pancreatic NETs. First 5-year survival of EAS patients was shorter compared with non-EAS patients.

European Journal of Endocrinology (2016) **174**, 271–280

Table 1 Clinicopathological characteristics of 918 patients with thoracic and GEP-NETs evaluated for the presence of EAS. Group analysis has been conducted between thoracic and GEP-NET patients with and without the EAS.

Clinicopathological characteristics	All patients ($n=918$)		Non-Cushing NET ($n=889$)		Ectopic ACTH Cushing NET ($n=29$)		P value
	n	%	*n*	%	*n*	%	
Gender							
Male	469	51.1	459	51.6	10	34.5	0.069
Female	449	48.9	430	48.4	19	65.5	
Age at diagnosis NET (years)	58.7 (17.3–87.3)		58.9 (17.3–87.3)		48.1 (24.7–77.9)		<0.001
<50	205	22.3	189	21.3	16	55.2	<0.001
50–69	555	60.5	543	61.1	12	41.4	0.033
>70	158	17.2	157	17.7	1	3.4	0.045
Primary localization							
Lung/bronchus	51	5.6	42	4.7	9	31	<0.001
Thymus	6	0.7	2	0.2	4	13.8	<0.001
Stomach	18	2	17	1.9	1	3.4	0.442
Small intestine	267	29.1	267	30	0	0	<0.001
Appendix	16	1.7	15	1.7	1	3.4	0.404
Ileocecal	43	4.7	43	4.8	0	0	0.393
Large intestine	47	5.1	47	5.3	0	0	0.394
Rectum	32	3.5	32	3.6	0	0	0.62
Other[a]	12	1.3	12	1.3	0	0	1.000
Cancer of unknown primary	131	14.3	127	14.3	4	13.8	1.000
Pancreas							
Non-functioning	221	24.1	212	23.8	9	31	0.373
Insulinoma	41	4.5	41	4.6	0	0	0.636
Glucagonoma	6	0.7	6	0.7	0	0	1.000
Gastrinoma	16	1.7	15	1.7	1	3.4	0.404
VIPoma	10	1.1	10	1.1	0	0	1.000
Somatostatinoma	1	0.1	1	0.1	0	0	1.000
Metastasis localization							
Lymph node	648	70.6	631	71	17	58.6	0.151
Liver	716	78	700	78.7	16	55.2	0.003
Bone	214	23.3	207	23.3	7	24.1	0.915
Lung	77	8.4	69	7.8	8	27.6	0.002
Other[b]	127	13.8	123	13.8	4	13.8	1.000
Tumor grade							
G1	240	26.1	236	26.5	4	13.8	0.124
G2	240	26.1	226	25.4	14	48.3	0.006
G3	43	4.7	40	4.5	3	10.3	0.15
Unknown	395	43	387	43.5	8	27.6	0.088
ENETS stage							
I–IIIa	77	8.4	73	8.2	4	13.8	0.296
IIIb	90	9.8	83	9.3	7	24.1	0.018
IV	751	81.8	733	82.5	18	62.1	0.005

[a]Other primary tumors included: oesophagus, kidney, and ovary NETs.
[b]Other metastasis included: adrenal, heart, brain, spleen, breast, skin, thyroid, testis, eye, and uterus.

Table 2 Clinical symptoms and signs at presentation including complications in patients with EAS ($n=29$).

Clinical presentation and complications	*n*	%
Clinical symptoms and signs		
Muscle weakness	23	79
Hypokalemia	21	72
Body weight	20	69
Increase	17	59
Decrease	3	10
Truncal obesity	19	66
Full moon face	19	66
Hypertension	17	59
Diabetes	17	59
Edema	16	55
Bruising	15	52
Hirsutism	14	48
Buffalo hump	13	45
Psychiatric disorders	11	38
Osteopenia or osteoporosis	9	31
Acne	7	24
Hyperpigmentation	7	24
Insomnia	6	21
Impaired cognition or memory	5	17
Violaceous striae	4	14
Menstrual irregularities or amenorrhea	2	7
Libido	2	7
Fractures	2	7
Complications		
Uncontrolled diabetes	17	59
Severe or opportunistic infections	12	41
Severe hypertension	5	17
Thrombosis or pulmonary embolism	4	14
Psychosis	4	14

Eur J Endocrinol. 2016 Mar;174(3):271-80.

Eur J Endocrinol. 2015 Oct;173(4):M23-32.

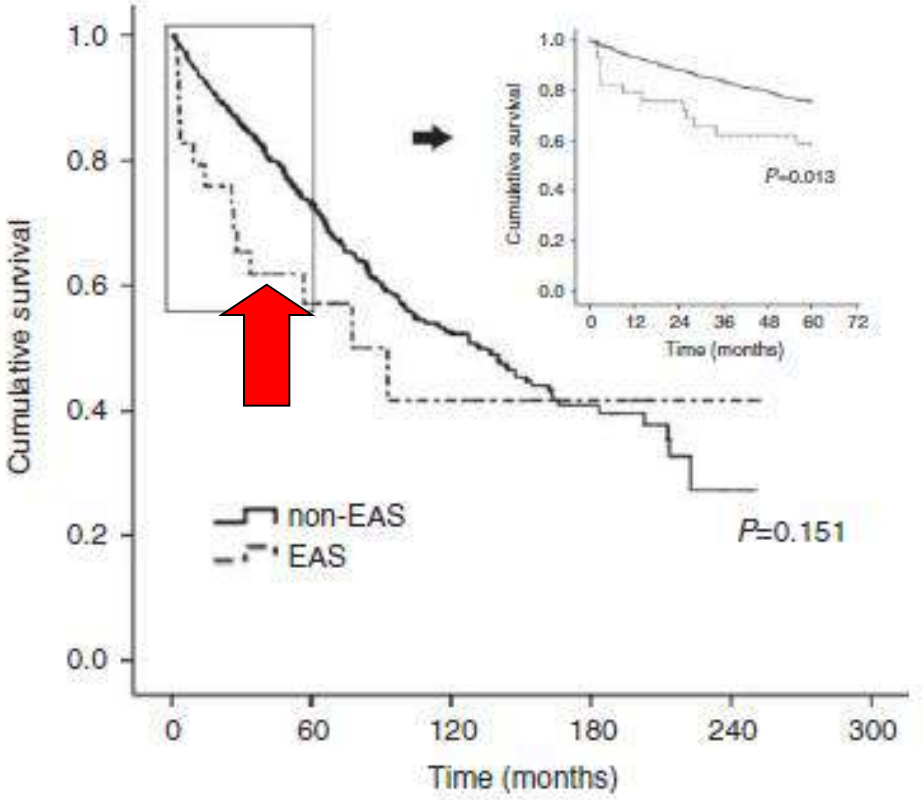
In total, 22 out of 29 patients underwent a bilateral adrenalectomy to control the hypercortisolism caused by EAS.
--late BADx: 5.2 months (range: 2.2–20.9)
--early BADx: 6.2 months (range: 5.0–20.9)

Table 2 Diagnostic criteria and specific treatment of emergency BADx in catastrophic Cushing's syndrome.

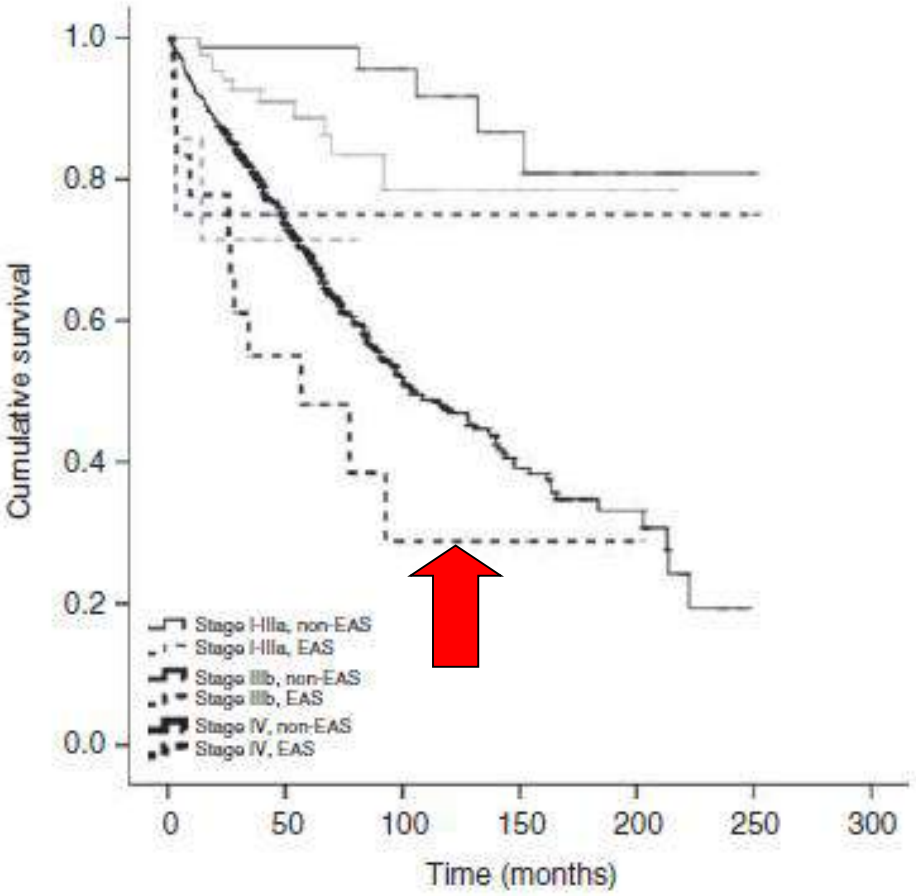
Clinical criteria
A patient with Cushing's syndrome and recent onset of one or more of the following:
- sepsis, opportunistic infection;
- intractable hypokalaemia, uncontrolled hypertension;
- heart failure;
- gastrointestinal haemorrhage;
- glucocorticoid-induced acute psychosis;
- progressive debilitating myopathy;
- thromboembolism; and/or
- uncontrolled hyperglycaemia and ketoacidosis.

Biochemical criteria
A patient with Cushing's syndrome and at least one of the following conditions:
- serum cortisol of ≥41 μg/dl (1100 nmol/l) (27); and/or
- severe hypokalaemia (<3.0 mmol/l).

Treatment
Consider transfer to ICU
Control hypercortisolism with 2.5–3.0 mg/h etomidate i.v. (safe cortisol levels: in physiologically stressed patients, 500–800 nmol/l; in non-stressed patients, 150–300 nmol/l) (31)
Treat complications
Plan BADx at the next available possibility



First 5-year survival shorter in EAS compared with non-EAS



Aggressive treatment of hypercortisolism with (combination) medical therapy or rescue bilateral adrenalectomy is an essential part of patient management.

LIVER TRANSPLANTATION FOR METASTATIC NEUROENDOCRINE CARCINOMA: An Analysis of 103 Patients

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Transplantation. 66(10):1307-1312, November 27, 1998.

Author Information

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Abstract

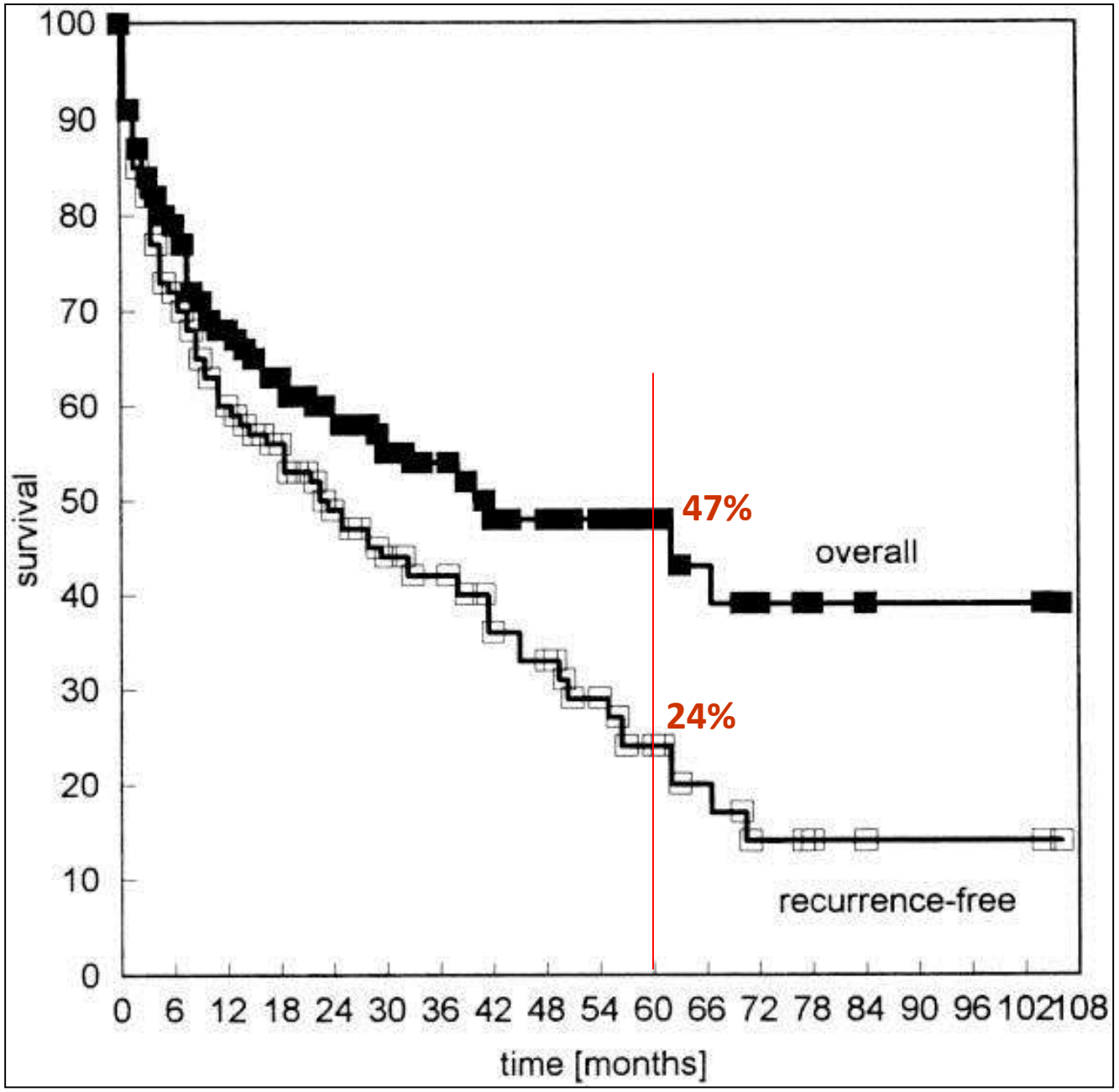
Background. Patients with neuroendocrine carcinoma often present with liver metastases not amenable to hepatic resection. For them, liver transplantation has been considered a viable treatment option, especially if hormonal symptoms and pain cannot be controlled medically. Still, little is known regarding potential prognostic factors and long-term survival after liver transplantation for neuroendocrine tumors.

Methods. A search of English, French, and German literature identified patients with liver transplantation for extensive metastases from neuroendocrine carcinoma for whom follow-up data were available.

Results. Overall, 2-year and 5-year survival for all 103 patients was 60% and 47%, respectively, but recurrence-free 5-year survival did not exceed 24%. Univariate analysis identified age less than 50 years, primary tumor location in lung or bowel, and pretransplant somatostatin therapy as favorable prognostic factors, whereas extended operations combining liver transplantation with upper abdominal exenteration or Whipple's procedure were associated with poor prognosis. Multivariate analysis identified age greater than 50 years ($P<0.03$) and transplantation combined with upper abdominal exenteration or Whipple's operation ($P<0.001$) as adverse prognostic factors.

Conclusions. Liver transplantation may be justified in selected patients to provide immediate relief of otherwise intractable pain or hormone-related symptoms. Transplantation with curative intent appears worth-while in young patients with only hepatic disease. In older patients with extrahepatic disease requiring extended operations, long-term results are discouraging, and the small benefit achieved by liver transplantation must be weighed against medical treatment options and the natural course of often slowly progressing disease.

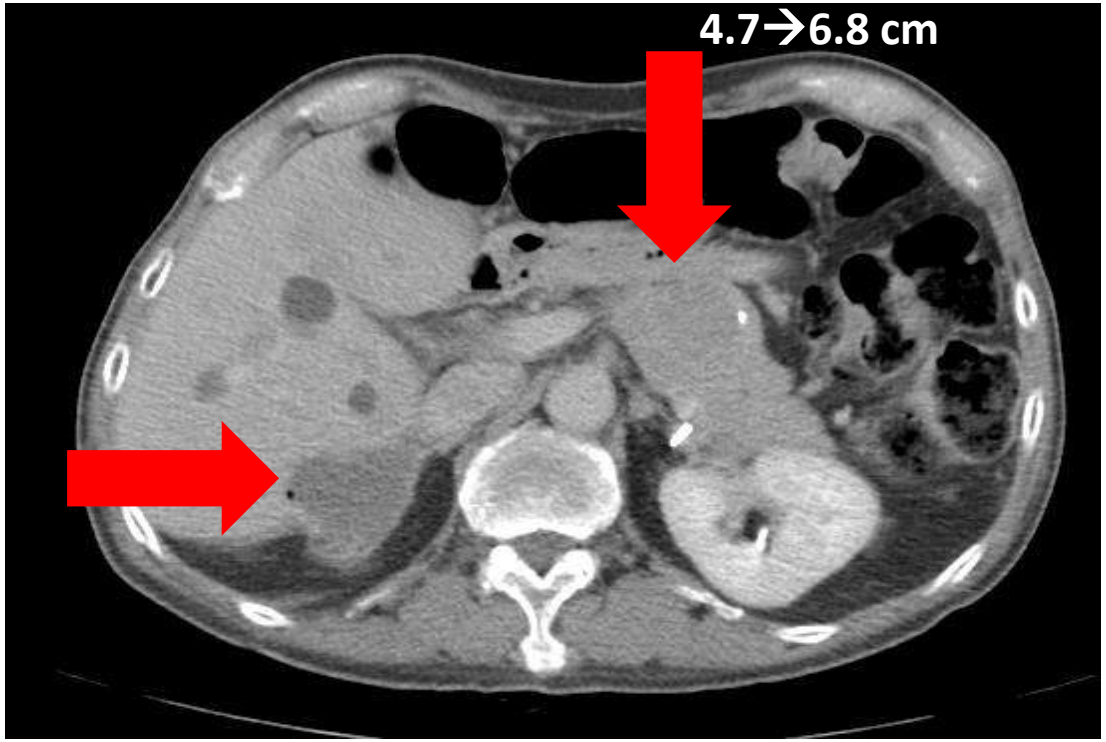
Location	n	Type	n
Lung	8	Carcinoid	7
		Nonfunctioning	1
Stomach	4	Carcinoid	3
		Nonfunctioning	1
Small bowel	16	Carcinoid	14
		GHRFoma	1
		Nonfunctioning	1
Colon and rectum	5	Carcinoid	5
Pancreas	48	Gastrinoma	12
		Carcinoid	6
		Glucagonoma	5
		VIP	3
		PPoma	2
		ACTH	1
		PTH	1
		Insulinoma	1
		Nonfunctioning	14
		Not reported	3
Adrenals	1	Phaeochromocytoma	1
Kidney	1	Nonfunctioning	1
Primary not detected	5	Carcinoid	1
		Gastrinoma	1
		Nonfunctioning	2
		PPoma	1
Not reported	1	Gastrinoma	1
Not reported	14	Not reported	14
Sum	103		


100
90
80
70
60
50
40
30
20
10
0
survival
47%
overall
24%
recurrence-free
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96 102 108
time [months]

Risk factor	Relative risk	95% Confidence limit	*P*
Extended operation	4.8	2.3–10.0	<0.0001
Age >50 years	2.1	1.1–4.0	0.027
Location of primary			0.20
Somatostatin treatment			0.23

Transplantation with curative intent
appears worth-while in young patients with only hepatic disease

Clinical course



2016/11/08

Whole body CT: **progressive disease** after 3rd Octreotide LAR 30mg

→Everolimus 10mg QD (RADIANT-3 trial: 11 vs 4.6 months[1]); (PFS in Taiwan: 18.9months[2])

→Lanreotide 120mg Q4W (Median not reached; **65.1% with 2 yrs PFS**[3])

[1]N Engl J Med. 364.6 (2011): 514-523.

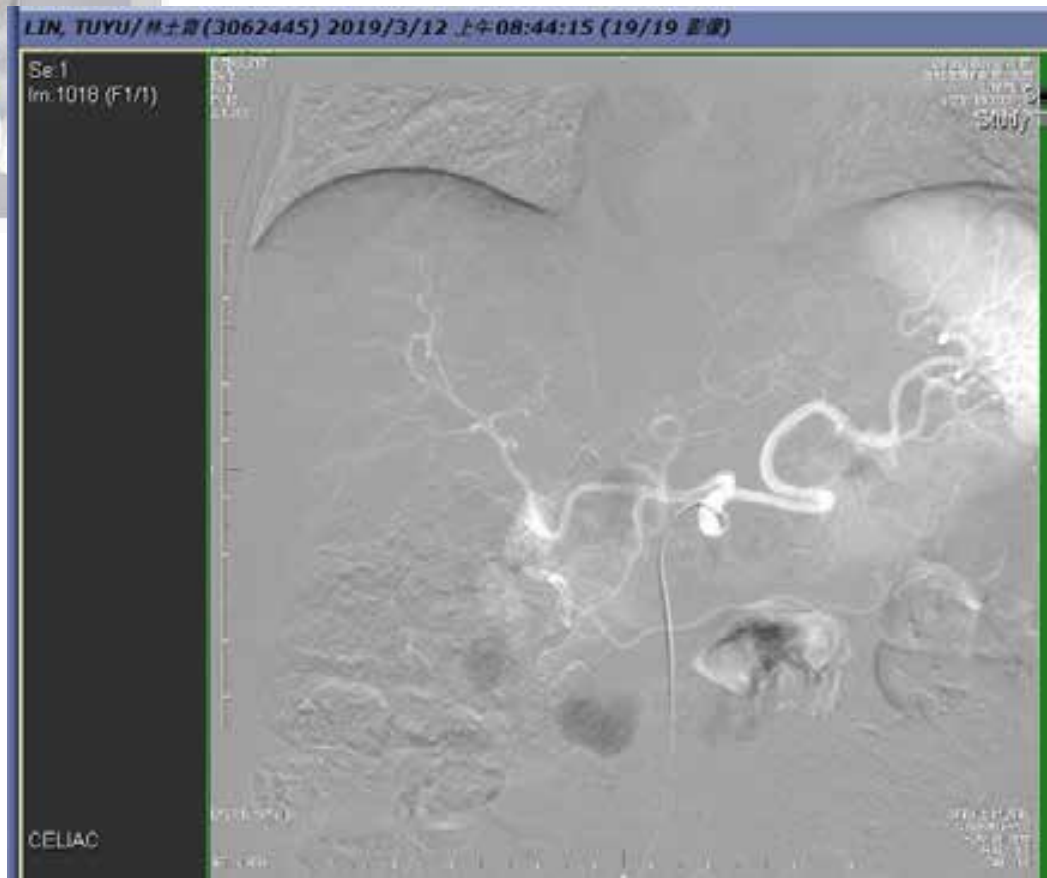
[2]Asia Pac J Clin Oncol. 2016 Jun 30. doi: 10.1111/ajco.12571.

[3]N Engl J Med. 2014 Jul 17;371(3):224-33.

編　　號 PZA240P
藥　　名 Octreotide LAR 30mg/2.5ml/vial
英文商品名　Sandostatin LAR 30mg
中文商品名　善得定長效緩釋注射劑
製造廠　SANDOZ GMBH, SCHAFTENAU PLANT
健保碼　BC22655243

編　　號 PDA258M
藥　　名 Everolimus 5mg/tab
（腎細胞癌、乳癌、胰臟神經內分泌腫瘤）
英文商品名　Afinitor 5mg
中文商品名　癌伏妥錠(Novartis)
製造廠　NOVARTIS
健保碼　BC25165100

編　　號 PZA254P
藥　　名 Lanreotide 120mg/pre-filled syringe
英文商品名 Somatuline Autogel
中文商品名 舒得寧長效型注射凝膠劑
製造廠 IPSEN PHARMA BIOTECH
健保碼 B023925257




thank you
danke
謝謝
рахмат
ngiyabonga
teşekkür ederim
gracias
merci
obrigado
dziękuję
bedankt
спасибо
Баярлалаа
go raibh maith agat
mochchakkeram
sukriya
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terima kasih
grazie
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감사합니다
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rahmat