Carcinoid tumor (유암종)

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Primary site of a carcinoid cancer of gut

Neuroendocrine tumors in the small intestine
1. Definition

- **Carcinoid** (also *carcinoid tumor*) is a slow-growing type of *neuroendocrine tumor* originating in the cells of the *neuroendocrine system*.
- In some cases, *metastasis* may occur.
- *Carcinoid tumors* have more *benign features* than neuroendocrine cancers.
2. History

• 1907 by Siegfried Oberndorfer, a German pathologist at the University of Munich, who coined the term karzinoide, or "carcinoma-like", to describe the unique feature of behaving like a benign tumor despite having a malignant appearance microscopically.

• And now these tumors are now known to arise from the enterochromaffin (EC) and enterochromaffin-like (ECL) cells of the gut.

• Some sources credit Otto Lubarsch with the discovery.
• In 2000, the World Health Organization redefined "carcinoid (유암종)", but this new definition has not been accepted by all practitioners.

• According to the American Cancer Society, the 2000 WHO definition states: “The WHO now divides these growths into neuroendocrine tumors and neuroendocrine cancers.

1. Neuroendocrine tumors are growths that look benign but that might possibly be able to spread to other parts of the body.

2. Neuroendocrine cancers are abnormal growths of neuroendocrine cells which can spread to other parts of the body.”
• 위장관계 내분비종양의 전통적인 병리학적 분류
1. 유암종(carcinoid)
   - 유암종(carcinoid)
   - 비정형 유암종(atypical carcinoid)
2. 저분화 신경내분비암종(poorly differentiated neuroendocrine carcinoma)
   - 소세포암종(small cell carcinoma)
   - 대세포 신경내분비암종(large cell neuroendocrine carcinoma)
3. Presentation

• GI tract: 54.5% of the tumors
• Within the GI tract:
  a. Small intestine was the most common site (44.7%)
  b. Rectum (19.6%)
  c. Appendix (16.7%)
  d. Colon (10.6%)
  e. Stomach (7.2%).
• The next most common affected area is the *respiratory tract*, with 28% of all cases — per PAN-SEER data (1973 – 1999).
2.1 Gastrointestinal

- **Carcinoid tumors** are *apudomas* that arise from the *enterochromaffin cells* throughout the gut.
- Over **two-thirds** of carcinoid tumors are found in the gastrointestinal (GI) tract.
- Some sources list the **appendix** as the most common site.

*Apudoma* is an endocrine tumor that arises from an APUD cell from structures such as the *ampulla of Vater, pancreas*, and *prostate*. They are derived from neural crest cells.

- **Enterochromaffin (EC) cells:**
  - A type of enteroendocrine and neuroendocrine cell occurring in the epithelia lining the lumen of the digestive tract and the respiratory tract.
  - Contain about 90% of the body's store of serotonin (5-HT).
  - In the GI tract, 5-HT is important in response to chemical, mechanical or **pathological** stimuli in the lumen.
  - It activates both secretory and peristaltic reflexes, and activates **vagal** afferents (via 5-HT<sub>3</sub> receptors) that signal to the brain (important in the generation of nausea).
  - They are stimulated by **gastrin**, a molecule that is produced at the antrum of the stomach by **G cells**.
2.2 Lung

- Carcinoid tumors are also found in the lungs.
- Typical pulmonary carcinoid tumor is an uncommon low-grade malignant lung mass that is most often in the central airways of the lung.
- It is also known as typical lung carcinoid tumor, lung carcinoid, and typical lung carcinoid.
2.3 Other sites / metastases

- Carcinoid metastasis can lead to **carcinoid syndrome**.
- This is due to the over-production of many substances, including **serotonin**, which is released into the systemic circulation, and which can lead to symptoms of cutaneous flushing, **diarrhea**, **bronchoconstriction**, and right-sided **cardiac valve disease**.
- It is estimated that less than 10% of carcinoid patients will develop **carcinoid syndrome**.
4. Epidemiology

- Approximately 1 out of every 100,000 individuals
- Male >> Female = 2:1
- More frequent in people older than 50 years old
- Rare in children
- Location:
  - 28.5% small intestine
  - 5% appendix
  - 14% rectum
  - 28% bronchial system of the lungs
  - 5-7% colon
  - 4% stomach
  - 1% pancreas
  - >1% liver
  - 8% other

- Up to 25% of all GI tract carcinoids are associated at some time with another tumor of non-carcinoid type, such as the typical colon cancer, cancer of the lung, breast cancer and prostate cancer.
- Of all carcinoids, those arising in the appendix are the most benign, having only very rare distant spread and 87% of people with carcinoid of the appendix diagnosed and removed by surgery remaining alive after 5 years.
- A carcinoid is found usually by accident in 1 of every 200-300 appendices removed at surgery.
5. Symptoms

- Most carcinoids are asymptomatic; finding of coincidental carcinoids.

- 3가지 단계별 증상:

  A. 무증상: 초기

  B. 장관에 생긴 carcinoid: 여타 종양과 마찬가지로 위치에 따라 증상이 다름

  C. Carcinoid 종양의 특이 증상: 생성되는 호르몬에 의한 증상; 10% 이하에서 다음과 같은 증상을 동반; 이와 같은 증상을 동반할 때 카르시노이드 증후군 동반

- About 10% of carcinoids secrete excessive levels of a range of hormones, most notably serotonin (5-HT), bradykinin, histamine, and prostaglandins causing carcinoid syndrome:

  - Flushing (안면홍조)
  - Diarrhea (설사)
  - Abdominal cramping (심한 복통)
  - Asthma like wheezing attacks (씨근거림, 천명)
  - Heart failure (심장기능상실, 심부전)
  - Peripheral edema (말초 부종)
1. Flushing(홍조):
   • 혈관확장이 홍조의 원인
   • 종양세포에서 유리되는 히스타민, 칼시토닌 등 유전자 관련 펩티드 등의 복합작용으로 발생
   • 유발인자: 알코올·카테콜라민·칼슘·펜타가스트린 등
   • 임상적 양상: 4가지
     a. 미만성 홍반성 홍조: 얼굴 뿐 아니라 등·복부·손바닥 피부에 도 발생하는데, 발작적이고 대개 2~5분간 지속
     b. 진홍색 홍조: 안면 피부정맥과 모세혈관 확장증, 눈물과 안결막 충혈이 동반; 오래 지속된 카르시노이드 증후군 환자에 자주 발생
   c. 선흔색 조각 홍조: 위 카르시노이드에서 히스타민의 과다 유리
   d. 기관지 카르시노이드 환자에서 홍조와 안면 피부부종, 눈물과 침샘부종, 저혈압, 설사, 심계항진 등이 동반되는데, 이것이 홍조반응의 가장 심한 형태

2. Diarrhea(설사):
   • 홍조 없이도 일어날 수 있음
   • 설사는 복통과 급박한 배변을 동반한 물 같은 대변의 형태
   • 어떤 환자는 하루 20회 정도의 점액성 대변을 봅
   • 설사는 증가된 장운동으로 나타나고, 세로토닌은 장운동을 자극과 점액분비를 증가시킴
3. Abdominal cramping(복통):
• 위장관 카르시노이드 환자에게 자주 발생하는 증상
• 장 운동의 항진에 의한 것
• 직장의 카르시노이드 종양이 대량으로 간 전이를 일으키면 발열과 통증이 나타남

4. 기관지 수축 with Wheezing:
• 카르시노이드 증후군 환자의 15~20% 정도에서 나타남.
• 천식발작은 안면 홍조와 함께 나타나고, 타키키닌과 브라디 키닌에 의해 발생
• 마취 중에도 기관지 수축이 나타날 수 있으며, 카테콜라민은 기관지 수축을 더 악화시키므로 전신적으로 투여하면 됨

5. 카르시노이드 심질환:
• 카르시노이드 종양에서 동반된 심질환은 유병률과 사망률을 증가시킴
• 카르시노이드 증후군 환자의 70% 정도에서 심질환 발생
• 가장 자주 나타나는 증상은 삼첩판의 형태적·기능적 이상
• 삼첩판의 유두근이 단축되고, 섬유화가 나타나 판막의 운동이 제한을 받음
• The outflow of serotonin can cause a depletion of tryptophan leading to niacin deficiency.
• Niacin deficiency (pellagra), is associated with dermatitis, dementia, and diarrhea.
• This constellation of symptoms is called carcinoid syndrome or (if acute) carcinoid crisis.
• Occasionally, hemorrhage or the effects of tumor bulk are the presenting symptoms.
• The most common originating sites of carcinoid is the small bowel, particularly the ileum; carcinoid tumors are the most common malignancy of the appendix.
• Carcinoid tumors may rarely arise from the ovary or thymus.
V-B3 (Niacin) Nicotinic acid Deficiency: 니아신 결핍증

- Pellagra (거친 피부증)
- 3Ds:
  a. Dermatitis (피부병)
  b. Diarrhea (설사)
  c. Dementia (치매)

- Cheilosis (구순증)
- Seborrheic dermatitis (지루성 피부염)
- Corneal interstitial keratitis (각막의 간질성 각막염)
The pathway for the synthesis of serotonin from tryptophan.
5. Diagnosis

1) 내시경검사 ⇒ 조직에서의 면역조직화학 검사[chromogranin A, neuron-specific enolase (NSE), synaptophysin (SYP)];

- The measurement of CgA is considered "the gold standard" of chemical tests.

2) 소마토스타틴 수용체 신티그래피: 특수한 방사선동위원소를 사용한 특수촬영법[^11]In 이 붙여진 Somatostatin analogs인 Octreotide를 정맥내로 주입, 신티그라피를 시행함; 일반적인 CT 혹은 MRI 촬영이나 내시경적 방법으로 확인되지 않는 원발 병소 혹은 전이 병소를 찾아내는데 도움을 줄 수 있음. 원리는 종양에서 발현되는 2번과 5번 소마토스타틴 수용체에 Octreotide가 강한 결합을 보이는 것을 이용

Micrograph of a paraganglioma stained with chromogranin A immunostain.

• Chromogranin A: a member of the granin family of neuroendocrine secretory proteins, i.e., it is located in secretory vesicles of neurons and endocrine cells (enterochromaffin-like cells)
A. Octreotide scan (Somatostatin receptor scintigraphy, SRS)

\[ \text{\^{111}In-pentetretotide scintigraphy of a 41 year-old man with ectopic Cushing' syndrome caused by a neuroendocrine carcinoma of the mesentery. Radiotracer accumulation in the left thyroid in 10/2003 (arrow). The mesenterial neuroendocrine tumor became clearly visible in 4/2005 (arrow).} \]

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B. Iobenguane $[^{131}\text{I}]-\text{mIBG}$ (meta iodo benzyl guanidine, mIBG, MIBG)]
- a radiopharmaceutical, used in a scintigraphy method called MIBG scan.
- Iobenguane is a radiolabeled molecule similar to noradrenaline.
- Product labeling for diagnostic iodine-131 iobenguane recommends potassium iodide administration one day before injection and continuing 5 to 7 days following.
- Iodine-131 iobenguane used for therapeutic purposes requires a different pre-medication duration, beginning 24–48 hours prior to iobenguane injection and continuing 10–15 days following injection.

[Chemical structure of Iobenguane]

Pheochromocytoma seen as dark sphere in center of the body (it is in the left adrenal gland). Image is by MIBG scintigraphy, with radiation from radiiodine in the MIBG. Two images are seen of the same patient from front and back.
3) CT
4) MRI
5) PET
6) Urine 5-HIAA test (24시간 소변 5-HIAA)
   • 5-Hydroxyindoleacetic acid (5-HIAA)는 세로토닌(serotinin) 대사로 인해 생성되는 산으로 암종 환자의 소변에서 상승하는 물질
   • 24시간 소변 5-HIAA는 중요한 유암종의 표지자로 특이도는 88%이며 암의 진단 뿐 아니라 치료에 대한 반응 정도를 평가하는데도 유용한 검사
   • 24시간 채집한 소변에서 5-HIAA의 정상치는 1~5mg
   • 소변 채집 도중 바나나, 파인애플, 키위, 건포도, 토마토, 땅콩 등을 섭취할 경우 5-HIAA가 상승할 수 있으므로 주의 요함
6. Treatment

1) **Surgery**: if feasible, surgery is the only curative therapy.
2) Chemotherapy:

- Chemotherapy for carcinoid given by intravenous injection or by mouth has been in use for over 20 years.
- There are many drugs available.
- Individual drugs used alone have been disappointing but a number of combinations of these drugs have been beneficial.
- Some of these combinations: leucovorin-fluorouracil and streptozotocin, cytoxan- Doxorubicin and cisplatin, dacarbazine-fluorouracil, etoposide-cisplatin.
- One or another of these combination has produced good response in only 20-30% of the cases.
• The site of the origin has considerable influence on likelihood of the tumor(s) responding to chemotherapy.

• For instance pancreatic and lung carcinoids respond to some forms of chemotherapy better than intestinal carcinoid.

• A number of newer drug combinations are currently approved or under investigation, including:
  
  • **Everolimus (Afinitor)**
  • **Sorafenib (Nexavar)**
  • **Sunitinib (Sutent)**
  • **Atiprimod**
  • **SOM230**
  • **Bevacizumab (Avastin)**
  • **Temozolomide (Temodar)**
  • **Capecitabine (Xeloda®)**, and others.
• **Somatostatin analogues**
  a. Octreotide
  b. Lanreotide
  c. Vapreotide

• Injections of these analogues not only usually squelch the symptoms of Carcinoid Syndrome but are now believed to sometimes inhibit or even reverse growth of the tumors.

• This has become the mainstay of treatment for most carcinoid tumors, with or without the Carcinoid Syndrome.

• In a few patients needing large amounts of octreotide continuous injection of Sandostatin s.c. is given by a special tiny injection pump as is used for insulin in some diabetics.
a. Octreotide

- Brand name **Sandostatin** by the Sandoz Pharmaceutical (now **Novartis Pharmaceuticals**) is an **octapeptide** that mimics natural **somatostatin** pharmacologically, though it is a more potent inhibitor of **growth hormone**, **glucagon**, and **insulin** than the natural hormone.

- It was first synthesized in 1979 by the chemist **Wilfried Bauer**.

- Approved uses by FDA
  - Acromegaly
  - Gigantism
  - Thyrotropinoma
  - Diarrhea and flushing episodes associated with carcinoid syndrome
  - Diarrhea in patients with vasoactive intestinal peptide-secreting tumors (VIPomas)
• Octreotide is used in nuclear medicine imaging by labeling with indium-111 (Octreoscan) to noninvasively image neuroendocrine and other tumors expressing somatostatin receptors.

• More recently, it has been radiolabelled with gallium-68, enabling imaging with positron emission tomography (PET), which provides higher resolution and sensitivity.

• Octreotide can also be labelled with a variety of radionuclides, such as yttrium-90 or lutetium-177, to enable peptide receptor radionuclide therapy (PRRT) for the treatment of unresectable neuroendocrine tumors.

• 한국노바티스 Octreotide 주사제 “산도스타틴주”: 초산옥트레오티드 100μg/mL

• 적응증
  - 말단비대증
  - 위·장·췌장계 내분비성 종양에 관계된 증상의 경감
  -췌장 수술 후 발생하는 합병증의 예방
  - 위, 식도 정맥류 출혈
b. Lanreotide (INN):
- a long-acting analogue of somatostatin, like octreotide.
- Lanreotide (as lanreotide acetate) is manufactured by Ipsen; the trade name Somatuline.
- approved for sale in the United States by the FDA in August 30, 2007

소마툴린피.알.주 (Somatuline P. R. Injection)
- 한국입센
- 초산 랜레오티드 40mg
- 효능/효과
  1. 수술 및 / 또는 방사선치료 등으로 성장호르몬 분비가 정상화되지 못한 말단비대증 치료
  2. 카르시노이드 종양과 관련하여 일어나는 임상증상의 치료
  3. 갑상샘항진증이 나타나는 갑상선자극호르몬 분비(TSH) 뇌하수체 선종의 치료: 수술 및 / 또는 방사선 치료를 위한 전처 리 또는 보조치료제로서 병용, 또는 수술 및 방사선 치료가 부적합한 경우
c. Vapreotide

- Vapreotide (Sanvar) is a synthetic **somatostatin** analog.
- It is used in the treatment of **esophageal variceal bleeding** in patients with cirrhotic **liver disease** and **AIDS**-related diarrhea.
If carcinoid tumor has metastasized (most commonly, to the liver) and is considered incurable, there are some promising treatment modalities, for arresting the growth of the tumors and prolonging survival in patients with liver metastases, though these are currently experimental.

a. Radiolabeled octreotide [e.g. Lutetium (\(^{177}\)Lu) DOTA-octreotate]

b. Radiopharmaceutical, lobenguane \([^{131}\)I-mIBG (meta iodo benzyl guanidine, mIBG, MIBG)]
• While the metastatic potential of a coincidental carcinoid is probably low, the current recommendation is for follow up in 3 months with CT or MRI, labs for tumor markers, like serotonin, and a history and physical, annual physicals thereafter.
7. Prognosis

- Of all carcinoids, **those arising in the appendix are the most benign**, having only very rare distant spread and 87% of people with carcinoid of the appendix diagnosed and removed by surgery remaining alive after 5 years.

- The second most least malignant of these tumors are **the rectal carcinoids with a 72% 5 year survival**. If distant metastases are present when a carcinoid from any site of origin is found, the 5 year survival rate drops to 27% **if not treated**.

- The **5-year survival rates** for the most common gastrointestinal sites: **stomach (75.1%)**, **small intestine (76.1%)**, **appendix (76.3%)**, and **rectum (87.5%)**.
8. Carcinoid syndrome

1) Definition:

• refers to the array of symptoms that occur secondary to carcinoid tumors.

• The syndrome includes flushing and diarrhea, and, less frequently, heart failure and bronchoconstriction.

• It is caused by endogenous secretion of mainly serotonin and kallikrein.

• Other substances: substance-P, pancreastatin, eurotensin, pancreatic polypeptide, neurokinin-A, motilin and atrial natriuretic hormone (ANH), as well as other peptide hormones.
Carcinoid syndrome

Heart
- pulmonic and tricuspid valve thickening and stenosis
- endocardial fibrosis

Liver
- hepatomegaly

Skin
- cutaneous flushes
- apparent cyanosis

Respiratory
- cough
- wheezing
- dyspnea

Gastrointestinal
- diarrhea
- cramps
- nausea
- vomiting

dermo-peritoneal and pelvic fibrosis
2) Clinical presentation

- **Carcinoid syndrome** is the pattern of symptoms sometimes seen in people with carcinoid tumors. These tumors are rare, and often slow growing. About 70% of carcinoid tumors are found in the gastrointestinal tract.

- **Carcinoid syndrome** occurs in about 1 in 10 people with carcinoid tumors, usually after the tumor has spread to the liver or lung.

- These tumors release too much of the hormone serotonin, as well as several other chemicals that cause the blood vessels to open (dilate).
• The most important clinical finding is **flushing** of the skin, usually of the head and the upper part of thorax.

• **Secretory diarrhea** and **abdominal cramps** are also characteristic features of the syndrome.

• When the **diarrhea** is intensive it may lead to electrolyte disturbance and dehydration.

• Other associated symptoms are **nausea**, and **vomiting**.

• **Bronchoconstriction**, which may be **histamine**-induced, affects a smaller number of patients and often accompanies **flushing**.
• About 50% of patients have cardiac abnormalities, caused by serotonin-induced fibrosis of the tricuspid and pulmonary valves, called cardiac fibrosis.

• Elevated levels of circulating serotonin have been associated with cardiac failure, due to fibrous deposits on the endocardium.

• These deposits are thought to be responsible for the fibrous degeneration of the valve apparatus.

• "TIPS" is an acronym for Tricuspid Insufficiency, Pulmonary Stenosis (fibrosis of tricuspid and pulmonary valves).
Abdominal pain is due to desmoplastic reaction of the mesentery or hepatic metastases.

Although the most common site of a carcinoid tumor is the appendix or terminal ileum, liver metastases, releasing serotonin directly into the systemic circulation are required for the carcinoid syndrome to occur.

This is because serotonin created by a GI carcinoid tumor and released into the hepatic portal system is broken down at the liver and does not reach the systemic circulation.

Serotonin is also metabolized in the lungs.

However: If the tumor is bronchogenic in origin, then metastasis does not need to occur in order for carcinoid syndrome to occur.
3) Pathophysiology

- Carcinoid tumors produce the vasoactive substance, serotonin.
- It is commonly, but incorrectly, thought that serotonin is the cause of the flushing.
  - results from secretion of kallikrein, the enzyme that catalyzes the conversion of kininogen to lysyl-bradykinin.
  - The latter is further converted to bradykinin, one of the most powerful vasodilators known.
- Other components of the carcinoid syndrome:
  - diarrhea (probably caused by serotonin),
  - pellagra-like syndrome (probably caused by diversion of large amounts of tryptophan from synthesis of the vitamin B\textsubscript{3}, niacin, to the synthesis of 5-hydroxyindoles including serotonin)
  - fibrotic lesions of the endocardium, particularly on the right side of the heart resulting in insufficiency of the tricuspid valve and, less frequently, the pulmonary valve and, uncommonly, bronchoconstriction.
The pathogenesis of the cardiac lesions and the bronchoconstriction is unknown, but the former probably involves activation of serotonin 5-HT2B receptors by serotonin.

When the primary tumor is in the gastrointestinal tract, as it is in the great majority of cases, the serotonin and kallikrein are inactivated in the liver; manifestations of carcinoid syndrome do not occur until there are metastases to the liver or when the cancer is accompanied by liver failure (cirrhosis).

Carcinoid tumors arising in the bronchi may be associated with manifestations of carcinoid syndrome without liver metastases because their biologically active products reach the systemic circulation before passing through the liver and being metabolized.

In most patients, there is an increased urinary excretion of 5-HIAA (5-hydroxyindoleacetic acid), a degradation product of serotonin.
• The biology of these tumors is interesting as it differs from many other tumor types.
• Ongoing research on the biology of these tumors may reveal new mechanisms for tumor development.

4) Localization of tumor
• Tumor localization may be extremely difficult.
• Barium swallow and follow-up examination of the intestine may occasionally show the tumor.
• Capsule video endoscopy has recently been used to localize the tumor.
• Often laparotomy is the definitive way to localize the tumor.
5) Treatment

A. For symptomatic relief of carcinoid syndrome:

- **Octreotide** (a somatostatin analogue which decreases the secretion of serotonin by the tumor and, secondarily, decreases the breakdown product of serotonin (5-HIAA))

- Peptide receptor radionuclide therapy (PRRT) with lutetium-177, yttrium-90 or indium-111 labelled to octreotate is highly effective

- **Methysergide maleate** (antiserotonin agent but not used because of serious side effect of retroperitoneal fibrosis)

- **Cyproheptadine** (an antihistamine drug with antiserotonergic effects)
B. Alternative treatment for qualifying candidates:

• Surgical resection of tumor and chemotherapy (5-FU and doxorubicin)

• Endovascular, chemoembolization, targeted chemotherapy directly delivered to the liver through special catheters mixed with embolic beads (particles that block blood vessels). For patients with liver metastases.
6) Prognosis

- Prognosis varies from individual to individual.
- It ranges from a 95% 5 year survival for localized disease to an 80% 5 year survival for those with liver metastases.
- The average survival time from the start of octreotide treatment has increased to about 12 years.
Case study-1

- A 35 year old man complains of episodic flushing and diarrhea. His flushing is occasionally precipitated by alcohol consumption. It begins suddenly, is accompanied by pruritus and lasts usually 5-10 minutes. The diarrhea is watery and often accompanies the episodes of flushing. Which statement best describes the tumors that are responsible for the carcinoid syndrome this patient demonstrates?

- Answer: Carcinoid syndrome is more commonly seen with hepatic metastasis.
Case study-2

- Recognizing and Diagnosing the Subtleties of Carcinoid Syndrome

- This case and the associated images have been provided by Rodney Pommier, MD (Professor of Surgery, Division of Surgical Oncology, Oregon Health & Science University, Portland, OR.)

Patient Background

- 54-year-old postmenopausal woman
- Married with 2 adult children
- History of hypertension
- Previously diagnosed with mild irritable bowel syndrome (IBS) with diarrhea
  – Family history is negative for both

Case History

- Presents to internist for care of hot flashes that have returned 2 years after menopause
  – Occur mostly after meals, when she drinks wine and when she goes running
- Referred to gynecologist
  – Physical examination is entirely normal
  – Experiences 2 hot flashes with no sweating during the examination
- Hormone-replacement therapy (HRT) is prescribed
- Referred to gastroenterologist for IBS treatment

3-Month Follow-up

- Patient has experienced no improvement of hot flashes
- A different formulation of HRT is prescribed
12-Month Follow-up
• Returns to gastroenterologist with worsening of her IBS like symptoms
  – Reports cramping
  – Abdominal pain
  – Increased episodes of diarrhea
• Wakes up at night with diarrhea
• Patient discontinued her HRT medication, feeling they were ineffective
• Patient is prescribed an antidiarrheal and antispasmodics, for control of diarrhea

21-Month Follow-up
• Patient is in need of emergency care
• Patient presents with acute bowel obstruction and is taken to operating room
  – There is marked fibrosis of the terminal ileum with multiple hairpin turns of the bowel and a small tumor in the terminal ileum (Figure 1)
- Tumor is surgically resected (Figure 2)

**Figure 2. Bowel Resection Surgical Specimen**

Surgical investigation revealed multiple metastatic tumors in lobes of the liver (Figure 3).

**Figure 3. Liver Metastases**

- Biopsies of the liver tumors were taken

**Pathological Report**

- Small bowel and cecal resection reveals:
  - Carcinoid tumor, 1.5 cm, with intense peritoneal sclerosis
  - Metastatic carcinoid in 10 of 23 mesenteric lymph nodes
  - Liver masses determined to be metastatic carcinoid tumors

**Diagnostic Conclusion**

- The patient had carcinoid syndrome
Oncologist Consulted:

- Postsurgical follow-up with an oncologist included:
  - OctreoScan™
  - 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A (CgA) level evaluation
    - Both levels were markedly elevated
  - Patient was advised to maintain a record of symptom frequency and severity
  - Follow-up appointment scheduled

* OctreoScan is a trademark of Covidien AG or one of its affiliates

Decipher the Evidence Early

- Evidence 1
  - The patient was experiencing nocturnal diarrhea

- Conclusion
  - IBS-associated diarrhea stops during sleep, so this patient may not be experiencing IBS

- Evidence 2
  - Hot flashes were not associated with sweating and did not improve with HRT

- Conclusion
  - Menopausal hot flashes and most other causes of flushing are associated with sweating, so the patient may not be experiencing menopausal hot flashes
  - Carcinoid-associated flushing has no sympathetic component, and thus is "dry"
Evidence 3
The patient's diarrhea was exacerbated by eating, drinking wine, and running.

Conclusion
Carcinoid syndrome is exacerbated by the 5 E's:
- Eating
- Epinephrine
- Emotion
- Ethanol
- Exercise

This patient may be experiencing carcinoid syndrome.

Carcinoid Tumors—Diagnose early to help gain control over debilitating symptoms
- Many patients with carcinoid tumors remain misdiagnosed for up to 5 to 7 years
- The 5-year survival rate decreases based on the extent of metastatic disease
  - 78.2% survival rate with localized tumor
  - 71.7% survival rate with regional metastases
  - 38.5% survival rate with distant metastases
- Carcinoid syndrome can be commonly misdiagnosed as IBS or menopause

If Carcinoid Syndrome is Suspected:
- 5-HIAA and serum CgA level testing can help confirm the diagnosis
- OctreoScan™ is helpful for imaging and tumor staging
유암종: 경계성 종양?

• 유암종: 양성종양? 악성종양? 경계성 종양?

• 경계성 종양: 양성과 악성의 성질을 모두 갖고 있어 언제 어떻게 악성으로 변할지 모르는 종양 (예, 유암종)

• 대법원: 유암종은 크기가 작아도 기타 다른 장기로 전이가 가능하여 암보험금 지급 대상이 맞다고 판결 (2012.5.28; 직장유암종 수술 문모씨의 경우; 보험금 2천만원 지급해라!)

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