มหาวิทยาลัยมหิดล
คณะแพทยศาสตร์
ศิริราชพยาบาล

# Interhospital Conference Case 4

## 24th Dec 2021

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# Topic Review Case 4

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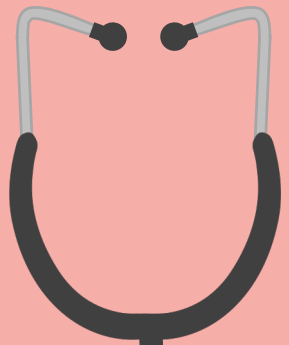
# Doege–Potter syndrome



Solitary fibrous tumor (SFT) that is associated with non-islet cell tumor hypoglycemia (NICTH).

# NICTH

Syndrome of hypoglycemia produced by or associated with **any neoplasm other than insulinoma**

- True incidence is unknown, it is generally believed to be much less frequent than hypoglycemia from insulinomas.
- Most commonly, IGF-2–linked hypoglycemia has been observed in patients with solid tumors that are either of **mesenchymal or epithelial origin**.

| Tumor Type | Prevalence, % |
|---|---|
| Epithelial origin | 45 |
| Hepatocellular carcinoma | 20 |
| Adrenocortical carcinoma | 5 |
| Stomach | 4 |
| Pancreas (non-islet cell) | 4 |
| Lung | 3 |
| Colon, rectum, esophagus | 3 |
| Carcinoid, neuroendocrine, medullary thyroid | 2 |
| Breast, ovary, prostate | 1 |
| Others: seminoma, pseudomyxoma, sarcomatous teratoma, melanoma, Wilms' tumor, dysgerminoma of the ovary, cervix, bladder, uterus, cholangioma | 3 |

| Tumor Type | Prevalence, % |
|---|---|
| Mesenchymal origin | 42 |
| Fibrosarcoma, fibroma | 23 |
| Mesothelioma | 8 |
| Hemangiopericytoma, hemangioendothelioma, hemangiosarcoma | 7 |
| Hematologic: lymphoma, leukemia, lymphosarcoma, myeloma | 1 |
| Others: rhabdomyosarcoma, liposarcoma, neurofibroma, neurofibrosarcoma, histiocytoma, neuroblastoma, mesoblastic nephroma, neurilemmoma, meningioma, reticulum cell sarcoma, pelvic clear cell sarcoma | 3 |
| Unknown etiology | 13 |

Endocrine Reviews, December 2013, 34(6):798 – 826

# Doege–Potter syndrome

- **Common origins of SFT: pleural cavity > pelvis > liver,** retroperitoneum, kidney, mediastinum, sella, utera, bladder, intestinal tissue, mandibular, and thigh
- **Benign VS Malignant:** United Kingdom's pathologic criteria (hypercellularity, >4 mitotic figures/10 high-power fields (HPFs), pleomorphism/atypia, infiltrative growth pattern, necrosis, and hemorrhage)
- **SFTs with NICTH** were **more likely to be malignant**.
- **Extrathoracic SFTs were more likely to be malignant than thoracic SFTs**.

Malignant: Thoracic SFTs (pleural cavities, lungs, and mediastinum) 56.1% VS Extrathoracic SFTs 66.7%

Medicine (2017) 96:27(e7417)

# Clinical features

- Mean age of onset 59 years
- More common in males than in females (47 vs 28 cases)
- SFT diameter varied from 3.2 to 30 cm

Symptoms characteristic:

- Hypoglycemia (predominant symptom) might develop before/after discovery of the tumor, during tumor recurrence or distance metastases
- Compression and mass effects

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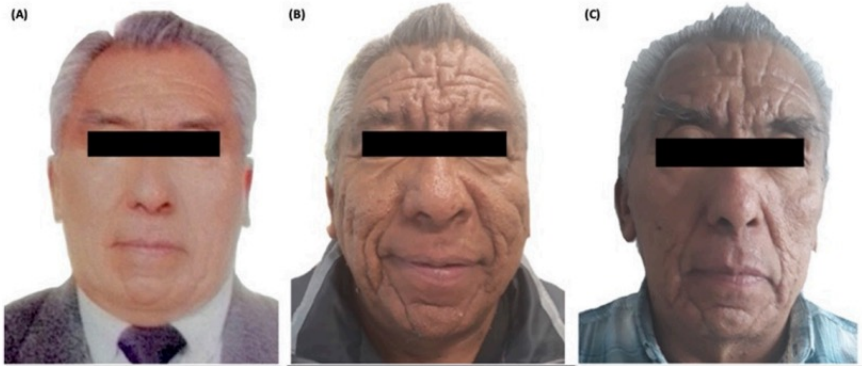
# Acromegaloid changes

- Skin lesions such as **seborrheic keratosis, skin tags, and rhinophyma** have all been described in patients with IGF-2–producing tumors.
- IGF-2–mediated stimulation of multiple subclasses of insulin-related and IGF-1–related receptors
- Combination of acromegalic features and tumor-associated hypoglycemia may not be unique to IGF-2-oma.
- MEN 1 have both insulin-secreting and GH-secreting tumors.




Endocrine Reviews, December 2013, 34(6):798 – 826
Journal of the Endocrine Society, March 2019, 3(3):537–543

# Diagnosis

- Confirm Whipple's triad

1) Symptoms and/or signs of hypoglycemia

2) Low plasma glucose

3) Resolution of signs and symptoms upon reversal of hypoglycemia

- Identify any systemic conditions that may be causing or contributing to hypoglycemia

| | |
|---|---|
| 1. Hormone deficiencies | Primary AI |
| | Hypopituitarism with secondary AI |
| 2. Critical illness | Severe renal, hepatic or cardiac failure |
| | Sepsis |
| 3. Starvation | |
| 4. Drugs | Salicylates, quinine, pentamidine, alcohol, insulin, OHA |

Endocrine Reviews, December 2013, 34(6):798 – 826

# Diagnosis

- Focus on IGF-2-omas in patients with hypoglycemia with low insulin, C-peptide, pro-insulin, and β-hydroxybutyrate levels

| Symptoms, Signs, or Both | Glucose (55 mg/dL) | Insulin (3 μU/mL) | C-Peptide | β-Hydroxybutyrate (2.7 mmol/L) | Sulfonylureas and Other Insulin Secretagogues | Antibody to Insulin | Hypoglycemia Pattern | Diagnostic Interpretation |
|---|---|---|---|---|---|---|---|---|
| No | Below | Below | Below | Above | No | No | NA | Falsely low |
| Yes | Below | Much above | Below | Below | No | No/Yes | Fasting or postprandial | Exogenous insulin |
| Yes | Below | Above | Above | Below | No | No | Fasting | Insulinoma |
| Yes | Below | Above | Above | Below | No | No | Postprandial | Postgastric bypass hypoglycemia, noninsulinoma pancreatogenous hypoglycemia syndrome |
| Yes | Below | Above | Above | Below | Yes | No | Fasting or postprandial | Oral hypoglycemic agent |
| Yes | Below | Much above | Much above | Below | No | Yes | Postprandial | Autoimmune: agonist antibodies to insulin |
| Yes | Below | Above | Below | Below | No | Yes | Fasting or postprandial | Autoimmune: antibodies to IR |
| Yes | Below | Below | Below | Below | No | No | Fasting | IGF-2 |

0.6 ng/ml

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# Investigation

- **GH** concentrations are usually **low** along with **low plasma levels of total IGF-1**
- Levels of **total IGF-2 may be elevated or normal**, whereas levels of the **IGF-2 precursors are often elevated**
- An elevated ratio of IGF-2 to IGF-1 may be helpful in the diagnosis when IGF-2 levels are within the normal range.

| Conditions | Molar ratio of IGF-2 to IGF-1 in plasma |
|---|---|
| Normal | 3:1 |
| IGF-2–linked hypoglycemia with recurrent hypoglycemia | >10:1 (64:1) |

- Abnormally high IGF-2 to IGF-1 ratios can also occur in patients with sepsis and severe cachexia (with subnormal IGF-2 and IGF-1 levels).

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# Imaging

- **CT scanning and MRI** are very effective tools in determining the invasion of the surrounding structures, distant metastasis and follow-up.

CT imaging of SFTs

- Typically shows a **smooth, well circumscribed, and homogenous mass**.
- Large heterogeneous masses can be seen with a necrotic area and probably with/without calcification.

MRI

- Multinodular tumors of **isointensity or low intensity on T1W** images and **high signal intensity on T2W** images.
- Mature fibrous tissue has a low signal strength due to the high content of fibrous tissue or collagen, with intense enhancement on postcontrast dynamic MRI.
- Malignant fibrous tissue tends to show a high signal intensity.

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# Imaging

FDG-PET VS Tyrosine-PET

- Malignant SFTs: usually false-negative on FDG-PET but can be benign positive on tyrosine-PET
- **High levels of IGF-II induce liver, heart, and muscle uptake of FDG**, leaving less available FDG for the tumor to take up.
- Using **radiolabeled amino acid C-11-tyrosine** as a tracer permits **visualization of the tumor**.
- Functional tumor imaging techniques like **FDG-PET may lead to false-negative** results.

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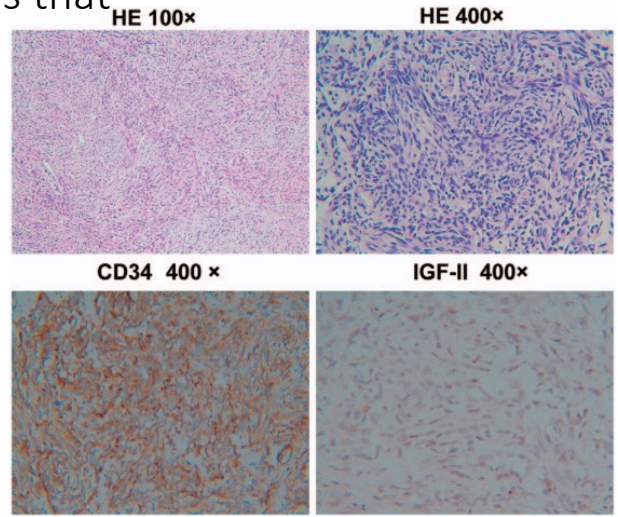
# Pathology

- Most of the identified tumors were large, solid, and well circumscribed, with a lobular, firm, and gray-white cut surface.
- **Microscopic examination** demonstrated a **bland spindle-cell proliferation** (arranged in fascicles), and hypo- and hypercellular areas that were separated by thick and thin collagen bundles.
- Most malignant tumors revealed hemorrhagic, high cellularity, pleomorphic, or necrotic changes.
- **IHC:** CD34+, B-cell lymphoma-2 (Bcl-2)+, Vimentin+ and S100- expression

Strong **positive CD34, CD99, Bcl2,** and **negative** (pancytokeratin) **AE1/AE3, synaptophysin, S-100, and calretinin** were shown to be important markers related to the diagnosis of SFTs.

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# Treatment: Tumor therapy

Tumor therapy

- Definite treatment: Complete tumor resection
- Neoadjuvant therapy (chemoradiation and consecutive selective embolization of the feeding vessels of the tumor) were reported to be effective.
- However, SFTs are considered relatively chemoresistant.
- Chemotherapy is used for metastatic or symptomatic nonresectable SFTs.
- Akt/mTOR pathway was considered a candidate therapeutic target for SFTs.

**The adjunctive therapy, including embolization, chemotherapy, and radiotherapy, for Doege–Potter syndrome, 1898–2016.**

| Reference | Location | Pathology | Embolization | Chemotherapy | Radiotherapy | Effects |
|---|---|---|---|---|---|---|
| [46] | Sella | Borderline | | | Gamma-knife stereo radiotherapy | The postoperative course was uneventful |

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# Treatment: Hypoglycemia therapy

Hypoglycemia therapy

Increase in oral food intake (amount of food, caloric density, and/or frequency)

1) Glucocorticoids
   - Most effective therapy for long-term remission of hypoglycemia
   - **Prednisolone at a dose ≥25mg/d (0.5mg/kg/d),** dexamethesone at 2.0mg/d, and methylprednisolone at 32mg/d could effectively relieve hypoglycemia.
   - When the dose was reduced to less than 20mg/d, prednisolone was unable to abolish episodes of hypoglycemia.
2) **GH:** Previous studies have suggested that at **daily doses of 4 to 12 U**, rhGH markedly increased IGFBP-3 and alleviated hypoglycemia in 3 patients with NICTH.
3) Glucagon
   - Effect of glucagon in recovering tumor hypoglycemia remains controversial.
   - 7 patients with hypoglycemia and liver metastasis had an acceptable glycemic response to long-term treatment with **glucagon (0.06–0.3mg/h, via intravenous infusion pump).**

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ABSTRACT | MAY 6, 2021

# Doege-Potter Syndrome: A Case of Tumor-Induced Hypoglycemia

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Case report


A 54 year-old man with solitary fibrous tumor (SFT) of the brain and metastases to the liver developed acute onset right-sided hemiparesis, confusion, and dysarthria. EMS was called, and blood glucose was noted to be 38. The patient was given D50 during transport to the hospital with improvement in his blood sugar and resolution of his neurologic symptoms. He described slightly diminished oral intake over the preceding week but was able to eat a full meal a few hours prior to symptom onset. He had no history of diabetes or recent medication changes. In the emergency department, his initial glucose after D50 was 102 but then dropped to 50 on subsequent check. He was started on D5LR at 125cc/hr and admitted to the hospital. Non-contrasted head CT scan showed no abnormalities. Over the next 48 hours, he had recurrent hypoglycemia when the D5LR infusion was weaned. Lab workup revealed normal liver function tests, Hgb A1c of 4.2%, low serum insulin level (<1.0), low serum C-peptide (0.5 ng/mL), and low insulin-like growth factor 1 (IGF-1) (21 ng/mL). Cortisol stimulation test demonstrated appropriate rise in cortisol levels. Infectious workup including UA, CXR, and blood cultures were unrevealing. CT abdomen/pelvis demonstrated multiple hepatic metastases from SFT.

Final Working Diagnosis:
Doege-Potter syndrome secondary to solitary fibrous tumor

Management/Follow-Up:
In this case, the patient had previously received bevacizumab/temozolomide, pazopanib, sorafenib, and trabectedin, and had disease progression with all of these agents. Due to need to control the SFT in order to wean the glucose drip, the patient was evaluated by surgical oncology and interventional radiology. His disease was not considered resectable, and the patient underwent transarterial chemoembolization (TACE) of the left lobe of the liver. He was started on oral steroids with the hope of suppressing IGF-2 (3, 7). Over a few weeks, the steroids were weaned. The patient later received a second TACE to the right lobe of the liver; however, within two months he began to experience recurrence of his hypoglycemia and was restarted on an increased steroid dose. He continues to follow with his primary oncologist and will undergo radiation therapy to his largest liver lesion in an attempt to treat both his disease progression and hypoglycemia.

Case Report

# Metastatic extrapleural malignant solitary fibrous tumor presenting with hypoglycemia (Doege–Potter syndrome)

Case report

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A B S T R A C T

We report a rare case of metastatic malignant solitary fibrous tumor (SFT) that presented with hypoglycemia because of insulin growth factor-2 production. Initial workup included computed tomography imaging that revealed a large, partially necrotic liver mass, a hypervascular pancreatic head lesion, and 2 renal lesions. Following hepatic resection, pancreatic head resection and nephrectomy, all these lesions demonstrated pathological findings that were consistent with SFT. The patient also had a history of an intracranial mass that had been previously resected and treated with gamma knife therapy at an outside institution, which was found to also be SFT. Six months after initial pancreatic head resection, the patient developed a new lesion involving the pancreatic tail that was found to represent recurrent metastatic SFT. This case emphasizes the highly aggressive nature of extrapleural SFT, while rare, and the role of imaging in follow-up for disease recurrence.

# Thank you