

July 2, 2017

Manuscript Title: First Report of Small Cell Lung Cancer with PTHrP-induced Hypercalcemic Pancreatitis causing Disconnected Duct Syndrome. First Report of Small Cell Lung Cancer with PTHrP-induced Hypercalcemic Pancreatitis causing Disconnected Duct Syndrome.

Manuscript NO.: 34928

Dear Drs. Gong and Peters,

Thank you again for your investment in our case submission. My colleagues and I have carefully reviewed the comments by the reviewers that have submitted revisions to our manuscript. Our responses are provided in a numbered manner below. Changes to the manuscript are shown in red, italics, and bold. My colleagues and I hope that this revision of our manuscript suits the publication standards for acceptance. We look forward to your correspondence soon.

Sincerely,

Eric M Montminy, MD

Internal Medicine Resident Physician

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Answers to reviewers:

Reviewer #1

1. Question: "Was there any bone metastasis from the lung CA?"

--Response: All imaging obtained during the June 2016 and July 2016 admissions for pancreatitis flares did not demonstrate any bone metastasis. Radiology reports do not note any lytic lesions or pathologic fractures.

--Revision to manuscript: "*No evidence of bone metastasis was seen on imaging.*" added after sentence three of Case Report section.

2. Question: "How about the PTH levels of the patient"

--Response: PTH levels are stated in the fifth sentence of the Case Report section. "Labs demonstrated a serum lipase of 2030 U/L (normal <90 U/L), serum calcium of 11 mg/dL (normal 8.4-10.3 mg/dL), **parathyroid hormone less than 9 pG/mL (normal 12-65 pG/mL)** and parathyroid-related peptide of 3.9 pmol/L (normal <2 pmol/L).

--Revision to manuscript: None due to PTH level already included.

Reviewer #2

1. Question: "Did the patient diagnose of small cell lung cancer or not when he was first admit for pancreatitis one month prior? If yes, why he did not run MRCP that time? If not, when was he diagnose of SCLN and how?"

--Response: The patient was diagnosed during the first admission after presenting with hypercalcemic pancreatitis. Imaging during the first admission was positive for a lung mass that was biopsied. Biopsy showed small cell lung cancer. The manuscript revision will reflect that a diagnosis of small cell lung cancer was made by biopsy.

--Revision to manuscript: Sentence three of Case Report will be changed to "He denied alcohol history or previous gall stones at that time, and imaging work up was only

positive for pancreatic inflammation and a lung mass determined *by biopsy* to be SCLC."

2. Question: "Did the patient with a condition of hypercalcaemia at the first administration?"

--Response: Hypercalcemia was present during the first admission. Sentence two of the Case Report section states, "He was admitted one month prior for acute pancreatitis secondary to a **calcium of 13.7 mg/dL (normal 8.4-10.3 mg/dL).**"

--Revision to manuscript: None due to serum calcium level already included for the first admission.

3. Question: "Did the patient perform EUS-FNA? Why not apply it to drain the cystic to decrease the compression?"

--Response: EUS was performed at the same time as ERCP. A drain was not placed due to failure of access to the lesion via intra-ductal means and patient was improving with symptomatic management at the time.

--Revision to manuscript: "*Endoscopic ultrasound visualized the walled off necrosis, but transmural drainage was avoided due to symptomatic improvement with conservative management.*" is added to the Case Report section in paragraph 1, after sentence 14.

4. Question: "More information about paraneoplastic hypercalcemia should be discussed."

--Response: More text regarding paraneoplastic hypercalcemia will be added to the Discussion section paragraph two, after sentence twelve. Revision to manuscript: "*Hypercalcemia results typically from either elevated PTHrP production or osteolytic activity from bone metastasis. Paraneoplastic hypercalcemia is most commonly associated with squamous cell carcinoma of the lung as opposed to small cell lung cancer. [7] The presence of paraneoplastic hypercalcemia in lung cancer has been*

associated with poorer survival outcomes.[8]" added in Discussion section, paragraph 2, sentence twelve. "*Kanaji N, Watanabe N, Kita N, et al. Paraneoplastic syndromes associated with lung cancer. World Journal of Clinical Oncology 2014; 5: 197-223. [PMID 4127595]*" added to references. "*Takai E, Yano T, Iguchi H, et al. Tumor-induced hypercalcemia and parathyroid hormone protein in lung carcinoma. Cancer 1996; 78: 1384-1387. [PMID 8839542]*" added to references.