Peer Review File

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Reviewer A:

Comment 1: 1. Line 179-180. This statement is no longer correct. Somatostatin analogues such as octreotide/lanreotide are now widely used for their anti-growth effects on neuroendocrine tumors .

Reply 1: We have modified this statement so that it accurate with what we know of SSAs to not only temporize hormonal secretion but also apoptotic effects.

Changes in the text: Please see line 199-201: **SSAs primarily bind to SSTR-2, primarily associated with temporizing hormonal and modest downstream SSTR effects of apoptosis and cell growth with variable interaction with SSTR 3 and 5, though low rates of durable radiologic response are reported (9).**

Comment 2: 2. A paragraph should be added of the problems managing these cushing's syndrome patients after the initial control of the cortisol excess, their prognosis and whether this patients subsequent course is unusual.

Reply 2: The authors included a paragraph to describe reported long term residual effects of Cushing Syndrome after serum cortisol control that the patient's course was likely normal for what could be expected in that time frame.

Changes in the text: Please see lines 250-264: **Despite serum cortisol normalization in treating EAS, clinical recovery is variable across patient populations. Long-term effects of EAS despite definitive treatment include cognitive dysfunction, psychiatric disorders, chronic fatigue, cardiac dysfunction, and adrenal insufficiency. EAS induced myopathy may persist for months and even years, time is needed for muscle fibers to regenerate after prolonged muscle wasting in the setting of hypercortisolism. A German study that reported on the recovery of CS induced myopathy found that grip strength worsened after cortisol levels decreased, hypothesizing that this could be do due to time needed for other anabolic hormones, such as growth hormone and sex hormones, to recover after prolonged suppression in florid CS (22). For our patient, the recovery of motor strength did not worsen after cortisol levels decrease and in fact, she was noted to have made some progress in terms of strength prior to hospital discharge. Her death was ultimately due to several factors including prolonged hospitalization, exposure to hospital-acquired infections and poor pulmonary hygiene due to reduced mobility, resulting in hospital acquired pneumonia. Due to the abrupt nature of her death, it is premature to determine if the patient would have fared well in terms of an improvement in her motor strength over time.**

Reviewer B:

Comment 3: The recent WHO classification requires a change in the general description from NET to NEN. please change that ini the Background where Ki-67 index and morphology is not described.

Reply 2: The authors added an additional paragraph to eleborate on the the subclassifications of NEN of NET vs NEC based on histlogic fingdings, tumor grade, mitotic rate, and Ki-67.

Change in the text: Please see lines 63-73: **Neuroendocrine neoplasms (NENs) are a heterogeneous group of neoplasms that vary in presentation and prognosis. NENs are broadly divided into two groups, neuroendocrine tumors (NETs) being well-differentiated tumors with the potential to metastasize and invade other tissues, the group subdivides into grades of low, intermediate, and high; and neuroendocrine carcinomas (NEC) which are poorly differentiated carcinomas that are highly malignant and aggressive in nature, histologically they may resemble small or large cell carcinomas. According to the revised WHO guidelines on classification of NENs considers the grade, mitotic count, and Ki-67, both of which carry prognostic relevance: NET, G1 with mitotic rate <2 mitoses/2 mm^2 , Ki-67 <3%; NET, G2 with mitotic rate of 2-20 mitoses/2 mm^2 , Ki-67 between 3-20%; NET, G3 with mitotic rate of >20 mitoses/2 mm^2 , Ki-67 >20% (1); NEC are poorly differentiated with mitotic rate of >20 mitoses/2 mm^2 (1).**

Comment 4: Please describe morphology in the pathology report according to the newest recommendations. Is it well- or low-differentiated?

Reply: The authors have clarified the patients pathology and modified the description to be in line with current guidelines.

Change in text: Please see lines 134-137: **Biopsy of a liver lesion was reported to be metastatic neuroendocrine tumor, G1 (NET, G1) per recent WHO criteria. The histology of the NET was further described as well differentiated neuroendocrine tumor (NET), grade-1, with a Ki-67 proliferative index <3%, the mitotic rate was not reported.**

Comment 5: Which doses were used of Ketoconazole and Octreotide, and how long was the treatment sustained?

Reply: The authors have included specific dosing/timing of the above treatments.

Change in text: Please see lines 159 -64, 164-166:
She was started on ketoconazole at 400 mg twice daily and later titrated up to 600 mg three times daily, there was minimal decrease in cortisol levels and no improvement in motor strength. The patient received a total of 38 days of oral ketoconazole, the clinical reasoning of continuing ketoconazole was to reduce the

risk of worsening hypercortisolism although it did not particularly lower the serum cortisol levels.

She was then started on subcutaneous octreotide injections at 100 mcg three times daily. The patient received daily octreotide for a total of 14 days