

Dear editor:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled "Simultaneous rectal neuroendocrine tumors and a pituitary adenoma: A report of a rare case". We have studied reviewer's comments carefully and have made revision which marked in red with yellow background in the paper. We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration. We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Reviewer #1:

Introduction is short, try to extend and outline for the rarity and the diagnostic challenge of such cases.

Response: We have conducted a review of the problem you mentioned and found that the background section lacks a detailed description of the rarity of the case and the challenges of diagnosis. We have made significant revisions to the text of the background section and added relevant missing content. Please refer to Line-76 to Line-85 and Line-90 to Line-104 for details.

Line-76 to Line-85:

GH stimulates the liver to produce insulin-like growth factor-1 (IGF-1), which can lead to excessive proliferation of soft tissue, bone, and cartilage due to long-term excessive secretion of GH and IGF-1. This results in typical symptoms and signs of enlarged limbs, which can have a significant impact on various organ systems, such as the respiratory, cardiovascular, digestive, and glucose metabolism systems. Compression or invasion of pituitary adenomas can result in headaches, visual impairments, and adeno-hypophysis. The median age of diagnosis for acromegaly ranges from 40.5 to 47.0 years, with delays in diagnosis lasting from 4.5 to 9.0 years. Delayed diagnosis can significantly increase the incidence of complications and difficulty in treating patients with large limbs.

Line-90 to Line-104:

To diagnose this disorder, patients may undergo both ¹⁸F-ALF-NOTATATE-PET/CT and ¹⁸F-FDG-PET/CT scans, which can reveal small lesions that cannot be detected through conventional imaging. However, routine imaging examination (CT) may fail to identify patients' pelvic metastatic lymph nodes. Due to abnormal blood sugar, a patient may initially be suspected of having diabetes and given hypoglycemic treatment. However, if the patient's blood glucose control remains poor, their clinical manifestation may be hidden, and changes in their limbs and face may only be detected long after the onset of symptoms. A multidisciplinary approach involving various departments such as endocrinology, neurosurgery, imaging, pathology, oncology, and others is required for the diagnosis and treatment of neuroendocrine tumors. The multi-disciplinary treatment mode of diagnosis and treatment can significantly enhance the standardization, accuracy, and individualization of treatment. Collaborative diagnosis and treatment can lead to an improved quality of life for patients, early diagnosis of diseases, better symptom management, prevention of complications, and reduced psychological distress.

You can use the abbreviation of MRI.

Response: We have thoroughly reviewed the manuscript and made corrections based on your specifications. The following revisions have been implemented:

Line-53: magnetic resonance imaging corrected to magnetic resonance imaging (MRI).

Line-145: magnetic resonance imaging corrected to MRI.

Line-174: magnetic resonance imaging corrected to MRI.

Line-232: magnetic resonance imaging corrected to MRI.

The second lesion was touching the surgical margin, however you did not comment and discuss this finding and the follow up for this point.

Response: We have made a specific supplement to address this issue, as described in Line-179 to Line-189 and Line-261 to Line-276 in the discussion section.

Line-179 to Line-189:

The patient's skin condition improved significantly, becoming smoother and more refined after undergoing neuroendoscopic pituitary gland surgery. Moreover, the patient's biochemical indicators have consistently remained within the normal range post-operation, especially with regards to blood sugar control, which has normalized without the need for hypoglycemic drugs. Given that the patient's pituitary growth hormone tumor was a macroadenoma, direct surgery was challenging and complete removal was difficult. However, thanks to three cycles of octreotide acetate microspheres treatment, the tumor size gradually decreased, allowing for successful R0 resection through timely surgical intervention. To date, follow-up head MRI and serum GH and IGF-1 level measurements have been consistently within the normal range.

Line-261 to Line-276:

Surgical resection of adenoma is the preferred treatment option for patients diagnosed with pituitary GH adenoma. This approach can effectively eliminate or reduce adenomas, and decrease the levels of GH and IGF-1. The transsphenoidal approach is the primary method utilized to perform surgical interventions on pituitary adenomas, while craniotomy is only required in rare cases. Despite significant advancements in surgical techniques, there are still inherent risks associated with major extremity surgery such as olfactory disturbance, hypopituitarism, temporary or permanent central diabetes insipidus, damage to vital nerves, blood vessels, brain tissue and blood supply of the skull base, resulting in postoperative cranial nerve dysfunction such as optic nerve impairment, cerebrospinal fluid rhinorrhea, meningitis, bacteremia, sepsis, hypothalamic syndrome, and even death of the patient. Patients with pituitary GH adenomas are at a significantly higher risk when undergoing general anesthesia compared to other types of pituitary adenomas. These risks include abnormal cardiopulmonary function, increased perioperative risk, and difficulty in tracheal intubation and extubation due to soft tissue hyperplasia, making the operation more challenging and imposing no small challenge for surgeons.

Legends of the histopathology should contain a bit microscopic description of the shown lesions, however you provided stain and power.

Response: We have modified the corresponding figure legends as follows:

Line-392 to Line-397:

A. The two lesions at the lower rectum under colonoscopy. B-C. HE staining shows the pathological feature of neuroendocrine tumor at the rectum from the bigger and smaller tumor tissue respectively (20x). D-F. IHC staining of neuroendocrine marker CD56, Syn and CgA in representative tumor tissue selected by the physician (4x). G. Ki-67 expression in neuroendocrine tumor at the rectum by IHC (10x). Brown nuclear stain highlights Ki-67 positive tumor cells.

Line-406 to Line-412:

Tumor metastasis was observed at the peri-intestinal lymph nodes (4/15). A-B. Laparoscopic low anterior resection with total mesorectal excision was performed five months after diagnosis of the rectal lesions, central lymph nodes were selected from the lesion for HE staining to evaluate the metastasis of neuroendocrine cells. C-E. IHC detection to evaluate the expression and distribution of neuroendocrine markers SSTR2,

Syn and CgA in central lymph nodes (400x). F. Ki-67 expression in central lymph nodes by IHC (400x).

Language editing is essential.

Response: The manuscript has been deeply polished by professional institutions, and the corresponding proofreading has been submitted.

Thank you for your inquiry. We have reviewed your request and believe that our response meets your needs. If you have any additional questions or concerns, please do not hesitate to reach out to us.

Best regards

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