CASE REPORT

Efficacy of intravenous catheter hormone sampling for growth hormone-secreting pituitary adenoma: a case report

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Abstract：

Excess secretion of growth hormone（GH）causes acromegaly, which is associated with increased morbidity and mortality. Primary GH hypersecretion from pituitary adenomas（PAs）is the most common cause of acromegaly, but sometimes microadenomas（<10 mm）cannot be detected by magnetic resonance imaging（MRI）of the head, resulting in delayed treatment by surgical resection. In this study, selective catheter hormone sampling of the venous sinus provided evidence of the localization of GH-secreting PAs.

A 47-year-old male, admitted to a previous hospital due to a hypertensive right thalamic hemorrhage, was incidentally suspected of acromegaly due to his physiological findings. Acromegaly is diagnosed by a combination of enlarged extremities and extremely high serum levels of GH and insulin-like growth factor-1（IGF-1）. A GH-secreting microadenoma was suspected by repetitive MRIs and selective intravenous hormone sampling in the head, resulting in left-side dominant high serum levels of GH. In an endoscopic trans-sphenoidal surgery（TSS）, the tumor was first apparent on the right side inside the normal pituitary gland, but we followed the lesion based on the results of the catheter examination. The tumor stretched to the left side and attached to the medial wall of the left cavernous sinus. The tumorous lesion was resected, and this was confirmed by a post-operative MRI and peripheral serum GH/IGF-1 level measurement. Serum GH and IGF-1 levels decreased at 108 days after surgical resection. Pathological diagnosis resulted in the observation of a sparsely granulated GH-secreting PA.

There are often cases where it is difficult to diagnose acromegaly with localization of the pathological lesion. The reason is that more than 50% of GH-secreting PAs are <10 mm, making it difficult to visualize the tumor in imaging examinations.

Here, we diagnosed a GH-secreting PA in a patient who received TSS and subsequently regained normal serum GH/IGF-1 levels.

Key words: GH secreting Pituitary Adenoma, Bilateral inferior petrosal sinus sampling, acromegaly, transphenoidal surgery

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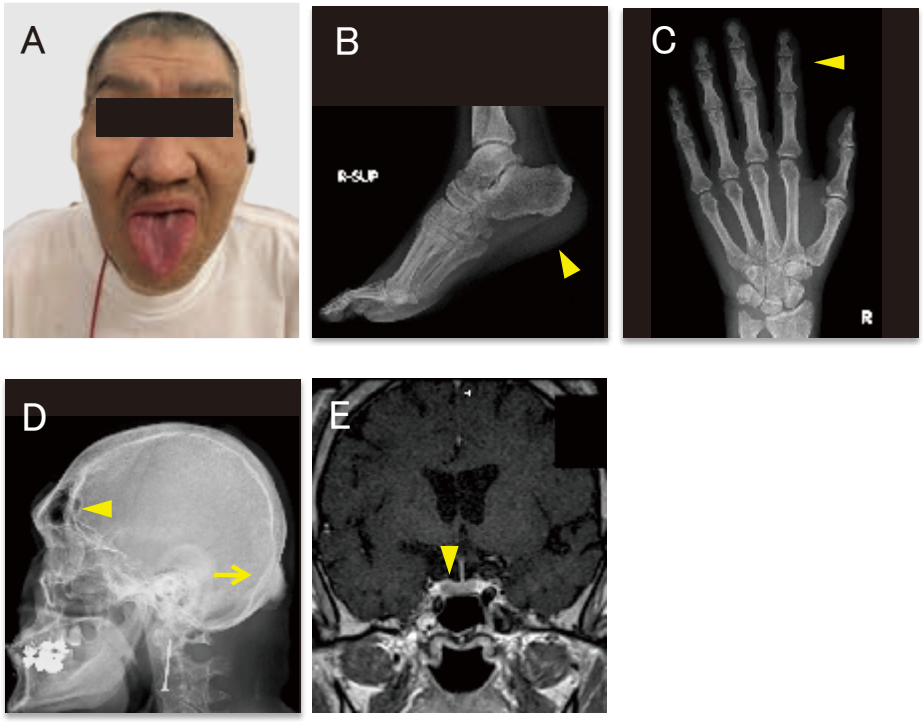

Fig. 1 : Pre-therapeutic images

A: Photo shows physiological findings of enlarged lip, nose, tongue, forehead, and lower jaw in the face. **B:** Right foot X-ray shows heel pad thickness (22 mm). **C:** Right hand X-ray shows cauliflower-like tufting. **D:** Head X-ray shows frontal sinus protrusion (arrow head) and outer occipital uplift (arrow). **E:** Head MRI T 1 -weighted contrast enhancement image shows a tumor in the pituitary gland.

Introduction

Excess secretion of growth hormone (GH) causes acromegaly, which is associated with increased morbidity and mortality related to cardiovascular, respiratory, cerebrovascular, and colonic cancer[1]. Acromegaly can be caused by different types of adenomas, including pure GH-cell adenomas or tumors with both GH and prolactin (PRL) secretion[1]. GH-secreting pituitary adenomas (PAs) constitute 8-16% of all PAs. While primary GH hypersecretion from PAs is the most common cause of acromegaly, several heterogeneous disorders—such as pituitary hyperplasia, excess ectopic GH release from the bronchial carcinoid, and ectopic GH secretion by malignant tumors—have been reported to cause excessive GH secretion[2]. It is therefore essential to diagnose acromegaly with the location of the pathology for proper treatment. Acromegaly caused by GH-secreting PAs is diagnosed by an enlargement of the hands, feet, and tongue, accompanied by high serum levels of GH and insulin-like growth factor (IGF-1) and the detection of PAs in neuroimaging examinations of the head, according to the guidelines published by the Japanese Society for Hypothalamic and Pituitary Tumors (JSHPT). However, microadenomas (<10 mm) can sometimes remain undetected by magnetic resonance imaging (MRI) of the head and cause a delay in treatment by surgical resection. Although selective intravenous hormone sampling by catheter intervention is a useful and required procedure for diagnosing hypersecretion of adrenocorticotropic hormone (ACTH) from PAs (Cushing's disease), hormone sampling of GH and IGF-1 is still not recommended for the diagnosis of GH-secreting PAs according to the official guidelines.

Here we present a case study of a patient with GH-secreting microadenoma as suspected by repetitive MRIs and selective intravenous hormone sampling, who received surgical resection and showed the decrease of hormone levels.

Case presentation

A 47-year-old male admitted to a previous hospital due to a hypertensive right thalamic hemorrhage was kept under observation with blood pressure management according to the patient's stable condition and the localization of the hemorrhage. He was incidentally suspected of acromegaly due to his physiological findings (Fig. 1A) and transferred to Yokohama City University Hospital. We took X-rays of foot, hand and head which showed characteristic findings of acromegaly (Fig. 1B-D). According to the guidelines for the

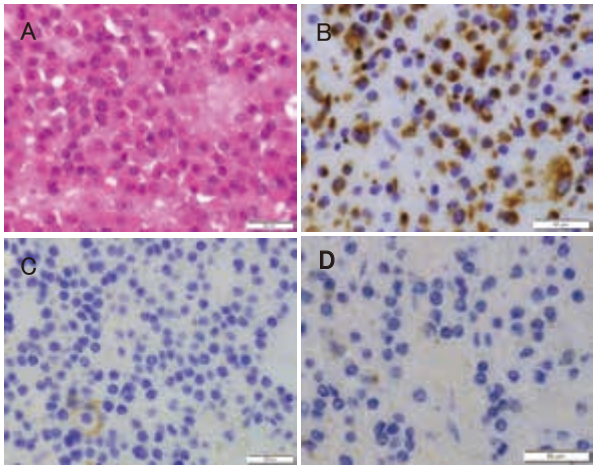

Fig. 2 : Histopathological analysis

A: Sparsely granulated somatotroph adenoma with nuclear pleomorphism in hematoxylin-eosin stain **B:** Low molecular weight keratin displays a cytoplasmic, perinuclear pattern in Cam 5.2 stain. **C:** GH is expressed focally. **D:** PRL is not expressed in the tumor tissue.

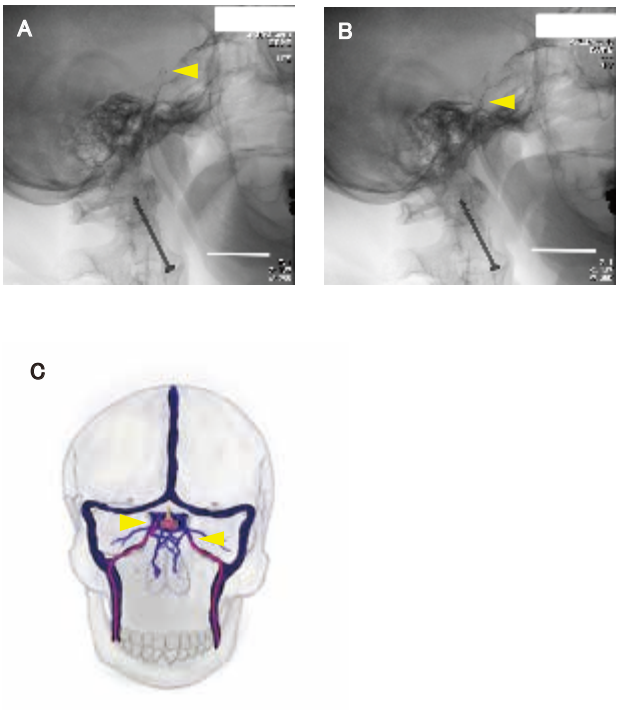

Fig. 3 : Catheter intervention images

A: Arrow head shows the leading edge of a micro-catheter for bilateral cavernous sinus sampling.
B: Arrow head shows the leading edge of a micro-catheter for bilateral inferior petrosal sinus sampling.
C: In the schema, arrow head shows cavernous sinus sampling and arrow shows inferior petrosal sinus sampling.

diagnosis and treatment of acromegaly from JSHPT, a set of measurements was taken, including serum GH/IGF-1 levels, nadir serum GH level during 75 g oral glucose tolerance test (OGTT), and an MRI. Peripheral serum GH and IGF-1 levels at rest were 3.31 ng/mL (Normal range: ＜2.47ng/mL) and 357 ng/mL (Normal range: 90-250ng/mL), respectively, while the blood sugar level and serum GH level after two hours on 75 g OGTT were 152 mg/dL and 5.51 ng/mL (Normal range: ＜ 1ng/mL), respectively. Increase of nadir serum GH level after two hours on 75 g OGTT is one of the diagnostic criteria of acromegaly. While the patient was diagnosed with acromegaly, MRI of the head for the detection of GH-secreting PAs did not show any signs of a tumor. Subsequently, the patient received bi-weekly subcutaneous injections of 90 mg lanreotide, and his serum GH level at rest decreased to 2.04 ng/mL for twelve months. However, serum GH levels increased again to 7.10 ng/mL in the fourteen months following initiation of the lanreotide treatment. Repetitive MRIs revealed a tiny lesion in the right side of the pituitary gland (Fig. 1E). Therefore, we conducted selective catheter intravenous sampling and found that serum GH and IGF-1 levels were much higher than the normal range with a left-side dominance as shown in Table 1. We conducted an endoscopic trans-sphenoidal surgery (TSS) for GH-secreting PAs. During the surgery, the tumor was first apparent on the right side inside the normal pituitary gland, but we followed the lesion according to the results of the catheter examination. The tumor stretched to the left side and attached to the medial wall of the left cavernous sinus. The tumorous lesion was resected, which was confirmed by a postoperative MRI and peripheral serum GH/IGF-1 measurements. Serum GH/IGF-1 levels decreased to 1.26 ng/mL and 134 ng/mL at 108 days after surgical resection, respectively.

Pathological Findings

We performed pathological diagnosis from the tumor sample. Under microscopic examination after hematoxylin-eosin staining, we observed a sparsely granulated adenoma with chromophobic features and nuclear pleomorphism (Fig. 2A). Low molecular weight keratins, displayed a cytoplasmic, perinuclear pattern after Cam 5.2 staining (Fig. 2B). GH was expressed focally (Fig. 2C), and PRL was not expressed in the tumor tissue (Fig. 2D). Taken together, we used these findings to diagnose the tumor as a sparsely granulated GH-secreting PA.

Discussion

There are often cases where it is difficult to diagnose acromegaly with localization of the pathological lesion. The first reason for this is that about 50% of PAs are <10 mm[2]. Of

Table 1: Cathertel venous sampling of serum GH and IGF-I

Target cathertel position	serum GH (ng/mL)	IGF-1 (ng/mL)
right cavernous sinus	0.86	349
right inferior petrosal sinus	2.76	339
left cavernous sinus	0.85	337
left inferior petrosal sinus	108	345
peripheral blood	1.2	331

GH-secreting PAs (comprising 8-16% of all PAs), more than half are expected to be <10 mm at the time of diagnosis. Although computer tomography (CT) scanning of the head may show moderate contrast-enhancement, or positron emission tomography (PET) may show high uptake of fluorodeoxyglucose, microadenomas (<10 mm) may not be detected because of the low resolution of the images[3, 4]. The second difficulty in diagnosing acromegaly with localization of the pathological lesion is that GH hypersecretion can also be a product of systemic diseases such as bronchial carcinoids or ectopic GH-secreting malignant tumors.

Selective intravenous sampling enables us to measure the values of GH and IGF-1 levels. Though selective intravenous sampling is recommended for only ACTH-secreting PAs in the guideline, still now, the technique is not recommended for the diagnosis of GH-secreting PA. In the diagnosis process of ACTH-secreting PAs, the selective intravenous sampling is most reliable examination with high sensitivity and specificity[2]. While GH-secreting PAs is relatively larger microadenomas comparing to ACTH-secreting PAs. And larger microadenomas can be found in images or intraoperative situation, so lateralization by selective intravenous sampling is usually not so critical[5].

In the case of microadenomas, selective intravenous sampling is useful for localization of the tumor. There are supposed to be a reason in the discrepancy between the hormone sampling values in cavernous sinus and inferior petrosal sinus.

Cavernous sinus and inter cavernous sinus makes complicated network structure like a net and trivial positioning difference of micro-cathertel causes data-variabilities. While inferior petrosal sinus is a outlet, so it is more reliable as othe reports noted before.

The possible complications of this test include thrombosis leading to arterial and venous cerebral infarction, and cerebral hemorrhage caused by damaged cerebral vessels [6]. Moreover, there are a lot of variations in the intracranial venous drainage system which makes it difficult to interpret the results of the catheter sampling. Therefore, every catheter result should be discussed in consultation with experts. While GH level on left side is higher than that of right side, the values of IGF-1, a liver mainly producing factor, are mostly equal in both sides.

Trans-sphenoidal surgery (TSS) is the first-line treatment for GH-secreting PAs in patients with acromegaly. With recent refinements in surgical instruments and techniques, surgical results are improving, and in approximately 70% of patients there is a chance of achieving biochemical remission after a single TSS performed by an experienced surgeon. Therefore, evidence of the localization of GH-secreting PAs using selective intravenous sampling may help the treatment strategy.

Disclosure Statement

The authors have no conflict of interest.

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