Clinical characteristics of acromegalic patients with empty sella and their outcomes following transsphenoidal surgery

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Carotid artery protrusion and dehiscence in patients with acromegaly

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Abstract

Purpose: Acromegaly is a systemic disease which causes multiple bony alterations. Some authors reported that acromegalic patients have risk factors for an intraoperative vascular injury due to the specific anatomical features of their sphenoid sinus. The objective of our study was to analyze the anatomic characteristics of sphenoid sinus in acromegalic patients compared with controls, by evaluation of computed tomography (CT) findings.

Methods: We examined 45 acromegalic (acromegaly group) and 45 non-acromegalic patients (control group) with pituitary adenomas who were matched for sex, age, height, tumor size, and cavernous sinus invasion (Knosp grade). Preoperative CT of the pituitary region including the sphenoid sinus was used to evaluate the following anatomic characteristics: type of sphenoid sinus (sellar or pre-sellar/conchal); intrasphenoid septa (non/single or multiple); carotid artery protrusion; carotid artery dehiscence; intercarotid distance.

Results: Sixteen acromegalic patients (35.5%) and 6 controls (13.3%) had carotid artery protrusion. Additionally, 10 acromegalic patients (22.2%) and 3 controls (6.6%) had carotid artery dehiscence. Carotid artery protrusion and dehiscence were more frequent in the acromegaly group than in control group ($p = 0.013$ and $p = 0.035$, respectively).

Other anatomic characteristics (type of sphenoid sinus, intrasphenoid septa, and intracarotid distance) showed no significant differences between acromegaly and control groups.

Conclusions: Our study suggests that carotid artery protrusion and dehiscence occur more frequently among acromegalic patients, compared with non-acromegalic patients. It is important for surgeons to be aware of these anatomic variations to avoid vital complications, such as carotid injuries, during surgery.

Keywords: Acromegaly, Sphenoid sinus, Carotid artery protrusion, Carotid artery dehiscence

Introduction

Acromegaly is a rare systemic condition that results in decreased life expectancy because of excessive production of growth hormone (GH) [1]. Approximately 98% of patients with acromegaly harbor a pituitary adenoma. Transsphenoidal surgery is the most commonly used procedure for pituitary adenomas because of its safety and effectiveness. Nevertheless, intraoperative bleeding from internal carotid artery during transsphenoidal surgery is a well-reported complication and may have catastrophic results, unless managed properly [2].

Some authors reported that patients with acromegaly have risk factors for an intraoperative vascular injury because of anatomic characteristics such as complex sphenoid sinus (e.g., multiple septa or presellar/conchal type pneumatization), carotid artery protrusion, and narrow intercarotid distance [3, 4, 5]. These anatomic features are very important for neurosurgeons who perform the transsphenoidal approach for pituitary tumor resection. The objective of our study was to analyze the anatomic characteristics of the sphenoid sinus in patients with acromegaly compared with control patients, by radiographic evaluation using computed tomography (CT).

Methods

Patient population

We retrospectively reviewed medical records of 48 patients with newly diagnosed acromegaly treated between May 2005 and June 2015 at Kanazawa Medical University Hospital (Ishikawa, Japan). The diagnosis of acromegaly was based on established criteria [6]. Three patients were excluded from the study since we were not able to evaluate their radiological data, and 45 patients with acromegaly were finally enrolled. We used as a control group 45 patients with pituitary adenoma, who were matched for sex, age, height, tumor size and cavernous sinus invasion (Knosp grade). In the control group, 20 patients had a non-functioning pituitary adenoma (gonadotropin secreting or null-cell adenoma), 8 had a prolactin- secreting adenoma, 6 had an adrenocorticotropic hormone-secreting adenoma, 2 had a thyrotropin -secreting adenoma, and 9 patients had a Rathke cleft cyst. Patients of both groups underwent transsphenoidal surgery for pituitary adenoma removal by the second author (O. T.). Standard histological examination of paraffin-embedded tissue sections and immunohistochemical studies confirmed a type of pituitary adenoma in each patient.

Imaging protocol

A preoperative magnetic resonance (MR) image and CT scan of the pituitary region were obtained for all 90 patients.

MR images were obtained using a 3-Tesla magnet strength scanner (MAGNETOM Trio, A Tim system T-Class VB17, Siemens, Germany) with a 32-channel head coil. All patients underwent pre-enhanced T1-weighted fluid-attenuated inversion recovery (T1-FLAIR) and T2WI, and post-enhanced T1-FLAIR in sagittal and coronal planes. The imaging parameters were as follows: T1-FLAIR and post-enhanced T1-FLAIR images, repetition time (TR) 2000ms, echo time (TE) 11ms, inversion time (TI) 860ms, flip angle (FA) 130°, echo train length (ETL) 6, scan time 2m54s; T2-weighted fast spin-echo images: TR 4000 ms, TE 76 ms, FA 150°, ETL 12, scan time 2 min 58 s. All sequences used a field of view (FOV) of 200 × 200 mm; slice thickness, 2 mm; matrix size, 320 × 320; and intersection gap, 0.0 mm. A rapid bolus injection (3 ml/s) of 0.1 mmol contrast medium (Magnevist; Schering, Germany or Omniscan; Daiichi Sankyo Company, Japan) per kilogram of body weight was followed by a 20 ml flush of normal saline solution. A total of 6 phase images were obtained with an acquisition time of 14 seconds for each phase.

CT scans of 1 mm slice thickness with a bone window image were performed to observe bony structures and internal carotid arteries. CT was performed immediately after an intravenous injection of 70 ml of an iodinated contrast medium (Omnipaque Injection; Daiichi Sankyo Company, Japan) using a 64-multidetector row CT (Brilliance 64; Philips Healthcare, Andover, MA, USA and Best, the Netherlands). The collimation was

64 × 0.625 mm and the gantry rotation time was 0.4 s. Scan parameters were as follows: voltage, 120 kV; tube current, 300 mAs (228 mA); FOV, 250 mm; matrix, 512 × 512 mm; and Brain Smooth (UV) filter.

All available images were interpreted independently by two observers who were blinded to the clinical diagnosis. The maximum tumor size was measured in the coronal plane on a T1-FLAIR post-enhanced image. Cavernous sinus invasion of the tumor was estimated using the Knosp grade [7] on T2-weighted coronal image. The following parameters were investigated on CT scans: (a) type of sphenoid sinus (sellar or pre-sellar/conchal) on sagittal view: pre-sellar/conchal type was defined as a pneumatization of half or less sphenoid of the sinus space; (b) number of intrasphenoid septa (non/single or multiple) on axial view; (c) carotid artery protrusion (present or absent): carotid artery protrusion was present when a half or more cross-sectional area of carotid artery protruded into sphenoid sinus space on axial view; (d) carotid artery dehiscence (present or absent): present when carotid artery was not covered with carotid canal wall on axial view; (e) intercarotid distance between cavernous carotid arteries: the smallest distance between the medial walls of the horizontal intracavernous portion of the cavernous carotid arteries. Figure 1 shows the pre-sellar type of sphenoid sinus (a), multiple septa in the sphenoid sinus (b), carotid artery protrusion (c), carotid artery dehiscence (d), and intercarotid distance (e) on preoperative CT, respectively.

Statistical analysis

Data are presented as mean (± standard deviation) for parametric and median (± standard deviation) for non-parametric variables. Statistical analyses were performed using Excel 2013 (Microsoft, Redmond, WA, USA) with the add-in software Ekuseru-Toukei 2015 version for Windows (Social Survey Research Information, Tokyo, Japan). The unpaired Student *t* test was used to compare data between acromegaly and control group when a normal distribution was observed. When the distribution of the values was non-Gaussian, the Mann–Whitney test was used. The Fisher extract test was performed for categorical data. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

Characteristics of acromegalic and control patients are shown in Table 1. The median age in the acromegaly group was 59 ± 10.8 years (32–75 years). Twenty-six patients were female and 19 were male. Median height was 163.0 ± 9.6 cm (146.1–181.4 cm).

Median tumor size was 12.2 ± 6.4 mm; 21 patients had microadenoma and 24 had macroadenoma. According to the degree of cavernous sinus invasion, tumors were classified as noninvasive (n = 37; Knosp grade 0-2) or invasive (n = 8; Knosp grade 3 and 4). There was no statistically significant difference between the acromegaly and control group by sex, age, height, tumor size, and Knosp grade. In contrast, the prevalence of hypertension or diabetes was significantly higher in acromegalic patients than in controls.

Anatomical analysis of the sphenoid sinus on CT images

The comparison of the anatomical data obtained by CT scan between acromegalic and control patients is presented in Table 2. Ten patients with acromegaly (22.2%) and 13 control patients (28.9%) had the pre-sellar/conchal type of sphenoid sinus ($p = 0.315$). Twenty-two patients with acromegaly (48.9%) and 27 control patients (60.0%) had multiple intrasphenoid septa ($p = 0.199$). Sixteen patients (35.5%) in the acromegaly group and 6 patients (13.3%) in the control group had carotid artery protrusion (acromegaly group: 9 unilateral and 7 bilateral carotid artery protrusions; control group: 4 unilateral and 2 bilateral carotid artery protrusions). The difference in occurrence of artery protrusion between the two groups was statistically significant (p =

0.013). Carotid artery dehiscence was present together with carotid artery protrusion in 10 acromegalic patients (7 unilateral, 3 bilateral) and in 3 (all unilateral) control patients ($p = 0.035$). The mean intercarotid distance was smaller in acromegalic patients compared with the control patients (15.6 vs. 17.1 mm). However, this difference in the mean values between two groups was not statistically significant ($p = 0.632$). Figure 2 shows CT images of bilateral carotid artery protrusion with dehiscence (a, b) and intraoperative view (c and video) in an acromegalic patient.

Discussion

Our results showed that patients with acromegaly more frequently experience carotid artery protrusion. Additionally, we found carotid artery dehiscence in more than half of acromegalic patients with carotid artery protrusion, which may represent a higher risk of carotid injury during transsphenoidal surgery.

To date, very few studies have focused on the morphologic features of the sphenoid bone in patients with acromegaly. Saeki et al. [3] performed bone CT scans in 13 acromegalic and 44 control patients and found that 7 of 13 (53.4%) patients with acromegaly had a marked carotid artery protrusion, compared with 8 of 44 (18.3%)

control patients. The data from our study with a matched control group are consistent with those reported by Saeki et al. The internal carotid artery is the most medial element of the cavernous sinus, and it lies in a direct relation to the lateral wall of the sphenoid sinus. Protrusion of the internal carotid artery into the sphenoid sinus appears in 5–28% of patients with rhinosinusitis or facial trauma on CT examination [8, 9, 10]. Accordingly, patients with acromegaly are likely to more frequently have carotid artery protrusion. In this study, we found that patients with acromegaly more frequently had carotid artery dehiscence in addition to carotid artery protrusion. In about 20% of patients with acromegaly, the bone that usually covers the internal carotid artery is dehiscent, leaving the artery exposed to the sinus cavity. Carotid artery dehiscence has been reported in 1.1–8.3% of cases in cadaver or radiological studies [8, 10, 11]. The incidence of 6.6% found in our control group is consistent with previous reports.

The pathophysiology of internal carotid artery protrusion and dehiscence phenomenon in patients with acromegaly is unknown. It may be associated with vascular alterations, including arteriosclerosis. Structural and functional alterations of the artery wall in acromegaly have been unveiled by the observation of increased aortic stiffness [12], ectasia [13], and hypertrophic remodeling of small resistance arterioles in subcutaneous fat [14]. Additionally, alterations of internal carotid arteries, such as tortuosity and ectasia, narrow intercarotid distance, and fusiform dilatation were seen in acromegalic patients [4, 15, 16]. In fact, the mean intercarotid distance in acromegalic patients was reduced in our study (15.6 vs. 17.1 mm of control group), although there was no statistically significant difference. The vascular alterations of the internal carotid artery (protrusion and dehiscence) are likely to be a systemic phenomenon probably caused by arterial hypertension and a loss of elastic tissue. Additionally, in our study, the prevalence of hypertension or diabetes was higher in acromegalic patients than in controls. We believe that acromegalic patients tend to have arteriosclerosis, which causes carotid protrusion and dehiscence.

To our knowledge, no comparative risk evaluation exists for transsphenoidal surgery in patients with acromegaly compared with other tumor entities. Iatrogenic internal carotid artery injury during transsphenoidal surgery is a rare complication, occurring in approximately 0.2–1% of cases [2]. Nevertheless, some authors reported internal carotid injury during transsphenoidal surgery in acromegalic patients [17, 18, 19]. Griauzde et al. [20] recently reported 5 cases of intraoperative complication involving the internal carotid artery during transsphenoidal surgery. Two of 5 cases had carotid artery dehiscence associated with acromegaly. Our results and previously reported findings regarding the anatomic changes in the surgical corridor seen in acromegalic individuals suggest that these patients are more susceptible to carotid injury during the transsphenoidal approach. Detailed preoperative diagnostic examination and planning, as well as selection of appropriate instruments, are mandatory for safe and successful pituitary adenoma removal in patients with acromegaly.

This study has some limitations. The limited number of patients limited the study's significance. In addition, there are no confirmed correlations of intraoperative and CT findings. Shin et al. compared CT and endoscopic findings for the presence of Onodi cells and found a good correlation between the two modalities [21]. Clearly, this is an area that requires further research; but certainly, the usefulness of CT scans in determining anatomic variations and in preoperative planning is evident. In summary, our data confirmed that patients with acromegaly require an in-depth preoperative evaluation of the sphenoid morphology, particularly in terms of a route of the internal carotid artery.

Conclusion

Our study suggests that patients with acromegaly more frequently have carotid artery protrusion and dehiscence, compared to patients without acromegaly. It is important that neurosurgeons keep in mind these anatomic variations in order to avoid vital complications during transsphenoidal surgery.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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Figure legends

Fig. 1: Sagittal CT image of presellar type sphenoid sinus (a). Axial CT image of multiple intrasphenoid septa (b), carotid canal protrusion (arrow) (c), carotid canal dehiscence (arrow) (d) and intercarotid distance (the distance was 11.2 mm in this case) between cavernous portions (e).

Fig. 2: Axial CT image of bilateral carotid canal protrusion with dehiscence in an acromegalic patient (a). The left carotid cavernous artery has a protrusion into sphenoid sinus with no ossification of carotid canal (b). Endoscopic intraoperative view of the left cavernous carotid artery. In this case, the pulsation of the artery is depicted. Vigorous sound of the pulsation is detected with intra-operative micro-Doppler ultrasonography (c).

Table 1. Baseline characteristics of acromegalic and control patients

Characteristic	acromegalic patients (n=45)	control patients (n=45)	p value
Histopathological type	GH: 45	gonadotrophic or null-cell: 20; PRL: 8; ACTH: 6; TSH: 2; RCC: 9	-
Male/female ratio	19:26	16:29	0.333
Age (years)	59±10.8	54±12.2	0.061
Height (cm)	163.0±9.6	161.0±6.8	0.554
Hypertension	19 (42.2%)	6 (13.3%)	0.002*
Diabetes	11 (24.4%)	4 (8.9%)	0.044*
Tumor size (mm)	12.2±6.4	12.5±10.5	0.175
Knosp grade	0-2: 37 3-4: 8	0-2: 39 3-4: 6	0.386

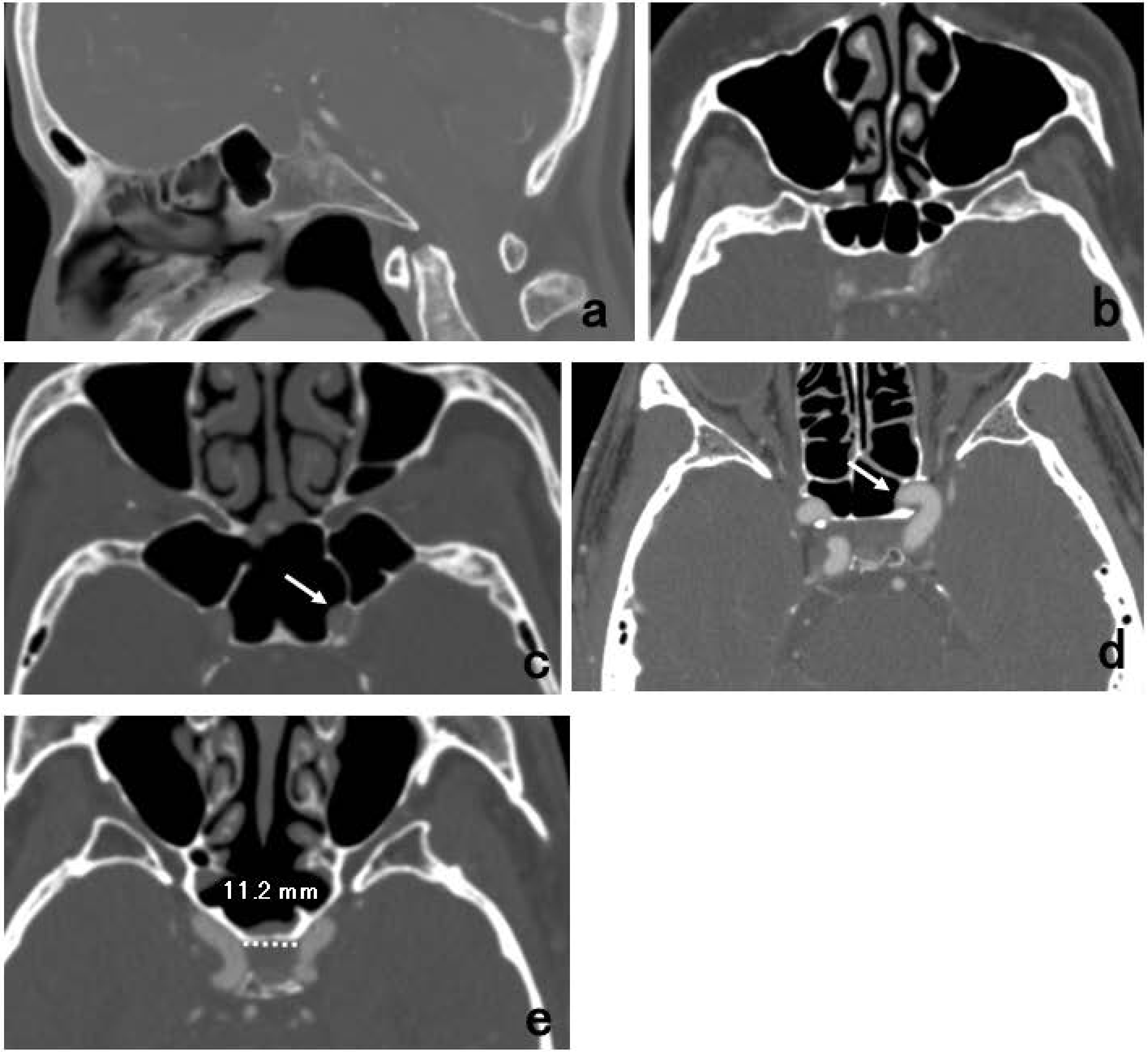
GH: growth hormone, PRL: prolactin, ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, RCC: Rathke cleft cyst

* $P < 0.05$

Table 2. Comparison of the anatomical data obtained using CT between acromegalic and control patients

	Acromegalic patients (n=45)	Control patients (n=45)	p value
Pneumatization (presellar/concha)	10 (22.2%)	13 (28.9%)	0.315
Intrasphenoid septa (multiple)	22 (48.9%)	27 (60%)	0.199
Carotid protrusion	16 (35.5%) (unilateral: 9, bilateral: 7)	6 (13.3%) (unilateral: 4, bilateral: 2)	0.013*
Carotid dehiscence	10 (22.2%) (unilateral: 7, bilateral: 3)	3 (6.6%) (unilateral: 3)	0.035*
Intercarotid distance (mm)	15.6±3.2	17.1±2.7	0.632

* $P < 0.05$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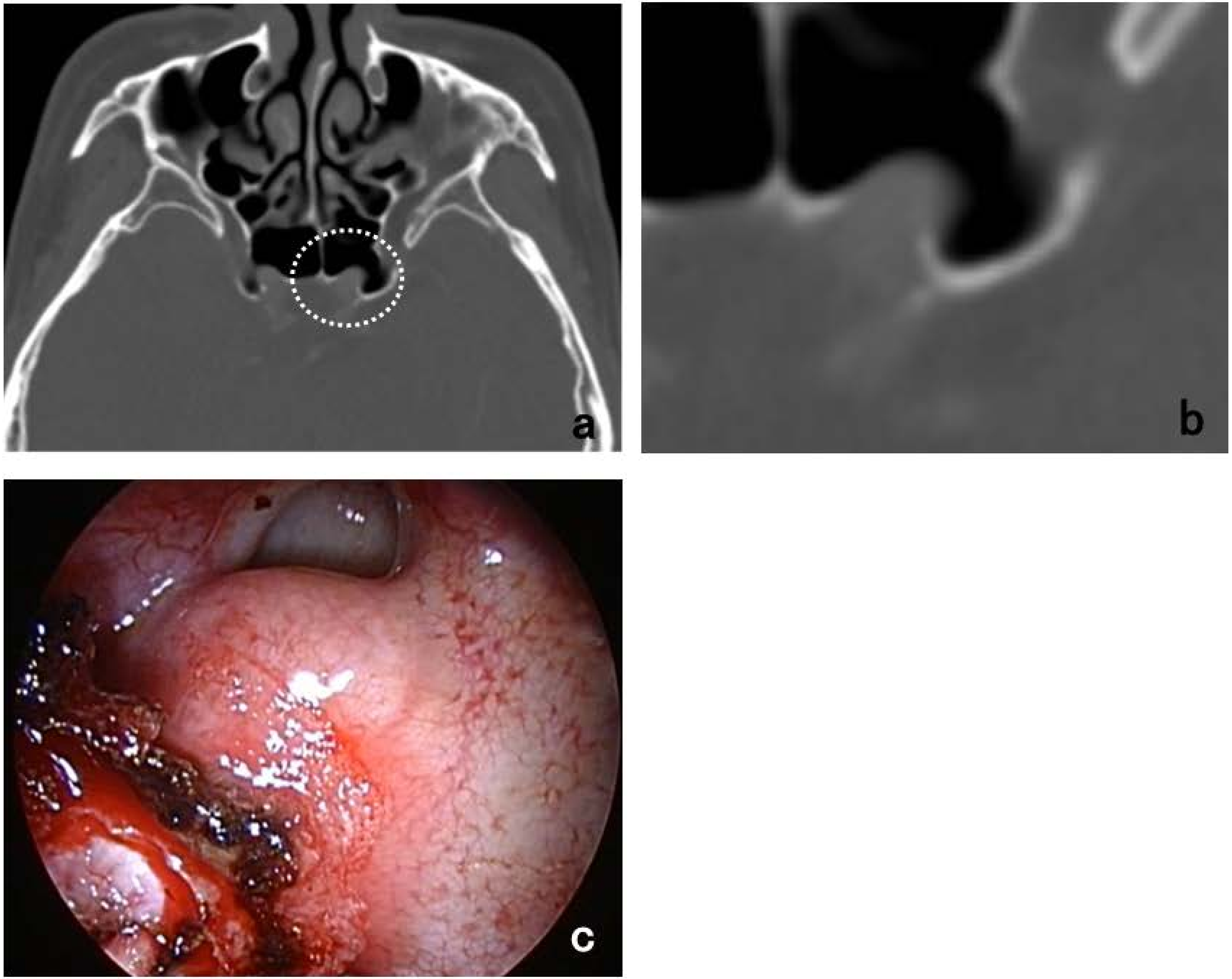
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