Giant pituitary adenoma (GPA) is defined as a tumor that extends more than 40 mm from the midline of the jugum sphenoidale in any direction, or to within 6 mm of the foramen of Monro, or that shows lobules extending to the suprasellar region in more than two directions [1]. The surgical and medical management and imaging findings of GPA have been thoroughly described [1–3]. However, the extent to which computed tomography (CT) and magnetic resonance (MR) imaging provide accurate information about the extent of tumor invasion is less clear. Once GPA invades the surrounding tissue, complete resection is difficult and is associated with a higher risk of morbidity and mortality[1, 4, 5]. Therefore, preoperative demonstration of the extent of invasion is essential for planning appropriate surgical and medical management. The purpose of this study was to characterize the CT and MR imaging features of GPA and to define the routes of tumor invasion.

**Materials and Methods**

Three hundred fifty-six patients with a single pituitary adenoma underwent CT and/or MR imaging focused on the sella and skull base for preoperative evaluation.

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Among these 356 pituitary adenomas, 14 tumors (4%) fulfilled the radiologic criteria for GPA. There were 10 male and four female patients, with ages ranging from 22 to 71 years (mean, 52 yr).

Within 2 months prior to the surgical removal of the tumors, nine patients underwent both CT and MR imaging studies, three underwent MR imaging only, and two underwent CT only. MR images were obtained by using a 1.5-T GE Signa MR Scanner (Milwaukee, WI, USA). The MR imaging protocols included 1) axial section of both spin-echo T1-weighted (TR/TE, 700/15 ms) images; 2) T2-weighted (TR/TE, 2000/100 ms) images; and 3) proton density-weighted (TR/TE, 2000/30 ms) images. Post-contrast enhanced T1-weighted images on axial, coronal, and sagittal views with emphasis on the sella were obtained using the same protocol following injection of gadolinium-DTPA (Magnevist [Schering AG, Allemagne, Germany]; 0.2 mmol/kg). The slice thickness used was 3 mm. Contrast-enhanced CT scans of the sella were obtained using the spiral mode of a third-generation scanner at a slice thickness of 2 mm on both axial and coronal sections after intravenous administration of 100 mL iodinated contrast agents.

All CT and MR images were analyzed in detail and data on the size, extension, and invasiveness of the GPA, especially the routes of tumor extension, were recorded. Histopathologic findings and pituitary hormone assay results were correlated with radiologic features in all cases. In addition, the clinical manifestations of the patients were reviewed.

**Results**

The clinical manifestations and tumor extension in the 14 patients with GPA are shown in the Table. All 14 patients presented with symptoms resulting from the mass effects of the GPA, including visual impairment (n = 13), headache (n = 9), vomiting (n = 3), and seizure (n = 3). Three patients had symptoms associated with hyperprolactinemia such as impotence, decreased libido, and galactorrhea (Table). The serum pituitary hormone concentrations were within normal limits in seven patients; the other seven patients had elevated concentrations of pituitary hormones corresponding to the individual tumor (Table). Histopathologic analysis revealed that five of these 14 GPAs were gonadotropin-secreting tumors, four were prolactinomas, two were null-cell adenomas, one was a plurihormone-secreting tumor, one was an invasive gonadotropin-secreting tumor, and one was an invasive null-cell adenoma.

On image analysis, these tumors measured from 5.5 to 9 cm at their greatest dimension (mean, 6.5 cm). All tumors appeared to be lobulated in shape, well contrast-enhanced, and with multi-directional invasion to the surrounding tissues. Thirteen tumors (93%) extended upward to the suprasellar cistern and/or the third ventricle and hypothalamus, resulting in obstructive hydrocephalus (Figs. 1–3). Infrasellar extension along the floor of the sella, from the sphenoid sinus to the ethmoid sinus or nasopharynx as well as the skull base, was noted in seven patients (50%) (Figs. 1–3). Eight tumors (57%) invaded laterally to the cavernous sinus (Figs. 1 and 2). Seven tumors (50%) exhibited temporal extension and six (43%) exhibited frontal extension (Figs. 1–3). Five tumors (36%) extended posteriorly to the posterior fossa or interpeduncle cistern (Fig. 2).

Histologically, only two tumors showed invasive features; one was a null-cell adenoma, the other was a gonadotropin adenoma. No correlation was found among histologic features, hormone assays, and image invasiveness (Table).

**Discussion**

GPAs are uncommon tumors. Jefferson was the first to report a series of massive adenomas, some of which had a suprasellar extension of more than 7 cm [6]. There have been few reports regarding the imaging features of GPA [2, 3]. Three types of GPA have been reported based on spreading behavior: invasive adenoma infiltrating into the brain [7, 8]; giant globular adenoma displacing the adjacent brain structures [2, 9]; and malignant adenoma with distant metastasis to the central nervous system [10].

The pituitary gland lies in the pituitary fossa of the sphenoid bone just below the optic chiasm, and is covered by the diaphragma sella. It is bordered on each side by the cavernous sinus. While pituitary microadenomas are usually associated with hypersecretion of pituitary hormones, GPA frequently presents with a mass effect on and/or invasion of adjacent structures with or without pituitary hormone hypersecretion. In this study and in previous reports, the size of the tumors was not correlated with serum hormone concentration (Table) [2, 11].

On CT and MR images, GPA typically appears as a large, lobulated, well-enhanced soft tissue mass at the sellar and suprasellar regions, with multi-directional invasion of adjacent structures; calcification and cystic change are rare. The reported rate of gross extrasellar expansion by pituitary adenomas of all types is approximately 35% to 38% [11, 12]. Several reports have demonstrated patterns of spread of invasive pituitary...
Table. Clinical data and routes of invasiveness in 14 patients with giant pituitary adenomas

<table>
<thead>
<tr>
<th>Age (yr)/sex</th>
<th>Major clinical features</th>
<th>Tumor size (cm)</th>
<th>Tumor extension</th>
<th>Routes of invasiveness</th>
<th>Types of tumors</th>
<th>Hormone concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>69/M</td>
<td>Visual impairment, seizures</td>
<td>5.5*</td>
<td>Third ventricle, cavernous sinus, temporal, pre-pontine cistern</td>
<td>S, CS, T, P</td>
<td>Gonadotropin</td>
<td>GH: 13 ng/ mL</td>
</tr>
<tr>
<td>65/M</td>
<td>Visual impairment, headache, seizures</td>
<td>9*‡</td>
<td>Frontal, third ventricle to nasopharynx, temporal, pre-pontine cistern</td>
<td>F, S, I, T, P</td>
<td>Gonadotropin</td>
<td>WNL</td>
</tr>
<tr>
<td>67/M</td>
<td>Visual impairment</td>
<td>5.5*</td>
<td>Frontal, third ventricle, cavernous sinus, temporal</td>
<td>F, S, CS, T</td>
<td>Plurihormone</td>
<td>GH: 20 ng/ mL, PRL: 102 ng/ mL</td>
</tr>
<tr>
<td>63/M</td>
<td>Visual impairment, headache, vomiting</td>
<td>6.5*†</td>
<td>Frontal, third ventricle, cavernous sinus</td>
<td>S, CS</td>
<td>Gonadotropin</td>
<td>FSH: 98 mIU/ mL</td>
</tr>
<tr>
<td>26/M</td>
<td>Visual impairment</td>
<td>6*†</td>
<td>Frontal, third ventricle</td>
<td>F, S</td>
<td>Gonadotropin</td>
<td>WNL</td>
</tr>
<tr>
<td>61/F</td>
<td>Visual impairment, headache, vomiting, seizures</td>
<td>6.5*†</td>
<td>Frontal, third ventricle, cavernous sinus, temporal, pre-pontine cistern</td>
<td>F, S, CS, T, P</td>
<td>Gonadotropin</td>
<td>WNL</td>
</tr>
<tr>
<td>67/F</td>
<td>Headache</td>
<td>6*</td>
<td>Sphenoid and ethmoid sinus, divus, skull base</td>
<td>I</td>
<td>Invasive gonadotropin</td>
<td>WNL</td>
</tr>
<tr>
<td>62/F</td>
<td>Visual impairment</td>
<td>6*</td>
<td>Suprasella to nasopharynx</td>
<td>S, I</td>
<td>Null-cell</td>
<td>WNL</td>
</tr>
<tr>
<td>36/M</td>
<td>Headache, visual impairment, decreased libido</td>
<td>6*†</td>
<td>Third ventricle, temporal, cavernous sinus</td>
<td>S, T, CS</td>
<td>Prolactinoma</td>
<td>5,930 ng/ mL</td>
</tr>
<tr>
<td>22/M</td>
<td>Headache, visual impairment, impotence</td>
<td>6.5*†</td>
<td>Third ventricle to sphenoid sinus</td>
<td>S, I</td>
<td>Prolactinoma</td>
<td>1,096 ng/ mL</td>
</tr>
<tr>
<td>29/M</td>
<td>Visual impairment, impotence, galactorrhea</td>
<td>7*†</td>
<td>Third ventricle, cavernous sinus, temporal</td>
<td>S, T, CS</td>
<td>Prolactinoma</td>
<td>8,695 ng/ mL</td>
</tr>
<tr>
<td>31/M</td>
<td>Visual impairment, headache</td>
<td>8.5*†</td>
<td>Third ventricle to skull base, temporal, cavernous sinus, ethmoid sinus, nasal chambers, cerebellopontine angle</td>
<td>S, I, T, CS, P</td>
<td>Prolactinoma</td>
<td>376 ng/ mL</td>
</tr>
<tr>
<td>54/F</td>
<td>Visual impairment, headache</td>
<td>6.5*†</td>
<td>Frontal, third ventricle to nasopharynx, cavernous sinus, ethmoid sinus</td>
<td>F, S, I, CS</td>
<td>Invasive null-cell</td>
<td>WNL</td>
</tr>
<tr>
<td>71/M</td>
<td>Visual impairment, headache, vomiting</td>
<td>6*</td>
<td>Frontal, third ventricle to sphenoid sinus, interpeduncular cistern</td>
<td>F, S, I, P</td>
<td>Null-cell</td>
<td>WNL</td>
</tr>
</tbody>
</table>

*Tumor within 6 mm of the foramen of Monro; †tumor more than 40 mm from the jugum sphenoidale; ‡suprasellar extension in more than two directions; F = frontal extension; S = upward extension; T = temporal extension; I = infrasellar extension; CS = cavernous sinus invasion; WNL = within normal limits.
adenomas [11, 13–16]. The classic pathways of tumor spread for pituitary adenomas include hypothalamic extension, frontal extension, temporal extension, protrusion into the cavernous sinus, protrusion into the nasopharyngeal region and posterior fossa, as well as orbital invasion. Factors affecting the extrasellar extension of pituitary adenomas include the growth tendency of the tumor, the status of fixation of the optic chiasm, the shape of the sella, and the thickness and dehiscence of the diaphragm [17].

Upward extension through the diaphragma sella into the suprasellar cistern is the most frequent pathway for GPA invasion [11, 17]. Although the diaphragma sella, the firm dural covering of the sella, is composed of connective tissue and forms an anatomic barrier against tumor expansion, a large GPA may invade the

Fig. 1. A 54-year-old woman with invasive null-cell adenoma and multi-directional tumor involving surrounding tissues. Contrast-enhanced magnetic resonance (MR) images (A, B) and computed tomography (CT) scans (C, D) show upward hypothalamic extension of the tumor to the third ventricle; lateral extension to the bilateral cavernous sinuses with encasement of internal carotid arteries (black arrows) and to the left medial temporal region; and inferior extension to the sphenoid sinus, skull base, clivus, posterior ethmoid sinus, and nasopharyngeal roof (white arrows). Skull bone destruction is more evident on the CT scans.

Fig. 2. A 31-year-old man with prolactinoma and multi-directional involvement of surrounding tissues. Serum prolactin was 376 ng/dL. Magnetic resonance (MR) images (A, B) and computed tomography (CT) scan (C) reveal upward hypothalamic extension of the tumor to the third ventricle and septum pellucidum causing hydrocephalus (white arrows); lateral extension to the bilateral cavernous sinuses and temporal region; inferior extension to the sphenoid sinus; and posterior extension to the right cerebellopontine angle (large white arrow). There are two extra-tumoral cystic components (white arrowheads).
A 65-year-old man with gonadotrophic cell adenoma. Serum follicle-stimulating hormone and luteinizing hormone concentrations were within normal limits. Magnetic resonance images (A, B) show upward hypothalamic extension of the tumor to the foramen of Monro; lateral extension to the right temporal region and basal ganglion; and inferior extension to the nasopharynx (white arrowheads).

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suprasellar space through an incompetent, relaxed, or stretched diaphragma sella. The upward growth of the GPA may compress and damage the optic nerves and chiasm or the hypothalamus, and further deeply indent the floor of the third ventricle. Therefore, the clinical manifestations include disturbances of vision or cranial nerve palsies, headache, nausea or dizziness due to increased intracranial pressure, loss of consciousness, epilepsy, hydrocephalus, and dysfunction of the hypothalamus [2, 11].

Downward growth of an adenoma involves erosion and penetration of the sphenoid dura, bone, and sinus. An aggressive GPA causes an increase in intrasellar pressure, resulting in attenuation of the sellar floor, enlargement of the sella, and eventual erosion of the sella. This can result in the generation of a pathway to the sphenoid sinus, the nasopharynx, ethmoid sinus, or nasal cavity. Occasionally, a GPA may behave as a large destructive skull-base mass filling the sphenoid, and invade the sphenoid base. In this situation, the differential diagnoses must include sphenoid sinus carcinoma, metastasis, plasmacytoma, chordoma, and nasopharyngeal carcinoma with skull base invasion. Nasopharyngeal extension of a pituitary adenoma is very uncommon, with an incidence of approximately 2% [15, 18]. The clinical features may include nasal obstruction, recurrent epistaxis, intermittent mucoid nasal discharge, or nasal dripping [15, 16].

Lateral growth of a GPA into the parasellar region is the least common type of growth because the lateral boundaries of the sella, composed of bone and firm connective tissue, provide a substantial anatomic barrier. Tumor extension into the cavernous sinus occurs in about 5% to 20% of cases [11, 12]. The most sensitive image pattern indicating cavernous sinus invasion by the tumor is an asymmetry in signal intensity between the two sides [19]. In contrast, the most specific sign is carotid artery encasement [19]. In this study, carotid artery encasement was considered a sign of cavernous sinus invasion. GPA invasion of the cavernous sinus was identified in five cases (36%) (Table, Figs. 1 and 2). Cavernous sinus invasion by GPA has been shown to be associated with a relatively low surgical cure rate because of the complexities of surgical exploration [20]. In most cases, the pituitary tumors simply indent and laterally displace the cavernous sinus and its contents. However, adenomas occasionally invade the wall of the cavernous sinus and the sinus itself, compressing or infiltrating the cranial nerves within. These findings are compatible with the infrequent clinical presentation of cranial nerve impairment. The mass effect of the tumor on the adjacent temporal lobe may result in seizures.

Posterior extension may result in destruction of the clivus and petrous apices, and further compression of the cerebellopontine, interpeduncle cisterns, and brain stem.

The differential diagnoses of GPA based on the image appearances include craniopharyngioma, germinoma, giant aneurysm, cavernous sinus meningioma, sphenoid sinus tumor, metastasis, skull-base bone tumor, and nasopharyngeal carcinoma. It may be difficult to differentiate GPA from craniopharyngioma. However, GPA seldom shows calcification, while craniopharyngiomas calcify in about 90% of cases [2]. In addition, infrasellar extension is unusual for craniopharyngioma, whereas most GPAs extend through the floor of the sella. In cases of GPA with massive global displacement of the adjacent structures, differential diagnosis between a well-enhanced brain tumor such as a meningioma, germ cell tumor, or lymphoma may be difficult (Fig. 3).

In our series and in others [1, 21, 22], males predominated. In addition, more men than women had larger
and more aggressive tumors. Symptoms such as decreased libido, impotence, and perhaps sterility tended to be either ignored by patients or undiagnosed. This may explain why the diagnosis of pituitary tumor is more likely to be made later in men, and consequently, why the tumor is usually considerably larger at presentation in men.

The histologic features of invasive tumors on the images in this study were no different from those of their non-invasive counterparts. The tumors showing invasive behavior in our studies demonstrated the benign microscopic appearance typical of adenoma, except for two cases in which invasive features were depicted microscopically. There was no correlation among histologic features, hormone concentrations, and imaging findings. Because of the histologically benign nature of GPA in most cases and because of the difficulty of performing complete tumor removal, GPA has frequently been treated by partial resection of the tumor to decompress the optic apparatuses and other surrounding structures [20]. Postoperative radiation is used for adjuvant management [23, 24].

In conclusion, GPA has the potential for multidirectional, widespread extension. Our data indicate that any type of GPA, regardless of its histologic features and endocrinologic activity, is able to invade the surrounding structures. No correlation was found among histologic features, hormone concentrations, and tumor aggressiveness. As yet, there is no explanation for why a tumor with a histologically benign appearance would exhibit invasive features. Upward invasion to the suprasellar region and/or hypothalamus is the most common pathway for the spread of GPA, followed by the infrasellar and nasopharyngeal pathway, the lateral route, and the anterior and posterior subtentorium routes. MR imaging is the most useful imaging technique available for preoperative evaluation and post-therapeutic follow-up, while CT provides better information about bony invasion and tumor calcification.

References