Microanatomy of the hypophyseal fossa boundaries

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Object. The authors studied the heads of 17 adult cadavers and one fetus to clarify the anatomy of the sellar region, particularly the lateral boundaries of the hypophyseal fossa.

Methods. Vascular injections and microdissection or histological techniques were used in this study. The roof of the cavernous sinuses and diaphragma sellae were part of a single horizontal dural layer that joined the two anterior petroclinoid folds. Laterally, the direction of this layer changed; it became the lateral wall of the cavernous sinus and joined the dura mater of the middle cerebral fossa. On the midline, this layer ballooned toward the sella through the diaphragmatic foramina, created a dural bag containing the hypophysis, and attached to the inferior aspect of the diaphragma sellae. As a consequence, no straight sagittal dural wall existed between the pituitary gland and cavernous sinus; the lateral border of the hypophyseal fossa was part of this anteroposterior and superoinferior convex bag. The authors stress the importance of the venous elements of the region and discuss the structure of the cavernous and coronary sinuses.

Conclusions. Invasion of the cavernous sinus makes surgery more risky and difficult and may necessitate modification of the surgical treatment plan. The preoperative diagnosis of cavernous sinus invasion is thus of great interest, but the possibility of normal lateral expansions of the pituitary gland must be kept in mind. A lateral expansion of this gland into the cavernous sinus was encountered in 29% of the specimens, and an adenoma that developed in such an expansion could easily mimic cavernous sinus invasion.

Key Words • pituitary gland • cavernous sinus invasion • anatomical study • pituitary adenoma

The hypophyseal fossa is situated in the center of the base of the skull. It is located in the sella turcica of the sphenoid bone, between the two cavernous sinuses laterally, and contains the hypophysis. In classic anatomical textbooks, the lateral walls of the hypophyseal fossa are said to be inserted cranially along a sagittal line separating the roof of the cavernous sinus from the diaphragma sellae and caudally at the lateral aspect of the sella turcica. In other words, the lateral walls of the hypophyseal fossa are described as linear sagittal dural walls, completely separating the hypophyseal gland medially from the cavernous sinuses laterally.

Usually, hypophyseal adenomas develop inside the hypophyseal fossa, with no extension outside it. Nevertheless, a lateral invasion of the homolateral cavernous sinus by an adenoma is described in approximately 10% of patients. Surgical treatment of adenomas invading the cavernous sinus remains a challenge for many neurosurgeons because of the difficulty associated with total removal of the tumor, particularly its lateral aspects, and because of possible bleeding of the cavernous sinus. Thus, a preoperative diagnosis of invasion of the cavernous sinus is important in planning the surgical strategy. Despite advances in neuroradiological imaging, the preoperative diagnosis of cavernous sinus invasion remains difficult and controversial. Some false positive diagnoses can be explained by anatomical variations; physiologically, the hypophysis may sometimes exhibit lateral expansion toward the cavernous sinus. An adenoma that develops in such a lateral expansion can mimic invasion of the cavernous sinus, while remaining completely separated from this structure by the lateral wall of the hypophyseal fossa. To better understand the variations observed by neuroradiologists and to aid magnetic resonance (MR) imaging interpretation, the authors studied the microanatomy of the hypophyseal fossa.

Materials and Methods

Heads from 17 adult cadavers and one 5-month-old fetus (age determined by crown–rump length) were studied. After severing the heads of 13 of the adult cadavers, red neoprene latex was injected into the primitive carotid and vertebral arteries, and blue neoprene latex was injected into the jugular veins. Red latex was injected into the umbilical arteries and blue latex into the umbilical vein of the fetus. The specimens were then embalmed using a 10% formalin solution and whitened in a 10% hydrogen peroxide solution. The brain was removed from each head and the hypophyseal region was...
Fig. 1. Photograph showing a superior view of the sellar and right parasellar spaces. The brainstem (Bs) and basilar artery (Ba) were sectioned. The anterior and posterior petroclinoid folds (Apcf and Ppcf) ran from the anterior and posterior clinoid processes, respectively, to the petrous bone apex. The posterior petroclinoid fold ran above the trigeminal nerve (V). The roof of the cavernous sinus (RCs) and the diaphragma sellae (Ds) were parts of a dural layer joining the two anterior petroclinoid folds. The pituitary stalk penetrated the sella through the diaphragmatic foramen. The oculomotor (III) and trochlear (IV) nerves entered the cavernous sinus laterally past the insertion of the tentorium at the upper petrous bone apex, medially to the trigeminal incisura, and directed posteriorly in a sagittal direction, ran above the petrous bone apex, medially to the trigeminal incisura, and was continued by the free edge of the tentorium. The posterior petroclinoid fold extended from the posterior clinoid process to the petrous bone apex and continued postero-laterally past the insertion of the tentorium at the upper rim of the petrous bone. It ran above the trigeminal nerve and cavanum, and contained the superior petrosal sinus, draining into the petroclival venous confluence. Because of the different distance between the anterior and posterior clinoid processes, the petroclinoid folds crossed at the superior aspect of the petrous bone apex, with the anterior petroclinoid fold lying above the posterior one. This X-shaped crossing delineated four quadrants: 1) an anterolateral one, which was the middle cranial fossa containing the anterior part of the temporal lobe; 2) a posterolateral quadrant consisting of the tentorium; 3) a postero-medial quadrant, the tentorial incisura, that contained the mesencephalon; and 4) the antero-medial quadrant, which was covered by a horizontal dural layer that ran from one anterior petroclinoid fold to the other (Fig. 2). It was continued anteriorly by the dura mater covering the tuberculum sellae and posteriorly by the dura mater surrounding the upper clivos. Laterally, its direction changed at the anteri-
or petroclinoid fold and it became nearly vertical to reach the line joining the rotundum and ovale foramina. This vertical part of the dural layer constituted the lateral wall of the cavernous sinus. The continuous horizontal layer spreading between the two anterior petroclinoid folds was the roof of the sellar and parasellar regions. Laterally it is called the roof of the cavernous sinus and on the midline it is known as the diaphragma sellae, because it is pierced by the diaphragmatic foramen. The latter was round or oval and contained the hypophyseal stalk and the terminal segment of the superior hypophyseal arteries that followed the stalk. The diameter of the diaphragmatic foramen was always more than twice the diameter of the hypophyseal stalk. We found no sagittal ligament or dural structure dividing the roof of the cavernous sinus from the diaphragma sellae. A dural bag containing the hypophysis (Figs. 2 and 3) was attached to the inferior aspect of the diaphragma sellae and was an evagination of the dural layer into the sella, extending to the diaphragmatic foramen. In the fetal specimen (Fig. 4), the maximum diameter of the bag was nearly the same as its opening (as if the bag were open). In the adult brains, the diaphragmatic foramen was smaller than the bag (as if the bag were half closed). The bag closely surrounded the hypophysis, had the same shape, and isolated the hypophysis from all the structures around it, particularly the cavernous sinuses. In other words, the lateral walls of the hypophyseal fossa were not straight sagittal dural layers, but rather the lateral parts of this anteroposterior and superoinferior convex dural bag (Fig. 3).

**Contents of the Hypophyseal Fossa**

The dural bag contained the anterior and posterior parts of the hypophysis. The former bulged laterally into the cavernous sinuses and the latter bulged dorsally, creating a small posterior lodge (Fig. 3). The hypophyseal stalk arose from the infundibulum, extended through the diaphragmatic foramen, and reached the posterior part of the hypophysis (Fig. 2). The portion of the hypophysis located just below the diaphragmatic foramen, around the hypophyseal stalk, was concave superiorly, similar to the small depression around an apple stem. This small depression was less than 2 mm deep and contained the hypophyseal cistern, which was located between the hypophyseal stalk, the upper limit of the hypophysis, and the border of the hypophyseal foramen. The hypophyseal cistern was an expansion of the chiasmatic subarachnoidal cistern and was separated from the interpeduncular or prepontine subarachnoidal cistern by the Liliquist membrane (Fig. 5).

**Nerve Relationships of the Hypophyseal Fossa**

The nerve relationships of the hypophyseal fossa were numerous: the fossa was located below the floor of the third ventricle, the optic nerves, and chiasm. The oculomotor (third) and trochlear (fourth) cranial nerves perforated the roof of the cavernous sinus just medial to the anterior petroclinoid fold (Fig. 1). The dural foramina of the third and fourth cranial nerves were located at the medial and posterior thirds, respectively, of the anterior petroclinoid fold (near the junction of the two petroclinoid

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**Fig. 2.** Photograph showing a posterior view of the sellar and parasellar spaces. The posterior boundaries of the cavernous sinus and sella were removed. A continuous dural layer joined the two anterior petroclinoid folds (Apcf) and corresponded laterally to the roof of the cavernous sinus (RCs) and to the diaphragma sellae (Ds) on the midline. It was continued laterally by the lateral wall of the cavernous sinus. The pituitary gland (Pg), which was partially removed on the right in this specimen, was embedded in a dural bag (Db), and bulged laterally and posteriorly. The coronary sinus (arrows), located between the dural bag and the roof of the sphenoidal sinus, joined the cavernous sinuses. The pituitary stalk (Ps) and supraclinoid ICA (Ca) were located below the optic chiasm (X) and optic nerves (II). The oculomotor nerve (III) ran near the lateral wall of the cavernous sinus. The carotid artery gave rise to the inferior hypophyseal arteries (IHa), and the superior hypophyseal arteries (SHa). c = caudal; r = right.
of the intracavernous ICA, alone or from a common trunk with the medial and lateral arteries of the clivus. The superior hypophyseal arteries (Fig. 2) arose from the supraclinoidal ICA near the origin of the ophthalmic artery, and vascularized the anterior part of the hypophysis.

The hypophyseal bag was surrounded by numerous venous structures. Laterally, it was flanked by the paired, so-called cavernous sinuses. Superiorly, each cavernous sinus was bordered by the lateral–horizontal part of the dural layer joining the two anterior petroclinoid folds. Laterally, the cavernous sinus was limited by the vertical part of this dural layer, before it reached the dura mater of the middle cerebral fossa. Posteriorly, the cavernous sinus was continued by another venous space: the petroclival venous confluence. The cavernous sinus, the superior petrosal sinus, and the basal sinus of the clivus filled this confluence. This petroclival venous confluence then gave rise to the inferior petrosal sinus. The border between the cavernous sinus and the petroclival venous confluence was the virtually vertical plane containing the posterior petroclinoid fold. The anterior limit of the cavernous sinus was difficult to delineate and was connected to the ophthalmic veins. Inferiorly, the cavernous sinus was limited by the roof of the sphenoidal sinus, and covered by a connective layer. We were unable to determine whether this connective layer corresponded to the periosteal dura mater or to the perieteum proper. The medial limit of the cavernous sinus was the lateral part of the hypophyseal bag applied to the irregular surface of the gland (Fig. 7). We never found a straight sagittal dural wall between the gland and the cavernous sinus.

A venous space located on the midline connected the two cavernous sinuses. This space was more or less wide and surrounded the hypophyseal gland and bag, except...
cranially and anteroinferiorly. There were numerous fibrous trabeculations joining the dural hypophyseal bag and the connective layer covering the roof of the sphenoidal sinus (Fig. 7). Those trabeculations delineated venous channels (Fig. 3), which were less numerous in the anteroinferior part of the bag; at that point, the bag and the connective layer covering the roof of the sphenoidal sinus were not separated by venous structures. These venous channels are known as coronary sinuses.

The cavernous sinus contained the intracavernous carotid artery (posterior bend, horizontal segment, anterior bend, and vertical segment), flanked laterally by the abducent (sixth) cranial nerve, and surrounded by venous blood. Macroscopic observations revealed 26 cavernous sinuses of two types: in 20 cases, the cavernous sinus was filled with blue latex mixed with fat, with no visible veins (Fig. 8). This organization corresponds to the cavernous structure described by others.\textsuperscript{5,11,23} The six other cavernous sinuses contained well-limited venous channels (Fig. 3). The space between those veins, the intracavernous carotid artery, and the sixth cranial nerve contained fat. This corresponded to descriptions published by Parkinson\textsuperscript{20} and Taptas.\textsuperscript{24} On histological studies, we found loose connective and fat tissue filling the free spaces in the cavernous sinus between nerves and the intracavernous carotid artery, but no veins. In this loose connective tissue, numerous vascular splits containing red blood cells showed continuous staining with factor VIII antibody at their inner aspect, but their walls were thin, with no muscle cells.

Whether or not it contained veins, the cavernous sinus was divided into four venous spaces, as previously described by Harris and Rhoton\textsuperscript{11} and Inoue, et al.\textsuperscript{12} The medial and lateral spaces were located between the intracavernous carotid artery and the dural hypophyseal bag and the lateral wall of the cavernous sinus, respectively. The anteroinferior space was located between the intracavernous carotid artery and the roof of the sphenoidal sinus. The posterosuperior space was located between the intracavernous carotid artery and the roof of the cavernous sinus.
The medial venous space is of great interest because the relationship of the hypophyseal bag to the intracavernous carotid artery depends on its width. The medial space was free in 24 (71%) of 34 instances (Fig. 2): the hypophyseal bag was isolated from the intracavernous carotid artery by blood most of the time, although sometimes only by a small contact point. In two specimens (6%) the hypophyseal bag demonstrated a small expansion onto the carotid artery containing a small tongue of pituitary gland. In eight instances (23%), the hypophyseal bag and the intracavernous carotid artery were in close contact, with no blood between them, and contained a lateral expansion of the pituitary gland and bag onto or below the intracavernous carotid artery (Figs. 8–10).

The 10 lateral expansions of the pituitary gland and bag are described in Table 1, according to the three techniques described by Moreau, et al. The medial carotid line (Fig. 11A) joins the medial walls of the intra- and supracavernous portions of the carotid artery. This line was crossed in the 10 specimens with lateral expansion. The medium carotid line, joining the center of the intra- and supracavernous carotid artery, was crossed four times. The lateral carotid line, between the lateral wall of the intra- and supracavernous carotid artery, was never crossed.

According to the horary quadrants method (Fig. 11B), the “hour” of each lateral expansion was measured on a frontal view, at the largest part of the expansion. Moreau, et al., used a clockwise rotation for the left cavernous sinus, and a counterclockwise rotation for the right cavernous sinus. The quadrants were graduated from 0 to 11 hours. Nine expansions involved the intracavernous carotid artery (eight at < 0 hours, one at 1 hour), whereas the remaining expansion was below the intracavernous carotid artery (7 hours).

The percentage of contact (Fig. 11C) between the intracavernous carotid artery and the lateral expansion was measured for each specimen in its widest frontal plane; it...
corresponds to the ratio of the perimeter of the intracavernous carotid artery in contact with the pituitary gland to the total perimeter of the artery. It exceeded 25% of contact in only one case (specimen 17, right hemisphere: 28%).

The 10 expansions were described in seven heads; three heads exhibited bilateral expansions. All of them were free of adenoma.

One of our specimens (Fig. 8) displayed an empty sella turcica and the pituitary tissue was located posteriorly, and in two there were lateral expansions above the right and left intracavernous carotid arteries.

Discussion

The anatomy of the sellar and parasellar spaces is of great interest with respect to surgery of the pituitary gland and cavernous sinuses. Nevertheless, it is not easy to understand this anatomy because of the numerous structural relationships in the region, particularly those between bone and dura mater.

The hypophysis consists of two embryologically different elements: an ectodermal part (antehypophysis) that migrates caudocranially, and a neuroectodermal one (neurohypophysis) that migrates craniocaudally. According to Chi and Lee, the whole hypophysis is surrounded by a fibrous capsule that originates from the mesenchymal cells located around the developing antehypophysis. Although these authors state that the capsule differentiates later than the diaphragma sellae, it probably corresponds to the dural bag we observed in the adults. The consequence is that the dura mater probably does not herniate caudally during craniocaudal migration of neurohypophysis; the dural bag progressively organizes around the developing and migrating hypophysis in the same way that the whole dura mater of the central nervous system does, by increased density of the surrounding mesenchymal tissue.

Nevertheless, to clarify the complex anatomy of the region, it is easier to imagine a specimen with no hypophysis. In this case, a continuous dural layer would join the two anterior petroclinoid folds (roof of the cavernous sinuses and hypophyseal diaphragm). Afterward, this layer would run vertically to reach the dura mater of the middle cerebral fossa (lateral wall of the cavernous sinuses). Between this dural layer and the roof of the sphenoidal sinus, a large venous space would be delineated. The hypophysis bulges at the midline of this dural layer, with the dura mater remaining closely apposed. This results in the dural layer covering the hypophysis as a layer of soap or rubber would surround a ball dropped into it. The dura then borders a small bag containing the gland. The venous space is thinner where the gland bulges (Fig. 4), and fibrous trabeculations (Fig. 7) joining the bottom of the dura bag to the roof of the sphenoid sinus delineate venous channels, or coronary sinuses (Figs. 3 and 7). The coronary and cavernous sinuses can thus be considered to be parts of a large median venous structure, although it is smaller where the hypophysis is larger.

The nature of the fibrous layer covering the roof of the
sphenoidal sinus remains unclear. According to Taptas,\(^24\) this layer is the periosteum, the whole dura mater of the middle cerebral fossa having been reflected to become the lateral wall of the cavernous sinus. In this case, the cavernous sinus is considered to be extradural (interperiosteodural) and continuous with the orbit. According to Paturet,\(^21\) only the inner, or encephalic, layer of the dura mater of the middle cerebral fossa reflects. Consequently, the roof of the sphenoidal sinus is considered to be covered by the outer, or periosteal, layer of the dura mater, whereas the cavernous sinus is intradural (between the two layers of the dura mater). We failed to demonstrate whether the connective layer covering the roof of the sphenoidal sinus is dura mater or periosteum, because there is a lack of distinctive macroscopic and histological features between those two structures. According to Haines, et al.,\(^10\) ultrastructural studies show that the dura mater is made of three distinct layers: an external or periosteal dura (attached to the inner surface of the skull), an internal or meningeal dura, and dural border cells (joining meningeal dura to the arachnoid membrane). The meningeal dura contains more fibroblasts and less collagen than the periosteal dura. In other words, these authors believe that there is no periosteum at the inner aspect of the skull because the external part of the dura mater is directly attached to the skull. As a consequence, the variations observed by different authors may be semantic differences rather than anatomical ones: the outer or periosteal layer of dura mater described by Paturet\(^21\) may be the same anatomical structure as Taptas’ periosteum\(^24\) (external or periosteal dura).

The diameter of the hypophyseal foramen was always larger than the pituitary stalk. The depth of the hypophyseal cistern (located in the free space around the pituitary stalk) was less than 2 mm. In the fetus we studied (Fig. 4), the diameter of the hypophyseal foramen was particularly large. The foramen is said to become proportionally smaller during development, and some empty sella turcica are considered to be the consequence of persistence in the adult of a large hypophyseal foramen. According to Ferreri, et al.,\(^7\) a large hypophyseal foramen is associated with a small hypophysis located at the posterior part of the sella turcica, the sella being filled with the arachnoid cistern. An arachnoid space ballooning into the sella was found in 20% of the 225 autopsies performed by Bergland, et al.\(^3\) Normally the arachnoid membrane ends at the upper part of the pituitary gland, preventing cerebrospinal fluid from filling the sella via the foramen. It has been hypothesized that normally the diaphragm sellae performs a protective role for the sellar contents, but dehiscence of the diaphragm could allow the pulsating cerebrospinal fluid to enlarge the hypophyseal cistern, leading to an empty sella.\(^8,18\) Gibby, et al.,\(^9\) corroborate this theory.

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<th>Passed Carotid Lines</th>
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* MdlL = medial carotid line; MdmL = medium carotid line.
raised intracranial pressure occurring during pseudotumor cerebri was associated with an empty sella in 94% of 17 patients. In the case we studied (Fig. 8), the dural bag was empty except laterally and posteriorly, where the remaining gland was located. The hypophyseal foramen was large, but we found no continuity between this free sella turcica and the hypophyseal cistern; above them, a thin layer of gland connected to the pituitary stalk seemed to obliterate the hypophyseal foramen. It would have been of great interest to have had a clinical history of symptoms usually related to an empty sella syndrome. Unfortunately, the medical history in this case was not available.

During the intrauterine period, the antehypophysis migrates from the base of the tongue to the sella turcica through the craniohypophyseal canal. Ectopic adenomas developing in the sphenoid sinus may be the consequence of abnormal migration or arrest of hypophyseal tissue in the craniohypophyseal canal. The absence of this canal in all the adult specimens we studied can be explained by its regression during growth: it is present in 0.42 to 0.5% of adults and in 5 to 9% of children younger than 3 months.

The structure of the cavernous sinus remains controversial. In classic textbooks and some modern papers, venous blood is not said to be contained in veins, but in a large space bordered by dura mater and containing fibrous trabeculations and fat tissue. This organization was found 28 times (20 latex-injected and eight histological specimens). On the other hand, in studies by Taptas and Parkinson, the authors state that this cavernous structure does not exist. The so-called cavernous sinus was identified as a plexus of veins. We found venous structures that resembled veins macroscopically in six specimens. Unfortunately, the technique we used (latex injection) did not permit histological studies on the same specimens; therefore, we were unable to determine whether those venous channels had a venous wall. Nevertheless, the 28 "cavernous-organized" paraseptal spaces we studied were not large venous spaces filled with blood. We believe that they were spaces containing loose connective and fat tissue that were pierced by numerous splits lined by endothelium and containing venous blood. The structure of the cavernous sinus may vary according to the age of the specimen: a plexiform organization in the fetus may become cavernous in the adult by fusion of adjacent veins. We did not study children, and the venous injection of latex in the fetus in our series was not sufficient to allow correct dissection. The structure of the cavernous sinus may also vary according to the anteroposterior level. The anterior portion of the cavernous sinus, which is continuous with the ophthalmic veins, may exhibit a venous organization; the posterior portion, which is continued by the petroclival venous confluence (Dorello’s canal), has a sinuslike organization. The junction between those two structures may correspond to a cavernous organization by progressive fusion of the veins. It may be postulated that the size of this cavernous transition zone changes from one specimen to another, with a large fusion zone corresponding to a cavernous organization, and a small one to a plexiform organization.

The existence of a dural bag (Figs. 2, 3, 6, and 8) surrounding all but the cranial part of the gland differs from traditional descriptions; the so-called medial wall of the cavernous sinus (or lateral wall of the hypophyseal fossa) is in fact the lateral part of this bag, instead of a sagittal fold of dura mater. As we describe, the absence of lateral bone limits of the sella turcica may lead to the development of the lateral expansions of the pituitary gland that were previously described by Harris and Rhoton in 28% of cases, and by Bergland, et al., in 22%. We found a similar frequency of lateral expansions (29%).

The physiological presence of lateral expansions of the pituitary gland (Figs. 8–10) makes it difficult to diagnose cavernous sinus invasion by using MR imaging. Moreau, et al., retrospectively studied 51 MR images obtained in patients who underwent surgery for pituitary adenomas. Invasion of 13 of those 102 cavernous sinuses was proven perioperatively. These authors described three signs that are useful for the diagnosis of cavernous sinus invasion (Fig. 11). 1) Crossing “0 o’clock” on the intracavernous carotid artery. The cavernous sinus was rarely invaded when the adenoma did not extend beyond “0 o’clock” (negative predictive value 97.1%), but some of the adenomas that extended beyond “0 o’clock” did not correspond to cavernous sinus invasion (positive predictive value 66.7%). In our series, pituitary gland expansions were located before “0 o’clock” except for one that was at “1 o’clock.” 2) When more than 25% of the intracavernous carotid artery was covered by the adenoma it was very suspicious. In our study, this exceeded 25% in only one case (28%). In the other specimens, it ranged between 10% and 25%. 3) The surest sign Moreau, et al., described was the crossing of the lateral carotid line (sensitivity 84.6%; specificity 95%). Conversely, extension beyond the medial and median carotid lines was not a good sign of cavernous sinus invasion. Similar data were reported by Knoop, et al. Our results corroborate those of Moreau, et al., because the medial line was passed in the 10 specimens with lateral expansion, the medium line was passed four times, and the lateral line was never passed in our anatomical series.

Conclusions

The medial wall of the cavernous sinus is the lateral part of the dural bag enveloping the hypophysis, and it is too thin to be seen easily on MR imaging. As a consequence, it is difficult to be sure preoperatively whether this wall has been invaded by an adenoma. Indirect signs are therefore of great importance for the diagnosis of cavernous sinus invasion, particularly the relationships between the hypophysis, the intracavernous carotid artery, and the venous spaces.

This study confirms the presence of lateral expansions of the hypophysis in approximately 29% of normal specimens, which makes the neuroradiological diagnosis more difficult: the development of an adenoma on a lateral pituitary expansion could easily mimic cavernous sinus invasion. Careful preoperative evaluation of neuroradiological data, taking into account these anatomical variants, must be performed.

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