Giant Prolactinoma Embedded by Pseudoaneurysm of the Cavernous Carotid Artery Treated with a Tailored Therapeutic Scheme

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Abstract

The coexistence of intracranial aneurysm (IA) is generally thought to be highest in patients with pituitary adenomas (PAs). Different mechanisms may play a role in aneurysm formation, but whether the PA contributes to aneurysm formation is still unclear. In the literature, there are numerous reported cases of this association; however, the analyses of the characteristics of PAs, aneurysms, and treatment management are rare and limited to a restricted number of case reports. We report a rare case of an embedded aneurysm in a macroprolactinoma treated with therapeutic management tailored to the clinical, neurological, and radiological characteristics of the patient. To select the best treatment, we reviewed the literature and reported the only cases in which the radiological characteristics of aneurysms, PAs, therapeutic management, and patient outcome are described. We aimed to understand what are the variables that determine the best therapeutic management with the best possible outcome. The presence of a large pseudoaneurysm of the internal carotid artery completely embedded in a giant macroprolactinoma is rare and needs a tailored treatment strategy. The importance of the preoperative knowledge of asymptomatic IA coexisting with PA can avoid accidental rupture of the aneurysm during surgical resection and may lead to planning the best treatment. A high degree of suspicion for an associated aneurysm is needed, and if magnetic resonance imaging shows some atypical features, digital subtraction angiography must be performed prior to contemplating any intervention to avoid iatrogenic aneurysmal rupture. Our multimodal approach with the first-line therapy of low-dose cabergoline to obtain prolactin normalization with minimum risks of aneurysms rupture and subsequent endovascular treatment with flow diverter has not been described elsewhere to our knowledge. In the cases, we suggest adopting a tailored low-dose cabergoline therapy scheme to avoid rupture during cytoreduction and initiate a close neuroradiological follow-up program.

Keywords
- prolactinoma
- pituitary adenoma
- cerebral aneurysms
- internal carotid artery
- cavernous sinus
- flow diverter

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Introduction

Brain tumors and intracranial aneurysms (IAs) are the most common cerebral lesions, and these two pathologies frequently could coincide and occur concurrently. The incidence of such coexistence is approximately 0.5% of all intracranial tumors as reported, but the assessment of the real incidence rate is difficult, as angiography is not routinely performed for all brain neoplasms.[1] Among all types of brain tumors, this coexistence is generally thought to be highest in patients with pituitary adenomas (PAs).[2] There is a general consensus that IAs occur more frequently in association with PAs than among the general patient population.[3] By mean of both autoptic and retrospective studies, with incidence rates ranging from 0.5 to 7.4%,[4–6] coincidental aneurysms are reported almost seven times more frequently in patients with PAs than in patients with other types of brain tumors.[3,7]

Several mechanisms of aneurysm formation associated with PA have been proposed, including local circulatory stress, endocrine effect, mechanical effect, and direct invasion. It is possible that one or more mechanisms play a role in aneurysm formation at locations, but whether the PA contributes to aneurysm formation is still unclear.[7] In the literature, over the decades, there have been sporadically numerous reported cases of this association, in some cases even very large series have been presented with more than 500 cases; however, the analyses of the characteristics of PAs, aneurysms, and treatment management are very rare and limited to a restricted minimum of case reports or clinical images. The great majority of these aneurysms are located outside the tumor itself. The presence of an internal carotid artery (ICA) aneurysm embedded within a PA located inside the sella turcica has rarely been reported.[7] So, reported cases of giant PA are even rarer where extrasellar growth may result in fully embedded intracranial aneurysm (IA) in the tumor. Giant prolactinomas are a rare subset of macroadenoma characterized by large size (more than 40 mm in diameter), high aggressiveness, and massive extrasellar involvement. In this study, we report a rare case of an embedded aneurysm in a large PA treated with therapeutic management tailored to the clinical, neurological, and radiological characteristics of the patient. To select the best treatment for our case, we performed a review of the literature and reported the only cases in which the radiological characteristics of aneurysms, PA and therapeutic management, and patient outcome are described. With this study, we want to understand what are the main variables that determine the best therapeutic management with the best possible outcome of this uncommon but not even rare coexistence of pathologies.

Methods

We performed a review of the literature by analyzing all reported cases of PAs associated with IAs. We aimed to identify the clinical features of patients suffering from this unusual and coincidental relationship and to describe the best treatments proposed and performed. We also added our experience with an unusual case of carotid aneurysm embedded in PA.

Eligibility Criteria

Our target was to define the clinical and radiological criteria to deem a PA associated with IA by analyzing all cases reported in the relevant literature.

Therefore, while screening the literature, we adopted the following inclusion and exclusion criteria.

Inclusion criteria were meta-analysis, case series, clinical study, or clinical image reporting cases of patients who suffered from PA and IA.

Conversely, we excluded the following: cases reported without detailed clinical features of patients, cases reported without the description of radiological images, papers that report other pathologies (out of topic), papers written in languages other than English, papers published before 1985, and before the introduction of magnetic resonance imaging (MRI) and digital subtraction angiography for diagnosis and treatment.

Information Sources and Search

The English literature was systematically investigated using MEDLINE, the NIH Library, PubMed, and Google Scholar. The last search date was 15 February 2022. The following search terms were used: Pituitary Adenoma AND Intracranial aneurysm or Cerebral Aneurysm. Duplicated articles were removed after the first investigation through the libraries.

Results

The search returned a total of 526 results, including radiological, molecular, and clinical studies. To this initial cohort, the aforementioned exclusion criteria for the title and abstract selection were applied, accordingly eliminating a total of 165 publications. The resulting 361 papers were included in our analysis. We subsequently excluded 315 articles after complete revision of the paper for inconsistent or incomplete case descriptions of cases reported, out of topic, or duplicated cases. A flowchart showing the article selection method is given in ►**Fig. 1**.

From the final 46 articles enrolled, we selected 150 patients for this review, including our representative cases. The 150 patients are listed in ►**Table 1**.

The total number of patients was 150, with a mean age of 52.15 years (reported for 144 cases; minimum = 18, maximum = 73), 62 males (43.05%), and 82 females (56.94%). Details are given in ►**Table 2**.

The histological type of PAs reported document-wide variability, where nonsecreting adenomas accounted for the majority of cases (41 cases, 42.7%), followed by GH-secreting adenomas (33 cases, 34.4%), and prolactinomas (17 cases, 17.7%).

Description of aneurysm onset symptomatology and its correlation with diagnosis and management of PA was reported in 71/150 patients. We observed that in 36.62% (26/71 patients) of cases, the diagnosis of IA occurred incidentally following routine radiological examinations, and in

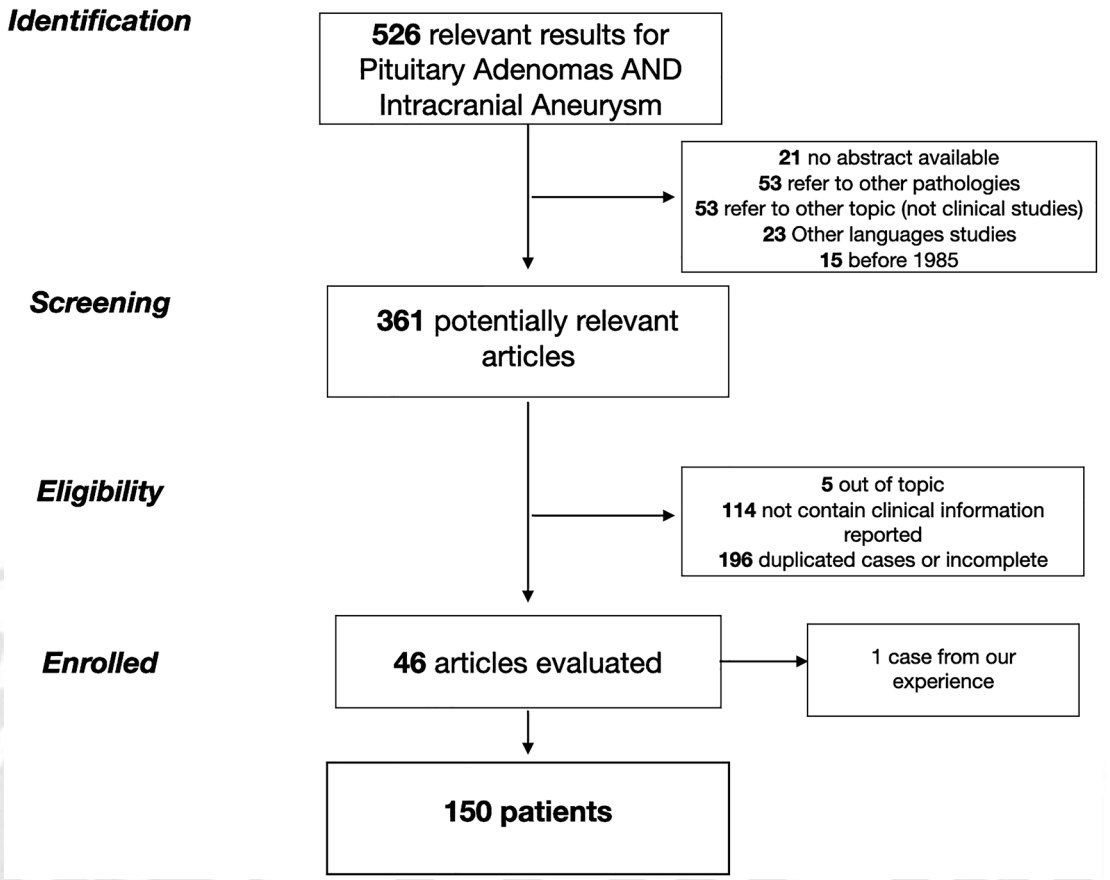

Fig. 1 The flow-chart of article selection.

6/71 patients (8.45%), it occurred during the follow-up after the PA removal procedure, in the absence of symptomatology. In 16 patients, the presence of aneurysm was diagnosed after the persistence of symptoms after surgery or after abnormalities found during the transsphenoidal (TS) surgery procedure. From these, seven patients (9.86%) manifested progressive worsening of visual acuity after treatment of PA, three patients (4.23%) manifested acute headache in the absence of intracranial bleeding, three patients presented epistaxis (4.23%), and two patients (2.82%) exhibited severe intracranial hemorrhage symptoms with loss of consciousness and severe neurologic deficits. We report one patient with transitory ischemic attack.

The most common location for an IA associated with a PA was the ICA with 89/126 cases reported (70.6%). The most frequent site of the aneurysm was at the intracavernous ICA (reported as carotid sinus ICA) with 50/126 reported cases (39.68%), followed by the supraclinoid ICA (37/126 patients, 29.37%) and the superior hypophyseal artery-ICA segment (2 cases, 1.59%). Other reported localizations were in decreasing order: anterior communicating artery (12/126 patients, 9.5%), anterior cerebral artery (9 patients, 7.14%), medium cerebral artery (8 patients, 6.35%), posterior cerebral artery (6 patients, 4.76%), and basilar artery (2 patients, 1.59%). The mean major dome diameter measured in the involved aneurysms was 2.69 mm (minimum 2.1 mm and maximum 14 mm).

The mode and timing of treatment was found to be highly variable and dictated, first, by the early and contextual diagnosis of the aneurysm along with the presence of PA and, second, based on the symptomatology and the presence of embedded aneurysm in PA.

In most of the reported cases (27/62, 43.5%), it was chosen to treat IA first by endovascular approach followed by the performance of TS approach for PA. In 12/62 patients (19.35%), the choice was made to treat the aneurysm and PA by a transcranial approach at the same surgical time.

In view of the fact that a considerable number of IAs were diagnosed during or after the procedure, a large number of PAs (12/62, 19.35%) were treated by the TS approach followed by the TC approach (5/62 patients 8%) and by the endovascular procedure in 4/62 patients (6.4%). In four cases, IA was not treated after TS surgery, and in another four cases, only a medical approach on PA was attempted before considering subsequent treatments. The other procedure modalities are shown in the tables.

Approaches on aneurysms were in most cases by the endovascular route, as also a consequence of the fact that most of them were located in the intracavernous compartment. Individual details of the procedures are given in the tables.

Outcome Analysis

The success rate of documented cases of aneurysm diagnosed at the same time as a PA was considered high with 60.41% of patients having an excellent outcome with endocrinological and neurological symptoms regressed or improving. The

Table 1 Study selection

Author	Year	Patients	Sex	Age	Aneurysm location	Aneurysm symptoms	Aneurysm treatment	Embedding	Dimensions aneurism (mm)	Adenoma Symptoms	Type	Adenoma treatment	Timing-Modality	Outcome
Acqui et al[8]	1987	2	M	48	AcoA	Incidental	Clipping	No	\	Acromegaly, visual loss	GH	Transcranial	Same	Diabetes insipidus
			F	38	ICA	Visual loss	Clipping	Yes	\	Acromegaly	GH	Transcranial	Same	Good
Onishi et al[16]	1989	1	F	31	ICA	Visual loss	Clipping	\	\	Acromegaly	GH	Transsphenoidal	TS-TC	Impaired visual acuity
Fedder et al[17]	1990	1	\	\	AcoA	Incidental	Clipping	No	\	\	Nonsecretory	Transsphenoidal	TC-TS	Good
Fujiwara et al[18]	1991	3	\	\	ICA	Hemorrhage	Clipping	\	\	None	GH	Transcranial	Same	Good
			\	\	ICA	Incidental	Clipping	\	\	Acromegaly	GH	Transcranial	Same	Good
			\	\	ICA	Incidental	Clipping	\	\	Acromegaly	GH	Transcranial	Same	Good
Weir[19]	1992	1	\	\	ICA	Visual loss	Clipping	Yes	\	Acromegaly	GH	Transsphenoidal	TS-TC	Good
Hermier et al[20]	1994	1	M	58	AcoA	Incidental	Clipping	No	4	Visual loss	TSH	Transcranial	Same	\
Salpietro et al[21]	1997	1	F	71	ICA	Incidental	Balloon ICA occlusion	Yes	\	Visual loss	Nonsecretory	Transsphenoidal	TS-wait and see-EV	Good
Pant et al[22]	1997	25	14F, 11M	30	20 ICA, 2 AcoA, 2 MCA, 1 PCA	Incidental	Clipping	\	3.5 (mean)	\			\	
Imamura et al[23]	1998	1	\	\	CS-ICA	Epistaxis fatal	Wait and see	\	\	Incidental		None	\	Hemorrhage, Death
Dolenc et al[24]	1999	1	F	39	CS-ICA	Incidental	Clipping	No	\	Galactorrhea, amenorrhea	PRL	Transsphenoidal	TS-TC	Good
Revuelta et al[25]	2002	1	F	60	ICA	Incidental	Clipping	No	14;19	Visual loss	Nonsecretory	Transcranial	Same	Good
Sade et al[26]	2004	1	F	39	CS-ICA	Incidental	Coiling	Yes	6	Acromegaly	GH	Transsphenoidal	EV-TS	Good
Pany et al[27]	2004	1	F	53	ICA	Headache	Coiling	Yes	\	Visual loss	\	Transsphenoidal	TS-EV	Good
Yang et al[28]	2005	1	F	53	CS-ICA	Incidental	Clipping	Yes	8	Hyperprolactinemia	PRL	Transcranial	Same	Good
Kulseng and Myhre[15]	2006	2	F	73	\	\	\	\	\	\	GH	Transsphenoidal	\	\
			M	59	CS-ICA	Incidental	Coiling	\	\	Incidental	GH	Transsphenoidal	EV-TS	Hemorrhage, died after 6 months
Chuang et al[29]	2006	1	M	60	CS-ICA	Incidental	Coiling + transcranial	Yes	\	Visual loss	TSH	Transsphenoidal	EV-TS	Good
Bulsara et al[30]	2007	1	M	73	AcoA	Visual loss	Clipping	No		Visual loss	\	Transcranial	Same	Good
Curto et al[31]	2007	1	F	61	CS-ICA	Incidental	Balloon	No	\	Acromegaly	GH	Medical	TC-Medical	Re-growth
Soni et al[32]	2008	1	M	53	CS-ICA	Incidental	Balloon	Yes	20	Hyperprolactinemia	PRL	Medical	Medical-EV	Good
Seda et al[33]	2008	1	F	58	ICA	Incidental	Clipping	Yes	12	Acromegaly	GH	Transsphenoidal	TC-TS	Re-growth
Wang et al[34]	2009	1	F	61	ICA	Incidental	Coiling	Yes	8.0 ;7.5; 4.8	Hyperprolactinemia, visual loss	PRL	Transsphenoidal	EV-TS - gamma knife	Good
Rustagi et al[35]	2011	1	M	39	AcoA	Postsurgery	\	\	\	Visual loss	Nonsecretory		\	\

(*Continued*)

Table 1 (*Continued*)

Author	Year	Patients	Sex	Age	Aneurysm location	Aneurysm symptoms	Aneurysm treatment	Embedding	Dimensions aneurism (mm)	Adenoma Symptoms	Type	Adenoma treatment	Timing-Modality	Outcome
												Transsphenoi-dal		
Yu et al[36]	2011	1	F	54	ICA	Incidental	Coiling	Yes	5.3	Visual loss	Nonsecretory	Transsphenoi-dal	EV-TS	Good
Oh et al[9]	2012	18	F	52	MCA	\	Coiling	No	8	\	Nonsecretory	Transsphenoi-dal	EV-TS	\
			F	54	ICA	\	Coiling	\	3.5	\	GH	Transsphenoi-dal	EV-TS	\
			M	59	Basilar artery	\	Coiling	No	3	\	Nonsecretory	Transsphenoi-dal	EV-TS	\
			F	49	MCA	\	Coiling	No	2.8	\	GH	Transsphenoi-dal	EV-TS	\
			F	53	AcoA	\	Coiling	\	2.3	\	Nonsecretory	Transsphenoi-dal	EV-TS	\
			F	64	ICA	\	Coiling	\	3.2	\	GH	Transsphenoi-dal	EV-TS	\
			M	60	ICA	\	Coiling	\	3.2	\	Nonsecretory	Transsphenoi-dal	EV-TS	\
			F	33	ICA	\	Coiling	\	4	\	GH	Transsphenoi-dal	EV-TS	\
			F	53	AcoA	\	Coiling	\	6	\	GH	Transsphenoi-dal	EV-TS	\
			F	41	MCA	\	Coiling	No	3.8	\	Nonsecretory	Transsphenoi-dal	EV-TS	\
			F	59	ICA	\	Coiling	\	7;3;2.3	\	Nonsecretory	Transsphenoi-dal	EV-TS	\
			F	38	MCA	\	Coiling	No	4.2	\	ACTH	Transsphenoi-dal	EV-TS	\
			F	46	ICA	\	Coiling	\	7	\	GH	Transsphenoi-dal	EV-TS	\
			F	65	MCA	\	Coiling	No	8	\	Nonsecretory	Transsphenoi-dal	EV-TS	\
			F	64	ACA	\	Coiling	\	3	\		Transsphenoi-dal	EV-TS	\
			F	18	ICA	\	Coiling	\	4.2	\	PRL	Transsphenoi-dal	EV-TS	\
			M	39	ICA	\	Coiling	\	3.7	\	GH	Transsphenoi-dal	EV-TS	\
			M	57	ICA	\	Coiling	\	5	\	\	Transsphenoi-dal	EV-TS	\
Yamada et al[37]	2012	1	F	57	ICA	Incidental	Coiling	No	6	Incidental	Nonsecretory	Transsphenoi-dal	EV-TS	\
Xia et al[38]	2012	1	F	48	CS-ICA	Incidental	Coiling	No	4;4	Incidental	GH	Transsphenoi-dal	EV-TS	Good
Choi et al[39]	2013	1	F	70	ICA-SHA	Incidental	Coiling	Yes	6.27;3.99	Visual loss	Nonsecretory	Transsphenoi-dal	EV-TS	Good
Takeuchi et al[40]	2013	1	M	49	ACA A2	TIA	Bypass	No	\	Incidental		Transcranial	Same	Good

Table 1 (*Continued*)

Author	Year	Patients	Sex	Age	Aneurysm location	Aneurysm symptoms	Aneurysm treatment	Embedding	Dimensions aneurism (mm)	Adenoma Symptoms	Type	Adenoma treatment	Timing-Modality	Outcome
											Craniopharyng-ioma			
Yoon et al[41]	2014	1	F	44	PCA	Incidental	Coiling	No	\	\	Nonsecretory	Transsphenoi-dal	TS-EV	CSF leak
Almeida Silva et al[42]	2014	1	M	53	AcoA	Headache	Clipping	Yes	1	Hyperprolacti-nemia, visual loss	PRL	Transsphenoi-dal	TS-TC	Good
Xu et al[3]	2015	1	M	49	AcoA	Headache vi-sion loss	Clipping	Yes	\	Note, in follow-up	PRL	Transcranial	Same + gamma knife	Good
Peng et al[7]	2015	1	M	53	CS-ICA	Epistaxis, visual loss	Balloon	Yes	14	Incidental	PRL	Transsphenoi-dal	TS-EV-Medical	Good
Tian et al[43]	2015	1	F	63	AcoA	Postsurgery	Coiling	No	3.5;8	\	PRL	Transsphenoi-dal	TS-EV	Good
Lee et al[44]	2015	1	F	32	PCA	Postsurgery	\	Yes	2.1;2.9	Visual loss	Nonsecretory	Transsphenoi-dal	TS-wait and see-EV	Good
Habibi et al[45]	2015	1	F	35	SCA	Postsurgery	\	\	\	\	Nonsecretory	Transsphenoi-dal	TS	Hemorrhage, died
Khalsa et al[46]	2016	1	M	61	CS-ICA	Hemorrhage	Coiling + onyx	Yes	1.2	Hyperprolacti-nemia	PRL	Medical	Medical + Wait and see	Hemorrhage
Satyarthee and Raheja[1]	2017	1	M	52	ICA	Worsening vi-sual acuity	Clipping	Yes	10.2;10.1	Visual loss	GH	Transcranial	Medical + TC	Good
Khachatryan et al[47]	2018	1	F	37	ICA	Incidental	Coiling	Yes	2.5	Acromegaly	GH	Medical	Medical + TS + EV	Good
Hu et al[2]	2019	36	21 M, 15 F	58	CS-ICA 13, ICA 17, ACA 8, MCA 1, PCA 3, Basi-lar artery 1	\	\	\	3.1 (mean)	\	21 Nonsecre-tory, 9 GH, 5 PRL, 1 ACTH	Transsphenoi-dal	\	\
Nakahara et al[13]	2019	1	F	61	CS-ICA	Postsurgery	Coiling	Yes	11;9	Headache	PRL	Transsphenoi-dal	Medical-EV	Good
Morinaga et al[48]	2019	1	M	68	PcoP	Postsurgery	Coiling	No	\	Acromegaly	GH	Transsphenoi-dal	TS-EV	Good
Inoue et al[49]	2019	1	M	41	CS-ICA	Acute epistaxis after RT for surgery residual	Bypass	Yes	\	Acromegaly	GH	Transsphenoi-dal	TS-TC	Good
Kino et al[12]	2020	1	F	53	ICA-SHA	Incidental	Clipping	\	3.3;2.7	Visual loss	Nonsecretory	Transsphenoi-dal	EV-TS-TC	Hemorrhage
Ogawa et al[50]	2021	24	10 M, 14 F	56	\	\	\	\	\	\	\	\	\	\
Piper et al[6]	2021	1	M	67	CS-ICA	Incidental	Flow diverter	Yes	3.7;3.4	Incidental	Nonsecretory	Transsphenoi-dal	EV-TS	Good
Wang et al[51]	2021	1	F	38	CS-ICA	Incidental	Wait and see	Yes	\	Visual loss	Nonsecretory	Transsphenoi-dal	TS	Good
Our case 2022	2022	1	F	73	CS-ICA	Visual loss	Flow diverter			Headache, diplopia	PRL	Transsphenoi-dal	TS-EV-Medical	Good

Abbreviations: ACA, anterior cerebral artery; AcoA, anterior communicating artery; ACTH, adrenocorticotropic hormone; CS-ICA, carotid sinus internal carotid artery; EV, endovascular; F, female; FSH, follicle-stimulating hormone ; GH, growth hormone; ICA-SHA, internal carotid artery–superior hypophyseal artery; M, male; MCA, medium cerebral artery; PRL, prolactin; RT, radiography; Same, during the same surgery; TC, transcranial; TS, transsphenoidal; TSH, thyroid-stimulating hormone.

Table 2 Population study

Patients reported 150	
Sex (144)	F = 82/144, 57.94%
Age (144)	Mean age = 52.15 minimum = 18, maximum = 73
Adenoma histology (reported in 96 pts)	Nonsecreting = 41/96, 42.7%
	GH = 33/96, 34.4%
	PRL = 17/96, 17.7%
	TSH = 2/96, 2%
	ACTH = 2/96, 2%.
	Craniopharyngioma = 1/96, 1%
Aneurysm symptomatology	Incidental = 26/71, 36.62%
	Visual loss = 7/71, 9.86%
	Postsurgery = 6/71, 8.45%
	Epistaxis = 3/71, 4.23%
	Headache = 3/71, 4.23%
	Hemorrhage = 2/71, 2.82%
	TIA = 1/71, 1.41%
Aneurysm location	CS-ICA = 89/126, 70.6%
	AcoA = 12/126, 9.5%
	ACA = 9/126, 7.14%
	MCA = 8/126, 6.35%
	PCA = 6/126, 4.76%
	Basilar artery = 2/126, 1.59%
Aneurysm dimension (113)	Mean = 2.69 mm (minimum = 2.1, maximum = 14)
Treatment modality	EV-TS = 27/62, 43.5%
	TC in same procedure = 12/62, 19.35%
	TS-TC = 5/62, 8%
	TS-EV = 4/62, 6.4%
	TS-wait and see = 4/62, 6.4%
	TC-TS = 4/62 - 6.4%
	EV-TC-Gamma-knife = 1/62, 1.6%
	Medical + TC = 1/62, 1.6%
	Medical + TS + EV = 1/62, 1.6%
	Medical + Wait and see = 1/62, 1.6%
	Medical + EV = 1/62, 1.6%
	TC + Medical = 1/62, 1.6%
Aneurysm treatment (86)	Coiling = 33/86, 38.37%
	Clipping = 19/86, 22.1%
	Balloon occlusion = 4/86, 4.65%
	Pipeline = 2/86, 2.33%
	Wait and see = 2/86, 2.33%
ICA aneurysm embedded	24/67, 35.8%
Adenoma treatment (101 pts)	Medical = 4/101, 3.9%
	Transcranial = 12/101, 11.9%
	Transsphenoidal = 84/101, 83.1%
	None = 1, 0.9%
Outcome (43 pts)	Good = 29/43, 60.41%
	Hemorrhage/rupture = 5/43, 11.62%
	Adenoma regrowth = 3/43, 6.98%
	Aneurysm rehabilitation = 3/43, 6.98%
	Worsening visual acuity = 1/43, 2.33%
	Diabetes insipidus = 1/43, 2.33%
	CSF leak = 1/43, 2.33%

Abbreviations: ACA, anterior cerebral artery; AcoA, anterior communicating artery; ACTH, adrenocorticotropic hormone; CSF, cerebrospinal fluid; CS-ICA, carotid sinus internal carotid artery; EV, endovascular; GH, growth hormone; MCA, medium cerebral artery; PCA, posterior cerebral artery; PRL, prolactin; TC, Transcranial; TIA, transitory ischemic attack; TS, transsphenoidal; TSH, thyroid-stimulating hormone.

most common complications reported were hemorrhage from aneurysm rupture in the postoperative phase or if the patient refused treatment (five cases, 11.62%), followed by incomplete regression of endocrinological symptoms or mass effect of the adenoma on parasellar structures (two cases, 4.65%). One patient died before the procedure, and one patient was not treated and was managed (at his preference) with wait-and-see management.

Two of these cases were reported in cases where only PAs were treated, two were evidenced after endovascular treatment with coiling and TS surgery, and one patient had rupture before starting any form of treatment. The only reported case of cerebrospinal fluid (CSF)-leak after procedures was reported in the case where the EV approach was performed after the TS approach.

During the follow-up, the presence of aneurysm grown in size, rehabilitated, or with the presence of bleeding was identified in 3/42 cases, 2 of which were in situations where only TS treatment for the PA had been opted for; in 1 case, only aneurysm rehabilitation occurred after the coiling procedure.

Representative Case

A 73-year-old woman with a history of arterial hypertension and amenorrhea since the age of 27 with no further investigation was admitted to our Hospital for headache and diplopia. Ophthalmological examination confirmed horizontal diplopia on the extreme lateral gaze. Examination of the fundus oculi ruled out papilledema. Apart from a slight left hemifacial hypoesthesia in the territory of V2, neurological examination was unremarkable. A gadolinium-enhanced brain MRI was performed and showed an intracranial lesion involving the left cavernous sinus and carotid internal

carotid artery. Gadolinium-enhanced T1 sequences documented a more parenchymatous area of the lesion that constituted the periphery of the neoformation. The inner portion of the lesion presented signs of flow in continuity with the cICA (►**Fig. 2A-D**). A digital subtraction angiography confirmed the presence of a giant pseudoaneurysm of the cICA (►**Fig. 2E-F**). Pituitary hormones blood levels were tested: prolactin (PRL) > 4,000 ng/mL, follicle-stimulating hormone 1.2 mIU/mL, luteinizing hormone 0.1 mIU/mL; thyroid-stimulating hormone, free triiodothyronine, free thyroxine, adrenocorticotropic hormone, cortisol, growth hormone, and insulin-like growth factor 1 were all within normal limits. An endoscopic endonasal three-dimensional-navigated paraseptal approach[8] was performed to collect samples of the lesion abutting in the sphenoethmoidal recess. We deemed any further resection pointless because the likelihood of a histological diagnosis of prolactinoma was extremely high and, to mitigate the risk of aneurysm rupture, increased by any decompressing surgical maneuvers around the aneurysm itself. Histological examination confirmed the diagnosis of a PRL-secreting adenoma with an accumulation of amyloid-like amorphous material, expression of estrogenic receptors, with a K_i-67 of 2%. We decided to treat the cICA aneurysm in case of any further neurological deterioration. Low-dose cabergoline (0.5 mg twice a week) treatment was started. At discharge, visual symptoms were stable and headache responded well to common analgesics. After 6 months of medical therapy, the patient was stable and serum PRL was 45 ng/mL. After 1 year following the same regimen, serum PRL normalized (16 ng/dL).

Approximately, 12 months later, the patient was referred to our institution for a sudden severe headache, associated with nausea and photophobia, and deficiency of abduction of the left eye. A head computerized tomography scan was performed and excluded a subarachnoid hemorrhage (SAH). A control brain MRI showed no changes in tumor size but an increase in the size of the cICA pseudoaneurysm. Endovascular occlusion of the left ICA was not viable because occlusion tests revealed an insufficient contralateral blood supply, so a flow diverter (FD) (Pipeline embolization device) was deployed along the left cICA after adequate loading doses of aspirin and clopidogrel. The patient tolerated the procedure and discontinued clopidogrel 3 months afterward. At discharge, visual symptoms remained stable.

Five months after, diplopia completely regressed, and we observed a reduction in the size of the pathological tissue at the edges of the aneurysm. The dose of cabergoline was reduced to 0.5 mg 1/2 cp twice a week. Control brain MRI at 1 year revealed almost complete regression of the prolactinoma **(►Fig. 3)**.

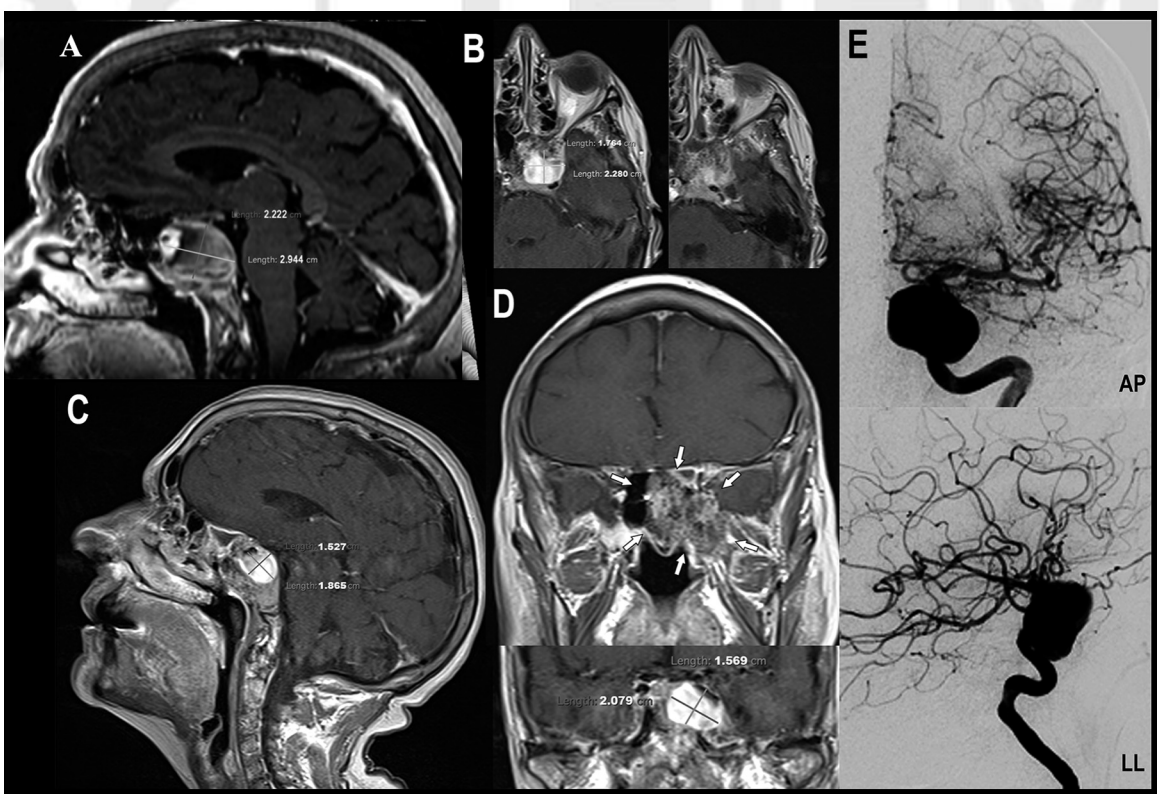

Fig. 2 **(A)** Head CT scan three-dimensional volume reconstruction showing the cICA pseudoaneurysm, the petrous internal carotid artery (pICA), the basilar artery (BA), and anterior cerebral artery (ACA). Note the fetal origin of the left PComA (#) and hypoplastic left A1 segment (*) and the extensive erosion of the middle cranial fossa caused by the giant prolactinoma (*white arrows*); **(B–D)** gadolinium enhanced brain MRI T1-weighted sequences in the three planes showing a voluminous neoformation packing the sphenoid sinus (*white arrows*) with an extension into the cavernous sinus, infiltration of the mesial temporal dura, middle cranial fossa, and initial involvement of the infratemporal fossa presenting an inner portion with flow signal in continuity with the ICA. **(E–F)** Digital subtraction angiography demonstrating a large pseudoaneurysm of the cICA.

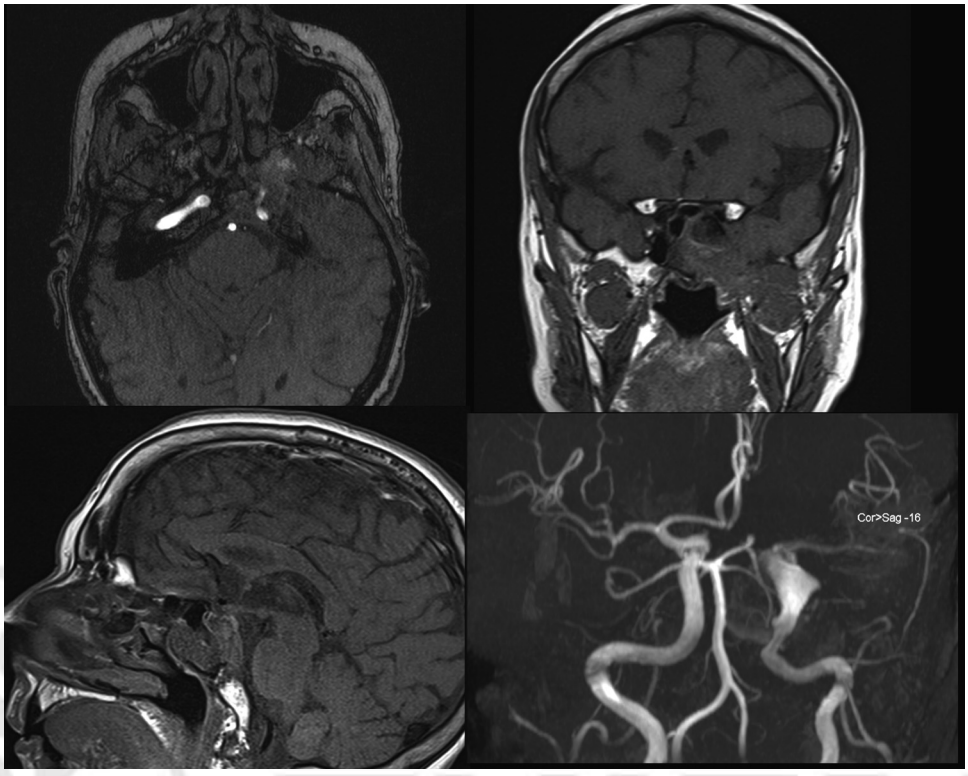

Fig. 3 Contrast-enhanced MRI performed 1 year after treatment documents extensive reduction of the mass with disappearance of compression on nerve structures. The aneurysm isolated from the circulation is maintained under observation at follow-up.

Discussion

PA with coexisting IA is not uncommon. The clinical symptoms are mainly caused by hormones secreted by PAs or by compression on the surrounding brain tissues and optic nerve, while for associated IA, the diagnosis is often incidental (51/94, 54.26%).[3] It seems that older age[9] and cavernous sinus invasion increase the rate of coexistence[6]; some studies[9] have also hypothesized that female sex may be a risk factor for AIs in patients with pituitary tumors, but the reported data do not suggest this difference.

There are many explanations regarding the causes of so high association between PAs and IAs. The mass effect and invasion of tumors change the hemodynamics and vascular structure, respectively, of the intracranial arteries.[1] As PA is a hormone-secreting tumor, the secreted hormones can induce aneurysm occurrence and growth.[3] Among the full-detailed reported cases, the most commonly detected endocrinopathies were hyperprolactinemia (58/96, 60.4%) and GH-secreting tumors (33/96, 34.4%). ICA aneurysms have been correlated to hyperprolactinemia in the so-called vasculogenic hyperprolactinemia,[10] much more than the presence of a true prolactinoma (reported in 17.7% of cases).

GH-secreting tumors could be considered an independent risk factor for IA formation.[2] A prolonged elevated GH level can induce arteriosclerosis, degenerative changes in the arterial wall, and collagen metabolism,[1] but considering that in the majority of cases (42.7%) PAs are inactive, this role in the pathogenesis of IAs, thus, remains to be fully elucidated.[11]

Another explanation for the high coexistence between PA and IA lies in the size and invasiveness of pituitary tumors. PAs occur the majority of times near the intracavernous segment of the ICA; as a tumor grows, it may compress or invade the cavernous sinus, potentially changing the hemodynamics of the ICA and inducing the formation of an IA.[2] Neoplastic infiltration over the cavernous sinus might strongly influence the incidence rate of IAs, especially in the case of pseudoaneurysms involving the cICA as in our presented case. IA with coexisting PA can be classified as nonadjacent, adjacent, intra-adenoma types. In nonadjacent types, the aneurysm is located apart from the adenoma such that they are not in direct contact and are separated by other tissues. These are the cases where IA were outside the cavernous sinus (37 cases, 29.37%); in adjacent types, PAs and aneurysms were in close or partial contact, and the capsule of PA was intact; in intra-adenoma types, the aneurysm body was partially or completely embedded in the PA[7] (reported in 24/150, 16%). The last situation refers especially to the giant PAs that represent approximately 6–10% of all pituitary tumors. This rare subtype of PA is characterized by high aggressiveness and massive extrasellar involvement. They are usually associated with high serum PRL levels (>1,000 ng/mL, so they are also defined as giant prolactinomas).

The method for treating a PA associated with a cerebral aneurysm is controversial, and the problem occurs especially in cases with cerebral aneurysms embedded in PAs or in cases where the IA is not radiologically identified. The best strategy has to be tailored to the patient to adopt the best medical treatment, avoid accidental rupture of IA during the surgical procedure, and plan treatment for the removal of the adenoma. The choice for the best procedure also has to take in account the need for long-term antiplatelet drugs before

the removal of the PA. The strategies outlined in the various reports are numerous and varied, of these the four main and most used are treatment of the IA using the endovascular procedure before transsphenoidal surgery for the PA, transsphenoidal surgery as the first treatment step, the use of a combined surgical treatment for both pathologies, and the choice to adopt a medical treatment for PA before the decision on surgical procedures. In our analysis, the most adopted strategy in the last years was to subject the patient first to endovascular treatment (41.9%).

Management strategies for the treatment of cerebral aneurysms have greatly expanded,[6] and endovascular therapy has almost replaced direct clipping in the last years, but the strategy treatment for this occurrence partially depends on the angiographic features of the aneurysm and ability to tolerate single or dual antiplatelet agents to prevent thromboembolic complications[6] in the presence of a PA. In general, the preferred treatment for aneurysms associated with a PA was the endovascular coiling and, more recently, the FD device. The endovascular procedure has been performed in the majority of cases (28/62, 45.52%) prior to tumor resection and has led to avoid long-term antiplatelet drugs.[12] In these procedures, antiplatelet therapy is generally not required and this intervention has been shown to provide aneurysm protection with low morbidity and facilitate transsphenoidal resection of the adenoma.[6] For these reason, the treatment of the coexistence pathology can be performed within the same procedure (in this study is reported in 19.35% of cases). In cases of direct clipping,[12] the surgical approach and the timing become problems (it was performed just in 11 cases reported). Performing both treatments with a transcranial approach is an alternative choice, but tumor resection via the endoscopic endonasal approach has more advantages than the transcranial approach in terms of preservation of endocrinological and ophthalmological function.[12]

Regarding the outcome of patients, the results of the various treatments reported were good, with functional recovery and complete exclusion of the aneurysm achieved in 74.42% of cases. The most frequently reported complication was hemorrhage from aneurysmal rupture occurring during TS surgery (in only one case) and during the time between the two treatments.

If ICA-cavernous aneurysms rarely rupture because the aneurysm is surrounded by hard tissues such as the dura and other bony structures,[7] the risk of rupture may increase if there is no longer the protection exerted by the presence of the tumor mass near or around the aneurysmal dome or in case of a rapid change in the intra- and parastellar pressure conditions. With this condition, the rupture could become dramatic once rupture and hemorrhage occur; the aneurysm may not be confined inside the tumor and may enter into the subarachnoid space to combine with SAH.

So, the most important risks could be apoplexy combined with SAH,[3] severe epistaxis (reported in one case), or the genesis of a carotid-cavernous fistula.

In our case, we considered the possibility of aneurysm rupture during endovascular internal trapping because the prolactinoma might have invaded and increased the fragility of the aneurysmal wall.[13] For these reasons, we suppose that in case of giant PAs, medical treatment of PA (in case of prolactinoma) must be performed at first. Objectives of the medical treatment include shrinkage of the lesion and normalization of serum PRL. First-line therapy is conducted with dopamine agonists, among which cabergoline is the most widely adopted. Some giant prolactinomas are responsive to a low dose of cabergoline; in this case, we observed normalization of serum PRL within 1 year. The average time needed to obtain a normalization of PRL levels is approximately 2 years. This variability is not associated with tumor size or baseline PRL serum level, and it is not correlated with tumor shrinkage. In this particular case, our therapeutic strategy was strongly influenced by the coexistent cICA aneurysm. The decision to use the minimum effective dose of cabergoline was determined by the need to avoid rapid shrinkage of the lesion, which could have induced aneurysm rupture.

After the occlusion test, in our case we preferred to select the use of FD as an approach for the IA. FD represents the mainstay of treatment of IAs not manageable with traditional coiling, as well as for the treatment of iatrogenic or posttraumatic pseudoaneurysms. FDs might be used in association with endosaccular coiling or to manage aneurysms already treated with coils. The use of FDs to treat cICA aneurysms embedded in pituitary macroadenoma has been already described[14] and recently reported in a similar case.[15]

Conclusion

IA are more frequently associated with PAs than with other tumor types, and the underlying reasons for this require continued exploration and study. Their diagnosis and management are extremely varied and poorly described in the literature. The importance of the preoperative knowledge of asymptomatic aneurysms coexisting with PA can avoid accidental rupture of aneurysm during surgical resection of PA and/ or may lead to the planning of a special medical and surgical strategy to deal with both pathologies simultaneously.[1] High degree of suspicion for associated aneurysm is needed, and if MRI shows some atypical features, DSA must be performed prior to contemplating surgical intervention to avoid iatrogenic aneurysmal rupture.[1] The presence of a large pseudoaneurysm of the cavernous segment of the ICA (cICA) completely embedded in a giant macroprolactinoma is exceedingly rare and needs a tailored treatment strategy.

Our multimodal approach with the first-line therapy of low-dose cabergoline to obtain PRL normalization with supposedly minimum risks of aneurysms rupture and subsequent endovascular treatment with FD upon neurological deterioration has not been described elsewhere to our knowledge.

Authors' Contributions
All authors have contributed equally to the draft of this manuscript.

Conflict of Interest
None declared.

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