Neurosurg Focus 32 (6):E2, 2012

Spontaneous and medically induced cerebrospinal fluid leakage in the setting of pituitary adenomas: review of the literature

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Object. Spontaneous and medically induced CSF leaks are uncommonly associated with pituitary adenomas. The aim of this study was to further characterize the clinical scenarios most closely associated with this phenomenon.

Methods. A review of the literature was conducted to identify all cases of nonsurgical CSF leaks associated with pituitary adenomas. The authors aimed to identify associated risk factors and management strategies used to treat these tumors and repair the CSF leak site.

Results. Fifty-two patients with spontaneous or medically induced CSF leaks in the setting of a pituitary adenoma were identified from 29 articles published from 1980 through 2011. In 38 patients (73%), CSF rhinorrhea developed following initiation of medical therapy, whereas spontaneous CSF leakage developed as the presenting symptom in 14 patients (27%). The patients' mean age was 42.8 years (range 23–68 years). There were 35 males and 17 females. Forty-two patients (81%) had a prolactinoma, with the remaining patients having the following tumors: nonfunctioning pituitary adenoma (6 patients), growth hormone–secreting adenoma (2 patients), mammosomatotroph cell adenoma (1 patient), and ACTH-secreting adenoma (1 patient). Infrasellar tumor invasion into the paranasal sinuses was specifically reported in 56% of patients. The medical agents associated with CSF leakage were dopamine agonists (97%) and somatostatin analogs (3%). The average time from initialization of medical treatment to onset of rhinorrhea was 3.3 months (range 3 days–17 months). Nonsurgical management was successful in 4 patients, including 1 who had successful resolution with a temporary lumbar drain. Forty-six patients (88%) underwent surgical intervention to treat the CSF leak and/or resect the tumor. In 2 patients, surgery was not performed due to medical contraindications or patient preference.

Conclusions. Nonsurgical development of CSF rhinorrhea may occur in the setting of pituitary adenomas, especially following favorable response of invasive prolactinomas to initiation of dopamine agonist therapy. Additional cases have been reported as the presenting symptom of a pituitary adenoma and are likely to be related to decreased tumor volume due to intrinsic infarction or hemorrhage, ongoing invasion, and/or increases in intracranial pressure. Surgical repair, preferentially via a transsphenoidal approach, is the recommended initial treatment for definitive repair of the CSF leak and achievement of maximal tumor resection.
(http://thejns.org/doi/abs/10.3171/2012.4.FOCUS1268)

Key Words • **pituitary adenoma** • **cerebrospinal fluid leak** • **rhinorrhea** • **transsphenoidal** • **prolactinoma** • **dopamine agonist**

Spontaneous CSF leakage has been reported extensively in the literature. The etiologies of spontaneous CSF leaks are numerous, and leaks have been associated with various factors, including obesity, trauma, and multiparity.[22,29] There have also been several reports of development of CSF rhinorrhea following the initiation of medical treatment for pituitary adenomas. The classical description of this phenomenon has been in the setting of DA therapy for prolactin-secreting tumors;[1] however, patterns in the patient and tumor characteristics, types of medications resulting in the development of CSF rhinorrhea, and successful treatment paradigms used to repair the leakage and treat the tumor have to date never been characterized. We aimed to review the literature with regard to CSF leakage associated with nonsurgical treatment of pituitary adenomas in order to further understand the clinical and pathological situations in which this entity typically arises. Additionally, we discuss the most suitable management strategies employed to treat the CSF leak and concurrently address the tumor.

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; DA = dopamine agonist; GH = growth hormone.

Methods

We performed a PubMed literature review to identify any case reports or clinical series of patients developing CSF leakage as a presenting symptom or in the setting of nonsurgical treatment of pituitary adenomas. These in-

cluded any spontaneous, medically induced, or radiotherapy-induced CSF leaks. Any patients developing postsurgical iatrogenic CSF leaks or CSF leaks not associated with any underlying sellar pathology were excluded. The following MeSH search terms were used: pituitary neoplasms, prolactinoma, dopamine agonists, cerebrospinal fluid leak, cerebrospinal fluid rhinorrhea. In addition, the PubMed search terms pituitary tumor, pituitary adenoma, spontaneous, rhinorrhea, and medical therapy were all searched individually and in combination to identify any previous articles matching these inclusion criteria. In addition, the citation lists of any articles matching the inclusion criteria were also searched to provide the most comprehensive search possible for any patients reported in the literature with spontaneous CSF leaks in the setting of a pituitary adenoma. Any studies describing patients with nonadenomatous sellar lesions were excluded from the analysis. Patient and tumor characteristics, including age, sex, symptoms, and tumor pathological subtype, location, pattern of extension, and size were recorded. The type and duration of treatment prior to onset of spontaneous rhinorrhea was also recorded. Finally, the treatment(s) used to treat both the CSF leak and the underlying tumor were recorded. Standardization of prolactin concentrations was performed by converting prolactin concentrations expressed in mIU/L to to μg/L by dividing by 21.2.[7] All values were converted and reported in ng/ml. The Student t-test was used for statistical analysis, with a p value < 0.01 being considered significant.

Results

Patient and Tumor Characteristics

Twenty-nine articles were identified from between the years 1980 and 2011, describing 52 patients with spontaneous or medically induced CSF leaks in the setting of a pituitary adenoma. A majority of these cases (38 patients, 73%) occurred following initiation of medical therapy, whereas the CSF leak developed as the presenting symptom of a pituitary adenoma in the remaining 14 patients (27%). The mean age was 42.8 years (range 23–68 years). There were 35 men and 17 women. Forty-two patients (81%) had a prolactinoma. The remaining 10 patients had the following tumor subtypes: nonfunctioning pituitary adenoma (6 patients, 11%), mammosomatotroph cell adenoma (1 patient, 2%), GH-secreting adenoma (2 patients, 4%), and ACTH-secreting adenoma (1 patient, 2%). Thirty-eight patients (73%) had a previously diagnosed pituitary tumor and developed CSF rhinorrhea following initiation of medical treatment. Thirty-six of the 38 patients who developed CSF leaks following initiation of medical therapy had prolactinomas, whereas patients who developed spontaneous (noniatrogenic) CSF leaks had a variety of pituitary adenomas (6 prolactinomas, 6 nonfunctioning pituitary adenomas, 1 GH-secreting adenoma, and 1 ACTH-secreting adenoma). The medical agents most closely associated with CSF leakage were DA medications in 37 patients (97%) and a somatostatin analog (lanreotide) in 1 patient (3%). Of the patients who developed CSF rhinorrhea while taking DA medications, 24 were taking bromocriptine and 13 were taking cabergoline. The average time from initiation of medical therapy to onset of rhinorrhea was 3.3 months (range 3 days–17 months). Seven patients (14%) presented with meningitis in conjunction with CSF rhinorrhea. Tumor size was reported in 9 of 52 cases (17%), with a mean maximum tumor diameter of 3.6 cm. Forty-nine of 52 patients (94%) were reported to have tumors with neuroimaging evidence of extrasellar tumor invasion. Specific invasion into the sphenoid sinus, ethmoid sinus, or clivus was documented in 29 patients (56%). In 47 patients, a discrete skull base defect could be identified on imaging studies, most frequently with thin-slice CT images in the coronal plane. The average initial prolactin level in patients with spontaneous CSF leakage was 9169 ng/ml, compared with 4917 ng/ml in those with medically induced leakage. Due to a small number of values from the spontaneous leakage group, however, this difference was not statistically significant. Interestingly, no cases of spontaneous CSF leakage following radiation therapy or radiosurgery for pituitary adenomas were identified. One case of a spontaneous CSF leak developing 4 months following Gamma Knife surgery for a metastatic renal cell carcinoma to the skull base was identified, but this case was excluded from the present study.[22] The patient underwent successful CSF leak repair via an endoscopic sinus approach.

Treatment Characteristics in Patients With CSF Leaks and Underlying Pituitary Adenomas

In 4 patients, nonoperative management was successfully employed. Of these, 1 patient was successfully treated with temporary lumbar drainage,[37] and the other 3 with bed rest or withdrawal of medications. Forty-six patients (88%) ultimately underwent surgical intervention as the definitive treatment for the CSF leak. Definitive procedures for the CSF leaks included: transsphenoidal surgery (32 patients), craniotomy (5 patients), lumboperitoneal shunt (2 patients), and unknown approach (7 patients). In 2 patients, surgery was not performed, due to medical contraindications or patient preference, resulting in ongoing CSF rhinorrhea.

In nearly 90% of cases reported, operative repair of the CSF fistula was eventually required. In 21 of 38 cases of DA-induced leak, there was no documented recurrence after the initial treatment. In these cases, the initial treatment strategies were as follows: transsphenoidal surgery (in 16 cases), transsphenoidal surgery combined with lumbar puncture (1 case), frontal craniotomy (1 case), unspecified surgery (1 case), and treatment withdrawal or bed rest (2 cases).

Recurrence was documented in the remaining 17 cases, and a combination of treatment approaches was employed. In 8 cases, temporary cessation of rhinorrhea occurred with treatment reduction or withdrawal, but the rhinorrhea recurred within days or weeks of restarting medical treatment. Of these cases, definite resolution of rhinorrhea was achieved via transsphenoidal surgery in 5 cases[1,15–17,27] and a combination of craniotomy and transbasal surgery in the sixth.[16] In the seventh and eighth cases, surgical repair was not performed because of pa-

tient refusal or contraindications to surgery, and rhinorrhea continued to occur.[17,19]

In 7 cases, rhinorrhea recurred despite initial surgical treatment. Of these cases, rhinorrhea was ultimately resolved with a transsphenoidal approach in 3 patients, a transfrontal approach in 1 patient, lumboperitoneal shunt placement in 1 patient, and craniotomy in 1 patient, and it subsided without treatment in 1 patient.[10,13,17,24,25,28]

In 2 cases, the rhinorrhea initially subsided with bed rest. Of these cases, the first recurred 3 three years later, even though treatment was uneventfully reinstated a month after the initial rhinorrhea episode ceased, and the recurrence subsided again with bed rest. The second was promptly resolved with transsphenoidal surgery.[2]

Finally, CSF rhinorrhea occurred spontaneously as the presenting symptom of pituitary adenoma in 14 cases, of which 7 resolved with surgical repair via a transsphenoidal approach, and 2 resolved with unknown operations.[3,5,8,18,20,21,25,26] In 1 patient, a temporary lumbar drain was successfully used as the only definitive treatment.[37] In the remaining 4 cases, initial management with frontal craniotomies[12,23] or transsphenoidal surgery failed to resolve the leak.[18,33] One of these patients was treated with bed rest,[18] and the others were treated definitively with first-time or repeat transsphenoidal surgery.[12,33]

Discussion

A comprehensive search of the published literature revealed 29 articles with 52 cases of spontaneous and medically induced CSF leaks associated with pituitary adenomas. Although this phenomenon has been described anecdotally or as single case reports in the past, the purpose of this review was to provide an improved characterization of the clinical and pathological settings in which this phenomenon occurs. The majority of cases of nonsurgical CSF leaks, the leaks occur in the setting of invasive pituitary tumors (typically prolactinomas) following initiation of standard medical management (Table 1). In addition, some patients may present with spontaneous CSF leaks as the presenting symptom of a newly diagnosed pituitary tumor (Table 2). Aside from prolactinomas, other (typically invasive) tumors that may result in nonsurgical CSF rhinorrhea include nonfunctioning macroadenomas, GH-secreting adenomas, and ACTH-secreting adenomas.

Based on the observations made and an understanding of the anatomy and pathophysiology of these lesions and the sellar space, the following mechanism has been proposed to explain the development of CSF rhinorrhea in the setting of pituitary adenomas. In larger and more invasive pituitary adenomas, tumor expansion into the surrounding dural and bony structures is commonly observed. In addition, various functional subtypes of pituitary adenomas are known to preferentially invade various regions of the parasellar spaces. For instance, GH-secreting adenomas and prolactinomas are known to frequently invade the sellar floor and infrasellar space (sphenoid sinus and clivus), whereas nonfunctioning macroadenomas have a tendency to invade the suprasellar space via bowing or invasion of the diaphragma sellae.[40] In cases where the arachnoid and/or brain parenchyma have also been violated, the potential for developing a CSF fistula has been established. These communications have little clinical significance as long as the tumor occludes the opening and serves as a "plug," thus preventing the escape of CSF. Any significant reduction in tumor size, however, can provide a conduit for the escape of CSF, typically resulting in CSF rhinorrhea.[24] Rapid tumor shrinkage is frequently associated with initiation of dopamine agonist therapy for prolactin-secreting tumors.[6] In cases of spontaneous (noniatrogenic) rhinorrhea, the cause of tumor shrinkage is not well understood, but it is likely related to intratumoral infarction and/or hemorrhage with subsequent reduction in tumor volume,[23] ongoing invasion through the arachnoid or bony skull base, and/or increases in intracranial pressure resulting in a CSF fistula.[32] The development of meningitis should be anticipated and addressed in advance in cases of nonsurgical CSF leak.

Surgical repair is the recommended initial treatment for definitive management of DA-induced rhinorrhea, and was ultimately required in nearly 90% of patients reviewed in the literature. Our preferred operation in the majority of cases is the endoscopic endonasal approach, although open surgical repair via a craniotomy may be warranted in a minority of cases. Depending on the tumor subtype and growth patterns, tumor resection may be concurrently achieved prior to reconstruction of the skull base in these instances, although complete tumor resection may be limited in many of these cases as these tumors are by definition invasive into bone and dura. Following tumor debulking, standard techniques for repairing the skull base can be used. For smaller "weeping" CSF leaks, dural substitutes and/or fibrin glue may be used to achieve a successful repair.[11] For larger CSF leaks, the use of autologous fat or fascia is recommended, with or without a sellar floor buttress.[9] For extremely large or refractory CSF leaks, rotation of a pedicled nasoseptal flap may be required to definitively address the CSF fistula.[35] If the location of CSF leakage is not obvious, the use of intrathecal fluorescein may also be attempted to achieve a more targeted repair.

Although reduction or discontinuation of medical therapy was attempted as the primary treatment in 24% of cases, we do not recommend this strategy in patients who are candidates for surgical repair. The half-life of cabergoline is 63–69 hours and that of bromocriptine is 12–14 hours, suggesting that no immediate effects from medication discontinuation will be achieved via this strategy and that patients may be at risk for the development of meningitis. Furthermore, the effects on tumor volume and the CSF fistula may be irreversible in the short term, often mandating eventual surgical repair of the CSF leak. We recommend surgical repair of spontaneous or medically induced CSF leaks in the setting of pituitary adenomas, along with safe maximal tumor resection, in patients who are surgical candidates. In patients who are not surgical candidates, a more conservative approach would include temporary cessation of medical therapy and temporary insertion of a lumbar drain, but this strategy is not recommended as a first-line therapy unless deemed medically necessary.

TABLE 1: Summary of cases of medically induced CSF leak*

Authors & Year	Age (yrs), Sex	Tumor	PRL (ng/ml)	Medical Tx	Meningitis	Rhino After Tx	Site of Defect	1st Tx	Recurrence	2nd Tx
Afshar & Thomas, 1982	28, F	P	283	Br, 5 mg/day	−	1 wk	sella, sphenoid	TS	no	
Baskin & Wilson, 1982	27, F	P	1,920	Br, 2.5 mg 2×/day	−	2 mos	sphenoid	w/drew	yes	op
Landolt, 1982	39, M	P	23,000	Br, 15 mg/day	−	5 mos	sella, sphenoid	TS	no	
	60, M	P	3,120	Br, 15 mg/day	−	3 mos	sella, sphenoid, clivus	op	no	
	33, M	P	24,500	Br	+	4 mos	sella, ethmoid, sphenoid, clivus	w/drew	yes, upon restarting Br	bifrontal craniotomy & transbasal op
Wilson et al., 1983	32, F	P	>200	Br, 7.5 mg/day	−	3 wks	sella	transfrontal	yes, 2 wks	TS
	50, M	P	454	Br, 7.5 mg/day	−	6 wks	sella, sphenoid	TS	yes, 6 wks	transfrontal
Holness et al., 1984	38, M	P	3,535	Br, 15 mg/day	−	NR	sella	frontal craniotomy	yes, 6 wks	craniotomy
Kok et al., 1985	47, M	P	636	Br, 15 mg/day	−	8 mos	sella	w/drew	yes, 3 days after restarting Br	TS
Hildebrandt et al., 1989	43, F	P	2,200	Br, 50 mg long-acting	−	2 wks	sella	frontobasal craniotomy	no	
	28, M	P	6,650	Br, 2.5 mg 3×/day	−	6 mos	sella, sphenoid	TS	no	
Bronstein et al., 1989	52, F	P	1,110	Br, 5 mg/day	−	16 mos	sella	TS	NR	
	33, M	P	1,700	Br, 10 mg/day	+	17 mos	sella, sphenoid	TS	NR	
Eljamel et al., 1992	52, F	P	20,660	Br, 5 mg 2×/day	−	4 wks	sphenoid	transethmoidal	yes, 2 wks	LP shunt
Barlas et al., 1994	27, F	P	9,500	Br, 10 mg/day	−	8 days	sella	bed rest	yes, 3 yrs	bed rest
	54, M	P	3,100	Br, 15 mg/day	+	1 yr	sella	w/drew	no	
	46, F	P	310	Br, 5 mg/day	+	15 days	sella	bed rest	yes, 3 days	TS
Russell et al., 1994	34, M	P	11,075	Br, 2.5 mg 3×/day	−	3 wks	sella	TS	yes, 40 days	TS
Leong et al., 2000	34, M	P	23,584	Br, 1.25 mg/day	−	1 wk	sphenoid	w/drew	yes, days of restarting Br	op
	52, F	P	18,867	Br, 5 mg 2×/day	−	8 wks	ethmoid	op	yes	LP shunt
	39, M	P	4,481	Br, 5 mg/day	−	6 wks	sphenoid	reduced Br to 2.5 mg/day	yes	op
	47, F	P	18,867	Br, 5 mg 2×/day	−	4 mos	sella	w/drew	yes, 1 yr of restarting Ca	w/drew
	24, M	P	23,584	Ca, 0.5 mg 2×/wk	−	4 wks	sella, sphenoid	intradural repair	yes, intermittently for 6 wks then stopped	
Hewage et al., 2000	42, M	P	2,783	Br, 5 mg 2×/day	−	6 days	sella, sphenoid	TS	no	
Cappabianca et al., 2001	53, M	P	9,715	Ca, 0.5 mg 2×/wk	−	4 mos	sella	TS	no	
	42, M	P	40,000	Ca, 0.5 mg 3×/wk	−	4 mos	sphenoid	TS	no	
	39, M	P	2,000	Ca, 0.5 mg 3×/wk	−	2 mos	sella	TS	no	

(continued)

TABLE 1: Summary of cases of medically induced CSF leak* *(continued)*

Authors & Year	Age (yrs), Sex	Tumor	PRL (ng/ml)	Medical Tx	Meningitis	Rhino After Tx	Site of Defect	1st Tx	Recurrence	2nd Tx
Nadesapillai et al., 2004	50, M	P	2,028	Br, 2.5 mg/day	−	3 days	sella	TS	NR	
Netea-Maier et al., 2006	57, M	P	18,396	Ca, 0.5 mg 3×/wk	−	10 days	NR	bed rest	no	
	65, M	P	13,207	Ca 0.5 mg/day	−	8 days	sphenoid	TS	no	
	48, M	P	1,367	Ca, 0.5 mg 2×/wk	−	10 days	sella, sphenoid	decreased Ca to 0.125 2×/wk	yes	refused op
de Lacy et al., 2009	50, F	P	18,867	Ca, 0.5 mg 2×/wk	−	2 mos	sella	TS	NR	
	42, M	P	3,702	Ca, 0.5 mg 2×/wk	−	10 mos	sella	TS	NR	
	48, M	P	6,603	Ca, 0.5 mg 2×/wk	−	10 wks	sella	TS	NR	
	64, M	P	4,716	Ca, 0.5 mg 2×/wk	−	10 wks	sella	TS	NR	
Chapin et al., 2010	58, F	P	12,190	Ca, 0.5 mg 2×/wk	−	1 wk	sella, sphenoid, ethmoid	TS	no	
Thakur et al., 2011	68, M	M	352	Ca	−	NR	sella	w/drew	yes, days of restarting Ca	TS
	36, M	GH	NR	lanreotide	−	NR	sella	TS, lumbar drain	no, but pt had meningitis	craniotomy

* A = ACTH-secreting adenoma; Br = bromocriptine; C = chromophobe adenoma; Ca = cabergoline; GH = GH-secreting adenoma; LP = lumboperitoneal; M = mammosomatotroph cell adenoma; NR = not reported; P = prolactinoma; PRL = Prolactin Level; pt = patient; Rhino = Rhinorrhea; TS = transsphenoidal surgery; Tx = Treatment; w/drew = withdrew DA treatment; − = absent; + = present.

TABLE 2: Summary of cases of spontaneous CSF leakage*

Authors & Year	Age (yrs), Sex	Tumor	PRL (ng/ml)	Medical Tx	Meningitis	Rhino After Tx	Site of Defect	1st Tx	Recurrence	2nd Tx
Nutkiewicz et al., 1980	45, F	NFPA	WNL	NR	–	presentation	sella, sphenoid	op	no	
Cole & Keene, 1980	41, M	P	>1200	NR	–	presentation	sella, sphenoid	TS	no	
	28, F	NFPA	63	NR	–	presentation	sella, sphenoid	frontal craniotomy	yes, 3 wks	TS
	38, M	NFPA	WNL	NR	+	presentation	sella, sphenoid	frontal craniotomy	yes, 4 mos	TS
Rothrock et al., 1982	24, M	NFPA	NR	NR	+	presentation	sella, sphenoid	TS	yes, 8 days	TS
Bilo et al., 1984	42, M	P	6200	NR	+	presentation	sella, sphenoid	TS	no	
Obana et al., 1990	63, M	P	3300	Br	–	presentation	sphenoid	op, lumbar drain	NR	
	36, F	P	2290	Br, 2.5 mg 2×/day	–	presentation	sphenoid, ethmoid	TS	NR	
Spaziante & de Divitiis, 1991	28, M	NFPA	compl hypopit	NR	–	presentation	sella	TS	no	
Carroll et al., 1991	23, M	ACTH	NR	NR	–	presentation	sella, sphenoid	TS	no	
Hanel et al., 2001	26, F	P	20	Br, 7.5 mg/day	–	presentation	sella, sphenoid	TS	yes, 2 mos	bed rest
Telera et al., 2007	48, F	NFPA	NR	NR	–	11 yrs postop	sella	lumbar drain	no	
	36, M	P	2000	NR	–	presentation	sella	TS & lumbar drain	no	
Makin et al., 2011	68, M	GH	NR	octreotide	–	presentation	sella, sphenoid	TS	NR	

* compl hypopit = complete hypopituitarism; Medical Tx = subsequent medical treatment; NFPA = nonfunctioning pituitary adenoma; WNL = within normal limits.

Although the current review provides improved characterization of factors associated with CSF fistulas associated with nonsurgical treatment of pituitary tumors, there are inherent limitations of this particular study design. There is a certain degree of publication bias associated with amassing data from numerous case reports and small clinical series to describe a relatively uncommon phenomenon. In an attempt to further understand the clinical scenarios in which this type of CSF leak most commonly occurs, however, we aimed to identify which tumor subtypes and particular treatments posed the greatest risk for the development of CSF rhinorrhea.

Conclusions

Nonsurgical development of CSF rhinorrhea may occur in the setting of pituitary adenomas, especially following initiation of medical therapy. The most common situation occurs in the setting of invasive prolactinomas that respond favorably to dopamine agonist therapy. Additional cases of spontaneous CSF leakage have been reported as the presenting symptom of a pituitary adenoma and are likely to be related to decreased tumor volume due to intrinsic infarction or hemorrhage, ongoing tumor invasion, and/or increases in intracranial pressure. In almost all cases, surgical treatment is warranted to repair the CSF leak and achieve maximal tumor resection.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lam. Acquisition of data: Mehta. Analysis and interpretation of data: Mehta. Drafting the article: Mehta. Critically revising the article: Zada. Reviewed submitted version of manuscript: Zada, Lam. Approved the final version of the manuscript on behalf of all authors: Zada. Study supervision: Lam.

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Manuscript submitted February 16, 2012.
Accepted April 4, 2012.
Please include this information when citing this paper: DOI: 10.3171/2012.4.FOCUS1268.

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