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Coagulative necrotic pituitary adenoma apoplexy: A retrospective study of 21 cases from a large pituitary center in China

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Abstract

Purpose Coagulative necrotic pituitary apoplexy (CNPA) is a clinical entity with unique intraoperative and histopathological manifestations. We aimed to improve the knowledge of this rare disease through the largest case series published to date.

Methods A retrospective review of 21 CNPA patients was performed from among 5095 patients who underwent surgery for pituitary adenomas at a single institution between January 2009 and June 2017. The demographic, clinical, endocrine, neuroimaging, intraoperative, and histopathological findings, management and prognosis were summarized.

Results Headache was the most common symptom that was observed in 21 patients, followed by visual disturbances (17/21, 81.0%), nausea and vomiting (16/21, 76.2%), electrolyte disturbance (13/21, 61.9%), and oculomotor palsies (10/21, 47.6%). Hypopituitarism with at least one anterior pituitary deficiency, especially panhypopituitarism (10/21, 47.6%), was present in 81.0% of patients. Most patients (81.0%) showed typical MRI appearances. All 21 patients underwent transsphenoidal surgery (TSS), and 16 patients had total tumor resection demonstrated by postoperative MRI. Cottage cheese-like necrosis was observed in 16 patients (76.2%) intraoperatively. Histopathology showed large areas of pink, acellular, coagulative necrotic areas in the central zone, and a pseudocapsule in the border zone. After follow-up for 4.3 ± 2.3 years, only 28.6% of patients still suffered from corticotropic deficiency, and 9.5% of patients had gonadotropic deficiency. These patients were administered the appropriate corresponding hormones for life.

Conclusions CNPA can be correctly diagnosed preoperatively by typical clinical and MRI characteristics. Early surgery combined with hyperbaric oxygen therapy early postoperatively usually yields satisfactory endocrine and neuro-ophthalmic outcomes.

Keywords Pituitary apoplexy · Pituitary adenoma · Infarction · Necrosis · Transsphenoidal surgery

Introduction

Pituitary apoplexy (PA) is an uncommon clinical syndrome mostly caused by hemorrhage and/or infarction of a pituitary adenoma. PA occurs in 2–12% of patients with all types of pituitary adenomas [1–4]. Brougham et al. [5] first reported the clinical entity of PA in 1950, and there have been many case series describing the spectrum of PA in the literature since then. However, coagulative necrotic PA (CNPA), which is generally considered as a rare subtype of infarctive PA, is a clinical entity with unique intraoperative and histopathological manifestations, remarkably different from the classical PA. It has been rarely reported in previous studies, and the concept of coagulative necrotic PA has not been clearly defined by any expert consensus statement. Most of our understandings of CNPA is mainly derived from some

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isolated case reports [6–9]. To the best of our knowledge, we present the largest series summarizing the clinical features, endocrine manifestations, neuroimaging manifestations, intraoperative findings, histopathological characteristics, management and prognosis of 21 patients with CNPA from Peking Union Medical College Hospital (PUMCH), which is one of the largest pituitary centers in China. We hope to improve the knowledge of this rare type of PA through our study.

Materials and methods

Patient population

We retrospectively analyzed 21 patients who were diagnosed with pituitary adenoma apoplexy with coagulative necrosis confirmed by histopathology at PUMCH between January 2009 and June 2017. During this period, 5095 patients underwent surgery for pituitary adenomas, and 437 patients underwent surgery for PA in our center. The inclusion criteria were as follows: (1) patients with isolated infarctive apoplexy due to a pituitary adenoma, excluding those with hemorrhagic apoplexy or a mixture of hemorrhagic/ischemic apoplexy, and (2) coagulative necrosis of a pituitary adenoma confirmed by intraoperative findings and postoperative histopathology. This study was approved by the Ethics Committee of PUMCH, and written informed consent was obtained from all patients.

Perioperative assessment

All the patients underwent endocrinological, neuroradiological and ophthalmologic evaluations preoperatively, postoperatively and during long-term follow-up. Endocrinological assessments mainly included measurement of plasma cortisol (F), adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone (P), testosterone (T), estradiol (E2), prolactin (PRL), growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels, which indicated pituitary function. The MRI scans were performed on a 1.5- or a 3.0-Tesla system (GE, Co., Fairfield, Connecticut, USA). Sagittal, coronal and axial MR images, including T1-weighted imaging (T1-WI) and T2-weighted imaging (T2-WI), were evaluated for all patients. T1-weighted sequences were performed after intravenous injection of gadopentetate dimeglumine (Gd-DTPA) at a dose of 0.1 mmol/kg. Tumor size was classified as a microadenoma (< 1 cm), macroadenoma (1–3 cm) or giant pituitary adenoma (> 3 cm). The Knosp classification system was used to evaluate cavernous sinus invasion of the pituitary tumor on preoperative MRI. Ophthalmologic evaluations included assessments of binocular visual acuity, visual field and cranial nerve functions, including eye movements, the size and shape of the pupils, and the presence of ptosis. Sex, age, clinical manifestations, the interval from initial onset to progression, subtype of pituitary adenoma, precipitating factors and PA score were also recorded for each patient before surgery [10, 11]. Based on the interval from initial onset to progression, PA patients can be classified into acute onset (< 7 days), subacute onset (7–14 days) and chronic onset (> 14 days) [2].

Treatments

All 21 patients underwent transsphenoidal surgery (TSS) performed by experienced neurosurgeons via a similar method. The surgical specimens were histopathologically examined via hematoxylin-eosin (HE) staining and immunohistochemical (IHC) staining. Routine antibiotic prophylaxis was performed intraoperatively and postoperatively. Hydrocortisone acetate tablets (20 mg, tid) were administered for at least 3 days before surgery as a component of our routine preparation for TSS. Preoperative hypopituitarism was determined by endocrine measurements, and empirical hormone replacement of glucocorticoids was performed for all patients with signs of PA before surgery. Hydrocortisone (100 mg) was administered intravenously every 12 h for patients with adrenocorticotropic hormone deficiency, and levothyroxine sodium tablets (100 μg) were administered every day preoperatively for patients with hypothyroidism. Hyperbaric oxygen therapy (HBOT) was performed for patients without contraindications such as chest pathology, inner ear disease, claustrophobia or pregnancy. Patients received 100% oxygen at 2.0 atmosphere absolute (ATA) daily for 1–2 h for 2 weeks.

Follow-up

After surgery, all patients were followed up at 3 months, 6 months, 1 year and long term, which was the latest one especially for this study. The follow-up evaluations included assessment of treatment outcomes, endocrinological findings, sellar MRI findings and ophthalmologic examinations.

Results

Demographics

Among the 21 patients, 15 (71.4%) were male, and 6 (28.6%) were female. The age at the time of surgery ranged from 27 to 77 years, with a mean of 50.7 ± 15.0 years. The mean interval from initial onset to progression was

40.7 ± 64.9 days (range 1–240 days). Five patients (23.8%) had an acute onset, 8 patients (38.1%) had a subacute onset, and 8 patients (38.1%) had a chronic onset. Six patients (28.6%) had a PA score of 0–3, and 15 patients (71.4%) had a PA score ≥ 4. The subtypes of pituitary adenoma mainly included nonfunctioning pituitary adenomas (18/21, 85.7%), prolactinomas (2/21, 9.5%) and growth hormone-secreting pituitary adenomas (1/21, 4.8%), as determined by postoperative immunohistopathology. Precipitating factors were found in 85.7% (18/21) of all patients including hypertension (10/21, 47.6%), coagulation disorders (9/21, 42.9%), diabetes mellitus (4/21, 19.0%), initiation of dopamine receptor agonists (1/21, 4.8%) and other factors. The average follow-up duration was 4.3 ± 2.3 years (range 1.2–9.0 years) (Table 1).

Clinical manifestations

Headache was the most common symptom and was observed in every patient (21 patients). Among them, 4 patients presented with a sudden, severe headache that frequently involved the whole cranium or retro-orbital area, and the other 17 patients presented with intermittent episodes of mild to moderate headache, lacking specific patterns and degrees. Seventeen patients (81.0%) complained of visual disturbances including decreased visual acuity (17 patients), visual field impairment (17 patients), absence of a pupillary light reflex (PLR, 5 patients) and diplopia (3 patients). Among them, 3 patients had the most severe visual acuity impairments with no light perception (NLP); 5 patients had the most severe visual field impairments with monocular (3 patients) or binocular (2 patients) blindness. Nausea and vomiting were observed in 16 patients (76.2%). Oculomotor palsies were present in 10 patients (47.6%; Fig. 1). Among them, the oculomotor nerve (the third cranial nerve) palsies were the most frequent (10 patients) and were characterized by ptosis (10 patients), limited eye movements in adduction (9 patients), and mydriasis (4 patients) (Fig. 1). Abducens nerve (sixth cranial nerve) palsies were observed in 8 patients and were characterized by limited eye movements in abduction. Combined palsies of cranial nerves III, IV and VI were observed in 4 patients who presented with ophthalmoplegia and eyeball fixation. In addition, 1 patient had dysfunction of the ocular branch of the left trigeminal nerve, which was characterized by prefrontal sensory disturbances and the absence of a corneal reflex. Other clinical presentations also included unconsciousness (3 patients), fever (3 patients) and acute cerebral stroke (1 patients).

Endocrine dysfunction was observed in all patients in our study. Seventeen patients (81.0%, 17/21) presented anterior pituitary hypofunction. Among them, panhypopituitarism was most frequently found (10 patients, 47.6%), followed by isolated corticotropic deficiency (2 patients, 9.5%), isolated gonadotropic deficiency (2 patients, 9.5%), combined thyrotropic and gonadotropic deficiency (2 patients, 9.5%), and combined corticotropic and gonadotropic deficiency (1 patient, 4.8%). Furthermore, 5 patients (23.8%) also had hyperprolactinemia to various degrees. Symptoms consistent with pituitary endocrine dysfunction mainly included electrolyte disturbances (13 patients), menstrual disturbances/amenorrhea and galactorrhea (4 patients), fatigue (3 patients), and hyposexuality (2 patients). Thirteen patients (61.9%) complained of electrolyte disturbances including hyponatremia (12 patients), hypochloremia (7 patients), hypokalemia (4 patients) and hypocalcemia (3 patients).

MRI characteristics

Thirteen patients (61.9%) had macroadenomas, and 8 (38.1%) had giant pituitary adenomas. Two patients were classified as Knosp grade I, 9 as Knosp grade II, 4 as Knosp grade III, and 6 as Knosp grade IV. All 21 patients showed isointensity to hyperintensity on T1WI (Fig. 2), of which 17 mainly showed hyperintensity, and 4 mainly showed isointensity. Seventeen patients (81.0%) showed isointensity to hyperintensity on T2WI (Fig. 2); 3 patients showed T2 signal isointensity or hyperintensity; and the other 1 patient showed heterointensity (a mixture of hypointensity, isointensity and hyperintensity) on T2WI. After gadolinium administration, 15 patients (71.4%) showed rim enhancement on T1WI with internal hypointensity (Fig. 2), and 6 patients (28.6%) showed uneven rim enhancement on T1WI with several hyperintense flocculent foci within an internal hypointense region. Mucosal thickening and enhancement of the sphenoid sinus was observed in all patients, 7 of whom also showed uneven thickening and enhancement of the ethmoid, maxillary or frontal sinus mucosa. Enhancement of the sellar dura and peripheral meninges was also found in all patients. Furthermore, large areas of T1 hypointense and T2 hyperintense cerebral infarcts were visible in the bilateral frontal, right temporal, parietal and occipital lobes in one patient (case 5). In another patient (case 6), ischemic signals in the right basal ganglia and multiple ischemic lesions were observed on MRI.

Intraoperative findings

Consistent with the MRI appearances, 21 patients all had solid tumor masses with poor or no blood supply during surgery, without bleeding or cystic changes. Yellow-gray or yellow-white tumors were observed in 13 patients, and gray-white tumors were observed in 8 patients. After excising the sellar dura, soft or brittle, cottage cheese-like necrotic tissues were observed in 16 patients; brittle or rubbery, mass-like solid tissues were observed in 3 patients; and thin and soft tissues that leaked out were observed in 2 patients (Table 1).

Table 1 Clinical characteristics of the 21 PA patients with coagulative necrosis

No.	Age/sex	Tumor types	Course (d.)	PAS	Precipitating factors	Clinical manifestations	Ophthalmologic examinations	Endocrine examinations	MRI[a]	Op. appro	Intraoperative findings	Histopathology	Follow-up time (mo.)	Outcomes
1	47/M	NF	30	4′	Hypertension	H/A, fatigue, hyposexuality	Binocular VA impairment and bitemporal VF defects	Panhypo	Typical	TSS	Yellow-gray, soft, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues	74.7	Tumor total resection; VA and VF normalized; HRT (prednisone + sex hormone)
2	35/F	PRL	90	4′	Initiation of bromocriptine	H/A, menstrual disturbances, galactorrhea	Binocular VA impairment and bitemporal VF defects	PRL↑, E↑	Typical	TSS	Yellow-gray, soft, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues; chronic sphenoidal mucosal sinusitis; Ki-67:1%	51.8	Tumor sub-total resection; VA and VF normalized; long-term bromocriptine therapy
3	44/M	NF	240	3′	Hypertension	H/A	Left-eye VA impairment and bitemporal VF defects	PRL↑, T↑	Typical	TSS	Grey-white, soft, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures surrounded by granulation tissues; Ki-67:1%	73.9	Tumor total resection; VA and VF normalized; full recovery
4	59/M	NF	7	0′	APTT↑, Fbg↑, APTT-R↑	H/A, nausea, vomiting, fatigue, electrolyte disturbance	Normal	Gonadotropic deficiency	T1 iso/hyperintensity, T2 mixed signals, uneven rim enhancement	TSS	Yellow-gray, brittle, and massive solid tissues, mixed up with fibrinoid necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration; sphenoidal mucosal sinusitis	71.0	Tumor total resection; full recovery

Table 1 (continued)

No.	Age/sex	Tumor types	Course (d.)	PAS	Precipitating factors	Clinical manifestations	Ophthalmologic examinations	Endocrine examinations	MRI[a]	Op. appro	Intraoperative findings	Histopathology	Follow-up time (mo.)	Outcomes
5	42/M	NF	9	7′	Hypertension, long-term oral intake of aspirin, INR↑, Fbg↑, D-Dimer↑	H/A, nausea, vomiting, unconsciousness (GCS 9′, E2V2M5), stroke, fever, electrolyte disturbance	Binocular VA impairment (right-eye NLP), binocular blindness; abnormal right direct and consensual pupillary reflex, abnormal left consensual pupillary reflex; right ptosis, limited right-eye movements in adduction and abduction	Panhypo	Typical; large-scale T1-hypointense and T2-hyperintense foci of bilateral frontal, right temporal, parietal and occipital lobe (acute cerebral infarction)	TSS	Yellow-white cottage cheese-like necrotic tissues with rubbery and brittle texture	Large areas of coagulative necrotic structures, with peripheral proliferation and hyaline degeneration of fibrous tissue; Ki-67 < 1%	69.5	Tumor total resection; left-eye VA normalized, VF improved; right-eye blindness; left hemiplegia; HRT (prednisone)
6	77/M	NF	20	7′	Hypertension, diabetes mellitus, chronic renal insufficiency	H/A, nausea, vomiting, unconsciousness (GCS 13′, E4V4M5), fever, electrolyte disturbance	Binocular VA impairment and bitemporal VF defects; abnormal left consensual pupillary reflex; left ptosis, limited left-eye movements in adduction and abduction	Panhypo	T1 iso/hyperintensity, T2 hypo/isointensity, uneven rim enhancement	TSS	Yellow-white, soft, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration; chronic sphenoidal mucosal sinusitis	14.9	Tumor total resection; VA and VF normalized; full recovery

Table 1 (continued)

No.	Age/sex	Tumor types	Course (d.)	PAS	Precipitating factors	Clinical manifestations	Ophthalmologic examinations	Endocrine examinations	MRI[a]	Op. appro	Intraoperative findings	Histopathology	Follow-up time (mo.)	Outcomes
7	67/M	NF	5	5′	Hypertension	H/A, nausea, vomiting, electrolyte disturbance	Binocular VA impairment and bitemporal VF defects; absence of left direct and consensual pupillary reflex; left ptosis, mydriasis, and eyeball fixation (ophthalmoplegia)	Panhypo	T1 hyperintensity, T2 iso/hyperintensity, uneven rim enhancement with internal mixed signals	TSS	Grey-white, brittle, and cottage cheese-like necrotic tissues, partially mixed up with solid tissues	Large areas of coagulative necrotic structures surrounded by granulation tissues	67.9	Tumor total resection; VA and VF normalized; full recovery
8	48/M	NF	120	4′	None	H/A, nausea, vomiting, fatigue, hyposexuality	Binocular VA impairment and bitemporal VF defects	Panhypo	T1 iso/hyperintensity, T2 hypo/iso-intensity, uneven rim enhancement	TSS	Grey-white, soft, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures surrounded by granulation tissues; Ki-67:1%	52.6	Tumor total resection; VA and VF normalized; HRT (prednisone + sex hormone)
9	32/M	NF	7	5′	None	H/A, nausea, vomiting, electrolyte disturbance	Binocular VA impairment and bitemporal VF defects; diplopia; left ptosis, limited left-eye movements in abduction	Thyrotropic and gonadotropic deficiency	T1 iso/hyperintensity, T2 iso/hyperintensity, uneven rim enhancement with internal mixed signals	TSS	Yellow-gray, brittle, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration; Ki-67:1%	22.2	Tumor subtotal resection; VA and VF normalized; residual tumors did not increase significantly after prolonged follow-up and observations

Table 1 (continued)

No.	Age/sex	Tumor types	Course (d.)	PAS	Precipitating factors	Clinical manifestations	Ophthalmologic examinations	Endocrine examinations	MRI[a]	Op. appro	Intraoperative findings	Histopathology	Follow-up time (mo.)	Outcomes
10	72/M	NF	30	7′	None	H/A, nausea, vomiting, unconsciousness (GCS 14′, E3V5M6), electrolyte disturbance	Binocular VA impairment, binocular blindness; left ptosis, limited left-eye movements in adduction	Panhypo	T1 iso/hyperintensity, T2 iso/hyperintensity, uneven rim enhancement with internal mixed signals	TSS	Yellow-white and cottage cheese-like necrotic tissues, surrounded by soft, grey tumor tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues	39.0	Tumor total resection; VA and VF improved; full recovery
11	27/M	GH	2	5′	Hypertension, PT↑, INR↑, Fbg↑, APTT↑, APTT-R↑, D-Dimer↑	H/A, nausea, vomiting, electrolyte disturbance	Binocular VA impairment (right-eye NLP), left temporal VF defect, right blindness; absence of right direct pupillary reflex, absence of left consensual pupillary reflex; right ptosis, limited right-eye movements in adduction, and mydriasis	Panhypo, GH↑	Typical	TSS	Yellow-white and cottage cheese-like necrotic tissues; no tumor tissue found	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration	20.2	Tumor total resection; left-eye VA and VF normalized, right-eye VA and VF improved; full recovery

Table 1 (continued)

No.	Age/sex	Tumor types	Course (d.)	PAS	Precipitating factors	Clinical manifestations	Ophthalmologic examinations	Endocrine examinations	MRI[a]	Op. appro	Intraoperative findings	Histopathology	Follow-up time (mo.)	Outcomes
12	27/F	PRL	14	5′	None	H/A, nausea, vomiting, amenorrhea, galactorrheate, electrolyte disturbance	Binocular VA impairment and bitemporal VF defects; right ptosis, mydriasis, and eyeball fixation (ophthalmoplegia)	PRL↑	T1 iso/hyperintensity, T2 hypo/isointensity, uneven rim enhancement	TSS	Grey-white, rubbery and massive solid tissues	Large areas of coagulative necrotic structures, surrounded by granulomatous and fibrous tissues; Ki-67:25%	36.7	Tumor partial resection; VA and VF normalized; long-term bromocriptine therapy, followed by one additional TSS, radiotherapy, 9-course temozolomide chemotherapy, PRL normalized
13	68/M	NF	6	5′	Hypertension	H/A, nausea, vomiting, electrolyte disturbance	Binocular VA impairment and bitemporal VF defects; left ptosis, mydriasis, and eyeball fixation (ophthalmoplegia)	Panhypo	Typical	TSS	Yellow-gray, soft, and cottage cheese-like necrotic tissues, with shapeless tumor tissues	Large areas of coagulative necrotic structures, surrounded by fibrous capsule; acute and chronic sphenoidal mucosal sinusitis; Ki-67 < 1%	87.9	Tumor subtotal resection; VA and VF normalized; residual tumors did not increase significantly after prolonged follow-up and observations
14	59/M	NF	9	2′	Hypertension, diabetes mellitus, old myocardial infarction, atrial fibrillation	H/A, nausea	Left VA impairment and left blindness	Thyrotropic and gonadotropic deficiency	T1 iso/hyperintensity, T2 iso/hyperintensity, uneven rim enhancement with internal mixed signals	TSS	Yellow-white, brittle, and massive solid tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues; Ki-67 < 1%	78.6	Tumor total resection; VA and VF improved; full recovery

Table 1 (continued)

No.	Age/sex	Tumor types	Course (d.)	PAS	Precipitating factors	Clinical manifestations	Ophthalmologic examinations	Endocrine examinations	MRI[a]	Op. appro	Intraoperative findings	Histopathology	Follow-up time (mo.)	Outcomes
15	58/M	NF	8	4′	PT↑, INR↑, Fbg↑, APTT↑, APTT-R↑, D-Dimer↑	H/A, nausea, electrolyte disturbance	Binocular VA impairment and bitemporal VF defects	Gonadotropic deficiency	T1 iso/hyperintensity, T2 iso/hyperintensity, uneven rim enhancement with internal mixed signals	TSS	Yellow-gray, brittle, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues; Ki-67: 5%	23.0	Tumor total resection; VA and VF normalized; full recovery
16	48/F	NF	180	4′	APTT↑, APTT-R↑	H/A, amenorrhea, galactorrheate	Binocular VA impairment and bitemporal VF defects	PRL↑	Typical	TSS	Grey-white, thin and soft tissues flowing out	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues; Ki-67: 3%	14.7	Tumor total resection; VA and VF normalized; full recovery
17	59/M	NF	1	4′	Hypertension	H/A, nausea, vomiting	Binocular VA impairment (right-eye NLP) and right blindness; diplopia; absence of right direct and consensual pupillary reflex; right ptosis and eyeball fixation (ophthalmoplegia)	Panhypo	Typical	TSS	Grey-white, thin and soft tissues flowing out, mixed up with fibrous stripes	Large areas of coagulative necrotic structures, surrounded by hyaline degeneration of fibrous tissue; Ki-67 < 1%	78.6	Tumor subtotal resection; VA and VF normalized; residual tumors did not increase significantly after prolonged follow-up and observations

Table 1 (continued)

No.	Age/sex	Tumor types	Course (d.)	PAS	Precipitating factors	Clinical manifestations	Ophthalmologic examinations	Endocrine examinations	MRI[a]	Op. appro	Intraoperative findings	Histopathology	Follow-up time (mo.)	Outcomes
18	68/M	NF	60	0′	PT↑, APTT↑, APTT-R↑, Fbg↑, factor X coagulant activity↓	H/A, electrolyte disturbance	Normal	Panhypo	T1 iso/hyperintensity, T2 iso/hyperintensity, uneven rim enhancement with internal mixed signals	TSS	Grey-white, soft, and cottage cheese-like necrotic tissues, mixed up with gray tumor tissues	Large areas of coagulative necrotic structures, surrounded by granulation tissues; Ki-67: 1%	20.9	Tumor total resection; HRT (prednisone)
19	45/F	NF	8	0′	Diabetes mellitus, PT↑, APTT↑, APTT-R↑, Fbg↑	H/A, nausea, vomiting, fever, electrolyte disturbance	Normal	Corticotropic deficiency	Typical	TSS	Yellow-gray, soft, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues; Ki-67: 5%	21.0	Tumor total resection; HRT (prednisone)
20	32/F	NF	7	0′	APTT↑, APTT-R↑, Fbg↑	H/A, nausea, vomiting, menstrual disturbances, galactorrhea	Normal	Corticotropic deficiency, PRL↑	Typical	TSS	Yellow-gray, soft, and cottage cheese-like necrotic tissues	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration and granulation tissues	108.6	Tumor total resection; HRT (prednisone)
21	50/F	NF	2	4′	Hypertension, diabetes mellitus, PT↑, INR↑, Fbg↑	H/A, nausea, vomiting, electrolyte disturbance	Binocular VA impairment and bitemporal VF defects; diplopia; left ptosis, limited left-eye movements in adduction and abduction	Corticotropic and gonadotropic deficiency	Typical	TSS	Grey-white and massive solid tissues with rubbery and brittle texture	Large areas of coagulative necrotic structures, surrounded by inflammatory cell infiltration; Ki-67 < 1%	66.2	Tumor total resection; VA and VF normalized; full recovery

Table 1 (continued)

PA pituitary apoplexy, *M* male, *F* female, *d.* day, *PAS* Pituitary Apoplexy Score, *Op* operation, *appro* approach, *mo.* month, *NF* nonfunctioning pituitary adenoma, *H/A* headaches, *VA* visual acuity, *VF* visual field, *Panhypo* panhypopituitarism, *TSS* transsphenoidal surgery, *HRT* hormone replacement therapy, *APTT* activated partial thromboplastin time, *Fbg* fibrinogen, *INR* International Normalized Ratio, *GCS* Glasgow Coma Scale, *NLP* no light perception, *PT* prothrombin time

[a]Typical signs of MRI, including T1 isointensity and hyperintensity, T2 isointensity and hyperintensity, uneven rim enhancement with internal hypointensity after gadolinium injection, sphenoid sinus mucosal thickening and enhancement, as well as enhancement of sellar dura and adjacent meninges

Histopathological results

HE staining showed large areas of pink, acellular, coagulative necrosis in the central zone under microscopy (Fig. 2e). The most specific characteristics of coagulative necrosis were "ghost cells", which are tumor cells with only ghost outlines and no cellular structure. Only a small number of broken cells with karyopyknosis and karyorrhexis could be seen in the necrotic regions, especially in the periphery. In the border zone, residual tumor tissues, inflammatory cell infiltration, fibroblast proliferation, and granulation tissue proliferation were observed in most patients (Fig. 2f). IHC staining identified nonfunctioning pituitary adenomas in 18 patients (85.7%), prolactinomas in 2 patients (9.5%) and a growth hormone-secreting pituitary adenoma in one patient (4.8%) (Table 1).

Treatment outcomes

Headache, nausea, vomiting, electrolyte disturbances and other clinical manifestations were improved to varying degrees in all patients postoperatively. The visual disturbances of 17 patients started to improve from the first day after surgery. At the last follow-up, the visual acuity and visual fields of 13 patients (76.5%) had recovered to normal, and those of 4 patients (23.5%) were improved but were not normalized. All 10 patients with oculomotor palsies resolved completely within 3 months after surgery. The fastest full recovery of oculomotor palsy was achieved within 3 days after surgery. No permanent diabetes insipidus or CSF leakage was present in any patient postoperatively. According to postoperative MRI findings, total tumor resection was achieved in 16 patients (76.2%), subtotal resection was achieved in 4 patients (19.0%), and partial resection was achieved in 1 patient (4.8%). For the three patients with nonfunctioning adenomas who underwent subtotal resection, residual tumors did not increase significantly after follow-up for 1.8 years, 7.3 years and 6.6 years, so no additional surgery was performed for them. For the one patient (case 2) with a prolactinoma who underwent subtotal resection, residual tumor shrinkage and normal serum PRL were obtained following long-term bromocriptine therapy. For the one patient (case 12) with an aggressive prolactinoma who underwent partial resection, sustained hyperprolactinemia had not improved following long-term bromocriptine therapy, one additional TSS procedure, and radiotherapy. However, after 9 courses of temozolomide chemotherapy, sellar MRI suggested that the residual tumor was significantly reduced, and serum PRL became normalized (Table 1).

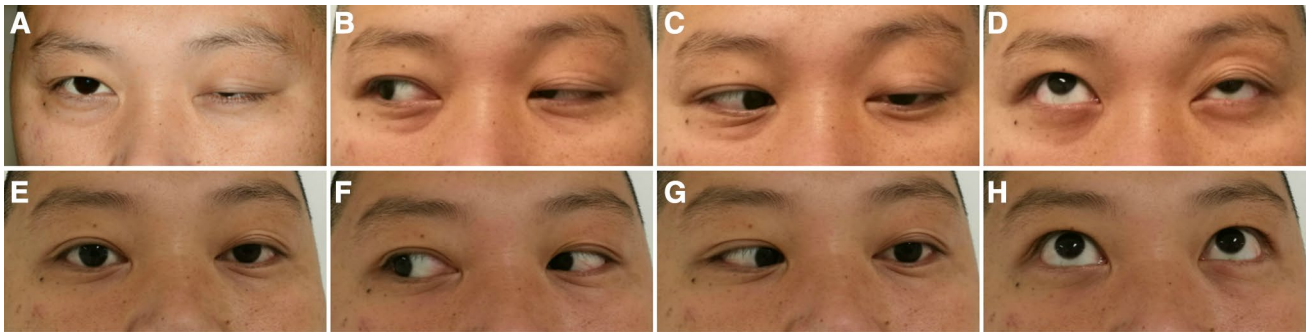

Fig. 1 Cranial nerve palsies (case 9, M/32 years, 7 days after the onset of symptoms): **a** before surgery, looking forward, left ptosis (left oculomotor nerve palsy); **b** before surgery, looking right, normal binocular eye movements in adduction; **c** before surgery, looking left, limited left eye movements in abduction (left abducens nerve palsy); **d** before surgery, looking upward; **e** 3 days after surgery, looking forward, left ptosis fully recovered; **f** 3 days after surgery, looking right, normal binocular eye movements in adduction; **g** 3 days after surgery, looking left, partial improvement of limited left eye movements in abduction; **h** 3 days after surgery, looking upward, left ptosis fully recovered

Postoperative hormone replacement therapy (HRT)

Immediately postoperatively (within 1 week), hypopituitarism was still present in 14 patients (66.7%) who had received hormone replacement therapy (HRT). Among them, 9 patients with panhypopituitarism received prednisone acetate tablets and levothyroxine sodium tablets for HRT; 3 patients with isolated corticotropic deficiency received prednisone acetate tablets for HRT; and 2 patients with combined corticotropic and thyrotropic deficiency received prednisone acetate tablets and levothyroxine sodium tablets for HRT. At the last follow-up, 6 patients (28.6%) continued to take low-dose prednisone for maintenance treatment due to failure to discontinue the glucocorticoid drugs. Sex hormones were administered correspondingly in 2 patients (9.5%) for hypogonadotropism beginning 3 months after surgery. The other 15 patients all showed normal endocrine function and did not require long-term HRT at the last follow-up. Thanks to the excellent follow-up and supervision system of our medical center, no patient died of a life-threatening pituitary crisis due to a lack of HRT.

Discussion

PA with coagulative necrosis, a rare subtype of infarctive PA, is a clinical entity with unique intraoperative and histopathological manifestations, remarkably different from the classical PA. It has only been reported in some isolated case reports in the literature [6–9]. Our study presents a consecutive series of 21 histopathologically confirmed PA cases with coagulative necrosis, constituting the largest case series collected to date. According to the data obtained from our institution from 2009 to 2017, 8.6% of patients with all types of pituitary adenomas experienced apoplexy, which is similar to the occurrence rate of 2–12% reported in the literature [1–4, 10, 12, 13]. Only 4.8% of PA patients in our center were determined to have coagulative necrosis by histopathology. Our study summarized the clinical characteristics, and combined treatment and prognosis of CNPA, demonstrating that this severe condition commonly has satisfactory endocrine and neuro-ophthalmic outcomes following early, adequate and comprehensive therapy.

The pathophysiology of CNPA is still unclear. Based on previous studies reported in the literature, we hypothesize that the possible mechanisms are as follows [14]: (1) Direct compression of portal vessels or the hypophyseal arteries by large tumor masses [4], high intracranial pressure, low blood pressure [15], or other factors lead to an absolute reduction in blood supply to the tumor; (2) rapid growth of the tumor outpaces the rate of angiogenesis [5], and increased metabolic activity after administration of hypothalamic releasing factors leads to relatively insufficient blood supply to the tumor [16]; and (3) vulnerability and fragility due to vascular lesions in pituitary tumors are inclined to cause tumor infarction or hemorrhage [17]. We hypothesize that CNPA is the result of infarction of pituitary adenomas. Various reasons lead to acute or chronic ischemia or infarction, rather than hemorrhage, of the tumors, which form large areas of necrosis at the earliest stage of onset. The autoimmune response may also play an important role during this period [6]. However, the reasons why isolated infarctive necrosis of tumors appear, rather than extensive bleeding, are still unknown. Chacko et al. [7] considered coagulative necrosis to be a late pathological outcome of hemorrhagic apoplexy, which is obviously inconsistent with the findings of our study and other reports in the literature [8–10, 13].

In our study, men significantly outnumbered women, and patients with nonfunctioning adenomas significantly outnumbered patients with other types of pituitary adenomas,

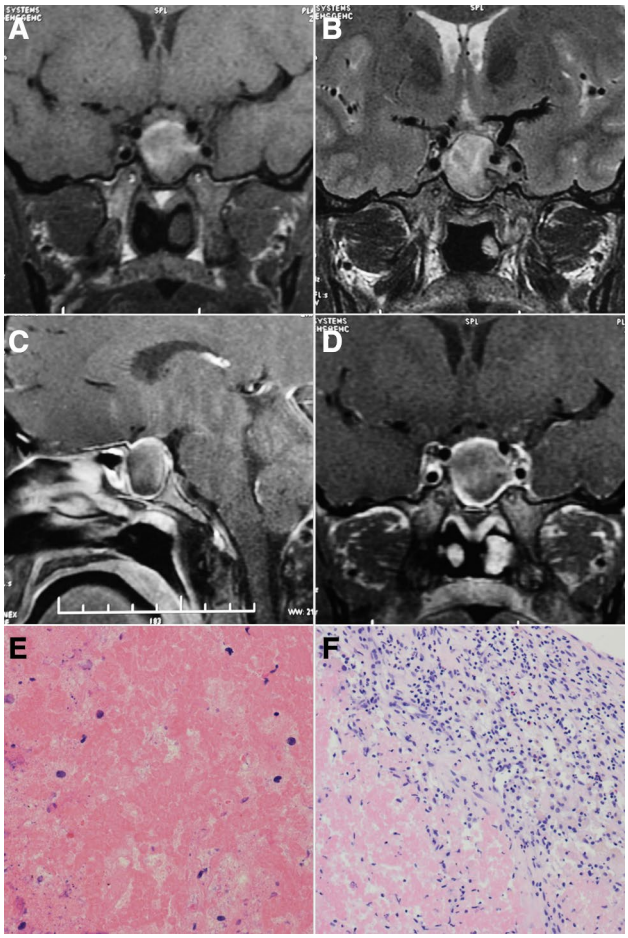

Fig. 2 Typical MRI characteristics of PA with coagulative necrosis (case 19, F/45 years, 8 days after the onset of symptoms): solid tumor mass without cystic change or fluid debris levels; isointensity to hyperintensity on T1WI (**a** coronal), isointensity to hyperintensity on T2WI (**b** coronal), and uneven rim enhancement with internal hypointensity after gadolinium injection (**c** sagittal, **d** coronal); mucosal thickening and enhancement of the sphenoid sinus. Histopathological findings: e- central zone of the lesions (HE×300) showing large areas of pink, acellular, coagulative necrosis. "Ghost cells" are tumor cells with only ghost outlines and no cellular structure. **f** Border zone of the lesions (HE×150) showing the pseudocapsule formed by the compressed normal pituitary gland, residual tumor tissues, infiltrating inflammatory cells, and granulation and fibrous tissues

both of which were similar to the features of classic PA [1, 3, 11]. Precipitating factors are commonly identified in 10–40% of cases of PA reported in previous studies [1, 11, 14]. However, 85.7% of patients with CNPA in our study were found to have precipitating factors. Hypertension (10/21, 47.6%) was the most frequent precipitating factor, followed by coagulation disorders, diabetes mellitus and initiation of dopamine receptor agonists, all of which may induce apoplexy of pituitary adenomas by lowering blood pressure or plasma glucose and/or by increasing tumor metabolism and demands for blood supply [14–17].

Different from classic PA, most patients (16 patients, 76.2%) with CNPA had a subacute or chronic onset and presented progression of symptoms from initial onset including visual disturbances, cranial nerve palsies, endocrine dysfunction and other symptoms. In our study, headache was present in all patients and was associated with nausea/vomiting in nearly 76.2% of patients. Headache was the most common complaint and lacked a specific pattern and severity, which is a classic symptom of PA [1]. Visual disturbances were observed in 81.0% of patients, which is slightly higher than the 50% of affected classic PA patients reported in the literature [1]. Varying degrees of visual acuity or visual field impairments mainly due to progressive compression of the optic nerve or optic chiasm by upward expansion of tumor masses were present. Some patients even had loss of visual acuity (3/21) and total blindness (5/21), which is extremely rare in classic PA and may be due to the relatively long course of CNPA. Oculomotor palsies were observed in nearly half of the patients (47.6%), similar to the 14–81% of affected classic PA patients reported in the literature, due to functional impairment of cranial nerves III (the most frequently affected), IV and VI [1, 2, 11, 18, 19]. However, the proportion of ophthalmoplegia and eyeball fixation (19.0%) was significantly higher in CNPA patients than in classic PA patients, which may result from progressive intracavernous invasion of the tumor mass and pressure increases in the pituitary region leading to combined impairment of cranial nerves III, IV and VI [1, 19]. In addition, other clinical presentations in our study, with no special significance, such as unconsciousness, fever and acute cerebral stroke can also be seen in patients with classic PA [1, 3, 11].

The majority of the patients (81.0%) in our study had at least one anterior pituitary deficiency at the onset of PA due to progressive tumor mass effect on the normal pituitary gland, which is close to the nearly 80% of patients with classic PA reported in the literature [11, 20, 21]. In our study, gonadotropic deficiency was the most common deficit observed in patients with CNPA, occurring in 71.4% of patients, followed by corticotropic deficiency (61.9%) and thyrotropic deficiency (57.1%). As reported by previous studies, corticotropic, thyrotropic and gonadotropic deficiencies have been observed in 50–80%, 30–70% and 40–75% of PA patients, respectively [1, 11, 21, 22]. However, it is worth noting that 58.8% of these hypopituitarism patients had panhypopituitarism, which was much higher than percentage of patients with classic PA who had panhypopituitarism, indicating that the slow-onset, progressive expansion of CNPA causes overall and comprehensive damage to pituitary function. Symptoms of pituitary endocrine dysfunction were present before PA onset. Similar to previous studies, electrolyte disturbances (especially hyponatremia) were the most common symptoms, followed by menstrual disturbances/amenorrhea and galactorrhea, fatigue, and hyposexuality [11, 20, 21].

The MRI appearances of classical PA can be very variable [21, 23–25]. Generally, within the first 7 days, known as the acute phase, isointensity or slight hypointensity on T1WI and hypointensity on T2WI can be observed. During the subacute phase, from 7 to 14 days, hyperintensity on T1WI and T2WI can be observed. During the chronic phase, after 14 days, hypointensity on T1WI and T2WI can be observed. According to our study, we found that patients with CNPA invariably showed isointense to hyperintense signal on T1WI and T2WI regardless of what phase they were in, which may be due to the special pathological type of CNPA. In contrast to classic PA, the typical MRI characteristics of CNPA, which were observed in 81.0% of patients in our study, are as follows: (1) solid tumor mass without cystic changes and fluid debris levels; (2) isointensity to hyperintensity on T1WI, isointensity to hyperintensity on T2WI, and uneven rim enhancement with internal hypointensity after gadolinium injection; (3) mucosal thickening and enhancement of the sphenoid sinus during the acute, subacute or chronic phase, sometimes with uneven thickening and enhancement of the ethmoid, maxillary or frontal sinus mucosa; and (4) enhancement of the sellar dura and adjacent meninges.

Combined with the intraoperative findings and postoperative pathological results, we hypothesize that the cottage cheese-like tissues, which present with isointensity to hyperintensity on T1WI and nonenhancement after gadolinium injection on MRI, are consistent with large areas of pink, acellular, coagulative necrosis in the central zone under microscopy. The most specific characteristics of coagulative necrosis were "ghost cells", which are tumor cells with only ghost outlines and no cellular structure. The uneven enhanced walls of different thickness on MRI are mainly the pseudocapsule formed by the compressed normal pituitary gland, residual tumor tissues, infiltrating inflammatory cells, and granulation and fibrous tissues.

In conclusion, we think that coagulative necrotic PA should meet the following criteria: (1) intraoperative findings: cottage cheese-like necrotic tissues with poor or no blood supply are observed during operation, instead of stale hemorrhage or cystic fluid; (2) postoperative histopathology: large areas of pink, acellular, coagulative necrosis are observed in the central zone, especially "ghost cells", and the pseudocapsule formed by the compressed normal pituitary gland, residual tumor tissues, infiltrating inflammatory cells, and granulation and fibrous tissues are observed in the border zone; (3) typical MRI characteristics: solid tumor mass showing isointensity to hyperintensity on T1WI, isointensity to hyperintensity on T2WI, uneven rim enhancement with internal hypointensity after gadolinium injection, and sphenoid sinus mucosal thickening; (4) clinical manifestations of apoplexy, such as visual disturbances, cranial nerve palsies, and endocrine dysfunctions, especially panhypopituitarism. The first two criteria are the most specific and indispensable diagnostic indicators of CNPA, and the last two criteria are nonspecific indicators.

As far as PA management is concerned, the indications and optimal therapeutic strategy including conservative or surgical treatment are still controversial [3, 11, 18, 22, 26, 27]. Nishioka et al. [9] have reported that 2 patients with coagulative necrotic PA who had improved symptoms and endocrine functions after conservative treatment, but their treatment options were quite doubtful without considering the possible progression of symptoms. According to the experience of our center, we suggest early and active transsphenoidal surgery for CNPA including adequate glucocorticoid replacement and hydroelectrolytic support, even though 6 patients in our study had a PA score of less than 4 (surgery is indicated for patients with a PA score ≥ 4 according to the UK Guidelines for PA) [11]. Because of the cottage cheese-like necrosis present in the central zone, which can easily be totally removed, and the presence of a pseudocapsule around the tumor, which prevents the tumor from adhering to the surrounding structures, it is easy to achieve total resection of these tumors and simultaneously protect the normal pituitary gland. In addition, early surgery can relieve compression of local structures, such as the pituitary gland and optic nerve, and provide improved endocrine and neuro-ophthalmic outcomes. Considering the rarity of CNPA, randomized controlled trials comparing both strategies with strong evidence are quite difficult to perform to determine the optimal management of this disease.

In addition, we recommend that each patient, especially those with cranial nerve palsies, receive HBOT early after surgery. In our center, patients with PA commonly receive 100% oxygen at 2.0 ATA daily for 1–2 h for 2 weeks. Many current studies have confirmed the value of HBOT for improving the prognosis of acute cerebral stroke patients [28, 29], and we are also actively exploring improvements in the prognosis of acute PA with HBOT, especially for PA with coagulative necrosis.

As corticotropic deficiency is present in the vast majority of patients (81.0%) preoperatively, hormone replacement with glucocorticoids is necessary as soon as the diagnosis is confirmed. Long-term close monitoring of endocrine function is required after surgery, and a good follow-up and supervision system can prevent a life-threatening pituitary crisis due to random withdrawal of HRT. Most patients require long-term but nonpermanent HRT after surgery. In our study, only 28.6% of patients with CNPA still suffered from corticotropic deficiency, and 9.5% of patients suffered from gonadotropic deficiency. However, as reported in the literature, long-term hormone replacement following classic PA involves corticosteroids in 60–80% of patients, thyroid hormone in 50–60% of patients, desmopressin in 10–25% of patients and testosterone in 60–80% of men [11, 20, 30]. Our study indicated that the frequency of postoperative anterior

pituitary hypofunction in patients with CNPA was similar to that in patients with classic PA before surgery. However, the recovery of postoperative pituitary function in patients with CNPA was significantly better than that in patients with classic PA. Furthermore, significantly fewer patients with CNPA require HRT for life than patients with classic PA.

Conclusions

Coagulative necrotic PA is a clinical entity with unique intraoperative and histopathological manifestations, remarkably different from the classical PA. It is generally considered as a rare subtype of infarctive PA, and has rarely been reported in the literature. Most patients with CNPA have a subacute or chronic onset and present with progressive symptoms of visual disturbances, cranial nerve palsies and endocrine dysfunction, especially panhypopituitarism. The vast majority of patients commonly showed typical MRI appearances, intraoperative findings and histopathological features (ghost cells are the most specific feature of coagulative necrosis). According to the abovementioned unique clinical characteristics, correct diagnosis of CNPA before surgery is not very challenging. Early and active TSS combined with HBOT early after surgery usually yield better endocrine and neuro-ophthalmic outcomes than those of classic PA.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures involving human participants were performed in accordance with the ethical standards of the Institutional Ethics Committee of Peking Union Medical College Hospital at the Chinese Academy of Medical Sciences & Peking Union Medical College and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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