Case Report

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Morphological optic nerve changes in a patient who has not undergone surgery for her giant pituitary adenoma: a case report

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We report a lethal case of a female patient who has not undergone surgery for her giant invasive infrasellar/endosellar/suprasellar/parasellar/retrosellar pituitary adenoma. The paper presents results of histological examination of optic nerves and considers the mechanisms of vision loss in prolonged chiasmal and optic nerve compression.

Keywords:

pituitary gland, anterior pituitary tumors, compressive optic neuropathy, pathohistological changes, invasive expansion

Introduction

According to the 2021 5th edition WHO Classification of Central Nervous Tumors, pituitary neuroendocrine tumors (PitNET) are neuroendocrine tumors of the anterior pituitary gland that are composed of secretory cells with pituitary hormone production [1]. Characteristics used when developing pituitary adenoma (PA) classification may be grouped into several categories: anatomical topographic characteristics (based on the location relative to the sella turcica and the major direction of tumor expansion), measurement-based characteristics (those based on linear measurements of the space-occupying lesion), shape-based characteristics (those based on the shape of the space-occupying lesion), density characteristics (based on imaging findings), characteristics based on the type of expansion to critical vascular and nervous structures, and pathomorphological and immunophenotype characteristics [2].

PA is classified pathohistologically into chromophobe (e.g., fetal), eosinophil, basophil and mixed. Immunohistochemically, PAs are classified with respect to their hormonal activity on the level of protein synthesis, via the determination of receptors on the surface of neuroendocrine cells; the rare tumor that is completely negative for all hormones and transcriptive factors is classified as a "null-cell pituitary adenoma" [3].

The modified Hardy classification (1970) is that most commonly used to determine metric characteristics, with pituitary adenomas grouped into four types based on their size: grade I (≤ 10 mm, within the sella (microadenoma)), grade II (10-20 mm, with a suprasellar extension within 10 mm of planum sphenoidale), grade III (20-40 mm, with a suprasellar extension ≤ 30 mm, distorting or invading the anterior third ventricle), and grade IV (≥ 40 mm, extending far beyond the sellar space, with lateral or multi-directional expansions (giant pituitary adenoma or GPA)) [4].

GPAs are usually described as tumors larger than 40 mm which is consistent with grade IV PA as per the modified Hardy classification; they account for 6-10% of all pituitary adenomas [5-9]. Surgical resection of GPAs is challenging, and is associated with a higher complication rate than resection of PAs less than 40 mm [6].

They are in close proximity to the vascular and nervous structures such as the internal carotid artery and anterior cerebral arteries and their branches, cavernous sinuses, chiasm, optic nerves and pituitary gland [6, 10].

Their features include the development of neuroophthalmological symptoms, pituitary hormonal deficit, and the invasive and destructive growth pattern, which is caused by a significant extracellular growth component at presentation. Vetricular system expansion results in the development of abnormal cerebrospinal fluid (CSF) dynamics and cerebral symptoms due to elevated intracranial pressure [6, 10]. Visual disability is caused by the development of descending optic atrophy due to prolonged chiasmal compression, which is observed in 29%-74.3% of patients, and may result in blindness in as much as 25% of patients [11-12].

Therefore, PitNETs (or generally termed PAs) are still considered as mostly benign neoplasms. However, the tumor growth rate may vary for each patient, and in some cases the tumor may grow to a giant size, and not only causing chiasmal syndrome and severe general brain symptoms and focal neurological symptoms, but also threatening the life of the patient [13].

The changes in the visual system may be directly assessed without the impact of surgical manipulations only on the autopsy material from the patients who have not undergone surgery for their GPA, which very rarely occurs in clinical practice.

The purpose of the study was to retrospectively review a case of the diagnosis and treatment of a giant pituitary adenoma which has not undergone surgery, and to assess morphological optic nerve changes in this case.

Methods

A female patient with a giant invasive infrasellar/ endosellar/suprasellar/ parasellar/retrosellar pituitary adenoma pituitary adenoma received treatment at the Departments of Skull Base Endoscopic Surgery and Neurosurgical Intensive Care, and her autopsy was performed at Neuropathomorphology Department, the Romodanov Neurosurgery Institute, National Academy of Medical Sciences of Ukraine. A clinical neurological and ophthalmological examination was performed.

Neuroimaging included T1-weighted magnetic resonance imaging (MRI) of the brain with a 1.5-T MRI system (Intera 1.5T/I system, Philips Medical Systems, Best, the Netherlands) and multispiral computed tomography (MSCT). MSCT was performed using a multiple-row detector CT scanner (Philips Brilliance CT 64-channel scanner; Philips Medical Systems) at a 1.25-mm slice thickness.

An ophthalmological examination included best-corrected visual acuity assessment, biomicroscopy, Maklakoff tonometry, kinetic and static perimetry, and direct and indirect ophthalmoscopy. Chiasmal syndrome severity was assessed with consideration of visual acuity and visual field mean defect (MD) in both eyes.

Pathomorphological examination

Pituitary adenoma bed, changes in the relief of bones of the skull base and changes in the removed PA fragments were assessed macroscopically. Post-mortem histological examination was performed microscopically in compliance with current industry standards and histological categorization was done as per the WHO classification. Tissue fragments and sites with evidence of tumor growth into adjacent tissue were examined using general and special histological methods. Paraffin processing and staining were performed using routine methods. Tissue sections not thicker than 5 μm were cut from paraffin blocks, placed on glass slides, dried in a dry oven at 36°C, and deparaffinized in a descending alcohol series as per relevant standards. Thereafter, glass slides with tissue sections were stained under visual microscopic control, cleared with xylene, and mounted in balsam. A Leica microscope (Leica MZ6, Leica Microsystems, Wetzlar, Germany) with an objective magnification of ×10–80 and eyepiece magnification of ×20 was used for observation.

This study followed the ethical standards of the Declaration of Helsinki and was approved by the Local Ethics Committee of the Romodanov Institute. Informed consent was obtained from the patient.

Results

A female patient born in 1971 was hospitalized urgently for further examination and treatment of her GPA to the Department of Skull Base Endoscopic Surgery on July 1, 2012. She complained of headache, reduced visual acuity, speech difficulties, inability to get around on her own, and general weakness.

The patient complained of a gradual reduction in visual acuity over more than a year, and headache over the most recent months. She reported that after she did not see a doctor for her symptoms “for a long time”, she had brain MRI due to deterioration in her general health condition. There was MRI evidence of a space-occupying brain lesion, and she was referred to the Romodanov Institute for further treatment.

Clinical neurological examination findings included profound obtundation, sopor, and a Glasgow coma score (GCS) of 12. The vital functions were preserved, blood pressure was 120/70 mmHg, pulse 78 bits per minute, and the pulse was rhythmic. The patient’s general condition was severe. Headache was the most prominent general cerebral symptom. Neurological findings were as follows: left pupil wider than the right, pupillary light reflex was diminished in the right eye and absent in the left eye, and normal ocular motility. Facial sensation was preserved and the face was symmetrical. Hearing was preserved. Her swallowing and speech were intact. Tendon and periosteal reflexes were equal and normal. The patient was able to extend her tongue along the midline, sensation was preserved, and tendon and periosteal reflexes were equal in the arms and ankles. Other neurological findings were dysmetria on finger-to-nose test and a positive Romberg’s sign. The patient was able to control her pelvic finction.

Brain MRI showed a space-occupying infrasellar/ endosellar/suprasellar/, parasellar/ retrosellar lesion measuring 52x40x66 mm. The lesion caused a defect in the suprasellar cisterns, extended retrosellularly and compressed the prepontine cistern (Fig. 1).

On objective visual examination, uncorrected visual acuity was 0.04-0.05 OD and zero OS. Maklakoff IOP measurements were 20 mmHg OD and 21 mmHg OS. The patient had a residual nasal visual field only in the right eye, and visual field was not measurable in the left eye. Ophthalmoscopy showed pale optic discs with clear margins and narrowed vessels. Other ocular structures were unremarkable.

The patient was diagnosed with bilateral descending optic atrophy, partial descending optic atrophy in the right eye, and chiasmal syndrome.

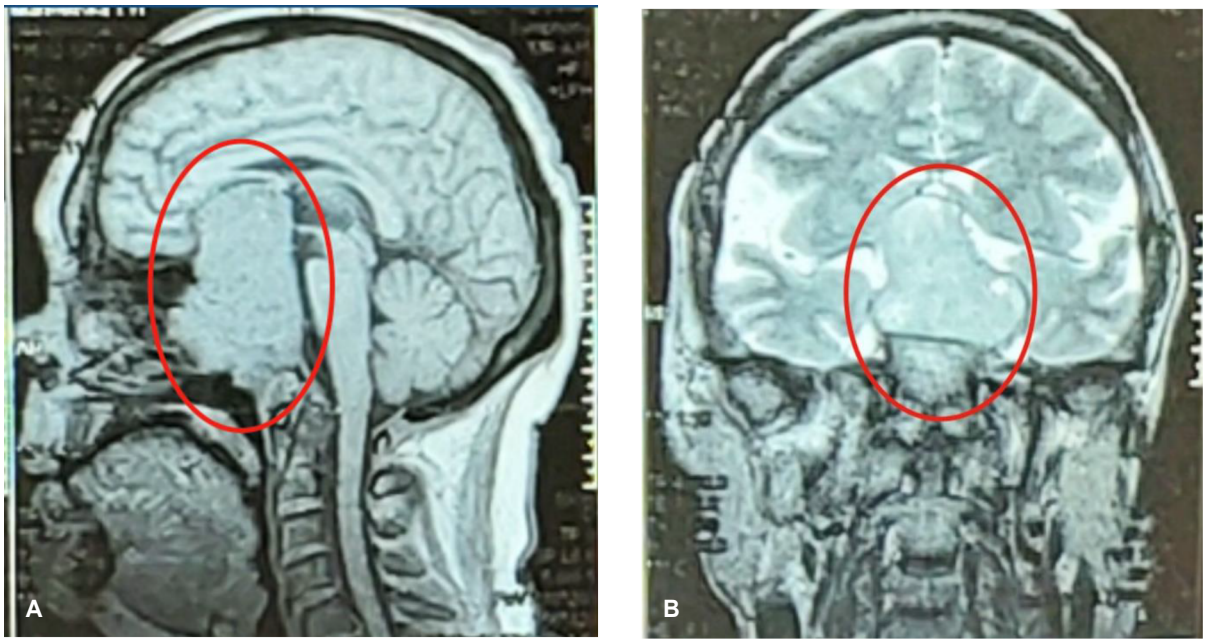

Fig. 1. A giant invasive infrasellar/endosellar/suprasellar/parasellar/ retrosellar pituitary adenoma in a female patient born in 1971. T1-weghted MRI, sagittal (A) and coronal (B) views.

She was administered medical therapy for edema.

The patient's condition worsened within a day: her headache increased in severity and was not relieved with over-the-counter analgesics, she had impaired consciousness (profound obtundation), with blood pressure elevated to 160/90 mmHg and pulse rate to 80 bits per minute, and the pulse was rhythmic. Neurological findings were as follows: left pupil wider than the right, and pupillary light reflex was diminished in the right eye and absent in the left eye. The patient was found to be alert and was able to follow simple instructions. General cerebral symptoms increased in severity and included severe headache and vomiting. Focal neurological symptoms appeared and included left facial nerve paresis and severe left hemiparesis. The patient was transferred to the intensive therapy unit. Her GCS was 12/15. A repeat 64-slice CT was performed and found hemorrhage in the superior-posterior portion of the lesion, a distorted third ventricle, and effusion of blood into the posterior lateral ventricles. The right lateral ventricle (the second ventricle) and third ventricle were tamponated with blood. The maximum width of anterior horns of lateral ventricles was 16 mm.

Resection of the tumor was contraindicated because the patient's condition was severe and the most prominent symptoms were those related to intracranial hypertension. An external ventricular drainage system was urgently installed. The patient continued receiving treatment (medical therapy for edema, treatment for the maintenance of homeostasis and antibiotic therapy) at the intensive care unit. Her general condition was poor, she had impaired consciousness (profound obtundation), and her GCS was 10/15. The function of the ventricular drainage system and the function of the drained ventricle were checked. Thereafter, the general condition was still poor, the patient exhibited impaired consciousness (sopor), and her GCS was 10/15. The patient's condition deteriorated over the day, her general condition was extremely poor, she exhibited impaired consciousness, her GCS was 8/15, and she was breathing through the tracheostomy. Clinical death in the form of asystolia was observed in the presence of an extremely poor condition, resuscitation efforts were unsuccessful, and the patient's biological death was pronounced.

The final clinical diagnosis was a giant infrasellar/ endosellar/suprasellar/ parasellar/retrosellar pituitary adenoma, with intratumoral hemorrhages and effusion of blood into the ventricular system and the development of occlusive hydrocephalus, which caused death.

The pathological anatomical diagnosis was threefold:

(1) a giant pituitary adenoma (ICD-10 code D35.2) located in the infrasellar/ endosellar/suprasellar/parasellar/ retrosellar region,

(2) acute cerebrovascular event (intratumoral hemorrhage), edema and dislocation of the brainstem, hemorrhage into cavity of the third ventricle, multiple dislocations (axial dislocation of the brainstem; engagement of the cerebellar tonsils into the foramen magnum; and compression of the optic nerves and mammillary bodies) and deformation of skull base bones, and

(3) parenchymatous dystrophy of the internal organs and cardiosclerosis.

The autopsy conclusion stated that the death of the patient with a giant infrasellar/endosellar/suprasellar/ parasellar/retrosellar pituitary adenoma was directly caused by edema and dislocation of the brainstem.

The autopsy showed the cavity of the sella turcica measuring 1.7x2.1x0.8 cm, with extremely thin dorsum

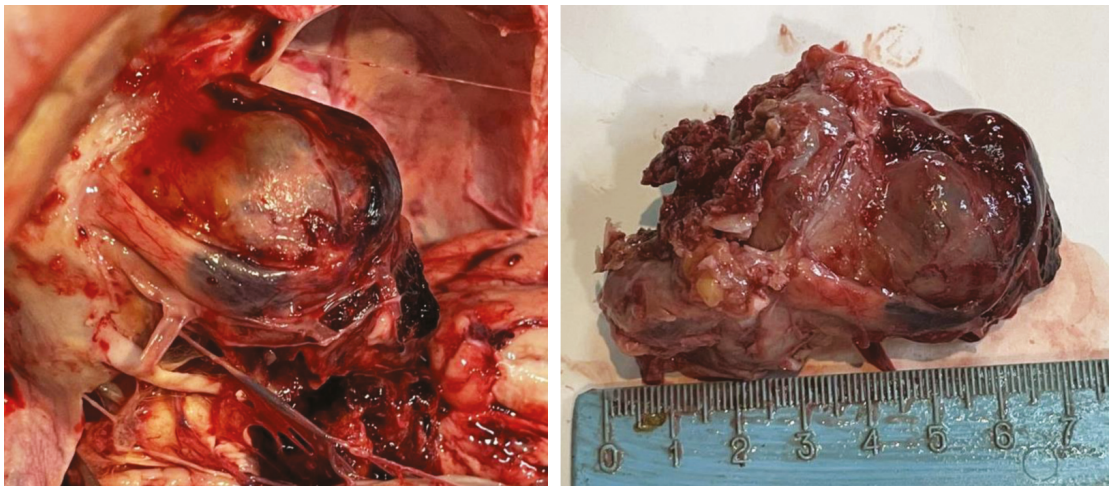

Fig. 2. Exterior of the tumor. The right optic nerve is very thin, stretched out and lying flat on the anterior superior surface of the tumor capsule. The left optic nerve is severely edematous, passing along the lateral surface of the tumor, and could be easily separated from the tumor capsule.

sellae with evidence of left-side surface erosion and a partial right-side bone loss, and a thinned anterior superior clinoid process. A round mass measuring 7.3x5.4x4.6 cm (Fig. 2) was located in the infrasellar-ante-supra-retrosellar region, showing right parasellar extension into the right cavernous sinus, and displacing and compressing backwards the siphon and intracavernous segment of the right internal carotid artery. The right optic nerve was extremely thin, stretched out and lying flat on the anterior superior surface of the tumor capsule. The left optic nerve was severely edematous, passing along the lateral surface of the tumor, and could be easily separated from the tumor capsule. At the left, the tumor approached the cavernous sinus wall. In addition, the tumor extended retrosellarly to the clivus, displacing the posterior communicating and basilar arteries. Moreover, the tumor extended upwards (antesellarly) to the interpeduncular fossa and from there penetrating into cavity of the anterior/inferior third ventricle. The tumor filled the third ventricle, occluding the foramen of Monro. Mammillary bodies were not consistently observed, but severely crushed and displaced backwards. A sagittal view showed an hourglass-shaped tumor with a constriction developed at the site of the defect in the third ventricle, tumor tissue appeared soaked with blood, and the tumor capsule was very tense. In addition, the site of capsular rupture was identified in the intraventricular portion of the tumor, and there was evidence of effusion of blood into, and tamponade of, the cavity of the third ventricle. The anterior brainstem appeared swollen, rotated and compressed. The brain was of normal size and shape, the cerebral hemispheres were symmetrical, and the cerebellar tonsils were engaged into the foramen magnum.

Post-autopsy histological examination classified the tumor as a pituitary neuroendocrine tumor (PitNET) 8272/2 (as per the 2021 5th edition WHO Classification of Central Nervous Tumors) or mixed chromophob-eosinophil pituitary adenoma.

The brain tissue showed marked paracellular edema, swollen endotheliocytes of small vessels passing through the pia mater, and ischemic neural cells.

The structural features of some small fragments of optic nerve tissue conformed to that reported in reactive perineural gliomatosis. Macroscopic examination of optic nerve biopsy specimens showed that their tissue had structure similar to that of a degenerated optic nerve. The optic nerve was thinned and swollen, and endoneural and perineural tissue was of non-uniform density. At some sites, the optic nerve sheaths appeared thickened, yellowish, and very dense. The cut surface of the tissue was fibrous and whitish to yellowish in color.

Microscopically, a thinned optic nerve showed isolated neural bundles with degenerative changes, and the volume percentage attributed to bundles was significantly lower than normal. In these bundles, there were predominantly nucleus-free fibrous sites (sheets) separated by connective tissue trabeculae (endoneurium), and the latter appeared fragmented with signs of fibrosis and focal hyalinosis (fibrous structures with hyperchromic rod-shaped fibroblast nuclei). In parenchymal sheets, nucleus-free fibrous sites showed a certain non-concentric pattern with a smooth curved structure. The number of glial cells was moderate inside neural bundles. Nuclei of these cells were monomorphic, mostly elongated and bipolar with moderately dense chromatin. No mitosis figures were noted. Vessels were few, had no signs of endothelial hyperplastic changes, and were seen in optic nerve stroma; walls of small vessels appeared thickened and hyalinized (Fig. 3).

Discussion

The optic nerve is unique since it has special microanatomy and macroanatomy. The pathophysiological mechanisms in lesions of the peripheral nerve are similar to the morphogenesis of degenerative and destructive changes in the optic nerve, which facilitates our understanding of the mechanisms of vision loss in compression and traction lesions of these nerves.

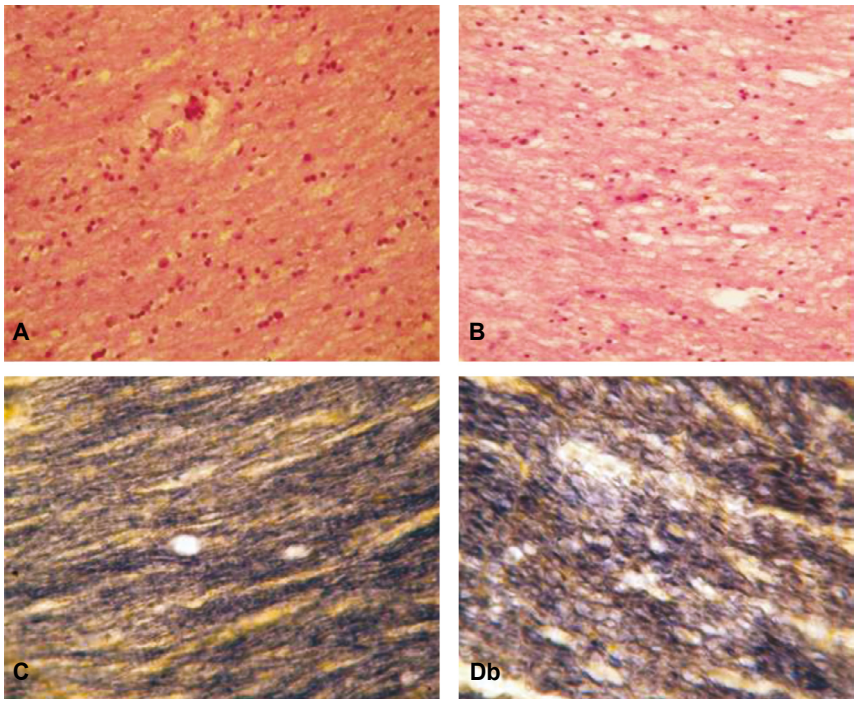

Fig. 3. Microscopic examination of optic nerves. (A) Right optic nerve (hematoxylin and eosin staining). (B) Left optic nerve (hematoxylin and eosin staining). (C) Right optic nerve (hematoxylin and picro-fuchsin staining). (D) Left optic nerve (hematoxylin and picro-fuchsin staining).

The mechanisms of vision loss in prolonged chiasmal and optic nerve compression are, however, still elusive. Studies in recent decades have reported that changes in the optic nerve are caused by the development of demyelination, glial proliferation, remyelination, Wallerial proliferation, retrofrade degeneration, conduction block, axoplasmic stasis and ischemic injury [14].

Seddon [15] was the first to classify nerve injuries to the peripheral nerve into three categories based on the presence of demyelination and the extent of damage to the axons and the connective tissue of the nerve.

The mildest form of injury is called neurapraxia, defined by focal demyelination without damage to the axons or the connective tissue. Neurapraxia typically occurs from mild compression or traction of the nerve and results in a decrease in conduction velocity. Depending on the severity of demyelination, the effects can range from asynchronous conduction to conduction block, causing muscle weakness. There is a temporary loss of function which is reversible within hours to months of the injury [15].

The next level is caused axonotmesis, which involves direct damage to the axons in addition to focal demyelination while maintaining continuity of the nerve's connective tissues. Changes take place in both the axon and the cell body. These changes include leakage of intra-axonal fluid from the injured nerve, swelling of the distal nerve segment and disappearance of neurofibrils in the distal segment [15].

The most severe form of injury is neurotmesis, which is a full transaction of the axons and connective tissue layers wherein complete discontinuity of the nerve is observed [15].

In 1951, Sunderland [16] expanded Sendon's classification to five degrees. Axonotmesis is divided into Sunderland type II (axonal injury), Sunderland type III (axonal and endoneural injury), and Sunderland type IV (axonal, endoneural and perineural injury) [16].

The most notable feature of vision loss with chiasmal compression is that decompression can result in immediate improvement in visual function (within minutes to hours after decompression). Such a rapid visual recovery does not occur with other forms of optic nerve injury [14].

In the case reported herein, the vision loss mechanism is a combination of chronic compression and traction injury to the optic nerve (which conforms to Seddon type I injury), which was complicated by acute massive intratumoral hemorrhage, with the latter contributing to the traction injury (Seddon type II-III injury). There was microscopical evidence of the changes typical of optic nerve atrophy in the form of reduced volume of, and degenerative changes in, neural bundles; predominance of nucleus-free fibrous sites; smooth parenchyma; non-concentric pattern, and endoneurium with signs of fibrosis and focal hyalinosis. Endoneurial fragmentation and edema developed due to the changes resulting from intracranial hypertension and intratumoral hemorrhage.

Conclusion

Chronic compression and traction injury to the optic nerve is characterized by a reduced volume of, and degenerative changes, signs of local fibrosis and focal hyalinosis in, neural bundles. An abrupt increase in optic nerve traction results in endoneurial edema.

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Disclosures

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All authors reviewed the results and approved the final version of the manuscript.

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Abbreviations: *GCS, Glasgow coma score; GPA, giant pituitary adenoma; PA, pituitary adenoma; MD, man defect; MRI, magnetic resonance imaging; MSCT, multispiral computed tomography*