CASE REPORT

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

# Complete oculomotor nerve palsy – first manifestation of gastric adenocarcinoma: clinical experience and literature review

IRINA ANDREEA PAVEL[1,2], CLAUDIA FLORIDA COSTEA[1,3], CĂTĂLIN CONSTANTIN ANTON[1,2], IOANA ROXANA MĂRIUŢA[1,2], DELIA GABRIELA CIOBANU APOSTOL[4], ANCA SAVA[5], ANDREI IONUŢ CUCU[6], SIMONA DELIA NICOARĂ[7], MIHAELA DANA TURLIUC[6,8], SPERANŢA SCHMITZER[9], DANIELA MARIA TĂNASE[10], DRAGOŞ VIOREL SCRIPCARIU[11], CAMELIA MARGARETA BOGDĂNICI[1,2]

[1] *Department of Ophthalmology, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

[2] *Department of Ophthalmology, St. Spiridon Emergency Clinical Hospital, Iaşi, Romania*

[3] *2nd Ophthalmology Clinic, Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iaşi, Romania*

[4] *Department of Morpho-Functional Sciences I, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

[5] *Department of Anatomy and Embryology, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

[6] *2nd Neurosurgery Clinic, Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iaşi, Romania*

[7] *Department of Ophthalmology, Faculty of Medicine, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[8] *Department of Neurosurgery, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

[9] *Department of Ophthalmology, Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[10] *Department of Internal Medicine, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

[11] *Department of General Surgery, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, Iaşi, Romania*

## Abstract

The diagnosis and management of the alteration of the normal function of the oculomotor nerve (third cranial nerve) varies depending on the characteristics of the paralysis, the age of the patient, and the associated symptoms and signs. Oculomotor nerve palsy may be caused by lesions located anywhere from the oculomotor nucleus to the termination of the third nerve in the extraocular muscles. Although there have been significant advances in neuroimaging to facilitate early diagnosis, the management of a patient presenting with isolated oculomotor palsy is still challenging. This review tackles the case of a 52-year-old patient, with a history of pulmonary tuberculosis (at the age of five), referred to the Department of Ophthalmology, St. Spiridon Emergency Clinical Hospital, Iaşi, Romania. The patient had diplopia accompanied by right eyelid ptosis, symptoms that began suddenly 10 days before hospitalization. The clinical examination showed right eye grade II palpebral ptosis, exotropia with limitation of eyeball movements in adduction, supra-/infraduction. Biomicroscopic examination of the anterior pole revealed the presence of anisocoria and light-near dissociation on the affected side. Numerous investigations were performed to identify the cause, starting with tumoral markers, which were within normal limits. Magnetic resonance angiography (MRA) was performed, and posterior communicating artery aneurysm was ruled out. The endocrinology examination and hormonal laboratory tests were also within normal parameters. Due to suspicions of generalized tuberculosis raised by the infectious disease doctor or presence of secondary lesions, thoraco-abdomino-pelvic computed tomography (CT) scan with contrast agent was done and its findings required gastroenterological exploration. After various explorations, the certainty diagnosis was set by histopathological examination, which revealed gastric adenocarcinoma.

***Keywords***: third nerve palsy, anisocoria, MRA, metastasis, gastric adenocarcinoma.

## Introduction

Paresis of the third cranial nerve is a frequent neurological condition in patients presenting ptosis or diplopia. Patients present either isolated or non-isolated paralysis, which may or may not affect the pupils. These clinical features are useful in locating the lesion along the course of the nerve and in determining its most likely cause [1]. The third nerve is a motor nerve and is involved in eye movements. The muscles supplied by the third nerve are the superior, inferior, and medial *rectus*, and also the inferior oblique muscle, which are responsible for elevation, depression, adduction, and extortion of the eyeball. The *levator palpebrae superioris* muscle is also supplied by the oculomotor nerve and is responsible for the elevation of the eyelid. Furthermore, the sphincter pupillae and ciliary muscle are supplied by the parasympathetic fibers from the Edinger–Westphal nucleus and are responsible for pupillary constriction and accommodation [2].

The oculomotor nucleus complex is located in the superior *colliculus* of the midbrain and is composed of the principal motor nucleus and Edinger–Westphal nucleus. The fibers pass through the interpeduncular fossa to reach the cavernous sinus and then the nerve divides into a superior and an inferior branch and enters the orbit [3]. The superior branch supplies the *levator palpebrae superioris* and superior *rectus*, while the inferior branch supplies the medial and inferior *rectus*, and also the inferior oblique muscle. Before

reaching the orbit, the fibers innervating the pupillary muscles are located superficially in the nerve trunk and may be affected by different lesions, such as aneurysms or tumors [2, 4].

A rare complication associated with cancer is tumor metastasis located in the pituitary gland (MPG). This accounts for <1% of all sellar or parasellar tumors and approximately 5.1% of all metastatic tumors located in the brain. MPG from gastric cancer (GC) is a topic rarely mentioned in literature. GC usually metastasizes through the lymph nodes, blood, peritoneum, or bone marrow, and the most common locations of metastases are the liver, lung, peritoneum, and bones [5]. GC diagnosis is set by histopathological (HP) examination of the biopsied tissue or cytological evaluation of the gastric brushing/washes. To help describe GC, several classification systems have been suggested.

Two of the most widely used classifications are the Laurén and *World Health Organization* (WHO) systems. The Laurén classification divides gastric adenocarcinomas into intestinal, mixed, diffuse, and indeterminate subtypes and varies from a morphological, epidemiological, progression pattern, genetic and clinical point of view. The *WHO* classification is based on purely histo-morphological appearance. Thus, the *WHO* classifies GCs into tubular, mucinous, poorly cohesive, papillary, and mixed carcinomas [6].

### Aim

The aim of this paper was to report a rare case of metastatic GC in the pituitary gland (PG) and to review other similar cases in literature. Our case report provides important clinical information for diagnosis and management. Gastric biopsy and HP assessment are key to accurate diagnosis setting and therapy. The treatment in these cases is oncological, so the need for accurate identification of biological tumor behavior requires complex immunohistochemical staining.

## Case presentation

We searched the *PubMed* database using the following keywords: 'third nerve palsy', 'anisocoria', 'MRA', 'metastasis', 'gastric adenocarcinoma' to find relevant papers on the selected topic. We will compare all relevant literature papers with our findings.

A 52-year-old man, with a history of pulmonary tuberculosis at age of five, presented for sudden onset of painless right ptosis, binocular horizontal diplopia, which was exacerbated in levoversion, symptoms that had begun 10 days before presentation. Remote visual acuity (VA) was best corrected visual acuity (BCVA) 0.1 *log*MAR (logarithm of the minimum angle of resolution) in the right eye (RE) and 0 *log*MAR in the left eye (LE). Intraocular pressures measured using Goldmann applanation tonometry was 17 mmHg in both eyes (*oculus uterque* – OU). Ishihara pseudoisochromatic plates were used to test color vision, which was not affected, with 14/14 plates being correct in OU. External slit lamp evaluation revealed stage II RE ptosis (Figure 1). The patient's pupillary responses were unequal. We also noted anisocoria, pupillary diameter measuring 5 mm in the RE, with sluggish pupillary reflex and 3 mm in the LE, more significant in the light without relative afferent pupillary defect (Figure 2). Ocular motility examination revealed right exotropia of 45 prism diopters (PD) in primary position, a deficit in adduction, supraduction and infraduction for the right eyeball; abduction was normal (Figures 3–7). No restriction was noted with forced duction testing. Fundus examination showed physiological cupping of the optic discs, with distinct and pink neural retinal rims for OU. Evaluation of the vasculature revealed no arterial attenuation. The maculae were without lesions. Based on the clinical presentation, complete third nerve palsy was considered (with pupil involvement). Assuming the presence of complete acute-onset third nerve palsy with pupillary involvement and the age of the patient, emergent magnetic resonance angiography (MRA) was performed, and posterior communicating artery aneurysm was ruled out. Brain MRA revealed an expansive sellar and parasellar mass, with inhomogeneous structure, measuring 23/23.5/33 mm. The described mass was extending in the right cavernous sinus, occupying it, and encompassing the right internal carotid artery (permeable) (Figures 8 and 9). Multiple osteolytic lesions were revealed in the C1–C5 vertebral bodies and in the paravertebral soft tissue corresponding to C1. Laboratory tests were performed, including liver function tests, full blood count, urea and electrolytes, and the results were within normal limits. The endocrinology examination findings and hormonal laboratory tests results, such as free triiodothyronine (FT3), free thyroxine (FT4), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), cortisol and testosterone were also within normal parameters. Tumoral markers were negative [carcinoembryonic antigen (CA)125, CA19-9, alpha-fetoprotein (AFP)]. Abdominal ultrasound revealed a hypoechoic mass in the right lobe of the liver, without mediastinal adenopathy, and free fluid in the pouch of Douglas. Thoracic radiography found an opacity with blurred outlines, which breached the cortical bone and invaded the soft tissue around the C7–T1 transverse apophyses. Due to suspicions of generalized tuberculosis raised by the infectious disease doctor or presence of secondary lesions, a thoraco-abdomino-pelvic computed tomography (CT) scan with contrast agent was done. Numerous secondary bone disseminations in the thoracic and lumbar spine, ischium, pubis, and femur were identified. We suspected liver metastasis, and the gastric parietal thickening of the lesser curvature was highly suggestive of malignancy. Abdomino-pelvic CT pathological findings required gastroenterological exploration. Superior digestive endoscopy revealed a vegetative tumor extending from the cardia to the lesser gastric curvature from which a biopsy was taken. During hospitalization and the first follow-up, he progressed towards complete ptosis and 20 kg weight loss over two weeks. The certainty diagnosis was set by HP examination, which revealed low-grade infiltrative gastric adenocarcinoma (moderately differentiated), with solid papillary and focal tubular architecture, and with reduced desmoplastic stroma (Figures 10, A and B). For tumor phenotyping, several markers were immunohistochemically assessed: cytokeratin AE1/AE3 (CK AE1/AE3) result was positive (Figure 11); synaptophysin result was negative (Figure 12); human epidermal growth factor receptor 2/neu (HER2/neu) – 2+ (slightly positive): complete membrane marking and moderate basolateral, weakly positive over 10% of tumor process (>5 cohesive tumor cells) (Figure 13). As the immunoexpression of HER2/neu was equivocal, *in situ* hybridization (ISH) HER2 testing was recommended. Given the advanced stage of the tumor, the patient could only benefit from oncological treatment. He was referred to the Regional Institute of Oncology, Iaşi, Romania. The patient's vital prognosis is guarded considering his stage IV GC.

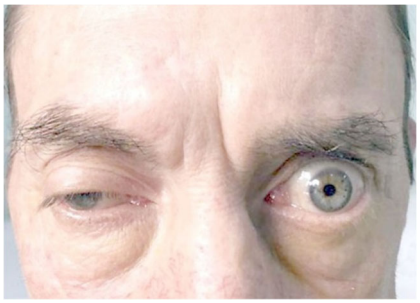

**Figure 1** – *RE: Grade II right ptosis. RE: Right eye.*

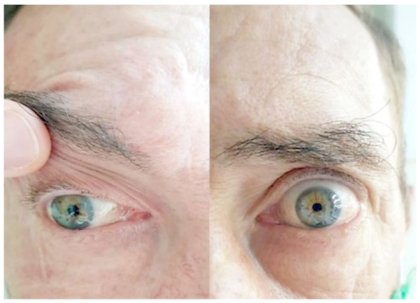

**Figure 2** – *Anisocoria.*

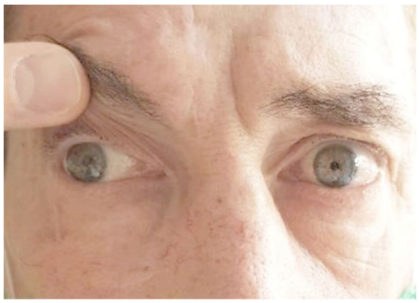

**Figure 3** – *RE: Exotropia in primary position.*

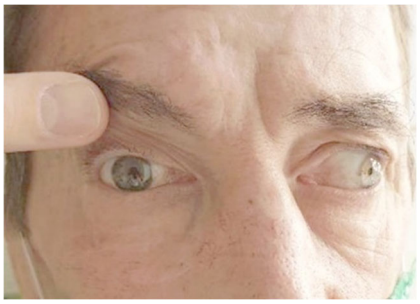

**Figure 4** – *RE: Adduction deficit.*

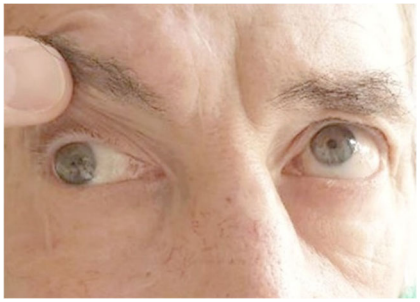

**Figure 5** – *RE: Supraduction*

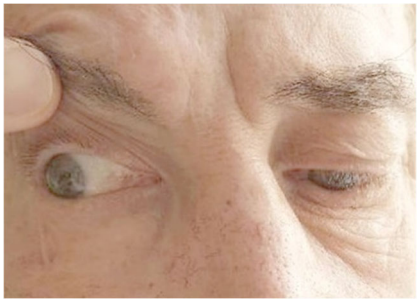

**Figure 6** – *RE: Infraduction deficit.*

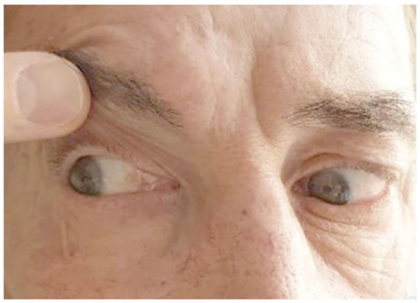

**Figure 7** – *RE: Normal abduction.*

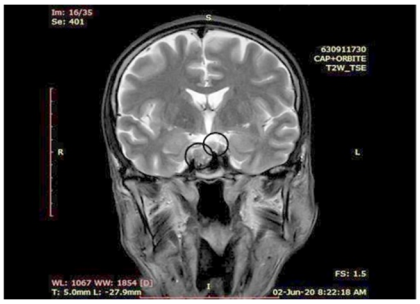


**Figure 8** – *Sellar mass extended in the right cavernous sinus.*

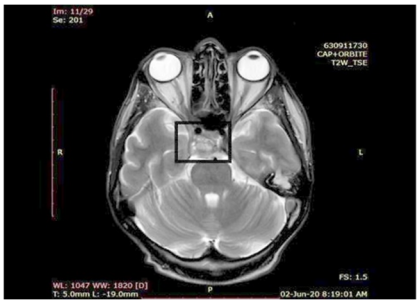


**Figure 9** – *Sellar and parasellar mass in contact with internal carotid artery.*

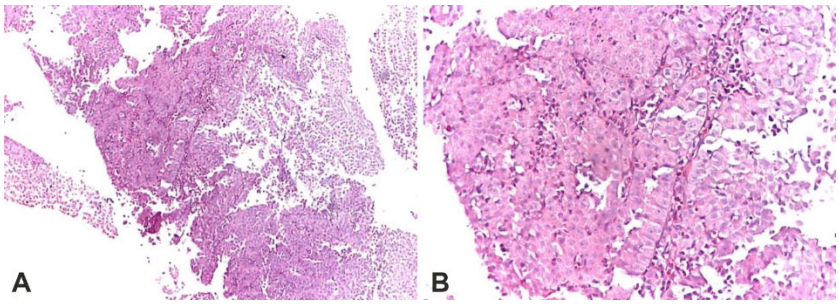


**Figure 10** – *(A and B) Moderately differentiated gastric adenocarcinoma. HE staining: (A) ×40; (B) ×100 (detail). HE: Hematoxylin–Eosin.*

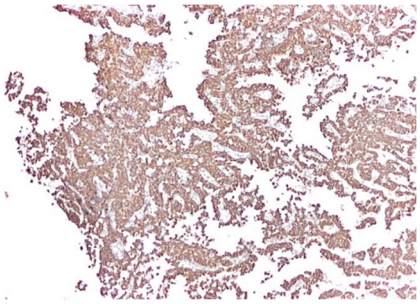

**Figure 11** – *Positive CK AE1/AE3 diffuse immunolabeling in tumor proliferation (×40). CK: Cytokeratin.*

**Figure 12** – *Negative synaptophysin immunostaining (×40).*

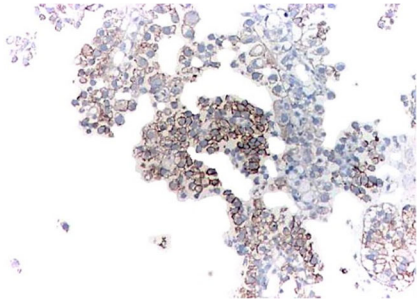

**Figure 13** – *Slightly HER2/neu positive immunostaining (×100). HER2: Human epidermal growth factor receptor 2.*

## Discussions

Carcinomas can metastasize to the PG but are extremely rare. It is even less common for the metastasis to result from gastric adenocarcinoma [5, 7]. Metastatic tumor cells can spread to juxtasellar tissues by hematogenous dissemination or lymphatic microvessels [8].

The most common metastases located in the PG are determined by lung and breast cancers, followed by intestinal, liver, and prostate cancers. Gastric metastases in the PG are rarely described although metastases from GC, such as adenocarcinomas, are common [9]. There are only five cases of MPG from GC reported in literature until 2015 [5].

In our patient, MPG was manifested by impairment of the intracavernous section of the oculomotor nerve. By sparing the lateral *rectus* and superior oblique muscle, the ocular deviation appeared in exotropia [10]. The pupil was involved, with the occurrence of anisocoria due to impairment of the parasympathetic fibers and paralysis of the pupillary sphincter muscle [11]. Diplopia was due to ocular deviation, with the projection of the image in an extrafoveal point. Complete third nerve palsy indicates total dysfunction of the extraocular muscles and *levator palpebrae superioris* [10].

Advances in the field of diagnosis depending on the genetic profile of cancer help to evaluate cancers from a molecular point of view as well. The best method of treating GC nowadays is surgical resection. Also, chemotherapy is still used as an elective therapy when surgical intervention is not possible or when metastases are present, as in the present case [12, 13].

The therapeutic approach is first and foremost dependent on HP characterization. It is often necessary to perform immunohistochemistry (IHC) staining [14]. As specified, several immunohistochemical markers were determined. When morphology is not enough, the first diagnostic IHC panel will include several antibodies directed against epithelial antigens (broad-spectrum pan-CK antibody cocktail). CKs are intermediate filaments specific to epithelial cells expressed in some normal human tissues, having 20 different subunits. Nowadays, anti-CK antibody cocktails are widely used to predict the anatomic origin of adenocarcinomas [15]. In our case, CK AE1/AE3 was positive. The broad type of cancer was thus detected (carcinoma). To detect the origin of gastric adenocarcinoma, phenotypic expressions of CKs were used: CK7–/CK20+; CK7+/CK20+ [16]. Since the stomach is the most important human neuroendocrine organ, synaptophysin was assessed to rule out a possible neuroendocrine tumor. The result was negative. The immunohistochemical expression of HER2 was also evaluated, and the result was slightly positive. When the findings are equivocal, HER2 (ERBB2) ISH is recommended [17]. HER2 is a transmembrane tyrosine kinase and a member of the epidermal growth factor receptor (EGFR) family, which is involved in the regulation of cell adhesion, differentiation, and proliferation. HER2 overexpression occurs in 10% to 40% of GCs and is more frequent in intestinal and gastroesophageal junction (GEJ) tumors. Trastuzumab, a recombinant humanized anti-immunoglobulin G1 (IgG1) antibody against the extracellular domain of HER2, blocks the cell surface HER2 receptor, sensitizes cancer cells to tumor necrosis factor (TNF), and inhibits neoangiogenesis. Trastuzumab also exhibits anti-cancer activity by inducing antibody-dependent cytotoxicity. This drug inhibits proliferation, enhances apoptosis, and reduces neoangiogenesis. Although the patient had poor HER2 expression, this type of therapy could be instituted as an adjuvant in the first line with fluoropyrimidines and Cisplatin [18–20]. Instead, our patient was administered only one course of chemotherapy and never came to subsequent follow-ups (the cause is unknown).

The particularity of our case is the presence of extremely rare MPG from GC whose only manifestation was the occurrence of complete oculomotor nerve palsy. In this case, resection of the primary tumor is not indicated. Chemotherapy treatment is the only solution with better survival rates and increased quality of life. As for the ophthalmic prognosis, it is also reserved. It may remain stationary, regress or progress to aberrant regeneration. This usually occurs following nerve compression by a slowly growing tumor. The torn myelin sheath and perineurium determine the regenerating axons to misdirect and innervate surrounding muscles, such as the superior oblique, *levator palpebrae superioris*, and occasionally the iris sphincter muscle. This causes clinical manifestations, such as elevation of the eyelid during attempted adduction (inverse Duane syndrome) or depression (pseudo-Von Graefe sign) or miosis in an otherwise unreactive pupil (pseudo-Argyll Robertson pupil) [2].

Oculomotor nerve dysfunction may cause doubling of vision, dropping of upper eyelid, eye pain, headache, glare, monocular blurred vision, or any combination of these [21]. When a patient comes with an acute onset of movement limitation in one eye, classifying the defect as complete or partial with or without pupil involvement is helpful in setting a diagnosis and further evaluation. In 25% of cases, isolated paralysis of the oculomotor nerve is idiopathic and is frequently caused by basilar lesions. The most common cause of isolated oculomotor nerve involvement is intracranial aneurysms or a tumor. Therefore, imaging investigations are necessary [22, 23].

In the literature, there is very little information regarding the association between oculomotor nerve palsy and gastric adenocarcinoma. Ocular symptoms can be developed as an initial manifestation of cancer in patients without cancer history [24].

A study conducted by Lee *et al.* (2015) studied the association between sixth cranial nerve palsy and gastric adenocarcinoma. The authors presented a rare case of clival metastasis of gastric adenocarcinoma in a 42-year-old female patient, manifesting as bilateral sixth nerve palsy [25].

Kong *et al.* (2019) reported a case of a 56-year-old male patient who presented vertical diplopia for 1.5 months. In this case, fourth cranial nerve palsy was reported as an initial presentation of advanced GC [26].

A study published by Ebert *et al.* (2009) reported the case of a patient with rapidly progressive bilateral total ophthalmoplegia due to bilateral cavernous sinus metastasis from gastric adenocarcinoma. Unilateral metastasis in the cavernous sinus occurs quite frequently, but a bilateral tumor infiltration of both cavernous sinus is very rare [27].

Carcinomas originating from almost every tissue can metastasize to the pituitary, but metastatic GC in the pituitary is extremely rare [7]. A study conducted in 2015 analyzed

the case of a 57-year-old woman who presented oculomotor paralysis, postorbital pain, and hypopituitarism as onset symptoms, but in this case, the patient had a history of surgical removal of GC [5].

Pozzessere *et al.* (2007) investigated the case of a 60-year-old male with liver and PG metastasis from GC. Despite the hormonal deficits, the patient did not report any specific symptom and no ophthalmological signs [28].

Izumi *et al.* (1999) analyzed the case of a patient with meningeal carcinomatosis accompanied by a small pituitary metastatic lesion from GC. The patient did not have any ophthalmological symptoms either [29].

Oculomotor nerve palsy can represent the initial manifestation in various malignant tumors. A recent study conducted in 2020 analyzed an isolated third nerve palsy presenting as the primary manifestation of a B-cell lymphoma [30]. Another study researched the case of a 72-year-old male whose final diagnosis was palsy of the oculomotor nerve by meningeal carcinomatosis in the context of urothelial carcinoma [31].

As can be seen in the previously mentioned studies, the oculomotor nerve palsy as first manifestation of gastric adenocarcinoma was not sufficiently investigated. The literature mentions the association between fourth and sixth cranial nerve palsy and gastric adenocarcinoma, but not the third cranial nerve palsy. Bilateral total ophthalmoplegia due to bilateral cavernous sinus metastasis from gastric adenocarcinoma is also mentioned in the literature.

There are studies in the literature that describe the MPG from GC, but they do not mention any ophthalmological symptoms. Moreover, oculomotor nerve palsy was described as first manifestation in other malignant tumors, but not gastric adenocarcinoma. Only one study mentions oculomotor paralysis in a female patient, but in this case, the patient was already known with GC.

## Conclusions

In this paper, we report a rare case of onset of a gastric neoplastic condition with an ophthalmological manifestation (oculomotor nerve palsy). The patient had a metastatic sellar mass that extended in the right cavernous sinus occupying it and encompassing the right internal carotid artery. We also discussed the importance of ophthalmic clinical signs in oculomotor nerve palsy, the necessary investigations, and HP and IHC examination approaches for an accurate final diagnosis.

### Conflict of interests

The authors do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interests in the context of the subject of the manuscript.

### References


[1] Blake PY, Mark AS, Kattah J, Kolsky M. MR of oculomotor nerve palsy. AJNR Am J Neuroradiol, 1995, 16(8):1665–1672. PMID: 7502972 PMCID: PMC8337757

[2] Ganger A, Yadav S, Singh A, Saxena R. A comprehensive review on the management of III nerve palsy. Delhi J Ophthalmol, 2016, 27(2):86–91. https://doi.org/10.7869/djo.215 https://www.djo.org.in/articles/27/2/a-comprehensive-review.html

[3] Roarty J. Third-nerve palsy. Knights Templar Eye Foundation, Pediatric Ophthalmology Education Center, ONE Network, The Ophthalmic News and Education Network – Strabismus, American Academy of Ophthalmology, Sep 28, 2017. https://www.aao.org/disease-review/third-nerve-palsy-2

[4] Flanders M, Hasan J, Al-Mujaini A. Partial third cranial nerve palsy: clinical characteristics and surgical management. Can J Ophthalmol, 2012, 47(3):321–325. https://doi.org/10.1016/j.jcjo.2012.03.030 PMID: 22687316

[5] Yang C, Zhang H, Zhang S, Liu L, Ma B, Lou J, Sun X, Zhang B. Oculomotor paralysis, postorbital pain, and hypopituitarism as first presentations of metastatic gastric cancer in the pituitary flourished by internal carotid aneurysm: a case report. Medicine (Baltimore), 2015, 94(50):e2317. https://doi.org/10.1097/MD.0000000000002317 PMID: 26683972 PMCID: PMC5058944

[6] Cisło M, Filip AA, Arnold Offerhaus GJ, Ciseł B, Rawicz-Pruszyński K, Skierucha M, Polkowski WP. Distinct molecular subtypes of gastric cancer: from Laurén to molecular pathology. Oncotarget, 2018, 9(27):19427–19442. https://doi.org/10.18632/oncotarget.24827 PMID: 29721214 PMCID: PMC5922408

[7] Fassett DR, Couldwell WT. Metastases to the pituitary gland. Neurosurg Focus, 2004, 16(4):E8. PMID: 15191337

[8] Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J. Structural and functional features of central nervous system lymphatic vessels. Nature, 2015, 523(7560):337–341. https://doi.org/10.1038/nature14432 PMID: 26030524 PMCID: PMC4506234

[9] Mocellin S, Verdi D, Pooley KA, Nitti D. Genetic variation and gastric cancer risk: a field synopsis and meta-analysis. Gut, 2015, 64(8):1209–1219. https://doi.org/10.1136/gutjnl-2015-309168 PMID: 25731870

[10] Katz B. Basic and clinical science course (BCSC) 2010–2011. Section 5: Neuro-ophthalmology. 1st edition, American Academy of Ophthalmology, San Francisco, USA, 2011, 228–229. https://www.bookdepository.com/Basic-Clinical-Science-Course-BCSC-2010-2011-Section-5-American-Academy-Ophthalmology/9781615251124

[11] Capó H, Warren F, Kupersmith MJ. Evolution of oculomotor nerve palsies. J Clin Neuroophthalmol, 1992, 12(1):21–25. PMID: 1532596

[12] Biagioni A, Skalamera I, Peri S, Schiavone N, Cianchi F, Giommoni E, Magnelli L, Papucci L. Update on gastric cancer treatments and gene therapies. Cancer Metastasis Rev, 2019, 38(3):537–548. https://doi.org/10.1007/s10555-019-09803-7 PMID: 31486976

[13] Clements WM, Wang J, Sarnaik A, Kim OJ, MacDonald J, Fenoglio-Preiser C, Groden J, Lowy AM. beta-Catenin mutation is a frequent cause of Wnt pathway activation in gastric cancer. Cancer Res, 2002, 62(12):3503–3506. PMID: 12067995

[14] Selves J, Long-Mira E, Mathieu MC, Rochaix P, Ilié M. Immunohistochemistry for diagnosis of metastatic carcinomas of unknown primary site. Cancers (Basel), 2018, 10(4):108. https://doi.org/10.3390/cancers10040108 PMID: 29621151 PMCID: PMC5923363

[15] Pavlidis N, Pentheroudakis G. Cancer of unknown primary site. Lancet, 2012, 379(9824):1428–1435. https://doi.org/1016/S0140-6736(11)61178-1 PMID: 22414598

[16] Pavlidis N, Briasoulis E, Hainsworth J, Greco FA. Diagnostic and therapeutic management of cancer of an unknown primary. Eur J Cancer, 2003, 39(14):1990–2005. https://doi.org/10.1016/s0959-8049(03)00547-1 PMID: 12957453

[17] Curea FG, Hebbar M, Ilie SM, Bacinschi XE, Trifanescu OG, Botnariuc I, Anghel RM. Current targeted therapies in HER2-positive gastric adenocarcinoma. Cancer Biother Radiopharm, 2017, 32(10):351–363. https://doi.org/10.1089/cbr.2017.2249 PMID: 29265917

[18] Shiroiwa T, Fukuda T, Shimozuma K. Cost-effectiveness analysis of Trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial. Br J Cancer, 2011, 105(9):1273–1278. https://doi.org/10.1038/bjc.2011.390 PMID: 21959871 PMCID: PMC3241558

[19] World Health Organization (WHO) Classification of Tumours Editorial Board. Digestive system tumours. WHO Classification of Tumours, 5th edition, vol. 1, International Agency for Research on Cancer (IARC) Press, Lyon, France, 2019, 93–95. https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Digestive-System-Tumours-2019

[20] Park JY, Ryu MH, Park YS, Park HJ, Ryoo BY, Kim MG, Yook JH, Kim BS, Kang YK. Prognostic significance of

neuroendocrine components in gastric carcinomas. Eur J Cancer, 2014, 50(16):2802–2809. https://doi.org/10.1016/j.ejca.2014.08.004 PMID: 25201164

[21] Biousse V, Newman NJ. Third nerve palsies. Semin Neurol, 2000, 20(1):55–74. https://doi.org/10.1055/s-2000-6833 PMID: 10874777

[22] Wiebers DO, Whisnant JP, Huston J 3rd, Meissner I, Brown RD Jr, Piepgras DG, Forbes GS, Thielen K, Nichols D, O'Fallon WM, Peacock J, Jaeger L, Kassell NF, Kongable-Beckman GL, Torner JC; International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. Lancet, 2003, 362(9378):103–110. https://doi.org/10.1016/s0140-6736(03)13860-3 PMID: 12867109

[23] Rush JA, Younge BR. Paralysis of cranial nerves III, IV, and VI. Cause and prognosis in 1,000 cases. Arch Ophthalmol, 1981, 99(1):76–79. https://doi.org/10.1001/archopht.1981.03930010078006 PMID: 7458744

[24] Yan J, Gao S. Metastatic orbital tumors in southern China during an 18-year period. Graefes Arch Clin Exp Ophthalmol, 2011, 249(9):1387–1393. https://doi.org/10.1007/s00417-011-1660-6 PMID: 21468734

[25] Lee A, Chang KH, Hong H, Kim H. Sixth cranial nerve palsy caused by gastric adenocarcinoma metastasis to the clivus. J Korean Neurosurg Soc, 2015, 57(3):208–210. https://doi.org/10.3340/jkns.2015.57.3.208 PMID: 25810862 PMCID: PMC4373051

[26] Kong E, Koh SA, Kim WJ. Rapid progression from trochlear nerve palsy to orbital apex syndrome as an initial presentation of advanced gastric cancer. Yeungnam Univ J Med, 2019, 36(2):159–162. https://doi.org/10.12701/yujm.2019.00129 PMID: 31620630 PMCID: PMC6784629

[27] Ebert S, Pilgram SM, Bähr M, Kermer P. Bilateral ophthalmoplegia due to symmetric cavernous sinus metastasis from gastric adenocarcinoma. J Neurol Sci, 2009, 279(1–2):106–108. https://doi.org/10.1016/j.jns.2009.01.006 PMID: 19187943

[28] Pozzessere D, Zafarana E, Buccoliero AM, Pratesi C, Fargnoli R, Di Leo A. Gastric cancer metastatic to the pituitary gland: a case report. Tumori, 2007, 93(2):217–219. https://doi.org/10.1177/030089160709300221 PMID: 17557575

[29] Izumi Y, Sakaguchi K, Udaka F, Tsujimura T, Kameyama M. [A patient with meningeal carcinomatosis accompanied by a small pituitary metastatic lesion from gastric cancer who developed cerebral salt wasting syndrome]. Nihon Ronen Igakkai Zasshi, 1999, 36(9):657–662. https://doi.org/10.3143/geriatrics.36.657 PMID: 10572452

[30] Khaleefah MM, Narayanan S, Dallal HAA, Jones CM, Friedland RP, Palade AE, Remmel KS, Shah JJ. Isolated oculomotor nerve palsy as a manifestation of diffuse large B cell lymphoma: a case report. Oncol Lett, 2020, 20(6):285. https://doi.org/10.3892/ol.2020.12147 PMID: 33014163 PMCID: PMC7520722

[31] Sousa FC, Barata AD, Teixeira F, Silva V. Unusual third cranial nerve palsy presentation with unexpected distant departure point. Int J Case Rep Images, 2017, 8(9):613–616. https://doi.org/10.5348/ijcri-201794-CR-10833 https://www.ijcasereportsandimages.com/archive/2017-articles-archive/009-2017-ijcri/CR-10833-09-2017-sousa/ijcri-1083309201733-sousa-full-text.php

***Corresponding authors***

Claudia Florida Costea, Associate Professor, MD, PhD, Department of Ophthalmology, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy, 16 University Street, 700115 Iaşi, Romania; Phone +40744–972 648, e-mail: costea10@yahoo.com

Dragoş Viorel Scripcariu, MD, Department of General Surgery, Grigore T. Popa University of Medicine and Pharmacy, 16 University Street, 700115 Iaşi, Romania; Phone +40723–913 425, e-mail: dscripcariu@gmail.com

*Received: June 23, 2022*

*Accepted: December 20, 2022*