LATE SIMULTANEOUS CARCINOMATOUS MENINGITIS, TEMPORAL BONE INFILTRATING MACRO-METASTASIS AND DISSEMINATED MULTI-ORGAN MICRO-METASTASES PRESENTING WITH MONO-SYMPTOMATIC VERTIGO – A CLINICO-PATHOLOGICAL CASE REPORT

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Background – Although vertigo is one of the most common complaints, intracranial malignant tumors rarely cause sudden asymmetry between the tone of the vestibular peripheries masquerading as a peripheral-like disorder. Here we report a case of simultaneous temporal bone infiltrating macro-metastasis and disseminated multi-organ micro-metastases presenting as acute unilateral vestibular syndrome, due to the reawakening of a primary gastric signet ring cell carcinoma.
Purpose – Our objective was to identify those pathophysiological steps that may explain the complex process of tumor reawakening, dissemination. The possible causes of vestibular asymmetry were also traced.
Methods – A 56-year-old male patient's interdisciplinary medical data had been retrospectively analyzed. Original clinical and pathological results have been collected and thoroughly reevaluated, then new histological staining and immunohistochemistry methods have been added to the diagnostic pool.
Results – During the autopsy the cerebrum and cerebellum was edematous. The apex of the left petrous bone

HEVENY VESTIBULARIS SZINDRÓMA KÉPÉBEN JELENTKEZŐ KÉSŐI MENINGITIS CARCINOMATOSA – KLINIKOPATOLÓGIAI ESETISMERTETÉS

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Célkitűzés – Bár a szédülés a leggyakrabban előforduló panaszok egyike, a vestibularis perifériák hirtelen kialakult tónusaszimmetriája hátterében mégis ritkán találunk perifériás eredetű betegséget utánzó malignus koponyaűri tumorokat. Dolgozatunk egy heveny vestibularis szindróma klinikai képében jelentkező, késői, temporalis csontot is beszűrő, disszeminált, generalizált mikrometasztázisokkal járó meningitis carcinomatosa esetet mutat be, ami egy primer pecsétgyűrűsejtes gyomorcarcinoma felébredését követően jelent meg.
Kérdésfelvetés – Célul tűztük ki, hogy azonosítjuk azon patofiziológiai folyamatokat, melyek magyarázatul szolgálhatnak a daganat felébredésére, disszeminációjára. A vestibularis tónusaszimmetria lehetséges okait szintén vizsgáltuk.
A vizsgálat alanya és módszerei – Ötvenhat éves férfi betegünk interdiszciplináris orvosi adatait retrospektíven elemeztük. Összegyűjtöttük és részletesen újraértékeltük az eredeti klinikai és patológiai vizsgálatok leleteit, majd új szövettani festésekkel és immunhisztokémiai módszerekkel egészítettük ki a diagnosztikus eljárásokat.

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was infiltrated and destructed by a tumor mass of 2x2 cm in size. Histological reexamination of the original gastric resection specimen slides revealed focal submucosal tumorous infiltration with a vascular invasion. By immunohistochemistry mainly single infiltrating tumor cells were observed with Cytokeratin 7 and Vimentin positivity and partial loss of E-cadherin staining. The subsequent histological examination of necropsy tissue specimens confirmed the disseminated, multi-organ microscopic tumorous invasion.

Discussion – It has been recently reported that the expression of Vimentin and the loss of E-cadherin is significantly associated with advanced stage, lymph node metastasis, vascular and neural invasion and undifferentiated type with $p<0.05$ significance. As our patient was middle aged and had no immune-deficiency, the promoting factor of the reawakening of the primary GC malignant disease after a 9-year-long period of dormancy remained undiscovered. The organ-specific tropism explained by the "seed and soil" theory was unexpected, due to rare occurrence of gastric cancer to metastasize in the meninges given that only a minority of these cells would be capable of crossing the blood brain barrier.

Conclusion – Patients with past malignancies and new onset of neurological symptoms should alert the physician to central nervous system involvement, and the appropriate, targeted diagnostic and therapeutic work-up should be established immediately. Targeted staining with specific antibodies is recommended. Recent studies on cell lines indicate that metformin strongly inhibits epithelial-mesenchymal transition of gastric cancer cells. Therefore, further studies need to be performed on cases positive for epithelial-mesenchymal transition.

Keywords: *carcinomatous meningitis, signet ring cell carcinoma, epithelial mesenchymal transition, acute vestibular syndrome*

Eredmények – Kórboncolás során a nagyagy és a kisagy oedamás volt. A bal piramiscsont csúcsát egy 2 × 2 cm nagyságú daganatmassza szűrte be. A gyomorreszekátum eredeti szövettani metszeteinek újraértékelése submucosus daganatinfiltrációt igazolt vascularis invázió jeleivel. Immunhisztokémiai vizsgálatokkal dominálóan magányosan infiltráló daganatsejteket láttunk cytokeratin 7- és vimentinpozitivitással, valamint részleges E-kadherin szövettani festésvesztéssel. A kórboncolás során nyert szövetminták ezt követő hisztológiai vizsgálatai igazolták a disszeminált, többszervi mikroszkopikus daganatinváziót.

Megbeszélés – Az újabb eredmények igazolták, hogy a vimentin kifejeződése, valamint az E-kadherin elvesztése szignifikáns ($p < 0,05$) kapcsolatot mutat az előrehaladott stádiummal, a nyirokcsomóáttétek jelenlétével, a vascularis és neuralis invázióval, valamint a nem differenciált szöveti típussal. Betegünk középkorú volt és nem volt immunhiányos állapotban, így a gyomorcarcinoma kilenc éven át tartó alvó állapotot követő felébredését nem tudtuk megmagyarázni. A daganat szervspecifikus tropizmusa, melyet a „seed and soil" teóriával magyaráznánk, kifejezetten váratlan volt, mivel a gyomorrákok ritkán képeznek áttétet az agyburkokon, hiszen a daganatsejtek elenyésző számban jutnak át a vér-agy gáton.

Következtetések – Az előzményben szereplő malignus folyamat, valamint egy új neurológiai tünet megjelenése fel kell, hogy keltse a klinikus figyelmét a központi idegrendszer daganatos érintettségére, melyet adekvát, célzott diagnosztikus és terápiás stratégia megtervezése kell, hogy kövessen. Ehhez célzott szövettani festési eljárások, specifikus antitestek alkalmazása szükséges. A közelmúlt eredményei sejtkultúrákon igazolták a metformin epithelialis-mesenchymalis transitiót erősen gátló hatását gyomorrák esetében. Így további kutatást kell végezni azon esetekben, amelyekben az epithelialis-mesenchymalis transitióra pozitív eredményeket kapunk.

Kulcsszavak: *carcinomatosus meningitis, pecsétgyűrűsejtes gyomorcarcinoma, epithelialis-mesenchymalis transitio, heveny vestibularis szindróma*

Based on the estimation of global cancer statistics (GLOBOCAN), gastric cancer (GC) was responsible for over 1,000,000 new cancer cases in 2018 and the cause of an estimated 783,000 deaths. Incidence rates are significantly higher in Eastern Asia. Mortality is varying between the two sexes from 6.5 to 9.5% for females and males respectively[1]. The prognosis of GC is highly dependent on its stage at verification. Gastric carcinogenesis and the metastatic cascade is a multistep and multifactorial process. GC commonly causes metastasis to the peritoneal cavity, lymph nodes, liver and lung. The intracranium is a very rare site for metastasis. From a retrospective cohort of 8080 subjects with advanced GC, only 13 patients developed intracranial metastases (~1.6‰). Out of these 13 patients, 5 were shown to have carcinomatous meningitis (CM) while the remaining 8 presented with parenchymal metastasis[2].

ABBREVIATIONS

ALP: alkaline phosphatase
AVS: acute vestibular syndrome
CM: carcinomatous meningitis
CSF: cerebrospinal fluid
CT: computer tomography
EMT: epithelial-mesenchymal transition
GC: gastric cancer
IHC: immunohistochemistry
MRI: magnetic resonance imaging
SRCC: signet ring cell gastric carcinoma

Dizziness is one of the most common complaints in medicine, affecting 15–35% of the general popu-

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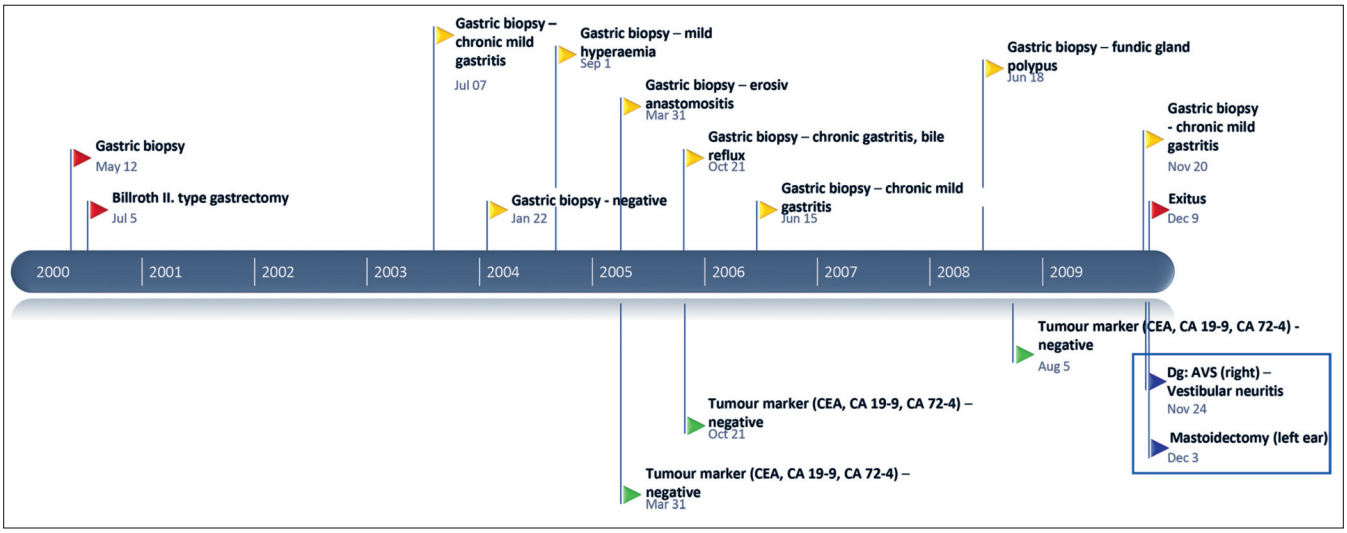

Figure 1. *Timeline of past history*

lation at some point in their lives[3]. In a multi-national, non-interventional observational study-cohort of 3,676 patients with vertigo, only 133 (3.6%) had cranial tumors, neoplasms[4]. Malignant tumors even more rarely cause acute vestibular syndrome (AVS), characterized by a sudden asymmetry between the tone of the vestibular peripheries. In patients with AVS the differentiation between vestibular neuritis and cerebellar stroke is the key differential diagnostic question[5–7].

In this report we present a patient who complained of imbalance and showed the clinical signs of AVS. Ten years earlier, this patient had gastrectomy due to primary gastric signet ring cell carcinoma (SRCC). In the background of the fulminant neurological symptoms, the post-mortem examinations revealed the unrecognized CM and the concomitant multi-organ micrometastases.

Case report

BRIEF PAST HISTORY

In July 2000 partial gastrectomy was executed according to Billroth II. (Dg: SRCC, diffuse mucosa type early carcinoma, on the basis of peptic ulcer; Dukes 2c type, pT1Nx). The patient received no adjuvant postoperative chemo- or radiotherapy. Repeated gastric biopsy until July 2003 and June 2006 showed only mild chronic gastritis of the anastomosis. In 2008 fundic gland polypus was found. Signs of dysplasia, malignancy, Helicobacter pylori infection were not seen at any point of the follow-up. Repeated tumor marker analysis for CEA, CA 19-9 and CA 72-4 form March 2005 to August 2008 were also unremarkable. For milestones of patient past history see timeline **(Figure 1)**.

PRESENTING COMPLAINTS AND INVESTIGATION RESULTS

In 2009, the 56-year-old male patient admitted to the Department of Otolaryngology, Head-Neck Surgery, with 2.5 weeks long leading complaints of intense nausea and vomiting. He was also mildly imbalanced with fluctuating, left temporal and retro-auricular headache. On physical examination the eardrums were normal. Pure tone audiometry showed symmetric, mild-moderate sensorineural hearing impairment. On routine vestibular tests, left-beating fast component horizontal jerk nystagmus was seen at left gaze position. By clinical head-impulse test overt saccades were seen on both sides. Furthermore, the stance and gait deviated to the right side. Signs were regarded as AVS, supporting that the right labyrinth was less active. Although the laboratory examinations at the point of the initial hospitalization showed only elevated alkaline phosphatase (ALP) level (212 U/l; normal value: <129), and otherwise were within or around normal ranges, the patient was hospitalized with vestibular neuritis, due to a suspected gastrointestinal infection (complaints of intense nausea and vomiting) as a primary cause. As the patient's blood pressure was elevated following the administration of intravenous pentoxiphyllin (200 mg diluted in 500 ml NaCl), and the oral betahistine was not prescribed due to the past history of gastric surgery, only vestibular training was advised to perform regularly.

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After the patient had been discharged with the complaints of mild imbalance and headache, 5 days later he was re-admitted with the symptoms of general malaise, nausea and vomiting. While observing at the intensive care unit the patient developed generalized seizure. Neurological examination revealed the following symptoms: *i)* exophthalmos of the left eye, *ii)* left-beating fast component horizontal jerk nystagmus at left and center gaze position with *iii)* truncal ataxia, *iv)* uncoordinated gait and *v)* latent right sided hemiparesis.

The diagnostic lumbar puncture showed 9 lymphocytes, 7 monocytes and 1 macrophage in 1 μL. The total protein level was 1.52 g/L, while the glucose level was 0.6 mM/L (serum: 5.34 mM/L). Cytological examination did not confirm cerebrospinal fluid involvement with SRCC features.

Abdominal ultrasound identified mild hepatosplenomegaly without pathological lymph nodes.

On repeated ear examination infiltrated (i.e. thick) tympanic membrane was observed on the left side, therefore myringotomy was performed, and only a few drops of serous discharge was drained.

Horizontal plane skull computer tomography (CT) with intravenous contrast material showed the bone destruction with ragged edges of the left petrous bone apex **(Figure 2)**.

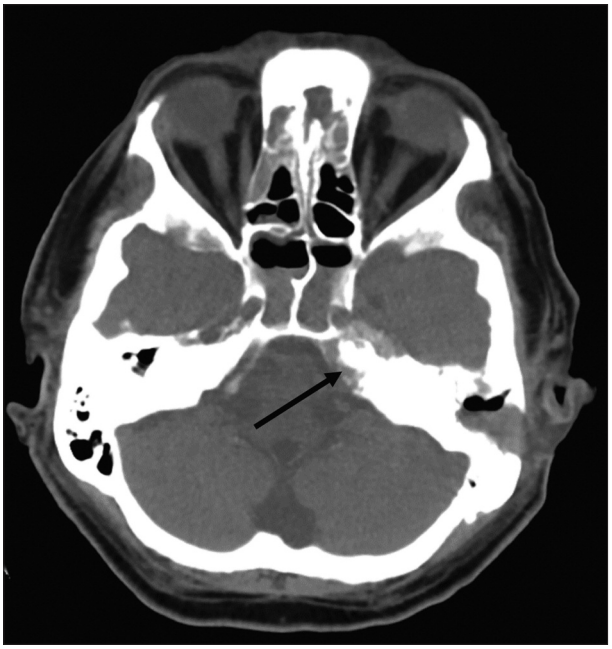

Figure 2. *Horizontal plane skull CT with intravenous contrast material showed the bone destruction with ragged edges of the left petrous bone apex (black arrow)*

Comparing the native and gadolinium enhanced T1-weighted magnetic resonance image (MRI) scans, contrast enhancement is showed at the apex of the left petrous bone, while the meninges were evaluated as normal **(Figure 3)**. The most frequent signs of CM (i.e. subarachnoid and parenchymal enhancing nodules, diffuse or focal pial enhancement, nerve root enhancement and brain parenchymal metastases) were not identified.

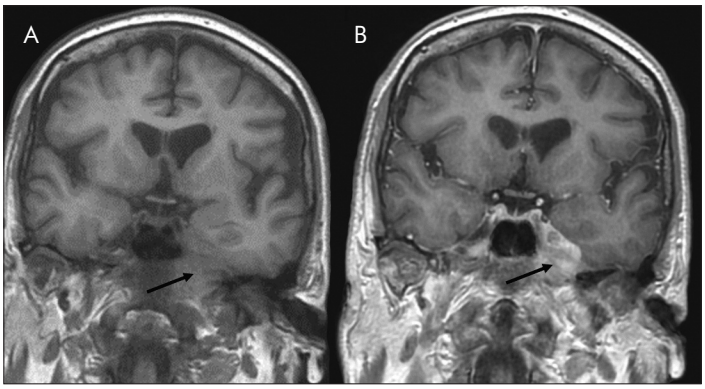

Figure 3. *Comparing the native* **(A)** *and gadolinium-enhanced* **(B)** *T1-weighted magnetic resonance image (MRI) scans, contrast enhancement is showed at the apex of the left petrous bone (black arrows)*

In order to exclude an unrecognized middle ear infection, the patient finally underwent mastoidectomy, that revealed air filled mastoid cells without any sign of infection of the left middle ear. After surgery, the patient was observed at the intensive care unit with continuous leaking hemorrhage from the surgical area. Subsequently the patient's state of consciousness began to fluctuate. Finally, deep coma developed, and the patient passed away. The cause of death was brain herniation due to increased intracranial pressure.

POSTMORTEM EXAMINATION AND REEVALUATION OF THE ORIGINAL GASTRIC RESECTION MATERIAL

During the autopsy the skull bones were intact. The dura mater was smooth and greyish-white in color. The venous sinuses and the arachnoid mater were intact. The cerebrum and cerebellum was edematous (1620gr). The sulci were shallow; the gyri were flattened. The cerebellar tonsils' surface was excavated. The apex of the left petrous bone was infiltrated and destructed by a tumor mass of 2x2 cm in size **(Figure 4)**. Other, remarkable macroscopic discrepancy was not revealed. The subsequent histological examination of necropsy confirmed the microscopic invasion of the meninx, the trigeminal ganglion and nerve trunks. Hematogenous micro-metastases were seen in the mediastinal hilar lymph nodes, in the lung and in the liver.

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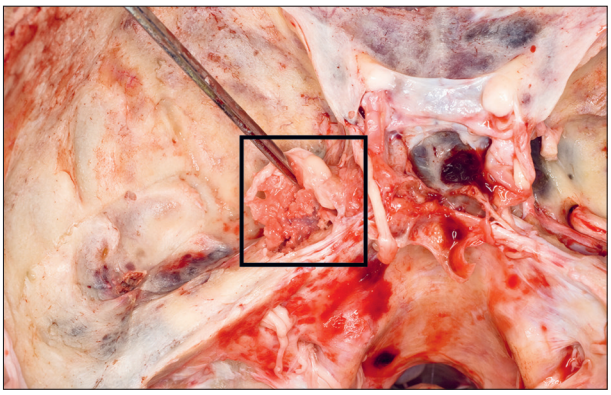

Figure 4. *Destructive tumor mass at the apex of the left petrous bone (black frame, the tumor mass is held by a forceps)*

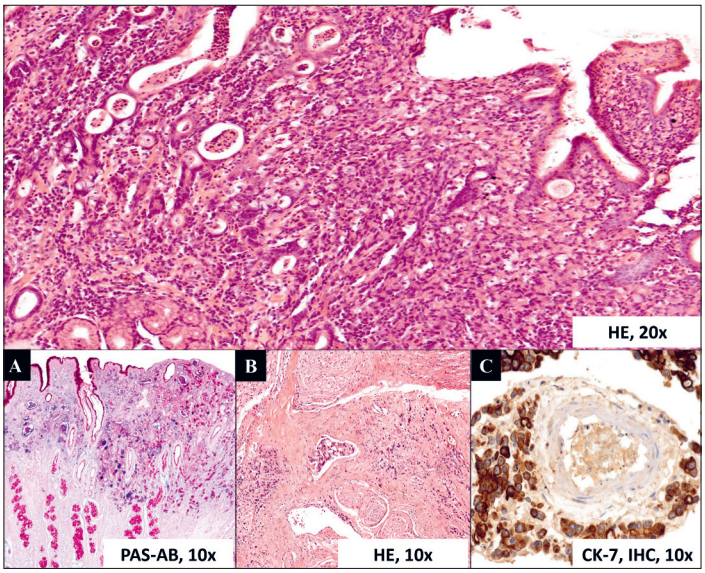

Figure 5. *Surgical specimen histology. Top image: Intramucosal diffuse sigillocellular infiltration (HE, 20x).* **A:** *Staining confirmed the intracellular mucus vacuole (PAS-AB at pH 2.5, 10x).* **B:** *Vascular invasion and nerve trunks (HE, 10x).* **C:** *Perivascular Cytokeratin 7 positive single tumor cells (IHC, 10x)*

HE: hematoxylin and eosin, PAS-AB: periodic acid-Schiff-AB, IHC: immunohistochemistry, CK-7: cytokeratin 7

Histological reexamination of the original gastric resection specimen slides revealed focal submucosal tumorous infiltration with a vascular invasion, but lymph node metastasis was not noted within the perigastric adipose tissue. By immunohistochemistry (IHC) mainly single infiltrating tumor cells were observed with Cytokeratin 7 and Vimentin positivity. Furthermore, gastric tumor cells showed partial loss of E-cadherin staining. These alterations indicate the epithelial-mesenchymal transition (EMT) phenomenon which can be a sign of a metastatic phenotype **(Figure 5.A–C)**. By IHC partial loss of E-cadherin membrane positivity was observed in the metastatic gastric carcinoma, with some perineural Vimentin positive carcinoma cells **(Figure 6.A–C)**.

This case report was authorized by the University of Szeged and National Scientific Research Ethical Review Board (No.4620; 21. Oct. 2019). All therapeutic and diagnostic departments involved, consented to this retrospective study, with data security kept in mind.

Discussion

The initial neurootological tests suggested that the right peripheral vestibular organ was hypo-functioning, but the pathological examination revealed the left middle ear infiltrated by the metastasis, thus we retrospectively hypothesized that the symptoms of the AVS were attributable to an excitatory pathology of the left inner ear. Although both the weakness of the right labyrinth and the excitation of the left labyrinth were equally possible explanation. Please note, that at the terminal stage of the disease neurootological examination couldn't not be performed. The left temporal and retro-auricular headache was attributable to the involvement of the trigeminal nerve trunk and ganglion **(Figure 6.A)**, while further neurological and psychomotor signs then the central origin of the disease.

During the course of the metastatic cascade, malignant cells must adapt to new environments very different from the tissue of origin. This process includes local invasion, intra- and extravasation, and colonization, while becoming an apparent, detectable metastatic disease. This period may last for years as the dynamic equilibrium between tumor promoting and suppressing activities are in balance, termed as tumor dormancy and reawakening[8]. As our patient was middle aged and had no immunedeficiency, the promoting factor of the reawakening of the primary GC malignant disease after a 9-year-long period of dormancy remained uncovered.

The tropism of tumor cells to form metastases in preferred tissues gave the illustrative analogy of "seed and soil" theory[9]. However, in our case presentation this tropism was a rare occurrence of GC to metastasize in the meninges given that only a minority of these cells would be capable of crossing the blood brain barrier. The explanation may be due to a cancer cell derived C3. This C3 activates the C3a receptor in the choroid plexus epithelium which leads to a disruption of the blood-cerebrospinal fluid (CSF) barrier. This would allow

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plasma components, including amphiregulin and other mitogens to enter the CSF and promote cancer cell growth, probably also in the meninges[10].

Recent studies emphasize the influence of tumor microenvironment on the characteristics of malignant cells, where pathological gastric EMT activation is considered to be significant[11]. This switch between these two histological modalities of the GC cells in which epithelial cells exhibit reduced intercellular adhesion and acquire migratory fibroblastoid properties, increase initiation and invasion, metastasis formation and chemo-resistance[11–14]. It has been recently reported that the expression of Vimentin and the loss of E-cadherin are significantly associated with advanced stage, lymph node metastasis, vascular and neural invasion and undifferentiated type with $p<0.05$[15]. From the mechanistic aspect, the leptomeningeal dissemination probably occurred via the Batson's vertebral venous plexus that might give the explanation for paradoxical, intracranial tumor spread[16–19]. CSF abnormalities were nonspecific in this case. The sensitivity could be increased with obtaining large sampling volumes or a repeated CSF analysis[20, 21]. The most sensitive technique of radiology is MRI with gadolinium enhancement[22, 23]. The prognosis of CM is poor; the treatment is almost always palliative[24]. In a single-center retrospective study with 155 consecutively analyzed patients with CM the overall median survival time was 4.8 months[25].

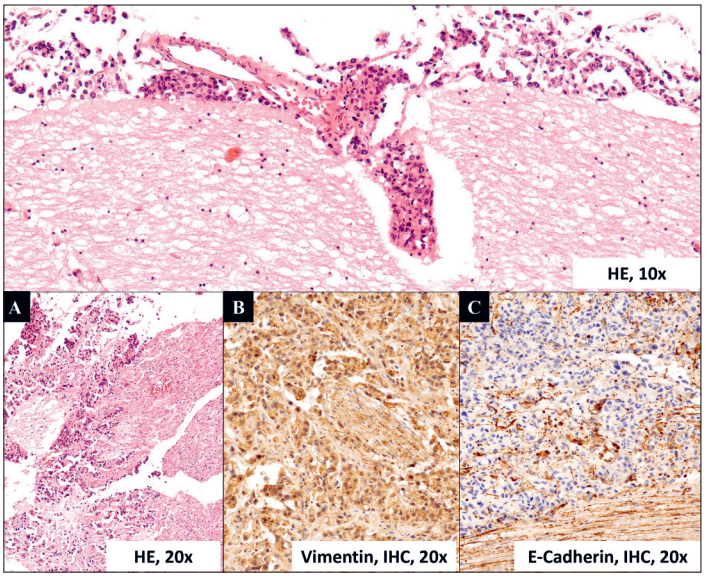

Figure 6. *Necropsy histology. Top image: Meningeal carcinomatous infiltration from gastric carcinoma (HE, 10x).* **A**: *Tumorous infiltration around of trigeminal nerve trunks (HE, 20x).* **B:** *some Vimentin positive carcinoma cells around a nerve (IHC, 20x).* **C:** *Partial loss of E-cadherin membrane positivity in metastatic gastric carcinoma (IHC, 20x)*

HE: hematoxylin and eosin, IHC: immunohistochemistry

Conclusion

Patients with past malignancies and new neurological symptoms should alert the physician to central nervous system involvement. Consequently, the appropriate, targeted diagnostic and therapeutic work-up should be established immediately. On the other hand, EMT is a significant predictor of aggressive metastatic behavior. Therefore, targeted staining with specific antibodies is recommended. Recent studies on cell cultures indicated that metformin strongly inhibited EMT of gastric cancer. Furthermore, wound-healing and invasion assays showed a significant decrease in cell migration and invasion after metformin treatment[26]. Therefore, further clinical studies need to be performed on cases positive for epithelial-mesenchymal transition.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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