

CLINICAL STUDY

Meningeal carcinomatosis as the first manifestation of malignant carcinomatosis

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Abstract: Meningeal carcinomatosis (MC) is a malignant infiltration of the leptomeninges and subarachnoid space and can be a devastating complication of a systemic malignancy. Although often found in patients with known metastatic malignancies, MC can also be the initial manifestation of an underlying malignancy. We report four case studies where back pain, dizziness, cognitive decline, headache and headache with the cranial nerve VI palsy were the first signs of MC. In two cases, adenocarcinoma ventriculi was found, in other one, the markers of the gastrointestinal tract malignancy were highly positive but malignancy was not found, and in the last one, there was a known breast carcinoma. The diagnosis of MC requires the finding of malignant cells in the cerebrospinal fluid, but sometimes several lumbar punctures are required to establish the diagnosis, and also MRI with gadolinium. Finally, we would like to highlight the fact that markedly decreased glycorrachia in cerebrospinal fluid (CSF) can also be the first sign of MC (Fig. 6, Tab. 2, Ref. 23). Full Text (Free, PDF) www.bmj.sk.

Key words: meningeal carcinomatosis, adenocarcinoma ventriculi, breast carcinoma, malignant carcinomatosis.

Meningeal carcinomatosis (MC) was first reported in 1970, and occurs most commonly in adults with a history of breast carcinoma, lung carcinoma and melanoma. MC is an infrequent sign of malignancy dissemination. Pure MC implies the involvement of the leptomeninges with no other metastasis in the central nervous system (CNS) (1). The incidence of MC appears to be increasing, perhaps due to a longer survival of patients with malignancy. MC has been reported to occur in 2 % to 25 % of patients with malignancy or cancer (2, 3) and typically has a poor prognosis even with an aggressive treatment (4). Nevertheless, MC is still considered infrequent, and its variable clinical manifestations make clinical diagnosis difficult to achieve (5). Signs of meningeal irritation, confusion, headache, cranial nerve deficits and seizures may indicate the leptomeningeal dissemination of a neoplasm primarily located outside the CNS (2). The presence of neoplastic cells in the cerebrospinal fluid (CSF) is diagnostic, but repeated CSF cytological examination is sometimes necessary (2). Diagnosis is supported by a cerebral MRI,

but only MRI with gadolinium reveals the pathology, while cerebral CT or MRI without contrast may be negative.

Case 1

A 40-year-old woman with a negative medical history experienced back pain at the end of August 2005. On October 21st, she was admitted to the hospital due to pain in the cervical spinal column and weakness of the lower extremities. On examination she was well orientated, without headache, she had a light nuchal rigidity and positive Kernig sign, and her gait was unstable. At that time, there were no other abnormalities in her clinical examination. Plain X-rays of the cervical and lumbal vertebrae were negative.

Because of the light meningeal syndrome, lumbar puncture and CSF examination was carried out with resulting increased protein at 1355 mg/l (normal: 150–400 mg/l) and lymphocytes – 66/3, only 6/3 leucocytes, but CSF glucose was markedly decreased at 0.6 mmol/l (blood sugar was 8.7 mmol/l).

The patient was transferred to the faculty hospital for further differential diagnosis on October 27th. At that time, she had the same clinical signs as described above, and she started to experience headache. Repeated lumbar puncture again revealed hypoglycorrachia – 1.1 mmol/l (glycemia – 5.2 ml/l), increased proteins: 2375 mg/l, increased leucocytes and erythrocytes (CSF was macroscopically clear). Brain CT was negative. On October 29th, the patient was confused, and she had an upward deviation of the eyes, so we decided (in combination with decreased glycorrachia) to start an antituberculosis therapy. On October 30th, the patient died due to cardiorespiratory failure after an unsuc-

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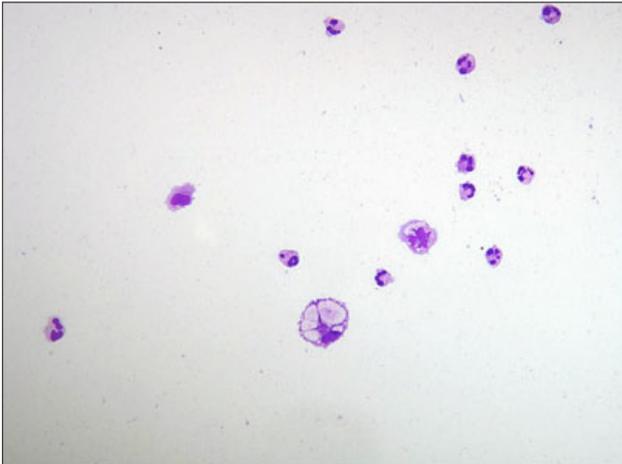


Fig. 1. Malignant cells with a central signet-ring cell in the cerebrospinal fluid (May-Grunwald-Giemsa 400x).

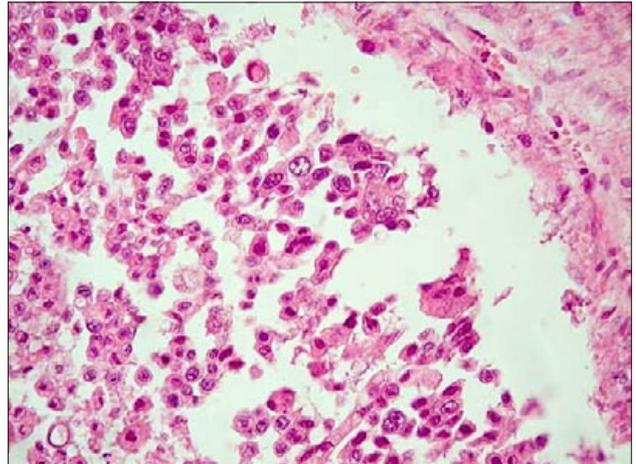


Fig. 3. Krukenberger tumor – carcinoma of the stomach spread to the ovary (Hematoxylin and eosin x40).

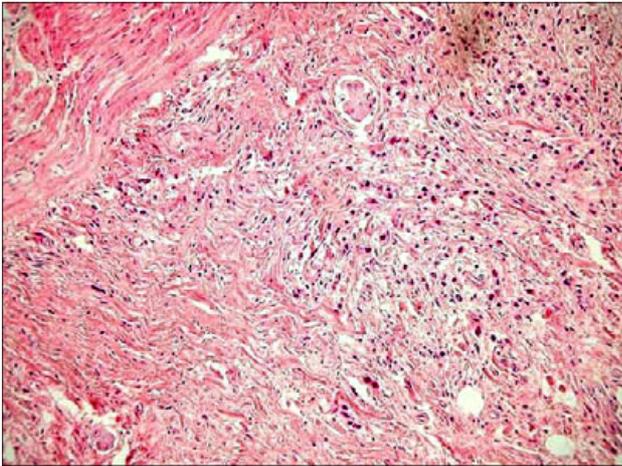


Fig. 2. Adenocarcinoma ventriculi (diffuse type according to Lauren) (PAS 20x). Lymphogenically spreading adenocarcinoma in the stomach wall, signet ring cells – intracellular mucin displaces the nuclei to the periphery of the tumor cells.

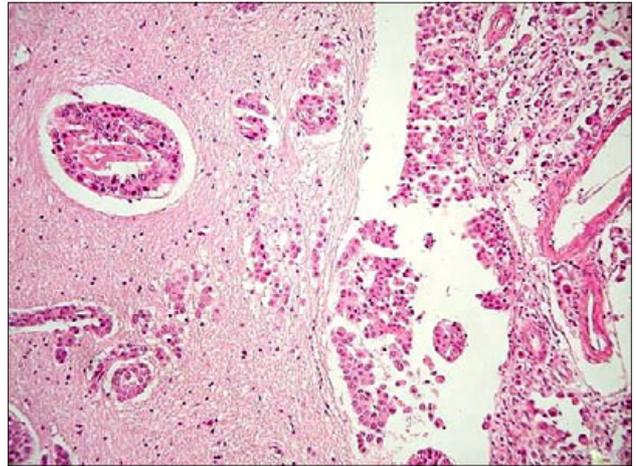


Fig. 4. Meningeal carcinomatosis with infiltration of the brain gray matter and perivascular malignant cells (Hematoxylin and eosin x20).

cessful resuscitation. Polymerase chain reaction (PCR) of CNS for mycobacterium tuberculosis was negative, and viral and bacterial cultures did not confirm any organisms. Cytology revealed malignant cells (Fig. 1). An autopsy revealed adenocarcinoma ventriculi (Fig. 2) with metastasis to lymphatic node, ovary (Fig. 3) and peritoneum, infiltration of leptomeninges of hemispheres (Fig. 4), cerebellum, and adenohypophysis.

Case 2

The neurological history of this 49-year-old woman with arterial hypertension, diabetes mellitus type II, ulcer ventriculi in her medical history started in April 2006 with headache and vomiting. A CT scan of her head was normal, but on lumbar puncture the cerebrospinal fluid contained 65 lymphocytes, and 830 mg/l proteins. She was treated at the Department of Infectious

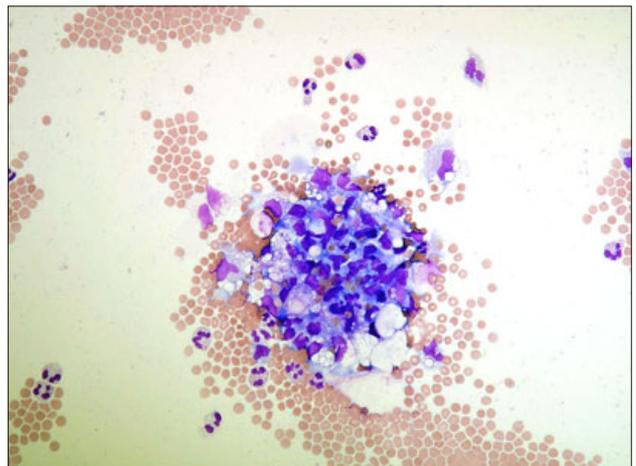


Fig. 5. Cluster of malignant cells with high pleomorphic appearance, multiple nuclei, prominent nucleoli and large vacuoles in the cytoplasm in cerebrospinal fluid (May-Grunwald-Giemsa 400x).

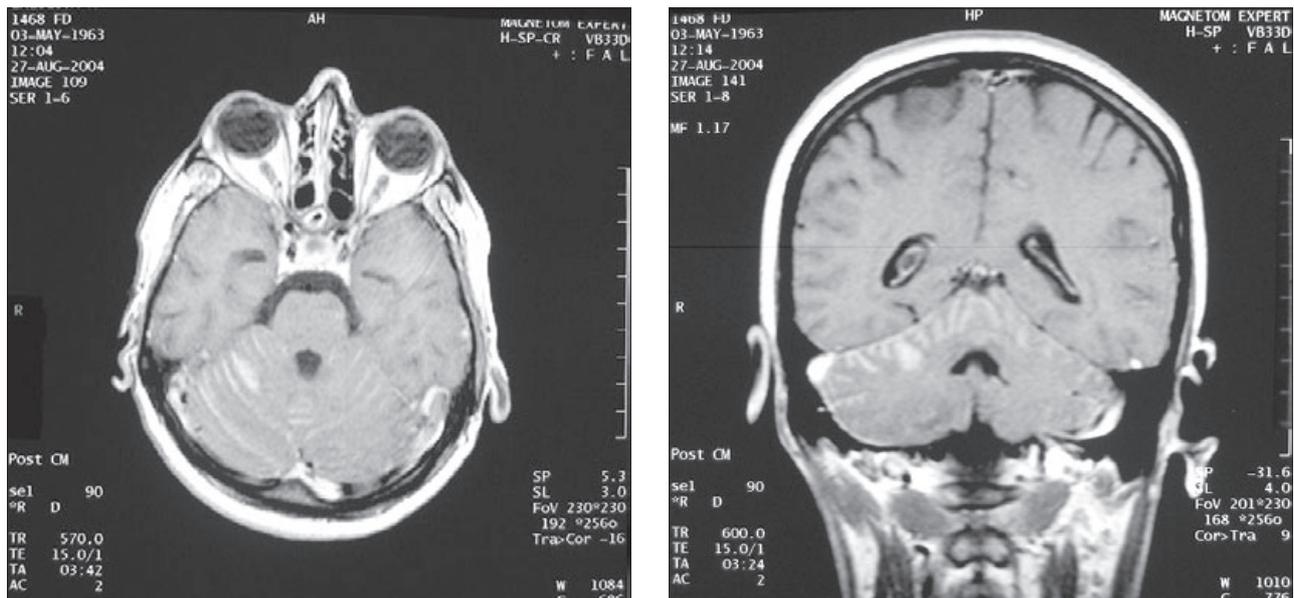


Fig. 6a, b. MR images (a – axial, b – coronal) – contrast enhanced T1 weighted MR image showing enhancement along the surface of the cerebellum.

Diseases for viral meningitis. She improved after therapy, but two days later she suffered again from headache and vomiting, and her neurological condition deteriorated over the following days; quadraparesis and the cranial nerve VII peripheral palsy appeared on the right side. MRI of the cervical spinal cord and cervical enlargement did not indicate malignancy. On May 31st, she was admitted to our department. The patient's neurological condition continued in deterioration with dysarthria, dysphagia and the cranial nerve III right-side palsy. Lumbar puncture again revealed mildly elevated elements: 36/3 lymphocytes, 24/3 leucocytes, 3/3 monocytes, elevated proteins: 925 mg/l (normal: 150–400 mg/l), and cytological examination discovered numerous malignant cells – clusters of cells with signet ring type (Fig. 5). Carcinoembryonic antigen (CEA) was increased – 250.4 (normal range to 7). Brain MRI with gadolinium demonstrated the pia-arachnoid enhancement (Fig. 6a, b). The diagnosis of meningeal carcinomatosis was made and the search for the primary tumour started. Gastroscopy, which was the first investigation, revealed a callous mediogastric ulcer as well as peptic ulcerations in the duodenal bulb, but urgent histological examination revealed carcinoma ventriculi. The patient died on June 3rd, three days after admission to our department.

Case 3

A 55-year-old woman was admitted to the regional hospital due to a 4-month history of dizziness, problems with walking balance and memory in June 2005. From her history, the most important diseases were rheumatic arthritis, sclerotic cholangitis and arterial hypertension. On admission, cognitive deficit, memory loss and ataxia were present. Blood count was normal, erythrocyte sedimentation rate was elevated – 34/70, hepatic

enzymes were increased – aspartate aminotransferase – AST, alanine aminotransferase – ALT, gamma-glutamyltranspeptidase – GMT, alkaline phosphatase – ALP, and cholesterol was increased, too. Lumbar puncture and CSF examination showed only a few elements – leucocytes 15/3, erythrocytes 8/3, but markedly increased proteins – 5442 mg/l, glycorrachia was 2.9 mmol/l (glycaemia – 4.4 mmol/l) and chlorides at 116 mmol/l. Borelia antibodies IgG and IgM were normal in serum and in CSF, as well as venereal disease research laboratory test (VDRL) and rapid protein reagin (RPR) tests. C-reactive protein (CRP), anti-streptolysin O (ASLO), and latex fixation (LATEX) were normal. Brain CT was negative, brain MRI revealed only brain and cerebellar atrophy. In an attempt to explain proteino-cytological dissociation, MRI of the cervical, thoracic and lumbar spinal cord was performed, but no pathology was found. On June 30th, 2005 she was transferred to our department. Clinical examination on admission showed no progression except for worsening of cognitive functions. Examination of CSF was repeated with resulting elevation of proteins to 9393 mg/l and a slight elevation of elements. Also, malignant cells with highly pleomorphic appearance, some of them large, with multiple nuclei, were found. The diagnosis of meningeal carcinomatosis was made and the search for the primary tumour started. However, the following investigations failed to demonstrate the presence of malignancy: X-rays of the lung, abdomen ultrasound, gynaecological examination, mammography, gastroscopy. Colonoscopy discovered only two polyps. CT of the abdomen revealed thickened colon wall with narrowed lumen. Increased tumour markers were present: carcinoembryonic antigen (CEA) – 116 ng/l (normal: less than 7), carbohydrate antigen (CA) 19-9: 76 IU/ml (normal: less than 37), CA 15-3: 93.6 IU/ml (normal: less than 30), CA 125: 109 IU/ml (normal: less than 35) and hepatic enzymes were increased

Tab. 1. Clinical features of the patients.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|----------------------------------|---|----------------------|---|---|
| Age | 40 | 49 | 55 | 41 |
| Sex | female | female | female | female |
| Diagnosis at the admission | tbc meningitis? carcinomatosis? | meningitis | progressive cognitive deficit | subarchnoid haemorrhage? metastasis cerebri? |
| History of malignancy | not known | not known | not known | breast carcinoma |
| First clinical symptoms | pain of cerviacal spinak column, weakness of lower extremities | headache, vomitus | dizzines, gait balance, memory problems | headache, vomitus |
| Meningeal signs at the beginning | ± | + | – | + |
| Cranial nerves palsy | – | – | – | VI, VII |
| Dizziness, vertigo | – | + | + | + |
| Other neurology symptoms | diabetes insipidus | cerebellar signs | ataxia | headache with sudden onset |
| Date of first symptoms | August 2005 | April 2006 | February 2005 | August 2004 |
| Admission at our department | 27.10.2005 | 31.5.2006 | 30.6.2006 | 25.8.2004 |
| Exitus | 1.11.2005 | 3.6.2006 | 8.8.2006 | 3.9.2004 |

CSF – cerebrospinal fluid

three times compared to the admission. On July 20th, 2005 the patient was transferred to the internal department, where she died one month later (August 8th, 2005). The primary tumour was not found. The relatives did not agree with the autopsy.

Case 4

The last patient was a 41-year-old woman, with a known history of malignant disease – breast carcinoma. In February 2004, she underwent surgery and later chemotherapy and radiotherapy due to breast carcinoma. On August 25th, 2004 she presented with headache, nausea and vomiting and she was admitted to our department. Clinical examination revealed a nuchal rigidity, a positive Kernig sign and the cranial nerve VI right-side palsy. Her blood count was normal, there was a mildly increased sedimentation rate – 12/17, but serum electrolytes, urea, creatinine, glucose were normal. Examination of the cerebrospinal fluid revealed moderate pleocytosis: lymphocytes 456/3, leucocytes 87/3 and moderate elevation of proteins: 930 mg/l (normal: 150–400 mg/l). Viral and bacterial cultures did not show any organisms. Brain CT was negative, and brain MRI with gadolinium demonstrated an enhancement around both hemispheres of the cerebellum. Based on the brain MRI, the diagnosis of meningeal carcinomatosis was made and the patient was indicated for oncological therapy, but she died on September 3rd, 2004 before the transfer to the oncology department.

Neurologic symptoms, signs and cerebrospinal fluid results in our four patients are presented in Tables 1 and 2.

Discussion

Meningeal carcinomatosis, an uncommon complication of disseminated neoplasia, can nevertheless present as its initial manifestation (3, 5, 6). MC is most commonly seen in patients with haematological tumours (leukemia and lymphoma), breast cancer, lung cancer and melanoma (3, 6), rarely in renal cell carcinoma, colon carcinoma, bladder carcinoma, medulloblastoma, or pancreas carcinoma (7). Our first patient also demonstrated carcinoma ventriculi.

Clinical manifestations of MC are heterogeneous and symptoms are typically widespread, involving multiple levels of the central and peripheral nervous system (7). This is supported by our four patients, in whom MC started as back pain, headache, and dizziness with ataxia, and cognitive dysfunction, and in the last one as the meningeal syndrome.

Traditionally, establishing a definitive diagnosis requires the presence of malignant cells in CSF (8). It has been reported that initial cytologic examination is diagnostic only in approximately 50% of causes, but this increases with serial CSF examinations (9, 10); several lumbar punctures may be required to establish the diagnosis (2, 3). Accordingly, in three of our patients malignant cells were found only in the second lumbar puncture.

Tab. 1. Clinical features of the patients.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|------------------------|--|-------------------------------|----------------|-----------------|
| 1. sample | 23.10.2005 | 27.5.2006 | 27.6.2005 | 25.8.2004 |
| CSF proteins mg/l | 1355 | 570 | 6600 | 1100 |
| CSF glucose mmol/l | 0.6 | 5.07 | 3.1 | 2.1 |
| CSF chlorides mmol/l | 124 | 120 | 118 | 127 |
| CSF elements No/ml | 66 lymphocytes | 35 elements | 60 leukocytes | 456 lymphocytes |
| Malignant cells in CSF | not examined | cell atypia, blasts? | notexamined | not examined |
| 2. sample | 28.10.2005 | 1.6.2006 | 3.7.2005 | |
| CSF proteins mg/l | 2375 | 925 | 9393 | |
| CSF glucose mmol/l | 1.1 | 8.5 | 2.3 | |
| CSF chlorides mmol/l | 111 | 119 | 113 | |
| CSF elements No/ml | plenty of white and red blood cells | 36 segments 24 lymphocytes | 21 lymphocytes | |
| Malignant cells in CSF | signet ring cell type | signed ring cell type | cell atypia | |

CSF — cerebrospinal fluid

What was interesting in the first patient, the initial CSF examination showed marked hypoglycorrhachia and mildly elevated protein with few elements. Low glucose content of the fluid was found in a number of occasions, and this has been also observed in fluids when tumour cells were not found during life, although necropsy later revealed carcinomatous meningitis. For this reason we advise intensifying the search for malignant cells if the glucose content is found to be low (11). Though hypoglycorrhachia in MC is recognised, it can also occur in viral, bacterial and fungal infections of the central nervous system (12, 13). The lowest glycorrhachia from the above-mentioned infectious diseases is known in tuberculous meningitis. Since CSF laboratory findings are similar, without other signs of malignancy, an often diagnostic problem is to distinguish MC from tuberculous meningitis. That is why, given a rapid progression of the disease, we started an anti-tuberculosis therapy before obtaining results from CSF cytology and PCR for mycobacterium tuberculosis.

The pathophysiology of hypoglycorrhachia is still an unsolved problem. Levinsky (14) suggested an increased utilization rate of CSF glucose by tumour cells infiltrating the meningeal membranes. This theory, however, does not explain the low level of CSF glucose, frequently observed in combination with moderate pleocytosis in tuberculous or sarcoid meningitis or, conversely, the normal levels of CSF glucose in aseptic meningitis despite the presence of marked pleocytosis (15). Fishman (16) hypothesized that lowering of CSF glucose occurs after an abnormality of the transport mechanism of the glucose molecule across the blood-brain barrier. The theory of an abnormal transport of glucose from blood to CSF by neoplastic infiltration of the leptomeninges as a major mechanism of hypoglycorrhachia is supported by Jann (6), who tested the transport of glucose from plasma to CSF after an intravenous infusion of sugar.

We decided to present our patient in case 1 to show that hypoglycorrhachia without signs of malignancy is not always caused by infectious disease of CNS, but it can also be the first sign of meningeal carcinomatosis.

Neuro-imaging is an additional tool to assess in MC. CT and MRI without contrast (2) is suboptimal for the detection of MC. MRI with gadolinium is the imaging modality of choice in suspected neoplastic leptomeningeal disease (3, 17). In comparing the three MRI sequences, the contrast-enhanced fast FLAIR sequences are less sensitive than the standard contrast-enhanced T1-weighted MR sequences in detecting intracranial neoplastic leptomeningeal disease (18). However, Nardone (3) reported that MRI of the brain may also appear completely normal, as in our patient 3. In fact, MRI reveals abnormalities in 23–70 % of patients with positive results on CSF cytology (19, 20).

Every patient with a known malignancy and presenting with neurologic symptoms or signs must be suspected of having MC, although the literature reports that some malignancies are more likely to cause MC than others (9, 18, 21). MC may arise any time during the course of disease.

What is very important is that as many as 9 % of patients present with MC as the first manifestation of cancer (7). Despite the results of vanOostenbrugge (7) that MC as first manifestation was seen especially in patients with high-grade hematologic tumours, all our four patients had different types of solid tumours.

The pathways by which neoplastic cells reach the meninges are still the subject of controversy. Proposed routes are vascular (arterial or through chorioid and Batson venous plexuses), perivascular and perineural lymphatics, or spread by contiguity with adjacent bone or from CNS parenchymatous metastasis (1). Cytokines secreted by tumour cells are also believed to play an important role in this kind of dissemination (22).

The treatment of meningeal carcinomatosis is decided on the basis of the patient's general condition and the control status of the primary lesion, but still has a poor prognosis. Radiotherapy, systemic chemotherapy and palliative therapy are used. It is often thought that systemic therapy has a minimal role in the management of central nervous system metastases due to impermeability of the blood-brain barrier. However, treatments directed at the CNS such as radiation or intrathecal chemotherapy are not effective in managing concurrent non-CNS metastases (4). In spite of this, Tham (4) referred to long-term response to capecitabine therapy after a whole-brain radiation, and Stemmler (23) discussed the parenteral or intrathecal use of trastuzumab in MC caused by breast cancer. After an intravenous application, infiltration of trastuzumab into CSF is facilitated under impaired blood-brain barrier, what is known for the meningeal carcinomatosis.

In conclusion, variable clinical manifestations of MC make its diagnosis difficult to achieve. Reporting our clinical presentations is relevant for three reasons. Firstly, MC can be the first presentation of different types of malignity. The initial symptoms are very different, but the most common presentation consists of multiple neuraxis syndromes with central nervous system, spinal and cranial nerve symptoms and signs. Furthermore, MC is not frequently considered, particularly as the time course of the disease is very rapid, with three of our patients being admitted at our department a few days before their death. And the last reason is that markedly decreased glycorrhachia in CSF can be the first sign of MC, and not merely a sign of an infectious disease of CNS.

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