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Grand Rounds

A 56-year-old man with acute vision loss

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History

A 56-year-old man was referred to the Department of Ophthalmology, General Hospital of Kavala, for evaluation of vision loss in his right eye. He had undergone surgical removal of a gastric tumor 15 days previously. Two days before surgery, he complained of slightly blurred vision and mild bulbar pain exacerbated by ocular movement. Immediately after surgery he reported considerable visual impairment. His past ocular history was otherwise unremarkable.

Except for the recently diagnosed and treated gastric tumor, he had no other known chronic medical conditions; he did not use scheduled medications and had no known allergies. His family history was remarkable for diabetes mellitus. He worked as a civil servant and did not smoke, drink, or use drugs.

Examination

On initial examination, the patient's visual acuity in the right eye was light perception; uncorrected visual acuity in the left eye was 8/10 (Snellen chart at 6 meters; equivalent to 20/25). Intraocular pressure (IOP) measured by Goldmann tonometry was 14 mm Hg in the right eye and 15 mm Hg in the left eye. Ocular motility was normal in both eyes. Anterior segment examination of both eyes was unremarkable. Fundus examination (Figure 1) revealed advanced optic disc edema in the right eye, with no retinal or choroidal lesions; the left eye was normal. Ocular echography (Figure 2) confirmed optic disc swelling in the patient's right eye.

Neurological examination on admission was normal. Although the patient had no neurological signs or symptoms, he was closely monitored. Two days later, he complained of further visual impairment. On reexamination, visual acuity in his right eye was no light perception, with no other neurological symptomatology. Up to then, all blood analysis and diagnostic tests were normal. On the 4th day after hospitalization, neurological signs and symptoms were apparent, and a lumbar puncture was performed.

On subsequent evaluation, 2 days later, there was further visual loss in the right eye, with no light perception; uncorrected visual acuity in the left eye was stable at 8/10 (20/25). The IOP was 15 mm Hg in both eyes and fundus examination was essentially unchanged. Neurological examination remained normal. On the 4th day of hospitalization the patient complained of severe headache and nausea, and he had epileptic seizures.

Ancillary Testing

Blood analysis including full blood count, basic biochemical analysis, C-reactive protein, and blood coagulation examinations were normal; serum antibodies (rheumatoid factor, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies) were negative. All radiological and echographical controls were normal. Magnetic resonance imaging (MRI) and computed tomography (CT) of the brain and orbits revealed no abnormalities.

After the patient complained of neurological symptoms (severe headache with nausea, and epileptic seizures), lumbar puncture was performed. Cerebrospinal fluid (CSF) was colorless and slightly cloudy/turbid. CSF glucose was 70 mg/dl, and CSF protein level was 80.5 mg/dl. CSF total cell number was 180 per cubic millimeter, with lymphatic cells at 10% and dysplastic/atypical cells at 90%. CSF cytology revealed the presence of a few white cells, a few round shaped epitheliod cells with eccentric nuclei, and some atypical multinucleated cells. The examination was positive for malignant cells, and the presence of dysplastic/atypical cells confirmed the diagnosis of meningeal carcinomatosis.

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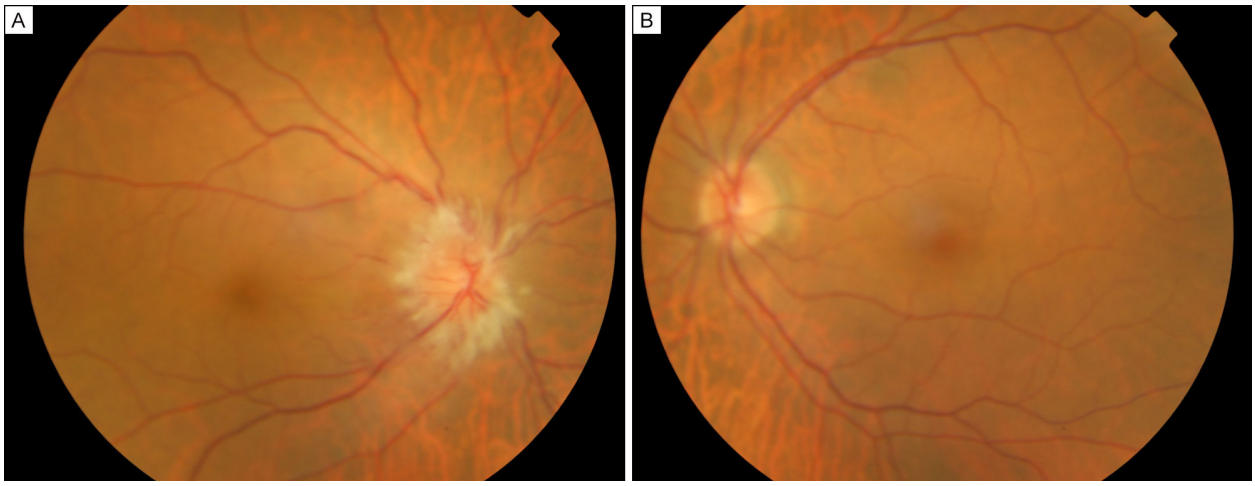

Figure 1. Fundus photographs of the right eye (A) and left eye (B).

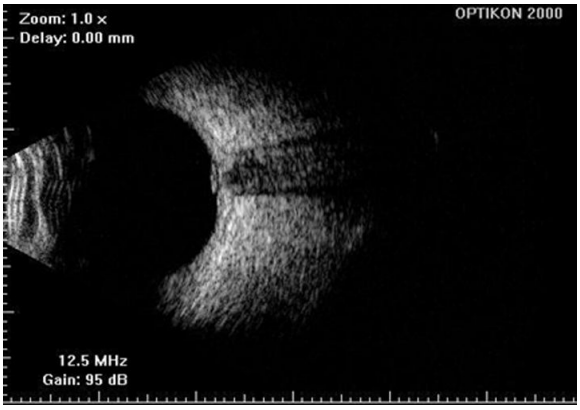

Figure 2. Ultrasound of the right eye showing the optic disc swelling.

Treatment

The patient was started on systemic intravenous chemotherapy, but his condition rapidly deteriorated, and he died 20 days later. Autopsy was not performed.

Differential Diagnosis

The differential diagnosis includes all of the most common causes of unilateral optic disc swelling,[1,2] such as anterior ischemic optic neuropathy, central retinal vein occlusion (unilateral, associated with an acute loss of vision), demyelinating optic neuritis, intracranial tumors, and orbital tumors and lesions (usually there are also motility defects and proptosis). However, optic disc swelling can also be a sign of papillitis (inflammatory, infiltrative, and infective conditions that cause true disc edema—typically unilateral condition with an accompanying vitritis), papillophlebitis (with mild visual loss and disc swelling in young, healthy patients), and diabetic papillopathy (frequently with a unilateral disc edema with minimal visual loss and resolving spontaneously). Finally, compressive optic neuropathy and Graves' ophthalmopathy, which may include thyroid dysfunction, lid lag, and proptosis, can cause optic disc edema, as can Leber optic neuropathy, which occurs typically in young males (at an early stage there is unilateral acute and severe visual loss).

Causes of pseudopapilledema should also be considered. Finally, oblique insertion of the optic nerve head, small (heaped up) optic nerve head, myelinated nerve fibers, buried disc drusen (swelling of the optic nerve head due to infiltration by hyaline bodies, which can be associated with visual field defects or afferent pupillary defect) and remnants of the hyaloid canal can simulate real optic disc edema.

Diagnosis and Discussion

The MRI and CT results, combined with a negative laboratory work-up for other possible causes of optic disc edema and the development of neurological symptomatology, led to the decision to perform a lumbar puncture. CSF analysis confirmed the diagnosis of meningeal carcinomatosis, because the examination was positive for malignant cells and dysplastic/atypical cells were present.

Meningeal carcinomatosis is a rare condition, but it is associated with devastating complications and high mortality. Ocular involvement is a frequent and early clinical

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manifestation of meningeal carcinomatosis and may mimic different diseases. Our patient manifested optic disc edema as the first sign of meningeal carcinomatosis. The exclusion of the most common causes of optic nerve head swelling, his medical history, and the close monitoring led to an early diagnosis of this condition.

Meningeal carcinomatosis should be included in differential diagnosis and CSF analysis should be requested in any patient with ocular symptoms when the most common causes of ocular symptomatology are excluded, especially in patients who have a known history of malignancy.

Meningeal carcinomatosis is defined as a diffuse infiltration of the meninges by metastatic cancer.[3,4] It is the first manifestation of systemic cancer in only 5%–10% of patients, although it is frequently seen in patients with disseminated systemic disease.[5,6]

Hematologic tumors are the most frequent cause of meningeal carcinomatosis, particularly acute lymphoblastic leukemia and non-Hodgkins lymphoma.[5] The incidence of clinically diagnosed meningeal carcinomatosis in patients with solid tumors is approximately 5%, but the incidence of undiagnosed or asymptomatic meningeal carcinomatosis may be higher.[7] Although any cancer can metastasize to the leptomeninges, breast cancer (12%–35%), lung cancer (10%–26%), melanoma (5%–25%), gastrointestinal cancer (4%–14%), and cancers of unknown primary origin (1%–7%) are the most common causes of solid-tumor-related meningeal carcinomatosis.[6–8]

Neoplastic cells may spread to the subarachnoid space through arterial circulation or, less frequently, through retrograde flow in venous systems or as a direct consequence of preexisting brain metastasis or through migration of neoplastic cells from the original tumor along perineural or perivascular spaces.[9–11] Clinical presentation is highly variable and may affect both central and peripheral nervous system. It is usually organized into three categories: cerebral, cranial nerve, and spinal.[6] Central nervous system involvement may lead to generalized symptoms such as seizures, confusion, encephalopathy, or intracranial hypertension as well as, less frequently, focal neurological symptoms, mainly consisting of hemiparesis or aphasia; peripheral nervous system involvement may present with lumbar and cervical radiculopathies or cranial neuropathies.[7,9] The most common manifestation of cranial nerve involvement is diplopia due to abducens nerve palsy, followed by oculomotor and trochlear nerve involvement. The trigeminal and vestibulocochlear nervew may also be affected.[9,12]

Ocular involvement represents a frequent manifestation of meningeal carcinomatosis.[13,14] Visual impairment as an important component of the syndrome received little attention in ophthalmological and neurological literature until 1955, when Fischer-Williams et al reported that partial or complete blindness occurs in one-third of such patients.[15,16] In 1961 Katz et al in a review of the neuro-ophthalmological findings of meningeal carcinomatosis, described decreased vision in 44% of cases.[17,15] The most common ocular manifestation was visual loss (70%), followed by diplopia (41%), ptosis (19%), papilledema (10%), anisocoria (7%), exophthalmos (5%), orbital pain (5%), scotomas (5%), hemianopsia (2%) and nystagmus (2%).[9]

The exact mechanism by which meningeal carcinomatosis produces visual impairment is not well defined. The implicated mechanisms could be direct infiltration of the optic nerve, tumor cuffing of the leptomeninges with compression of the nerve, compromised vascular supply, humoral toxin, or retinal photoreceptor degeneration as a remote effect of cancer. Some cases, however, remain inadequately explained by any of these mechanisms.[18–20]

Because ocular involvement is a frequent and early clinical manifestation of meningeal carcinomatosis and may mimic different diseases, early diagnosis is challenging. Clinical suspicion of the condition is based on the finding of neurological signs and symptoms at more than one level of the neuraxis. Multifocal neurological symptoms and signs are strongly suggestive of the diagnosis of meningeal carcinomatosis in patients with known cancer, but patients may also present with isolated and subtle neurologic symptoms.[7]

Currently, the diagnostic approach includes neuroimaging studies (cranial and spinal CT and MRI), which allow identification of the pathological process eventually involving the leptomeninges, and CSF analysis. Although the presence of malignant cells in CSF is the pathognomonic laboratory examination for meningeal carcinomatosis, the sensitivity of this test is suboptimal. Wasserstrom et al reported that the sensitivity of single lumbar puncture is only 54%, and 91% sensitivity could be achieved with repeated tests.[8,10,14]

The diagnosis of meningeal carcinomatosis may be ascertained according to the National Comprehensive Cancer Network guidelines.[21] The guidelines suggest that any one of the following diagnostic criteria are sufficient to diagnose meningeal carcinomatosis; CSF positive for tumor cells (positive CSF cytology); radiologic findings in the central nervous system consistent with

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meningeal carcinomatosis irrespective of supportive clinical findings or alternatively and more controversial, clinical signs and symptoms consistent with meningeal carcinomatosis, and a nonspecific but abnormal CSF analysis (high white blood cell count, low glucose <60 mg/dl, and elevated protein >50 mg/dl) in a patient known to have a cancer.[4,7]

Although meningeal carcinomatosis occurs in only 3%–8% of all cancer patients, it is associated with devastating neurologic complications and high mortality.[10] The median survival of patients with this disorder is 4–6 weeks without treatment; even in response to therapy, median survival in these patients is limited to 18.6 weeks.[7,22]

Early diagnosis is important, although treatment is intended to reduce the symptoms and at best extend survival, especially when neurologic symptoms are already present.[5] Because there are no well-established regimens, the treatment of meningeal carcinomatosis varies, and treatment options are very limited. Options are intrathecal (IT) chemotherapy, radiotherapy, and best supportive care. IT chemotherapy is the mainstay of treatment because it is a more selective and relatively less toxic. Methotrexate, cytosine arabinoside, and thiotepa in combination with hydrocortisone are the most frequently used drugs, although there are other substances tested in several clinical trials.[5,10,14]

Treatment is only palliative and cannot provide lasting clinical benefit for the majority of cases. Patients with meningeal carcinomatosis have a guarded prognosis with a mean survival rate of 3–6 months.[4,5,22]

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