Deafness and Blindness as a Presentation of Colorectal Meningeal Carcinomatosis

Beau B. Bruce, MD[1,2]
Mahtab Tehrani, MD[3]
Nancy J. Newman, MD[1,2,4]
Valérie Biousse, MD[1,2]

Departments of [1]Ophthalmology, [2]Neurology, [3]Pathology, and [4]Neurological Surgery, Emory University, Atlanta, Georgia

Introduction

Multiple cranial nerve palsies often reveal a meningeal process that may be infectious, inflammatory, or neoplastic in origin. Even when there is a known history of malignancy, the rarity with which a given primary cancer causes meningeal carcinomatosis can influence diagnostic decision making and lead to delays in diagnosis. We present a unique case of a patient with deafness and blindness secondary to carcinomatous meningitis from colorectal adenocarcinoma.

Case Report

A 65-year-old man with a history of hypertension presented with 6 weeks of progressive balance difficulties, 4 weeks of acute hearing loss in both ears, and 2 weeks of acute vision loss in the right eye prior to our initial evaluation. His course was also complicated by delirium, which developed after he was started on high-dose oral steroids for presumed giant cell arteritis at an outside facility.

His visual acuity was "hand motion" in the right eye and 20/25 in the left eye. He had a right relative afferent pupil defect, full extraocular movements, and profound hearing loss in both ears. Visual fields were very constricted by confrontation in both eyes. Fundus examination showed bilateral optic nerve head edema, suggesting bilateral optic neuropathies. Communication with the patient was made very difficult by his poor vision, deafness, and altered mental status. His neurologic and general examinations were otherwise unremarkable. Erythrocyte sedimentation rate (ESR) was 82 mm/h and C-reactive protein (CRP) was 18.3 mg/L (normal <0.9 mg/L). Lumbar puncture showed a cerebrospinal fluid (CSF) opening pressure of 28 cm H_2O, with 1 red cell and 138 white cells, which were 85% macrophages and 15% lymphocytes. CSF protein was greater than 300 mg/dL; glucose was 27 mg/dL. CSF Venereal Disease Research Laboratory (VDRL) test was 1:8, and serum rapid plasma regain was negative. CSF cytology was negative. Antinuclear antibodies were positive at 1:160. Anti-neutrophil cytoplasmic antibody was negative, and magnetic resonance imaging (MRI) of the brain with contrast was normal.

A meningeal process (infectious, inflammatory, or neoplastic) was suspected, given the multiple cranial nerve involvement and CSF findings. The CSF profile and positive VDRL raised suspicion for neurosyphilis and tuberculosis (TB), for which the patient was treated with penicillin and 4-drug TB therapy. The initial differential diagnosis also included vasculitic processes such as giant cell arteritis and Wegeners granulomatosis, given his age and biologic inflammatory syndrome. Cytology was repeated on 2 subsequent lumbar punctures, and both samples showed rare atypical epitheloid cells (Figure 1A). Carcinoembryonic antigen (CEA) was 55.9 ng/mL (range, 0–5.0 ng/mL). A computed tomography scan of the abdomen suggested that the patient had had previous colorectal surgery but there was no mass lesion. Upon further interview of distant family members, we discovered that the patient had a history of rectal cancer diagnosed 2 years prior, which was treated with chemotherapy, surgery, and radiation; however, the exact type of cancer and staging were unknown. Repeat neuroimaging showed bilateral enhancement of the proximal optic nerves, left nodular enhancement of the trigeminal nerve, and bilateral enhancing cerebellopontine angle mass lesions (Figures 1B and 1C). Biopsy of the right cerebellopontine angle lesion showed signet ring adenocarcinoma (Figure 1D), immunohistochemically positive for cytokeratin and histochemically positive for mucicarmine, suggestive of gastrointestinal origin. The

Address correspondence to:
Beau Bruce, MD, Neuro-ophthalmology Unit, Emory Eye Center, 1365-B Clifton Road, NE, Atlanta, Georgia 30322; Phone: 404-778-5360; Fax: 404-778-4849; E-mail: bbbruce@emory.edu.
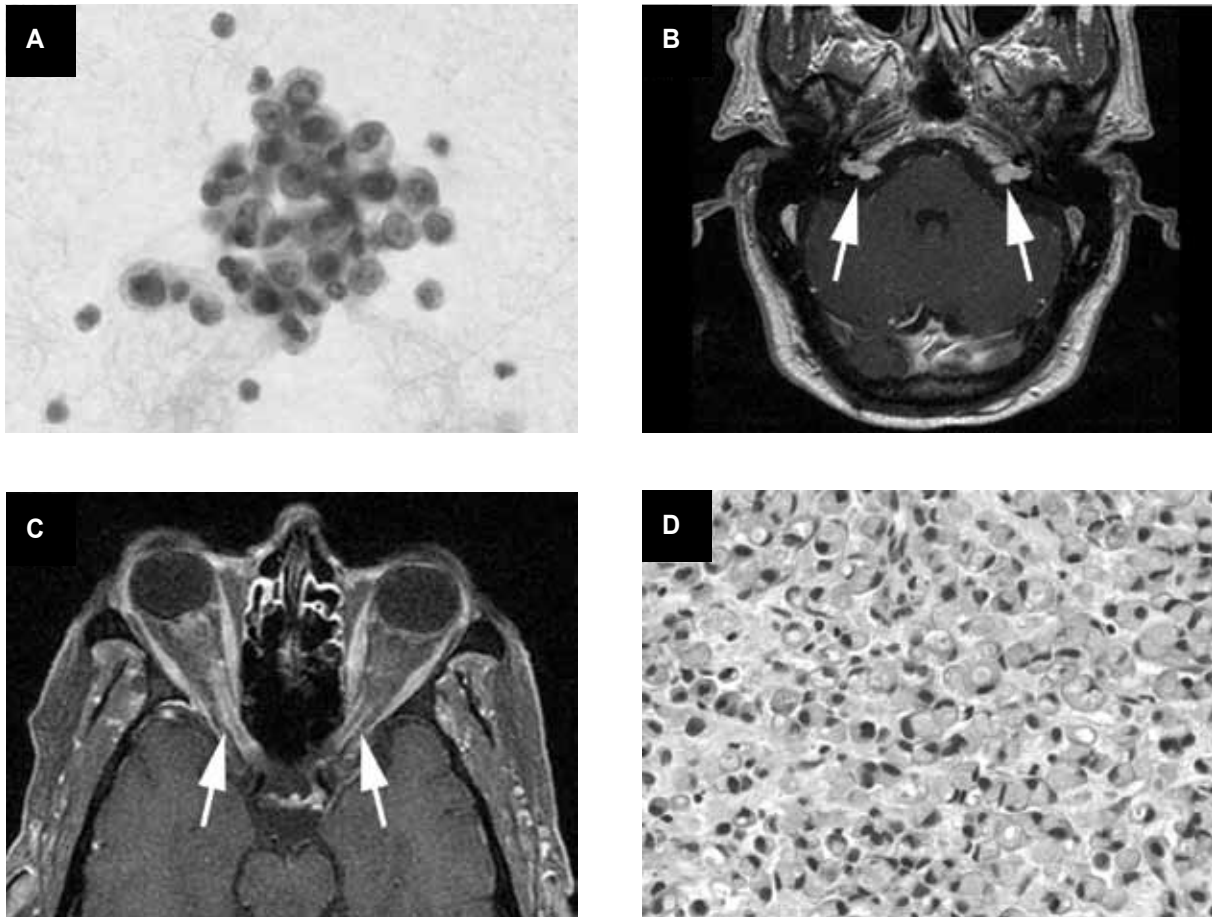
Figure 1. Rectal meningeal carcinomatosis. A) Cerebrospinal fluid cytology with rare, atypical epitheloid cells. B) Bilateral, nodular enhancement in the cerebellopontine angles (magnetic resonance imaging [MRI] T1 post-contrast administration). C) Bilateral enhancement of the proximal optic nerves (MRI T1 post-contrast administration). D) Cerebellopontine angle biopsy showing signet ring adenocarcinoma (hematoxylin and eosin section).

patient's clinical status deteriorated rapidly to death following whole brain radiation, and before chemotherapy could be initiated.

Discussion

We present an unusual case of meningeal carcinomatosis from rectal carcinoma. Meningeal processes can be caused by infectious, inflammatory, and neoplastic processes, but differentiation can be difficult. As in this case, the typical CSF profile of meningeal carcinomatosis is that of elevated opening pressure, low glucose, and elevated protein. However, this CSF profile is also seen in various inflammatory and infectious etiologies. Contrast-enhanced MRI is about 70% sensitive for leptomeningeal metastases, but differentiation from alternate etiologies is also difficult with this technique.[1] Positive CSF cytology remains the gold-standard diagnostic technique; however, it is positive in only 50–70% of cases on the initial lumbar puncture.

The sensitivity increases to nearly 100% after 3 attempts, and thus, as in this case, vigilance in repeating the lumbar puncture is necessary when initial results are negative.[1,2] Sensitivity can be further increased by obtaining at least 10.5 mL of CSF for cytologic analysis and immediately processing the sample.[2]

Breast, small-cell lung cancer, and melanoma are the most common solid tumors reported to cause meningeal carcinomatosis, while other tumors such as head and neck, cervical, ovarian, renal, and bladder cancer have been reported to do so with much less frequency.[1,3] Colorectal carcinoma is particularly unlikely to metastasize to the meninges, occurring in only 0.019% of patients with this primary cancer. It is the responsible tumor in only 0.56% of cases of meningeal carcinomatosis.[4]

Reviewing the English literature after 1960, we identified 10 cases of meningeal carcinomatosis where colorectal cancer was the underlying neoplasm.[5-10] Some presentations had only mild symptoms, such as mild,

isolated, upper extremity paresthesias,[6] whereas others had significant alterations of consciousness.[10] In some of these cases, the presentation of meningeal carcinomatosis occurred over a year after initial diagnosis,[5] while in others it was the only clue to an underlying, occult neoplasm.[10] We identified a single report of blindness[8] and a single report of acute hearing loss[5] from carcinomatous meningitis related to colorectal cancer.

Wasserstrom and colleagues reviewed 90 cases of leptomeningeal metastasis from solid tumors and found that blindness occurred in only 3 (3%) and some degree of hearing loss was reported in 7 (8%).[11] Our literature review identified 11 additional cases of blindness from meningeal carcinomatosis[12-20] related to a variety of mechanisms, including papilledema from increased intracranial pressure,[12] direct infiltration of the optic nerve/sheath complex,[17] treatment-related toxicity,[15] and retinal vascular occlusions.[19] The responsible neoplasms included breast,[15,16,19] lung,[12-14] ovarian,[17] gastric,[18] and endometroid sarcoma.[13] While bilateral hearing loss is a more frequent symptom of meningeal carcinomatosis, as seen in Wasserstrom and colleagues' series, it is exceptional that it occurs in isolation.[21-24] The dramatic, simultaneous presentation of blindness and deafness seen in our patient has not, to our knowledge, been previously reported in association with meningeal carcinomatosis from any cause.

Prognosis in this setting is extremely poor. In the absence of treatment, median survival is a mere 4–6 weeks. Aggressive therapy with radiation to symptomatic sites combined with intrathecal chemotherapy prolongs median survival to 3–6 months, but fixed neurologic deficits rarely improve. Because radiation combined with the most commonly used chemotherapeutics for meningeal carcinomatosis (methotrexate, Ara-C, and thiotepa) can result in significant neurologic and systemic toxicity, it is important to balance the patient's functional status, degree of fixed neurologic dysfunction, and natural history of the underlying malignancy to help guide the decision between therapy and supportive care.[25]

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Review
Visual and Hearing Loss Due to Colorectal Meningeal Carcinomatosis: A Case-based Review

Panteleimon Kountourakis, MD, PhD,[1]
and Alexandros Ardavanis, MD, PhD[2]

[1]Bank of Cyprus Oncology Centre, Nikosia, Cyprus;
[2]First Department of Medical Oncology, Saint Savas Anticancer Hospital, Athens, Hellas

Introduction

Bruce and colleagues[1] report on a 65-year-old man who developed progressive vision and hearing loss. The patient's course was also complicated by balance disturbances and altered mental status. Clinical and laboratory examination led to the initial differential diagnosis of infectious, inflammatory, vasculitic, or neoplastic process. The initial magnetic resonance imaging (MRI) of the brain was normal, and lumbar puncture results could not differentiate the etiology. Furthermore, the patient's past medical history was significant for a rectal cancer diagnosis 2 years prior, which was treated with chemotherapy, surgery, and radiation. Therefore, a repeated contrast-enhanced MRI of the brain was performed, and bilateral enhancing cerebellopontine angle mass lesions, bilateral enhancement of the proximal optic nerves, and left nodular enhancement of the trigeminal nerve were observed. A guided biopsy of the right cerebellopontine angle revealed a signet ring adenocarcinoma of gastrointestinal origin. The patient received whole brain radiation, but in a short period of time had a rapid decline and died.

Discussion

Meningeal carcinomatosis (MC) is a late complication and occurs in 1–15% of patients with solid malignancies.[2] Virtually any type of cancer can disseminate into the leptomeningeal space. The most frequent primary tumors responsible for meningeal spread are carcinomas of the breast and lung and melanomas.[3] Cases from other solid tumors such as gastric, colorectal, ovarian, prostate, cervical and thyroid cancer have also been reported in the literature.[4-8] MC is characterized by a diffuse or multifocal seeding of the meninges by neoplastic cells. MC can cause a variety of neurologic symptoms including headache, seizures, sensory abnormalities, memory loss, mental status disorders, stroke-like symptoms, nausea, vomiting, and fatigue. In addition, the most commonly affected cranial nerves are III, V, VI, VII, VIII, with analogous signs and symptoms such as diplopia, hearing loss, decreased taste, and problems with hoarseness and swallowing.

At least 4 distinct pathways exist to explain the biologic basis for diffuse or multifocal dissemination of meninges by malignant cells: a) hematogenous dissemination, b) perivenous spread from the bone marrow within the skull, c) direct extension along peripheral nerves to the subarachnoid space, and d) direct extension from subdural or extradural tumors, or from sites outside but adjacent to the central nervous system.[9]

The diagnosis of meningeal involvement is based on cytologic confirmation by either a meningeal biopsy or cerebrospinal fluid (CSF) cytology.[10] Gadolinium-enhanced MRI appears to have a 2-fold greater sensitivity and specificity in lesion detection when compared with CT, and is the preferred imaging modality.[11] Contrast-enhanced MRI revealing abnormal leptomeningeal enhancement of the brain, spinal cord, cauda equina, or subependymal areas could support the diagnosis. Suggestive of leptomeningeal involvement are findings regarding the enhancement of cranial nerves and superficial cerebral lesions, and also the presence of communicating hydrocephalus.[12] Several investigators agree that when there is strong evidence of leptomeningeal carcinomatosis on MRI, cytologic confirmation is not necessary, and clinicians can proceed with treatment.[13]

It should also be noted that MRI imaging and CSF cytology exhibit high rates of false negative results[14]; 40–50% of patients with neoplastic meningitis have negative CSF cytology. Obstruction of CSF flow, inadequate amount of CSF collection, and delayed handling of the specimen could lead to false negative results. Findings such as decreased glucose levels (<60 mg/dL), increased amount of white blood cells (>4/mm^3; in 75% of patients), elevated protein levels (>50 mg/dL), and increased opening pressure of CSF (>150 mm H_2O) are consistent with MC even when cancer cells are not identified. It should be highlighted that CSF cytology is positive in only 50% of cases on the first lumbar puncture. Repeat CSF cytologic evaluations over time will increase diagnostic sensitivity to 80% after 2 attempts and nearly 100% after 3 analyses.[15] Tumor cells may be demonstrable with all types of solid tumors,

Address correspondence to:
Alexandros Ardavanis MD, PhD, First Department of Medical Oncology, Saint Savas Anticancer Hospital, 171 Alexandras Ave 11522, Athens, Hellas; Phone: +30 6944421525; Fax: +302106409508; E-mail: ardavanis@yahoo.com.

but absence of tumor cells does not exclude meningeal carcinomatosis.

Prognosis in this patient's setting is ominous; typically, median survival without treatment is 4–6 weeks. Current therapies, such as radiation therapy in combination with intrathecal chemotherapy, are palliative rather than curative, and prolong median survival for 3–6 months.[16]

To our knowledge, a few cases of MC due to rectal cancer have been reported.[17-20] The symptoms were mild (eg, headache and mild paresthesias) to severe (eg, alterations of mental status), with unilateral or bilateral hearing loss as one of the more frequently reported symptoms. On the contrary, blindness occurred more rarely. Reviewing the literature, simultaneous presentation of deafness and blindness, as reported by Bruce and colleagues, in a patient with rectal cancer has not been previously reported.

Colorectal malignancies remain one of the major causes of cancer death, and the incidence has been rapidly increasing worldwide over the past few decades. It is the second most common malignancy (13.1%) and the second most common cause of cancer death in Europe.[21] In the last decade, newer cytotoxic agents such as oxaliplatin and irinotecan have shown promise. The administration of these agents has increased the overall survival rate as well as the time to progression in patients with metastatic cancer.[22,23] Despite significant improvements in traditional chemotherapy regimens, over the last several years, more effective treatments such as monoclonal antibodies against epidermal growth factor receptor (cetuximab [Erbitux, Bristol-Myers Squibb/ImClone]) and anti-angiogenetic agents (bevacizumab [Avastin, Genentech]) have been administered and have improved patient outcome.[24,25] As the life expectancy of patients is prolonged, more patients are expected to be diagnosed with late and severe complications of MC. For that reason, clinicians should be aware of early signs of meningeal involvement even if initial tests are negative.

Given the ominous prognosis and the limited options of therapy in this setting, further evaluations are needed to determine whether earlier diagnosis of MC could have led to prolonged survival and improvement of neurologic deficits. In the current era of targeted therapeutics, advances in our knowledge of cancer biology and elucidation of carcinogenesis and signal transduction pathways could reveal potential targets for novel agents, which may help establish an efficacious tailored-made therapy with minimal toxicity.

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