2

Rapid #: -1405108 **Ariel IP: 155.100.78.5**

Status	Rapid Code	Branch Name	Start Date
New	UUE	Eccles Library	10/22/2007 1:04:47 PM
Pending	ORU	Main Library	10/22/2007 1:05:58 PM
Batch Not Printed	ORU	Main Library	10/22/2007 1:06:19 PM
Batch Printed	ORU	Main Library	10/22/2007 1:06:43 PM
Filled	ORU	Main Library	10/22/2007 6:51:46 PM
New Resend	UUE	Eccles Library	10/23/2007 8:24:00 AM
Pending	ORU	Main Library	10/23/2007 8:24:07 AM

Resend Notes: line all the way through page. please check scanner, and resend better copy

CALL #: **WEB SITE**
LOCATION: **ORU :: Main Library :: oruc**

TYPE: Article CC:CCG
JOURNAL TITLE: Journal of neuro-oncology
USER JOURNAL TITLE: Journal of neuro-oncology
ORU CATALOG TITLE: Journal of neuro-oncology
ARTICLE TITLE: Carcinomatous meningitis as the presenting manifestation of gallbladder carcinoma: case report and review of the literature
ARTICLE AUTHOR: Digre, Kathleen B.
VOLUME: 70
ISSUE: 1
MONTH:
YEAR: 2004
PAGES: 67-71
ISSN: 0167-594X
OCLC #:
CROSS REFERENCE ID: 428849
VERIFIED:

RESEND

BORROWER: **UUE :: Eccles Library**
PATRON: **Gorton,Grace**

PATRON ID:
PATRON ADDRESS:
PATRON PHONE:
PATRON FAX:
PATRON E-MAIL: gegorton@gmail.com
PATRON DEPT: Main Campus
PATRON STATUS: Staff
PATRON NOTES:

Journal of Neuro-Oncology 70: 67–71, 2004.

Clinical Study

Carcinomatous meningitis as the presenting manifestation of gallbladder carcinoma: case report and review of the literature

Yue Shen[1], Deborah T. Blumenthal[1,2,3], Kathleen Digre[1,4], Melissa H. Cessna[5] and Evelyn V. Gopez[5]
[1]*Department of Neurology;* [2]*Department of Neurosurgery;* [3]*Division of Oncology, Department of Medicine;* [4]*Department of Ophthalmology;* [5]*Department of Pathology, University of Utah Hospital, Salt Lake City, UT, USA*

Key words: carcinomatous meningitis, gallbladder carcinoma, leptomeningeal metastasis, meningeal carcinomatosis and cranial neuropathy

Summary

The primary tumors that typically cause carcinomatous meningitis include lung cancer, breast cancer, leukemia, lymphoma and melanoma. A variety of neurological signs and symptoms can be seen depending on the extent and location of the meningeal metastasis. Once the diagnosis of carcinomatous meningitis is confirmed, the search for the primary tumor can be a challenge and at times may require extensive radiographic or even surgical evaluation to obtain specimen for pathological confirmation. Here we report a patient who presented with bilateral cranial nerve VIII and cerebellar symptoms, and was diagnosed with carcinomatous meningitis. Only after an exploratory laporatomy did it become clear that the initial symptoms were related to a metastatic gallbladder carcinoma.

Introduction

Although numerous primary cancers have been reported to cause carcinomatous meningitis, primary gallbladder carcinoma rarely metastasizes to the meninges. There are only five such reported cases in the English literature [1–5]. Here we report a woman who presented with cranial nerve VIII symptoms and ataxia and was found to have carcinomatous meningitis. An extensive search for the primary tumor ultimately led to the diagnosis of gallbladder carcinoma.

Case report

A 51 year old woman with history of alcoholism and hypothyroidism was referred to ENT clinic for evaluation of 1-month history of progressive right ear tinnitus and hearing loss, vertigo, and ataxia without headache or weight loss. Neurological examination revealed hypometric saccades and impaired hearing in both ears, right worse than the left. The patient had a wide-based ataxic gait. On a high-resolution MRI of the internal auditory canals, bilateral enhancement of cranial nerve VIII and cerebellar folia was noted, suggestive of an inflammatory process such as meningitis.

Initial blood chemistry and metabolic screens were normal other than a macrocytic anemia and elevated liver function enzymes. Cerebral spinal fluid (CSF) showed 28 mg/dl glucose (serum glucose 101 mg/dl), 166 mg/dl protein, 0 red blood cells, and 145/μl white blood cells with 74% lymphocytes. The opening pressure during the lumbar puncture was 15 cm H_2O. CSF cytology revealed malignant cells with characteristic signet ring morphology that were cytokeratin and carcinoembryonic antigen (CEA) positive, consistent with metastatic adenocarcinoma (Figure 1). A repeat MRI 1 week later showed progressive enhancement along the ventral surface of the brainstem, cranial nerves II, V, VII and VIII, as well as many

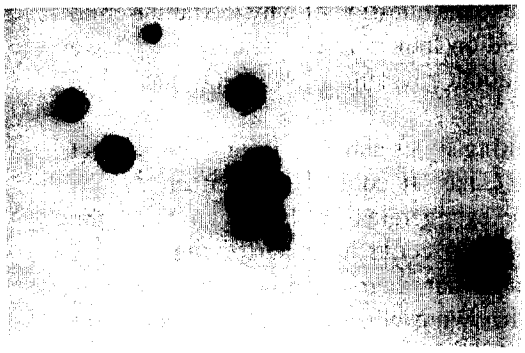

Figure 1. Cerebrospinal fluid. Cytospin of the patient's cerebrospinal fluid (Papanicolau stain) shows single cells and clusters of malignant cells having signet ring morphology.

cerebral sulci and the right sylvian fissure (Figure 2).

An extensive work-up to identify a primary malignancy ensued. The serum CEA was elevated at 12.7 ng/ml (normal range 0.0–3.0). Serum tumor markers were negative for bladder tumor associated antigen, alpha-fetoprotein (AFP), CA (cancer antigen) 15–3, CA 27.29 (breast cancer), CA 19–9 (pancreatic cancer) and CA 125 (ovarian cancer). Mammogram and pap smear were unremarkable. Computed Tomography (CT) of chest was normal. Abdominal and pelvic CT demonstrated complex appearing cystic masses in the ovaries and a gallbladder with abundant gallstones and sludge. There were no enhancing lesions in the liver. Because of the abnormal appearing ovary and gallbladder on the CT scan, positive serum and CSF markers for CEA, and positive cytokeratin immunohistochemical stain on the malignant cells in CSF, ovarian or GI tract cancer was suspected as the primary source. In order to obtain pathological specimen for definite diagnosis and possibly resection of the tumor, the patient underwent an exploratory laparotomy. She had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, cholecystectomy after intraoperative biopsy proved adenocarcinoma, and portal lymph node excision. During the operation, the gallbladder was found to be slightly enlarged, irregular in shape and firm to palpation. Microscopic examination of the ovaries showed cystic corpus luteum and follicles but no neoplastic changes. Pathological examination of the gallbladder demonstrated cholelithiasis and chronic cholecystitis with diffuse intestinal metaplasia and poorly differentiated signet ring cell adenocarcinoma localized to the gallbladder fundus. The carcinoma extended through the full thickness of the wall and out to the external cauterized margin of the gallbladder fundus. The morphology of the signet ring cells was similar to that seen in the CSF (Figure 3). Interestingly, the portal lymph nodes were negative for metastases.

Figure 2. Enhancing cranial nerves. Postcontrast-enhanced coronal MRI of the Brain demonstrating enhancing bilateral cranial nerve VIII and cerebellar folia.

Eight days after the laporatomy, an Ommaya reservoir was placed and the first dose of intrathecal thiotepa was given. The second dose was given 6 days later. Two days later the patient developed decreased oral intake, intractable vomiting, worsened ataxia, and became progressively obtunded. Empiric intravenous antibiotics were started for possible bacterial meningitis but repeated CSF analysis did not show evidence of infection. Repeat MRI of the brain showed more extensive leptomeningeal enhancement consistent with progression of carcinomatous meningitis. She subsequently developed respiratory distress and required intubation 7 days after the second dose of intrathecal chemotherapy. She was treated with

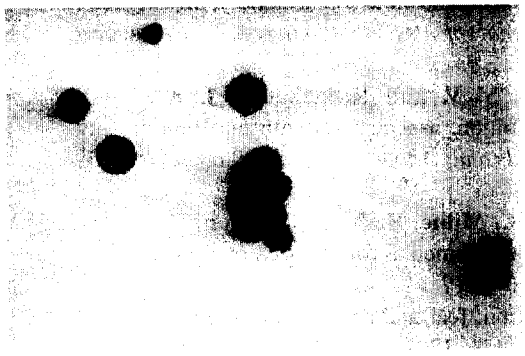

Figure 1. Cerebrospinal fluid. Cytospin of the patient's cerebrospinal fluid (Papanicolau stain) shows single cells and clusters of malignant cells having signet ring morphology.

cerebral sulci and the right sylvian fissure (Figure 2).

An extensive work–up to identify a primary malignancy ensued. The serum CEA was elevated at 12.7 ng/ml (normal range 0.0–3.0). Serum tumor markers were negative for bladder tumor associated antigen, alpha-fetoprotein (AFP), CA (cancer antigen) 15–3, CA 27.29 (breast cancer), CA 19–9 (pancreatic cancer) and CA 125 (ovarian cancer). Mammogram and pap smear were unremarkable. Computed Tomography (CT) of chest was normal. Abdominal and pelvic CT demonstrated complex appearing cystic masses in the ovaries and a gallbladder with abundant gallstones and sludge. There were no enhancing lesions in the liver. Because of the abnormal appearing ovary and gallbladder on the CT scan, positive serum and CSF markers for CEA, and positive cytokeratin immunohistochemical stain on the malignant cells in CSF, ovarian or GI tract cancer was suspected as the primary source. In order to obtain pathological specimen for definite diagnosis and possibly resection of the tumor, the patient underwent an exploratory laparotomy. She had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, cholecystectomy after intraoperative biopsy proved adenocarcinoma, and portal lymph node excision. During the operation, the gallbladder was found to be slightly enlarged, irregular in shape and firm to palpation. Microscopic examination of the ovaries showed cystic corpus luteum and follicles but no neoplastic changes. Pathological examination of the gallbladder demonstrated cholelithiasis and chronic cholecystitis with diffuse intestinal metaplasia and poorly differentiated signet ring cell adenocarcinoma localized to the gallbladder fundus. The carcinoma extended through the full thickness of the wall and out to the external cauterized margin of the gallbladder fundus. The morphology of the signet ring cells was similar to that seen in the CSF (Figure 3). Interestingly, the portal lymph nodes were negative for metastases.

Figure 2. Enhancing cranial nerves. Postcontrast-enhanced coronal MRI of the Brain demonstrating enhancing bilateral cranial nerve VIII and cerebellar folia.

Eight days after the laporatomy, an Ommaya reservoir was placed and the first dose of intrathecal thiotepa was given. The second dose was given 6 days later. Two days later the patient developed decreased oral intake, intractable vomiting, worsened ataxia, and became progressively obtunded. Empiric intravenous antibiotics were started for possible bacterial meningitis but repeated CSF analysis did not show evidence of infection. Repeat MRI of the brain showed more extensive leptomeningeal enhancement consistent with progression of carcinomatous meningitis. She subsequently developed respiratory distress and required intubation 7 days after the second dose of intrathecal chemotherapy. She was treated with

Figure 3. Gallbladder histology. Hematoxylin and eosin stained section of the gallbladder showing a poorly differentiated invasive adenocarcinoma, which focally exhibits signet ring morphology.

Figure 5. Meningeal histology. Hematoxylin and eosin stained section of the meninges reveals a subarachnoid infiltrate of poorly differentiated malignant cells, many of which exhibit signet ring morphology.

one dose of whole brain radiation therapy on the second day after being intubated. On the same day she developed EKG abnormalities and elevated cardiac enzymes indicating acute cardiac injury. CT angiogram and duplex ultrasound did not reveal any evidence of pulmonary embolism or deep venous thrombosis, respectively. On the following day she developed asystole and was not resuscitated. At autopsy, there was tumor infiltration in cranial nerves II, V, VII, VIII, and X, and the cerebral hemispheres, in addition to dorsal and ventral roots of the spinal cord (Figures 4–6). There was no evidence of hydrocephalus or significant coronary atherosclerosis. We presumed her terminal cardiac events were related to metastatic involvement of the brainstem autonomic centers. Interestingly, the metastatic tumor was not found

Figure 6. Cranial nerve histology. Hematoxylin and eosin stained section of cranial nerve V illustrating infiltration of nerve by poorly differentiated malignant cells with signet ring morphology.

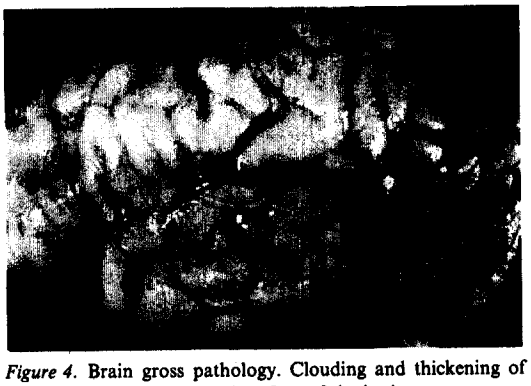

Figure 4. Brain gross pathology. Clouding and thickening of the meninges on the ventral surface of the brainstem.

outside of the nervous system. In summary, the disease progression in her case was rapid and resulted in her death one month after the initial neurologic presentation.

Discussion

The incidence of carcinomatous meningitis has increased in the past few decades. This increase has been attributed to the prolonged survival of cancer patients as a result of the advances in anti-cancer treatment, as well as heightened index of clinical

suspicion [6]. In one autopsy study, 8% of patients with systemic cancer were found to have tumor cell metastases in their meninges [7]. In those with leptomeningeal metastases, 24% had concomitant parenchymal brain metastases [8]. The most likely solid tumors found to spread to the leptomeninges include lung cancer, breast cancer and melanoma. Other primary tumors that less commonly spread to leptomeninges include ovarian cancer [9], cervical cancer [10], renal cell carcinoma [11] and gastric adenocarcinoma [12]. Gallbladder carcinoma involving the leptomeninges has only been reported in very few instances. The symptoms of carcinomatous meningitis are not specific to the primary cancer type. Our patient presented with hearing loss, tinnitus, vertigo and ataxia. Meningeal irritation from tumor infiltration can produce headache, nausea, vomiting and altered mentation. Visual loss and diplopia can be due to either direct cranial nerve damage or papilledema from hydrocephalus. Spinal cord leptomeningeal involvement can result in radicular pain, weakness and paresthesia, and bowel and bladder dysfunction.

Definitive diagnosis requires identification of malignant cells in the CSF. The diagnosis can be supported by findings on CT with contrast or MRI with gadolinium and occasionally meningeal biopsy. The sensitivity of cytological diagnosis with one CSF examination is 54% but increases to 91% with two-examinations [8]. Therefore, multiple lumbar punctures may be required to achieve a definitive diagnosis. Other CSF abnormalities associated with carcinomatous meningitis include low glucose, high protein, and lymphocytic pleocytosis. CSF markers can be helpful in supporting the diagnosis of carcinomatosis. These include β-glucuronidase, CEA (carcinoembryonic antigen), β-microglobulin, cancer specific monoclonal antibodies, lactate dehydrogenase, and others [13]. These markers may prove helpful to increase the diagnostic yield in those patients with multiple taps with negative cytology or help to delineate the origin of the primary tumor, as this case illustrates.

CSF cytology and neuroimaging are complementary in the diagnosis of carcinomatous meningitis. Gadolinium-enhanced MRI of brain is considered more sensitive than contrast-enhanced CT in demonstrating the abnormalities caused by leptomeningeal metastasis [14]. The classic radiographic findings on MRI for carcinomatous meningitis include leptomeningeal enhancement, either in the brain (extending into the sulci of the cerebral hemispheres or the folia of the cerebellum), spinal cord, caudal equina, or subependymal areas. Enhancement of cranial nerves is highly suggestive of leptomeningeal involvement. Neuroimaging abnormalities can be observed in 79% of patients with positive cytological studies [15].

The treatment of carcinomatous meningitis includes intrathecal chemotherapy, radiation therapy or systemic chemotherapy. Treatment is palliative rather than curative even though prolonged responses may be seen in more chemosensitive primary neoplasms such as lymphoma, breast cancer and small cell lung cancer. Intrathecal chemotherapeutic agents include methotrexate, thiotepa, cytarabine, or the recently available liposomal cytarabine [16]. These agents may be used either alone or in combination, but there is no evidence to support the superiority of combination over single agent therapy, and patients treated with combination drug therapy have markedly increased toxicity [17]. Intrathecal methotrexate and thiotepa, if used alone, will both convert the CSF cytology to negative in one-third of previously untreated patients. However, 75% of those patients will develop neurological progression within 8 weeks of initiating therapy [18]. High-dose intravenous methotrexate may deliver a cytotoxic CSF methotrexate concentration and minimize the neurologic side effects associated with intrathecal injection [19], but with greater systemic side effects. The average survival following diagnosis of carcinomatous meningitis is 4–6 months [20], which can be prolonged to a mean of 9 months by aggressive treatment [21], with isolated cases of survival up to 29 months [8]. Radiation therapy is often given palliatively to bulky tumor mass for symptomatic relief.

Overall survival for patients with gallbladder adenocarcinoma is 25% at 5 years with median survival of 9.7 months [22]. Early (stage I and II) lesions have a good prognosis and do not require further treatment after surgery. Survival with advanced disease is measured in weeks to months.

In summary, patients with symptoms of cranial neuropathy, increased intracranial pressure, or spinal cord dysfunction should have carcinomatous meningitis on the list of differential diagnoses, especially if the patient has systemic cancer. As in our case, neurologic symptoms of carcinomatous meningitis may be the presenting feature of a rare neoplasm. Although the prognosis of patients with

carcinomatous meningitis is very poor, prompt diagnosis and treatment could possibly prolong survival and improve quality of life.

References

1. Tans RJ, Koudstaal J, Koehler PJ: Meningeal carcinomatosis as presenting symptom of a gallbladder carcinoma. Clin Neuro Neurosur 95: 253–256, 1993
2. Gaumann A, Marx J, Bohl J, Kommoss F, Kohler H, Tews DS: Leptomeningeal carcinomatosis and cranial nerve palsy as presenting symptoms of a clinically inapparent gallbladder carcinoma. Pathol Res Pract 195(7): 495–499, 1999
3. Higes-Pascual F, Beroi-Groh P, Bravo-Guillen AL, Palomo-Martinez V, Cuevas-Santos J: Leptomeningeal carcinomatosis as presenting symptoms of a gallbladder carcinoma. Rev Neurol 30(9): 841–844, 2000
4. Homa K, Hamashima H: Fulminating gallbladder carcinoma presenting as leptomeningeal carcinomatois and acute renal failure. Wien Klin Wochenschr 102: 654–656, 1990
5. Naylor RA, MacGregor JE, Hutcheon AW, Best PV: Meningeal carcinomatosis from clinically undiagnosed signet-ring cell primary in the gallbaldder. Surg Neurol 29: 315–318, 1988
6. Zachariah B, Zachariah SB, Varghese R, Balducci L: Review: carcinomatous megingitis: clinical manifestations and management. Int J Clin Pharmacol Ther 33(1): 7–12, 1995
7. Posner JB, Asbury AK, McKhann GM, McDonald WI: Secondary neoplastic disease. In: Disease of the Nervous System: Clinical Neurobiology, 2nd ed. 1992, pp 1093–1141
8. Wasserstrom WR, Glass JP, Posner JB: Diagnosis and treatment of leptomeningeal metastasis from solid tumors: experience with 90 patients. Cancer 2: 759–772, 1982
9. Bakri YL, Lewis JJ, Lublin GCJ, Dannof B: Meningeal carcinomatosis complicating gynecologic malignancies: a literature review and report of a case. Obst Gynecol Sur 38: 1–5, 1983
10. Aboulafia DM, Taylor LP, Crane RD, Yon JL, Rudolph RH: Case report: carcinomatous meningitis complicating cervical cancer: a clinicopathologic study and literature review. Gynecol Oncol 60: 313–318, 1996
11. Crino PB, Sater RA, Sperling M, Katestos C: Renal cell carcinomatous meningitis: pathologic and immunochemical features. Neurol 45: 189–191, 1995
12. Deeb LS, Yamout BI, Shamseddine AL, Shabb NS, Uthman SM: Case Report: Meningeal carcinomatosis as the presenting manifestation of gastric adenocarcinoma. Am J Gastroenterol 92(2): 329–331, 1997
13. Chamberlain MC: Current concepts in leptomeningeal metastasis. Curr Opin Oncol 4: 533–539, 1992
14. Chamberlain MC, Sandy AD, Press GA: Leptomeningeal metastasis: a comparison of gadolinium-enhanced MR and contrast-enhanced CT of the brain. Neurology 40(3 Pt 1): 435–438, 1990
15. Freilich RJ, Krol G, DeAngelis LM: Neuroimaging and cerebrospinal fluid cytology in the diagnosis of leptomeningeal metastasis. Ann Neurol 38: 51–57, 1995
16. Jaeckle KA, Batchelor T, O'Day SJ, Phuphanich S, New P, Lesser G, Cohn A, Gilbert M, Aiken R, Herons D, Rogers L, Wong E, Fulton D, Gutheil JC, Baidas S, Kennedy JM, Mason W, Moots P, Russell C, Swinnen LJ, Howell SB: An open-label trial of sustained-release cytarabine (DepoCyt) for the intrathecal treatment of solid tumor neoplastic meningitis. J Neurooncol 57(3): 231–239, 2002
17. Hitchins RN, Bell DR, Woods RL: A prospective randomized trial of single-agent versus combination chemotherapy in meningeal carcinomatosis. J Clin Oncol 5: 1655–1662, 1987
18. Grossman SA, Finkelstein DM, Ruckdeschel JC, Trump DL, Moynihan T, Ettinger DS: Randomized prospective comparison of intraventricular methotrexate and thiotepa in patients with previously untreated neoplastic meningitis. J Clin Oncol 11: 561–568, 1993
19. Tetef ML, Margolin KA, Doroshow JH, Akman S, Leong LA, Morgan RJ Jr, Raschko JW, Slatkin N, Somlo G, Longmate JA, Carroll MI, Newman EM: Pharmacokinetics and toxicity of high-dose intravenous methotrexate in the treatment of leptomeningeal carcinomatosis. Cancer Chemother Pharmacol 46: 19–26, 2000
20. Chamberlain MC, Kormanik PA, Barba D: Complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases. J Neurosurg 87: 694–699, 1997
21. Grant R, Naylor B, Greenberg HS, Junck L: Clinical outcome in aggressively treated meningeal carcinomatosis. Arch Neurol 51: 457–461, 1994
22. North JJ, Pack MS, Hong C, Rivera DE: Prognostic factors for adenocarcinoma of the gallbladder: an analysis of 162 cases. Am Surg 64(5): 437–440, 1998

Address for offprints: Yue Shen, Department of Neurology, University of Utah Hospital, 50 North Medical Room, Rm 3R210, UT 84132, Salt Lake City, USA; Tel.: +1-801-585-0932; Fax: +1-801-581-4192; E-mail: jason.shen@usa.net