Journal of Neuro-Oncology **00:** 1–5, 2003.

Clinical Study

Meningeal carcinomatosis as the first manifestation of a transitional cell carcinoma of the bladder

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Key words: meningeal carcinomatosis, transitional cell carcinoma, bladder tumor, CSF cytology, urine cytology, seizures

Summary

Meningeal carcinomatosis (MC) as first manifestation of a transitional cell carcinoma (TCC) of the bladder is rare. We report a 66-year-old man, smoker, who presented with two episodes of secondarily generalized partial motor seizures. The routine blood test, brain computed tomography (CT) scan, brain magnetic resonance imaging and electroencephalogram were normal. Cerebral spinal fluid (CSF) revealed a significant pleocytosis and a morphology compatible with non-differentiated non-small cell carcinoma. Broncofiberscopy, gastrofiberscopy, thoracicoabdominopelvic CT-scan and bone scintigraphy were normal but the urine cytology revealed malignant cells similar to those found in the CSF. TCC was diagnosed by cystoscopy and later necropsy confirmed the MC of this tumor. In this report we review the literature and analyze patient survival.

Introduction

Meningeal carcinomatosis (MC) is an uncommon complication of solid tumors (1–8%) [1–3]. In recent years, an increased incidence of MC is reported due to the development of new antineoplastic treatments and, subsequently, a longer patient survival [4]. Prevalence of the various primary tumors leading to MC has changed over the years due to variation in its incidence and the applied novel therapies [4]. The most frequently involved tumors are, in order of frequency: breast, lung, melanoma and genitourinary tumors. The most common histological type is adenocarcinoma [5–8]. In 6–38% of patients the primary tumor is unknown at the time of the MC presentation [5,9]. The usual clinical presentation is a multifocal involvement of the neuraxis with headache and radicular pain being the most common initial symptoms. The most frequent signs are motor deficits, altered mental status and cranial nerve involvement. Seizures are rare as first manifestation and occur in 6% [1,5–7,9].

Transitional cell carcinoma (TCC) of the bladder is the most common neoplasm of the urinary tract. Metastases are the first manifestation of this tumor in 4–17% of patients. Lymph nodes (78%), liver (38%), bones (27%) and adrenal glands (21%) [10] are the most common localization for metastases. MC is rare as a first manifestation of TCC [11–13]. We describe a patient who presented with MC as a first manifestation of a TCC and review the literature.

Case report

A 66-year-old man, smoker of 15 cigarettes/day, was admitted in July 2001 for two episodes of secondarily generalized partial motor seizures with origin in the upper right extremity. Physical examination was normal. Brain computed tomography (CT) scan, brain magnetic resonance imaging (MRI), electroencephalogram and routine blood tests were normal, determinations of PSA, alpha-fetoprotein, CEA and CA-125

in serum were normal. Blood levels of CA 19-9 were of 1479 kU/l (normal range <39 kU/l). Cerebral spinal fluid (CSF) analysis revealed an elevated protein concentration of 0.69 g/l and 85 cells/mm^3. Twenty-seven percent of cells had morphology compatible with non-differentiated non-small cell carcinoma (Figure 1a). The subsequent bronchofiberscopy, gastrofiberscopy, thoracicoabdominopelvic CT-scan and bone scintigraphy were normal. The urine cytology revealed malignant cells of a similar lineage to those cells found in the CSF (Figure 1b). TCC of the bladder was diagnosed by cystoscopy. A pyelography showed no evidence of abnormalities in the upper urinary tract. Intrathecal chemotherapy (methotrexate) was started by means of an Ommaya reservoir. The patient died 2 months after admission due to a *Staphylococcus aureus* meningitis. He had received one unique dose of intrathecal methotrexate (12 mg per dose). Autopsy was performed and confirmed the diagnosis of MC due to TCC ($pT3_aN_xM1$) after staining the cells that infiltrated the meninges with low-molecular weight cytoqueratin (CAM 5.2) (Figure 2).

Statistical analysis of literature review

We undertook a revision of the literature of MC complicating a TCC of the bladder. To calculate the median of survival, we estimated the function of survival via the method of Kaplan–Meier. To compare the functions of survival we used the log-rank test. Although most patients underwent intrathecal chemotherapy and some of them followed adjuvant radiotherapy, in any case their survival did not exceed 9 months (median: 52 days, range: 15–270 days). According to a survival analysis on the patients reported in the literature we have noticed a higher median survival in patients who received treatment (intrathecal chemotherapy ± radiotherapy) against those who did not (90 vs. 20 days; log-rank = 0.0107). This is a retrospective study and therefore we cannot rule out the influence of a significant selection bias, so that patients with a better initial prognosis a priori are prone to receive treatment.

Discussion

MC as a first manifestation of TCC is rare. Until now, only three patients have been reported in the literature. In two patients these tumors were localized in the bladder [11,13] and the third patient's tumor was in the renal pelvis [12]. The second case reported by Vidal et al. [13] has not been included in this review since there is no anatomopathological confirmation of meningeal infiltration, and the initial MRI was normal. We have only found 19 patients reported in the literature with MC due to TCC (Table 1). There is a predominance of men aged from 40 to 71 years. The initial clinical symptomatology is the same as those reported for other MC etiologies [1,5–7,9]. Seizures due to leptomeningeal cellular infiltration, with no evidence of intraparenchymatous nests, may be explained by different mechanisms. A local depletion of glucose levels, ischemia produced by local 'steal' phenomena or hydrocephalus, may lead to focal epileptiform abnormalities [1,18,24]. When MC is manifested, many patients present other distant metastases and locoregional adenopathies. Central nervous system has traditionally been considered as a 'sanctuary' for neoplastic cells due to the blood–brain barrier impermeability

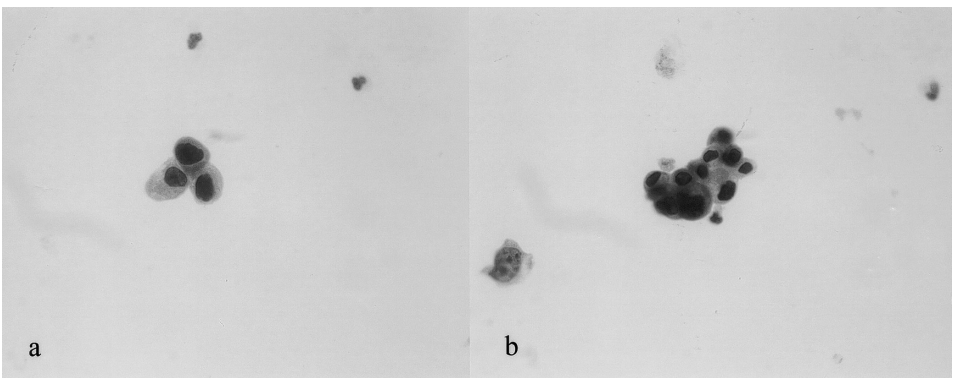

Figure 1. (a) Urine, papanicolaou, ×200; (b) cerebrospinal fluid, ×200. Oval or polyhedral cells whith moderate basophilic cytoplasma and central hyperchromatic nuclei.

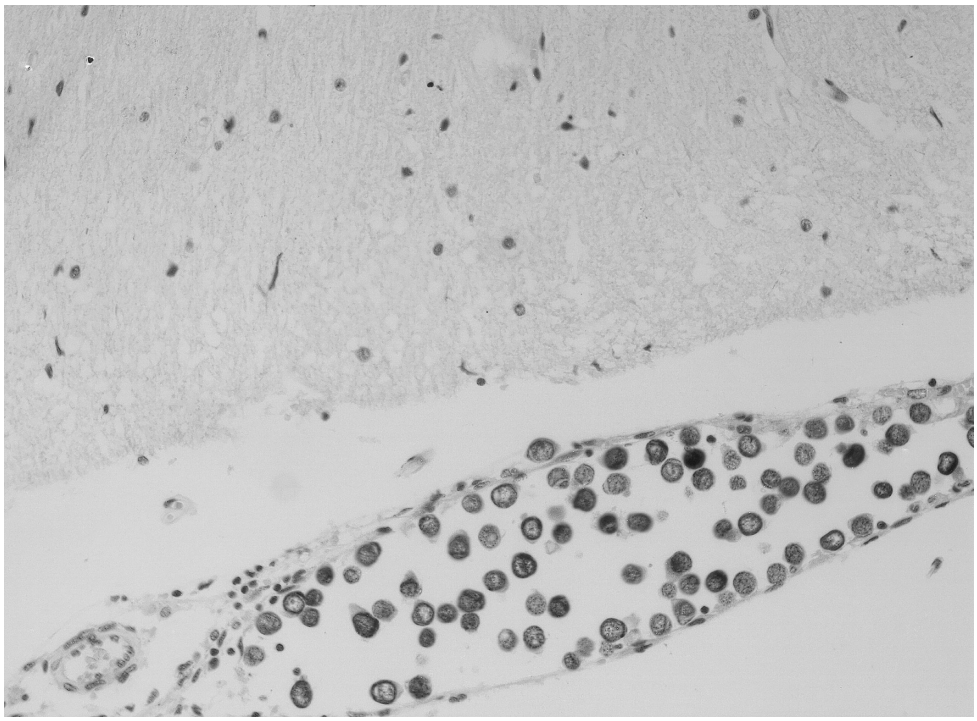

Figure 2. Histologic section of tissue showing meningeal infiltration by cells similar to the ones seen in the urine and cerebrospinal fluid, all of them positive for epithelial markers (CAM 5.2).

Table 1. Patient characteristics and survival

Patient	Author	Year	Sex	Age (years)	Systemic chemotherapy	Intrathecal chemotherapy	RDT	Survival (days)
1	Mandell [4]	1985	M	59	−	+	cs	n.r.
2	Bishop [14]	1990	M	60	−	+	cs	35
3	Bishop [14]	1990	M	55	−	−	—	20
4	Santarossa [15]	1997	F	52	−	+	wb	270
5	Loizaga [16]	1999	M	60	+	−	—	15
6	Raghavan [17]	1991	M	42	+	+	—	134
7	Steg [18]	1993	M	68	−	−	wb	38
8	Eng [19]	1993	M	71	−	−	—	25
9	Eng [19]	1993	M	64	−	+	sp	90
10	Hust [11]	1982	M	52	−	−	—	30
11	Hust [11]	1982	F	66	−	−	—	15
12	Vidal [13]	2000	M	46	+	+	wb	162
13	Bloch [20]	1986	M	67	−	−	—	107
14	Hussein [21]	1991	M	60	−	+	—	164
15	Hasbini [22]	1997	M	63	−	−	—	18
16	Imamura [12]	1997	M	71	n.r.	n.r.	n.r.	90
17	Cozzarini [23]	1999	M	46	−	+	—	150
18	Cozzarini [23]	1999	M	40	−	+	—	30
19	Wieczorek*	1964	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
20	Current	2001	M	66	−	+	—	66

M – male; F – Female; n.r – not reported; wb – whole brain; cs – craniospinal; sp – spinal.
*Referred in [23].

for systemic chemotherapy [25]. However it has also been postulated that patients treated with systemic chemotherapy present an increased permeability which would enhance the dissemination of tumor cells [26]. Meningeal dissemination in our patient may be explained by different mechanisms: (a) retrogade dissemination through the pudendal nerves, the sacral plexus or the obturator nerve [27], (b) dissemination through Batson's venous plexus is possible but the absence of vertebral metastases makes it unlikely [28,29], (c) finally, the meningeal invasion could be secondary to hematogenous dissemination enhanced by the expression of specific organ/endothelial adhesion molecules, as has been described in melanomas and other tumors [30].

We conclude that the performance of a non-invasive and simple examination such as urine cytology should be considered in cases of MC due to epithelial carcinomas, when basic examinations cannot prove the primary tumor, especially in men.

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