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Clinical Study

High incidence of asymptomatic brain lesions in metastatic renal cell carcinoma

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Summary

The metastatic pattern of renal cell carcinoma has been well established. Studies have revealed a relatively high incidence of spread to lung, liver, bone and brain. A retrospective review of the records of ninety patients with metastatic renal cell carcinoma showed seven to have evidence of brain metastases. Six of the seven were asymptomatic at time of diagnosis. This study shows a significant incidence of asymptomatic brain metastases in patients with metastatic renal cell carcinoma. Subsequent to our chart review, an additional two patients have presented to our institution with asymptomatic brain lesions from metastatic renal cell carcinoma.

Introduction

American Cancer Society statistics estimate the incidence of new cases of kidney and other urinary cancer to be 26,500 in 1992, with approximately 10,000 deaths [1]. The incidence of renal cell carcinoma has previously been reported to be 7.5 per 100,000 in the USA with roughly 15,000 new cases presenting each year [2, 3]. About 25% of patients with renal cell carcinoma present with metastatic disease. Of those patients with metastatic renal cell carcinoma, as many as 10% will have brain lesions [4–6]. Generally, once renal cell carcinoma has metastasized to distant sites, the prognosis is poor with a median survival of six to eight months [7–9].

In the metastatic workup of renal cell carcinoma, brain scans are not routinely employed and brain lesions are usually detected after patients become symptomatic. Perhaps as a result, brain metastases have been considered to be a late manifestation of renal cell carcinoma [8]. We conducted a retrospective review of the records of 90 patients with metastatic renal cell carcinoma in order to assess the frequency of asymptomatic brain metastases. Our series shows a higher than expected incidence of asymptomatic brain lesions among patients with metastatic disease. These findings suggest a role for routine brain scans in patients with metastatic disease in order to guide therapy appropriately.

Materials and methods

90 patients with documented metastatic renal cell carcinoma were enrolled in the randomized controlled survival study of autolymphocyte therapy as reported in Lancet, April 1990 [10]. To participate in the study, all patients were required to have a full evaluation including initial comprehensive history and physical examination by a physician, laboratory indices, chest and abdominal computerized tomography (CT), bone scan and head CT. A retrospec-

tive analysis of their records was performed with particular attention to the presence of brain metastases, and signs and symptoms of neurologic dysfunction.

Results

During evaluation for study eligibility, 7 of the original 90 patients were noted to have lesions on head CT consistent with metastatic disease. Of these 7, 6 were free of related neurologic signs and symptoms at the time of diagnosis and subsequent radiographic evaluation. One patient developed neurologic symptoms 2 months after the diagnosis of brain metastasis (Table 1). The patient who presented with visual symptoms at the time of head CT was found to have a brain lesion. Patients # 1–4 were enrolled in the control arm of the protocol receiving cimetidine only, and patients # 5–7 were enrolled in the ALT arm; however, patient # 6 did not receive ALT due to his brief survival.

A review of the records of all 90 patients enrolled in the autolymphocyte therapy (ALT) protocol revealed a mean survival of 646 days for the ALT group versus 265 days for the control arm [11]. Patients not receiving ALT with asymptomatic brain metastases had a mean survival of 173 days, as compared to a mean survival of 245 days for the ALT group.

Discussion

Renal cell carcinoma most commonly metastasizes to lung, liver, and bone and can metastasize to brain. Brain metastases from renal cell carcinoma usually occur in the setting of widespread metastatic disease. Maor *et al.* reviewed a series of 46 patients with renal cell carcinoma metastatic to the brain [12]. In only 3 cases was the brain the only organ involved with metastatic disease. All 7 patients mentioned in this study had widespread metastatic disease with 6/7 having pulmonary involvement.

Although renal carcinoma metastasizes more commonly to lung, liver and bone, metastases to the brain are by no means rare. The incidence of brain metastasis from renal carcinoma has been documented in several large autopsy series to be approximately 10%.

Table 1. Lesions, symptoms and survival in patient with brain metastases

Patient	# of lesions	Site of lesion	Symptom	Survival
# 1) Control	2	Left frontoparietal 1 cm Right parietal 1 cm	None	237 d
# 2) Control	1	Right occipital 2 cm Right occipital 1 cm	None	82 d
# 3) Control	1	Right calvarium with extension into brain	None	498 d
# 4) Control	1	Left parietaloccipital	Expressive aphasia Visual symptoms Neurologic symptoms appeared 2 months after diagnosis of Renal cell	37 d
# 5) ALT	1	right frontal 1 cm	Visual symptoms	202 d
# 6 ALT*	2	right temporal 1 cm	None	12 d
# 7 ALT	1	left occipital	None	288 d

* patient did not receive treatment.
Mean survival patients not receiving ALT with brain lesions = 173 d (#1–4,6)
Mean survival ALT treated patients with brain lesions = 245 d (# 5, 7)
Mean survival all patients in with brain lesions = 193 d (# 1–7)
Mean survival overall for ALT (All patients with metastatic disease) = 646 d
Mean survival patients not receiving ALT = 265 d
(All patients with metastatic disease)
Expected mean survival for metastatic renal cell = 180–240 d (no therapy).

Table 2. Reports of renal cell carcinoma with brain metastases

Investigator	Series	Number brain mets	Total	Percent brain mets
1) Saitoh	Autopsy	177	1828	10%
2) Weiss	Autopsy	66	687	10%
3) Murphy	Autopsy	4	42	10%
4) Ohkoshi	Autopsy	35	409	9%
5) Gay	Clinical	36	926	3.9%
6) Osband	Clinical	6	90	7.8%
7) Lavin	Clinical	31	335	9%

Despite several autopsy studies, as well as reports of solid tumors metastasizing to the brain, there are few clinically oriented reports of a large series of renal cell carcinoma with spread to the brain [13–19]. A recent clinical series by Gay reports the incidence to be 3.9% (36/926) [8]. The data for this series was generated from review of medical records and therefore there was no prospective control of metastatic workup. It is particularly striking that such a difference in reported incidence exists between autopsy and clinical series. A recent report on the results of ALT in a multicenter study revealed a 9% incidence (31/335 patients). The incidence of brain lesions in this study was 7.8% (See Table 2) [20].

Currently, there is no standard therapy effective for patients with advanced disease. However, with the advent the biologic response modifiers, there are now therapies available which, in selected patients, can increase response rates. Forms of immunotherapy such as alpha interferon, adoptive immunotherapy with interleukin 2 and lymphocyte activated killer (LAK) cells, tumor infiltrating lymphocytes (TILS) therapy and autolymphocyte therapy have shown response rates of 18–35% [21, 22]. In addition, previous experience with metastatic disease response to chemotherapy has shown that the presence of brain metastases confers a poor prognosis [23]. It is difficult to assess what effect the use of biologic response modifiers will have on the prognosis of patients with brain metastases. Of the 7 patients reviewed in the Lancet cohort, the 2 patients receiving autolymphocyte therapy had a limited increase in mean survival compared to patients not receiving ALT, and had a significantly less mean survival compared to the entire ALT group mean survival of 450 days. In fact, CNS metastases are frequently an exclusion criterion for participation in such studies.

It is therefore important to determine the presence or absence of brain metastases in patients with metastatic renal cell carcinoma as it may impact on their overall treatment response and survival. By not screening for these lesions, one may miss them in their early stages. This is unfortunate as brain lesions are often controlled by treatment with radiation therapy alone or in combination with surgical excision. In Maor's series, 7 patients were treated with excision and post operative radiation. In 5/7, the excision was complete and associated with clinical improvement. Other patients in the series were treated with whole brain radiation with a mean survival of 17 weeks [12]. In Gay's series 7 patients who underwent excision and post operative radiation had a 66 week mean survival, and a 13 week mean survival was noted in patients treated by radiation alone [8]. Although the early treatment of these lesions may not improve overall survival, it may improve a patient's quality of life.

Other clinical series have noted the significance of asymptomatic brain lesions. Only 2/36 patients in the Gay's clinical study presented with neurologic complaints. Of the remaining patients, 8 went on to develop focal neurologic symptoms after diagnosis and another 5 had seizures, leaving only 58% (21/36) patients asymptomatic from their CNS involvement. It is possible that more patients in their series had asymptomatic neurologic involvement, but did not undergo head CT. In our series, one patient exhibited focal neurologic symptoms and one additional patient developed symptoms 2 months after diagnosis of the lesion.

Subsequent to our review, 2 additional patients have presented to our institution with asymptomatic brain lesions from renal cell carcinoma. Neither of the two patients have developed neurologic symptoms. One has been treated with radiation therapy and surgical excision in addition to autolymphocyte therapy, this patient is currently alive with a 845 day survival. The other patient received external beam radiation therapy; however his performance status rapidly deteriorated precluding systemic therapy with a biological response modifier.

From the data reviewed and presented, it would appear that renal carcinoma brain metastases occur in a significant number of patients and are often asymptomatic. Therefore, in the setting of metastatic renal cell carcinoma, brain imaging would seem indicated to perform proper initial assessment of extent of disease and the initiation of appropriate therapy.

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