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Clinical case

Sustained response of sarcomatoid renal-cell carcinoma to MAID chemotherapy: Case report and review of the literature

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Summary

The sarcomatoid variant of renal-cell carcinoma (SRCC), a clinically aggressive subtype of renal parenchymal tumors, is typically resistant to systemic treatments and carries a poor prognosis. The authors report a case of a 57-year-old male with advanced SRCC who had a durable complete response after MAID (mesna, adriamycin, ifosfamide and dacarbazine) chemotherapy, and remains free of disease four years after completing treatment. To the authors' knowledge, this is the first report of a remission from MAID chemotherapy in SRCC. A review of published literature revealed occasional responses after systemic chemotherapy. Notably, all responses were seen with doxorubicin containing regimens, suggesting that doxorubicin is a critical component in chemotherapy regimens for SRCC.

Key words: complete response, doxorubicin-based chemotherapy, MAID, sarcomatoid renal-cell carcinoma

Introduction

Sarcomatoid renal-cell carcinoma (SRCC) is an uncommon histological variant of renal carcinoma representing 0.7%–13.2% of renal parenchymal tumors [1]. Pathologically, these tumors consist of pleomorphic spindle cells and/or malignant appearing giant cells, which resemble a sarcoma interspersed with clear cells and granular cells [2]. The clinical course of SRCC is characterized by a high rate of local recurrence and metastasis, and shortened survival [2, 3]. There is no uniform therapy for this disease, and rare responses have been reported with systemic chemo- and/or immunotherapy. Here we report a case of metastatic SRCC who, after failing to respond to high-dose immunotherapy with IL-2, had a complete and sustained response to MAID (mesna, adriamycin (doxorubicin), ifosfamide and dacarbazine) chemotherapy. To our knowledge, this is the first report of a response to MAID, a chemotherapy generally used for soft tissue sarcomas, in SRCC. We also review the literature on treatment of SRCC with systemic therapies.

Case report

A 57-year-old Caucasian male, who had previously been in good health, presented with left upper abdominal discomfort in February of 1996 and was found to have a 10 cm mass at the inferior aspect of the left kidney by CT scan. Radical nephrectomy revealed a 9.5 cm tumor, which microscopically consisted of conventional (clear cell) renal-cell carcinoma with extensive areas of malignant spindled cells and necrosis (Figures 1a and b). The Fuhrman grade was 4 of 4, and the high-grade sarcomatoid pattern comprised >95% of the tumor. A separate nodule, consisting of low grade granular renal-cell carcinoma without sarcomatoid features was noted in the renal cortex, and was thought to represent an intra-renal metastasis or a second primary cancer. Microscopic tumor thrombi were seen in several intrarenal veins, but hilar lymph nodes showed no evidence of metastasis. The pathologic stage was $T_{3a}N_0M_0G_4$.

Two months later, the patient developed lung metastasis with a 2 cm nodule in the right lung and hilar lymphadenopathy. A needle biopsy of the lung nodule confirmed the presence of metastasis from the primary SRCC. Systemic treatment was started with high-dose IL-2 (720,000 U/kg q 3 weeks), but the patient experienced severe toxicity consisting of renal insufficiency, cardiac ischemia and arrythmias requiring discontinuation of therapy after 10 doses. A CT scan at the conclusion of IL-2 therapy revealed progression of disease with large mediastinal and lung nodules, and a left pleural effusion. The patient was treated with palliative radiotherapy to the mediastinum (total dose of 3720 cGy), but a CT scan after completion of radiotherapy revealed further progression of disease in the lungs with new pleural metastases (Figure 2a).

The patient presented to our clinic one month after completing radiotherapy, and was noted to have dyspnea and fatigue. It was decided to treat him with MAID chemotherapy consisting of dacarbazine (250 mg/m^2/day), adriamycin (doxorubicin, 15 mg/m^2/day) and mesna (2.5 g/m^2/day) on days 1–4, and ifosfamide (2.5 g/m^2/day) on days 1–3, all given as a continuous i.v. infusion, once every three weeks. The patient tolerated

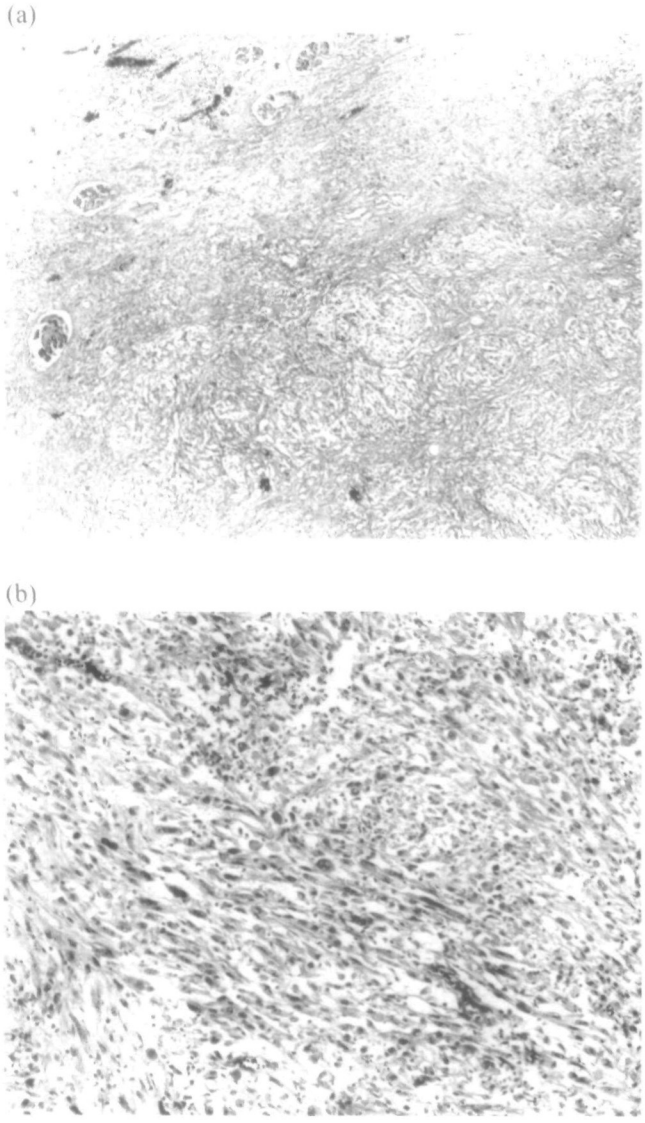

Figure 1. (a) Sarcomatoid renal-cell carcinoma, composed of neoplastic, spindle shaped cells (right lower half of the figure) along with residual normal kidney (left upper corner). Hematoxylin and eosin, × 100. (b) Higher magnification showing high-grade, granular, spindled cell arranged in fascicles, with nuclear hyperchromasia, pleomorphism and abnormal tripolar mitosis (center). Hematoxylin and eosin, × 500.

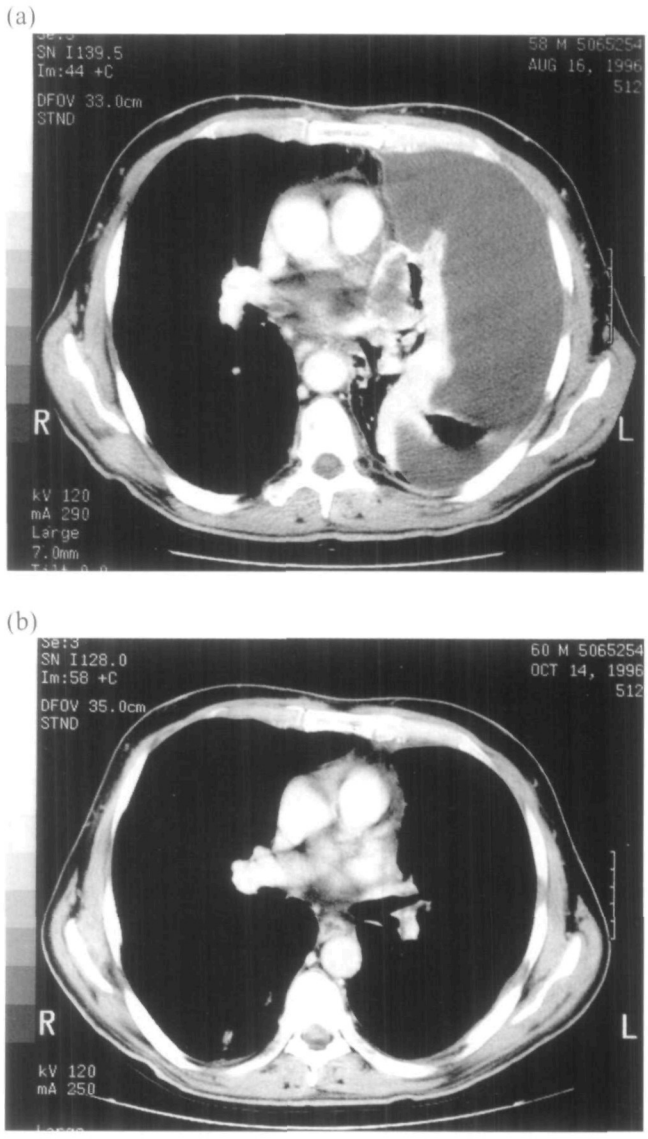

Figure 2. (a) CT scan of the chest at the time of presentation showing a 4.0 × 2.6 cm left hilar mass and a large left-sided pleural effusion; (b) a follow-up CT scan after two cycles of MAID chemotherapy showing a complete resolution of the left hilar mass and a dramatic improvement in the left-sided pleural effusion.

the treatments well and had significant symptomatic improvement after two cycles of chemotherapy. A CT scan revealed a dramatic improvement in the large left sided pleural effusion, and complete resolution of the left hilar mass and several pulmonary and pleural nodules (Figure 2b). The patient had a complete response at the end of four cycles, and received a total of six cycles of MAID. At this time, the patient continues to do well without any evidence of recurrence more than four years after completing chemotherapy.

Discussion

Renal-cell carcinomas are generally chemoresistant tumors [4]. The sarcomatoid variant of renal-cell carcinoma, in particular, is characterized by an aggressive clinical course, wherein most patients present with locally advanced or metastatic disease at the time of diagnosis [5–10]. Hence, SRCC carries a poorer prognosis, with a median survival of seven months in untreated patients [6, 11]. A new classification for renal-cell carcinoma based on molecular markers has been recently devised, whereby the clinical course can be correlated with specific genetic abnormalities [12]. While this contemporary classification does not distinguish SRCC as a distinct clinicopathologic entity, it recognizes that any histological variant of renal-cell carcinoma may have sarcomatoid areas, the presence of which indicate a high-grade lesion with poor prognosis [13]. Information regarding molecular markers was not available on our patient; however, the microscopic features and clinical course are consistent with a conventional (clear cell) renal-cell carcinoma with extensive sarcomatoid areas. For the

purpose of this report, we have described our patient's tumor as SRCC based on established morphologic criteria [2] to enable comparison with existing literature.

Due to the rarity of this disease, there have been few clinical trials, and long-term survival data is limited. While there is no standard treatment currently available for metastatic SRCC, many treatment modalities have been tried including chemotherapy, hormone therapy [11, 14, 15], immunotherapy [1], and combination of chemotherapy with hormones or immunotherapy [16–18]. A few responses have been observed with each of the aforementioned modalities. However, sustained complete remissions (CRs) have been reported only after treatment with chemotherapy (with or without immunotherapy). Table 1 summarizes the published literature on treatment of SRCC with chemotherapy based regimens.

The chemotherapy regimens used for SRCC have generally consisted of modifications of regimens used for soft-tissue sarcomas. These include doxorubicin based regimens such as CYVADIC [19], DECAV [15], and DI [20], and non-doxorubicin containing regimens using CCNU, streptozotocin, hydroxyurea, vincristine, and ethanesulforic acid or single agent elliptinium [14]. It is interesting to note that durable CRs have been reported only after treatment with doxorubicin containing regimens. Sella et al. reported durable CRs in 2 of 7 patients treated with CYVADIC (11) while 11 patients treated with non-doxorubicin containing chemotherapy had no response. Similarly, Lupera et al. noted one complete response to DECAV [15].

Immunotherapy regimens, similar to those used in clear-cell renal carcinoma, have also been used for the treatment of SRCC with little success. Alpha interferon as a single agent has been disappointing with no responses noted in two retrospective studies with small number of patients [11, 14]. However, in spite of a lack of response patients treated with alpha interferon appeared to have a longer median survival [11]. In a retrospective analysis of 31 patients with SRCC treated with immunotherapy after radical nephrectomy, treatment with high-dose IL-2 was found to correlate with improved overall survival [1]. There were no CRs and 22% partial responses (PRs) in patients treated with high-dose IL-2. As shown in Table 1 there have been few reports about the efficacy of combination of chemotherapy with immunotherapy in SRCC. Krutchik et al. reported one patient who had a very good PR to a combination of CYVADIC, BCG and sarcoma viral oncolysate lasting at least 24 months (16), while Friedland at al reported one patient with CR following therapy with a combination of 5-FU, low-dose IL-2 and IFN-α [18].

Since our patient had already progressed on high-dose IL-2, we elected to treat him with MAID chemotherapy regimen which has been shown to be effective in advanced soft tissue sarcomas (10% CR and 37% PR) [21]. Although a total of six cycles were administered to our patient, he had a dramatic response with an almost complete remission after the second cycle of MAID and his CT scans demonstrated a CR after four cycles. It was elected to treat him with additional two cycles due to the aggressive nature of his disease. His remission has been durable with no evidence of disease four years after treatment.

Table 1. Response of SRCC to various chemotherapy based regimens.

Author [reference]	Treatment regimen	Number of patients with SRCC	Response	Duration (months)
Culine et al. [14]	CYVADIC	3	1 PR	12
	DECAV	3	2 PRs	6 & 8
	DI	2	1 PR	5
	Elliptinium	2	None	
Sella et al. [11]	CYVADIC	7	2 CRs	50 & 65
	Non doxorubicin chemotherapy ± hormones	11	None	
Krutchik et al. [16]	CYVADIC + immunotherapy	1	Very good PR	24
Lupera et al. [15]	DECAV	1	1 CR	6
Wood et al. [17]	DI + IFN-α	12	1 MR	NA
			1 PR	5+
			1 CR	6+
Friedland et al. [18]	5-FU + IL-2 + IFN-α	3	1 CR	NA

Abbreviations: CYVADIV – cyclophosphamide + vincristine + doxorubicin + dacarbazine, DECAV – darbazine + cyclophosphamide + cisplatin + doxorubicin; DI – doxorubicin + ifosfamide; CR – complete response; PR – partial response; MR – minimal response; NA – not available.

It is noteworthy that the only consistent feature between our patient's regimen (MAID) and the previously reported chemotherapy regimens (CYVADIC, DECAV, DI) is the similarity of doxorubicin dose. All previously reported regimens administered doxorubicin at a total dose of 50 mg/m^2 while the doxorubicin dose in MAID is 60 mg/m^2. This observation gives rise to several important considerations: (1) could doxorubicin alone have a similar efficacy profile in SRCC?; (2) could response rates be increased with higher cumulative doses of doxorubicin, especially with the availability of cardioprotective agent like dexrazoxane? [22]; and, (3) would a combination of doxorubicin and high-dose IL-2 and/or IFN-α be more effective than the individual drugs alone?

In summary, although sarcomatoid renal carcinomas are highly aggressive tumors with a poor prognosis, durable remissions may be achieved in some patients with doxorubicin-based chemotherapy as demonstrated by this case. Emerging data regarding molecular abnormalities in sarcomoatoid renal cell carcinomas may help elucidate the role of chemotherapy and biologic agents in the treatment of sarcomatoid renal tumors.

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