Malignant Ascites Associated with Carcinoma of the Prostate

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ABSTRACT:

Background: Prostate cancer is the most common malignancy in men in the United States. Both at diagnosis and throughout the disease progression, it can metastasize to multiple organs, most commonly bone and lymph nodes. Effusions (either pleural or abdominal) are relatively uncommon.

Patients and Methods: We reviewed the medical literature including the case reports and post-mortem studies relating ascites to prostate cancer, identified through a MEDLINE search (human; all languages; 1969-2004).

Results: We found 12 published cases. Forty two percent of patients presented initially with ascites, in 50% ascites developed later with progressive disease, and 8% had ascites being the only site of recurrence. The response rate to endocrine therapy, including orchiectomy, was 25%. Ascites in these patients conferred a poorer prognosis.

Conclusion: The development of ascites secondary to prostate cancer, either as an initial manifestation or recurrent disease, is not well known and may be unfamiliar to many physicians. If patients with history of prostate cancer develop malignant effusions, prostate specific antigen (PSA) immunohistostaining of the fluid can serve as a valuable adjunctive study for the diagnosis. This clinical situation becomes particularly important in patients with ascites with a carcinoma of unknown primary. Palliation can be achieved in patients with ascites secondary to prostate cancer using hormone manipulation. Lack of knowledge about this complication of prostate cancer may delay the diagnosis and treatment of this hormonally responsive malignancy.

INTRODUCTION

Carcinoma of the prostate is predominantly a tumor of older men. Some patients have prolonged survival even after the cancer has metastasized to distant sites, such as to bone.[1] Since the median age at diagnosis is 72 years, many patients, especially those with localized tumor, may die of other illnesses without ever having suffered significant morbidity from their cancer.[2] Survival of the patient with prostate carcinoma is related to the extent of the tumor. Patients with locally advanced cancer are not usually curable, and a substantial fraction will eventually die as a result of their tumor, although median survival may be as long as 5 years.[1,2] If prostate cancer has spread to distant organs, current therapy is not curative. Median survival is usually 1 to 3 years, and the majority of such

patients will die of prostate cancer.[3] Even in this group of patients, however, indolent clinical courses lasting for many years may be observed. Other factors affecting the prognosis of patients with prostate cancer that are useful in making therapeutic decisions include histological grade of the tumor, patient's age, other medical illnesses, and the serum level of PSA.[4] Poorly differentiated tumors are more likely to have metastasized at the time of diagnosis and are associated with a poorer prognosis.[5]

The evaluation of metastatic carcinoma of an unknown primary site is often a challenging problem encountered by oncologists. Despite extensive clinical evaluation, the origin of the primary tumor may remain undetected. This clinical situation can be more exhausting if a patient presents with an atypical feature of the underlying tumor. Prostate cancer usually presents as obstructive uropathy with a predilection to spread to the axial skeleton. This situation can be compounded if ascites are manifested as an initial presentation or the only site of recurrent disease. This association of prostate cancer and ascites may be unknown to many physicians, and thereby, diagnosis of a hormone-responsive tumor may be delayed.

PATIENTS AND METHODS

We reviewed the medical literature including the case reports and postmortem studies relating ascites to prostate cancer, identified through a MEDLINE search (human; all languages; 1969-2004). A manual retrieval of bibliographies of the identified literature was performed to collect information pertaining to age, race, clinical features, sites of metastases, treatment, outcome to treatment, and survival.

RESULTS

We found 12 published cases with where the patients' mean age was 70 years (range: 29–83).[6-16] Five patients were diagnosed with ascites at the time of initial diagnosis (42%), while six patients developed ascites later with wide-spread metastatic cancer (50%). Only one patient had ascites manifesting as the sole manifestation of recurrent prostate cancer (8%) (Table 1).

After review of these cases with prostate carcinoma, it is apparent that metastatic effusions responded to endocrine therapy. Heffner et al[17] reported a case of a 64-year-old man with metastatic prostate cancer who responded to diethylstilbestrol diproprionate therapy evidenced by resolving pleural effusion, partial clearing of the parenchymal infiltrates, and improved oxygenation. Disdier et al[8] reported a 78-year-old man whose ascites responded to nilutamide (150 mg/24 hours x 2 months) along with a decrease in serum PSA level from 150 ng/mL to 40 ng/mL. Catton et al[6] reported a response to orchiectomy with control of ascites for 9 months in which no other immediate therapy was instituted. Orchiectomy has also been tried in patients with prostate cancer who developed ascites and resulted in mixed responses.[6,10,14] Intraperitoneal chemotherapy (5-FU, thiotepa) was not successful in another patient.[10] These data support that endocrine or hormonal therapy should be tried in patients with ascites resulting from prostate cancer. In patients with androgen independent prostate cancer, a secondary hormonal therapy, chemotherapy or experimental agents should be tried. The role of the new anti-angiogenesis therapy, either as a therapy or a potential cause resulting in fluid retention, is not known at present. However, one patient was on thalidomide at the time when he developed ascites.[11]

Malignant effusion development in cases of prostatic adenocarcinoma seems to correlate with a poorer outcome. The

Table 1. Case Reports of Patients with Prostate Cancer Who Developed Ascites*

Patient No.	Age	Race	Time of presentation of ascites	Other sites of met. disease	Therapy	Outcome/ Duration of response	Reference
1	63	NK	Initial	Visceral, direct extension, lymph nodes	Orchiectomy	9 months	6
2	29	Arab	Initial	Bones	Refusal of therapy	Death	7
3	78	NK	Initial	Lymph nodes	Nilutamide	Ameliorated ascites along with PSA	8
4	58	Black	Initial	None	Diethylstilbe-strol	6 months	9
5	76	NK	Late	Lymph nodes, direct extension into surrounding organs	5-FU + thiotepa (intraperi-toneally)	Disease progression	10
6	45	NK	Late	Prostate bed recurrence	Orchiectomy	Death	10
7	70	White	First site of recurrence	None	Thalidomide	Disease progression	11
8	60	NK	Late	Bone; lymph nodes	No	Death within 6 weeks	12
9	80	NK	Late	Bone; others	No	Death within 12 weeks	13
10	76	NK	Initial	Omentum	Orchiectomy	Remission (18 months)	14
11	83	NK	Late	Lymph nodes	Hormonal Rx withdrawal	Death within 6 weeks	15
12	68	NK	Late	Metatstatic Toremifene	Interferon +	Death within 16 weeks	16

*NK indicates not known.

median survival after development of ascites ranged from 4 weeks to 16 weeks. However, 3 patients achieved more than 6 months of survival upon administration hormonal therapy, with one patient still in remission after 18 months.

DISCUSSION

Clinical manifestations of carcinoma of the prostate can be protean. One of the main reasons is the varying and widespread dissemination of the metastases. Carcinoma of the prostate can metastasize to nearly every organ, but metastasis without bone involvement is rare. A catalog of metastatic sites in patients with prostate cancer was first described by Arnheim in 1948 in a study of the postmortem findings in 176 cases.[18] In this study, the most common sites of metastatic disease were bones, lymph nodes, and lungs. Uncommon sites of metastatic disease included adrenal gland, kidney, brain, pancreas, genitalia, and breasts. Malignant effusions, whether pleural or peritoneal, are an extremely rare.[18] Broghamer et al[19] described a series of 33 patients with carcinoma of prostate and the ascites. The peritoneal fluid involvement in most cases (2%-21%) was caused by a secondary primary malignancy or con-

comitant reactive conditions, such as pancreatic cancer, bronchogenic cancer and gastric carcinoma.[19] In contrast, gastrointestinal malignancies are the most frequent etiology of malignant ascites in men.[20] Megalli et al[9] noted that ascites in patients with prostate cancer were also caused by second primary malignancies, and gastrointestinal malignancies were the most common among them.

Rapoport et al[10] reviewed the autopsy of 523 cases of prostate cancer and found 13 cases with peritoneal deposits with no disease elsewhere, demonstrating the fact that effusions can occur in patients with prostate cancer without the involvement of the more common sites of metastatic disease.

There are several aspects of these published cases of ascites in patients with prostate cancer, which warrant comment: First**,** malignant effusions, whether peritoneal or pleural, are associated extremely rarely with carcinoma of prostate and so much less so without osseous or lymph node involvement. Second, 42% patients developed ascites as their first presenting sign, but only two of these patients had ascites with no other sites of metastatic disease (including bones and lymph nodes). Only one patient developed ascites as the only sign of recurrent disease. Third, the exudative nature of the effusion and positive papanicolou stain for malignant cells supports a pathogenetc mechanism of mesothelial invasion. This in contrast to the transudative nature of ascitic fluid reported in few of these cases suggesting lymphatic obstruction as the mechanism in the development of malignant effusion associated with carcinoma of prostate. Two patients had chylous ascites.[7,15] One patient had hemorrhagic ascites.[16] Fourth, the mean age of these patients was 70 years. The relationship to race cannot be assessed due to the unavailability of such information in the reported cases. Fifth, malignant effusions secondary to carcinoma of the prostate have been reported to resolve with endocrine therapy, even if ascites constitutes the initial manifestation of prostate cancer and in patients with or without previous hormonal ablation. This fact is further strengthened by the presence of malignant prostate cells in the malignant effusion, as evidenced by special staining by Broghamer et al.[19] He suggested that the benefit from hormonal therapy may be derived in such conditions and hence should be used.[19] Sixth, we also found that these malignant effusions in patients with prostate cancer are associated with a poorer prognosis. Finally, a difficult problem for the physician and the patient can be the evaluation of metastatic carcinoma of unknown primary site.[21] Despite extensive clinical evaluation, the original tumor may remain undetected, especially if the sole presenting feature is a malignant effusion. In this situation, it may be prudent to stain the fluid for both PSA and prostate acid phosphatase (PAP).

Invasion of the mesothelial lining by malignant cells is regarded as a triggering factor in the pathogenesis of a body cavity effusion such as ascites. It is suggested that neoplastic cells in an effusion may be exfoliated from the cancer of the origin, if the cytological examination of these fluids reveals the presence of cancer cells. It is also suggested that the effusion may develop secondary to lymphatic obstruction, or that it may be the result of prostatic lymphatic carcinomatosis. Other benign and malignant etiologies should be excluded in these patients, as suggested by the literature review of cancers of non-prostatic origin, especially in cancer of the gastrointestinal tract, which can be the reason for the development of ascites in patients with carcinoma of the prostate.[9] Two cases of chylous ascites as a presenting sign of prostate adenocarcinoma have also been reported.[7,15] In these

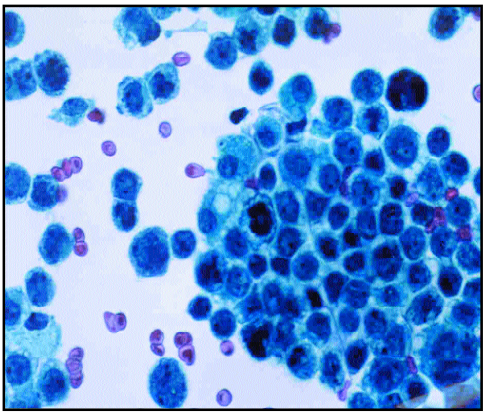

Figure 1. Papinacolou stain showing malignant cells in peritoneal fluid.

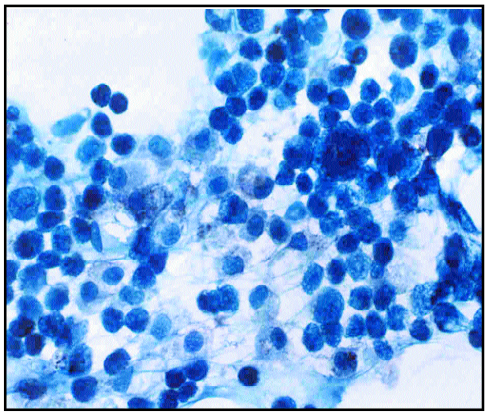

Figure 2. Positive staining with prostate specific antigen of the peritoneal fluid.

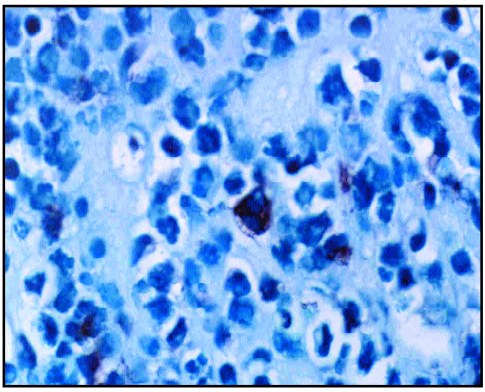

Figure 3. Positive prostatic acid phosphatase staining of the peritoneal fluid.

patients, with enlarged retroperitoneal lymph nodes and wide dissemination of the carcinoma, development of chylous ascites were thought to be secondary to diffuse metastases to periaortic lymph nodes and regional lymphatics draining the prostate carcinoma.[7,15] We reported a similar case earlier in which thalidomide was initially thought to be the cause of the patient's ascites and leg edema.[11] This presumption was based on the preliminary data from a Phase II trial involving thalidomide that revealed the development of peripheral edema in approximately 50% of cases, but no ascites or other effusions were seen. However, immunostaining of the ascitic fluid confirmed the diagnosis of prostate cancer.[11]

Satz N et al[22] found that the usual parameters like protein content, LDH ratio, albumin gradient and albumin quotient, fibronectin, cholesterol, and cell count did not reliably distinguish the etiology of ascites. They suggested that the best separation between malignant ascites and benign effusions, for example, from hepatic or cardiac causes, might be made by monitoring ferritin levels, with sensitivity of 97% and specificity of 100%. They found values of ferritin less than 150 ng/mL in benign cases and ferritin of more than 170 ng/mL in malignant ascites.[22] The immunohistochemical staining method for the diagnosis of prostate cancer (Figures 1,2,3) in a patient presenting with malignant effusion using prostatic acid phosphatase and/or prostate specific antigen as a specific marker serve as important tools.[11] The immunohistochemical staining of PAP is both specific and sensitive.[11,22] PAP shows a positive staining reaction in more than 95% of prostatic tissues and is weakly positive in non-prostatic tissues in about 3% of prostatic tissues.[22] Also, the activity of prostatic acid phosphatase antigen in the prostatic cells often parallels the degree of anaplasia of malignant cells, as evi-

denced by scarce enzyme antigen in cells of poorly differentiated carcinoma. PSA is a nonenzymatic protein which shows no cross antigenicity with the PAP. PSA may be found in anaplastic tumor cells where there is scanty PAP activity.[22] Therefore, the use of PSA in conjunction with PAP enhances the diagnostic sensitivity in metastatic carcinoma of the prostate. Hence, it may be prudent to stain the tumor or cell in a malignant effusion associated with a tumor to establish its origin.[11,12,22]

The general management of ascites including the three D's—that is D1 for diet, D2 for diuretic, and D3 for drainage, should be applied in individual cases. Our review supports the view that endocrine therapy should be tried in patients with ascites resulting from the prostate cancer. In patients with androgen independent prostate cancer, a secondary hormonal therapy, chemotherapy or experimental agents should be tried. The role of intraperitoneal chemotherapy remains investigative. Similarly, the effect and role of newer chemotherapies such as docetaxel, which can potentially cause fluid retention, needs to be explored in this rare presentation of prostate cancer.

CONCLUSION

We conclude that malignant effusions like ascites are a potential complication of carcinoma of the prostate. Although these effusions may constitute the initial manifestation of prostatic adenocarcinoma, such effusions may be the only signs of recurrence of prostate cancer. Prostate cancer is a common disease in elderly men and presents typically with obstructive uropathy or disease in the axial skeleton. However, an unusual presentation like malignant effusions may be encountered, therefore, oncologists, urologists, and primary care physicians should be aware of this complication of the prostate cancer. We suggest that PSA measurement may be a valuable adjunctive study for the diagnosis of malignant effusions in prostate cancer. This situation is of particular significance in cases of metastatic carcinoma of unknown primary site, where ascites may be the only manifestation. Immunohistochemical staining should be performed in sorting out the tumor origin. Worthwhile palliation can be achieved in patients with massive effusions secondary to metastatic prostate cancer using hormone manipulation.

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