Malignant Ascites

Clinical and Experimental Observations

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Malignant ascites formation is a grave prognostic sign, but palliative efforts seem justified in some patients. Lack of knowledge concerning the natural history of this process hinders the choice of therapeutic options. Over 5 years, 107 patients with untreated malignant ascites were reviewed to define their survival. Pancreas (20), ovary (18), and colon (18) were the most frequent tumors, with 52% of patients presenting with ascites at the time of the initial cancer diagnosis. Cytology evaluation of the ascitic fluid was positive for tumor cells in 57% of cases and a high protein content was noted in 65%. Mean survival of the entire series was only 20 weeks from the time of diagnosis of ascites, with tumors of ovarian and lymphatic origin having better mean survivals of 32 and 58 weeks, respectively. Patients with high ascitic protein levels fared better than those with low levels. In an effort to explain this correlation of elevated protein levels and a favorable survival rate, a hypothesis was proposed that certain tumors secrete a factor, which alters vascular permeability and causes fluid accumulation in the absence of lymphatic obstruction. In an experimental rat model of malignant ascites, the intraperitoneal infusion of cell-free malignant ascitic fluid caused an increase in edema formation and a significant increase in capillary permeability to protein in the omentum. This demonstrated change in the leak of protein explains the formation of ascites by some tumors in the absence of tumor obstruction of the draining lymphatics of the peritoneal cavity and suggests another important mechanism in the genesis of malignant ascites.

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THE FORMATION OF ASCITES as part of the continuum of a malignant process has been recognized as a grave prognostic sign.[1] Despite the limited survival of many of these unfortunate patients, discomfort and overall well-being are sufficient problems to justify palliative efforts. Multiple treatments directed at the fluid accumulations have been recommended for such patients, and a few individuals seem to benefit significantly from these therapeutic interventions.[2–4] However, the choice from among the various treatment options is difficult because little is known about the natural history of patients with malignant ascites. In an effort to better define the clinical factors that determine the length of survival of patients who develop a peritoneal effusion in association with a malignancy, our clinical experience with untreated malignant ascites over a 5-year period was reviewed.

During this review, it became apparent that patients with a high protein concentration in the ascitic fluid fared better in length of survival when compared to those patients with low ascitic protein levels. The formation of peritoneal fluid is usually a transudative process, and a change in the vascular permeability to large molecules is necessary to account for these elevated protein levels. However, previous studies[5,6] have emphasized the importance of obstruction of diaphragmatic lymphatics as the primary etiologic process in the formation of malignant ascites, although lymphatic blockage alone should not change vascular permeability and increase peritoneal fluid protein concentration.

Based on these clinical findings, we hypothesized that certain tumors produce diffusable factors, which are present in extracellular fluid and are responsible at least in part for an alteration in microvascular permeability, thus favoring fluid and protein accumulation in the interstitium and body cavities. To substantiate this theory, the effects of malignant ascitic fluid on peritoneal microvascular permeability were studied in a rat model. Using the Walker 256 carcinoma as a source of cell-free ascitic fluid, we measured the permeability of protein in the omentum of normal rats after 3 days of an intraperitoneal infusion

Presented at the 97th Annual Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 1–4, 1985.

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Submitted for publication: December 23, 1985.

of fluid. An increase in the leak of protein in this model where no lymphatic obstruction was present would give evidence for the presence of permeability factors in malignant ascitic fluid.

Clinical Material

The records, from three University of Louisville affiliated hospitals, of patients who had ascites secondary to a cancer from January 1980 through December 1984 were reviewed. Malignant ascites was defined as a clinically evident fluid accumulation within the abdominal cavity associated with a disseminated malignancy in the absence of hepatic cirrhosis. All ovarian tumors where fluid was submitted to the laboratory simply as peritoneal washings were excluded, unless gross clinical ascites was present at the time of laparotomy or developed during the subsequent course of the disease. Any patient who had therapy specifically directed toward the peritoneal effusion was similarly excluded from further analysis. All of the clinical features of these patients were reviewed, with particular attention focused on the time of diagnosis of the ascites and the chemical or cellular makeup of the fluid.

Results

One hundred seven patients developed clinically apparent ascites associated with a malignancy during the period surveyed. None of these patients had specific therapy primarily directed toward the peritoneal effusion, although the majority were administered diuretic medication. There were 57 men and 50 women ranging in age from 28 to 83 years. The primary malignancies are listed in Table 1. The tumors most commonly associated with ascites formation were of intra-abdominal origin, with pancreas, colon, and ovary the predominant sites of the primary malignancy. The most frequent extra-abdominal tumors responsible for malignant ascites were of lymphatic origin.

The diagnosis of ascites was apparent in all of the patients from clinical findings, as noted from the entries made by the physicians in the chart. Abdominal distention with a palpable fluid wave was listed as the primary diagnostic finding in 96 patients, while shifting dullness was noted in the remainder. Radiographic studies were obtained in 94 patients at the time of ascites diagnosis. The plain abdominal film confirmed the presence of peritoneal fluid in 40 of these cases (43%). The radiographic report of the computed tomography (CT) scan mentioned the presence of ascites in 30 of 38 studies (79%), while the ultrasound noted the presence of fluid in only 18 of 26 readings (69%).

Fifty-six patients (52%) had clinically apparent ascites at the time of their initial cancer diagnosis. The advanced stage of the disease was evident in the majority of patients, with only 17 undergoing an attempted curative resection at the time of diagnosis of the primary tumor. A palliative or diagnostic procedure could be done only in 71 patients at this time, while 19 patients had no operative therapy attempted when the malignancy first became apparent. An attempt at estimating the extent of disease at the time of onset of ascites was made by the authors from the data available in the hospital record. Forty-seven patients had primarily liver and nodal involvement, while another 50 were thought to have a significant amount of diffuse peritoneal spread of tumor. Ten patients either had extremely small tumor burdens or could not be classified into one of these two groups based on the data that were available. Further evidence of the widespread extent of the disease is evident from the fact that 44 patients (41%) in this series had clinically apparent pleural and/or pulmonary involvement at the time of ascites presentation.

Cytologic and/or biochemical analyses of the ascitic fluid were available in 94 patients (Table 2). Sixty-four were obtained by percutaneous needle aspiration of the

TABLE 1. *Malignant Ascites: Site of Primary Tumor*

	No. of Tumors	Ascites as Primary Complaint
Pancreas	20	14
Ovary	18	15
Colon	18	5
Lymphatic system	10	6
Uterus/cervix	9	3
Stomach	8	5
Lung	7	2
Liver/biliary	4	3
Breast	3	—
Renal	3	1
Unknown	2	2
Prostate	2	—
Testes	1	—
Bladder	1	—
Retroperitoneal sarcoma	1	—
Total	107	56 (52%)

TABLE 2. *Malignant Ascites Characteristics*

	No. of Patients (%)
Cytology positive	52 (57)
Cytology negative	40 (43)
RBC* > 20,000 cells/ml	23 (34)
RBC < 20,000 cells/ml	45 (66)
WBC† > 1,000 cells/ml	20 (40)
WBC < 1,000 cells/ml	30 (60)
Protein > 2.5 g/100 ml	34 (65)
Protein < 2.5 g/100 ml	18 (35)

* RBC = red blood cell.
† WBC = white blood cell.

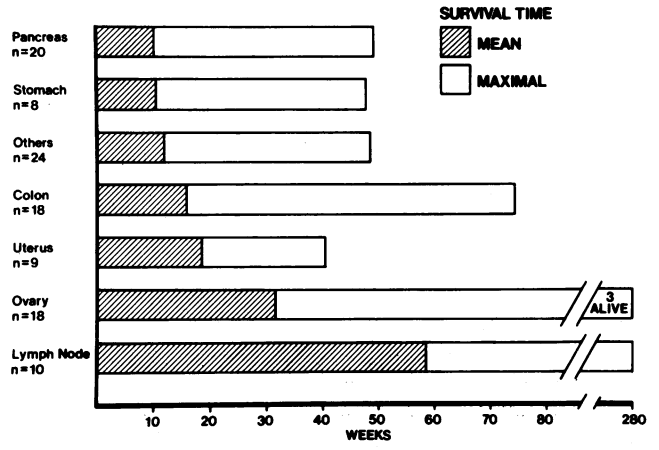

FIG. 1. Mean and maximal patient survival times from the time of diagnosis of ascites for different tumor groups.

abdominal cavity, while 30 specimens were collected at the time of celiotomy. A protein content of greater than 2.5 g/100 ml was found in 65% of determinable cases. This high ascites protein content, when compared to the serum protein level, showed an ascites/serum ratio of greater than 0.4, implying a change in the peritoneal permeability to protein in 71% of cases. Essentially all of the tumors of reproductive origin (ovary, uterus, and testes) had a ratio of greater than 0.4 (12 of 12), as did tumors of lymphatic origin (9 of 10). On the other hand, ascites from adenocarcinomas of the alimentary tract had a ratio below 0.4 in 10 of 16 measurements.

Mean and maximal survival times from the time of diagnosis of ascites are shown in Figure 1. Tumors of lymphatic and ovarian origin have the longest survivals among the 107 patients studied, with three women who had primary ovarian tumors alive and free of disease and ascites at the time of this review. Adenocarcinomas of the upper alimentary tract had the poorest survivals, with a mean survival from the onset of ascites of only about 10 weeks. Patients with colonic and female reproductive tract tumors fared a little better, with mean survivals of 16 and 19 weeks, respectively. Overall, once a tumor progresses to the formation of ascites, the survival is on average less than 20 weeks, with a few long-term survivors and apparent cures noted in patients with ovarian carcinomas (Fig. 2). Tumors with a high protein concentration within the ascitic fluid have longer survivals than tumors that form a simple transudate within the peritoneal cavity.

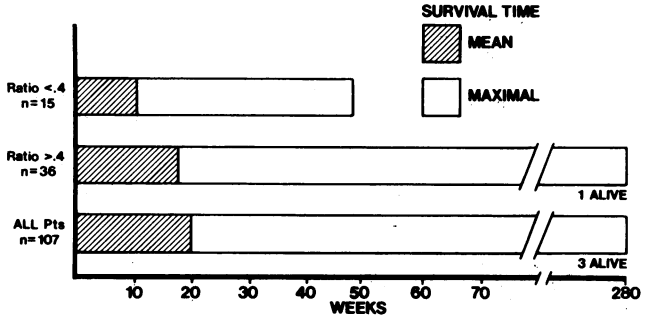

FIG. 2. Mean and maximal patient survival times from the time of diagnosis of ascites comparing the protein content of the ascitic fluid.

Experimental Studies

To study the significance and validity of the change in permeability noted in these patients, we used the Walker 256 carcinoma, which establishes multiple tumor implants on the peritoneal surfaces of rats when injected into the abdominal cavity. Clear ascites formation follows soon after tumor implantation and becomes bloody within 7 days. Intramuscular tumors from carrier animals were harvested, diced, and forced through a wire mesh under sterile conditions. A 2-ml suspension of tumor cells (1×10^6 cells/ml) in saline was injected into the peritoneal cavity of Sprague-Dawley rats (175–225 gm). Palpable ascites was noted on day 6 or 7, at which time the animals were killed by decapitation and the ascites aspirated under sterile conditions.

The collected ascites was centrifuged and the supernatant aspirated. The absence of cellular material was confirmed by hemocytometer examination under a light microscope. A small amount was cultured on blood agar plates to assure sterility of the sample. All sterile, cell-free specimens were then pooled, the protein concentration determined by the method of Lowry,[7] and the osmolarity was determined by freezing point depression using an osmometer. Eight-ml volumes were then individually packaged in syringes and kept frozen at −20 C until used for infusion.

Serum was prepared by sterile exsanguination of tumor-free animals by cardiac puncture. Specimens were allowed to clot, centrifuged, and the supernatant aspirated using sterile technique. Once sterility was assured by culturing on blood agar plates, all specimens were pooled and the protein and osmolarity determined. Adjustment of the protein and osmolarity concentrations to coincide with those of the ascites was accomplished by a 1:1 volume dilution with Ringer's solution. The final pool then was divided into 8-ml volumes and kept frozen until used for infusion.

Male Sprague-Dawley rats weighing 175–205 g were used for the infusion protocols. All animals were anesthetized with ketamine (35 mg/kg) and xylazine (5 mg/kg) prior to surgical manipulation. Under sterile conditions, a silicone rubber infusion catheter was placed in the peritoneal cavity at laparotomy and tunneled subcutaneously to exit in the midtail. The exit site was protected by a wire mesh shield, and the tail and catheter were suspended from the top of the cage. Following cath-

eter placement, animals were individually housed, weighed daily, and allowed free access to food and water. Catheters were connected to a pump set to deliver 8 ml by slow infusion over a 24-hour period. Following 3 days of baseline infusion with normal saline, animals were randomized to receive either saline, serum, or cell-free malignant ascitic fluid at 8 ml/24 hours for a subsequent 72-hour period. All animals that were not fully acclimated to the infusion apparatus or had not recovered from the surgical procedure, as evidenced by a stable or gaining weight pattern, were not used in the infusion protocol.

Capillary permeability to protein was quantitated by a technique using Evans blue dye. This technique has been used to measure the vascular permeability of proteins in previous experiments.[6,8,9] Intravenous Evans blue combines with plasma proteins and is distributed within the intravascular space. An increase in capillary permeability will be reflected by an increased concentration of dye within the interstitial space. Three hours before termination of the infusion period, animals were anesthetized lightly, and an intravenous (I.V.) injection of Evans blue dye (2 mg/100 g body weight) was given. When the animals were killed, blood was obtained for determination of hematocrit and plasma protein concentration. A 0.5-ml aliquot of plasma then was diluted with formamide to a 3% solution by volume and the color intensity of Evans blue dye measured at 620 mm in a spectrophotometer. Omental specimens were blotted dry, halved, and weighed. One-half of the tissue then was placed in a drying oven and the weight determined daily until stable. The other half of the omentum was eluted in 3 ml of formamide solution for 72 hours and the optical density of the eluate read at 620 mm in a spectrophotometer.

Results were expressed in terms of tissue wet-to-dry weight ratios, which reflect the amount of fluid present within the tissues. The optical density of the eluated tissue supernatant per dry weight tissue (OD eluted/dry wt) and the optical density of the eluate per optical density of the plasma per dry weight (OD eluted/OD plasma/dry wt omentum) were calculated. OD eluted/dry wt is indicative of the amount of plasma and interstitial protein within the omentum, while the OD eluted/OD plasma/dry wt calculation corrects for the amount of plasma within the tissue itself at the time of harvest. Both of these numbers are indicators of the degree of plasma protein leak from the intravascular space into the interstitium. Values for each study group were expressed as the arithmetic means ± the standard deviation. The data were analyzed by one-way analysis of variance and differences between individual groups by the Student's t-test.

Results

Intraperitoneal implantation provided consistent ascites formation after 6 to 7 days. Each animal provided 20–25 ml of fluid for processing. Once pooled, the resultant mixture of cell-free malignant ascites fluid contained 3.75 g/100 ml of protein, with an osmolarity of 290 miliosmoles. The collected serum pool from normal animals had 6.76 g/100 ml of protein and thus was diluted 1:1 with Ringer's solution to yield a closer protein concentration and osmolarity to the ascitic fluid. The final serum infusate had 3.38 g/100 ml of protein and an osmolarity of 283.

TABLE 3. *Final Blood Values of Rats Following Three Days of an Intraperitoneal Infusion*

Infusion Group (*N* = 8)	Hematocrit		Plasma Protein (g/100 ml)	
	Mean	SD	Mean	SD
Catheter (no infusion)	4.39	0.31	5.56	0.72
Saline (0.9%)	4.13	0.48	5.54	0.63
Serum	4.15	0.34	6.07	0.87
Malignant ascites	4.06	0.33	5.84	0.89

Tables 3 and 4 show the results obtained from the infusion groups along with a control group, where only an intraperitoneal catheter was placed for the 6-day period but no infusions were admininstered. All animal groups were comparable with respect to hematocrit and plasma protein concentration when the animals were killed (Table 3). Significant differences are noted for each study parameter of the excised omental tissues ($p \leq 0.05$). An increase in tissue edema is noted for each study group, as evidenced by the increased wet/dry weight ratios. However, animals infused with cell-free malignant ascitic fluid had significantly more omental edema formation than saline controls or animals infused with a comparable osmotic and protein content ($p \leq 0.05$).

A similar difference was noted in the Evans blue dye studies of vascular permeability. The optical densities of the omental eluates are greater in each successive group.

TABLE 4. *Measurements of Edema and Vascular Permeability in the Rat Omentum Following Three Days of Intraperitoneal Infusion*

Infusion Group (N = 8)	Wet Wt/Dry Wt of Omentum		OD Eluted/ Dry Wt Omentum		OD Eluted/ Plasma OD/ Dry Wt Omentum	
	Mean	S.D.*	Mean	S.D.	Mean	S.D.
Catheter (no infusion)	3.07	0.37	1.52	0.39	3.92	0.75
Saline (0.9%)	3.39	0.26	1.55	0.15	4.52	0.56
Serum	3.61	0.36	1.57	0.30	4.81	1.32
Malignant ascites	3.91	0.25†	2.06	0.45†	6.55	1.32†

* S.D. = Standard deviation.
† $p \leq 0.05$.

A significant difference is seen in the animals infused with cell-free malignant ascitic fluid when compared to each of the other infusion groups ($p \leq 0.05$). This difference in the permeability of the microvasculature to macromolecular molecules remains even when an adjustment for the contribution of the plasma dye within the omental tissue is compared (OD eluate/plasma OD/dry wt).

Discussion

Peritoneal effusions are a common terminal path for many tumors of diffuse origin. Various treatments have been advocated for the relief of this disabling complication of malignant disease, but no single regimen has been shown to yield superior results.[1-4] Generally, the prognosis of patients at this stage of the disease is very poor, as has been confirmed by our patient review, and only minimal supportive therapy is indicated. In the absence of a clear understanding of the natural history and etiology of malignant ascites, a rational choice of the many palliative options available to the clinician can be made only with difficulty. A few patients have a better survival than the group as a whole, and therapies that help to relieve the discomfort of the ascites fluid accumulation would be best applied to these few individuals.

In this retrospective review of 107 patients with malignant ascites, a variety of tumors was found. Males predominate, and pancreas adenocarcinoma was the most prevalent tumor partially because of the inclusion of patients from a Veterans Administration Medical Center. Tumors of ovarian origin were the most common to produce malignant ascites in a general hospital population. Except for an occasional ovarian tumor, the development of ascites can be seen as a preterminal event, with the average patient surviving only 20 weeks. In 56 of our patients, ascites was a major component of the presenting complaints, which led to the diagnosis of malignancy. Malignant ascites tends to be a process seen in untreated, neglected, and far-advanced disease, as evidenced by the fact that only 16% of our patients had an attempted curative resection of the primary tumor during the course of the malignancy.

The ascitic fluid characteristics were highly variable in our patients, and no single finding except for the presence of malignant cells was diagnostic of tumor. A positive cytology was found in 57% of our patients but was not predictive of life expectancy. One long-term survivor of 4 years had malignant cells in her initial ascites specimen. This finding is contrary to the studies of Yamada and associates,[10] where the size of the cancer cell clusters found in the fluid specimen correlated with a longer survival than patients with diffuse noncluster-forming cells. This study used a positive cytology in the criteria for the diagnosis of a malignant peritoneal effusion, and the majority of tumors analyzed were of alimentary tract origin; our study includes all patients with ascites and a malignancy who did not have hepatic cirrhosis as an etiology for the fluid collection. Since our cytology specimens were not classified according to cluster formation, we cannot verify the predictive value of cluster cell formation.

A comparison of the ascitic protein concentration in our series was helpful in anticipating a longer survival. Patients who had an ascites/serum protein ratio greater than 0.4 had a mean survival of 18 weeks, with three patients alive at 3, 4, and 5 years, while patients with a ratio lower than 0.4 had no long-term survivors and a mean of only 10 weeks. Tumors of the reproductive tract (ovary, uterus, and testes) and the lymphatic system were grouped into this high protein ratio category, with only one exception, while tumors of the alimentary tract tended to have a low protein ratio and short mean survival. The one patient who did not fit this grouping suffered from a lymphocytic lymphoma and died only 8 weeks following ascites formation. Patients with reproductive or lymphatic tumors who have a high protein concentration in the peritoneal fluid appear to benefit mostly from an invasive procedure to drain or relieve the ascitic fluid, while other patients would be better managed by temporary drainage. Our data contains only two patients with tumors of the breast, so meaningful comments cannot be made for this tumor; however, other investigators[11] have noted good palliative results with peritoneovenous shunts in breast cancer patients.

Radiologic evaluation of the abdomen was helpful in confirming the presence of fluid in our patients. All of these patients had physical exam findings consistent with the diagnosis of an intra-abdominal fluid accumulation; this was confirmed by plain abdominal films in 43% of the cases where the study was obtained (N = 94). The ultrasound report mentioned the presence of fluid in 69% of 26 studies, while the CT scan was positive in 79% of 38 exams. Ultrasonography and computed axial tomography are considered quite sensitive in detecting as little as 100 ml of ascitic fluid, while physical exam yields varying results.[12] This discrepancy between our results and the literature demonstrates that the accuracy of any exam rests on the astute observer. Four of these negative exams were blindly reviewed by another radiologist, and fluid was evident on all four, although not mentioned on the first report.

Endothelial permeability has received little attention for its role in the formation of malignant ascites. The degree to which an increase in fluid production contributes to the accumulation of peritoneal fluid is poorly defined. Coates and associates[13] showed that 85% of patients with ascites secondary to a malignancy had no detectable radioactivity above the diaphragm by mediastinal lymphoscintigraphic examination following the injection of

radiocolloid into the peritoneal cavities, although the remaining patients had no obstruction of diaphragmatic lymphatics. In the present experimental study, lymphatic obstruction was eliminated as a cause of increased edema formation because the ascitic fluid infused was free of tumor cells.

In our clinical patients reported herein, malignant ascites from a large variety of tumors had a high concentration of protein in 71% of cases. This high protein content in the ascitic fluid was more consistent with a change in vascular permeability as a factor in the accumulation of the edema. In the absence of a permeability change, peritoneal fluid would have the characteristics of a transudate with a low protein concentration. Our hypothesis that tumor-secreted factors might alter capillary permeability is consistent with these facts.

The intra-abdominal growth of Walker 256 carcinoma in the rat serves as an animal model of diffuse abdominal carcinomatosis and malignant ascites. Heuser[14] has shown that protamine sulfate, a known inhibitor of angiogenesis, when topically infused into the peritoneal cavities of tumor-bearing animals, prevented the diffuse proliferation of tumor; however, ascites continued to be formed. This implied that the Walker 256 carcinoma might produce a factor that alters the macromolecular permeability of normal vessels, causing edema and fluid accumulation within the abdomen. In an effort to explain experimentally the high protein concentration we observed in our patients, we used this tumor model to test the effect of cell-free malignant ascitic fluid on the permeability of normal rat omental vessels.

In this experiment, cell-free malignant ascitic fluid was infused intraperitoneally for 3 days, after which edema formation and macromolecular permeability in omental vessels were measured. Both edema formation and protein permeability were altered significantly when malignant ascites was topically administered into the peritoneal cavity. The wet/dry ratios of the excised omentums in our animals were clearly higher than comparable volume and protein infused controls. Similarly, the concentration of interstitial Evans blue dye, a compound that binds to intravascular protein and reflects the concentration of protein that has leaked into the interstitial space, was significantly higher than control groups in our studies. It is implied from these data that our hypothesis was confirmed in this model and that some tumors produce a factor that can alter the permeability of normal vessels, causing edema and an increased protein concentration within the interstitial space. The role this change in permeability plays in the formation of clinical malignant ascites remains to be defined.

The obstruction of subdiaphragmatic lymphatics is reported to be the primary etiologic factor preventing the absorption of intraperitoneal fluid and thus the formation of ascites. This clinical and experimental report focuses on another important mechanism in the genesis of malignant ascites. There appear to be tumor-induced factors, that alter macromolecular permeability favoring interstitial fluid accumulation. Whether this leak of protein is reflective of the process of tumor angiogenesis and the friability of the newly formed vessels[15] or is an actual alteration of the permeability of existing vessels remains to be defined. We suggest that the purpose of a specific tumor factor to increase macromolecular permeability is to provide an enriched nutrient supply for the excessive growth needs of the malignancy.

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