Management of Recurrent Malignant Effusions*

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At least half of all patients with carcinoma of the breast or lung develop a pleural effusion at some time in the course of their disease; in patients with an abdominal neoplasm, particularly ovarian carcinoma, ascites commonly occurs. The clinical findings of an effusion are well known: pleuritic pain, dyspnea, cough and fever from a pleural effusion; swelling or a feeling of fullness due to ascites; chest pain and weakness as the result of fluid in the pericardial cavity. With recurrent effusions, frequent taps may result in hypoproteinemia and further fluid retention.

Obviously not all effusions are neoplastic; Lowell found that only 25 percent of 1,231 pleural effusions were due to carcinoma.1 Therefore, histologic confirmation is essential to determine malignancy and to rule out such non-neoplastic conditions as infection, congestive heart failure, pulmonary embolism or the nephrotic syndrome as the cause of effusion in a patient with cancer.

A neoplastic pleural or peritoneal effusion may occur as the first evidence of disease or as a late manifestation; a malignant pericardial effusion, however, is generally a late manifestation. Ariel et al. found in a study of 267 patients with malignant effusions that the duration of life following the development of effusion was 6.3 months in the case of solid tumors, and 16 months in lymphomas.2 Adequate control of an effusion which is the sole manifestation of disease may result in months or years of effective palliation.

In the more common situations where the effusion is part of a generalized malignancy, local control, while it does not affect prognosis, will greatly improve the patient’s well-being.

Laboratory Studies

At the time of the first thoracentesis or abdominal paracentesis, note the appearance of the fluid and determine the specific gravity and protein content. If the fluid is bloody and there is no evidence of pulmonary infarction, if the specific gravity is greater than 1.016 and the protein content in excess of 3 gm/100 ml, a malignant effusion is strongly suggested. The white cell differential is not specific in malignant effusions, except for leukemias and lymphomas.

Cytologic examination of the fluid may confirm the diagnosis of malignancy when a tissue diagnosis is not possible. However, atypical cells may be noted in some patients due to mesothelial cell proliferation or as a result of prior chemotherapy. Since cytologic examination usually cannot determine the spe-
specific site of origin, pleural biopsy may be attempted, using a Cope needle. Pleural biopsy is also useful in ruling out tuberculosis since biopsy is positive in up to 50 percent of such patients.

Various special studies may also be done, including Sudan III stains to verify the fat content in chyloous ascites or chylothorax. An elevation in the effusion amylase level may indicate pancreatitis as well as pancreatic carcinoma and other carcinomas metastatic to serous cavities. Ultmann has discussed the significance of these various laboratory studies. 3

Certain unusual effusions that are not associated with direct involvement of the mesothelial space by tumor may also be found in patients with neoplastic disease. These include pleural effusion in ovarian tumor (Meig's syndrome) and radiation pneumonitis, as well as benign pleuritis associated with carcinoma of the pancreas.

Pathogenesis of Neoplastic Effusions

It is important to determine, in each patient, the probable pathogenesis of the effusion as this influences the decision to use local or systemic therapy. Generally, neoplastic effusions arise from several mechanisms including: (1) serosal involvement by tumor nodules in the pleura or peritoneum with resulting irritation; (2) venous or lymphatic obstruction by tumor, particularly common in lymphomas, including Hodgkin's disease; and less commonly, (3) the presence of large numbers of free-growing cancer cells within the chest or abdominal cavity, corresponding to experimental ascites tumors in animals. An example of the latter mechanism would be abdominal carcinomatosis associated with ovarian cancer. In this instance of transcoelomic metastasis, the free tumor cells are apparently capable of producing damage to the coelomic lining and inciting an inflammatory reaction. Lymph and fibrin exudates then become organized, providing a suitable stroma for growth of the enmeshed tumor cells.

Some clues to the pathogenesis of the effusion can be obtained from the number and appearance of the cancer cells present in the effusion. It has been noted that human malignant effusions are of three main types:

1. In the most common type, there is irritation of serous membranes from solid tumor implants, with exfoliation of cancer cells. The tumor cell count is usually 50-1,000 cells/mm. 3 These cancer cells are differentiated and pleomorphic, although they tend to form organoid structures. The cells may simulate acini or else simply form clumps. Extensive solid invasion of viscera is almost always present in association with this type of effusion. Intracavitary therapy has little effect on the associated solid tumor, although it may have a lethal effect on the free tumor cells and may induce fibrosis of the serous membrane.

2. Suspect transudation of fluid as the result of obstruction in the small vessels and lymphatics or, less commonly, solid implants or portal hypertension as the cause if the effusion is relatively acellular. This type of effusion is associated with large solid tumor masses. It is better to treat this type of patient systemically, as the solid tumor mass will almost certainly not respond to intracavitary drug therapy.

3. Suspect an effusion similar to the ascitic cell tumor in animals if the cancer cell count is as high as 4,000 cells/mm. 3 These cells are fairly uniform in appearance, isolated and are apparently viable and able to survive singly. Distinguish these cells from those which are merely exfoliated from adjacent serous membranes. This type of effusion usually responds well to intracavitary treatment with either radioactive isotopes or chemotherapeutic agents.
When to Use Local Chemotherapy

In general, local chemotherapy is indicated if: (1) a surgically non-
resectable cancer has a malignant effusion as the only manifestation of
disease or known site of involvement; or (2) a patient with generalized disease,
including involvement of the serous cavity, has had some type of systemic
treatment, either radiotherapy or chemotherapy (with control of the systemic
disease but persistence of local disease in the serous cavity with effusion). For
optimum results of local chemotherapy, large numbers of cancer cells should
be present in the fluid and there should be no associated large tumor masses.

Initial treatment is, of course, a thoracentesis or paracentesis; occasionally,
one or two taps will control the effusion so that it does not recur. Local therapy is then reserved for patients
with recurrent effusions following several taps. It may be useful to obtain a
lateral decubitus radiograph of the chest immediately following the tap to reveal possible areas of metastatic involve-
ment hidden by the effusion.

Besides local chemotherapy, surgical methods are also used to control the
effusion (see page 146) and, occasionally, radiotherapy is given to one hemi-
thorax if there is known extensive involve-
ment of only one side of the chest. This, however, is infrequently used, since it carries the risk of radiation fibrosis of the lung.

Chemotherapeutic agents

Nitrogen mustard

Nitrogen mustard was first used for the intracavitary treatment of malignant pleural effusions in 1949 and has since been used extensively. ¹ Weisberger et
al. report 43 patients treated with nitrogen mustard, with therapeutic benefit in 65 percent; ² subsequently, he treated 88 patients with either pleural, peritoneal or pericardial malignant ef-
fusions with improvement in 65 percent.

The vast majority of these patients had no recurrence following intracavitary instillation with nitrogen mustard; ³ none of the three patients with pericardial effusion had recurrence following in-
trapericardial nitrogen mustard. Patients with primary breast or ovarian tumors responded most favorably and some patients who had not responded to previ-
ous therapy with radioactive gold responded to nitrogen mustard. ⁴ Four-
teen of the 65 patients survived 12 to 42 months, with complete relief of
symptoms due to effusion. Factors that seemed to correlate with poor response included chylous effusions and a specific gravity below 1.014.

Kinsey et al. treated 62 patients with malignant pleural effusions, mostly
due to lung or breast carcinoma, and demonstrated complete control of the
effusion in 87 percent of the cases. ⁵ Those cases that did not respond often
had a thick fibrous peel on the surface of the lung, preventing re-expansion.
Mark et al. treated 32 patients with intrapleural nitrogen mustard and found
that 92 percent of those who lived at least one month after treatment had
subjective and objective improvement. ⁶ It was noted that side effects encoun-
tered at the first instillation may not occur at second or subsequent instilla-
tions due to scarring of the pleura at the time of the first exposure, with
resultant limitation on systemic ab-
sorption.

Since at least one half to two thirds
of patients will respond, nitrogen
mustard is the initial treatment of
choice for the local management of
malignant effusions in most situations. The usual intracavitary dose of nitrogen mustard is 0.4 mg/kg—the same as that given systemically. Reduce this
dose by half in patients with poor bone
marrow reserve or those who have had
Three Types of Human Malignant Effusions

| Pathogenesis | Typical Tumor Cell Count | Appearance of the Cells | Treatment |
|--------------|--------------------------|-------------------------|-----------|
| 1. Serosal involvement by tumor nodules in the pleura or peritoneum with resulting irritation (Common) | 50-1,000 cells/mm³ | Differentiated and tend to form clumps or organoid structures | Intracavitary treatment has little effect on an associated solid tumor — almost always present — but may have a lethal effect on free tumor cells |
| 2. Obstruction of the small vessels or lymphatics and, less commonly, solid implants or portal hypertension (Common) | acellular | | Treat systemically as intracavitary drug therapy has little effect on an associated solid tumor |
| 3. Presence of free growing tumor cells within the chest or abdominal cavity — corresponding to experimental ascites tumors (Rare) | as high as 4,000/mm³ | Fairly uniform and isolated | Intracavitary treatment with either radioactive isotopes or chemotherapeutic agents is indicated |

extensive previous radiotherapy to marrow-bearing areas and chemotherapy, since systemic absorption may occur in some patients.

To administer the drug, remove most of the fluid prior to injection. Remember that although nitrogen mustard is stable in the syringe for at least one hour, it alkylates proteins and nucleic acids in the body within five minutes of administration. Therefore, immediately following administration, ask the patient to change positions frequently during the first five minutes to help distribute the drug. Have the patient lie prone, left side, supine, right side and knee-chest for one minute each. The injection may be repeated in two to three weeks if the patient requires more than one injection for control.

Side effects including nausea, vomiting and leukopenia are usually mild. Pain is rare after intrapleural injection but is frequently seen after intraperitoneal injection. Sometimes, there is a temporary increase in the serous effusion due to irritation of the serosal surface by the drug; this may require one or two additional taps in the next few weeks. Explain this to the patient beforehand so that he does not interpret reaccumulation of fluid as a necessarily bad prognostic sign. The advantages of nitrogen mustard over other agents include its ease of administration, ready availability and inexpensiveness.
**Quinacrine (Atabrine®)**

Quinacrine was found to be of value in the local treatment of neoplastic disease by Gellhorn, Ultmann and their associates. This observation was later confirmed by Rochlin et al. and Dollinger et al. The response rate with this agent varies from 64 to 88 percent and is therefore higher and more predictable than with other drugs given intracavitarily. Some patients who did not respond to radioisotopes did respond to this agent. Rochlin demonstrated response to this treatment in a wide variety of tumors and obtained a 64 percent response rate, including seven of 13 patients with carcinoma of the breast and two of five patients with carcinoma of the lung. Hickman and Jones reported control of effusion in all of 12 patients treated. Generally, cancer of the lung and breast appear most responsive to quinacrine; lymphomas respond poorly. Some patients who did not respond to radioisotopes now responded to this method.

Quinacrine produces a local cytocidal action on neoplastic cells as well as an inflammatory reaction, frequently resulting in adhesions which partially or completely obliterate the serous cavity. This latter effect seems to be the more important factor in producing a favorable response. Since quinacrine does not produce hematopoietic depression it is useful in patients who have impaired bone marrow function due to disease or treatment. However, because of its acute toxicity—the drug may cause pain and fever—and the need for hospitalization and multiple injections, other drugs such as nitrogen mustard or radioactive isotopes are generally given a trial before quinacrine.

Quinacrine is obtained as a hydrochloride salt in 200 mg ampuls and is dissolved in 10 ml of saline. Dosage varies with patient response, however, 100-200 mg daily or on alternate days is an average dose for pleural effusions; 200-400 mg for ascites. The first dose is usually half of subsequent doses as a check on sensitivity or idiosyncrasy. The drug is injected at the conclusion of a thoracentesis or abdominal paracenteses, after about two thirds of the fluid has been removed. The doses are continued daily or on alternate days, according to toxicity, until a mild sterile pleuritis or peritonitis occurs, generally after three to five doses. Local toxicity includes: local pain, which occurs in as many as half the patients and usually begins several hours after instillation and lasts about two hours, and fever, sometimes as high as 103° or 104°F, which occurs in almost all patients.

Response may occur within two weeks or may take as long as three months. Following the use of this drug, a frequent source of confusion is the interpretation of chest X-rays. While the chest X-ray seems to show a "consolidated hemithorax" or "massive effusion," repeated thoracentesis at multiple sites produces only a few milliliters of fluid. Autopsy studies on several of these patients revealed severe pleural fibrosis (fibrothorax), without fluid, indicating that the radiographic changes were due to the fibrosis and may be misleading.

**Thio-TEPA**

Results similar to those reported with nitrogen mustard in the treatment of pleural effusions have been reported with thio-TEPA by Bateman. Remissions lasting from one to nine months occurred in 10 of 17 patients with pleural effusions, and there was decreased ascites formation in four other patients. Effusions secondary to breast or ovarian carcinoma responded most favorably. However, this agent may also be useful in malignant pericardial effusions where an acute inflammatory response, as observed with nitrogen mustard, may be undesirable. The usual injected dose—similar to tho
systemic dose—is 0.8 mg/kg, although many patients have been treated with empirical doses of 20-50 mg, somewhat lower than the calculated dosage above.

**Other chemotherapeutic agents**

Suhrland and Weisberger instilled 5-fluorouracil in the serous cavities of 55 patients with malignant effusions, with significant improvement in 32 patients (68 percent), 21 of whom had no recurrence of effusion. Although this drug has been used principally in the treatment of breast cancer, response to intracavitary 5-fluorouracil is generally observed in patients with ascitic neoplasms (large numbers of free-floating cancer cells). Treatment is ineffective when large tumor masses are present. The usual dose is 2-3 gm. Side effects are minimal, and in most patients, the white blood count will fall moderately between the seventh and tenth days.

Although there have been reports on the use of other chemotherapeutic agents by the intrapleural route, including actinomycin D, hydroxyurea and daunorubicin, experience is not adequate to permit a conclusion to be made about the value of these agents.

**Radioactive isotopes**

**Radioactive Gold (198 Au)**

Radioactive gold may be better tolerated than alkylating agents such as nitrogen mustard in severely leukopenic patients. However, it is contraindicated in patients with an open or draining fistula, those likely to require early surgery or those with known intra-abdominal adhesions. However, when radiogold is used, most reports cite about 50 to 60 percent improvement.

Dybiicki et al. summarized results with radiogold therapy up to 1959. Of the 635 patients treated for recurrent pleural effusions, 49 percent showed good control; of 566 patients treated with intraperitoneal therapy for malignant ascites, 47 percent improved. Remissions lasted from a few months to two years and improvement, if it did occur, was present by the sixth week after treatment.

Botsford reported 85 patients, most with breast cancer, of whom 57 had relief from recurrent pleural effusions from one instillation. Of 28 patients who failed to respond to the first treatment, 12 responded to a second treatment given within one month. Card et al. summarized the world literature, including 2,110 patients treated with radiogold and found 53 percent benefited either by complete fluid suppression or by definite diminution in accumulation.

Radioactive gold is a beta and gamma emitter with a half path of 0.4 mm and a physical half life of 2.7 days. Applied as a colloidal suspension, which is phagocytosed by cells in the mesothelium lining the cavity, it is not significantly absorbed and leukopenia is unusual. Its action is due to a radiation effect on cancer cells in the fluid and on implants on the serosal surface, as well as the creation of an obliteratorive fibrosis of serosal blood vessels. Radiation is delivered only to the first 2 mm of tissue below the serous membrane.

The dosage is usually 75-100 mc for pleural effusions and 150-225 mc for peritoneal effusions. Particularly with malignant ascites, the patient must move about frequently following administration to insure exposure of the entire peritoneal surface and to prevent pooling with resultant radiation necrosis. Administration may be followed by mild radiation sickness after three to four days.

Radiogold has several disadvantages: (1) it is expensive; (2) it has a short half life which necessitates ordering the agent immediately before use; and (3) it has a radiation hazard. This is related...
## Common Modalities of Treatment

| Agent                  | Indications                                      | Dose                                                                 |
|------------------------|--------------------------------------------------|----------------------------------------------------------------------|
| Nitrogen Mustard       | Malignant pleural, peritoneal and pericardial effusions | Usual intracavitary dose = 0.4 mg/kg<br>Reduce this dose by ½ in patients with poor bone marrow reserve or extensive previous radiotherapy to marrow-bearing areas or chemotherapy |
| Quinacrine (Atabrine®) | Effusions in wide variety of cancers, especially lung and breast<br>Causes no hematopoietic depression and is useful in patients with impaired bone marrow function | Average dose for pleural effusion = 100-200 mg daily or on alternate days<br>Average dose for ascites = 200-400 mg daily or on alternate days<br>First dose is ½ of subsequent doses |
| Radioactive Gold (¹⁹⁸Au) | Recurrent pleural malignant effusions and malignant ascites<br>Tolerated in severely leukopenic patients better than alkylating agents such as nitrogen mustard | For pleural effusion = 75-100 mc<br>For peritoneal effusion = 150-225 mc |
| Radioactive Phosphorus (³²P) | Recurrent pleural malignant effusions and malignant ascites<br>Tolerated in severely leukopenic patients better than alkylating agents such as nitrogen mustard | For pleural effusion = 5-10 mc<br>For peritoneal effusion = 10-15 mc |
| Administration                                                                 | Side Effects                                                                 | Contraindications                                                                 |
|--------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 1. Remove most of fluid prior to injection                                    | Mild nausea, vomiting, leukopenia; pain after intraperitoneal injection; temporary increase in serous effusion | Severe leukopenia or thrombocytopenia (however, absorption is variable; further marrow depression may not occur with half doses) |
| 2. Have patient change positions (prone, right/left side, supine, knee-chest) following injection to distribute drug | Side effects at first instillation may not occur at subsequent instillations |                                                                                  |
| 1. Administer at conclusion of thoracentesis or paracentesis                   | Local pain lasting about 24 hours; fever possibly as high as $103^\circ$-$104^\circ$; transient ileus after intraperitoneal injection | Seizures are an unusual toxic effect; therefore, use cautiously in patients with cerebral metastases or those taking corticosteroid agents which lower the seizure threshold |
| 2. Dissolve dose in 10 ml of saline                                            |                                                                             |                                                                                  |
| 3. Continue doses until mild sterile pleuritis or peritonitis occurs after 3-5 doses |                                                                             |                                                                                  |
| 1. Following administration, have patient move about frequently to insure exposure of peritoneal surface and to prevent pooling with resultant radiation necrosis | Mild radiation sickness                                                     | Open or draining fistula                                                         |
| 2. Isolate patient for several days due to radiation hazard                    |                                                                             | Need for early surgery                                                           |
|                                                                                |                                                                             | Intra-abdominal adhesions                                                        |
| 1. Administer at conclusion of thoracentesis or paracentesis                   | No appreciable side effects                                                 | Open or draining fistula                                                         |
| 2. No patient isolation required                                              |                                                                             |                                                                                  |
to the gamma component, which has no therapeutic effect, but requires isolation of the patient for the first few days with limited physician/nurse contact and monitoring by specially trained personnel, not available in all hospitals. Despite these disadvantages, however, in appropriate facilities, this agent has a definite role in the management of neoplastic effusions.

**Radioactive phosphorus (\(^{32}\)P)**

Radioactive colloidal chromic phosphate (Cr\(^{32}\)PO\(_4\)) has been used extensively in recurrent neoplastic effusions with results similar to radiogold. Card et al. reported a 52 percent response rate in 222 patients collected in the literature; \(^{19}50\) percent of the patients treated with radiophosphorus required no further treatment. Jacobs reported improvement in 25 of 41 patients with pleural effusions and five of 16 patients with peritoneal effusions.\(^{21}\)

Card et al. concluded that radiophosphorus is preferred over radiogold; it is less expensive and has a physical half-life of 14.3 days which makes it easier to obtain and use than radiogold which has a half-life of 2.7 days. Also, since radiophosphorus produces only beta particles, it is safer to use than radiogold and the patient need not be isolated.

The dosage of radiophosphorus is 5-10 mc for intrapleural instillation and 10-15 mc for abdominal instillation. There is no appreciable radiation sickness or bone marrow depression since systemic absorption is minimal. Be careful to request colloidal radiophosphorus, and not the soluble form which is used to treat polycythemia vera and other hematologic neoplasms.

Other radioactive isotopes have been used for recurrent neoplastic effusions, including radioactive yttrium (\(^{89}\)Y), a pure beta emitter, colloidal lutecium (\(^{177}\)Lu) and colloidal oils containing \(^{131}\)I. Ariel et al. administered \(^{90}\)yttrium chloride to 10 patients but found that the results were no better than with other agents.\(^{2}\)

**Surgical Treatment**

Since it is usually not possible to remove all the pleural fluid and obtain a full lung expansion with needle aspiration, pleurectomy has been employed.\(^{3,22-25}\) Decortication of the lung may be indicated particularly for long-term pleural effusion with resultant development of a pleural peel. However, pleurectomy is more difficult after alkylating agents or radioisotopes have been used intrapleurally.

A closed trocar tube drainage to treat malignant pleural effusions has been used by Lambert.\(^{26}\) The recurrence rate with this method was 14 percent, as compared to 100 percent following thoracentesis alone. Talc poudrage was employed by Starkey in six patients, with no operative deaths and no recurrence of the pleural effusion.\(^{21}\) Iodized talc insufflated over the pleural surface through a cannula was used by Jones.\(^{28}\) Twenty of 21 patients did not require further removal of fluid.

A recent and novel surgical approach to the treatment of malignant ascites called "ileal entectomy" isolates an everted ileal segment, and exposes the mucosal surface to the free peritoneal cavity.\(^{29,30}\) Some patients with ascites due to ovarian carcinoma have had control of the effusion using this method.

The creation of a window between the pericardial space and the pleural space may be effective in the palliation of malignant pericardial effusions. This technique can relieve cardiac tamponade and decompress the pericardial space, without the need for an extensive surgical procedure, such as pericardectomy, which is not usually indicated in such patients.\(^{31}\)
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