Intrapleural Tetracycline for Malignant Pleural Effusions

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After drainage by closed-tube thoracostomy, tetracycline was instilled in seven patients with malignant pleural effusions. None of the patients had clinically significant recurrence of effusion, even though four patients worsened while receiving systemic chemotherapy and died.

Recurrent pleural effusion is a problem frequently seen in patients with malignant neoplasms, particularly carcinomas of the breast and lung. Most often the etiology of the effusion is secondary to metastatic pleural implants with positive fluid cytologic findings. Negative fluid cytologic findings, however, may occur with pleural tumor being found only at autopsy. At other times, autopsy reveals only mediastinal or parenchymal involvement by tumor, and effusion is believed to be secondary to lymphatic blockage. Regardless of the mechanism, simple thoracocentesis is associated with a high rate of recurrence of the effusion.1 Mechloroethamine (nitrogen mustard)1 and quinacrine,2 the two most commonly used agents for intrapleural instillation, have their disadvantages. Both can cause local pain and systemic febrile reactions. Mechloroethamine has the potential for marrow toxicity, especially in a host already compromised and debilitated by a malignant neoplasm. Quinacrine (Atabrine**) hydrochloride requires two or three doses; and when one large dose is used, morbidity, including hypotension, can be significant.3

Considering alternatives, we felt that tetracycline, with its effect on pleural effusions previously demonstrated by Rubinon and Bolooki,3 could be a useful agent, particularly if the associated morbidity were mild and easily tolerated.

METHODS

Closed-tube thoracostomy is performed in the eighth or ninth intercostal space at the posterior axillary line and attached to water-seal drainage with gentle suction for at least 24 hours or until drainage has stopped. Removal of all fluid is confirmed by upright and decubitus chest x-ray films. Five hundred milligrams of tetracycline diluted with 50 ml of saline solution is injected through the tubing. This is followed by another 20 ml of saline solution to clear the tubing of all medication. The tube is then clamped for 30 minutes, and the patient's position is changed at five-minute intervals to ensure adequate dispersal. The tube is then unclamped and allowed to drain again with gentle suction for at least 24 hours or until drainage is no longer obtained. A follow-up x-ray film is taken to ensure that all fluid has been removed and no loculations have occurred. If no effusion is present, the tube is removed. If loculations are present and appear to be clinically significant, another closed tube thoracostomy is performed in an appropriate interspace to free the loculations, and drainage with suction is continued for at least another 24 hours. Another x-ray film is taken to confirm clearing of fluid, and the tube is removed.

One hour before instillation of tetracycline, the patient is treated with 10 mg of morphine sulfate. In addition, 15 mg of alphaprodine hydrochloride (Nisentil†) is given immediately prior to instillation, and the patient's pain is titrated with another 25 mg over the next 20 to 30 minutes.

RESULTS

As seen in Table 1, seven patients received treatment. None had recurrence for at least 30 days. In fact, no patient had a clinically significant effusion during any time of follow-up. Four patients worsened while receiving chemotherapy and died from progressive disease. Only one patient (case 3) had effusion at autopsy. He had 300 ml of fluid in the treated cavity with marked thickening and invasion of the pleura with adenocarcinoma. Three patients with metastatic breast carcinoma (cases 1, 6, and 7) responded to systemic chemotherapy and had no recurrence of effusion. Only one patient (case 1) was given a second instillation. She actually responded to the first instillation but developed an air leak through the first chest incision leading to a 40 percent pneumothorax. She was given a second instillation, though only 50 ml of fluid was recovered with the second tube.

Initially, local pain was a problem. In spite of morphine premedication, the first patient complained of severe "internal" burning pain over the

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510 HOWARD W. WALLACH

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CHEST, 68: 4, OCTOBER, 1975
entire hemithorax. We then began using alphaprodine hydrochloride, a short-acting synthetic narcotic with rapid onset of action. The next six patients had little trouble with local pain, which seemed in all cases to abate spontaneously 30 to 45 minutes after drug instillation.

Two patients developed temperature elevations to 37.8°C (100°F) orally the day following instillation, but this elevation was transient and without associated chills or sweats. The patient with pneumothorax (case 1) developed pneumonia within 48 hours of the occurrence of her pneumothorax but responded to antibiotic therapy. A second patient (case 7) developed fever within 24 hours. When all cultures proved negative, antibiotic therapy was discontinued after eight days, and the fever responded to indomethacin administration.

Six of the seven patients had very little drainage after drug instillation and had their tubes removed 24 to 36 hours after tetracycline was instilled. One patient (case 5) drained about 2,000 ml of fluid over eight days before the tube could be removed. She, however, had no recurrence of effusion.

Another patient (case 7) had several loculations 24 hours after drug instillation. It was felt, however, that these were not clinically significant, so another closed-tube thoracostomy was not performed. The loculations were no longer present on a chest x-ray film taken two weeks later.

**DISCUSSION**

Intrapleural instillation of tetracycline appears to be an effective treatment for recurrent malignant pleural effusion. When one combines our small series with that of Rubinson and Bolooki, our success rate is comparable to that with mechlorethamine, triethylene thiophosphoramide (Thiotepa), and quinacrine. The combined total of 19 patients had a success rate of greater than 80 percent.

Morbidity was mild, consisting mainly of poten-

tially severe local pain controlled with a combination of long-acting and short-acting analgesics. Temperature elevations occurred in four patients. One had pneumonia developing after a pneumothorax. The other two patients with fever had no associated symptoms. The fourth (case 7) probably had a tumor-related fever secondary to chest wall involvement.

The elevated diaphragms did not appear to be associated with any respiratory problems. However, the elevated diaphragms did lead to problems with interpretation of follow-up chest x-ray films, which were resolved by the use of decubitus films.

Six of seven patients had previous thoracocenteses (Table 1) but had reaccumulation of fluid in short periods of time. We feel that at least one attempt with needle thoracocentesis alone should be made, particularly if there is the possibility that systemic chemotherapy or hormonal manipulation might be successful. If the patient becomes symptomatic from effusion after chemotherapy has been initiated and given an adequate trial, then closed-tube thoracostomy should be done and tetracycline instilled. The tube drainage is essential in order to remove as much fluid as possible, since a needle thoracocentesis frequently is inadequate. The removal of all fluid then ensures adequate dispersal of the tetracycline.

The tetracycline solution is quite acidic, and it is probably the destructive-irritant effect of this acidic solution on the mesothelial cells of the pleura which leads to pleural symphysis. This non-specific property is important, because tetracycline can be effective whether the mechanism for the effusion is tumor implants or mediastinal lymphatic obstruction. Five of our patients (Table 1) had positive malignant findings on fluid cytologic examination or positive malignant findings on pleural biopsy and responded. Two other patients responded even though their fluid cytologic findings and biopsy results were negative.
Intrapeural instillation of tetracycline has several advantages. Morbidity is mild and tolerable. The treatment is effective whether or not chemotherapy or hormonal manipulation proves successful. Tetracycline allows full doses of chemotherapy, because it does not appear to have any depressive effects on the bone marrow.

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ADDENDUM

Since submitting the manuscript, cases 1 and 7 have died of disseminated breast carcinoma. Case 1 died 490 days after drug instillation. Autopsy revealed no effusion. Case 7 died 110 days after drug instillation. Autopsy revealed only 200 ml of effusion. Both patients had diffuse bilateral pulmonary and pleural metastases.

REFERENCES


Saxophone

Antoine Joseph (known as Adolphe) Sax (1814-1894) grew up with his ten brothers and sisters in the paternal workshop in Brussels where even as a child he worked side by side with his father making wind instruments. The bass clarinet was his particular interest, and while trying to improve its tone, he invented the saxophone. While still in Brussels, Sax met Berlioz, and it was no doubt he who persuaded him to try his luck in Paris. But in spite of such influential friends as Meyerbeer, Halevy, Donizetti, and of course Berlioz, Sax could not break into the Paris market. Sax invited musicians to little performances to stimulate their interest in his instrument. One such occasion was organized at the Salle Herz and was to include a piece especially written by Berlioz for Sax's instrument. Each instrument had its moment in Berlioz's little composition—last of all the saxophone, which had never been heard publicly in Paris. The saxophone was unfortunately not quite finished when the appointed day arrived and had to be patched together with string and sealing wax. Sax was so preoccupied whether his instrument would hold out that he temporarily forgot the score and was forced to sustain a single note at great length and with many delicate nuances of tone until his memory returned. The audience was delighted with the display, and the saxophone solo brought great applause.