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Chemical Pleurodesis with Mitoxantrone in the Management of Malignant Effusions

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METASTATIC DISEASE of the pleura is a frequent cause of exudative pleural effusions. The epidemic of lung cancer today and the increase of most forms of cancer make malignant effusion a common pathology in pulmonary practice. Optimal treatment for these patients with often limited life expectancy has to be effective, as assessed by a low recurrence rate of pleural fluid. Furthermore, the treatment should be inexpensive and should have minor morbidity. None of the various reported methods fulfil all these demands [1].

The standard treatment for controlling malignant pleural effusions is tube thoracostomy with instillation of a sclerosing or cytotoxic drug. Most commonly employed sclerosing agents include talc, tetracycline and tetracycline analogues such as doxycycline and minocycline. Bleomycin is frequently proposed as an important cytotoxic agent for pleurodesis of malignant pleural effusions [2]. Mitoxantrone, an anthracycline derivative, has recently been demonstrated to be effective in the treatment of peritoneal and pleural effusion. Mitoxantrone with its high molecular weight and high polarity exhibits a decreased pleural clearance with prolonged high peak concentrations intrapleurally, favourable factors for local intrapleural treatment. The mechanism of intrapleural action of mitoxantrone has not yet been established. Both the inflammatory and antineoplastic activity of mitoxantrone intrapleurally have been described [3, 4]. There are only limited data about the efficacy of mitoxantrone in the treatment of malignant pleural effusions. In a prospective study in 18 patients, Musch and associates [5] reported a success rate of 75%. A comparative study including bleomycin and mitoxantrone showed almost an equal response rate of 64% and 67%, respectively [6].

Table 1. *Total response (CR + PR) according to primary malignancy*

	No. (%)
Breast cancer	10/11 (91%)
Lung cancer	4/8 (50%)
Mesothelioma	4/5 (80%)
Cancer of unknown origin	7/12 (58%)
Ovarian cancer	2/3 (67%)
Sarcoma	1/1 (100%)

We studied 40 patients with cytologically proven malignant pleural effusion. Patients were treated following standard procedures. In all patients thoracostomy and tube drainage were performed. After adequate drainage and expansion of the lung, 30 mg of mitoxantrone was instilled through the chest tube. In patients with persistent pleural fluid production of more than 200 ml/24 h after the first instillation of mitoxantrone, a second dose of mitoxantrone (30 mg) was administered. Four weeks after pleurodesis, the response rate was assessed radiographically (chest X-ray). The criteria for complete or partial response were defined according to Paladine and associates [2]. A complete response (CR) was obtained in 18 patients (45%) and a partial response (PR) in 12 patients (30%), resulting in an overall response rate (CR + PR) of 75%. 7 patients showed sustained pleural fluid production after the first mitoxantrone instillation, and needed a second instillation of mitoxantrone. In this latter group of 7 patients, a failure rate of 57% was found. The highest success rate was found in patients with breast cancer (Table 1). Remarkably, pleural effusion in mesothelioma patients seemed to respond well, although the patient number was limited. The procedure was well tolerated and side-effects of the intrapleural instillation of mitoxantrone were rare. Importantly, no complaints of pain were noted during and after instillation. The present study confirms previous data that prolonged excessive production of pleural fluid with sustained pleural drainage, after initial treatment with a sclerosing agent, is an unfavourable prognostic factor for successful pleurodesis. The results in our study confirmed the high effectiveness of mitoxantrone for pleurodesis in the absence of significant morbidity. Our reported data justify further longitudinal and biochemical studies in a controlled setting to elucidate the biological action and prognostic relevance of mitoxantrone in the treatment of malignant pleural effusions, and to compare this agent with other treatment procedures for malignant effusions.

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Proteinuria: a Frequent Paraneoplastic Phenomenon in Colorectal Cancer?

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THE TERM paraneoplastic syndrome is used to describe the indirect effects of cancer that are secondary to the production of biologically active hormones, growth factors, antigen–antibody interactions induced by the tumour, or yet undefined substances. The prevalence of paraneoplastic phenomena is estimated to be 7–15% in cancer patients [1]. Proteinuria is one of the symptoms of paraneoplastic renal damage, usually a type of glomerulopathy [2].

In 1995 we collected, pre-operatively, fasting early morning urine samples of 58 patients with recently diagnosed colorectal cancer. No samples were obtained from patients with a history of renal disease. The control group comprised 42 patients admitted for elective surgery. In patients with colorectal cancer, the urine samples were again provided between 1 and 2 weeks postoperatively. In colorectal cancer patients, serum carcinoembryonic antigen (CEA) levels were measured pre-operatively and in case of an abnormal value (> 5 μg/l) a repeated CEA measurement was done 1 week postoperatively.

Proteinuria appeared to be more common in patients with a colorectal tumour (62%) than in controls (24%) ($P < 0.001$, Mann–Whitney U test). Patients with colorectal cancer had significantly higher urinary protein concentrations compared with controls (0.26 [range 0.17–2.03] versus 0.18 [0.16–0.5], $P < 0.01$). Abnormal CEA levels were present pre-operatively in 23 of 55 colorectal patients (42%). There was no significant correlation between the pre-operative urine protein concentrations and serum CEA levels (Spearman's $r = 0.12$, $P = 0.46$). The results of postoperative urinalysis in 22 patients with pre-operatively detected proteinuria but without metastatic disease are shown in Figure 1. The difference between pre-operative and postoperative urine protein excretion in this group was significant ($P < 0.01$, Wilcoxon-signed rank test).

A link between cancer and renal disease, manifested primarily by the nephrotic syndrome, was first suggested by Galloway in 1922 [3]. Patients with nephrotic syndrome have a high prevalence of cancer, more than age-matched controls [2]. The actual prevalence of overt renal disease in patients with cancer is unknown, but is probably quite small. Subclinical disease is undoubtedly much more common [2, 4]. However, relatively little attention has been paid to this paraneoplastic phenomenon in comparison to the huge interest that is given to the role of several tumour markers. Sawyer and associates showed that, in patients with several types of disseminated malignancies, the presence of proteinuria was significantly associated with a substantially reduced survival time [5]. Our data show that paraneoplastic proteinuria is not rare in patients with newly diagnosed colorectal cancer. The proteinuria is probably a symptom of a membranous glomerulonephritis caused by immune complex formations [2]. Evidence for this was provided by Constanza and associates, who showed CEA and anti-CEA-antibody

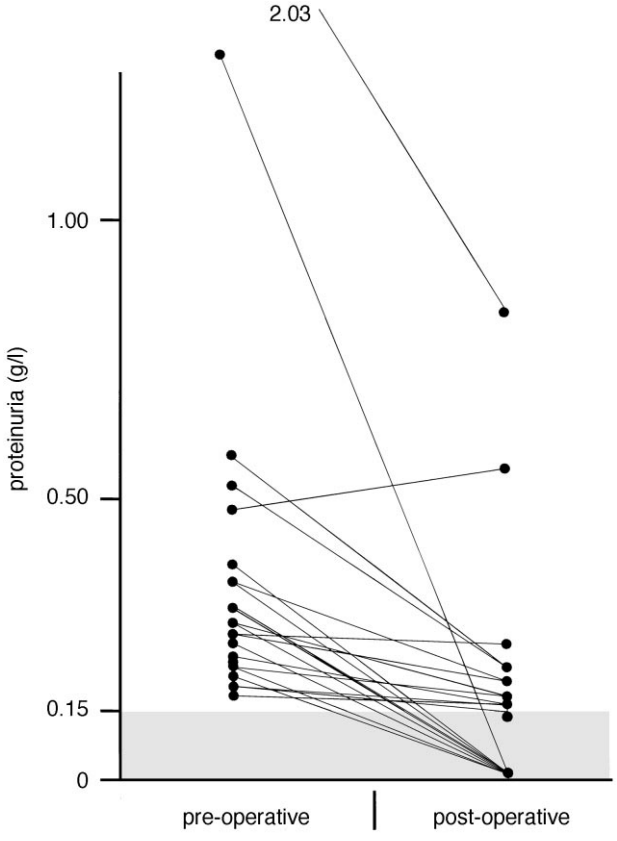

Figure 1. Illustration of pre-operative and postoperative urine protein concentrations in 22 patients with colorectal cancer without disseminated disease. The shaded area represents the detection limit of urine protein excretion (0.15 g/l). The difference between pre-operative and postoperative urine protein concentration was significant ($P < 0.01$).

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