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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

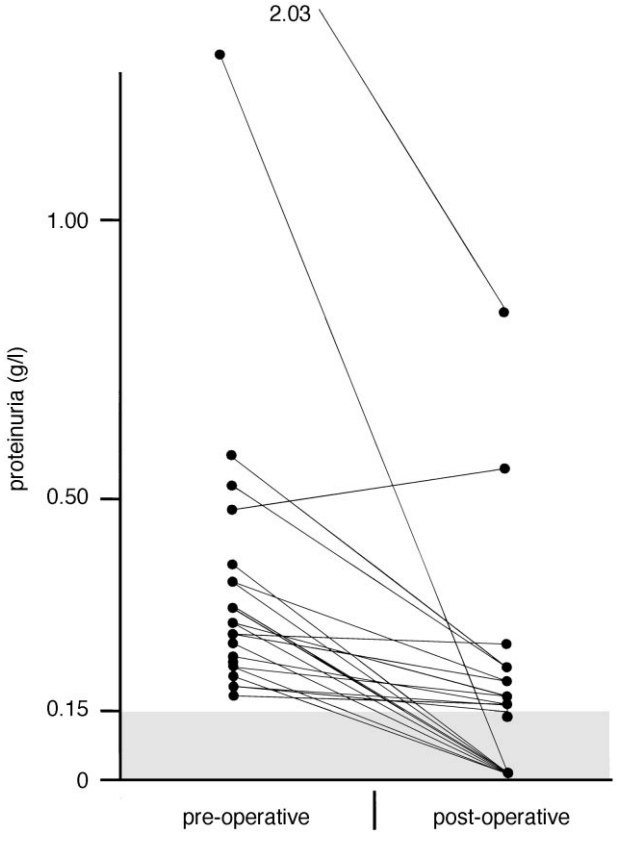

Figure 1. Illustration of pre-operative and postoperative urine protein concentrations in 22 patients with colorectal cancer without disseminated disease. The shaded area represents the detection limit of urine protein excretion (0.15 g/l). The difference between pre-operative and postoperative urine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

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deposits along the glomerular basement membrane in a patient with colonic carcinoma and membranous glomerulonephritis resulting in a nephrotic syndrome [6]. It has been shown that as many as 82% of patients with neoplasia may have soluble immune complexes in their plasma that might result in frequent glomerular injury developing by the deposition of these complexes [5]. However, it is still thought to be an unusual feature. We hope that the present data are convincing enough to indicate the contrary. As we did not find a relevant correlation between the presence of CEA in serum and proteinuria, this might indicate that probably other tumour-related substances play a role in the formation of immune complexes responsible for the development of glomerulonephritis. A feature strongly supporting the idea that the paraneoplastic glomerulopathy is tumour related is the reversal of the renal lesion after removal of the primary tumour, something that occurred 1 week postoperatively in more than half our patients without disseminated disease.

More extensive studies are needed to provide data on the prevalence of proteinuria in colorectal cancer and the usefulness of urine protein excretion follow-up for the possible detection of recurrent disease.

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