

SHORT COMMUNICATION

THE RELIABILITY OF HIGHLY ELEVATED CA 19-9 LEVELS

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SUMMARY

CA 19-9 is used as a tumour marker of the upper gastrointestinal tract. However, extremely elevated CA 19-9 levels are found also in patients with benign diseases. Cholestasis was present in 97.1% of patients with high elevated CA 19-9, independent of their primary disease. 50% of patients with non-malignant diseases and increased CA 19-9 levels showed liver cirrhosis, cholecystitis, pancreatitis and/or hepatitis. In 8.8% no explanation was found for the extremely high CA 19-9 level. The results provide evidence of different factors influencing the CA 19-9 level.

KEY WORDS CA 19-9 Tumour markers Cholestasis Malignancy

INTRODUCTION

Highly elevated CA 19-9 levels are seen predominantly in patients with gastrointestinal malignancies. The higher the CA 19-9 level, the more likely is a diagnosis of malignancy. Some quite contrary clinical observations (Klee *et al.*, 1993) provoked further investigation of the sensitivity and specificity of this marker.

MATERIALS AND METHODS

832 CA 19-9 measurements have been analysed, in relation to clinical findings, from patients of the Departments of Surgery and the Department of Internal Medicine. Indication for measurement were suspicion of malignancy or monitoring of proven tumours. All measurements were performed using the CA 19-9 IMx® assay [enzyme immunoassay; normal range <45 U/ml] (Abbott).

RESULTS

We found highly elevated CA 19-9 levels (more than 500 U/ml) in 4.6% (n=38) of the total measurements. Levels between 45 U/ml and 499 U/ml occurred in 26.8% (n=223), normal values were obtained in 68.6% (n=571).

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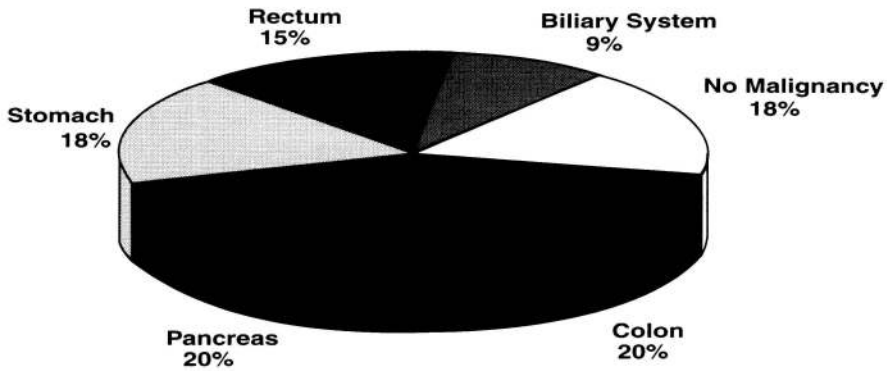


Figure 1. Distribution pattern of malignant tumors in highly elevated CA 19-9 levels (> 500 U/ml).

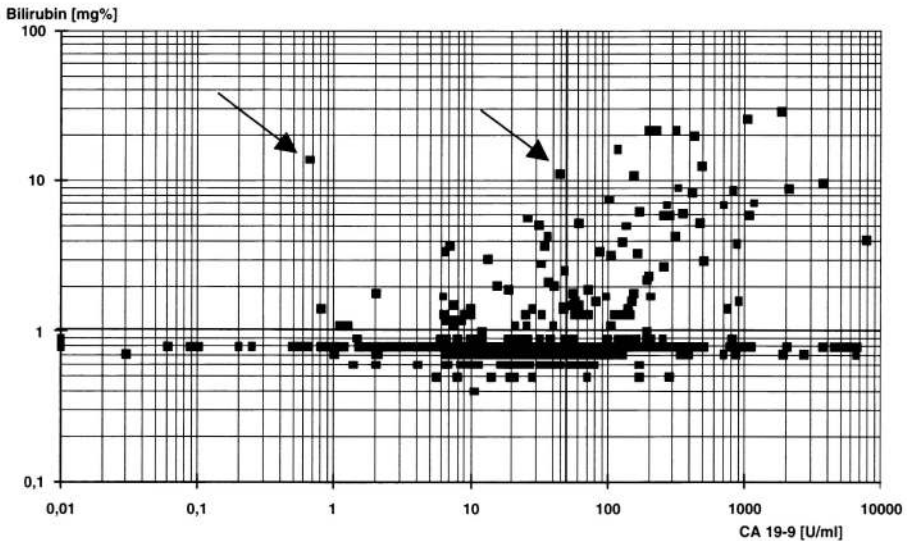


Figure 2. Bilirubin and CA 19-9 levels [log]. High bilirubin serum levels combined with normal CA 19-9 levels (arrows).

Cholestasis, accompanied by bilirubin levels from 3.8 mg/dl to 25.7 mg/dl was found in 97.1% of the group with highly elevated CA 19-9, independent of the underlying diagnosis.

CA 19-9 levels >500 U/ml were associated with malignant tumours in 82.3% (colon and pancreas in 20.6 each, stomach in 17.6%, rectum in 14.7%, gallbladder and/or bile ducts in 8.8%) (Fig. 1).

50% of the group with non-malignant diseases and highly elevated CA 19-9 levels had liver cirrhosis, cholecystitis, pancreatitis and/or hepatitis. 41.2% of this group has

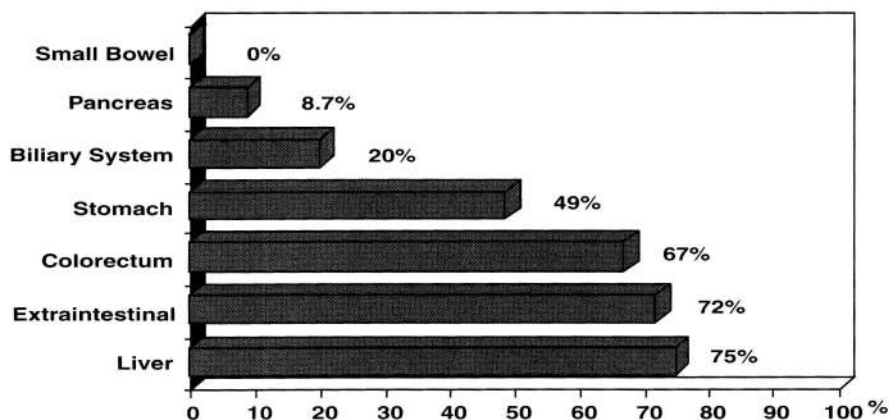


Figure 3. Rate of false negative CA 19-9 levels in different tumor localizations.

bilirubin levels of more than 2.9 mg/dl. In 8.8% an explanation for the extremely high CA 19-9 level was not established.

Cholestasis is well known as an important factor causing false positive CA 19-9 results. However, in this study we also found bilirubin levels of 13.8 mg/dl and 11.2 mg/dl accompanied by CA 19-9 levels of 0.67 U/ml, and 44 U/ml respectively (Fig. 2).

The high rate of false negative CA 19-9 values seen in colorectal cancer (67%), stomach malignancies (49%), liver malignancies (75%) and in other tumours such as kidney, breast and ovary (72%) reflects the relatively poor sensitivity of 41.2%. This was even true for carcinomas of the biliary system, pancreas and small bowel (Fig. 3). The specificity was 71.8%. The positive predictive value of 51.8% and the negative predictive value of 62.4% emphasize the risk of false interpretation of CA 19-9 levels.

DISCUSSION

In evaluating CA 19-9 levels, a number of different factors possibly influencing the result must be considered. Iwase *et al.* (1992) found CA 19-9 levels in the cystic fluid of benign biliary liver cysts to be increased more than one hundred-fold compared with corresponding serum levels. In addition, they observed positive immunohistochemical staining for CA 19-9 in the cytoplasm of the epithelial cells of the cyst wall. Involvement of the bile duct epithelium in benign as well as malignant disorders may therefore account for elevated peripheral CA 19-9 levels.

In malignant tumours, the sensitivity and specificity of CA 19-9 are strikingly enhanced with advanced tumour stage (Kouri *et al.*, 1992) and are positively correlated with the grade of tumour differentiation (Iwamura *et al.*, 1992; Ohshio *et al.*, 1990).

False negative CA 19-9 values are common in patients who are negative for the Lewis blood group phenotype (Tempero *et al.*, 1987). Kawa *et al.* (1991) examined different tumour markers in healthy subjects and patients with pancreatic carcinoma. Within the tumour group, 30% of the patients with false negative CA 19-9 levels were Lewis

negative. However, the reason for negative CA 19-9 levels in the majority of cases of clinically proven pancreatic cancer is still unknown.

Cholestasis is the most common cause for false positive CA 19-9 levels, but even in the absence of gross cholestasis, hepatitis, liver cirrhosis, pancreatitis and cystic fibrosis can be associated with elevated serum CA 19-9 levels (Jalanko *et al.*, 1984; Duffy *et al.*, 1985).

Increased CA 19-9 levels must therefore be interpreted with caution in the investigation of possible malignancy. Nevertheless it should be stressed that where there have been high preoperative CA 19-9 levels and a substantial drop after surgical treatment, CA 19-9 measurement represents one of the most important parameters in the monitoring of tumour growth.

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