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CA 19-9 Determination in Gastric Juice: Role in Identifying Gastric Cancer and High Risk Patients

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Abstract—*Gastric juice CA 19-9 levels were determined in 23 patients affected by gastric cancer, in 57 patients affected by chronic atrophic gastritis of different severities and in 55 'healthy' controls, undergoing endoscopy for upper gastrointestinal tract symptoms. Increased CA 19-9 levels were documented in chronic atrophic gastritis patients as well as in gastric cancer patients, the difference with respect to controls being statistically significant. However, there was considerable overlap between different groups. In particular, gastric cancer patients had CA 19-9 levels similar to those detected in moderate and severe chronic atrophic gastritis. CA 19-9 correlated with gastric juice pH and CEA concentration. Its values were not influenced by the patients' age or sex. In our opinion CA 19-9 gastric juice determination, although not useful in singling out patients harboring gastric neoplasia, may be used in identifying patients 'at risk' for gastric cancer and who might then be referred for more accurate investigations.*

INTRODUCTION

TUMOR-ASSOCIATED antigens have proven useful in the diagnosis of gastrointestinal malignancies, including liver, pancreatic and colon cancer. Serum determination of alphafetoprotein, CEA and CA 19-9 are routinely performed and provide useful clinical information [1–6].

However, no useful serum markers are presently suitable for screening gastric cancer [GC], since all the tests described are of unacceptably low sensitivity and specificity [7, 8]. We have previously shown that the determination of CEA in gastric juice may represent a more useful tool in investigating the presence of GC as well as precancerous conditions [9]. This approach is indeed more valuable in terms of sensitivity and specificity and its results are less affected by extra-gastric factors, such as the age of the patient [10]. The aim of the present study was to assess whether the determination of gastric juice CA 19-9, a sialylated carbohydrate first described by Koprowski in tumor tissue of colorectal carcinoma [11], might add to endoscopic and bioptic procedures in screening for GC and gastric precancerous changes. CA 19-9, which proved relatively useful in the diagnosis of malignant tumors of the pancreas [12, 13], intra- and extra-hepatic bile ducts [14] and to a lesser extent, of the stomach [12, 14] has in fact been recently described in benign and malignant gastric tissues [15].

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MATERIALS AND METHODS

The series included 23 patients affected by GC, admitted to a department of surgery or undergoing endoscopy, and 112 consecutive patients referred to our endoscopy unit for dyspepsia. In all patients routine antral and fundic biopsies (2 + 2 at least) were obtained. Biopsies were also performed on any focal lesion. The group included:

- 55 healthy controls, in whom no macroscopic lesions and no atrophic histological changes were observed;
- 57 patients affected by chronic atrophic gastritis (CAG) as classified according to Whitehead *et al.* [16] (26 mild, 23 moderate, 8 severe).

Eighteen patients also presented dysplastic changes, mostly of low grade, as classified according to Ming [17]. In 10 cases epithelial dysplasia was associated with CAG, in eight it was detected in a non-atrophic mucosa.

No patients with severe liver function impairment entered the study. The male/female ratio and age of the patients are summarized in Table 1. In each

Table 1. Mean age (± S.D.), males, females and male/female ratio in control subjects and in CAG and GC patients

	Tot.	Age	Males	Females	Ratio
Controls	55	46 ± 11.8	43	12	3.6
CAG (mild)	26	49.7 ± 12.8	18	8	2.2
CAG (moderate)	23	55.1 ± 10.4	19	4	4.7
CAG (severe)	8	55.7 ± 17.7	4	4	1.0
GC	23	58.1 ± 11.4	16	7	2.3
	135				

patient a sample of gastric juice was obtained at the beginning of the endoscopy (by means of an appropriate cannula) or prior to surgery. The pH of the sample was recorded and the juice was then stored at −20°C, up to the determination, which was carried out within 1 month. After thawing, the samples were centrifuged at 2000 rpm for 5 min, the pH of the supernatants adjusted to 7 and CA 19-9 levels were determined by using a R.I.A. method (Sorin, Sallugia, Italy). Inter- and intra-assay variations were calculated (8 and 5.5% respectively).

CA 19-9 levels in controls, CAG and GC patients were compared by using Student's t test. Possible effects of age and pH in affecting CA 19-9 gastric juice levels were assessed by linear regression between CA 19-9 values and the two factors. Possible variations due to gender were looked for by comparing CA 19-9 levels in males and females, pair-matched for presence and extent of histological changes and age. In a subgroup of patients ($n = 74$), CA 19-9 gastric juice levels were correlated with gastric juice CEA levels, as determined by a R.I.A. method, previously described [9], and the sensitivity and specificity of the two methods were compared. As reported, data were analyzed by using Student's t test for paired and unpaired data and linear regression; sensitivity, specificity, positive and negative predictive values, performance index according to Youden [18] were also calculated.

RESULTS

CA 19-9 levels in control patients, mild, moderate and severe CAG patients and GC are reported in Fig. 1. All but two control subjects presented CA 19-9 levels lower than 450 U/ml. This was identified as the upper normal limit, calculated by considering the mean + 2 S.D. All groups of CAG (mild, moderate and severe) and GC patients showed statistically higher CA 19-9 levels than control subjects, but a large overlap among groups was present. Sensitivity for GC (patients showing CA 19-9 exceeding the cut-off) was 65%, specificity was 71%, positive and negative predictive values were 30% and 90% respectively. Overall diagnostic accuracy (Youden's performance index) was 20%. No significant correlation was documented between age and CA 19-9 levels ($r = 0.11$). Table 2 shows CA 19-9 values (mean ± S.D.) in 72 patients (36 males, 36 females), pair-matched for age and presence/degree of histological changes. No difference was detected. A relatively good correlation was demonstrated between gastric juice pH and CA 19-9 ($r = 0.45$, $P < 0.001$) as well as between CEA and CA 19-9 ($r = 0.47$, $P < 0.001$). Due to the small amount of juice available in some instances, CEA determination was performed only in 74 patients (Fig. 2). In this group of patients, CEA sensitivity and specificity were slightly higher than those of CA 19-9 (72% and 74% respectively).

CA 19-9 levels were determined in 18 patients with epithelial dysplasia (Table 3). CA 19-9 values in this group of patients were statistically higher than in controls ($t = 4.4$, $P < 0.001$). The mean value however fell within the normal range and only 7/18 patients (39%) showed abnormal levels. In patients with epithelial dysplasia associated with CAG CA 19-9 values were higher and exceeded, as a mean, the normal range.

DISCUSSION

Even though the incidence of GC is decreasing throughout the Western world [19], this tumor still remains a major cause of death from cancer worldwide. The dramatic improvement in early diagnosis achieved in Japan has not been matched in Western countries [20, 21], where most often GC is still diagnosed at an advanced stage. New perspectives come from the identification of gastric precancerous changes, particularly epithelial dysplasia, but reliable data on the evolution of these changes are still scanty [22, 23].

Particular interest has been focussed on the search for markers which could single out patients with GC or at high risk for the lesion. With respect to GC however, serum markers have not provided encouraging results, since the overall sensitivity and specificity of the methods has been low [7, 8]. Better results have been obtained by determining gastric juice markers, such as CEA [9, 24], lactic dehydro-

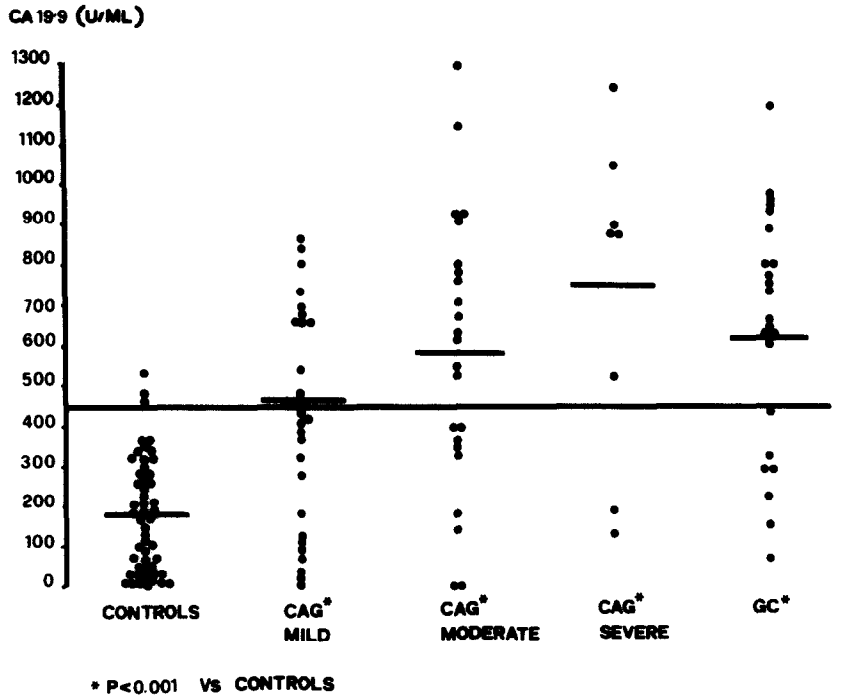

Fig. 1. Gastric juice CA 19-9 levels in control subjects and in patients affected by mild, moderate or severe CAG and GC.

Table 2. CA 19-9 gastric juice levels in males and females (included in control group, CAG and GC) pair-matched for age, presence and extent of histological damage

	No.	CA 19-9 (mean ± S.D.)
Males	36	330.8 ± 324.8
Females	36	315.6 ± 307.1

genase [25], beta-glucuronidase [26] and others.

CA 19-9 is a monosialoganglioside which shares some structural features with Lewis blood group substances [27] and has been identified as a sialylated lacto-*N*-fucopentose [28]. In our experience, this marker proved to be a useful tool in the identification of pancreatic cancer [29] and its presence was associated with an increased risk for GC in a preliminary study of a family at high risk for this neoplasia [30].

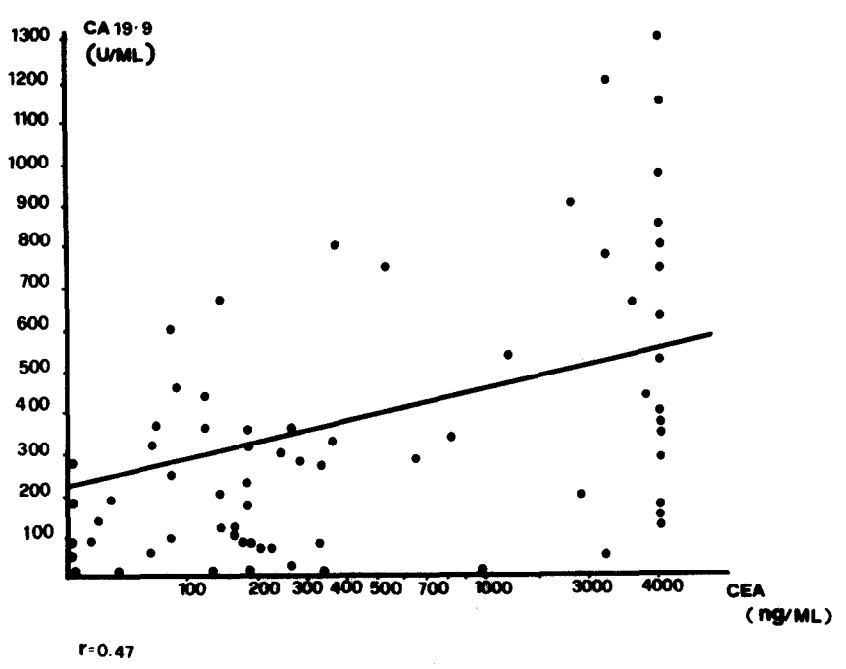

Fig. 2. Correlation between CA 19-9 and CEA gastric juice levels.

Table 3. Gastric juice CA 19-9 levels in patients affected by epithelial dysplasia, with or without CAG, with respect to controls

	CA 19-9 (mean ± S.D.)
Controls (normal range 0–450 U/ml)	177.4 ± 136.4
Dysplastic patients (Tot.)	431.9 ± 358.5*
Dysplastic patients (no CAG)	351.8 ± 342.2
Dysplastic patients (with CAG)	495.9 ± 364.9†

*$t = 4.4$, $P < 0.001$ with respect to controls.
†$t = 4.9$, $P < 0.001$ with respect to controls.

The data presented show that patients with precancerous conditions (i.e. CAG) and lesions (i.e. epithelial dysplasia) as defined by Morson *et al.* [31], synthesize and secrete abnormal amounts of CA 19-9 in their gastric juice. Even though statistically significant for all groups considered, the rise in CA 19-9 levels is not sharp enough to allow a clear cut distinction between groups. In particular patients affected by GC do not present higher CA 19-9 levels than CAG patients and even epithelial dysplasia is associated with high levels of CA 19-9 only when detected in an atrophic mucosa. It appears therefore that CA 19-9 synthesis depends more on the presence of diffuse atrophic changes than on the development of neoplastic or pre-neoplastic alterations. These data seem to confirm the recent report by Sipponen and Lindgren [15] who reached the same conclusions by studying CA 19-9 expression in human mucosa. In this respect, CEA gastric juice determination is probably still to be preferred, due to its higher sensitivity and specificity. It should be stressed however that, if we consider patients with epithelial dysplastic changes in CAG at risk for GC [23], CA 19-9 detemination allows us to identify a large share of this group of patients independently of factors such as age, which have been shown to affect CEA determination. With respect to gastric pH, which has been also shown to affect CEA determination, this is influenced by the presence and extent of CAG [32] and most probably correlates with gastric juice CA 19-9 levels because they are both controlled by the same process. It might be proposed to use the two markers in association but, as always happens in these cases, the gain in sensitivity would be offset by a reduction in specificity and overall diagnostic accuracy.

In conclusion, even though interesting results have been obtained by studying gastric juice CA 19-9, we do not think that the routine use of this marker is indicated in clinical practice. The attempt to identify cohorts of patients at risk for GC for inclusion in a follow-up protocol might, however, justify exceptions to this rule.

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