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Persistent elevation of serum CA 19-9 with no evidence of malignant disease

M. Ventrucci [a,*], P. Pozzato [a], A. Cipolla [a], G. Uomo [b]

[a] *Department of Internal Medicine and Gastroenterology, Bentivoglio Hospital, Via Marconi 35, Bologna, Italy*
[b] *Department of Internal Medicine, Cardarelli Hospital, Naples, Italy*

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Abstract

Background. Serum CA 19-9 is the mainstay marker for the diagnosis of biliopancreatic malignancies, though a persistent elevation can also be observed in various benign diseases.

Aims. In this study, a marked increase of serum CA 19-9 was seen in 10 patients who had no evidence of malignant disease. The possible causes of this finding are discussed.

Patients. Nine women and one man were studied, whose admitting diagnoses were as follows: pulmonary fibrosis in two, diabetes in two, non-ulcer dyspepsia in two, obesity in one, acute diarrhoea in one, colon diverticula in one and gastric ulcer in one.

Methods. Routine blood tests, tumour marker determinations, imaging studies and endoscopy were carried out at admission.

Results. Serum CA 19-9 levels ranged from 112 to 1338 IU/ml (mean 517 IU/ml). Abdominal ultrasonography, CT-scan, upper gastrointestinal X-ray series and gastrointestinal endoscopies were negative for malignancy. During the follow-up period (range 2–7 years) serum CA 19-9 values were persistently elevated in all patients.

Conclusions. Our study shows that persistent and significant elevation of serum CA 19-9 can be found in non-malignant and non-cholestatic disease.

Keywords: CA 19-9; Tumour markers

1. Introduction

Serum CA 19-9 is tumour marker carbohydrate antigen that is expressed in tissue as a monosialoganglioside and as a mucous protein [1]. It is secreted into the blood, saliva, bronchial secretions as well as gastric and bile juice. It is the most important tumour marker for the diagnosis of biliopancreatic malignancies, and it has become the standard for predicting recurrence of pancreatic carcinoma during follow-up [2]. The sensitivity and specificity of CA 19-9 for pancreatic cancer as assessed by an analysis of 22 studies that included almost 1000 patients and 5000 controls, were 83% and 82%, respectively [3]. Its diagnostic accuracy is hampered by the fact that an increase in serum levels can also be found in other digestive carcinomas [4–9] and in a number of benign diseases [11–31] (Table 1). However, since the elevation of CA 19-9 in the non-malignant diseases is minor, the use of an appropriate cut-off far above the upper normal limit could improve the specificity of this marker for the diagnosis of digestive cancers [32–33].

In this paper we report 10 cases of marked and persistent increase of CA 19-9 in serum with no evidence of malignant disease. The possible causes of this finding are discussed.

2. Materials and methods

The inclusion criteria of the study were frank elevation of serum CA 19-9 (>100 IU/ml) persisting for at least 2 years and absence of malignant disease, which was determined by

* Corresponding author. Tel.: +39 051 6644554; fax: + 39 051 6644076.
E-mail address: maurizio.ventrucci@ausl.bo.it (M. Ventrucci).

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Table 1
Causes of serum CA 19-9 elevation (numbers in brackets correspond to the listed references)

Aetiology	Serum CA 19-9 levels	
	Marked elevation (>1000 IU/ml)	Mild elevation (<200 IU/ml)
Malignancies of:		
Biliary tract [4]	+	
Pancreas [5,6]	+	
Colon [7,8]	+	
Stomach [9]	+	
Female reproductive system [1,10]		+
Cholestasis [11,12]	+	
Acute hepatitis [13,14]		+
Chronic liver disease [15]		
Non-alcoholic [13,14]		+
Alcoholic [16]		+
Cystic fibrosis [17]		+
Pancreatitis [18,19]		+
Diabetes mellitus [20]		+
Interstitial pulmonary disease [21,22]		+
Collagen vascular diseases [23]		+
Endometriosis [24]		+
Case reports:		
Hydronephrosis [25]		+
Splenic cyst [26]		+
Bronchogenic cyst [27]		+
Hepatic steatosis [28]		+
Colon diverticulitis [29]		+
Hypothyroidism [30]		+
Heavy tea consumption [31]		+

physical examination, laboratory findings, imaging studies and endoscopy.

The 10 patients included in the study were referred during the period from 2000 to 2007 to the GI Units of two Hospitals (Bentivoglio, Bologna and Cardarelli, Naples, Italy) because of abdominal symptoms. The baseline characteristics of the patients are shown in Table 2. In their clinical histories, previous colon polypectomy was reported in two of the patients, diabetes in two, interstitial pneumonia in two, hypertension in two, mastectomy for cancer in one, papillosphincterotomy due to common bile duct stone in one, and chronic bronchitis in one.

Routine blood tests, in addition to CA 19-9, CEA, CA 125, CA 15-3, amylase and lipase determinations were carried out at admission. Serum levels of CA 19-9 were measured by a radioimmunometric assay; the cut-off value was 37 IU/ml [34]. In addition, study for cystic fibrosis transmembrane conductance regulator (CFTR) mutation was performed in order to look for cystic fibrosis heterozygosis [35]. Abdominal ultrasonography and/or CT scan, upper gastrointestinal (GI) endoscopy and colonoscopy or barium studies were performed to exclude malignancies. Chest X-ray was done to check for interstitial pneumonia. In the two patients with pulmonary fibrosis, bronchoscopy and bronchoalveolar lavage fluid examination were carried out. The study follow-up period ranged from 2 to 7 years (mean 5 years).

Serum CA 19-9 and other tumour marker determinations as well as abdominal ultrasonography were repeated at least once in all patients; for all patients the last study was done at the end of follow-up.

3. Results

Abnormal blood test results were found in eight patients: neutrophil leucocytosis in three patients, mild anaemia in two, C-reactive protein elevation in three, slight increase in gammaglutamyltranspeptidase (GGT) in two, hypercholesterolaemia in three. The tumour markers, other than CA 19-9, were in the normal range except for elevated CEA in three patients, CA 15-3 in two and CA 125 in one. CFTR mutation research was negative in all patients.

Chest X-ray was normal in all but three patients (fibrosis in two and increased radiolucency of the lung in one). In the two patients with interstitial pneumonia, bronchoscopy and bronchoalveolar lavage fluid examination did not reveal any abnormal findings.

GI endoscopies showed no evidence of neoplasia. Abdominal ultrasound, CT scan, upper GI X-ray series, endoscopic ultrasound (UES), magnetic resonance cholangiopancreatography (RMCP) and positron emission tomography (PET) with 18F-FDG were negative for tumour presence and for biliary tract obstruction.

Most of the patients were undergoing medical treatment: proton pump inhibitors (PPI), steroids and insulin were the drugs most frequently administered. Results of blood tests and imaging studies as well as the concomitant medication are reported in Table 3.

During the follow-up period all patients were apparently healthy except those suffering from interstitial pneumonia, who complained of dyspnoea and coughing. At present, 9 of the 10 patients studied are alive; 1 died of end stage renal disease secondary to amyloidosis 2 years after the entry into the study. Leucocytosis and anaemia disappeared in all four of the patients with these conditions and GGT levels normalized in one of the two subjects who shoved elevation of this enzyme.

Levels of CA 19-9 remained persistently elevated in all 10 patients during follow-up. Fig. 1 illustrates CA 19-9 serum levels in four of the nine patients studied in whom the determinations of tumour markers were performed each year for a minimum follow-up period of 6 years. The behaviour of CA 19-9 serum levels was stable over time for two patients, but variable for the others. The other tumour markers (CEA, CA 15-3, CA 125) maintained the same serum concentrations found at admission throughout the study.