C reactive protein: an aid to assessment and monitoring of acute pancreatitis

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SUMMARY An evaluation of C reactive protein as an indicator of the progress of acute pancreatitis has been made, and the data have been compared with the information given by the white cell count, erythrocyte sedimentation rate, and temperature and by two antiproteases— α_1 protease inhibitor and α_1 antichymotrypsin. The main value of C reactive protein is to provide a guide to the severity of the inflammation and to increase clinicians' awareness of the patient's enhanced risk of developing pancreatic collections when the C reactive protein concentration remains high (>100 mg/l) at the end of the first week of the illness. In this respect C reactive protein concentrations are superior to white cell count, erythrocyte sedimentation rate, and temperature and the concentrations of antiproteases.

An increased serum C reactive protein concentration is well recognised as a non-specific response to a wide variety of tissue injuries.^{1,2} Sequential measurements of C reactive protein concentration can be helpful in providing a warning of inflammatory complications in disease—for example, postoperative sepsis and thrombosis—and its response to treatment.^{3,4} But in complex inflammatory diseases there is no a priori way of forecasting whether C reactive protein is going to provide useful information in clinical decision making.

Nevertheless, the rapid response of C reactive protein to changes in the intensity of the inflammatory stimulus suggest that it might be valuable in the assessment and monitoring of acute pancreatitis. The clinical problem of particular interest was to test whether C reactive protein measurements could reflect the severity of the attack and thereby provide a warning of the likely development of pancreatic collections (pseudocyst, abscess, and necrosis), which can arise insidiously and be life threatening.^{5,6}

Most pancreatic collections probably arise when part of the duct system is affected in an area of necrosis which forms early in the attack of acute pancreatitis. Although a collection of fluid or a sequestrum may subsequently develop over the course of days or weeks, it is probable that

inflammation around the necrotic focus exists throughout the period of evolution. For this reason we thought it might be possible to screen for "occult" collections using plasma indicators of the inflammatory response.

We have studied the intensity of the C reactive protein response and its rate of change in cases of acute pancreatitis of varying severity. The value of this test was compared with the information provided by the concentration of α_1 antichymotrypsin and α_1 protease inhibitor. The white cell count and erythrocyte sedimentation rate, standard indices of inflammation, were used as reference data.

The design precluded using the new data for clinical decision making; however, the results indicate that C reactive protein can identify severe pancreatitis which may not be obvious at its onset, and lay the basis for prospective trials.

Patients and methods

Fifty-five patients with acute pancreatitis were studied. The diagnosis was based on a plasma amylase value in excess of 1200 IU/l combined with consistent clinical features in 48 patients and on the findings at laparotomy in seven patients.

The patients were treated conventionally, which in 30 patients included a diagnostic peritoneal lavage. They were discharged from hospital when the

Table 1 Fifty-five patients with acute pancreatitis

	Mild*	Severe
No of patients	39	16
Men: Women	19:20	6:10
Age range (yr)	22-85	26-80
(median)	(60)	(65)

*See text for definition of mild and severe.

attack was thought to have settled according to routine clinical criteria. Investigations such as ultrasound examination and computed tomography were carried out only when there was clinical suspicion of a pancreatic collection. After discharge from hospital all patients were followed up for six months. The first 49 patients were consecutive, but in order to provide sufficient numbers for analysis data from a further six patients who had developed a pancreatic collection were added to the series.

Each attack was classified as mild or severe according to clinical criteria. A severe attack was defined as one which resulted in more than 14 days in hospital, one which gave rise to a complication such as a pseudocyst or abscess, or one which was fatal. According to these criteria, there were 39 mild and 16 severe attacks (Table 1). Pancreatic collections developed in 11 patients (eight pseudocysts and three abscesses), six of whom were treated by operation.

Two patients in this study were discharged without recognition of their collection, only to be readmitted six and 10 days later. Pancreatic collections were diagnosed 4 to 29 days after admission to hospital with pancreatitis and confirmed by computed tomography in six patients, ultrasound in four, and at laparotomy in one.

During the initial 13 days in hospital, plasma samples were collected on roughly alternate days and stored at -20°C . C reactive protein, α_1 -protease inhibitor, and antichymotrypsin were measured by radial immunodiffusion,⁸ using antisera and standards obtained from Behringwerke AG, Marburg/Lahn, FRG, and Seward Immunostics,

London, UK. White cell count and erythrocyte sedimentation rate were measured at the time the blood samples were taken using standard methods. The highest sublingual temperature recorded during each 24 h period was noted.

Data were collected to enable the prognostic criteria of Ranson *et al*⁹ and Imrie *et al*¹⁰ to be calculated.

Results

The criteria which are currently used to make an early prediction of the severity of acute pancreatitis failed to recognise several of the severe attacks in this study. This was because of their failure to predict severe pancreatitis (as defined) unless the patient developed evidence of the early shock like component of the illness. Only eight of the 16 severe attacks exhibited this shock like pattern.

Of the severe attacks 36% were correctly recognised by peritoneal lavage, and the multiple criteria

Fig. 1 Plasma concentrations of antichymotrypsin in patients with mild and severe acute pancreatitis. Each point shows the mean value recorded on that day and the hatching indicates the 95% confidence limits of the mean of each group.

Table 2 Prognostic techniques currently used to predict the severity of acute pancreatitis

	Proportion of patients with correct prognostic criteria			
	Initial clinical assessment	Diagnostic peritoneal lavage ⁷	Imrie's criteria ¹⁰	Ranson's criteria ⁹
Severe attacks (n = 16)	7 (44%)	4 (36%) (n = 11)	7 (44%)	10 (62%)
Mild attacks (n = 39)	33 (100%) (n = 33)	18 (100%) (n = 18)	28 (76%) (n = 37)	16 (43%) (n = 37)

Fig. 2 Leucocyte count in patients with mild and severe acute pancreatitis. Hatching indicates the 95% confidence limits.

Fig. 3 Plasma concentration of C reactive protein in patients with mild and severe acute pancreatitis. Hatching indicates 95% confidence limits.

of Ranson *et al*⁹ and Imrie *et al*¹⁰ recognised 62% and 44% respectively (Table 2). Body temperature, erythrocyte sedimentation rate, and α_1 protease inhibitor concentrations failed to discriminate between severe and mild attacks. Although high values were often found in severe attacks, there was overlap of the 95% confidence limits of the means of the mild and severe groups throughout the study.

Better discrimination was provided by white blood cell count, antichymotrypsin and C reactive protein concentrations (Fig. 1, 2, 3). A difference in the white blood cell count between the severe and mild attacks was apparent on the day of admission to hospital, but the initial concentration of C reactive protein and antichymotrypsin could not differentiate the two groups. As the acute phase response became established, higher concentrations of C reactive protein and antichymotrypsin were sustained in severe attacks, reaching their maximum values towards the end of the first week and then falling. C reactive

protein appeared to provide considerably better discrimination between mild and severe pancreatitis than the white blood cell count or antichymotrypsin concentration. The fall of C reactive protein towards normal in severe cases was consistently delayed. Individual C reactive protein data are shown in Fig. 4. The overlap of C reactive protein concentrations between the two groups was relatively small.

In analysing these results severe attacks have been considered as a single group. Fig. 5 shows mean C reactive protein concentrations in severe attacks subdivided into two groups according to the development of a pancreatic collection. The rise and fall of C reactive protein concentration in these two groups was similar, indicating that the concentrations of C reactive protein did not appear to differentiate the attacks which were severe because a collection developed from those that were severe for other reasons.

Fig. 4 Plasma C reactive protein concentration in patients with acute pancreatitis during the second week of the attack. Oblique line indicates suggested levels of discrimination between mild and severe attacks.

Fig. 5 Plasma concentrations of C reactive protein in patients with severe acute pancreatitis. Closed circles are mean values from 11 patients who developed a pancreatic collection; open circles are mean values from five patients who did not.

Discussion

Of the indices of inflammation studied, C reactive protein differentiated mild and severe attacks with greatest precision. Differentiation became clearer after the first week, and the overlap in the data during the initial phase of the disease is consistent with other findings.¹¹ α_1 -protease inhibitor, another acute phase reactant protein, usually rises more slowly and reaches its peak later, the time course of antichymotrypsin being intermediate. Both these types of response were reflected in the results of this study. C reactive protein rose to higher concentrations in patients with severe disease, as has been shown previously,¹⁵ but it was the rate of fall from peak concentrations which provided greater differentiation between grades of severity.

There was no suggestion that C reactive protein was able to separate patients who developed pancreatic collections from those who were classified as severe but who did not develop collections. A high concentration of C reactive protein (> 100 mg/l) at the end of the first week, however, suggests that the

patient will have an illness needing two or more weeks to recover—hence, clinical awareness of the risk of a pancreatic collection in the patient is reinforced. Collections are more common in patients with an overtly severe or prolonged attack of pancreatitis¹² and their presence should be sought in such patients using computed tomography and other appropriate radiological and ultrasonic investigations.

High concentrations of C reactive protein seem to give a warning of severe local inflammation in the patient whose initial illness is relatively mild and whose clinical course is apparently benign. This study supports the view that pancreatic collections which develop in such patients have their origins at an early stage in the attack. The C reactive protein response is similar in magnitude to that in patients with more overtly severe pancreatitis. Our experience, and that of others, suggests that the identification of pancreatic collections in some patients is a problem^{13 14} and the data from this pilot study support the concept that a sensitive marker of continuing inflammation may be of value to select

patients who are at high risk of a complication. We believe that measurement of C reactive protein concentration during the second week of the illness may enable radiological imaging techniques to be used to search fruitfully for pancreatic collections in a high risk group. Its measurement before the patient's discharge from hospital seems a wise precaution. A prospective study to examine this thesis is being carried out.

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