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Serum C-reactive Protein Levels in the Management of Infection in Acute Leukaemia*

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Abstract—*C-reactive protein (CRP) was measured serially in 29 patients with acute leukaemia. Sixty-four febrile episodes (≥38°C) occurred during 37 periods of neutropenia (<0.5 × 10⁹/l). In all of 41 microbiologically or clinically documented infections the maximum CRP level exceeded 30 mg/l, and in 25 it was greater than 100 mg/l. In no case in which the CRP level remained below 30 mg/l for 48 hr after the onset of fever was any clinical or microbiological evidence of infection obtained. The CRP level during documented infection began to fall 24–48 hr after appropriate treatment was begun. A CRP level above 30 mg/l in neutropenic patients was associated with early recurrence of fever if systemic antibiotics were discontinued. Graft-vs-host disease, without infection, did not result in high levels of CRP.*

INTRODUCTION

THE MANAGEMENT of infection in neutropenic patients with acute leukaemia continues to present difficulties, and infection is the major cause of death before remission is achieved [1]. C-reactive protein (CRP) is the classical acute-phase reactant, the serum level of which increases rapidly and extensively in response to tissue damage, inflammation and infection [2]. It has been reported that the serum CRP concentration is significantly higher in leukaemia patients with intercurrent microbial infections than in non-infected patients and that in some cases the CRP level may rise before clinical signs of infection occur [3–5]. More recent studies have suggested that the rise in CRP may be smaller in viral infections than in bacterial or protozoal infections [6] and that failure of the CRP to fall after starting treatment indicated that the infection had not resolved [5], even if there had been an apparent clinical response [6].

In view of the possible value of the measurement of CRP levels in the recognition and management of infection in acute leukaemia, we undertook a prospective study of serum CRP in an attempt to confirm its usefulness in clinical management.

MATERIALS AND METHODS

Twenty-nine patients with acute leukaemia were studied (Table 1); each underwent at least one period of neutropenia (neutrophils <0.5 × 10⁹/l). Patients were nursed in single cubicles with 'reverse-barrier' precautions and received a cooked-food diet. Cotrimoxazole and amphotericin B were given routinely by mouth as antimicrobial prophylaxis [7].

'Surveillance' cultures were obtained from the throat, nose, groin and faeces on admission, and once or twice weekly thereafter or when infection was suspected. A chest radiograph was obtained on admission, and twice weekly if a patient was febrile or if there were symptoms or signs in the chest. Blood (60 ml) and urine were cultured when a patient became febrile and again if the fever did not resolve.

A fever was defined as a body temperature of 38°C or greater which persisted for 2 hr or longer; the end of a febrile episode was defined as when the body temperature had remained at or below 37.0°C for 24 hr. Documented infections were those in which it was possible to identify either the site of infection (a clinically documented

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Table 1 Characteristics of patients studied

	Primary diagnosis	
	Acute myeloid leukaemia	All other patients*
No. of patients	19	10
Male:female	13:16	7:3
Mean age in years (range)	35.3 (13–70)	37.7 (23–57)
No. of periods of neutropenia	27	10
Mean duration of neutropenia† in days (± S.D.)	24.7 ± 10.7	15.8 ± 4.4
Febrile episodes without documented infection	10	13
Clinically documented infections	15	6
Microbiologically documented infections	16	4

*CGL in blast-cell transformation treated by buffy coat autografting and patients whose treatment included bone-marrow allografting.
†Neutrophil count $<0.5 \times 10^9/l$.

infection or CDI) or the causative organism (a microbiologically documented infection or MDI). All other febrile episodes were termed pyrexias of unknown origin (PUO). An organism was considered to be the cause of infection if it was isolated from a clinically defined site of infection or from blood cultures. Organisms usually regarded as normal skin flora that were isolated from blood cultures were taken to be the cause of the infection only if they were present in four or more of the 12 bottles inoculated.

When a patient became febrile systemic broad spectrum antibiotic therapy was begun empirically. If there was no response after 72–96 hr antibiotics were changed if this was indicated by the results of cultures, or daily granulocyte transfusions were given. If there was still no response after a further three to four days then systemic treatment with amphotericin B and 5-fluorocytosine was begun, even without laboratory confirmation of a fungal infection. In these circumstances serum was examined for the presence of *Candida albicans* antigen by gas–liquid chromatography [8]. If an infection with Herpes simplex or Herpes varicella-zoster virus was suspected then treatment with acyclovir was begun [9]. Antimicrobial treatment was usually stopped 5 days after the end of a febrile episode.

Nineteen patients with acute myeloid leukaemia (AML) received cytotoxic chemotherapy and seven patients with chronic granulocytic leukaemia (CGL) in blast-cell transformation received high-dose chemotherapy followed by an autograft of cryopreserved autologous chronic phase buffy coat cells [10]. Three patients received bone marrow allografts, of whom one had acute lymphoblastic leukaemia and two had CGL in chronic phase. All three patients who received allografts developed acute graft-vs-host disease (GVHD) despite prophylaxis with cyclosporin A [11].

Venous blood was taken for CRP estimation approximately twice weekly from all patients. Serum was stored at −20°C and assayed in batches at the end of the study. The electroimmunoassay which was used was calibrated with standards of isolated pure CRP, and had a coefficient of variation of 10% [12]. Up to five CRP estimations were carried out in each patient in each of the following circumstances: on admission, during and after chemotherapy or radiotherapy, when apyrexial, when the body temperature was 37.1 to 37.9°C, when febrile, and 1–3 and 4–7 days after the end of a febrile episode. The significance of differences in maximum CRP levels in different circumstances was sought by Wilcoxon's rank sum test.

RESULTS

CRP levels in uninfected patients

Maximum CRP levels in apyrexial, uninfected patients were usually below 40 mg/l before, during or after chemotherapy (Fig. 1). Four patients had higher maximum levels: in one this followed insertion of a central venous line, in two the CRP was falling after a documented infection, and in one the finding was unexplained.

Fifteen clinically uninfected patients whose body temperature was 37.1–37.9°C had maximum CRP levels of 5–130 mg/l (median 38 mg/l), which was significantly higher than values in apyrexial patients ($P<0.001$). Eleven of these mildly pyrexial patients became truly febrile (≥38°C) 1–5 days after the CRP estimation, but the CRP level did not predict who in this group would become febrile, nor did the interval before fever developed.

CRP levels during episodes of fever

The maximum CRP levels reached during a febrile episode were significantly higher than when patients were afebrile, and the maximum levels during MDI (median 163 mg/l) were significantly higher than those during CDI

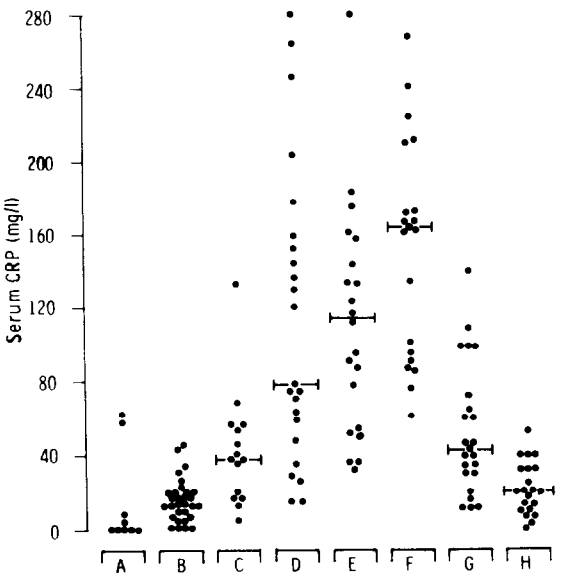

Fig. 1. Maximum levels of serum CRP recorded in individual patients. Horizontal bars are medians. A = on admission, temperature 37.0°C or less; B = during or after chemotherapy, temperature 37°C or less; C = body temperature 37.1–37.9°C; D = temperature ≥38°C, no infection documented (PUO); E = clinically documented infection; F = microbiologically documented infection; G = after infection, afebrile for 1–3 days; H = after infection, afebrile for 4–5 days.

(median 115 mg/l; $P<0.001$) and during PUO (median 78 mg/l; $P<0.001$). In CDI the CRP levels 24 hr after the onset of fever (32–112 mg/l, median 63 mg/l) remained lower than the maximum levels (32–280 mg/l, median 115 mg/l; $P<0.001$), but in the MDI the levels at 24 hr (55–235 mg/l, median 108 mg/l) were already near to the maximum levels (62–270 mg/l, median 166 mg/l) (Fig. 1).

In all microbiologically documented infections the maximum CRP level was above 60 mg/l. In a number of clinically documented infections the maximum levels were between 30 and 60 mg/l (Table 2), although in most cases the maximum value was above 60 mg/l (Table 3). Febrile episodes in which infection was not documented were sometimes accompanied by modest elevations of CRP level, the highest being 63 mg/l, but the CRP remained below 30 mg/l during two episodes of PUO, a transfusion reaction and an allergic response to an antibiotic (Table 2).

There was no difference in the maximum levels of CRP in relation to the infecting organism if this was a bacterium or a fungus (Table 4). Two viral infections were documented; in one a typical 'cold sore' resolved without treatment and the maximum CRP level was 36 mg/l. In the other a nasal cellulitis was accompanied by a rise of Herpes simplex antibody titre from 1:32 to 1:1024, and the maximum CRP level was 178 mg/l. The infection resolved with bone marrow recovery.

CRP levels after treatment of infection

In most patients CRP levels started to fall within 48 hr of the start of the treatment that proved successful (Fig. 2). The CRP levels in documented infections that did not respond to the treatment being given were usually still rising 48 hr after the onset of fever.

After patients had been afebrile for 1–3 days the median CRP level was 45 mg/l, and by 4–5 days it was 20 mg/l (Fig. 1). In five out of nine patients whose neutrophils remained below 0.2×10^9/l and whose CRP level remained greater than 30 mg/l more than 4 days after resolution of fever

Table 2. Possible or documented causes of febrile episodes associated with a maximum CRP level below 65 mg/ml

Maximum CRP level (mg/l)	CDI or MDI	Probable cause of fever
17	—	transfusion reaction
18	—	PUO
26	—	PUO
28	—	allergy to mezlocillin
32	CDI	swelling and tenderness at I-V line site
35	—	pulmonary embolism
36	CDI	'cold sore' on lip
37	CDI	redness and tenderness at I-V line site
48	—	following insertion of intravenous catheter
57	CDI	redness and tenderness at I-V line site
52	CDI	sore throat and cough, normal chest radiograph
54	CDI	redness and tenderness at I-V line site
54	—	acute graft-vs-host discase
59	—	pneumothorax and insertion of chest drain
62	MDI	*Staph epidermidis* bacteraemia: organism grown from all of 12 culture bottles
63	—	transfusion reaction

CDI = clinically documented infection; MDI = microbiologically documented infection.

Table 3. Details of clinically documented infections in which the maximum CRP level was greater than 61 mg/l

Maximum CRP level (mg/l)	Clinical details of infection
78	cellulitis of the nose
87	cellulitis of the nose and consolidation on CXR
91	oropharyngitis ('mucositis')
94	acute tracheitis
112	thrombophlebitis proximal to I-V line site
117	redness and tenderness at I-V line site
123	abscess overlying left mandible
132	tenderness along I-V line skin tunnel
133	consolidation on CXR; discharging sinus in left axilla
144	consolidation on CXR
158	*Candida* oesophagitis (barium swallow)
161	cellulitis of the nose
176	consolidation on CXR
183	acute appendicitis (appendectomy)
406	consolidation and pleural effusion on CXR

CXR = chest radiograph.

Table 4. Maximum C-reactive protein levels recorded during documented systemic fungal infections

Site	Organism	How diagnosed*	Maximum† CRP (mg/l)
Blood	*Candida albicans*	GLC‡	167
Blood	*Candida albicans*	GLC‡	164
Oesophagus	*Candida albicans*	barium swallow	158
Paranasal sinuses	*Aspergillus fumigatus*	nasal washings	87
Lungs	*Aspergillus fumigatus*	sputum culture chest radiograph	101
Lungs	*Aspergillus fumigatus*	autopsy	144
Lungs	*Aspergillus fumigatus*	autopsy	224

*In addition, all patients in whom the diagnosis was made before death had failed to respond to antibacterial therapy but had responded to antifungal therapy.

†In 14 microbiologically documented bacterial infections the median maximum CRP = 165 mg/l, range 52–242 mg/l.

‡GLC = gas-liquid chromatography of serum for *Candida albicans* mannan antigen [8].

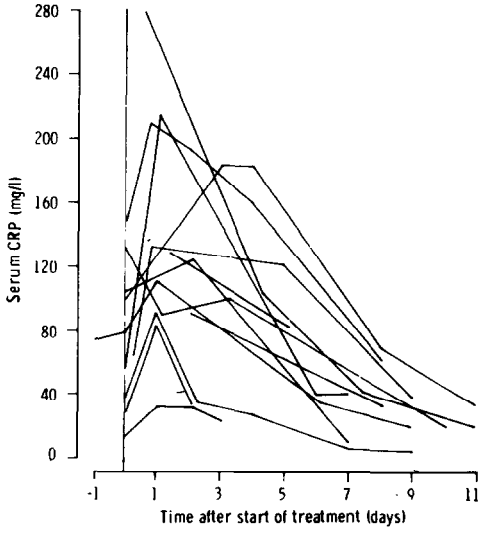

Fig. 2. Serial C-reactive protein levels in patients with clinically or microbiologically documented infections which were responding to therapy.

there was early recurrence of infection when antibiotics were stopped (Fig. 3). This did not happen in neutropenic patients whose CRP was 20 mg/l or less, nor in patients whose neutrophil count had risen above 0.2×10^9/l.

CRP levels during acute graft-vs-host disease

The occurrence of acute GVDH did not greatly change the CRP level. Of the three allografted patients the first (Fig. 4) developed grade II GVHD [11] but had a steadily falling CRP level and the second developed grade IV GVHD affecting mainly the gastrointestinal tract, with a small increase in CRP from 20 to 54 mg/l during the first 24 hr of GVHD. The third patient developed grade I GVHD but his maximum CRP level was 144 mg/l; he developed pneumonia, and at autopsy *Aspergillus fumigatus* was found in the lungs.

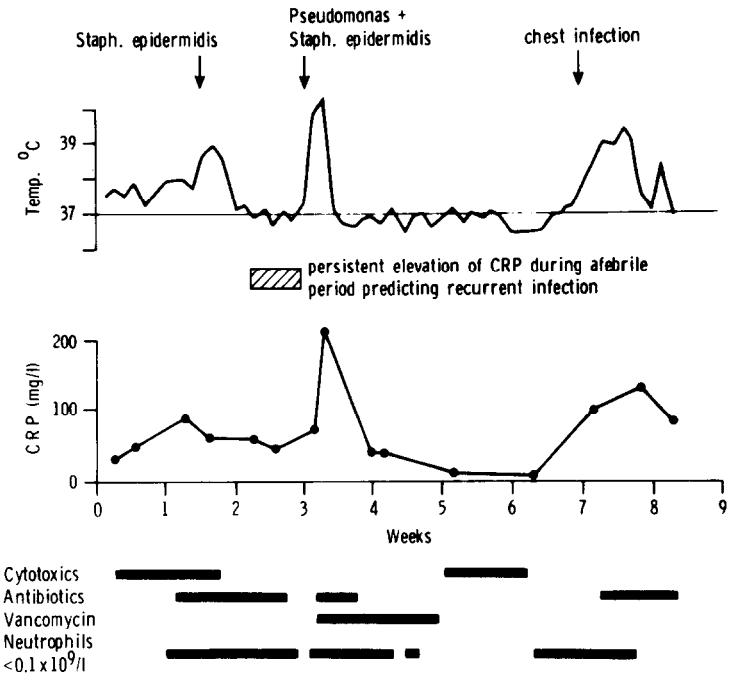

Fig. 3. Clinical course of a 49-yr-old male with acute myeloid leukaemia. A Staph. epidermis *infection on day 11 responded to antibiotics but the CRP level did not fall between weeks 2 and 3. When antibiotics were stopped the same infection recurred and both the temperature and the CRP level returned to normal by week 5, after a further course of antibiotics.*

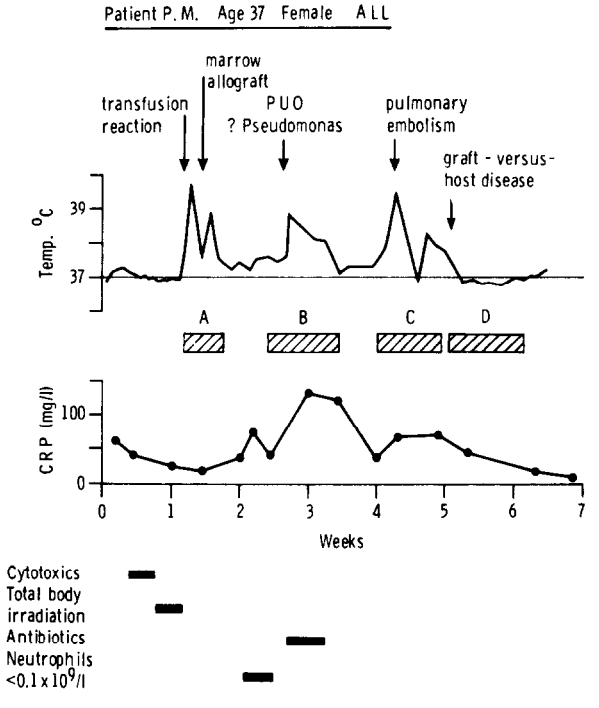

Fig. 4. Clinical course of a 37-yr-old female undergoing bone marrow allografting. Episodes of fever followed a transfusion reaction and the bone marrow allograft (A) but the CRP did not rise. An oropharyngeal infection with Pseudomonas *spp. (B) was accompanied by a maximum CRP level of over* 100 mg/l. *Only a small rise in CRP was associated with a fever due to pulmonary embolism (C). The CRP then continued to fall steadily despite the development of GVHD (D).*

DISCUSSION

Microbial infection is known to be a potent stimulus to CRP production and high serum levels of CRP have been reported, particularly in association with serious bacterial infections [2]. This is the case both in patients with no other underlying disease and in those predisposed to inter-current infection by a non-infectious

primary condition such as systemic lupus erythematosus [13–15] or acute leukaemia [3–6].

In this study a serum CRP level above 100 mg/l was highly suggestive of infection, as has been reported by others [3, 4], but in 16 out of 41 documented infections the maximum CRP level remained below 100 mg/l. This is consistent with another recent report that suggests that 60 mg/l may be a more appropriate threshold for the diagnosis of infection [6]. To be certain of detecting the maximum CRP level the assay should be repeated 24 and 48 hr after the onset of a febrile episode, and failure of the CRP concentration to exceed 30 mg/l during this period in this study indicated that infection was not the cause of the fever. Chemotherapy, radiotherapy and transfusion reactions did not cause elevation of the CRP to levels greater than 30 mg/l, but a small number of local infections raised the CRP level to between 30 and 60 mg/l.

Some have suggested that an elevated level of CRP is a useful early indication of the presence of infection [3, 6], but others have observed that a rising temperature may precede, accompany or follow the rise in CRP [4, 5]. In only nine out of 41 documented infections in this study did the CRP level rise to between 35 and 80 mg/l 1–4 days before the temperature rose to 38°C; in eight of these infections the temperature was already above 37.1°C when the CRP rise was detected, and in the ninth the site of infection was apparent clinically.

It did not, therefore, seem worthwhile to carry out twice weekly CRP estimations in an attempt to detect rising levels in afebrile patients who did not have clinical signs of infection, although it remains possible that more frequent CRP estimations would have detected an increase in levels before the patient became febrile. Five documented infections were preceded by a period when the patient's temperature remained between 37.1 and 37.9°C for several days. In all these episodes the CRP level rose steadily, and daily CRP estimation may therefore be useful in the diagnosis of infection in these circumstances.

Measurement of the CRP levels seems to provide additional information on the efficacy of antimicrobial therapy, as reported by others [6]. In microbiologically documented infections the maximum CRP occurred 24–48 hr after the onset of fever or after the start of the correct therapy, and a falling CRP was frequently an earlier indication of response that the return of the temperature to normal. In contrast, in clinically documented infections the maximum CRP level was recorded later and the falls in CRP and in body temperature were more likely to be concurrent.

Antibiotics were usually discontinued 5 days after the resolution of fever. If, at this time, the CRP level remained greater than 30 mg/l and the patient remained neutropenic, then there was an increased chance of infection recurring if antibiotics were stopped. A recent study suggested that if the CRP level fell below 100 mg/l with a rate of fall equivalent to the normal half-life of 3 days, then it was generally safe to stop antibiotics, with continued monitoring of CRP level if the patient remained neutropenic [6]. Our results appear to suggest that rather greater caution than this should be applied to the discontinuation of antibiotic therapy, but there were few true recurrent infections: recurrent fever in the other cases could have been due to a second, new infection.

In conclusion a serum CRP concentration of less than 30 mg/l throughout the 48 hr after the onset of fever was useful in excluding infection as the cause. A persistently elevated serum CRP in a neutropenic patient receiving antibiotic treatment suggested that recurrence of infection was possible if antibiotics were stopped.

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