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C-reactive Protein for Detection and Follow-up of Bacterial and Fungal Infections in Severely Neutropenic Patients with Acute Leukaemia

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Abstract—*To evaluate the aetiology of febrile episodes and to rationalize our politics with antibiotics, C-reactive protein (CRP) was determined immunoturbidimetrically in 20 consecutive neutropenic adults with acute leukemia. They had 35 febrile episodes, 89% of which were infectious. Twenty per cent of infections were fungal. A similar CRP response was seen both in bacterial and in fungal infections. In 84% of infections the peak value for CRP rose >100 mg/l. Thirty-five apyrexial patients with acute leukaemic and 20 healthy adults served as controls. Their CRP was <10 mg/l in 87%. CRP proved most valuable in the follow-up of infections, in the detection of infectious complications and in the detection of possible invasive fungal infections. Although relapse itself did not effect on CRP levels, extramedullary bone infiltration in two of our patients resulted in increased CRP production, which normalized with cytostatics only.*

INTRODUCTION

A LEUKAEMIC patient with agranulocytosis and fever represents both a diagnostic and a therapeutic problem. Fever can be due to infection, leukaemia, blood products or cytostatics. Fever over 38°C for more than 2 hr has been empirically regarded as if there were septicaemia. Currently two synergistic bactericidal [1] antibiotics are given based on high mortality experienced with pseudomonas and klebsiella septicaemias in the past [2-4]. Further, it is known that approximately 70-80% of early deaths in leukaemia are due to infection in adults who failed to achieve remission after initial induction therapy [5]. On the other hand, it is supposed that 20-40% of patients with acute leukaemia treated empirically with antibiotics do not have any infection [6].

Fever is generally associated with increased hepatic synthesis of acute phase-reactant proteins, which include fibrinogen, haptoglobin, ceruloplasmin, transferrin, plasminogen and C-reactive protein. Electrophoretic strips of serum proteins reflect this increase in febrile patients. The increase, for example, in erythrocyte sedimentation rate seen in both infectious and non-infectious febrile episodes is due to fibrinogen. The rise and fall of sedimentation rate, however, are slower than those of CRP in bacterial infections [7]. All of the acute phase-reactant proteins, including C-reactive protein, suffer from a lack of sensitivity in discriminating between infectious and non-infectious causes of fever [8]. The profits of CRP in the differential diagnostics of acute bacterial and non-bacterial meningitis were already observed in the fifties [9, 10]. Along with better quantitative determination methods [11, 12] CRP has lately been rediscovered.

We decided to study the characteristics of CRP in pyrexial occurrences of neutropenic patients with acute leukaemia. Special attention was paid to the following questions: can CRP estimation differentiate bacterial infections from fungal infections and, on the other hand, can pyrexia caused by these microbes be distinguished from fever of non-infectious origin?

MATERIALS AND METHODS

Twenty consecutive patients, ten women and ten men aged 17-78 (mean 49) yr, with acute leukaemia were treated with multiple cytostatics as inpatients either because of remission induction

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or relapse of the disease at Oulu University Hospital between May 1982 and March 1983. Some of them were febrile on admission, while pyrexia, i.e. >38°C for more than 2 hr, developed in others in hospital. The absolute granulocyte count was $<0.5 \times 10^9$ cells/l. A combination antibiotic treatment was begun in all except two febrile episodes. Neither prophylactic antibiotics nor granulocyte transfusions were used.

Blood cultures, bacterial and fungal swabs from throat, sputum, urine, rectum and possible local infectious focuses were taken immediately before and during antibiotic therapy. Surveillance cultures were not used. Blood and differential counts, thrombocytes, liver function tests, serum creatinine and blood electrolytes were investigated approximately thrice a week.

Venous blood for CRP determination was taken in admission and serially on several days per week during the follow-up of pyrexia. Serum CRP concentrations were determined by an immunoturbidimetric assay using specific antiserum against CRP (Orion Diagnostica, Finland) [12]. A limit of <10 mg/l was regarded as normal according to literature [13, 14].

Patients with fever were divided into four groups: I, patients with positive blood cultures; II, patients with positive microbial cultures, blood excluded; III, patients with negative cultures but with positive focal signs of an infection and/or fever responding to antibiotics; and IV, patients with negative cultures without signs of infection and no response to antibiotics.

There were 55 patients in three control groups. The first consisted of the study patients (groups I-IV), when they were afebrile either in remission or in relapse. The second group was made up of another 20 apyrexial adult patients with acute leukaemia diagnosed after the afore-mentioned group. Twenty healthy adults formed the third group.

RESULTS

Altogether 35 febrile episodes were found in 20 patients. Eight (23%) of these were due to septicaemia (group I). In 15 (43%) patients local bacterial or fungal cultures were positive (group II). In two patients both bacterial and fungal aetiology were concurrently found. Clinical evidence of infection and/or fever responding to antibiotics but with negative culture was observed in eight (23%) patients (Group III). In only four (11%) cases with fever were no signs of infection nor response to antibiotics found (group IV). Distribution of pyrexial occurrences in different groups of patients is detailed in Fig. 1.

Twelve infectious focuses were located in the respiratory tract. While there were eight documented septicaemias, the site of infection was in eight cases in the gastrointestinal tract and in eight additional cases in the skin, and only in two cases in the urinary tract. Thrombophlebitis was found in two cases. Species of bacteria and fungi isolated are enumerated in Table 1.

In group I the mean value for the highest individual CRP was 195 mg/l (range 112-354), in group II 219 mg/l (range 36-440), in group III 147 mg/l (range 69-210) and in group IV 86 mg/l (range 10-204). In Fig. 2 we can see the highest CRP values of patients in different groups. The sensitivity, specificity, accuracy and positive and negative predictive values of CRP are 82, 75, 80, 96 and 33% respectively.

The corresponding mean value was <10 mg/l in 13/14 control patients (one patient 14 mg/l) in remission and in 15/21 control patients (six patients 11-26 mg/l) in relapse. CRP concentration was <10 mg/l in 28/35 (80%) and <27 mg/l in all control patients with acute leukaemia. In 20 healthy adults the mean value was <10 mg/l.

In fungal infections the mean CRP value of 219 mg/l (range 36-426) rose to the same level as in bacterial infections, 204 mg/l (range 46-440). We had three patients with fungal infections and

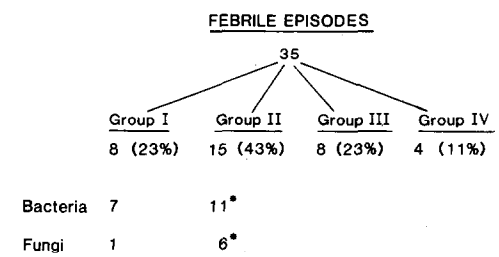

Fig. 1. Distribution of 35 febrile episodes in different febrile groups of patients with acute leukaemia. Group I = septicaemia; group II = patients with positive microbiological cultures, blood excluded; group III = patients with negative cultures but with positive focal signs of an infection and/or fever responding to antibiotics; group IV = patients with negative cultures without signs of infection and no response to antibiotics. × = two patients with bacterial and fungal infection concurrently.

Table 1. Species of bacteria and fungi isolated

Organism	No. of episodes
Escherichia coli	5
Staphylococcus aureus	4
Streptococcus β-hemolyticus	4
Enterobacter cloacae	3
Klebsiella pneumoniae	2
Proteus mirabilis	1
Clostridium difficile	1
Diplococcus pneumoniae	1
Candida albicans	7
Aspergillus fumigatus	2

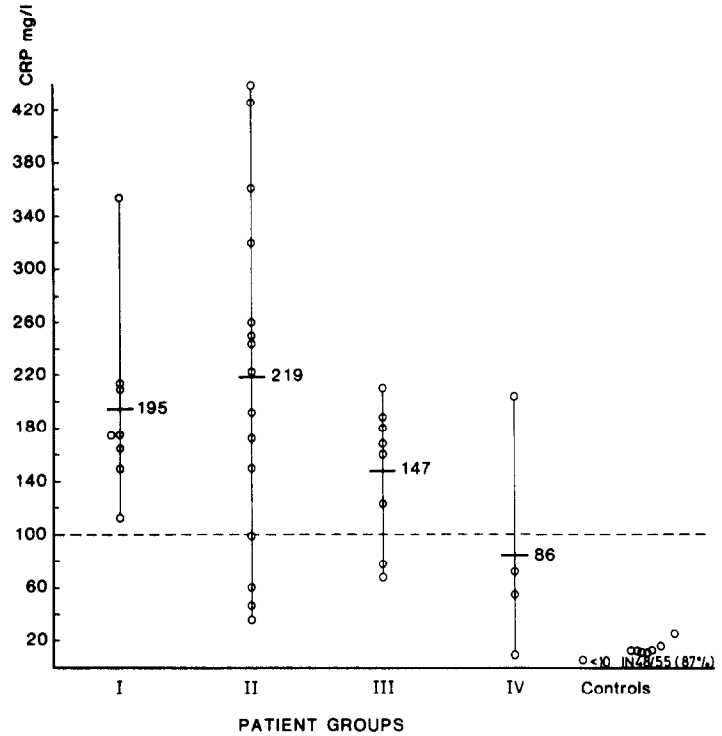

Fig. 2. Highest individual and mean concentrations of CRP in different febrile groups (I–IV) of leukaemic febrile patients and afebrile controls.

high CRP values of 354, 175 and 426 mg/l. The first two were caused by candida septicaemia and oesophagitis and the third by candida- and aspergillus-induced stomatitis. All these resolved with intravenous fungicides.

In 84% of our pyrexial episodes the peak value of CRP rose above 100 mg/l in microbiologically documented or clinical infections (groups I–III). Three patients exist as an exception to this finding. In group II there was a lady with candidiasis in the mouth and paronychium in the finger. Her highest CRP was 60 mg/l and she responded to intravenous fungicides. During another febrile episode of 40°C for 3 days caused by candidiasis in the mouth and reactive to intravenous fungicides, her CRP response was 36 mg/l only. In another lady with a pyrexia of 39°C for 2 days and *Staphylococcus aureus* in the throat swab, the CRP concentration rose merely to 46 mg/l, though her fever responded to intravenous antibiotics. A third lady belonging to group III had two culture-negative infectious episodes; the first was caused by furuncle in her face with a CRP level of 78 mg/l.

Curiously, in group IV there were two patients with peak CRP values of 204 and 76 mg/l, whose CRP and fever fell during cytostatic treatment without any antibiotics. The former had a diagnosis of acute lymphatic leukaemia with bone pain. His bone pain, fever and elevated CRP disappeared during cytostatics.

In nine pyrexial episodes it was possible to make CRP measurements daily. The peak levels were attained after a mean of 72 (24–144) hr from the rise of fever. At defervescence nobody had normal CRP levels. Antibiotics were stopped after 3 days and afebrile patients with reasonable blood counts were allowed to return home. However, we were able to follow the fall of CRP along with fever serially for several days in seven patients, who had no complications after pyrexia. After an average of 4 (range 3–6) days the mean value for CRP in them was still 48 (range 24–75) mg/l. Figure 3 depictures the slowness in the fall of CRP concentrations.

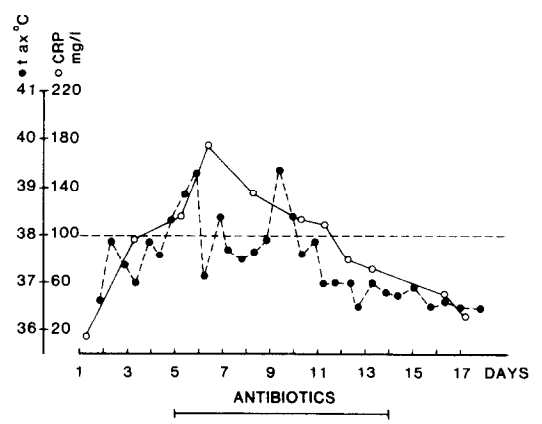

Fig. 3. Similar trends of CRP and fever curves provide useful information regarding clinical response.

In a number of patients CRP values did not seem to normalize, but were high or rising during antibiotic therapy. The reasons for elevation could be divided into three categories (Table 2). For the first, in four patients with ongoing septicaemia and fever the aim of changing antibiotics was strengthened by high CRP values, which did not begin to fall before the change of antibiotics. On the other hand, even though there were sporadic febrile spikes in connection with a continuing fall of CRP values, we needed not to hesitate in changing antimicrobial therapy, but went on with the former. Figure 4 demonstrates how CRP values provide additional data but are not the final arbiter in making a decision of changing antibiotics. For the second, in three patients the aetiology for increased CRP production was abscesses developed as a complication of infections. Two of these were incised without the change of antibiotics (Fig. 5). CRP concentration began to fall rapidly in both of them. In a man with multiple liver abscesses we continued with antibiotics solely and observed a fall in CRP level and defervescence. For the third there were six patients with increasing CRP levels. They all died of refractory acute leukaemia

Table 2. Usefulness of serial CRP determinations in the follow-up of fever in granulocytopenic patients with acute leukaemia

Category	No. of patients	Consequence
Ongoing septicaemia and fever	4	antibiotics were changed
Indolent fever and persistently elevated CRP	3	drainage of abscess in 2
Rising CRP levels on antibiotics	6	died of refractory leukaemia

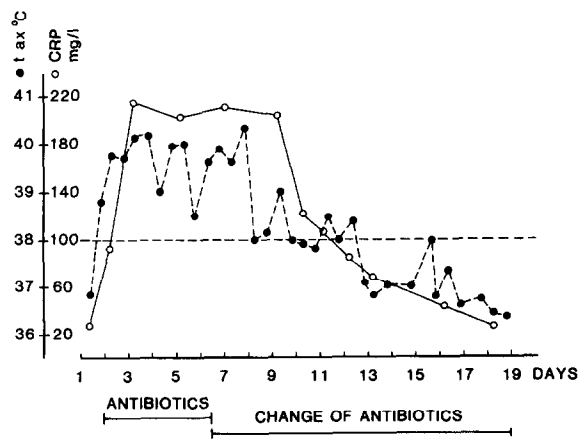

Fig. 4. In addition to fever CRP gives further information regarding the change of antibiotics.

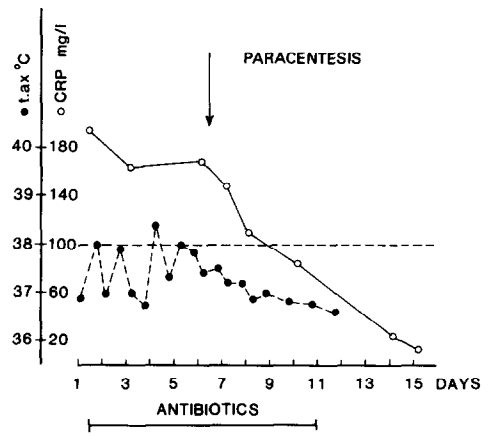

Fig. 5. Low-grade fever and a high CRP level normalize after paracentesis in a leukaemic patient with otitis media.

in spite of appropriate antibiotics sensitive to the underlying micro-organism. All the other infectious patients survived.

DISCUSSION

In remission induction of acute leukaemia with multiple cytostatics practically every patient becomes neutropenic and gets fever. It is recognized that approximately 60% of all fevers in acute leukaemia are due to infections requiring antibiotics [7, 15]. We found that 31/35 (89%) febrile episodes were infectious in origin. Why does this surpass the data in the literature? Blood products and cytostatic agents did not cause fever. The rather high percentage (71%) of culture-positive samples might have been influenced by thorough physical search for signs of infectious focuses daily during the doctor's round. Secondly culture specimens were taken during fever on several consecutive days. X-ray pictures taken repeatedly revealed additional focuses of infection, because pneumonic infiltrations did not appear until late in agranulocytosis. The fact that we did not use prophylactic antibiotics may have contributed to growth positivity, too. Because the majority of febrile events was infectious, our non-fectious group became too small to discriminate these groups based on CRP.

We had a few patients with high fever but with a normal CRP value at the beginning and negative cultures. Their fever was regarded as abacterial at first, but in the follow-up most of them turned out to be infectious. With our present knowledge and experience, even with a low CRP level at the onset of fever, one dare not delay starting antibiotics in neutropenic leukaemic patients. Observation of a patient's physical status, temperature and CRP production discloses in a few days whether to continue or to stop with the antibiotics.

Although CRP levels of >20 mg/l have been considered as induced by bacterial infection [7,

16], a CRP concentration of >100 mg/l has been regarded as a diagnostic level of bacterial infection in acute leukaemia [17-19]. Our results with a CRP of >100 mg/l in 84% of infections support this view. On the other hand, in local, non-invasive and clinically mild bacterial and fungal infections, as well as in non-infectious situations, CRP values <100 mg/l were encountered. We therefore want to emphasize that in cases of slightly or moderately increased concentrations CRP assays should be repeated on consecutive days. This reveals whether the level is rising or falling and enables the clinician to draw proper conclusions.

The rate of rise and fall of CRP concentration has practical implications. The achievement of peak values after 72 hours was longer than in the literature [20]. Therefore slightly elevated CRP values within the first 48 hours had little role in the evaluation of febrile episodes. In some of our patients CRP began to fall before fever during an infection. In them there was no need to change antibiotics as previously would have been done in the morning of the fourth day [6, 21] with continuous fever, but to wait for defervescence. However, in our patients CRP never normalized before fever, still taking a mean of 4 days to fall to 48 mg/l after fever. This is in concord with earlier observations which recorded half-life of approximately 3 days in the fall [19]. It would be interesting to investigate whether a decreased amount of leukocyte endogenous mediator [22] could result in the delay of reaching peak levels or normalization in agranulocytosis. In practice antibiotic susceptibility and rapidity of rise in granulocyte counts influence the recovery of an infection and thus on the normalization of CRP. In patients whose CRP was rising or remained high regardless of temperature, the determination gave a valuable hint for the need to search for a complication of an infection, such as an abscess to be incised, fungi to be treated with fungicides or a new or the same bacteria to be treated with a change of antibiotics.

We suspected that high CRP values in acute leukaemia are not all due to infection, but could originate from the extramedullary activity of the disease. In a man with fever, bone pain and high CRP at diagnosis all these parameters were observed to normalize with cytostatics only. At the onset of relapse 1 yr later he claimed of leg pain and fever and his CRP rose to 212 mg/l. This time a bone scan was made and increased uptake of ^{99}Tc was found in his other tibia. Repeatedly his symptoms disappeared with cytostatics and CRP fell down. In the same group IV there was another patient, whose CRP and fever normalized solely with cytostatics. A third patient with refractory acute leukaemia had intense pain in her bones and at the same time high CRP values without any infection were observed. Also, she had increased uptake of ^{99}Tc in bone scan. On these grounds we believe that, for example, tissue necrosis in bone could explain increased CRP in these patients.

The significance of CRP in connection with fungal infections has not been reported earlier in clinical praxis to our knowledge. We observed that CRP can elevate during fungal infections to as high a level as in bacterial ones, the concentration range being wide. Though one cannot differentiate fungal and bacterial infections with CRP measurements, highly increased CRP levels in connection with local signs of fungal infection such as candidiasis in the mouth, but with negative bacteriological cultures, support the usage of systemic intravenous fungicides in acute leukaemic patients, especially if correlative fungal serology—not used in our study—is available.

In our study only 11% of patients had a non-infectious rise in temperature (group IV). Therefore we cannot conclude about the differential diagnostic capacity of CRP between infectious and non-infectious groups. Also, CRP does not seem to differentiate bacterial infections from fungal ones. Instead, we could summarize the practical uses of serial CRP measurements in febrile patients with acute leukaemia as follows: (1) response to antibiotics and need for change of antibiotics; (2) detection of a complicating abscess; and (3) detection of possible invasive fungal infection.

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