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Characteristics of Febrile Patients with Normal White Blood Cell Counts and High C-reactive Protein Levels in an Emergency Department

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Fever is one of the more common chief complaints of patients who visit emergency departments (ED). Many febrile patients have markedly elevated C-reactive protein (CRP) levels and normal white blood cell (WBC) counts. Most of these patients have bacterial infection and no previous underlying disease of impaired WBC functioning. We reviewed patients who visited our ED between November 2003 and July 2004. The WBC count and CRP level of patients over 18 years of age who visited the ED because of or with fever were recorded. Patients who had normal WBC count (4,000–10,000/μL) and high CRP level (>100 mg/L) were included. The data, including gender, age and length of hospital stay, were reviewed. Underlying diseases, diagnosis of the febrile disease and final condition were recorded according to the chart. Within the study period, 54,078 patients visited our ED. Of 5,628 febrile adults, 214 (3.8%) had elevated CRP level and normal WBC count. The major cause of febrility was infection (82.24%). Most of these patients were admitted (92.99%). There were 32 patients with malignant neoplasm, nine with liver cirrhosis, 66 with diabetes mellitus and 11 with uremia. There were no significant differences in age and gender between patients with and those without neoplasm. However, a higher inhospital mortality rate and other causes of febrility were noted in patients with neoplasm. It was not rare in febrile patients who visited the ED to have a high CRP level but normal WBC count. These patients did not necessarily have an underlying malignant neoplasm or hematologic illness. Factors other than malignant neoplasm or hematologic illness may be associated with the WBC response, and CRP may be a better indicator of infection under such conditions.

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Fever is one of the more common chief complaints of patients who visit the emergency department (ED). As the cause of fever may be the common cold or fatal sepsis, it is a great challenge to emergency room physicians to make the correct diagnosis. In addition to the patient's symptoms and signs, many tests are used to

examine febrile patients. Sometimes, they have significant symptoms and signs, and the diagnosis can be made by suitable examination. On other occasions, however, patients do not have obvious symptoms and signs, although physicians need an indicator to avoid a failure to diagnose severe disease.

In febrile patients, white blood cell (WBC) count is a common examination. In addition, procalcitonin, C-reactive protein (CRP) and interleukin-6 levels will be elevated in cases of severe infection [1–7]. Some studies suggest that these examinations could help to differentiate between less threatening fever and septic patients. CRP is a common available examination item in Taiwan's hospitals. In practice, however, WBC count and CRP are not always elevated at the same time [8–10]. Some obviously septic patients do not have elevated WBC count but their CRP is markedly elevated. Such a condition can also be found in some patients with hematologic disease and neoplasm [11,12].

We found that many patients without hematologic disease and neoplasm have normal WBC count and markedly elevated CRP. These patients usually have obvious infection or inflammation. Therefore, we analyzed the characteristics of these patients, and then compared them with those of patients with malignancy.

Methods

We retrospectively reviewed patients who visited the ED of Kaohsiung Medical University Hospital between November 2003 and July 2004 because of fever or high body temperature (tympanic temperature >38.3°C). Because the period of study was within 1 year of the severe acute respiratory syndrome (SARS) outbreak, all febrile patients received blood examinations including WBC count and CRP level. Adult patients (>18 years) who had normal WBC counts (4,000–10,000/μL) and high CRP levels (>100 mg/L) were included for further analysis. Patient characteristics including gender and age were recorded. Underlying diseases including diabetes mellitus, end-stage renal disease, liver cirrhosis and malignant neoplasm were recorded by history taking and examination in hospital. The diagnosis and final condition on discharge from hospital were determined according to the chart records filled in by the doctor in charge of the ward or ED. Student's *t* test was used to compare age and days of hospitalization between patients with and those without underlying malignant neoplasm and/or hematologic disease. χ^2 and Fisher's exact tests were used to examine the correlation between gender, cause of fever, hospitalization, type of infection and mortality with underlying malignant neoplasm and/or hematologic disease.

Results

Within the study period, 54,078 patients visited our ED. Of 5,628 febrile adults, 214 (3.8%) had an elevated CRP level and normal WBC count. The age of these patients ranged from 20 to 97 years. The characteristics of these patients are shown in Table 1. There were 32 patients with malignant neoplasm, nine with liver cirrhosis, 66 with diabetes mellitus and 11 with uremia. The major cause of febrility was infection (82.24%). Pneumonia and urinary tract infection were the leading diagnoses of infection (Table 2). Most of the patients

Table 1. Characteristics of patients with high C-reactive protein levels and normal white blood cell counts*

Age (yr)	61.9 ± 18.2
Gender	
Female	96 (44.86)
Male	118 (55.14)
Underlying disease	
Malignancy	32 (14.95)
Liver cirrhosis	9 (4.21)
Diabetes mellitus	66 (30.84)
Uremia	11 (5.14)

*Data presented as mean ± standard deviation or *n* (%).

Table 2. Causes of febrility and patient outcome*

Infection	176 (82.24)
Infection focus	
Urinary tract	44 (25)
Lung & bronchus	70 (39.77)
Gastrointestinal tract	10 (5.68)
Soft tissue	9 (5.11)
Liver	12 (6.82)
Multisite	11 (6.25)
Others	20 (11.36)
Number of hospitalizations	199 (92.99)
Days of hospitalization	14.06 ± 12.91
Mortality	9 (4.52)

*Data presented as *n* (%) or mean ± standard deviation.

Table 3. Comparison of characteristics and outcomes between patients with and those without malignancy*

	With malignancy ($n=32$)	Without malignancy ($n=182$)	p
Age (yr)	61.9 ± 19.3	61.8 ± 10.6	0.969†
Male gender	17 (53.1)	101 (55.5)	0.804‡
Infection	19 (59.4)	157 (86.3)	< 0.005‡
Infection focus			< 0.005‡
Urinary tract	3 (15.8)	41 (26.1)	
Lung & bronchus	10 (52.6)	60 (38.2)	
Multisite	5 (26.3)	6 (3.8)	
Others	1 (5.3)	50 (31.8)	
Hospitalization	30 (93.8)	169 (92.9)	0.855‡
Days of hospitalization	17.4 ± 12.2	13.5 ± 13.4	0.131†
Mortality	4 (13.3)	5 (3)	0.031‡

*Data presented as mean ± standard deviation or n (%); †t test; ‡χ^2 test or Fisher's exact test.

were admitted (92.99%). There were no significant differences in age and gender between patients with and those without neoplasm (Table 3). However, a higher inhospital mortality rate and other causes of febrility were noted in patients with neoplasm.

Discussion

Febrile patients who have normal WBC counts and elevated CRP levels usually have infection (82.24%). CRP is an acute-phase reactant produced by the liver that can increase markedly in response to infection or inflammation. In a previous study [13], markedly increased CRP level (> 100 mg/L) was highly associated with severe sepsis. This makes it possible to distinguish pyelonephritis from cystitis, bacterial pneumonia from acute bronchitis, acute bronchitis from uncomplicated acute or chronic obstructive pulmonary disease, and bacterial meningitis from aseptic meningitis. However, the range of elevation is large: the higher the CRP level, the more sensitivity there is to an association with sepsis. For this reason, a cutoff point of 100 mg/L was selected in this study for its higher ability to detect the factor results in normal WBC counts in those patients. In Putto et al's study [14], CRP of > 40 mg/L could detect 79% of bacterial infection with 90% specificity. However, CRP of 20–40 mg/L has been recorded in both viral and bacterial infections. Many studies found that CRP was more sensitive than WBC counts in distinguishing bacterial infection [1,10].

Many studies have focused on the use of CRP in patients with malignancy, hematologic disease or neutropenia, because these patients do not have normal WBC response to infection [3,4,12,15–22]. Such studies have shown that CRP could help to diagnose sepsis in such patients. In a study of children with cancer, Santolaya et al [18] showed that patients with CRP level > 40 mg/L had bacterial infection (sensitivity of 100%, specificity of 76.6%). Arber et al [12] found that levels of CRP in sepsis were higher than in graft-versus-host disease. Although CRP is elevated in cancer itself, fever with elevated CRP could still reveal infection. Most of the patients in our study did not have malignancy or hematologic disease, but WBC count did not increase in those with infections. Although some of these patients had chronic disease, further study is needed to determine the cause of impaired WBC response in these patients. Other biomarkers like CRP may be more suitable to detect infection in such patients. In our study, there were no differences in age and gender between patients with and those without malignancy. Although most causes of febrility were infection in both types of patients, patients with malignancy still had higher incidences of causes of febrility other than infection. The inhospital mortality rate was higher in patients with malignancy. Our data did not attribute the mortality to the difference in severity of infection or underlying malignancy. The patients with malignancy had a greater possibility of having a rare infection or multiple site infection.

As fever is one of the most common complaints of patients who visit the ED, it is very important to

determine whether the cause is severe infection or inflammation. Many standard medical tests have aided clinical diagnosis, such as WBC counts, interleukin-6, interleukin-8, CRP, procalcitonin, soluble Fcγ receptor type III and mannose-binding protein [1,4,5,7,23]. Although studies have shown the value of these examinations, the majority, except for CRP and WBC count, are unavailable in the ED of most hospitals. Most infections can be diagnosed by clinical symptoms and signs, but diagnosis may be difficult in patients who cannot express their symptoms well, such as children. Accordingly, CRP could be used in febrile children [1,7,16,18,23–26] to distinguish bacterial infection. Furthermore, the causes of febrility may be difficult to distinguish in some situations including trauma [27] and bone marrow transplantation [12]. The CRP level test has value in such cases. Furthermore, many infectious or inflammatory diseases have no specific symptoms; marked elevation of CRP has significant diagnostic value in such cases as well.

There are several limitations to this study. First, the major goal of the study was to analyze the characteristics of febrile patients with normal WBC count and high CRP level. We lacked the data to confirm the roles in differential sepsis in this study. Secondly, this study did not determine whether CRP itself affects the disposition of the doctors. Further study is necessary to determine if doctors tend to suggest that patients with high CRP level be hospitalized. Finally, this study analyzed the data in an ED, so the results can be applied to patients in an ED, but it did not determine if these patients had normal WBC counts throughout the course of disease or whether some patients developed high CRP levels during the course of the disease.

It was not rare for febrile patients who visited the ED to have high CRP level but normal WBC count. These patients usually had significant infection or inflammation and needed hospitalization and further treatment, but they did not necessarily have an underlying malignant neoplasm or hematologic illness. This suggests that some factors other than malignant neoplasm or hematologic illness may be associated with the WBC response, and that CRP may be a better indicator of infection under such conditions. Further studies are needed to elucidate what these factors may be. We believe that it is reasonable to check CRP level in addition to WBC count for patients who visit the ED due to fever.

References

1. Galetto-Lacour A, Zamora S, Gervaix A. Bedside procalcitonin and C-reactive protein tests in children with fever without localizing signs of infection seen in a referral center. *Pediatrics* 2003;112:1054–60.
2. Kawasaki Y, Hosoya M, Katayose M, et al. Correlation between serum interleukin 6 and C-reactive protein concentrations in patients with adenoviral respiratory infection. *Pediatr Infect Dis J* 2002;21:370–4.
3. Kallio R, Bloigu A, Surcel H, et al. C-reactive protein and erythrocyte sedimentation rate in differential diagnosis between infections and neoplastic fever in patients with solid tumours and lymphomas. *Support Care Cancer* 2001;9:124–8.
4. Engel A, Mack E, Kern P, et al. An analysis of interleukin-8, interleukin-6 and C-reactive protein serum concentrations to predict fever, gram-negative bacteremia and complicated infection in neutropenic cancer patients. *Infection* 1998;26:213–21.
5. Herrmann J, Blanchard H, Brunengo P, et al. TNF alpha, IL-1 beta and IL-6 plasma levels in neutropenic patients after onset of fever and correlation with the C-reactive protein (CRP) kinetic values. *Infection* 1994;22:309–15.
6. Fassbender K, Pargger H, Muller W, et al. Interleukin-6 and acute-phase protein concentrations in surgical intensive care unit patients: diagnostic signs in nosocomial infection. *Crit Care Med* 1993;21:1175–80.
7. Lehrnbecher T, Venzon D, de Haas M, et al. Assessment of measuring circulating levels of interleukin-6, interleukin-8, C-reactive protein, soluble Fc gamma receptor type III, and mannose-binding protein in febrile children with cancer and neutropenia. *Clin Infect Dis* 1999;29:414–9.
8. Verkkala K, Valtonen V, Jarvinen A, et al. Fever, leucocytosis and C-reactive protein after open-heart surgery and their value in the diagnosis of postoperative infections. *Thorac Cardiovasc Surg* 1987;35:78–82.
9. Gozzard D, Yin J, Delamore I. The clinical usefulness of C-reactive protein measurements. *Br J Haematol* 1986; 63:411–4.
10. Povoa P, Almeida E, Moreira P, et al. C-reactive protein as an indicator of sepsis. *Intensive Care Med* 1998;24: 1052–6.
11. Grutzmeier S, von Schenck H. C-reactive protein during chemotherapy for acute leukemia with special reference to non-infective causes of fever. *Med Oncol Tumor Pharmacother* 1986;3:71–5.
12. Arber C, Passweg J, Fluckiger U, et al. C-reactive protein and fever in neutropenic patients. *Scand J Infect Dis* 2000;32:515–20.
13. Morley J, Kushner I. Serum C-reactive protein levels in disease. *Ann NY Acad Sci* 1982;389:406–18.
14. Putto A, Ruuskanen O, Meurman O, et al. C reactive protein in the evaluation of febrile illness. *Arch Dis Child* 1986;61:24–9.
15. Timonen T, Koistinen P. C-reactive protein for detection and follow-up of bacterial and fungal infections in

severely neutropenic patients with acute leukaemia. *Eur J Cancer Clin Oncol* 1985;21:557–62.
16. Katz J, Mustafa M, Bash R, et al. Value of C-reactive protein determination in the initial diagnostic evaluation of the febrile, neutropenic child with cancer. *Pediatr Infect Dis J* 1992;11:708–12.
17. Rintala E, Irjala K, Nikoskelainen J. Value of measurement of C-reactive protein in febrile patients with hematological malignancies. *Eur J Clin Microbiol Infect Dis* 1992;11:973–8.
18. Santolaya M, Cofre J, Beresi V. C-reactive protein: a valuable aid for the management of febrile children with cancer and neutropenia. *Clin Infect Dis* 1994;18:589–95.
19. Gunther G, Gardlund B, Hast R, et al. Endotoxaemia and inflammatory mediators in febrile patients with haematological disease. *J Intern Med* 1995;237:27–33.
20. Manian F. A prospective study of daily measurement of C-reactive protein in serum of adults with neutropenia. *Clin Infect Dis* 1995;21:114–21.
21. Kostiala A, Kostiala I, Valtonen V, et al. Levels of C-reactive protein in patients with hematologic malignancies. *Scand J Infect Dis* 1985;17:407–10.
22. Harris R, Stone P, Hudson A, et al. C reactive protein rapid assay techniques for monitoring resolution of infection in immunosuppressed patients. *J Clin Pathol* 1984;37:821–5.
23. Heney D, Lewis I, Evans S, et al. Interleukin-6 and its relationship to C-reactive protein and fever in children with febrile neutropenia. *J Infect Dis* 1992;165: 886–90.
24. Lembo R, Marchant C. Acute phase reactants and risk of bacterial meningitis among febrile infants and children. *Ann Emerg Med* 1991;20:36–40.
25. Gervaix A, Galetto-Lacour A, Gueron T, et al. Usefulness of procalcitonin and C-reactive protein rapid tests for the management of children with urinary tract infection. *Pediatr Infect Dis J* 2001;20:507–11.
26. Pulliam P, Attia M, Cronan K. C-reactive protein in febrile children 1 to 36 months of age with clinically undetectable serious bacterial infection. *Pediatrics* 2001; 108:1275–9.
27. Miller P, Munn D, Meredith J, et al. Systemic inflammatory response syndrome in the trauma intensive care unit: who is infected? *J Trauma* 1999;47:1004–8.

高 C 反應蛋白和正常白血球數的急診發燒病患特徵

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發燒是到急診就診病患常見的主訴之一，其中有許多病人其 C 反應蛋白值明顯上升而白血球數正常，多數的這些病患有細菌感染但無明顯的白血球功能異常的慢性疾病，我們收集了從 2003.11 到 2004.7 間到本院急診就診的病患，18 歲以上的發燒病患其 C 反應蛋白值大於 100 mg/L 而白血球數正常者,收集病患年齡、性別等基本資料,並記錄其慢性疾病、該次發燒診斷、住院日數及預後做為分析，期間共有 54,078 位病患到本院急診就診，其中有 5,628 位發燒的成人病患，共有 214 (3.8%) 位病患合乎本研究有高的 C 反應蛋白值和正常的白血球數。這些病人大部份發燒的原因是感染 (82.24%)，並大多數都有住院 (92.99%)。其中有 32 位有惡性腫瘤，9 位有肝硬化，66 位有糖尿病和 11 位有尿毒症。在有無惡性腫瘤的兩組病人之間，年齡及性別並無差異，但有惡性腫瘤的病患的死亡率較高，並且有較多感染以外的發燒原因。到急診就醫的發燒病人中，白血球正常而 C 反應蛋白值的病人並不罕見，這些病人多半有感染或組織發炎需要住院進一步治療，這些病患並不一定有惡性腫瘤或血液疾病。除了惡性腫瘤及血液疾病以外可能有些因素會影響白血球反應，而 C 反應蛋白在這些情況可能會是比較好的感染指標。

關鍵詞：C 反應蛋白，急診，發燒

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