Relationships between Causes of Fever of Unknown Origin and Inflammatory Markers: A Multicenter Collaborative Retrospective Study

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Abstract

Objective Although inflammatory markers, such as the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and levels of C-reactive protein (CRP) and procalcitonin, are widely used to differentiate causes of fever of unknown origin (FUO), little is known about the usefulness of this approach. We evaluated relationships between the causes of classical FUO and the levels of inflammatory markers.

Methods A nationwide retrospective study including 17 hospitals affiliated with the Japanese Society of Hospital General Medicine was conducted.

Patients This study included 121 patients ≥18 years old diagnosed with “classical FUO” (axillary temperature ≥38.0°C at least twice over a ≥3-week period without elucidation of the cause on three outpatient visits or during three days of hospitalization) between January and December 2011.

Results The causative disease was infectious diseases in 28 patients (23.1%), non-infectious inflammatory disease (NIID) in 37 patients (30.6%), malignancy in 13 patients (10.7%), other in 15 patients (12.4%) and unknown in 28 patients (23.1%). The rate of malignancy was significantly higher for a WBC count of <4,000/μL than for a WBC count of 4,000-8,000/μL (p=0.015). Among the patients with a higher WBC count, the rate of FUO due to NIID tended to be higher and the number of unknown cases tended to be lower. All FUO patients with malignancy showed an ESR of >40 mm/h. A normal ESR appeared to constitute powerful evidence for excluding a diagnosis of malignancy. In contrast, the concentrations of both serum CRP and procalcitonin appeared to be unrelated to the causative disease.

Conclusion The present study identified inflammatory markers that should be considered in the differential diagnosis of classical FUO, providing useful information for future diagnosis.

Key words: white blood cell, erythrocyte sedimentation rate, C-reactive protein, procalcitonin

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**Introduction**

Fever of unknown origin (FUO) may be caused by many diseases, and the underlying cause can vary depending on the region and time period. FUO was first reported in the medical literature 80 years ago (1). Since then, the causative diseases have changed greatly in association with the many recent changes in the social environment and widespread adoption of diagnostic imaging (2-9). We previously conducted a multicenter collaborative retrospective study of patients with FUO at hospitals affiliated with the Japanese Society of Hospital General Medicine (10). That study represented the first nationwide trial in this country on diseases causing FUO and the related diagnostic workup and identified diseases that should be considered when evaluating FUO in Japan.

Measurement of the levels of inflammatory markers, such as the white blood cell (WBC) count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, are useful for detecting acute inflammation that may indicate specific diseases (11-17). The levels of inflammatory markers increase in association with a wide variety of disorders, including infection, malignant tumors and non-infectious inflammatory disease (NIID). Wacker et al. recently provided a systemic review of another inflammatory marker, procalcitonin, and concluded that this peptide is a helpful marker for diagnosing sepsis in critically ill patients (18).

However, few assessments of the tests used in the diagnostic evaluations of classical FUO have been reported. In particular, very few studies have assessed the clinical utility of inflammatory markers, even though use of these parameters is now widespread. We therefore investigated the relationships between the category of causative disease of FUO and the levels of inflammatory markers in the present study. This represents the first study to evaluate the association between classical FUO and the serum procalcitonin level.

**Materials and Methods**

Among 99 hospitals affiliated with the Japanese Society of Hospital General Medicine that were invited to contribute to this study, 17 participated. The hospitals participating in our study showed a wide geographic distribution throughout Japan, including seven hospitals in Eastern Japan and 10 hospitals in Western Japan. These 17 hospitals included 13 university hospitals and four community hospitals. The data were collected by the participating hospitals from patients ≥18 years of age who were diagnosed with classical FUO between January and December, 2011. All data were recorded on standardized case report forms and collected via fax.

Classical FUO was diagnosed based on the definition of Durack et al. (19) in patients meeting all of criteria <1> to <4> below:

<1> Fever with an axillary temperature of ≥38.0°C at least twice over a ≥3-week period;
<2> Unknown cause after three outpatient visits or during three days of hospitalization;
<3> No diagnosis of immunodeficiency prior to fever onset; and
<4> No confirmed infection with human immunodeficiency virus (HIV) prior to fever onset.

The axillary temperature is usually measured in Japan. Therefore, fever was defined as an axillary temperature of ≥38.0°C.

The data described below were collected. No additional testing was performed in this study due to the lack of sufficient data.

- Patient characteristics: sex; age; concomitant diseases; past medical history; and medication history.
- Clinical findings: subjective symptoms; and objective physical findings.
  - Blood tests: blood count; biochemical examination; and inflammatory markers (CRP, ESR, procalcitonin level).
  - Results of blood cultures if performed.
  - Results of imaging studies and endoscopy if performed.
  - Results of cytology, histology and genetic testing or autopsy findings if performed.
- Final diagnosis, day of diagnosis and outcome.

The causes of FUO were classified as infection, NIID, malignancy, other and unknown. Because the categorization of specific diseases has sometimes differed among prior studies, previous articles were used as references for the present study (5, 6).

Differences in the demographic data of the groups who underwent each test were statistically analyzed. The statistical analysis of sex was performed using the Pearson chi-square test. Differences in age, body temperature and disease duration were analyzed using a one-way analysis of variance. Characteristic features of the four types of inflammatory markers for each cause were compared among causes using a one-way analysis of variance. The incidence and 95% confidence interval (CI), as determined using standard methods, showed significant differences.

**Results**

A total of 121 patients with FUO were enrolled from the 17 participating hospitals, comprising 112 patients from 13 university hospitals and nine patients from four community hospitals. There were 52 women (43.0%), and the median age was 59 years (range, 19-94 years). Most patients were 70-79 years of age.

The causative disease for FUO was infectious disease in 28 patients (23.1%), NIID in 37 patients (30.6%), malignancy in 13 patients (10.7%), other in 15 patients (12.4%) and unknown in 28 patients (23.1%). We previously reported the details of these findings (10). Parameters assessed in the diagnostic evaluations included the WBC count in 100% of the subjects, the ESR in 76.0% of the subjects, the serum CRP level in 100% of the subjects and the quantita-
The rate of malignancy was 6.25% in the patients with a WBC count of 4,000-8,000/μL (incidence, 1 as reference) (Fig. 1), compared to 25.0% in the patients with a WBC count of <4,000/μL (5.875; 95%CI, 1.864-29.092, p=0.015). The proportion of patients exhibiting FUO due to NIID increased in association with an increase in the WBC count. In contrast, the frequency of unknown cases decreased in association with an increase in the WBC count.

Table 2 shows the characteristic features of the tests for each cause, with the results of the statistical analyses comparing the causes. No significant differences were identified among the five causative disease groups.

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Discussion

The causative diseases underlying FUO vary by region and time period, and assessing these causes over a wide area using recent data is therefore important. Although a previous study in Japan reported tuberculosis as being the most common cause of FUO (8), the present study identified NIID as the most common cause (10). In the present study, infections, including tuberculosis, were diagnosed based on appropriate culture and/or serological tests before meeting the definition of classical FUO. Polymyalgia rheumatica (PMR) was the most common disease causing FUO (nine patients) in the present study.

The ESR and procalcitonin levels were measured in only 92 (76.0%) and 45 (37.2%) patients, respectively. Since the procalcitonin level is widely used to make the differential diagnosis of infectious disease in Japan, selecting patients who underwent measurements of the procalcitonin level may have resulted in bias toward subjects with infectious dis-
Figure 1. Relationship between the cause of fever of unknown origin and the white blood cell count. NIID: non-infectious inflammatory disease. *p=0.015

Figure 2. Relationship between the causative disease for fever of unknown origin and the erythrocyte sedimentation rate (ESR). NIID: non-infectious inflammatory disease

Figure 3. Causative disease and the serum levels of C-reactive protein (CRP) in the FUO patients. NIID: non-infectious inflammatory disease

Figure 4. Relationship between the cause of fever of unknown origin and the serum procalcitonin level. NIID: non-infectious inflammatory disease

eases. However, the demographic data of the patients who underwent each test (measurements of the WBC/CRP, ESR or procalcitonin values) showed no significant differences between the three groups (Table 1).

The WBC count has been widely used to differentiate febrile patients. Weinstein et al. reported an association between the WBC count and mortality in patients experiencing episodes of bacteremia and fungemia (20). However, as shown in Fig. 1, no relationships were evident between an underlying cause of infectious disease and the WBC count in our study. The WBC count changes widely in individuals with chronic infections and is decreased in cases of viral infections, such as HIV/acquired immunodeficiency syndrome. In the present study, a WBC count of <4,000/μL was found to be significantly related to the presence of malignant disease. This relationship may be related to the fact that many of the malignant diseases presenting as FUO are hematological diseases. Eleven of the 13 patients (84.6%) with malignant disease in our study had hematological diseases (malignant lymphoma, n=8; Castleman’s disease, n=2; acute lymphoblastic leukemia, n=1). The number of FUO cases for which no cause was identified increased with a decreasing WBC count. The onset of FUO due to non-specific viral infection may play a role in this relationship.

Findings vary regarding the usefulness of ESR for diagnosing FUO (6). Well-known diseases associated with an ESR of >100 mm/h include PMR, tuberculosis, multiple myeloma and osteomyelitis (vertebral discitis), and malignancies have also been reported in approximately 60% of such cases (21). In the current study, 18 of the 121 patients (14.9%) showed an ESR of >100 mm/h, including five with an unknown cause of FUO, two with PMR and two with antineutrophil cytoplasmic antibody-associated vasculitis. As shown in Fig. 2, all of the FUO patients with malignancy had an ESR of >40 mm/h, and this finding therefore appears to prove helpful when diagnosing FUO.
Tillett et al. reported the discovery of serum CRP in patients with pneumococcal pneumonia in 1930 (22). Among several markers of an inflammatory state, the serum CRP level is well known and useful for detecting infection, most often bacterial infections (11-15, 23). Despite acting as a sensitive parameter of infection, this parameter is not specific, as an elevated CRP level may also reflect NIID, malignant tumors, drug allergies, smoking, aging and/or other non-inflammatory states (24, 25). Although its predictive ability in patients with classical FUO was evaluated in the present study, we found no associations between the serum CRP level and the category of causative disease for FUO (Fig. 3). Hence, the serum CRP concentration may not be useful for differentiating diseases in patients with classical FUO.

In recent years, the usefulness of the serum procalcitonin level for making the differential diagnosis of bacterial infections has increasingly been reported, and testing of this parameter is now in wide application in Japan. Simon et al. reported that, for the differential diagnosis of bacterial infection from non-infectious disease, the serum procalcitonin level offers a higher sensitivity (88%) and specificity (81%) than the CRP level (75% and 67%, respectively) (26). In the present study, quantitative serum procalcitonin testing was performed in 37.2% of the patients. Although the use of this test is widespread in Japan, 5.9% of the patients with a serum procalcitonin level of ≥0.25 ng/mL in this study showed bacterial infection, while 10.7% of the patients with a level of <0.25 ng/mL had a bacterial infection. Based on these findings, using the procalcitonin level to evaluate patients with classical FUO may not be effective. Serum procalcitonin testing is also more expensive than determining the WBC count or ESR, and indiscriminate measurements of the serum procalcitonin level in febrile patients should be avoided.

The present study is associated with several limitations. Only 17 hospitals participated in this research; therefore, the results may not be generalizable to the overall situation in Japan. We hope that more hospitals will participate in future studies. Furthermore, this study was a retrospective summary of cases, and the individual diagnoses were made by the treating physician at specific times in each case. We are currently planning a prospective study of patients who fulfill the criteria for FUO at the time of enrollment in order to allow for periodic follow-up observations.

Conclusion

We conducted the first nationwide study of FUO and inflammatory markers in Japan. This study identified the role of inflammatory markers in the differential diagnosis of causes of FUO. Based on our findings, the WBC count and ESR represent useful markers for diagnosing the causative disease in FUO patients. In contrast, neither the CRP nor procalcitonin levels appear to be helpful for obtaining the differential diagnosis in patients with classical FUO. These observations will serve as a reference for differentiating causes of FUO in the future.

The authors state that they have no Conflict of Interest (COI).

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