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Fever of unknown origin: a retrospective study of 78 adult patients in Taiwan

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To elucidate the causes of fever of unknown origin (FUO) in Taiwan, we retrospectively analyzed the characteristics of 78 adult patients meeting the classic criteria for fever of unknown origin who were treated at National Taiwan University Hospital from July 1999 through June 2002. Cause of FUO was due to infections in 42.3% of patients, neoplasms in 6.4%, noninfectious inflammatory diseases in 20.5%, and miscellaneous causes in 7.7%, whereas the cause was not established in 23.1% of patients despite every effort. Tuberculosis (14.1%) and acquired immunodeficiency syndrome (7.7%) were the most common causes of infection in patients with FUO, while intraabdominal abscess, infective endocarditis, and tumor were less frequently found. Noninfectious inflammatory diseases were still a very important cause of FUO and were difficult to diagnose. In conclusion, infection remains the most important cause of classic FUO in Taiwan, confirming the findings in previous series. The importance of tuberculosis and AIDS as frequent causes of FUO should be emphasized.

Key words: Fever of unknown origin, Taiwan

A long list of diseases may cause fever of unknown origin (FUO). Despite the continuous improvement of diagnostic methods, including new microbiological techniques and radiographic tools, identification of the cause of FUO remains a challenge in clinical practice. Epidemiological data on FUO in Taiwan remains limited. Only one study, conducted in 1976 [1], has been reported while a recent report of a 7 cases series emphasized Q fever as an uncommon cause of FUO in Taiwan [2].

The major causes of FUO include infections, malignancy, collagen vascular diseases, and undiagnosed [3,4]. However, the spectrum of diseases causing FUO appears to change with time. Recent studies have found that the proportion of patients without a definite diagnosis as a cause of FUO was increased compared with previous studies [5-8]. Furthermore, the frequency of endemic diseases such as tuberculosis and some emerging diseases has been rising, which may also change the spectrum of FUO. This retrospective study evaluated the clinical characteristics of 78 Taiwanese patients with FUO. Also, comparison of data with other studies is mandatory in original articles.

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Patients and Methods

This study included patients treated at National Taiwan University Hospital from July 1999 through June 2002. National Taiwan University Hospital is a tertiary care medical center in northern Taiwan receiving patients transferred from other hospitals and also provides a primary care outpatient service. Medical records of all patients with an initial diagnosis of fever of unknown causes were retrieved from a computer database for review. Patients included in this study were more than 18 years old, and fulfilled the following classic FUO criteria of Durack and Street [9]: (1) body temperature exceeding 38.3°C on several occasions; (2) duration of illness more than 3 weeks; and (3) failure to reach a diagnosis after 3 outpatient investigations or 3 days of inpatient investigation. Patients with a diagnosis of human immunodeficiency virus infection, nosocomial infection, or febrile neutropenia due to anticancer therapy were excluded.

Demographic information and detailed medical history including familial disorders, medications, previous illness, occupations, travel and animal exposure were recorded. Any abnormal physical examination findings such as lymphadenopathy, skin rash and cardiac murmur were also recorded. Other data included in the assessment were complete blood cell count and differential count; routine blood chemistry, urinalysis, erythrocyte sedimentation rate, C-reactive

protein, ferritin, blood cultures, other body fluid or pus cultures, antinuclear antibody, rheumatoid factors, serologic tests for syphilis, cryptococcal antigen, rickettsial serology, cytomegalovirus or Epstein-Barr virus serology tests, human immunodeficiency virus tests and other viral isolation, chest and abdomen radiographs, ultrasonographs, and computed tomographs (CT) or magnetic resonance images (MRI), radionuclide scan or fluorodeoxyglucose-positron emission tomographs (FDP-PET). All information was collected on a standardized form.

The cause of FUO was determined at the time of discharge or during follow-up. The causes were classified into 5 groups: (1) infections; (2) neoplasms; (3) noninfectious inflammatory diseases; (4) miscellaneous; and (5) no diagnosis. Drug fever and factitious fever were classified into the miscellaneous group. The method that identified the cause of FUO was also recorded. If there were multiple tests which provided the diagnosis in an individual case, the one that first identified the etiology was considered the method that yielded the diagnosis.

Data between groups of patients were compared using chi-square test. A p value of <0.05 was considered significant.

Results

During the 3-year study period, 78 patients admitted to NTUH met the inclusion criteria. The mean age of these patients was 49 ± 19 years (range, 19-88 years). Twenty-one patients (26.9%) were older than 65 years. Thirty-six (46.2%) patients were female and 42 (53.8%) were male. Twenty-six (33.3%) patients were referred from other hospitals, 36 (46.2%) were referred from primary practitioners, and 16 were admitted from the outpatient service of NTUH. The mean duration of hospitalization was 18.8 ± 18.9 days (range, 3-113 days). Eleven patients (14%) were hospitalized for more than 4 weeks. The mean interval between admission and diagnosis was 14.2 ± 13.7 days (range, 2-72 days).

The mean hemoglobin level was 11.1 ± 1.9 g/dL, leukocyte count was 8.4 ± 4.8 x 10^3/μL, platelet count was 257 ± 145 x 10^3/μL. Serum creatinine level was 1.1 ± 1.4 mg/dL, sodium was 134.3 ± 14.9 mmol/L, potassium was 4.2 ± 0.7 mmol/L. Aspartate aminotransferase was 46.6 ± 54.9 IU/L, γ-glutamyl transpeptidase was 95.2 ± 87.1 IU/L, lactate dehydrogenase was 599.1 ± 386.9 IU/L. C-reactive protein level was 6.65 ± 6.67 mg/dL.

Infectious disease (42.3%) was the most common cause of classic FUO in this study (Table 1). *Mycobacterium tuberculosis* infection was the most frequent type of infection and included patients with pulmonary and extrapulmonary infections. Tuberculosis was diagnosed in 11 (14.1%) patients based on the findings of microbial culture, tissue pathology, radiographic evidence, or antituberculosis trial. Acquired immunodeficiency syndrome was the second most common cause of FUO in this study (6 patients, 7.7%), and 5 of these cases were complicated with opportunistic infection such as pulmonary tuberculosis, *Pneumocystis carinii* pneumonia, *Penicillium marneffei*

Table 1. Cause of fever in 78 patients with classic fever of unknown origin

Cause of fever	No. of cases (%)
Infection	33 (42.3)
Bacterial	21 (26.9)
Tuberculosis	11 (14.1)
Scrub typhus	3 (3.9)
Atypical pneumonia or recurrent pneumonia	2 (2.6)
Urinary tract infection	2 (2.6)
Tuboovarian abscess	1 (1.3)
Osteomyelitis	1 (1.3)
Chronic parasinusitis	1 (1.3)
Parasitic	1 (1.3)
Malaria	1 (1.3)
Viral	10 (12.8)
Acquired immunodeficiency syndrome	6 (7.7)
Other viral infection	4 (5.1)
Fungal	1 (1.3)
Cryptococcal meningitis	1 (1.3)
Neoplasms	5 (6.4)
Hematologic	2 (2.6)
Hodgkin's lymphoma	1 (1.3)
Non-Hodgkin's lymphoma	1 (1.3)
Solid	3 (3.9)
Ovarian	2 (2.6)
Lung	1 (1.3)
Noninfectious inflammatory diseases	16 (20.5)
Adult Still's disease	3 (3.9)
Ankylosing spondylitis	2 (2.6)
Autoimmune vasculitis	2 (2.6)
Kikuchi's disease	2 (2.6)
Systemic lupus erythematosus	1 (1.3)
Mixed connective tissue disease	1 (1.3)
Rheumatoid arthritis	1 (1.3)
Polymyositis	1 (1.3)
Palindromic rheumatica	1 (1.3)
Reactive arthritis	1 (1.3)
Kimura's disease	1 (1.3)
Miscellaneous	6 (7.7)
Granulomatous hepatitis	1 (1.3)
Subacute thyroiditis	1 (1.3)
Hashimoto's disease	1 (1.3)
Hypereosinophilia	1 (1.3)
Rapidly progressive glomerulonephritis	1 (1.3)
Drug fever	1 (1.3)
No diagnosis	18 (23.1)

infection, cryptococcal fungemia, and anal fistula, respectively. The other infectious causes of FUO were scrub typhus (n = 3), intraabdominal abscess (n = 1), recurrent pneumonia (n = 1), atypical pneumonia (n = 1), prostatitis (n = 1), osteomyelitis (n = 1), chronic paranasal sinusitis (n = 1), malaria (n = 1), and cryptococcal meningitis (n = 1). However, 4 patients had clinical manifestations, which suggested viral infection but no virus was identified or isolated.

Five patients (6.4%) were found to have neoplastic diseases. Among them, 2 had ovarian cancer, one had Hodgkin's disease, one had non-Hodgkin's lymphoma, and one had metastatic carcinoma with unknown origin.

The noninfectious inflammatory diseases group (20. 5%) included patients with adult Still's disease (3), ankylosing spondylitis (2), autoimmune vasculitis (2), Kikuchi's disease (2), systemic lupus erythematosus (1), mixed connective tissue disease (1), rheumatoid arthritis (1), polymyositis (1), reactive arthritis (1), palindromic rheumatica (1), and Kimura's disease (1).

The miscellaneous causes group (7.7%) included patients with granulomatous hepatitis (1), subacute thyroditis (1), Hashimoto's thyroditis (1), hyper-eosinophilic syndrome (1), glomerulonephritis (1) and drug-induced fever (1). Even after detailed investigations, there were still 18 patients (23.1%) without an identified cause for FUO.

Four of the patients died during hospitalization. One patient with Hodgkin's disease and one with metastatic carcinoma of unknown origin died due to bacterial sepsis. One patient died due to hepatic failure secondary to severe *M. tuberculosis* infections, and one patient died because of fulminant cryptococcal meningitis. All of the patients with AIDS survived during the period of FUO in this study.

Discussion

Our review of the literature revealed that the proportion of FUO cases grouped in specific disease categories has changed during the past decades (Table 2) [5,6,8, 10-17]. Infections have been the most important cause of FUO in nearly all reports including this study, with a relative frequency ranging from 22% to 54%. However, intraabdominal abscess, hepatobiliary infection, and infective endocarditis were less common causes in this study compared with previous reports [10-12]. In the past 2 decades, the introduction of ultrasonography, computer tomography, and magnetic resonance imaging represent major advances in diagnostic armamentarium that have a sensitivity of more than 90% for the diagnosis of abdominal abscess, liver and renal tumor, hepatobiliary disease, and mediastinal or hilar abnormalities [18-22]. This study confirmed the trends suggested by Larson *et al* [11] that bacterial endocarditis has become a less important cause of FUO. This trend may be attributable to the use of echocardiography, especially transesophageal echocardiography [23].

Unlike other FUO series from western countries, tuberculosis was the most common infectious etiology (14.1%) in this series. The forms of tuberculosis that caused FUO in this series were either disseminated disease without the characteristic pulmonary radiographic pattern or extrapulmonary disease without clear localizing features. Compared with previous studies in Taiwan, the proportion of cases of FUO

Table 2. Comparison of cause of the percentage of FUO with previous and present studies

Diagnostic category	Petersdorf, 1961 [10] (n = 100)	Eyckmans, 1973 [12] (n = 80)	Larson, 1982 [11] (n = 105)	Barbado, 1984 [5] (n = 133)	Knockaert, 1992 [6] (n = 199)	Kazanjian, 1992 [13] (n = 86)	de Kleijn, 1997 [8] (n = 167)	Liu, 2002 [Present] (n = 78)
Infection	36	33.7	30.4	30.8	22.7	33	25.7	42.3
Abscess	4	2.5	10.4	3	2.1	12.8	3.6	1.3
TB	11	8.7	4.7	11.2	5	4.7	1.8	14.1
AIDS	-	-	-	-	-	1.2	-	7.7
Endocarditis	5	2.5	0	1.5	1.5	4.7	2.4	0
Neoplasm	19	18.7	31.4	18	7	24	12.6	6.4
Noninfectious inflammatory diseases	19	9.9	15	14.2	21.5	26.7	24	20.5
Still's disease	2	0	3.8	0.7	3	5.8	3.6	3.8
Drug-related fever	1	1.2	0	0	3	0	1.8	1.3
Factitious fever	3	2.5	2.8	4.5	3.5	1.2	1.2	0
Miscellaneous	15	8.7	8.5	9.7	14.5	8	4.8	7.7
No diagnosis	9	25	16	21.7	25.6	9	29.9	23.1

Note: Values are expressed as percentage of total.

Abbreviations: TB = tuberculosis; AIDS = acquired immunodeficiency syndrome

Table 3. Causes of FUO in Taiwan, expressed as percentage of total

	Hsieh[a], 1960 (n = 105)	Hsieh[a], 1964 (n = 112)	Hsieh[a], 1974 (n = 71)	Chen[b], 1986-1989 (n = 47)	Liu, Present study (n = 78)
Infection	71	62	54	25.5	42.3
TB	11	10	8	10.6	14.1
AIDS	-	-	-	-	7.7
Neoplasm	16	4	19	4	6.4
Noninfectious inflammatory diseases	1	6	11	21	20.5
Miscellaneous	5	6	7	15	7.7
No diagnosis	7	24	9	34	23.1

Abbreviations: TB = tuberculosis; AIDS = acquired immunodeficiency syndrome
[a]From reference 1.
[b]Author's unpublished data.

attributable to tuberculosis has been increasing in recent years (Table 3). As the suggestion of some recent studies [13,24], acquired immunodeficiency syndrome has become another important cause of FUO in Taiwan. Although the prevalence of human immunodeficiency virus remains quite low in Taiwan, the number of HIV-infected patients is increasing rapidly [25]. It is important that clinicians should keep maintain vigilance so as to not delay the diagnosis of AIDS. Interestingly, 5.1% of cases in this series, presented with a typical viral infection course but without positive diagnosis by viral serology and culture including enterovirus, cytomegalovirus or Epstein-Barr virus serology tests. Although not included in routine practice, human herpesvirus 8 is considered one of the causes of FUO [26] that can infect immunocompetent adults. However, this hypothesis needs to be confirmed.

Only 6.4% of cases in this series were due to malignancy, a result that is much lower than in previous series from university hospitals, which ranged from 7% to 31.4% [5,6,8,10-13]. A similar result was reported by Knockaert *et al* in 1992 [6], who suggested that the low proportion of cases in patients with tumors may have been due to the widespread use of ultrasonography, CT, and MRI. In this study, ultrasonography was used in 73%, CT in 46%, and MRI in 12% of cases. The frequent use of image studies may have helped to detect solid tumors earlier and thus reduced the proportion associated with FUO.

Noninfectious inflammatory diseases are common causes of FUO because fever could precede weeks or months without specific clinical manifestations. In this study, 20.5% of cases were diagnosed as noninfectious inflammatory diseases. Patients who were the cases of rheumatic fever and systemic lupus erythematosus rarely meet the criteria of FUO in recent decade [5]. There is a low prevalence of rheumatic fever in Taiwan, and the rapid immunologic diagnosis by an assay of antinuclear and anti-DNA antibody could be used to diagnose the systemic lupus erythematosus. However, adult Still's disease remains a common cause of FUO among noninfectious inflammatory diseases, as the suggestion of Knockaert *et al* [6], because of either typical signs or clinical courses. Moreover, Kikuchi-Fujimoto's disease and Kimura's disease were among the causes of FUO in this series, and both have been reported to present with prolonged fever [27-30].

Cases of factitious fever have been found in most series of FUO, but not in this series or a previous series from National Taiwan University Hospital. This may be partially because we excluded all cases with undocumented fever even if patients reported prolonged fever.

It is difficult to explain why the number of undiagnosed cases remained high in this study, and several possible explanations may have played a role. First, some complex cases were referred from other centers, and these cases were more likely to have lower chance of identifying an underlying cause of fever. Second, the strict diagnostic criteria employed may have influenced the percentage cases, which remained undiagnosed. Third, some patients delayed seeking more aggressive medical care due to the mild illness and self-limiting courses, which made the diagnosis more difficultly. Furthermore, the restrictions of the National Heath Insurance system might hesitate physicians to repeatedly perform some investigations including image studies such as CT or other laboratory studies.

In conclusion, the spectrum of diseases causing FUO in Taiwan continues to change. Infections remain the most common cause, and the high percentage of cases with tuberculosis and AIDS suggests the need to be alert to these likely causes of FUO. Noninfectious inflammatory diseases remain very important causes of FUO, which are difficult to diagnose. Although there

is increasingly widespread use of newer image studies such as Gallium-67 scan and invasive procedures such as bone marrow aspiration early in the course of FUO, the proportion of undiagnosed cases remains high. Because of the wide spectrum of causes and often atypical illness manifestations, accurate diagnosis of the cause of FUO requires careful history taking, physical examinations, aggressive laboratory work up, and image studies. However, the approach used in the diagnosis of FUO has not been standardized. Further studies with prospective designs and long-term follow up are needed to track the changing etiology of FUO and facilitate its early diagnosis and appropriate management.

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