Int J Clin Exp Med 2014;7(12):5862-5866
www.ijcem.com /ISSN:1940-5901/IJCEM0002911

Original Article

Fever of unknown origin: report of 107 cases in a university hospital

Kang-Kang Yu, Sheng-Sen Chen, Qing-Xia Ling, Chong Huang, Jian-Ming Zheng, Qi Cheng, Ning Li, Ming-Quan Chen, Guang-Feng Shi

Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China

Received October 1, 2014; Accepted December 8, 2014; Epub December 15, 2014; Published December 30, 2014

Abstract: Fever of unknown origin (FUO) is a challenging problem in clinical practice. Evaluation of patient's characteristics may illustrate the etiologies of FUO. In present study, 107 patients with FUO hospitalized in our inpatient department between 2010 and 2011 were investigated. The median age of the patients was 48 years (15-94). The median fever duration was 8.5 weeks (3-104). The median hospital stay was 8.5 days (1-51). Etiologies of FUO were identified as follows: infectious diseases 32 (29.9%), malignancies 19 (17.8%), inflammatory rheumatic diseases 18 (16.8%), and miscellaneous diseases 15 (14.0%). In 23 (21.5%) patients, the diagnosis remained unclear. Infection group had relative shorter average fever duration and hospital stay than other groups. Shortened mean fever duration was observed in geriatric age group. In conclusion, as the most common cause of FUO in the present study, infectious cases had relative shorter average fever duration and hospital stay, and geriatric patients had shortened average fever duration as well.

Keywords: Fever of unknown origin, etiology, infection

Introduction

Fever of unknown origin (FUO) was first defined as the body temperature higher than 38.3°C on several occasions and lasting more than 3 weeks, with no identified etiology after one week of investigation [1]. The definition was revised 30 years later by Durack and Street, meanwhile, FUO was divided into classic FUO, nosocomial FUO, neutropenic FUO, and HIV-associated FUO [2]. Now FUO is still a challenging clinical problem worldwide, with changed proportion of its major etiologies, despite the advances in diagnostic methods and tools [3]. In this study, we analyzed the clinical data of patients with FUO retrospectively and revealed their clinical features which may help with the management of FUO.

Patients and methods

Subjects

One hundred and seven patients meeting the criteria of classic FUO were enrolled in this study between Jan 2010 and Dec 2011 in Huashan Hospital, Department of Infectious Diseases. The complete blood count, routine serum biochemical analysis, erythrocyte sedimentation rate, C-reaction protein, urine analysis, auto-antibodies, cultures of blood, T-SPOT. TB test, coagulation function, direct chest X-ray, computed tomography (CT), ultrasonography were examined. Serologic examination for various tumor biomarkers and several viruses, Wright agglutination and Gruber-Widal tests, blood smear and bone marrow aspiration and biopsies, magnetic resonance imaging and positron emission tomography/computed tomography (PET/CT) were performed according to the clinical findings. Tissue biopsies were engaged when indicated.

Statistical analysis

Data were analyzed with SPSS version 17 (SPSS Inc., Chicago, IL, USA), and a value of $P \leq 0.05$ was considered statistically significant. Continuous variables were expressed as mean ± standard deviation (SD), and were assessed

Table 1. Etiologic classification of FUO cases

Diagnosis	Case number (%)
Infections	32 (29.9)
Mycobacterium	9
Tuberculosis	8
Non-tuberculosis mycobacteria	1
Bloodstream infection	7
Staphylococcus	6
Virus	4
Streptococcus	3
Syphilis	1
Histoplasma	1
Penicillium marneffei	1
Malignancies	19 (17.8)
Hematologic	14
Lymphoma	13
Myelofibrosis	1
Solid	5
Meningioma	2
Hepatocellular carcinoma	1
Gastric adenocarcinoma	1
Pituitary adenoma	1
Inflammatory rheumatic diseases	18 (16.8)
Adult-onset Still's disease	10
Vasculitis	4
Reiter's syndrome	1
Polyarteritis nodosa	1
Antiphospholipid syndrome	1
Crohn's disease	1
Miscellaneous diseases	15 (14.0)
Functional fever	10
Drug fever	3
Centric fever	1
Artificial fever	1
Undiagnosed	23 (21.5)

using unpaired Student's t-test. Categorical variables were expressed as absolute frequency (%), and were assessed using the nonparametric Mann-Whitney test.

Results

Of the 107 patients, 54 (50.5%) were male and 53 (49.5%) were female. The mean age of the patients was 46.8 years (standard deviation, 18.7). The median age was 48 years, ranging from 15 to 94 years. The mean fever duration was 14.3 weeks (standard deviation, 19.3). The median fever duration was 8.5 weeks, ranging from 3 to 104 weeks. The mean hospital stay was 13.4 days (standard deviation, 9.1). The median hospital stay was 8.5 days, ranging from 1 to 51 days.

Infectious diseases, as the most common cause of FUO, were diagnosed in 32 (29.9%) patients. Mycobacterium infection was observed in 9 patients, including 8 mycobacterium tuberculosis infection and one non-tuberculosis mycobacterium infection. Among the 8 patients with tuberculosis, two had pulmonary involvement, the extra-pulmonary tuberculosis including vertebral tuberculosis (n = 2), military tuberculosis (n = 1), peritoneal tuberculosis (n = 1), lymphatic tuberculosis (n = 1) and tuberculous meningitis (n = 1). The average duration of fever in infection group (9.8 ± 18.9 weeks) was shorter than that in inflammatory rheumatic disease group (14.1 ± 11.1 weeks), malignancy group (14.5 ± 13.3 weeks), and miscellaneous disease group (20.4 ± 26.6 weeks) (P = 0.014, P = 0.009, P = 0.043, respectively). The average hospital stay in infection group was 12.3 ± 7.6 days, shorter than malignancy group's 16.7 ± 8.4 days (P = 0.038). Malignancies were diagnosed in 19 (17.8%) patients, among which 13 (12.1%) were lymphomas. Inflammatory rheumatic diseases were observed in 18 (16.8%) patients, and 10 (9.3%) of the cases had adult-onset Still's disease (AOSD). Miscellaneous diseases were diagnosed in 15 (14.0%) patients. There were 23 (21.5%) patients with unidentified FUO (**Table 1**).

In male group, the mean age (mean ± SD, 48.8 ± 18.1 years) was older than the female group's (mean ± SD, 44.7 ± 19.3years), but there was no statistical significance (P = 0.264). The fever duration in male group (mean ± SD, 11.6 ± 16.5 weeks) was shorter than the female group (mean ± SD, 17.0 ± 21.6 weeks), but the difference was still not statistically significant (P = 0.059). The leading cause of FUO in male group was infection (23/54), and in female group was inflammatory rheumatic disease (12/53).

Table 2 shows the diagnosis of FUO in geriatric patients (≥ 60 years) and non- geriatric patients. In this study, 30 (28%) patients were in geriatric age group. Their average duration (mean ± SD, 8.8 ± 9.3 weeks) was shorter than the non-geri-

Table 2. Diagnosis of FUO in geriatric patients and non-geriatric patients

Diagnosis	Geriatric (%) (n = 30)	Non-geriatric (%) (n = 77)
Infections	10 (33.3%)	22 (28.6%)
Malignancies	7 (23.3%)	12 (15.6%)
Inflammatory rheumatic diseases	4 (13.3%)	14 (18.2%)
Miscellaneous diseases	2 (6.7%)	13 (16.9%)
Undiagnosed	7 (23.3%)	16 (20.8%)

atric age group (16.4 ± 21.7 weeks) (P = 0.012). Infections (n = 10), malignancies (n = 7), and inflammatory rheumatic diseases (n = 4) were the top 3 etiologies of FUO in geriatric patients.

Discussion

More than fifty years have passed since FUO was first described in 1961 [1], despite the advances of diagnostic techniques, FUO is still a significant clinical problem. In the present study, the etiologies of FUO were identified as follows: infections 29.9%, malignancies 17.8%, inflammatory rheumatic diseases 16.8%, miscellaneous diseases 14.0%, and unidentified 21.5%. The causes of FUO were in agreement with previous study [4].

Infectious disease remains the most common cause of FUO, which account for about 30% cases. As reported in former investigations, tuberculosis was the most frequent infection [4, 5], but the cases of FUO caused by tuberculosis declined, this probably due to the widely use of T-SPOT.TB, a T-cell-based assays for the diagnosis of tuberculosis [6].

Malignancies and inflammatory rheumatic diseases were the second and third leading cause of FUO in this study. Lymphoma was the most common malignancy and adult-onset Still's disease was the most frequent inflammatory rheumatic disease, which is similar to previous researches [4, 5]. The increased proportion of lymphoma in malignancy may attribute to its climbed incidence rate [7]. AOSD has no specific diagnostic tool, it relies on clinical and laboratory findings and need to exclude other diseases [8], study have reported that AOSD was not a rare cause of FUO in China [9].

Twenty-three (21.5%) patients with no identified etiologies, this rate closed to the previous reports [4, 5] in our country (**Table 3**). Among the undiagnosed cases, 6 patients were referred from other hospitals and rejected further investigations, only stayed 1 or 2 days in our hospital before discharge.

In our study, the mean fever duration was 14.3 weeks (standard deviation, 19.3), longer than reported, while the mean hospital stay was 13.4 days (standard deviation, 9.1), shorter than previous studies [10, 11]. The average duration of fever and hospital stay of infection group was observed to be contracted, which was different to previous study [10]. Male predominance was observed in infectious diseases (P = 0.004). Inflammatory rheumatic diseases were more common in women than men, as we known. In malignancy group, hematological neoplasm was the most frequent neoplasm, which accounts for 73.7% (14/19) of the cases.

In geriatric age group, the average duration of fever was shorter than the non-geriatric age group. The most common etiologies of FUO in elderly patients were infection and malignancy, which was quite different from previous report [12].

In conclusions, despite a portion of undiagnosed patients, most causes of FUO can be identified by careful history, detailed examination, and targeted laboratory tests. In our country, infectious diseases, malignancies, and infectious diseases remain the leading cause of FUO, but syphilis and other rare infectious diseases should not be ignored. Hematological neoplasm (especially lymphoma) and adult-onset Still's disease are the most common cases in malignancies and inflammatory rheumatic diseases respectively. Infectious diseases had contracted mean fever duration and hospital stay. In geriatric population, the average fever duration was shortened, and infections and malignancies are the most common causes of FUO in this group. FUO do poses a challenge to health service, but it is believed that with the development of laboratory tests and diagnostic technologies, the identification of causes of FUO will become easier and earlier.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Guang-Feng Shi, Department of Infectious Diseases, Huashan Hospital,

Table 3. Fever of unknown origin series recently reported in the literatures

Diagnosis	Erten N et al. [11] Turkey n = 57	Colpan A et al. [10] Turkey n = 71	Zenone T [12] France n = 144	Zong ZY et al. [4] China n = 208	Shi XC et al. [5] China n = 997	Present study (%) China n = 107
Infections	24 (42.1%)	32 (45.1%)	33 (22.9%)	66 (31.7%)	479 (48.0%)	32 (29.9%)
Tuberculosis	12 (21.1%)	13 (18.3%)	1 (0.7%)	28 (13.5%)	217 (21.8%)	8 (7.5%)
Malignancies	10 (17.5%)	10 (14.1%)	14 (9.7%)	35 (16.8%)	79 (7.9%)	19 (17.8%)
Hematologic	3 (5.3%)	8 (11.3%)	6 (4.2%)	27 (13.0%)	56 (5.6%)	19 (17.8%)
Solid	7 (12.3%)	2 (2.8%)	8 (5.6%)	8 (3.8%)	23 (2.3%)	5 (4.7%)
Inflammatory rheumatic Diseases	17 (29.8%)	19 (26.8%)	38 (26.4%)	46 (22.1%)	168 (16.9%)	18 (16.8%)
AOSD	6 (10.5%)	5 (7.0%)	4 (2.8%)	18 (8.7%)	53 (5.3%)	10 (9.3%)
Undiagnosed	6 (10.5%)	13 (18.3%)	4 (2.8%)	50 (24.0%)	200 (20.0%)	23 (21.5%)
Miscellaneous diseases	0	4 (5.6%)	22 (2.8%)	11 (5.3%)	71 (71.2%)	15 (14.0%)

Fudan University, 12 Middle Urumqi Road, Shanghai 200040, China. Tel: 86-21-52887965; Fax: 86-21-62480170; E-mail: gfshi@shmu.edu.cn

References

[1] Petersdorf RG and Beeson PB. Fever of unexplained origin: report on 100 cases. Medicine (Baltimore) 1961; 40: 1-30.

[2] Durack DT and Street AC. Fever of unknown origin--reexamined and redefined. Curr Clin Top Infect Dis 1991; 11: 35-51.

[3] Horowitz HW. Fever of unknown origin or fever of too many origins? N Engl J Med 2013; 368: 197-199.

[4] Zhiyong Z, Bingjun L, Xiaoju L, Xinjian F, Ping F and Wenya W. Fever of unknown origin: a report from China of 208 cases. Int J Clin Pract 2003; 57: 592-596.

[5] Shi XC, Liu XQ, Zhou BT, Zhang LF, Ma XJ, Deng GH, Li TS, Sheng RY and Wang AX. Major causes of fever of unknown origin at Peking Union Medical College Hospital in the past 26 years. Chin Med J (Engl) 2013; 126: 808-812.

[6] Pai M, Zwerling A and Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med 2008; 149: 177-184.

[7] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012; 62: 10-29.

[8] Cagatay Y, Gul A, Cagatay A, Kamali S, Karadeniz A, Inanc M, Ocal L, Aral O and Konice M. Adult-onset Still's disease. Int J Clin Pract 2009; 63: 1050-1055.

[9] Chen PD, Yu SL, Chen S and Weng XH. Retrospective study of 61 patients with adult-onset Still's disease admitted with fever of unknown origin in China. Clin Rheumatol 2012; 31: 175-181.

[10] Colpan A, Onguru P, Erbay A, Akinci E, Cevik MA, Eren SS and Bodur H. Fever of unknown origin: analysis of 71 consecutive cases. Am J Med Sci 2007; 334: 92-96.

[11] Erten N, Saka B, Ozturk G, Karan MA, Tascioglu C, Dilmener M and Kaysi A. Fever of unknown origin: a report of 57 cases. Int J Clin Pract 2005; 59: 958-960.

[12] Zenone T. Fever of unknown origin in adults: evaluation of 144 cases in a non-university hospital. Scand J Infect Dis 2006; 38: 632-638.