



Etiology of Fever of Unknown Origin in Shiraz: A Southern Iranian Experience

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Abstract

Background: Although infectious diseases are the most common cause of fever of unknown origin (FUO) in many countries, the spectrum of its etiology is changing over time.

Objectives: The purpose of this study was to determine the clinical spectrum and the pattern of FUO in Shiraz.

Methods: This study was undertaken from 2011 to 2015 in the main hospitals of Shiraz, southern Iran. The data of 60 patients fulfilling the modified criteria for FUO referring to the main hospitals in Shiraz were used for analysis. The data were extracted from the patients' medical charts and probable etiologies responsible for FUO were assessed. The patients were followed up by further ambulatory and readmission assessment.

Results: Of the identified etiologies, infections were the most common cause of FUO in 30% of the patients, followed by collagen vascular diseases with 15% and malignancies with 11.6%. However, 25 patients (41%) remained undiagnosed for their fever causes.

Conclusions: The pattern of FUO in the region has changed in recent years and complicated cases are admitted to hospitals. With improving ambulatory tests and diagnostic modalities, most of the patients with FUO are being diagnosed in outpatient settings and it will cause some changes in the classic percentage of FUO etiologies among admitted patients in the future.

Keywords: FUO, Infection, Malignancy

1. Background

Prolonged fever has always been a challenging problem for physicians since it needs time-consuming examinations to find the underlying cause. Suspected causes of prolonged fever in antiquity were malaria, typhoid fever, and plague as the primary infectious causes (1). The prolonged fever remained a problem until the previous decade that was defined by Petersdorf as a new entity. According to this definition, classic Fever of Unknown Origin (FUO) in adults is a temperature of higher than 38.3°C, which lasts more than three weeks with no clear source after one week of proper investigation (2). However, the definition was revised later and FUO was divided into classic FUO, nosocomial FUO, neutropenic FUO, and HIV-associated FUO (3).

The most important causes of "classic" FUO are infections, collagen vascular diseases, and malignancies, alongside undiagnosed etiologies. The proportion and spectrum of these major causes are variable in different geographic areas, due to multiple local parameters such as

specific environment, climate, and different endemic infectious diseases. Moreover, the difference in access to facilities for diagnostic procedures in hospitals may have led to the diversity in defined causes of FUO in various reports (4).

Despite advances in diagnostic methods and tools, the proportion of patients with the undiagnosed cause of FUO has shown increases in recent studies than before (5, 6). It might be due to the rapid and better diagnosis of fever causes in febrile patients in initial days of disease development and labeling of complicated cases as FUO in recent series.

2. Objectives

In this study, we retrospectively analyzed the clinical data of patients who were admitted to the main hospitals affiliated to the Shiraz University of Medical Sciences with the impression of FUO to emphasize the determination of the spectrum of clinical manifestations and etiologic causes.

3. Methods

This retrospective cross-sectional study was conducted in two referral hospitals (Namazee and Faghihi Hospitals) affiliated to the Shiraz University of Medical Sciences in Fars province, southern Iran, from March 2010 to February 2015. The referral hospitals have specialties in internal medicine, pediatrics, gynecology, general surgery, dermatology, and other health-related specialties. Each of the hospitals serves more than five million people in its inpatient and outpatient departments. These referral hospitals serve not only the large community of people from the Fars region but also patients from other nearby regions. Furthermore, they are teaching hospitals and have clinical attachment sites for different health professionals.

The medical records of all patients with a primary diagnosis of FUO were obtained from the hospitals' database archiving systems for review. Patients included in this study were older than 18 years and achieved the classic FUO criteria of Durack and Street (7) as follows: a fever of higher than 38.3°C (100.9°F) without definite diagnosis persisting for at least three weeks in spite of at least two outpatient investigations or three days of inpatient examinations. Patients who had a human immunodeficiency virus infection, nosocomial infection, or neutropenic fever were excluded from the study.

We carefully reviewed the patients' demographic data such as age, sex, occupation, detailed history, physical examinations, lab data, radiological findings, medications administered during the hospital course, and final diagnosis in their charts. In addition, for some undiagnosed discharged patients, we considered ambulatory follow-ups and telephone calls for the determination of final diagnosis.

According to the charts, we assessed the results of the complete blood count, leukocyte differential count, serum electrolytes such as sodium, potassium, calcium, and phosphorus, blood urea nitrogen, creatinine, liver function test, erythrocyte sedimentation rate, C-reaction protein, urine analysis, urine culture, blood culture, cerebrospinal fluid analysis and culture, coagulation function tests, serological examinations for various tumor biomarkers and various viruses, Wright agglutination and Widal tests, malaria smear, peripheral blood smear, bone marrow aspiration and biopsies, PPD skin test, electrocardiography, chest radiography, sonography, computed tomography, whole body bone scan, and magnetic resonance imaging. All information was collected in standardized forms.

3.1. Statistical Analysis

Data were analyzed using SPSS version 16 software (SPSS Inc., Chicago, IL, USA), and P values of ≤ 0.05 were consid-

ered statistically significant. Continuous variables such as age were expressed as means and standard deviation (SD) and some lab data were compared between groups by the chi-square test.

4. Results

During the review of the 5-year admission charts in the two hospitals, 60 patients met the criteria of enrolling in the study, including 29 (48.3%) male patients and 31 (51.7%) female patients. The median age was 46.5 years, ranging from 19 to 80 years. The duration of fever was 44 days. The mean duration of hospital admission was 13.98 days. Infectious diseases as the most common causes of defined etiology of FUO were found in 18 patients (30%) including tuberculosis (TB) in five patients (8.3%), which was diagnosed based on the findings of tissue pathology, radiographic evidence, or anti-TB trial. The other important infectious causes of FUO were brucellosis (n = 4), chronic prostatitis (n = 2), subacute endocarditis (n = 2), intra-abdominal abscess (n = 1), splenic abscess (n = 1), chronic complicated pyelonephritis (n = 1), visceral leishmaniasis (n = 1), and chronic osteomyelitis (n = 1).

Collagen vascular diseases were diagnosed in nine patients (15%) including adult-onset Still disease in two patients (3.3%), early undifferentiated arthritis in one patient (1.7%), giant cell arteritis in one patient (1.7%), systemic lupus erythematosus in one patient (1.7%), bullous pemphigoid in one patient (1.7%), Wegener's granulomatosis in one patient (1.7%), Behcet's disease in one patient (1.7%), and rheumatoid arthritis in one patient (1.7%).

Seven patients (11.6%) were found to have malignant diseases among whom, three (5.0%) had non-Hodgkin lymphoma, two had a final diagnosis of multiple myeloma (3.3%), one had colon cancer (1.7%), and one had pelvic malignant mass (1.7%). The cause of fever remained undiagnosed in 25 patients (41%) regardless of extensive workups during hospital stays and ambulatory follow-ups after hospital discharge (etiologies are listed in Table 1).

Fifty-five (91.7%) patients were discharged. Three patients (5.0%) did not complete their hospital course and left the hospital with their own release sheet. Two of the patients (3.3%) died during the hospital course, including one patient with non-Hodgkin lymphoma and bacterial sepsis and another with the undiagnosed cause of fever.

5. Discussion

The FUO syndrome always remains a big challenge and nightmare for clinicians (6). For proper management of FUO cases, we need to know the diversity and spectrum of

Table 1. Etiology of Fever in 60 Patients Admitted with the Diagnosis of Classic Fever of Unknown Origin

Cause of Fever	No. of Cases (%)
Infections	18 (30)
Tuberculosis	5 (8.3)
Brucellosis	4 (6.6)
Chronic prostatitis	2 (3.3)
Subacute bacterial endocarditis	2 (3.3)
Intra-abdominal Abscess	1 (1.7)
Chronic osteomyelitis	1 (1.7)
Splenic abscess	1 (1.7)
Chronic pyelonephritis	1 (1.7)
Visceral leishmaniasis	1 (1.7)
Collagen vascular diseases	9 (15)
Adult-onset Still's disease	2 (3.3)
Early undifferentiated arthritis	1 (1.7)
Wegener's granulomatosis	1 (1.7)
Giant cell arteritis	1 (1.7)
Systemic lupus erythematosus	1 (1.7)
Behcet's disease	1 (1.7)
Bullous pemphigoid	1 (1.7)
Rheumatoid arthritis	1 (1.7)
Neoplasms	7 (11.6)
Non-Hodgkin lymphoma	3 (5)
Multiple myeloma	2 (3.3)
Colon cancer	1 (1.7)
Pelvic malignant mass	1 (1.7)
Miscellaneous	1 (1.7)
Kikuchi disease	1 (1.7)
Undiagnosed	25 (41)

etiologies of the disease in our region. With a review of the literature, we found limited publications about adult FUO in Iran (8-11).

Infections have been the most important defined cause of FUO in the majority of reports including our study, with a relative frequency ranging from 27% to 42% (10-15). In our study, the etiologies of FUO were infections in 30% of the cases, followed by collagen vascular diseases in 15% and malignancies in 11.6%. According to many FUO surveys in our region and all over the world, infectious diseases are the most common causes of FUO and noninfectious inflammatory diseases and malignancies are the second and the third causes, respectively (8, 11, 16-18). With developing medical facilities and experience, the spectrum

of FUO causes is changing over time. The proportion of FUO patients diagnosed with infectious diseases is decreasing while the ones diagnosed with collagen vascular diseases and malignancy are increasing, specifically in developed countries (19-21).

Regarding the infectious causes, *Mycobacterium tuberculosis*, visceral abscess, and endocarditis are reported as the most frequent infections in different FUO cases (4, 19, 20). Among them, tuberculosis remains an important cause of FUO. In a study conducted in Pakistan, most of the infectious cases were pulmonary TB (22) but most researchers in our region found that extrapulmonary TB was more common than pulmonary TB (8, 16, 23, 24). In our series, tuberculosis constituted 27.7% of the infectious cases. We had two cases of TB peritonitis diagnosed by laparotomy, one case of miliary TB, and one case of smear-negative pulmonary TB confirmed by culture; one of the TB cases was a patient whose diagnosis was confirmed after starting the trial of anti-TB agents. It should be considered that the diagnosis of extrapulmonary TB is challenging due to the diversity of symptoms, the low level of suspicion among physicians, and the difficulty in obtaining an adequate sample for confirmation. Moreover, the diagnosis of this type of TB might require several diagnostic procedures by different medical disciplines and this adds to the difficulty and delay in diagnosis (25). Therefore, extrapulmonary TB should be considered in the differential diagnosis of all cases of FUO and adequate examinations must be done.

Another important infectious cause of FUO is brucellosis, which was found to be the most common cause of FUO in some series in our region (11, 26). In our study, we found the disease as the second prevalent infectious cause of FUO, which is in agreement with some FUO surveys in our neighboring countries such as Iraq, Turkey, and Saudi Arabia (16, 23, 27, 28).

Recent studies have shown an increase in FUO cases caused by collagen vascular diseases. It may be due to developments and new achievements in sophisticated serological and immunological diagnostic tests (19, 20, 29). In a Dutch prospective FUO study between 2003 and 2005, noninfectious inflammatory diseases were reported as the most common cause of FUO (21). Among connective tissue diseases, adult-onset Still's disease (juvenile rheumatoid arthritis), other variants of rheumatoid arthritis, and systemic lupus erythematosus were more prevalent in younger patients whereas temporal arteritis and polymyalgia rheumatic syndromes were more common in elderly patients (29). In our study, rheumatologic diseases were found as the second cause of FUO, which accounted for 15% of our patients. Of them, adult-onset Still's disease in two patients was the most common

rheumatologic disease. This rheumatologic disease has also been reported as the most common noninfectious inflammatory cause of FUO in other studies in our region (28, 30). On the other hand, some researchers have found systemic lupus erythematosus as the most common connective tissue disease among FUO cases (16, 22, 24, 26). Other connective tissue diseases as the causes of fever in our FUO cases were undifferentiated polyarthritis, rheumatoid arthritis, systemic lupus erythematosus, giant cell arteritis, Wegener's granulomatosis, Behcet's diseases, and bullous pemphigoid, each of which was found in one patient.

Malignancies as the other important cause of fever in patients with FUO can produce fever directly through the production and release of pyrogenic cytokines and indirectly by inducing spontaneous necrosis and/or creating secondary infections (31). Imaging studies such as computed tomography, magnetic resonance imaging, and especially PET/CT have facilitated the diagnosis of solid tumors recently (32, 33), but when it comes to hematologic malignancies, due to the absence of localized symptoms, they are still difficult to be diagnosed and they may present as FUO. According to various FUO studies all over the world, lymphoma was found to be the most common malignancy among FUO patients (4, 11, 16, 21, 23, 30). In our study, three out of seven malignant cases were diagnosed as non-Hodgkin lymphoma; one of the lymphoma cases was transferred to another hospital, ending up of a final diagnosis there. Based on our follow-up, he passed away in his further admission after the diagnosis of lymphoma. The other malignancy was pelvic malignant mass as sarcoma, which was found in one patient. Because the most common malignancies diagnosed in patients presenting with FUO are hematologic malignancies, it is very crucial for better management of patients with FUO to conduct careful lymph node examination of all palpable lymph nodes and radiological surveys for other lymph nodes, followed by taking biopsies, if indicated, and bone marrow aspiration biopsy.

In the present study, we could not find the cause of the fever in 41% of the patients during their hospital courses, which is the same as other studies (ranging from 9% to 51% since 1990) (20, 34, 35). Part of this undiagnosed fraction is possibly due to the limitations of our study because we had inadequate access to outpatient clinical data; the other part might be attributed to the lack of more specialized tests used in the FUO protocol, including PET scan or other new laboratory tests. Moreover, we should consider that compared to previous years, currently with the availability of more precise outpatient workups, more complicated cases are admitted to hospitals with an impression of FUO; thus, it is not surprising that fewer cases of FUO are admitted to hospitals and at the end of admission, the percentage of patients with undetermined diagnosis is in-

creased.

We found infections and rheumatologic diseases more frequently in women and malignancies more frequently in men. Higher mean age was noticed in patients with malignancies; mean fever degree was higher in patients with infectious causes and mean fever duration was longer in patients diagnosed with malignancies. We had longer mean hospital stay in patients diagnosed with infectious causes of FUO.

Fortunately, most of the FUO cases whose fever remains undiagnosed after extensive evaluations have a good prognosis (36) and their fevers mostly resolve spontaneously. As we followed up further admissions of our cases, they had a low rate of repeated hospital admissions due to internal medicine problems related to the fever or any FUO causes. Elderly patients and patients with malignancies have the poorest prognosis.

5.1. Conclusions

Improved technology and availability of more sophisticated laboratory tests and imaging studies with advances in interventional radiology might have led to better diagnosis of FUO etiologies in ambulatory settings. Therefore, more complicated, mysterious cases are currently admitted to hospitals, making it difficult for physicians to determine the etiologic causes of fevers. Like previous studies, we found infectious diseases as the most common cause of FUO among determined causes in our region. Collagen vascular diseases and malignancies were diagnosed as the second and the third common causes of FUO, respectively. Further prospective studies with close observation of FUO patients in future years, along with the focus on a new spectrum of diseases such as autoinflammatory spectrum and the use of new diagnostic procedures, will be helpful in decreasing the undetermined part of FUO.

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Footnotes

Authors' Contribution: Study concept and design: Mohsen Moghadami; analysis and interpretation of data: Mitra Amini and Mahsa Kiani; drafting of the manuscript: Fortes; critical revision of the manuscript for important intellectual content: Sina Bagheri and Mohsen Moghadami; statistical analysis: Mitra Amini.

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