

Clinical Profile and Etiologies of Classical Fever of Unknown Origin

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Abstract:

Objective: The causes of fever of unknown origin (FUO) vary depending on the region and time period. We herein present a study of patients with classic FUO, to investigate differences based on patient background factors, such as age and causative diseases, and changes that have occurred over time and diagnosis of FUO and provide the basis for the treatment of FUO.

Methods: From March 2016 to May 2017, the clinical data of 103 patients with FUO in Hunan People's Hospital, Changsha was retrospectively analyzed. The diagnosis, methods, etiologies, and their relationship with age, sex, fever duration, and period.

Results: Of these 103 FUO patients, 93 were confirmed to be with fever caused by infectious diseases in 55 cases out of 93 cases with 53.4%, connective tissue disease in 19 patients (18.5%), neoplasms in 13 cases (12.6%) and miscellaneous cause in 6 cases (5.8%). The causes were not identified in 10 cases. The total rate of diagnosis is 90.3%. The proportion of connective tissue disease in female patients was higher than in male patients, whereas the proportion of neoplasm was higher in male patients was higher than female patients. Infectious disease was the most common cause of FUO in all groups. CTD ranked the second in 21-39-year group and 40-59-year group, and neoplasm was second more common cause over 60-year group.

Conclusion: Infectious diseases (in particular, tuberculosis) remains the major cause of FUO. CTD and neoplasms also play important role in the development of FUO. The distribution of the FUO etiologies have certain difference on term of age, sex, duration of fever and period.

Keywords: Fever of unknown origin; Causes; Retrospective investigation.

1 Introduction

The term 'fever of unknown origin' (FUO) was first introduced by Petersdorf and Beeson in 1961 based on an analysis of 100 cases, and it was defined as recurrent fever $>38.3^{\circ}\text{C}$, lasting for >3 weeks, remaining undiagnosed after 1 week of in-hospital evaluation¹. Several decades later, the criteria of FUO diagnosis have changed and it is currently defined by lack of a definitive diagnosis after appropriate inpatient or outpatient evaluation. In view of the patient's clinical circumstances and underlying immune status, FUO was categorized into classic, nosocomial, neutropenic and human immunodeficiency virus (HIV)-associated FUO by Durack and Street in 1991². Now FUO is still a challenging clinical problem worldwide, with changed proportion of its major etiologies, despite the advances in diagnostic methods and tools³. 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 and diagnosis.

2 Patients and Method

2.1 Subject

One hundred and three patients meeting the criteria of classic FUO were enrolled in this study between March 2016 and May 2017 in Hunan People's Hospital, Department of Infectious Diseases. After detailed medical history and clinical examination of the patients had fever $>38.3^{\circ}\text{C}$ for more than three week processed for different diagnostic tests. The complete blood count, routine serum biochemical

analysis, erythrocyte sedimentation rate, C-reactive 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.

2.2 Statistical Analysis

Data were analyzed with SPSS version 22 and a value of $P \leq 0.05$ was considered statistically significant. Continuous variables were expressed as mean \pm standard deviation (SD), and were assessed using unpaired Student's t-test. The cross data was analyzed by chi-square test.

2.3 Results

Of the 103 patients, 62(60%) were male and 41 (40%) were female. The mean age of the patients was 42.6 ± 8.35 years. The median age was 43 years, ranging from 14 to 84 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. Of the 103 patients with FUO, Infectious disease in 55 cases, accounting for FUO 53.4%, 19 cases of connective tissue diseases, accounting 18.5%, tumor disease in 13 cases, accounting 12.6%, Other

diseases in 6 cases, accounting 5.8%, Diagnosis of unknown disease in 10 cases, accounting 9.7%.The most common findings on clinical examination were pallor, lymphadenopathy and splenomegaly. All the three findings were predominantly seen in patients with malignancy as a cause of F.UO. The mean hemoglobin of patients varied from 7.71±3.2 mg/dl, total leukocyte count of 4.84±3.0 cells/mm³, MCV from 76.95±3.3 and ESR from 21.66±2.8 mm. Hemoglobin tends to be on lower side in malignancy and connective tissue group (malignancy group 8.48±2.7, connective tissue group 7.71±3.2).The largest proportion of infectious diseases usually bacterial infection was the primary infection factor (37 cases, accounting for 67.3%). After collection of specimens from patients of F.UO were sent to the specimen line pathogen detection, and Co-culture. During the culture ,19 strains of bacteria were isolated. The positive rate of pathogens was 48.6%. Among them, 11 strains of gram-negative bacteria (61.1%), gram-positive bacteria (38.9%). There were following pathogen distribution: (1) 6 strains of Escherichia coli. (2) 1 strain of Klebsiellapneumoniae.(3)1 strain of Salmonella typhimurium. (4) 2 strains of brucella. (5) 3 strain of Staphylococcus. (6) 1 strain of Enterococcus faecium. (7) 1 strain of Enterococcus faecalis. (8) 1 strain of Actinobacillus. (9) 3 strains of Micro-coccu.

Table 1: Infectious disease and diagnostic methods

Etiology	Diagnostic Method
Septicemia serology, Blood culture	
Lung infection	Sputum culture, CT
T.B	CT,CXR, Sputum staining
Meningitis	Lumbar puncture,CT
Typhoid fever	Blood culture, Serology
UTI	Urine culture
Tonsillitis	Serology, Sputum culture
Viral Encephalitis	Lumbar puncture, Serology
H7N9 Influenza	Serology
Biliary tract Infection	CT, Blood culture
Herpes Simplex	Serology, DN
Fungal Infection	Skin culture,KOH preparation

Table 2: Non-infectious diseases and diagnostic Methods

Etiology	Diagnostic Methods
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Lymphoma	Bone marrow biopsy, PET, CT
Leukemia	Bone marrow biopsy, Ct
R.A	Immunological Investigation
SLE	ANA (+), DNA (+)
Non-Hodgkin lymphoma	Bone marrow biopsy, CT
Rheumatic Fever	Throat culture,ECG,Blood culture
Polymyositis	Muscle Biopsy
Dermatomyositis	Muscle Biopsy
Sjogren’s Syndrome	Gland Biopsy,SSB(+),SSA(+)
Lung Cancer	CT, Bone scan,CXR
Temporal Arthritis	Temporal artery Biopsy
Takayasa Arthritis	Aortography
Poly Arthritis Nodosa	Skin Biopsy
Reiter’s Syndrome	Stool culture, urine culture , Serology

3 Diagnosis

After a detailed medical history, physical examination, related inspection and diagnostic methods, 93 cases were diagnosed for F.UO from 103 patients.The diagnosis rate was 90.3%.According to diagnostic methods the classification of 93 F.UO patients, respectively, by serology and / or bacteriological examination in 31 cases (33.4%), body fluid or bone marrow examination in 10 cases (10.7%), imaging examination in 13 cases (13.9%),tissue biopsy in 12 cases (12.9%), surgery (laparoscopic) exploration in 2 cases (2.2%), Clinical procedure and / or treatment response in 25 patients (26.9%) . The rest of 24 cases were diagnosed by invasive test,accounting 25.8%, including 1 case of retro-peritoneal abscess puncture,thoracic puncture in 2 cases, lumbar puncture in 3 cases, bone marrow puncture in 5 cases, lymph node biopsy in 6 cases, skin biopsy in 1 case, 1 case of muscle biopsy, sub-lingual gland biopsy in 2 cases, colonoscopy (intestinal mucosal biopsy) 1 case, surgery (laparoscopic) exploration in 2 cases.

Table 3: Composition ratio of confirmed diagnosis of F.UO

Diagnosis	Numbers	Percentage
Serology	31	34.4%
Body Fluid	10	10.7%
Film Examination	13	13.9%
Biopsy	12	12.9%
Laproscopy	2	2.2%
Treatment	25	26.6%
Total	93	100%

4 Discussion

More than fifty years have passed since F.UO was first described in 1961¹, despite the advances of diagnostic techniques, F.UO is still a significant clinical problem. In the present study, the etiologies of F.UO were identified as follows: infections 53.4%, malignancies 12.6%, connective tissue diseases 18.5%, miscellaneous diseases 5.8%, and unidentified 9.7%. The causes of F.UO were in agreement with previous study .In our series of 103 cases of classical F.UO, that were observed over a period of one year, the

diagnosis of a specific cause was established in 93 cases (90.3%), with 10 cases (9.7%) remained undiagnosed.

We observed that in most of the cases of FUO were due to infectious diseases. Similar results were reported by various studies from Asia and the Middle East⁴. Infection still remains the most common cause of classical FUO all over the world even though the demographics vary from region to region¹⁰. As reported in former investigations, tuberculosis was the most frequent infection⁵, 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 tuberculosis⁶.

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 researches⁵. The increased proportion of lymphoma in malignancy may attribute to its climbed incidence rate⁷. AOSD has no specific diagnostic tool, it relies on clinical and laboratory findings and need to exclude other diseases, study have reported that AOSD was not a rare cause of FUO in China⁸.

For the diagnosis of FUO, the most common methods for the diagnose were serology, bacteriology, imaging and clinical diagnosis (clinical process and / or treatment response). A small number (25.8%) required invasive tests such as puncture of body fluids or bone marrow, tissue biopsy and laparoscopic exploration

FUO patients diagnosed with infectious diseases, among them the bacterial infection was common, accounting for 67.3%. The gram-negative bacteria detection rate was higher than gram-positive bacteria. The most common bacterial infections are sepsis, pulmonary infection and tuberculosis. Suppurative bacterial infections are commonly caused by Staphylococcus and Enterobacteriaceae. Among them, Escherichia coli is the most common bacteria followed by Staphylococcus aureus, mainly diagnosed by blood culture and bone marrow biopsy.

Most patients have received antibiotic treatment before admission so the detection rate of etiology was low in lung infection, biliary tract infection, abdominal (organ) abscess and urinary tract infection. There are also associated with the body immune function of the underlying diseases such as diabetes, granulocyte deficiency and resulting in clinical unclear manifestations, and the diagnosis is unknown. The diagnosis of Such depends mainly on imaging, puncture and drainage and empirical anti-infected treatment.

According to domestic and international reports, in the patients of FUO, the proportion of tuberculosis infectious diseases was slightly lower than other types of infection. The possible decline in the rate of TB development because the development of specific diagnostic tools and advancement in the treatment of tuberculosis.

In the diagnosis of tuberculosis, the number of extra-pulmonary tuberculosis accounted for more than half. Pulmonary tuberculosis mainly includes tuberculous pleurisy, tuberculous peritonitis,

tuberculous meningitis, intestinal tuberculosis, spinal tuberculosis and so on. The Biochemical examination, tuberculosis culture, smear positive rate is low, and imaging examination of typical lesions was difficult to find and unclear. So the diagnosis the pulmonary tuberculosis was confirmed Often through the puncture, colonoscopy, surgical exploration and other invasive examination to take pathological biopsy found typical lesions, and diagnostic anti-TB treatment.

In this group of patients, autoimmune diseases in 19 cases and accounting 18.5%. The systemic lupus erythematosus and adult Still disease are the most common (52.6%)⁹. Such diseases have their general characteristics, generally more common in young women (this group of women accounted for 84.2%, the average age of 34.1 years). Nearly all cases happened to be females, because the incidence of CVD is higher in females. SLE was missed initially because of less common presenting symptom. Most of them had fever, lymphadenopathy and arthritis. The other common signs and symptoms are anorexia, psychosis, malar rash, butterfly rash, oral ulcer, leukopenia, plural effusion and vasculitis. The mostly involved organs are the lung, kidney, blood system and endocrine system. In SLE the level of ESR mostly elevated. Auto-antibodies such as ANA, DNA and smith antibodies were positive.

In this this group of patients, Sjogren's syndrome diagnosed by lower lip gland biopsy in 2 cases. The CTD, Polymyositis and dermatomyositis diagnosed in 1 case muscle biopsy. Such diseases glucocorticoid treatment effect is obvious, antibiotics ineffective. Serum ferritin was significantly elevated in adult Still disease. Studies have shown that it can be used as adult Still disease diagnosis and determine the degree of disease activity specific indicator⁵.

Other causes of FUO in this group of patients, including drug hypersensitivity syndrome, Infectious mononucleosis, sub-acute thyroiditis, acute sub-mandibular gland inflammation. In these, the drug hypersensitivity syndrome and infectious mononucleosis more common. Through history, symptoms, signs, laboratory tests and refer to the relevant diagnostic criteria can be diagnosed in general.

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. The infections, CTD and malignancies are the most common causes of FUO. 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.

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