Retrospective Analysis of 1,641 Cases of Classic Fever of Unknown Origins

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Abstract

Background We present a study of the etiological factors and clinical features of classic fever of unknown origins (FUO) to provide evidence for related clinical diagnosis and treatment. **Methods** We analyzed 1,641 cases of patients with classic FUO hospitalized in West China Hospital of Sichuan University during January 1, 2011 and December 31, 2017, analyzed the etiological factors of classic FUO, explored and screened the laboratory indicators related to infectious diseases, and compared the above data with the clinical features of tuberculosis and lymphoma, which are difficult to diagnose. **Results** 1,504 patients were diagnosed through various examination or diagnostic treatment methods, and the diagnosis rate was 91.65%. 48.69% (799) were infectious diseases, of which tuberculosis was the most common, accounting for 19.50% (320). 19.26% (316) were connective tissue diseases, among which adult-onset Still's disease (AOSD) was the most common, accounting for 5.42% (89). 16.94% (278) were neoplastic diseases, and lymphoma was the most common malignant tumor, accounting for 8.71% (143). 6.76% (111) were other diseases; and 8.35% (137) were unclear. We found that there were no significant differences between the symptoms, signs, and non-specific routine examination results of tuberculosis and lymphoma. Tuberculosis-related examinations and pathological examinations used more frequently. **Conclusion** The causes of classic FUO are mostly infectious diseases, in which tuberculosis accounts for a large proportion. Non-infectious diseases that cause FUO are mainly connective tissue diseases and malignant tumors. Tuberculosis and lymphoma are relatively difficult to diagnose. The causes of most cases of classic FUO could be ascertained.

Background

Fever of unknown origins (FUO) is a special type of fever and a common disease in internal medicine. However, due to its complex etiology, lack of characteristic clinical manifestations, and insufficient laboratory examination indicators, it often baffles clinicians in diagnosis. Petersdorf and Beeosn suggested the following criterion for FUO: fever higher than 38.3 °C (101 °F) on several occasions; persisting without diagnosis for at least 3 weeks; at least 1 week's investigation in hospital. The advantage of this diagnostic criterion is the elimination of short-term self-healing but unexplained acute fever, certain self-limiting viral infections, and functional fever characterized by hypothermia. Therefore, symptoms that meet the criterion are called classic FUO^[1]. We retrospectively analyzed 1,641 cases of patients with classic FUO hospitalized in West China Hospital of Sichuan University between January 1, 2011 and December 31, 2017, analyzed the etiological factors of classic FUO, and compared the above data with the clinical features of tuberculosis and lymphoma, which are difficult to diagnose, in order to provide help for related clinical diagnosis. The report is as follows.

Methods

Clinical Data

We collected cases of patients with fever hospitalized in West China Hospital, Sichuan University between January 1, 2011 and December 31, 2017 and selected the medical records of patients with classic FUO. The selected patients were 14 years old and older, were hospitalized for more than a week, and had a fever higher than 38.3 °C (101 °F) on several occasions and persisted for at least 21 days. We screened out patients who were diagnosed with HIV infection before hospitalized in West China Hospital, patients with immunodeficiency, and pregnant women. 1,641 cases of classic FUO were finally selected.

Diagnostic Methods

Diagnosis can be based on one of the following five criteria: 1) clinical manifestation and positive histopathological examination (including bone marrow examination) results; 2) clinical manifestation and obtained pathogenic evidence (the same strain or body fluid is produced through blood culture of more than 2 times, and pathogen is found in it one time or more); 3) clinical manifestation and obtained radiographic evidence and 1 pathogenic evidence; 4) there is clinical manifestation, antigen is detected positive once or more times, and therapeutic reaction is observed; 5) the diagnostic criteria for a certain disease are met. The clinical diagnostic criteria are: in the case of the diagnostic criteria are not met, clinical manifestation shall be observed, radiographic evidence or general laboratory evidence shall be obtained, and therapeutic reaction shall be observed.

Results

Brief Introduction of the Cases Selected for Study

Among the 1,641 patients, 46.13% (757) were male and 53.87% (884) were female; 10.60% (174) patients were under the age of 20; 36.14% (593) were between the ages of 20 and 39; 30.23% (496) were between 40 and 59; and 23.03% (378) were aged 60 or older. 91.65% (1,504) of the 1,641 cases of classic FUO were diagnosed and the causes of 65.69% (1,078) cases were ascertained; 25.96% (426) cases of clinically diagnosed; and the causes of 8.35% (137) cases were unclear. The causes of the various cases of FUO are shown in Table 1. The percentages of causes ranked by gender and age are shown in Tables 2 and 3, respectively. The durations of FUO caused by different diseases vary. When no diagnosis is made, the duration from the onset of fever to the discharge time is counted. The durations of the various cases of FUO and percentage of each cause are shown in Table 4. Different types of diseases are often diagnosed in different ways, and the percentages of methods through which the different diseases were finally diagnosed are shown in Table 5.

Comparison between the Clinical Data of Lymphoma and Tuberculosis

The results of our study showed that the most common infectious disease that caused FUO was tuberculosis, and the most common non-infectious disease that caused FUO was lymphoma; the diagnosis of these two diseases took a long time. The clinical manifestations of lymphoma other than long-term fever are often not characteristic, which brings many difficulties to diagnosis of the disease. In this respect, the infectious disease of tuberculosis is similar to lymphoma. Lymphoma and tuberculosis

are the neoplastic and infectious diseases that are most difficult to diagnose, which can be glimpsed in their fever durations. Both tuberculosis and lymphoma account for a large proportion of diseases that cause fever over 90 days. The clinical manifestations of tuberculosis and lymphoma also have many similarities. For example, some tuberculosis and lymphoma patients have enlarged lymph nodes or spleen, and have higher peak of body temperature, so sometimes the two are difficult to distinguish. We conducted a comparative study of the clinical manifestations of the two diseases, as shown in Table 6.

Through the comparison between the above basic clinical manifestations and laboratory investigation, no sufficient factors ($P>0.05$) suggestive of lymphoma could be found. Therefore, specific investigations are needed to distinguish lymphoma from tuberculosis.

Discussion

The results of our retrospective analysis showed that the most common cause of classic FUO is infectious disease, which are followed by connective tissue disease. The results are consistent with most previous studies at home and abroad [2] [3] [4]. The causes of FUO are related to diseases, among which the incidence of connective tissue disease is higher in women than men, while the incidence of infectious disease is more common in men, and the incidence of neoplastic disease is not significantly correlated with gender. There is no significant difference in the incidence of infectious disease in all age groups, and connective tissue disease is more common in patients under 40 years of age, and the incidence of neoplastic disease in patients over 40 years old increases. The time from onset to final confirmation of the cause of FUO also varies. Through the retrospective study, we found that the diagnoses of infectious diseases in West China Hospital were not significantly associated with durations of fever, while foreign studies have shown that the time required for diagnosis of infectious disease is usually short [4]. The lung infections and biliary tract infections involved in this study could not be diagnosed until more than 30 days after the onset of fever. This may be related to the fact that Chengdu is located in the western part of China, and the distribution of primary medical resources is uneven, resulting in some patients unable to seek medical treatment in time. Generally, after hospitalization, FUO patients will routinely undergo chest and abdominal radiographic, bone marrow needle biopsy, and immune function examinations. Therefore, most of the connective tissue diseases and neoplastic diseases involved in this study were diagnosed quickly.

Among the infectious diseases that cause FUO, tuberculosis is the most common, but a large number of tuberculosis patients were not diagnosed by pathogenic investigation, but were diagnosed based on the effectiveness of diagnostic anti-tuberculosis treatment. By reviewing the results of adjuvant examinations, we found that in most tuberculosis patients with long-term fever, the white blood cell count was normal or increased, the proportion of neutrophil was increased, the erythrocyte sedimentation rate and C - reactive protein were increased, and the increase of procalcitonin was lower than that in patients with common bacterial infections. Some other tuberculosis patients, through bone marrow biopsy, were

found to have DNA fragments of mycobacterium tuberculosis, or that their bone marrow smears were positive for acid-fast staining, which further reminds clinicians of the importance of bone marrow biopsy for patients with FUO. In addition to tuberculosis, some infectious diseases such as kala-azar also require bone marrow biopsy to be effectively diagnosed.

Due to the popularity of radiographic examination methods such as CT and MRI, FUO caused by deep abscess has become rare, and only 19 cases were involved in our study. FUO caused by sepsis is still common, and there are some special pathogens like brucellosis. Therefore, patients with FUO should receive blood culture examination during fever. When deep abscess exists and is not easy to drain, positive blood cultures can also help reasonable selection of antibacterial drugs.

Among the connective tissue diseases that cause FUO, AOSD is the most common. By reviewing the results of adjuvant examination of cases diagnosed as AOSD, we found that, in most AOSD patients serum iron ferritin was significantly increased, and procalcitonin was also increased. Procalcitonin, as an indicator of serologic evaluation of the presence of bacterial infection, has attracted increasing attention from clinicians. However, exclusion of infection is necessary in diagnosis of AOSD, so the increase of procalcitonin brings some interference to the diagnosis. AOSD is characterized by increased white blood cell count and mainly neutrophil. It is sometimes difficult to distinguish AOSD from bacterial infection. Therefore, the typical signs of rash and the increase of ferritin should receive special attention. Compared with AOSD patients, ferritin in patients with bacterial infections tends to be normal or only slightly increased.

Some connective tissue diseases have positive autoantibodies, but they cannot be classified as a specific autoimmune disease. The diagnoses of undifferentiated connective tissue diseases in our hospital usually require diagnostic treatment of glucocorticoids or immunosuppressive agents to be confirmed.

Similar to FUO caused by deep abscesses, FUO caused by solid tumors has become rare due to the popularity of radiographic examination methods. Only 32 solid tumors were involved in our study, accounting for 1.95% of the causes of all the cases of FUO. Hematological tumors, especially lymphoma, were the most common neoplastic diseases causing FUO. In our retrospective study, many cases of diffuse large B-cell lymphoma and NK\T-cell lymphoma were found, and a large proportion of them were secondary to EB virus infection. The clinical manifestations of lymphoma are diverse. We found that a large proportion of the lymphoma patients had skin lesions and nasopharynx ulcers. The lymphoma patients were diagnosed by skin or mucosal biopsy. It should be noted that the bone marrow biopsy of such patients often has no positive results, so it is necessary to pay attention to physical examinations to

understand whether there are skin and mucous membrane related lesions in order to facilitate timely biopsy. In addition to bone marrow biopsy, attention should be paid to the flow cytometry of bone marrow, serous membrane effusion, and peripheral blood. Some lymphoma and multiple myeloma's bone marrow biopsies do not produce specific indications, but can be diagnosed by flow cytometry.

Sometimes, patients with hematological tumors cannot receive invasive examinations such as bone marrow puncture due to reasons such as thrombocytopenia and coagulation dysfunction, but they should actively receive routine blood tests and blood biochemical tests. In patients diagnosed with hematological malignancies, the probability of finding abnormal cells by routine blood tests is high; the detection of significant increase in lactate dehydrogenase and triglycerides through blood biochemical tests is suggestive. It has also been reported at home and abroad that 66.66% of patients with non-Hodgkin lymphoma have increased lactate dehydrogenase; the increase of lactate dehydrogenase in patients with highly malignant lymphoma is greater than that in patients with low-grade malignant lymphoma ($P<0.05$)^[5]. Some scholars even suggested that the level of lactate dehydrogenase could be used as an independent indicator^[6] to judge the prognosis of patients with lymphoma. Our study also shows that lymphoma accounts for the highest proportion of neoplastic diseases causing FUO, so clinicians should pay more attention to markedly increased lactate dehydrogenase.

The clinical manifestations of lymphoma and tuberculosis causing FUO are not characteristic, and it is often difficult to distinguish between the two, but we failed to find the clinical features and routine laboratory investigation methods for distinguishing between lymphoma and tuberculosis. Diagnosis of lymphoma often needs to be confirmed by pathological examination, but serological and pathogenic examinations of tuberculosis are often suggestive, which reminds clinicians to complete specific examinations (such as tuberculosis infection T-cell interferon release test, PPD skin test, tuberculosis antibody test, etc.) related to tuberculosis for patients with FUO caused by diseases that are difficult to diagnose, so as to shorten the time required for diagnoses and reduce invasive examinations.

Of the 137 patients who were discharged from the hospital with unclear causes of their FUO, only a few were seriously ill and most were well. These patients are characterized by a long course of disease, non-suggestive adjuvant investigations, slightly increased inflammatory indicators such as blood sedimentation and C - reactive protein, and effective treatment with anti-inflammatory drugs such as glucocorticoids and non-steroidal anti-inflammatory drugs. PET-CT has been reported at home and abroad to be of great significance for the diagnoses of cases of classic FUO that are difficult to identify^[7]^[8]. However, due to the constraints of economic development in western China, few FUO patients can receive PET-CT examination in our hospital, which needs further improvement in the future.

Conclusions

The causes of classic FUO are mainly infectious diseases, among which tuberculosis accounts for a large proportion. Non-infectious diseases causing FUO are mainly connective tissue diseases and malignant tumors. Many cases of connective tissue diseases that cause FUO are AOSD. And lymphoma is the most common malignancy that causes FUO. Lymphoma and tuberculosis are difficult to distinguish only by routine examinations, and tuberculosis-related serology, pathogen examinations and pathological examinations are needed in diagnoses of the two diseases. Clinicians should conduct detailed consultation and physical examination for classic FUO patients, and attach importance to laboratory, radiographic, pathogenic, and pathological investigations and other adjuvant methods. Through detailed clinical investigations and analyses, most cases of classic FUO can be diagnosed.

Declarations

Ethics approval and consent to participate

All data collection was approved and supervised by the ethical committees of West China hospital of Sichuan University. All the experiments were performed in accordance with the Helsinki Declaration ethical guidelines. All patients provided informed written consent for the collection of samples and subsequent analysis. The written informed consents have been obtained from the parents or legal guardians of the subjects under 18.

Consent for publication

Not applicable.

Availability of data and materials

The data are available from the first author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

1. Study conception and design: GYZ, XJL
2. Acquisition, analysis and/or interpretation of data: GYZ, YZ, CJZ, HY
3. Drafting/revision of the work for intellectual content and context: GYZ, ZZL, YBL, GGT, JYQ
4. Final approval and overall responsibility for the published work: LS. All authors have read and approved the manuscript, and ensure that this is the case.

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Tables

Table 1 Causes of the 1,641 Cases of FUO

Cause of FUO	Number of Cases	Percentage (%)
Infectious Diseases	799	48.69
Bacterial Infections	591	36.01
Tuberculosis	320	19.50
Septicemia	117	7.13
Infective Endocarditis	47	2.86
Biliary Tract Infection	32	1.95
Pulmonary Infection	15	0.91
Urinary Tract Infection	13	0.79
Peritonitis	11	0.67
Liver Abscess	7	0.43
Brucellosis	7	0.43
Abdominal Abscess	6	0.36
Renal Abscess	5	0.30
Non-tuberculosis Mycobacteria Infection	4	0.24
Chronic Tonsillitis	3	0.18
Typhoid	3	0.18
Retropharyngeal Abscess	1	0.06
Viral Infections	168	10.24
Epstein-Barr Virus Infection	83	5.06
Cytomegalovirus Infection	33	2.01
Herpes Simplex Virus Infection	12	0.73
Viral Meningitis	9	0.55
HIV Infection	8	0.49
Rubella Virus Infection	3	0.18
Parvovirus Infection	1	0.06
Other Viral Infections	19	1.16
Invasive Fungal Infections	15	0.91
Pulmonary Aspergillosis	7	0.43
Histoplasmosis	5	0.30
Aspergillus Sinusitis	3	0.18
Parasitic Infection	16	0.98
Kala-azar	11	0.67
Paragonimiasis	2	0.12
Toxoplasma Gondii Infection	2	0.12
Malaria	1	0.06
Other Pathogen Infections	9	0.55
Mycoplasmal Pneumonia	7	0.43
Tsutsugamushi	2	0.12
Connective Tissue Diseases	316	19.26
AOSD	89	5.42
Systemic Lupus Erythematosus	31	1.89
Systemic Vasculitis	29	1.77
Necrotic Lymphadenitis	28	1.71
Sjogren Syndrome	23	1.40
Polymyalgia Rheumatica	12	0.73
Dermatomyositis	12	0.73
Rheumatoid Arthritis	11	0.67
Erythema Nodosum	9	0.55
Reactive Arthritis	8	0.49
Ankylosing Spondylitis	5	0.30
Autoimmune Liver Disease	5	0.30
IgG4-related Diseases	5	0.30
Systemic Sclerosis	4	0.24
Polymyositis	2	0.12
Behcet's Disease	2	0.12
Autoimmune Encephalitis	1	0.06
Rheumatic Fever	1	0.06
Mixed Connective Tissue Disease	18	1.10

Undifferentiated Connective Tissue Disease	21	1.28
Neoplastic Diseases	278	16.94
Lymphoma	143	8.71
Leukemia	61	3.72
Multiple Myeloma	31	1.89
Hepatoma	12	0.73
Malignant Histiocytosis	11	0.67
Lung Carcinoma	7	0.43
Renal Carcinoma	4	0.24
Soft Tissue Sarcoma	3	0.18
Prostate Cancer	3	0.18
Thyroid Carcinoma	2	0.12
Ovarian Cancer	1	0.06
Other Diseases	111	6.76
Undetermined	137	8.35
Total	1,641	100

Table 2 Percentages of Causes of FUO Ranked by Gender

Gender	Infectious Diseases [%]	Connective Tissue Diseases[%]	Neoplastic Diseases[%]	Other Diseases[%]	Undetermined [%]	Total
Male	439 [58.11]	107[14.13]	127[16.67]	40[5.28]	44[5.81]	757
Female	360 [40.73]	209[23.64]	151[17.08]	71[8.03]	93[10.52]	884
Total	799 [48.69]	316[19.26]	278[16.94]	111[6.76]	137[8.35]	1,641

Table 3 Percentages of Causes of FUO Ranked by Age

Age	Infectious Diseases [%]	Connective Tissue Diseases[%]	Neoplastic Diseases[%]	Other Diseases [%]	Undetermined [%]	Total
≤20	80[45.97]	50[28.74]	23[13.22]	10[5.75]	11[6.32]	174
20-39	290 [47.90]	185[31.20]	49[8.26]	16[2.70]	53[8.94]	593
40-59	253 [51.01]	34[6.85]	117[23.59]	42[8.47]	50[10.08]	496
≥60	176 [46.58]	47[12.43]	89[23.54]	43[11.37]	23[6.08]	378
Total	799 [50.11]	316[20.07]	278[16.17]	111[4.31]	137[8.35]	1,641

Table 4 Durations of the Various Cases of FUO and Percentage of Each Cause

Duration Of FUO (Days)	Infectious Diseases %	Connective Tissue Diseases %	Neoplastic Diseases %	Other Diseases %	Undetermined %	Total
21-30	239 46.96	135 26.52	62 12.18	62 12.18	11 2.16	509
31-60	230 42.83	93 17.32	166 30.91	41 7.64	7 1.30	537
60-90	162 59.79	24 8.85	46 16.97	8 2.95	31 11.44	271
91-180	81 55.86	38 26.21	4 2.76	0 0	22 15.17	145
180	87 48.60	26 14.53	0 0	0 0	66 36.87	179
Total	799 48.69	316 19.26	278 16.94	111 6.76	137 8.35	1,641

Table 5 Methods through which the Diseases were diagnosed

Type Of Disease	Laboratory Investigation %	Radiographic Investigation %	Invasive Investigation %	Diagnostic Treatment %	Total
Infectious Diseases	257(32.16)	216(27.03)	90(11.26)	236(29.55)	799
Connective Tissue Diseases	164(51.90)	0(0)	74(23.42)	78(24.68)	316
Neoplastic Diseases	0(0)	53(19.06)	225(80.94)	0(0)	278
Other Diseases	19(17.12)	27(24.32)	5(4.50)	60(54.06)	111
Total	440(29.25)	296(19.68)	394(26.19)	374(24.88)	1504

Note: diagnostic treatment includes drug discontinuance and clinical observation

Table 6 Comparison between the Clinical Data of Lymphoma and Tuberculosis Patients

	Lymphoma n=86	Tuberculosis n=174	P-value
Age ¹	32(17-67)	33(20-71)	0.082
Gender (Male) ²	42(48.3%)	91(52.87%)	0.394
Duration of Fever (Days) ³	50(25-380)	49(23-100)	0.342
Highest Body Temperature (°C) ³	39.0(38.4-40.1)	39.0(38.3-39.8)	0.451
Type of Fever ⁴			0.089
Intermittent Fever	21	53	
Remittent Fever	42	104	
Irregular Fever	23	17	
Duration of Fever ⁴			0.063
6: 00-12:00	1	2	
12:00-18:00	52	112	
18:00-next day 6:00	23	41	
Irregular	10	19	
Chills ⁴			0.071
No	31	74	
Yes	55	100	
Shiver ⁴			0.195
No	62	138	
Yes	24	36	
Peripheral Lymphadenopathy ⁴			0.570
No	67	131	
Yes	19	43	
Splenomegaly ⁴			0.613
No	69	129	
Yes	17	45	
WBC $\times 10^9/L$ ³	6.27(1.27-12.65)	8.44(3.22-15.02)	0.071
HB g/L ³	105(74-129)	102(76-132)	0.174
PLT $\times 10^9/L$ ³	211(89-337)	206(81-382)	0.067
ESR mm/h ³	29(2-120)	62(15-120)	0.057
CRP mg/dL ³	66.8(1.73-166)	59.2(10.4-169)	0.054
PCT ng/mL ³	0.52(0.04-3.16)	0.66(0.04-4.43)	0.192
LDH U/L ³	317(162-764)	235(118-629)	0.063

Note: 1: T test; 2: chi-square test; 3: Mann-Whitney U test; 4: Fisher's exact test