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Research Article

Fever of Unknown Origin: A Diagnostic Pitfall

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Abstract

Objectives: The prevalence of the underlying disease in fever of unknown origin (FUO) has changed due to emerging laboratory and imaging methods. This study aims to present the recent etiological classification of FUO in Turkey.

Methods: Physical examination, laboratory analysis, imaging methods and histopathology of the interventional procedures were analyzed, and the diagnosis were reported in a total of 50 patients those admitted to Istanbul University, Istanbul Faculty of Medicine Hospital and Memorial Bahcelievler Research Hospital, between January 2023 and January 2024.

Results: A total of 50 patients (mean age 54.7±19.6 years, 58% males) were included in the study. After detailed examination, infectious diseases were diagnosed in 30% of the patients, followed by non-infectious inflammatory diseases (NIID) in 28%, malignancies in 20%, other etiology in 6% and undiagnosed in 16% of the patients. Extra-pulmonary tuberculosis was diagnosed in 6 patients (40% of the infectious diseases). In NIID group (n=14), 5 patients had adult Still's disease, and in malignant diseases group (n=10), 8 patients had lymphoma. Subacute thyroiditis was diagnosed in 2 patients.

Conclusion: Infectious diseases remain the primary cause of FUO, although the associated prevalence was decreased significantly when compared to previous reports. The prevalence of NIID in FUO etiology was increased in the last decades.

Keywords: Fever of unknown origin, inflammation, etiology

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Petersdorf and Beeson defined the concept of Fever of unknown origin (FUO) in 1961.[1] In 1991, Durack and Street suggested a modification which include the diagnosis could not be made despite three outpatient clinic visits or three days in hospital.[2]

Classic FUO has been associated with hundreds of diseases in the literature, and its causes are generally categorized into four main groups: Infections, non-infectious inflammatory diseases (NIID), malignancies, and others.[3] In addition to classic FUO, the investigative approaches and etiological factors may vary among healthcare-associated, immunosuppressed patients, and travel-related FUO.[4] There are various diagnostic and work-up protocols in the approach to FUO. Baseline biochemical parameters and appropriate advanced imaging techniques are applied by analyzing the patient's age, gender, geographical region of residence, family history, and detailed physical examination findings.[5] Despite this, the cause cannot be found in 10-25% of cases of FUO. Although the use of PET-CT has led to a significant decrease in FUO cases, it has been observed that most unexplained FUO causes are inflammatory and malignant rather than infectious diseases.[6]

In this article, we aimed to determine our current diagnostic practice on FUO.

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Methods

In this study, physical examination, laboratory analysis, imaging methods and histopathology of the interventional procedures were analyzed, and the diagnosis were reported in a total of 50 patients those admitted to Istanbul University Faculty of Medicine Hospital and Memorial Bahcelievler Research Hospital, between Jan 2023 and Jan 2024. Patients with a temperature of more than 38.3°C on intermittent measurements and a fever for more than three weeks that could not be diagnosed despite a 3-day hospital stay and one week of further investigations and tests were included in the study. Patients under 18 years of age were not included in the study.

After a detailed anamnesis taking and physical examination, a complete blood count was performed, including leukocytes, Hgb, Hct, MCV, platelets, neutrophils, lymphocytes, erythrocyte sedimentation rate, creatinine, BUN, AST, ALT, ALP, GGT, LDH, ferritin, CRP, procalcitonin and d-dimer. Specific microbiological tests (Wright, EBV, CMV, HIV, PPD, Quantiferon, etc.) and rheumatological tests (RF, ANA, ENA, etc.) were recorded. Imaging studies, including direct radiography, CT, MR, PET-CT, and ECHO, were performed during hospitalization. Interventional studies were also conducted, and histopathological examination of biopsy tissues was carried out.

The distribution of patient diagnoses, age groups, diagnostic methods, and laboratory parameters were examined.

Statistical Methods

SPSS (Statistical Package for the Social Sciences) program version 21.0 (IBM, Armonk, NY, USA) was used for statistical data analysis. The parameters were assessed for normality using the Kolmogorov-Smirnov test. Descriptive statistics were expressed as mean±standard deviation or median (minimum-maximum) for discrete and continuous numerical variables and as number of cases and (%) for categorical variables. Cross-tabulation statistics were used to compare categorical variables (Chi-square, Fisher). Non-parametric data that did not conform to normal distribution were compared using Kruskal Wallis tests. After utilizing Kruskal-Wallis and chi-square tests to assess pairwise comparisons, Post Hoc analysis with Bonferroni correction was applied. Results were defined as $p<0.05$ statistical significance.

Results

Fifty patients, 29 males (58%) and 21 females (42%), were included in our study. The mean age of the patients was 54.7±19.6 years (59.2±17.9 in females and 51.5±20.4 in males). The median time from admission to diagnosis was 8 (0-27) days, and the total hospital stay was 12 (2-41) days. After detailed examination, 15 patients had infectious diseases (30%), followed by NIID in 14 patients (28%), malignancies in 10 patients (20%), and other etiology in 3 patients (6%). No etiology could be found in 8 patients (16%). In the infectious disease group (n=15), tuberculosis was diagnosed in 6 patients and 2 patients had infective endocarditis. In the NIID group, 5 patients had adult Still's disease, followed by 4 patients with idiopathic recurrent pericarditis and 2 patients with vasculitis. In the malignancy group, 6 patients had non-Hodgkin's lymphoma and 2 patients had Hodgkin's lymphoma. In the other group, 2 patients had subacute thyroiditis (Table 1).

All patients complained of fever and 76% experienced involuntary weight loss. Physical examination revealed lymphadenomegaly in 52%, hepatosplenomegaly in 32%, skin findings in 6%, and joint findings in 6% of the patients. When analyzing the patients' laboratory parameters, the

Table 1. Etiological distribution of patients

	Number of patients	(%)
Infection Disease	**15**	**30**
Tuberculosis	6	12
Infective endocarditis	2	4
Hepatic abscess	1	2
Brucellosis	1	2
Spondylodiscitis	1	2
Intra-abdominal Abscess	1	2
Prostate abscess	1	2
Osteomyelitis	1	2
Cat scratch disease	1	2
Non-infectious inflammatory diseases (NIID)	**14**	**28**
Adult Still's Disease	5	10
Idiopathic recurrent pericarditis	4	8
Vasculitis		
Giant Cell Arteritis	1	2
Cryoglobunemic Vasculitis	1	2
Inflammatory Bowel Diseases	1	2
Hemophagocytic Lymphohistiocytosis	1	2
Acute pericarditis	1	2
Malignancies	**10**	**20**
Non-Hodgkin Lymphoma	6	12
Hodgkin Lymphoma	2	4
Pancreatic adenocarcinoma	1	2
Larynx Ca	1	2
Other Diseases	**3**	**6**
Subacute Thyroiditis	2	4
Common Variable Immunodeficiency	1	2
Undiagnosed	**8**	**16**

median (min-max) Hgb was found to be 10.3 (7-15.9) g/dL lower. Median ALT levels were 22.1 (4.9-455) U/L, ALP 93 (20.8-787) U/L, GGT 53.5 (9-880) IU/L, LDH 227. 5 (107-1353) mg/dL, ferritin 523 (34-35438) ng/mL, CRP 93 (3-443) mg/l, procalcitonin 0.2 (0.01-45.34) ng/mL and erythrocyte sedimentation rate 58 (9-125) mm/h were found to be elevated. There was no significant difference in mean age, physical examination findings (skin involvement, joint findings, lymphadenopathy, and hepatosplenomegaly), biochemical parameters (leukocytes, Hgb, platelets, neutrophils, lymphocytes, erythrocyte sedimentation rate, creatinine, AST, ALT, ALP, GGT, LDH, ferritin, CRP, procalcitonin) between males and females (p>0.05).

As there were only three patients in the other disease group, this group was excluded, and the other groups were compared in terms of physical examination findings, biochemical parameters, imaging methods, and interventional procedures performed.

When the physical examination findings (lymph adenomegaly hepatosplenomegaly, skin findings, joint findings) and biochemical parameters were compared with the patient groups, a significant difference was observed only in serum GGT levels (p=0.037). When post-hoc Kruskal-Wallis analyses were performed, a significant difference was observed between the undiagnosed group and the malignant group (p=0.048), and no significant difference was observed in other comparisons (p>0.05) (Table 2).

When the imaging studies (direct radiography, CT, MR, PET-CT, ECHO), and interventional procedures (thoracentesis/paracentesis, bronchoscopy, lumbar puncture data, colonoscopy/gastroscopy results, and biopsy results include lymph nodes, bone marrow, liver, skin, temporal artery, thyroid, kidney) were compared with the patient groups, a significant difference was observed only for PET-CT imaging and bone marrow biopsy (p=0.017 and p=0.031, respectively) and when post-hoc chi-squared analyses were performed for PET-CT, a significant difference was observed between the malignant and undiagnosed infectious disease and NIID groups (p<0.05). In addition, when post hoc chi-squared analyses were performed for bone marrow biopsy, a significant difference was observed between the infectious disease group and the malignant group (p<0.05), and no significant difference was observed in other comparisons (p>0.05) (Table 3).

Discussion

Our study revealed that infectious causes of FUO are decreasing in Turkey with the concurrent increase in the prevalence of NIID as diagnostic and imaging facilities have improved.

Fever of unknown origin has been important since the 1960s. Despite changes in living conditions, the transition to modern life, technological developments, and biochem-

Table 2. Comparison of physical examination, diagnostic and biochemical parameters in different groups

Laboratory Findings	Infection disease	NIID	Malignancies	Undiagnosed	p
Lymphadenomegaly	7 (46.7%)	7 (50%)	6(60%)	4 (50%)	0.931
Hepatosplenomegaly	5 (33.3%)	3 (21.4%)	4 (40%)	2 (25%)	0.766
Skin findings	0 (0%)	1 (7.1%)	0 (0%)	2 (25%)	0.095
Joint findings	0 (0%)	2 (14.3%)	0 (0%)	1 (12.5%)	0.300
Hemoglobin (g/dL)	9.8 (7.2-13.4)	10.2 (7-12.6)	9.5 (7.9-15.9)	12.4 (8.7-13.2)	0.252
Platelets (x10^9/L)	206 (110-413)	276 (260-552)	180 (25-341)	294 (82-633)	0.300
Neutrophils (x10^9/L)	6800 (2910-18700)	8000 (900-15800)	3500 (1600-23680)	5720 (400-14100)	0.763
Lymphocytes(x10^9/L)	1100 (100-3300)	1100 (400-2790)	1125 (300-35100)	12000 (200-23000)	0.948
Creatinine (mg/dl)	0.9 (0.4-1.3)	0.79 (0.55-1.6)	0.77 (0.47-1.95)	0.7 (0.3-1.13)	0.684
AST (U/L)	28.5 (15-193)	22.5 (6.2-317)	35 (15-164)	14.8 (10-37)	0.099
ALT (U/L)	29 (9.9-455)	26.4 (4.9-202.4)	16 (7-245)	12.5 (6.7-47.5)	0.144
ALP (U/L)	85 (20.8-268)	106 (56-702)	137 (54-787)	102 (64-200)	0.257
GGT (IU/L)	29 (14-170)	88.5 (9-435)	75 (18-880)	19 (10-80)	0.037*
LDH (mg/dL)	246 (132-380)	174 (107-662)	270 (191-1353)	206 (121-477)	0.139
Ferritin (ng/mL)	437 (40-1561)	570 (138-35918)	698 (59-18054)	468 (34-1310)	0.599
CRP mg/l	95 (22-443)	125 (27-241)	74 (3-344)	35 (4-229)	0.208
Procalcitonin (ng/mL)	0.24 (0.07-12.6)	0.19 (0.01-2.13)	0.95 (0.02-8.2)	0.04 (0.01-45.3)	0.112
Sedimentation (mm/h)	44 (9-125)	59 (10-84)	61 (26-118)	34 (11-90)	0.324

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; CRP: C-reactive protein; GGT: Gamma-glutamyl transpeptidase; ESR: Erythrocyte sedimentation rate; LDH: Lactate Dehydrogenase; NIID: Non-infectious inflammatory diseases. *Post-hoc Kruskal-Wallis analyses undiagnosed vs. malignant group (p=0.048).

Table 3. Comparison of imaging methods, and interventional procedures in different groups

	Infection disease, n (%)	NIID, n (%)	Malignancies, n (%)	Undiagnosed, n (%)	p
PET-CT					0.017*
Not applied	8 (53.3)	5 (35.7)	3 (30)	4 (50)	
Applied but not diagnostic	4 (26.7)	8 (57.1)	1 (10)	4 (50)	
Involvement consistent with disease	3 (20)	1 (7.1)	6 (60)	0 (0)	
Bone marrow biopsy	2 (13)	4 (28.6)	7 (70)	3(37.5)	0.031+

NIID: Non-infectious inflammatory diseases; *Post-hoc chi-square analyses malignant group vs. infection disease and NIID group (p<0.05); +Post-hoc chi-square analyses malignant group vs. infection disease (p<0.05).

ical and imaging techniques in the health field, 10-25% of FUOs are still undiagnosed.[7] Infectious diseases are still the most common cause of FUO, and that has not changed for decades.

Tuberculosis is the most common infectious cause of FUO in the world and Turkey. While the prevalence of infectious diseases in FUO worldwide is between 17 and 57%, it is between 26 and 59% in Turkey.[8-11] These rates may vary depending on the centers, the socioeconomic status of the individuals, and the region in which the study was conducted. In a recent multicentric study from 21 countries of different levels of development, including Turkey, tuberculosis is still the leading infectious cause of FUO, followed by infective endocarditis and brucellosis.[7] There are many reasons for this, meager rate of in vitro growth in the culture media, low probability of bacterial isolation from the tissue biopsies, interferon-gamma dependent biochemical tests do not work in those with poor interferon response.[12] In most of the tuberculosis cases in our study, patients were diagnosed with granulomatous reactions on histopathological examination of the pathological lymph nodes and other involved tissues, while in some patients the diagnosis can be achieved with clinical suspicion associated with the systemic signs and symptoms, diagnosis of exclusion and positive clinical response to treatment. All patients were completely cured after treatment. Infective endocarditis is the most common cause of FUO after tuberculosis, and it should be remembered that in this group patients, repeated echocardiography (transthoracic and/or transesophageal) is necessary in the presence of a positive blood culture to avoid misdiagnosis.[13] Brucellosis questioning rural life and dietary habits in our cases are the most important indicators for this diagnosis. Elevated cholestatic liver enzymes are important signs of liver involvement and granulomatous reaction in tuberculosis and brucellosis.[14] In our study, mean serum GGT was significantly higher in FUO patients diagnosed with malignancy compared to others. This was associated with possible liver involvement or metastasis. Serum ALP and GGT levels were elevated in 50% of patients diagnosed with tuberculosis, whereas they were normal in the brucellosis case in our study.

Shang et al. reported an increased prevalence of adult Still's disease and lymphoma in FUO cases.[15] Mulders-Manders CM et al. suggested early PET-CT for diagnosis in FUO patients.[16] The prevalence of NIID in FUO varies between 2% and 34% worldwide[12,17] and between 11.6% and 38% in Turkey.[13,14] The most common cause of NIID is adult Still's disease in adults.[7] In our study, one third of the FUO patients with an identified diagnosis had NIID (n=14), and the most common diagnosis in this group of patients was adult Still's disease (n=5). In FUO patients, Bilgin et al. claimed that serum ferritin >1680 ng/ml with arthralgia was associated with a positive predictive value (PPV) of 96.7% for adult Still's disease. They also showed that, serum ferritin between 336-1680 ng/ml, neutrophilic leukocytosis and sore throat together were associated with a PPV of >90.7% for adult Still's disease.[18] In our study, 60% of the patients diagnosed with adult-onset Still's disease diagnosis had serum ferritin >1680 ng/ml, another 20% had serum ferritin 336-1680 ng/ml, 20% had neutrophilic leukocytosis and 20% had joint involvement. Autoimmune diseases were associated with idiopathic recurrent pericarditis (IRP), and concurrent autoimmune disease was previously reported in 6.1% of patients with IRP.[19] More recently, IRP cases were associated with COVID-19 infection, especially in post-COVID period.[20]

Malignant diseases were diagnosed in 10-17.8% of FUO cases, with a 9.4-16.7% prevalence in Turkey.[21-24] Lymphomas, constituting more than half of FUO-associated malignancies, prevail due to the typical persistence of fever in lymphoma's etiopathogenesis. A multicenter study from 21 countries reported a diagnosis of lymphoma in 75% of FUO associated with malignant diseases.[7] In our study, lymphomas constituted 80% of the malignant diseases associated FUO cases. Recent research accentuates the pivotal role of PET-CT in elucidating FUO etiology, underscoring its integration into FUO examinations.[25,26] The augmented

utilization of PET-CT in FUO coincides with increased lymphoma diagnoses. We also emphasize that the diagnostic contribution of PET-CT in our study was significantly higher in the malignancy group than in the infectious disease group. This divergence arises because many infectious diseases can be diagnosed utilizing biochemical parameters and interventional procedures, obviating the necessity for PET-CT. As for other causes of FUO, there has been a significant increase in cases of subacute thyroiditis following COVID infection and other similar infectious diseases. And in some of these patients, FUO may be present because of normal thyroid function tests in blood tests taken in the early stages of the disease.[27]

Despite the advances in medicine, it is still estimated that 20% of patients with NIID and genetic disorders remain undiagnosed. However, this number is expected to decrease as genetic testing, such as whole exon sequencing and fever panels, becomes more affordable and widely available. A study that followed up undiagnosed FUO patients found that mortality was low and not typically related to the high fever itself.

Our study has some limitations: First, the small number of study participants, which was only 50. This was partly due to study method and schedule. The recruitment was done in the last 12 months. And many of the previous FUO reports also had similar numbers of patients. Secondly, our study was conducted in two centers from the same province of Turkey. A multicenter study from different regions of the country might give more definitive results. The study centers are located in the largest city in Turkey, with a population of over 15 million. They are university and research hospitals with a total of more than 1300 beds. The patients admitted to these hospitals come from all regions of Turkey. Still, advanced imaging and interventional procedures cannot be performed in every center.[28]

Conclusion

Infectious diseases are still the most common cause of fever of unknown origin in Turkey, and extrapulmonary tuberculosis is still the leading cause of infectious diseases. FUO associated with NIIDs is getting more prevalent in the last years, which has similar rates with the infectious diseases. The most frequent NIID is adult-onset Still's disease. Lymphomas can present with FUO.

Disclosures

Ethics Committee Approval: This study has been approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine Hospital: 24 January 2024. Number: 2382181.

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Conflict of Interest: None declared.

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