

The clinical characteristics and outcomes of patients with fever of unknown origin caused by parasitic infection

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Abstract

There are over 200 causes of fever of unknown origin (FUO), and although parasitic infection is an increasingly uncommon cause, a definitive diagnosis remains important to ensure rapid treatment and to prevent adverse sequelae through delay. Here, we studied the clinical features and outcomes of patients admitted with FUO and diagnosed with parasitic infection to improve our understanding of the features of parasitic FUO.

Medical records of patients admitted to Peking Union Medical College Hospital between 2013 and 2019 with FUO and diagnosed with parasitic infection were reviewed. The clinical features and outcomes of patients for whom follow-up data were available were summarized.

Six patients were admitted with FUO and diagnosed with parasitic infections (6/1013; 0.59%). Patients were more commonly middle-aged men and had a relatively long disease course. Most suffered from hyperpyrexia and other non-specific symptoms. Routine examinations were non-specific, and some patients had positive tumor markers, antinuclear antibodies, or positron emission tomography/computed tomography results. Diagnoses were confirmed by bone marrow smears, serum antibody testing, or feces examination. All 6 cases received anthelmintic treatments and recovered well.

Parasitic infections must be screened for and actively excluded in FUO patients so that targeted therapy can be rapidly administered to ensure optimal outcomes.

Abbreviations: ANA = antinuclear antibodies, anti-RNP = anti-ribonuclear protein antibody, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FUO = fever of unknown origin, Hb = hemoglobin, NSAIDs = non-steroidal anti-inflammatory drugs, PET/CT = positron emission tomography/computed tomography, PUMCH = Peking Union Medical College Hospital, WBC = white blood cell.

Keywords: diagnosis, fever of unknown origin, parasitic infections

1. Introduction

Fever of unknown origin (FUO) was originally defined by Petersdorf and Beeson in 1961 as an illness of more than 3 weeks'

duration with a fever $> 38.3^{\circ}\text{C}$ (101°F) on several occasions and of uncertain cause after 1 week of in-hospital investigations.^[1] Changes were proposed to the quantitative criteria (diagnosis uncertain after 1 week or 3 days of investigation) and the qualitative requirement that fever remained undiagnosed after a minimal diagnostic work-up^[2]; however, the investigations that should be included in the work-up remain a matter of debate. There are over 200 reported causes of FUO, with the spectrum of underlying causes changing not only due to the increasing number of causative conditions but also the availability of new diagnostic techniques.^[3] Nevertheless, some causes still lack a specific diagnostic method, often making the diagnosis and treatment of FUO a perplexing clinical puzzle.

The common causes of FUO are infections, connective tissue diseases, neoplasms, and miscellaneous diseases, of which infection is the most frequent cause.^[4] As most patients with parasites have a suggestive epidemiological history and as medical care and diagnostics (appropriate serology and imaging) have improved, parasitic infections can often be promptly diagnosed and treated. As a result, parasitic infections account for an ever smaller proportion of the total causes of FUO.^[5] In our own institution, 1446 patients presented with prolonged unexplained fever and fulfilled the clinical criteria of FUO between 2000 and 2010, of whom only 4 were finally diagnosed as parasite infection^[4]; these data suggest that parasitic infection is a rare cause of FUO. Nevertheless, parasitic infections must still be considered in the differential diagnosis of FUO, not least because therapeutics are often available that lead to complete and

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rapid recovery. If the parasitic infection is misdiagnosed or the diagnosis delayed, outcomes are suboptimal.

2. Materials and methods

There has been little research on the clinical characteristics of patients with FOU caused by parasites, so it is difficult to distinguish these patients from others admitted with FOU. To comprehensively describe the clinical manifestations of patients admitted with FOU caused by parasitic infections, here we reviewed the medical records of all patients hospitalized with FOU at Peking Union Medical College Hospital (PUMCH) between January 2013 and December 2019 to clarify their clinical characteristics, diagnosis, treatment, and outcomes to improve our understanding of the features of parasitic FOU and benefit future clinical practice.

This was a retrospective study of patients admitted to PUMCH, a 2000-bed university-affiliated tertiary hospital in Beijing, China. Two experienced physicians reviewed the medical records of 1013 patients admitted to PUMCH with FOU between January 2013 and December 2019, of whom 6 were finally determined to have causative parasitic infections. FOU was diagnosed according to 1961 criteria.^[2]

The medical records were reviewed to extract demographic, clinical, diagnostic, medical history, and contact history data. Treatments prior to admission such as antibiotics and glucocorticoids were also summarized, together with the therapeutic protocols administered after the final diagnosis. Outcomes were also recorded. The research was approved by the PUMCH ethics committee and the ethical approval was uploaded together with the article.

Data were collected and summarized using a standard form. Descriptive statistics were used to characterize the study population. For continuous variables, the data are presented as means \pm standard deviations or medians and ranges, depending on the distribution. Categorical data are presented as numbers and percentages.

3. Results

3.1. Demographic characteristics

One thousand thirteen patients were diagnosed with FOU between 2013 and 2019, of whom 0.59% (6/1013) had parasitic infections. The median age of these 6 patients was 48.5 years (range 18–62 years). Four were male and 2 were female. The

Table 1

Demographic characteristics of 6 patients admitted with fever of unknown origin and diagnosed with parasitic infections.

Variable	n (%)	Median (range)
Age		48.5 (18–62)
Gender		
Male	4 (66.7)	
Female	2 (33.3)	
Time with fever before admission (mo)		18 (0.75–48)
Time of hospitalization (wk)		4 (3–5)
From prevalent regions of the parasite infection or not		
Yes	3 (50)	
No	3 (50)	
Underlying disease or not		
Yes	1 (16.7)	
No	5 (83.3)	

median duration of fever prior to admission was 18 (range 0.75–48) months, and the median duration of hospitalization was 4 (range 3–5) weeks. The demographic characteristics of the 6 patients are detailed in Table 1.

3.2. Clinical features

The clinical manifestations of the 6 cases varied, but most (5/6) had hyperpyrexia. Other clinical features included chill, fatigue, myalgia, muscle pain, weight loss, anemia, night sweats, nausea, vomiting, headache, and lymphadenectasis. Two patients suffered from splenomegaly. One patient had hypertension, osteoclastoma, and received mitral valve replacement due to infectious endocarditis about 10 years previously, while the other 5 patients were in previously good health. Half (3/6) lived in regions with endemic parasite infections, ie, areas with a high prevalence of these infections. All 6 patients had been prescribed 1 or more antibiotics prior to admission, and 4 had been given oral or intravenous corticosteroids without effect. The specific clinical information for each patient is presented in Table 2.

3.3. Laboratory findings

Most patients (5/6) had normal white blood cell counts; 4/6 patients had eosinophilia (mean $0.68 \pm 0.83 \times 10^9/L$). Two were anemic and 3 were thrombocytopenic, 2 of whom were diagnosed with leishmaniasis. The biochemical profiles of all cases were within normal limits.

Table 2

Clinical characteristics of 6 patients admitted for FOU and diagnosed with parasite infections.

Case number	Clinical feature		Treatment before hospitalization	
	T _{max}	Clinical manifestation	Antibiotics	Glucocorticoid
1	39.5°C	Muscle pain, fatigue, weight loss, anemia, enlarged lymph nodes, and progressive enlargement of the spleen	Vancomycin, meropenem, Moxifloxacin, voriconazole, isoniazid, rifapentine, and ethambutol	Short-term use of intravenous medium-dose glucocorticoids
2	40°C	Fever and chills	Clindamycin, azithromycin, and penicillin	No use of glucocorticoids
3	39.1°C	Fever and chills	Cefuroxime	No use of glucocorticoids
4	40°C	Headache, chills, and low back pain	Azithromycin and levofloxacin	Intravenous dexamethasone 10 mg once
5	41°C	Chills, night sweats, dizziness, fatigue, cough, more white sputum, nausea, vomiting, jaundice, and splenomegaly	Azithromycin	Oral prednisone 10 mg qd for 1 month
6	38°C	Hoarseness, painful swallowing, right occipital neck pain, and purple extremities	Moxifloxacin, ornidazole, and amoxicillin clavulanate potassium	Oral prednisone, unknown dose

Table 3**Clinical, hematological, radiological, and immunological details of patients with parasite-related FUO.**

Case number	1	2	3	4	5	6
Age/gender						
52/F	36/M	62/M	47/M	18/F	50/M	
Splenomegaly						
Yes	No	No	No	Yes	No	
Routine blood tests						
WBC ($10^9/L$; normal 4–10)	8.06	4.08	5.84	7.09	0.79	7.74
Hb (g/L; normal 110–150)	79	124	130	137	80	142
Platelets ($10^9/L$; normal 100–300)	85	65	209	122	88	130
Eosinophils (%) ($10^9/L$; normal 0.02–0.50)	1.02 (12.6)	0	0.61 (10.4)	0.1 (1.4)	0	2.33 (30.1)
Inflammatory indicators						
CRP (mg/L; normal 0–3.00)	14.24	106.51	7.24	67	24.43	88.58
ESR (mm/H; normal 0–20)	50	31	6	130.69	39	17
Autoantibody profiles						
ANA S1:160 +, anti-Ro-52-kd +, anti-PM/Scl +	Negative	Negative	Negative	ANA S1:80	ANA(-), anti-Ro-52-kd+++ anti-RNP++, anti-Sm+, anti-SSA++	
Lymphocyte subtype analysis						
B cells (/ul; normal 180–324)	43	141	59	43	33	148
CD4 ⁺ T cells (/ul; normal 561–1137)	380	590	806	256	201	766
CD38 ⁺ CD8 ⁺ T cells (%; normal 32.4–57.4)	83.7	79.1	51.5	64.7	68	37.2
DR ⁺ CD8 ⁺ T cells (%; normal 6.3–23.8)	71.9	43.8	29.9	43.9	41.6	37.9
PET/CT findings						
NA	NA	Negative	Negative	Abnormally enlarged, highly metabolically enhancing lymph nodes and spleens	NA	
Diagnosis						
Ancylostomiasis	Leishmaniasis	<i>Angiostrongylus cantonensis</i>	<i>Schizophrenia mansonii</i>	Leishmaniasis	<i>Schizophrenia mansonii</i>	
Diagnosis method						
Finding worms and eggs in feces	Bone marrow smear, serum antibody	Serum antibody	Serum antibody	Bone marrow smear	Serum antibody	

ANA = antinuclear antibodies, anti-RNP = anti-ribonuclear protein antibody, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FUO = fever of unknown origin, Hb = hemoglobin, PET/CT = positron emission tomography/computed tomography, WBC = white blood cell.

To exclude neoplastic disease, half of the patients underwent tumor marker testing, with 1 with leishmaniasis having slightly elevated 2-phospho-D-glycerate hydrolase levels; the others were within normal limits. In addition, positron emission tomography/computed tomography (PET/CT) scans were arranged for 3 patients, 1 of whom had abnormally enlarged, highly metabolically enhancing lymph nodes and spleens, while the other 2 patients had normal scans.

All patients had complete immune cell profiling. Average B cell counts were 77.8 ± 47.8 /ul; CD4⁺ T cell counts were 499.8 ± 236.9 /ul; CD38⁺CD8⁺ T cell proportions were $64.0 \pm 15.9\%$; and the average DR⁺CD8⁺ T cell proportion was $44.8 \pm 13.0\%$. Inflammatory indicators were significantly higher than normal, with average C-reactive protein values of 51.33 ± 38.13 mg/L and mean erythrocyte sedimentation rates of 45.62 ± 40.63 mm/h. Three patients had negative antinuclear antibodies and the others were positive.

Two patients were diagnosed as having leishmaniasis through bone marrow smears. Two were diagnosed with *Schizophrenia mansonii* and with *Angiostrongylus cantonensis* by serology. The other patient was diagnosed with ancylostomiasis after finding worms and eggs in feces. The clinical, hematological, radiological, and immunological details of patients with parasite-related FUO are presented in Table 3.

3.4. Treatment and prognosis

All 6 cases received anthelmintic treatments. The 2 leishmaniasis cases received sodium stibogluconate 1g daily for 28 days. Albendazole was prescribed to the other patients, combined with praziquantel in 1 case. All 6 patients recovered.

4. Discussion

Although nearly 60 years have passed since the first definition of FUO, it still remains a diagnostic challenge. Notwithstanding that the proportion of FUO cases caused by infectious diseases has decreased over recent years, they remain an important cause of FUO.^[6] Parasitic infections accounted for 0.59% of FUO patients in this study, so parasite infections cannot be discounted when managing patients with FUO.

With increasing globalization, population mobility has also increased, meaning that even individuals not living in endemic areas can be exposed to and get infected with parasites. Particularly in these patients, the diagnostic delay could be a problem if they subsequently present in non-endemic areas where there is a relative lack of awareness or knowledge about parasitic infections.

Our previous study of nearly 1000 FUO patients admitted to our hospital between 2004 and 2010 revealed that 46.7% were

male^[4]; in the present study, two-thirds of our patients were male. The mean age of the entire FUO population was 42.9 ± 17.4 years (range 14–85 years), consistent with the median age of the parasite-infected patients presented here (median 48.5 years; range 18–62 years). Similarly, most general FUO cases had no pre-existing disease and, although most were hyperpyrexia, their clinical manifestations were non-specific. The lag time to reaching a diagnosis was a median of 13 weeks (range 4–520 weeks), which compares to a median duration of fever prior to admission of 18 months (range 0.75–48 months) in the parasite-infected group. This significant delay in diagnosing parasite-related FUO may be due to the non-specific clinical manifestations creating diagnostic difficulties but, more importantly, this diagnostic delay led to the administration of inappropriate treatments prior to definitive diagnosis including antibiotics and even glucocorticoids.

The blood abnormalities in these patients were non-specific (anemia, thrombocytopenia). Although high eosinophil levels are classically thought to indicate parasitic infections,^[7] not all patients had elevated eosinophils and in most patients the eosinophil levels were only slightly elevated. White blood cell levels were usually within normal ranges, and inflammatory markers were only slightly elevated or even normal. Therefore, the clinical index of suspicion for parasitic infection must remain high in FUO patients, even when routine tests are normal or only slightly abnormal.

Some patients had clinical features suggestive of cancer such as enlarged lymph nodes and spleens with increased metabolism on PET/CT or slightly elevated tumor markers together with fatigue and weight loss. All FUO patients therefore require clear pathological evidence of cancer to make the diagnosis of cancer as an underlying cause since parasitic infection might at least partially mimic neoplastic disease.^[8]

Half of our patients had positive antinuclear antibodies. However, none had specific symptoms of autoimmune disease or a relevant medical history, and most were middle-aged men, who tend not to suffer from autoimmune diseases. Parasitic infections must not be excluded when anti-nuclear antibodies are positive in patients with FUO.^[9]

A misdiagnosis of FUO caused by neoplastic or autoimmune diseases with the subsequent administration of chemotherapy or immunosuppressants could result in serious adverse sequelae. Therefore, given the lack of specific clinical indicators, testing for parasites must be exhaustive in FUO patients. With improvements in diagnostics, many parasitic infections are now easy to identify and rapidly treat, so parasites are now forming a smaller proportion of FUO cases than previously. Cases tend to be concentrated in natural endemic areas, and most present with typical clinical manifestations, allowing local experienced clinicians to make the diagnosis early in the course of the illness. Most parasitic diseases are susceptible to anthelmintic drugs, so relatively few parasite infections finally manifest as FUO, with visceral leishmaniasis and malaria the most common parasitic causes of FUO,^[5] although *S. mansoni*, *A. cantonensis*, and ancylostomiasis can also lead to FUO, as in this series. Moreover, according to the previous data from our hospital, amoebic infection may also cause FUO.^[4] Serum antibody testing for parasites is a critical examination in FUO patients, with bone

marrow smears and urine, fecal, or even sputum smears or cultures important in some cases.

This study had several limitations. The sample size was small and from a single center, so the results may not be generalizable. In addition, PUMCH is a specialist tertiary center for complicated and severe diseases in China, so many cases with typical symptoms may have been successfully diagnosed and cured in local hospitals, ie, there may have been selection bias. Furthermore, as most patients were non-local residents, some follow-up information was lost.

5. Conclusions

In summary, screening for parasitic infections should not be ignored in FUO patients so that targeted anthelmintics can be administered earlier to improve outcomes. This is particularly true in non-endemic areas, where a clinical index of suspicion must remain given the possibility of exposure in the increasingly mobile global population.

Author contributions

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References

- [1] Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)* 1961;40:1–30. 10.1097/00005792-196102000-00001.
- [2] Fusco FM, Pisapia R, Nardiello S, et al. Fever of unknown origin (FUO): which are the factors influencing the final diagnosis? A 2005-2015 systematic review. *BMC Infect Dis* 2019;19:65310.1186/s12879-019-4285-8.
- [3] Unger M, Karanikas G, Kerschbaumer A, et al. Fever of unknown origin (FUO) revised. *Wien Klin Wochenschr* 2016;128:796–801. 10.1007/s00508-016-1083-9.
- [4] Shi XC, Liu XQ, Zhou BT, et al. Major causes of fever of unknown origin at Peking Union Medical College Hospital in the past 26 years. *Chin Med J (Engl)* 2013;126:808–12.
- [5] McGregor AC, Moore DA. Infectious causes of fever of unknown origin. *Clin Med (Lond)* 2015;15:285–7. 10.7861/clinmedicine.15-3-285.
- [6] Tan Y, Liu X, Shi X. Clinical features and outcomes of patients with fever of unknown origin: a retrospective study. *BMC Infect Dis* 2019;19:19810.1186/s12879-019-3834-5.
- [7] Ravin KA, Loy M. The eosinophil in infection. *Clin Rev Allergy Immunol* 2016;50:214–27. 10.1007/s12016-015-8525-4.
- [8] Schonau V, Vogel K, Englbrecht M, et al. The value of (18)F-FDG-PET/CT in identifying the cause of fever of unknown origin (FUO) and inflammation of unknown origin (IUO): data from a prospective study. *Ann Rheum Dis* 2018;77:70–7. 10.1136/annrheumdis-2017-211687.
- [9] Lakhal S, Benabid M, Sghaier IB, et al. The sera from adult patients with suggestive signs of autoimmune diseases present antinuclear autoantibodies that cross-react with *Leishmania infantum* conserved proteins: crude *Leishmania* histone and soluble *Leishmania* antigens [corrected]. *Immunol Res* 2015;61:154–9. 10.1007/s12026-014-8589-x.