



ETIOLOGY OF CLASSIC FEVER OF UNKNOWN ORIGIN (FUO) AMONG IMMUNOCOMPETENT ADULTS IN INDIA

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Background

- India is a diverse country with different cultures, ethnicities and geographical predilection to infections
- The adequacy of medical care also varies with each region resulting in often a delay in diagnosis of classic FUO
- The advent of imaging, functional scans, guided procedures and molecular techniques has enabled earlier diagnosis of most FUO
- Information regarding FUO in India is scarce with variable definitions

Methods

- We recruited 300 consecutive patients presenting with classic FUO as defined by Durack and Street to a tertiary care centre in South India
- A preliminary workup was done to rule out delayed diagnosis of an acute febrile illness
- Potential diagnostic clues (PDCs) were identified and workup proceeded on those lines
- A persistent attempt was made to establish a confirmatory microbiological diagnosis for infections and histopathological diagnosis for neoplasms in all cases
- Empirical therapy was withheld in most cases on the first admission if patient was stable and no diagnosis was obtained
- Disease states were grouped into the three major etiological groups i.e., infections, neoplasms and non-infectious inflammatory diseases (NIIDs)

Sample size was calculated to be 96 based on the prevalence of tuberculosis of 40% (25-50%) among FUO studies in India

$$\text{Sample size} = [1.96^2 \times P \times (1-P)] / D^2$$

P=prevalence of the disease (%), D= confidence interval (taken as 10%). Summary statistics and tests of significance (Chi square test for categorical variables and student t-test for continuous variables) were done using statistical software package SPSS version 16.

Institutional review board approval and funding

- IRB approval was obtained prior to starting the study and funding was provided through an internal fluid research grant

Results

- 300 patients with classic FUO were recruited into the study
- Infections contributed to 48%, neoplasms 21.6% and NIIDs 20.6% (Table 1)
- The 3 most important infections included Tuberculosis in 61%, Melioidosis in 10% and Visceral abscesses in 4.8% (Figure 1)
- Hematological malignancies contributed to 82% and solid tumors to 18% of FUO
- Among NIIDs, SLE and Vasculitis contributed to 41% of classic FUO and 58% were evenly distributed among other granulomatous and rheumatological conditions

Results

Miscellaneous results

- Infection was the most common cause of FUO across all age groups
- The second most common was NIIDs in the < 50 year age group vs neoplasms in the > 50 year age groups (Table 2)
- Only 1.6% of the cases in our series were undiagnosed and we attribute that to strict inclusion of only documented FUOs which lasted > 3 weeks, availability of excellent radiology and pathology departments and perseverance towards obtaining a diagnosis
- Mortality in our series was 5%

Table 1: Differential diagnoses of FUO in India

| DIAGNOSIS | NUMBER OF PATIENTS | % OF TOTAL FUO PATIENTS | % OF SPECIFIC DIAGNOSTIC CATEGORY |
|---------------------------------------------|--------------------|-------------------------|-----------------------------------|
| INFECTIOUS | | | |
| Tuberculosis | 88 | 29 | 61 |
| Melioidosis | 16 | 5 | 10 |
| Infective endocarditis | 6 | 2 | 4 |
| Visceral Abscesses | 7 | 2.3 | 4.8 |
| Disseminated | | | |
| Histoplasmosis | 4 | 1.3 | 2.7 |
| ungal endocarditis | 1 | 0.3 | 0.7 |
| Enteric fever | | | |
| Visceral Leishmaniasis | 3 | 1 | 2 |
| Lepra reaction | 3 | 1 | |
| Brucellosis | 2 | | |
| Others (1 case each)* | 8 | | |
| NEOPLASMS | | | |
| Non Hodgkin's lymphoma | 20 | 7 | 31 |
| Hodgkin's lymphoma | 17 | 6 | 26 |
| Lymphoma unclassified | 2 | 2 | 3 |
| Leukemia | 6 | | 9 |
| Multiple Myeloma | 6 | 2 | 9 |
| Solitary plasmacytoma | 1 | | |
| Myelodysplastic syndrome | 1 | | |
| Solid organ tumours | 12 | 4 | 18 |
| NON INFECTIOUS INFLAMMATORY DISEASES | | | |
| SLE | 16 | 5 | 26 |
| Vasculitis | 9 | 3 | 14.5 |
| Inflammatory bowel disease | 4 | | |
| Sarcoidosis | 2 | | |
| Kikuchi's disease | 5 | | |
| Mixed connective tissue disorder | 5 | | |
| Still's disease | 5 | | |
| Rheumatoid Arthritis | 4 | | |
| Seronegative spondyloarthropathy | 2 | | |
| Others ** | 9 | | |
| MISCELLANEOUS | | | |
| Self limited | 17 | 5 | |
| UNDIAGNOSED | | | |
| Hyperthyroidism | 6 | 2 | |
| Others*** | 3 | 1 | |
| Undiagnosed | 5 | 1.6 | |

Figure 1: Etiology of Classic FUO in India

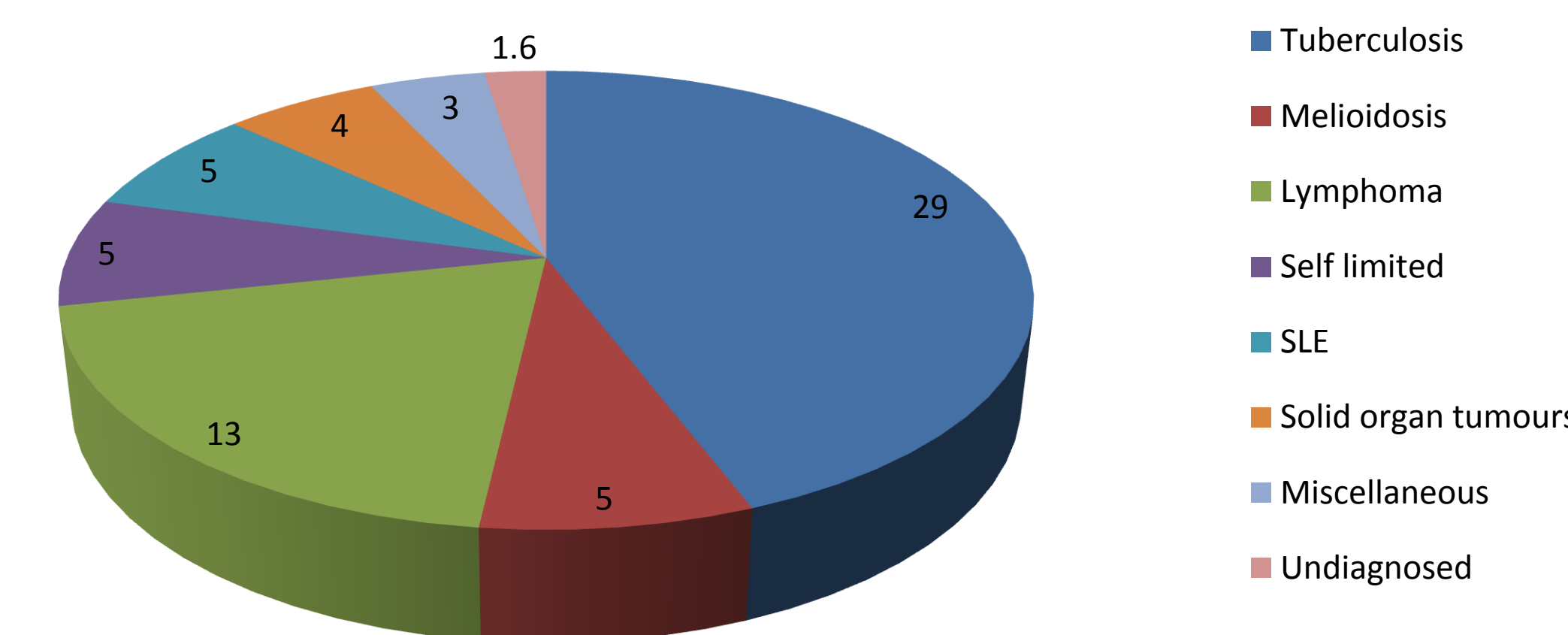


Table 2: Specific categories of FUO across age groups

| Age Group | Infection | Neoplasm | NIID | Miscellaneous | TOTAL |
|--------------------|-----------|----------|------|---------------|-------|
| <20 years | 9 | 3 | 7 | 4 | 23 |
| % within age group | 39.1 | 13 | 30.5 | 17.4 | 100 |
| 20-29 years | 33 | 8 | 23 | 6 | 70 |
| % within age group | 47.1 | 11.4 | 32.9 | 8.6 | 100 |
| 30-39 years | 24 | 9 | 10 | 7 | 50 |
| % within age group | 48 | 18 | 20 | 14 | 100 |
| 40-49 years | 38 | 20 | 13 | 3 | 74 |
| % within age group | 51.4 | 27 | 17.6 | 4 | 100 |
| 50-59 years | 20 | 15 | 3 | 7 | 45 |
| % within age group | 44.4 | 33.3 | 6.7 | 15.6 | 100 |
| Above 60 years | 20 | 9 | 6 | 3 | 38 |
| % within age group | 55 | 23 | 15 | 7 | 100 |
| TOTAL | 144 | 64 | 62 | 30 | 300 |

Table 3: Potential diagnostic clues in each category

| | Infection | Neoplasm | NIID | P Value |
|------------------------------------------|-----------|----------|-------|---------|
| SYMPTOMS | | | | |
| Cough | 64.5% | 24.8% | 9.7% | 0.019 |
| Diarrhea | 50% | 0 | 50% | 0.028 |
| Headache | 84.6% | 0 | 15.4% | 0.050 |
| Arthritis | 22.2% | 2.8% | 75% | 0.000 |
| Rash | 9.5% | 23.8% | 66.7% | 0.000 |
| SIGNS | | | | |
| Pallor | 42.5% | 38.1% | 19.5% | 0.000 |
| Lymphadenopathy | 38.4% | 36% | 25.6% | 0.001 |
| Hepatosplenomegaly | 43.4% | 45.3% | 11.3% | 0.000 |
| Arthritis | 22.2% | 2.8% | 75% | 0.000 |
| BASIC INVESTIGATIONS | | | | |
| Anemia (Hb <8g%) | 58.1% | 18.6% | 23.3% | 0.000 |
| Thrombocytopenia | 39.2% | 45.1% | 15.7% | 0.000 |
| Leukopenia (WBC count <4000 cells/mm.cu) | 43.9% | 39.0% | 17.1% | 0.044 |
| DIAGNOSTIC TESTS | | | | |
| Blood Culture | 100% | 0 | 0 | 0.001 |
| Bone marrow studies | 34.9% | 62.8% | 2.3% | 0.000 |
| CT Thorax | 58.6% | 13.8% | 27.6% | 0.019 |
| CT Thorax with abdomen | 56.8% | 32.4% | 10.8% | 0.006 |
| Lymph node biopsy | 50.0% | 41.3% | 8.7% | 0.000 |

Diagnostic yield of various tests

- Among the diagnostic tests CT thorax and Abdomen had the highest localising value of 83% followed by lymph node biopsies (Table 4)
- Among the invasive tests lymph node biopsies were the most frequent with a diagnostic yield of 70%, splenectomies had a 100% yield and the least helpful was a bone marrow aspiration with biopsy and cultures at 18.5%
- Using symptoms, signs and laboratory tests we used a bootstrapping analysis to derive potential diagnostic clues for each category of FUO namely infections, neoplasms and NIIDs (Figure 2)

Table 4: Diagnostic yield of various tests in the diagnosis of FUO

| Sl no | Diagnostic test | Diagnostic yield (%) |
|-------|------------------------------------------|----------------------|
| 1. | Chest X-ray | 25.3 |
| 2. | Ultrasound abdomen | 66.8 |
| 3. | CT thorax and abdomen | 83.2 |
| 4. | Bone marrow aspiration, biopsy, cultures | 18.5 |
| 5. | Lymph node biopsies | 69.6 |
| 6. | PET scan | 66.7 |
| 7. | Liver biopsy | 50 |
| 8. | Diagnostic splenectomy | 100 |

Limitations

- Ours is a tertiary referral center and patients have usually been elsewhere for a detailed evaluation before they come here.
- The disease process would have likely evolved by the time they present here
- In some cases they would have been given a therapeutic trial with no response and hence our suspicion for an alternate diagnosis would likely be higher
- In some cases a therapeutic trial for tuberculosis was given without culture confirmation

Conclusions

- Infections continue to be the most common cause of FUO in India across all age groups
- Unusual forms of tuberculosis continue to be the commonest cause of FUO in India-29%
- Melioidosis is a newly described cause of FUO among infections in India
- Lymphoma is the commonest cause of neoplastic FUO
- SLE is the commonest cause of FUO among the NIIDs
- It is possible to obtain a diagnosis in 99% of FUOs with use of advanced imaging, guided procedures and molecular techniques
- Using potential diagnostic clues from history, physical examination and lab tests we were able to create algorithms to evaluate classic FUO

