Changing Face of Fever of Unknown Origin (FUO): A Single Hospital Study

Thesis

Submitted for partial fulfillment of Master Degree in Tropical Medicine

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LIST OF ABBREVIATIONS

4-MTA	4-Methylthioamphetamine
ACPAs	Anti-citrullinated protein antibodies
ACR	American college of rheumatology
AFB cultures	Acid-Fast Bacilli
AIDS	Acquired immunodeficiency syndrome
ANA	Anti-nuclear antibody
ANCA	Anti-neutrophil cytoplasmic antibody
anti-CCP	Cyclic citrullinated peptide
anti-ENA	Extractable nuclear antigen
ASO	Antistreptolysin O
BCG	Bacillus Calmette–Guérin
CD4	cluster of differentiation 4
CDC	Centers for disease control and prevention
CMV	Cytomegalovirus
CNS	Central nervous system
CRP	C-reactive protein
CSD	Cat scratch disease
CSF	Cerebro spinal fluid
CT	Computer tomography
DNA	Deoxyribonucleic acid
EBNA	Epstein-Barr nuclear antigen

EBV	Epstein-Barr virus
ELISA	Enzyme linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
FBT	Fecal bacteriotherapy
FDA	US Food and Drug Administration
FMF	Familial Mediterranean fever
FUO	Fever of unknown origin
HAART	Highly Active Antiretroviral Therapy
HCQ	Hydroxychloroquine
HHV-6	Human herpesvirus 6
HIV	Human immunodeficiency virus
IAAT	Immunosorbent agglutination assay test
IBD	Inflammatory bowel disease
IFA	Indirect fluorescent antibody assay
IL	Interleukin
IM	Intramuscular
IV	Intravenous
IVIGs	Intravenous immunoglobulins
LAT	Latex agglutination test
MDMA	3,4-methylenedioxy-N-methylamphetamine
MDR	Multi drug resistant
MEFV	Mediterranean fever
MPT	Metaraminol Provocative Test
MRI	Magnetic resonance imaging

NSAIDs	Non-steroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PMA	para-Methoxyamphetamine
PMR	Polymyalgia rheumatica
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SLE	Systemic Lupus Erythematosus
SPEP	Serum Protein Electrophoresis
TB	Tuberculosis
UC	Ulcerative colitis
VCA	Viral capsid antigen
VDRL	Venereal Disease Research Laboratory
XDR	Extensively drug resistant

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Introduction

One of the problems most frequently encountered in medical practice is thediagnosisof prolonged fever, with or without local signs of disease. Thisproblem confuses both the physician and the patient.

Unlike the 1910's when most cases of FUO were restricted to a few infectious diseases, the differential diagnosis for FUO today comprises over 200 disorders and is among the longest of any condition in medicine. Fortunately, a meticulous history, a thorough physical examination, the use of investigative procedures, and constantreassessment of the evidence will usually reveal the cause of the patient's fever. A valuable measure is to know how to apply available diagnostic tools appropriately and knowing when careful patient observation is better than further investigative or therapeutic intervention.**(Dykewic, 2003).**

Most febrile conditions are readily diagnosed on the basis of presenting symptoms and a problem-focused physical examination. Occasionally, simple testing such as a complete blood count or urine culture is required to make a definitive diagnosis. Viral illnesses (e.g., upper respiratory infections) account for most of these self-limiting cases and usually resolve within two weeks.**(Dykewicz, 2003).**

Fevers of unknown origin (FUO) were first described in 1961 by Petersdorf and Beeson, when the pair outlined 100 patients that presented with FUO. Their research is best remembered for establishing the three criteria that define FUO. First, a minimum measured temperature of 38.3ºC was required. Secondly, the febrile states should occur on several occasions over a period of at least three weeks. Finally, a minimum of one week of investigations was required to allow adequate time for test results to return.**(Petersdorfand Beeson,1961).**

The modern definition of FUO is based on modifications around these criteria. These adaptations take into account four specific patient subtypes: classic, nosocomial, immune deficient (neutropenic), and HIV–associated. In addition to

having a documented fever of 38.3ºC, each category has a different set of criteria and list of likely causes.

1. **Classic FUO** - When temperature > 38ºC (>101ºF) recorded on several occasions occurring for more than three weeks in spite of investigations on three outpatient visits or three days of stay in hospital or one week of invasive ambulatory investigations is called classic FUO.

2. **Nosocomial FUO** - When temperature more than >38.3ºC(> 101°F) is recorded on several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifest or incubating on admission is called nosocomial FUO. Three days of investigations including at least two days incubation of cultures, is the minimum requirement for this diagnosis.

3. **Neutropenic FUO** - When temperature of > 38.3ºC (>101ºF) on several occasion is observed in a patient whose neutrophil count is less than 500/microliter or is expected to fall to that level in 1 or 2 days is called neutropenic FUO. This diagnosis should be considered when investigation including at least two days of incubation of cultures. It is also called immunodeficient FUO.

4. **HIV associated FUO** - When temperature of > 38.3ºC (>101ºF) on several occasions is found over a period of more than 4 weeks for our patient or more than three days for hospitalized patients with HIV infection is called HIV associated FUO. This diagnosis is considered if appropriate investigations over three days including two day of incubation of cultures reveals no source.**(Durack and Street, 1991)**

The differential diagnosis for FUO can be divided into four suggested classes: infection, malignancy, collagen vascular disease, and miscellaneous.**(ArnowandFlaherty, 1997).**

The following table outlines the proportion each class contributes, and provides the most common etiologies within each.