Case Report

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A case of fever of Unknown Origin (FUO): Problems, Pitfalls and Eventually Diagnosis

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Abstract

Fever of unknown origin (FUO) or pyrexia of unknown origin (PUO) is a real medical issue at times. Modern investigations can help in diagnosing but in some rare cases, it remains a medical challenge. Patients and clinicians are worried about unexplained fevers. Causes of most of the fevers is identified and approach to diagnosis in such cases is usually related to history, physical examination and basic laboratory clues. The correct approach in such cases is to follow clues and start with the least invasive evaluation. This will help in avoiding unnecessary harm and cost to the patient. Miscellaneous conditions also cause FUO.

Keywords: Fever of unknown origin (FUO); Non-Hodgkin's lymphoma (NHL); Pyrexia of unknown origin (PUO).

Case Report

A 72 year-old-female was admitted with presenting complains of fever and weight loss of about six kg in one month. Fever was not associated with cough, shortness of breath, sore throat, earache, headache, palpitation, joint pain and burning micturition. She had normal bowel movements. The patient received complete course of empirical antibiotic but there was no improvement. There was history of travelling abroad fourteen days before this illness. She is a diagnosed case of diabetes mellitus and hypertension on treatment.

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Her general physical examination was unremarkable, she was pale but vitally stable. No lymphadenopathy was present and joint examinations were normal. Systemic Examination was unremarkable. Examination of other systems were normal.

Her baseline investigations were : Haemoglobin 105g/L,WBC count $7.8x10^9$/L, Platelet count $168x10^9$/L, ESR 30 mm/1st hour. Her glycated haemoglobin (HbA1C) was 6.7%. Blood for malarial parasite, HBsAg, Anti-Hb e Ag, Anti-HBc IGM, Anti -Hbs, HbeAg, Anti- Hbc, Anti- HCV, HIV, RA factor, ANA, Brucella antigen were all negative. C reactive protein was 5 mg/L. No AFB was seen on microscopy. Bone and coagulation profiles were normal. Liver function tests, TSH, Free T3, Free T4 were normal. Peripheral smear showed RBC mild anisocytosis, normochromic, polychromasia and no abnormal cells seen. X ray chest was unremarkable.

Serum ferritin level was 1229 ng/mL (Raised), Dengue RNA virus PCR was negative. IgA, IgG, IgM was non-reactive for *Mycoplasma pneumoniae* and *Legionella pneumoniae*. Direct Coombs test was negative. Blood culture and sensitivity showed no growth. Quantiferon TB Gold test was negative. Echocardiography and CT scan of the chest, abdomen, pelvis with contrast were unremarkable. Bone marrow biopsy done at Royal Hospital showed hypercellular spaces, trilineage hematopoiesis are present with good maturation. There is slight increase in megakaryocytes seen by CD61, CD117. No increase in the blast cells, no granuloma or atypical infiltrates were seen. All workup has been negative. The patient was advised to undergo FDG PET-CT. The findings of the report were: Head and neck, nasopharynx, hypopharynx, oropharynx were unremarkable. Thorax showed multiple tissue lesions as shown in Figure 1. No metabolically active disease was seen elsewhere in the body. The patient also had special investigations like endoscopic biopsy, colonoscopy for gastric and colonic evaluation with no evidence of dysplasia and malignancy. Under CT guidance, trucut biopsy

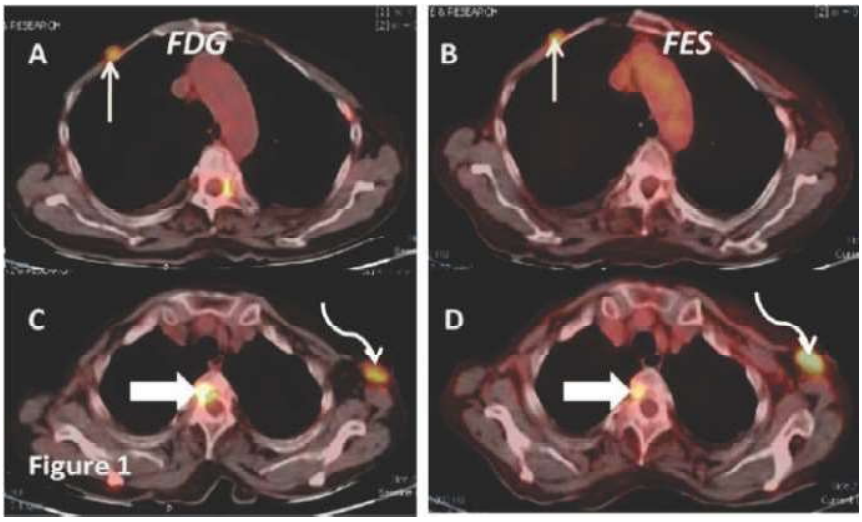

Fig. 1: FDG- PET CT showing multiple lesions (as shown by arrows) in thorax.

of the lesion and histopathology of the biopsy material revealed non - Hodgkin lymphoma with a cytotoxic phenotype of possible T cell type. The tumor cells express CD 3, CD 56, Tia and granzyme B. CD 30 is very focally & weakly expressed. The Mib-1 labeling index is 70%. (There is no expression of CD 20, CD 5, CD 23, ALK-1, CD 4, CD 8, CD 7 & CD 25, EBERs by ISH are not expressed). Immunohistochemistry report/Immunophenotype report was highly suggestive for extranodal NK T cell lymphoma. The patient was referred to higher medical centre for further management.

Discussion

The syndrome of fever of unknown origin (FUO) is defined as a temperature greater than 38.3°C on several occasions, more than 3 weeks' duration of illness, and failure to reach a diagnosis despite one week of investigation on indoor basis [1,2].

Others grouped FUO as classical, hospital-acquired, immunocompromised or neutropenic, and HIV-related based on human HIV virus and immunomodulating therapy. Modern imaging techniques (e.g, ultrasonography, computed tomography (CT) scanning, magnetic resonance imaging (MRI) and positron emission tomography (PET) are helpful in reaching a diagnosis [3].

Non-Hodgkin lymphomas (NHLs) are tumours originating from lymphoid tissues. They present with fatigue/weakness, temperature above 38°C, lymphadenopathy, extra-nodal involvement, thyroid, CNS involvement besides other organs.

Table 1: Causes of fever of unknown origin (FUO).

Types of FUO	Common examples
Infectious Causes of FUO	• Tuberculosis • HIV infection • Brucellosis • Cat scratch disease • Epstein-Barr virus infection • Cytomegalovirus infection • Enteric (typhoid) fever • Toxoplasmosis • Extra - pulmonary TB • Subacute bacterial endocarditis • Chronic sinusitis/ mastoiditis • Chronic prostatitis • Vascular graft infections • Cholecystitis
Noninfectious Inflammatory Causes of FUO (Connective Tissue and Granulomatous Disorders, Vasculitides)	• Giant cell (temporal) arteritis • Adult Still disease • Systemic lupus erythematosus • Rheumatoid arthritis • Gout • Pseudogout • Antiphospholipid syndrome • Behçet disease • Felty's syndrome
Malignant and Neoplastic Causes of FUO	• Lymphoma, renal cell carcinoma • Myeloproliferative disorder, acute myelogenous leukemia • Multiple myeloma, breast/ liver/pancreatic/colon cancer, atrial myxoma, metastases to brain/liver, malignant histiocytosis
Miscellaneous Causes of FUO	• Cirrhosis • Thyroiditis • Crohn disease • Familial periodic fever

Staging: Staging of the disease is essential for treatment selection and determining prognosis. Staging of lymphoma is based on biopsy and bone

marrow examination, CT scans of the neck, chest, abdomen, and pelvis. Ann Arbor staging system is the most commonly used for patients with NHL. In addition to the 4 stage designations, letters designate involvement of other organs, as follows:

- L - lung
- H - Liver
- P - Pleura
- B - Bone
- M - Bone marrow
- D - Skin
- E - Extranodal lymphoid malignancies

The stages can also be appended by A or B designations. Patients with A disease do not have systemic symptoms. The B designation is applied in patients with any of the following symptoms:

- Loss of more than 10% of body weight in the 6 months before diagnosis
- Fever with temperature above 38°C
- Drenching night sweats

Approach Considerations: The treatment of non-Hodgkin lymphoma (NHL) varies depending on the following factors:

- Tumor stage
- Histology (i.e, low, intermediate,or high grade)
- Phenotype (B-cell, T-cell or natural killer [NK] cell/null-cell)
- Symptoms
- Performance status
- Patient age
- Comorbidities

Most of the chemotherapy for NHL can be administered in an outpatient setting. Growth factor support (e.g, granulocyte-colony stimulating factor (GCSF), granulocyte macrophage–colony stimulating factor (GM-CSF), erythropoietin is also administered in an outpatient treatment setting. Infusional chemotherapy comprising of doxorubicin, etoposide and cyclophosphamide should be administered. High-dose chemotherapy and bone marrow and/or stem cell transplantation are also helpful.

Management of Indolent NHL:

Indolent stage I and contiguous stage II NHL

Radiotherapy is the standard therapy. Manus MMP et al [4] reported that 40% of patients with limited-stage disease at 10 years remained disease-free. Rossier et al [5] reported that low-dose involved-field radiotherapy is helpful in low-grade lymphoma patients.

Indolent noncontiguous stage II, III, and IV NHL

The treatment paradigm of patients with B-cell lymphomas is changing with use of monoclonal antibodies. The use of rituximab, a monoclonal antibody, in combination with systemic chemotherapy has resulted in an improved duration of remission and survival for patients with indolent B-cell lymphomas, compared with chemotherapy alone.

Combination agents are useful in bulky and rapidly growing disease and have higher response rates than single agents, but there is no improvement in overall survival [6,7,8]. Peyrade F et al. [9]found that in patients older than 80 years, rituximab plus low-dose CHOP (R-mini CHOP) was helpful.

Conflict of Interest None

Financial Disclosure None

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