Anatomy of Undiagnosed Fever - A Physician’s Perspective

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Abstract
Undiagnosed fever is a vexing problem. The reasons why fever remains undiagnosed can be inherent to the underlying pathology, our shortcoming(s) or both. This article describes “our” causes based on cases seen over the years. It is apparent that with proper attention to details mystery of at least some undiagnosed fevers can be solved.

Fever is a common clinical problem. Diagnosis of its cause and management are both an art and a science. Oxford Text-Book of Medicine states “Most fevers are readily explained or resolve rapidly. Fever with unclear cause or source at first sight should not be labelled fever of unknown origin (FUO). FUO is uncommon...........” It goes on to advise “The clinician must rely on a very careful and thorough clinical history and examination that does not neglect any part of the body, followed by appropriate targeted investigations..... the approach should follow all possible diagnostic clues which may sometimes be subtle”.1 The original criteria for diagnosis of FUO suggested by Petersdorf and Beeson (1961)2 have been modified and now need a minimum defined diagnostic evaluation before a fever can be called FUO.1 The components of diagnostic evaluation are comprehensive history, a meticulous physical examination and a fairly elaborate set of investigations. The investigations suggested are pretty exhaustive and may not always be possible (especially in our milieu) and may not be always necessary. Adhering to the basic ground rules of clinical medicine the number of ‘FUOs’ encountered can be decreased.

In this communication common pitfalls in the application of the ground rules (which probably we all sometime or the other commit), are illustrated with a series of cases. The article is based on cases seen by me at least 20 years back, and hence lack modern investigations. The cases represent my (re)learning process. Fever has been a great teacher. This account is by no means all inclusive. It does not include patients with nosocomial infections, infections in neutropenic and significantly immunosuppressed (e.g. oncology) patients. For brevity only essentials of cases are provided. Since many are in a way “iatrogenic” (because of our short comings) I prefer the term undiagnosed fever to FUO as in our set ups, diagnostic criteria of FUO cannot always be satisfied.

History and Physical Examination

It is said that history and physical examination form almost 90-95% (70% history) of data base.3

Case 1

A forty-two year old female, family physician by profession, had moderately high grade fever of 4-6 weeks duration, fatigue, and weight loss. Investigations had revealed high ESR, and a positive TB IgG (?) test. Tuberculosis was suspected and treatment advised. She consulted us at this point. Her illness had started with pain in the throat and upper part of left side of neck below the mandible. In a few days
the pain had tracked down and settled at the root of neck. Examination had revealed an exquisitely tender nodular swelling of about 1.5 cms in diameter at the lower pole of left lobe of thyroid. Sub acute thyroiditis was suspected. Nuclear scan confirmed the diagnosis. The nature of illness was explained, assured, and symptomatic treatment advised. She recovered fully over the next few weeks, regained weight and was fully functional. In her case careful history recording provided clue to the seat of the disease and its diagnosis.

However, sometimes patients do not volunteer full information, even hide it (commonly of drug addiction and extramarital sex). Thus, there was a physician with a pararectal abscess who did not volunteer history of painful defaecation to his physician. When diagnosed, it was too late. The infection had spread to abdominal cavity (Figures 1a, b); septicaemia supervened and he succumbed to the infection. The reason for not disclosing the symptom ? He was a case of Klinefelter’s syndrome and did not want his external genitalia to be seen.

Case 2

A 25 year old male, was admitted for recurrent bouts of fevers, each of a few days duration, for previous 2 months or so. No definite diagnosis had been arrived at. When seen, he complained of pain in the left lower abdomen and hip region. On examination there was spasm of left psoas muscle. X-rays of hip with pelvis and lumbar spine were normal. A CT scan of abdomen and pelvis including hips revealed (Lt) psoas abscess. (MRI was not available those days). Vertebrae were normal. The abscess was drained. Culture grew Staphylococcus aureus. He was treated accordingly. He recovered fully and had no recurrence of fever.

Learning point – It is important to locate the seat of the disease. Sometimes this may require repeated history taking and physical examination. e.g. when I joined Nair Hospital in 1973 we had a patient admitted to our ward for fever of more than one month’s duration. Investigations had not revealed the cause of fever. After 2-3 weeks a repeat examination revealed a supraclavicular lymph node which on biopsy proved tubercular. Incidentally during hospital stay the patient had complained of abdominal pain. A barium study was normal. One and half year later he was readmitted with intestinal obstruction secondary to stricture (tubercular) of small intestine.

Investigations

Investigations (laboratory, and imaging) have become (and rightly so) an integral part of clinical medicine. However wrong choice of investigation(s), improper interpretation of reports, lack of reliable laboratory services can convert an otherwise diagnosable fever into undiagnosed fever. (This is what happened with Dombivali fever – diagnosis of enteric fever and the resistant nature of the organism (to chloramphenicol) was missed until quality laboratories came into picture). A not uncommon pitfall or approach is to spread the net of investigations wide, a fishing expedition. This strategy increases the chances of landing with false positive (misleading) result(s).

Case 3

A male paediatrician, (age around 35 years) had prolonged, moderate to high grade fever that had not responded to treatment. Usual investigations were non contributory. On enquiry he complained of localised right lower chest pain. On examination swelling and tenderness of one of the right lower ribs was detected. Radionuclide bone scan revealed multiple hot spots suggestive of multiple osseous metastasis. He was advised diagnostic biopsy. However, based on the nuclear bone scan report he was fully investigated (at another facility) for the primary. None could be detected. Ultimately rib biopsy was performed and diagnosis of tuberculosis was made on the basis of histopathology. (On enquiry his practice involved many children with pulmonary tuberculosis). Undoubtedly the most common cause
of multiple hot spots on bone scan is secondaries. The slip was instead of a direct approach, a winding process was adopted with loss of time and a lot of mental anxiety to the patient.

Lesson learnt : Osseous tuberculosis (and arthritis) can be multicentric. Go for the lesion.

Case 4

A female patient suffering from dermatomyositis was on treatment with steroids and immunosuppressive agents. She developed persistent fever with cough and mutton fat like tongue lesions (Figure 2a). X-ray chest showed a cavity with fluid level involving left upper lobe (Figure 2b). Pulmonary tuberculosis (though fluid level is not a feature of tubercular cavity) and candidiasis of oral cavity were suspected. Treatment was initiated for candidiasis. Repeated sputum smears were negative for AFB as also tongue lesions for candida. Further, the tongue lesions did not respond to anti-fungal treatment. Sputum culture grew *Nocardia asteroides* while tongue lesions grew *Pseudomonas aeruginosa*. (Double infection is not unusual with immunosuppression). Appropriate treatment for both the infections lead to complete recovery. Few important points emerge (i) reliable microbiology service is of paramount importance and (ii) clinicians should be willing to believe laboratory report(s) and change the (clinical) diagnosis. Money and time spent on appropriate investigations can in the long run save money and importantly life. This patient without treatment of nocardia infection would certainly have succumbed to the infection. (The case was reported in JAPI).

Lesson learnt – Pseudomonas tongue infection (saw it for the first time).

Case 5

A young man in early twenties had been having fever for a few months along with neck swellings (Figure 3). Based on FNAC done elsewhere a diagnosis of tuberculosis of lymph nodes was made. However, anti-tuberculosis treatment did not help. Examination showed lymphadenopathy involving almost all lymph nodes of the neck. Lymphoma was suspected. This was confirmed with surgical biopsy of a lymph node. Biopsy is essential for definite diagnosis of lymphoma. Further, biopsy permits precise diagnosis of malignancy, (squamous cell carcinoma, adenocarcinoma etc.) permits histochemistry, genetic studies and guides therapy.

Lesson learnt : The case reiterates the dictum “when malignancy is suspected FNAC is not the investigation of choice”.

Case 6

A 26 year old male had been having fever for 2½ years. There was profound weight loss (> 20 kg). He had enlarged supraclavicular lymph nodes in the neck along with a mediastinal mass and had undergone two mediastinal and three neck lymph node biopsies without reaching a diagnosis. We advised to repeat neck lymph node biopsy. With great reluctance (understandably) on the part of the patient and also the surgeon, biopsy was performed and this time (luckily) diagnosis was made. It was lymphoma.
Lesson learnt – Repeating the appropriate investigation(s) is often the only way to arrive at the diagnosis (though because of reluctance on the part of patients and the costs incurred this is often not possible).

- A particularly difficult situation used to be to localise diseases involving hidden sites (sites not readily accessible/recognised and requiring specialised investigations) such as heart (infective endocarditis), mediastinum, retroperitoneum, spine, thyroid, prostate, and seminal vesicles.
- Careful attention to routine investigations is important e.g. microscopic haematuria can be a clue to renal cell carcinoma presenting as “undiagnosed fever”, an increasing lymphocyte count could be the fore-runner of leukaemia and an unexplained macrocytosis of myelodysplastic syndrome.

Case 7

Beyond the science of history, physical examination, and investigations the ability to make the best diagnosis in the presence of uncertainty constitutes the art of medicine.³

A 40 year old female had suffered from Falciparum malaria two months back. She was treated appropriately and cured. A few days later, she again started getting mild fever. Suspecting relapse of malaria, treatment was repeated with no relief. Resistance was considered. She consulted us at this stage. Physical examination was noncontributory. X-ray chest was suspicious of widening of superior mediastinum. A CT scan of chest showed caseating mediastinal lymph nodes (Figure 4). She improved on antitubercular treatment (ideally a CT guided needle aspiration biopsy should have been done. Possibly patient had refused).

Learning point - It is not uncommon for one disease to be unmasked by another illness or by its treatment. The dictum is if the diagnosis of (first) fever is correct and it has been treated correctly and fully, with recurrence of fever one should suspect either a complication secondary of the illness or an unrelated pathology. e.g. In one of our patients the cause of recurrence of fever after full and appropriate treatment of enteric fever was an abscess secondary to intestinal perforation and not recurrence of enteric fever.

Learning point : One infection can predispose to another infection. It is well documented that an attack of malaria can predispose to salmonella septicaemia.⁵

Case 8

A 38 year old orthopaedic surgeon had sustained traumatic fracture of left femur. He was treated with plating (Figure 5). Post-operatively he developed high grade fever with rigors. Clinical examination including local examination was non contributory. There was no evidence of infection. Investigations revealed leucocytosis with eosinophilia, raised ESR and elevated liver enzymes. He had received antibiotics, but the fever had persisted. Typically in between episodes of fever he would look quite normal. Drug fever (antibiotic induced – being the commonest cause) was suspected. Antibiotics were discontinued. Over the next 4-5 days he became afebrile and had no recurrence of fever.

Lesson : Drugs are an important cause of fever,
especially these days with freely applied empirical antibiotic treatment of fevers. It seems any drug except possibly digitalis and aminoglycosides can cause fever. Generally patients with fever due to infection, do not look normal in between episodes of fever. Other important causes of patient looking normal in between fever or otherwise are Still’s disease and fictitious fever (especially in medical and paramedical personnel). Adult onset Still’s disease is a diagnosis of exclusion. There are no diagnostic tests or features. Fictitious fever is not associated with tachycardia and temperature of normally voided urine is normal.

Case 9

A young girl in her teens was treated outside for “tuberculosis” with standard drugs. She developed fever, facial swelling, and a body rash (Figure 6). Drug reaction was suspected and TB treatment was discontinued. She was treated with steroids with control of the reaction. However, on tapering steroid, the rash reappeared. She was a case of juvenile systemic lupus erythematosus (SLE) that was precipitated by anti tuberculosis medications (INH). Differential diagnosis would be drug induced lupus.

Learning point - Acute SLE can be precipitated by a drug reaction especially in children.

Case 10

A 50 year old male, known diabetic was admitted with a history of fever of four months duration and left upper abdominal pain radiating to left shoulder. USG abdomen had revealed a “splenic abscess” (Figure 7a). Splenectomy was performed. Histopathologic diagnosis was tuberculosis. However, despite antituberculosis treatment his fever persisted. Intermittent moderate high fever had continued over the next 2½ years with no specific localising manifestations. Repeated investigations were non diagnostic. At this point he developed persistent cough with hiccups and progressive respiratory discomfort. CT scan of chest showed a mass in the left main bronchus (Figure 7b). Bronchoscopic biopsy specimen revealed only inflammatory tissue. There was no evidence of malignancy. He was started on steroids with dramatic response. He however remained on long term maintenance dose (5-10 mg/d) of prednisolone. A review of splenic histology was suggestive of Wegener’s granulomatosis. ANCA test was not available then.

The case illustrates the value of long-term follow-up (observation) to arrive at a correct diagnosis e.g. SLE may evolve over years. Waiting till the cause of fever surfaces (provided patient’s condition is otherwise stable) is an important ‘investigation’.

Lesson : Time is the greatest diagnostician, but should be used wisely.

And the rest.

Case 12

An important cause of undiagnosed fever is lack of familiarity with the disease or total ignorance of the disease entity. A forty plus muslim patient came to us with a history of recurrent bouts of fever accompanied by severe abdominal pain of more than 20 years duration. He was extensively investigated, empirically treated without relief. On enquiry his abdominal pain mimicked acute abdomen. Once or twice a diagnostic laparotomy was contemplated. Each attack lasted roughly 48-72 hours. Clinical examination during afebrile periods was non contributory. Mediterranean fever (MF) was suspected. He did not have a family history of FMF. The genetic test (MEFV gene) for Mediterranean fever was not available then. He was started on colchicine with dramatic relief from the febrile attacks. The diagnosis in this case of Mediterranean fever is tentative but possibly correct. Luckily he had not developed secondary amyloidosis. Ironically one senior physician had suggested FMF quite sometime back but the suggestion was ignored.
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This case is an example of empirical treatment as a diagnostic aid. Empirical treatment is commonly practiced. The rule is to set a limit to trial period, and predefined end points to decide success or failure of the trial. Indefinite continuation is not justified.

A major obstacle to any diagnosis is dogma. “It is rare”. “It does not happen in India”. Because of this mental block we took a long time to accept diseases like ulcerative colitis, Crohn’s disease, sarcoidosis and multiple sclerosis.

Learning point - “Rare does not mean Never”. It should not become a blind spot.

Are there no cases of FUO then? Undoubtedly there are. I do remember them. However with each new diagnostic facility added and experience gained, the number of such cases decreases. But new causes continue to enter the arena. Apparently nature does not give up. There is no doubt that some patients are beyond one’s capability. At such point seeking out help, a second opinion is worth it. There is nothing wrong. It is to the patient’s and one’s own benefit.

**Conclusion**

Undiagnosed fever is a source of anxiety not only to the patient, and his family, but also to the treating physician. A methodical approach, patience, and (shall one say) luck are necessary to reach a correct diagnosis.

**References**


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**Nomination for the Post of ICP Faculty Council Member**

Nominations are invited to fill the vacancy for the post of “Faculty Council Member” of The Indian College of Physician created due to the sad demise of Dr. Shrenik M. Shah.
Eligibility:- A member of API for at least 10 years and a Founder Fellow or a Fellow of the college of 3 year standing.
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Nominations shall be made on prescribed forms stating the office for which nominations are filled. The nominations for ICP post shall be proposed by one valid member and seconded by another valid member of ICP and duly signed by them and shall also be signed by the candidate signifying his/her willingness to stand for election and serve on the Faculty Council of ICP if elected.
The nomination should reach Dr. Milind Y. Nadkar, the Hon. General Secretary of API, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400 011 not later than 30th January 2014. Applications that are received after the due date will not be considered.
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