Fever of Unknown Origin in a Nigerian Doctor: An unusual case

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Abstract

The causes of persistent fever in sub-Saharan Africa are enormous and unraveling the diagnosis could be a daunting task when investigations for common infective and non-infective conditions and treatment response to the most logical differential diagnoses have proved disappointing. We report the case of a 29 year old Nigerian medical practitioner with recurrent high grade fever, petechie and body weakness for over three weeks, whose condition remained largely undiagnosed after rigorous laboratory investigations. He received numerous antimicrobials without remission of fever but withdrawal of all medications was associated with cessation of fever which left us wondering if it was a case of drug fever. The possibility of drug fever should be entertained in patients being investigated for fever of unknown origin who have received several medications without change in the height and pattern of fever.

INTRODUCTION

Fever of unknown origin (FUO) was defined by Petersdorf and Besson as a temperature above 38.3°C on several occasions, persisting for more than three weeks with failure to reach a diagnosis after one week of inpatient investigation (1). Although FUO remains a challenging medical problem, the causes are usually familiar diseases with uncommon presentations with infections being the commonest causes (1, 2). We report a 29 year old medical practitioner with recurrent high grade fever, petechie and body weakness for over three weeks, who received numerous antimicrobials without relief. Withdrawal of all medications was associated with cessation of fever. Is this a case of drug fever?

CASE REPORT

A 29 year old doctor, in a federal medical center at an urban capital city in South East Nigeria, presented with a two week history of recurrent high grade fever up to 40^{o}C, accompanied by rigors. He also had headache, sore throat, malaise and skin eruptions at the trunk and extremities. There was no history of weight loss, bone pain or bleeding tendency. He had received antimalarial therapy using two different artemisinin-based combinations. Four days before presentation to us, he commenced ciprofloxacin tabs 500mg BD, and had continued this till presentation to us. There was no history of use of recreational drugs. Risk factors for enteric fever, tuberculosis, retroviral infection, brucellosis, and endocarditis were absent and there was no history of recent travel outside South East Nigeria. He however had a risk factor for Lassa fever, having occasionally visited a restaurant notorious for rat infestation. There was no family history of recurrent fevers or cancers. Apart from pyrexia, hyperaemic oropharynx, petechial rashes on the trunk and extremities, and tachycardia, other physical findings were unremarkable.

Several stool and urine cultures as well as initial blood culture were negative for growth. A repeat blood culture yielded staphylococcus aureus, sensitive to ofloxacin, ciprofloxacin, and gentamycin only. Urinalysis had blood deposits, with numerous white blood cells (WBC) and red blood cells (RBC). Thin blood film showed Plasmodium falciparum parasitaemia (+). Other blood tests with positive findings included full blood count and blood film analysis, which showed significant polymorph leucocytosis on two occasions with associated left shift of neutrophils. Enzyme-linked immunosorbent assay (ELISA) for HIV antibodies (using two different kits), hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV); tuberculin skin test (Mantoux), WIDAL test, blood film for trypanosomal organisms and microfilaria, Veneral Disease Research Laboratory test (VDRL), antineutrophil cytoplasmic antibodies, rheumatoid factor and antinuclear antibodies were all negative. Blood clotting profile, liver and renal function tests, chest x-ray and abdominal ultrasound

were all normal.

Based on a working diagnosis of sepsis, he was treated with numerous intravenous antibiotics including Gentamycin 80mg 8 hourly plus Ofloxacin 500mg 12 hourly, both for 72 hours; cefriaxone 1g 12 hourly for 72 hours; ceftazidime 1g 8 hourly for 4 days; Meropenem 1g 8hourly for 5 days, but fever persisted. He was repeatedly exposed and tepid sponged and was placed on antipyretics at moments when the temperature was ≥ 40°c. In the fourth week of his illness, the differential diagnosis was expanded to include viral exanthema, Lassa fever and rickettsial infection. He was commenced on tabs ribavirin scheduled as a loading dose of 33mg/Kg then 16mg/Kg 6 hourly for 4 days and 8mg/Kg 8 hourly for another 6 days; alongside doxycycline caps 100mg BD scheduled for 7 days. He remained febrile more than 48 hours on this regimen, with worsening of most symptoms. All medications were consequently discontinued to enable us re-investigate him. Fever however stopped on the third day after discontinuation of all medications, and he has remained symptom free since then. He has since resumed his normal duties.

DISCUSSION

Despite the wealth of literature on FUO, diagnosis of FUO remains a daunting task to physicians. This is partly due to the enormousity of causes and the lack of useful algorithms (1). Although there are geographical variations in the aetiology of FUO, the spectrum of diseases found in most studies investigating FUO shows that infections continue to be the commonest causes accounting for about 20-40% of cases, followed by neoplastic lesions and collagen vascular disorders (1-3). Studies in developing countries have revealed that tuberculosis, enteric fever and intra-abdominal abscesses are the commonest infections associated with FUO (3). There is no identifiable cause in 5-15% of cases (2).

Based on the well-recognised epidemiology of FUO, we considered that our patient's fever had an infective aetiology at the time of presentation. Having completed two different antimalarial regimens without resolution of fever, the fever was unlikely to be attributable to malaria. Positive post-therapy thin blood film is not unusual in individuals living in a malaria endemic region where asymptomatic carriage of malaria parasites is common and fever co-existing with malaria parasites does not necessarily mean the parasites are causal (4). The initial working diagnosis of sepsis in our patient was based on fulfillment of the diagnostic criteria for sepsis in addition to the fact that it is a common cause of fever in Nigerian adults. While Staphylococcus aureus is a recognised cause of sepsis, its isolation in a subsequent blood culture in our patient might be due to nosocomial acquisition or skin contamination of blood sample. Following non-response to several broad-spectrum antibiotics including those to which the organism was reportedly sensitive to, we felt it was more likely to be a contaminant.

The clinical scenario was further complicated by the negative investigation results for other common infective conditions and the negative auto-immune serology. Although acute HIV infection could be missed by ELISA, the chances of diagnosing acute HIV infection in our patient was increased by a repeat ELISA carried out in the fourth week of his illness about two weeks after the first using a different kit. While the clinical presentation could be explained by Lassa fever, the finding of neutrophil leucocytosis is not a feature of Lassa fever. We were further constrained by non-availability of facilities for Lassa virus serology. Unfortunately, our trial of ribavirin therapy was halted by the worsening of his symptoms which prompted discontinuation of all his medications to re-investigate him.

While it may be clinically logical to try to narrow the differential diagnosis in individual cases of FUO by focusing on specific clinical features, it often yields disappointing results (5). In majority of patients, the height, pattern, or duration of fever does not relate to the diagnosis (6). The challenge in making a diagnosis is further deepened by the observation that non-invasive laboratory tests provide a diagnosis in only 25% of cases while invasive procedures are only able to identify less than 50% of causes (7, 8). In resource-limited settings where laboratory facilities are far from optimal, clinicians investigating FUO even face greater frustration. While we were about to label our patient a case of undiagnosed FUO, the resolution of fever on discontinuation of all his medications made a strong case for drug fever. The clinical characteristics of drug fever are not distinctive but may include rigors, body rashes and white blood cell abnormalities, and the list of implicated drugs includes antibiotics and analgesics (5). While the temporal profile between commencement of the drug and on-set of fever is not consistent, diagnosis becomes more difficult when infection prompted administration of the drug which might be the case in our patient (5). Once the causative drug is stopped, fever almost always resolves within two to three days as observed in our patient (5).

CONCLUSION

We have presented a young Nigerian medical practitioner whose high grade persistent fever remained unraveled after rigorous investigations and medications but resolved following discontinuation of all the drugs. As a learning point, while FUO may remain undiagnosed in 5-15% of cases after rigorous management, the possibility of drug fever should be entertained in FUO cases that have been exposed to several drugs without change in the height and pattern of fever.

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