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FEVER OF UNDETERMINED ORIGIN IN PATIENTS WITH THE ACQUIRED IMMUNODEFICIENCY SYNDROME IN BRAZIL: REPORT ON 55 CASES

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SUMMARY

The medical records of patients with AIDS admitted to a general hospital in Brazil from 1989 to 1997 were reviewed retrospectively with the aim at defining the frequency and etiology of fever of undetermined origin (FUO) in HIV-infected patients of a tropical country and to evaluate the usefulness of the main diagnostic procedures. 188 (58.4%) out of 322 patients reported fever at admission to hospital and 55 (17.1%) had FUO. Those with FUO had a mean CD4+ cell count of 98/ml. A cause of fever was identified for 45 patients (81.8%). Tuberculosis (32.7%), *Pneumocystis carinii* pneumonia (10.9%), and *Mycobacterium avium* complex (9.1%) were the most frequent diagnoses. Other infectious diseases are also of note, such as cryptococcal meningitis (5.5%), sinusitis (3.6%), *Salmonella-S. mansoni* association (3.6%), disseminated histoplasmosis (3.6%), neurosyphilis (1.8%), and isosporiasis (1.8%). Four patients had non-Hodgkin's lymphoma (7.3%). We conclude that an initial aggressive diagnostic approach should be always considered because biopsies (lymph node, liver and bone marrow) produced the highest yield in the diagnosis of FUO and the majority of the diagnosed diseases are treatable. The association of diseases is common and have contributed to delay the final diagnosis of FUO in most cases. In our study area the routine request of hemocultures for *Salmonella* infection and the investigation of cryptococcal antigen in the serum should be considered.

KEYWORDS: Fever; Fever of unknown origin; AIDS; Acquired immunodeficiency syndrome; Fever of undetermined origin

INTRODUCTION

The clinician confronted with a febrile HIV-infected patient may feel overwhelmed by the potentially large differential diagnosis. Prolonged fever is frequently observed in this setting and it is a challenge to the attending physician to unveil the diagnosis and to define the best therapeutic approach.

A systematic search for both infectious and non-infectious etiologies is warranted for all episodes of fever.

Several reports have investigated the most frequent causes of fever of undetermined origin (FUO) in the general population[12], but only a small number of articles have studied the causes of fever in patients with AIDS[10, 15, 22]. Moreover, regional differences are to be expected. In Spain[16] and France[2] , for instance, leishmaniasis is an important cause of FUO in AIDS patients. In Subsaharan Africa Gram-negative bacteremia is second only to tuberculosis as an explanation for death among HIV-infected individuals[7].There has been no reports on FUO in AIDS patients from Brazil.

We reviewed the medical records of all HIV-infected patients admitted to a general hospital in Brazil from 1989 to 1997, with the aim at defining the frequency of fever and of FUO in this population. The usefulness of the main investigative procedures in the diagnosis of FUO and the results of empiric therapy have also been analyzed.

PATIENTS AND METHODS

Patients

The medical charts of all HIV-infected patients who were admitted to the hospital of the Federal University of Minas Gerais (Brazil) between July 1989 and November 1997 were reviewed retrospectively. Each episode of FUO was recorded, along with its etiology, epidemiologic data and all tests contributing to a diagnosis. The information obtained was stored in a computer data bank using the EpiInfo version 6 software.

Definition of FUO

Fever of undetermined origin was defined as axillary temperature higher than 37.8°C, in different occasions, persisting for more than 4 weeks, and confirmed during hospital investigation[5, 19, 24]. We did not include patients who developed FUO during hospitalization.

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Other definitions

Specific diseases were defined as follows. *Pneumocystis carinii* pneumonia (PCP) was defined in patients who responded to trimethoprim-sulfamethoxazole and had a convincing clinical picture and radiologic findings; in one patient *P. carinii* was identified in the sputum. The diagnosis of tuberculosis was based on the identification of the agent in tissues or sputum; in 8 patients a response of the fever after treatment with rifampin, isoniazid and pyrazinamide was considered diagnostic. The diagnosis of *Mycobacterium avium* complex (MAC) was accepted when acid fast bacilli were recovered from tissues, the symptoms were consistent with MAC infection, the CD4 cell count was below 100, and a good response was obtained with clarithromycin associated with ethambutol.

Toxoplasmic encephalitis was diagnosed when a patient with serum IgG antibody to *T. gondii* and an abnormal and suggestive computed tomographic scan of the brain responded to antitoxoplasmosis therapy. Sinusitis was diagnosed if a patient had a sensation of congestion and tenderness on palpation of sinuses, plus radiologic evidence of sinusitis and good response to appropriate treatment. Cryptococcal meningitis was diagnosed when there was neurologic involvement and a lumbar puncture revealed positive India ink preparation for fungi.

More than one infectious agent has been identified in 38 patients with FUO. We have chosen the agent most likely to be responsible for the fever based on the treatment that terminated the fever.

HIV serology

All samples were tested by an enzyme-linked immunosorbent assay (Abbot Laboratories, California-USA). Positive samples were retested by ELISA and subsequently by western blot (Sanofi Diagnostics, Pasteur Inc., France). A western blot was judged to be positive if both core and envelope bands (p24 and gp 120/160 or gp41) were present (CDC/ASTPHLD criteria).

RESULTS

General data

Medical records of 322 HIV-positive patients who were hospitalized for investigation and treatment have been studied. 188 (58.4%) gave a history of fever during admission, and 55 of them (29.3%) presented one episode of FUO. 46 were male (83.6%): 23 homosexuals/bisexuals, 21 heterosexuals, 2 contaminated by blood transfusions; and 9 female (16.4%): one intravenous drug addict, one by blood transfusion, one prostitute, 3 contaminated by their husbands and 3 unknown.

The age range varied from 18 to 69 years (median: 33). The mean CD4 cell count was 98.2 ± 111.9 (range = 2-452/ml). 27 out of 40 (67.5%) had a CD4 cell count below 100/ml. Fever persisted before admission for a median of 90 days (range = 30-320).

Causes of FUO

In 45 patients (81.8%) the cause of fever was identified (Table 1). An infectious disease was documented in 41 patients (74.5%). Tuberculosis, pneumocystosis, and *Mycobacterium avium* complex infection were the most frequent diagnoses. 16 out of the 18 cases of tuberculosis had extrapulmonary involvement. Four remaining patients had non-Hodgkin's lymphoma (in two cases the diagnosis was confirmed by liver biopsies and the other two by bone marrow biopsies).

TABLE 1
Diagnostic categories and causes of fever of undetermined origin in 55 HIV-infected patients

Diagnostic categories (Causes)	Cases n = 55 (%)
Infectious diseases	**41** (74.5)
Tuberculosis	18 (43.9)
Pneumocystosis	6 (14.6)
MAC	5 (12.2)
Cryptococcal meningitis	3 (7.3)
Salmonella-S. mansoni association	2 (4.9)
Sinusitis	2 (4.9)
Histoplasmosis	2 (4.9)
Syphilis	1 (2.4)
Toxoplasmosis	1 (2.4)
Isosporiasis	1 (2.4)
Neoplasias	**04** (7.3)
Non-Hodgkin's lymphoma	4 (100.0)
Without a diagnosis	**10** (18.2)

MAC = *Mycobacterium avium* complex

Diagnostic procedures

Both noninvasive and invasive procedures were used in the evaluation of the patients. Table 2 shows those procedures that led to diagnoses. Biopsies of different tissues defined a diagnosis in 22 out of 51 patients (43.1%). Tuberculosis was the main disease diagnosed by biopsies. Lumbar puncture with CSF examination revealed the cause of fever in 4 patients, 3 with cryptococcal meningitis and in 1 with tuberculosis. Blood cultures isolated *Salmonella* sp in 3 patients (2 associated with schistosomiasis and 1 with lymphoma).

TABLE 2
Diagnostic procedures in 55 HIV-infected patients with FUO.

Procedures	N° performed	N° (%) positive
Lymph node biopsy	12	7 (58.3)
Liver biopsy	18	8 (44.4)
Bone marrow biopsy	07	4 (57.1)
Lumbar puncture	07	4 (57.1)
Skin biopsy	02	0 (00.0)
Blood cultures	25	5 (20.0)
Rectal biopsy	04	1 (25.0)
Parasitological stool examination	32	9 (28.1)
Brain biopsy	02	0 (00.0)
Pleural biopsy	02	2 (100.0)
Autopsy	01	1 (100.0)
Empiric therapy		
antimycobacterial	12	8 (66.6)
pneumocystosis	10	6 (60.0)

Some procedures were helpful because they showed abnormalities that guided diagnostic testing. The following are worth mentioning: imaging techniques (abdominal ultrasonography and computed tomographic scan) were helpful in 12 of 28 cases (42.9%), tuberculin skin test suggested the diagnosis of tuberculosis in 4 of 19 patients (21.1%); 6 out of the remaining 15 anergic patients had tuberculosis, serological tests for syphilis (VDRL, FTA) identified one patient with neurosyphilis, white blood cell count documented cytopenias in 14 patients and prompted the indication of bone marrow biopsy in 7 with diagnosis in 4 cases. Liver function tests (alkaline phosphatase, gamma-glutamyl transpeptidase) pointed the liver as the target organ in 18 patients and liver biopsy defined a diagnosis for the fever in 8. Stool examination identified 1 patient with schistosomiasis and one with isosporiasis.

Empiric therapy

22 patients received empiric therapy and 14 (63.6%) responded well to treatment. 12 cases were treated for mycobacterial infections and 10 for pneumocystosis.

Patients without a diagnosis

The 10 patients with FUO for which a diagnosis was not determined had fever for a mean of 120 days (range: 30-210). The mean CD4 cell count was 156 (range: 2-238ml). One patient died while febrile and autopsy was not authorized by his family. 9 patients left the hospital against medical advice and did not return for control.

Association of diseases

The association of diseases was common. 38 patients (69.1%) had more than one disease during hospitalization, and 15 patients (27.3%) more than 3. The following diseases (among others) were diagnosed in our patients with FUO but were not the explanation for their fevers: aspergillosis (1), Kaposi sarcoma (1), bacterial pneumonia (1), pneumocystosis (5), gram-negative bacteremia (2), urinary tract infection (3), candidiasis (22).

The cases of 3 patients have been selected and summarized below as examples of the association of diseases:

Patient 1 (Non-Hodgkin's lymphoma): He was a 32 year old man with persistent fever for 2 months, pain in the right leg, jaundice and weight loss of 10 kg. His chest x-ray on admission showed a diffuse interstitial pattern suggesting PCP, and 3 blood cultures grew *Salmonella* sp. Radioisotope bone scan showed concentration of radioisotope in the head of the right femur and in a lumbar vertebra (alterations were confirmed by CT scan). Biopsy of the femur disclosed the diagnosis of lymphoma. Urine culture revealed *Escherichia coli* (> 100,000 colonies/ml). The fever disappeared after starting treatment for the lymphoma.

Patient 2 (Tuberculous encephalitis): This was a 53 year old man with a history of fever during 39 days that was brought to hospital because he had a recent episode of seizures. A CT scan of the brain showed a solitary enhancing lesion surrounded by edema. He was treated for cerebral toxoplasmosis with sulfadiazine and pyrimethamine with no response. In the chest x-ray a homogeneous consolidation in the right lung base was diagnosed as aspiration pneumonia and he was treated accordingly. He died 19 days after admission without any improvement. Autopsy diagnosed the brain lesion as tuberculous meningoencephalitis and the lung involvement as caused by *Aspergillus* sp.

Patient 3 (Cryptococcal meningitis): a 33 year old black man was admitted to hospital with a 30-days history of fever. He was treated for "pneumonia" 6 months earlier and was receiving prednisone (5 mg) until 8 days before admission for psoriasis. He was also being treated for cytomegalovirus retinitis (maintenance dose) with ganciclovir. A biopsy of an inguinal lymph node revealed Kaposi's sarcoma. Because he complained of persistent headache a lumbar puncture was performed and an India ink preparation disclosed *Cryptococcus neoformans*.

Deaths

Nine patients died during the hospitalization or within the first month after dismissal. They had the following diseases: pneumocystosis (2 cases), disseminated tuberculosis (3 cases),

cryptococcal meningitis (1 case), tuberculous meningoencephalitis and pulmonary arpergillosis (1 case), histoplasmosis (1 case). One patient died without a diagnosis.

DISCUSSION

Infectious diseases were predominant as causes of FUO in the study herein presented (74.4%), and mycobacterial infections represented 56.1% of the infectious diseases. Our results also indicate that liver and lymph node biopsies are the most efficient and rapid methods for diagnosing mycobacterial infection, and that antimycobacterial empiric therapies deserve a trial in doubtful cases. These findings corroborate previous studies reporting the major role of mycobacteria as a cause of FUO in patients with HIV infection[1, 2, 16].

All 5 patients considered as having MAC infection were resistant to standard antituberculous drugs (rifampin, isoniazid, pyrazinamide) but presented a good response to a 2 drug combination regimen of clarithromycin, and ethambutol or rifampin. It should be noted that the newer macrolide antimicrobial agents that are effective against *M. avium* complex do not have significant activity against *M. tuberculosis*[9].

P. carinii pneumonia commonly presents with fever and slowly progressive dyspnea on exertion[17]. One study found nearly 1 month of constitutional symptoms prior to presentation in most HIV-infected patients[11]. Six patients had PCP in our study and 2 died. Of note, two other patients with FUO, one with lymphoma and another with pulmonary tuberculosis, also presented with associated PCP. Previous works have pointed out PCP as a cause of FUO in HIV-infected patients.

Cryptococcal meningitis was the cause of FUO in 3 patients in the present series. The onset of cryptococcal disease usually is insidious. The median time between the onset of symptoms and the diagnosis of cryptococcal disease is 30 days[4]. In our patients the median time until diagnosis was 45 days. Diagnosis often is delayed by the waxing and waning course of the disease and the absence of specific symptoms, making the prolonged febrile prodrome indistinguishable from that of other opportunistic infections.

Salmonella bacteremia was a commonly reported AIDS-defining opportunistic infection in the 1980s but is now reported to be uncommon. This decrease in incidence has been attributed to the antibacterial activity of zidovudine and TMP/SMX, which are frequently administered chronically to patients with AIDS[21]. In the present series two patients with FUO and AIDS had the *Salmonella-S. mansoni* association[13, 20]. In both patients treatment of schistosomiasis alone with oxamniquine cured the *Salmonella* bacteremia. Our patients were not receiving zidovudine or TMP/SMZ (one did not accept the diagnosis of AIDS and the other was unaware of the diagnosis). Recognition of the *Salmonella-S. mansoni* association as a cause of FUO in patients with AIDS, in endemic areas for schistosomiasis, is important because treatment of schistosomiasis improves the prognosis of this potentially fatal bacteremia.

Bacterial sinusitis is a common complication of advanced HIV disease and a reported cause of FUO[27]. Of our 2 patients, one responded well to treatment with antibiotics; the other, however, improved only after surgical drainage of the right maxillary sinus.

The patient with neurosyphilis and FUO had skin and ocular involvement (nodular eruptions in the legs and bilateral papillitis in the fundus oculi). Treatment with penicillin caused termination of the fever, disappearance of the skin lesions and improvement of the papillitis[8, 14, 23]. This is the first description of syphilis as a cause of FUO in patients with AIDS.

A CT scan showed cerebral toxoplasmosis in one patient who had no neurological manifestations but headache. Treatment with sulfadiazine/pyrimethamine produced resolution of the cerebral lesion and of her fever.

One patient with FUO, diarrhea and isosporiasis improved after treatment with TMP/SMX, and this is the second case of *Isospora belli* infection causing FUO[6]. Fever seems to be common during the course of isosporiasis. PAPE et al.[18], for instance, reported intermittent fever in 18 out of their 32 patients with isosporiasis.

Within endemic areas, histoplasmosis represents 5% of the opportunistic infections among AIDS patients. However, in hyperendemic areas, the incidence is as high as 25%[25]. Owing to the nonspecific symptoms of disseminated histoplasmosis, the disease may be difficult to diagnose. Histopathologic evaluation of tissues is more rapid than culture and establishes the diagnosis in up to 50% of patients. In some areas of Brazil histoplasmosis seems to be an important associated infection in patients with AIDS[3]. In our series one patient with FUO presented with pancytopenia; the bone marrow biopsy defined the diagnosis of disseminated histoplasmosis.

Widespread disease involving extranodal sites is the hallmark of AIDS-associated lymphoma at the time of diagnosis. ZIEGLER et al.[26] reported that 95% of patients had evidence of extranodal disease, 42% of patients had CNS disease, and 33% had bone marrow involvement. Our four patients with FUO, in the neoplasia group, had a disseminated non-Hodgkin's lymphoma and, on the occasion, a mean CD4+ cell count of 80 (range 26-425). Non-Hodgkin's lymphoma as a cause of FUO has previously been reported. It is interesting that all cases were seen in the last 3 years and this may be indicative of improvement in the treatment of other opportunistic infections (i.e., our patients are living longer and developing neoplasias).

In summary, the data from this retrospective study in a tropical country indicate at least two scenarios. On one side, our AIDS patients with FUO share a common profile with other countries (infectious diseases predominate as causes of FUO in AIDS patients and the importance of mycobacterial infection as a leading cause of FUO is also confirmed, non-Hodgkin's lymphoma represent a secondary cause of FUO, and immunologic diseases have not been observed). There are, however, regional differences. Other infectious diseases have got to be given a second thought

in Brazil such as, cryptococcal meningitis, *Salmonella-S. mansoni* association, histoplasmosis, syphilis and isosporiasis.

Finally we wish to emphasize 4 main lessons learned from this study:

1) The clinician should always consider an initial aggressive diagnostic approach in HIV-infected patients with FUO because biopsies (especially of lymph node, liver, and bone marrow) produced a high diagnostic yield in our study and the majority of the diagnosed diseases are treatable; 2) The frequent association of diseases in AIDS patients have contributed to delay the definition of the final diagnosis of FUO in most cases; 3) In endemic areas for schistosomiasis hemocultures should be ordered routinely in the search for *Salmonella* bacteremia; 4) Serum cryptococcal antigen must be added to the protocol of investigation of prolonged fever in patients with AIDS.

RESUMO

Febre de origem indeterminada em pacientes com a síndrome da imunodeficiência adquirida no Brasil: relato de 55 casos

Revisaram-se os prontuários médicos de pacientes com AIDS e febre de origem indeterminada (FOI) com o objetivo de definirem-se as causas de FOI em indivíduos HIV positivos em um país tropical e, ainda, determinar o valor dos procedimentos diagnósticos mais utilizados. Cento e oitenta e oito (58,4%) de 322 pacientes apresentavam febre à internação e 55 (17,1%) preencheram os critérios de FOI. A contagem média de CD4+ no grupo com FOI era de 98 células/ml. Definiu-se a causa da febre em 45 pacientes (81,8%). As seguintes doenças infecciosas predominaram como causa de FOI: Tuberculose (32,7%), pneumonia pelo *Pneumocystis carinii* (10,9%) e *Mycobacterium avium* complex (9,1%). Outras doenças infecciosas merecem destaque: meningite criptocócica (5,5%), sinusite (3,6%), associação *Salmonella-S. mansoni* (3,6%), histoplasmose disseminada (3,6%), neuro-sífilis (1,8%) e isosporíase (1,8%). No grupo das neoplasias, quatro pacientes (7,3%) apresentaram linfomas não-Hodgkin disseminados. As biópsias de linfonodos, de fígado e de medula óssea responsabilizaram-se pelo maior número de diagnósticos definitivos na presente casuística. A associação de doenças mostrou-se comum e atrasou o diagnóstico da febre na maioria dos casos. Em nossa região, a realização rotineira de hemoculturas visando identificar os indivíduos com salmonelose prolongada associada à esquistossomose e a pesquisa de antígeno circulante para *Cryptococcus neoformans* devem ser consideradas nos pacientes com AIDS e FOI.

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