Fever of Unknown Origin in Adults: Two Case Reports and Review

Erişkinlerde Sebebi Bilinmeyen Ateş: 2 Olgu Sunumu ve İncelemesi

Sebebi Bilinmeyen Ateş / Fever of Unknown Origin

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Özet

Sebebi bilinmeyen ateş (SBA) tanısal bir sorundur. SBA'nın sebepleri listesi muhtemelen tüm tıp dünyasındaki en uzun listedir. Doğru tanının temeli, öykü ve fizik muayeneye ait tanısal ipuçlarının aktif olarak incelenmesinde yatar. Biz iki ayrı SBA vakası sunacağız. Febril sendromun asıl nedeni insan immün yetmezlik virüsü (HIV) ile enfeksiyondur. Doğru kesin tanı için anahtar nokta, klinik belirtiler ve laboratuvar incelemelerin detaylı analizidir.

Anahtar Kelimeler

Uzamış Ateş; HIV Enfeksiyonu; AIDS

Abstract

Fever of unknown origin (FUO) is a diagnostic challenge. The list of causing disorders of FUO is probably the longest in the medicine. The active searching of diagnostic clues of history and physical examination is the base to the correct diagnosis. We present two cases of FUO. The finding reason of the febrile syndrome is infection with Human immunodeficiency virus (HIV). The detailed approach in clinical manifestation and laboratory investigation should be the key to final diagnosis with beneficial outcome.

Keywords

Prolonged Fever; HIV Infection; AIDS

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Introduction

The persisting fever is a puzzle in the general medicine. In 1961 Petersdorf and Beeson [1] introduced the definition of fever of unknown origin (FUO) with aim to limit the spontaneously self-limited infection from the prolonged undiagnosed fever. It includes three criteria: 1.) fever higher than 38.30C on several occasions, 2.) duration of illness more than three weeks, 3.) the diagnosis is uncertain after one week of investigations in hospital [2]. In 1991 FUO is separated in four groups by Durrack and Street [3]: classic, nosocomial, neutropenic and HIV-associated [4]. Classic FUO is a modified version of the first definition by Petersdorf and Beeson. The definition is: a) fever ≥ 38.30C on several occasions; b) duration ≥ 3 weeks; c) diagnosis uncertain after 3 days despite appropriate in-hospital investigation or three outpatient visits [3, 5]. More than 200 diseases are the causes of FUO [5]. The disorders causing classical FUO are included in five categories: infections, neoplasms, connective tissue diseases, miscellaneous other disorders and undiagnosed illnesses [6]. In the differential diagnosis of any unexplained prolonged febrile syndrome HIV infection should be taken [6]. It is in the list of causes in classic FUO [2, 4, 6]. On the other hand the immunodeficiency-related infections as Pneumocystis carinii pneumonia (PCP) and Mycobacterium avium/Mycobacterium intracellulare complex (MAC) infection are presenting as causes of FUO [7].

In this report, we present two cases of FUO. HIV infection was the leading cause of the illnesses. In the first case it is presenting as opportunistic infection in HIV positive man, the second case is HIV/HBV co-infection. A brief review of the literature is also presented.

Case Report 1

A 42-year-old man, white, heterosexual was admitted to our department because of fever of unknown origin (FUO) at February 2013. The patient had had high fever since one month. At the first week of his illness the family doctor examined him and did a few investigations. In the view of elevated acute phase proteins she prescribed an antibiotic – Amoxicillin/Clavulanic acid 875mg/125mg twice orally. The man took the medicine seven days without any result. At the third week of the illness because of the continuing the fever second antibiotic was prescribed – Levofloxacin 500mg once daily. The generalized itching rash was appeared after the first accepting of the drug. The man was hospitalized at the Department of Toxicology in Military Medical Academy. There he was treated with intravenous corticosteroids for five days because of allergic reaction presenting with headache, maculo-papula itching disseminated rash and fever. After the specific therapy the rash was disappeared and the man was directed to the Department of Infectious Diseases for diagnostic specification. He complained of fever, fatigue, sickness, and weight loss. He had a history of respiratory disease and common oral thrush one year before this evaluation. He had no known allergies before the admission to the Department of Toxicology. He didn't have an underlying disease. He has been born in Burgas (Bulgaria) – a sea town but has been living in the the capital of Bulgaria. He was not married, without permanent partner. He worked in a restaurant. He didn't smoke cigars, drank alcohol infrequently, and didn't use illicit drugs or systemic medicines. No travel abroad was mentioned. No pet and animal exposition. On an examination the man was intoxicated, frightened and nervous. The temperature was 38.80C, the blood pressure was 115/70 mmHg, the pulse 90 beats per minute. There wasn't any rash on body. Eyes were with flushing and exophthalmia. Herpes labialis was presented. The oropharynx was with inflammation, the tonsils were enlarged with curdlike patches. Oral mucosae, tongue longitudinal angle and pharynges were covered with white patches. The lymph nodes in cervical region were enlarged. The lung auscultation found coarse breath sounds without wheezes. The abdomen was soft, with normal bowel sounds and without tenderness. The physical examination did not reveal liver or spleen enlargement. The remainder of the examination was normal.

The complete investigations were performed. The urinalysis was normal. The blood samples are presented in Table 1. The ESR, CRP, AST, ALT, GGT, and LDH were elevated.

Table 1. Laboratory data in patients with fever of unknown origin

Variable (SI units)	Reference range	Case 1		Case 2	
		Admission	Discharge	Admission	Discharge
Hemoglobin (g/L)	136-175*	125	ND	152	145
Erythrocyte count (x1012/L)	4.7-6.1	4.2	ND	4.9	4.5
White blood cell count (x109/L)	4.8-10.8	9.5	ND	4.5	3.1
Fibrinogen (mcmol/L)	5.15-12.73	11.76	ND	12.348	ND
Erythrocyte sedimentation rate (mm/h)	< 12#	66	ND	46	26
Glucose (mmol/L)	3.33-6.11	4.1	ND	5.3	4.1
Creatinine (mcmol/L)	50-100	74	ND	79	69
Total bilirubin (mcmol/L)	2-21	19	ND	15	30
Total protein (g/L)	60-80	77	ND	89	67
Albumin (g/L)	34-47	33	ND	39	31
C-reactive protein (mg/L)	< 10	23.2	ND	1.4	ND
Aspartate transaminase (mckat/L)	0.0-0.58	1.04	ND	15.46	28.64
Alanine transaminase (mckat/L)	0.0-0.7	3.04	ND	22.20	28.64
Gamma-glutamyl transferase (mckat/L)	0.15-1.42	3.38	ND	2.72	5.50
Alkaline phosphatase (mckat/L)	0.7-2.2	3.96	ND	4.52	7.08
Lactate dehydrogenase (mckat/L)	1.46-3.82	10.16	ND	25.86	ND
Ferritin (pmol/L)	36-674	1381.905	ND	1617.84	ND

Note: * reference for male; # reference for male younger than 50 years. ND – no data available.

The intravenous infusions were applied. Ademetionine was added to the therapy. The patient continued to be febrile and cough was appeared. This was the reason to extend the diagnostic protocol. The culture samples were obtained: blood, sputum, throat and feces. The throat culture was positive for Candida albicans, which corresponded to the physical present-

ing of thrush. The sputum was submitted to the microbiology laboratory for acid-fast smears and mycobacterial cultures. The results were negative.

Anti-streptolysin titer (ASO) and rheumatoid factor (RF) were negative. T. Pallidum haemagglutination assay (TPHA) was negative. Thyroid hormones were in reference. The serological tests were done using Enzyme-linked immunosorbent assay (ELISA). Anti-influenza type A and B IgM and IgG, anti-CMV IgM and IgG, anti-Q fever II IgM were negative. The abdomen ultrasound found a slight liver enlargement. The chest X-ray was performed because of the processing the respiratory signs. The finding was diffuse infiltrates. Non-culture methods for invasive fungal infection were performed. Test for Mannan antigen was positive and Galactomannan antigen was negative. Fluconazole 200mg daily was applied. The diagnostic protocol was purposed in the thinking of immunodeficiency. Basing on the history, physical findings, laboratory findings, chest X-ray and the progressing respiratory illness the opportunistic infection as PCP was suspected. Sulfamethoxazole/Trimethoprim 960mg three times daily intravenously was added to the therapy. ELISA screening test for HIV was done. The result was reactive (positive), HIV-1 antibodies were found. Second blood samples were sent to the National Reference Laboratory for a confirmation. Western blot confirmatory assay was performed. HIV-1 infection was confirmed. But the respiratory symptoms get worsen and the respiratory failure has been developed. Despite the adequate reanimation procedures the patient died. The autopsy was not performed. We supposed that the opportunistic infection as PCP was the reason of the death. In case 1 FUO was established as HIV/AIDS, developing immunodeficiency-related infections.

Case Report 2

A 43-year-old homosexual, white man was admitted to the Department of Infectious Diseases because of FUO at May 2013. He has been ill since April 2013. He had high temperature with chills and sweating, sore throat with acute tonsillitis, muscle and joint pain. Because of these complaints he has been hospitalized at the Department of Internal Medicine, General Hospital in Burgas (Bulgaria). The empirical antibiotic therapy has been started: Ceftriaxone 2g once daily intravenously for 7 days, after that Moxifloxacin 400mg one tablet per day for the period of 7 days. The result of this treatment was the reduction of the temperature to low grade value. After three days the symptoms came back. Fever, fatigue, weight loss of 6 kilogrammes for 14 days, dark urine and weakness were the leading signs. Because of the prolonged febrile syndrome the man was hospitalized in our department.

The man was born in Aytos (Bulgaria) – a small town at the seacoast. After his thirty years he came to the capital of the country. He was single, homosexual man. The man worked as a waiter. There were no underlying diseases. The patient mentioned common tonsillitis in the last three years. No travel history. No blood transfusion. He smoked cigars, drank alcohol infrequently, and didn't use illicit drugs or systemic medicines. No pet and animal exposition.

On the physical examination the man was febrile, without skin eruptions. Herpes labialis was presenting. There were creamy white patches on the tongue and oral mucosal surfaces. The liver was slight enlargement. The remainder examination was normal.

The complete investigations were obtained. The urinalysis showed increased urobilinogen. From the biochemical parameters the liver enzymes were elevated, LDH also was high elevated. The culture of blood, throat, urine and feces were negative. The serology for Toxoplasmosis and Toxocariasis were negative. The ELISA tests for Mycoplasma pneumoniae and Chlamydophila pneumoniae were negative.

Serological tests for hepatotropic viruses were done by ELISA. The results are following: anti HAV was negative; HBsAg – positive; anti-HBe – positive; anti-HBc IgM – positive; anti-HBc total – negative; anti-HCV – negative; anti-EBV VCA IgM – negative. The test confirmed acute viral hepatitis type B.

The abdomen ultrasound was performed. The liver and spleen were enlarged without local lesion.

The symptomatic treatment for acute viral hepatitis was started. The patient continued to be febrile and full of weakness and muscle pain. A screening test for HIV was performed. Using ELISA the result was reactive (positive) for HIV-1 antibodies. The second blood samples were sent to the National Reference Laboratory for confirmation. Western blot was performed. The result was positive. Basing on the national legislation the man was transferred to Department of Immunodeficiency, National Hospital of Infectious Diseases.

Discussion

The presenting two cases have some similar things: male sex, age group of young adults, an occupation in the field of service, inconstant sexual partner. They suffered of prolonged unexplained fever. Oropharyngeal candidiasis and oral hairy leukoplakia were presented. The men were admitted to the Department of Infectious Diseases after one month unsuccessful diagnostic investigations. The diagnostic protocol of FUO was started. The examination for HIV is a part of the investigations. In carefully research and complete exam few diagnostic clues suggest the final diagnosis. The findings of history and physical exam are sexual behaviour, fever, weight loss, oral thrush and oral hairy leukoplakia. The clinical keys in case 1 are the aggravation of the respiratory manifestation and following acute respiratory distress syndrome (ARDS). In case 2 the persisting fever and oral ulceration in the course of acute viral hepatitis. These two cases are part of a prospective study on FUO, conducting in the Department of Infectious Diseases, Military Medical Academy, Sofia (Bulgaria). The presenting cases of HIV infection are only 2.85 % of all 70 patients with febrile syndrome in our study. These results are similar to the data of other articles made in USA, Europe and Asia (Table 2) [7-13]. The total number in these articles is 18 patients with HIV/AIDS. Acute HIV infection was found in 4 cases and 14 had AIDS. Mycobacterium tuberculosis and MAC infection was presented in 3 cases, PCP was described in 3 cases, Cryptococcosis - 1, Penicillium marneffei infection – 1, and unmarked infection in 4 cases with AIDS. Co-infection with HBV or HCV is not noted. The total percentage of HIV/AIDS as a part of all FUO cases in mentioned seven studies (Table 2) is 1.99 %, respectively 6.06 % of infectious disorders as causes of FUO. This number is not high, but the social and economic meaning of HIV/AIDS made the count

Table 2. HIV/AIDS cases in patients with fever of unknown origin

Study, Reference	Country	Period	Methodology	HIV/AIDS, №(%)	
				of all infections	of all patients
Kazanjian PH [7]	USA	1984-1990	Prospective	3/28 (10.7)	3/86 (3.5)
Baicus C et al [8]	Romania	1997-1998	Prospective	4/74 (5.4)	4/164 (2.4)
Vanderschueren S et al [9]	Belgium	1990-1999	Prospective	1/57 (1.8)	1/290 (0.3)
Tabak F et al [10]	Turkey	1984-2001	Retrospective	2/40 (5)	2/117 (1.7)
Liu KS et al [11]	Taiwan	1999-2002	Retrospective	6/33 (18.2)	6/78 (7.7)
Chin C et al [12]	Taiwan	2001-2002	Prospective	1/54 (1.9)	1/94 (1.1)
Ben-Baruch S et al [13]	Israel	2005-2010	Retrospective	1/11 (9.1)	1/75 (1.3)

Note: HIV - Human Immunodeficiency Virus; AIDS - Acquired Immunodeficiency Syndrome; USA - United States of America.

important. HIV infection and immunodeficiency syndrome are conditions with leading world, healthy and considerable meaning. Basing on these facts the investigations for HIV have to be a part of the guidelines in the case of fever of unknown origin. In the era of modern technology and investigation the basic medical principles of completed medical history and entire physical examination couldn't be leaving out. Sometimes they are the key to the correct diagnosis.

In conclusion we would mark a few points: 1.) suspect every case of

prolonged fever for immunodeficiency, 2.) do not forget the fundamental medical rules – repeat the history and complete physical examination, 3.) optimize and improve the collaboration between laboratory and clinicians because early diagnosis and an appropriate specific therapy is basically for the final outcome in case of immunodeficiency.

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Conflicts of Interest

None of the authors have any associations that might be deemed a conflict of interest to the publication of this manuscript.

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Abbreviations

Human immunodeficiency virus (HIV); Fever of unknown origin (FUO); Acquired Immunodeficiency Syndrome (AIDS); Pneumocystis carinii pneumonia (PCP); Mycobacterium avium/Mycobacterium intracellulare complex (MAC); Erythrocyte sedimentation rate (ESR); C-reactive protein (CRP); Aspartate aminotransferase (AST); Alanine aminotransferase (ALT); Gamma-glutamyl transferase (GGT); Lactate dehydrogenase (LDH); Anti-streptolysin titer (ASO); Rheumatoid factor (RF); T.Pallidum haemagglutination assay (TPHA); Enzyme-linked immunosorbent assay (ELISA); Hepatitis B virus (HBV); Hepatitis C virus (HCV); Acute respiratory distress syndrome (ARDS).

Author's Contributions

Magdalena Baymakova conceived study design, data collection, data interpretation, manuscript preparation and literature search. Benjamin Sakem assisted with data interpretation and manuscript preparation. Kamen Plochev, Raynichka Mihaylova-Garnizova, Georgi T. Popov, Ginka Delieva and Diana Dimitrova assisted with data collection. Valentina Kovaleva did the serological studies.

All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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