Katarzyna DĄDELA[1]
Andżelika SIWIEC[1]
Jarosław JARCZEWSKI[1]
Marcin KOSTAŃSKI[1]
Joanna SULICKA-GRODZICKA[2]
Magdalena STRACH[2]

Fever of unknown origin: a current problem in clinical practice – case report

Gorączka o nieznanej przyczynie: aktualny problem w praktyce klinicznej – opis przypadku

[1]Student's Research Group of Rare Diseases, Jagiellonian University Medical College, Cracow, Poland
[2]Clinic of Internal Diseases and Geriatrics, University Hospital in Cracow, Department of Internal Medicine, Poland
Head:
Prof. Tomasz Grodzicki, MD, PhD

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Fever of unknown origin (FUO), defined in 1961, is a clinical syndrome known as one of the major diagnostic challenges of internal medicine. This case report documents a 28-year-old female with episodic fever accompanied by: arthralgia, rash, lymphadenopathy and the elevation of acute phase reactants. Between the episodes, the patient felt well and regained her normal daily functions (work, household chores). Treatment with oral corticosteroids resulted in the regression of the symptoms but did not affect the frequency of relapses. Diagnostic evaluation, including x-rays, ultrasound scans, CT scans, bone marrow biopsy, lymph node biopsy and laboratory investigations did not confirm the major causes of FUO: infections, malignancies and autoimmune diseases. The genetic screening panel did not confirm any of known periodic fever syndromes (familial Mediterranean fever, hyper-IgD syndrome, TNF receptor-associated periodic syndrome, muckle-wells syndrome, familial cold autoinflammatory syndrome, neonatal onset multisystem inflammatory disease). Fifty five years after the first definition, fever of unknown origin still remains a diagnostic challenge.

**Gorączka nieznanego pochodzenia (FUO - fever of unknown origin), zdefiniowana w 1961 roku, jest zespołem klinicznym znanym jako jedno z największych wyzwań diagnostycznych medycyny wewnętrznej.
W niniejszej pracy opisano przypadek 28-letniej kobiety z epizodyczną gorączką, której towarzyszyły: bóle stawów, wysypka, powiększenie węzłów chłonnych i podwyższenie markerów stanu zapalnego. Pomiędzy epizodami gorączki pacjentka czuła się dobrze i powracała do normalnego, codziennego funkcjonowania (praca, obowiązki domowe). Leczenie doustnymi kortykosteroidami powodowało ustąpienie objawów, jednak nie wpływało na częstość ich nawrotów. Badania diagnostyczne, w tym rentgenogramy, badania ultrasonograficzne, tomografia komputerowa, biopsja szpiku kostnego i węzłów chłonnych oraz badania laboratoryjne nie potwierdziły głównych przyczyn FUO: zakażeń, nowotworów złośliwych oraz chorób autoimmunologicznych. Wykonany panel badań genetycznych nie potwierdził obecności mutacji charakterystycznych dla zespołów gorączek nawrotowych (tj.: gorączki śródziemnomorskiej, zespołu Hyper-IgD, gorączki związanej z mutacją receptora dla czynnika martwicy nowotworów, zespołu Muckle-Wells, rodzinnej zimnej pokrzywki, noworodkowej choroby wielonarządowej). W okresie 55 lat po pierwszej definicji, gorączka o nieznanej przyczynie wciąż pozostaje wyzwaniem diagnostycznym.**

Introduction

Fever of unknown origin (FUO), as defined by Petersdorf and Beeson in 1961, is a rare clinical syndrome well known as one of the major diagnostic challenges of internal medicine [1]. In the last two decades several modifications have been proposed for the FUO criteria and nowadays it is defined as a fever of 38.3°C or more lasting at least 3 weeks and for which no cause can be identified after 3 days of investigations in hospital or after 3 or more outpatient visits [2-4]. There are only a few other clinical presentations that produce such a wide array of differential diagnoses.

Recurrent or episodic fever represents probably the most intriguing FUO subtype. Recurrent fever is defined as relapses of fever that lasts from a few days to few weeks, separated by symptom-free intervals of variable duration [5]. It represents between 18% and 42% of the cases in large series of FUO patients and up to 50 % cases remain unsolved [6-10]. In contrast to patients with classic FUO, the evaluation of patients with recurrent fever often requires a different approach since:

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Address for correspondence:
Katarzyna Dądela, Śniadeckich St. 10
31-351 Cracow, Poland
tel. (12) 424 88 00, fax (12) 424 88 54
e-mail: katarzyna.dadela@gmail.com

(a) patients often consult a specialist during an attack-free period; (b) patients usually have a long history of frequent attacks of fever; (c) patients have been subjected to numerous invasive procedures and repeated courses of corticosteroids [11].

Case presentation

A 28-year-old female presented to the Immunology and Rare Disease Clinic with an 8-year history of episodic fever. The first episode of 40°C fever with accompanying shivers, cough and diffuse salmon-coloured rush appeared at the turn of September and October 2008 and lasted for 36 days. After hospitalization and extensive evaluation the fever was attributed to dental and urinary tract infections (positive urine culture). Dental extractions with antibiotics were introduced and the symptoms subsequently subsided. However, after 2 months the fever relapsed and within the following years occurred from 5 to 7 times a year. These episodes lasted from 2 to 4 weeks and were additionally associated with cervical, axillary and inguinal lymphadenopathy, arthralgia and uncharacteristic musculoskeletal complaints.

The patient's past medical history was remarkable for the total retinal detachment of the right eye (retinopathy of prematurity), drug-induced angioedema (sulphamethoxazole/trimethoprim), uterine fibroid, conjunctivitis and aphthous stomatitis. She was allergic to amoxicillin with clavulanic acid. She denied any travel, contact with animals and any known exposure to potential toxins. Her family history was unremarkable and none of the family members had similar complaints.

Despite prolonged course of disease the patient did not develop substantial weigh loss or other sign of a serious underlying disease. Between attacks she felt well and regained her normal daily activities.

The patient's laboratory studies revealed that febrile episodes were marked by increased levels of C-reactive protein within range 30-70 mg/l (N<5.00) and presence of hypergammaglobulinemia (17.91 g/dl N: 6.50-11.50) and hyperbetaglobulinemia (11.68 g/dl N: 5.70-7.90) (Tab. I). Immunology tests detected antinuclear antibodies (ANA) with no antigen's specificities in enzyme-linked immunosorbent assay (ELISA) (Tab. II). Because of the history of angioedema she underwent the oral provocation testing with nonsteroidal anti-inflammatory drugs. This result was negative. The remaining biochemistry, haematological, serological and immunological tests as well as cultures were within normal ranges. The genetic screening panel for periodic fever syndromes did not demonstrate mutations in suspected disease-related genes (Tab. III). An extensive radiological investigation was also inconclusive. In addition she underwent excisional lymph node biopsy and trepanobiopsy which showed unspecific inflammatory changes. The biopsy of gastrointestinal tract did not disclose amyloid deposits.

Table I
Laboratory results.
Wyniki badań laboratoryjnych.

Parameters	Units	Results	Normal ranges
	Routine biochemistry investigations		
CRP during attacs	mg/l	30-70 ↑	<5.00
CRP between attacs	mg/l	<5.00	<5.00
ALT	U/l	38 ↑	5 – 33
AST	U/l	27	5 – 32
Total bilirubin	µmol/l	7.20	0.00 – 21.00
Cholinesterase	U/l	7999	5320 – 12920
Glucose	mmol/l	4.38	3.30 – 5.60
Creatinine	µmol/l	53.00	44 – 80
	Protein electrophoresis – serum		
Total protein	g/l	78.9	66.00 – 87.00
	%	48.40 ↓	60.00 – 71.00
Albumin	g/l	38.19	35.00 – 50.00
	%	2.30	1.40 – 2.90
Alpha-1 globulin	g/l	1.81	0.90 – 2.10
	%	11.80 ↑	7.00 – 11.00
Alpha-2 globulin	g/l	9.31 ↑	5.00 – 7.90
	%	14.80 ↑	8.00 – 13.00
Beta globulin	g/l	11.68 ↑	5.70 – 7.90
	%	22.70 ↑	9.00 – 16.00
Gamma globulin	g/l	17.91 ↑	6.50 – 7.90
	%	22.70 ↑	9.00 – 16.00
	Complete blood count		
RBC	10^6/µl	4.69	3.50 – 5.00
HGB	g/dl	12.90	11.00 – 15.00
HCT	%	39.30	37.00 – 47.00
PLT	10^3/µl	259.00	125.00 – 340.00
WBC	10^3/µl	5.59	4.00 – 10.00
LYM	10^3/µl	1.90	0.80 – 4.00
MONO	10^3/µl	0.70	0.16 – 0.80
EOS	10^3/µl	0.10	0.04 – 0.30
BASO	10^3/µl	0.00	0.00 – 0.10
IgG	10^3/µl	0.01	0.00 – 0.09

CRP C – reactive protein, ALT alanine transaminase, AST asparate transaminase, RBC red blood cell count, HGB haemoglobin, HCT haematocrit, PLT platelets, WBC White blood cell count, LYM Absolute lymphocyte count, MONO absolute monocyte count, EOS absolute eosinophil count, BASO absolute basophil count, IgG immunoglobulin G

Discussion

The conditions underlying recurrent fever are numerous. Infections, malignancies and non-infectious inflammatory diseases, which account for 60% to 70% of the FUO cases, are responsible for only 20% of the recurrent fevers causes [12].

Only a restricted number of infections produce a pattern of episodic fever. The bacterial seeding from a silent site such as tooth and sinusitis can be the reason for relapsing symptoms. However, despite initial suspicion, this was not the leading cause of fever FUO in our patient. Other causes of fever include an inappropriate treatment of infections and an enhanced susceptibility to infections due to primary or secondary immunodeficiencies [13]. These reasons were also ruled out by evaluation of patient's immune system (Tab. I, II) with complete blood count with differential, the levels of the immunoglobulin, peripheral blood lymphocyte flow cytometry, in vitro studies of T cell function and cytokine measurements. The persistent Yersinia enterocolitica infection [14] and, in endemic areas, the Borreliarecurrentis infection [15] and trypanosomiasis [16] have been reported as a cause of episodic fever. These causes were not evaluated in our patient because of the absence of particular risk factors and suggestive symptoms.

Recurrent fever may be seen in the cases of neoplastic diseases, especially in lymphomas. Pel-Ebstein fever, which cyclically increases then decreases over an average period of one or two weeks, is typical of Hodgkin's disease [17]. Other less common malignant disorders reported as a cause of FUO include angioimmunoblastic T cell lymphoma, multicentric Castleman disease, myeloproliferative disorder, solid cancers or paraneoplastic syndromes. To

Table II
Clinical evaluation and differential diagnosis of the febrile patient.
Ocena kliniczna i diagnostyka różnicowa gorączkującej pacjentki.

Tested parameters	Results	Medical conditions associated with a positive test result
	Infectious disease	
HBsAg	(-)	Hepatitis B
Anti-HCV	(-)	Hepatitis C
Blood culture	(-)	Blood infection, endocarditis
Bile culture	(-)	Biliary tract infection
Parasitological stool examination	(-)	Gastrointestinal parasitic infection
Mycological stool examination	(-)	Gastrointestinal fungal infection
Anti-HIV (p24)	(-)	HIV infection
***Borrelia* (ELISA-IgM, IgG)**	(-)	Lyme disease
EBV DNA detection by PCR	(-)	Chronic active EBV infection
	Diseases of the Immune System	
ANA	(+/-)*	SLE
AMA	(-)	Primary biliary cirrhosis
ASMA	(-)	Primary biliary cirrhosis
APCA	(-)	Pernicious anemia
Anti-LKM	(-)	Autoimmune hepatitis
RF	WNL	Rheumatoid arthritis
Waller-Rose assay	(-)	Rheumatoid arthritis
Anti-CCP	WNL	Rheumatoid arthritis
ASO	WNL	Reactive arthritis
C3, C4, C1-inh	WNL	Complement deficiency
IgG, IgM, IgA, IgE levels	WNL	Primary immunodeficiency diseases
IgD level	WNL	HIDS
Lymphocyte immunophenotyping	WNL	Immunodeficiency
Lymphocyte proliferation to mitogens	WNL	Immunodeficiency
Ferritin level	WNL	Adult-onset Still's disease
Subcutaneous sulphonamide testing	(+)	Drug hypersensitivity
Oral provocation test with NSAIDs	(-)	Drug hypersensitivity
Congo red staining for amyloidosis	(-)	Amyloidosis
	Malignancies	
Complete blood count with peripheral smear	WNL	Lymphoma
CA 19-9	WNL	Digestive system neoplasms
CA-125	WNL	Serous ovarian cancer

WNL within normal limits, (-) negative test result, (+) positive test result HBsAg surface antigen of the hepatitis B virus, Anti-HCV antibody to hepatitis C virus, anti-HIV antibody to human immunodeficiency virus, p24 capsid protein, ELISA enzyme-linked immunosorbent assay, EBV DNA detection by PCR Epstein-Barr Virus DNA detection by polymerase chain reaction, ANA antinuclear antibodies, ASMA Anti-smooth muscle antibody AMA anti-mitochondrial antibody, APCA anti-parietal cell antibody, anti-LKM1 anti-liver-kidney microsome antibody, RF rheumatoid factor, Anti-CCP anti-citrullinated protein antibody, ASO antistreptolysin O titer, C3 complement component 3, C4 complement component 4, C1-inh C1 esterase inhibitor, NSAIDs nonsteroidal anti-inflammatory drugs, CA cancer antigen, HIDS Hyperimmunoglobulinemia D with recurrent fever.

** Indirect immunofluorescence assays on Hep-2 cells showed homogenous and grainy ANA pattern (1:320) but ELISA did not detect specific antibodies.*

Table III
Genetic testing of periodic fever syndromes.
Badania genetyczne w kierunku występowania zespołów gorączek nawrotowych.

Disease	Gene (Chromosome)	Select sequences
Familial Mediterranean fever (FMF)	MEFV (16p13.3)	Exon 2, 3 and 10
Hyperimmunoglobulin D syndrome (HIDS)	MVK (12q24)	Exon 9 and 11
Tumor necrosis factor alpha receptor-1 associated syndrome (TRAPS)	TNFRSF1A (12p13)	Exon 2-3, 4-5, 6-7 intron 2, 4 and 6
Muckle-Wells syndrome (MWS)	NLRP3 (1q44)	Exon 3
Familial cold autoinflammatory syndrome (FCAS)	NLRP3 (1q44)	Exon 3

MEFV Familial mediterranean fever gene, MVKMevalonate kinase gene, TNFRSFIA Tumor necrosis factor receptor 1 gene, NRLP3 NACHT, LRR and PYD domains-containing protein 3 gene. References: Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/

exclude hematologic conditions our patient underwent the lymph node and bone marrow biopsy which have shown only unspecific inflammatory changes.

Habitual hyperthermia, drug-induced fever as well as factitious fever were considered in the differential diagnosis of this FUO case. Although habitual hyperthermia occurs mainly in young females and can be accompanied by fatigue and malaise, it is characterized by rather low grade fever and the normal CRP level [18]. Similarly, drug hypersensitivity was not the leading cause of recurrent fever. The fever in the patient relapsed despite the discontinuation of sulphonamides therapy. The factitious fever was excluded because the temperature corresponded with tachycardia during hospitalization.

Multisystem diseases including rheumatic disorders, vasculitis, and granulomatous diseases are common FUO causes because fever may precede the other, more typical manifestations. The presence of antinuclear antibody (ANA) and skin lesions directed the evaluation to systemic lupus erythematosus (SLE). However, the cutaneous eruptions of SLE and changes in the white blood count were unlike that seen in our patient. Furthermore, the C3 and C4 complement levels were within normal ranges. The high, spiking fever accompanied by arthralgia, transient rash as well as response to corticosteroids, were highly suggestive of adult Still's disease (ASD), a classic FUO cause. Whereas, the normal leukocyte count and the ferritin level together with self-limited attacks of fever made this diagnosis unlikely. It is worth mentioning that ASD is, in part, a diagnosis of exclusion that can generally be made in the absence of another condition that may cause similar symptoms and findings. The disease is associated with leucocytosis in 80 % of patients and markedly elevated serum ferritin concentrations in 70% of patients [19]. ANA and RF are predominantly negative in ASD.

Autoinflammatory diseases, and in particular periodic fever syndromes, may have similar clinical manifestations as autoimmune diseases. From a pathogenetic point of view, autoinflammatory diseases are determined by dysregulation of the innate immunity, without the involvement of the acquired immunity (auto reactive T cells and auto antibodies). The prolonged attacks of fever lasting even 3-4 weeks suggested TNF receptor associated periodic syndrome (TRAPS). TRAPS is the most common autosomal dominant autoinflammatory disease manifested as self-limiting episodes of fever recurring at variable intervals. In addition to fever, localized pain and tightness of one muscle group and a migratory pattern of the symptoms are prominent features, present in more than 80% of patients [5]. Other symptoms include abdominal pain and headache [20]. Painful conjunctivitis and periorbital oedema are also common. During febrile attacks, painless cutaneous lesions may develop on the trunk or extremities and migrate distally [5]. Arthralgia of the large joints is common, but arthritis is rare [21]. The average age of patients at onset is around 3 years, but the adult-onset has been reported up to the sixth decade. The most thoroughly characterized pedigree is an Irish and Scottish family; nonetheless TRAPS has been reported in many ethnic groups [22] and can occur in a single family member as a result of de novo-mutation. Periodic fever syndrome was considered in this case as a possible diagnosis, albeit the absence of mutations in suspected disease-related genes (Tab. III) were not in line with the diagnosis.

In summary, all previously described investigations did not lead to the diagnosis. 55 years after the first definition, FUO still remains a diagnostic challenge. The approach for such patients may be as follow: (a) a wait and see strategy, (b) a whole body inflammation scan, (c) a staged approach or (d) a therapeutic trial. The 18F-fluoro-deoxyglucose positron emission tomography (18F-FDG PET) has the potential to play a role in approaches b and c. However, high diagnostic sensitivity of PET is addressed to infectious and neoplastic diseases which were excluded in our case. 18F-FDG PET appears to have a very low negative predictive value in ruling out miscellaneous FUO causes that cannot be reliably visualized by conventional techniques [23-25].

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