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Interpretation of Biomarkers in Fever of Unknown Origin–demonstration in A Clinical Case

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Abstract

Workup of fever of unknown (FUO) is challenging due to non-specific clinical manifestations. We report the case of a patient who presented with FUO for two months. Further workup with laboratory test, image study and tissue sample confirmed the diagnosis of lymphoma. Our case illustrates the importance of careful interpretation of laboratory test during the workup of FUO. For example, abnormal ferritin and hemoglobin levels are associated with higher risk of hematology maligancy. (J Intern Med Taiwan 2022; 33: 383-388)

Key Words: Fever of unknown origin, Biomarker, Hemoglobin, Lymphoma

Introduction

Classical fever of unknown origin (FUO) is defined by Durack et al. as fever lasting more than 3 weeks, with a temperature higher than 38.3°C on several occasions, the cause of which remains uncertain after days of in-hospital diagnostic workups[1]. Important etiologies of FUO include infectious disease, autoimmune disease, malignancy and others. The severity of FUO varies according to the underlying etiology and ranges from self-limiting courses to life-threatening conditions. Choosing appropriate diagnostic tools in clinical settings is an important issue in the current era. Here, we presented a challenging case of FUO and discussed ways to improve the workup algorithm.

Case presentation

A 64-year-old woman presented to this hospital due to fever for 3 weeks. Three weeks prior to this hospital visit, she started to have fever and chills. She also had headache, decreased appetite and poorly localized abdominal discomfort. Antipyretics partially improved the symptoms. Her past medical history only included mitral valve prolapse. She lived in New Taipei City, Taiwan. She did not travel abroad or have contact with a sick person in the preceding months. There was no documented local transmission of coronavirus disease (COVID-19) infection in Taiwan during that period of time. She did not smoke or use illicit drugs (recreational drugs). Her father had gastric cancer, and her sister had lung cancer.

Due to persistent symptoms, she was evaluated in the emergency room at Hsin-Chu Branch,

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National Taiwan University Hospital. On examination, she was alert and oriented. The physical examination revealed fever with temperature of 38°C, a pale conjunctiva, and there was no heart murmur or skin rash. The meningeal sign was negative. The laboratory tests showed normocytic anemia. The chest radiograph and electrocardiogram were unremarkable. She was admitted for further workup.

Despite receiving empirical antibiotics, she continued to have intermittent fever after admission. Blood, urine and sputum cultures were performed repeatedly, while later exams revealed negative results. On hospital Day 4, abdominal ultrasound and transthoracic echocardiography did not reveal evidence of abnormalities. A computed tomography (CT) scan with contrast of the brain, neck, chest, abdomen and pelvis did not reveal an infection focus. She underwent further examination, including B2 microglobulin, protein electrophoresis, serum free light chains, and anti-double stranded DNA (anti-dsDNA) tests, all of which showed normal results. Further workup was performed for anemia, and it revealed a reticulocyte index value of 0.77, an elevated level ferritin of 6575 (ng/mL), a total iron binding capacity (TIBC) of 252 (ug/dL), a transferrin saturation (TSAT) of 23%, a lactate dehydrogenase (LDH) level of 612 (U/L), and a haptoglobin level of 151.7 (mg/dL). On hospital Day 18, positron emission tomography (PET) revealed hypermetabolism in the spleen and axial bone marrow (Figure 1). A bone marrow examination was performed the next day, and a diagnosis of high-grade B-cell lymphoma with hemophagocytosis was made. The hospital course was complicated with febrile neutropenia with pneumonia and respiratory failure. After the first cycle of immunochemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), the fever was completely resolved, and her functional wellbeing and anemia were much improved. She is regularly followed up and remains disease-free for more than 11 months after the completion of eight cycles of chemotherapy.

Laboratory exams for FUO

The guidelines recommended by the Infectious Diseases Society of America, Bleeker-Rovers et al. and Wright et al. [2-4] are mostly consistent and include the following key steps in the workup of FUO: 1. obligatory exam; 2. PET scan; and 3. tissue sampling. Required exams include a thorough history taking, physical examination, essential laboratory examinations and imaging studies. The essential laboratory exams include (a) complete

Table 1. Blood tests within the first five days of hospital stay

WBC (K/μL)	RBC (M/μL)	HB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	PLT (K/μL)
6.5 (3.25-9.16)	2.21	7.2 (11.0-15.2)	21.5	97.3 (80.9-99.3)	32.6	33.5	238 (150-378)

Blast (%)	Promyl. (%)	Myel. (%)	Meta (%)	Band (%)	Seg (%)	Eos. (%)	Baso. (%)	Mono. (%)	Lym. (%)
0	0	0	0	0	78.4	0.3	0.3	5.3	15.7

CRP (mg/dL)	CRE (mg/dL)	Na (mmol/L)	K (mmol/L)	ALT (U/L)	Lipase (U/L)	T-bil (mg/dL)	LDH (U/L)
11.4 (<1)	0.7 (0.6-1.3)	130 (136-145)	3.6 (3.5-5.1)	8 (0-41)	20 (11-82)	0.89 (0.3-1.0)	612 (140-271)

ESR (mm/hr)	Ferritin (ng/mL)	ANA	RF (IU/mL)	Urine analysis	Blood culture
111 (2-15)	3973 (4.63-204.0)	1:160 + nucleolar	< 10	WBC 0-2 RBC 0-2	(-)

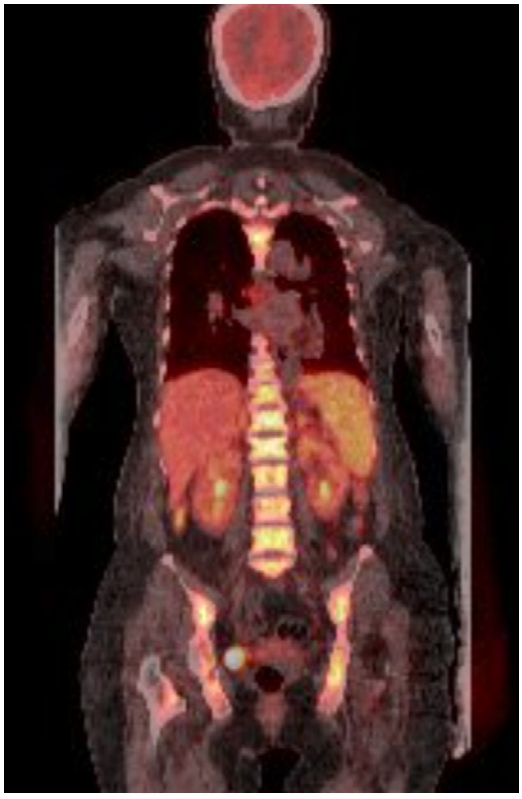

Figure 1. Positron emission tomography (PET) scan.

blood count, (b) biochemistry studies, (c) C-reactive protein (CRP) levels or the erythrocyte sedimentation rate (ESR), (d) anti-nuclear antibody and rheumatic factor levels, (e) blood cultures, and (f) interferon-gamma release assays (IGRA) or tuberculin skin tests (TSTs). Here, we describe how to better interpret these easily available biomarkers, with a focus on hemoglobin, CRP and IGRA results.

Hemoglobin

Inflammatory cytokines impair normal erythropoiesis by inhibiting the production of erythropoietin and erythroid cell differentiation. Besides, inflammation induces the iron regulatory hormone hepcidin, restricting the supply of iron for erythropoiesis. These factors lead to clinical anemia, but rarely for hemoglobin levels <8 g/dL[5,6]. Table 2 lists the FUO cohorts with information on hemoglobin levels. We concluded that anemia is fairly common, with a mean value of approximately 10-11 mg/dL in patients with FUO. In this case, a hemoglobin level of 7.2 mg/dL was significantly below the average and was considered an unusual finding. Bone marrow study was warranted for this patient with regard to the severity of anemia being well beyond the average that is seen in FUO and a lower reticulocyte index value. Further studies are needed to delineate a cut-off point of hemoglobin level in the evaluation of FUO.

C-reactive protein (CRP) and other inflammatory markers

CRP and procalcitonin levels were shown to be useful biomarkers for bacterial infection in hospitalized patients[7,8]. However, their use in patients with prolonged fever without an obvious infection focus remains uncertain. In patients evaluated for FUO, those with elevated CRP or ESR levels are more likely to receive a diagnosis[9]. A normal CRP level predicts a negative finding on subsequent PET scans[10]. In the setting of FUO, studies have shown that CRP levels are not useful for differentiating infectious disease from noninfectious disease[11-14]. Procalcitonin is increasingly used as a biomarker of bacterial infection[13-15]. Its use in prior studies is

Table 2. Hemoglobin level in cohorts with fever of unknown origin

1st author	Design	Country, yr.	n	Mean Hb level (g/dL)
Vanderschueren S [20]	prospective	Belgium, 2000-2010	60	11.7
A Hot et al. [21]	retrospective	France, 1995-2005	130	11.1
Kucukardali Y et al. [11]	prospective	Turkey 2003-2004	154	10.7
HY Wang et al. [22]	retrospective	Taiwan 2006-2013	38	10.2

Abbreviation: Hb, hemoglobin; yr., year.

Table 3. C-reactive protein and procalcitonin levels in cohorts with fever of unknown origin

1st author	Design	Country, yr.	n	Etiology of ID %	PCT for ID	CRP for ID
Efstathiou SP et al.[23]	prospective	Greece 1992-2000	112	29% IE, 24%TB		Useful
Kucukardali Y et al.[11]	prospective	Turkey 2003-2004	154	39% TB		Not useful
Ryuko H et al., [12]	retrospective	Japan 2004-2010	174	17% UTI		Not useful
Liu CP et al.[13]	retrospective	China 2009-2015	383	50% TB	Useful	Not useful
Naito T, et al.[14]	retrospective	Japan 2011	121	9% TB	Not useful	Not useful
Teng Xu, et al.[15]	Retrospective Prospective	China 2014-2017 China 2017-2019	527 185	NA	Useful Not useful	Useful Useful

Abbreviation: CRP, C-reactive protein; IE, infective endocarditis; ID, infectious disease; NA, not applicable; PCT, procalcitonin; TB, tuberculosis; yr., year.

Table 4. Ferritin level in cohorts with fever of unknown origin

1st author	Design	Country, yr.	n	Ferritin level (mean, μg/L)			p value
				infectious	neoplasm	noninfectious inflammatory disease	
Liu CP, et al.[13]	Retrospective	China 2009-2015	383	293	1,913	782	0.026
Teng Xu et al.[15]	Retrospective Prospective	China 2014-2017 China 2017-2019	527 185	349 371	664 566		<.001
Kima SE, et al.[24]	retrospective	Korea	77	282	1818	563	0.048
Efstathiou SP, et al.[23]	prospective	Greece 1992-2000	112	301	612.3		<0.001

Abbreviation: yr., year.

summarized in Table 3. The evidence of its use in FUO was limited, and further prospective studies with large-cohorts are needed.

Interferon-Gamma Release Assays (IGRA)

IGRAs were not tested in this clinical case, even though the guidelines suggest that the exam be performed. IGRAs were demonstrated to be useful for testing for latent tuberculosis (TB) infection. In active TB, both the sensitivity and specificity were shown to be poor[16,17]. In FUO workups, only active TB is considered clinically relevant, but latent TB is not. In the setting of FUO in areas with a high TB prevalence, IGRA test results could neither reject nor confirm active TB, so it is reasonable not to perform the test in this setting.

Other useful markers

The ferritin level was previously discussed in many FUO cohorts (Table 4). The cohorts consistently showed that individuals with infectious disease tended to have lower ferritin levels compared to that of other etiologies. The high ferritin level in this case correctly predicted noninfectious disease. The “bone marrow score”, a simple scoring system proposed by Dr. Wang et al, combines biomarkers, including the neutrophil count, hemoglobin level, platelet level, LDH level, ferritin level and other clinical parameters, to predict hematological disease in FUO[18]. The high “bone marrow score” of this patient also implied underlying hematological disease.

Conclusion

The workup of FUO remains a challenge. The rationale provided in this article is largely consistent with the recently published review article from the *New England Journal of Medicine*[19]. In this clinical

case, an unusually low hemoglobin level warranted an early bone marrow examination, regardless of the result of the PET scan. This would have led to earlier diagnosis of underlying malignancy. Although not included as part of the mandatory tests in the guidelines, the ferritin level and other biomarkers also have the potential to help identify the underlying etiology more quickly and potentially improve patient outcomes.

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The authors declare no conflicts of interest.

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不明熱的生物標記判讀—以一個臨床個案為例

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摘 要

不明熱為臨床診斷上常遇到的難題。本文描述一個困難診斷的不明熱個案，藉由討論不明熱的評估與診斷流程，並著重於血液與生化檢查方面。文中呈現一位64歲女性，以兩個月不明熱的臨床表現，最後診斷為骨髓中的惡性淋巴瘤。在不明熱的病人中，血紅素、血鐵質等指標，都可能暗示著血液疾病的診斷。至於發炎指標、潛伏結核菌的檢查結果，在不明熱的病患都需要小心判讀。