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A Rare Cause of Fever of Unknown Origin: A Case of Secondary Adrenal Insufficiency

Nedeni Bilinmeyen Ateşin Nadir Sebebi: Sekonder Adrenal Yetmezlik Olgusu

Erbağcı and Erbağcı. A Case of Secondary Adrenal Insufficiency

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Abstract
Fever is one of the most common symptoms observed in infectious diseases. However, non-infectious causes should also be considered in the differential diagnosis. In patients presenting with a common symptom such as fever, it is important to keep adrenal insufficiency in mind as a rare but possible underlying cause. A 54-year-old woman with a history of coronary artery disease, hypertension, and hypothyroidism presented with complaints of fatigue, weakness, nausea, vomiting, abdominal pain, headache, and fever. Her past medical history was notable for a previous pituitary adenoma surgery. Laboratory tests revealed elevated C-reactive protein (65 mg/L) and procalcitonin levels (33.2 ng/mL). To investigate a possible infectious etiology, neck, thoracic, and abdominal computed tomography, transthoracic echocardiography, blood and urine cultures, and other infectious disease workups were performed, but no pathology was identified. Pituitary magnetic resonance imaging revealed a macroadenoma. Laboratory findings showed hyponatremia and decreased early morning cortisol levels (1.82 µg/dL), while adrenocorticotropic hormone (ACTH) levels were within the normal range. A high-dose ACTH stimulation test confirmed the diagnosis of secondary adrenal insufficiency. The patient showed a dramatic clinical improvement after glucocorticoid replacement therapy and was discharged with an appropriate treatment plan. When investigating the cause of fever, a thorough medical history, repeated physical examinations, and appropriate use of laboratory and imaging studies are essential. Common etiologies should be considered first, and if no diagnosis is established, rare causes must be carefully evaluated.
Keywords: Adrenal insufficiency, case report, fever, fever of unknown origin (FUO)

Özet
Ateş, enfeksiyon hastalıklarının sık görülen semptomlarından birisidir. Ancak enfeksiyon dışı nedenlerinin de olduğu unutulmamalıdır. Ateş gibi yaygın bir semptom ile başvuran hastalarda nadir de olsa adrenal yetmezliğin tanıda akla gelmesi önem taşımaktadır. Koroner arter hastalığı, hipertansiyon ve hipotiroidi tanıları olan 54 yaşında kadın hasta halsizlik, yorgunluk, bulantı-kusma, karın ağrısı, baş ağrısı ve ateş nedeniyle başvurdu. Özgeçmişinde hipofiz adenomu nedeniyle operasyon öyküsü mevcuttu. C reaktif protein (65 mg/L) ve prokalsitonin (33,2 ng/mL) yüksekliği dikkat çekmekteydi. Olası enfeksiyöz patolojilerin araştırılması için boyun, toraks, abdomen bilgisayarlı tomografi, transtorasik ekokardiyografi, kan, idrar kültürleri ve bulaşıcı hastalıklar açısından yapılan diğer testlerde patoloji saptanmadı. Hipofiz manyetik rezonans görüntülemede makroadenom olduğu tespit edildi. Hiponatremi ve sabah erken kortizol seviyesinde düşüklük (1,82 µg/dL) tespit edildi. Adrenokortikotropik hormon (ACTH) ise normal düzeylerdeydi. Yüksek doz ACTH stimülasyon testi ile sekonder adrenal yetmezlik tanısı konuldu. Glukokortikoid tedavisine dramatik yanıt alınan hasta, tedavi planı yapılarak taburcu edildi. Ateşin nedeni araştırılırken iyi bir anamnez, tekrarlayan fizik muayeneler, uygun laboratuar ve görüntülemeler akıllıca kullanılmalıdır. Öncelikle sıklıkla görülen nedenler düşünülmeli ve tanı konulamıyorsa nadir sebepler açısından değerlendirmeler yapılmalıdır.
Anahtar Kelimeler: Adrenal yetmezlik, vaka sunumu, ateş, nedeni bilinmeyen ateş (NBA)

Introduction
Fever is one of the most common symptoms encountered in infectious diseases; however, it should be kept in mind that there are also numerous non-infectious causes[1]. These include malignancies, autoinflammatory and autoimmune diseases, medications, and various other conditions[2]. In patients presenting with fever, a thorough medical history, detailed physical examination, and appropriate laboratory and imaging studies should be systematically utilized to elucidate the underlying etiology[1].
Adrenal insufficiency presents with non-specific symptoms such as weight loss, loss of appetite, fatigue, abdominal pain, nausea, vomiting, fever, and hypotension[3]. In primary adrenal insufficiency, the adrenal glands are affected; in secondary adrenal insufficiency, the pituitary

gland; and in tertiary adrenal insufficiency, the hypothalamus. The diagnosis is established through evaluation of adrenal-related hormones and stimulation tests. Treatment is achieved by hormone replacement therapy[4].

In this case report, we present a patient with secondary adrenal insufficiency as a rare cause of a common symptom, fever. It is important to consider adrenal insufficiency in the differential diagnosis, even though it is uncommon, in patients presenting with a common symptom such as fever.

Case Report

A 54-year-old woman with a medical history of coronary artery disease, hypertension, and hypothyroidism presented with complaints of fatigue, nausea, vomiting, headache, and abdominal pain that had persisted for approximately three weeks, accompanied by high-grade fever for the past 10 days. Her regular medications included acetylsalicylic acid 100 mg, rivaroxaban 20 mg, and levothyroxine 100 µg.

Her medical history was notable for four previous surgeries due to pituitary adenoma, the most recent occurring three months prior to admission. The patient's long-term low-dose glucocorticoid therapy (prednisolone 5 mg) had been discontinued about 4 months prior. She had also been hospitalized two months earlier with a diagnosis of acute cholecystitis and biliary pancreatitis. During that hospitalization, she developed deep vein thrombosis, pulmonary embolism, and a cerebrovascular event. The patient reported receiving amoxicillin/clavulanate 1000 mg every 12 hours during the past seven days without clinical improvement. She denied any history of animal contact, consumption of well water, or recent travel.

On physical examination, the patient was in moderate general condition. Her blood pressure was 100/70 mmHg, and body temperature was 38.5 °C. Tachycardia was present during febrile episodes. She was conscious and fully oriented to time and place. No neck stiffness or other meningeal irritation signs were observed. Head and neck examination was unremarkable. Breath sounds were equal bilaterally, with no rales, rhonchi, or additional sounds. Cardiac auscultation revealed a regular rhythm without murmurs or extra heart sounds. Abdominal examination was normal, and no abnormalities were detected in the extremities. No prosthetic devices or indwelling catheters were present.

At admission, the patient's C-reactive protein (CRP) level was 65 mg/L and procalcitonin was 33.2 ng/mL, both markedly elevated. Leukocytosis was not present, and urinalysis showed no pyuria. No infectious focus explaining the elevated acute-phase reactants was identified during the initial examination. Two sets of blood cultures and a urine culture were obtained, and empirical ceftriaxone therapy (1 g every 12 hours) was initiated. Subsequently, contrast-enhanced computed tomography (CT) scans of the neck, thorax, and abdomen were performed to identify a possible infectious focus. Imaging revealed only a 3-mm hypodense lesion in the gallbladder consistent with a cholesterol stone. Additionally, various blood tests were ordered to investigate both infectious and non-infectious causes, and the requested tests and their results are presented in Table 1.

On the 48th hour of hospitalization, the patient continued to have a fever of 38.5 °C. Follow-up blood cultures were obtained, and empirical antibiotic therapy was changed to piperacillin–tazobactam 4.5 g every 6 hours. The initial urine culture showed no bacterial growth. Staphylococcus epidermidis was isolated twice from blood cultures; therefore, transthoracic echocardiography was performed to evaluate for possible endocarditis, but no vegetations or findings suggestive of endocarditis were detected.

Considering the patient's history of pituitary surgery, a contrast-enhanced pituitary magnetic resonance imaging (MRI) was performed, which revealed a 2-cm macroadenoma within the pituitary fossa. Laboratory evaluation showed thyroid-stimulating hormone <0.02 mIU/L, morning cortisol 1.82 µg/dL, adrenocorticotropic hormone (ACTH) 26.3 pg/mL, and serum sodium 130 mmol/L. To confirm the diagnosis of secondary adrenal insufficiency, a high-dose ACTH stimulation test was performed. After intravenous administration of 250 µg of synthetic ACTH (cosyntropin), cortisol levels were measured at 30 and 60 minutes, with a peak value of 4.2 µg/dL. These findings confirmed the diagnosis of secondary adrenal insufficiency.

On the fourth day of hospitalization, the patient developed neutropenia (neutrophil count: 1.19×10^9/L). Peripheral blood smear revealed no abnormal cell morphology or pathological findings. Follow-up blood cultures obtained during the febrile period showed no bacterial growth. Based on the available findings, infectious pathology was deemed unlikely, and antibiotic therapy was discontinued due to concern for antibiotic-associated neutropenia.

Following confirmation of secondary adrenal insufficiency, methylprednisolone therapy was initiated at a dose of 60 mg daily. The patient showed a dramatic clinical response to glucocorticoid replacement, with rapid improvement in fatigue and malaise and resolution of fever. The methylprednisolone dose was gradually tapered (60 mg for three days, followed by 30 mg, and subsequently reduced over one month until discontinuation). On the fourth day of glucocorticoid therapy, laboratory results showed a neutrophil count of 2.1×10^9/L, serum sodium of 141 mmol/L, CRP of 9 mg/L, and procalcitonin of 0.7 ng/mL. After a total hospital stay of seven days, the patient demonstrated both clinical and laboratory improvement and was discharged with a recommendation for outpatient endocrinology follow-up.

At the three-month follow-up visit after discharge, the patient was clinically stable and had experienced no further febrile episodes. She reported regular adherence to her medications with good tolerance and was being followed on a maintenance dose of 5 mg prednisolone daily.

Discussion

While infectious diseases are often the leading causes of fever of unknown origin (FUO), non-infectious causes should not be overlooked. The definition of FUO has evolved over time. It was first described in 1961 by Petersdorf and Beeson as cases presenting with a fever of ≥38.3 °C lasting for at least three weeks and remaining undiagnosed after one week of inpatient evaluation[5]. In 1991, Durack and Street proposed modifying the definition by replacing the inpatient duration with either three days of hospitalization or three outpatient visits[6]. Later, in 1997, De Kleijn et al.[7,8] suggested defining FUO based on the failure to establish a diagnosis after a set of specific investigations, regardless of hospitalization duration or visit number. These investigations include a complete blood count, serum calcium, liver function tests, a comprehensive metabolic panel, erythrocyte sedimentation rate, CRP, ferritin, at least three sets of blood cultures (incubated for a minimum of five days), urinalysis and urine culture, tuberculin skin test (TST) or interferon-gamma release assay (IGRA), abdominal ultrasonography, chest radiography, and CT of the thorax, abdomen, and pelvis[7,8].

Recent studies have reported that the etiologies of FUO comprise infections in 12–59% of cases, non-infectious inflammatory diseases in 11–34%, malignancies in 3–32%, miscellaneous causes in 0–23%, and undiagnosed conditions in 2–51%[9]. In our patient, who presented with a 10-day history of fever, we performed most of the initial diagnostic investigations mentioned above but could not establish a definitive diagnosis. Therefore, further evaluation was undertaken for less common causes.

Adrenal insufficiency is a clinical condition characterized by impaired cortisol secretion from the adrenal cortex. It typically presents with non-specific symptoms such as fatigue, weakness, and hypotension. Laboratory findings may include hyponatremia and hyperkalemia. The diagnostic evaluation begins with measurement of early morning serum cortisol levels (between 6:00 and 9:00 a.m.). A low morning cortisol level should prompt further investigation for adrenal insufficiency. A cortisol level ≥18 µg/dL effectively rules out adrenal insufficiency, whereas a value ≤3 µg/dL in the presence of compatible clinical findings is diagnostic without the need for an ACTH stimulation test. For cortisol levels between 3 and 18 µg/dL, an ACTH stimulation test is required to confirm the diagnosis. The standard high-dose ACTH stimulation test involves intravenous administration of 250 µg synthetic ACTH (cosyntropin), followed by measurement of serum cortisol at 30

and 60 minutes. A peak cortisol value <18 µg/dL confirms adrenal insufficiency. Measurement of plasma ACTH levels helps differentiate between primary and secondary adrenal insufficiency: If the plasma ACTH level is above the reference range, primary adrenal insufficiency is diagnosed, whereas values within the lower half of the reference range indicate secondary adrenal insufficiency. The cornerstone of adrenal insufficiency treatment is glucocorticoid replacement therapy[10]. In our case, a low early morning cortisol level raised suspicion for adrenal insufficiency, prompting a high-dose ACTH stimulation test, which confirmed the diagnosis. Plasma ACTH levels were within the reference range, suggesting secondary adrenal insufficiency. Subsequent pituitary MRI revealed a macroadenoma, supporting the diagnosis. Glucocorticoid therapy was initiated, resulting in a rapid clinical improvement. The patient's history of previous pituitary surgery played a crucial role in guiding the diagnostic process.

Adrenal insufficiency is among the rare causes of FUO. In a 2019 systematic review, Fusco et al.[11] reported that conditions categorized as "other causes," including adrenal insufficiency, accounted for 6.5% of FUO cases. In a 2017 study, Hung et al.[12] evaluated 58 patients using nuclear imaging methods and identified adrenal insufficiency in 2 cases (3.4%). More recently, Ko et al.[13] assessed 202 patients and diagnosed adrenal insufficiency in 61 of them (30.1%).

Patients with adrenal insufficiency may present with fever. In a 2017 study, Lee et al.[14] reported that 33 (18%) of 183 patients with adrenal insufficiency presented with fever. In their 2019 systematic review, Lee et al.[15] also found that fever occurred in 33.3% of adrenal insufficiency cases. Similarly, Jang et al.[16] analyzed 150 patients with adrenal insufficiency and observed that 45 (30%) presented with fever. Glucocorticoids released under the influence of cortisol suppress proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha. In adrenal insufficiency, cortisol deficiency can lead to increased levels of these cytokines. The elevation of proinflammatory cytokines may, in turn, cause an increase in inflammatory markers such as CRP and procalcitonin. Elevated inflammatory markers often suggest an infectious etiology, thereby complicating the diagnostic process[17]. Procalcitonin is now widely recognized as a clinically valuable biomarker for evaluating systemic inflammatory responses, particularly in distinguishing bacterial infections from non-infectious inflammation[18]. Although elevated procalcitonin levels are typically associated with infections, they may also be seen in various non-infectious conditions (e.g., trauma, burns, surgery, malignancy, acute pancreatitis)[19-21]. In our case, markedly elevated CRP and procalcitonin levels initially led to an extensive infectious workup. However, no infectious pathogens were identified, and subsequent hormonal testing and imaging confirmed the diagnosis of secondary adrenal insufficiency. Despite receiving broad-spectrum antibiotic therapy for approximately four days, the patient showed no clinical or laboratory improvement, whereas a dramatic response was observed following the initiation of glucocorticoid therapy.

A peripheral blood smear for malaria was not performed due to the absence of a travel history. TST or IGRA could not be performed because these tests were not available at our institution.

Conclusion

In the evaluation of FUO, a thorough medical history, repeated physical examinations, and appropriate laboratory and imaging studies should be used judiciously. Common causes should be considered first, and when a diagnosis cannot be established, rare etiologies must also be evaluated. In our case, the patient's history of pituitary surgery prompted suspicion, and subsequent diagnostic testing led to the identification of secondary adrenal insufficiency—a rare cause of FUO.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the anonymous publication of their medical data and images in this case report..

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.E., B.E., Concept: E.E., B.E., Design: E.E., B.E., Data Collection or Processing: E.E., B.E., Analysis or Interpretation: E.E., Literature Search: E.E., Writing: E.E., B.E.

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Table 1. Initial diagnostic evaluation.

Parameters	Result	Reference range
Leukocyte	4.26	4–10 10^9/L
Neutrophil (n, %)	2.62 (61.6%)	2–7 10^9/L
Lymphocyte (n, %)	1.38 (32.3%)	0.8–4 10^9/L
Haemoglobin	11.9	11–16 g/dL
Platelet	228	150–400 10^9/L
Creatinine	0.8	0.51–0.95 mg/dL
Urea	15.6	17–43 mg/dL
Glucose	85	74–106 mg/dL
Sodium (Na)	130	136–145 mmol/L
Potassium (K)	4.7	3.5–5.1 mmol/L
Lactate dehydrogenase (LDH)	254	0–247 U/L
Aspartate aminotranferase (AST)	32	0–35 U/L
Alanine aminotranferase (ALT)	8.5	0–35 U/L
Total bilirubin	1.22	0.3–1.2 mg/dL
Direct bilirubin	0.22	0–0.2 mg/dL
Alkaline phosphatase (ALP)	35.1	30–120 U/L
Gamma-glutamyl transferase (GGT)	12.7	0–38 U/L
Lipase	31.5	0–67 U/L
Amylase	36.3	28–100 U/L
C-reactive protein (CRP)	65	0–5 mg/L
Procalcitonin	33.2	ng/mL
Erythrocyte sedimentation rate (ESR)	29	mm/hour
INR	1.51	0.8–1.24
Prothrombin time (pT)	19.2	11–16 sc
Activated partial thromboplastin time (aPTT)	53.7	27–45 sc
D-dimer	0.86	0–0.5 ug/mL
Fibrinogen	401	200-400 mg/dL
Brucella Rose Bengal test	Negative	
Brucella Coombs gel test	Negative	
HbsAg	0.22 (negative)	0-1
Anti-HCV	0.05 (negative)	0-1
Anti-HIV	0.24 (negative)	0-1
Syphilis Ig total	0.06 (negative)	0-1
Anti nucleer antibody (ANA)	0.1 (negative)	0–1.2 index
Rheumatoid factor (RF)	8.3	0–14 IU/mL
Complement C3	1.19	0.9–1.8 g/L
Complement C4	0.41	0.1–0.4 g/L

HCV, hepatitis C virus; HIV, human immunodeficiency virus; Ig, immunoglobulin; dL, deciliter; g, gram; INR, international normalized ratio; IU, international unit; L, liter; mg, miligram; mL, mililiter; mm, milimeter; ng, nanogram; n, number; U, unit; ug, microgram.