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Case Report

Internal Medicine Section

Pyrexia of Unknown Origin due to Secondary Adrenal Insufficiency: A Case Report

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ABSTRACT

Adrenal insufficiency is a critical condition that can often present with non specific symptoms, posing a diagnostic challenge in the context of co-existing conditions. Authors hereby, report a complex case of secondary adrenal insufficiency revealed through persistent fever and hyponatremia in a 73-year-old female with a multifaceted medical history, including hypertension, diabetes, and Takotsubo cardiomyopathy. Her symptoms of intermittent fever and diarrhoea were refractory to treatment, leading to hospital readmission. Initial laboratory investigations highlighted hyponatremia, low haemoglobin, elevated inflammatory markers, and low cortisol levels. Although a urinary tract infection with multidrug-resistant *Klebsiella* was identified and treated, her febrile state persisted. Extensive serological testing for a broad range of infectious diseases yielded negative results, excluding infectious etiologies as the cause of her fever. Imaging studies, including chest X-ray, Electrocardiogram (ECG), echocardiogram, Positron Emission Tomography (PET) scan, Computed Tomography (CT), and transesophageal echocardiography, failed to identify a source of infection or malignancy. Notably, a low random cortisol level coupled with an inappropriately low Adrenocorticotropic Hormone (ACTH) level prompted further endocrine evaluation. Magnetic Resonance Imaging (MRI) revealed an empty sella turcica, confirming secondary adrenal insufficiency. This diagnosis was substantiated by the patient's positive response to steroid therapy, which led to clinical improvement and eventual discharge. The present case underlines the importance of considering adrenal insufficiency in patients presenting with unexplained hyponatremia and fever, particularly when other common aetiologies have been ruled out. It also illustrates the potential for critical endocrine disorders to mimic sepsis, underscoring the necessity of a comprehensive diagnostic approach in the face of complex presentations.

Keywords: Computed tomography, Empty sella, Hyponatremia, Magnetic resonance imaging

CASE REPORT

A 73-year-old female with a medical history of hypertension for 18 years, diabetes for 10 years, and Takotsubo cardiomyopathy for one year, presented with intermittent fever and diarrhoea that persisted for 20 days. She had been on a regimen of Aspirin (150 mg) and Clopidogrel (75 mg), taken once daily for her co-morbid conditions, alongside Amlodipine (5 mg) once daily for hypertension. Her diabetes was managed with a daily dose of Metformin (500 mg), Glimepiride (3 mg), and a combination of Voglibose (0.3 mg) with Metformin (500 mg). Despite adherence to her treatment, her symptoms did not improve, leading to her readmission to the hospital for further care and evaluation.

Upon admission, the patient's initial investigations revealed several notable findings. Arterial blood gas analysis showed hyponatremia, although her haemodynamic status remained stable with a blood pressure reading of 120/70 mmHg. Laboratory tests indicated a low haemoglobin level (10.5 gm/dL), elevated C-Reactive Protein (CRP) (82 mg/dL), high procalcitonin levels (7.3 ng/mL), low random cortisol levels (6.5 mcg/dL), and hyponatremia (130 mmol/L). Chest X-ray, 12-lead ECG, and echocardiogram did not provide any significant contributions towards establishing a diagnosis.

However, urine analysis demonstrated the presence of 10-15 pus cells. Further microbiological examination of urine culture revealed a multidrug-resistant *Klebsiella* infection, which was appropriately treated with injection Cefoperazone Sulbactam 3 gm i.v. 12 hourly, resulting in the normalisation of routine urine findings. However, despite the treatment, the patient continued to have a high-grade fever, following which six blood cultures were done throughout the evaluation process which remained sterile.

An extensive infectious disease laboratory work-up was conducted to investigate the cause of the patient's pyrexia. This included tests for malaria, dengue, widal (detecting Salmonella antibodies), scrub typhus antigen (detecting antibodies against *Orientia tsutsugamushi*), Tuberculosis (TB) gamma interferon (testing for tuberculosis), Mantoux test (tuberculin skin test), detecting Hepatitis B Virus Surface Antigen (HBsAg), anti-Hepatitis C Virus antibodies (antiHCV antibody), Human Immunodeficiency Virus (HIV) serology (testing for HIV antibodies or antigens), detecting Epstein-Barr Virus Deoxyribonucleic Acid (DNA) via Polymerase Chain Reaction (EBV PCR), detecting Cytomegalovirus DNA Via Polymerase Chain Reaction (CMV PCR), and Antinuclear Antibody Test (ANA). However, all the results from these tests were negative, ruling out infectious etiologies as the cause of the patient's symptoms. Furthermore, a PET CT scan, and transesophageal echocardiography were also done, which were essentially normal and showed no significant findings.

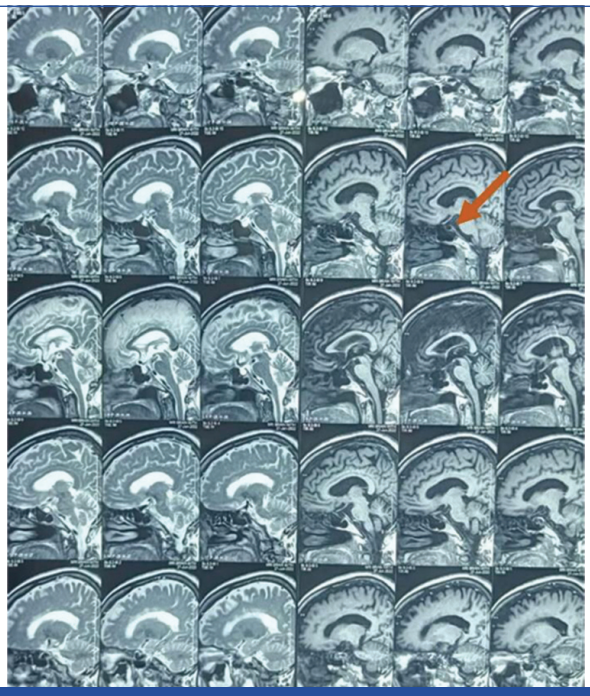
Further investigations were performed to explore the underlying cause of the patient's low sodium levels, revealing low random cortisol levels and normal Thyroid Stimulating Hormone (TSH) levels. The short Synacthen test yielded negative results; however, 8 am ACTH levels were found to be lower than normal [Table/Fig-1].

Parameters	Random	At 8 am	Just before SST	1 hr after SST
Serum cortisol (mcg/dL)	6.5	-	11.6 (6.2-19.4)	24 (6.2-19.4)
ACTH (pg/mL)	-	4.5 (7.2-63.3)	-	-
Prolactin (ng/mL)	7.3 (4.79-23.3)	-	-	-
TSH (micro IU/mL)	3.2 (0.27-4.2)	-	-	-

[Table/Fig-1]: Serum levels of cortisol, ACTH, prolactin, and TSH of the patient.
ACTH: Adrenocorticotropic hormone; SST: Short synacthen test; TSH: Thyroid stimulating hormone.
( ) - Normal value

Based on the patient's clinical presentation and the results of various investigations, infectious etiologies such as sepsis or an undetected source of infection were ruled out, as the fever persisted post-antibiotic therapy and various serological tests. To explore and delve further into several potential causes for the condition, PET/CT and transesophageal echocardiography were performed without

any clinically significant findings. The patient succumbed to shock with high-grade fever (102°F) during the course of the investigation and had to be intubated and put on ventilatory support. The patient was treated with Inj. Piperacillin Tazobactam 4.5 gm i.v. eight hourly, Inj. Hydrocortisone i.v. (≤300 mg/day), and Dopamine infusion maintained at 10-15 µg/kg/min. Subsequently, after extubating, an MRI of the brain revealed an empty sella [Table/Fig-2].



[Table/Fig-2]: MRI brain-visualisation of empty sella (red arrow).

The MRI examination revealed an empty sella turcica leading to secondary adrenal insufficiency with Prolactin and Angiotensin Converting Enzyme (ACE) levels within the normal range. The patient gradually responded to intravenous followed by oral steroid treatment. Ultimately, she was discharged home in a haemodynamically stable condition and followed-up for three weeks while on Chest Physiotherapy (CPT) to promote airway clearance and reduce secretions.

DISCUSSION

Pyrexia of Unknown Origin (PUO) poses a continuous challenge to physicians, as it refers to a prolonged fever without a definitive diagnosis despite thorough evaluation. The concept of PUO was initially introduced in 1961, defining it as a prolonged fever exceeding 38.3°C (100°F) that remains undiagnosed for a minimum of three weeks, with at least one week of hospital investigation [1]. However, this definition has evolved over time due to advancements in diagnostic techniques and changes in healthcare practice, and the necessity of a week-long hospitalisation is no longer considered essential in the evaluation of PUO. The causes of PUO can be categorised into infectious and non infectious causes. Infectious causes include conditions like endocarditis (especially culture-negative endocarditis), discitis, osteomyelitis, occult abscesses, and infected implanted devices. Non infectious causes encompass inflammatory disorders, haematological malignancies, solid tumours, and miscellaneous conditions [2]. The landscape of PUO management has evolved, with an increasing number of patients remaining undiagnosed, accounting for up to 51% of cases. The proportion of cases attributed to infectious causes ranges from 17% to 35%, while inflammatory, neoplastic, and miscellaneous causes account for 24-36%, 10-20%, and 3-15%, respectively [3].

The current case deals with a 73-year-old female who presented with complaints of intermittent fever and diarrhoea persisting for 20 days. She continued to have daily intermittent fever even after the urinary tract infection resolved, as indicated by a negative urine culture. The incidences of PUO are high in geriatric patients; therefore, it is essential not to discount the possibilities of tuberculosis, HIV, or syphilis [2]. An extensive infectious work-up was conducted, which provided negative results ultimately ruling out the possibility of an infectious and inflammatory cause. Extensive imaging evaluation, including PET/CT and transesophageal echocardiography, were unremarkable, indicative of the absence of neoplastic causes. Evaluation of hyponatremia revealed low cortisol levels, but the short synacthen test was negative. The patient experienced shock and required intubation. Later in the course of investigations, secondary adrenal insufficiency was suspected and later confirmed by low ACTH levels and an MRI revealing an empty sella. Notably, her prolactin and TSH levels were normal.

Adrenal deficiency is characterised by insufficient production of certain hormones by the adrenal glands. Primary adrenal insufficiency results from adrenal gland failure, while secondary adrenal insufficiency stems from inadequate ACTH production, either directly from the pituitary gland or due to hypothalamic disease affecting CRH production [4]. Adrenal insufficiency can manifest as either an adrenal crisis or chronic insufficiency. Adrenal crisis primarily presents as shock but may also include symptoms such as anorexia, nausea, vomiting, abdominal pain, weakness, fatigue, lethargy, fever, confusion, or coma. The incidence of adrenal crisis is similar in patients with primary and secondary adrenal insufficiency [4].

Fever is not a common symptom of chronic adrenal insufficiency, which typically manifests with non specific signs and symptoms that often lead to a delayed diagnosis. These include fatigue, weight loss, nausea, vomiting, abdominal pain, muscle and joint pain, skin hyperpigmentation, postural hypotension, and salt craving. There are limited case reports of secondary adrenal insufficiency presenting as fever. For instance, one such report represents a 43-year-old obese, non insulin-dependent diabetic patient presenting with fever, nausea, and vomiting for four months, who was eventually diagnosed with ACTH deficiency as an unusual cause of PUO. Another case reported a 62-year-old man who experienced 10 hospital admissions over 12 years due to PUO [5]. Through dynamic tests involving clomiphene, Luteinising Hormone Releasing Hormone (LRH), Thyrotropin Releasing Hormone (TRH), and chlorpromazine stimulation, the patient was diagnosed with hypothalamic hypopituitarism [6]. Dental infection and isolated splenic tuberculosis have been identified as potential causes of PUO in several case reports [7,8].

In these cases, the patients presented with fever, malaise, and weight loss, and the underlying cause was only discovered after extensive investigation. Treatment with tooth extraction or anti-tuberculous therapy led to the resolution of the fever. These reports highlight the importance of extensive investigations to reach the cause of PUO. Adrenal insufficiency should be considered in patients with PUO exhibiting specific and non specific signs and symptoms of adrenal dysfunction. It is worth noting that the patient had a history of Takotsubo cardiomyopathy, which has been associated with both empty sella syndrome and adrenal insufficiency in previous case reports [9-12]. Numerous publications have reported similar cases of secondary adrenal insufficiency associated with isolated ACTH deficiency and an empty sella [13,14].

CONCLUSION(S)

The case highlights the diagnostic challenges associated with PUO, particularly in the geriatric population. Despite a thorough infectious and inflammatory work-up, the patient's persistent intermittent fever remained unexplained until secondary adrenal insufficiency was suspected and later confirmed. The present case underscores the importance of considering adrenal insufficiency as a potential cause of PUO, especially in patients presenting with specific and non specific signs of adrenal dysfunction, even in the absence of overt adrenal crisis. Moreover, the association between Takotsubo cardiomyopathy, empty sella syndrome, and adrenal insufficiency

underscores the need for a comprehensive approach to evaluation and management in such cases.

REFERENCES

[1] Petersdorf RG, Beeson PB. Fever of unexplained origin: Report on 100 cases. Medicine (Baltimore). 1961;40:01-30.
[2] Fernandez C, Beeching NJ. Pyrexia of unknown origin. Clin Med (Lond). 2018;18(2):170-74.
[3] Bleeker-R CP, Vos FJ, de Kleijn EMHA, Mudde AH, Dofferhoff TSM, Richter C, et al. A prospective multicenter study on fever of unknown origin: The yield of a structured diagnostic protocol. Medicine (Baltimore). 2007;86(1):26-38.
[4] Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, et al. Epidemiology of adrenal crisis in chronic adrenal insufficiency: The need for new prevention strategies. Eur J Endocrinol. 2010;162(3):597-602.
[5] Page RC, Alford F. Adrenocorticosteroid deficiency: An unusual cause of fever of unknown origin. Postgrad Med J. 1993;69(811):395-96.
[6] Marilus R, Barkan A, Leiba S, Arie R, Blum I. Pyrexia of unknown origin. Presenting sign of hypothalamic hypopituitarism. Postgrad Med J. 1981;57(667):310-13.
[7] Ho PL, Chim CS, Yuen KY. Isolated splenic tuberculosis presenting with pyrexia of unknown origin. Scand J Infect Dis. 2000;32(6):700-01. Available from: https://www.tandfonline.com/doi/abs/10.1080/003655400459685.
[8] Samra Y, Barak S, Shaked Y. Dental infection as the cause of pyrexia of unknown origin- two case reports. Postgrad Med J. 1986;62(732):949-50.
[9] Yang C, Han X, Du Y, Ma AQ. Takotsubo cardiomyopathy and pituitary apoplexy: A case report. BMC Cardiovasc Disord. 2020;20(1):236. Doi: 10.1186/s12872-020-01521-1.
[10] Eto K, Koga T, Sakamoto A, Kawazoe N, Sadoshima S, Onoyama K. Adult reversible cardiomyopathy with pituitary adrenal insufficiency caused by empty sella--a case report. Angiology. 2000;51(4):319-23.
[11] Bagnall T, Tow YR, Bunce N, Astroulakis Z. Takotsubo cardiomyopathy associated with adrenal insufficiency in the context of long-term steroid use mimicking acute coronary syndrome. BMJ Case Rep. 2021;14(1):e234983. [cited 2024 Feb 21]. Available from: https://casereports.bmj.com/content/14/1/e234983.
[12] Garrahy I, Nicholas P, Oladiran O, Nazir S. Takotsubo cardiomyopathy secondary to adrenal insufficiency: A case report and literature review. Case Rep Cardiol. 2020;2020:e6876951.
[13] Shima H, Miya K, Okada K, Doi T, Minakuchi J. Adrenal insufficiency associated with empty sella syndrome and steroid malabsorption complicated with septic shock due to post-transplant pyelonephritis: A case report. Cureus. 2023;15(4):e38234.
[14] Usuda D, Takagi S, Takanaga K, Izumida T, Sangen R, Higashikawa T, et al. Adrenal insufficiency due to total primary empty sella syndrome. J Endocrinol Metab. 2020;10(5):144-53.

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