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Internal Medicine

INTERLEUKIN-6 AS A BIOMARKER IN PYREXIA OF UNKNOWN ORIGIN

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ABSTRACT In cases of pyrexia of unknown origin (PUO), inflammatory and non-infective markers like C-reactive protein (CRP), procalcitonin, total leucocyte count (TLC), erythrocyte sedimentation rate (ESR) are widely and frequently used to differentiate the cause of fever. It becomes a very difficult case when all these markers are normal and non-contributory. However, their absence does not rule out inflammation. We describe a 48-year-old woman with prolonged low-grade fever and normal inflammatory markers. Extensive investigations, including imaging and infection screening, were inconclusive. A markedly elevated interleukin (IL) -6 level guided a trial of anti-inflammatory therapy, resulting in complete symptom resolution. IL-6 may serve as a valuable biomarker in PUO when conventional inflammatory and infectious markers are non-contributory.

KEYWORDS : Inflammatory markers, Interleukin-6, Pyrexia of Unknown Origin, SIADH

INTRODUCTION:

PUO presents a diagnostic challenge, particularly when common inflammatory and infectious markers are within normal limits. CRP, procalcitonin, ESR, and TLC are routinely used in clinical algorithms for fever evaluation. (Takahashi et al., 2023) However, these may occasionally fail to identify subtle or atypical inflammatory states. This case illustrates the value of IL-6 measurement in such scenarios.

Case Presentation:

A 48-year-old lady was admitted to the hospital with history of intermittent low-grade fever for 20 days and was accompanied initially by self-remitting diarrhoea, nausea and vomiting. She also reported non-specific body ache and tingling sensation. On examination her oral temperature was 100.4 deg F with BP 120/76 mm Hg and pulse rate 88/min. Systemic examination was unremarkable with no sensory deficit.

Initial haematological and biochemical parameters were unremarkable except hyponatremia (121 mEq/L). **Table 1.0**

Table 1.0 Laboratory Findings

Parameter	Result	Reference level
Haematology		
Haemoglobin	14.1 g/dL	13-17 g/dL
White blood cell count	7400 /cumm 70% neutrophils	4000 - 10000 /cumm
Platelet count	2.29 lac/cumm	1.5 - 4 lac/cumm
Biochemistry		
Creatinine	0.7 mg/dL	0.9 - 1.3 mg/dL
Random blood sugar	101 mg/dL	70 - 140 mg/dL
Sodium	121 mEq/L	136 - 145 mEq/L
Potassium	4.2 mEq/L	3.5 - 5.2 mEq/L
Bicarbonate	26 mEq/L	22 - 28 mEq/L
Chloride	96 mEq/L	96 - 106 mEq/L
Phosphorus	3 mg/dL	2.5 - 4.5 mg/dL
Magnesium	2 mg/dL	1-7 - 2.8 mg/dL
Calcium	10 mg/dL	8.6 - 10.2 mg/dL
Total bilirubin	0.7 mg/dL	up-to 1 mg/dL
Albumin	4.6 g/dL	3.5 - 5.1 g/dL
Alkaline phosphatase	85 U/L	53 - 128 U/L
Aspartate aminotransferase	24 U/L	10 - 42 U/L
Alanine aminotransferase	38 U/L	10 - 40 U/L
Creatine phosphokinase	64 U/L	40 - 171 U/L

For evaluation of fever, broad screening for infections including tropical infections were done like malaria, typhoid, dengue, chikungunya, scrub typhus, brucellosis - all were negative. Blood cultures on several occasions (a total of four samples) were negative. CRP and procalcitonin were normal (less than 0.306 mg/dL and less than 0.5ng/ml respectively) on four occasions. Tests sent for autoimmune work-up such as, Anti-nuclear antibody by Hep2 method and Antineutrophil Cytoplasmic Antibodies were negative. Ferritin was 32 ng/ml. Stool sample analysed via Polymerase Chain Reaction (PCR) method for common bacterial and viral pathogens was non-contributory. Urinalysis was unremarkable. Further work-up of hyponatremia revealed low serum osmolality (259mOsm/kg) with low urine osmolality (148mOsm/kg) and Urine sodium of 38 mmol/L-suggestive of Syndrome of Inappropriate Anti-diuretic Hormone Secretion (SIADH). Thyroid and adrenal functions were normal. Imaging including abdominal ultrasound and echo cardiography were unremarkable except for a uterine fibroid. With all negative septic markers and negative results for common infections, a Fluorodeoxyglucose Positron Emission Tomography / Computed Tomography (FDG-PET CT) scan was done to look for any focal source of infection or malignancy. FDG PET CT scan did not show any evidence of focal infection or malignancy. **Figure 1.0**

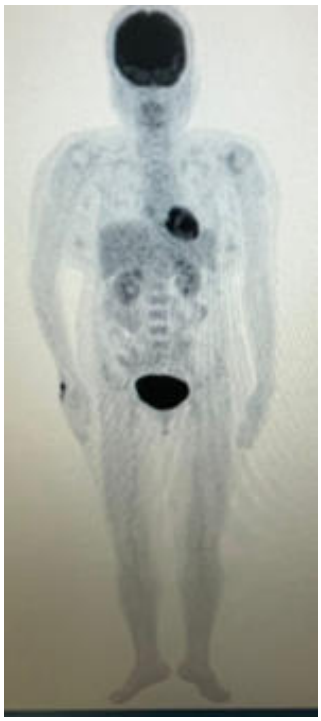

Figure 1.0 Whole body FDG PET CT scan

Given the persistently normal markers and imaging, IL-6 was measured and found to be significantly elevated at 30pg/ml (normal range <7pg/ml). A trial of low-dose naproxen for 7 days led to resolution of fever, and repeat IL-6 dropped to 9 pg/mL. She was then discharged in a haemodynamically stable condition and followed up in the out-patient department. The patient remained afebrile on follow-up.

DISCUSSION:

The case represents a diagnostic challenge in PUO, where standard inflammatory markers were unhelpful. The patient had long duration of low-grade fever for 20 days on admission which was initially associated with self-resolving loose motion, nausea and vomiting. The patient's fever, hyponatremia due to SIADH and elevated IL-6 suggest a low-grade inflammatory process, possibly post viral. Inflammatory markers like TLC, CRP, procalcitonin, ESR were normal throughout and they are widely used to differentiate the causes in case of PUO (Takahashi et al., 2023; Naito et al., 2013; Roy and Tan, 2001). Viral enteric infection can result in low grade inflammatory response from small intestine with production of IL-1, IL-6 and Tumour necrosis factor - alpha which reach hypothalamus and augment synthesis of Prostaglandin (PG) E2 via cyclooxygenase 2. PGE2 is released from pre-optic area and increases body temperature (Evan et al., 2015; Kruger, 1979). It can be assumed in this case that prolonged release of cytokines due to self-limiting enteric infection was the cause of fever and is a case of altered thermoregulation due to viral insult. Viral infections have also been documented to cause SIADH and hyponatremia (Krolicka et al., 2020; Obaid et al., 2024; Liamis et al., 2011).

The clinical course and response to NSAIDs further support a cytokine-mediated process. This case highlights the potential role of IL-6 as an adjunct biomarker in PUO, particularly when conventional tests are inconclusive.

CONCLUSION:

Self-limiting viral gastroenteritis can cause prolonged low-grade fever through persistent IL-6-mediated inflammation, even when traditional markers are normal. In rare cases of PUO with normal inflammatory markers, elevated IL-6 may provide a crucial diagnostic clue. Its use, in conjunction with clinical history, can aid in diagnosis and guide therapy.

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