Perspective

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Journal of Neoplasm
ISSN 2576-3903

2024
Vol.9 No.1:63

Neoplastic Fever: A Sign of Underlying Malignancy

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Received date: February 19, 2024, Manuscript No. IPJN-24-18878; **Editor assigned date:** February 22, 2024, PreQC No. IPJN-24-18878 (PQ); **Reviewed date:** March 07, 2024, QC No. IPJN-24-18878; **Revised date:** March 14, 2024, Manuscript No. IPJN-24-18878 (R); **Published date:** March 21, 2024, DOI: 10.36648/2576-3903.9.1.63

Citation: Jen C (2024) Neoplastic Fever: A Sign of Underlying Malignancy. J Neoplasm Vol.9 No.1: 63.

Description

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) like naproxen or indomethacin have shown effectiveness in managing NF. The naproxen test serves as a clinical tool in the differential diagnosis of fever of uncertain origin in cancer patients. The standard naproxen trial involves administering a 500 mg dose every eight hours for two days. However, a minority of patients with NF fail to respond to naproxen, raising questions about its diagnostic value in fever management related to malignancy. Neither markers of inflammation, radiographic tests, nor the naproxen test can definitively confirm the diagnosis of NF. While C-reactive protein and procalcitonin have been utilized to differentiate infections from NF, studies have failed to establish their ability to distinguish between infective and noninfective causes of fever.

Antibiotics and standard antipyretic medications such as acetaminophen (paracetamol) often prove inadequate in managing NF. A negative blood culture and fever unresponsive to antibiotics cannot rule out an underlying bacterial infection. Neoplastic Fever (NF) represents a paraneoplastic phenomenon triggered directly by the presence of malignant tumors. However, fever in cancer patients often stems from infections. Pinpointing the cause of fever in these patients is crucial. They commonly undergo extensive laboratory and radiographic investigations, along with prolonged courses of antimicrobial therapies, all of which are time-consuming, resource-intensive, increase the risk of drug toxicity and may delay essential chemotherapy.

In lammatory cytokine

However, the exact mechanism behind this timing in fever spikes remains unclear. It is well-established that body temperature follows circadian rhythms, both in normal and febrile states, with higher values typically seen at night and lower values in the early morning hours. The secretion of serum cortisol peaks in the morning and remains low at night. Circadian rhythms of cytokines have also been demonstrated in individuals with advanced neoplasms, with significant fluctuations observed in gastrointestinal cancer patients. Moreover, cancer and its treatments can lead to an increase in proinflammatory cytokine release, dampening cortisol sensitivity, reducing glucocorticoid responsiveness to stress, and activating cytokine signaling pathways, including Nuclear Factor kappa B (NFκB) and p38 mitogen-activated protein kinase in the brain. These circadian fluctuations in cytokine levels, reduced cortisol sensitivity and activation of cytokine signaling pathways in the brain likely contribute to the observed patterns of fever spikes and their daily peak temperatures. Complex self-regulation mechanisms among the neuroendocrine system, the hypothalamic-pituitary-adrenal axis and the cytokine network have been proposed in advanced cancer patients. Elevated serum cytokine levels, coupled with cortisol rhythm, have been shown in patients with metastatic colorectal cancer. High-grade neoplastic diseases may alter cortisol levels and disrupt its circadian release, potentially due to increased proinflammatory cytokine release associated with cancer and its treatment.

Neoplastic fever

During febrile episodes, vital signs including body temperature (measured using an ear thermometer), blood pressure, heart rate and respiratory rate were monitored from vital sign flow sheets. If fever persisted for at least five days despite appropriate antibiotic therapy, without evidence of infection or positive culture and with stable vital signs, it was considered treatment-related fever. Naproxen was administered to patients suspected of having NF. The dosage ranged from 125 to 250 mg every six hours. Acetaminophen, tramadol, codeine, morphine and transdermal fentanyl were commonly prescribed medications for pain control in these patients.

The definition of NF needed to be stringent. Individuals who died, were lost to follow-up, or developed an infection within at least two weeks of NF suspicion were excluded from this study. Diagnosis of drug fever was challenging. There was no evidence that any medications taken by patients in this study could lead to fever. If patients who were suspected of having NF received chemotherapy without significant adverse effects, the onset of their fever from cancer was ruled out. The characteristics of NF were described as including the highest peak body temperature, typically the daily maximum temperature; hemodynamic instability; presence or absence of chills; association with other paraneoplastic disorders; and white blood cell counts and their band forms.