Case Report

Neoplastic Fever in a Cancer Patient: A Case Report and Review of Literature

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Abstract

Fever is a common symptom presented in cancerous patient, either through state of infection or developed by tumour itself in certain malignancies. At many instances it is described as para neoplastic syndrome in patient with lymphoma, acute leukaemias and renal cell carcinoma. Neoplastic fever is characterised as intermittent fever, with no signs of rigors, chills and any mental disturbance. The alternate fever spikes and regular pulse rate is monitored for definitive diagnosis. Certain diagnostic imaging are necessary for definitive diagnosis. CT scan and MRI are essential for tumour location and identification. Adjuvant diagnostic aid are naproxen test, ESR and blood hormones test. Treatment modalities comprises of surgical therapy, radiotherapy and chemotherapy. A case of a squamous cell lung cancer patient who was initially evaluated and managed as a case of pyrexia of unknown origin.

Keywords: Neoplastic fever; Para-neoplastic syndrome; Pyrexia of unknown origin; Squamous cell lung cancer

Introduction

Fever is an evident sign of inflammatory reactions taking place in the body. It is a well known common symptom observed in 67% of the infectious cases in contrast, neoplastic fever arises from the tumour itself or invasive procedure [1]. Neoplastic fever is a paraneoplastic syndrome that originates from cancer. In 27% of cases, the fever is associated with non-infectious febrile episodes [1]. Neoplastic fever is a unique feature in certain malignancies such as hematological malignancies, colon cancer, renal cell carcinoma, and cholangiocarcinoma [2]. However, an unusual case of non-small cell lung carcinoma was presented in the outpatient department with a high-grade intermittent fever at the stage of diagnosis that was later suggested as neoplastic fever.

Fever is divided into two categories septicemic infection in a cancer patient or non-infectious condition arising from the tumour itself. The neoplastic fever accounts for 20% of patients with an undetermined origin. It is important to diagnose the disease at the initial stage and provides a cure on time for minimal morbidity and mortality. During the management of cancer, it becomes critical for the doctors to present a definite diagnosis as the fever could be a side effect of chemotherapy, cancer or the underlying infection. At the time of growth and development of the tumour the body is vulnerable to infection; therefore, fever as a result of the infection is associated with the tumor in each case. Neoplastic fever is characterised as an intermittent fever with alternative febrile periods over a period. In non-infectious condition, a visible change noticed is the alterations of the oral mucosa, mucositis mainly occurring due to medication, blood transfusions, radiation, endocrine disturbances, surgery, and neoplastic fever [3]. It is recommended by the surgeons to surgically remove the mass in addition to follow-ups with radiotherapy and chemotherapy to avoid future relapse. The neoplastic fever disappears within 24 hrs after the surgical treatment assuring definite diagnosis of neoplastic fever.

Case Report

A 44-year-old Filipino married women reported to our outpatient department with History of recurrent high grade fever, weight loss and occasional dry cough. The patient was admitted and investigated thoroughly. She underwent series of investigations including blood, urine and sputum cultures. She was also screened for tuberculosis, fungal and viral infections. But all these investigations couldn’t detect any kind of infective factor. During all this period she was put on empirical antibiotics for 2 weeks with a broader coverage, and antifungal for 7 days. But with no significant clinical improvement and no relief in fever, while the high-grade fever continued to persist. Naproxen was also tried and had limited effect of short-term relief. Her initial X Ray chest had a small suspicious small right upper lobe lesion, which was reported as consolidation path. But it couldn’t disappear with antibiotics and antifungal treatment. So, a CT Scan and bronchoscopy was planned, which revealed a right upper lobe mass 4cm x 3 cm on right upper lobe with associated mediastinal lymphadenopathy. To confirm tissue diagnosis, an image guided biopsy was performed that confirmed the malignancy as squamous cell carcinoma. The fever was between 38 degrees to 40 degrees without associated chills and rigors. Her blood test showed high Erythrocyte Sedimentation Rate (ESR) of 80 mm/h and the White Blood Cell Count (WBC) was 24109 /l.

The patient was planned for chemotherapy based on taxeme’s and platinum. After first cycle of chemotherapy, the fever vanished for 6 days. But with no significant clinical improvement and no relief in fever, while the high-grade fever continued to persist. At the stage of diagnosis that was later suggested as neoplastic fever.

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for several days, it recurred again but with decreased frequency and intensity. Also Blood tests show some improvement with decrease in WBC, ESR levels. This type of fever is commonly termed as neoplastic fevers. It is a type of paraneoplastic syndrome. So, her paraneoplastic syndrome (neoplastic fever) responded to chemotherapy with relief in fever after one month of persistent fever.

**Discussion**

The neoplastic fever is a unique type of fever that can only be treated by the removal of the cause, cancer. The pathophysiology of the fever manifestation is still unknown. As per Fever Of Unknown Origin (FUO) classification if any patient has fever more than 38.3 for more than 3 weeks without a definite known cause is obliged to undergo certain sets of investigation [4,5]. This type of fever accounts for 27% of non-infectious illness [5].

Authors have reported that patient with cancer commonly shows sign of intermittent fever [2,5]. In addition, there are other causes also for fever which include drug or transfusion reaction, central nervous system metastasis, and chemotherapy or radiation-induced fever [4].

The administration of antibiotics is a way to discriminate between neoplastic fever and infectious fever. Infection fever is characterised as rigors, temperature, and periodic sweating occasionally accompanied by tachycardia, hypotension, and mental status changes [14]. Alsirafy, et al. tried differentiating the two types of fever by closely monitoring the effect of anti-inflammatory, naproxen to reduce the fever within 24 hrs. the positive response was achieved [12]; however, some demonstrated conflicting results.

Cancer patients prolonging hospitalisation period often cause infections, which might be the leading reason for the induced fever [8]. Moreover, blood transfusions and medicinal administration equally causes similar symptoms. The explanation for such induced fever is the immunological reactions in the body to the antigens or the bacteria. In the case of viral and bacterial infections, the acute and convalescent serologies including the urine test that has 70% sensitivity for detecting the infections [3,9]. In contrast for diagnosing the neoplastic fever, acute phase reactants supplemental testing offers reliable source for definite diagnosis. Many laboratory tests conducted are nonspecific in nature. The acute phase reactants testing includes the ESR, a systematic nonspecific test that measures the length a drop of blood falls within a microtube in one hour [10]. The results greater than 100mm/hr confirms the diagnosis of the tumour, autoimmune infection or hidden infection [10]. ESR offers a general overview of the systematic inflammation; however, does not provide definite diagnosis. In addition, similar results can be observed evaluating the levels of C-reactive protein [11].

Metastasis is commonly associated with the primary tumour masses such as lymphadenopathy. Lymph node examination presented with tender, fixed enlarged lymph nodes indicated reactive hyperplasia. The increase in the infiltrative cells was due to the induction from the neoplastic cells. A further explanation for neoplastic cancer could be the tumour necrosis, dead tissue releasing the pyrogens or the TNF release [12]. Our patient test result showed no significant evidence of necrosis of tumour. In certain cases, the brain metastasis invades the brain tissue leading to activation of phospholipase A2 causing the neurogenic fever [13]. However, no such metastasis was suspected.

The pathophysiology is still a question regarding neoplastic fever. One of the explanations for neoplastic fever is that either the tumour cells or the host cells are intrigued by the tumour to produce some pyrogenic cells such as Interleukin (IL)-1, IL-6, IL-8 Tumor Necrosis Factor (TNF)-α, and interferon [11]. These cytokines induce a change in the hypothalamus to raise the set point temperature through alteration in prostaglandin E2 levels [9]. The detailed histopathological examination of our patient revealed the dedifferentiated carcinoma infiltrated by a large number of lymphocytes and multiple aggregated PMNs.

Confirmatory diagnosis can be achieved through radiological imaging. The latest diagnostic modality used to detect the abnormal masses is through computed topographical scanning. Neoplastic patients who presented with fever revealed primary tumour masses, metastatic lesion and body cavity effusions, pneumonia, hydronephrosis, biliary dilatation, and lymphadenopathy [2,13]. Best way to use these modalities is in combination with needle biopsy in cancer patients. Mostly recommended in febrile patients suspected of the underlying tumour. Furthermore, MRI, magnetic resonance imaging is recommended in the condition where there is soft tissue neoplasm in muscle, bone sarcomas and brain tumour. In our patient only CT scan was sufficient to diagnose the lesion in the lung.

Definitive diagnosis is important to be achieved to proceed with appropriate treatment modalities such as surgical operation, radiotherapy, and chemotherapy. Studies have portrayed that 41% of the patients responded to systematic anti-neoplastic therapy [3]. NSAIDS have equally displayed superior efficacy in treating neoplastic fever. Our patient showed a timely reduction in the fever; however, it re-occurred when the NSAIDS were withdrawn. Kudlowitz, et al. [14], explained that as the tumour increases in the size it increases the production of IL 6. Thus, the naproxen does not show promising effect.
in reducing the size of the tumour; however, it can cause haematological disturbance as a side effect of NSAID [14]. Therefore, the use of naproxen should be used in a controlled form other randomised trial compared indomethacin and diclofenac sodium that displayed comparable results in contrast naproxen has a quick effect [15].

These types of fevers are distressful for the patients causing delirium and fatigue. Intense clinical investigation and diagnostic tests necessary builds a great deal of stress. In addition, the chemotherapy in the patient with extensive metastasis causes some adverse effects. Neutropenic fever is a common complication of chemotherapy. Surgeons have administered certain growth factors such as Granulocyte Colony Stimulating Factor (G-CSF) and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) to control the neutropenic fever [8]. Research in the US has successfully shown that filgrastim was able to control the episodes of neutropenic fever [3,8]. Likewise, studies in Europe also displayed similar results. In contrast, the steroid component has a palliative effect. The NSAIDS have shown symptomatic cure. The use of naproxen at a certain point is considered a distinguishing feature between neoplastic fever and non-neoplastic fever. In some patients, naproxen provides fever lysis. The previous study has shown 7 out of 10 patients demonstrated lysis of the fever after the withdrawal within 24hrs [12]. The dose of both chemotherapy and naproxen can be reduced once the patients start responding to the therapy.

The evidence of naproxen effects is limited due to small sample sizes in the study. Before the administration of naproxen, it is essential to perform physical and laboratory and diagnostic test including empirical antibiotic treatment and imaging. This often leads to prolonging hospitalisation and extensive evaluation in the case of advanced cancer. The dose is a critical factor for treatment in any condition. A dose of 250 mg twice a day displayed successful lysis of fever. Moreover, small dose of 125 mg naproxen, 375 mg twice a day, and 250 mg 3 times a day is considered useful. Doctors have recommended 125 to 750 mg/ day, stabilising the concentration level after 3 days [3], if the fever persists than naproxen should be discontinued and further evaluation will be required for the treatment.

Studies have displayed that 60% of the patient did not present with fever until after their admission to the hospital. Few patients exhibited unique symptoms as those enlisted for neoplastic fever such as high peak fever, chills, and leucocytosis. Physicians have always recommended to administer antibiotic, measure the vital signs, and blood and other cultures monitoring necessary to exclude possible fatal infections. A study demonstrated that 92% of the patient showed one spike daily in fever commonly observed between the time 9 am to 5 pm [9], 28% of patients showed a spike twice a day between 9 am and 9 pm and 9 am and 5 pm [9].

Literature states that circadian rhythm is maintained throughout the body in health and febrile period [9,15]. Statistical analysis displayed high levels during the night and low levels during early morning [9]. In addition, cortisol levels were measured in certain trials presenting with high peaks in the morning while lower in the night. Therefore, circadian rhythm of cytokines was successfully proven to be related to neoplasm. In case of gastro intestinal cancer cortisol and TNF-a displayed a significant relation with circadian rhythm fluctuation [2,11]. In the advanced cancer patient a self-regulation system between neuroscience and the hypothalamic-pituitary adrenal axis, and the cytokine network activates. Further investigation proved that cortisol rhythm had a positive relation with elevated levels of serum cytokines in colorectal cancer. Limper, et al. reported that cancer and its treatment causes a release of proinflammatory cytokines [7], flat levels of cortisol, reduced sensitivity of glucocorticoid, lower cortisol response to stress, and activates the cytokine signal pathway such as Nuclear Factor-Kappa B (NFkB) and p38 mitogen activated protein kinase in the brain. Any fluctuation in the cytokine levels and reduction in the cortisol sensitivity has shown to have a profound influence in the neoplastic fever pattern.

Tumor growth, cancer treatment, and related complications cause a rise in the expression of inflammatory cytokines and NF-κB activation. However, the fluctuating pulse rate is not addressed as a confirmatory value unless monitored over a period. Chemotherapy instigates the production of cytokines. 7 percent of the patients in a study showed transient elevated pulse rates after discontinuation of post chemotherapy dexamethasone although the cessation does not reduce the cytokines level [9]. Under such circumstances, fever origin from infection or neoplasia is critical to differentiate. Naproxen and corticosteroids displayed antipyretic effect on neoplastic fever. Bearing in mind NFκb has a profound effect on the number of cytokine production. The use of NSAIDS caused the suppression of NFκb and COX thus palliating the fever. In contrast, naproxen was found in 87% of patient to show complete lysis of neoplastic fever [9]. The febrile stage response to the corticosteroids by blocking the activity of phospholipase A2 leading of reduction in PGE2 synthesis and production of pyrogemic cytokines can be stopped through blocking the transcription of the mRNA. In 14% of patient’s dexamethasone mask the neoplastic fever during cancer therapy [9]. An unusual behaviour was noted in the patient who did not respond to naproxen demonstrated lysis of fever after chemotherapy. Therefore, it was stated that a septic fever do not respond to naproxen. Nevertheless, 10 - 20% of the patient failed to respond to complete lysis of fever after naproxen administration [3,9]. However, NSAID exhibited successful lysis of neoplastic fever in 38% patient with no neoplasm.

**Conclusion**

Our patient displayed symptoms that were indicative of neoplastic fever; however, all necessary steps were followed as suggested by physicians for definitive diagnosis. This unusual case points out the chances of a unique and rare condition to exhibit a well-known symptom.

**Reference**


