Clinical Medicine 2015 Vol 15, No 3: 292–4

# Malignant causes of fever of unknown origin

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ABSTRACT

**The presence of fever in malignancy usually indicates infection, though transfusion, thrombosis and drugs are also culprits. However, particularly in some tumour types, fever can also be a paraneoplastic syndrome, caused by the malignancy itself. This can be a difficult diagnosis to establish and presents a therapeutic challenge to the physician when the underlying malignancy is not easily treated.**

## Introduction

The mechanisms by which malignancies induce fever are not fully understood. The release of pyrogenic cytokines either directly from tumour cells or from macrophages responding to tumour are likely to play a major role, particularly interleukin (IL)-1, IL-6 and tumour necrosis factor (TNF)α. Cytokines induce prostaglandin E2 which acts on the hypothalamus, causing a change in the thermostatic set point. Although cancer is often a concern in fever of unknown origin (FUO), malignancy appears to account for a decreasing proportion of those investigated.[1] In 1961, 19% of FUO were attributed to cancer and by 2007 this had fallen to 7%. Neoplastic fevers are now most commonly encountered in the setting of febrile patients with a known malignancy and presents a diagnostic challenge in differentiating whether fever is attributable to infection, therapy or disease.

Unfortunately there is no fever pattern pathognomonic of cancer. Classically, neoplastic fever may be less associated with rigors, tachycardia and hypotensive episodes than other causes. Fevers may be only partially relieved by paracetamol and may respond better to nonsteroidal anti-inflammatory drug (NSAIDs). Cyclical fever patterns may occur. The most well known of these is Pel–Ebstein fever associated with Hodgkin's lymphoma.[2] However, the pattern of a week of high fevers, followed by an afebrile period of similar duration, is rare, and both its specificity for Hodgkin's lymphoma and its existence as an entity at all are contentious.[2]

## Naproxen test

An interesting series of small studies published by Chang and Gross[3] in 1984 observed that neoplastic fever was suppressed by naproxen. Defervescence occurred in 14 of 15 patients with neoplastic fever in contrast to none of the 5 patients with fever due to infection. Two patients with connective tissue disease had partial lysis of fever. In patients with neoplastic fever, the fevers resolved within 24 hours and patients remained afebrile as long as they continued on naproxen. This led to the description of a naproxen test and the suggestion of diagnostic criteria for neoplastic fever.[4]

Follow-up data of larger groups of cancer patients has supported that the naproxen test has a high degree of sensitivity and specificity, with a high positive predictive value.[5,6] Particularly when clinical suspicion is high, this may provide an effective aid in differentiating neoplastic from infectious fever in cancer patients in whom naproxen is not contraindicated (see Box 1).

Fever can serve an important purpose in alerting clinicians to the presence of an underlying malignancy. However, in the investigation of oncology patients with fever, it should remain a diagnosis of exclusion. Once the diagnosis of neoplastic fever is established, clearly the priority is to treat the malignancy. When that is not possible, naproxen may be able to provide some symptom relief. There is some evidence that other NSAIDs, including indomethacin and diclofenac, are also effective.[7]

## Cancers most associated with neoplastic fever

Among cancers, the common culprits for neoplastic or paraneoplastic fever include: Castleman's disease, Hodgkin's

### Key points

- Presence of fever in patients with cancer usually indicates infection.
- The first priority should be to treat underlying infection and only once infection is excluded should other causes of fever be considered.
- Malignancy is well known to cause fever, particularly in association with certain tumour types.
- In cancer patients with fever of unknown origin, the naproxen test may help diagnose neoplastic fever (see Box 1).
- NSAIDs, and other anti-inflammatory agents may help control symptoms of fever until the cancer can be treated.

KEYWORDS: Neoplastic fever, fever, FUO, malignancy

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and non-Hodgkin's lymphoma, renal cell carcinoma, hepatocellular carcinoma, acute myeloid leukaemia, hairy cell leukaemia, glioblastoma multiforme, blast crisis of chronic myelogenous leukemia, ovarian cancer and atrial myxoma. Neoplastic fever has differing manifestations and significance depending on the underlying tumour type, and may hold prognostic value.

### Castleman's disease

This rare lymphoproliferative disorder can be localised or multicentric. In both types there can be hyperactivation of the immune system, hypersecretion of cytokines and proliferation of B and T cells. The condition, when seen in patients with HIV is associated with human herpes virus (HHV)-8 infection. Systemic symptoms include fever, night sweats, fatigue, anorexia and cachexia. Patients can have lymphadenopathy, hepatosplenomegaly and anaemia. The acute phase proteins are increased, including CRP and fibrinogen. IL-6 is the most commonly elevated cytokine and is pivotal to the pathophysiology of Castleman's disease. It is the excess production of IL-6, which appears to lead to the constitutional symptoms, as well as proliferative features of the disease. This may result from dysregulated production by tumour cells, or in HHV-8-associated disease production of a viral homolog of IL-6.[8–10]

Unicentric Castleman's disease is treated by surgical resection. The poor prognosis of multicentic Castlemans has been improved by the introduction of anti-IL-6 agents. In a recent randomised controlled trial,[11] patients who received siltuximab demonstrated durable tumour and symptomatic responses. As use of this drug widens, it will be interesting to see it has therapeutic benefit in other cancers associated with systemic inflammation.

### Lymphoma

High levels of IL-6 and IL-10 have been observed in lymphomas, and the presence of B symptoms correlates with serum levels of IL-6.[12]

**Box 1. Diagnostic criteria for neoplastic fever.**

- Temperature over 37.8°C at least once each day.
- Duration of fever over two weeks.
- Lack of evidence of infection on:
  - physical examination
  - laboratory examinations eg sputum smears or cultures, cultures of blood, urine, stool, bone marrow, spinal fluid, pleural fluid and discharge from local lesions
  - imaging studies eg chest radiograph and CT scans of the head, abdomen, and pelvis.
- Absence of allergic mechanisms eg drug allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction.
- Lack of response of fever to an empiric, adequate antibiotic therapy for at least seven days.
- Prompt, complete lysis of fever by the naproxen test[a] with sustained normal temperature while receiving naproxen.

[a]naproxen 375 mg (by mouth) every 12 hours for three days. Reproduced with permission.[4]

B symptoms, including fever, night sweats and weight loss, are present in approximately 25% of patients with Hodgkin's lymphoma. B symptoms are associated with a worse prognosis, so are included in disease staging and impact on choice of treatment regimes.

### Haemophagocytic lymphohistiocytosis

Haemophagocytic lymphohistiocytosis (HLH) is a rare severe inflammatory disease characterised by high fevers and pancytopenia. Other features include lymphadenopathy, hepatosplenomegaly, rash and neurological symptoms. Evidence of haemophagocytosis (histiocytes eating other blood cells) is found on bone marrow or lymph node biopsy. The disease can be inherited or associated with infection, rheumatological disorders or malignancy, particularly T- or NK-cell leukaemias and lymphomas. Its genetic and immunological basis is increasingly well understood. Genetic defects of cytotoxicity and/or acquired absence of NK-cell function leads to immune activation and inflammatory cytokine production, with consequent disease development.[13,14] Patients have strikingly high levels of inflammatory cytokines whose production may drive fevers and other clinical features. Treatment strategies combine immunotherapy and chemotherapy to achieve remission of symptoms, often as a bridge to bone marrow transplantation.

### Renal cell carcinoma

In some series, up to 20% of patients with renal cell carcinoma (RCC) present with fever, and systemic symptoms, including fever, weight loss, hypertension and paraneoplastic phenomena, do seem to correlate with tumour size. In a previous study, Song[15] reported a 1.54 increased odds of systemic symptoms with every 1 cm increase in tumour size. It seems logical that larger tumours might produce or provoke greater concentrations of inflammatory mediators.

In patients with RCC, increased serum IL-6 levels have been associated with neoplastic fever and also with advanced stage, poor performance status and decreased responsiveness to immunotherapy.[16–18]

## Therapy

In most cases, treatment targets the underlying neoplastic condition, however this is not always successful or feasible. Fever can be a distressing symptom of advanced malignancy in the palliative setting. The metabolic demands associated with frequent generation of fever can contribute to cancer cachexia. In palliative care, we frequently attempt to control the symptoms with paracetamol, NSAIDS and corticosteroids. Steroids such as dexamethasone inhibit a variety of cytokines, including IL-2, IL-4, IL-6, IL-10, IL-12, interferon (IFN) γ and TNFα. Although a blunt tool with many side effects, they are often used in this setting, particularly when paracetamol or NSAIDS are ineffective.

## Novel therapies

One interesting development has arisen out of the discovery that thalidomide has a marked effect on fever associated with

leprosy.[19] Thalidomide is an immunomodulatory agent with a wide spectrum of activity. It acts on the protein cereblon and its interaction with the enzyme complex formed by cereblon results in the drug's antiproliferative and teratogenic effects. Thalidomide enhances the release of IL-2 and IFN from activated T cells, inhibits the immunosuppressive activity of regulatory T cells and increases NK-cell mediated cytotoxicity. It inhibits the release of TNFα and other cytokines including IL-6.[20] This may explain the potential anti-pyretic effect. Thalidomide has been found to be effective in cancer cachexia, chronic nausea, insomnia, profuse sweating and pain.[21] In the context of advanced malignancy, the catastrophic teratogenetic effects are irrelevant and other side effects including neuropathy may be less of a concern. However, thalidomide is a relatively expensive drug which needs careful control and regulation. It may prove inaccessible to many patients in this setting until proven to offer benefit.

Hopes for future treatments rest on better understanding the pathophysiology of malignancy-induced fever and exploiting unique features to improve symptom control. ■

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