



Case Report

Bring Back the Naproxen Challenge: Neoplastic Fever Resolved with Naproxen in the Setting of Recurrent Invasive Papillary Thyroid Carcinoma

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Abstract

While there have been several small studies and a review article discussing the naproxen challenge for neoplastic fever or fever of unknown origin, it seems to be an underutilized diagnostic and therapeutic tool. We present a case of an 81-year-old man with recurrent papillary thyroid cancer with laryngeal invasion requiring tracheostomy and feeding tube placement who spiked daily fevers to 102 despite being on antibiotic treatment for MSSA bacteraemia secondary to presumed hospital acquired pneumonia. Other sources of infection were effectively ruled out and his fevers resolved with administration of naproxen, indicating he was experiencing neoplastic fevers. Naproxen can be an effective tool for treating neoplastic fever, yet little is known about the mechanism of this effect. It stands to reason that more frequent use of the naproxen challenge may prevent unnecessary medical workup and reduce hospital length of stay, but more studies are needed.

Keywords: Neoplastic Fever; Fever of Unknown Origin; Naproxen; Naproxen Challenge

Introduction

Neoplastic fever, a fever caused by the cancer itself, has been reported as the most common cause of fever of unknown origin in cancer patients [1]. Neoplastic fever is a diagnosis of exclusion, once other causes of fever such as infectious, rheumatologic, inflammatory, and allergic have been ruled out. Neoplastic fever can occur in both hematological and solid tumors and has previously been reported to occur in about 15-20% of cancer patients [2,3]. Neoplastic fever is defined as meeting the following six criteria [4,5]:

1. Temperature $>37.8^{\circ}\text{C}$ at least once a day;
2. Duration of fever >2 weeks;
3. Lack of evidence of infection (eg physical examination, laboratory examinations, and imaging studies);

4. Absence of allergic mechanisms (eg, drug allergy, transfusion reaction, and radiation or chemotherapeutic drug reaction);
5. Lack of response of fever to an empiric, adequate antibiotic therapy for at least 7 days;
6. Prompt complete lysis by the naproxen test with sustained normal temperature while receiving naproxen.

The naproxen challenge was first mentioned in 1984 by Chang and Gross and then again in 2005 by Zell and Chang [1,4]. Studies to date have shown that naproxen has been extremely effective at eliminating neoplastic fevers within 24 hours of it being started and has demonstrated superiority to steroids and other NSAIDs [6]. Nevertheless, based on anecdotal evidence, the naproxen challenge seems to be underutilized and often unheard of amongst practicing physicians. The naproxen test can be used to help differentiate between malignancy versus infectious as the cause of fevers. If due to underlying malignancy, fevers will abate immediately or within three days of starting naproxen. However, if the fevers are due to an infectious cause, there may be only a

slight drop in the temperature or no change at all with naproxen. We present a case of an 81-year-old man with recurrent papillary thyroid cancer with laryngeal invasion requiring tracheostomy and peg tube placement who spiked daily fevers to 102, despite antibiotic treatment, and responded to the naproxen challenge. To our knowledge, this is the first paper examining the naproxen challenge since a systematic review in 2019 [6].

Case

An 81-year-old man with a past medical history of thyroid cancer treated with total thyroidectomy 2 years prior was sent to the emergency department by his outpatient ENT provider after CT of the neck showed significant airway compression. The patient noticed an enlarging neck mass for the past year but did not seek medical care. He also noticed increased difficulty breathing for the past year along with worsening dysphagia. He was afebrile and hemodynamically stable while in the emergency department and was started on dexamethasone and admitted to the ICU for airway observation and management. During the hospitalization, biopsy confirmed recurrent papillary thyroid carcinoma. Patient underwent tracheostomy due to concern for acute hypoxic and hypercapnic respiratory failure due to the large thyroid mass compressing on his airway. Patient also underwent feeding tube placement due to his inability to tolerate intake by mouth due to the mass compression. On day five of his hospitalization, the patient started spiking high fevers. Patient was found to have MSSA bacteremia and E coli/MSSA hospital acquired pneumonia due to continued aspiration pneumonia/pneumonitis given patient was having thick and copious secretions, related to his neck mass with interval development of cystic/necrotic centre as noted on his admission CT neck. However, the patient continued to spike daily fevers to 102 while on treatment with Ciprofloxacin and Nafcillin. Given his lack of response to antibiotics, further work up was initiated to search for other sources of infection. Repeat blood cultures remained negative, fungal blood cultures were negative; MRI of the neck was ordered and ruled out infected mass and prevertebral abscess. The patient had a negative urinalysis and transthoracic echocardiogram. Nine days after the patient started spiking fevers, he was started on naproxen to evaluate for neoplastic fever as the cause for his fevers in lieu of an infectious process. After receiving the first dose of naproxen, the patient remained afebrile throughout the rest of the hospitalization. He also subjectively reported feeling better, denying any fevers or chills. He received a total of 8 doses of naproxen dosed at 250 mg BID, after which it was converted to as needed, which he did not receive. He was treated with a proton-pump-inhibitor while receiving naproxen. His dysphagia improved during the hospitalization as well and he was able to tolerate limited intake by mouth at time of discharge. He was deemed stable for discharge and was discharged home with plan to follow-up with ENT, radiation oncology, and medical oncology

and was presented at the institution's Tumor Board.

Discussion

Our patient met five of the six aforementioned criteria for neoplastic fever detailed in the introduction. He did not meet the criteria of duration of fever for >2 weeks before the naproxen challenge was attempted. However, given his lengthy hospital stay and the extensive negative infectious workup, our clinical suspicion was high for neoplastic fever, and we made the decision to move forward with the naproxen challenge rather than waiting longer. We dosed naproxen at 250 mg twice daily for our patient as this is the most used dose in the literature and saw an immediate response in fever and subjective symptoms [6]. Other doses that have been reported included 375 mg twice daily and 250 mg three times daily. We made the decision to stop the naproxen due to the risk of gastrointestinal and renal side effects from extended NSAID use but made naproxen available on an as-needed basis for fevers and chills. Interestingly, even after stopping naproxen, our patient remained afebrile throughout the remainder of his hospital stay (due to placement issues was another twenty days in the hospital). The exact mechanism as to how naproxen can treat neoplastic fever is uncertain; however, it is thought to be distinct from fevers of infectious etiology. Neoplastic fever is thought to occur in part due to pyrogenic cytokines including IL-1, IL-6, and TNF-alpha; however, the differences between neoplastic and other causes of fever are uncertain [5]. Naproxen, like other non-steroidal anti-inflammatory drugs, is a cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitor that ultimately blocks prostaglandin synthesis [7].

Conclusion

The naproxen test was first described in 1984 for neoplastic fever and the use of naproxen can be diagnostic and therapeutic for patients with neoplastic fever if they cannot immediately undergo chemotherapy and/or radiation therapy. Classically, it is only used after all sources of infection have been ruled out, however earlier use of the naproxen challenge may provide immediate symptom relief for those with neoplastic fever, prevent unnecessary medical workup, and reduce hospital length of stay. An early trial of naproxen is inexpensive and, in patients who can tolerate NSAIDs, may provide good control for neoplastic fever [8].

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