Antipyretic Effects of Indomethacin in Liver Metastases of Solid Tumors

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Six cases of fever in patients with dominant hepatic metastases from a variety of solid tumors are presented. The elevated temperature in each case was due to the malignant process itself without evidence of infection. After failure to control fever with various antipyretics and antibiotics, indomethacin promptly controlled fever in all six patients. Prior reports of antipyresis from indomethacin in hematologic malignancies and solid tumors are reviewed. Both the mechanism of fever due to the malignant process itself and the possible mechanism of indomethacin's antipyretic effect are presented. The major thrust of this report is the clinical usefulness of indomethacin for the management of liver metastases with uncontrollable fever.

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FEVER IS a common symptom of malignant disease.[1-3] Such temperature elevations are encountered most frequently with lymphoproliferative, myeloproliferative, renal, bone (Ewing's sarcoma) and primary and metastatic hepatic malignancies.[4-6] In most cancer patients, the fever is due to secondary infection. But in a considerable number of cases, the fever is directly related to the basic malignant disease process itself.[7,8] Such fevers are disabling to patients leading to malaise, headache, anorexia, weakness, debilitation, and can be a major contributor to death. If pyrexia is due to infection, antibiotic therapy is appropriate. However, when infectious cause for fever cannot be found effective antineoplastic agents and/or suitable antipyretic agents are indicated.

The efficacy of several antipyretic drugs in various lymphoproliferative diseases has been reported. While aminopyrine, phenylbutazone and adrenal corticosteroids are more effective than aspirin and acetaminophen they are also more toxic.[9] Indomethacin has been noted to control fevers in a number of patients with lymphoproliferative malignancies. Only a few instances of beneficial effects in fever due to solid, nonreticuloendothelial tumors have been reported.[10-13]

Case Reports

Case 1

A 50-year-old man who underwent total cystectomy following failure of 6500 rad of external radiation to control a Grade 3 transitional cell carcinoma of the bladder, developed confirmed pelvic recurrence which regressed following chemotherapy with cyclophasphamide, cisplatinum and doxorubicin. His abdominal pain and rectal mass completely disappeared for more than a year, but in January of 1980, he developed spiking fevers (to 40.6°C) that failed to respond to acetaminophen, aspirin, ampicillin, tetracycline, trimethoprim, sulfamethoxazole, gentamicin and carbenicillin. Chest roentgenogram intravenous pyelogram, gallium scan, multiple ilial loop urine and blood cultures all failed to demonstrate any infection or urinary obstruction. In February 1980, a palpably enlarged liver elevated alkaline phosphatase, multiple, large cold defects on liver scan and anaplastic carcinoma on liver biopsy, confirmed spread of his urinary bladder tumor to the liver. Within two hours of commencing indomethacin 25 mg every four hours, his temperature dramatically lysed. Further attempts with antineoplastic drugs were unsuccessful, but for the remaining four months of his life indomethacin controlled his fever.

Case 2

A 50-year-old woman, despite sigmoid resection, 5400 rad of postoperative external radiation to residual abdominal disease, six monthly five-day cycles of 5-fluorouracil (5-FU) and two monthly cycles of lomustine (CCNU) and 5-FU, demonstrated progressive local spread of her adenocarcinoma. In October 1980, a rising alkaline phosphatase level, enlarging palpable liver and multiple large cold defect on liver scan confirmed progressive cancer in the liver and was treated with doxorubricin, mitomycin C and 5-FU without benefit. In January 1981, the patient developed three weeks of high temperatures (to 39.4°C) unresponsive to acetaminophen, aspirin, tetracycline, ampicillin, trimethoprim and sulfamethoxazole. Chest roentgenogram, multiple urine, blood and sputum cultures failed to reveal an infection. Within two hours of starting indomethacin her temperature returned to normal and it controlled her fever (25 mg every six hours) during the remaining four weeks of her life.

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Case 3

A 63-year-old white man who underwent anterior perineal resection for invasive adenocarcinoma of the rectum with histologically positive regional lymph nodes, did well for 1½ years, when he developed a rising CEA level, elevated alkaline phosphatase and multiple, cold defects on liver scan. Despite four months of 5-FU chemotherapy his metastatic liver disease progressed. In December 1979, the patient developed high spiking fevers (to 39.2°C). His physical examination and workup including chest roentgenogram, multiple blood and urine cultures failed to demonstrate infection. After one month of fever, the patient was started on indomethacin 25 mg every six hours. Within several hours of starting this medicine his temperature dramatically returned to normal. The patient refused any further attempts at cytotoxic, antineoplastic therapy. During the remaining eight months of his life, he discontinued indomethacin on two occasions with prompt reappearance of high fever. Twice he reinstituted indomethacin and each time his fever was rapidly controlled.

Case 4

A 59-year-old woman who underwent a left radical mastectomy for poorly differentiated invasive adenocarcinoma with microscopic spread to multiple left axillary lymph nodes did well for 2½ years when she developed biopsy-positive left supraclavicular lymph node recurrence (estrogen-receptor negative), with bone scan positive, painful rib metastases, but a negative liver scan. The patient had a complete clinical remission to 42 monthly cycles of CMF (cyclophosphamide, methotrexate and 5-FU). Subsequent metastases to the right breast, sternum, ribs and a left-sided malignant pleural effusion partially remitted with the instillation of nitrogen mustard into the pleural cavity and six cycles of doxorubicin and vincristine. In May 1980, she developed extensive liver metastases as manifested by a palpable, hard, irregular liver and multiple, cold defects on her liver scan. Despite two months of tamoxifen, Velban (Lilly) and mitomycin C, the patient's liver metastases increased and she developed ascites and bone marrow metastases. In June 1980, she developed spiking fevers (up to 39.4°C) which were unresponsive to acetaminophen, aspirin, penicillin, erythromycin, gentamicin and carbenicillin. Multiple blood, urine, peritoneal effusion and pleural effusion cultures all failed to demonstrate infection. In July 1980, she had a defervescence of her fever one hour after starting indomethacin and was continued at a dosage of 25 mg every six hours for the remaining six weeks of her life with control of her fever. On two occasions, the patient discontinued indomethacin briefly with prompt recurrence of fever on both occasions. On each occasion temperature was controlled within one hour of resuming treatment.

Case 5

A 48-year-old woman who underwent sigmoid resection for an adenocarcinoma with spread to the small bowel and multiple liver metastases, was given seven months of weekly 5-FU, but demonstrated progressive liver metastases. The patient refused any further cytotoxic, antineoplastic drugs. In November 1980, she developed fevers (to 38.3°C) which persisted for three weeks despite aspirin, tetracycline and erythromycin. Chest roentgenogram, multiple urine and blood cultures were negative for infection. Fever fell immediately when indomethacin was started (25 mg every six hours). She survived another five weeks before dying of overwhelming liver metastases. During this time, she remained afebrile while on indomethacin.

Case 6

A 50-year-old woman who underwent right radical mastectomy for invasive adenocarcinoma with microscopically negative axillary lymph nodes, did well for 3½ years when she presented with tumor cells in her bone marrow biopsy, multiple osteoblastic areas on bone scan elevated alkaline phosphatase, a pulmonary nodule on chest roentgenogram and a large left occipital brain lesion on CT cranial scan. Two excellent partial clinical remission were achieved with CMF for two years and vincristine and doxorubricin for six months, but she had increased pain and sustained a pathologic fracture of her left proximal femur. Despite orthopedic repair and a trial of tamoxifen, the patient's bone metastases progressed. In February 1980, she developed a palpable, painful hepatomegaly, high fevers, elevated SGOT, GGT and multiple, large cold defects on radionuclide liver scan. Multiple blood and urine cultures were sterile and her high fevers (to 39.4°C) despite aspirin, acetaminophen, ampicillin, erythromycin and tetracycline. Within two hours of starting indomethacin (25 mg every six hours) her temperature returned to normal. After two weeks on indomethacin her temperature recurred, but was controlled for the remaining three weeks of her life by increasing the dose of indomethacin to 50 mg every six hours.

Discussion

While neoplasms of the reticuloendothelial system are the cancers most frequently characterized by fever without infection, kidney (Wilm's tumor, hypernephromas), liver (hepatomas and metastases to liver), bone (Ewing's sarcoma) and ovarian malignancies have also been noted to cause pyrexia by virtue of the malignant disease process itself.[2,14-19] The proportions of fevers due to infections and noninfectious etiologies will vary depending on the types of tumor populations surveyed. In Browder's report most the patients had solid tumors, and only 5.4% of their febrile episodes were due to the tumor itself.[8] On the other hand, Luft reports 50% of fevers were due to the tumor itself, when the majority of cases reported were lymphoproliferative neoplasms.[3]

The distinction between fever due to infection and fever due to neoplasia itself is clinically quite important. Unfortunately, tumor-induced pyrexia and infection-induced pyrexia can't be differentiated by the analysis of fever charts.[1] Fever due to malignancy itself is "typeless," *i.e.*, continuous, intermittent, remittent, low grade, hectic or any combination of the above.[19] Only with

TABLE 1. Clinical Features in 6 Cases of Hepatic Metastases with Fever

	Age (yrs)/Sex	Diagnosis & clinical status	Prior antipyretic and response	Antibiotic therapy and response	Indomethacin dose and response
Case 1	50/M	Transitional cell carcinoma of bladder, dominant liver metastases, no infection	Acetaminophen, aspirin, no response	Ampicillin, tetracycline, trimethoprim, sulfamethoxazole, gentamycin and carbenicillin, no response	25 mg Q 4 H, control of fever
Case 2	50/F	Adenocarcinoma of sigmoid colon, massive liver metastases, no infection	Acetaminophen, aspirin, no response	Tetracycline, ampicillin, trimethoprim, sulfamethoxazole, no response	25 mg Q 4 H, control of fever
Case 3	63/M	Adenocarcinoma of rectum, multiple liver metastases, no infection	None	None	25 mg Q 6 H, control of fever
Case 4	59/F	Adenocarcinoma of breast, extensive liver metastases, no infection	Acetaminophen, aspirin, no response	Penicillin, erythromycin, gentamycin, carbenicillin, no response	25 mg Q 6 H, control of fever
Case 5	48/F	Adenocarcinoma of sigmoid colon, multiple liver metastases, no infection	Aspirin, no response	Tetracycline, erythromycin, no response	25 mg Q 6 H, control of fever
Case 6	50/F	Adenocarcinoma of breast, multiple liver metastases, no infection	Aspirin, acetaminophen, no response	Ampicillin, erythromycin, tetracycline, no response	25 mg Q 6 H, transient control of fever; 50 mg Q 6 H, recontrolled fever

Q: every, H: hour.

negative cultures and failure of empiric trials of antibiotics can one exclude infection as a cause of fever.

Fever occurring in cancer patients can be of three different causes. First and most common, is that of secondary infection. Second, fever can be a consequence of noninfectious complications of neoplastic disease such as hemolytic anemia, hemorrhage into the adrenal glands or the brain, congestive heart failure and reactions to drugs or transfused blood products.[19] Third, fever can be due to the malignant process itself. It is the control of this category of fever that is the thrust of this report. Four older hypothesized mechanisms include: (1) necrosis of tumor when it outgrows its blood supply with the release of substances which cause fever; (2) leukocytic infiltration of infarcted or necrotic neoplasms, with the release of pyrogens; (3) metastasis to the liver which may interfere with the conjugation of etiocholanolone and the production of fever; and (4) rarely, metastases may involve the temperature-regulating center of the hypothalamus.

A hypothesis more consistent with clinical observations and recent laboratory investigations is that some neoplastic cells elaborate a substance (tumor pyrogen) that can act directly on the hypothalamus or act indirectly by causing release of another substance (endogenous pyrogen) from polymorphonuclear leukocytes blood mononuclear phagocytes or macrophages from the lung and liver which is responsible for hypothalamic stimulation and pyrexia.[20,21] Such tumor pyrogens have been extracted from renal tumors of febrile patients with hypernephromas and from splenic and lymphoid tissue of febrile patients with Hodgkin's disease.[22,23] These tumor pyrogens and endogenous pyrogens appear to cause fever by altering the activity of the temperature-sensitive neurones in the preoptic area of the anterior hypothalamus that determine the set-point for normal body temperature. They act directly on these neurones or through prostaglandins and other intermediates.[20] Injection of prostaglandin E_1 (PGE_1) into the anterior hypothalamus of animals produces a rapid rise of body temperature.[24,25] One of the actions of indomethacin is to prevent the synthesis of PGE_1. In animal studies, the drug attenuates endotoxin-induced fevers and concomitantly lowers PGE_1 levels in the cerebral spinal fluid.[26-28]

In our six patients (Table 1) with dominant liver

metastases and uncontrollable fever without infection, indomethacin dramatically controlled fever. Fever has previously been reported in as many as 23% of patients with dominant liver metastases.[6] Hepatic macrophages (Kupffer's cells) stimulated by intravenous endotoxin have been demonstrated to be a potent source of endogenous pyrogen.[29] Our clinical observations could be explained as follows: massive hepatic metastatic disease stimulated the release of endogenous pyrogen from the Kupffer cells of the liver. The action of this endogenous pyrogen on the temperature-sensitive neurones of the hypothalamus could be inhibited by indomethacin decreasing the synthesis of PGE_1, an essential intermediate. Unfortunately, we did not monitor the PGE_1 levels in our patients.

Antipyretic effects of indomethacin in individuals with malignancies has been described previously in five reports. Silberman *et al.*[11] noted antipyretic effects of indomethacin in nine patients with Hodgkin's disease with fever despite chemotherapy, salicylates and corticosteroids.[11] Lusch *et al.*[12] reported antipyresis in 18 of 27 patients with leukemia and lymphoma most of whom had no evidence of infection. In that report, the antipyretic effect of indomethacin was noted in one patient with hypernephroma and one patient with ganglioneuroblastoma. Banerjee[10] successfully used indomethacin in six patients with malignant reticuloendothelial tumors and fevers of noninfectious etiology. Kiely[9] also attained symptomatic control of fever in five patients with hematologic malignancies. Finally, Clavel and Gazeau[13] described antipyretic responses in five patients with lymphoreticular malignancies and nine patients with metastatic solid carcinomas from a variety of primary sites. In none of the 11 previously reported patients with metastatic solid tumors was the presence of hepatic metastases specifically noted.

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