

## Case Report

# Carcinoma of Colon: A Rare Cause of Fever of Unknown Origin

Wei Dai<sup>1</sup>, Kyu-sung Chung<sup>2\*</sup><sup>1</sup>Department of Gastroenterology, the First Affiliated Hospital of Kunming Medical College, Kunming 650032, China<sup>2</sup>Department of Gastroenterology, the Affiliated YanAn Hospital of Kunming Medical College, Kunming 650051, China

DOI: 10.1007/s11670-012-0157-0

©Chinese Anti-Cancer Association and Springer-Verlag Berlin Heidelberg 2012

## ABSTRACT

Fever of unknown origin (FUO) was originally defined as a body temperature greater than 38.3°C on several occasions longer than 3 weeks, with a diagnosis that remains unclear after 7 days of obligatory investigation. Only a few types of solid tumors have been associated with FUO. We described 2 patients who had recurrent fever but no other specific gastrointestinal symptoms where carcinoma of the colon was the only identifiable cause. In the first case, a mass arising from the sigmoid colon was found without any nodal metastasis, and the fever was resolved after three days of the surgical resection. In the second case, advanced adenocarcinoma was found in the ascending colon together with liver cirrhosis. Although it was not possible to surgically remove this tumor, prolonged fever in the patient was most likely due to the carcinoma. These cases indicate that clinicians should consider carcinoma of the colon in the differential diagnosis of patients with FUO.

**Key words:** Colon; Carcinoma; Fever; FUO

## INTRODUCTION

Fever of unknown origin (FUO) is defined as recurrent fever of 38.3°C or higher, lasting 2–3 weeks or longer, where a cause cannot be identified after one week of hospital evaluation. Nowadays, prolonged and undiagnosed fever is a serious clinical problem as the diseases underlying FUO are numerous and complicated. Pyrexia associated with tumors is sometimes noted in elderly patients, but underlying solid tumors and lymph nodes are usually easily detected by modern imaging modalities<sup>[1]</sup>. One large-scale Caucasian population-based study showed that FUO in cancer patients is associated not only with malignancies of hematologic origins but also with some solid tumors including colorectal adenocarcinoma<sup>[2]</sup>.

The objectives of this study were to report 2 cases of FUO that were eventually determined to be due to carcinoma of the colon, to discuss useful diagnostic modalities in this scenario, and to review the association of FUO with carcinoma of the colon through a computer-assisted search of the English-language literature and cross-checks from other review articles.

## CASE REPORT

### Case 1

A 47-year-old obese man was referred to the Department of Gastroenterology for evaluation of FUO (up to 38.8°C) that has been documented over the past 4 years. The patient had previously been admitted to hospitals for diagnostic work-up and definitive treatment. As the cause had not been determined, empirical trials with several antibiotics had been undertaken. The fever was controllable by a standard dose of acetaminophen and he habitually took this medication. In a previous diagnostic work-up in July 2006, a computerized tomogram (CT) of the abdomen, not including the pelvis, revealed tiny stones with a thickened gall bladder wall. On further questioning, he denied right upper quadrant pain and any food-related pain. A cholecystectomy was electively performed for the diagnosis of chronic cholecystitis due to gall bladder stones, but the fever was sustained thereafter as usual.

In April 2009, he was readmitted for further evaluation. His only complaint was that of fever and he denied weight loss, loss of appetite, diarrhea or constipation. Physical examination was normal including body temperature and rectal examination. The only abnormal result during a comprehensive work-up for FUO was an elevated C-reactive protein (CRP) at 2.4 mg/dl (normal range is below 0.8

Received 2011–04–28; Accepted 2011–06–15

\*Corresponding author.

E-mail: duloswife@hanmail.net

mg/dl)<sup>[1]</sup>. On this occasion, however, the gastrointestinal tract underwent endoscopic examination. Colonoscopy revealed a mass lesion in the sigmoid colon that extended from 16 cm through 30 cm from the dentate line of the anus (Figure 1). The colonoscope was readily passed through this segment and the remainder of the colon and the terminal ileum were normal. The mass was a multilobular tumor that the most part mildly protruded into the sigmoid lumen and had discrete pin-point mucosal ulcers and erosions over it. An abdominopelvic CT scan demonstrated a huge mass with wall thickness in the sigmoid area was present in ten consecutive scans of 1 cm interval (Figure 2). No lymph node enlargement was noted. He underwent a laparotomy and a 6 cm×8 cm mass growth arose from the sigmoid colon, with penetrating to the surface of the visceral peritoneum. A left hemicolectomy was performed. Pathological examination of the resected specimen showed well to moderately differentiated adenocarcinoma involving all layers and pericolic tissue (Figure 3). None of twenty-six lymph nodes were involved with adenocarcinoma, compatible with TNM stage IIb (T4aN0M0). From the fourth post-operative day, the fever that had been present pre-operatively, had been resolved. The patient received 6 cycles of oxaliplatin-based chemotherapy. He has had no recurrence of fever with a follow-up that is now 12 months.



**Figure 1.** Colonoscopic findings in Case 1: a multilobular tumor was protruding into the sigmoid lumen.

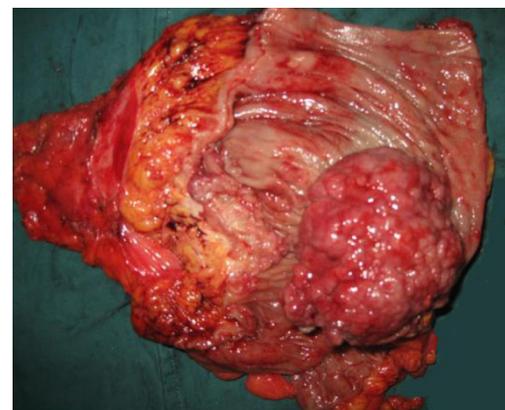
### Case 2

A 58-year-old woman presented for the evaluation of ascites and F.U.O. of up to 38.3°C for about two months. She had been diagnosed by another medical institute as having liver cirrhosis with ascites in October 2007. She denied any symptoms referable to hepatic encephalopathy, skin lesions, serious weight change, altered bowel habit or stool color change. In May 2008, physical examination showed body

temperature of 37.8°C, mild pallor of the conjunctiva and abdominal distension. Hemoglobin was 99 g/L and iron level was 15 (normal >50), compatible with iron deficiency anemia. Serum albumin was 31 g/dl and other blood indices were within normal ranges. Abdominal paracentesis showed a total leukocyte count of 250/mm<sup>3</sup> and cultures were negative. Repeated cultures of blood and urine, skin testing for tuberculosis and screening for autoimmune diseases were negative. A CT scan showed a cirrhotic liver, mild splenomegaly and ascites. A 7-day empirical trial with cefotaxime 2 g for every 8 h intravenously (iv) failed to lower body temperature. A culture of a bone marrow aspirate was negative. The patient was discharged herself and subsequently was able to control her fever and abdominal distension through acetaminophen and diuretics with intermittent iv albumin over the next year.



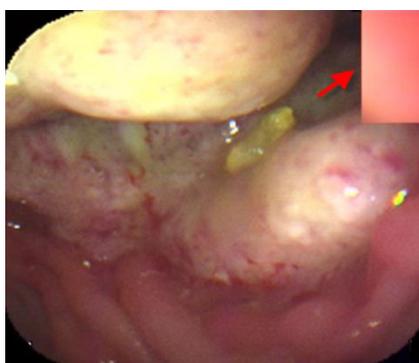
**Figure 2.** Contrast enhanced CT scan of the pelvis in Case 1: an inhomogeneous soft tissue mass and thickening of the wall of the sigmoid colon are seen.



**Figure 3.** Gross finding of the resected tumor in Case 1 shows polypoidal mass with an irregular surface.

In June 2009, she was readmitted with the same complaints as 2008 for a repeat comprehensive work-up including paracentesis, repeated cultures, auto-antibody tests, and upper and lower digestive endoscopies. Meanwhile, the fever persisted despite empiric therapy both moxifloxacin 400 mg for every

24 h iv and ampicillin 1.0 g plus sulbactam 0.5 g for every 6 h iv. Colonoscopy, however, demonstrated a non-obstructing, approximately 5 cm long multilobular mass protruding into the lumen of the ascending colon (Figure 4). Histopathology revealed poorly differentiated mucinous adenocarcinoma. A subsequent CT of the abdomen showed, apart from the findings of cirrhosis and ascites, a solitary lesion within the wall at the same level of intestine identified at colonoscopy and no lymph node enlargement was noted (Figure 5). The patient refused surgical intervention after receiving information regarding the risks associated with a major abdominal operation in the presence of liver cirrhosis. Therefore, she was discharged and, during six months' follow-up so far, the fever has been well controlled by moderate dosage of acetaminophen on demand (500 mg each time).



**Figure 4.** The red arrow indicates the scope could pass through a relatively narrow channel made by a circumferentially protruding mass in the ascending colon of Case 2.



**Figure 5.** The contrast enhanced CT scan in Case 2 suggests an irregularly thickened lesion along with the wall at the ascending colon level (arrow).

## DISCUSSION

FUO is challenging and frustrating for both physicians and patients because the diagnostic work-up frequently involves multiple modalities including invasive procedures that often do not clearly explain

the origin of the fever. From prolonged febrile illness to FUO, at least one-fifth to one-third of the cases, the diagnosis is not able to be made<sup>[1,3,4]</sup>. Vanderschueren, et al. quite reasonably have proposed to consider etiologic possibility of malignancy in patients with FUO as malignancies occupy a sizable proportion of FUO (15.1%) and further, are the major cause of FUO-related deaths<sup>[3]</sup>. Though the major cancer associated with FUO involves the reticuloendothelial system, solid tumors with FUO, such as hepatocellular carcinoma, hypernephroma and atrial myxoma, have also been reported. However, colorectal cancer, as observed in these two cases, has not been previously reported to be the likely cause of FUO in Chinese patients. For example, in a study of 78 Chinese adult patients with FUO, there were no cases of colorectal carcinoma<sup>[5]</sup>. The most extensive evaluation has occurred in Caucasian populations in Denmark. A population-based study using a cancer registry noted an association at least between colorectal cancer and FUO. While the association does not necessarily mean that the cancer was causing the FUO, it does justify investigation for colorectal cancer in the work-up of patients with FUO<sup>[2]</sup>.

If the relationship is causal, the mechanism could be infectious or non-infectious. Recurrent infection in the ulcerated mucosa may play a role. Some organisms, such as *Streptococcus bovis* (*S. bovis*) or *Escherichia coli*, may invade mucosa or express themselves as metastatic infections, especially among immune compromised hosts with colorectal cancer<sup>[6,7]</sup>. There is a well-established relationship between *S. bovis* bacteremia (SBB) and colorectal cancer, but this association is merely about causal sequence, not that FUO is likely accompanied by colorectal cancer concomitantly<sup>[6]</sup>. As a matter of fact, since *S. bovis* is just one of the normal flora of the digestive tract, it is not surprising that some patients with SBB have concomitant bowel diseases. In a report with three colon cancer patients who complained of fever for over three weeks to six months of time, none of them had specific digestive symptoms; interestingly, those surgical specimens appeared involving the whole muscular wall and pericolic fat, with abscess formation in the pericolic fat. As pathologic evaluation of the tumor tissues demonstrated a severe organized inflammatory process forming abscesses in the pericolic fat, along with microcytic anemia and high erythrocyte sedimentation rate (ESR), they speculated it was more likely to be associated with infection<sup>[7]</sup>. In our first case, gastrointestinal symptoms were absent, the cancer involved the entire colonic wall and pericolic tissue, and abscesses containing about 5-10 ml of pus inside were found. The nature of bacteria associated with these abscesses was not evaluated.

The cause of the FUO related colon cancer may be

explained by a non-infectious background. Tumors cause recurrent fever by intermittent necrosis with subsequent phagocytosis and cytokine production<sup>[8]</sup>. In certain kinds of tumors, it was speculated that interleukin I (IL-1) and tumor necrosis factor (TNF) were the major endogenous pyrogens identified. Circulating IL-1 and TNF centrally act on the thermoregulatory center of the hypothalamus<sup>[9,10]</sup>. However, since there are no data on whether carcinoma of the colon can produce IL-1 and TNF, this paraneoplastic mechanism for FUO remains speculative.

Currently, the evidence-based approach to investigating patients with FUO recommends a diagnostic spiral CT of the abdomen<sup>[1,8]</sup>. It should be one of the initial investigations in FUO, since it has a high diagnostic yield and is likely to identify two of the most common causes of FUO: intra-abdominal abscesses and histiocytic or lymphoproliferative disorders. Since various types of malignancies could accompany fever, CT of the abdomen should be a very useful tool to search for an origin of hidden malignancy with FUO<sup>[8]</sup>. In fact, many published cases of carcinoma of the colon with FUO, including our first case, have shown CT scans to reveal masses associated with the colon<sup>[7,11]</sup>. However, as its accuracy and sensitivity varies, it is complementary to the clinical assessment of the patient and to the use of other diagnostic modalities<sup>[12,13]</sup>. Thus, as an early investigation in patients with FUO, expectations of abdominal CT should be limited. This was illustrated by both our cases where the initial CT was negative. In the first case, the pelvis was not scanned and the tumor may have been picked up there. In the second case, the tumor was not readily visible on CT earlier in the patient's course. The presence of iron deficiency may have prompted earlier colonoscopy, but chronic systemic inflammation is often associated with iron deficiency due to poor iron absorption. It is well known that CT scanning is not the investigation of choice for detecting colon cancer. Therefore, it is reasonable to suggest that clinicians should seriously consider performing colonoscopy in patients with FUO, undiagnosed after a conventional work-up including abdominal CT scan. Colonoscopy is an essential investigation because both colon cancer and Crohn's disease are classic causes of recurrent FUO<sup>[14,15]</sup>. Colonoscopy definitely has a better yield than barium enema as the small sizes of tumor might be missed and it has the added advantage of providing tissue confirmation<sup>[16]</sup>.

In summary, we have described 2 patients who had fever for years: the first unequivocally related to

carcinoma of the colon and the second likely to be causally related. Neither patient had gastrointestinal symptoms. We conclude that in patients presenting with FUO where standard investigations including a CT scan of the abdomen have failed to reveal a cause, colonoscopy should be considered to search for colorectal cancer.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### REFERENCES

1. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med* 2003; 163:545–51.
2. Sorensen HT, Mellemejaer L, Skriver MV, et al. Fever of unknown origin and cancer: a population-based study. *Lancet Oncol* 2005; 6:851–5.
3. Vanderschueren S, Knockaert D, Adriaenssens T, et al. From prolonged febrile illness to fever of unknown origin: the challenge continues. *Arch Intern Med* 2003; 163:1033–41.
4. Cunha BA. Fever of unknown origin: focused diagnostic approach based on clinical clues from the history, physical examination, and laboratory tests. *Infect Dis Clin North Am*. 2007; 21:1137–87.
5. Liu KS, Sheng WH, Chen YC, et al. Fever of unknown origin: a retrospective study of 78 adult patients in Taiwan. *J Microbiol Immunol Infect* 2003; 36:243–7.
6. Alazmi W, Bustamante M, O'Loughlin C, et al. The association of *Streptococcus bovis* bacteremia and gastrointestinal diseases: a retrospective analysis. *Dig Dis Sci* 2006; 51:732–6.
7. Agmon-Levin N, Ziv-Sokolovsky N, Shull P, et al. Carcinoma of colon presenting as fever of unknown origin. *Am J Med Sci* 2005; 329:322–32.
8. Knockaert DC. Recurrent Fevers of Unknown Origin. *Infect Dis Clin North Am* 2007; 21:1189–211.
9. Liaw CC, Chen JS, Wang CH, et al. Tumor fever in patients with nasopharyngeal carcinoma: clinical experience of 67 patients. *Am J Clin Oncol* 1998; 21:422–5.
10. Sato K, Fujii Y, Ono M, et al. Production of interleukin 1[alpha]-like factor and colony stimulating factor by a squamous cell carcinoma of the thyroid (T3M-5) derived from a patient with a hypercalcemia and leukocytosis. *Cancer Res* 1987; 47:6474–80.
11. Varghese GM, Shenoy M, Subramanian S, et al. Colonic malignancy with recurrent bacteraemia presenting as pyrexia of unknown origin. *J Intern Med*. 2004; 255:692–3.
12. Ott DJ, Wolfman NT, Scharling ES, et al. Overview of imaging in colorectal cancer. *Dig Dis* 1998; 16:175–82.
13. Karachalios GN, Karachaliou IG, Bablekos G, et al. Fever of unknown origin in carcinoma of the colon. *Med Princ Pract* 2004; 13:169–70.
14. Knockaert DC, Vanneste LJ, Bobbaers HJ. Recurrent or episodic fever of unknown origin: review of 45 cases and survey of the literature. *Medicine* 1993; 72:184–96.
15. Gupta N, Bostrom AG, Kirschner BS, et al. Presentation and disease course in early- compared to later-onset pediatric Crohn's disease. *Am J Gastroenterol* 2008; 103:2092–8.
16. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; 134:1570–95.