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Fever of unknown origin as the first manifestation of colonic pathology

Moncef Belhassen-García, Virginia Velasco-Tirado, Amparo López-Bernus, Montserrat Alonso-Sardón, Adela Carpio-Pérez, Lucía Fuentes-Pardo, Javier Pardo-Lledías, Lucia Alvela-Suárez, Ángela Romero-Alegría, Alicia Iglesias-Gomez and Miguel Cordero Sánchez

ABSTRACT – Fever of unknown origin (FUO) is an entity caused by more than 200 diseases. Haematologic neoplasms are the most common malignant cause of FUO. Fever as a first symptom of colonic tumour pathology, both benign and malignant, is a rare form of presentation. Our work is a descriptive study of a series of 23 patients with colonic tumoral pathology who presented with fever of unknown origin. The mean age was 67.6 years; 56.5% of patients were men and 43.5% were women. Primary malignant neoplasia was the most common diagnosis. Blood cultures were positive in 45% of the samples. Coagulase-negative staphylococci were the most common cause of bacteraemia. Nine of 10 faecal occult blood tests performed were positive. Fever secondary to colon neoplasms, both benign and malignant, usually presents with a bacteraemic pattern, with positive results for blood-culture tests in a high percentage of cases.

KEY WORDS: bacteraemia, colonic neoplasms, fever of unknown origin, occult blood

Introduction

Ever since Petersdorf and Beeson described fever of unknown origin (FUO) as a clinical entity in 1961[1] and Durack and Street redefined it in 1991,[2] more than 200 diseases have been described as a cause of this condition. These diseases have been classified into infections, neoplastic processes, inflammatory disorders and a wide range of miscellaneous conditions.

The incidence of FUO within the different diagnostic groups has changed over the years. Infectious diseases were the main cause until the 1990s, with that position currently occupied by malignant processes (7–24% of cases).[3–8] Haematologic neoplasms are the most common malignant cause of FUO. Solid tumours are a much less common cause, with three predominating aetiologies in the kidneys, lungs and colon.[9] Colon cancer has a variable incidence depending on the series, ranging from 0% to 5% of all cases of FUO.[9,10] Apart from benign tumours and colorectal malignant tumours, the range of colonic disorders that can lead to FUO is wide, including inflammatory bowel disease, infections of the digestive tract, ischaemic colitis, etc. For this reason, we must point out that fever as a first symptom of colonic tumour pathology, both benign and malignant, is a rare form of presentation.

The objective of our study was to assess the clinical and analytical variables of a group of 23 patients with colonic tumour pathology who presented with FUO as the first symptom.

Methods

Our setting is the University Hospital of Salamanca (Western Spain) – a third-level medical centre with 1,000 beds that covers a population of 350,000 inhabitants. The period of our study was 1 January 1995–31 December 2009. Our work is a descriptive study of cases that were found through an active search developed by the Department of Clinical Documentation and the Department of Anatomical Pathology. We reviewed clinical records of all patients with colonic pathology and selected those who addressed the agreed criteria (Table 1). All epidemiological, clinical and analytical parameters were recorded according to a clinical protocol.

Box 1. Definition of case.

- Patient with classic Durack and Street criteria for FUO[2] as first reason for clinical consultation:
  - Fever ⩾38.3°C on several occasions
  - Fever >3 weeks in duration
  - Diagnosis uncertain despite appropriate investigations after ≥3 outpatient visits or ⩾3 days in hospital
- Final diagnosis presented by pathological analysis of anatomy with a result of colorectal carcinoma or polyp of any histological type
- Disappearance of fever after treatment of colonic pathology

FUO = fever of unknown origin.

Moncef Belhassen-García,[1] consultant; **Virginia Velasco-Tirado**,[1] consultant; **Amparo López-Bernus,** [1] consultant; **Montserrat Alonso-Sardón**,[2] professor of medicine; **Adela Carpio-Pérez**,[1] consultant; **Lucía Fuentes-Pardo**,[3] consultant; **Javier Pardo-Lledías,**[4] consultant; **Lucia Alvela-Suárez**,[1] consultant; **Ángela Romero-Alegría**,[1] consultant; **Alicia Iglesias-Gomez**,[1] consultant; **Miguel Cordero Sánchez**,[1] professor of medicine

[1]Department of Internal Medicine, Unit of Infectious Diseases, IBSAL, University Hospital of Salamanca, Spain; [2]Department of Preventive Medicine, Public Health and Medical Microbiology, Faculty of Medicine, University of Salamanca, Spain; [3]Department of Internal Medicine, 'Virgen de la Concha' Hospital, Zamora, Spain; [4]Department of Internal Medicine, General Hospital of Palencia 'Río Carrión', Palencia, Spain

Results

Twenty-three cases were selected (Table 2): 13 (56.5%) were men and 10 (43.5%) were women. The mean age was 67.6 (range 29 to 92) years. In 13 (56.5%) cases, there was a personal record of digestive pathologies. One (4%) case showed a family record with first-grade relatives who presented with colon neoplasm. Most of the patients presented with data compatible with an inflammatory process, with increased levels of phase reactants. In 19 (82.6%) cases, the patients presented with chronic and/or iron-deficiency anaemia, with average haemoglobin levels of 10.4 (range 6.1 to 12.0) g/dl. The fever at diagnosis lasted for fewer than 6 months in 14 (60.9%) cases, 6–12 months in four (17.4%) cases and ≥12 months in five (21.7%) cases. Sixteen (69.6%) patients had other clinical manifestations, including constitutional symptoms (asthenia, anorexia and weight loss) in 10 (43.5%) patients and abdominal pain in six (26%) patients. The fever was bacteraemia-like in all cases. Blood-culture tests were performed for 20 (86.9%) patients; they were not arranged for three patients because they did not have fever in the days they were studied. The results were positive in nine (45%) cases. Cultures with growth of coagulase-negative staphylococci were considered positive only when the growth was present in two consecutive samples. The following bacteria were isolated: *Escherichia coli* (n=2), *Streptococcus bovis* (n=2), *Staphylococcus hominis* + *Staphylococcus epidermidis* (n=2), *Staphylococcus capitis* (n=1), *S. hominis* (n=1) and *S. epidermidis* (n=1). The faecal occult blood (FOB) test was performed in 10 (43.5%) patients, with positive results in nine cases. Chest X-ray was performed on each patient, without any finding of note. Primary malignant neoplasia was the most common diagnosis, occurring in 18 (78.3%) cases, while polyps were diagnosed in three (13%) cases and tumour recurrence in two (8.7%) cases. The neoplasms were accompanied by hepatic metastases in four (17.4%) patients. In three (13%) patients, contiguity infiltration was present (two in the bladder; one in the stomach). Two (8.7%) patients had abscesses, one of which was perirectal and the other hepatic. One (4.3%) patient presented with endocarditis due to *S. bovis*.

Discussion

The series published by Peterson and Beeson in 1961[1] and Larson *et al* in 1982[11] show a certain variability with regard to the importance of different types of neoplasms in FUO. However, in most published series, haematological neoplasms are more common than solid tumours, with an approximate ratio of 2:1. Kazanjian *et al* report an incidence of neoplasms that reaches 24% of all cases, with Hodgkin's disease as the first cause and colon cancer as the most common solid tumor.[12] However, other authors, such as Hirschmann,[13] do not describe any cases of colon cancer, and Hirschmann's study includes only one case of kidney cancer. With regard to fever-inducing solid cancers, most are located in the abdominal cavity.[11] The global incidence of colon cancer in case series with FUO ranges from 0% to 5%.[9,10] Fever associated with neoplastic processes is due to the production of tumour-induced pyrogens, necrosis of large masses, hypothalamic involvement and infection, as well as secondary causes derived from the neoplastic process, such as blastic crises, paraneoplastic phlebitis, etc. The presence of FUO in patients with a known neoplasm is estimated to be due to an infectious concomitant cause in 50% of cases; it is related to an immunodepressed state and/or the rupture of mucous membranes, which, in most cases, implies an advanced stage of disease.[13] Colon cancer-induced FUO results from the same pathophysiological mechanisms underlying other tumours. Rupture of the mucous barrier facilitates invasion by intestinal bacteria.[10]

The fever pattern in our patients was bacteraemic in all cases: spikes in fever were lacking a stable periodicity and so could not be predicted and disappeared spontaneously or after antibiotic therapy.[11] In a previous series study of 23 patients with recurrent fever, the authors observed that 8.6% presented with colorectal cancer.[10] For this reason, we must point out that a recurrent or spiking fever may be the first and only manifestation of a hidden colon neoplasm.[10]

Although the literature usually describes negative blood cultures (due to the use of antibiotic therapy or the fact that the fever is caused by temporary bacteraemia), our study found positive results in 45% of patients in whom blood culture tests were performed. With regard to bacteraemia associated with colon cancer, two bacteria stood out: *Streptococcus bovis*[14,15] and *Clostridium septicum.*[16,17] The degree of association between the bacteraemias caused by these bacteria and colon cancer is so high that their presence makes it necessary to rule out colon cancer.[16] In addition, *Bacteroides fragilis* and *Escherichia coli* may cause bacteraemias in patients with colon tumours, although they do not have such a direct relation with colonic tumour pathologies as *S. bovis* and *C. septicum.*[10] In our case study, 'classic' germs were found in four patients (*S. bovis* in two; *E. coli* in two). According to the central line-associated bloodstream infection (CLABSI) criteria,[18] our series had a remarkably high number of cases with positive results for coagulase-negative staphylococci (n=5; 25% of all blood cultures and 55.6% of all positive blood cultures). Bacteraemia caused by these germs is generally associated with the iatrogenic context of intravenous catheters, but this was not the case in any of our 20 patients who underwent blood culture tests. We did not observe similar data in other studies,[19,20] and, to the best of our knowledge, an association of coagulase-negative staphylococci bacteraemia with colon cancer has not been described. However, the number of cases included in our study is not large and we cannot rule out the possibility that this is a 'chance finding'.

Apart from bacteraemia, other infectious disorders may lead to fever in patients with non-disseminated colon cancer, including appearance of a fistula; intra-abdominal infections[16] such as peritonitis; perilesional abscesses; distant infections such as empyema, endocarditis (4.3% of patients in our series) and arthritis;[21] urinary infections (secondary to colovesical fistulas; 6.4% of patients in our series);[16] extensions of other infections; necrotising cellulitis; and gaseous gangrene.[17,22] In our series,

Table 2. Main clinical and analytical characteristics of 23 cases presenting with fever of unknown origin.

Patient	Age (years)	Sex	Duration of fever	Other symptoms	Blood culture findings	FOB test	Hb (g/dl)	APR	TM	Diagnosis
1	69	W	12 months	None	*Escherichia coli*	Not performed	9.6	Increased	Increased	Sigmoid adenocarcinoma with bladder infiltration
2	74	M	9 months	Slight tenesmus	*Staphylococcus capitis* (2/2)	Positive	10.7	Increased	Increased	Stenosing sigma adenocarcinoma
3	85	W	3 weeks	Dysuria	*S. hominis* (2/2) *S. epidermidis* (2/2)	Not performed	9.7	Increased	Increased	Rectum adenocarcinoma with abscess
4	36	W	13 months	Weight loss	Negative	Not performed	12	Increased	Normal	Adenocarcinoma of splenic flexure
5	84	M	12 months	None	Not performed	Not performed	9.4	Increased	Not measured	Adenocarcinoma of left colon
6	77	M	6 weeks	None	Negative	Not performed	10.3	Increased	Not measured	Recurrent adenocarcinoma of rectum with liver metastases
7	74	W	7 weeks	Weight loss	*Streptococcus bovis*	Not performed	9.7	Increased	Not measured	Adenomatous polyps (2) of the transverse colon
8	69	M	2 months	Weight loss Asthenia	*S. hominis* (2/2)	Not performed	11.9	Increased	Increased	Sigmoid adenocarcinoma
9	74	M	2 months	None	Negative	Positive	9.2	Increased	Normal	Adenomatous polyp of the rectum
10	64	W	12 months	Asthenia RIF pain	Negative	Positive	13	Increased	Normal	Sigmoid adenocarcinoma
11	81	M	3 months	Abdominal pain	Negative	Not performed	13	Increased	Normal	Sigmoid adenocarcinoma with liver metastases
12	60	M	6 weeks	No	Negative	Positive	9.7	Increased	Normal	Sigmoid adenocarcinoma with liver metastases
13	31	M	3 months	Weight loss	Negative	Not performed	12.6	Increased	Normal	Adenocarcinoma of colon with bladder infiltration
14	92	M	2 months	Itches	Negative	Not performed	8.6	Increased	Normal	Adenocarcinoma of caecum
15	77	M	3 weeks	No	*S. hominis* (2/2) *S. epidermidis* (2/2)	Positive	10.7	Increased	Increased	Adenocarcinoma of caecum
16	70	M	5 months	Weight loss	*E. coli*	Not performed	11.5	Increased	Normal	Sigmoid adenocarcinoma and villo-glandular polyps (4)
17	57	W	6 months	Weight loss Abdominal pain	Not performed	Not performed	13	Increased	Increased	Adenocarcinoma of splenic flexure with gastric infiltration and inflammatory plastron
18	80	M	24 months	No	Negative	Positive	10.6	Normal	Normal	Villo-glandular polyps (2) in sigmoid colon

Continues

Table 2. Continued

Patient	Age (years)	Sex	Duration of fever	Other symptoms	Blood culture findings	FOB test	Hb (g/dl)	APR	TM	Diagnosis
19	29	W	7 weeks	Asthenia Anorexia	Negative	Not performed	6.7	Increased	Increased	Adenocarcinoma of colon with liver metastases
20	81	M	3 months	Slight alterations of intestinal activity	*S. bovis*	Positive	12	Increased	Normal	Ulcerated adenocarcinoma of rectum and endocarditis
21	71	W	6 months	Weight loss Asthenia Anorexia	Negative	Positive	6.1	Increased	Normal	Adenocarcinoma of splenic flexure
22	72	W	8 months	Weight loss (6 kg) Postprandial fullness	Not performed	Positive	13	Increased	Normal	Muco-secreting adenocarcinoma of caecum
23	44	W	3 weeks	No	*S. epidermidis* (two positive blood cultures of two cultures performed)	Negative	6.4	Increased	Normal	Recurrent mucosecreting adenocarcinoma of splenic flexure

APR = acute-phase reactants; FOB = faecal occult blood; Hb = haemoglobin; M = man; RIF = right iliac fossa; TM = tumour markers; W = woman.

17.4% of patients had hepatic metastases; none of these had a tumour fever pattern (a continuous and stable fever that does not respond to antibiotics), which is explained by the systemic inflammatory reaction in a disseminated disease caused by liver metastases, tumour-induced pyrogens, necrosis of the tumour itself or central involvement.[23]

In an analysis of time between symptom onset and diagnosis, we must highlight that fever lasted for ≥6 months in almost 40% of patients. This would suggest that fever is not a sign that practitioners associate immediately with the presence of colonic pathology. Whenever there is no initial clinical suspicion, invasive endoscopic tests are postponed to a second or third stage of the investigation pathway. The spiked fever pattern probably contributes to this fact, because it suggests an infectious pathology. In our patients, therefore, we found different initial suspected diagnoses, such as endocarditis, fistula and intra-abdominal abscesses (data not shown).

Ninety per cent of patients who underwent an FOB test showed a positive result. Although the number of patients in this situation was small (n=9), this fact may suggest the usefulness of a simple, inexpensive and non-invasive test in the rational and staged study of a patient with FUO.

Finally, we observed a high number of analytical tests (tumour markers and autoimmunity studies) and radiological tests (ultrasound imaging and abdominal computed tomography) in patients who presented with fever as a first symptom (data not shown).

In conclusion, fever secondary to colon neoplasms, both benign and malignant, usually presents with a bacteraemic pattern, with positive results from blood-culture tests in a high percentage of cases.

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Address for correspondence: Dr M Belhassen-García, Department of Internal Medicine, Unit of Infectious Diseases, IBSAL, University Hospital of Salamanca, CIETUS, University of Salamanca, Paseo San Vicente 58-182, 37007, Salamanca, Spain.
Email: mbelhassen@hotmail.com