

[CASE REPORT]

G-CSF-producing Undifferentiated Pleomorphic Sarcoma Adjacent to the Ascending Colon and in the Right Iliopsoas Muscle: A Case Report and Review of the Literature

Shinsuke Kazama¹, Tabu Gokita², Michitoshi Takano¹, Ayataka Ishikawa³, Yu Nishimura³, Hiroaki Ishii¹, Yusuke Nishizawa¹, Yoji Nishimura¹, Yoshiyuki Kawashima¹ and Hirohiko Sakamoto¹

Abstract:

Undifferentiated pleomorphic sarcoma (UPS) is a soft tissue sarcoma, occurring most commonly on the lower extremities. We herein report a rare case of primary UPS adjacent to the ascending colon and in the right iliopsoas muscle. Computed tomography of the abdomen revealed large masses, and the patient experienced a high-grade fever, leukocytosis, elevated serum C-reactive protein level, and hematopoietic activation on ¹⁸F-fluorodeoxyglucose-positron emission tomography. This inflammatory reaction was caused by granulocyte colony-stimulating factor secreted by tumor cells. Surgical resection was performed, and the inflammatory reaction disappeared immediately. The patient received adjuvant chemotherapy and survived one year after the operation without evidence of recurrence.

Key words: undifferentiated pleomorphic sarcoma, inflammatory reaction, granulocyte colony-stimulating factor, ascending colon, iliopsoas muscle

(Intern Med 58: 2783-2789, 2019)

(DOI: 10.2169/internalmedicine.2762-19)

Introduction

In adults, malignant fibrous histiocytoma (MFH) is a soft tissue sarcoma, occurring most commonly on the lower extremities and in the abdominal cavity or retroperitoneum (1). MFH in the viscera, particularly with gastrointestinal involvement, is rare (2-22). In 2002, MFH was re-classified as undifferentiated pleomorphic sarcoma (UPS) by the World Health Organization (23). It is classified into three types: UPS, UPS with giant cells, and UPS with prominent inflammation.

Among these types, inflammatory UPS occurring in the gastrointestinal tract is extremely rare (2, 8, 12, 17, 19, 24). Inflammatory UPS has been reported to be correlated with the production of granulocyte colony-stimulating factor (G-CSF) by tumor cells (12, 25).

We herein report a rare case of G-CSF-producing UPS adjacent to the ascending colon and in the right iliopsoas muscle. Although this inflammatory reaction caused by G-CSF was noted preoperatively, it disappeared immediately after complete surgical resection of the tumors.

Case Report

A 50-year-old man was admitted to a local hospital because of abdominal pain and numbness in the right lower limb accompanied by a slight fever. Computed tomography (CT) of the abdomen revealed large well-defined enhanced heterogeneous masses: a 7.2×6.0-cm mass on the right side of the abdomen (Fig. 1A), which was adjacent to the ascending colon, and a 3.7×3.6-cm mass in the right iliopsoas muscle (Fig. 1B).

The patient was referred to our hospital with a 15-kg loss

¹Department of Gastroenterological Surgery, Saitama Cancer Center, Japan, ²Department of Orthopedic Surgery, Saitama Cancer Center, Japan and ³Department of Pathology, Saitama Cancer Center, Japan

Received: January 31, 2019; Accepted: April 1, 2019; Advance Publication by J-STAGE: June 27, 2019

Correspondence to Dr. Shinsuke Kazama, kaz-tyk@umin.ac.jp

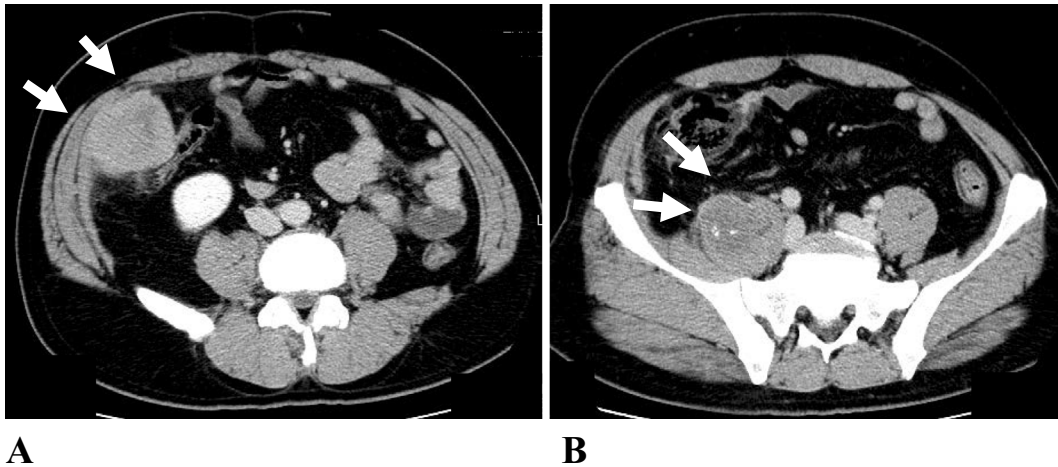


Figure 1. Computed tomography (CT) of the abdomen. A: A 7.2×6.0-cm mass on the right side of the abdomen (white arrows). B: A 3.7×3.6-cm mass in the right iliopsoas muscle (white arrows).

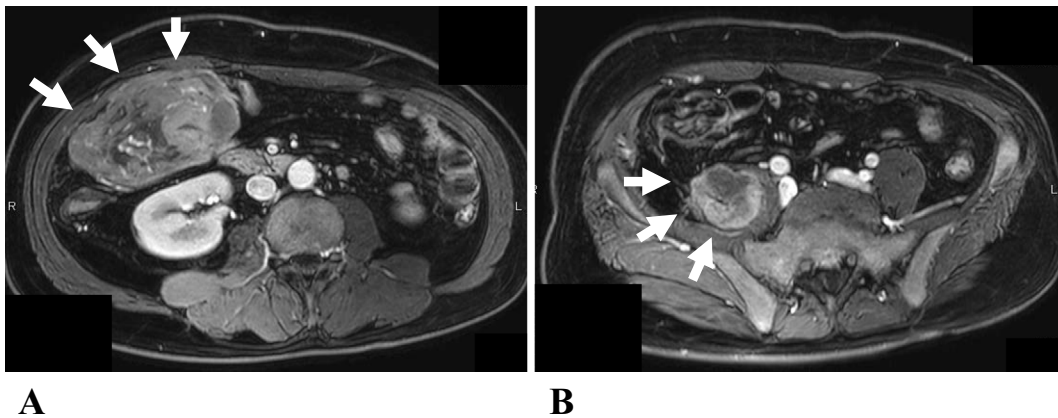


Figure 2. Magnetic resonance imaging (MRI) of the abdomen. A: A 12.9×6.8-cm mass on the right side of the abdomen (white arrows) with a high intensity in the early phase, as observed in enhanced images. B: A 3.7×3.6-cm mass in the right iliopsoas muscle (white arrows).

of weight in a month. On a physical examination, his body temperature was 37.4°C, and a large palpable mass was detected in the right lower abdomen. The hematological examination showed a hemoglobin level of 12.3 g/dL (normal range: 14.1-17.2 g/dL), white blood cell count of 21,440/mm³, and severe elevated serum C-reactive protein (CRP) level of 14.8 mg/dL. The levels of tumor markers, including CEA and CA19-9, were within the normal limits. While a CT-guided biopsy of the masses on the right side of the abdomen and right iliopsoas muscle was performed, the specimens revealed inflammatory changes, mainly composed of neutrophils, so the biopsy was not useful for the diagnosis.

The patient complained of a continuous high fever and was hospitalized for both a further examination and treatment. During hospitalization, his maximum temperature was 40.0°C despite antipyretic medication, with a maximum leukocyte count of 40,100/mm³ (84.1% neutrophils, 1.2% eosinophils, 0.1% basophils, 6% monocytes, and 8.6% lymphocytes) and serum CRP level of 21.3 mg/dL. The serum cytokine values were assessed by an enzyme immunoassay,

and elevated G-CSF levels of 339 pg/mL (normal range: 10.5-57.5 pg/mL) and elevated interleukin-6 (IL-6) levels of 110 pg/mL (normal range: 0-2.41 pg/mL) were noted. Magnetic resonance imaging (MRI) of the abdomen revealed a 12.9×6.8-cm mass on the right side of the abdomen, which showed marked enlargement in 1 month with a relatively homogenous intensity on T2-weighted imaging and high intensity in the early phase on enhanced images accompanied by bleeding caused by the CT-guided biopsy (Fig. 2A). The size of the mass in the right iliopsoas muscle was unchanged, showing the same intensity as that on the right side of the abdomen (Fig. 2B). Colonoscopy revealed only extramural compression in the ascending colon (Fig. 3). ¹⁸F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT showed the elevated uptake of FDG in the right abdominal tumor [maximum standardized uptake value (SUVmax) 25.12] (Fig. 4A) and tumor in the right iliopsoas muscle (SUVmax 17.84) (Fig. 4B). In addition, an increased FDG uptake in the systemic bone marrow, which indicated elevated bone marrow activity, was noted (Fig. 2B). Al-

though no obstruction of the large intestine was detected, tumor resection was nevertheless scheduled due to the fact that the patient's high fever persisted.

At the operation, two masses were detected adjacent to the ascending colon invading the right transverse abdominal muscle and right iliopsoas muscle. Right hemi-colectomy with regional lymph node dissection, composite resection of the right transverse abdominal muscle, and resection of the right iliopsoas muscle were performed. No evidence of liver or peritoneal metastases was found.

The high fever and leukocytosis immediately disappeared after resection of the tumors. Serum G-CSF was undetectable after the operation. The postoperative course was un-

eventful, and the patient was discharged 10 days after the operation. FDG-PET revealed that the elevated FDG uptake in both tumors and the systemic bone marrow had disappeared 1.5 months after the operation.

Grossly, the resected specimen of the ascending colon was a whitish circumscribed tumor, measuring 19×14×10 cm in size, that protruded extramurally from the colonic wall. The tumor in the right iliopsoas muscle was a whitish tumor, measuring 6.5×5.0×3.0 cm in size. Lymph node metastasis was not detected. A microscopic examination revealed that the tumor in the ascending colon consisted of many neutrophils and fibroblast-like spindle cells with atypical mitosis and widespread necrosis (Fig. 5A), and the tumor in the right iliopsoas muscle consisted of fibroblast-like spindle cells, giant cells, and cells undergoing osteogenesis. Immunohistochemical staining was positive for vimentin in both tumors and for SMA, desmin, and EMA (focally) in the right iliopsoas muscle tumor. S100, CD34, and AE1/AE3 were not expressed. On an immunohistochemical examination based on cytokine expression, both tumors were focally positive for G-CSF (Fig. 5B). Therefore, the pathological diagnosis was inflammatory UPS originating from the ascending colon and giant cell-type UPS originating in the right iliopsoas muscle, with G-CSF-producing tumors.

Following surgical treatment, the patient received 3 courses of adjuvant chemotherapy with doxorubicin (60 mg/m²) and was doing well 1 year after the operation without evidence of recurrence.

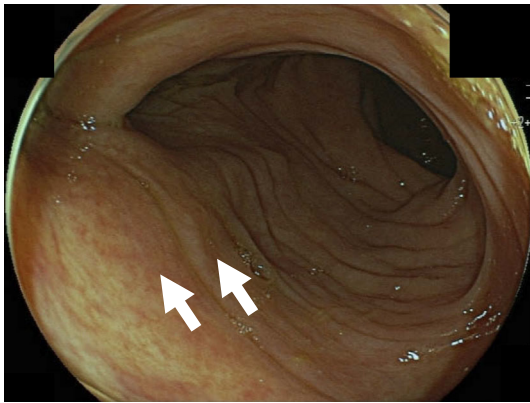


Figure 3. Colonoscopy findings. Extramural compression was revealed in the ascending colon (white arrows).

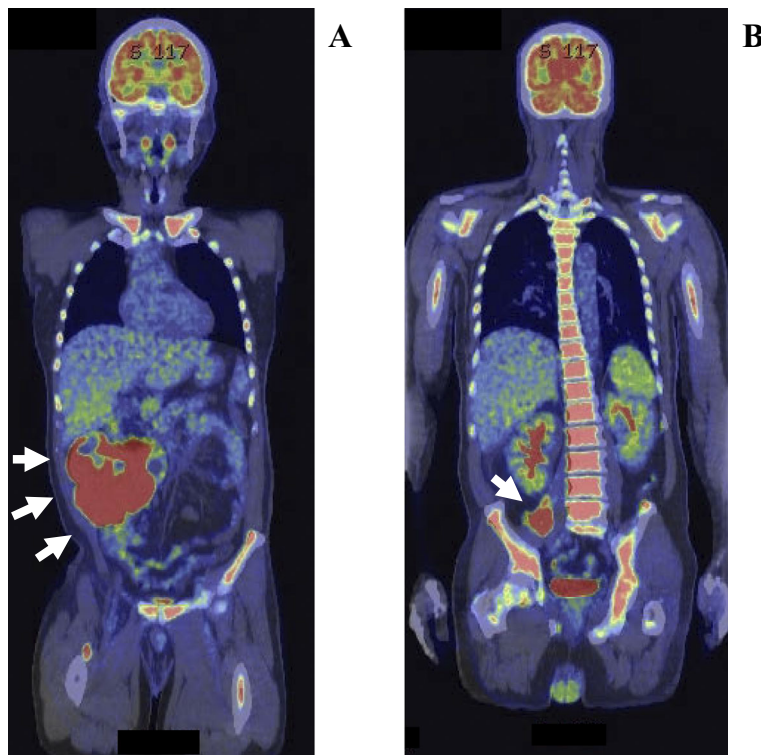


Figure 4. FDG-PET findings before the operation. A: A high uptake of FDG by the tumor in the ascending colon (white arrows). B: A high uptake of FDG by the tumor in the right iliopsoas muscle (white arrow) and a diffuse, low uptake of FDG in the bone marrow.

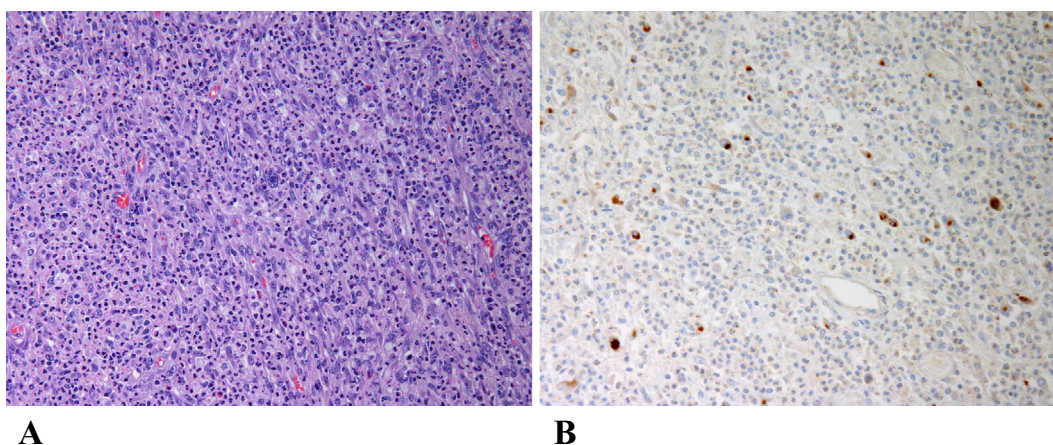


Figure 5. Histopathological findings of the resected specimen. **A:** Fibroblast-like spindle cells with many neutrophils (Hematoxylin and Eosin staining, $\times 200$). **B:** Tumor cells showing positivity for granulocyte colony-stimulating factor ($\times 200$).

Discussion

We encountered a case of G-CSF-producing UPS adjacent to the ascending colon and in the right iliopsoas muscle. The patient presented with a high-grade fever, and laboratory tests showed marked leukocytosis and severely elevated serum CRP levels. FDG-PET revealed the localized FDG uptake in both tumors and diffuse uptake in the systemic bone marrow. These inflammatory reactions were considered to have been caused by cytokines, such as serum G-CSF and IL-6 secreted by tumor cells, and they disappeared immediately after surgical resection.

MFH was first described by O'Brien and Stout in 1964 and it was the most common soft tissue sarcoma found in adults at that time (26). It consists of fibroblastic spindle cells, histiocytic round and polygonal cells, and unusual giant cells. Weiss et al. reported that this tumor most commonly occurred on an extremity (lower 49%, upper 19%) and in the abdominal cavity or retroperitoneum (16%) but rarely in the digestive tract (1). Recently, the classification of soft tissue sarcoma according to the line of differentiation rather than histogenesis has been considered. Therefore, MFH was re-classified as UPS by the World Health Organization in 2002 (23). This tumor did not have any of the typical diagnostic characteristics which could help in performing histological specific differentiation, and therefore an exclusion diagnosis was made by performing an immunohistochemical analysis.

UPS is classified as UPS, UPS with giant cells, and UPS with prominent inflammation.

Primary MFH/UPS of the large bowel is exceedingly rare. We reviewed a total of 23 reported cases of primary colorectal MFH/UPS, including our own case, published in the English literature and summarized the findings in the Table (2-22). The ratio of male to female patients was 19:4, with a median age of 62 years (range 12-80 years). The tumor originated from the cecum in three, ascending colon in

seven, transverse colon in four, descending colon in one, sigmoid colon in three, rectum in four, and anal canal in three, including two cases with multicentric tumors. Most of the tumors were large, ranging from 2 to 19 cm in diameter; their early detection was difficult. All of the patients, excluding one autopsy case, received surgical resection, four of whom received adjuvant chemotherapy, two radiotherapy, and one chemoradiotherapy. Synchronous metastasis was detected in the regional lymph nodes in three patients, the peritoneum in two, and the liver, lymph nodes, and peritoneum in one. Local recurrence was detected in three patients (local alone in one, local and lung in one, and local and liver in one) and lung and liver metastasis in one patient each. Local recurrence was most common in MFH/UPS of the large intestine; the tumors spread radially through the muscle, involving the surrounding structures. Seven cases were considered to be inflammatory MFH/UPS (2, 8, 12, 17, 19, 24).

Recently, inflammatory UPS has been reported to be correlated with the production of G-CSF by tumor cells (12). Furthermore, several studies have reported that G-CSF and IL-6 are produced by lung carcinoma (27). To our knowledge, this is the first study to report that G-CSF and IL-6 are produced by inflammatory UPS. IL-6 is known to play a role in stimulating the production of G-CSF (28). The elevated IL-6 level in previous reports might have contributed to the high-grade fever and elevated serum CRP level (29), and the elevated serum G-CSF level might have contributed to leukocytosis and hematopoietic activation (30). G-CSF-producing tumors are characterized by 1) an increased WBC count, predominantly neutrophils, in the absence of infectious and hematologic diseases; 2) an increased serum G-CSF level; 3) normalization of the WBC count and serum G-CSF level after removal of the tumor; and 4) the presence of G-CSF in the tumor tissue (31). In the present case, all of these criteria were fulfilled. FDG-PET imaging of patients with G-CSF-producing tumors has shown not only the elevated uptake of FDG by the primary tumors but also its dif-

Table. Reported Cases with Primary Malignant Fibrous Histiocytoma/Undifferentiated Pleomorphic Sarcoma of the Large Intestine.

| Reference | Age | Sex | Site | Size (cm) | Symptom | Inflammation | Cytokine | Therapy | Metastasis | Adjuvant therapy | Recurrence | Prognosis | |
|--------------|------|--------|-----------------------------|-----------------|--------------------------------------|-------------------------------|----------------------|-----------|-------------------------------|-------------------|-----------------|-------------|----------|
| 2 | 38 | Male | Rectum | 12 | loose bowel movement, abdominal pain | WBC 11,300, ESR 40 | | Operation | Lymph node | - | - | 2M Alive | |
| 3 | 74 | Male | Transverse | 8.5x5x5 | anorexia, diarrhea | - | | Operation | - | - | - | 1Y Alive | |
| 4 | 17 | Male | Transverse/ Rectosigmoid | 10, 8, 3x2 | abdominal pain, fever | - | | Operation | NS | - | NS | NS | |
| 5 | 68 | Male | Sigmoid | 7.5x6 | abdominal pain, fever | - | | Operation | - | - | Local | 9M Dead | |
| 6 | 60 | Male | Sigmoid | 7 | blood in stool | - | | Operation | Lymph node | Chemotherapy | Liver | 2Y4M Alive | |
| 7 | 52 | Female | Anorectal | 2x1.6x1 | blood in stool | - | | Operation | - | - | Local, Lung | 2Y Daed | |
| 8 | 73 | Male | Ascending | 15x7x4, 8x4x1 | anemia, anorexia | WBC 10,800 | | Operation | - | - | - | 6M Alive | |
| 9 | 62 | Male | Ascending/ Transverse | 17x10x8, 19x7x7 | palpable mass | - | | - | Peritoneum | - | - | NS | |
| 10 | 41 | Male | Anal canal | NS | palpable mass | - | | Operation | - | Radiation | - | 1Y4M Alive | |
| 11 | 62 | Female | Cecum | 2x1.8x1.1 | rectal bleeding | - | | Operation | - | - | - | 3M Alive | |
| 12 | 50 | Male | Ascending | 9.5x6x5 | abdominal fullness, anorexia | WBC 12,700, ESR 151, CRP 32.7 | G-CSF 78 | Operation | - | Chemotherapy | - | 10M Alive | |
| 13 | 12 | Male | Ascending | 3.5 | abdominal pain | - | | Operation | - | - | - | 1Y4M Alive | |
| 14 | 72 | Male | Transverse | 5x7 | periumbilical pain | - | | Operation | - | - | Local, Perineal | 4M Dead | |
| 15 | 50 | Female | Descending | 4.0x3.2 | abdominal pain, diarrhea | - | | Operation | - | Chemotherapy | - | 7Y Alive | |
| 16 | 64 | Male | Cecum | 4x5x3 | slightly tenderness | - | | Operation | Peritoneum | - | - | 9M Dead | |
| 17 | 47 | Male | Ascending | 7x5x4 | abdominal pain | WBC 10,400, CRP 2.21 | | Operation | - | - | - | 1Y1M Alive | |
| 18 | 55 | Male | Rectum | 4x2.5 | tennisism, perineal pain | - | | Operation | - | Chemoradiotherapy | - | 3Y10M Alive | |
| 19 | 66 | Male | Ascending | 14.5x8x4.5 | epigastralgia | WBC 10,900, CRP 7.74 | | Operation | - | - | - | 2Y9M Alive | |
| 20 | 73 | Male | Sigmoid | 3.2 | anemia | - | | Operation | - | - | - | 1Y10M Alive | |
| 21 | 70 | Male | Cecum | 12x10 | abdominal pain | - | | Operation | Lymph node, Liver, Peritoneum | - | Lung | 1M Dead | |
| 22 | 63 | Female | Anal canal | 1.7x1.3x0.3 | blood stool, anal mass | - | | Operation | - | Radiation | - | 1Y3M Alive | |
| 24 | 80 | Male | Rectum | 5x4x2.5 | rectal bleeding, fecal incontinency | ESR 45 | | Operation | - | - | - | NS | |
| Present case | 2018 | 50 | Male | Ascending | 19x14x10 | abdominal pain, numbness | WBC 40,100, CRP 21.3 | G-CSF 339 | Operation | - | Chemotherapy | - | 6M Alive |

NS: not stated, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein level

fuse uptake throughout the bone marrow. This FDG finding of bone marrow was thought to indicate that G-CSF-producing tumors enhanced bone marrow metabolism, potentially being useful for the diagnosis of G-CSF-producing tumors (32). In our case, the uptake of FDG was noted in both tumors and the systemic bone marrow, and this signal disappeared after resection of the tumors.

The strategy for treating MFH/UPS is early and complete excision with en-bloc regional lymph node dissection. It has been reported that this tumor in the extremities and limb girdles is not radiosensitive, but radiation therapy plays an important role in achieving local control, particularly in high-grade lesions or in cases with positive surgical margins (33). In the present case, radiation therapy was not performed because the resected margin was negative. Although the role of adjuvant chemotherapy in colorectal MFH/UPS is controversial, 3 patients treated by adjuvant chemotherapy survived for >10 months of follow-up (6, 12, 15). Inflammatory MFH/UPS has been reported to be aggressive with an ultimately fatal course, but four cases with either inoperable or recurrent inflammatory MFH have proven responsive to chemotherapy (34). Therefore, we considered that the present patient should receive adjuvant chemotherapy despite no signs of recurrence for six months after the operation.

In conclusion, although G-CSF-producing colorectal UPS is rare, the clinical condition of leukocytosis (especially of neutrophils), the elevated serum CRP level, and the uptake of FDG in the bone marrow may suggest this tumor type. Changes in these parameters may be useful as markers of tumor recurrence.

The authors state that they have no Conflict of Interest (COI).

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Intern Med 58: 2783-2789, 2019