Metastatic gastrointestinal stromal tumor and hypercalcemia in a patient with ulcerative colitis

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ABSTRACT

A 45-year-old man suffering from intermittent rectal bleeding was diagnosed with ulcerative colitis involving the descending colon and rectum. After 2 years on ulcerative colitis treatment, he presented with metastatic gastrointestinal tumor, liver and peritoneal spread, and a pelvic mass. Interestingly, he was found to have significant hypercalcemia. He was treated with Imatinib with significant symptomatic and clinical response.

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Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, but remain rare accounting for approximately 0.1-3% of all gastrointestinal neoplasms.[1] Most tumors (70%), occur in the stomach, and approximately 20-30% occur in the small intestine, but a small percentage of GISTs arise elsewhere in the GI tract, omentum, or retroperitoneum.[1,3] The identification of mutations in c-kit gene and the expression of the receptor tyrosine kinase CD 117 in GISTs, have resulted in better histopathological characterization and new therapeutic approaches.[2] Imatinib, is a competitive inhibitor of kit tyrosine kinase that has been demonstrated to be highly effective in the treatment of metastatic GIST.[2] We present a case of metastatic GIST and hypercalcemia in a patient affected with ulcerative colitis with subsequent significant response to treatment with Imatinib.

Case Report. A 45-year-old gentleman presented with a 6-month history of recurrent diarrhea and intermittent bleeding per rectum. Colonoscopic examination and biopsies revealed extensive colitis involving the rectum, and the left side of colon, and features of ulcerative colitis (**Figure 1**). He was started on prednisolone and salazopyrin; however, his illness was complicated with fissure in ano, perianal abscess, and pelvic abscess requiring surgical intervention. Two years after the initial diagnosis, he was referred to our service due to marked deterioration in his general condition over a period of 2 months, with frequent intermittent generalized abdominal pain, recurrent vomiting, loss of appetite, and significant weight loss associated with development of abdominal masses. On clinical examination, he was cachectic, pale, and mobilizing with difficulty. A firm tender hepatomegaly and 3 poorly defined firm tender masses in the left lower abdominal

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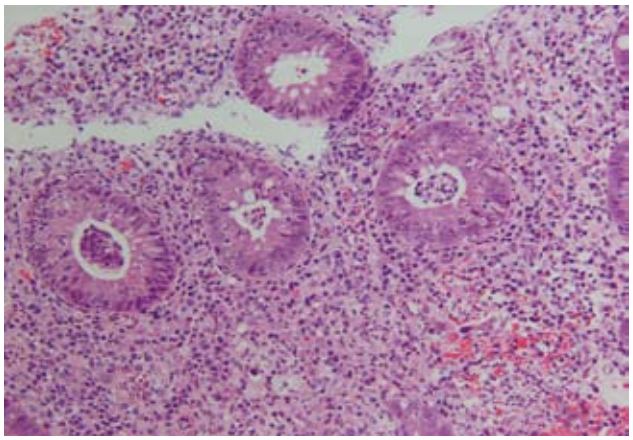

Figure 1 - Colonic mucosa shows crypt abscesses and inflammation of lamina propria with basal round cell infiltrate separating crypt from muscularis mucosae.

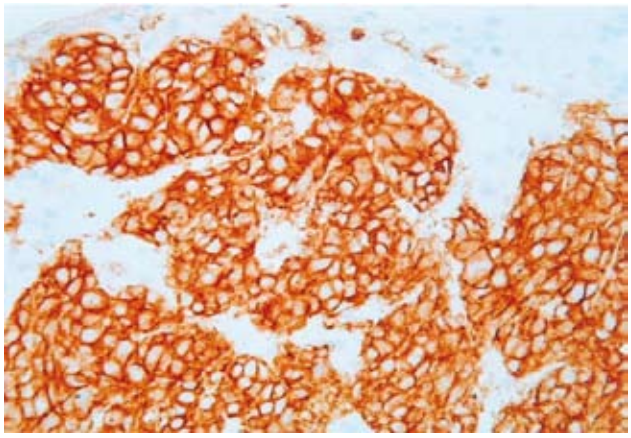

Figure 3 - A laparoscopic omental biopsy showing metastatic spindle shaped tumor with strongly positive CD117 staining.

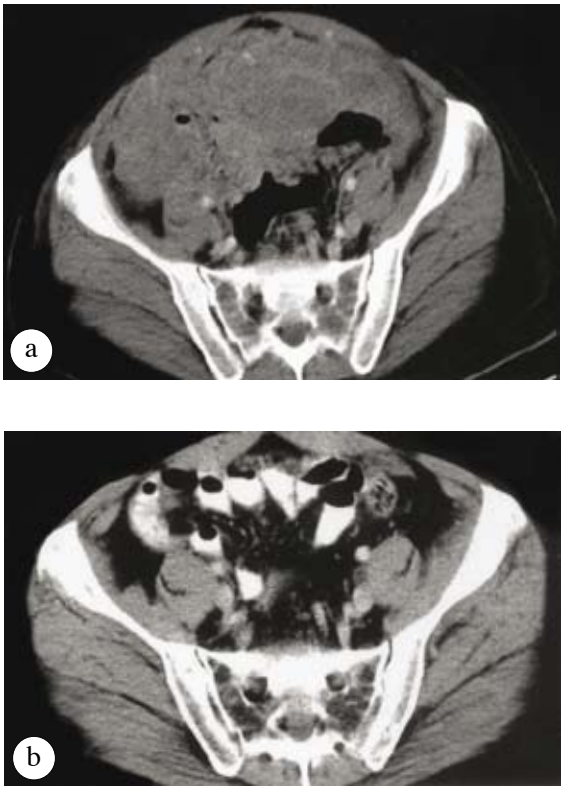

Figure 2 - Computerized tomographic scan of pelvis showing **a)** pelvic mass at time of diagnosis and **b)** a corresponding image showing significant response 24 weeks.

quadrant ranging in size between 3x5 cm to 4x6 cm were palpable. A CT scan of the abdomen and pelvis (**Figure 2**) showed multiple extensive hypodense lesions in both lobes of the liver; suggestive of liver metastases. There were extensive omental and peritoneal thickening associated with a large pelvic mass. A CT-guided liver biopsy and laparoscopic biopsy of peritoneal, and omental deposits, showed metastatic spindle cell tumor suggestive of malignant GIST (**Figure 3**). Immunohistochemically, the lesions were strongly positive for CD34 and CD117, and negative for cytokeratin with interspersed lesions with positivity for S100. His upper and lower gastrointestinal endoscopies showed normal mucosal surfaces. The other investigations showed significant hypoalbuminemia with albumin of 23 g/L, hypercalcemia with albumin corrected calcium of 3.02 mmol/l, and hypochromic microcytic anemia. His whole body ^{99}Tc methyl diphosphonate bone scintigraphy was normal.

In view of the metastatic GIST, he was started on Imatinib mesylate, 400 mg daily single dose. A gradual symptomatic and objective improvement was noted over the period of 12 weeks with significant improvement of performance status and softening, and shrinking of abdominal masses clinically. A follow up CT scan performed 24 weeks after the initiation of therapy showed a good radiological response (**Figure 2**). His hypercalcemia was treated with zoledronic acid (4 mg intravenous infusion over 15 minutes), and did not reoccur on follow up. His ulcerative colitis remained in

remission, but relapsed for 8 months after diagnosis of recurrent rectal bleeding. The inflammatory process involving the rectum and left side of the colon was biopsied during colonoscopy, and confirmed the reoccurrence of ulcerative colitis.

Discussion. The current case demonstrates the following observations: 1. The association between GIST and ulcerative colitis that has been described previously by a single case report with localized GIST, but not with such extensive metastases;[4] 2. The concomitant occurrence of hypercalcemia; 3. The good response to Imatinib with no major adverse effects on the natural course of his ulcerative colitis. Our patient presented with extensive liver and peritoneal cavity associated with a pelvic mass. Thus, he falls into the 10-30% of the malignant GIST category that behaves either with local invasion or distant metastasis, or both.[3,5] Usually, metastasis tends to occur in the liver, and within the peritoneal cavity, although, bony metastasis and metastasis to other visceral organs are also recognized.[3,5]

The biopsy proven ulcerative colitis involving the rectum and descending colon, preceded the diagnosis of metastatic GIST. The link between the GIST and ulcerative colitis is unclear; however, the progenitor interstitial cells of Cajal have been implicated.[6,7] The immunophenotypic (CD117 positive), and ultrastructural resemblance of GISTs to the interstitial cells of Cajal gastrointestinal pacemaker cells, which control gut motility, suggests a histogenesis from the latter cells.[6,7] It has been demonstrated that interstitial cells of Cajal, may undergo mutational changes in inflammatory bowel disease that may result in a malignant change.[8] Although in this particular case, it is difficult to ascertain where the GIST has risen from, due to the extensive metastasis and the normal colonoscopy at presentation. The presence of a large pelvic mass closely related to the rectal area, suggests that the tumor may have risen from the outer colorectal wall. This is particularly interesting, as several tumors, including adenocarcinoma and Kaposi sarcoma, complicate the natural course of inflammatory bowel disease.[4] It remains a postulate, whether the chronicity of the pre-existing inflammatory bowel disease besides the long-term exposure to steroids, and sulfasalazine may have favored the ground for an acquired c-Kit mutation.[4] The significant level of hypercalcemia without bony metastasis suggests an ectopic mechanism. Unfortunately, at the time of diagnosis, an ectopic cause could not be confirmed, due to unavailability of the parathyroid-hormone-related peptide assay in Oman. The prompt response and maintained remission to zoledronic acid, and Imatinib is particularly interesting.

In general, inoperable GISTs have demonstrated chemo and radio resistance. It has been demonstrated that 40-69% of inoperable and metastatic GISTs respond to targeted therapy using Imatinib, a synthetic tyrosine kinase inhibitor, which now has an established role in the management of chronic myeloid leukemia.[2] Chronic myeloid leukemia is characterized by a translocation between chromosomes 9 and 22, which produces a chimeric protein (BCR-ABL) with tyrosine kinase activity. Imatinib acts by occupying the kinase pocket of the BCR-ABL oncoprotein, preventing phosphorylation of its substrate. Imatinib is also effective against a number of other tyrosine kinases including c-kit and platelet derived growth factor.[2] Hence, irrespective of the underlying cause for such concomitant association between GIST and ulcerative colitis, he has responded remarkably well in treatment with Imatinib. Interestingly, the course of his inflammatory bowel disease remained unaltered by the treatment with Imatinib.

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