CLINICAL VIGNETTE

A Rare Gastrointestinal Cancer and the Use of Biological Agents Targeting Inflammation in Crohn's Disease

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A 57-year-old female had Crohn's disease since her mid-twenties. She had been on mesalamine and intermittent courses of glucocorticoids until age 55 when she developed progressive constipation and left lower quadrant abdominal pain. She had undergone a colonoscopy one year earlier which had not shown severe colon narrowing or cancer. She then attempted capsule endoscopy but could not pass the capsule. An MRI enterography of the abdomen and pelvis was attempted but stopped due to the retained capsule in the terminal ileum. She was referred to surgery for retrieval of the capsule and hemicolectomy for Crohn's bowel injury.

Her pre-operative labs included a normal complete blood count (CBC) with a normal hemoglobin (Hb) of 13.7 gm/dL and a normal comprehensive metabolic panel (CMP) with a creatinine of 0.90 mg/dL and an albumin of 4.2 gm/dL She underwent a right hemicolectomy and terminal ileum resection to remove the area with apparent luminal strictures and the retained capsule. Surprisingly pathology revealed a small bowel medullary cancer[1] with invasion into the muscularis propria (T2) and no evidence of lymph node involvement in 20 sampled lymph nodes (N0). The cancer was undifferentiated with loss of 2 mismatch repair proteins, MLH 1 and PMS 2.

She recovered uneventfully from surgery and received no adjuvant therapy. One year later, she began to have a flare in Crohn's symptoms of intermittent crampy abdominal pain and diarrhea and fatigue and weight loss. A CT of abdomen and pelvis was performed and was negative for cancer recurrence or other obvious bowel abnormalities. Her gastroenterologist recommended treatment with ustekinumab, a monoclonal antibody targeting interleukin 12 and 23,[2] based on efficacy in previously treated inflammatory bowel disease.[3] She presents to oncology discuss her risk of cancer recurrence if she were to receive ustekinumab.

Discussion

Crohn's disease is an inflammatory bowel disease (IBD), an autoimmune disorder characterized by transmural involvement of the small bowel and large bowel wall. This patient developed partial bowel obstruction due to progressive bowel wall injury which required urgent surgery. She was discovered to have an occult small bowel cancer in pathological review. Crohn's disease is associated with an increased risk of colorectal adenocarcinoma, with the relative risk influenced by the extent and duration of luminal injury.[4] While there is some variability in the estimate of increased colon cancer risk from longitudinal studies, there may be a 3% risk at 10 years and 8% risk at 30 years with Crohn's disease.[4] The standard of care recommends regular colonoscopic surveillance.

Medullary cancer of the bowel is a rare subtype of undifferentiated cancer characterized by different immune-histochemical markers, like loss of CDX2 & CK20 expression, and frequent microsatellite instability, particularly due to loss of MLH1 single stranded DNA repair protein by promoter hypermethylation.[1] While so rare that there are no randomized controlled clinical studies, medullary bowel cancer tends to have a good prognosis, since it is rarely metastatic at presentation.[1] Stage 1 T2 N0 medullary cancer has high likelihood of cure with surgery alone. There is no need for adjuvant therapy in Stage 1 cancer even with the more standard adenocarcinomas.

One year after her cancer was surgically removed, she developed a classic flare in her Crohn's disease prompting a need for additional therapy. Ustekinumab has proven efficacy even in patients treated with prior monoclonal antibodies targeting tumor necrosis factor (TNF) alpha, like infliximab or adalimumab.[3] However, there is a concern with a possible increased risk of malignancy with any biological therapy with monoclonal antibodies targeting inflammatory signaling molecules that are also involved in immune response. In clinical trials involving these agents there has been a slight increased risk of lymphoma with TNF inhibitors and possibly for colorectal adenocarcinoma.[5] The data is most limited with the newer biologics for IBD treatment including ustekinumab.[5] There is no reliable estimation for any increased risk of cancer recurrence after standard therapy for IBD patients receiving biologic therapy. With all approved therapies there are ongoing post marketing studies to allow for better assessment of long-term safety and efficacy.

I recommended proceeding with ustekinumab therapy given her excellent chance of cure with surgery alone and lack of evidence of increased relapse after standard cancer therapy. For more careful surveillance I recommended annual CT of abdomen and pelvis for 2 more years as is recommended for stage 3 colorectal cancer along with screening colonoscopies every 3-years.

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