CASE REPORT

Hodgkin's lymphoma rectosigmoid in a patient with ulcerative colitis on long-term azathioprine therapy

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SUMMARY

Hodgkin's lymphoma complicating chronic ulcerative colitis is extremely rare. We report a case of extranodal Hodgkin's lymphoma involving rectosigmoid in a patient of chronic ulcerative colitis on long-term azathioprine. A 67-year-old man presented with extensive ulcerative colitis, on follow-up since September 2005. He received long-term steroids, mesalamine and azathioprine. Serial surveillance colonoscopic examinations and colonic biopsies were performed. Surveillance colonoscopy performed 8 years after the onset of disease showed multiple deep ulcers and nodular masses involving the rectum and sigmoid colon. Histological examination of rectosigmoid biopsies showed classic Hodgkin's disease. Azathioprine was withdrawn. He received mechlorethamine, vincristine, procarbazine and prednisone (MOPP) chemotherapy protocol and was planned for total colectomy in follow-up. We believe patients with ulcerative colitis on long-term azathioprine should be on vigil for development of lymphomas by protocol surveillance colonoscopic examinations and biopsies. The risk of lymphoma in such patients is small and outweighs the benefits of long-term azathioprine therapy.

BACKGROUND

Inflammatory bowel disease is of global occurrence with considerable variation across the world. Ulcerative colitis (UC) and Crohn's disease has a high incidence in North America, Europe and Australia. However, the disease has a low incidence in Asia, Africa and Latin America.¹ In one study from India crude prevalence of inflammatory bowel disease was reported as 44.3/100 000 inhabitants and an incidence of 6.02 cases/100 000 inhabitants.² Patients with inflammatory bowel disease encounter a number of complications. These may be related to disease itself or concomitant drug therapy. Long-term pancolitis causes dysplasia. Such lesions are precursors to colorectal cancers.³ These dysplastic lesions can appear as flat or polypoid lesions. Flat dysplasia has a significant risk of progression, particularly for high-grade dysplasia. Polypoid dysplasia can present as sporadic adenoma, adenoma-like dysplastic lesions and atypical dysplasia-associated lesion/mass. The risk of colorectal cancer has been estimated to be 0.5–1%/year after 8–10 years of disease in patients with extensive UC. Long-term immunosuppression with azathioprine has been associated with haematopoietic malignancies.⁴

We report a case of extranodal Hodgkin's lymphoma limited to the rectosigmoid in a patient with chronic UC on long-term azathioprine therapy.

CASE PRESENTATION

A 67-year-old, North Indian man, presented to the clinic on 3 September 2005. Prior to onset of this illness he was in good health and denied history of hypertension, diabetes or thyroid disease. He presented with altered bowel habits with haematochezia of 6 months' duration. He passed 5–8 motions/day. The stool was liquid mixed with blood, mucus and pus. He had urgency, tenesmus and lower abdominal discomfort. He denied history of fever, weight loss, arthralgia or abdominal distension. Clinical examination was unremarkable except mild pallor. In September 2013, he presented with aggravation of symptoms, with frequent episodes of abdominal pain, tenesmus and urgency.

INVESTIGATIONS

Complete blood counts revealed haemoglobin of 8 g/dL (normal 13.8–17.2 g/dL), white cell count of $7.6 \times 10^9/L$ (normal $4-11 \times 10^9/L$) and platelet count of $300 \times 10^9/L$ (normal $150-400 \times 10^9/L$). Serum chemistry revealed normal liver and kidney function tests. Stool analysis did not reveal any parasites. Stool culture failed to reveal *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia*. Stool was negative for *Clostridium difficile* toxin A and B. Serology was negative for hepatitis B surface antigen, antihepatitis C virus and HIV 1 and 2, IgM cytomegalovirus (CMV) and CMV antigen.

Colonoscopy was performed which revealed findings suggestive of chronic ulcerative pancolitis with activity. There was no anorectal disease or fistulae. Colonic mucosa from rectum onwards until caecum revealed erythema, friability, granularity, mucosal haemorrhages and bleeding, ulcers and luminal exudate. Few inflammatory polyps were seen in the transverse and right colon. There was no cobblestoning, fissures, strictures or masses. Terminal ileum revealed erythema and congestion suggestive of backwash ileitis. Multiple biopsies were taken from ileum, right colon, proximal and distal transverse colon, left colon, sigmoid colon and rectum. Few polyps were removed for histological examination. Histological examination revealed mucosal glands with irregularity, goblet cell depletion, cryptitis and crypt abscesses. Lamina propria showed dense infiltrate by neutrophils, plasma cells and few eosinophils. All polyps revealed features of inflammatory polyps without dysplasia. An upper gastrointestinal endoscopy was normal, without any mucosal polyps. Video capsule endoscopy revealed normal jejunum and ileum without ulcers, strictures and polyps. Patient was started on wyselone 40 mg orally once daily

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Figure 1 Surveillance colonoscopy 2009. (A; Recto sigmoid) and (B; right colon mucosa) Features of acute exacerbation of chronic ulcerative colitis. Mucosa showed extensive erythema, granularity, mucosal haemorrhages and mucosal exudate. Lumen is compromised due to mucosal oedema. (B and D) Colonic biopsies revealing extensive chronic inflammatory infiltrate in the lamina propria with formation of lymphoid follicles. Cryptitis and crypt abscess also noted (arrow). There is marked crypt distortion and branching (curved arrow). No evidence of dysplasia or atypical cells. (H&E $\times 100$).

and mesalamine 800 mg orally three times daily. Over a 6-week period, his symptoms regressed and steroids were slowly tapered. However, he developed recurrence of symptoms after steroids were reduced to 7.5 mg/day. He was started on azathioprine 100 mg orally once daily and maintained with wyselone 7.5 mg and mesalamine 800 mg three times daily. He showed clinical, colonoscopic and histological remission over the next 3 months. He maintained a three monthly follow-up at the clinic. During his follow-up visits, he developed several relapses of the disease which were managed by enhancing dose of steroids. Azathioprine was continued throughout his follow-up. Surveillance colonoscopic examinations along with colonic biopsies were performed on a yearly basis and revealed findings consistent with UC with varying activity ([figure 1](#)). None of the biopsies had revealed dysplasia. He underwent a surveillance colonoscopy on 22 September 2013 which revealed

multiple large deep ulcers, nodules and polypoidal lesions involving the rectum and sigmoid colon ([figure 2](#)). Rest of the colon showed features of chronic UC in remission. Histological examination of the biopsies (along with immunohistochemistry) from rectosigmoid ulcers, nodules and polypoidal masses showed findings suggestive of Hodgkin's lymphoma classic type ([figure 3](#)). CT of the abdomen and pelvis with oral, rectal and intravenous contrast showed tumour limited to the rectum and sigmoid ([figure 4](#)). CT of the chest was normal. Bone marrow examination was normal.

TREATMENT

Azathioprine was withdrawn and he was started on chemotherapy with mechlorethamine, vincristine, procarbazine and prednisone (MOPP regimen). He underwent a total colectomy with ileostomy and had an uneventful postoperative course. The

Figure 2 Surveillance endoscopy September 2013. (A) Rectum at 5 cm. A large deep 5 cm ulcer with slough, nodularity and infiltration at the base is seen. (B) Rectum at 10 cm. Mucosa revealed ulceration, infiltration, nodularity and mucosal exudate. (C) Rectosigmoid at 15 cm. A large polypoidal mass with ulceration and mucosal slough is projecting in to the lumen. (D) Sigmoid at 20 cm. A large nodule with overlying ulceration is seen.

Figure 3 Colonic mucosal biopsy September 2013. (A) Sections showed sheets of mixed inflammatory infiltrate composed of lymphocytes, eosinophils, neutrophils and plasma cells. Large neoplastic cells with binucleate forms consistent with Reed-Sternberg cells (arrows) are also noted (H&E $\times 200$). (B) CD30 immunostain positive in Reed-Sternberg cells (arrows; $\times 200$). (C) CD15 immunostain positive in Reed-Sternberg cells (arrows; $\times 200$). (D) Cytokeratin immunostain negative in Reed-Sternberg cells ($\times 200$).

resected specimen showed disease limited to the rectosigmoid region.

OUTCOME AND FOLLOW-UP

The patient is clinically well and disease free in the follow-up.

DISCUSSION

Our patient had extensive UC of 8 years duration with multiple remissions of the disease. He was treated with steroids and mesalamine. Azathioprine was introduced very early in the disease as steroid sparing agent and also to maintain remission. Surveillance colonoscopy at 8 years of disease duration revealed extranodal Hodgkin's lymphoma involving the rectosigmoid region. The association of inflammatory bowel disease and development of haematopoietic neoplasms is unclear. Controversy exists whether there is an increased risk of development of lymphomas in inflammatory bowel disease. Over the past 9 years we have been following 252 patients with inflammatory bowel disease (137 UC and 15 Crohn's disease) and over a follow-up of 1134 patient-years have encountered two patients with colorectal cancer and one case of Hodgkin's disease in these patients (MSK unpublished data). Studies relying on cases at referral centres have found an increased risk of lymphomas, whereas population-based studies have not. The most likely explanation is either a referral bias or an increased risk confined to patients with more severe disease.⁴

The haematopoietic neoplasms associated with inflammatory bowel disease include non-Hodgkin's lymphomas and Hodgkin's lymphoma.¹ We searched the literature to find documented case reports and case series of lymphomas associated with inflammatory bowel disease. Of the 58 cases reported, 30 cases were of non-Hodgkin's lymphomas and 28 (10 nodal and 18 extranodal) were of Hodgkin's lymphoma. Crohn's disease was the underlying cause in 42 lymphomas (20 non-Hodgkin's lymphomas and 22 Hodgkin's lymphomas) and UC in 16 lymphomas (10 non-Hodgkin's lymphomas and 6 Hodgkin's lymphomas). Of the six cases of Hodgkin's lymphoma associated with UC, three had nodal disease while the other three had extranodal disease (two colon and one skin).⁵⁻⁷ These data suggest that association of UC with Hodgkin's disease is very rare, with only few published case reports in the literature.

Azathioprine therapy has an important role in the management of Crohn's disease and UC. Azathioprine is an inactive

Figure 4 CT of the abdomen and pelvis with oral, rectal and intravenous contrast showed irregular thickening of the rectum and distal sigmoid colon (arrows) with stranding of mesorectum and extra mesorectal fascia. There were few rectal and mesorectal lymph nodes. Fat planes with adjacent organs were maintained.

prodrug for thiopurines analogues. The thiopurines cause a reduction in the number of circulating natural killer cells.⁸ In addition, azathioprine has shown to activate Rac1 when costimulation of CD4T lymphocytes occurs via CD28, affecting apoptosis of the cells and diminishing the immune response.⁹ The question whether patients with inflammatory bowel disease who are treated with azathioprine are at increased risk of malignancy is unresolved. Azathioprine therapy given to patients after organ transplantation and other immune mediated conditions are associated with an excess of malignancies particularly non-Hodgkin's lymphoma.¹⁰ A number of studies carried out to define association between inflammatory bowel disease and lymphomas on azathioprine therapy have shown conflicting results. Hospital-based studies have shown a definite increased risk of lymphomas^{11–13}; whereas population-based studies failed to show such increased risk.^{14–16} Recent population-based cohort study showed a five times higher risk of lymphoproliferative disorder in patients exposed to thiopurines than in those not exposed to these drugs. Factors associated with increased risk of incident lymphoproliferative disorders included old age, male sex and longer duration of inflammatory bowel disease.¹⁷ Another prospective nationwide cohort-based study showed that patients with UC have a fourfold increase in risk of lymphoma while being treated with thiopurines compared with patients who have not been treated with thiopurines. The risk was seen to increase gradually with successive years of therapy; while, discontinuing azathioprine therapy reduces the risk of lymphoma.¹⁸ These data suggest that azathioprine therapy is associated with increased risk of lymphomas in patients with inflammatory bowel disease and a close vigilance needs to be kept on such patients by surveillance protocol colonoscopic examinations. While on that the risk of development of lymphomas in such patients is rather small and definitely outweighs the benefits of azathioprine in the management of such patients.

Learning points

- ▶ Patients with pancolitis need surveillance colonoscopy to pick up lesions that might be precursors of colonic malignancy.
- ▶ Haematopoietic malignancies are known to occur after long-term azathioprine therapy; rarely lymphomas may occur in colon as seen in this patient.
- ▶ Azathioprine is used as a steroid-sparing agent in patients with pancolitis as its use in such patients outweighs the adverse effects.

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Competing interests None.

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