CASE REPORT

Classical Enteropathy-Associated T-cell Lymphoma (EATL) Complicating A Crohn's Disease Patient on Thiopurine Monotherapy: A Case Report

Rozi NR[a], Jaafar KA[a], Kori AN[b], Che Aun A[b], M Salleh NH[c]*

[a]Kulliyyah of Medicine, International Islamic University Malaysia (IIUM), Kuantan, Pahang, Malaysia
[b]Department of Medicine, Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia
[c]Department of Pathology, Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia

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Corresponding Author
Dr Nur Raziana Binti Rozi
Department of Internal Medicine
International Islamic University Malaysia,
Jalan Sultan Ahmad Shah, 25200, Kuantan, Pahang, Malaysia
Email: razianarozi@iium.edu.my

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ABSTRACT

Thiopurine exposure from inflammatory bowel disease (IBD) treatment had been associated with a higher risk of lymphoproliferative disorders namely peripheral T-cell lymphoma, as early as 2 years after its initiation. We report a rare case of classical or type 1 enteropathy-associated T-cell lymphoma (EATL) with liver metastasis in a long-standing Crohn's disease 61-year-old patient treated with azathioprine monotherapy. He presented with acute, severe abdominal pain with cholestatic jaundice and pancytopenia. Colonoscopy showed multiple small, superficial ulcers at the terminal ileum and the biopsy taken was reported as classical EATL, an uncommon gastrointestinal non-Hodgkin's lymphoma with CD2, CD 3, CD 30 and CD 56 positivity and more than 90% Ki67 proliferative index. Computed tomography (CT) 3-phase liver scan suggested liver metastasis. This case highlights the unusual presentation of classical EATL in non-celiac disease patients and its risk association with thiopurine therapy in IBD.

INTRODUCTION

IBD primarily consists of ulcerative colitis and Crohn's disease which are both rare conditions in Asia.[1] It is an autoimmune, inflammatory condition mainly affecting the gastrointestinal tracts with several extra-intestinal manifestations. These include the skin, eyes, liver, kidney and musculoskeletal system.[2] Crohn's disease encompasses transmural inflammation of the gastrointestinal tract, commonly affecting the terminal ileum (80%). The clinical presentations are variable with relapsing symptoms which may occur years before diagnosis.[2]

Crohn's disease has been associated with the risk of malignancy. Yet, the relationship remains unclear. The complex relationship between this immune-mediated disease and malignancy is believed to arise from dysregulation of the immune response causing chronic inflammation which promotes malignancy.[3] A meta-analysis of 34 studies involving 60,122 patients in 2007 showed an increased risk of gastrointestinal malignancies as well as lymphoma among Crohn's disease patients. The overall relative risk of small bowel carcinoma was reported as 28.4 (95% confidence interval, 14.46–55.66) and 1.42 (95% confidence interval, 1.16–1.73) for lymphoma.[4] Another large study conducted in Taiwan to evaluate the risk of malignancy in Crohn's disease patients, which is also the first study in Asia, reported an increased risk of haematological malignancies, namely non-Hodgkin lymphoma and leukaemia.[3] However, the overall risk of cancer and that of colorectal cancer were rather not increased.[3] The data on population-based as well as site-specific studies in assessing the risk of cancer in IBD is scarce.[3]

Thiopurine treatment exposure in IBD has also been described to result in a higher incidence of lymphoproliferative disorders.[2,5,6]. The chance is reported to be higher in the combination therapy of thiopurine and anti-tumour necrosis factor (anti-TNF) for at least 2 years.[6,7] Hepatosplenic T cell lymphoma (HSTCL) is the

type of NHL that had been specifically reported in CD patients with thiopurine exposure.[6] Overall, there were 11 cases of HSTCL reported in patients receiving thiopurine monotherapy which were commonly attributable to young age less than 35 years male patients.[7] The prognosis is poor with the median survival described in previous cases of 7 to 8 months.[7]

In this article, we present a case of EATL which is a rare type of NHL and to our best knowledge, this is the first case of classical EATL in a Crohn's disease patient receiving thiopurine monotherapy.

CASE PRESENTATION

A 61-year-old gentleman had been diagnosed with Crohn's disease for 11 years with a history of right hemicolectomy in 2005. He was having a stable disease till April 2014 when he presented with relapsing episodes of abdominal pain and diarrhoea. A high dose of prednisolone and mesalazine were initiated for active Crohn's disease treatment. The colonoscopy findings were inflammatory mass at the anastomotic site with large surface ulcer and the biopsy taken showed chronic colitis with granulation tissue reaction. Faecal calprotectin level was 75 mg/g (normal range of <50 mg/g) which was slightly raised. He was initiated on azathioprine that was subsequently continued as the maintenance therapy of 150 to 200 mg daily dosage after remission was achieved. He was regularly followed up and his condition remained stable while on thiopurine therapy.

In 2017, he presented with an acute onset of abdominal pain and severe vomiting. No diarrhoea, fever or constitutional symptoms were reported. However, he was noted to be jaundiced. He then underwent a computed tomography (CT) 3 phase liver scan which showed multiple hypodense lesions bilaterally in both liver lobes on late arterial phase which were suggestive of metastatic lesions. Oesophagogastroduodenosocpy (OGDS) performed was unremarkable. Meanwhile, colonoscopy showed few small, superficial ulcers at the terminal ileum and several biopsies were taken.

Throughout the hospital admission, he was noted to have an increasing trend of conjugated hyperbilirubinaemia and C-reactive protein (CRP) levels. His transaminase enzymes levels were mildly elevated. The likelihood for the diagnosis of Crohn's disease flare was low at that point of time because of the negative colonoscopic findings. He was started on broad-spectrum antibiotic coverage to tackle the possibility of infection given his underlying immunocompromised state. Subsequently performed ERCP was also unremarkable. His hepatitis B and C screening tests were negative.

We were however alarmed by the worsening pancytopenia trend. The full blood picture revealed leucoerythroblastic anaemia, monocytosis with reactive lymphocytes but no abnormal cells. There was true thrombocytopenia with giant platelets seen. His serial blood investigation results are summarised in Table 1. The histopathological examination's result of his terminal ileal biopsy subsequently came back suggestive of enteropathy-associated T-cell lymphoma (EATL), of classical type. There was partial to complete effacement of lamina propria and submucosa by high-grade lymphoma cells which were predominantly large and markedly pleomorphic. The cells were expressing strong CD2+, CD3+, CD 30+ and high proliferative rate (Ki67 >90%). Weakly positive CD56+ and CD7+ cells were noted among the submucosal lymphoma cell population.

Our final diagnosis of this gentleman's condition was classical (Type 1) enteropathy-associated T-cell lymphoma (EATL) with liver metastasis. A diagnostic bone marrow examination was performed which did not show malignant infiltration. He then underwent chemotherapy (CHOP regimen; cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone). Despite the treatment, he clinically deteriorated after 90 days post -diagnosis due to severe sepsis with acute kidney injury.

DISCUSSION

Our case represents a rare complication of haematological malignancy in CD patients on thiopurine monotherapy.

Table 1: Blood investigation results

Date / Investigations	Baseline (February 2017)	7/4/17	9/4/17	11/4/17	12/4/17	13/4/17	17/4/17	21/4/17	25/4/17	27/4/17	2/5/17
Hb (g/dL)	13.9	17.0		12.8		12.5	9.5	7.4	7.5	7.0	5.3
TWC (X10^9/L)	4.75	6.2		11.4		11.2	10.0	3.5	2.3	1.4	2.1
Platelet (X10^9/L)	226.0	114.0		75.0		48.0	17.0	32.0	36.0	31.0	34.0
Total Bilirubin (µmol/L)	10.0	129.7	180.0	215.0	261.0	362.0	431.0	335.0	251.0	225.0	
ALP (IU/L)	100.0	394.0	375.0	340.0		334.0	447.0	240.0	188.0	175.0	
AST (IU/L)	14.0	193.0	184.0	190.0	199.0	148.0	107.0	98.0	71.0	67.0	
ALT (IU/L)	14.0	216.0	163.0	120.0	100.0	86.0	51.0	52.0	57.0	63.0	
Albumin (g/L)	43.0	43.0	34.0	25.0	24.0	31.0	27.0	23.0	20.0	19.0	
CRP (mg/L)		73.9		308.6	310.0		189.9			30.8	
ESR (mm/Hr)		41.0									
LDH (U/L)										1206.0	
Urea (mmol/L)						11.6	19.0	10.0		7.0	6.0
Sodium (mmol/L)						136.0	139.0	134.0		119.0	128.0
Potassium (mmol/L)						3.4	4.0	4.9		4.4	3.9
Creatinine (µmol/L)						121.0	112.0	98.0		90.0	72.0
AFP (ng/mL)				2.6							
CA 19-9 (U/mL)				57.0							
CEA (ng/mL)				1.0							

AFP-alpha fetoprotein, ALP-alkaline phosphatase, ALT-alanine aminotransferase, AST-aspartate aminotransferase, CA19-9-cancer antigen 19-9, CEA-carcinoembryonic antigen, CRP-C-reactive protein, ESR-erythrocyte sedimentation rate, Hb-haemoglobin, LDH-lactate dehydrogenase, TWC- total white count

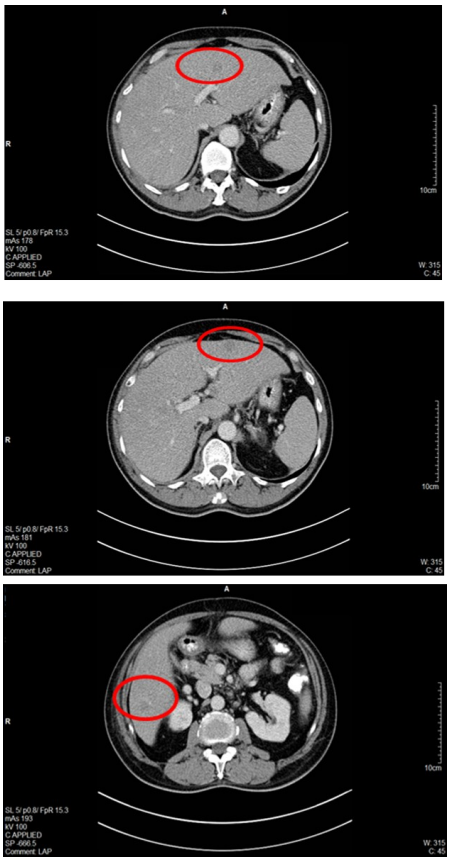

Figure 1: CT 3-phase liver scan demonstrating bilateral multiple hypodense lesions in both liver lobes on the late arterial phase.

This highlights the importance of a high level of suspicion for an early diagnosis and intervention. EATL is a rare malignancy that accounts for less than 1% of non -Hodgkin lymphoma (NHL).[8] Predominantly, it has been reported in areas such as Northern Europe, Italy, France and western parts of Ireland with a high incidence of celiac diseases.[8] In Northern Ireland for instance, the incidence was estimated at 0.10 per 100 000 person-years.[8] Studies had been reported on its association with celiac disease and therefore, adequate treatment of this condition prevents the occurrence of EATL.[9] EATL however, is never specifically reported in IBD-related haematological malignancies.

Figure 2: Terminal ileal tissue biopsy showing predominantly large and markedly pleomorphic neoplastic plasma cells.
A-residual small intestinal glands, B-neoplastic cells
Haematoxylin and eosin staining (magnification x40)

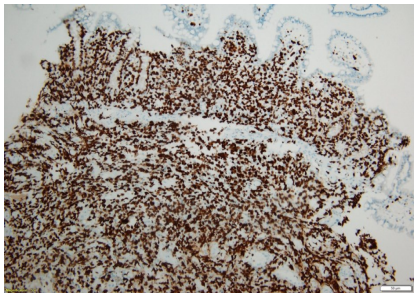

Figure 3: Terminal ileal biopsy showing high Ki-67 proliferative index (>90%).
Ki-67 staining (magnification x10).

It comprises two types; type 1 which is associated with celiac disease with a prevalence of 80 to 90%[9] while type 2 is characterised by its lack of association with gluten-sensitive enteropathy.[8] The 2016 revisions to the World Health Organization classification had renamed type 2 EATL to monomorphic epitheliotropic intestinal T cell lymphoma. Due to its distinctive nature and lack of association with celiac disease, it has been removed from EATL diagnostic category. Abdominal pain and systemic B symptoms are the predominant clinical manifestations and unfortunately, patients commonly present late. Bone marrow involvement has been reported in the disease, accounting for about 3%. In the majority of cases, it involves the small intestine as reported in an international series of 62 patients with EATL.[8] Dissemination to other organs including the liver and spleen is also common.[8] Histologically, many cases express pan-T antigens (surface CD7+) and the mucosal lymphoid antigen CD103. CD30 expression is positive in the large cell component of the tumour.[8]

This case report highlights the risk of lymphoproliferative disorders in IBD. This may arise either due to the disease's immune-mediated responses and chronic inflammation or the treatment used.[3] Thiopurine therapy, which has been the important maintenance drug in IBD, increases the risk of cancer by a variety of mechanisms.[10] These include direct DNA alteration, oncogenes activation, reduction in immunosurveillance of malignant cells and impairment of oncogenic viruses control.[10] Literature reviews have demonstrated the increased relative risk of cancer of 1.3 to 1.7, specifically lymphomas, myeloid disorders, and skin cancers in the setting of IBD.[10] It is difficult to determine if the thiopurine exposure may have caused lymphoma in this case independently. The combination of both underlying inflammatory disease and thiopurine, predisposing to lymphoproliferative disorder remains a likely possibility.

Nonetheless, the secondary cancer risk should be weighed against the proven benefits of thiopurine therapy in achieving mucosal healing and corticosteroid free clinical remission.[7] A recommendation to possibly limit treatment duration up to two years has been described in the recently published European Crohn's and Colitis Organisation guideline.[8] However, this has to be adjusted to several factors including extent and progress of the disease, remission duration, prior surgery as well as the history of malignancy.[7]

Although complications of EATL such as intestinal perforation and obstruction have been commonly described, our patient did not present with such. Previous cases also reported frequently a late presentation of the disease with dissemination to other organs. EATL is, unfortunately, an aggressive neoplasm that carries a poor prognosis and the median overall survival is 10 months with six months of failure-free survival.

CONCLUSION

While lymphoproliferative disorders have been reported in association with Crohn's disease and thiopurine monotherapy independently, it remains rare. Nonetheless, a low level of suspicion is imperative in early diagnosis and management. EATL, which is a rare type of non-Hodgkin lymphoma, had never been specifically described in association with thiopurine therapy in the setting of IBD. To our best knowledge, this is the first case to report classical EATL in a patient with non-celiac pathology.

Declaration of Conflicting Interests

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Patient consent

Informed consent has been obtained from the patient for publication of this case.

REFERENCES

1. Prideaux L, Kamm MA, De Cruz PP, Chan FKL, Ng SC. Inflammatory bowel disease in Asia: A

systematic review. *J Gastroenterol Hepatol.* 2012;27 (8):1266-1280. doi:10.1111/j.1440-1746.2012.07150.x

2. Peppercorn MA, Kane SV. Clinical manifestations, diagnosis and prognosis of Crohn disease in adults. In: UpToDate Gastroenterology [online]. Available at: https://www-uptodate-com. Accessed June 04, 2018
3. Wang L, Yang Y, Cheng W, Wang W, Lin S, Shieh C. Higher Risk for Hematological Malignancies in Inflammatory Bowel Disease : A Nationwide Population-based Study in Taiwan. 2016;111(9):1313 -1319. doi:10.1038/ajg.2016.239
4. von Roon AC, Reese G, Teare J, Constantinides V, Darzi AW, Tekkis PP. The Risk of Cancer in Patients with Crohn's Disease. *Dis Colon Rectum.* 2007;50(6):839-855. doi:10.1007/s10350-006-0848-z
5. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet.* 2009;374(9701):1617-1625. doi:10.1016/S0140-6736 (09)61302-7
6. Kotlyar DS, Osterman MT, Diamond RH, et al. A Systematic Review of Factors That Contribute to Hepatosplenic T-Cell Lymphoma in Patients With Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol.* 2011;9(1):36-41. doi:10.1016/ j.cgh.2010.09.016
7. Selvaraj SA, Chairez E, Wilson LM, Lazarev M, Bass EB, Hutfless S. Use of case reports and the Adverse Event Reporting System in systematic reviews: overcoming barriers to assess the link between Crohn's disease medications and hepatosplenic T-cell lymphoma. *Sys Review* 2013; 2: 53. doi:10.1186/2046-4053-2-53
8. Freedman AS, Aster JC. Clinical manifestations, pathologic features, and diagnosis of enteropathy-associated T cell lymphoma. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed June 04, 2018
9. Zhang JC, Wang Y, Wang XF, Zhang FX. Type I enteropathy-associated T-cell lymphoma in the colon of a 29-year-old patient and a brief literature review. *Onco Targets Ther.* 2016;9:863-868. doi:10.2147/ OTT.S96745
10. Axelrad JE, Roy A, Lawlor G, Korelitz B, Lichtiger S. Thiopurines and inflammatory bowel disease: Current evidence and a historical perspective. *World J Gastroenterol.* 2016;22(46):10103-10117. doi:10.3748/ wjg.v22.i46.10103