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Surgical management of monomorphic epitheliotropic intestinal t-cell lymphoma followed by chop and stem-cell transplant: A case report and review of the literature

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Abstract

BACKGROUND

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is a rare and rapidly progressive intestinal T-cell non-Hodgkin lymphoma associated with a very poor prognosis and a median survival of 7 mo. Advances in the identification of MEITL over the last two decades have led to its recognition as a separate entity. Predominant in male, MEITL patients typically present with vague and nonspecific symptoms and diagnosis is predominantly confirmed at laparotomy. Currently, there are no standardized treatment protocols, and the optimal therapy remains unclear.

CASE SUMMARY

We report a case of MEITL that was initially considered to be gastrointestinal stromal tumor (GIST) and Imatinib was administered for 1 cycle. The 62-year-old man presented with abdominal pain, abdominal distension and weight loss of 20 pounds. Within 2 wk, the size of the mass considerably increased on computed tomography scans. Our patient underwent surgery followed by chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and stem-cell transplant. Correct diagnosis of MEITL was established based on postoperative pathology. Immunophenotypically the neoplastic cells fulfilled the diagnostic criteria of MEITL as they were $CD3^+$, $CD4^+$, $CD8^+$, $CD56^+$, and $TIA\text{-}1^+$.

CONCLUSION

Given that MEITL has no predisposing factor and presents with vague symptoms with a rapid progression, the concomitant presence of abdominal symptoms and B symptoms (weight loss, fever, and night sweats) with hypoalbuminemia, anemia, low lymphocytic count and endoscopic findings of diffuse infiltrating type lesions should alert physicians to this rare disease especially when it comes to Asian patients. Immediate laparotomy should then be carried out followed by chemotherapy and stem cell transplant.

Key Words: Monomorphic epitheliotropic intestinal T-cell lymphoma; Gastrointestinal stromal tumor; Immunophenotypically; Chemotherapy; Stem-cell transplant; Case report

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Core Tip: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is a rare and rapidly progressive intestinal T-cell non-Hodgkin lymphoma. Currently, there is no standardized treatment or diagnostic protocols for MEITL. Chemotherapy followed by stem cell transplant post-operatively has shown promising results in terms of remission and progression free survival. Since MEITL is associated with a poor prognosis and high recurrence, it is crucial that the oncologist follow up and monitor any relapsing signs.

INTRODUCTION

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), formerly known as Enteropathy-associated T-cell lymphoma type II (EATL type II), is a rare non-Hodgkin primary lymphoma of the gastrointestinal tract arising from intraepithelial T cells[1].

Previously, EATL was recognized as a single entity of small intestinal lymphoma and was termed as enteropathy-type T-cell lymphoma. But in 2008, World Health Organization (WHO) classified the disease into 2 subtypes: (1) EATL type I, which comprises of 80%-90%; and (2) EATL type II, 10%-20% (a rather monomorphic variant)[2]. EATL accounted for 5.4% of all lymphomas based on an international survey[3].

However, post 2008 studies revealed noteworthy and remarkable clinical and pathological differences between the 2 types of lymphoma mentioned above. As a result, the WHO redefined these lymphomas as distinct and separate entities: Type I EATL was then termed as Enteropathy-associated T cell lymphoma and Type II, owing to its distinctive nature, was designated as MEITL[4]. The nomenclature and classification are illustrated in Figure 1.

The geographic distribution of the EATL and MEITL varies: EATL is seen more often in areas with a high prevalence of celiac disease (particularly Northern Europe) whereas MEITL has a broader geographic distribution and is seen in regions where celiac disease is rare, particularly in Asian countries[2,4]. The findings of a study conducted in Asia which included 38 cases of MEITL suggested that intestinal T-cell lymphomas might be merely MEITL in Asian patients[5].

A male predominance (ratio 2.6:1.0) has been observed in MEITL and the median age of onset is 58 years old with the small intestine as the most commonly involved site[6]. Upon consultation, MEITL patients typically present with vague and nonspecific symptoms such as abdominal pain, fatigue, weight loss, small bowel perforation, diarrhea, GI obstruction[2,5,7]. Low albumin, increased lactate dehydrogenase (LDH) and elevated C-Reactive protein (CRP) has been observed in most studies of MEITL cases[2,5].

Tumor cells expressing a monomorphic shape, an epitheliotropic pattern and $CD8^+$ $CD56^+$ are the diagnostic criteria for MEITL and serves to distinguish them from other types of T-cell lymphoma[8].

The vagueness of symptoms and/or lack of all symptoms at presentation can make the initial diagnosis of T cell lymphoma challenging in the primary care setting. In

addition, primary diagnosis of MEITL can be delayed until further investigation due to the similar symptoms/imaging manifestations of other GI cancers. Another challenge that may be encountered is intestinal obstruction and perforation. Thus, diagnosis is predominantly confirmed at laparotomy[9].

Herein, we present a case of MEITL, the treatment approach and follow up result. This case report and literature review will provide an up-to-date insight on the management of MEITL. Because of a relatively poor prognosis and a median survival of only 7 mo[5], weight loss, elevated LDH, CRP and low albumin should alert the physician especially when it comes to Asian patients. No standardized treatment is yet established for MEITL due to the rarity of the disease. However surgical resection followed by chemotherapy and/or autologous stems cell transplantation has been demonstrated to have better outcomes compared to surgery alone. In addition, new clinical trials using novel regimen of IVE/MTX (ifosfamide, vincristine, etoposide/methotrexate) followed by autologous stem cell transplant have proven to have significantly better outcomes with a 65% complete remission and 60% 5-year survival rate[10].

CASE PRESENTATION

Chief complaints

A 62-year-old man visited our hospital with a 2-mo history of abdominal pain and distension.

History of present illness

The patient had persistent epigastric pain half an hour after eating, which alleviated after a few hours. The patient's bowel habits varied between constipation and diarrhea. His symptoms gradually aggravated. He reported a weight loss of 20 pounds.

History of past illness

He has no history of other illnesses such as hypertension, diabetes or heart disease.

Interestingly, he had a full positron emission tomography (PET)/computed tomography (CT) scan in the previous year which revealed no abnormality, highlighting the rapid and aggressive progression of the disease.

At an outside hospital, he had a gastroscopy which showed chronic superficial gastritis and a colonoscopy which revealed multiple colorectal polyps and proctitis. Half a month later, he came to our hospital for further treatment and diagnosis.

Personal and family history

He had no significant personal and family history.

Physical examination

Physical abdominal examination revealed abdominal distension on inspection and decreased bowel sounds on auscultation. On palpation, a 15-cm mass could be felt. The mass had a clear boundary and an irregular shape. The abdomen was soft and deep palpation revealed left lower abdominal tenderness.

Laboratory examinations

Laboratory tests and blood workouts revealed an elevated C-reactive protein 163.5 mg/L, normal lactate dehydrogenase 180 IU/L, albumin 36.2 g/L, lymphocytic count 0.58% and hemoglobin 113 g/L. Other laboratory results are shown in Table 1. Tumor markers were all within normal range (Table 2).

Imaging examinations

The patient had 2 CT scans 2 wk apart at our hospital. An increase in the size of the mass was observed on the second CT scan, with significant necrosis (Figure 2). Reports estimated the size of the mass on the first and second CT scans to be approximately 85 mm × 74 mm × 107 mm and 113 mm × 97 mm × 146 mm respectively. Local mesenteric lymph nodes were enlarged.

FURTHER DIAGNOSTIC WORK-UP

He was consulted at the General Surgery department of our hospital and gastrointestinal stromal tumor (GIST) was initially considered due to the imaging presentation of the tumor (Figure 2) and the associated symptoms. Gleevec (Imatinib) was administered as empirical neoadjuvant targeting therapy. He had 5-8 times diarrhea/day after oral administration of Gleevec.

While the patient was on Gleevec, his symptoms further aggravated, with a higher accumulation of pelvic fluid accompanied with fever (maximum of 37.9). As intestinal perforation and peritonitis were suspected, the patient underwent emergency surgery in our department.

Postoperative immunohistochemistry findings revealed CD3 (+), CD20 (-), CD21 (residual FDC +), CD138 (-), Kappa (+), Lambda (+), Ki-67 (80%), CD117 (-), CD4 (+), CD5 (-), CD7 (+), CD8 (+), CD30 (-), CD10 (-), PD-1 (-), CK-PAN (-), GranzymeB (+), TIA-1 (+), CD56 (+) (Figure 3). EBER in situ hybridization for Epstein-Barr virus was negative. The results are listed in Table 3.

FINAL DIAGNOSIS

Based on post-operative immunohistochemistry findings, final diagnosis was validated as MEITL.

TREATMENT

The patient underwent surgery followed by chemotherapy and stem cell transplant.

Intraoperative findings

The size of the mass was estimated to be 15 cm × 14 cm × 10 cm and the margin was not clear. The texture was hard. Superficial purulent exudation was observed. The tumor had inflammatory adhesions with the mesentery of the small intestine, the descending colon and transverse colon. The relationship between the tumor and left psoas major

muscle and left ureter was unclear. Specimens were sent for pathology for further diagnosis after tumor resection.

OUTCOME AND FOLLOW-UP

After surgery and before systemic treatment, ^{18}F-fluorodeoxyglucose (FDG) PET/CT scan (Figure 4) revealed no remarkable abnormalities, no abnormal density focus and no significant increase or decrease in radioactivity uptake. There was no significant thickening and increase of radioactivity uptake in the anastomotic intestinal wall. The metabolism of FDG was increased in the middle abdomen subcutaneously. Several large lymph nodes were spotted in the left abdominal mesenteric area, the largest measuring 1.1 cm × 1.6 cm. The Standardized uptake value (SUV) of the left mesentery was 1.6. An increase in the metabolism of FDG was also noted in the ascending colon.

In addition, the patient underwent a bone marrow biopsy and the biopsy was without overt morphologic or flow cytometry evidence of T-cell lymphoma or metastatic malignancy (Figure 5).

A month after surgery, the patient was started on chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), scheduled for 4 cycles, every 3 wk. After chemotherapy, the patient had stem cell transplant. Between surgery and the first cycle of CHOP, the patient developed an itchy rash on his hands which subsequently alleviated after his first chemotherapy cycle.

Regarding the staging of MEITL, gastrointestinal lymphomas follow the Lugano staging system[11], which is tabulated in Table 4. Our patient was staged as IIE.

One and a half year after treatment, our patient is currently under complete remission.

DISCUSSION

Consistent with our patient, literature reported that the most common site of involvement is the small intestine, particularly the jejunum followed by the ileum and duodenum; rarely it could also involve the colon and stomach[12]. Metastasis to mesenteric lymph nodes is common[13]. Our patient had several enlarged mesenteric

lymph nodes, observed on CT but they were due to lymphoid hyperplasia rather than metastasis. Regarding imaging modalities, obstruction is not common in the small bowel. Multifocal involvement and perforation are more prevalent[14]. Necrosis, reported not to be usual in MEITL[6,8], was observed in our case (Figure 6).

The pattern of presenting symptoms greatly varied among previous studies with abdominal pain being the most common reported symptom. Our patient presented with a 2-mo history of abdominal pain, abdominal distension and weight loss. However abdominal pain has a wide range of diagnoses which can pose a great challenge in diagnosing MEITL upon clinical presentation. Weight loss, despite being regarded as a B symptoms, has not been found to be an exclusive symptom when it came to diagnosis of MEITL in Asian patients[5,6]. In contrast to classic EATL which can be suspected in sudden worsening of abdominal pain and diarrhea in a previously diagnosed celiac disease patient, MEITL has not been found to have any predisposing factor and was rather known to be sporadic. Clinically, diagnosis of MEITL is more challenging and delayed because of the low index of clinical suspicion and a vague inconsistent display of symptoms that can be easily confused with other malignancies[15-17].

Low albumin, elevated LDH, abnormally high C-reactive protein, low hemoglobin and abnormal lymphocyte count are common laboratory abnormalities detected[2,5,10,16]. Our patient had all the listed laboratory abnormalities except for a normal LDH.

In this case, post laparotomy and pathology reports, other malignancies such as poorly differentiated adenocarcinoma, B cell lymphoma and GIST were easily excluded because of the expression of monoclonal tumor cells expressing only T cell markers. In addition, negative staining of CD20[18,19] and CD117[20] excluded B cell lymphomas and GIST respectively. The positive staining of CD56 and CD8 Led to the diagnosis of MEITL and not the classical EATL form[2,3,9,21]. The panel of immunohistochemistry markers was consistent with MEITL. Epstein-Barr virus (EBV)-encoded RNA (EBER) by *in situ* hybridization was negative; thus, excluding the possibility of Natural Killer/T-cell lymphoma which most commonly presents as a facial mass, with a small percentage involving the GI tract[22,23].

Despite having been cited negative in several papers and studies for the occurrence of MEITL[17,24], CD4 was found be positive in our case. One of the largest multicenter studies of MEITL analyzed 38 patients where $CD4^+CD8^+$ was as low as 19%[5]. $CD4^+CD8^+$ however conclude the hypothesis of the cellular origin of MEITL, thus being type 'a' intestinal T-cell[6].

A literature review about the endoscopic findings of MEITL revealed a higher tendency of diffuse infiltrating type lesions compared to ulcerative and polypoid lesions. In a study of 9 MEITL patients[25], the endoscopic examination findings were: 6 (67%) diffuse infiltrating type lesions (colitis-like or proctocolitis-like); 2 (22%) polypoid type lesions; and 1 (11%) ulcerative type lesions. Another study of 15 MEITL[26] endoscopic findings showed 8 (53%) ulcero-infiltrative type lesions and 2 ulcerative type lesions.

Currently, there are no standardized treatment or diagnostic protocols for MEITL. Being a very rare entity, there exists very few trials and regimens in regards to MEITL, some having more promising results in eligible patients. Historically, MEITL has been treated with surgery, chemotherapy, autologous stem cell transplant or a combination. Several studies hypothesized that chemotherapy with or without surgery delivered better outcomes than surgery alone[21,27]. Moreover, different chemotherapy regimens have been investigated over the last decade[3,10,16,28], resulting in different prognosis (Table 5)[29-63].

Despite anthracycline-based regimens having better survival rates than those treated with other therapies or no therapy at all[3], Sieniawski *et al*[10] compared a novel regimen with anthracycline-based regimen. The novel regimen begins with 1 course of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), followed by 3 courses of IVE/MTX (ifosfamide, vincristine, etoposide alternating with intermediate-dose methotrexate). Autologous stem cell transplantation (ASCT) was then performed 3 wk after the last cycle of IVE/MTX. They found that the novel regimen had a better response (lower mortality and higher remission). Chiadamide combined with chemotherapy also slightly improved the survival time in 2 patients, with a mean

survival time of 16 mo[45]. The planned regimen for our patient was 4 cycles of CHOP every 3 wk, followed by stem cell transplant.

Given that (1) MEITL has no predisposing factor, (2) diagnosis of MEITL is predominantly made at laparotomy, (3) a bulky tumor, elevated serum LDH and CRP levels are risk factors significantly associated with a worse prognosis, and (4) MEITL has no standardized treatment; the concomitant presence of abdominal pain, systemic symptoms (weight loss, fever, and night sweating) together with laboratory parameters indicative for hypoalbuminemia, anemia (low hemoglobin), increased C-reactive protein and low lymphocytic count and endoscopic findings of diffuse infiltrating type lesions can be regarded as highly suspicious features of MEITL and should alert physicians to this rare disease and opt for immediate laparotomy.

Fluorine-2-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has been proven to be most useful diagnostic modality in the staging and follow-up for recurrence of aggressive lymphomas. The study of 12 MEITL cases[64] examined with PET concluded that MEITL is not restricted to the gut; many different anatomical sites were involved at presentation or at relapse with the infiltration of thoracic structures in 50% of the cases and central nervous system involvement in 25% of the cases. Our patient however had no abnormalities, no abnormal density focus and no significant increase or decrease in radioactivity uptake on his whole body ^{18}F-FDG PET scan after surgery and before his chemotherapy. The increase in metabolism of FDG in the middle abdomen subcutaneously is considered to be postoperative changes. Inflammation was considered for the increase in metabolism of FDG in the ascending colon. An increase in uptake of FDG is not distinct for malignancy; benign infectious and inflammatory processes as well as treatment-induced inflammatory changes can also account for an increase in FDG uptake[65]. In regards to uptake of FDG on PET scans in the setting of MEITL, clinicians must be careful as infectious and inflammatory processes can also lead to an increase.

As GIST was highly suspected as the primary diagnosis, no endoscopic biopsies was planned due to the risk of intraabdominal bleeding and tumor rupture (increasing risk

of dissemination and metastasis). However, after the mass was found to be significantly enlarged within 2 wk while on Gleevec, emergency surgery after acute abdomen (perforation and acute peritonitis) was performed and specimens were sent for pathology. This is consistent with previous studies, EATL and MEITL have been preponderantly diagnosed at laparotomy[16,21]. In the study by Sieniawski *et al*[21], 52 out of 57 patients underwent emergency laparotomy and Gale *et al*[16] reported that diagnosis was made at laparotomy in 25 out of 31 patients.

CONCLUSION

Understanding MEITL as an entity can be dismaying for both patients and physicians. Diagnosis should be correlated to clinical symptoms while the final diagnosis is mainly based on the pathological features and immunophenotypes. Since MEITL is associated with a poor prognosis and high recurrence, it is crucial that the oncologist follow up and monitor any relapsing signs. In the occurrence of a rapidly growing malignant tumor in the small intestine (otherwise not explained by any other pathologic processes), vague gastrointestinal symptoms, a poor suspicion of diagnosis due to lack of specific tests accompanied by elevated C-reactive protein, elevated LDH, hypoalbuminemia, anemia and low lymphocytic count, we suggest emergent laparotomy and specimens to be sent for pathology. Based on our case' relatively favorable prognosis and the literature review we conducted, surgical resection followed by chemotherapy and stem cell transplant lead towards a better prognosis and should be recommended as the standard treatment protocol.

Figure Legends

Figure 1 Evolution of the Classification of monomorphic epitheliotropic intestinal T-cell lymphoma.

Figure 2 Computed tomography. A: The first computed tomography (CT) scan; B: The second CT scan, 2 wk later. Multiple enlarged mesenteric lymph nodes and apparent necrosis on the second CT scan.

Figure 3 Pathologic and Immunohistochemistry findings. A and B: Low magnification (A) (× 40, H&E) and high magnification (B) (× 200, H&E) images of lymphocytes demonstrating an epitheliotropic pattern; C: The shape of the lymphoma cells is uniform throughout, emphasizing the monomorphism; D-H: The tumor cells were positive for (D) CD3, (E) CD8, (F) CD56, (G) GranzymeB and (H) TIA-1. (C-H, magnification × 200).

Figure 4 Post-operative positron emission tomography scan.

Figure 5 A (approximately 22.06% of non-erythroid cells) mature lymphocyte population (mainly T cells, a small amount of B and NK cells).

Figure 6 Computed tomography. Red arrow: Enlarged mesenteric lymph nodes; double headed-arrow: Necrosis.

Table 1 Patient's Laboratory results of blood chemistry

Items	Results	Reference value
White cell count (× 10^9/L)	7.8	3.5-9.5
Neutrophils (%)	88.2	40.0-75.0
Eosinophils (%)	0.6	0.4-0.8
Basophils (%)	0.3	0.0-1.0
Lymphocyte (%)	0.58	1.10-3.20
Monocyte (%)	0.28	0.10-0.60
Red blood cell count (× 10^{12}/L)	3.87	4.30-5.80
Hemoglobin (g/L)	113	130-175
Mean corpuscular volume (fL)	88.6	82.0-100.0
Platelet count (× 10^9/L)	380	125-350
Hematocrit (%)	0.34	0.11-0.28
Lactate dehydrogenase (IU/L)	180	120-250
C-reactive protein (mg/L)	163.5	< 6.0
Direct bilirubin (umol/L)	2.7	0.0-4.0
Indirect bilirubin (umol/L)	7.90	0.00-22.00
Creatine kinase (U/L)	45	50-310
Total protein (g/L)	67.7	65.0-85.0
Albumin (g/L)	36.2	40.0-55.0
Globulin (g/L)	31.4	25.0-35.0
Glucose (mmol/L)	6.34	4.30-5.90

Table 2 Tumor markers

Marker	Results	Reference value
CA211	1.05	0.0-3.3
SCC	1.08	0.0-1.5
CA724	1.36	0.0-6.9
CA242	4.89	0.0-20.0
CA125	31.51	< 35.0
CA-153	12.87	< 25.0
CEA	1.97	0.0-5.0
CA19-9	18.57	< 37.0

Table 3 Panel of Immunohistochemical stains

IHC stain	Result
CD3	+
CD4	+
CD5	-
CD7	+
CD8	+
CD30	-
CD56	+
CD117	-
CD138	-
Ki-67	80%
Kappa	+
Lambda	+
PD-1	-
CK-PAN	-
TIA-1	+
Granzyme B	+
EBER ISH	-

IHC: Immunohistochemistry; EBER: Epstein-Barr virus-encoded RNA.

Table 4 The lugano staging system

Stage		Features
I		Tumor confined to small bowel: Single or multiple primary lesions
II	II	Para-intestinal nodal involvement
	II-1	Involving mesenteric, aortic, caval, pelvic or inguinal nodes
	II-2	With penetration of serosa involving adjacent organs or tissues
	E (IIE, II-1E, II-2E)	Tumor extending into abdomen from primary small bowel site
III		NO stage III
IV		Disseminated extranodal sites or supra-diaphragmatic nodal involvement

Table 5 Details of previously published case reports

Case	Gender/age	Chief complaint	Treatment	Prognosis
Chen[29]	M/60	Abdominal pain	Emergency Surgery followed by CHOP + IVE/MTX + SCT, followed by ASCT	CR; liver recurrence 2.5 years later refractory to GDP regimen. Passed away 2 wk after recurrence
Ishibashi[30]	M/60	Diarrhea and 10 kg weight loss in 17 mo	CHASE followed by SCT	3 years
	F/40	Diarrhea and 6 kg weight loss in 3 mo	THP-COP followed by surgery 10m later	2 mo after surgery
	F/50	Abdominal distension	CHOP + High-dose MTX + SCT	9 mo
	M/70	Nausea	SMILE	9 mo
Aiempanakit[31]	M/67	Diarrhea for 4 months and 15 kg weight loss over 3 mo	Anthracycline-based regimen	2 mo
Antoniadu[32]	M/76	Severe dyspnea	N/A	5 d
Aoyama[33]	M/85	Fever and diarrhea	CHOP followed by DeVIC	Not stated but deceased subsequently due to progressive disease
Pan[34]	F/67	Abdominal pain	1 cycle of CEOP	3.7 mo
Liu[35]	F/48	Abdominal pain,	Unspecified chemo	1 mo after

		distension, vomiting, watery diarrhea, weight loss		chemotherapy initiation
Ozaka[36]	F/68	Melena and mild anemia	8 cycles of CHOP	Achieved complete remission and was still alive at the time of publication (68 mo after diagnosis)
Kasinathan[37]	F/70	Abdominal pain and vomiting for 4 wk	2 cycles of CHOP, followed by 2 cycles of GDP	Developed gastrointestinal bleeding and succumbed 4 wk after initiation of GDP
Mago[38]	M/59	SOB for 1 mo, abdominal distension for 2 wk	1 cycle of CHOEP	Passed away within few days after tumor lysis syndrome
Nato[39]	F/43	Abdominal distension, 2 mo' history of early satiety and nausea	4 cycles of GDP achieving a PR, CR was achieved after CBT conditioned with total body irradiation, cyclophosphamide, and cytarabine	Cogntive impairement (7 mo post transplantation) was improved after 3 cycles of MPV and whole

			brain radiotherapy and passed away 6 mo later	
Pan[40]	M/63	Diffuse abdominal pain for 1 mo	Emergency surgery followed by 2 cycles of CHOP	2 mo
	M/47	Diarrhea, dyspnea, orthopnea, weight loss for 1 year	1 dose of L-asparaginase, etoposide, and decadron regimen followed by emergency surgery, adjuvant chemo included etoposide, methylprednisolone, high-dose cytarabine, and cisplatin	9 mo
Umino[41]	M/41	Diarrhea and epigastric pain for 1 mo	3 neoadjuvant cycles of ICE followed by Autologous SCT	13 mo
Ferran[42]	F/45	Cutaneous lesions followed by abdominal perforation after chemotherapy initiation	6 neoadjuvant cycles of CHOP and 1 cycle of SMILE followed by surgery. 1 Adjuvant cycle L-GEMOX	8 mo
Aoki[43]	F/77	Abdominal	EPOCH for 6 months	Still alive 1 year

		discomfort, night sweats and fever for 1 mo		after diagnosis
Soardo[44]	M/65	2-wk history of weight gain, increased abdominal volume with progressive mild dyspnea, and fever in the last 2 d	Emergency laparotomy	1 mo post operatively
Liu[45]	M/61	Upper abdominal pain and black stool for 2 mo	Partial excision of small intestine and chidamide-based combination regimen	15 mo
	F/35	Abdominal distension for 1 mo	Sigmoid colostomy followed by chidamide-based combination therapy	17 mo
Samuel[46]	M/62	Hypovolemic shock secondary to severe chronic diarrhea and 100 pounds lost over a year	Forwent chemotherapy	1 mo
Ikeda[47]	M/61	3 episodes of ileal strangulation within 4 mo of gastrectomy	Ileal resection followed by 2 cycles of CHOP and 1 cycle of ICE	3 mo
Lenti[48]	F/63	Diarrhea and 10 kg	Surgery followed by a	27 mo

		weight loss in 6 mo	single course of CHOP	
	M/58	Diarrhea and 5 kg weight loss	Surgery	4 mo
Broccoli[49]	M/65	Petechiae at both limbs, Acute abdominal pain, diarrhea and clinical signs of bowel perforation	Emergency resection of 9 cm of small bowel	6 mo
Tabata[49]	M/72	Ileum perforation…severe constipation after 21 mo in CR	Emergency resection followed by anthracycline based regimen chemotherapy (CR for 21 mo), paltrexate therapy was administered during recurrence	Currently in CR after 52 mo
Fisher[50]	F/60	Abdominal pain, diarrhea and 30 lbs weight loss over 3 mo	EOCH chemotherapy (subsequently developing a large lymphoma 6 mo after therapy initiation)	N/A
Tian[8]	M/58	Abdominal pain, diarrhea and weight loss over 3 mo	1 course of CHOP	Died subsequently after the first cycle due to bone

				marrow suppression
	F/64	Abdominal pain and diarrhea for 5 years	5 wk of adjuvant chemotherapy consisting of romidepsin with Revlimid followed by laparotomy involving small bowel bypass	3 mo
Kubota[51]	M/41	Diarrhea for 1 mo and intermittent abdominal pain	Resection followed by CHOP and 3 cycles of ICE resulted in CR	Repeated intrathecal chemotherapy and high-dose chemotherapy followed by ASCT achieved CR
Gentille[52]	F/70	Intermittent abdominal pain, nausea, vomiting and diarrhea for 14 mo. 50 lbs weight loss	Right hemicolectomy followed by 5 cycles of EPOCH (with PEG-asparaginase added in the last cycle)	Developed abdominal pain 15 mo after initial therapy, subsequently passing away around 20 mo after initial diagnosis
Sato[53]	F/52	Diarrhea and anorexia for 8 wk + 6	CHOP followed by stem cell transplant	Unknown

		kg weight loss		
Kakugawa[54]	M/65	Watery diarrhea for 14 mo	8 cycles of CHOP followed by 5 cycles of ESHAP	Still alive 67 mo post chemotherapy
Felipe-Silva[55]	M/78	Diarrhea for 2 months + 20 kg weight loss	Surgical resection followed by 2 cycles of CHOP, which was changed to COP	6 mo
Okumura[56]	F/66	Abdominal distension for 1 mo presenting with acute abdomen	Surgical resection followed by high dose chemotherapy and stem cell transplant	Still alive at the time of publication, in complete remission
Yang[57]	M/39	Acute onset of lower abdominal pain and diffuse peritonitis	Surgical resection	Unknown
Fukushima[58]	M/60	Severe diarrhea	CHOP	1 year
Liong[59]	M/50	Diarrhea for 6 mo, presenting with acute abdomen due to intestinal perforation	Surgical resection followed by CHOP	4 mo
Noh[60]	M/68	Nausea and vomiting for 6 mo + 25 kg weight loss	Surgical resection followed by chemotherapy (unspecified)	Unknown
Hashimoto[61]	M/64	Diarrhea for several mo	Chemotherapy (unspecified)	Unknown
Liu[62]	F/43	Upper abdominal	4 cycles of CHOEP	11 mo after

		pain and weight loss for 3 mo	and 2 cycles of DHAP followed by surgery	diagnosis, 1 d after surgery due to septic shock	
Fukushima[63]	F/68	Upper abdominal pain and nausea	Laparoscopic intestinal resection followed by auto-peripheral blood SCT	22 mo without recurrence; passed away 1 mo after duodenal recurrence in 23rd mo	

M: Male; F: Female; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisolone; IVE: Ifosfamide, vincristine, and etoposide; MTX: Methotrexate; SCT: Stem cell transplant; CHASE: Cyclophosphamide, cytarabine, etoposide, dexamethasone; GDP: Gemcitabine, dexamethasone and cisplatin; THP-COP: Pirarubicin, cyclophosphamide, vincristine and prednisolone; SMILE: Dexamethasone, methotrexate, ifosfamide, L-asparaginase and etoposide; DeVIC: Etoposide, ifosfamide, and carboplatin; CEOP: Cyclophosphamide, epirubicin, vincristine, and prednisolone; SOB: Shortness of breath; CHOEP: Cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; PR: partial response; CR: Complete response; CBT: Cord blood transplantation; MPV: Methotrexate, procarbazine, vincristine; ICE: Ifosfamide, carboplatin, and etoposide; L-GEMOX: Gemcitabine, oxaliplatin, asparaginase, dexamethasone; EPOCH: Etoposide, prednisolone, oncovin, cyclophosphamide, hydroxydaunorubicin; ICE: Ifosfamide, carboplatin and etoposide; ESHAP: Etoposide, methylprednisolone, cytarabine, cisplatin; DHAP: Dexamethasone, high dose cytarabine, platinol.

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