Pegylated liposomal doxorubicin (PLD)-containing regimen as a novel treatment of monomorphic epithelial intestinal T-cell lymphoma (MEITL)

A case report and review of literature

Yue Chen, MDa, Hongzhi Xu, PhDab, Ningning Shan, PhDab, Huiting Qu, PhDab,*

Abstract

Introduction: Monomorphic intestinal T-cell lymphoma (MEITL) is a rare, aggressive peripheral T-cell lymphoma that arises from intestinal epithelial lymphocytes. Currently, MEITL lacks standard treatment options. Under the current treatment regimen, the median survival time for patients is only 7 months. Chemotherapy followed by hematopoietic stem cell transplantation may improve patient outcomes. New anti-lymphoma drugs, including chidamide and PEG-asparaginase, are being tested against MEITL. To our knowledge, there are currently no data on the pegylated liposomal doxorubicin (PLD) regimen for MEITL therapy. Patient concerns, diagnosis and interventions: We report the case of a 54-year-old patient diagnosed with MEITL who presented with abdominal pain and was treated with a cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide regimen containing PLD.

Outcomes: After 15 months of follow-up, the patient is currently alive and disease free. The application of doxorubicin liposomes in chemotherapy regimens may be a new way to treat MEITL.

Review: We searched the literature on MEITL and selected 52 case reports. We summarized the clinical characteristics and treatment of 53 patients (including the current patient).

Conclusion: It highlights 2 important clinical findings. First, for patients with MEITL treated with the cyclophosphamide, doxorubicin, vincristine, prednisone, etoposide regimen, PLD has fewer adverse reactions and better long-term survival than doxorubicin. Second, an early diagnosis is necessary for prompt treatment. We believe that this manuscript will be valuable to all the researchers who are interested in.

Abbreviations: CHOP = cyclophosphamide, vincristine, doxorubicin, and prednisone, CHOPE = cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide, CR = complete remission, CT = computed tomography, MEITL = monomorphic intestinal T-cell lymphoma, PLD = the pegylated liposomal doxorubicin, WHO = World Health Organization.

Keywords: MEITL, Diagnosis, Treatment, Pegylated Liposomal Doxorubicin

1. Introduction

Monomorphic intestinal T-cell lymphoma (MEITL) is a malignant tumor of extra nodal lymphoid tissue caused by proliferation of intraepithelial lymphocytes. MEITL is a relatively rare disease previously known as type II of Enteropathy-associated T-cell lymphoma, accounting for approximately 5% of gastrointestinal lymphomas and less than 1% of all non-Hodgkin lymphomas. MEITL has been independently identified as a subtype of lymphoma by the World Health Organization (WHO) since 2017. MEITL currently lacks a standard treatment regimen, and usually follows the cyclophosphamide, doxorubicin, vincristine, prednisone (CHOPE) regimen for T-cell lymphoma. However, the curative effect of current chemotherapy is not good. After chemotherapy, the median survival time is only 7 months. Hematopoietic stem cell transplantation may improve outcomes in patients with MEITL. In addition, new drugs including Chidamide and PEG-Asparaginase are in clinical trials for MEITL. Here, we introduce a case of MEITL patients treated with CHOPE regimen using doxorubicin liposome instead of doxorubicin.
A previously healthy 54-year-old male patient, presented with the upper abdominal pain for 1 month and the weight loss of about 10 kg for 6 months. He denied night sweat, fever and denied any tobacco or alcohol use. His family history was not notable. Initial vital signs at the physical examination were as follows: blood pressure, 105/65 mm Hg; heart rate, 76 beats/minute; respiratory 19 times/minute. The abdomen was soft, no obvious mass was touched on the abdomen, no swollen lymph nodes were touched, mild tenderness in the upper abdomen, no rebound pain.

Laboratory Examination showed no obvious abnormalities. X-ray of the thorax and lymph node sonography were unremarkable. Abdominal computed tomography (CT) with enhancement showed uneven thickening with the small bowel (Fig. 1A–F). The patient underwent an open small intestinal partial, transverse partial resection. These lesions were biopsied. An extensive lymphocytic infiltrate of atypical was observed in the biopsies from the small intestine and transverse colon with invasive growth and infiltration into the whole intestinal layer. The intestines adjacent to the tumor were without lymphocytic infiltrate abnormalities and so did the peripheral lymph nodes. Histopathologic examination of the tumor revealed sheets of relatively monotonous medium-sized cells with round or irregular nuclei, intensely concentrated chromatin and rim of pale cytoplasm. The tumor cells were positive for CD20, CD3 and CD43. But it is negative for CD5, CD10, PAX-5, MUM1, and BCL6. Ki-67 demonstrated a high proliferation index of 40% to 50%. In situ hybridization for Epstein–Barr virus remained negative. Positron emission computed tomography showed postoperative intestinal lymphoma, and no abnormal radioactive distribution was found at the anastomosis of intestinal lymphoma operation. Cord shadow can be seen under the skin of the abdominal wall operation area, with slightly high radiation distribution, and the highest SUV is 1.5 (Fig. 2A–J). The clinical findings, morphologic appearance as well as the immunohistochemistry staining pattern were consistent with the diagnosis of MEITL. Bone marrow aspiration and biopsy did not show any evidence of lymphoma. The patient was diagnosed as MEITL in Ann Arbor stage IV.

The patient with MEITL were treated with the pegylated liposomal doxorubicin (PLD) containing CHOPE regimen consisting of an intravenous administration of Cyclophosphamide (750 mg/m²), Liposomal doxorubicin (35 mg/m²), and Vincristine (1.4 mg/m²) on d1, an oral administration of Prednisolone (60 mg/m²) on d1–5, as well as an intravenous administration of Etoposide (50 mg/m²) on d1–3. The treatment with PLD 35 mg/m² was initiated in April 2021 and performed every 3 weeks, and a total of 5 cycles was performed. Interim assessment was done after 3 cycles of CHOPE regimen. His bellyache subsided significantly after completion at interim assessment. Abdominal CT scan after 3 cycles of CHOPE showed no evidence of lymphoma. No enlarged lymph nodes on physical examination and ultrasonic instrument were observed. He achieved complete remission (CR) after 3 full cycles of CHOPE therapy containing PLD. Because of these impressive results, the patient continued the 2-cycle CHOPE regimen consolidation therapy. Monitored by regular laboratory investigations and electrocardiography, adverse reactions were not observed after chemotherapy drugs including PLD therapy. There were no serious chemotherapy-related adverse events, except nausea and vomiting. After 5 cycles of CHOPE regimen, which were well tolerated without grade 3 or 4 toxicities, no further deterioration of disease had been measured. And this is different from the regimen containing doxorubicin. In December 2021, the patient was followed up regularly after discharge, and no lymphoma progression was found. The median overall survival of patients receiving anthracycline-containing chemotherapy was 7 months. The last follow-up was accomplished by telephone in May 2022. The patient has been in CR for 15 months after the initial diagnosis.

We performed a literature review of previous MEITL cases using the search terms “MEITL”, “type II of enteropathy associated T-cell lymphoma” and “intestinal lymphoma”. We performed a retrospective review of MEITL from January 2016 to June 2021 and identified 52 cases of MEITL with relatively detailed medical history reported in the English literature to date. The clinical characteristics and treatment of 53 patients (including the current patient) are summarized in Table 1.[3-32] Patients ranged in age from 35 to 88 years, and 71.7% were male. Among the reported cases, the main symptoms were abdominal pain.
MEITL occurs at a wide range of ages with a median age of 58 years and with a male to female ratio of 2:1. MEITL is an aggressive lymphoma that involves not only the gastrointestinal tract, but also extensive systemic involvement, and there are case reports of brain involvement. It is generally believed that patients with MEITL do not have celiac disease, but there are also reports in the literature that celiac disease is not a specific sign to identify MEITL. Patients with MEITL lack specific endoscopic findings, so diagnosis relies on pathological diagnosis and immunohistochemistry. The prognosis of MEITL is poor with a previously reported median overall survival of only 7 months and 1-year overall survival is only 36%.

Doxorubicin, an anthracycline antitumor agent, is widely used in the treatment of malignant tumors such as lymphoma. The CHOP regimen (cyclophosphamide, vincristine, doxorubicin, and prednisone) is a widely used treatment regimen for T-cell lymphoma. Unfortunately, the long-term use of this drug is limited by cardiac toxicity, especially drug-induced congestive heart failure, even chronic irreversible cardiotoxicity. Due to the cardiotoxicity of cumulative dose limitation, doxorubicin has been formulated in liposomes to selectively deliver the drug to tumors and limit the accumulation of drug in healthy tissues, especially in the heart. Wrapping doxorubicin in the liposome will significantly change its bioavailability and biological distribution, so as to change its biological activity. PLD has been shown to significantly reduce cardiotoxicity and is effective against tumors. To our knowledge, there is currently no standard treatment regimen for MEITL, and the CHOP regimen containing doxorubicin is less effective. Here, we report a patient with pathologically confirmed MEITL treated with a CHOP regimen containing liposome doxorubicin.

There are no specific guidelines for the treatment of MEITL. There is a report in the literature that a patient survived for 5 years after early diagnosis and 8 cycles of CHOP regimen. Various new treatments have been tried in MEITL, including chidamide and PEG-asparaginase, but chidamide does not appear to improve patient survival. Current consensus suggest a systemic anthracycline-containing chemotherapy with primary surgical resection to be an effective regimen. A multicenter retrospective study found that the CHOP regimen in MEITL was insufficient to achieve CR, which may be an important factor affecting survival. Hematopoietic stem cell transplantation may bring survival benefits to patients with MEITL, but there are also reported cases of early central nervous system (CNS) relapse after cord blood transplantation in the literature.

We report a case of MEITL diagnosed with CHOP regimen containing PLD. Our summary in this case emphasizes 2 important clinical points. Firstly, for patients with MEITL treated with CHOP regimen, PLD has less adverse reactions and long-term survival than doxorubicin. Secondly, there are few relevant reports and lack of characteristic clinical manifestations features, so the diagnosis is very challenging. It is easy to misdiagnosis and mistreatment, and the disease is invasive and progresses rapidly, with high mortality and very poor clinical prognosis. Effective treatment administered early is critical in order to long-term survival.

Doxorubicin is an active chemotherapeutic agent for MEITL, which shows efficacy in different types of cancer. But it can cause some adverse effects, such as myelosuppression, as well as heart...

Figure 2. (A–J): PET-CT: no abnormal radioactive distribution was found at the corresponding place. Cord shadow can be seen under the skin of the abdominal wall operation area, with slightly high radiation distribution, and the highest SUV is 1.5. PET-CT = positron emission computed tomography.
| Authors (yr) | Age and gender | Clinical presentation | Clinical stage of MEITL | Intestinal localization | Other involved sites | Chemotherapy | Follow-up |
|-------------|----------------|-----------------------|------------------------|------------------------|---------------------|--------------|-----------|
| Chen et al. (2016) | 60 yr/o, male | Abdominal pain | I A | Small bowel | – | CHOP + IVE/MT × 3 cycles + GDP | Died after 2 and a half years |
| Ishibashi et al. (2016) | 60 yr/o, male | Persistent diarrhea and weight loss | IV B | Duodenum, jejunum and cecum | Stomach bone marrow | CHASE | Died after 3 years |
| Ishibashi et al. (2016) | 40 yr/o, female | Diarrhea and weight loss | I B | Small bowel and colon | – | THP-COP | Died after 1 year |
| Ishibashi et al. (2016) | 50 yr/o, female | Abdominal distention | IV A | Small bowel, colon and rectum | Bone marrow | CHOP + high dose MTX/cytarabine | Died after 9 mos. |
| Ishibashi et al. (2016) | 70 yr/o, male | Nausea | IV A | Small bowel, colon, cecum and rectum | Bone marrow | SMILE | Died after 9 mos. |
| Hong et al. (2016) | 67 yr/o, male | Abdominal pain, night sweats and weight loss | II B | Terminal ileum, cecum and colon | – | 4 cycles of CHOP | Died after 4 mos. |
| Hong et al. (2016) | 50 yr/o, male | Abdominal pain and low grade fever | II A | Ileum and colon | – | 6 cycles of R-CHOP | Alive, 60 mos. |
| Hong et al. (2016) | 48 yr/o, male | Chronic diarrhea and weight loss | III B | Duodenum and jejunum | – | CHOP and chemotherapy regimen was changed (regimen not specified) | Died after 13 mos. |
| Hong et al. (2016) | 55 yr/o, female | Chronic diarrhea, abdominal pain, and weight loss | IV B | Small bowel | Lung, spleen and bone marrow | 2 cycles of cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone and a cycle of ICE | Died after 4 mos. |
| Liong et al. (2016) | 50 yr/o, male | Chronic diarrhea, and weight loss | I A | The small intestine | – | 1 cycle of CHOP | Died after 1 mos. |
| Nozari et al. (2017) | 35 yr/o, male | Chronic diarrhea | II | The small and large intestines | – | 5 course of chemotherapy (regimen not specified) | Died after 7 mos. |
| Komeda et al. (2017) | 65 yr/o, male | Left-sided ulcerative colitis | IV B | Duodenum and jejunum | The abdominal and chest walls | Anthracycline-based chemotherapy | Died after 2 mos. |
| Aiempanakit et al. (2017) | 67 yr/o, male | Chronic diarrhea and weight loss | I A | Small bowel | – | SMILE | Died after 136 mos. |
| Chan et al. (2017) | 44 yr/o, male | Abdominal pain | II A | Small bowel | – | SMILE | Died after 3 weeks |
| Chan et al. (2017) | 55 yr/o, male | Ascites and intestinal obstruction | IV A | Small bowel | Peritoneum, lung nodules and SCF LN | Dexamethasone, etoposide, ifosfamide, L-asparaginase, cisplatin and gemcitabine | Died after 1 month |
| Chan et al. (2017) | 57 yr/o, female | Abdominal pain | II A | Small bowel | – | Dexamethasone, etoposide, ifosfamide, L-asparaginase, cisplatin and gemcitabine | Died after 11 mos. |
| Chan et al. (2017) | 39 yr/o, male | Diarrhea | IV A | Small bowel and large bowel | Peritoneum, PT LN, IM LN, SCF LN, diaphragm and pleura | CHOP | Died after 11 mos. |
| Chan et al. (2017) | 61 yr/o, female | Abdominal pain and diarrhea | I A | Large bowel | – | SMILE | Died after 16 mos. |
| Chan et al. (2017) | 51 yr/o, female | Intestinal perforation | III A | Small bowel | – | Dexamethasone, etoposide, ifosfamide, L-asparaginase, cisplatin and gemcitabine | Died after 20 mos. |
| Chan et al. (2017) | 70 yr/o, female | Abdominal pain | I A | Duodenum | – | Dexamethasone, etoposide, ifosfamide, L-asparaginase, cisplatin and gemcitabine | Died after 6 mos. |
| Chan et al. (2017) | 51 yr/o, male | Diarrhea and weight loss | II B | Small bowel | – | CHOP | Died after 14 mos. |
| Authors (yr) | Age and gender | Clinical presentation | Clinical stage of MEITL | Intestinal localization | Other involved sites | Chemotherapy | Follow-up |
|-------------|----------------|-----------------------|-------------------------|-------------------------|----------------------|--------------|-----------|
| Chan et al[17](2017) | 65 yr/o, male | Gastrointestinal bleeding | IV A | Stomach, esophagus and lung | Dexamethason, etoposide, ifosfamide, L-asparaginase, cisplatin and gemcitabin | Died after 13 mos. |
| Chan et al[17](2017) | 57 yr/o, male | Abdominal pain | II A | Small bowel | Dexamethason, etoposide, ifosfamide, L-asparaginase, cisplatin and gemcitabin | Alive, 13 mos. |
| Chan et al[17](2017) | 68 yr/o, male | Gastrointestinal pain | II A | Large bowel | − | Alive, 13 mos. |
| Antoniadou et al[18](2017) | 76 yr/o, male | Severe dyspnea | IV A | Jeurum | Pleura | Died after 1 month |
| Gentilie et al[8](2017) | 70 yr/o, female | Abdominal pain, nausea, vomiting, diarrhea, and weight loss | Not given | Jejunoileal junction and colon | − | Died after 17 mos. |
| Zhao et al[19](2018) | 47 yr/o, female | Diarrhea and weight loss | II B | Rectum, sigmoid colon, and distal ileum | − | Could not undergo chemotherapy | Died after 4 mos. |
| Aoyama et al[20](2018) | 83 yr/o, male | Fever and diarrhea | II B | Colon | − | CHOP followed by Devic | Died: no stated time frame |
| Tian et al[19](2019) | 58 yr/o, male | Abdominal pain, diarrhea and weight loss | IIB | Colon and rectum | stomach | 1 cycles of CHOP | Died after 2 mos. |
| Tian et al[19](2019) | 64 yr/o, female | Chronic diarrhea and weight loss | II B | Small bowel and colon | − | Romidepsin with revlimid | Died after 7 mos. |
| Ikeda et al[20](2019) | 61 yr/o, male | 3 episodes of ileal strangulation | IV | Ileum | Bone marrow and pleura | 2 cycles of CHOP and 1 cycle of ICE | Died after 3 mos. |
| Kubota et al[20](2019) | 41 yr/o, male | Diarrhea and abdominal pain | IV A | An extramural tumor of the small intestine | Cerbospinal fluid | CHOP and 3 cycles of ICE chemotherapy, intrathecal chemotherapy and high-dose chemotherapy | Complete remission (CR) |
| Noh et al[21](2019) | 88 yr/o, male | Nausea, vomiting, and weight loss | Not given | Duodenum | − | Chemotherapy (regimen not specified) | Not given |
| Liu et al[22](2020) | 43 yr/o, female | Abdominal pain and weight loss | I B | duodenum | − | 4 cycles of the CHOPE and 2 cycles of the DHP with chidamide | 11 mos. since diagnosis |
| Fei et al[23](2020) | 58 yr/o, male | Persistent abdominal pain and weight loss | Not given | Small intestine | − | 3 cycles of EPOCH cycles | 7 mos. since diagnosis |
| Fei et al[23](2020) | 57 yr/o, male | Diarrhea and weight loss for 3 mos. | Not given | Small intestine, oceum, colon and rectum | − | 6 cycles of CHOP | 8 mos. since diagnosis |
| Fei et al[23](2020) | 80 yr/o, male | Small intestine perforation | Not given | Small intestine | − | Not given | Not given |
| Fei et al[23](2020) | 61 yr/o, male | Abdominal mass | Not given | Duodenum and jejenum | − | Not given | Not given |
| Fei et al[23](2020) | 61 yr/o, male | Upper abdominal pain and intermittent black stool | Not given | Small intestine | − | 2 cycles of CHOP combined with chidamide, CHOPE combined with chidamide for 4 cycles | 15 mos. since diagnosis |
| Liu et al[24](2020) | 35 yr/o, female | Abdominal distention, abdominal pain and high fever | Not given | Small intestine and colon | − | IVE and chidamide for 6 cycles | 17 mos. since her diagnosis |
| Gopalakrishna et al[25](2020) | 53 yr/o, male | Abdominal pain, fever, burning sensation and increased urinary | II B | Jejenum | − | 3 cycles of CHOPE | Not given |
| Suzuki et al[26](2020) | 74 yr/o, male | Diarrhea | IV A | Small intestine | The right cerebral hemisphere, bilateral lungs and pelvic cavity | Could not undergo chemotherapy | Not given |
| Susu Lu et al[27](2020) | 65 yr/o, male | Chronic diarrhea edema | I A | Colon | Stomach | 3 cycles of CHOP | Died after 13 mos. |

(Continued)
| Authors (yr) | Age and gender | Clinical presentation | Clinical stage of MEITL | Intestinal localization | Other involved sites | Chemotherapy | Follow-up |
|-------------|----------------|-----------------------|-------------------------|-------------------------|---------------------|--------------|-----------|
| Chuah et al.[28](2020) | 36 yr/o, male | Intractable diarrhea and weight loss | I B | The duodenojejunal junction | – | 7 cycles of CEOP, 2 cycles of MINE and ESHAP | Died after 9 mos. |
| Afzal et al.[4](2020) | 39 yr/o, male | Abdominal pain and intermittent diarrhea | IV A | Jejunum | The bilateral adrenal glands | Chemotherapy (regimen not specified) | Died after 7 mos. |
| Mago et al.[29](2021) | 59 yr/o, male | Intermittent shortness of breath exacerbated, abdominal distention and night sweats | IV B | Duodenum and jejunum | Pleura | CHOPE | Few days since diagnosis |
| Morimoto et al.[5](2021) | 74 yr/o, female | Abdominal distention and melena | IV A | Small intestine | Brain | 1 cycle of CHOP and 2 cycles of ESHAP | Died: no stated time frame |
| Ozaka et al.[7](2021) | 68 yr/o, female | Abdominal pain, diarrhea, fatigue and fever | I A | Duodenum | – | 8 full cycles of CHOP | Alive, 8 mos. |
| Zhong et al.[31](2021) | 49 yr/o, male | Abdominal pain, night sweats and fever | IV B | Jejunum and ileum | The ribs, spine and pelvic bone | EPOCH | Alive, 2.5 mos. since diagnosis |
| Aoki et al.[31](2021) | 77 yr/o, female | Abdominal pain, night sweats and fever | IV B | Jejunum and ileum | The ribs, spine and pelvic bone | EPOCH | Alive, 1 year |
| Kansoun et al.[32](2021) | 59 yr/o, male | Weight loss, recurrent nocturnal episodes of fever, night sweats and abdominal pain | I B | Small bowel and the sigmoid | Appendix and urinary bladder | 6 courses of adjuvant chemotherapy according to the following regimen: brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone. | Alive, beyond 1 year |
| Current patient | 54 yr/o, male | The upper abdominal pain and weight loss | IV B | Small intestinal and colon | – | 5 cycles of CHOPE (liposomal doxorubicin) | Alive, 13 mos. |

CEOP = cyclophosphamide, etoposide, vincristine and prednisone, CHASE = cyclophosphamide, cytarabine, etoposide, and dexamethasone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone, CHOP = cyclophosphamide, doxorubicin, vincristine, and predn
and digestive system toxicities, dose-dependent cardiac toxicity is a main side effect of doxorubicin, especially in elderly patients where there is a high rate of preexisting cardiac disease.\[^{[40]}\] Based this, Duncan found liposomal formulations with slow release of doxorubicin were developed and successfully reduced the cardiac toxicity in cancer treatment (Duncan, 2006; Gabizon and Papahadjopoulos, 1988; Gill et al, 1993). In our case report, after surgical resection, PLD containing CHOP regime was given. PLD has a stable spatial structure and encapsulated form. Its binding to plasma proteins is reduced. Compared to conventional doxorubicin injection, PLD has longer plasma circulation, lower clearance rate, higher blood concentration, and longer t\(1/2\) (68 hours).\[^{[41]}\] PLD has a longer retention time in blood circulation and releases more slowly, which can act directly on tumor tissues. Therefore, it can reduce the toxicities associated with doxorubicin, especially the myelosuppression and cardiotoxicity, and make doxorubicin more targeted delivery. Compared with doxorubicin solution, PLD have produced significant efficacy and toxicity profiles in solid tumor and lymphoma patient. The patient has survived for a year and has no adverse events of cardiotoxicity after chemotherapy drugs.

Although MEITL is an aggressive T-cell lymphoma with progresses rapidly, an extremely poor prognosis and high mortality rate, patients with MEITL might survive for a long term if effective treatment is administered early. In our case, the patient presented with nonspecific clinical manifestations, yet total excision revealed early stage of MEITL. The operation and diagnosis were timely and the treatment was positive. Therefore, it is significant to diagnose and treat at an early stage. Embarrassed the diagnosis of MEITL, it is difficult and prone to missed diagnosis, misdiagnosis and mistreatment. The main reasons for the difficult diagnosis of MEITL are as follows: A. The low incidence of MEITL had not attracted the attention of medical researchers and practitioners. B. The clinical manifestations of MEITL are nonspecific and mainly digestive tract symptoms. It is difficult to distinguish from other diseases. Diarrhea is the first symptom, and there will be symptoms such as abdominal pain, abdominal distension, abdominal mass, and changes in defecation rules. Other nonspecific clinical manifestations: hypoalbuminemia, anemia, etc. Systemic symptoms can appear fever, fatigue, poor appetite, progressive emaciation, etc. C. Small intestinal CT is helpful to detect lesions, and it is also helpful to judge the scope of the affected intestine, providing guidance for the next endoscopic examination. However, small intestinal CT lacks specificity and has a certain false-negative rate for MEITL diagnosis. No abnormality found under CT cannot completely exclude MEITL, so it plays a sufficient and unnecessary role in the diagnosis of MEITL. For endoscopic manifestations, MEITL may have mild and varied early mucosal changes, such as superficial ulceration, peripherally or 1/2 circumferential lumen, granular changes, and Mosaic signs.\[^{[40]}\] D. In the majority of MEITL, the lymphoma cells are positive for CD2, CD3, CD7, CD8 and CD56, and negative for CD4, CD5 and CD30.\[^{[42,43]}\] However, immunophenotypic variation occurs; some cases are negative for CD8 and/or CD56, and a minority co-expresses CD4 and CD8.\[^{[42,43]}\] The diagnosis of MEITL needs to comprehensively and carefully perform auxiliary examinations and clinical manifestations to rule out MEITL. Abnormally high uptake of fluorodeoxyglucose (18F-FDG) in tumor tissue during positron emission computed tomography may be helpful in diagnosing lymphoma.

Treatment with PLD containing CHOP is very rare in MEITL. Using the CHOP regime containing PLD is our new attempt in MEITL therapy. Would PLD offers an advantage for survival? It remains questionable. It is needed that further investigate and evaluate toxicity and efficacy of liposomal doxorubicin in the treatment of MEITL for an optimal treatment algorithm. Further investigations with more patients and randomized controlled studies in comparison to the Doxorubicin are warranted. Given that MEITL is a rare and newly proposed disease, international and multi-center efforts are needed to conduct prospective studies.

Acknowledgements

This work was supported by grants from Natural Science Foundation of Shandong Province (ZR2021HM019).

Author contributions

Conceptualization: Hongzhi Xu, Ningning Shan, Huiting Qu.

Data curation: Yue Chen, Ningning Shan, Huiting Qu.

Investigation: Yue Chen, Hongzhi Xu, Huiting Qu.

Project administration: Yue Chen, Huiting Qu.

Supervision: Hongzhi Xu, Huiting Qu.

Writing – review & editing: Yue Chen, Hongzhi Xu, Ningning Shan, Huiting Qu.

References

[1] Fontaine Kent L, Rodgers DL, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) within a Meckel’s Diverticulum. Am Surg. 2021;87:101–2.

[2] Tse E, Gill H, Loong E, et al. Type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia Lymphoma Study Group. Am J Hematol. 2012;87:663–8.

[3] Gopalakrishna H, Al-Abdouh A, Nair G, et al. Incidental diagnosis of monomorphic epitheliotropic intestinal T-cell lymphoma: a case report. Cureus. 2020;12:e10084.

[4] Afzal A, Easmeil A, Ibrahim S, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma with extraintestinal areas of peripheral T-cell lymphoma involvement. Cureus. 2020;12:e10021.

[5] Morimoto A, Fujioka Y, Ushiku T, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma invades brain. Intern Med. 2021;60:815–6.

[6] Tian S, Xiao SY, Chen Q, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma may mimic intestinal inflammatory disorders. Int J Immunopathol Pharmacol. 2019;33:2058738419829387.

[7] Ozaka S, Inoue K, Okajima T, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma presenting as melena with long-term survival: a case report and review of literature. World J Gastroenterol. 2021;27:6501–10.

[8] Geonlle C, Qin Q, Barbieri A, et al. Use of PEG-asparaginase in monomorphic epitheliotropic intestinal T-cell lymphoma, a disease with diagnostic and therapeutic challenges. ECancermedicalscience. 2017;11:771.

[9] Liu TZ, Zheng YJ, Zhang ZW, et al. Chidamide based combination regimen for treatment of monomorphic epitheliotropic intestinal T-cell lymphoma following radical operation: two case reports. World J Clin Cases. 2020;8:1278–86.

[10] Hong YS, Woo YS, Park G, et al. Endoscopic findings of enteropathy-associated T-cell lymphoma type II: a case series. Gut Liver. 2016;10:47–51.

[11] Chen Y, Tan SY, Petersson BF, et al. Occult recurrence of monomorphic epitheliotropic intestinal T-cell lymphoma and the role of MATK gene expression in diagnosis. Hematol Oncol. 2017;35:852–5.

[12] Ishibashi H, Nimura S, Kayashima Y, et al. Multiple lesions of gastrointestinal tract invasion by monomorphic epitheliotropic intestinal T-cell lymphoma, accompanied by duodenal and intestinal enteropathy-like lesions and microscopic lymphocytic pseudolymphocytic: a case series. Diagn Pathol. 2016;11:66.

[13] Liang CC, Ravindran S, Gnana Kumar G, et al. Enteropathy-associated T-cell lymphoma: an extremely rare cause of chronic diarrhoea. Med J Malaysia. 2016;1:88–90.

[14] Nozari N. Type II enteropathy-associated T-cell lymphoma: a rare report from Iran. Middle East J Dig Dis. 2017;9:55–7.

[15] Komeda Y, Kashida H, Sakurai T, et al. A case of type II enteropathy-associated T-cell lymphoma: a multicenter analysis from the Asia Lymphoma Study Group. Med Oncol. 2017;1:433.

[16] Asempanakit K, Amatawat C, Chiratikarnwong K, et al. Erythema multiforme-like cutaneous lesions in monomorphic epitheliotropic intestinal T-cell lymphoma: a rare case report. J Cutan Pathol. 2017;44:183–8.

[17] Chan TSY, Lee E, Khong PL, et al. Positron emission tomography computed tomography features of monomorphic epitheliotropic intestinal T-cell lymphoma. Hematology. 2018;23:10–6.
Antoniadou F, Dimitrakopoulou A, Voutsinas PM, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma in pleural effusion: a case report. Diagn Cytopathol. 2017;45:1050–4.

Zhao L, Yang Y, Zhang Y. Type II enteropathy-associated T-cell lymphoma: a case report and literature review. Niger J Clin Pract. 2018;21:812–5.

Aoyama Y, Tsunemine H, Zushi Y, et al. Colonal monomorphic epitheliotropic intestinal T-cell lymphoma with novel phenotype of cytoplasmic CD3 expression. J Clin Exp Hematop. 2018;58:102–6.

Ikeda C, Maruyama D, Oka H, et al. Bone marrow involvement by monomorphic epitheliotropic intestinal T-cell lymphoma. Br J Haematol. 2019;187:10.

Kubota Y, Kusaba K. Monomorphic epitheliotropic intestinal T-cell lymphoma involving the central nervous system. Blood. 2018;131:17651765.–1765.

Noh CK, Roh J, Lee KJ. Monomorphic epitheliotropic intestinal T-cell lymphoma presenting as weblike feature. Gastrointest Endosc. 2019;89:891–2.

Liu Z, He L, Jiao Y, et al. Type II enteropathy-associated T-cell lymphoma in the duodenum: a rare case report. Medicine (Baltim). 2020;99:e20050.

Fei F, Reddy V, Patel CR, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma: a study of four cases and review of literature. Ann Clin Lab Sci. 2020;50:806–12.

Suzuki Y, Minemura H, Tomita H, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma involving the lung and brain: a rare case study. Intern Med. 2020;59:2559–63.

Lu S, Zhou G, Chen M, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma of the stomach: two case reports and a literature review. Int J Surg Pathol. 2021;29:410–9.

Chuaah YY, Tashi T, Lee YY, et al. Enteropathy-associated T-cell Lymphoma (EATL) with intracranial metastasis: a rare and dismal condition. Acta Gastroenterol Belg. 2020;83:77–80.

Mago S, Mavilia M, Forouhar F, et al. Small bowel T-cell lymphoma: a MEITL-ing diagnosis. Clin J Gastroenterol. 2021;14:1071–83.

Zhong H, Zheng Y, Zhang F. Monomorphic epitheliotropic intestinal T-cell lymphomas: a case report. Diagn Pathol. 2021;16:80.

Aoki Y, Sujino T, Takabayashi K, et al. Various endoscopic features in monomorphic epitheliotropic intestinal T-cell lymphoma. Case Rep Gastroenterol. 2021;15:312–22.

Kansoun A, Chamma L, Sadek M, et al. Intestinal presentation of non-Hodgkin lymphoma: case report. Int J Surg Case Rep. 2021;86:106346.

Jaffe ET. 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematol Am Soc Hematol Educ Prog. 2009;523:531.

Bhatlapenumarthy V, Patwari A, Siddiqui AD. An unusual case of enteropathy-associated T-cell lymphoma type 2 with pulmonary metastasis. Cureus. 2019;11:e5714.

van Vliet C, Spagnolo DV. T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract: review and update. Pathology. 2020;52:128–41.

Lenti MV, Biagi F, Lucioni M, et al. Two cases of monomorphic epitheliotropic intestinal T-cell lymphoma associated with coeliac disease. Scand J Gastroenterol. 2019;54:965–8.

Huang D, Lim JQ, Cheah DMZ, et al. Whole-genome sequencing reveals potent therapeutic strategy for monomorphic epitheliotropic intestinal T-cell lymphoma. Blood Adv. 2020;4:4769–74.

Yi JH, Lee GW, Do YR, et al. Multicenter retrospective analysis of the clinicopathologic features of monomorphic epitheliotropic intestinal T-cell lymphoma. Ann Hematol. 2019;98:2541–50.

Nato Y, Miyazaki K, Imai H, et al. Early central nervous system relapse of monomorphic epitheliotropic intestinal T-cell lymphoma after cord blood transplantation. Int J Hematol. 2021;114:129–35.

Havlik RJ, Yancik R, Long S, et al. The National Institute on aging and the National Cancer Institute SEER collaborative study on comorbidity and early diagnosis of cancer in the elderly. Cancer. 1994;74(7 Suppl):2101–6.

Fan Y, Lin NM, Luo LH, et al. Pharmacodynamic and pharmacokinetic study of pegylated liposomal doxorubicin combination (CCOP) chemotherapy in patients with peripheral T-cell lymphomas. Acta Pharmacol Sin. 2011;32:408–14.

Delabie J, Holte H, Vose JM, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood. 2011;118:1448–55.

Ko YH, Karnan S, Kim KM, et al. Enteropathy-associated T-cell lymphoma–a clinicopathologic and array comparative genomic hybridization study. Hum Pathol. 2010;41:1231–7.