Immunopathologia Persa
http www.immunopathol.com
DOI:10.34172/ipp.2022.25261

Duodenal monomorphic epitheliotropic intestinal T cell lymphoma along with unpredictable intestinal Epstein-Barr virus infection; a rare newly redefined entity in a rare site and review of literature

Somaia Ahmed Saad El-Din[1,2*], Khalid Al Hashmi[3], Khaled Hamad[4], Fahad Al-Ghafri[3]

[1]Pathology Laboratory, Armed Forces Hospital, Muscat, Oman
[2]Pathology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt
[3]Medical Oncology Department, Armed Forces Hospital, Muscat, Oman
[4]Medical Department, Armed Forces Hospital, Muscat, Oman

***Correspondence to**
Somaia Ahmed Saad El-Din, Email: drsomaia2005@gmail.com, somiasd12@med.asu.edu.eg

Received 25 Apr. 2021
Accepted 10 Jul. 2021
Published online 30 Jul. 2021

Keywords: Monomorphic epitheliotropic intestinal T cell lymphoma, Panel of immunohistochemical markers, Clinical features, Chemotherapy

Abstract

Introduction: Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), previously known as type II enteropathy associated T-cell lymphoma (EATL), was redefined by the WHO (2016) as separate entity from the celiac disease-associated lymphoma. It is an extremely rare and highly aggressive peripheral T-cell lymphoma. It mainly involves jejunum and ileum and rarely duodenum.

Case Presentation: This was a 38-year-old male patient presented by daily vomiting related to meals for 8 months along with generalized colicky abdominal pain associated with constipation and marked weight loss. Upper endoscopy showed large ulcerated mass at the third part of the duodenum. Histopathological examination showed the diffuse malignant lymphoid infiltrate with morphology and immunophenotyping consistent with MEITL associated with unpredictable Epstein-Barr virus (EBV) in intestinal epithelial cells. The patient underwent five cycles of chemotherapy (cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone) followed by duodenectomy.

Conclusion: This case represents a rare newly redefined lymphoma entity in a rare site associated with unpredictable non-neoplastic epithelial EBV infection, which proved to be oncogenic agent involved in various hematopoietic and other neoplasms with unclear relationship to the development of this MEITL.

Citation: Saad El-Din SA, Al Hashmi K, Hamad K, Al-Ghafri F. Duodenal monomorphic epitheliotropic intestinal T cell lymphoma along with unpredictable intestinal Epstein-Barr virus infection; a rare newly redefined entity in a rare site and review of literature. Immunopathol Persa. 2024;10(1):e25261. DOI:10.34172/ipp.2022.25261.

Introduction

Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) which is previously known as type 2 EATL (enteropathy associated T-cell lymphoma) shows distinctive pathological and epidemiological features which warrant its designation as a separate entity from EATL (previously type I EATL) (1). In the contrary to EATL that is usually associated with celiac disease and thus It is common in areas where celiac disease is prevalent as Europe and North America, MEITL is not associated with celiac disease and occurs worldwide with increased incidence in Asian's population. It is twice more common in males. Thus, it has been renamed as MEITL (2).

MEITL is an aggressive gastrointestinal tract lymphoma with a short survival (3). Presentation is variable, with most of patients present by acute onset of bowel perforation or obstruction, while others show more gradual onset and presented with abdominal pain, diarrhea and weight loss (4).

MEITL can show ulcerating single or multiple masses. The malignant lymphoid cells are typically monotonous in appearance on low power magnification and mostly

Key point

Monomorphic epitheliotropic intestinal T cell lymphoma is a very rare and newly redefined entity in 2016 with poor prognosis. Histopathology is the gold standard for its diagnosis through morphology and immunohistochemical panel. Correct diagnosis can help in providing the proper aggressive therapy and close follow up of the patient. EBV is not known to be related to this type of lymphoma but it is found in the intestinal epithelial cells of our presented case, whether it is an incidental finding or it has an indirect rule in the development of this lymphoma as it has well-known oncogenic rule in different types of lymphomas, further researches are needed to assess this issue and on large number of cases.

medium-sized with inconspicuous nucleoli and a rim of pale or clear cytoplasm (5). The malignant T cells in MEITL express the cell surface molecules CD3, CD8, and CD56 and do not express CD4, CD5, and CD30. Epstein-Barr virus (EBV) infection is not found in the malignant lymphoid cells and thus, malignant lymphoid cells are negative for EBER virus's products (6).

To date, no highly effective therapeutic interventions have been known. The best but still only marginally effective therapy for this lymphoma, is to incorporate hematopoietic stem cell transplantation into chemotherapy plus surgical regimens (7).

This case represents a rare newly redefined type of lymphoma in a rare site (the duodenum as it is mostly developed in jejunum and ileum). MEITL is often a missed diagnosis as many clinicians and histopathologists are unaware of such a disease thus increase attention to this aggressive newly defined rare type of intestinal lymphoma is warrant. Moreover, EBV which is well known to be related to some B cell and T/NK cell lymphomas was found to infect the intestinal epithelial cells but not the lymphoma cells with unclear relationship to the development of this type of the MEITL which should be negative to EBV as part of its diagnostic criteria.

Case Presentation

We present a case of a 38-year-old male patient with past-history of renal stones and *Helicobacter pylori* infection. He came with few month history of vomiting about (two or three times per day) related to meals associated with colicky abdominal pain and constipation and he passed motion only after laxative. This was associated with loss of appetite, poor oral intake and marked weight loss about 40 kg within 8 months. Additionally, patient was complaining of odynophagia.

Physical examination

The patient had thin built and looked cachectic. He was afebrile with no lymphadenopathy or organomegaly. Abdomen is soft not distended with mild tenderness at epigastric region. The patient was dehydrated and found to have gastric outlet obstruction with metabolic alkalosis and renal impairment thus total parental nutrition was advised to him.

Investigation

Blood tests showed decrease serum calcium, albumin, phosphate, magnesium, chloride, and potassium along with increased serum sodium, and CO_2, urea and creatinine (renal impairment). CT scan showed thickened duodenal wall. Upper endoscopy revealed large obstructing ulcerating mass with raised edges at the third part of the duodenum, biopsy was taken. Celiac disease antibodies including anti-deamidated gliadin antibodies (IgA and IgG) and anti-transglutaminase (IgA and IgG) were negative.

Histopathology

H&E stained sections showed many duodenal mucosal fragments, some showed active ulcerating malignant lymphoid neoplasm along with fragments of non-neoplastic inflamed duodenal mucosa. The lymphoid neoplasm showed diffuse infiltrate destroying and replacing the duodenal architecture composed mostly of monomorphic medium size to large cells with moderate pale eosinophilic to clear cytoplasm and round to angulated hyperchromatic nuclei along with some pale vesicular nuclei associated with scattered mitosis and apoptosis with no appreciated necrosis (Figure 1C and D). Occasional eosinophils and plasma cells noted among the infiltrate. Blood vessels with fibrinoid necrosis noted mostly at the base of the ulcer. The malignant lymphoid cells appeared infiltrating into the intestinal crypts that are focally appreciated in the mucosa above the malignant lymphoid infiltrate (epitheliotropism) (Figure 1D) as well as at the sides of few villi. The non –neoplastic duodenal mucosa showed preserved villous architecture along with no significant increased intraepithelial lymphocytes at villi tip (> 6/20 enterocytes)/(> 40/100 enterocytes) thus celiac disease was not suggested (Figure 1E) instead there was frequent patchy prominent surface epithelial karyorrhexis with possible neutrophils (Figure 1F) along with villous expansion by dense mixed acute and chronic lymphoplasmacytic and eosinophilic infiltrate along with congested blood vessels with plump vascular endothelial cells, hemorrhage with fibrin deposition and some lymphoid aggregates.

On this level before immunophenotyping, the possibility of aggressive non-Hodgkin's diffuse large cell lymphoma was suggested with the differential diagnosis including diffuse large B cell lymphoma and in view of the site; some T cell lymphomas were needed to be assessed

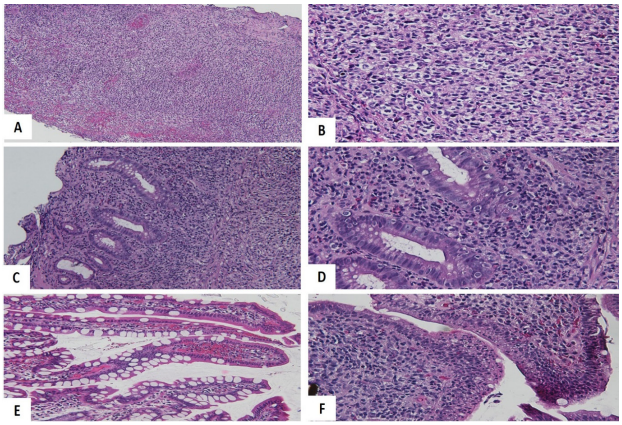

Figure 1. (A) Diffuse malignant lymphoid infiltrate (H&E x100). (B) Monomorphic medium to large lymphocytes with clear cytoplasm and mostly hyperchromatic nuclei (H&E x400). (C) Crypt epitheliotropism (H&E x200). (D) Higher view (H&E x400). (E) Non-neoplastic duodenal mucosa showed preserved villous architecture with no increased in intraepithelial lymphocytes at tip of the villi (H&E x200). F: Villi showed significant surface karyorrhexis that is suggested to be related to EBV infection (H&E x400).

including monomorphic epitheliotropic intestinal T cell lymphoma. Additionally, celiac disease related enteropathy associated T cell lymphoma that was mostly unflavored microscopically as no features of celiac disease but in view that sometimes occult celiac disease may be diagnosed concurrently with EATL, thus we also assess this type of lymphoma. Another T cell lymphoma to be assessed was extra-nodal natural killer cell T cell lymphoma nasal type that is related to EBV infection. Finally, the remote unexpected possibilities of T cell lymphoma not otherwise specified or anaplastic large cell lymphoma as there was no extra-intestinal manifestation for lymphoma.

A panel of immunohistochemical markers was applied to confirm the non-Hodgkin's lymphoma and for immunophenotyping as well as to rule out the remote possibility of undifferentiated carcinoma including pan CK, CD20, CD79a, CD10, BCL6, MUM1, BCL2, CD3, CD5, CD4, CD7, CD8, CD30, CD43, CD56, Granzyme B, perforin, Ki-67 and EBER/ISH (Epstein-Barr virus–encoded RNA/in situ hybridization).

Pan-cytokeratin was negative thus rule out the remote possibility of undifferentiated carcinoma. Ki-67 was about 50% to 60%. MUM1 was weakly expressed thus non-conclusive. CD20, CD10, BCL6 were negative with patchy moderate expression of CD79a along with intense positive diffuse stain to CD3 (both membranous and cytoplasmic), CD8, BCL2, CD7 and CD43 with loss of CD5 expression thus confirm the monoclonal T cell nature of the infiltrate with aberrant expression of CD79a (aberrant expression of one of the B cell marker is reported in some T cell lymphomas) (8). CD56 and granzyme B were also positive while CD4, perforin and CD30 were negative with negative ISH for EBER in lymphoma cells but it was positive in non-neoplastic intestinal epithelial cells (Figures 2 and 3). Thus, the immune stains along with the morphology were consistent with the MEITL.

Discussion

We present a case of MEITL in the duodenum which is a rare, newly described lymphoma entity and in a rare uncommon site (duodenum instead of jejunum and ileum) associated with the oncogenic EBV infection in the intestinal epithelial cells but not in the lymphoma cells with unclear relationship to the development of this lymphoma that should be negative to EBV as one of its diagnostic criteria. EBV is suggested to infect mostly about 90% of the world's population with a small subset would show neoplastic transformation (9). According to the WHO in 2008, there were two types of EATL, celiac disease associated lymphoma which is called type I and similar lymphoma that is not associated with celiac disease and called type II. Recent studies found significant clinical and pathologic differences between these two types of lymphoma. Consequently, the WHO redefined these two lymphomas as two separate entities, renamed the celiac disease-associated lymphoma as EATL and the lymphoma not associated with celiac disease as MEITL (10).

MEITL is representing less than 5% of all gastrointestinal lymphomas. It has a poor prognosis with a median survival of seven months (11).

Patients can presented with abnormal bowel movements, abdominal pain, B symptoms and/or bowel perforations and/or obstructions (12). In the present case, features of chronic intestinal obstruction was evident with repeated vomiting, colicky abdominal pain along with constipation and significant weight loss.

Investigations were conducted including abdominal CT scan and upper endoscopy that found large ulcerating mass at the third part of the duodenum suggestive of lymphoma versus carcinoma where biopsy was taken. Microscopic evaluation confirm the diffuse monomorphic malignant lymphoid infiltrate that lack an inflammatory background associated with epitheliotropism with the non-neoplastic duodenal mucosa showed no features of celiac disease. These microscopic features were in concordance with the morphological features described for MEITL (12).

The differential diagnosis was including diffuse large B cell lymphoma, EATL with occult concurrent celiac disease, extra-nodal NK/T lymphoma nasal type, and very remote possibilities of peripheral T cell lymphoma unspecified or anaplastic large cell lymphoma as there

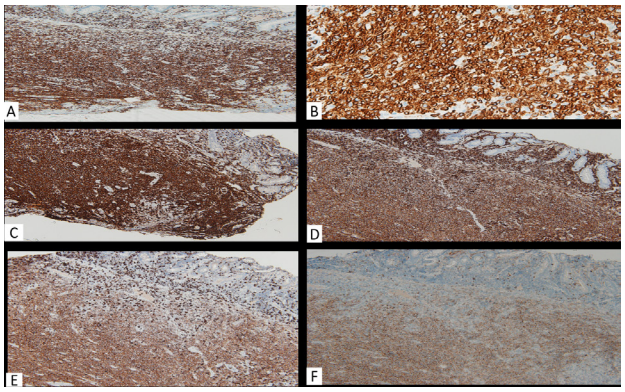

Figure 2. (A and B) CD3 positive diffuse intense membranous and cytoplasmic, x100, x400 respectively. (C) positive CD7 (x100), (D) Positive CD43 (x100, E: Positive CD8 (x100), (F) Positive CD56 (x100).

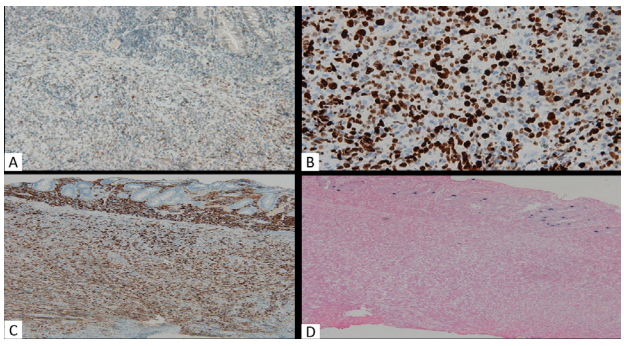

Figure 3. A: Positive patchy granzyme B (x200). B: Ki 67 is about 50% (x400). C: Aberrant expression of CD79a (x100). D: EBER ISH positive in epithelial cells and negative in lymphoma cells (x100).

was no extra-intestinal manifestation of lymphoma. Diffuse large B cell lymphoma was ruled out as malignant lymphoid infiltrate was negative for CD20 and express more than one pan T cell markers (CD3, CD7, CD43, BCL2). Both EATL (as it is positive to CD30 and negative for CD56) as well as extra-nodal NK/T cell lymphoma (as it showed positive EBER in neoplastic lymphoid cells and CD3 is expressed only cytoplasmic with mostly negative CD8) were also ruled out. The immunohistochemical panel showed positive CD3 membranous and cytoplasmic, CD7, CD8, CD43, CD56 and granzyme B that was classic for monomorphic epitheliotropic intestinal T cell lymphoma. According to the study by Perry et al (11), the diagnostic features of type II EATL are; (a) intestinal involvement with epitheliotropism, (b) the malignant lymphoid infiltrate composed of monotonous atypical medium-sized lymphoma cells, without extensive tumor necrosis, (c) proper T-cell immunophenotype (positive CD3, CD7, CD56 and CD8 with negative CD4, CD5 and CD30) along with variable expression of granzyme B and perforin and (d) EBV negativity in lymphoma cells (13).

Significant surface epithelial karyorrhexis was noted with positive EBER ISH in the intestinal epithelial cells. Does this oncogenic virus which was negative in lymphoma cells infect the intestinal epithelial cells after lymphoma had been developed or there was chronic intestinal infection that encourage the development of the lymphoma with somewhat similar pathogenesis to *Helicobacter pylori* in gastric MALT (mucosa associated lymphoid tissue) lymphoma? (14).

Regarding prognosis and treatment, according to literature, this is one of the dismal lymphomas as it is one of the cytotoxic lymphomas and generally very aggressive. They reported no ordinary effective therapy for MEITL. Most previous studies conducted in Europe are for type 1 EATL and not for MEITL. Combined treatment of chemotherapy and surgery with or without radiotherapy with even the need for autologous stem cell transplantation were recommended as lines of treatment. Anthracycline based polychemotherapy (cyclophosphamide, etoposide, vincristine and prednisolone) were applied as used in others peripheral T cell lymphomas (15). Although, the literature reported the dismal prognosis for this lymphoma, our case respond well to 5 cycles of chemotherapy with complete pathological response as was evident on negative repeated biopsy and PET scan follow up. However, significant fibrosis associated chemotherapy had been developed, thus patient underwent duodenectomy to relief secondary obstruction (excision of third and fourth parts of duodenum and part of jejunum).

Conclusion

MEITL is a rare aggressive newly redefined lymphoma entity by WHO 2016 that is not related to celiac disease and expresses CD3, CD7, CD56 along with variable expression of the cytotoxic markers with negative expression of CD4, CD7 and CD30. It is uncommon in the duodenum and by diagnostic criteria should show negative EBV infection in lymphoma cells. However in view of this case that showed intestinal EBV infection, does the well-known oncogenic EBV induce chronic antigenic stimulation that expand lymphoid cells and progress to lymphoma in similar way to *Helicobacter pylori* in gastric MALT lymphoma or it was just accidental finding.

Acknowledgments

Authors would acknowledge Dr. Lakshmi Roa, the senior consultant at Pathology Laboratory of Armed Forces hospital, Muscat, Oman for her confirmation of this rare diagnosis after revision of the slides and Dr. Masoud Al Kindy, the head of the Pathology Laboratory, Armed Forces Hospital, Muscat, Oman to allow us to take the photos.

Authors' contribution

Conceptualization: Somaia Ahmed Saad El-Din, Khalid Al Hashmi, Khaled Hamad, Fahad Al-Ghafri.
Data curation: Somaia Ahmed Saad El-Din, Khalid Al Hashmi.
Investigation: Somaia Ahmed Saad El-Din, Khalid Al Hashmi, Khaled Hamad, Fahad Al-Ghafri.
Project administration: Somaia Ahmed Saad El-Din.
Resources: Somaia Ahmed Saad El-Din, Khalid Al Hashmi, Khaled Hamad, Fahad Al-Ghafri.
Supervision: Somaia Ahmed Saad El-Din.
Validation: Somaia Ahmed Saad El-Din, Khalid Al Hashmi, Khaled Hamad, Fahad Al-Ghafri.
Visualization: Somaia Ahmed Saad El-Din, Khalid Al Hashmi, Khaled Hamad, Fahad Al-Ghafri.
Writing–original draft: Somaia Ahmed Saad El-Din, Khalid Al Hashmi, Khaled Hamad, Fahad Al-Ghafri.
Writing–review & editing: Somaia Ahmed Saad El-Din, Khalid Al Hashmi, Khaled Hamad, Fahad Al-Ghafri.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication or double publication) have been completely observed by authors. Informed consent was taken from the patient for publication of this report.

Funding/Support

None.

References

1. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76:182-8. doi: 10.1111/his.13975.
2. Van Vliet C, Spagnolo DV. T- and NK-cell lymphoproliferative disorders of the gastrointestinal tract: review and update. Pathology. 2020;52:128-141. doi: 10.1016/j.pathol.2019.10.001.
3. Weindorf SC, Smith LB, Owens SR. Update on Gastrointestinal Lymphomas. Arch Pathol Lab Med. 2018;142:1347-51. doi: 10.5858/arpa.2018-0275-RA.
4. Chan JK, Chan AC, Cheuk W, Wan SK, Lee WK, Lui YH, et al. Type II enteropathy-associated T-cell lymphoma: a distinct aggressive lymphoma with frequent γδ T-cell receptor expression. Am J Surg Pathol. 2011;35:1557-69. doi: 10.1097/PAS.0b013e318222dfcd.

5. Kikuma K, Yamada K, Nakamura S, Ogami A, Nimura S, Hirahashi M, et al. Detailed clinicopathological characteristics and possible lymphomagenesis of type II intestinal enteropathy-associated T-cell lymphoma in Japan. Hum Pathol. 2014;45:1276-84. doi: 10.1016/j.humpath.2013.10.038.
6. Tian S, Xiao SY, Chen Q, Liu H, Ping J. Monomorphic epitheliotropic intestinal T-cell lymphoma may mimic intestinal inflammatory disorders. Int J Immunopathol Pharmacol. 2019;33:2058738419829387. doi: 10.1177/2058738419829387.
7. De Baaij LR, Berkhof J, van de Water JM, Sieniawski MK, Radersma M, Verbeek WH, et al. A new and validated clinical prognostic model (EPI) for enteropathy-associated t-cell lymphoma. Clin Cancer Res. 2015;21:3013-9. doi: 10.1158/1078-0432.CCR-14-2195.
8. Tan SY, Chuang SS, Tang T, Tan L, Ko YH, Chuah KL, et al. Type II EATL (epitheliotropic intestinal T-cell lymphoma): a neoplasm of intra-epithelial T-cells with predominant CD8αα phenotype. Leukemia. 2013;27:1688-96. doi: 10.1038/leu.2013.41.
9. Rezk SA, Weiss LM. EBV-associated lymphoproliferative disorders: update in classification. Surg Pathol Clin. 2019;12:745-70. doi: 10.1016/j.path.2019.03.002.
10. Chander U, Leeman-Neill RJ, Bhagat G. Pathogenesis of enteropathy-associated T cell lymphoma. Curr Hematol Malig Rep. 2018;13:308-317. doi: 10.1007/s11899-018-0459-5.
11. Perry AM, Warnke RA, Hu Q, Gaulard P, Copie-Bergman C, Alkan S, et al. Indolent T-cell lymphoproliferative disease of the gastrointestinal tract. Blood. 2013;122:3599-606. doi: 10.1182/blood-2013-07-512830.
12. Chott A, Haedicke W, Mosberger I, Födinger M, Winkler K, Mannhalter C, et al. . Most CD56+ intestinal lymphomas are CD8+CD5-T-cell lymphomas of monomorphic small to medium size histology. Am J Pathol. 1998;153:1483-90. doi: 10.1016/S0002-9440(10)65736-7.
13. Wilson AL, Swerdlow SH, Przybylski GK, Surti U, Choi JK, Campo E, et al. Intestinal γδ T-cell lymphomas are most frequently of type II enteropathy-associated T-cell type. Hum Pathol. 2013;44:1131-45. doi: 10.1016/j.humpath.2012.10.002.
14. Sagaert X, Van Cutsem E, De Hertogh G, Geboes K, Tousseyn T. Gastric MALT lymphoma: a model of chronic inflammation-induced tumor development. Nat Rev Gastroenterol Hepatol. 2010;7:336-46. doi: 10.1038/nrgastro.2010.58.
15. d'Amore F, Relander T, Lauritzsen GF, Jantunen E, Hagberg H, Anderson H, et al. Up-front autologous stem-cell transplantation in peripheral T-cell lymphoma: NLG-T-01. J Clin Oncol. 2012;30:3093-9. doi: 10.1200/JCO.2011.40.2719.