



Monomorphic Epitheliotropic Intestinal T-Lymphoma – Case Report

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Abstract

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BACKGROUND: Monomorphic epitheliotropic intestinal T cell lymphoma (MEITL) (formerly termed enteropathy-associated T cell lymphoma, type II) is an extremely rare peripheral T-cell lymphoma that involves the malignant proliferation of a T-lymphocyte in the gastrointestinal tract. Over time, these T cells commonly spread throughout the mucosal lining of a portion of the GI tract (particularly the jejunum and ileum of the small intestine), lead to GI tract nodules and ulcerations, and cause symptoms such as abdominal pain, weight loss, diarrhea, obstruction, bleeding, and/or perforation. Its clinical, morphologic, and immunophenotypic features distinguishing it from the more common Enteropathy Associated T-Lymphoma (previously EATL type I) made it a separate entity.

CASE REPORT: We present a case of a rare extremely aggressive T cell lymphoma that originates from the gastrointestinal tract, spreads to surrounding organs and is refractory to surgery and chemotherapy. We describe a case report of 79 years old female Caucasian clinical features of acute abdomen and ileus, treated with surgery 2 times. During the first surgery, partial resection of jejunum was performed. Histopathology and immunohistochemistry findings of MEITL were confirmed. PET/CT scan was performed and revealed infiltration of intestine, uterus, and ovarium. During the second operation partial resection of ileum and hysterectomy with adnexectomy was performed. The patient is treated with anthracycline-based regimen CHOP21 (4 cycles). Re-evaluation with second PET/CT scan revealed residual tumor on the intestine and bladder. Despite aggressive treatment with extensive surgery and aggressive anthracycline-based chemotherapy, in a short time the tumor spread to surrounding organs (sigmoid colon and bladder). The patient deteriorated with acute renal failure and multi-organ failure, only survived 11 months from the initial definitive diagnosis.

CONCLUSION: MEITL is a challenging primary intestinal T cell lymphoma to treat as the outcome is frequently poor despite surgery and chemotherapy. Most patients are elderly with co-morbidities and they usually present late rendering any therapy ineffective. Young age, early Ann-Arbor/Lugano disease stage, good performance scale status, patients receiving autologous stem cell transplantation, and less bulky disease are associated with an improved survival outcome. Further research is needed to incorporate new therapeutic modalities based on molecular research for successful treatment of this aggressive lymphoma.

Introduction

In 2008, the World Health Organization (WHO) defined a specific type of lymphoma, enteropathy-associated T cell lymphoma (EATL), as having two different types: EATL type I, a lymphoma occurring in patients with the chronic, autoimmune GI tract disorder, celiac disease, and EATL type II, a similar bowel lymphoma that was not associated with celiac disease. However, subsequent studies found significant clinical, pathologic, and pathophysiological differences between these two types of lymphoma.

Consequently, in 2016, the WHO redefined these lymphomas as separate entities, terming the celiac disease-associated lymphoma as (EATL) and the lymphoma not associated with celiac disease as: Monomorphic Epitheliotropic Intestinal T cell Lymphoma (MEITL) [1].

MEITL is only 1/5 to 1/10 as common as EATL. It differs from EATL in that it predominantly affects Asian populations and is not associated with celiac disease and/or other malabsorption syndromes and inflammatory colitis. The WHO (2016) also termed a third type of intestinal T cell lymphoma that could not be classified as EATL or MEITL as intestinal T cell lymphoma, not otherwise specified.

Pathology

Monomorphic epitheliotropic intestinal T-cell lymphoma is a rare peripheral extranodal T-cell lymphoma (PTCL). It originates from intraepithelial intestinal T lymphocytes and tends to spread aggressively to surrounding tissue [1]. Most often MEITL involves the small bowel, particularly the jejunum and ileum, but it can also involve the stomach, colon, and other extra-intestinal sites [2].

Microscopically, the tumor tissue typically consists of small- to medium-sized monomorphic lymphocytes with hyper-chromatic nuclei with inconspicuous nucleoli and a moderate amount of clear to pale eosinophilic cytoplasm. There is a prominent epitheliotropism associated with MEITL, and it typically shows villous distortion without the villous atrophy and crypt hyperplasia often noted in the adjacent mucosa with EATL. Histologically, it is important to distinguish it from cryptitis and microscopic colitis due to the presence of intraepithelial lymphocytes (IELs). The number of IELs is far greater in lymphoma than in inflammatory conditions and there is marked cytologic atypia present [3], [4].

The most important features that can help us differentiating among MEITL and other types of T-cell lymphoma are the monomorphic cell shapes, epitheliotropic patterns, and immunopositivity for cluster of differentiation (CD): CD8 and CD56 positive. Immuno-phenotyping shows that the tumor cells typically are: CD3+, CD5-, CD4-, CD8+, CD56+, CD30-, gamma-delta T-cell receptor (GD TCR)+, alpha-beta TCR (AB TCR)-, T-cell intracellular antigen (TIA)+, megakaryocyte-associated tyrosine kinase (MAYK)+, and Epstein-Barr virus (EBV) encoded small nuclear RNAs (EBER)-. About 80% of the cases show TCR- γ and TCR- δ gene rearrangements.

Pathophysiology

The malignant T cells in MEITL can be identified by: Their expression of cell surface molecules CD3, CD8, and CD56; by their failure to express CD4, CD5, or CD30; and, in particular, by their overexpression of megakaryocyte-associated tyrosine kinase. They are not infected with the Epstein-Barr virus and therefore do not express this virus's products (e.g., EBER1 or EBER2). In most individuals with the disease, these T cells are $\gamma\delta$ rather than $\alpha\beta$ T-cells based on their expression of $\gamma\delta$ rather than $\alpha\beta$ T-cell receptors. They also commonly express cytotoxic T cell activation markers such as TIA1, granzyme B, and perforin. MEITL is thought to arise from intraepithelial lymphocytes that normally reside in the epithelial lining of the GI tract and over time acquire abnormalities that promote their survival, proliferation, avoidance of the immune system, and thereby malignancy. These cells are not infected with the Epstein-Barr virus and therefore have not become malignant as a consequence of this virus's malignancy-producing effects on lymphocytes as it does in other types of GI tract lymphomas. Rather, the malignant T cells in MEITL bear various genetic abnormalities that may promote their malignancy. Usually has complex cytogenetic abnormalities; mutations in *STAT5B*, *SETD2*, *JAK3*, *GNAI2*, and *CREBBP* are common [5].

Treatment

Patients with MEITL have a poor prognosis. Treatment usually consists of a combination of surgery,

chemotherapy, radiotherapy, and in patients with good performance status autologous stem cell transplantation (ASCT). Anthracycline-based polychemotherapy (CHOEP - cyclophosphamide, etoposide, vincristine, and prednisolone) followed by ASCT has been used with some improvement in overall survival.

Case Report

On April 12, 2021, 79 years old female Caucasian patient who was previously healthy, without gastrointestinal diseases, was hospitalized as an emergency in the City Surgical Hospital (Naum Ohridski). The clinical physical examination showed acute abdomen. An indication for urgent surgical treatment is given.

Intraoperative finding

Diffuse fibrino-purulent peritonitis is present. The jejunum shows a tumor that sticks to the large omentum. A resection of the jejunum (51 cm in length and 3.5 cm in circumference) was performed with a terminal anastomosis.

Histopathological finding

Macroscopic finding: After opening of the small intestine, ulcerative tumor tissue is seen on the wall of the jejunum with dimensions 6 × 6 cm which occupies the entire circumference of the intestine and infiltrates deep into the mesentery. The tumor is grayish-white and with areas of necrosis that in places have a sarcomatoid appearance. Seven intra-abdominal lymph nodes were isolated. The obtained sections are stained with LCA, CD3, CD20, bcl2, CD56, Synaptophysin, Chromogranin, CKAE1/AE3, and Ki-67.

Microscopic finding

Neoplastic cell growth with lymphoid morphology, ulceratively altering morphology, and infiltrating the mesangium with angiocentric arrangement. The cells have a morphology of medium-sized lymphocytes that have round hyperchromic nuclei with sparse cytoplasm. The cytoplasm showed pronounced epitheliotropism and villi destruction. Extensive areas of necrosis are present.

Immunohistochemical findings

The tumor cells showed immunopositivity for CD3 +, CD8 +, CD56 +, bcl2 +, Nucleophosmin +, and Ki67 > 70% (Figure 1).

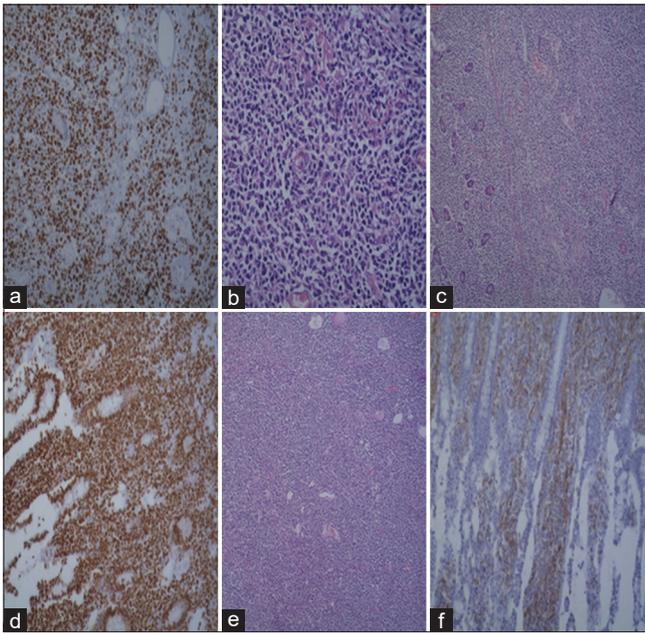


Figure 1: The immunohistochemical findings of the tumor cells. (a) Ki 67>70%, (b) PTCL-T, (c) PTCL, (d) Nucleophosmin, (e) PTCL, (f) CD-56. PTCL: Peripheral T cell lymphoma

Deferential diagnosis: Monomorphic epitheliotropic intestinal T cell lymphoma

On June 23, 2021, a ^{18}F -fluorodeoxyglucose (FDG) PET/CT scan was performed. Activity of FDG was 4.8 MBq kg^{-1} , with an uptake time of 60/min. PET images were analyzed visually and quantitatively. Positive uptake was defined as increased metabolic activity in locations incompatible with normal anatomy or anatomical variant. Areas with maximum standardized uptake value (SUVmax) were identified as index lesions.

Results: A malignant lesion is present in the wall of the ileum in the length of 20 cm. SUVmax = 29.6, (liver SUVmax = 2.7). No activity in other lymph nodes, liver, and spleen (Figure 2).

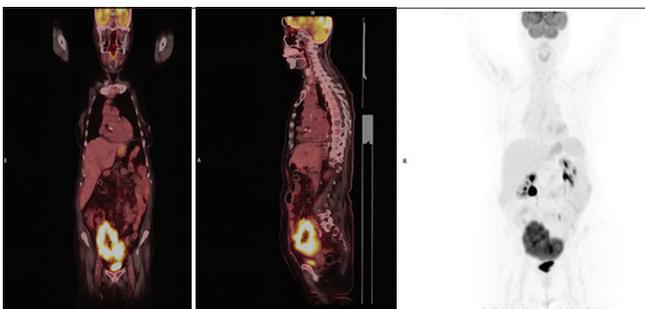


Figure 2: First PET/CT scan on 23.06.2021 (after first surgery)

Before starting chemotherapy treatment, it is necessary to perform a staging procedure. Prolonging the onset of chemotherapy led to a second attack on the disease.

On June 28, 2021, she was again hospitalized in the City Surgery Hospital (Naum Ohridski), again under clinical symptoms for ileus. On June 30, 2021, the second operative procedure was performed with

partial resection of the ileum (48.7 cm in length and 3.2–5.8 cm in volume) and terminal anastomosis. Due to infiltration and abscess present in the uterus, a total hysterectomy with adnexectomy was performed. 12 lymph nodes are isolated.

Histopathological finding

From isolated 12 intra-abdominal lymph nodes, five have tumor deposits. The pathohistological finding confirms the diagnosis: Monomorphic epitheliotropic intestinal T lymphoma.

Microscopic finding

Destructed small bowel mucosa from neoplasm with lymphoid morphology. The tumor lesion is transmural and penetrates the serosa. Ulcers of the mucosa infiltrated by a medium-sized lymphoid population are present. The neoplasm infiltrates the uterus and reaches the adnexa. Immunohistochemical findings: Atypical T cells show positive expression of CD3 +, CD4 +, CD8 +, CD56 +, Nucleophosmin +. Negative expression of: CD138 -, CD20 -, and MUM1 -. Proliferative index for Ki 67 is 80%. The initial diagnosis of MEITL is again confirmed.

Given the extremely aggressive course of the disease, the patient's age, and the limited success of the surgical treatment, we decided to continue the treatment with chemotherapy. Rare recommendations in the literature have suggested the use of an anthracycline-containing regimen. We applied chemotherapy according to the standard protocol for Non-Hodgkin Lymphomas CHOP21 (Oncovin 2mg, Cyclophosphamid 800 mg., Doxorubicyn 60mg. and Prednisolone 100 mg in 5 days.). Four cycles of chemotherapy have been completed. Clinical findings and laboratory parameters improve moderately (Hb 121 WBC 12.2 Plt 426).

On February 24, 2022, evaluation of the disease condition was performed with a control PET/CT scan. Tumor of the small intestine, sigmoid colon, and urinary bladder are present. Intensive acceptance of ^{18}F FDG with SUVmax = 20.0. A fistula is present between the bowel and the urinary bladder (Figure 3). Renal failure occurs, followed by multiorgan failure. As a result of cardiorespiratory failure, a fatal outcome occurred on March 15, 2022.

The patient survives 11 months from the initial diagnosis.

Discussion

MEITL is an aggressive T-cell lymphoma with a poor prognosis. T-cell lymphomas account for just 5%

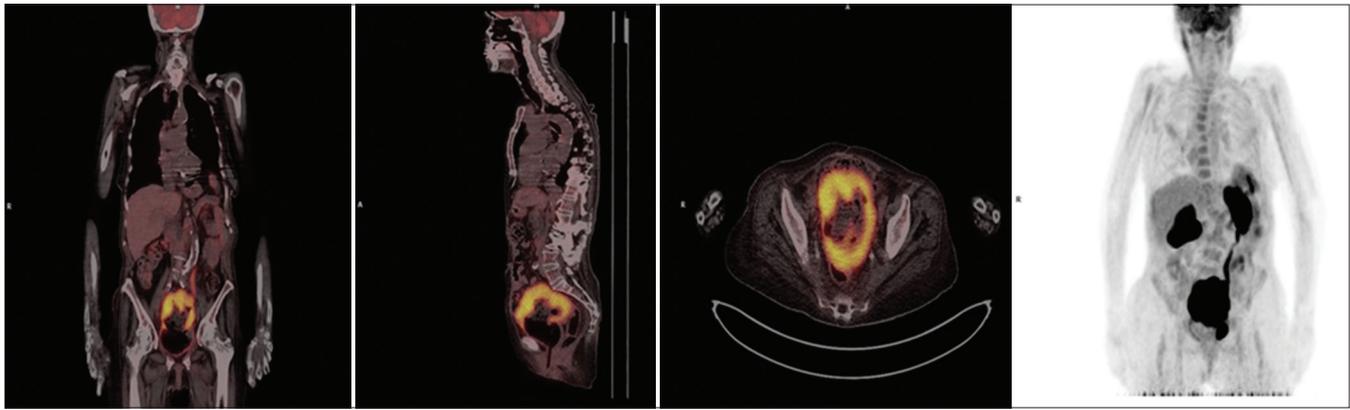


Figure 3: Second PET/CT scan on 24.02.2022 (after completed 4 cycle of CHOP chemotherapy)

of gastrointestinal tract lymphomas [6]. The disease occurs most often in elderly. The median age of onset of the disease is the sixth decade. Gender distribution is twice as common in favor of men. Unlike EATL, MEITL is less common in Northern Europeans but is more prevalent in Asian and Hispanic individuals. MEITL can have endoscopic features similar to various types of colitis. The prognoses of both the MEITL and EATL are extremely poor, showing identical median survival time of 7 months. These facts imply that when once clinically detected either tumor grows very aggressively. It is well known that malignant cells grow in a Gompertz model [7], suggesting both high proliferative capacity of clinical tumor and long-term low proliferative nature of subclinical malignant cell agglomeration. In our patient, at the initial diagnosis, the tumor is located in the small intestine, but in a short period of only a few months it spreads to the rest of the intestine, uterus, ovaries, sigmoid colon, and bladder. Extremely high Ki-67 labeling index (Ki-67 = 80%) in our patient proves the aggressiveness of the lymphoma and the unusually fast growth in the surrounding organs and tissues.

Unlike MEITL, which does not respond to conventional chemotherapy at all, CD20-positive lymphomas, such as Diffuse Large B Cell Lymphoma (DLBCL), which is the most common lymphoma, are completely cured with anti-CD20 monoclonal antibodies in combination with chemotherapy. Tan *et al.* [8] reported that one fourth of MEITL cases had aberrant CD20 positivity. Efficacy of adding rituximab to conventional chemotherapy should be explored in CD20-positive MEITL cases. In addition, PD-L1 positivity should be examined for the application of immune checkpoint inhibitor(s) to the treatment of both MEITL and other malignant lymphomas with dismal prognosis including EATL [9].

Ho *et al.*, in 2019, provides a multicenter retrospective analysis of the clinico-pathologic features of 42 patients with MEITL. The median age is 59 years and 27 are male patients (64%). Thirty-two patients (76%) were Ann-Arbor stages I–II and 28 (67%) were Lugano stages I–II_{1&2}. The most frequent site of involvement was the jejunum (n = 21). Most cases

expressed CD8 (79%) and CD56 (95%) and did not express CD30 (5%) or EBER (0%). The median progression-free survival is 6.9 months and the median OS is 14.8 months (2.4–27.2). Thirty-two patients (76 %) underwent surgery and 37 (88%) received chemotherapy. A complete response (CR) rate was 38 %. Sixteen patients had undergone autologous stem cell transplantation (ASCT). Relapse or progression was documented in 24 cases, most frequently in the primary site (n = 23). Four cases showed central nervous system relapse. Age over 55 years, poor performance scale, advanced Lugano stage (II_E–IV), not achieving CR, and not receiving ASCT were associated with inferior OS [3].

While the optimal management of MEITL remains undetermined, achieving CR and consolidative ASCT seem essential. Most individuals have been treated by surgical resections of involved areas with or without anthracycline-based chemotherapy. In these cases, responses have been short-lived and/or poor with 1-year overall survival rates, 1-year progression free survival rates, and median survival times of 36%, 21%, and 7 months, respectively. A retrospective study of patients treated with resection, chemotherapy and autologous hematopoietic stem cell transplantation had a higher 1-year and 5-year overall survival (100%, 33%) compared to 1-year survival (73%) and 5-year survival (14%) without transplantation; a second retrospective study supported the usefulness of transplantation in that high-dose lymphoma chemotherapy followed by transplantation and standard-dose lymphoma chemotherapy with or without surgical resection increased 5-year overall survival from 22% to 60% and 5-year disease progression-free survival from 22% to 52% [9].

L-Asparaginase based regimens show a higher complete remission rate than CHOP or anthracycline based chemotherapy. I-Asparaginase may be used as monotherapy in patients not fit for combination polychemotherapy. Anthracycline based chemotherapy such as CHOP chemotherapy is no longer used as standard regimens in other aggressive lymphomas such as NK/T cell lymphoma as it is

frequently ineffective. The ineffectiveness of CHOP chemotherapy could be explained by the expression of CD56 on tumor cells. While further studies, particularly randomized controlled trials, are needed to investigate the best treatments for MEITL, the use of lymphoma chemotherapy, hematopoietic stem cell transplantation, and, where needed, surgical resections are the currently recommended treatments for MEITL.

Conclusions

MEITL is an extremely rare disease, and therefore more prospective randomized multicenter studies are needed to establish more information on pathogenesis and appropriate target therapies or an effective combination of poly-chemotherapy strategies and autologous stem cell transplantation. Determining the entire MEITL genome using new NGS technologies will provide future target therapies for this currently difficult-to-manage disease with currently available therapies. We rarely diagnose MEITL in our daily clinical practice due to the lack of early diagnostic measures resulting in a poor prognosis. Therefore, any patient with gastrointestinal symptoms or perforation of the digestive tract where it is difficult to identify the primary lesion should consider the possibility of this disease.

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