Enteropathy-associated T-cell Lymphoma (EATL) with intracranial metastasis : a rare and dismal condition

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Abstract

***Background* : Enteropathy-associated T-cell lymphoma (EATL) is a rare type of gastrointestinal non-Hodgkin's Lymphoma. EATL with intracranial metastasis is even rarer. We report a case of EATL with intracranial metastasis.**

***Case Presentation* : A 36-years old man presented with five weeks history of intractable diarrhea. Colonoscopy was normal, but abdominal computed tomography (CT) scan revealed mural thickening at duodenojejunal junction, and subsequent jejuno-fiberoscopy showed a circumferential ulceration at the jejunum. Histo-immunopathology confirmed the diagnosis of enteropathy-associated T-cell lymphoma (EATL) type II. His disease course proved to be aggressive and refractory to standard front-line chemotherapy, and eventually progressed through second-line salvage regimen with CNS and intracranial involvement. He died nine months after the initial diagnosis.**

***Conclusion* : EATL with brain metastasis is a very rare occurrence with dismal prognosis.** (Acta gastroenterol. belg., **2020**, 83, **77-80**).

Key words : enteropathy-associated T-cell Lymphoma, intracranial metastasis.

Abbreviations : EATL: Enteropathy- associated T-cell Lymphoma ; CT : Computed Tomography ; GI : Gastrointestinal ; CEOP : Cyclophosphamide, Etoposide, Vincristine and Prednisone.

Background

A rare entity of Non-Hodgkin's Lymphoma, enteropathy-associated T-cell lymphoma (EATL) comprises about 5.4% of all lymphomas in the gastrointestinal (GI) tract (1). Intracranial metastasis associated with EATL is even rarer with only five reported cases so far (2-6). Here, we present a case of EATL with intracranial metastasis, and literature review on this extremely rare entity.

Case presentation

A 36-year-old Chinese male without any significant prior medical history presented with five weeks of intractable diarrhea. He had 4-5 loose stools (Bristol stool type 7) per day and reported weight loss of about 10 kg since the onset of symptoms. He did not have any travel history or antibiotics use. On examination, the patient appeared cachectic and dehydrated with poor skin turgor. The rest of his physical examination were unremarkable. His initial laboratory studies revealed leukocytosis with white cell counts of 15.8 K/mcl with 70% neutrophils and 16% lymphocytes, a hemoglobin count of 15.4 g/dl and a platelet count of 502 K/mcl. Stool studies for worms, parasites and *Clostridium difficile* were all negative. Serum anti-HTLV, anti-endomysial Ab and transglutaminase antibodies-IgA were negative as well, and colonoscopy did not show any significant findings. Subsequently, a jejuno-fiberoscopy revealed a circumferential ulcer at the proximal jejunum with aneurysmal dilatation and multiple biopsy samples were taken (Figure 1a). Abdominal CT scan with contrast demonstrated a segmental mural thickening with aneurysmal dilatation at the duodenojejunal junction (Figure 1b). H&E stains of the biopsied ulcer edge showed abundance of monotonous medium-sized lymphocytes with pale cytoplasm (Figure 2a). Immunohistochemistry staining was positive for b-F1, gd TCR, CD3, CD8, and CD56 (Figures 2b,2c and 2d) but negative for CD4 and EBV. These histologic and immunostaining results were consistent with EATL type 2, monomorphic variant. Staging scans did not show any additional areas of disease

The patient was then started on chemotherapy and received cyclophosphamide, etoposide, vincristine and

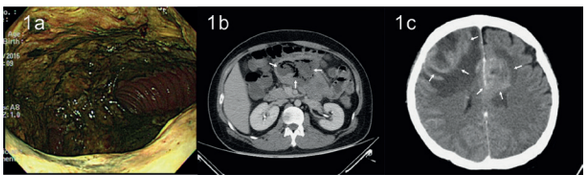

Figure 1. — Jejunofiberoscopy (1a) and abdominal CT scan (1b, arrows) showed a circumferential ulcer with aneurysmal dilatation at proximal jejunal junction. Computed tomography of brain showed heterogeneously-enhancing lesions in right frontal lobes and corpus callosum with extensive perifocal white matter edema. (1c, arrows).

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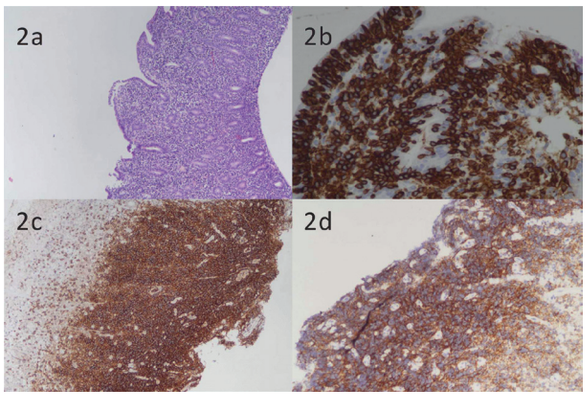

Figure 2. — H&E stains showed abundance of monotonous medium-sized lymphocytes with pale cytoplasm (2a). Immunohistochemistry staining was positive for CD3, CD8, and CD56 respectively (2b,2c and 2d).

prednisone (CEOP) for seven cycles, but achieved only partial response. The treatment course was complicated with bowel perforation requiring bowel resection. He then received second-line regimen consisting of mesna, ifosfamide, mitoxantrone, etoposide (MINE), but his disease remained refractory even after two cycles, and subsequently he was switched to a salvage regimen with etoposide, methylprednisolone, cytarabine, cisplatin (ESHAP), with high dose methotrexate. However, his condition deteriorated with altered mental status with left hemiplegia. CT scan of his brain found an ill-defined mass at both frontal lobes and the corpus callosum with extensive perifocal white matter edema (Figure 1c). These radiographic features were consistent with a secondary CNS lymphoma. Given the declining clinical condition and overall poor prognosis, brain biopsy was deferred and the patient was transitioned to a hospice facility and passed away shortly thereafter, approximately 9 months after the initial diagnosis.

Discussion and conclusions

EATL is a rare primary intestinal lymphoma which is often associated with poor prognosis due to its aggressive clinical behavior and high incidence of bowel perforation at diagnosis or during treatment, as exemplified by our case. Due to the GI complications, many of these patients are unable to receive or complete chemotherapy which further contributes to the poor outcome (7). Several single center and retrospective case series show the estimated median survival of about 7-8 months, and the most widely used chemotherapy is CHOP regimen, although many other lymphoma regimens have been used (7,8).

According to the recent 2016 WHO classification of lymphoid neoplasms, EATL is categorized into two subtypes which have distinct histological and molecular characteristics (9,10). EATL type 1, now simply named as enteropathy-associated T-cell lymphoma, is predominantly found in Western countries and is strongly associated with underlying antecedent celiac disease (9). Histologically, they can be medium to large size cells, and as with celiac disease, usually associated with HLA-DQ2 or HLA-DQ8 haplotype (1,11), and also express CD30, making an attractive target for brentuximab vendotin therapy. EATL type 2, which is now known as monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), has higher incidence in Asians and Hispanic population, and is usually not associated with celiac disease (9), consistent with our case here. A study of 600 cases of peripheral T-cell lymphoma (PTCL) from

Table 1. — **Clinical characteristics of EATLs with intracranial metastasis**

Authors [Ref]	Age	Sex	Celiac Disease	Primary lesion	Symptoms & Sign	Tx for primary lesion	Location of intracranial metastasis	Neurological symptoms	Tx for intracranial metastasis	Overall survival after initial diagnosis
Gobbi et al* [4]	56	F	(+)	Stomach Duodenum	Perforation	OP (+), C/T	Supratentorial (Subcortical & periventricular)	Headache, Depression, Cognitive decline	C/T, radiotherapy	9 M
Tutt et al* [2]	45	M	(+)	Small bowel	Abd pain, Diarrhea	Supportive	Supratentorial (Rt ventricle)	Headache, confusion, memory impairment	C/T, radiotherapy	11 M
Shams et al* [3]	54	M	(-)	Jejunum	Perforation	OP (+), C/T	Infratentorial (Lt cerebellum)	Ataxia, slurred speech	Nil	3 M
Berman et al. [5]	70	M	(-)	Jejunum	Abd pain, Weight loss	OP (+), C/T	Supratentorial (Bil occipital & temporal)	Seizure	Steroid (+), radiotherapy	16M
Defillo et al. [6]	65	F	(-)	Jejunum	Abd pain, Obstruction	OP (+), C/T	Supratentorial (Rt frontal-parietal)	Change in MS; Left facial brachial weakness	OP (+)	Nil
Our case	35	M	(-)	Jejunum	Diarrhea, Weight loss, Perforation	OP (+), C/T	Supratentorial (Frontal & corpus callosum)	Change in MS; Left sided weakness	Steroid (+)	9M

*cryptogenic EATL : present with initial neurological symptom and were diagnosed of EATL in gastrointestinal tract later ; OP : surgical operation ; C/T : Chemotherapy ; MS: mental status ; Ref : Reference.

Taiwan showed frequency of EATL to be about 8.1% in the Taiwanese population, which is similar to what is found in Western countries for EATL type 1(12). EATL type 2, or now MEITL, as name suggests, is monomorphic, and usually expresses CD8 and CD56, and positive for megakaryocyte-associated tyrosine kinase (MATK) (10,13). Majority of MEITL are of gd T-cell origin, although some are derived from ab T-cells (14). Additionally, mutations in STAT5B gene was reported in about one-third of MEITL cases, all of which expressed gd TCR (15).

Extraintestinal spreads of EATL to lymph nodes, spleen, liver and lung have been well-described in literatures but brain metastasis is an extremely rare occurrence. All five case reports were from the West (table 1) (2-6), and ours is the first case report from Asia. Based on the five cases, the mean age of patients was 54.1 (35-70) years old, two-thirds were males and two-thirds were without prior history of celiac disease. Half (3/6) reported abdominal pain and perforation, with diarrhea and weight loss in about one third (2/6) of the cases. Only 16.7% (1/6) of cases had intestinal obstruction. Half presented initially with neurological manifestations (cryptogenic type, shown in table 1) and another half presented initially with GI symptoms (including ours). All reported EATL with brain metastasis was originated from small bowel with the jejunum predominated. There was only one case with concomitant gastric involvement (16.7%) but none from the colon. (4) Another possible presentation of EATL and other types of intestinal lymphoma is intussusception (16).

All cases except for one underwent abdominal surgery mostly for bowel perforation, whilst the only case without surgery was a cryptogenic case who presented with initial neurological symptoms and was later proven to be EATL from autopsy. All reported cases except the abovementioned one had received chemotherapy. The overall survival of reported cases of EATL with brain metastasis was 9.6 months but appeared shorter with the cryptogenic group.

Eighty-three percent (5/6) of cases metastasized to the supratentorial region, while only one case (1/6) was found with infratentorial metastasis. (Table 1) The reason for supratentorial predilection was unclear, but it could be purely due to the fact that the supratentorial region comprises more than 60% of human brain. Headache, changes in mental status and extremities weakness were the most commonly encountered symptoms from supratentorial metastasis, while ataxia and slurred speech were seen with infratentorial metastasis, correlating with the site of metastasis. One half (3/6) of cases with intracranial metastasis underwent whole brain radiation and only 16.7% (1/6) underwent craniotomy for tumor resection.

In conclusion, EATL with brain metastasis is a very rare occurrence and the prognosis is often dismal.

Declarations

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