T-Cell Lymphomas: finally vision and mission !
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Indolent T-cell lymphoproliferative disorders of gastrointestinal tract

standard treatment in front-line
How I treat

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COI

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- Primary gastrointestinal(GI) lymphoma is accounting for 10-15 % of all non-Hodgkin lymphoma.
- Most primary GI lymphomas are non-Hodgkin lymphoma of B-cell lineage.
- T-cell types are relatively rare, comprising only 4-6% of all primary GI lymphoma.
- The GI involvement account for less than 10% of extranodal lesions in PTCL.
- The majority of GI T-cell lymphomas are aggressive types (more than 90%) , such as EATL, MEITL, ENKTL, Intestinal T-cell lymphoma (ITCL), NOS and other lymphomas involving the GI tract.

Indolent T-cell lymphoproliferative disorders of the gastrointestinal tract (ITLPD-GIT)

primary, GI

T-cell lymphoproliferative disorders with indolent behavior

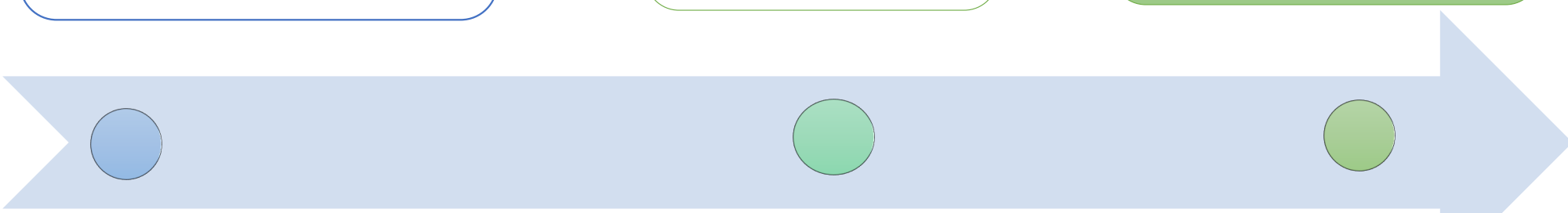
ITLPD-GIT

(provisional entity)

Indolent

T-cell lymphoma-GIT

(definite entity)



1994

First reported by Carbonnel et al.

2016

revised 4th edition WHO classification of lymphoid neoplasms

2022

5th edition WHO classification of lymphoid neoplasms

F Carbonnel et,al ; Cancer 1994

Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract (ITLPD-GIT)

■ Definition; revised 4th edition

・A clonal proliferation of T cells that can involve the mucosa in all sites of the GI tract, but is most common in the small intestine and colon.

・The lymphoid cells infiltrate the lamina propria but usually do not show invasion of the epithelium.

・The clinical course is indolent, but most patients do not respond to conventional chemotherapy.

・A subset of cases progress to a higher-grade T-cell lymphoma with spread beyond the GI.

Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract (ITLPD-GIT)

■ Epidemiology and Etiology

- Usually occurs in adulthood.
- Ages 15 - 79 years (median : 51 years).
- Slightly more common in males than females (M : F 1.5 : 1).
- No known ethnic and regional factors.
- Etiology is unknown.

Clinical features (1)

- Clinical manifestations
  - Mainly gastrointestinal symptoms ;

    chronic diarrhea, abdominal pain, dyspepsia, vomiting,

    indigestion, weight loss, bleeding

    non-specific !!

    → Symptoms overlap with other GI tract tumors

    → Differential diagnosis important

  - Some cases are asymptomatic.

Clinical features (2)

- Site of involvement
  - Any part of the GI tract can be affected. Often multiple lesions.
  - The most common site is the small intestine, followed by the large intestine.
  - Stomach, esophagus and oral cavity are uncommonly involved.
  - Usually confined to the GI tract.
  - Some patients show mesenteric lymphadenopathy.
  - Liver, bone marrow, and peripheral blood involvement has been infrequently described.

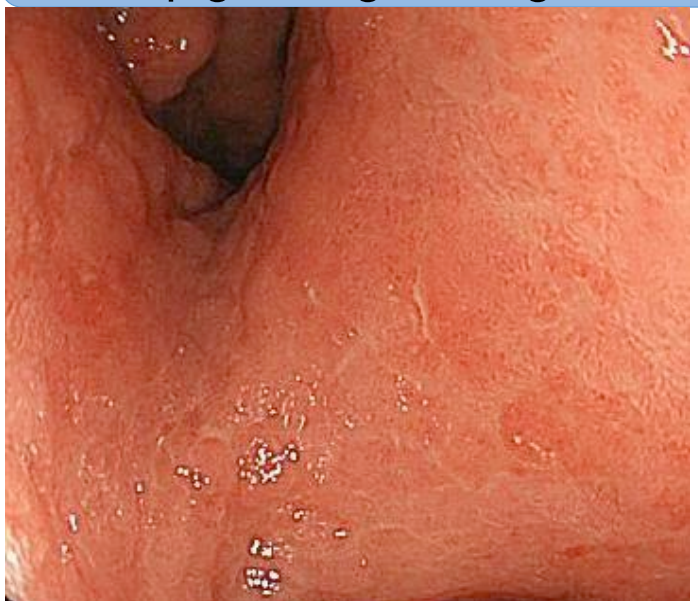
Clinical features (3)

■ Endoscopic findings

・Endoscopic examination shows normal or nodular mucosa, ulcers, polyps, erosions.

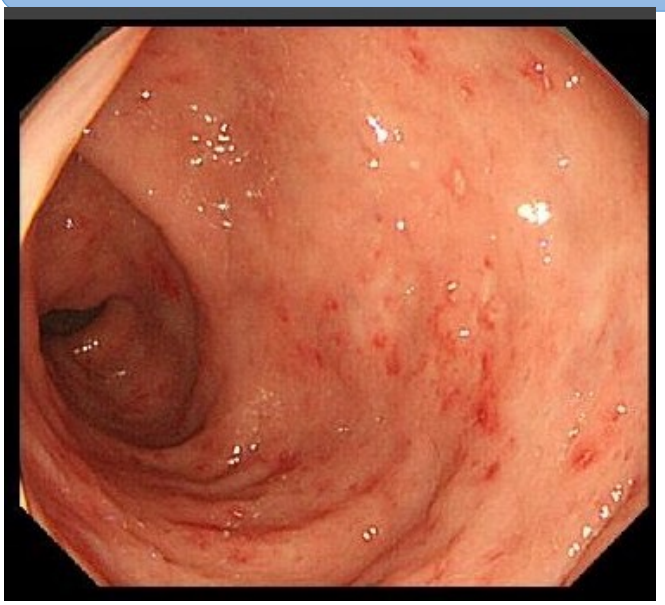
・Extremely varied and lack specificity.

Stomach; Case1
With epigastralgia, weigh loss



erosions

Colon; Case2
with chronic diarrhea



edematous mucosa

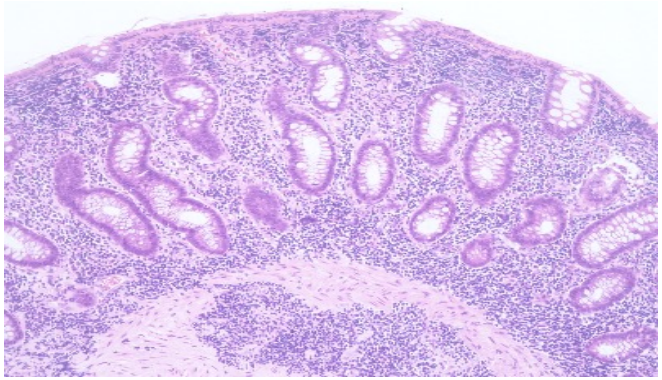
multiple aphthae

Kohri M, Tsukasaki K, et al; Leuk Res 2020

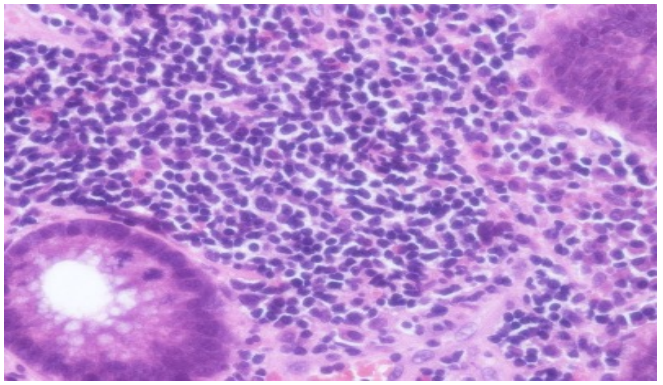
Pathological features (1)

- A dense, non-destructive infiltrate of small lymphocytes in the expanded lamina propria, with some extension into the muscularis mucosa and submucosa.
- Typically non-epitheliotropic.
- Tumor cells exhibit minimal atypia.

◆ Colon; Case2 in our hospital



low power



high power

(H&E stain)

Pathological features (2)

- Immunophenotype

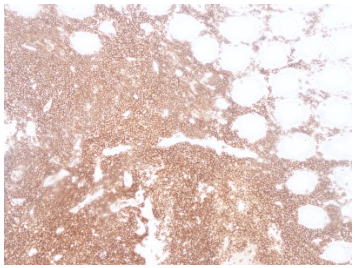
– **Typically** –

- CD2+, CD3+, CD5+, and CD4+ or CD8+.
- TIA1+, granzyme B -.
- CD56 -, EBER -.
- Ki - 67 expression < 10% (very low).
- TCRβ (βF1) +. in all cases

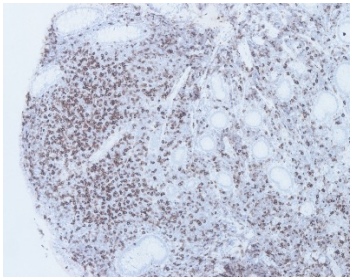
– Rare –

- CD4 + /CD8 + (double-positive),
- CD4 - /CD8 - (double-negative)

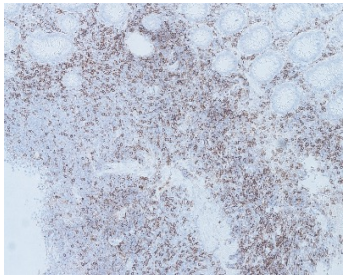
Case 2 (colon)
CD4 - /CD8 +



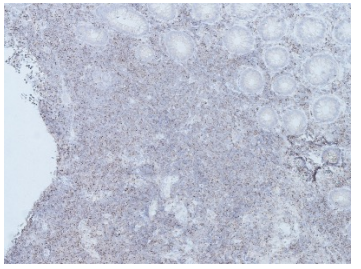
CD3+, low power



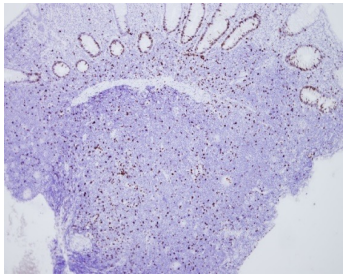
CD8+, low power



CD4 -, low power



TIA-1+, low power



Ki-67 index<10%, low power

Molecular and Genetic Alterations

clonal rearrangement of TCRβ or TCRγ

All cases of ITLPD-GIT

IL2 gene alteration
- IL2 3' UTR deletion
- IL2-RHOH rearrangement
- IL2-TNIP3 rearrangement

CD8+ phenotype

mutation of JAK-STAT pathway
- STAT3 SH2 domain hotspot mutations(D661Y, S614R)
- SOCS1 deletion
- STAT3-JAK2 rearrangement

mutation of epigenetic modifier genes (TET2, DNMT3A, KMT2D)

CD4+, CD4+/CD8+, CD4-/CD8- phenotype

Sharma et, al. blood 2018, Soderquist et, al. Haematologica 2020

Clinical course and Prognosis

- Indolent behavior and chronic relapsing course
  (Lasting for years to decades)
- Prolonged survival with persistent disease is common.
- A minor proportion of patients develope progressive and/or transformed disease.
  higher risk with CD4+ phenotype ?

Treatments

- The optimal treatment and management for patients with this disease are not clear.

■ Treatments reported in previous literature

(1) Watchful & Waiting 6cases AWD : All

(2) Steroids 15cases → Effective : 9, AWD : 9, Died : 1

(3) Chemotherapy 16cases → Effective : 0, AWD : 11, Died : 2

(4) Purine analogues 8cases → Effective : 0, AWD : 3, Died : 1

(5) Anti-CD52

- monoclonal antibody 2cases → Effective : 2, AWD : All

Other – Interferon, TNF-inhibitor, Immunosupressant and IFRT (30Gy)*

IFRT (30Gy)* 1case → Effective, CR

AWD : Alive with disease

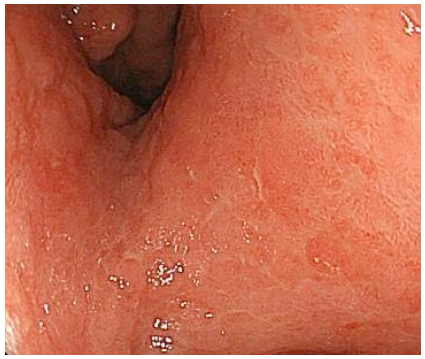
Soderquist, et al; Hematol Onco 2020, Chun-Yan, et al.;WJCC 2022
Malamut, et al; Clin Gastro 2014, Takahashi, et al; JCEH 2020,
Matnani, et al; Hematol Onco 2017

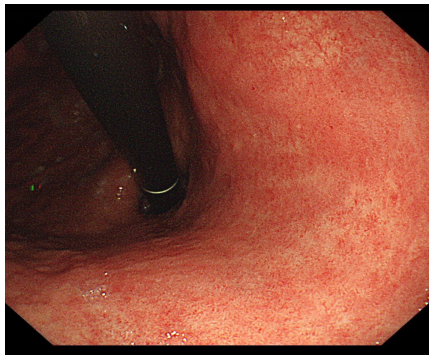
Radiotherapy for ITLPD-GIT with localized lesion

At diagnosis

30Gy/20fr

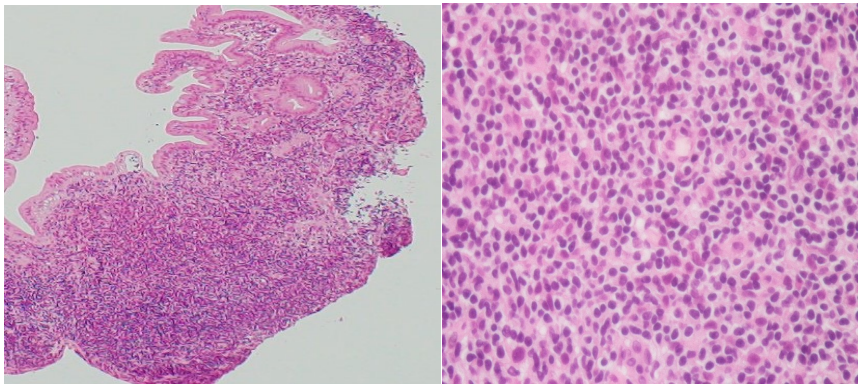
After radiotherapy



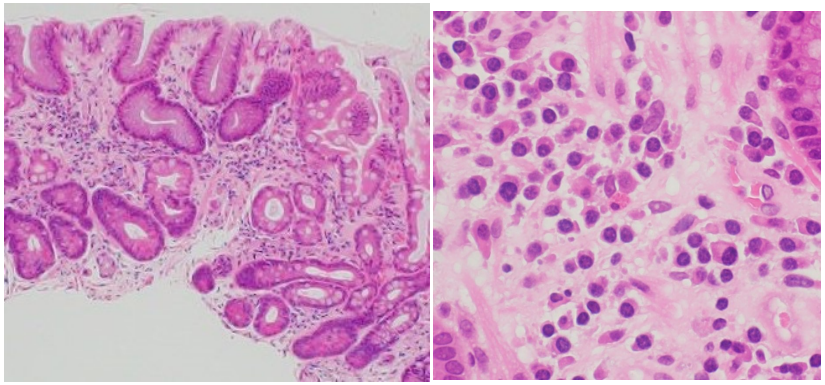


Superficial erosions improved.

H&E



×200 ×400



×200 ×400

Small to medium-sized tumour cells disappear.

Therapeutic Approach