

# The Morphologic Features of Primary Epstein-Barr Virus Infection in the Gastrointestinal Tract

## *An Approach to Correct Diagnosis*

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*Am J Surg Pathol* 2019;43:1253–1263

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# 2017版WHO分类中EBV相关淋巴组织疾病

- EBV+大B细胞淋巴瘤，NOS
- EBV相关皮肤黏膜溃疡
- 慢性炎症相关大B细胞淋巴瘤
- 淋巴瘤样肉芽肿
- 浆母细胞淋巴瘤
- 原发渗出性大B细胞淋巴瘤
- HHV8相关嗜生发中心LPD
- Burkitt淋巴瘤
- 经典型霍奇金淋巴瘤
- 侵袭性NK细胞白血病
- 儿童系统性EBV+T细胞淋巴瘤
- 慢性活动性EBV感染（CAEBV）
- 种痘样水疱病
- 蚊叮超敏反应
- NK/T细胞淋巴瘤，鼻型
- 免疫缺陷相关淋巴增殖性疾病



# 其他EBV相关的淋巴组织疾病

## B细胞

- 传染性单核细胞增多症
- 急性EBV性淋巴结炎
- 急性EBV性咽/鼻炎
- EBV+B-LPD
  - (1) EBV+ 淋巴组织增生
  - (2) EBV+ 结外多形性LPD
  - (3) EBV+结内多形性LPD
- AITL早期病变

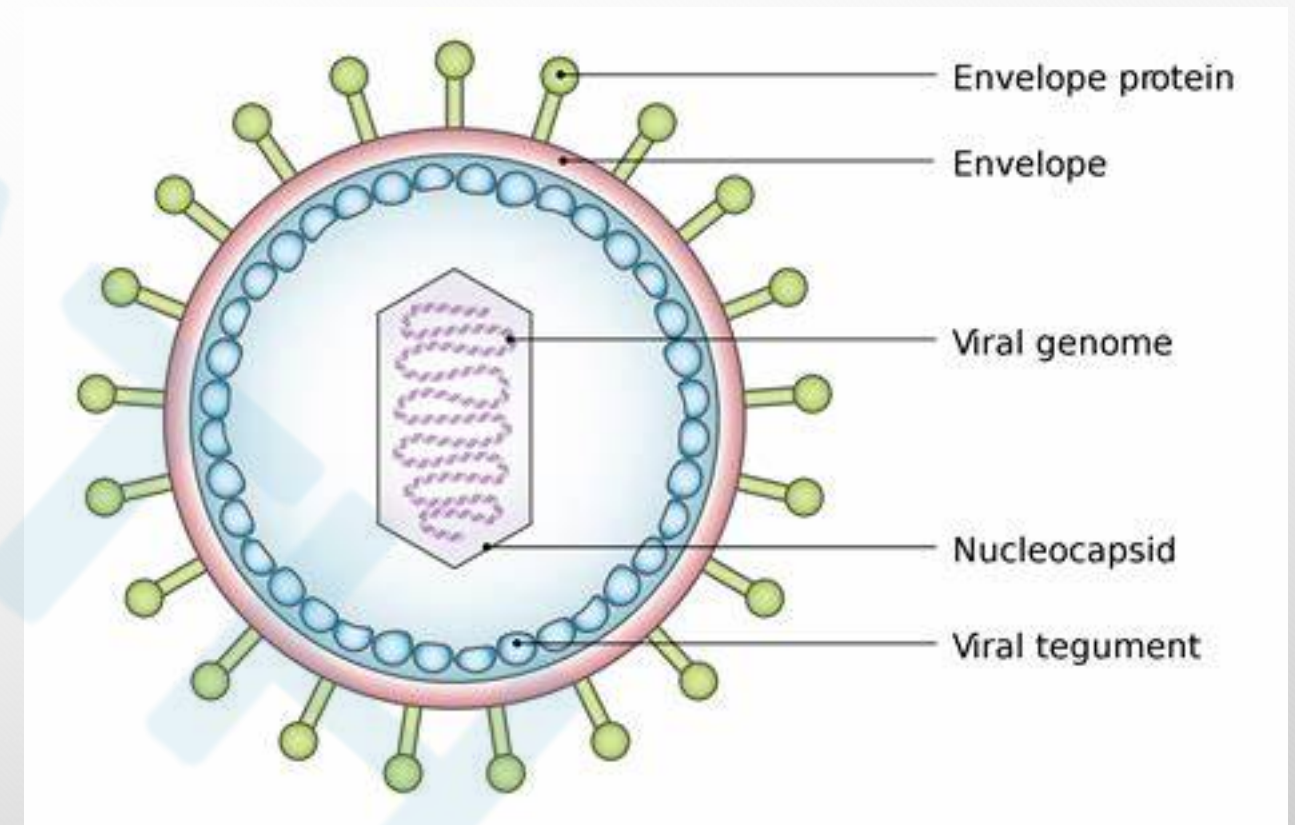
## T细胞

- 传染性单核细胞增多症
- 急性EBV性淋巴结炎
- 急性EBV性鼻/咽炎
- EBV相关的嗜血细胞综合征
- 重症传单
- EBV+结内NK/T细胞淋巴瘤
- EBV+结内细胞毒性T细胞淋巴瘤

Blood. 2011;117(18):4726-4735  
Kato S. et al Histopathol 2012;61:186  
Attygale AP, et al Histopathol 2014;64:171

# EBV的基本情况

- DNA疱疹病毒
- 172kbp
- 100个基因
- 糖蛋白gp350/220（结合B细胞受体 CD21）
- 两种形式：环形、线形





# EBV感染现状

- 全球90%以上人口被EBV感染：血清EBV抗体阳性；
- 中国儿童3岁>50%，8岁>90%被EBV感染

Q2 2.776 [PLoS One](#). 2014 Jun 10;9(6):e99857. doi: 10.1371/journal.pone.0099857. eCollection 2014.

## **Epstein-Barr virus (EBV) infection in Chinese children: a retrospective study of age-specific prevalence.**

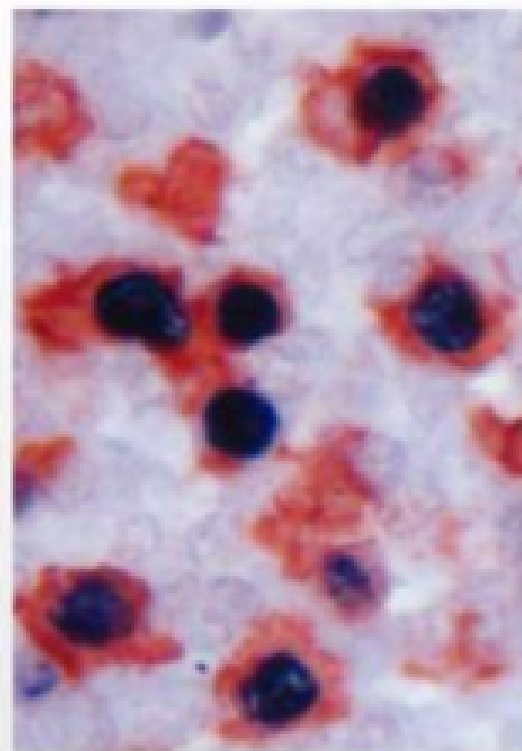
[Xiong G](#)<sup>1</sup>, [Zhang B](#)<sup>2</sup>, [Huang MY](#)<sup>1</sup>, [Zhou H](#)<sup>3</sup>, [Chen LZ](#)<sup>1</sup>, [Feng QS](#)<sup>1</sup>, [Luo X](#)<sup>4</sup>, [Lin HJ](#)<sup>5</sup>, [Zeng YX](#)<sup>1</sup>.

Q2 2.776 [PLoS One](#). 2015 Jan 23;10(1):e0115836. doi: 10.1371/journal.pone.0115836. eCollection 2015.

## **A large-scale seroprevalence of Epstein-Barr virus in Taiwan.**

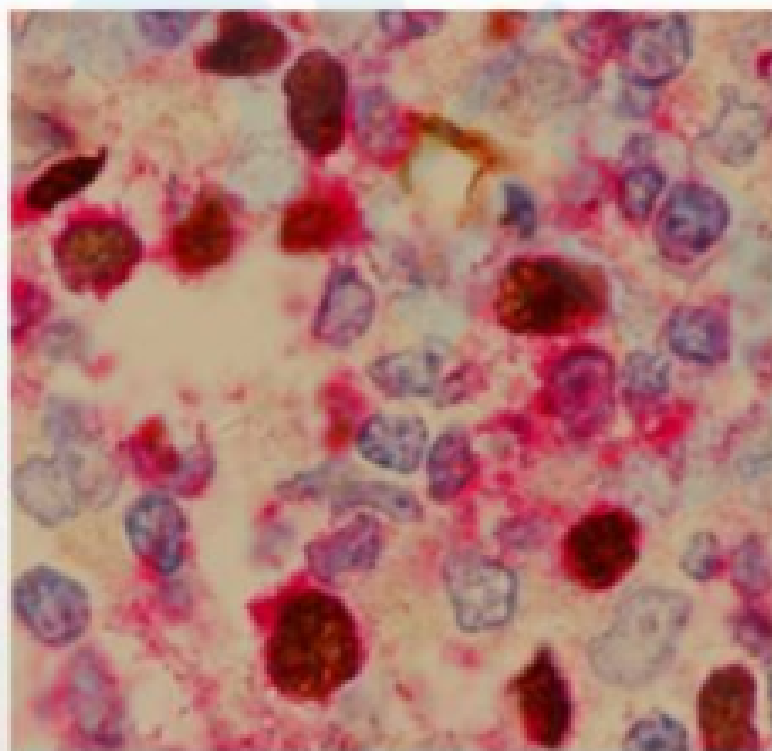
[Chen CY](#)<sup>1</sup>, [Huang KY](#)<sup>2</sup>, [Shen JH](#)<sup>1</sup>, [Tsao KC](#)<sup>3</sup>, [Huang YC](#)<sup>1</sup>.

# EBV感染何种细胞？



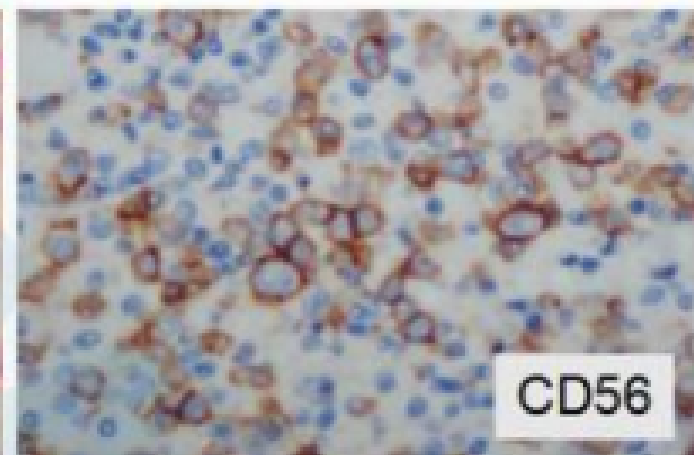
EBER/CD20

B细胞



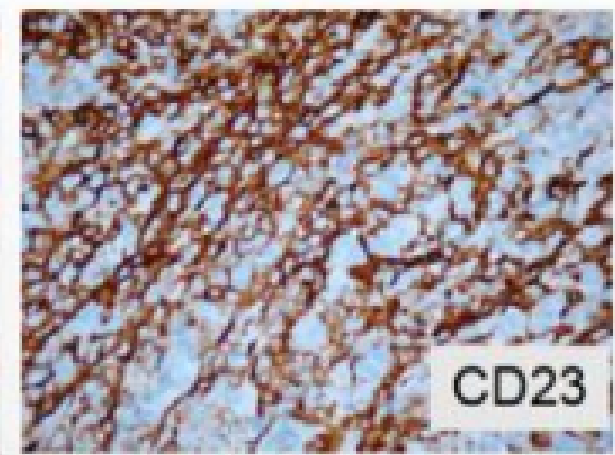
EBER/CD3

T细胞



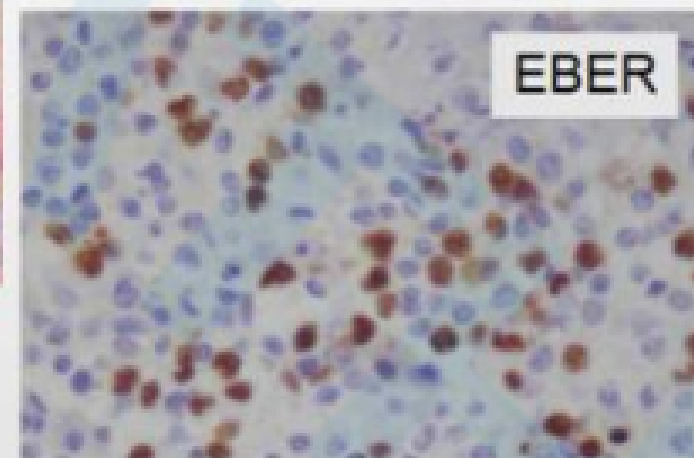
CD56

NK细胞

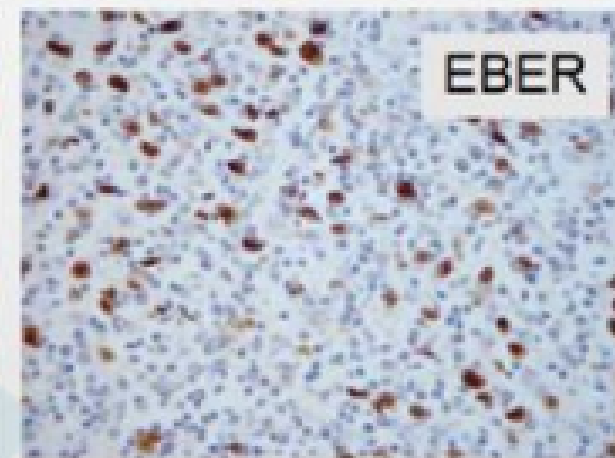


CD23

树突细胞



EBER



EBER



# EBV检测方法

- 血清抗体：酶联免疫法；
- 血液DNA含量：定量PCR；
- 组织中EBV抗原：免疫组化；
- 组织细胞中RNA：EBER原位杂交
- 组织细胞中DNA：EBV-DNA原位杂交
- EBV克隆性检测：Southern Blot
- EBV基因测序：一代、二代测序

# EBV相关淋巴组织疾病的可能关系



## 急性感染

潜伏感染

传单

EBV淋巴结炎

## CAEBV (LPD)

EBV+B-LPD:

- CAEBV-B type

EBV+T-LPD:

- CAEBV-T/NK type

- HV-like LPD/淋巴瘤

- 蚊叮超敏反应

## 淋巴瘤

Burkitt

EBV+DLBCL

HL

NK/T细胞淋巴瘤

etc.



# 慢性活动性 EBV 感染 (CHRONIC ACTIVE EBV INFECTION, CAEBV)

- 传染性单核细胞增多症样症状\*持续 3 个月以上
- 外周血 EBV DNA  $> 10^{2.5}$  copies/mg
- 器官病变的组织学证据
- 病变组织内 EBV 原位杂交 EBER+, 或 EB 病毒核抗原 (EBNA) +, 或 EB 病毒编码的潜伏性膜蛋白 (LMP1/2) +
- 患者无免疫缺陷、恶性或自身免疫性疾病

\*传单样症状：发热、肝脾肿大、淋巴结肿大

# CAEBV的形态学变化

细胞形态变化较大，多数是中小淋巴细胞，少数大细胞，可有轻度异型性

- 淋巴结：副皮质区扩张明显，滤泡缩小或消失（早期可增生）；可有灶状坏死和散在核碎片
- 结外病变：散在或灶状淋巴细胞浸润，数量不等，可有灶状坏死和核碎
  - 肝脏：肝窦内和汇管区数量不等的小淋巴细胞浸润
  - 脾脏：脾脏红髓内散在和灶状中小淋巴样细胞浸润
  - 骨髓：无明显异常或有散在淋巴样细胞浸润
  - 皮肤：淋巴细胞主要在真皮层的血管和皮肤附属器周围浸润



# CAEBV的分级

| 分级 | 细胞学 | 克隆性 | 性质  |
|----|-----|-----|-----|
| A1 | 多形性 | 多克隆 | 增生  |
| A2 | 多形性 | 单克隆 | 交界  |
| A3 | 单形性 | 单克隆 | 淋巴瘤 |
|    |     |     |     |
| B  | 单形性 | 单克隆 | 淋巴瘤 |



# CAEBV形态学评判标准

## 非皮肤、黏膜病变

- 1级：固有组织结构基本保留，破坏不明显；细胞轻度异型，形态以中小淋巴细胞为主；
- 2级：固有组织结构部分保留，部分破坏；细胞轻/中度异型，形态以中小淋巴细胞为主，核不规则；
- 3级：固有组织结构破坏消失；细胞中/重度异型，形态以中至大的多形性淋巴细胞为主，核明显不规则，染色质粗糙，核仁大而清晰。

## 皮肤、黏膜病变

- 1级（增生性）：病变累及真皮浅层，或黏膜层，细胞无明显或轻度异型性；
- 2级（交界性）：病变累及真皮深层，或黏膜下浅肌层，细胞有轻至中度异型性；
- 3级（肿瘤性）：病变累及真皮全层至皮下脂肪，或黏膜下深肌层（或全层），细胞单一，异型性明显



# 免疫表型及基因型

- T 细胞 59%
- NK 细胞 41%
- T and NK 混合 4%
- B 细胞：罕见
- CD4+ >> CD8+; TIA1+、GrB+
- 细胞可呈单克隆（多数）、寡克隆和多克隆
- EBER+

# 胃肠道EBV感染现状及研究目的

- 现状

- 无其他病毒感染特征（病毒包涵体）；
- 常误诊为IBD、EBV相关淋巴瘤或其他疾病；
- 死亡率高

- 研究目的——准确、及时诊断原发胃肠道CAEBV

- 原发胃肠道CAEBV（A1/A2级）形态学证据；
- 移植后免疫缺陷患者胃肠道EBV感染的特征；



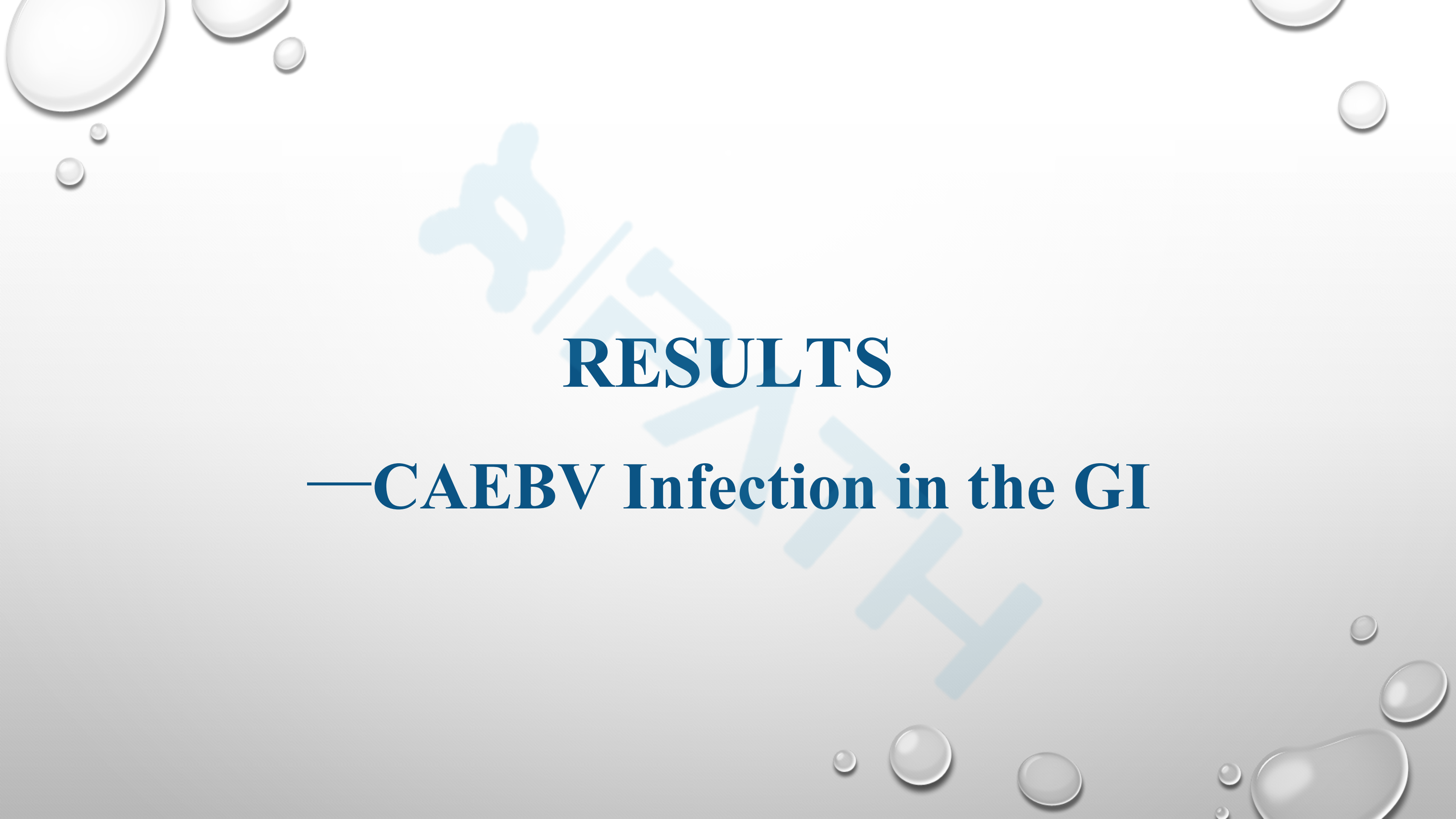
The background features a light gray gradient with several realistic water droplets of varying sizes in the corners. A large, faint, light blue watermark is also visible, consisting of a stylized figure and the text '© 2014 清华大学'.

# **MATERIALS AND METHODS**

# MATERIALS AND METHODS

|             | CAEBV组                     | 移植术后组  |
|-------------|----------------------------|--------|
| 病例来源        | 武汉大学中南医院、洛杉矶加州大学           |        |
| 病例数         | 16                         | 18     |
| 入组标准        | 同前                         | 器官移植术后 |
| EBER原位杂交临界值 | 活检：> 30个/HPF；切除术：> 50个/HPF |        |
| 免疫组化        | T细胞、B细胞、NK细胞标记             |        |
| 基因重排        | TCR                        |        |
| 分级          | G1、G2、G3                   | 无分级    |





# RESULTS

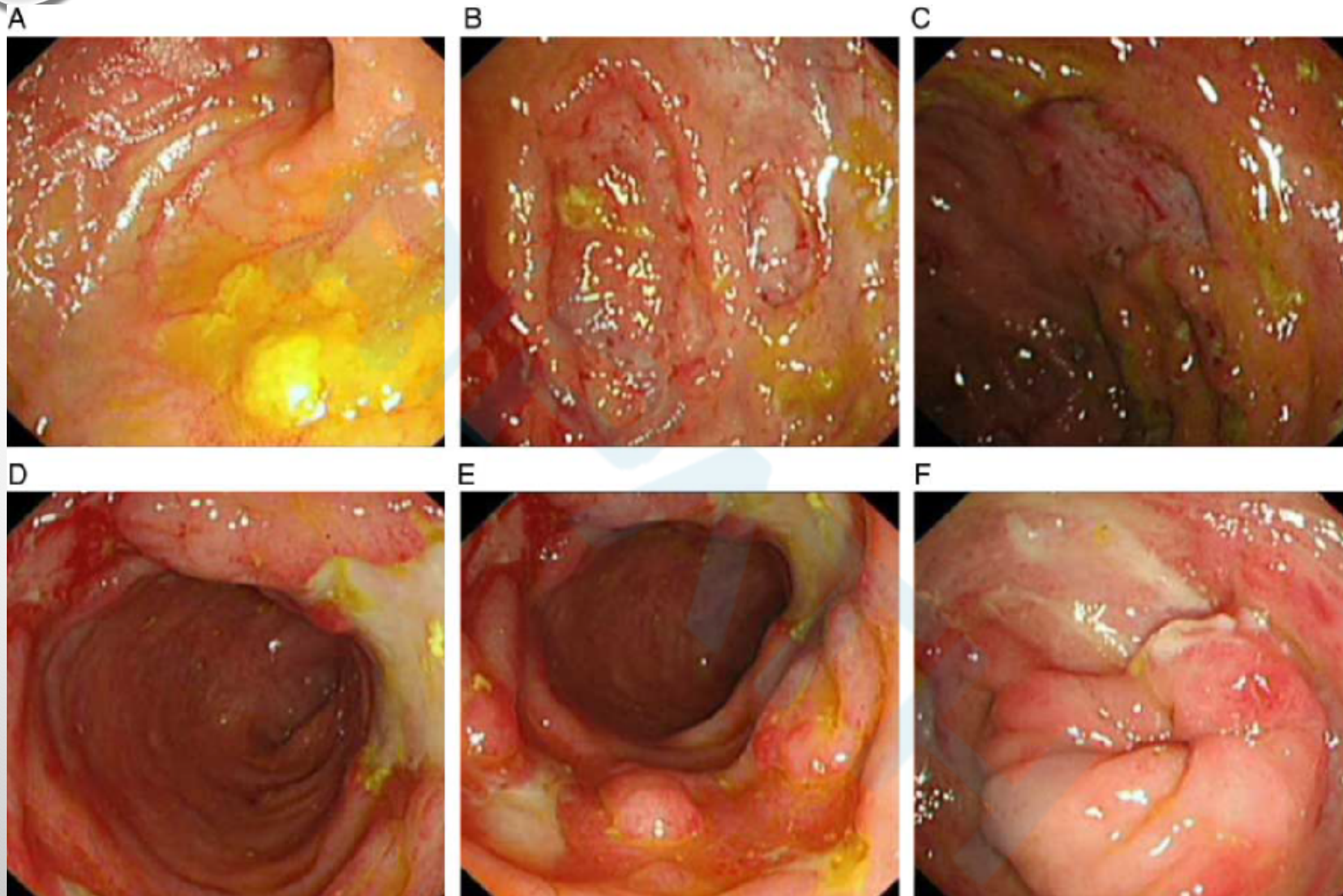
## —CAEBV Infection in the GI

**TABLE 1.** Clinical, Laboratory, and Pathologic Findings in Immunocompetent Patients

| Case No. | Age (y) | Sex    | Organ Involvement    | Sample    | EBV DNA | Duration | Subtype and Grade     | Summary of Pathologic Findings, EBER-positive Cells/HPF                                                                                                                                                                                          | Follow-Up |
|----------|---------|--------|----------------------|-----------|---------|----------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 1        | 50      | Male   | Small bowel          | Resection | 4.5E5   | 1 y      | CAEBV-T-cell, grade 2 | Ulceration, mild crypt distortion in the margin of the ulcer, aggregation of atypical lymphoid cells, and also infiltration of mixed inflammatory cells in submucosa, > 50                                                                       | PR        |
| 2        | 27      | Female | Colon                | Resection | 4.8E5   | 3 y      | CAEBV-T-cell, grade 1 | Ulceration and infiltration of small lymphocytes with little atypia in the mucosa. Lymphoid aggregates and vascular hyperplasia are prominent in the submucosa, > 100 only in mucosa                                                             | PR        |
| 3        | 26      | Male   | Duodenum, lymph node | Biopsy    | 2.52E5  | 1 y      | CAEBV-T-cell, grade 2 | Fragmented tissue with surface necrosis and diffuse lymphoid infiltrates in the lamina propria and submucosa. Atypical rounded, medium-sized lymphocytes infiltrate the epithelium, and karyorrhectic debris is noted, > 100                     | Recovered |
| 4        | 22      | Male   | Colon, spleen        | Biopsy    | 1.02E6  | 3 mo     | CAEBV-T/NK, grade 2   | Multiple biopsies show that the mucosa between ulcerations seems normal, with lymphoid hyperplasia mimicking follicles. The infiltrating lymphocytes exhibit a round shape and increased cytoplasm compared with mature small lymphocytes, > 100 | Died      |
| 5        | 15      | Male   | Ileum, skin          | Resection | 7.2E5   | 1 y      | CAEBV-T/NK, grade 2   | Diffuse infiltration of atypical lymphocytes in lamina propria, and karyorrhexis and focal necrosis are noted, > 200                                                                                                                             | Died      |
| 6        | 26      | Female | Colon                | Resection | 4.06E4  | 1.5 y    | CAEBV-T-cell, grade 2 | Ischemic change and ulceration in mucosa without obvious crypt abnormality. Scattered polymorphic lymphocytes infiltrates the intestinal wall (monoclonal TCR rearrangement), > 100                                                              | Recovered |
| 7        | 28      | Male   | Colon                | Biopsy    | 2.0E5   | 6 mo     | CAEBV-T/NK, grade 2   | No crypt abnormality, lymphoid infiltrates in mucosa and submucosa with mild atypia (monoclonal TCR rearrangement), > 100                                                                                                                        | PR        |
| 8        | 51      | Male   | Colon, mouth         | Biopsy    | 3.76E5  | 16 y     | CAEBV-T-cell, grade 1 | Ulceration of the mucosa with scattered small lymphocytes in the lamina propria and submucosa, > 200                                                                                                                                             | PR        |

患者年轻，平均年龄30岁；  
 病变持续3个月-16年；  
 1级患者持续时间长；  
 外周血EBV DNA拷贝数均超过10<sup>3</sup>；





**FIGURE 1.** Colonoscopic images from case 4 show sporadically distributed ulcerations in different parts of the GI tract, including the terminal ileum (A), ileocecal region (B, C), descending colon (D, E), and sigmoid colon (F). The clinical impression from the colonoscopy was Crohn disease.



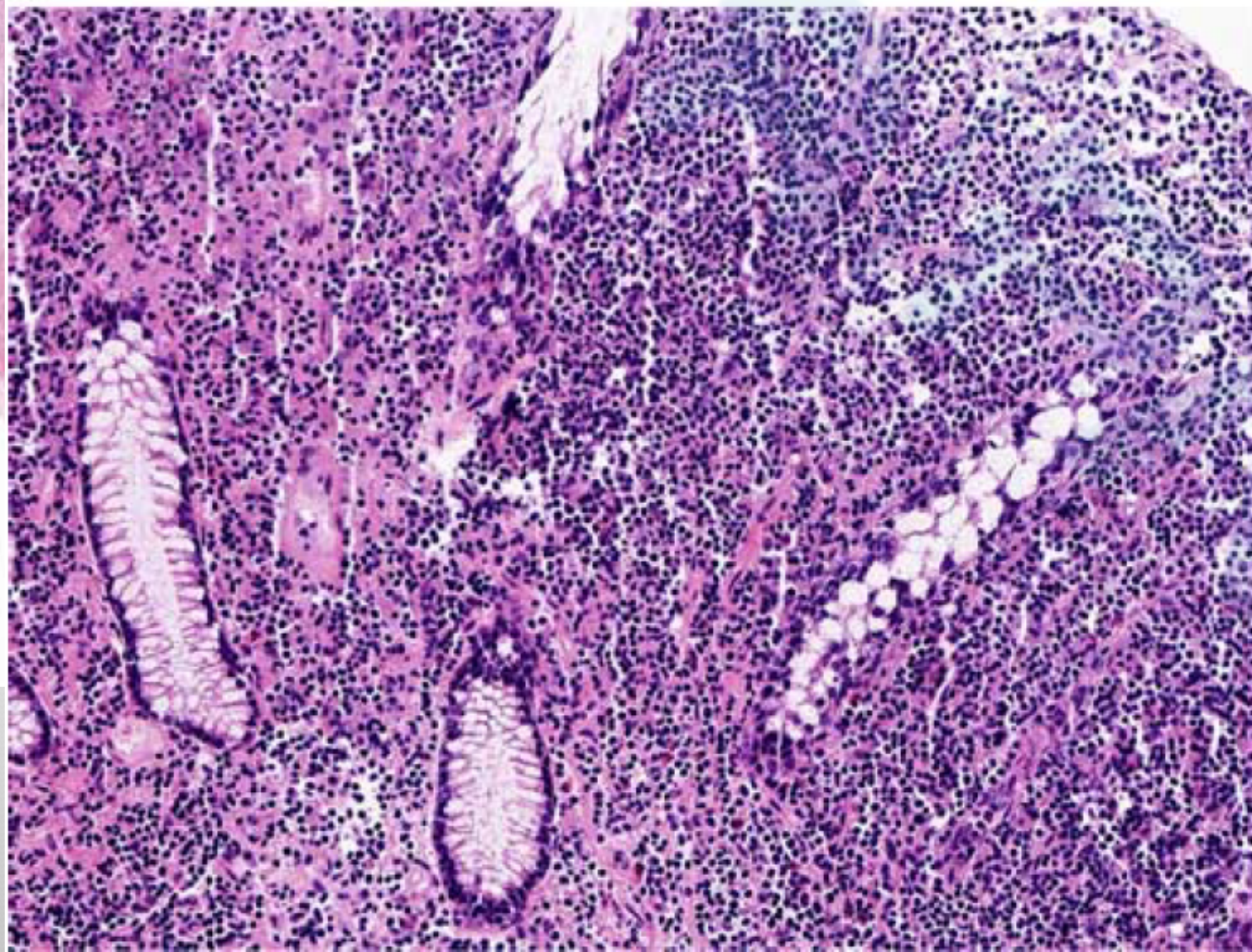
A



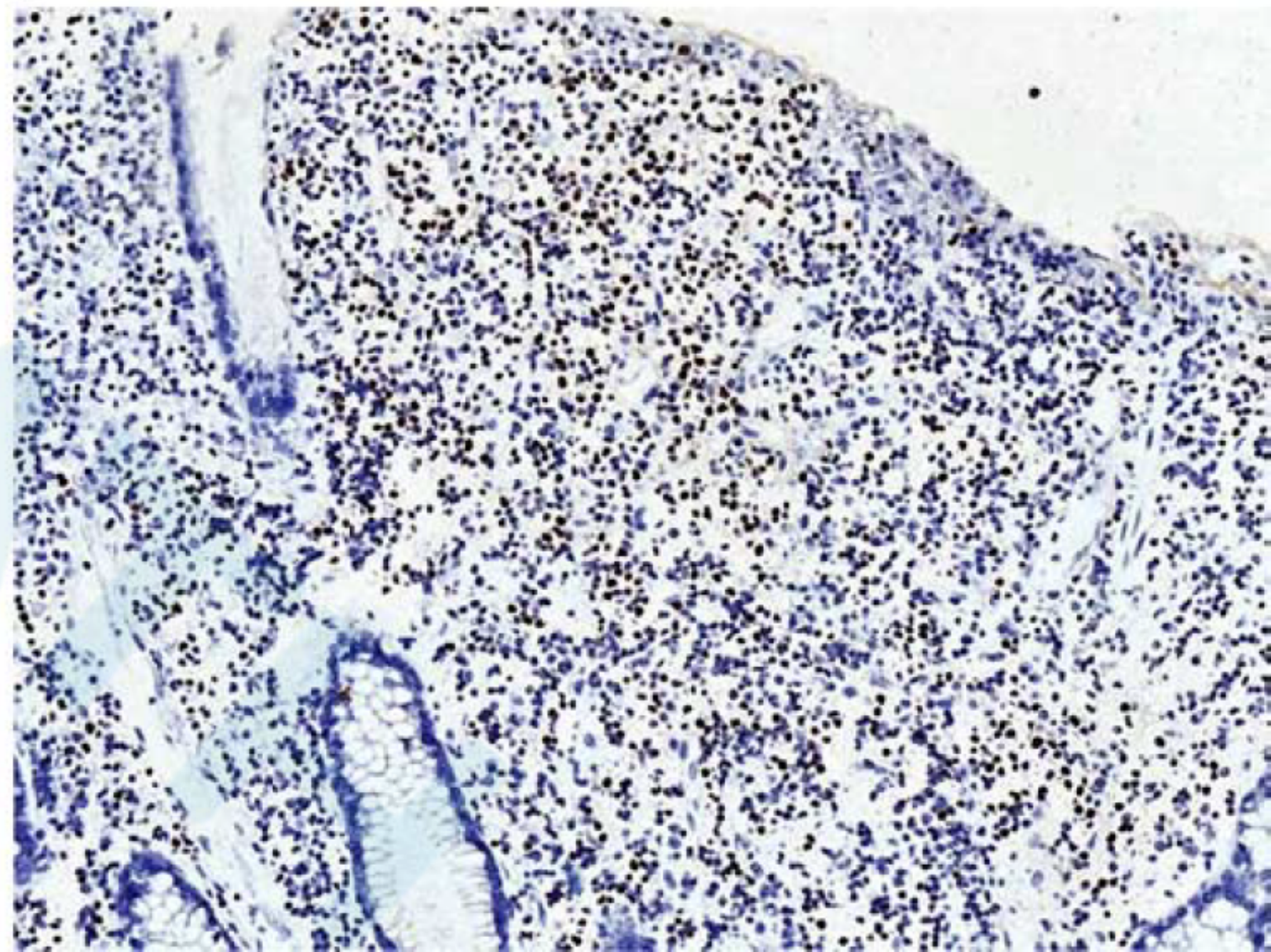
B



C

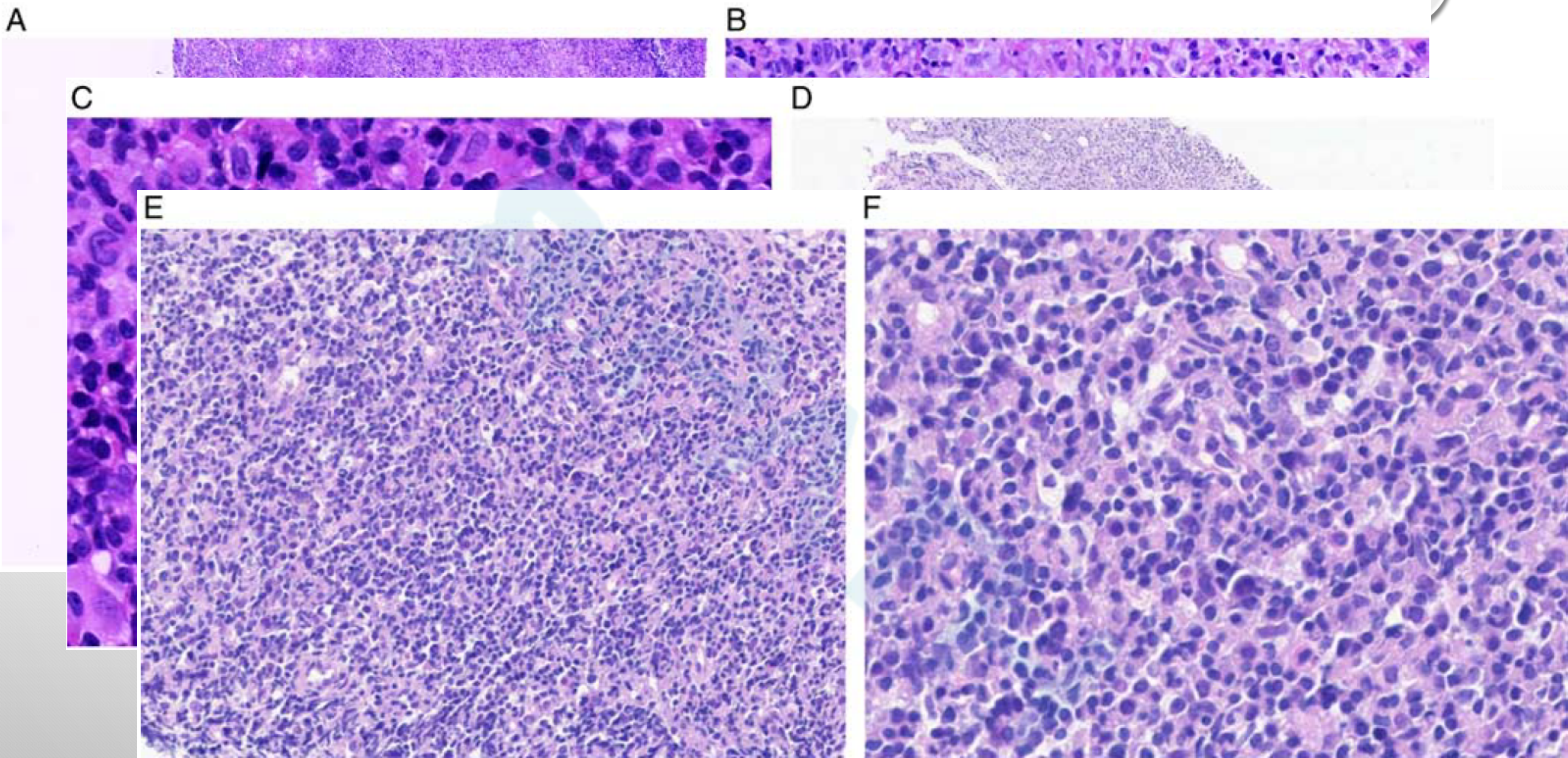


D



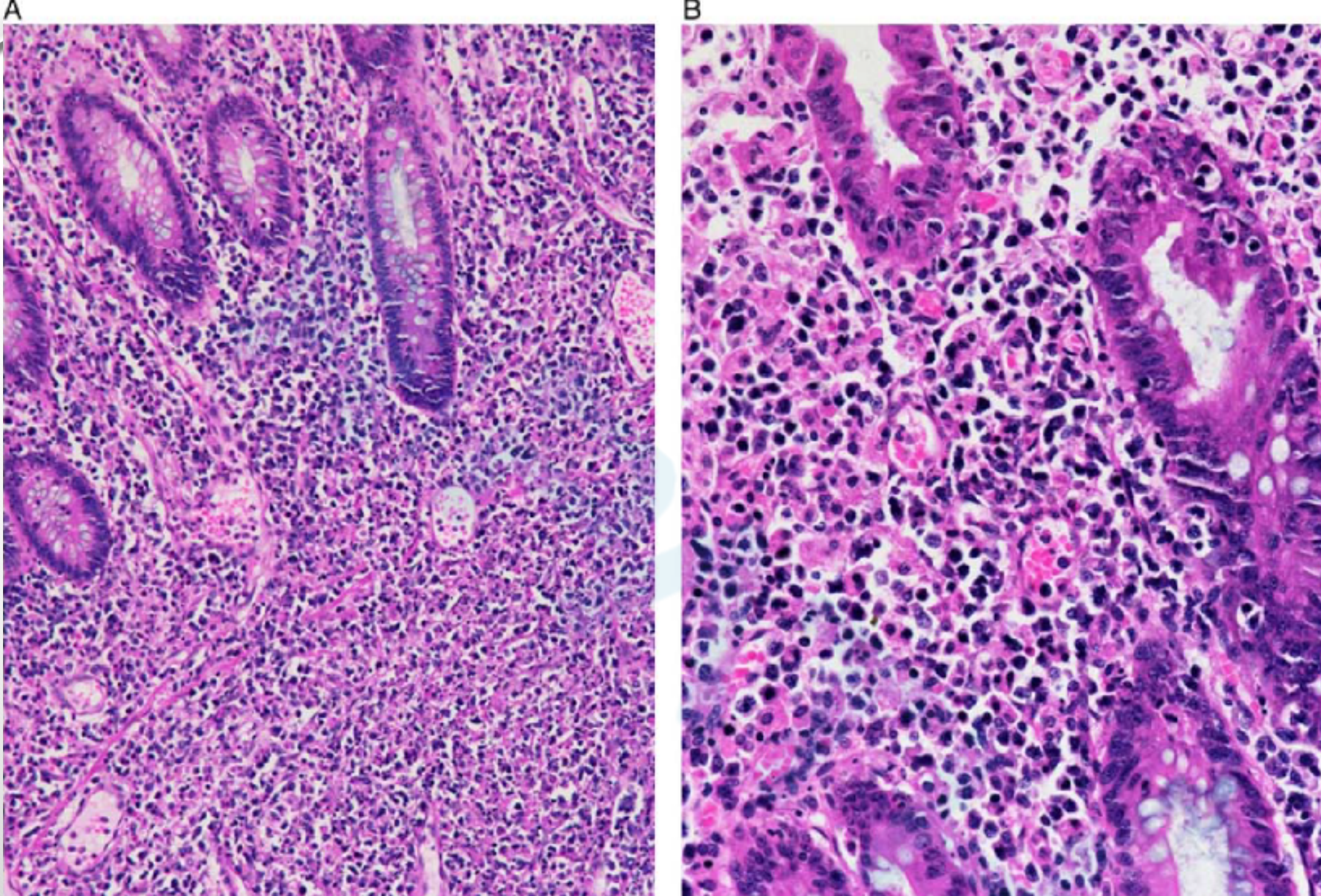
**FIGURE 2.** From case 2, sections of the resected colon from a 27-year-old woman with gastrointestinal symptoms for 3 years. A low-power view shows ulceration of the mucosa and an expanded submucosal layer (A, the box indicating the area shown in B and C at higher power view). Lymphoid aggregates and vascular hyperplasia are prominent in the submucosa as well (B). A high-power view shows small lymphocytes with minimal atypia infiltrating the mucosa (C), and ISH for EBER shows numerous positive cells present in the mucosa (D) but not in the deeper tissue.





**FIGURE 3.** From case 3 (A–C), a duodenal biopsy shows fragmented tissue with surface necrosis and diffuse lymphoid infiltrates in the lamina propria and submucosa. There are no lymphoid follicles (A). Karyorrhectic debris is noted (B). Atypical rounded, medium-sized lymphocytes infiltrate the epithelium (C). From case 4 (D–F), a 22-year-old man with fever of unknown origin, intermittent abdominal pain, and hematochezia for 3 months. His blood EBV DNA copy number was 1.02E6. Colon biopsies show that the mucosa between ulcerations appears normal, with lymphoid hyperplasia mimicking follicles (the box in D indicating the area shown in E and F at higher power view). The infiltrating lymphocytes exhibit a round shape and increased cytoplasm compared with mature small lymphocytes (E, F). He was ultimately diagnosed with EBV-associated T/NK LPD, grade 2.





**FIGURE 4.** From case 5, ileal resection due to perforation in a 15-year-old boy. The sections show diffuse infiltrates of atypical lymphocytes and prominent karyorrhexis (A, B). Similar findings were also seen in biopsies from other organs including the skin. He was diagnosed with EBV-positive T/NK-cell LPD and died after the operation.



## 免疫组化及基因型——G2

- 阳性：EBER原位杂交、CD3、CD8、CD56、CD30(强弱不等)
- 阴性：CD4
- 所有做TCR重排的病例均显示TCR单克隆性重排



# 随访结果

- 经过治疗后，6/8例患者部分或完全缓解；
- 2/8例在发展为淋巴瘤前死于EBV感染并发症（肠穿孔、大出血、血栓）





# RESULTS

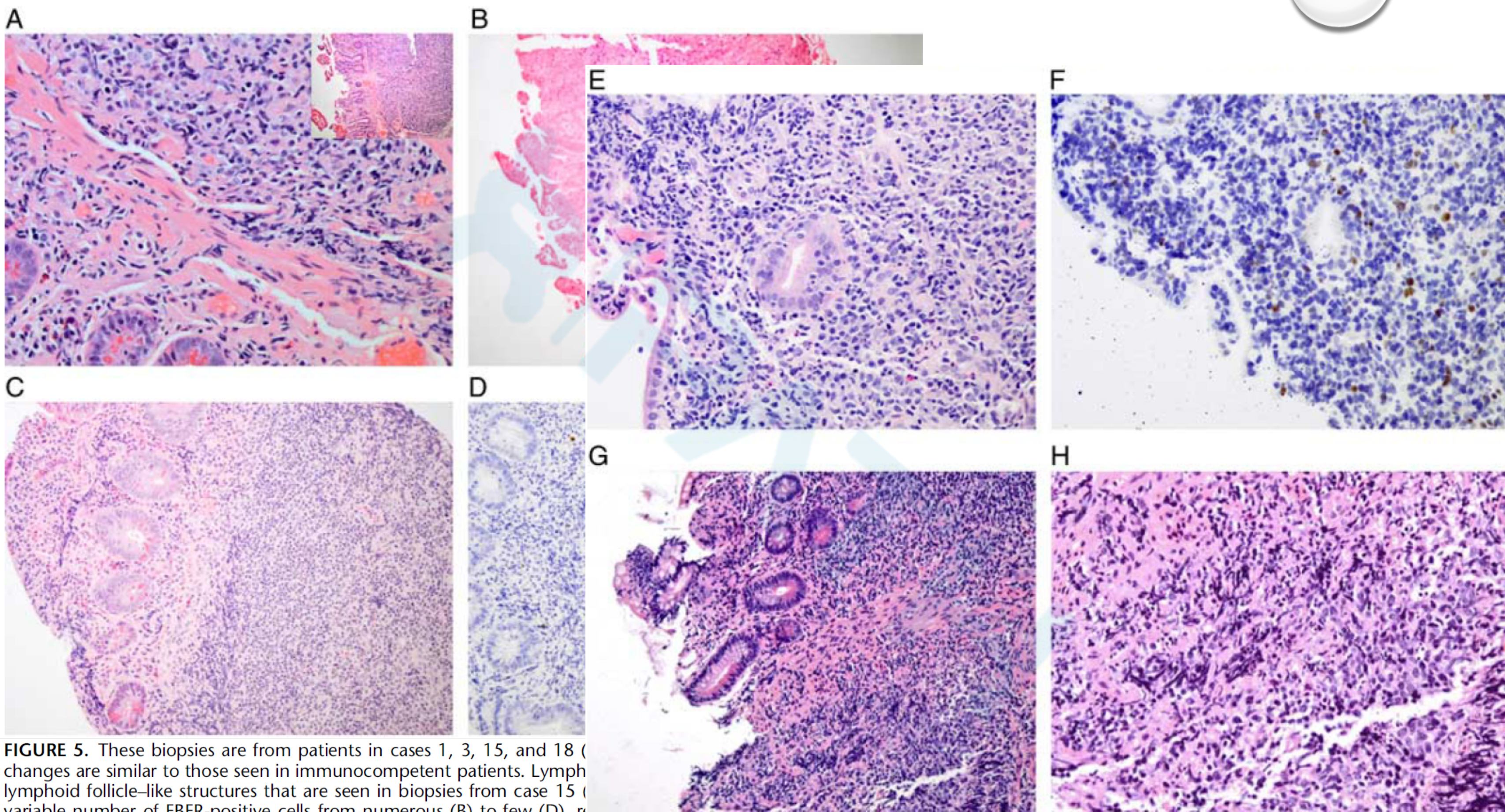
—EBV Infection in the GI After Transplantation



**TABLE 2.** Clinical and Laboratory Findings in Immunocompromised (Posttransplant) Patients

| Case No. | Age (y) | Sex    | EBV DNA<br>(Copies/mg)                                                                                                                                                | Summary of Pathologic Findings, and EBER-positive Cells/HPF                                   | Onset of EBV Viremia<br>After Transplant (y) |
|----------|---------|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------|
| 1        | 15      | Male   | 78                                                                                                                                                                    | Mildly increased lymphocytes in lamina propria with karyorrhexis, 15                          | 5                                            |
| 2        | 8       | Female | 334                                                                                                                                                                   | Lymphoid hyperplasia is noted with no increase in crypt apoptotic                             | 0                                            |
| 3        | 3       | Female | <ul style="list-style-type: none"> <li>● 移植后检测到外周血EBV阳性时间从1年-7年不等</li> <li>● 所有患者外周血EBV DNA10-2000拷贝，但大部分患者无临床症状；</li> <li>● 组织中EBER原位杂交阳性细胞数与外周血EBV载量不一致；</li> </ul> | erosion, > 100                                                                                | 3                                            |
| 4        | 5       | Male   |                                                                                                                                                                       |                                                                                               | 2                                            |
| 5        | 13      | Female |                                                                                                                                                                       |                                                                                               | 0                                            |
| 6        | 5       | Male   |                                                                                                                                                                       |                                                                                               | NA                                           |
| 7        | 28      | Female |                                                                                                                                                                       | 0                                                                                             | 1                                            |
| 8        | 57      | Female |                                                                                                                                                                       |                                                                                               | NA                                           |
| 9        | 13      | Male   |                                                                                                                                                                       |                                                                                               | 0                                            |
| 10       | 13      | Male   |                                                                                                                                                                       |                                                                                               | 0                                            |
| 11       | 13      | Female |                                                                                                                                                                       |                                                                                               | NA                                           |
| 12       | 28      | Male   |                                                                                                                                                                       | 2565                                                                                          | 5                                            |
|          |         |        |                                                                                                                                                                       | No histopathologic abnormality and a few benign-appearing lymphoid aggregates are noted, 30   |                                              |
| 13       | 39      | Male   | 10                                                                                                                                                                    | Minimally increased crypt apoptotic activity, 10                                              | NA                                           |
| 14       | 8       | Female | 188                                                                                                                                                                   | Benign-appearing lymphoid aggregates present, 10                                              | NA                                           |
| 15       | 34      | Male   | 186                                                                                                                                                                   | Large aggregate comprised of lymphocytes with round shape and increased cytoplasm, > 100      | NA                                           |
| 16       | 12      | Female | 54                                                                                                                                                                    | Atypical lymphoid proliferation with lymphoepithelial lesions, > 100                          | NA                                           |
| 17       | 10      | Male   | 752                                                                                                                                                                   | Focal dense lymphoplasmacytic infiltrates, 20                                                 | 0                                            |
| 18       | 20      | Male   | 116                                                                                                                                                                   | Mucosa with lymphoid hyperplasia mimicking lymphoid follicle and medium-sized lymphocytes, 20 | 0                                            |





**FIGURE 5.** These biopsies are from patients in cases 1, 3, 15, and 18 (changes are similar to those seen in immunocompetent patients). Lymphoid follicle-like structures that are seen in biopsies from case 15 (C) contain a variable number of EBV-positive cells from numerous (B) to few (D), respectively. Moreover, lymphoepithelial lesions are easily identified in case 3 (E), which is positive for EBV on EBV staining (F). Karyorrhexis is found in case 1 (G, H).



# DISCUSSION



# DISCUSSION

- 由于诊断经验受限，原发胃肠道EBV感染常被忽略或误诊
  - 传单样病变
  - CAEBV
- 本研究中患者均较年轻，与之前报道类似
- 内镜检查无特异性改变，对诊断本类疾病帮助较小
- 影像学可提示胃壁/肠壁轻微增厚，或肠系膜淋巴结肿大



# 如何准确诊断胃肠道CAEBV?

结合组织学改变、临床病史及实验室检查：

- 除实验室检查异常外，症状持续至少3个月；
- EBV阳性细胞数需超过临界值（ $\geq 30$ 个/HPF）；
  - G1：形态学改变轻微，EBER原位杂交更重要；
  - G2：细胞有异型，CD8+
- 需除外其他病变

单纯疱疹病毒感染，IBD伴/不伴EBV感染，NK/T细胞淋巴瘤，EBV+外周T细胞淋巴瘤，EBV相关皮肤黏膜溃疡



## CAEBV vs. IBD

- CAEBV除IBD样症状外，还可出现间断高热，不规则、小、表浅溃疡；
- EBER原位杂交；
- CAEBV更常出现：急骤/间断高热、肝脾肿大、广泛淋巴结肿大、EBV DNA载量升高；
- IBD可伴发EBV感染；IBD经治疗后可感染EBV；
- 炎症性黏膜更容易受EBV感染



# CAEBV vs. NK/T细胞淋巴瘤

两者组织学特征相似，并CD56、EBER均阳性；

## CAEBV

- 系统性症状；
- 疾病初期实验室检查异常；
- 疾病复发、持续几个月至几年，并逐渐恶化

## NK/T细胞淋巴瘤

- 疾病初期病变局限；
- 逐渐转移至全身



# CAEBV vs. EBV相关皮肤黏膜溃疡

- EBV相关皮肤黏膜溃疡是一种发生于口咽、皮肤、胃肠道的B细胞淋巴组织增殖性疾病；
- 发病机理、临床过程、大体、镜下及免疫表型与CAEBV均不相同；
  - 医源性免疫低下、老年患者；
  - 孤立的、局限性的溃疡；
  - 肿瘤细胞为B细胞
  - 自限性病变，停药或保守治疗效果好



# 治疗及预后

- 治疗方案依据感染的细胞类型及患者全身情况
  - B细胞感染：美罗华
  - T/NK细胞感染：输注血清球蛋白+糖皮质激素+环孢素
- 最有效的治疗方法：同种异体造血干细胞移植；
- 早期识别并发症是关键：血栓、多器官衰竭、胃肠道出血/穿孔、心肌炎、冠状动脉瘤、败血症



## 总结

- 识别形态学线索对于准确诊断胃肠道EBV感染至关重要；
- CAEBV G1：病变轻微，黏膜固有层可见小淋巴细胞聚集，黏膜腺体无破坏；
- CAEBV G2：不典型淋巴细胞，胞浆丰富，聚集成淋巴滤泡样结构，淋巴上皮内病变，局灶坏死、核碎裂；
- 对于可疑EBV感染病例，尤其是年轻患者，应详尽了解临床病史、实验室检查及EBER原位杂交情况；
- CAEBV分良性、交界性、恶性，预后差别大，准确诊断极为重要。



# ■ THANK YOU

Any questions?

