

## BACKGROUND

Age-related EBV-associated lymphoproliferative disorder (AR-EBVLPD) has emerged as a new subset of B-cell lymphoproliferative disorders. We report a unique case of AR-EBVLPD with a widespread gastrointestinal presentation and subsequent transformation to EBV-associated T-cell lymphoma. To our knowledge, this is the first report of a generalized polymorphic extranodal AR-EBVLPD with subsequent transformation to EBV-induced T-cell lymphoma

## CLINICAL HISTORY

The patient was a 70 year old woman who presented with worsening nausea, vomiting and weight loss over the preceding 2 months. The patient underwent upper gastrointestinal endoscopies with biopsy of esophagus, stomach and small bowel, which revealed severe chronic and active inflammation.

A repeat gastrointestinal endoscopy revealed gastric outlet obstruction with luminal narrowing and wall thickening from the gastric antrum to the 2nd portion of duodenum. She underwent exploratory laparoscopy with distal subtotal gastrectomy with Roux-en-Y and perigastric lymph node biopsies. Pathology again showed extensive chronic inflammation through-out the stomach and duodenum. Rare EBV positive cells were present in gastric and small bowel mucosa. Perigastric lymph nodes showed reactive follicular hyperplasia.

She initially did well, but her clinical condition worsened with persistent nausea and vomiting, failure to thrive and a new finding of generalized lymphadenopathy. Due to severe malnutrition with continuous weight loss, the patient was re-admitted and a jejunostomy tube was placed. Her course was further complicated by pulmonary embolism, aspiration pneumonia, upper urinary tract infection, and persistent atrial and ventricular tachycardia. Biopsy of the cervical lymph node, small bowel, stomach and esophagus showed EBV-positive polymorphic lymphoid infiltrate with evolving T-cell lymphoma in the lymph node and esophagus. Her condition continued to deteriorate with hypotension and increased GI bleeding. She ultimately expired 1 month after the admission (2 years after the initial presentation).

## MATERIALS AND METHODS

Formalin-fixed, paraffin-embedded (FFPE) tissue sections were processed for routine Hematoxylin and Eosin (H&E) stains. Immunohistochemistry was performed on FFPE sections using an automated immunohistochemical stainer according to the manufacturer's specification (Ventana Medical System, Tucson, AZ). Double staining for EBER/CD20 was performed on selected specimens. FFPE tissue sections were first stained with EBER using a standard procedure from the manufacturer (Ventana, Tucson, AZ). The EBER stained slides were then stained with CD20 using a manual procedure.

Immunoglobulin heavy chain (IGH) gene rearrangement and T-cell receptor (TCR) gamma gene rearrangement were analyzed by polymerase chain reaction (PCR) using BioMed2 kits and T-cell receptor gamma gene rearrangement assay respectively according to the manufacturer's specification (InVivoScribe Technologies, Carlsbad, CA). DNA was extracted from FFPE tissue sections and quantified using a spectrophotometer. The BioMed IGH kit frameworks 1, 2 and 3 master mix and T-Cell Receptor Gamma mix 1 and 2 were combined with patient's DNA and underwent PCR amplification according the manufacturer's specification. The amplified products were analyzed on an ABI 310 gene analyzer (Applied Biosystems, Foster City, CA).

## RESULTS

Histologic sections from esophagus, stomach and duodenum from the initial endoscopic biopsy and subsequent partial gastrectomy showed prominent expansion of lamina propria with a diffuse infiltration of polymorphic lymphoplasmacytic infiltrate. Rare scattered EBV positive cells were present (Figure 1).

Histologic sections of the esophagus, stomach and duodenum from the 2nd admission showed similar findings to the previous biopsies with marked polymorphic infiltration in all specimens. In addition, there were increased large cells in esophagus. Scattered EBV positive cells were present. Histologic sections from the cervical lymph nodes showed marked expansion of paracortical zone with a polymorphic infiltration containing blood vessels, plasma cells, small lymphocytes, and scattered large atypical lymphocytes. The large cells showed morphology of plasmablasts and/or immunoblasts. Focal clusters of large cells were present. Immunohistochemistry of the lymph node revealed a predominance of T cells that expressed CD2, CD3, CD4, CD5, CD7 and were negative for CD8, CD56. The T cells included both small mature cells and large atypical cells. Numerous EBV positive cells were present (Figure 2).

Histologic sections from the autopsy showed a widespread polymorphic lymphoplasmacytic infiltrate involving the gastrointestinal tract, lungs, liver, pancreas, adrenal glands, and lymph nodes. The esophageal mucosa was expanded by solid sheets of intermediate- to large-sized lymphocytes. These lymphocytes showed atypical morphology with an irregular nuclear contour. Immunohistochemistry showed uniform, strong expression of CD3 in all the atypical cells. The atypical cells were strongly positive for EBV by EBER in situ hybridization (Figure 3).

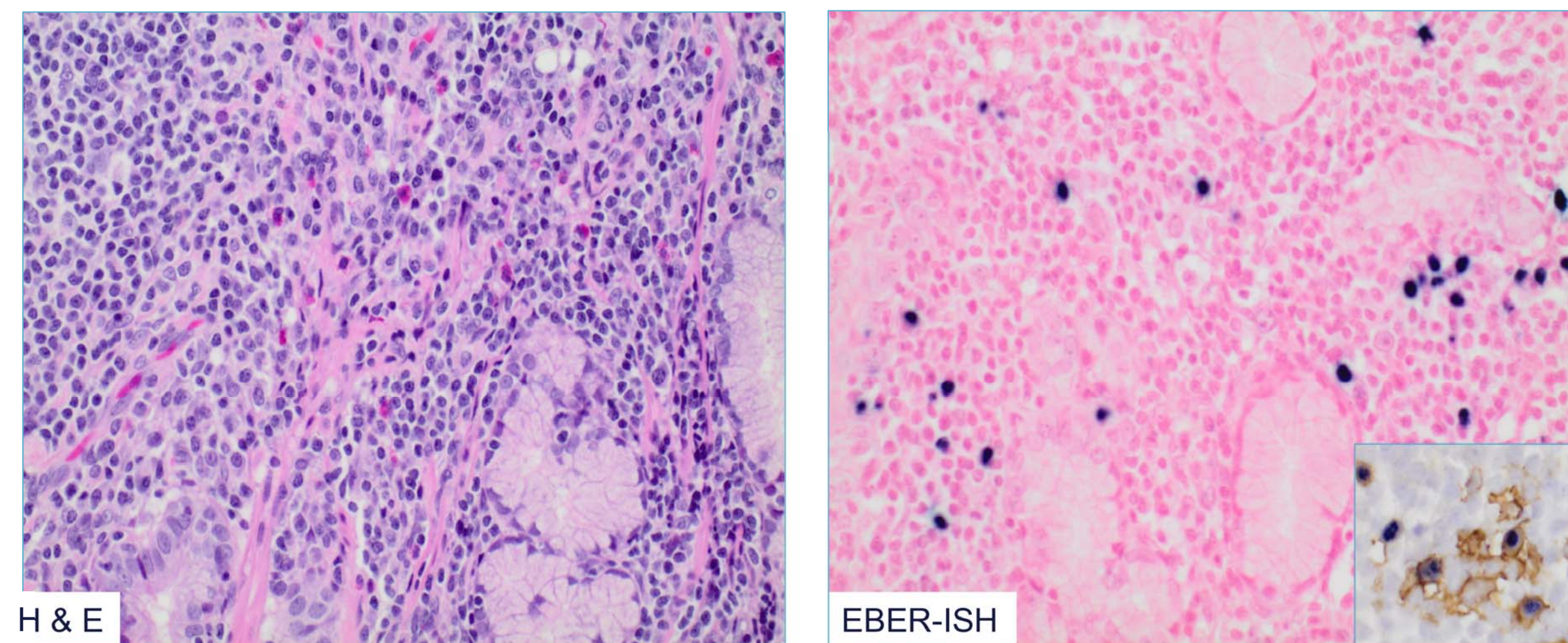


Figure 1: Gastrectomy specimen showing lymphoplasmacytic infiltrate and EBV positive (inset, double EBER and CD20 stains)

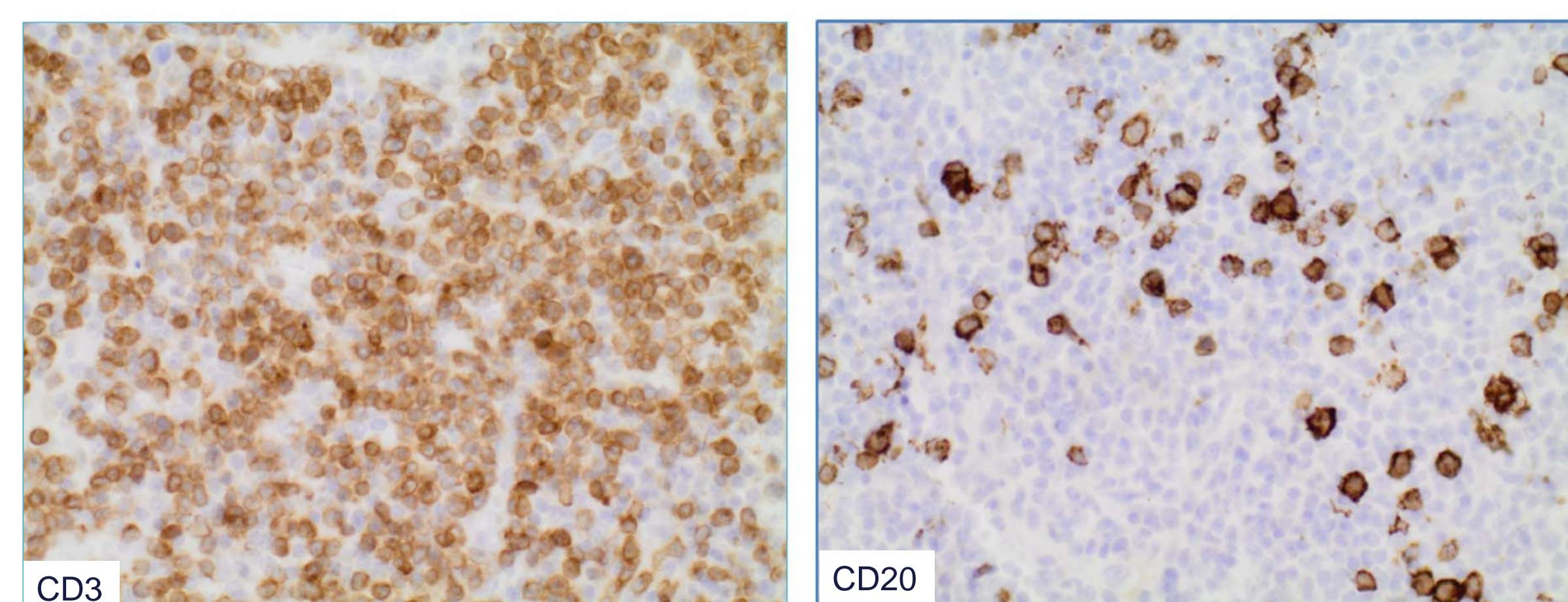
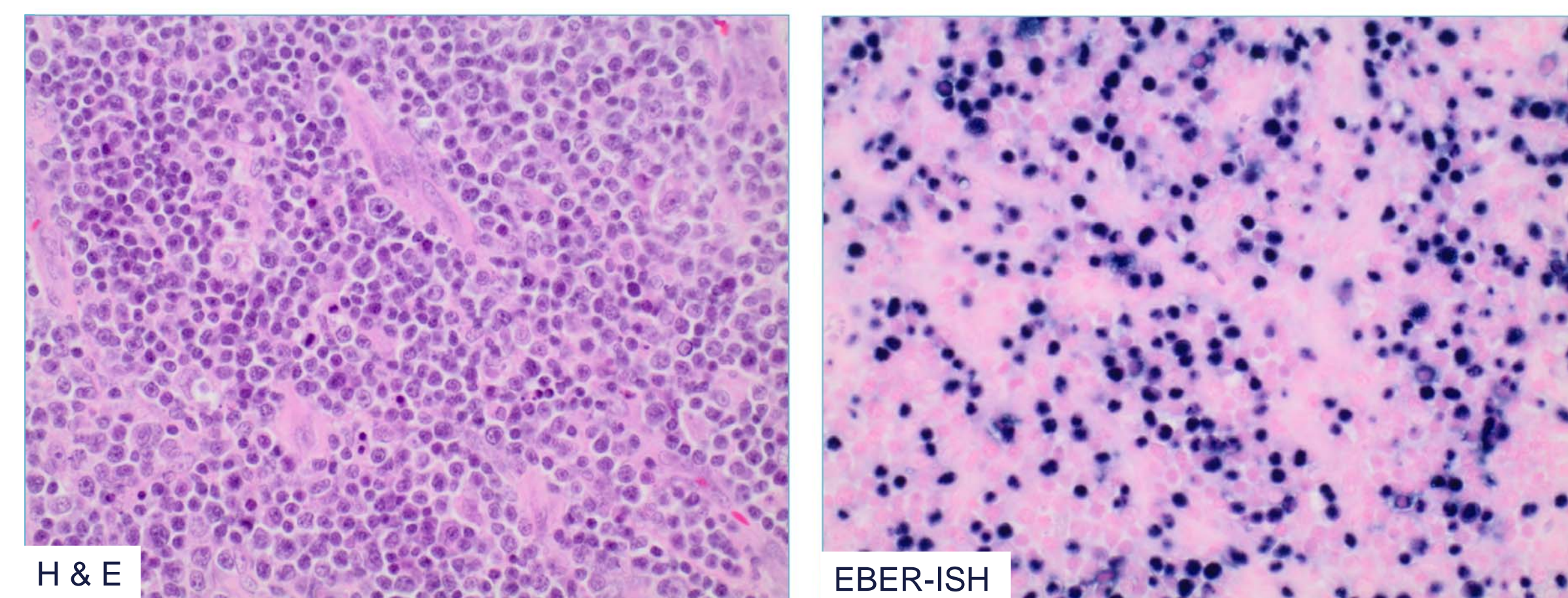


Figure 2: Lymph node biopsy with mixed infiltration of large and small cells. Many EBV infected cells are present

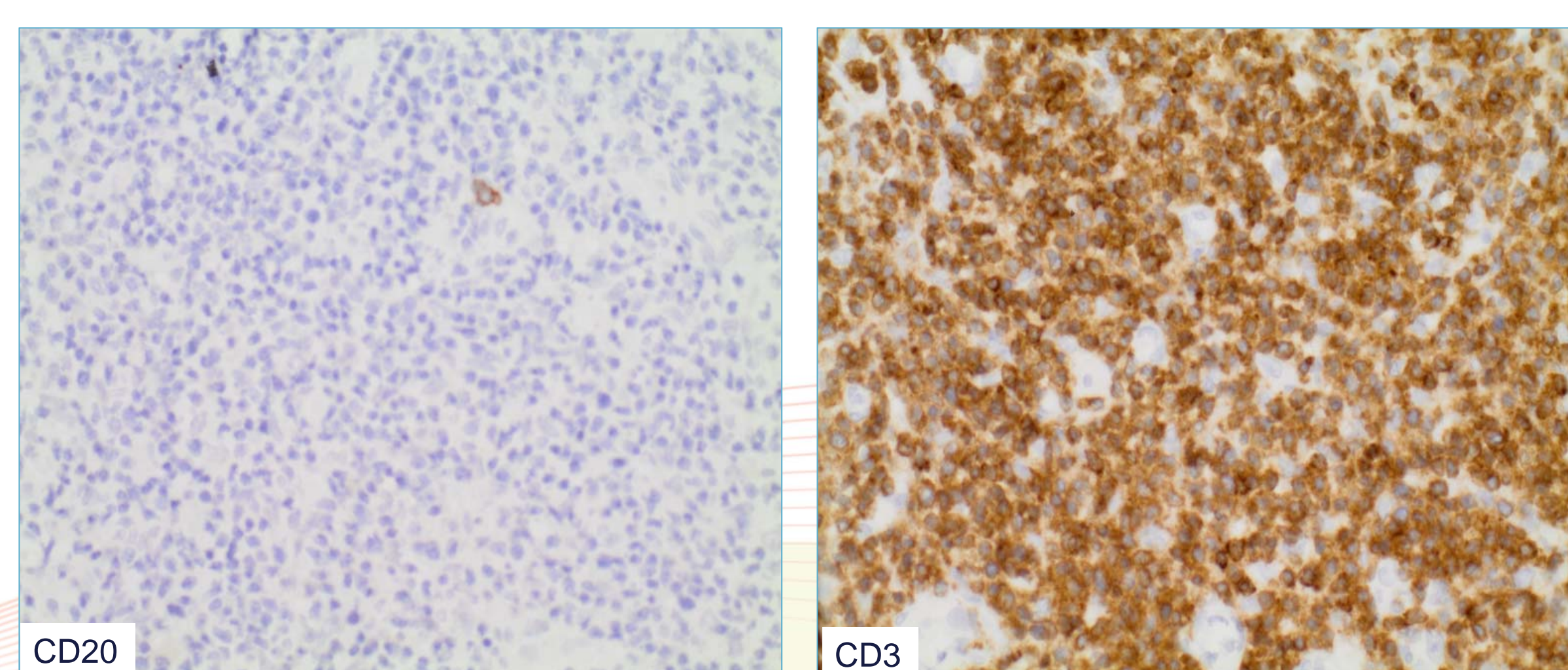
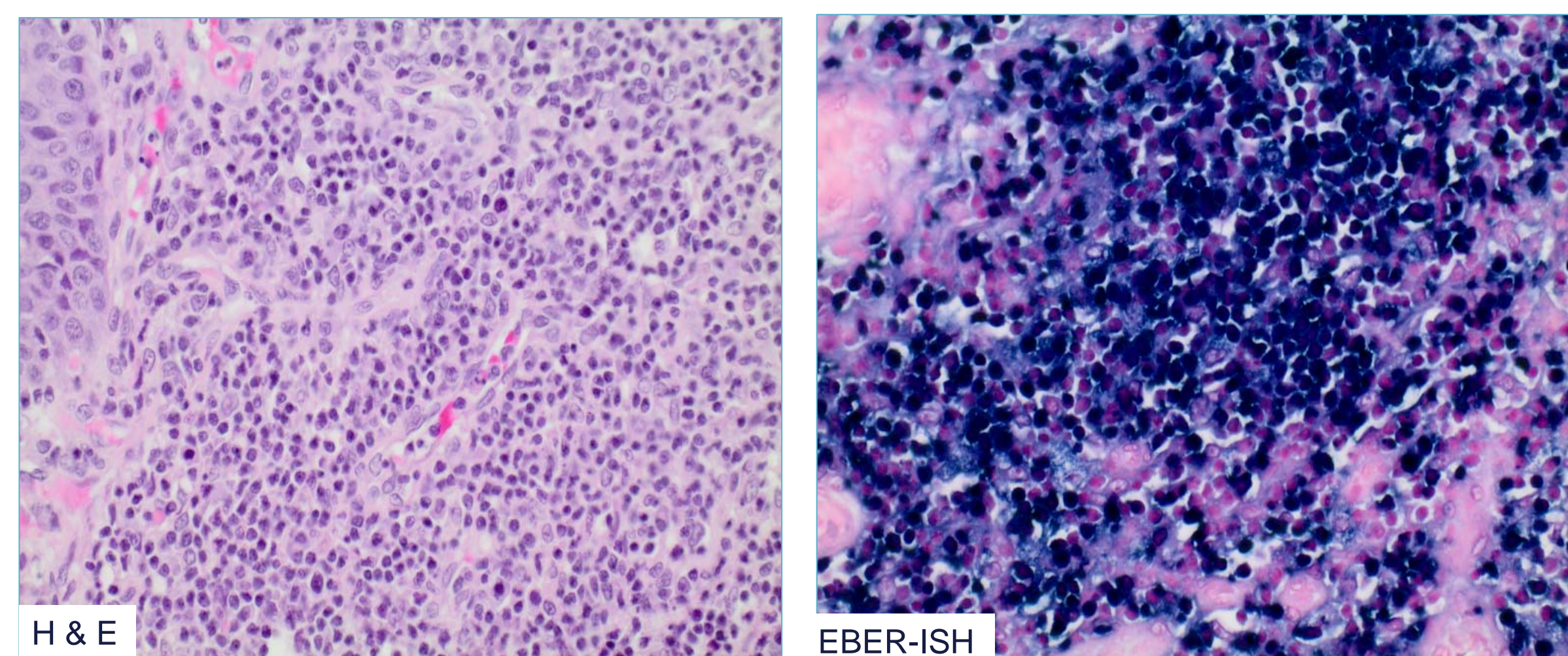
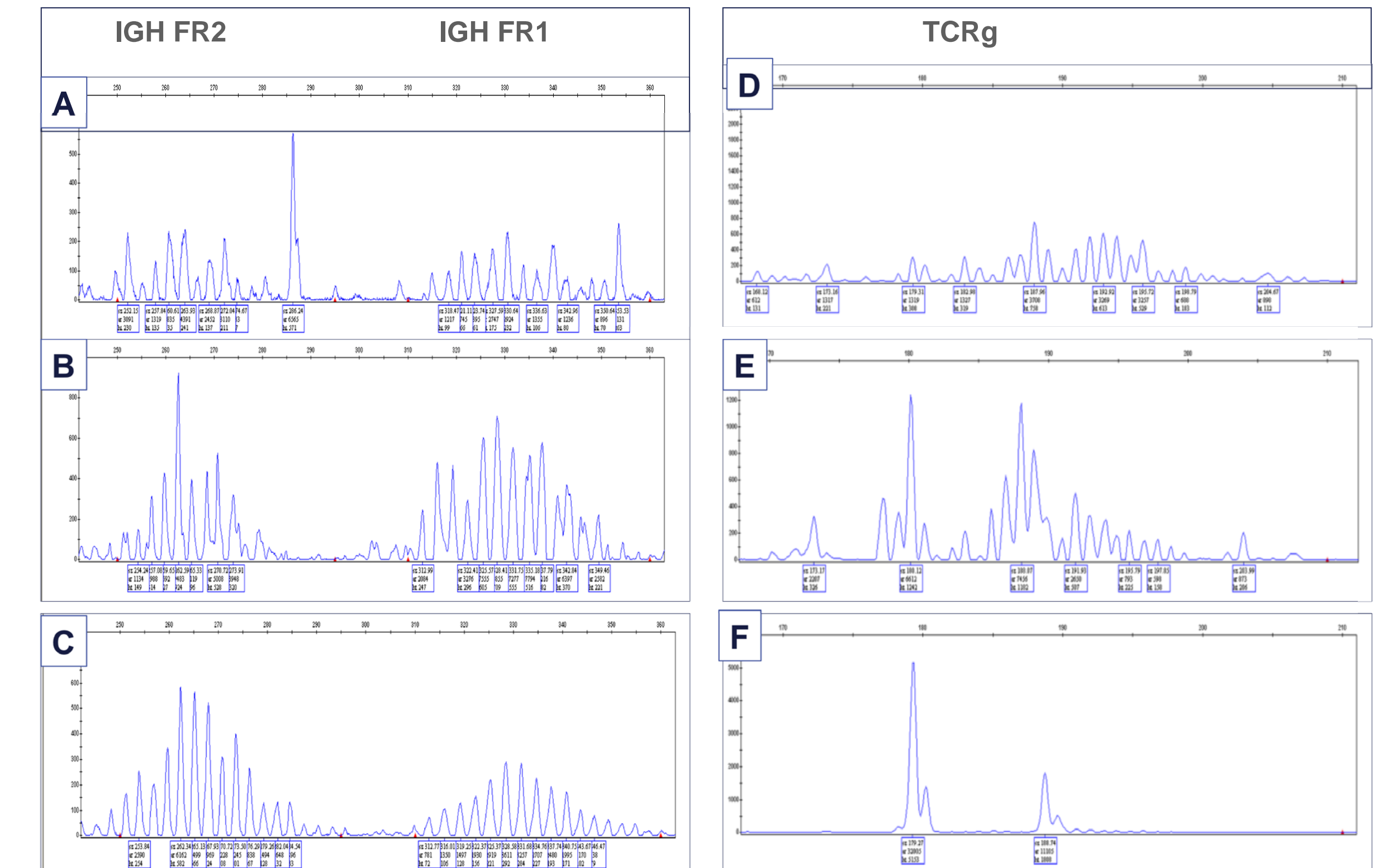


Figure 3: Histologic morphology, EBV in situ hybridization and immunohistochemistry of the esophagus from autopsy



Immunoglobulin heavy chain gene rearrangement (IGH) (A, B, C) and T-cell receptor (TCR) gamma gene rearrangement (D, E, F) in sequential samples. A clonal IGH peak was detected in the initial small bowel biopsy (A) and the clonal peak was absent in the subsequent small bowel biopsy (B) and esophageal biopsy (C). Polyclonal TCR gamma gene rearrangement in the initial small bowel biopsy (D) Monoclonal TCR gamma gene rearrangement in the subsequent small bowel biopsy (E) and esophageal biopsy (F).

## DISCUSSION

The presentation of AR-EBVLPD is associated with a wide clinicopathologic spectrum, ranging from a benign nodal reactive hyperplasia to the more aggressive EBV-positive DLBCL lesions. Clinically aggressive AR-EBVLPD with wide spread, polymorphic gastrointestinal disease appears to be a very rare form of this entity. Our patient experienced extensive gastrointestinal involvement at the initial presentation. Histologically, all areas showed a polymorphic proliferation of chronic inflammatory cells, mimicking inflammatory bowel disease. In our case, the diagnostic clues were rare EBV-positive cells and clonal immunoglobulin gene rearrangement. It is not uncommon to see rare EBV staining cells in inflammatory processes which are often deemed "nonspecific". The small number of EBV-positive cells in our case did not prompt a diagnosis of AR-EBVLPD early at the presentation. The detection of immunoglobulin gene rearrangement in one of the small bowel biopsies in our case was certainly an alarming feature. Morphologically, there was also an increase of large B cells in the same small bowel sample, although sheets of large cells were absent. Although an evolving large B-cell neoplasm was suspected, the morphologic features did not warrant a definitive diagnosis of DLBCL. Immunoglobulin gene rearrangement can be seen in up to 30% of the polymorphic extranodal AR-EBVLPD.

Polymorphic AR-EBVLPD in general has an indolent clinical course. Transformation to overt lymphoma is exceedingly rare. The peripheral T-cell lymphoma that developed in our case showed strong EBV expression in all tumor cells. The lymphoma developed after prolonged EBV stimulation in B cells in the GI tract and lymph nodes and subsequent EBV infection of T cells in the same organs, resulting in transformation of infected benign T cells to T-cell lymphoma. The patient's rapid decline coincided with an altered T-cell repertoire with subsequent development of a malignant clonal T-cell population. Oligoclonal and monoclonal T-cell populations are not uncommon in age-related lymphoproliferative disorders. The emergence of overt T-cell clones in these disorders is a result of enhanced restricted T-cell responses to the impaired B-cell functionality within the inflammatory lesions. However, these clonal T cells typically do not progress to T-cell lymphoma. In our case, clonal T-cell gene rearrangement was detected in relatively early stage of the disease, although the size of the T-cell clone is small and the morphologic evidence of T-cell lymphoma was absent. The continuous progression of the disease resulted in progressively impaired B-cell repertoire and immune surveillance, which in turn enabled EBV infection of T cells and ultimately clonal T-cell expansion and oncogenic transformation to T-cell lymphoma.

## CONCLUSION

We present a unique case of T-cell peripheral lymphoma arising in association with an EBV-driven B cell proliferation. This case demonstrates that, despite the polymorphic extranodal presentation, AR-EBVLPD may behave in an aggressive fashion and emphasizes the need for early recognition and optimal treatment.

## REFERENCES

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