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Expanding the Spectrum of EBV-positive Marginal Zone Lymphomas

A Lesion Associated With Diverse Immunodeficiency Settings

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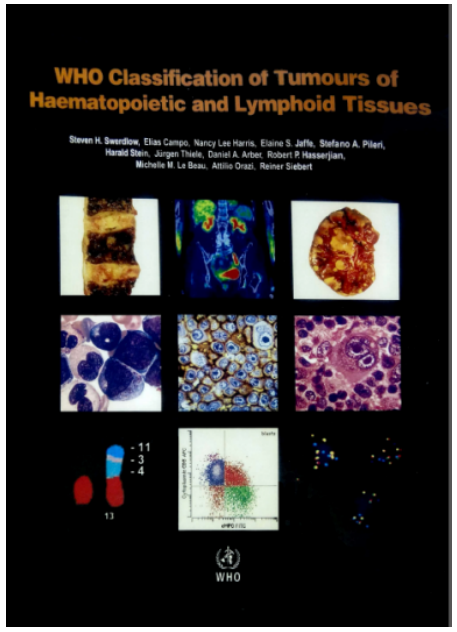


16 Immunodeficiency-associated lymphoproliferative disorders

Lymphoproliferative diseases associated with primary immune disorders

Lymphomas associated with HIV infection

Post-transplant lymphoproliferative disorders (PTLD)

Non-destructive PTLD

Polymorphic PTLD

Monomorphic PTLD (B- and T/NK-cell types)

Monomorphic B-cell PTLD

Monomorphic T/NK-cell PTLD

Classic Hodgkin lymphoma PTLD

Other iatrogenic immunodeficiency-associated lymphoproliferative disorders

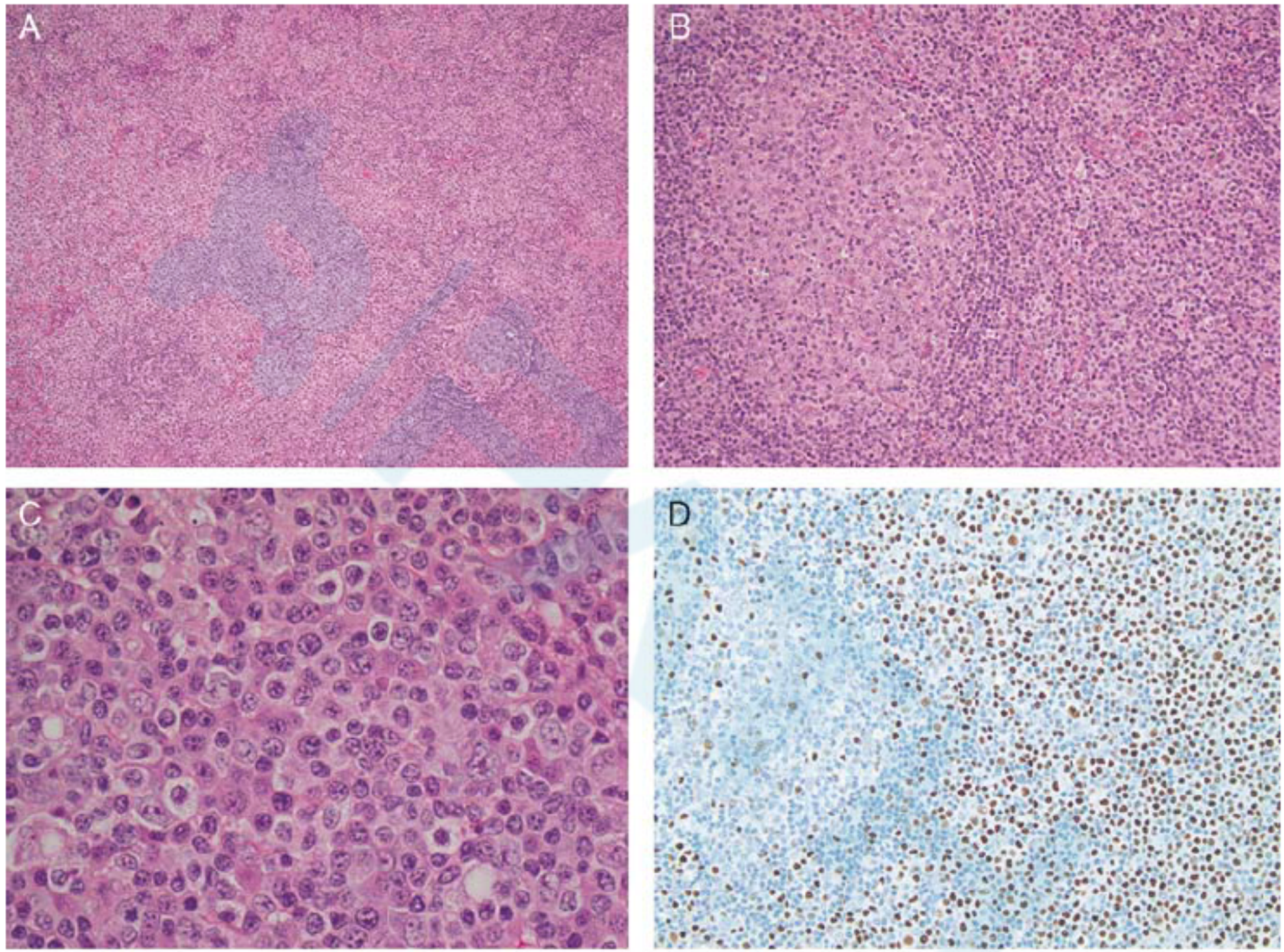
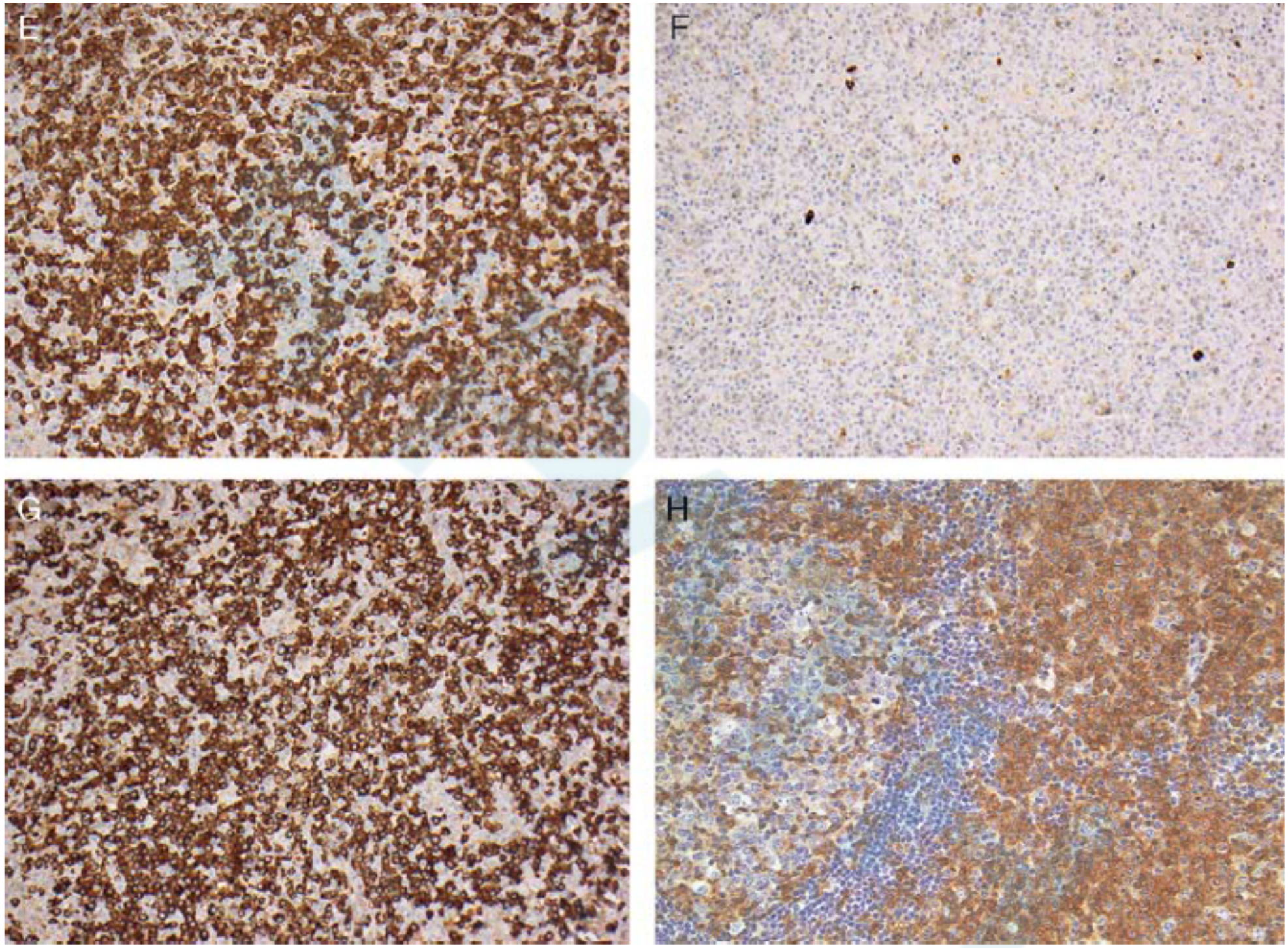
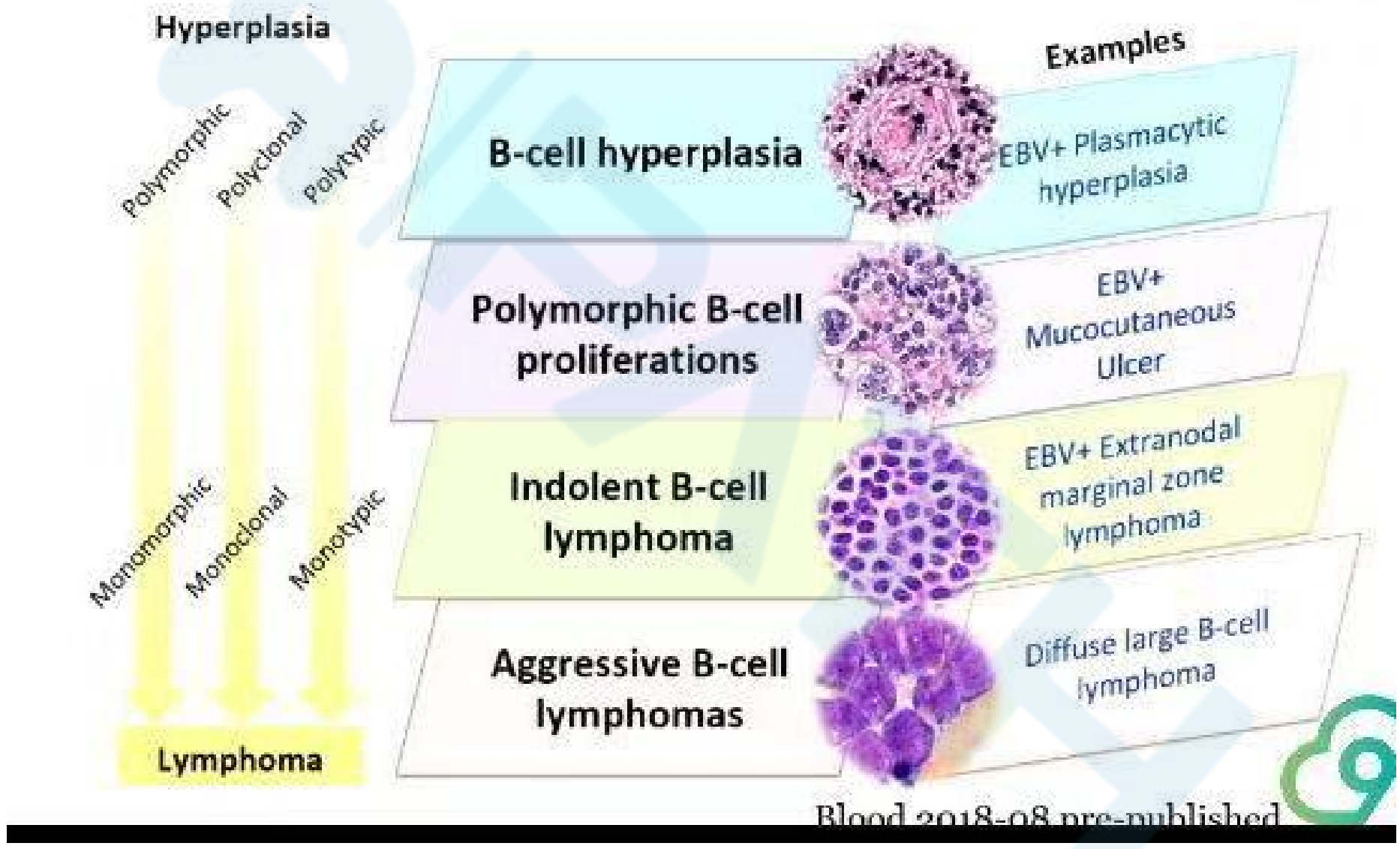


FIGURE 1. EBV-positive MALT lymphoma presenting as an inferior orbital soft tissue mass in a 12-year-old male patient who had previously received a heart transplant (case 1). A and B, The mass was composed of a diffuse and vaguely nodular proliferation of small lymphoid cells, many of which had a monocytoid cytology. Residual follicles surrounded and colonized by the monocytoid cells were identified. C, A prominent plasmacytic proliferation was also identified. D, Numerous EBER-positive cells were present mostly outside the residual non-neoplastic germinal centers (left).



E and F, The plasma cells were κ light chain restricted, with only infrequent λ-positive plasma cells seen . G, The plasma cells were also positive for IgA .H, The neoplastic B cells and plasma cells were positive for CXCR3,whereas the residual non-neoplastic germinal center and mantle zone cells appeared negative (left).

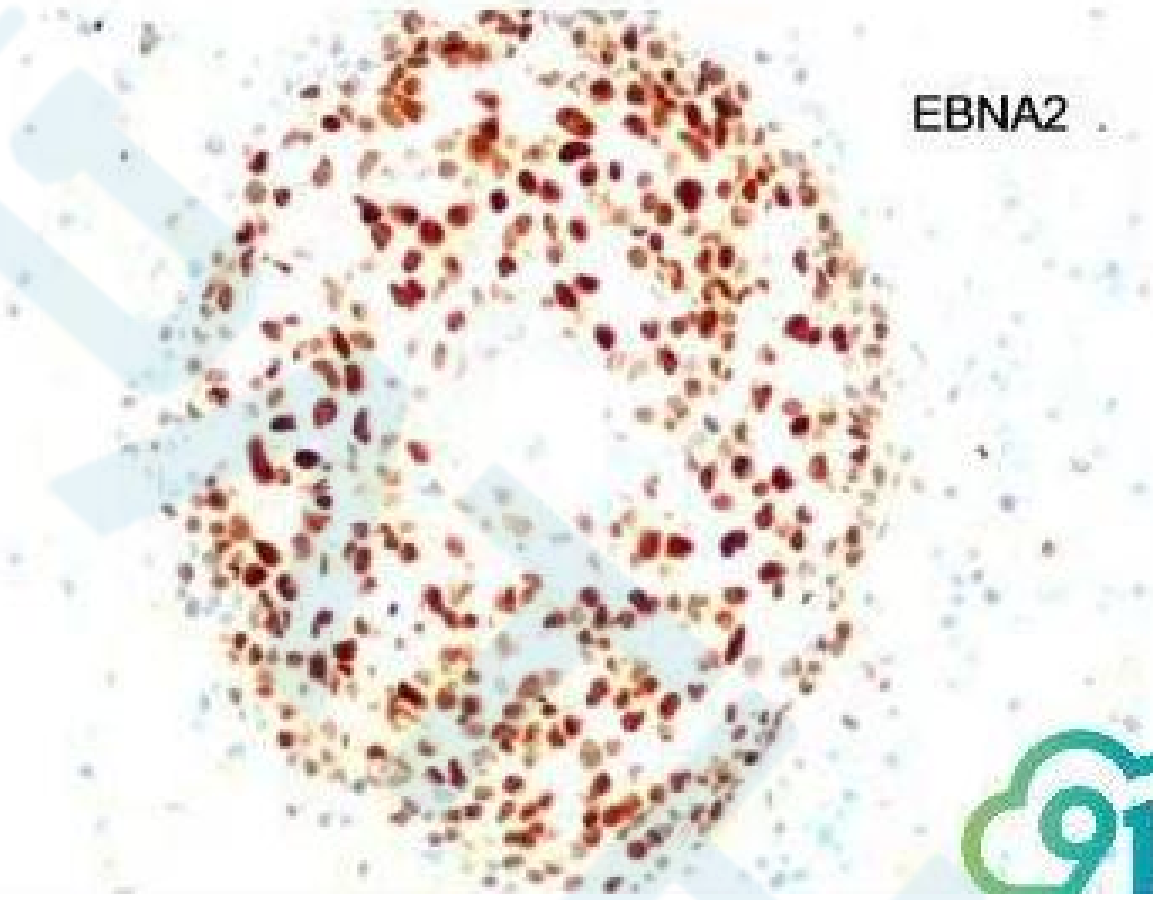
Immunodeficiency-associated B-cell proliferations



王主任课件

EBV Infection in Immunodeficiency

- History
- Ancillary test
- EBNA2
- Double staining



王主任课件

MATERIALS AND METHODS

- 10 EBV^+ marginal zone lymphomas (MZL) cases were identified.
- Immunohistochemistry and EBV-encoded Small RNA In Situ Hybridization.

CD3、CD20、CD79a、PAX-5、EBNA2、CD138、CD38、MUM-1、IgG、IgM、EBER

- Molecular Studies

polymerase chain reaction (PCR)

RESULTS

- Clinical Presentation and Risk Factors.

- Treatment and Clinical Outcome.

- Morphologic, Immunohistochemical, and Molecular Features.

TABLE 1. Summary of Patient Demographics, Clinical History, Treatment, and Follow-up of EBV$^+$ MZL

Patient	Anatomic Site	Age (y)/Sex	History	Treatment	Follow-up
1	Left inguinal LN	18 F	Heart/kidney combined transplant in 2002	Reduced immunosuppression; rituximab at relapse 1 y later	Relapsed 6 y after diagnosis, with similar histology, and clonality proven by Ig PCR. In continuous CR following rituximab
2	Subcutaneous masses, arm, abdomen	78 M	CHL in 2001, s/p chemotherapy; advanced Parkinson disease at the time of diagnosis. Subcutaneous masses in 2008 and 2009	Unknown	Received ABVD for CHL in 2001; R-ICE recommended in 2008 but patient lost to follow-up; died in 2014
3	Skin, flank, abdomen	70 M	No significant PMH	Unknown	Died in 2013
4	Skin, arm	69 M	Subcutaneous nodules, mediastinal and cervical LAD (2008)	R-CHOP and local radiation	CHL (EBV$^+$) was diagnosed 5 mo later. Recurrence of EBV$^+$ cutaneous MZL in 2011 and 2014. EBV$^+$ B-cell proliferation in oropharynx in 2016
5	Periparotid soft tissue	63 F	Rheumatoid arthritis and Sjogren syndrome, treated with methotrexate; presented with parotid mass (2014)	Unknown	Alive
6	Lung	26 M	Anterior chest wall mass in 2010, patient treated as Ewing Sarcoma; developed right lung nodule in 2011 which had been enlarging; lung wedge resection performed in 2016	Unknown	Alive
7	Breast	31 F	Status post liver transplant in 2004 for Wilson disease; developed multiple right breast lesions in 2011, 2015, residual breast mass was resected in 2016	DA R-EPOCH × 6 cycles in 2011; reduction of immunosuppression. Subsequent chemorx with bortezomib, dexamethasone, and valganciclovir HCL	Currently stable
8	Skin, arm	86 F	No significant PMH; presented with skin nodules on bilateral forearms, face, and trunk; she was also noted to have peripheral blood and bone marrow involvement (2016)	Received prednisone but no response	Currently stable
9	Parotid gland	54 F	History of rheumatoid arthritis, Sjogren syndrome, treated with methotrexate, etanercept, infliximab since 2014. Presented with parotid mass in 2017	Discontinued immunosuppression. Rituximab induction with rituximab maintenance	Currently stable and clinically improved with resolution of parotid symptoms
10	Parotid gland	18 F	History of chronic active EBV infection in 2015; parotid mass in 2017. Genetic testing showed mutation in RNA component of mitochondrial RNA processing endoribonuclease (*RMRP*) gene and congenital immune deficiency. Elevated viral load at 3382 copies/mL	Stem cell translant to correct immune deficiency	Complete response, NED

ABVD indicates adriamycin, bleomycin, vincristine, doxorubicin; chemorx, chemotherapy; CR, complete remission; DA R-EPOCH, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; F, female; LAD, lymphadenopathy; LN, lymph node; M, male; NED, no evidence of disease; PMH, past medical history; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; s/p, status-post.

- The 10 patients included 4 males and 6 females (ages 18 to 86 y）.
- nodal disease(1 case), skin or subcutaneous tissue(4 cases), with other sites being parotid gland (3 cases), lung (1 case), and breast (1 case).

TABLE 2. Summary of Pathologic and Major Laboratory Findings of EBV$^+$ MZL Cases

Patient	Anatomic Site	H&E	CD20	CD79a	CD138 or CD38	MUM-1	κ/λ	IgG/ IgM/ IgA	EBER /LMP1	Ki-67	*MyD88*	Ig PCR Clonality
1	Left inguinal LN	Nodular infiltrate of monocytoid cells	Pos	Pos	Both focally pos	Pos	Kappa	IgG	Pos /Neg	Low	WT	IgH pos
2	Subcutaneous masses, arm, abdomen	Lymphocytic/ plasmacellular, biphasic pattern	Pos	Pos	CD38 pos, CD138 neg	Pos	Kappa	IgG	Pos /Neg	Low	WT	Poor DNA
3	Skin, flank, abdomen	Lymphocytic/ plasmacellular, polymorphic	Partially pos	Pos	CD138 pos	Pos	Lambda	IgG	Pos /Neg	Moderate	WT	IgH and IgK pos
4	Skin, arm	Lymphocytic/ plasmacellular, biphasic pattern	Partially pos	Pos	CD138 partially pos	Pos	Lambda	IgG	Pos /Neg	Moderate	ND	IgH and IgK pos
5	Periparotid soft tissue	Lymphocytic/ plasmacellular, biphasic pattern	Partially pos	Pos	CD138 variably pos	Pos	Kappa	All neg	Pos /Neg	Low	WT	IgH pos
6	Lung	Lymphocytic/ plasmacellular, biphasic pattern	Partially pos	Pos	CD138 pos	Pos	Lambda	IgG	Pos /Pos	Moderate	ND	IgH and IgK pos
	Lymph node (2nd Bx)	Classical Hodgkin lymphoma, EBV$^+$, LD										IgH and IgK Pos (unrelated)
7	Breast	Monocytoid/ plasmacellular, biphasic, Mott cells and Russell bodies	Partially pos	ND	Pos	ND	Kappa	IgG	Pos /ND	Low	ND	ND
8	Skin, arm	Lymphocytic/ plasmacellular, polymorphic	Partially pos	Pos	ND	Pos	Lambda	ND	Pos /ND	Moderate	ND	ND
9	Parotid gland	Monocytoid/ plasmacellular, biphasic	Pos	ND	CD138 partially pos	Pos	Kappa	IgM	Pos /Neg	Moderate	WT	IgH and IgK pos
10	Parotid gland	Monocytoid/ plasmacellular, biphasic	Pos	ND	CD138 partially pos	Pos	Kappa	IgM	Pos /Pos	Low	WT	IgH and IgK pos

H&E indicates hematoxylin and eosin; LD, lymphocyte depleted; LN, lymph node; ND, not done; Neg, negative; Pos, positive; WT, wild type.

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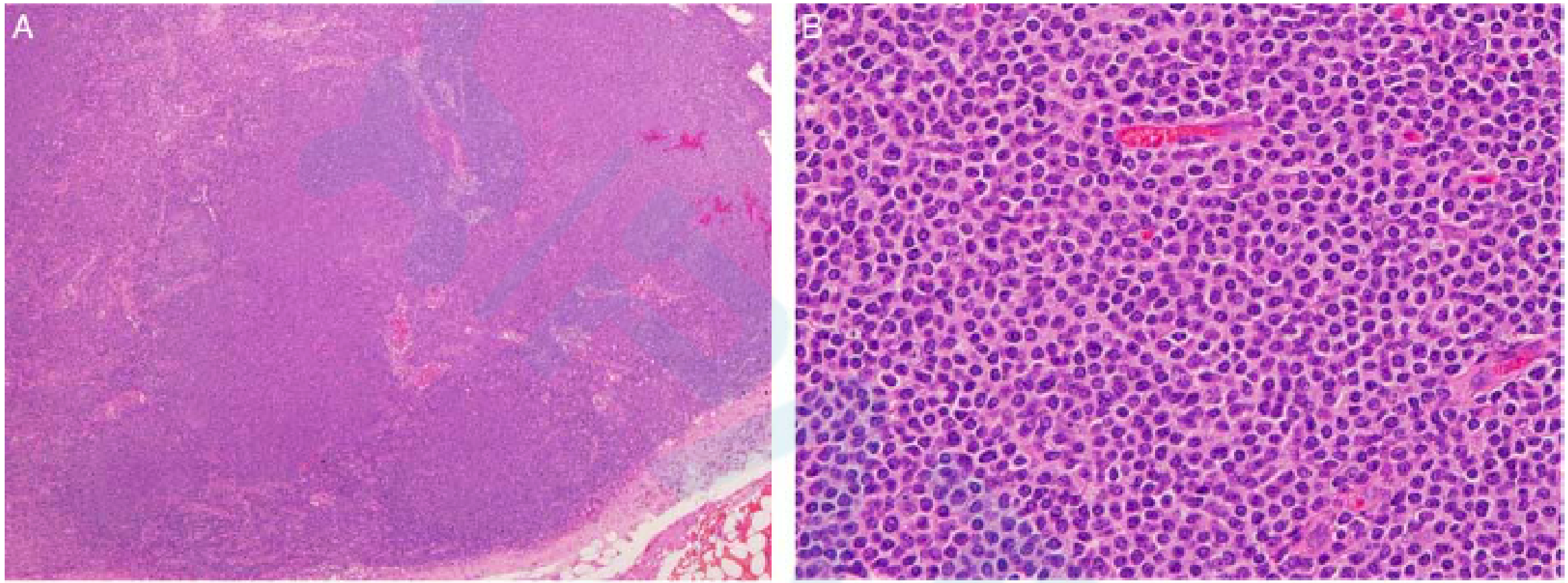
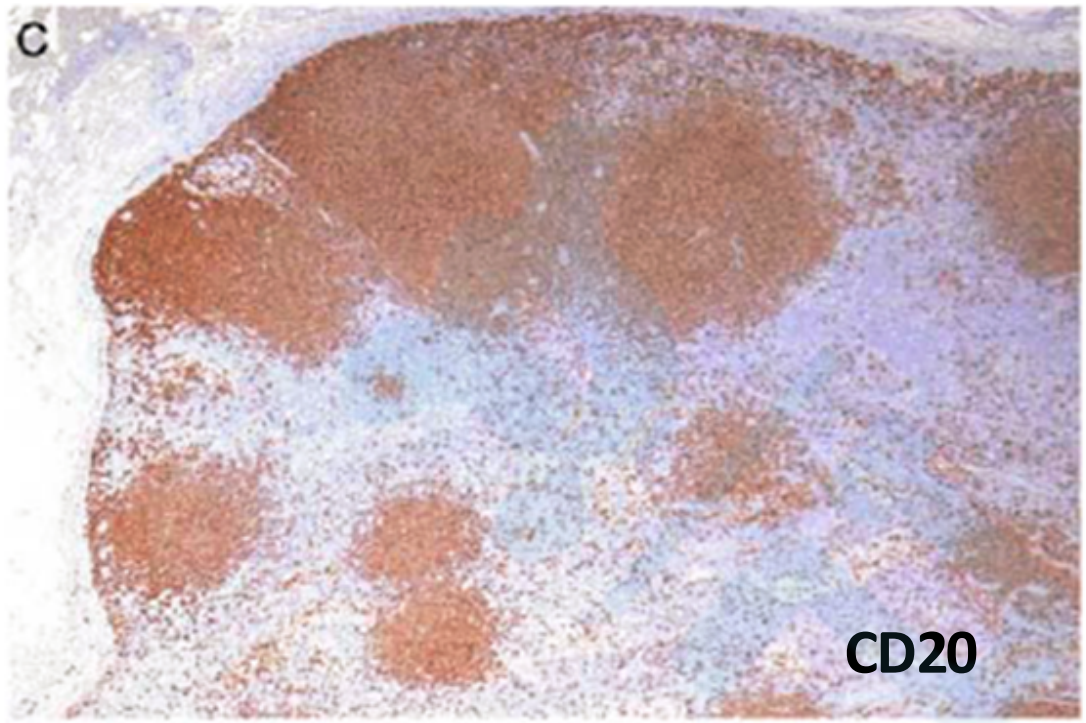


FIGURE 1. EBV+ nodal marginal zone lymphoma in an 18-year-old female with heart/kidney combined transplant (case 1). A and B, Nodal architecture is effaced by nodular infiltrates of monocytoid cells with a rim of pale cytoplasm.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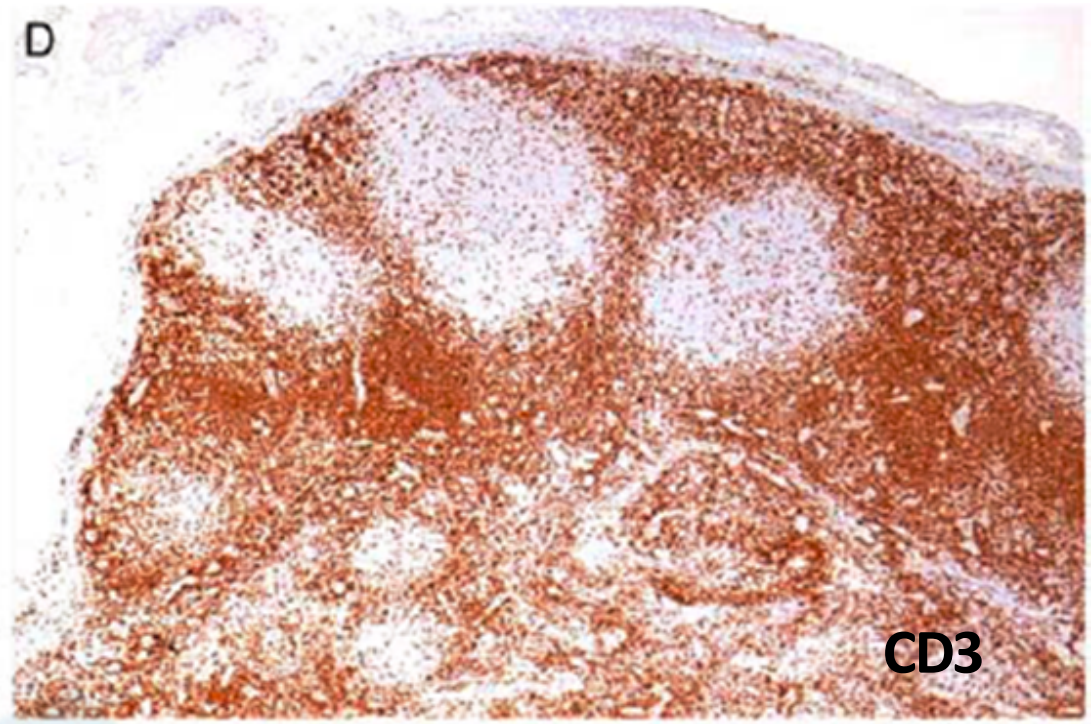
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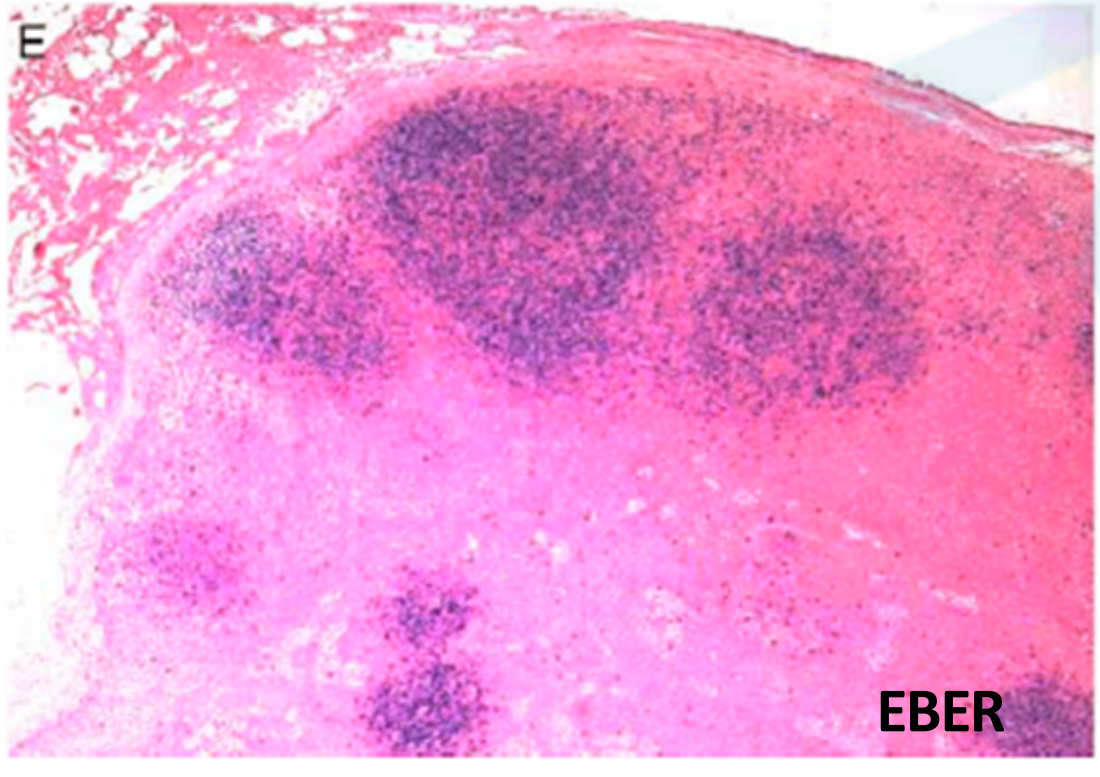
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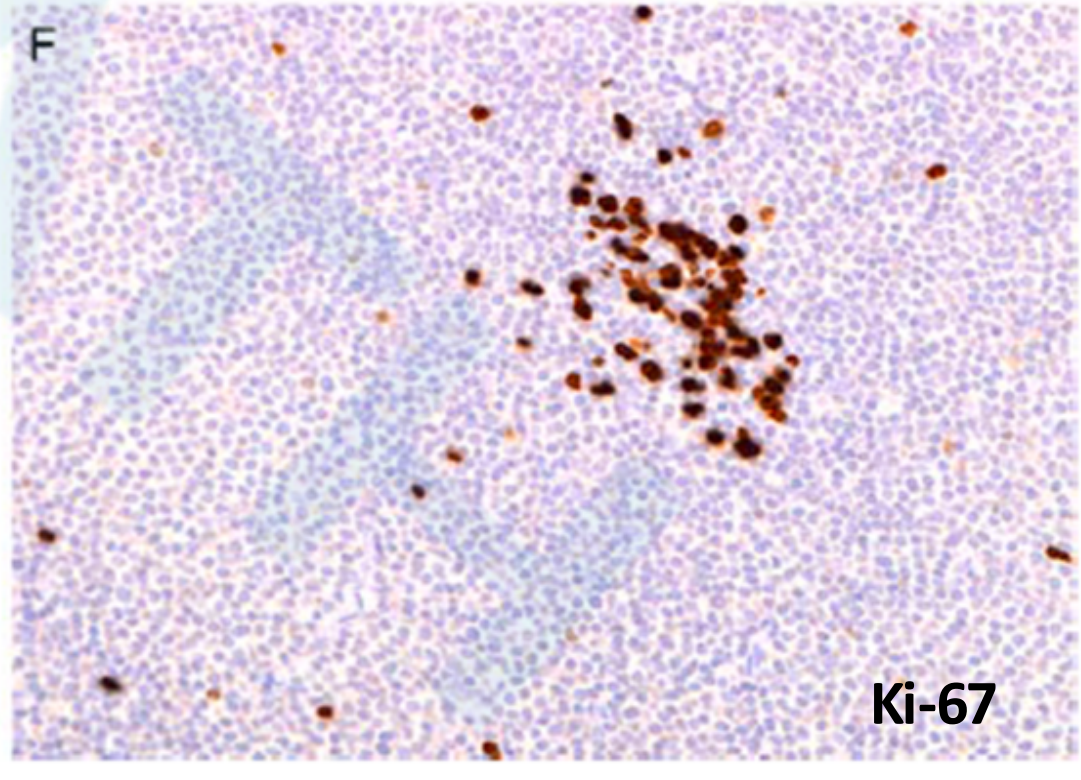
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Ki-67

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2	Subcutaneous masses, arm, abdomen	78 M	CHL in 2001, s/p chemotherapy; advanced Parkinson disease at the time of diagnosis. Subcutaneous masses in 2008 and 2009	Unknown	Received ABVD for CHL in 2001; R-ICE recommended in 2008 but patient lost to follow-up; died in 2014
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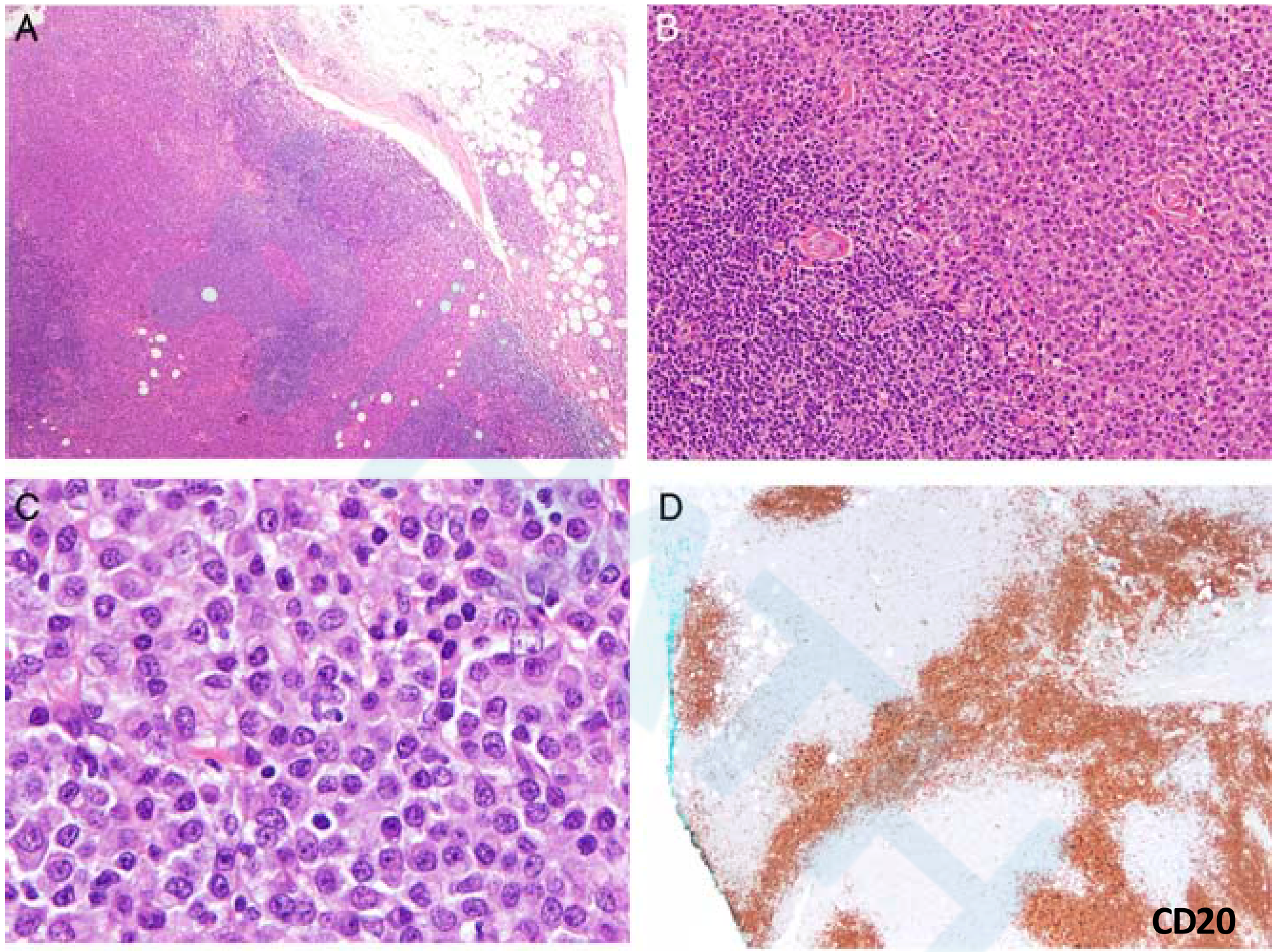
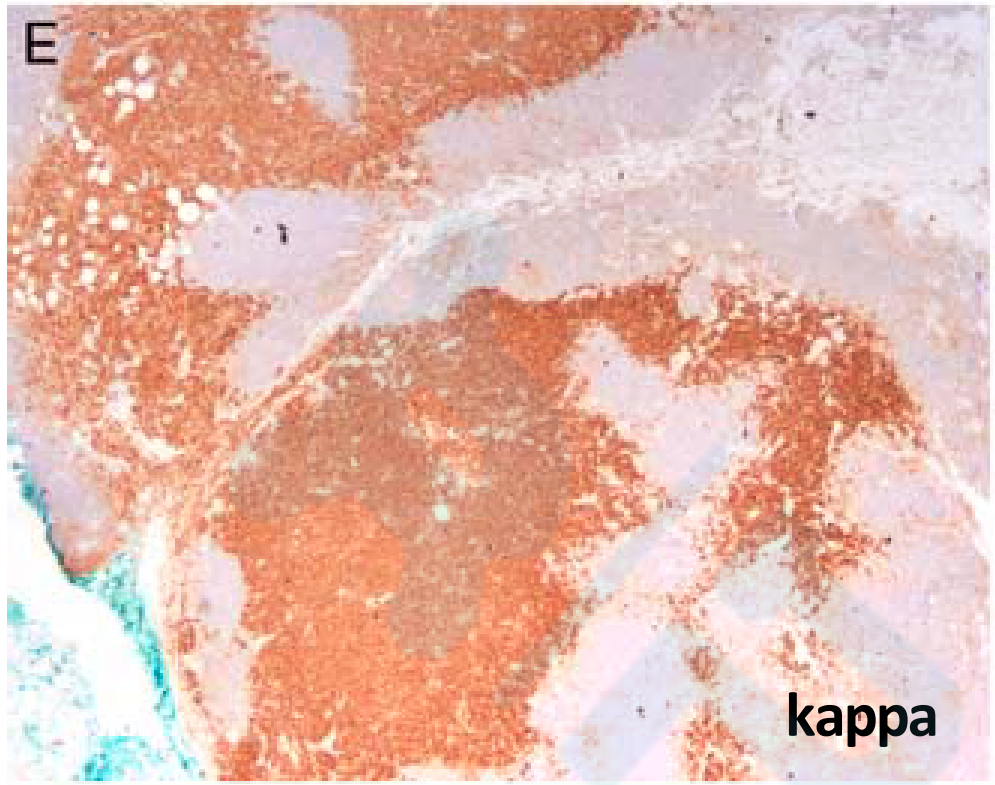


FIGURE 2. EBV+ MZL lymphoma in a 78-year-old male (case 2). A and B, The subcutaneous mass is composed of sheets of monotonous plasmacytoid cells rimmed by small lymphocytes. C, Plasmacytoid features are shown at high power.D, CD20+ small lymphocytes surround the atypical plasmacytoid cells, which are CD20−.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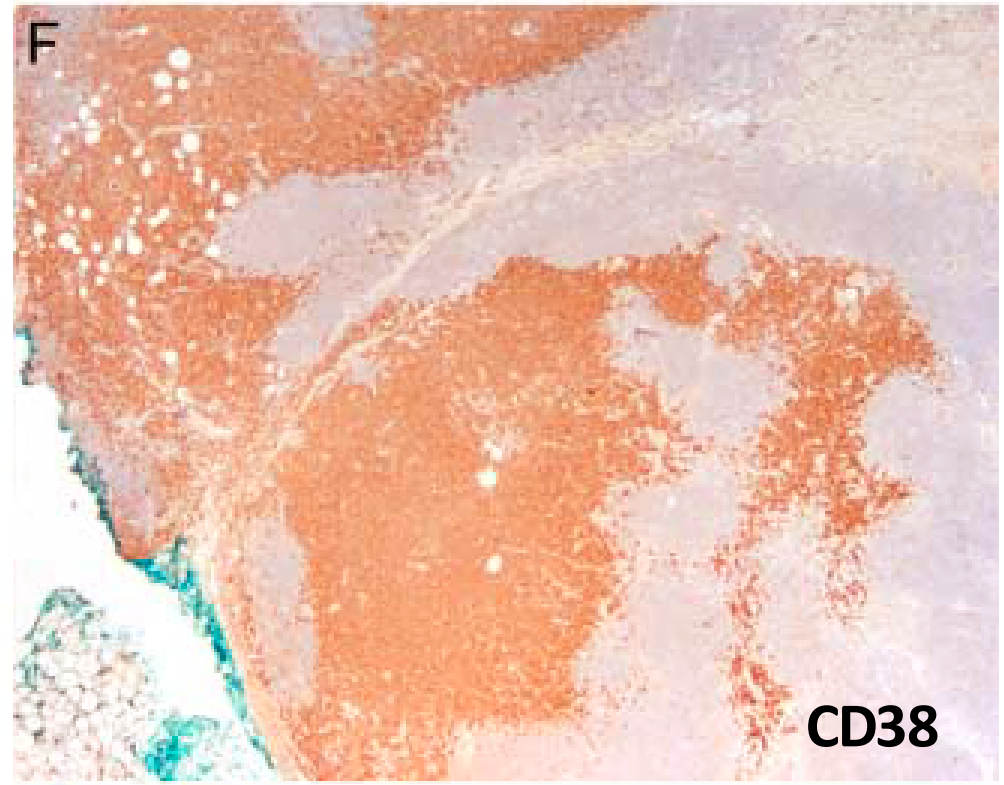
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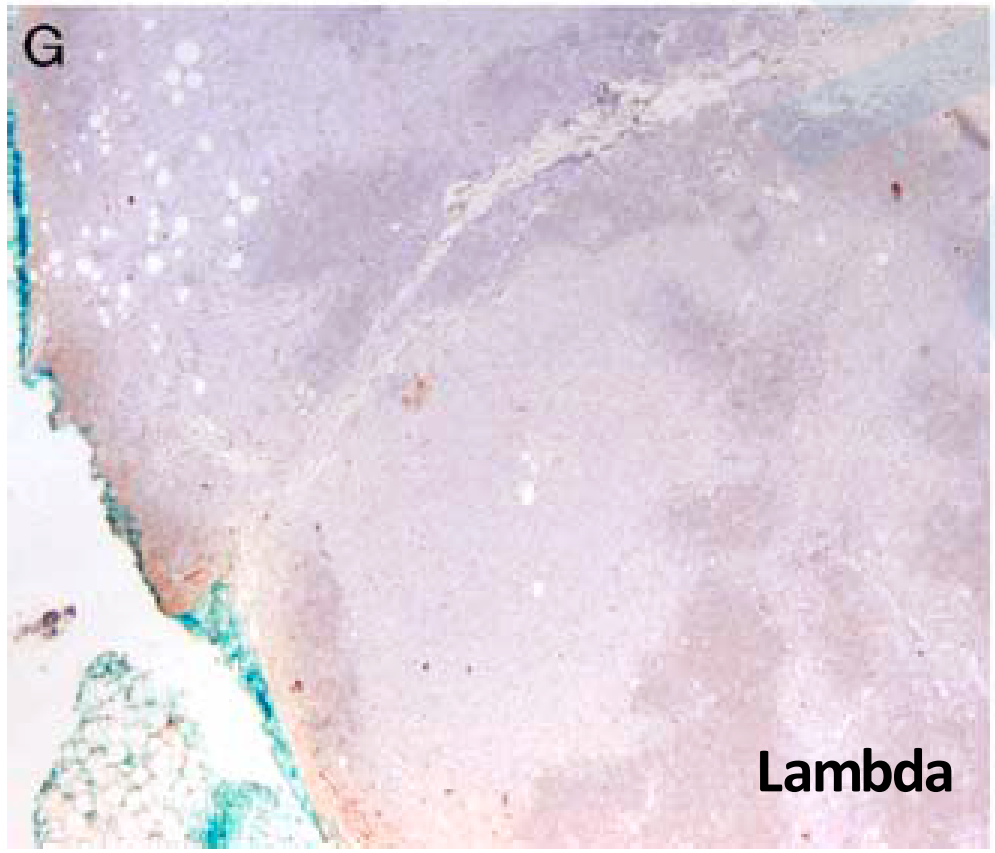
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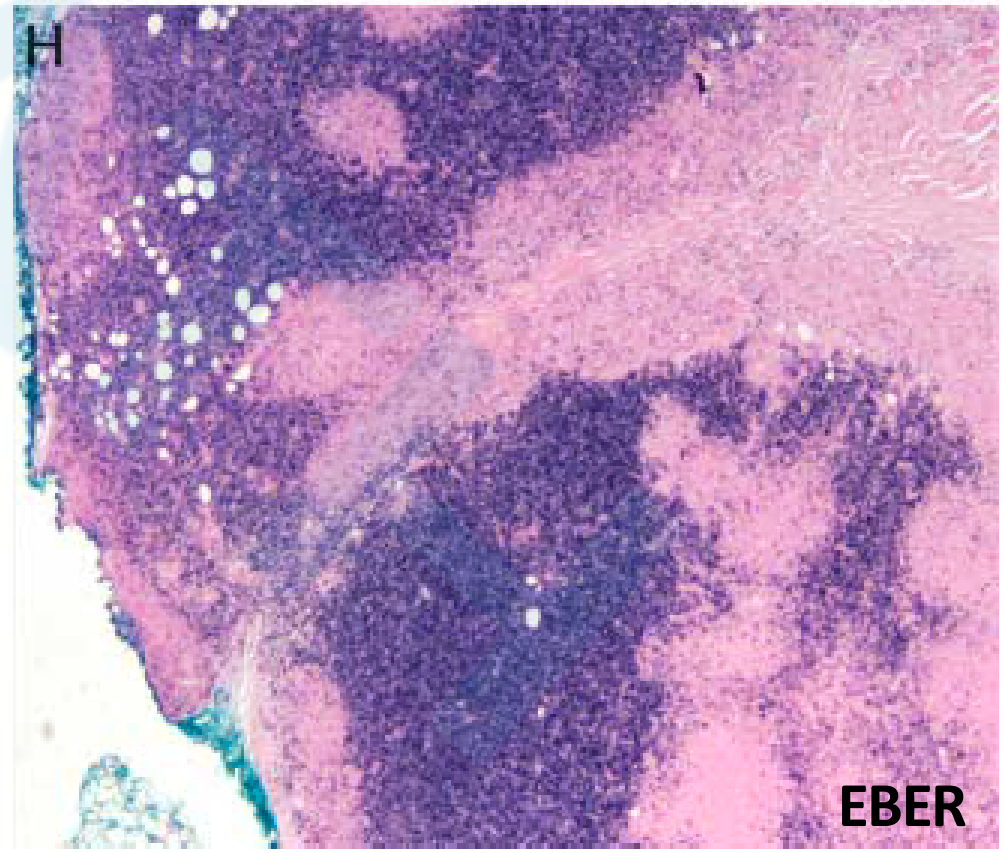

H
EBER

TABLE 1. Summary of Patient Demographics, Clinical History, Treatment, and Follow-up of EBV$^+$ MZL

Patient	Anatomic Site	Age (y)/Sex	History	Treatment	Follow-up
3	Skin, flank, abdomen	70 M	No significant PMH	Unknown	Died in 2013
4	Skin, arm	69 M	Subcutaneous nodules, mediastinal and cervical LAD (2008)	R-CHOP and local radiation	CHL (EBV$^+$) was diagnosed 5 mo later. Recurrence of EBV$^+$ cutaneous MZL in 2011 and 2014. EBV$^+$ B-cell proliferation in oropharynx in 2016
8	Skin, arm	86 F	No significant PMH; presented with skin nodules on bilateral forearms, face, and trunk; she was also noted to have peripheral blood and bone marrow involvement (2016)	Received prednisone but no response	Currently stable

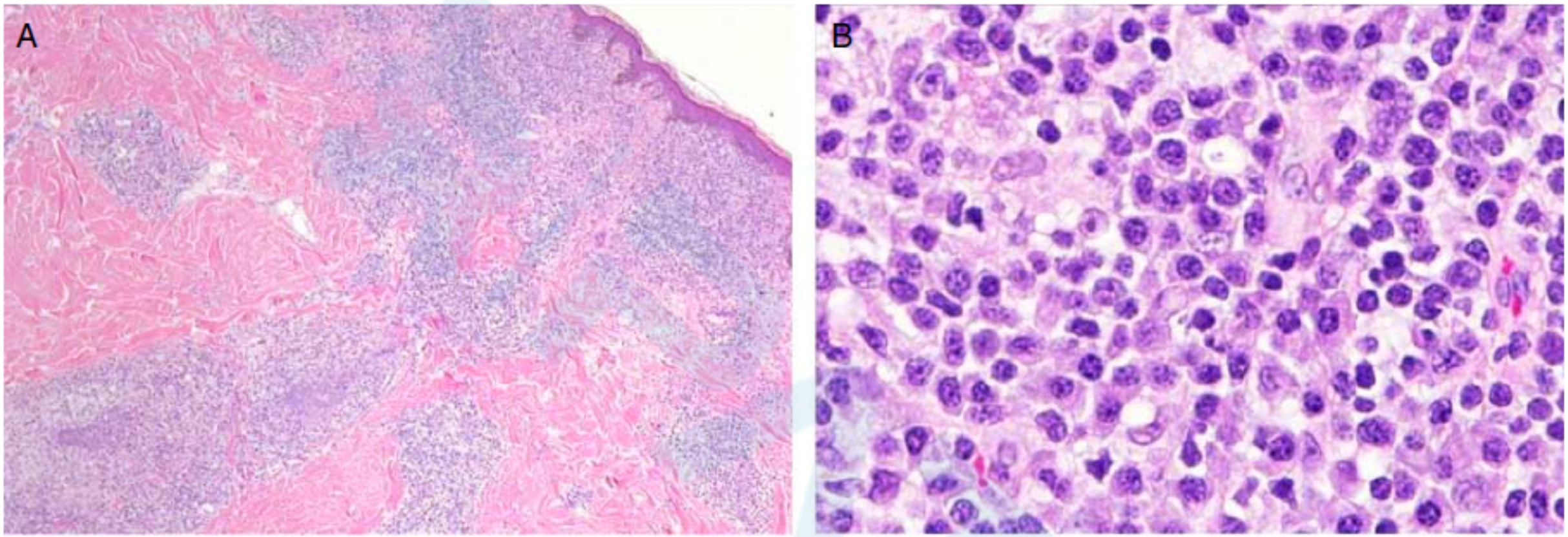
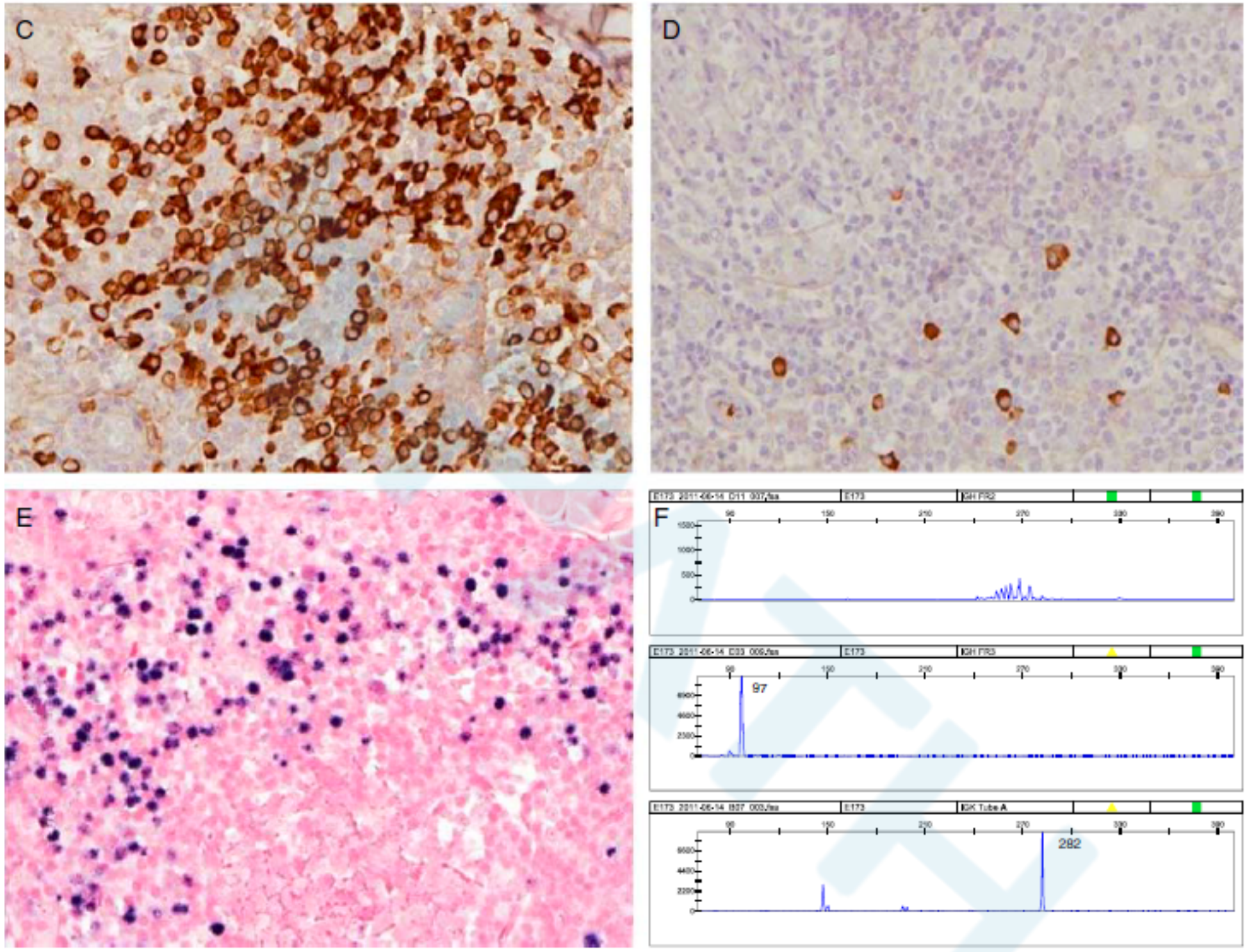


FIGURE 3. EBV+ MALT lymphoma in a 70-year-old male with no significant past medical history (case 3). A, The infiltrate involves the dermis and subcutaneous tissue with a perivascular and periadnexal distribution. B, The infiltrate is composed of monocytoid and plasmacytoid cells.



The plasmacytoid cells are positive for lambda (C) and negative for kappa (D) light chain. E, EBER shows a similar distribution to lambda. F, PCR for immunoglobulin gene rearrangements revealed a clonal pattern, with peaks in IGH Fr III, and Kd

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10	Parotid gland	18 F	History of chronic active EBV infection in 2015; parotid mass in 2017. Genetic testing showed mutation in RNA component of mitochondrial RNA processing endoribonuclease (*RMRP*) gene and congenital immune deficiency. Elevated viral load at 3382 copies/mL	Stem cell translant to correct immune deficiency	Complete response, NED

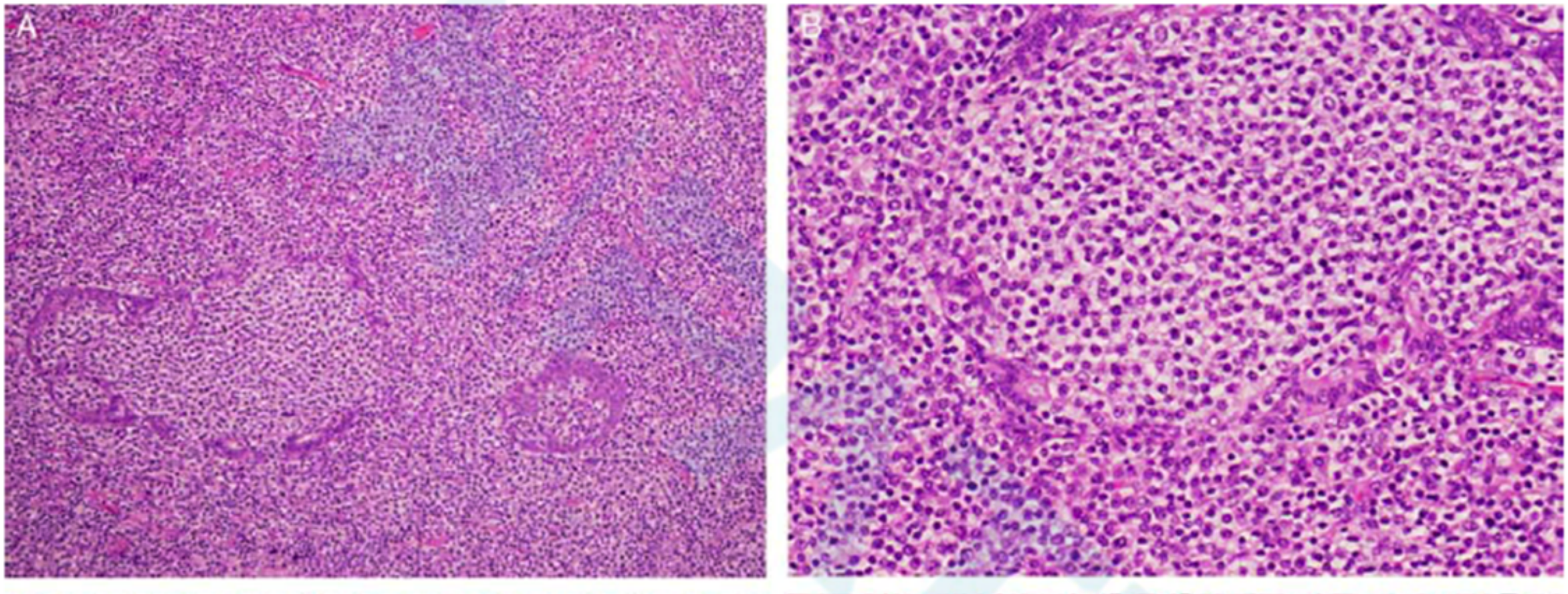
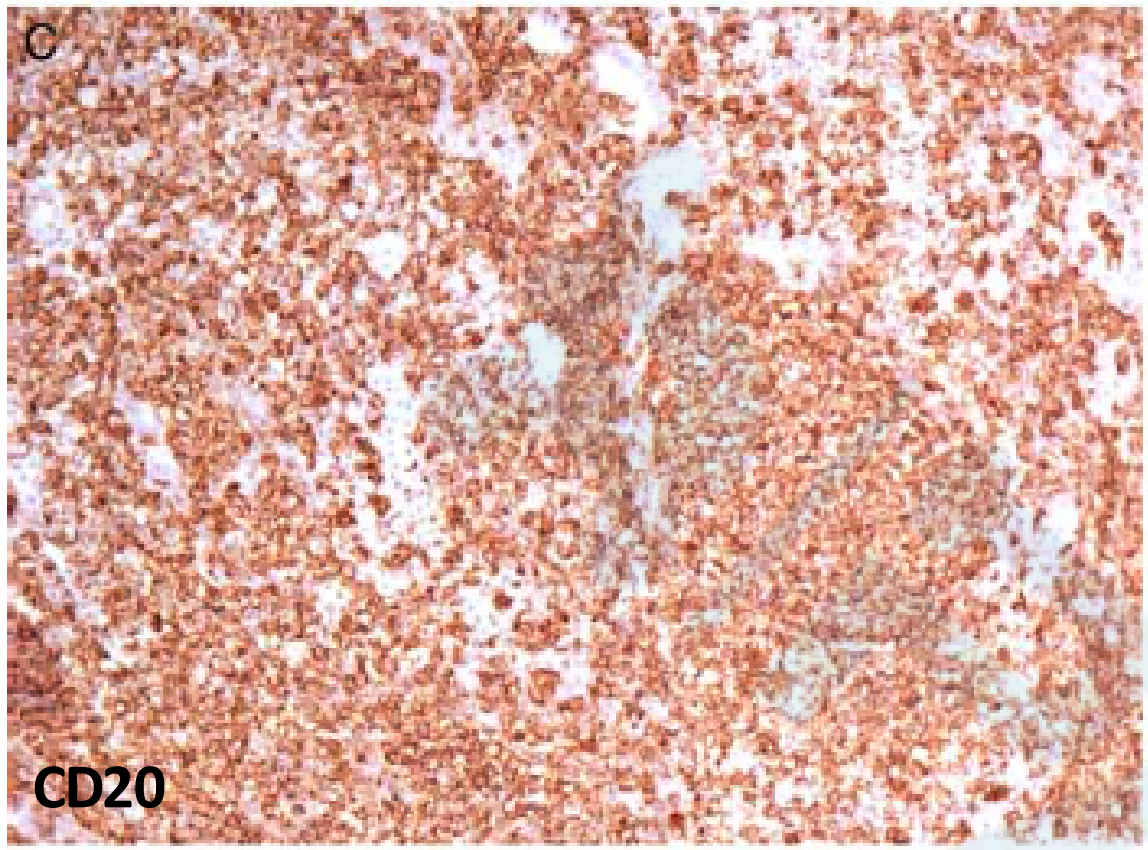


FIGURE 4. EBV+ MALT lymphoma in a 54-year-old female with history of rheumatoid arthritis and Sjogren syndrome (case 9). A, The parotid ducts are filled with monocytoid appearing cells. B, The cells have a rim of pale cytoplasm.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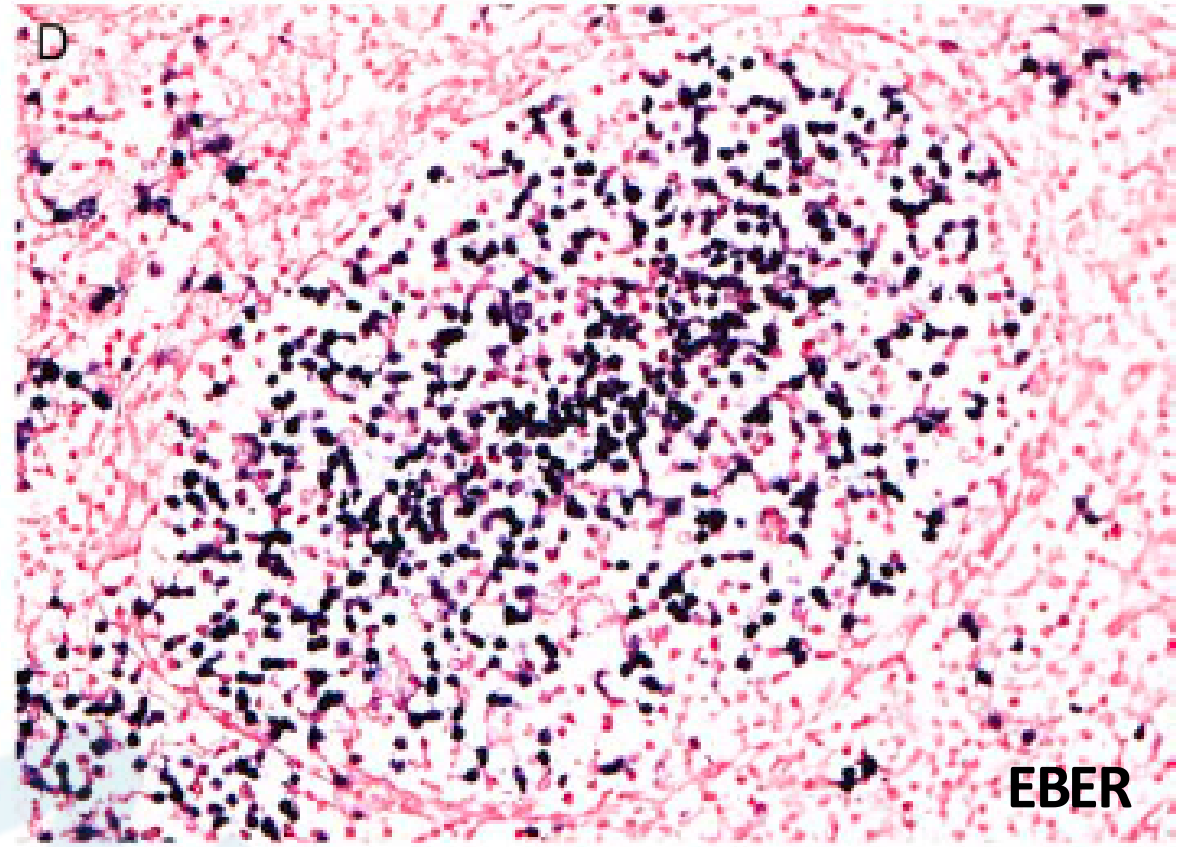
CD20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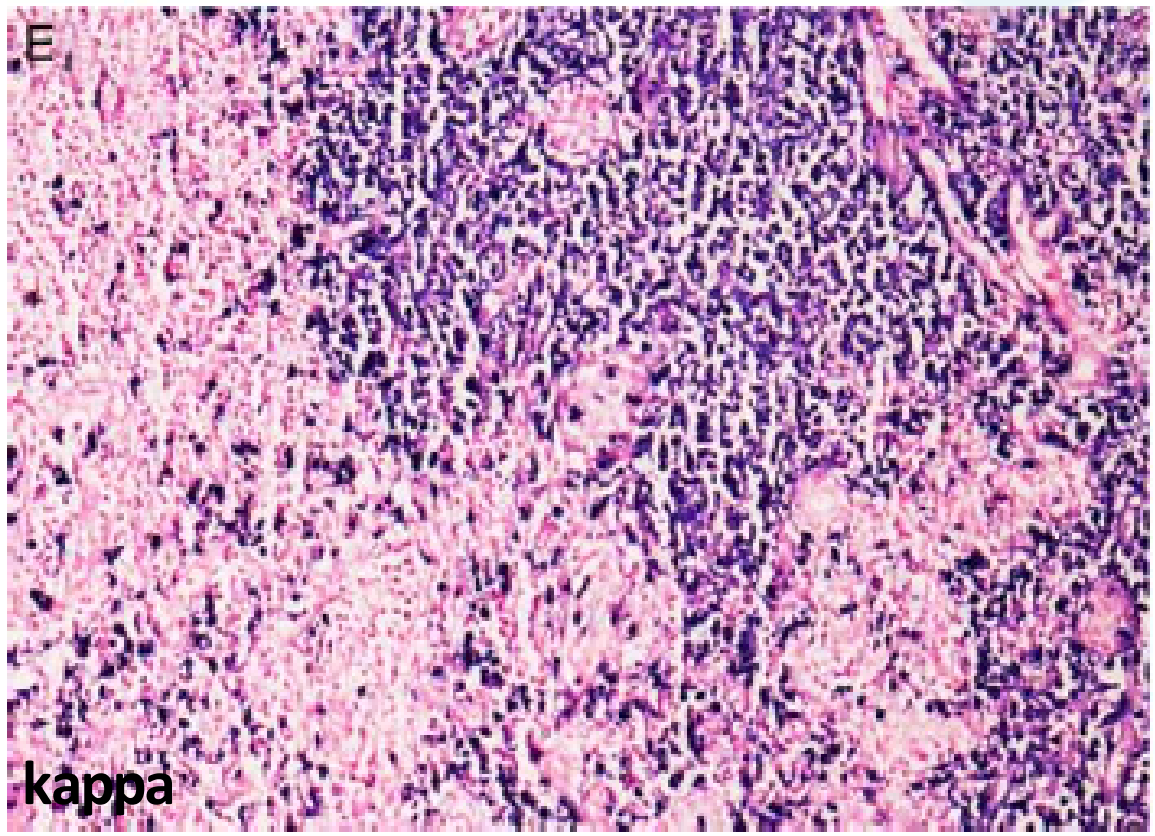
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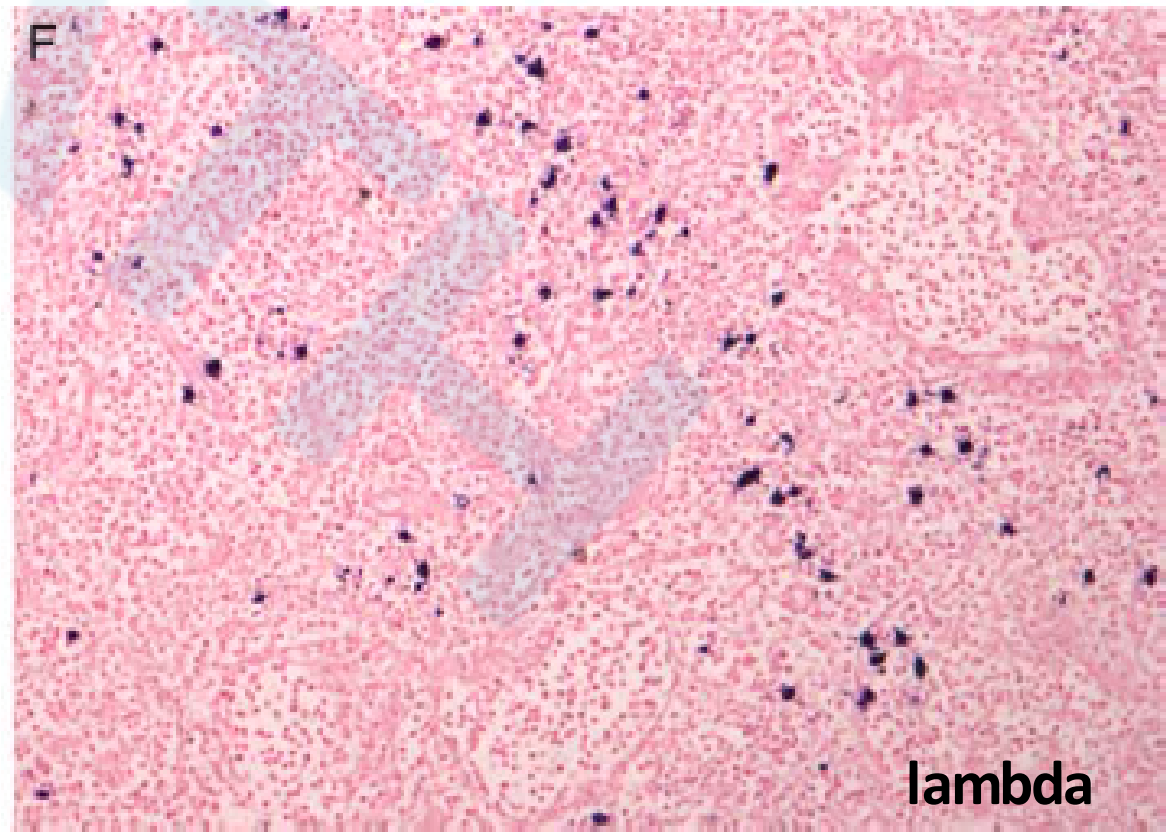
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lambda

DISCUSSION

- The EBV+ MZLs in this series lacked the necrosis and apoptosis that are key features of polymorphic PTLD.
- Notably, most of the cases in our series had a biphasic pattern, with the plasmacytoid cells segregated from the other cellular components, monocytoid cells and small lymphocytes.
- While the histologic appearance may raise a differential diagnosis with polymorphic PTLD, all of the cases studied for EBNA2 were negative.

- The differential diagnosis also includes lymphoplasmacytic lymphoma. Because of significant plasma cell differentiation seen in 9/10 cases, we performed PCR for evidence of MYD88 L265P mutation. All 6 cases tested exhibited MYD88 in the wild type state.

- Our series also expands the anatomic localization of EBV+ MZL. As noted, 3 cases involved the parotid gland and adjacent soft tissue. Two cases involved the lung and breast, both of which are commonly affected by MALT lymphoma. Notably, one posttransplant case was nodal in origin, a site not previously reported for EBV+ MZL.


谢谢！