Atypical infectious mononucleosis in the cervical region mimicking lymphoma in an adult: a case-based literature review

Shize Zheng
Jilin University Stomatology Hospital
Ce Shi
Jilin University Stomatology Hospital
Feilong Ren
Jilin University Stomatology Hospital
Chunxia Ren
Jilin University Stomatology Hospital
Lin Meng
Jilin University Stomatology Hospital
Yifan Hao
Jilin University Stomatology Hospital
Xinyi Fan
Jilin University Stomatology Hospital
Chunyan Qiao
Jilin University Stomatology Hospital
Hongchen Sun (hcsun@jlu.edu.cn)
Jilin University Stomatology Hospital

Case Report

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Abstract

Background

Infectious mononucleosis (IM) is an infectious clinical entity commonly seen in adolescence and early adulthood. It is caused in the majority of cases by Epstein-Barr virus (EBV) and it presents as pharyngitis, fever, and lymphadenopathy. As the viruses mainly target the lymphocytes and reticuloendothelial system of the body, leading to the proliferation of the lymphatic tissues, it is often mistaken as lymphoma. Most cases of IM can be easily distinguished from lymphoma by clinical presentations and laboratory findings. However, atypical clinical presentations or laboratory findings occasionally occur, including the ages of patients over 30, generalized or isolated lymphadenopathy at unusual sites, negative heterophile antibody tests, absence of atypical lymphocytosis in the peripheral blood smear, etc. These atypical cases may lead to confused diagnosis. Therefore, IM should be differentiated from malignant lymphoma. In this paper, we reported a case of atypical IM in the cervical region of an adult, with elder age and longer disease course than typical IM.

Case presentation

In this paper, we reported a case of IM in the cervical region of a 31-year-old man, and reviewed the recent literatures on the pathogenesis, as well as differential diagnosis of IM.

Conclusion

When facing enlarged tonsil or cervical lymph nodes, the pathologists should increase vigilance to the differential diagnosis between infectious diseases and lymphomas. Especially in ambiguous cases, it is essential to test for EBER by in situ hybridization to rule out IM before making a preliminary diagnosis of lymphoma.

Background

Infectious mononucleosis (IM) is a benign and self-limited lymphoproliferative disease mainly caused by Epstein-Barr virus (EBV) infection with a course of two to three weeks[1]. IM occurs mainly in adolescents and young adults[2]. Based on the current literature, 44% of IM patients present as triad of pharyngitis, cervical lymphadenopathy, and fever. Besides, some patients can also present hepatosplenomegaly (60.1%), tonsillar white coat (39.3%), headache (25.6%), cough (13.1%), abdominal tenderness (12.5%), abdominal pain (9.5%) and facial edema (8.3%)[3]. For most cases of IM, the diagnosis depends on clinical presentations and laboratory findings[4]. Clinical signs that make the diagnosis more likely include triad of pharyngitis, fever, and lymphadenopathy[2]. Serological diagnosis requires either (1) a positive anti-viral capsid antigen (VCA)-immunoglobulin M (IgM) and anti-VCA IgG, or (2) a positive monospot test and anti-VCA IgG, or (3) a positive monospot and anti-VCA IgM[5]. These clinical manifestations and laboratory examinations can easily lead to the diagnosis of IM. While, some patients with atypical presentations, including large or asymmetric lymph nodes or tonsillar masses (frequently out of the sizes of

pharyngitis/tonsillitis), may be biopsied to rule out lymphoma[6-8]. However, owing to the presence of extensive proliferation of immunoblasts and atypical Reed-Sternberg-like cells, IM is usually misdiagnosed as lymphoma in biopsies[9, 10]. To prevent pitfalls during diagnosis and inappropriate treatments due to misdiagnosis, pathologists should consider the possibility of infectious mononucleosis, based on disease history, clinical presentations, pathologic findings etc., before making a diagnosis of lymphoma.

Case Presentation

A 31-year-old man came to our hospital presenting with a mass in his left cervical region for 3 months. Three months earlier, the patient had a routine physical examination, and a chest radiograph showed asymptomatic lymphadenopathy in his left submandibular region. Ten days earlier, he got a fever with the temperature of 37.6 ℃ (99.68 ℉), and sometimes he felt pain on his shoulder. These symptoms were relieved after anti-inflammatory treatment (the name of the medicine was unknown), but the size of the mass kept unchanged. The patient was in good status without splenomegaly, rashes, or hepatomegaly. Physical examination revealed a 25 mm × 15 mm mass in the left submandibular region with clear boundaries and good mobility. The mass was in slight tenderness on palpation. Color Doppler revealed multiple lymph nodes in the left submandibular region and around the left internal jugular vein. An initial diagnosis of tuberculosis was made. The patient was then proceeded to surgery in our hospital. During the surgery, the mass was found in the left submandibular region, measuring 25 mm × 15 mm. The mass was sent for routine pathological examination.

Macroscopically, the mass was irregular in shape, measuring 28 mm × 15 mm × 10 mm, with intact capsule. On cross-section, it was solid, medium-textured and fleshy. Microscopically, it was a lymph node with an intact capsule and proliferative lymphocytes (Fig. 1a). At high magnification, there was expansions of the interfollicular areas by polymorphous infiltrations of small-, medium-, and large-sized lymphocytes, and occasionally histiocytes, resulting in expansion and distortion, but not obliteration of the architecture of the lymph node. The infiltrated cells within the interfollicular zones exhibited mild abnormalities, with mitotic figures easily seen (Fig. 1b).

Differential diagnosis of lymphoproliferative diseases was considered, and a panel of immunohistochemical stainings were performed using EnVision system. T cells were positive for CD2, CD3, and CD5 (Fig. 2a, 2b and 2c). B cells were positive for CD20 (Fig 2d). The patterns of the positivities of CD3 and CD20 immunostainings demonstrated the mixed nature of small-, medium-, and large-sized lymphocytes, including transformed active form of immunoblasts and mature plasma cells. Germinal centers were positive for Bcl-6 (Fig. 2e) and CD10 (Fig. 2f), but negative for Bcl-2 (Fig. 2g). Follicular dendritic cell (FDC) networks were delineated by the positivity of CD21 (Fig. 2h. More than 60% of the cells within the interfollicular regions were labeled by Ki-67 (Fig. 2i).

Due to the presence of enlarged T zones and T cells, differential diagnosis of T-cell lymphoma was made. However, the architecture of the lymph node was not obliterated and T cell-associated antigens (CD2,

CD3, CD5) was not lost, thus T-cell lymphoma could be excluded. Then, in situ hybridization (ISH) for EBV-encoded small RNAs (EBER) was performed to rule out IM. Positive signals of EBER could be detected, with 200 positive cells/HPF (Fig 3a). EBER+ cells were predominantly small lymphocytes and large immunoblasts located within the interfollicular regions, as well as small lymphocytes located within the germinal center beneath the capsule (Fig 3b and 3c).

Based on the normal structure of the lymph node, proliferative lymphocytes of mixed cell types, and positive signals of EBER in both large and small cells, a final diagnosis of IM was made.

Discussion

IM is a benign and self-limited lymphoproliferative disease, mainly occurs in adolescents and young adults, with most patients caused by EBV infection[11, 12]. While, approximately 10% of cases arise from infections by other viruses, such as cytomegalovirus, HIV, and hepatitis B[13]. The diagnosis of IM is usually made based on clinical presentations (triad of pharyngitis, fever, and lymphadenopathy) and serological examinations (positive anti-VCA IgG and IgM, or positive monospot test together with IgG or IgM)[5, 11, 12]. However, atypical clinical presentations occasionally occur, including the ages of patients over 30, generalized or isolated lymphadenopathy at unusual sites, negative heterophile antibody tests, absence of atypical lymphocytosis in the peripheral blood smear etc., in which biopsies are needed[6-8]. In this case, the patient is atypical, due to his elder age (31-year-old) and long disease course (3 months).

P*athological features* of IM are nonspecific. At low magnification, shrink of the lymphoid follicles are usually found, with interfollicular regions significantly enlarged. At high magnification, characteristic findings include B cells of different differentiation stages, i.e., activated lymphoblastic cells, immunoblasts, plasma-like cells, and mature plasma cells, with different sizes and morphologies. The specific feature is the proliferation of immunoblasts, which are large in size and rich in clear cytoplasm, giving a mottled appearance at low magnification. Mitotic figures and nuclear fragments are commonly detected. Increased small blood vessels, as well as necrosis can be seen in a few cases. In a minority of cases, small sheets of monocyte-like B cells can be found[6]. Immunohistochemical profiles revealed that $CD3^+$ T cells are the major small lymphocytes within the expanded interfollicular zone. Active lymphoid-like blasts and immunoblasts which are CD20 and CD30 positive are scatteredly distributed, and are partially positive for CD30 with variable intensity. In all EBV infectious cases, nuclear EBER positivity can be detected in large-, medium- and small-sized lymphocytes.

Actually, the pathogenesis of IM is a continuous spectrum following EBV infection, and can be divided into four stages, i.e., latent stage, early stage, middle stage, and late stage.

(1) Latent stage: as EB viruses invade the body, they first infect B cells, resulting in a massive proliferation of B cells and induction of humoral immune responses. To prevent the proliferation of B cells, cytotoxic T lymphocytes are activated. Thus, this stage presents as the proliferation of B lymphocytes in the lymphoid follicles and cytotoxic T lymphocytes in the interfollicular zone, with EBV-infected B

lymphocytes less than 5%. Latent stage of IM is similar to toxoplasmic lymphadenitis. However, the features of toxoplasmic lymphadenitis not only include the presence of immunoblasts and plasma cells, but also include necrosis and Langerhans cells. PCR and serological tests can be helpful to distinguish the pathogens[14].

(2) Early stage: this stage presents as the proliferation of the large-, medium-, and small-sized cells in the paracortex region, among which large B lymphocytes significantly proliferated (accounting for 5%~75%). At this stage, IM should be differentiated from diffuse large B-cell lymphoma, no otherwise specified (DLBCL, NOS) and EBV-positive DLBCL. IM can be distinguished from DLBCL, NOS by the intact structure of the lymph nodes, the reactive proliferation of mixed cell types, as well as the immunophenotypes (scattered CD20 positivity with different intensities in IM vs. diffusely strong CD20 positivity in DLBCL, NOS). EBV is generally negative in DLBCL[6]. In EBV-positive DLBCL, the positive signals of EBV can be exclusively detected in large neoplastic cells, distinguishing from IM which shows EBV positive signals in polymorphous lymphocytes[2].

(3) Middle stage: this stage presents as the continuous proliferation of the large-, medium-, and small-sized lymphocytes, most of which are medium- to large-sized T lymphocytes, with $CD8^+$ cytotoxic T lymphocytes accounting for 35%□50%. Meanwhile, the number of B lymphocytes is decreased. At this stage, IM should be differentiated from anaplastic large cell lymphoma (ALCL) and classic Hodgkin lymphoma (CHL). In ALCL, the proliferative cells are frequently adhesive to each other, with the nuclei exhibiting in horseshoe or kidney shapes, as well as the presence of characteristic Hallmark cells. ALCL also exhibits specific immunophenotypes, i.e., tumor cells are positive for CD30 and EMA; frequently positive for T lymphocyte-associated antigens and cytotoxic molecule (TIA-1, granzyme B, perforin, etc.); in some cases, tumor cells are positive for anaplastic lymphoma kinase (ALK). While, in IM, CD30 can be positively stained in some cases, and EMA is negative. The proliferative lymphocytes also show EBV latent membrane protein 1 (LMP1) positive[15]. Hodgkin lymphoma (HL) and IM are the most common EBV-associated diseases in western countries[16]. Although both IM and CHL have similar background of mixed cell types, eosinophils are rare in IM while usually numerous in CHL. Furthermore, the presence of Reed-Sternberg (RS)-like cells in IM can cause confusion with CHL. However, the RS-like cells in IM show OCT-2 and BOB.1 positive, but CD15 negative, whereas the RS cells in CHL show CD15 positive, with one of OCT-2 and BOB.1 lost[17]. In situ hybridization result shows that EBER can be detected in both large and small cells in IM, whereas EBER can only be detected in large cells in CHL, with much more positive cells in IM than in CHL.

(4) Late stage: Large T lymphocytes are continuously increased, with $CD8^+$ T lymphocytes accounting for 50-75%, and EBV-positive B lymphocytes less than 5%. The proliferative T lymphocytes show basophilic cytoplasm, irregular nuclei, coarse chromatin, and more frequent mitotic figures. At this stage, IM should be differentiated from peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS). PTCL is more common in elder adults. The tumor cells are proliferative in a monoclonal manner, which show irregular cell morphology and light or transparent cytoplasm. The tumor cells in PTCL express antigens related to

T lymphocytes, such as T cell receptor beta-chain (TCR beta). Clonal rearrangement of genes can be helpful in the differential diagnosis[6, 18].

As IM progresses, the interaction between T and B lymphocytes leads to enhanced activity of suppressor T cells and macrophages, which block the proliferation of B lymphocytes. Ultimately, both B and T lymphocytes are decreased. Thus, IM presents as a self-limited disease. The treatment strategy for IM includes supportive treatment, rest, and analgesics. Since the pathological changes of IM at different stages mimic HL or non-HL, misdiagnosis of IM as lymphomas is common, resulting in inappropriate treatments. Thus, the pathologists should consider the differential diagnosis of IM and lymphomas at different stages. It is believed that in situ hybridization using EBER probes is helpful for differential diagnosis of IM[2].

Conclusion

In this study, we reported one IM arising in the left submandibular region, with elder age (31-year-old) and long disease course (3 months). A final diagnosis of IM was made based on normal structure of the lymph node, proliferative lymphocytes of mixed cell types, and positive signals of EBER in both large and small cells by in situ hybridization. It suggested that when a lymph node is proliferative with mixed background, IM should be considered as differential diagnosis and in situ hybridization using EBER probes should be performed to rule out IM. The pathologists should avoid the misdiagnosis of lymphoma to prevent the patients suffering from unnecessary treatment and psychological burden.

Abbreviations

IM: Infectious mononucleosis; EBV: Epstein-Barr virus; VCA: Anti-viral capsid antigen; IgM: Immunoglobulin M; FDC: Follicular dendritic cell; DLBCL, NOS: diffuse large B-cell lymphoma, no otherwise specified; ISH: In situ hybridization; EBER: Epstein-Barr virus encoded small RNA; ALCL: Anaplastic large cell lymphoma; CHL: Classic Hodgkin lymphoma; ALK: Anaplastic lymphoma kinase; LMP1: Latent membrane protein 1; HL: Hodgkin lymphoma; RS: Reed-Sternberg; PTCL, NOS: Peripheral T-cell lymphoma, not otherwise specified; TCR beta: T cell receptor beta-chain

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hospital of Stomatology, Jilin University, Jilin, China(No. KY2021-18). Written informed consent was obtained from the patient for the storage of samples and data, follow-up contact, and further use of samples and data for research purposes.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

Shize Zheng contributed to draft the manuscript; Chunyan Qiao, Hongchen Sun contributed to conception and design; Ce Shi, provided the interesting case that we reported, as well as guidance and editing throughout the writing process. Feilong Ren, Chunxia Ren, Lin Meng, Yifan Hao and Xinyi Fan contributed to assisted with research and writing, particularly the discussion/conclusion portion. All authors gave final approval and agreed to be accountable for all aspects of the work.

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Not applicable.

Authors' information (optional)

1 Department of Oral Pathology, Hospital of Stomatology, Jilin University, Changchun 130021, China. 2 Department of Periodontology, Hospital of Stomatology, Jilin University, Changchun, 130021, China. 3 Department of Oral Radiology, Hospital of Stomatology, Jilin University, Changchun, 130021, China.

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Figures

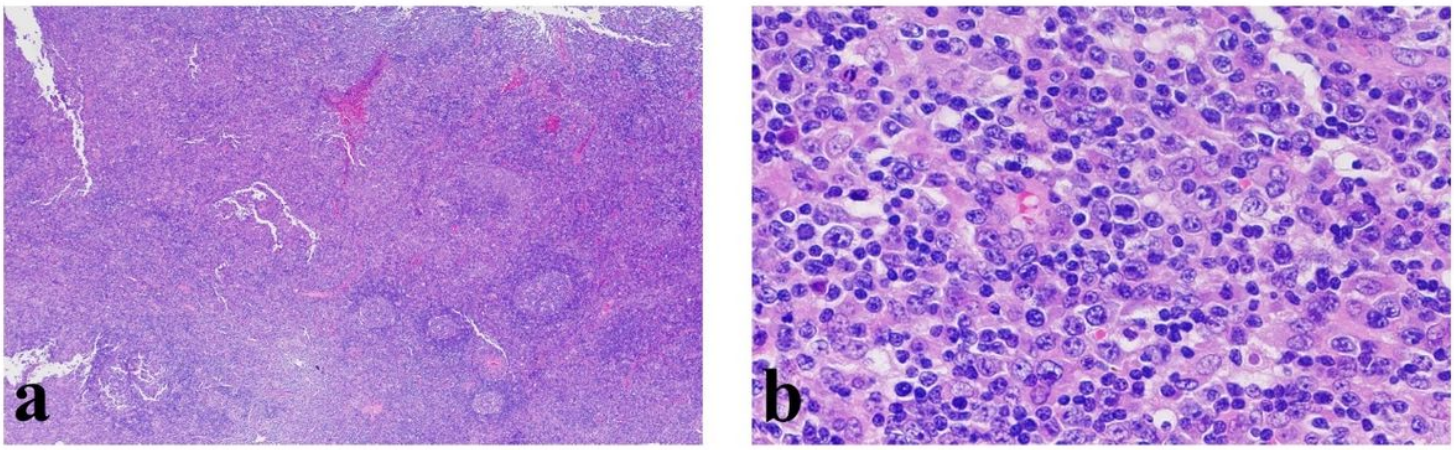

Figure 1

Characteristic morphological features of infectious mononucleosis.

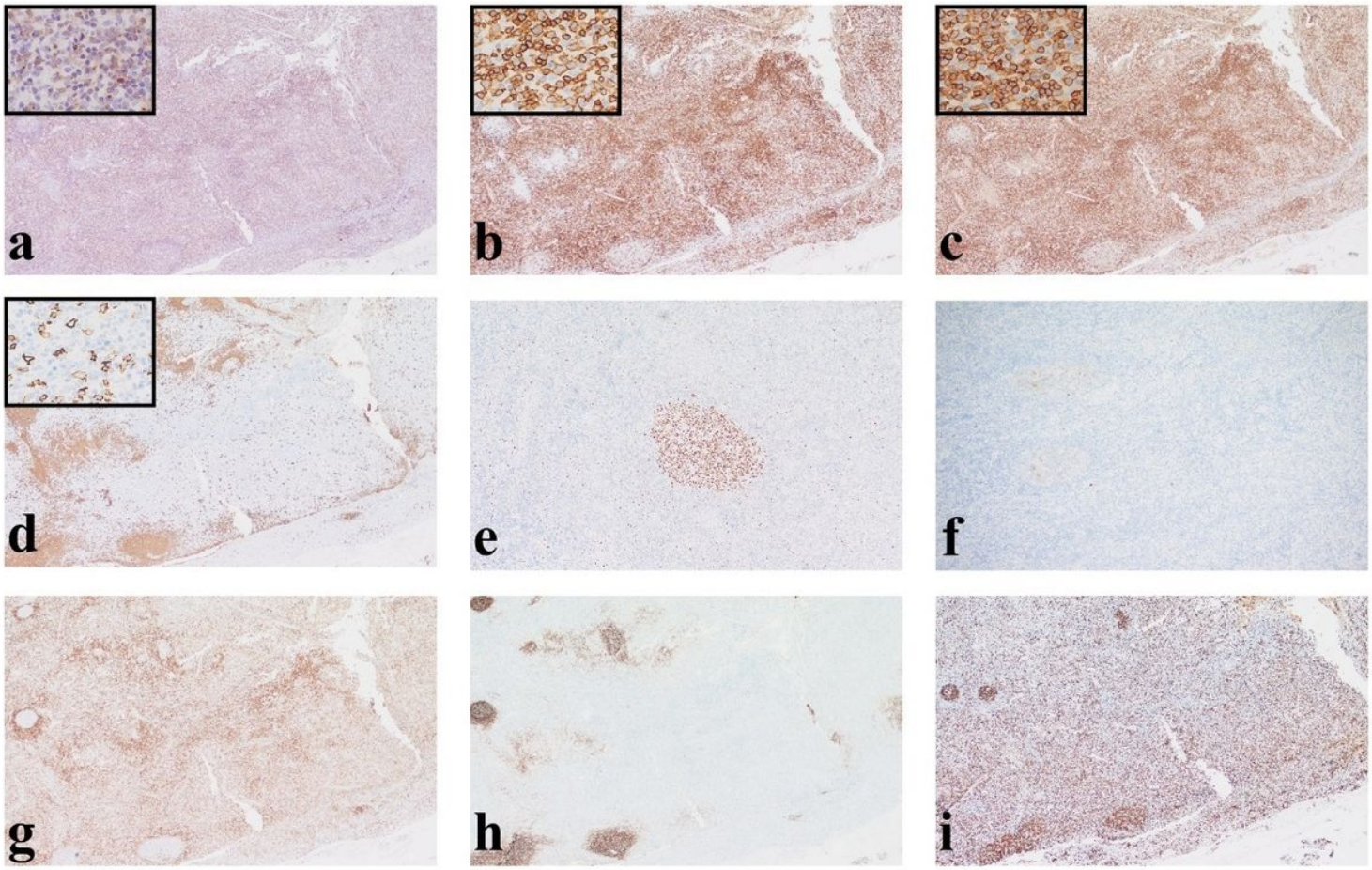

Figure 2

Immunohistochemical findings.

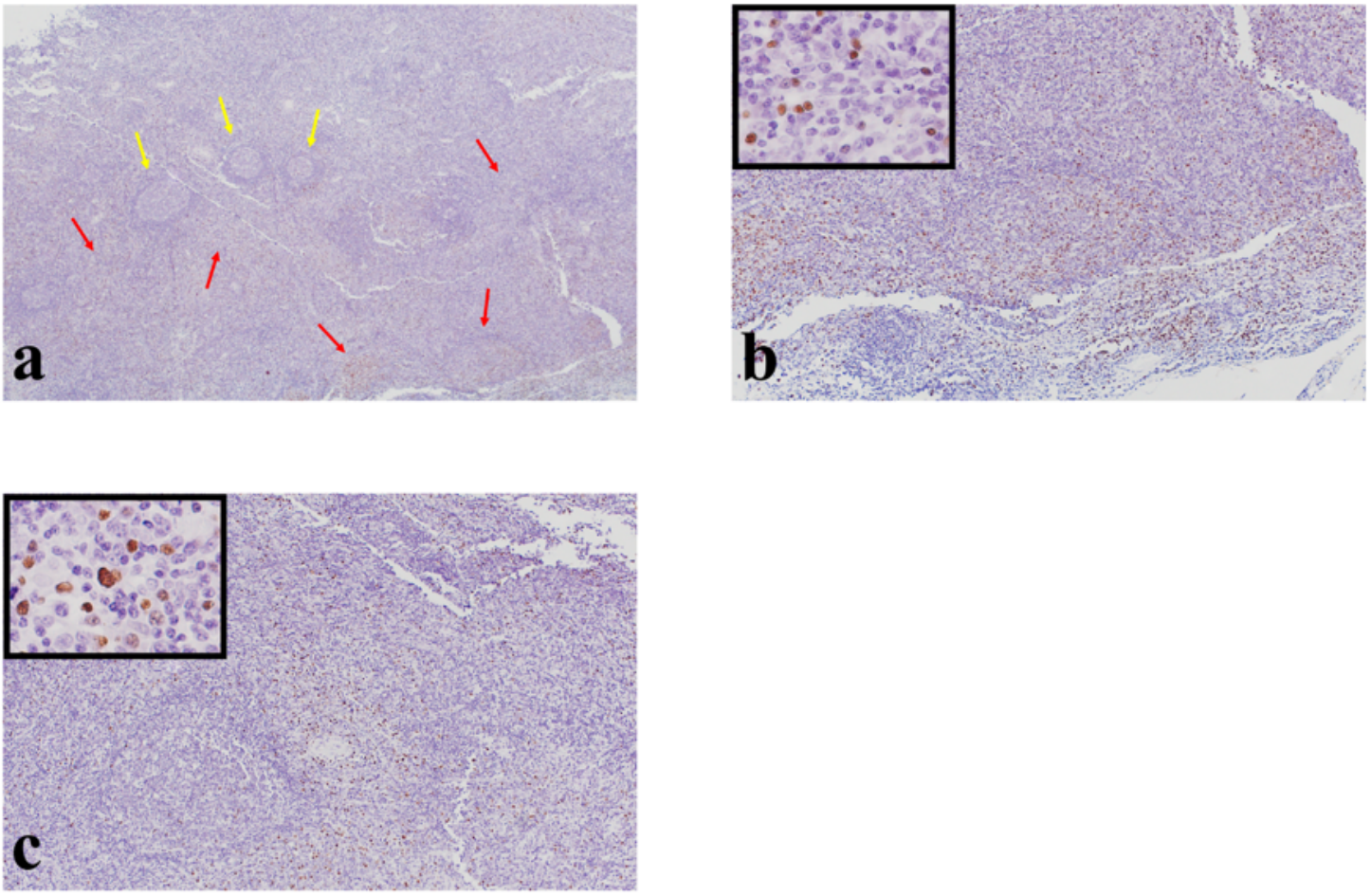

Figure 3

Detection of Epstein-Barr virus encoded small RNA (EBER) by in situ hybridization (ISH).

Supplementary Files

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- CAREChecklist.pdf