

Nodular lymphocyte predominant B-cell lymphoma involving an intraparotid lymph node: a case report

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Case Report

Keywords: Nodular lymphocytic-predominant B-cell lymphoma, NLPHL, Intraparotid lymph node, B-cell lymphoma, Parotid mass, Case report

Posted Date: September 24th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9546012/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Nodular lymphocyte predominant B-cell lymphoma (formerly known as nodular lymphocyte-predominant Hodgkin lymphoma) is a distinct B-cell neoplasm characterized by large neoplastic cells with multilobulated “popcorn-like” nuclei. It typically presents as peripheral lymphadenopathy and rarely involves the intraparotid lymph nodes, which may pose a diagnostic challenge due to overlap with other lymphoid neoplasms, particularly classical Hodgkin lymphoma.

Case presentation:

A 23-year-old man presented with a painless left parotid swelling. Ultrasound revealed a solitary intraparotid lymph node, and an excisional biopsy confirmed the diagnosis of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). After the PET/CT scan, it was classified as Stage IA. He was treated with localized radiotherapy and remained clinically stable at 3-months follow up.

Conclusion

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) rarely involves the parotid lymph nodes, presenting diagnostic challenges due to its indolent course and potential histologic mimicry of benign lesions. Accurate diagnosis requires excisional biopsy and immunohistochemistry, and treatment is stage-dependent. Despite a favorable prognosis, careful follow-up is essential because of the risk of relapse or transformation into aggressive B-cell lymphoma.

Background

Hodgkin’s lymphoma (HL) is a haematological malignancy of B-cell origin that primarily affects the lymph nodes and the lymphatic system (1). HL is distinguished from other lymphomas by its unique cellular composition and by the presence of Hodgkin and Reed–Sternberg (HRS) cells (2). There are two main subtypes of Hodgkin lymphoma: Classical HL (cHL), which accounts for approximately 95% of cases, and the less common Nodular Lymphocyte Predominant HL (NLPHL) (3). The distinction between these subtypes is based on the neoplastic cells involved. In cHL, the predominant cell type is HRS, whereas in NLPHL, the neoplastic cells are lymphocytic and histiocytic (LP) “popcorn” cells. They also differ in immunophenotype, EBV association, histologic pattern, cellular background, and origin (2).

Hodgkin lymphoma is one of the most common lymphomas in the Western world, with an annual incidence of 2–3 cases per 100,000 persons (4). NLPHL accounts for approximately 5–13% of all HL cases and predominantly affects men, typically between 35 and 40 years of age (5–7). There may be an inherited or immune-related predisposition, with certain Human Leukocyte Antigen (HLA) types

increasing the risk, sometimes triggered by infections such as *Moraxella catarrhalis* (8). Although NPLHL usually involves peripheral lymph nodes such as cervical, axillary, and inguinal regions, involvement of the parotid gland is rare but highly specific for this subtype (9).

In this report, we present a rare case of NPLHL involving the intraparotid lymph nodes in a young male, highlighting its clinical presentation, diagnostic considerations, histopathological findings, and treatment options. This case adds to the limited number of reported intraparotid NPLHL cases and supports a potential predilection for parotid lymph nodes

Case Presentation

Patient Information

A 23-year-old male patient from Palestine with no significant past medical or surgical histories presented with a painless swelling over the left parotid region that had been slowly increasing in size for more than a year but remained stable for the preceding six months and had no overlying skin changes. The patient denied any constitutional “B” symptoms such as fever, night sweats, or unintentional weight loss. He had no history of recent infections. Family history was free of hematologic or oncologic diseases, and he reported no smoking, alcohol consumption, illicit drug use, or exposure to radiation. There are no known drug or food allergies.

Clinical Findings

On physical examination, the patient was afebrile and hemodynamically stable. Local examination of the left parotid region revealed a firm, mobile, non-tender mass measuring approximately 3.5*2.5 cm with intact overlying skin and no facial nerve dysfunction. On examination, there was no palpable cervical, axillary, or inguinal lymphadenopathy, nor was there hepatosplenomegaly.

Diagnostic assessment

An ultrasonographic assessment demonstrated a solitary left intra-parotid lymph node enlargement measuring 3.8 X 2.3 cm hypoechoic with internal thin echogenic foci and two other adjacent lesions adherent to it, the largest being 2.3 X 1.3 cm with no hilum seen.

Laboratory investigations revealed a white blood cell count of 9.6×10^9 cells/L, haemoglobin of 16.3 g/dL, and a platelet count of 289 K/ μ L. Lactate dehydrogenase was 155 U/L, lower than the reference range (207–414); uric acid was 7.7 mg/dL, higher than the reference range (3.7–7.1); and C-reactive protein was 2.49 mg/L, indicating no systemic inflammation. Liver and renal function tests were unremarkable except for mildly elevated alanine aminotransferase of 55.7 U/L (0–41). Viral screening for hepatitis B and C was negative. Overall, the laboratory investigation was unremarkable for a patient with lymphoma.

An excisional biopsy of the left parotid lymph node was done and the histopathologic examination demonstrated nodular lymphoid architecture composed predominantly of small lymphocytes mixed with scattered large, atypical cells with rare multilobulated nuclei. Figure 1.

Immunohistochemical staining showed that the large cells were positive for CD20, CD45 also called Leukocyte Common Antigen (LCA) immunostain, PAX5 (weak), and BCL6 (weak), and negative for CD15, CD30, BCL2, CD3, and (Multiple Myeloma Oncogene 1) MUM1. CD21 highlighted expanded follicular dendritic cell meshwork, while CD3 highlighted T-cell rosettes surrounding the large cells. Negative BCL2 expression within the nodules confirmed the lack of reactive germinal center. With these findings the patient was diagnosed with nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). Figures (2).

For staging, a whole-body 18F-FDG PET/CT scan was obtained. It demonstrated a hypermetabolic left parotid lymph node measuring 1.6 X 1 cm with a maximum standardized uptake value (SUVmax) of 7.6, consistent with lymphomatous activity. No other hypermetabolic lymph nodes or extranodal lesions were identified throughout the body. Accordingly, the disease was classified as Stage IA according to the Ann Arbor staging system. Figure (3)

Therapeutic Intervention

The management plan included localized radiotherapy directed to the left parotid region, given the early-stage (IA) disease and the localized nature of the involvement without evidence of systemic spread on PET/CT imaging. The decision for localized treatment was made following multidisciplinary discussion, aiming to achieve local disease control while minimizing treatment-related morbidity.

Follow up and outcome

The patient remains clinically stable at 3- and 6-month follow-up, with no evidence of disease progression or development of new lymphadenopathy on physical examination. Follow-up assessments, including clinical evaluation and laboratory investigations, showed no significant abnormalities. There was no radiological evidence of recurrence or disease progression. The patient demonstrated good adherence to follow-up visits and tolerated the treatment well, with no reported significant adverse effects related to radiotherapy.

Discussion and Conclusions

Hodgkin Lymphoma (HL) is a rare monoclonal lymphoid neoplasm, with an incidence in the United States of around 2.6 cases per 100,000 persons. Hodgkin Lymphoma is broadly classified based on its clinicopathological features into two main categories: Classical Hodgkin Lymphoma (CHL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL). The Classical Hodgkin Lymphoma (CHL), accounts for about 95% of all Hodgkin Lymphoma cases (10, 11). Meanwhile, Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL) is a rare subtype that accounts for only 5% of all Hodgkin lymphoma cases (12).

Hodgkin Lymphoma generally has a bimodal distribution pattern — the first peak occurs in young adults aged between 20 and 40 years, followed by a second peak in individuals aging 55 years or older. It is also characterized by affecting males more than females, which is most apparent in the paediatric population (10). CHL subtypes are characterized by pathognomonic Reed-Sternberg cells, which typically express CD15 and CD30. In contrast, NLPHL is distinct from CHL by the presence of atypical lymphocyte-predominant cells (LP cells), also known as Popcorn Cells, which are positive for B-cell-associated antigens such as CD20 and negative for CD15 and CD30. (13, 14)

Regarding clinical manifestations of Hodgkin Lymphoma, each subtype has a unique pattern. However, patients often present painless supra-diaphragmatic lymphadenopathy. In a smaller proportion of cases (around 30%), patients present with B symptoms, including significant weight loss, high-grade fever, chills, and profuse night sweats. Occasionally, patients present chronic pruritus or paraneoplastic symptoms, such as pain in lymph nodes triggered by alcohol consumption (10). Patients with NLPHL often present in the early stages—usually stage I or stage II—complaining of lymphadenopathy, most located in the cervical, axillary, or inguinal regions, highlighting the rare location of our patient's tumor. Only 6% to 15% of patients present with constitutional B symptoms (12, 15).

NLPHL has a more indolent course and a better survival rate compared to CHL, but it is more often associated with late relapses and transformation into an aggressive type of Non-Hodgkin Lymphoma (NHL), such as Diffuse Large B-Cell Lymphoma (DLBCL) (10, 13). Another distinguishing feature of NLPHL compared to CHL is the rate of Epstein–Barr virus (EBV) association, with NLPHL being rarely associated with EBV, unlike CHL, where the association is strong (12), (16).

Most lymphomas involving the salivary glands are non-Hodgkin B-cell lymphomas, often associated with chronic autoimmune diseases, such as Sjögren's disease. Thus, the presentation of Hodgkin lymphoma in the parotid region is extremely rare, representing only 3.5% to 6% of primary parotid gland lymphomas and 0.3% of all Hodgkin lymphoma cases. In addition, it is worth mentioning that, up to 2015, fewer than 10 cases had been reported in the literature—only one of which was NLPHL (9, 17)

While cervical, inguinal, and axillary lymph nodes are the most common sites of NLPHL-induced lymphadenopathy, some studies suggest a distinct preferential pattern involving parotid lymph nodes. A remarkable and unusual association between intraparotid lymph nodes and NLPHL was demonstrated via a study reviewing 938 cases of Hodgkin and non-Hodgkin lymphomas, of which only six lymphomas were intraparotid. Among these six cases, 66% were NLPHL (15). Later, another review also confirmed that NLPHL is more commonly associated with parotid gland lymphomas than other Classical Hodgkin Lymphoma (CHL) subtypes (18).

The parotid gland is the largest among the salivary glands and is the only one that contains intraglandular lymph nodes, which are more concentrated in the superficial lobe, located between the gland and its capsule (18–20). It is difficult to diagnose NLPHL cases in general, with a particular focus on NLPHL intraparotid lymph nodes. The difficulty was attributed to the fact that LP cells may be

minimal or insufficient, and the nodular pattern of the disease can be misdiagnosed as any associated reactive response, especially if NLPHL is not considered in the differential diagnosis (17).

Primary Malignant Lymphoma (PML) of the parotid gland is a very rare disease, accounting for only (0.6% to 5%) of all parotid gland tumors and/or tumor-like lesions, often clinically unsuspected, due to nonspecific manifestations, which are indistinguishable from other much more common epithelial tumors (17, 21). Almost all primary lymphomas of the parotid gland are classified as subtypes of NHL, where the extra-nodal marginal-zone (MALT-) B-cell lymphomas, and nodal follicular and diffuse large cell B lymphoma constitute most of all cases (17, 21, 22).

According to a literature review, less than ten cases of Hodgkin lymphoma presenting as a primary nodal parotid tumor have been reported: six (n = 6) as NLPHL and three (n = 3) as Classical Hodgkin Lymphoma (CHL). This low prevalence, particularly the relative dominance of NLPHL cases (n = 6) compared to CHL (n = 3), sharply contrasts with the general Hodgkin lymphoma epidemiology where NLPHL accounts for only 5% of all cases (12, 17). To the best of our knowledge, we found no similar cases in the region. It significantly adds to the literature, reinforcing the observation of NLPHL's preferential involvement of parotid lymph nodes, and sheds new light on the clinical, radiological, and histopathological patterns.

A recent case series established the histopathological patterns of Hodgkin Lymphoma in primary parotid gland tumors, outlining them as a nodal-based lymphoproliferative disease with minimal or absent extension into surrounding parenchymal salivary tissue. Within the lymph node, unusual proliferation and metaplasia of salivary epithelial elements were noted; these inclusions, suggest an inherent tendency especially of NLPHL to induce secondary lymphoepithelial and oncocytic proliferations through epitheliotropism or a not yet understood immunological mechanisms. NLPHL may on occasion be a difficult diagnosis, given that the characteristic cellular elements of NLPHL (LP cells) might be sparse and the nodular architecture of NLPHL might be mistaken for a reactive process, highlighting the potential for misdiagnosis of NLPHL in intraparotid lymph nodes especially as non-sebaceous lymphadenoma, Warthin tumor, or autoimmune sialadenitis (17).

Hodgkin lymphomas that arise within intraparotid lymph nodes often present as well-circumscribed and surrounded by a fibrous capsule with or without minimal invasion to adjacent tissue. On the other hand, diffuse parenchymal infiltration lacks a capsule and may present as a multilobular structure (17,23). Typical intraparotid lymph nodes when evaluated by high resolution ultrasound, appear as reniform or oval tissue with echogenic hilum that is centrally located. Whereas, if lymphoma involves the lymph nodes, it can cause significant changes in the previously mentioned features, resulting in a homogeneous hypoechoic lesion with mild posterior acoustic enlargement, with no echogenic hilum and that could be like a cyst morphology (15, 18, 24). Parenchymal masses of the parotid gland, especially the mucosa associated lymphoid tissue (MALT) type, usually seen as heterogeneous mixed {solid, cystic} lesions, in which half of the cases may be diffused, and the other half is solitary mixed mass. In comparison, non-MALT lymphomas are usually purely solid or multifocal lesions (25). In this reported

case, the sonographic findings suggest three masses. The main lesion is 3.8 × 2.3 Cm, hypoechoic oval mass with internal thin echogenic foci, and the other two are also oval, hypoechoic with no hilum, the largest is 2.3 × 1.3 cm. They are likely well circumscribed, and the PET scan suggests no signs of invasion.

Fine needle aspiration cytology (FNAC) is a minimally invasive initial diagnostic step, which allows safe sampling that enables cytologic evaluation of the lesions (18). When supported by ancillary testing such as flow cytometry, its sensitivity for lymphoma can be significantly increased (26). In our case, cytologic evaluation showed large atypical lymphoid cells that were CD20+, CD45+, but negative for CD30, CD15, and CD3, compatible with B-cell immunophenotype (which is seen in NLPHL) (17). However, FNAC has important limitations in this context. The accuracy of diagnosis may be distributed by the presence of a mixture of the salivary and lymphoid tissue, for example, reactive or autoimmune cases such as lymphoid hyperplasia or sialadenitis can be similar cytologically to lymphoma, causing misclassification or false negative results, frequent causes are low grade lymphomas like NLPHL which may resemble reactive processes (27, 28). As a result, a confirmatory diagnosis is based on an excisional or core biopsy to evaluate tissue architecture, lymphocyte-predominant cell morphology, and nodularity (17).

Excisional/core biopsy is a crucial step for NLPHL definitive diagnosis. As it allows the assessment of nodular growth pattern, tissue architecture, and the extent of the lymphocyte-predominant cells, for an accurate diagnosis and subtyping (29). In our case, biopsy of the left parotid lymph node showed atypical lymphoid proliferation with partial nodular architecture, composed predominantly of small lymphocytes with scattered large atypical, cells with some multilobulated nuclei. For the immunohistochemical examination, the large cells were CD20+, CD15-, and negative for CD30, confirming the diagnosis of NLPHL.

Immunohistochemistry (IHC) is a vital part of the evaluation of lymphoproliferative disorders, including the differentiation of NLPHL from CHL as well as other lymphoid proliferation disorders. NLPHL has a distinctive B-cell immunophenotype, the LP cells are CD20 + and CD45+, and both CD15- and CD30-negative, whereas CHL has HRS cells that are CD30 and CD15 positive, weak PAX-5 positive, and CD20 negative. In addition to confirming the diagnosis, IHC can help to rule out benign conditions such as an autoimmune or reactive process, that may be histologically like lymphoma (18).

Among the lymphoid proliferations of the parotid gland, the differential diagnoses of salivary gland lymphomas include CHL, MALT lymphoma, diffuse large B Cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma and mantle cell lymphoma, and account for approximately 75 percent of all salivary gland lymphomas (28, 30). MALT lymphoma is often seen in association with Sjögren syndrome. MALT lymphoma typically consists of small polymorphic B cells with CD20 positivity and CD5 and CD10 negativity (31). Follicular lymphoma is characterized by centrocytic morphology, is often low-grade and therefore is CD10, BCL6, and BCL2 positive. DLBCL is characterized by large atypical lymphoid cells that are strongly positive for CD20. CLL/SLL usually expresses CD5 and CD23, whereas MCL is positive for CD5 and Cyclin D1 or has a CCND1 translocation (28)

There are also several benign parotid swellings that can cytologically or histologically resemble lymphoma. Reactive intraparotid lymph nodes present polymorphic lymphoid hyperplasia (28). Autoimmune sialadenitis may present lymphoepithelial lesions, or it can progress to MALT lymphoma, often with cystic changes (32). There is also tumor-associated lymphoid proliferation that may occur in epithelial neoplasms, like acinic cell carcinoma or mucoepidermoid carcinoma, where reactive lymphoid stroma can mimic lymphoma on FNAC (27, 28). Warthin tumors and non-sebaceous lymphadenoma could also be mistaken for non-Hodgkin lymphoma, especially with oncocytic or cystic change (32). Lymphoepithelial cysts in patients with HIV infection may have mixed lymphoid or inflammatory components that would be suspicious for lymphoma on cytologic review (32)

The German Hodgkin Study Group (GHSG) classified risk groups of NLPHL into early, intermediate, and advanced stages. this classification considers the presence of the following risk factors: A. Large mediastinal mass, defined as mass greater than one-third of the maximum horizontal chest diameter; B. Extranodal disease; C. Elevated ESR > 50 mm/h without B symptoms, or > 30 mm/h with B symptoms; D. At least three nodal areas. Early stages include stage I/II with no risk factors, stage I/IIA with at least one risk factor, or stage IIB with risk factors C/D, but not A/B. Advanced stages include Stage IIB with risk factors A/B or Stage III/IV. (33) Currently, regimens used for NLPHL treatment are used for CHL due to lack of randomized controlled trials on NLPHL treatment outcomes so more studies should be conducted for better understanding of management. (34)

Treatment options depend on the stage of the disease. For example, in early stages of NLPHL without extranodal or bulky disease, or radiotherapy cannot be used, or in asymptomatic patients, active surveillance may be possible (35). The recommended treatment for stage IA without risk factors is limited field Radiotherapy (RT) alone. Active surveillance can be considered in patients after LN resection or in complete remission on PET and CT scans (36). For early stages, limited-field RT and two cycles of Adriamycin (A) (Doxorubicin), Bleomycin (B), Vinblastine (V), Dacarbazine (DTIC) (D), sometimes given with Rituximab(R) abbreviated as ((R)ABVD) is recommended, other options include Bendamustine + Rituximab (BR) +/- RT, Rituximab + Cyclophosphamide + Vincristine + Prednisone (R-CVP) +/- RT if use of anthracycline is precluding. Rituximab +/- RT or RT alone (37). Options are the same for intermediate stages but four cycles instead of two (38–40).

In advanced stages, four or six cycles of Bleomycin, Etoposide, Adriamycin (Doxorubicin), Cyclophosphamide, Oncovin (Vincristine), Procarbazine, Prednisone (BEACOPP escalated) +/- RT (PET-2-guided: 4 cycles if PET-2 negative, 6 cycles if PET-2 positive) are recommended. Another option is 6 cycles of Rituximab, Cyclophosphamide, Doxorubicin (Adriamycin), Vincristine (Oncovin), Prednisone (R-CHOP) +/- RT. Other alternative treatments include BP +/- RT, R-CVP +/- RT if use of anthracycline is precluded. Active surveillance or (R-)ABVD +/- RT. (33)

NLPHL patients typically have risk of transformation and relapses, even the fact that they have a more favorable prognosis when compared with CHL patients (41). The ten-year overall survival rate is approximately 90%. Relapse of the disease occurs in 3–4 years in 20% of the diagnosed patients. 30% of

relapses occur within 2 years of the diagnosis ((42). And 20% within 10 years (8). Older patients (> 60 years) patients and those who relapses in 2 years of diagnosis has poorer outcomes (7, 42, 43).

It was observed that relapsed cases may undergo a transformation to a more aggressive B cell immunophenotype, for which, making it important to repeat biopsy in relapsed cases (44). And if a different histopathology is found, a different chemotherapeutic regimen should be selected, and hematopoietic cell transplantation (HCT) should be considered. (34)

Conclusion

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) of the parotid lymph node is an exceptionally rare entity, with few cases reported in the literature. This case highlights the importance of considering NLPHL in the differential diagnosis of parotid masses, particularly in young adults presenting painless, isolated lymphadenopathy. Accurate diagnosis relies on excisional biopsy and immunohistochemistry, as fine needle aspiration may be insufficient due to the sparse distribution of LP cells. Despite its generally favorable prognosis, NLPHL carries a risk of relapse and transformation into aggressive B-cell lymphomas. Reporting such rare cases contributes to a better understanding of the clinical, radiological, and histopathological characteristics of NLPHL in atypical locations, guiding future diagnosis and management strategies.

Declarations

Ethics approval and consent to participate

Writing this case report was approved by Al-Quds University, Faculty of Medicine, Palestine and Beit Jala Governmental Hospital, Bethlehem, Palestine, Department of Hematology and Oncology.

Consent for publication

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this article.

Availability of data and materials

All data generated during this study are included in this published article

Competing interests

The authors declare that they have no competing interests

Funding

Authors declare that no financial support was received for the research and/or publication of this article.

Authors' contributions

HH is the first author, performed literature review, contributed in the discussion section and review the case report data. PA identified the case, collected data, and documented it. All authors performed a literature review, and drafted the manuscript. GK, IH, RS, and HH contributed to data interpretation and drafting of the discussion. HH contributed to clinical interpretation and critically revised the manuscript. AK diagnosed the case and supervised the work, validated the findings, and critically revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable

Patient Perspective

The patient reported that the initial symptoms were distressing and affected his daily activities. He expressed concern about the uncertainty of the diagnosis and the progression of his condition. During the hospital stay, he felt reassured by the medical team and appreciated the explanations provided regarding his condition and treatment plan. Following treatment, the patient noted a significant improvement in symptoms and overall well-being. He expressed satisfaction with the care received and emphasized the importance of early diagnosis and proper medical attention.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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Figures

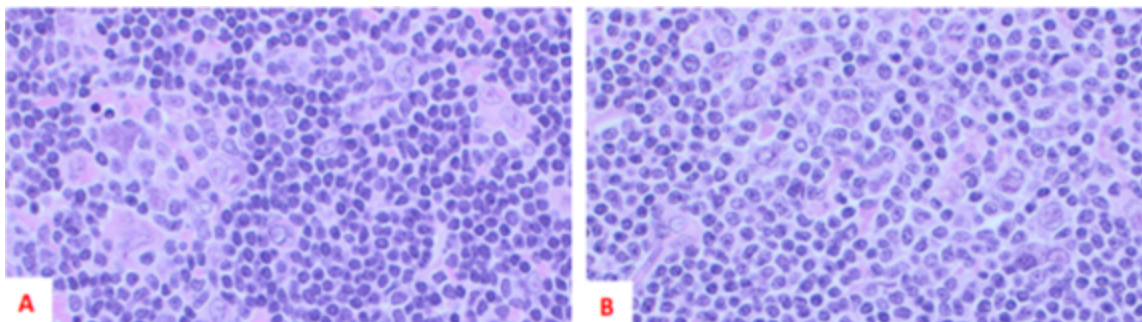


Figure 1

Hematoxylin and Eosin stain (H&E) (40X) : **A.** The lymph node architecture is effaced by vague nodular proliferation composed of many Reed-sternberg cells (RS). **B.** Few popcorn cells are identified.

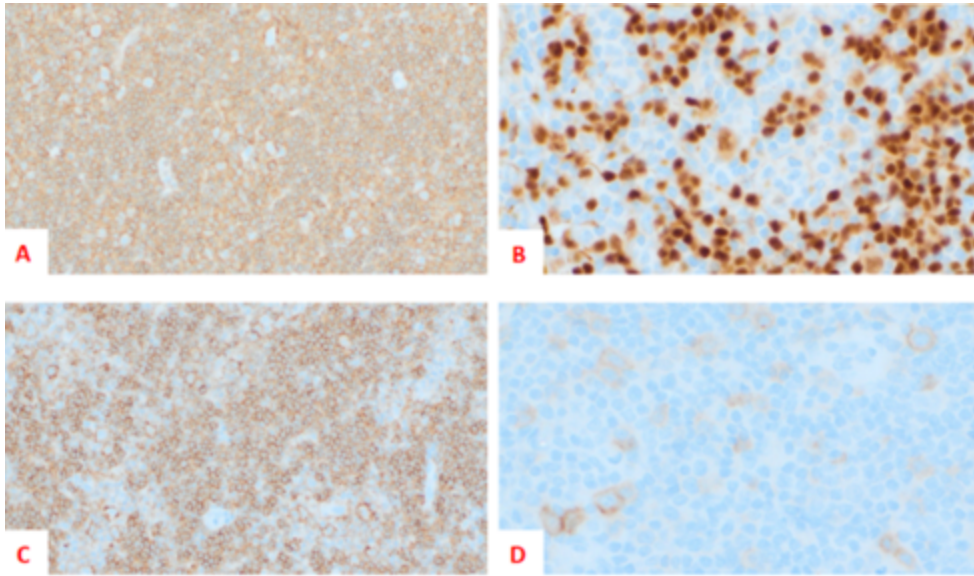


Figure 2

A. The neoplastic cells are positive for Leukocyte Common Antigen (LCA) (CD45) immunostain. **B&C:** The neoplastic cells are positive for CD20 and PAX5 (dim) immunostain. **D:** The neoplastic cells are focally positive for CD30 immunostain.

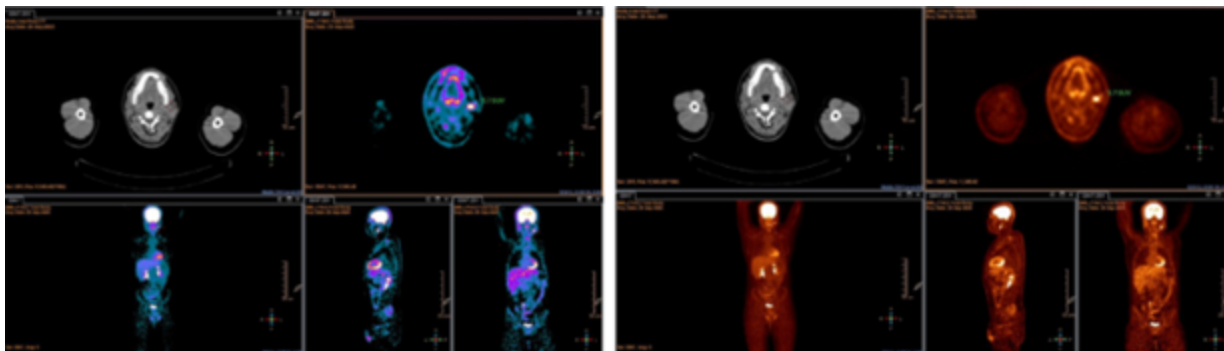


Figure 3

Full body 18F-FDG PET/CT. Hypermetabolic left parotid lymph node measuring 1.6X1 cm with a maximum standardized uptake value (SUVmax) of 7.6, consistent with lymphomatous activity.