

Best Initial Treatment Strategies for *EGFR*-Mutant Lung Cancer

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Abstract

EGFR activating mutations were described in lung cancer over a decade ago, and in that time, targeted therapy with epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) have become the treatment of choice as first-line therapy. Targeted therapy improves responses and progression-free survival when compared with chemotherapy in these patients with advanced disease. Despite improvements in outcomes, resistance develops and the majority of patients experience tumor progression and are not cured. The introduction of third-generation *EGFR* TKIs that effectively block activating mutations and the T790M resistance mutation while sparing wild-type *EGFR* has led to improved outcomes following the development of resistance. The future of *EGFR* therapy will explore the use of these agents and combinations to potentially delay or eliminate resistance to increase efficacy and ultimately survival. This review will focus on current therapies used in the first-line setting for advanced *EGFR* mutation positive non-small cell lung cancer (NSCLC) followed by emerging data that may lead to a transition in the choice for initial therapy in these patients.

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Introduction

Lung cancer is the leading cause of cancer related mortality worldwide in both men and women.¹ Patients with advanced epidermal growth factor receptor (*EGFR*) mutated non-small cell lung cancer (NSCLC) treated with tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and afatinib, show improved progression-free survival (PFS) compared with standard chemotherapy as first-line therapy.^{2,5} Unfortunately, patients develop resistance through multiple routes, including acquired *EGFR* mutations such as T790M.⁶ In order to combat this resistance, second- and third-generation *EGFR* TKIs have been developed. In order to prevent or delay the development of resistance, multiple strategies have been investigated, such as the combination of high-dose pulses with low-dose

continuous *EGFR* TKI therapy or co-targeting bypass signaling pathways as in the combined inhibition of both *EGFR* and *MET*.⁷ The development of third-generation TKIs has improved patient outcomes; however, therapeutic resistance still occurs. As the options for therapy increase, the available data should be considered in choosing a frontline treatment.

Current Options for First-Line Therapy

EGFR TKIs have been established as frontline therapy for patients with metastatic *EGFR* mutant lung. Differentiating between these treatment options requires an evaluation of the studies that have been performed.

The IPASS trial led the field, and was a randomized, phase III trial that compared gefitinib to carboplatin and paclitaxel in 1217 previously untreated never or light ex-smokers with advanced NSCLC, but did not require *EGFR* mutation. The primary endpoint was PFS, and at 12 months, the PFS was 24.9% with gefitinib and 6.7% with carboplatin/paclitaxel. In the subgroup of patients with an *EGFR* mutation, PFS was significantly longer among those who received gefitinib.² Importantly, those without *EGFR* mutation had improved PFS with chemotherapy, highlighting the importance of molecularly testing for activating *EGFR* mutations.

A randomized, phase III trial compared gefitinib versus carboplatin/paclitaxel in previously untreated patients with *EGFR*-mutated metastatic NSCLC.⁸ Analysis of the first 200 patients revealed that PFS was significantly longer in patients in the gefitinib group resulting in early termination. The gefitinib group had a median PFS of 10.8 versus 5.4 months in the chemotherapy group and a higher response rate of 73.7% versus 30.7%.

A third study comparing gefitinib and cisplatin plus docetaxel had similar results.⁹ This randomized, phase III study involved 177 previously untreated patients diagnosed with stage IIIB/IV NSCLC or postoperative recurrence with *EGFR* mutations and evaluated PFS as the primary endpoint. The gefitinib group had significantly longer median PFS compared with the cisplatin plus docetaxel group (9.2 versus 6.3 months).

A randomized, phase III trial compared erlotinib with carboplatin/gemcitabine in 165 patients with stage IIIB/IV NSCLC and

EGFR mutations.⁵ The analysis of PFS included 82 patients in the erlotinib group and 72 in the chemotherapy group. Median PFS was significantly longer in the patients treated with erlotinib than those treated with chemotherapy (13.1 versus 4.6 months).

The EURTAC trial compared erlotinib versus platinum-based chemotherapy for first-line treatment of patients with advanced NSCLC with EGFR mutations in a randomized, phase III trial.¹⁰ In that study, 86 patients received erlotinib and 87 received standard chemotherapy. The preplanned interim analysis showed the study met its primary endpoint and enrollment was stopped. The median PFS in the erlotinib group was 9.7 months compared with 5.2 months in the chemotherapy group.

The LUX-Lung 3 study was a randomized, phase III trial that compared afatinib to pemetrexed/cisplatin in previously untreated EGFR-positive stage IIIB/IV NSCLC patients.³ The study enrolled 345 patients who were randomly assigned in a 2:1 ratio and stratified by EGFR mutation (exon 19 deletion, L858R, or other). The median PFS was 11.1 months for the afatinib group and 6.9 months for the chemotherapy group. Median PFS among patients with exon 19 deletions and L858R deletions was 13.6 months for afatinib and 6.9 months for chemotherapy.

The LUX-Lung 6 trial randomized 364 patients with previously untreated EGFR mutation positive stage IIIB/IV NSCLC to receive either afatinib (242 patients) or gemcitabine-cisplatin (122 patients) a 2:1 ratio and stratified patients by EGFR mutation (exon 19 deletion, L858R, or other).⁴ Median PFS in the afatinib group was 11.0 months and 5.6 months in the gemcitabine-cisplatin group.

A pooled analysis of LUX-Lung 3³ and LUX-Lung 6⁴ included 631 of the 709 patients randomized and evaluated overall survival (OS) in patients with exon 19 (n = 355) and exon 21 mutations (n = 276).¹¹ OS was significantly longer in the del19-positive tumors in the afatinib group than in the chemotherapy group (31.7 versus 20.7 months). There were no significant differences by treatment group for patients with EGFR L858R-positive tumors. This study showed that OS was improved for patients with del19 EGFR mutations in the afatinib group.¹¹

The LUX-Lung 7 trial was a randomized phase IIB trial that compared first-line treatment with either afatinib or gefitinib in patients with EGFR-mutated stage IIIB/IV NSCLC.¹² In the study, 160 patients received afatinib and 159 patients received gefitinib until disease progression. PFS was 11.0 months with afatinib and 10.9 months with gefitinib and median time to treatment failure was 13.7 months with afatinib and 11.5 months with gefitinib, and the results were statistically significant. Furthermore, survival was increased with afatinib at 27.9 versus 24.5 months, but the result

was not significant.¹³

The current frontline options with afatinib, erlotinib, and gefitinib offer improved outcomes over standard chemotherapy in EGFR-mutant NSCLC patients. Toxicities are manageable and most commonly include rash, and skin toxicity, and diarrhea.^{2,5} Despite the benefit to patients, progression invariably occurs so we must consider novel strategies that might increase survival.

Emerging Frontline Options

Enhancing outcomes for patients may require combination therapy or new generation inhibitors that can prevent or overcome resistance mechanisms. The strategies with early results include combination erlotinib and bevacizumab, afatinib and cetuximab, and osimertinib as first-line therapy for EGFR-mutant NSCLC, and other agents and combinations are under investigation.

A randomized, phase II study in 154 patients with stage IIIB/IV or recurrent nonsquamous NSCLC with EGFR mutations and no previous therapy for advanced disease compared erlotinib alone versus erlotinib plus bevacizumab.¹⁴ The median PFS was 16.0 months in the erlotinib plus bevacizumab group and 9.7 months in the erlotinib alone group. Additional studies are ongoing to confirm these results and assess toxicities.

Osimertinib, a third-generation EGFR TKI, is approved as treatment for patients with EGFR TKI resistance due to emergence of the T790M mutation, and demonstrated over 50% objective response rate (ORR).¹⁵ With the hypothesis that early treatment with osimertinib can prevent the emergence of T790M as a mechanism of resistance and improve PFS, cohorts were studied using osimertinib as first-line therapy. Sixty patients from 2 phase I expansion cohorts of the original AURA trial received either 80 mg per day (n = 30) or 160 mg per day (30 patients) of osimertinib as first-line therapy. The ORR was 77%. Median PFS was 19.3 months for the 160 mg dose, and has not yet been reached for the 80 mg dose.¹⁶ This early data are promising, and a phase III trial (FLAURA) is evaluating the efficacy of osimertinib in treatment-naïve EGFR mutation-positive NSCLC patients (NCT02296125).

Afatinib plus cetuximab demonstrated clinical activity in EGFR-mutated lung cancers with acquired resistance compared with gefitinib or erlotinib, both with and without T790M mutations in a phase Ib study.¹⁷ This combination is now being studied as a frontline therapy for EGFR-mutant NSCLC (NCT02438722).

Central nervous system (CNS) metastases, including leptomeningeal carcinomatosis, are a challenge in patients with EGFR mutation positive lung cancer. Progression within the brain often occurs in the absence of systemic tumor growth due to inadequate drug

concentration in the CNS. Pulse dose erlotinib has been shown to be tolerated while increasing penetration into the brain.^{18,19} A phase I study evaluated twice-weekly pulse dose erlotinib at 1200 mg on days 1 and 2 followed by 50 mg on days 3 to 7 in treatment-naïve NSCLC patients with EGFR mutations.²⁰ The study demonstrated similar survival and responses seen in phase III trials, but of the 34 patients enrolled, none had progression in an untreated metastasis or developed new CNS metastases while on study. Additional trials evaluating activity of next-generation EGFR inhibitors in patients with CNS metastases are planned.

Future Directions

The use of EGFR TKIs is effective, but patients develop resistance, most commonly due to T790M. Molecular analysis of circulating tumor cells or cell-free DNA may provide a strategy for monitoring changes in tumor genotypes and the development of drug resistant mutations during treatment. One study found that the T790M was detectable in pretreatment tumor biopsies and circulating tumor cells during treatment and that T790M mutations were associated with reduced PFS (7.7 versus 16.5 months), and an increase in the number of cells with T790M mutations correlated with disease progression.²¹

A number of trials investigating EGFR TKIs in the frontline setting are ongoing and the results are forthcoming. These trials will help clarify the optimal use of TKIs in EGFR mutation positive NSCLC, and future studies will address the question of proper sequencing of therapy to provide the best outcomes for patients. The timing of third-generation EGFR inhibitors, such as earlier use of osimertinib will likely lead to new mechanisms of resistance, the emergence of the C797S EGFR mutation is one example.²² Additional studies to understand these mechanisms and therapies to overcome resistance will be needed.

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Hemophagocytic Lymphohistiocytosis in a Patient With Nodular Lymphocyte–Predominant Hodgkin Lymphoma: A Case Report

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare and rapidly progressing clinical syndrome with unknown incidence in adults that results from severe immune activation. Characteristic findings include fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, rash, and neurological symptoms with elevated triglycerides, ferritin, and hypofibrinogenemia.

HLH is often described as primary hemophagocytic lymphohistiocytosis (inherited), with underlying genetic abnormality, or secondary (acquired) to another underlying condition such as a viral infection, an autoimmune disease, or a malignancy.

To the best of our knowledge, this is the first case report of HLH

complicating a nodular lymphocyte–predominant Hodgkin lymphoma (NLPHL) in an adult treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone. The NLPHL showed the additional, unusual feature of cyclin D1 expression, which, to our knowledge, also has not been previously reported. The patient died after treatment failure following 3 regimens of therapy.

High clinical suspicion of HLH should prompt immediate immunotherapy to reverse the otherwise high likelihood of a fatal outcome.

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a syndrome caused by an exaggerated inflammatory response and cytokine defect resulting in organ infiltration by activated cytotoxic T lymphocytes and histiocytes.^{1,2} Disproportionate levels of TNF-alpha; interleukins (IL) 4, 6, 8, 10, and

12; and soluble IL-2 receptor (sCD25) have been recorded in patients with HLH in combination with impaired/absent natural killer (NK) cell activity.³ The aforementioned parameters can aid in distinguishing this syndrome from etiologies with similar manifestations. Primary HLH, which generally affects infants and young children, is attributed to

defects in perforin function. The incidence of secondary HLH in adults is unknown. Secondary HLH, either as a presenting phenomenon or developing during the course of a primary disease, has a broad range of associations, including infections (eg, Epstein-Barr virus [EBV] and cytomegalovirus [CMV]), rheumatic diseases, and malignancies, such as lymphoma).

Clinical and laboratory findings are characteristic yet nonspecific, which can delay the diagnosis. Findings include prolonged fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, rash, and neurological symptoms, usually with a rapidly progressing course.^{1,4} Classic laboratory features include elevated triglycerides, markedly elevated ferritin levels, hypo-fibrinogenemia, and abnormal liver function tests. Bone marrow examination often reveals characteristic hemophagocytes—histocytes with engulfed hematopoietic elements, including nucleated erythroid precursors, white blood cell precursors, and platelets—which are best depicted in marrow aspirate smears.

HLH is a challenging diagnosis due to its rarity and its nonspecific presentation, and laboratory findings. Prompt recognition and diagnosis is important, given the necessity of early treatment to assure the best possible outcome. The main goal of therapy, especially when HLH is associated with malignancy, is to direct therapy toward the underlying condition while attempting to control the amplified inflammatory reaction.⁴

Case Presentation

Our patient is a 26-year-old Caucasian man with past medical history significant for nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) stage IIIBs (lymph node involvement above and below the diaphragm with splenic involvement). Lymph node biopsy findings at diagnosis were typical of NLPHL, including macronodular architecture with a predominance of small lymphocytes, lesser numbers of histocytes, and a minor population of admixed lymphocyte-predominant (LP) cells (**Figure**). LP cells expressed CD45, CD20, CD79a, BCL6, and epithelial membrane antigen, and lacked expression of CD10, CD15, and CD30. Interestingly, cyclin D1 was also expressed by cells consistent with LP cells (large, pleomorphic cells having highly lobated nuclei). The patient completed 6 cycles of rituximab, doxorubicin, vincristine, and prednisone (R-CHOP) with resolution of the presenting symptoms following 2 cycles. The patient achieved unconfirmed complete remission at the end of therapy due to a small residual node on the left infraclavicular region.

After 4 months, a positron emission tomography/computed tomography (PET/CT) scan to follow up on the residual findings described above showed persistent local uptake. This was removed by surgery, with pathology showing extensive necrosis. A second PET/CT scan showed no further abnormal findings. One year after completion of therapy, the patient was seen in the office with recurrent symptoms (mainly night sweats) and was found to have pancytopenia upon blood count. A third PET/CT scan showed an enlarged left supraclavicular mass (4.3 × 1.3 cm) with a standardized uptake value of 13. Laboratory investigation showed the following results: white blood cell count, $1.2 \times 10^3/\text{mcL}$; absolute neutrophils, $0.6 \times 10^3/\text{mcL}$; hemoglobin,

11 g/dL; mean corpuscular volume, 87 fL; platelet count, $130,000/\text{mcL}$; ferritin, 1387 ng/mL; alanine transaminase, 122 U/L; aspartate transaminase, 121 U/L; total bilirubin, 2.5 mg/dL; alkaline phosphatase, 303 U/L; albumin, 3.5 g/dL; prothrombin time, 18 seconds; creatinine, 0.8 mg/dL. Bone marrow biopsy showed normal trilineage hematopoiesis and increased cellularity (70%) without evidence of lymphomatous involvement. The patient underwent local radiation therapy to the supraclavicular area.

Six weeks later the patient was hospitalized for possible sepsis, because he presented with fever, splenomegaly, and cytopenias. The laboratory investigations showed hypertriglyceridemia and hyperferritinemia, with elevated liver enzymes. A bone marrow biopsy showed scattered histocytes displaying hemophagocytosis of both myeloid and erythroid precursors, and normal to increased cellularity with no evidence of lymphoma. He was treated with oral prednisone 100 mg daily and rituximab 375 mg/m² intravenous once weekly for 4 weeks with mild improvement in his symptoms. He required intravenous hydration on 2 occasions following drenching sweating.

The patient developed severe jaundice due to progressive hepatic failure, acute kidney injury, and bloody diarrhea after a few weeks, which required readmission. Salvage therapy with alemtuzumab, per standard protocol, and dexamethasone 40 mg intravenous daily for 4 days was initiated with no significant response. The patient was subsequently treated with pentostatin 4 mg/m² without a response. His condition further deteriorated with the development of disseminated intravascular coagulation. The patient was transferred to hospice and died shortly thereafter.

Discussion

NLPHL is a rare type of Hodgkin lymphoma (HL), accounting for just 5% of cases. Unique findings include variants of Hodgkin Reed-Sternberg cells (HRS cells), also known as LP cells. These display an intact B-cell program, expressing pan B-cell markers including CD20 and CD79a; express CD45; and typically lack expression of CD15 and CD30, distinct from HRS cells found in classical HL. Morphologic and immunophenotypic features in this case were typical of NLPHL with notable cyclin D1 expression by LP cells.

We are unaware of any previous case report of HLH developing in the course of NLPHL. It can be argued that our patient had HLH at initial diagnosis of NLPHL but it was not pursued. The poor prognosis of HLH mandates initiation of therapy as soon as possible, not wait for confirmation investigations when clinically suspected. Updated diagnostic criteria used in the HLH-2004 trial by the Histiocyte Society are described in the **Table**.⁵

In our case, diagnosis of HLH was delayed at least 6 weeks following development of bicytopenia, fever, splenomegaly, and a markedly elevated ferritin. Four of 5 criteria required for HLH diagnosis were met. NK activity, soluble CD25, triglycerides, and fibrinogen were not assessed at that time, which might have been useful investigations. The patient was actually fulfilling the proposed diagnostic criteria, as HLH-2004 criteria are not specific and mainly used for clinical trials.⁵ The proposed criteria are 3 of 4 clinical manifestations (fever,

splenomegaly, cytopenias, and hepatitis) in addition to 1 of 4 investigational findings (hemophagocytosis, high ferritin, low fibrinogen, and absent/decreased NK cell function).

In a series of 34 patients with HL-associated hemophagocytic syndrome, most patients were male, predominantly lymphocyte depleted, and mixed cellularity subtypes of classical HL (85%) with EBV involvement (95%).⁶ None of these patients had NLPHL (14 patients with unknown type).

Treatment of triggering infection improves outcomes. Described culprits include EBV, CMV, HIV, herpes simplex virus, varicella zoster virus, and *Leishmania*. Our patient was EBV immunoglobulin (Ig) G positive and IgM negative. In adult patients, NK/T-cell degranulation, activity studies, and genetic testing can be used to explore the possibility of late onset of a congenital variety, which was not performed in our case.

Malignancy-associated HLH has a worse prognosis compared with other secondary forms and there are no evidence-based guidelines to direct therapy.⁷ A common practice is to initiate treatment aimed at the presenting malignancy and to add other measures to control the hyperimmune reaction based on the response to initial therapy.⁴

The Histiocyte Society initiated a prospective international collaborative therapeutic study in 1994 (HLH-94) that aimed to improve survival. Standard treatment for primary HLH (HLH-94 protocol) includes 8 weeks of initial therapy, consisting of etoposide (150 mg/m² twice weekly for 2 weeks and then weekly) and dexamethasone (initially 10 mg/m² for 2 weeks followed by 5 mg/m² for 2 weeks, 2.5 mg/m² for 2 weeks, 1.25 mg/m² for 1 week, and 1 week of tapering). The initial therapy was followed by a continuation therapy and bone marrow transplant for patients with persistent disease or known familial disease. Patients with unresolved nonfamilial disease stopped therapy. The continuation therapy included dexamethasone and etoposide alternating every second week in combination with daily oral cyclosporin. Intrathecal methotrexate was administered for patients with progressive neurological symptoms or consistent abnormal cerebrospinal fluid findings.

The HLH-94 study enrolled 119 patients who were younger than 15 years of age. The study excluded 6 patients who were subsequently found to have specific underlying disorders (4 with hematolymphoid malignancies). This study is the only known study to date to show an improved survival with an estimated 3-year probability of overall survival of 55% (95% CI, 46%-64%). However, given the patient demographics, we speculate that the majority of the patients enrolled had a familial predisposition.⁸

Rituximab showed good response if the trigger was EBV infection.^{8,9} So et al also reported a case of HLH and autoimmune hemolytic anemia associated with systemic lupus erythematosus successfully treated with rituximab that was refractory or intolerable to conventional therapy.¹⁰ During the second presentation, our patient did not respond to 4 weeks of rituximab and steroid treatment. He was also treated with cyclosporine, dexamethasone, and etoposide without significant improvement.

Alemtuzumab may be appropriate, instead of etoposide, in the case

TABLE. HLH 2004 Diagnostic Criteria⁵

The diagnosis of hemophagocytic lymphohistiocytosis (HLH) is established if any of the below are fulfilled:
1. A molecular diagnosis consistent with HLH is made.
2. Five of these 8 criteria are met:
- Fever
- Splenomegaly
- Cytopenias (affecting 2-3 lineages in the peripheral blood)
- Hypertriglyceridemia and/or hypofibrinogenemia
- Hemophagocytosis in bone marrow, spleen, or lymph nodes
- Low or absent natural killer cell activity
- Ferritin 500 g/L
- Soluble CD25 (ie, sIL2r) 2400 U/mL

Supportive criteria include neurological symptoms, cerebro-spinal fluid pleocytosis, abnormal liver function tests, hypo-natremia, high D-dimers, and lactate dehydrogenase. The absence of hemophagocytosis in the bone marrow does not exclude HLH.

of liver failure, clinical deterioration, or no improvement within 2 to 3 weeks of HLH-94 therapy.¹¹⁻¹³ Cyclophosphamide, doxorubicin, vincristin, prednisone (CHOP) therapy for 8 weeks in 17 adult patients showed a 2-year overall survival of 44%¹⁴; however, our patient received R-CHOP as an initial therapy for NLPHL and repeat of the same regimen was not entertained. Unfortunately, most trials in the literature included limited numbers of patients and the various regimens used in those trials were not compared with HLH-94-based therapy, which remains the standard of care. Although hematopoietic stem cell transplantation in familial HLH has been shown to improve outcomes, its role in secondary types has not been defined.³

Conclusion

Despite improvements in the diagnosis and treatment of HLH, this entity remains an often-fatal clinical syndrome that requires prompt recognition and intervention. HLH can be associated with NLPHL, and clinician awareness of early manifestations is crucial to avert fatal outcomes. More effective therapies are also required to improve patient outcomes and should be a focus of further studies.

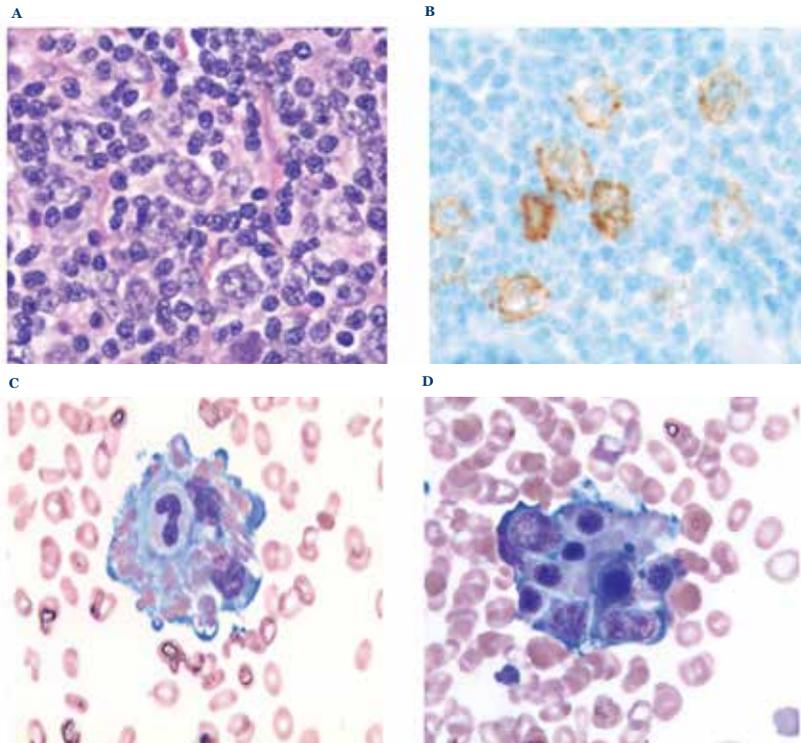
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FIGURE. Lymph Node Biopsy Findings at Diagnosis



(A) Typical histology of nodular lymphocyte predominant cells, including small lymphocytes and histiocytes (hematoxylin and eosin, 400x magnification). (b) The immunophenotype of LP cells included expression of epithelial membrane antigen (400x magnification). (c) Macrophage with engulfed band neutrophil (May-Grünwald-Giemsa, 600x magnification). (d) Macrophage with multiple engulfed nucleated erythroid precursors (May-Grünwald-Giemsa, 600x magnification).

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