PATHOLOGICA 2025;117:397-402
DOI: 10.32074/1591-951X-N831

Case report

Lung and nodal hairy cell leukemia with concurrent infectious granulomatosis: a mimic of metastatic lung epithelial neoplasia

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Summary

Hairy cell leukemia (HCL) is a rare, indolent B-cell neoplasm, typically involving bone marrow, spleen, and peripheral blood, with extranodal sites rarely affected. Herein, we present the unique case of a 52-year-old man with lung and lymph node involvement by HCL concurrently with atypical mycobacteriosis. Initial imaging showed mediastinal lymphadenopathy and a pulmonary nodule, which raised suspicion for lung neoplasia. A minimally invasive biopsy of the mediastinal nodes and hilar lesion revealed a lymphoid proliferation mixed with necrotizing granulomatous inflammation, with an immunophenotype consistent with HCL and BRAF V600E mutation, confirmed by digital PCR. Notably, molecular analyses detected atypical mycobacteria in lymph nodes. This unusual co-occurrence of HCL with atypical mycobacterial infection in the lung and lymph nodes poses a complex diagnostic and therapeutic challenge, highlighting the importance of recognizing such presentations to optimize patient management.

Key words: hairy cell leukemia, atypical mycobacterial infection, lung involvement, BRAF V600E mutation, lymphocytic interstitial pneumonia

Received: November 25, 2024
Accepted: February 14, 2025

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How to cite this article: Mancini M, Maurizi G, Rogges E, et al. Lung and nodal hairy cell leukemia with concurrent infectious granulomatosis: a mimic of metastatic lung epithelial neoplasia. Pathologica 2025;117:397-402 https://doi.org/10.32074/1591-951X-N831

Introduction

Hairy cell leukemia (HCL) is a rare, indolent mature B cell neoplasm characterized by the proliferation of medium-sized, mature lymphocytes that display "hairy" projections[1]. HCL is believed to originate from post-germinal center B cells carrying BRAF p.V600E mutation. Indeed, although the BRAF V600E mutation is thought to arise in hematopoietic stem and B-lymphoid progenitor cells [2] no normal counterpart along the continuum of developing B lymphocytes has been delineated as the cell of origin. Evidence has shown that the BRAFV600E mutation is present in hematopoietic stem cells (HSCs, approximately 90% of HCL patients exhibit a somatically hypermutated immunoglobulin heavy chain variable gene (IGHV) [3]. Alternative BRAF mutations [4] or BRAF translocation to the IGH locus [5] have been reported in less than 5% of cases. HCL primarily involves the bone marrow, spleen, and peripheral blood [6] including HCL variant (HCL-V)..

Infiltration of lymph nodes or other extranodal sites is infrequent, with rare and anecdotic reports in the literature [7–11]. Mass-forming lesions in patients with an undiagnosed HCL could represent a diagnostic dilemma with solid tumors.

Herein, we report the case of a patient diagnosed with lung and lymph node involvement by HCL associated with atypical mycobacteriosis.

Case presentation

A 52-year-old Caucasian man was referred to the Emergency Department of our University Hospital with a diagnosis of renal colic. During the diagnostic work-up, a computed tomography (CT) scan revealed a pathologic enlargement of mediastinal lymph nodes; moreover, a small nodule was found deeply in the hilum of the upper left lobe, situated near the bifurcation of the pulmonary artery (PA) and bronchial component. This nodule radiologically appeared solid with signs of necrosis.

PET/CT scan with fluorodeoxyglucose (18F) revealed high metabolic activity in the left pulmonary hilar lesion, with a standard uptake value (SUV) of 9. Various lymph nodes also showed increased metabolic activity, though lower than in the lung, including the cervical, supraclavicular, subclavicular, prevascular mediastinal, paratracheal, aortopulmonary window, subcarinal, and hilar-peribronchial regions. Additionally, heightened metabolic activity was observed in abdominal lymph nodes, particularly in the interposed-caval, peri-pancreatic, peri-gastric, celiac, pre- and para-aortic, interaortic-caval, paracaval, and bilateral common iliac regions.

A CT scan revealed splenomegaly, with the spleen measuring 15 x 15 cm, while an ultrasound indicated mild structural heterogeneity. The patient did not report weight loss, night sweats, fever, or bleeding symptoms. Hemocromocytometric analysis showed the following results: hemoglobin (Hg) 10.6 g/dL, hematocrit (HCT) 30%, mean corpuscular volume (MCV) 95, red blood cells (RBC) 3.15 x 10^6/uL, white blood cells (WBC) 2.32 x 10^3/uL (neutrophils 800/mm^3, lymphocytes 1,500/mm^3), and platelets (PLT) 121,000/mm^3.

The initial concern was the presence of lung neoplasia with a concomitant nodal N2 disease, leading to the patient's referral to the thoracic surgery unit for further evaluation. An endo bronchial ultrasound (EBUS) biopsy was done on the mediastinal lymph nodes with a report suspicious of a hematologic nodal disease; the biopsy of the hilar lesion was considered technically demanding due to the lesion's proximity to the upper lobe segmental branches of the pulmonary artery (PA); therefore, it was not performed. At this point, the only way to obtain histology of the PET-positive left hilar lesion was a surgical incisional biopsy.

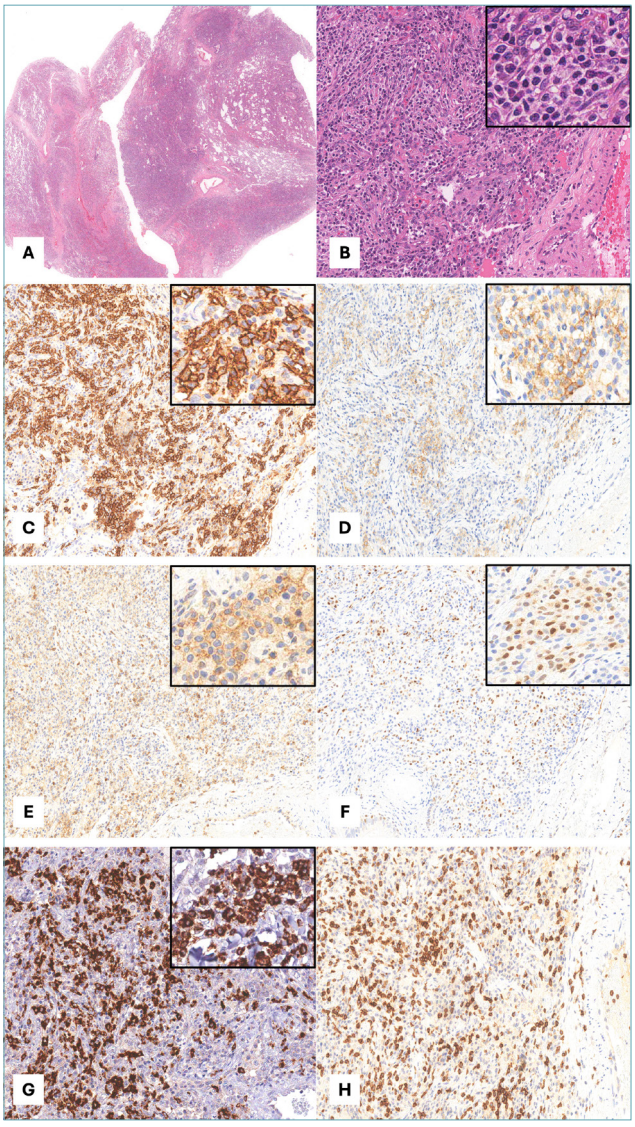


Figure 1. Histopathologic examination of the lung nodule showing features suggestive of lymphocytic interstitial pneumonia (LIP) (A, H&E o.m.x20). The infiltrate was composed by a monomorphic population of small lymphocytes with abundant clear cytoplasm with irregular margin (B, H&E o.m.x200, upper insert o.m.x400) expressing CD20 (C, o.m.x200, upper insert x400), CD25 (D, o.m.x200, upper insert x400), annexin A1 (E, o.m.x200, upper insert x400), cyclin D1 (F, o.m.x200, upper insert x400) and BRAF (G, o.m.x200, upper insert x400). Immunostaining for CD3 showed admixed small T-cells (H, o.m.x200, upper insert x400).

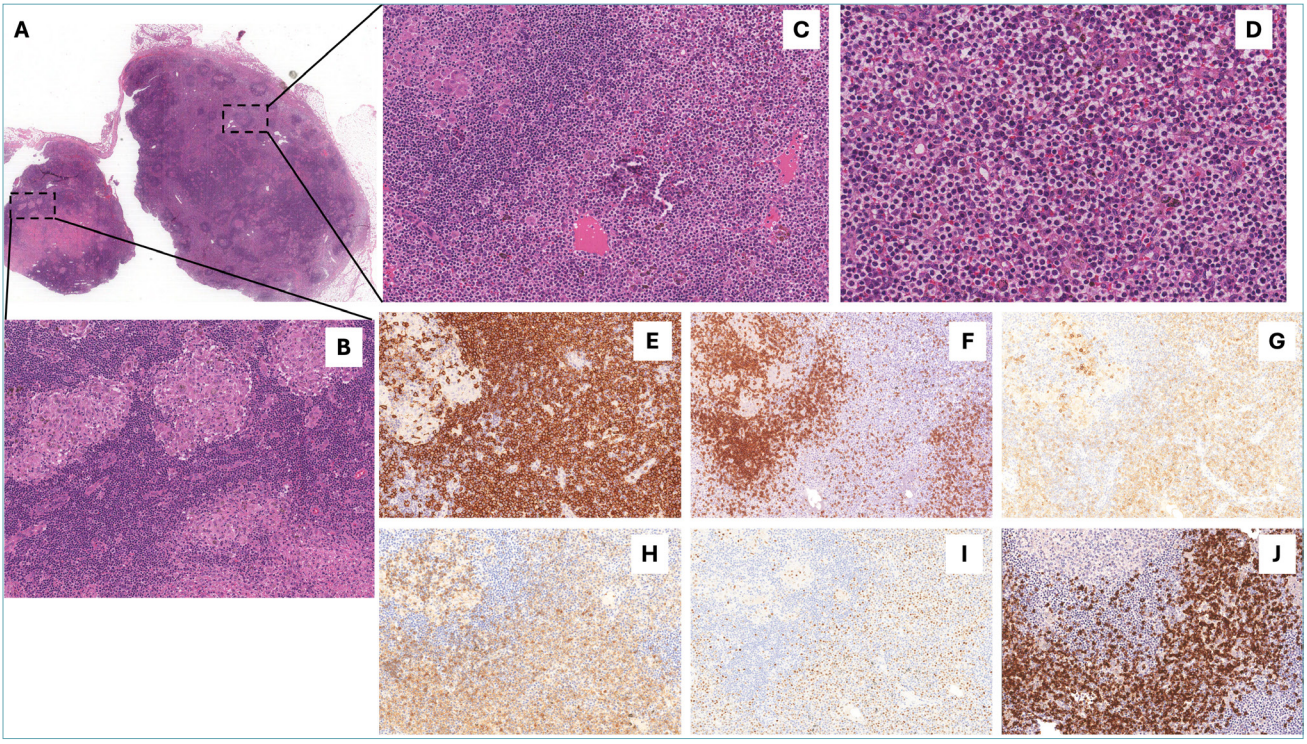


Figure 2. Lymph node biopsy (A, H&E o.m.x20) revealed the presence of non-necrotizing granulomas (B, H&E o.m.x200) associated with extensive infiltration by hairy cell leukemia (C, H&E o.m.x200, D H&E o.m.x300). Neoplastic cells were positive for CD20 (E, o.m.x200), CD25 (G, o.m.x200), annexin A1 (H, o.m.x200), cyclin D1 (I, o.m.x200) and BRAF (J, o.m.x200), and negative for CD3 (F, o.m.x200).

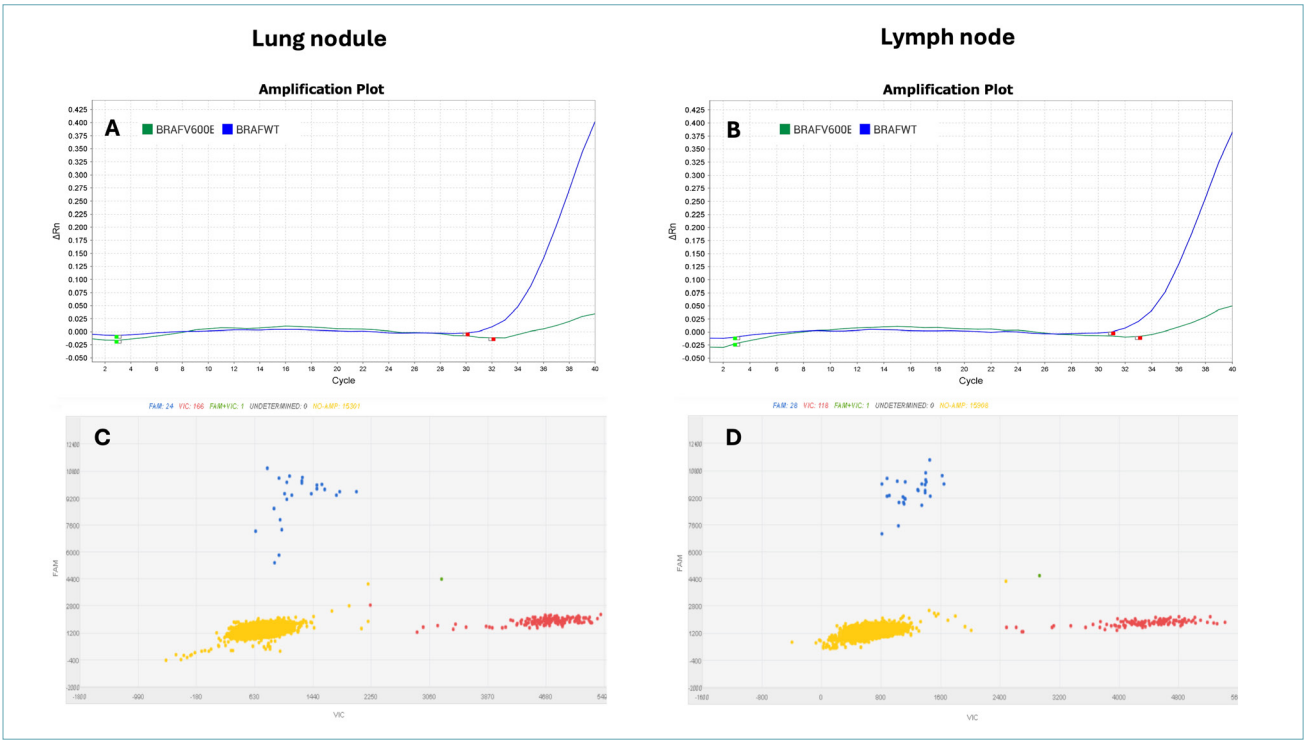
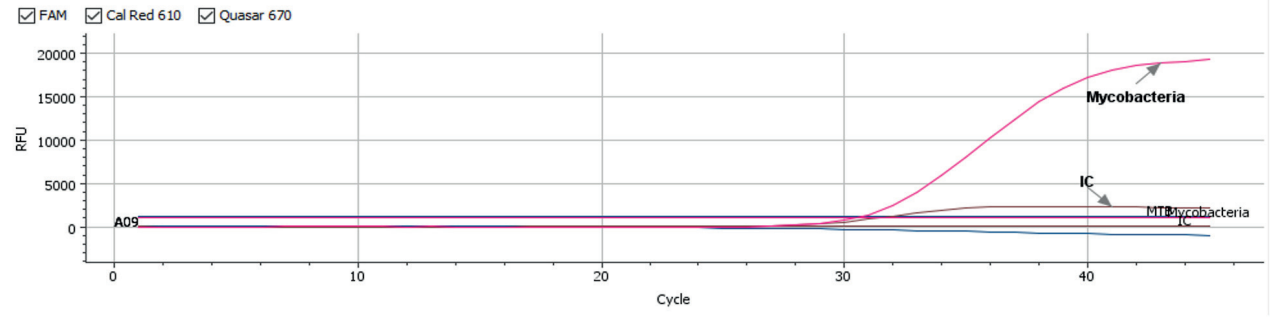


Figure 3. Real-time PCR (A, B) and digital PCR (C, D) detected BRAFV600E mutation in both the lung nodule and the lymph node biopsy.



Tipo	FAM		Cal Red 610		Quasar 670		Interpretazione automat...
	MTB	C(t)	Mycobact...	C(t)	IC	C(t)	
SAMPLE	-	N/A	+	30.43	+	27.16	NTM
NC	-	N/A	-	N/A	+	27.09	Negative Control(-)
PC	+	19.63	+	21.14	+	21.03	Positive Control(+)

Figure 4. Real-time PCR analysis detected the presence of DNA from atypical mycobacteria, as indicated by the pink amplification curve. An internal control (IC) was successfully amplified, shown by the yellow curve, confirming the validity of the assay. No amplification was observed for Mycobacterium tuberculosis DNA, as indicated by the absence of a fuchsia curve.

Via a minimally invasive left thoracic surgery, the left upper hilum lesion was revealed to be a node, and the intraoperative frozen section showed partial involvement characterized by granulomatous necrotizing inflammation. Moreover, a small area of increased parenchyma thickness in the upper segment of the lingula was palpatory, detected, and resected. The intraoperative pathologic exam showed no signs of epithelial neoplasm but revealed a mixed lymphocytic interstitial pneumonia (LIP) pattern and an organizing pneumonia (OP) pattern with lymphoid infiltrate. At the end of the intervention, a left mediastinal node sampling was performed to better understand the pattern of the suspected hematologic disease.

The lung nodule exhibited features suggestive of LIP pattern at routine histopathological examination. The infiltrate was composed of a monomorphic population (Fig. 1) of small lymphocytes with abundant cytoplasm with an immunophenotype CD20+, CD79a+, CD3-, C annexin A1 D25+, DBA44+, annexin A1+, BRAF+ [Ventana anti-BRAF V600E (VE1) Mouse Monoclonal Primary Antibody Roche Diagnostics International AG Rotkreuz, Switzerland] indicative of hairy cell leukemia (Fig. 2) Digital PCR analysis confirmed the presence of the BRAFV600E mutation in the lung specimen (Fig. 3). OP pattern was associated with granulomatous inflammation surrounding the lymphoid infiltrate.

The lymph node showed partial nodal involvement by a lymphoid population consistent with HCL and a concomitant granulomatous reaction, which was suspicious of infection. Molecular analyses identified the DNA of atypical mycobacterial species (Fig. 4) and the presence of the BRAFV600E mutation.

Subsequently, bone marrow trephine biopsy and flow cytometry analysis of peripheral blood confirmed involvement by HCL.

Discussion

In adherence to consensus guidelines, the diagnosis of HCL is suspected on the patient's clinical presentation and the presence of splenomegaly and subsequently confirmed through comprehensive analyses for the identification of the characteristic morphology (in a blood or marrow smear), immunophenotype of the lymphoid infiltrate and the BRAF V600E mutation[1]. According to guidelines, incorporating imaging into the initial diagnostic process is discretionary and reserved for specific cases. For example, chest X-rays are recommended for patients suspected of pneumonia, and ultrasound and PET/CT scans are recommended to determine the extent of disease involvement and identify affected lymph nodes, spleen, bone marrow, and

other organs [6] including HCL variant (HCL-V). However, it is crucial to note that the role of PET/CT in HCL evaluation is an area of ongoing research, as there is currently no universally accepted SUV value.

The novelty of the case reported herein lies in the rare simultaneous occurrence of HCL in the lung and lymph node coupled with nodal atypical mycobacterial disease.

Atypical mycobacterial disease typically occurs in children, immunocompromised patients, or individuals with impaired host defense of the lung [12,13]. It manifests as a chronic infection caused by acid-fast bacilli and is characterized by the formation of granulomas in various organs, particularly the lungs, lymph nodes, skin, and soft tissue, while HCL causes pancytopenia, increasing susceptibility to infection. Atypical mycobacterial infection has been reported in nine out of 186 patients with hairy cell leukemia diagnosed in 10 years [14]. The simultaneous lymph node involvement by atypical mycobacterial infection and HCL as the first presentation is rare and represents a diagnostic and clinical challenge. It suggests a complex interplay between the immune system, infectious agents, and malignant processes. Additionally, the leukemic involvement of the lung interstitium adds another layer of complexity to the case, as interstitial lung diseases encompass a heterogeneous group of disorders affecting the lung parenchyma, often leading to impaired gas exchange and respiratory symptoms.

Thickening of bronchovascular bundles, interlobular septa, prominence of peripheral pulmonary arteries, ground-glass opacities, air-space consolidation, and nodules are common imaging findings in leukemic lung infiltration [15,16] prominence of peripheral pulmonary arteries, ground-glass opacities, air-space consolidation, and nodules. The CT-pathologic correlations for leukemic infiltration were evaluated in 7 patients. Frequent parenchymal CT findings were thickening of bronchovascular bundles (81.8%). Histologically, these findings often correlate with lymphoid nodules and confluent expansion of alveolar walls, suggesting lymphocytic interstitial pneumonia (LIP) or mucosa-associated lymphoma. Subtle interstitial and septal infiltration with a LIP-like cellular pattern, occasionally paired with organizing pneumonia, has been documented, although differentiation from other interstitial pneumonia remains challenging.

Our case highlights the unusual presentation of a lymphoid interstitial pneumonia (LIP)-like pattern in pulmonary involvement by HLC, coupled with granulomatous inflammation. Typically, LIP manifests as a diffuse interstitial lymphoid infiltrate within the alveolar septa, often associated with immune dysregulation or autoimmune disorders rather than hematologic malignancies such as HCL. The presence of non-necrotizing granulomas in LIP-like lung lesions, as observed in our patient, further complicates the histopathologic landscape, as granulomatous inflammation is not a standard feature of typical HCL lung involvement. Interestingly, granulomas in LIP are frequently associated with autoimmune or infectious etiologies, as in granulomatous-lymphocytic interstitial lung disease (GLILD), raising questions about the interplay between the underlying malignancy and immune-mediated inflammatory responses in this patient [17-19], but the pulmonary pathologic features of these systemic diseases are poorly recognized by pathologists. It has been claimed that CVID cases show a characteristic combination of noncaseating granulomas-lymphoid proliferations termed granulomatous-lymphocytic interstitial lung disease (GLILD. This unique combination of LIP-like lymphoid proliferation with granulomatous features suggests that HCL may induce atypical pulmonary patterns that mimic benign lymphoid proliferations, underscoring the importance of thorough histopathological evaluation to accurately distinguish malignant from benign lymphoid patterns. Our findings advocate for further investigation into the pathophysiologic mechanisms linking lymphoid neoplasia, granulomatous inflammation, and LIP, especially in cases where atypical mycobacterial infection is present.

Conclusions

Understanding the underlying mechanisms driving the co-occurrence of granulomatous mycobacterial disease and HCL and their impact on the lung interstitium is crucial for accurate diagnosis, appropriate management, and predictive assessment. Further investigation and documentation of similar cases are necessary to elucidate the pathophysiological mechanisms and optimize therapeutic strategies for patients with rare and intricate clinical presentations.

Conflicts of interest statement

The authors declare no conflict of interest.

Funding

No funding to disclose.

Authors' contributions

Conceptualization MM and ADN; methodology MM, ER, GM; Clinical and Pathological data curation MM, GM, ER, KP, AV, ADN; Molecular biology data SS, DV; writing—original draft preparation MM, ADN; review and editing, MM, GM, ER, KP, SS, DV, AV, ADN.

All authors have read and agreed to the published ver-

sion of the manuscript.

Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

Written informed consent was obtained from each participant/patient for study participation and data publication.

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