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Persistent Fever and Splenic Abscess-like Lesions: A Diagnostic Trap in a Young Adult

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Introduction. Classic Hodgkin lymphoma (cHL) is a B-cell lymphoid malignancy characterized by Hodgkin and Reed-Sternberg cells within an inflammatory cellular microenvironment. In Asia, incidence rates range from 0.21 to 1.3 per 100,000 person-years.[1] Clinically, cHL is a great mimicker, and its presentation with constitutional symptoms in the absence of peripheral lymphadenopathy can lead to a misdiagnosis of infection. We report a case of cHL with a splenic-dominant and abscess-like presentation that masqueraded as a splenic abscess, illustrating this diagnostic challenge.

Report of the Case.

Case presentation and clinical history. A previously healthy 31-year-old Malay man, who worked as a construction site supervisor, presented with a three-day history of non-productive cough and fever. Over the preceding month, he had experienced an unintentional 4 kg weight loss. Although he had fever and weight loss, he did not meet the formal criteria for B symptoms, as his weight loss was less than 10% of body weight and he reported no drenching night sweats. Initial evaluation revealed non-tender splenomegaly. There was no other organomegaly, and no peripheral lymph nodes were palpable. Cardiovascular and lung examinations were unremarkable. He was started on intravenous (IV) amoxicillin-clavulanic acid and oral azithromycin for a presumed respiratory tract infection.

Due to poor response to antibiotics with persistent fever, an abdominal ultrasound was performed on hospital day 5, revealing multiple hypoechoic splenic lesions (**Figure 1A**). IV ceftazidime and oral trimethoprim-sulfamethoxazole were initiated for presumed melioidosis with splenic abscess, given the local endemicity of melioidosis.

A subsequent computed tomography (CT) scan of the thorax, abdomen, and pelvis (TAP) demonstrated splenomegaly with multiple small, ill-defined hypodense splenic lesions, initially interpreted as splenic microabscesses (**Figure 1B**). Multiple enlarged abdominal lymph nodes were noted (**Figure 1C**), attributed to reactive changes. Throughout the hospitalization, the patient had intermittent temperature spikes ranging from 38°C to 39.2°C, despite escalation of antibiotics to IV meropenem. Multiple sets of bacterial and fungal blood cultures were negative, and *Burkholderia pseudomallei* serology was also negative. Other investigations for pyrexia of unknown origin yielded unremarkable results. A follow-up ultrasound after multiple antibiotic courses (5 days of IV amoxicillin-clavulanic acid, 3 weeks of IV ceftazidime

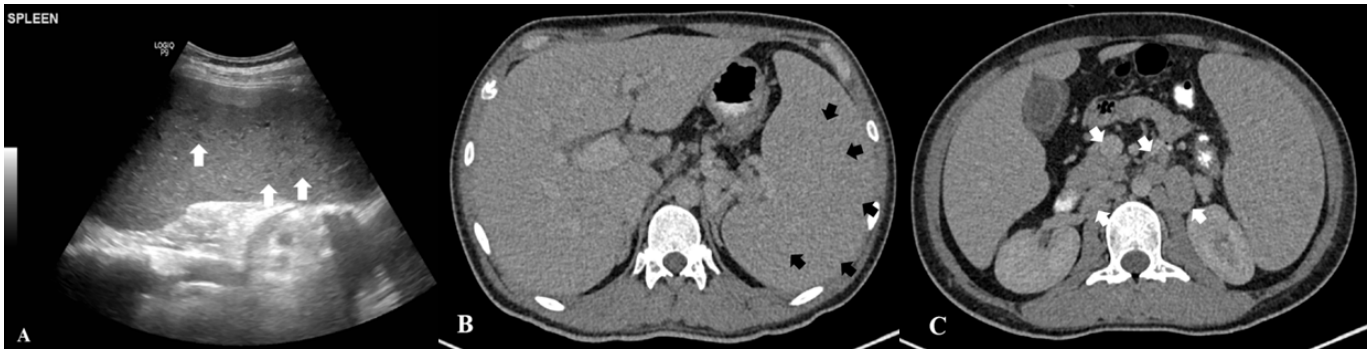

Figure 1. (**A**) Ultrasound abdomen shows enlarged spleen with multiple scattered ill-defined small nodules (miliary pattern) (arrow). (**B**) CT of the abdomen reveals an enlarged spleen measuring 20 cm in craniocaudal length, containing multiple small, ill-defined hypodense lesions without definite necrotic features (arrow). (**C**) Multiple enlarged and matted para-aortic, aortocaval, and paracaval lymph nodes (arrows) are seen, with the largest para-aortic node measuring 1.7 cm in short-axis diameter. No central hypodensities are present to suggest nodal necrosis.

and oral trimethoprim-sulfamethoxazole, and 1 week of IV meropenem) showed persistent splenic microabscesses.

Investigations. After four weeks of hospitalization, serial complete blood counts revealed pancytopenia. A trephine biopsy revealed bone marrow involvement by large atypical mononuclear cells (**Figure 2A**). Immunohistochemistry demonstrated CD30 positivity (**Figure 2B**), dim PAX5 (**Figure 2C**), MUM1 positivity, and negativity for CD15 (**Figure 2D**), CD20, CD79a, CD3, CD5, CD7, CD4, CD8, MPO, CD138, ALK, CD34, and TdT, with negative staining for acid-fast bacilli, fungi, and cytokeratin (CKAE1/AE3). Concurrently, a core biopsy of the right external iliac lymph node was performed. Section showed scattered Hodgkin and Reed-Sternberg cells (**Figure 3A**, **B**). Immunohistochemistry confirmed CD30 positivity (**Figure 3C**), with weak PAX5 (**Figure 3F**), MUM1 positivity, occasional weak CD15 (**Figure 3D**), and focal heterogeneous CD20 positivity (**Figure 3E**). The cells were negative for CD3, Gata3, CD79a, CD45/LCA, ALK, CD138, and CD34. EBER (Epstein-Barr virus-encoded small RNA) in-situ hybridization test was not performed. Final histopathology confirmed stage IV cHL with bone marrow involvement.

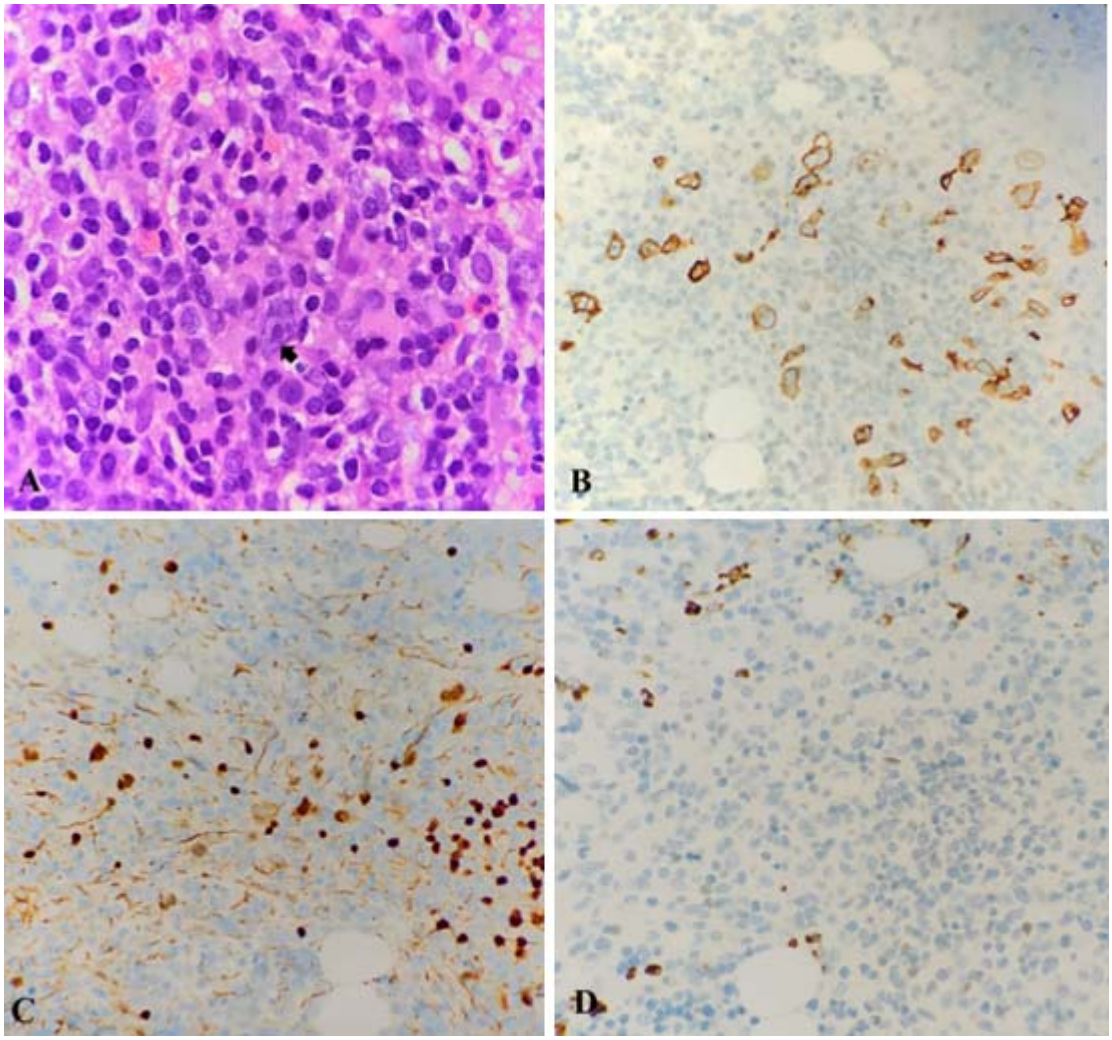

Figure 2. Histopathological examination (HPE) of trephine biopsy shows large atypical mononuclear cells (arrow) (**A**) with eosinophilic nucleoli, which are positive for CD30 (**B**), dim-positive PAX5 (**C**), and negative for CD15 (**D**).

Progression. Following the confirmation of Hodgkin lymphoma, the chemotherapy regimen doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) was initiated without delay. Unfortunately, the patient's clinical status had progressively deteriorated throughout the prolonged diagnostic period. His Eastern Cooperative Oncology Group (ECOG) performance status worsened significantly from grade 1 at admission to grade 4 prior to chemotherapy treatment. Despite intensive supportive care, he succumbed to complications of his advanced disease one week after the initiation of chemotherapy. The diagnostic timeline is summarized in **Figure 4**.

Discussion

Diagnostic delay in fever of unknown origin. Delayed diagnosis of Hodgkin lymphoma in patients presenting with fever of unknown origin (FUO) is not uncommon. Zhang *et al.* reported diagnostic delays in 42% of such cases, with 44% already demonstrating bone marrow

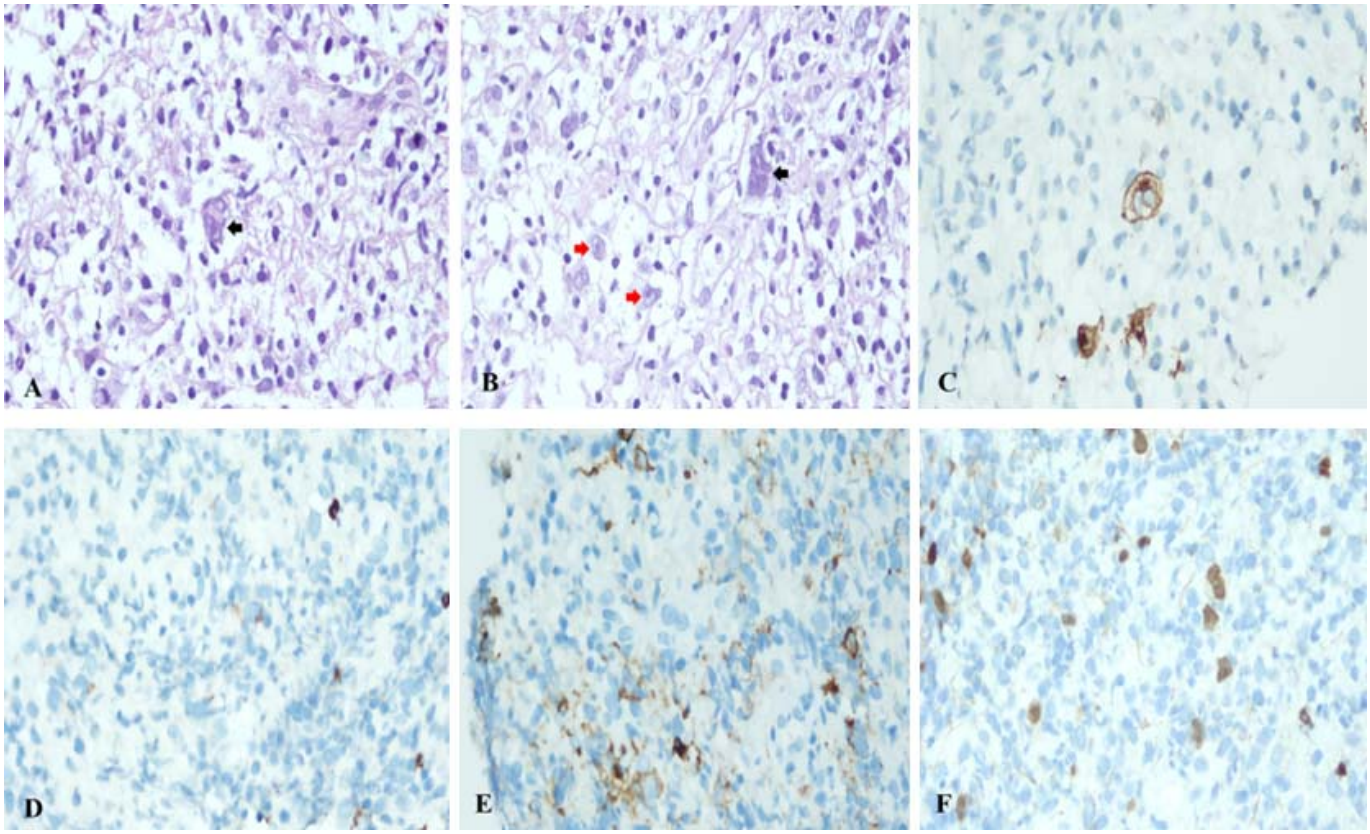

Figure 3. HPE of right external iliac node shows large mononuclear to multilobulated neoplastic Hodgkin (black arrow) and Reed-Sternberg (red arrow) cells with prominent nucleoli in a background of small lymphocytes, plasma cells and histiocytes (A, B), positive for CD30 (C) and CD15 immunohistochemistry (D), with weak heterogeneous expression of CD20 (E) and weak nuclear PAX5 positivity (F) (A, B hematoxylin-eosin stain, 400x).

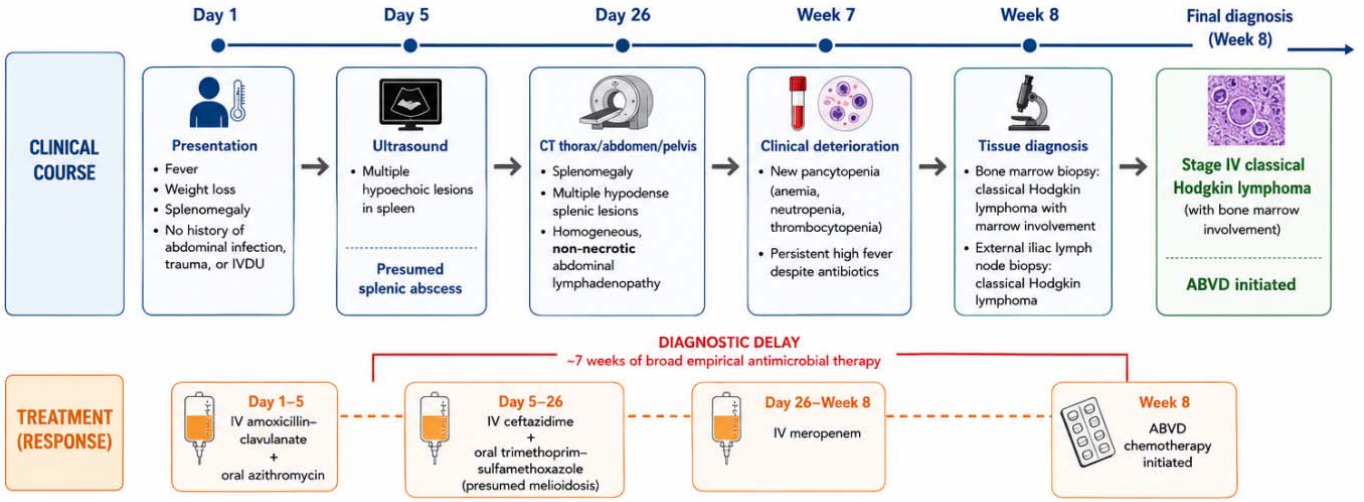

Figure 4. Diagnostic timeline from presentation to diagnosis.

involvement at diagnosis.[2] This may reflect a systematic cognitive bias, particularly in tropical regions, where FUO with splenic lesions is reflexively attributed to endemic infections, including tuberculosis and melioidosis, before malignancy is considered. This case exemplifies this cognitive bias, resulting in seven weeks of empirical antimicrobial therapy before the correct diagnosis was established.

Hodgkin lymphoma accounts for up to 11% of all lymphomas and typically presents with asymptomatic lymphadenopathy.[2] Retrospectively, the intermittent fever pattern, characterised by cyclical spikes every 4-6 days, was compatible with lymphoma-associated fever (Pel-Ebstein pattern). However, this observation should be interpreted cautiously, as it is neither sensitive nor specific for Hodgkin lymphoma and was recognised only after the diagnosis had been established.[3]

When should 'splenic abscess' be questioned? Splenic involvement is present at diagnosis in approximately one-third of Hodgkin lymphoma cases and 30-40% of non-Hodgkin lymphoma (NHL) cases.[4,5] While it is regarded as nodal disease in Hodgkin lymphoma, it is classified as extranodal disease in NHL. Importantly,

Table 1. Splenic abscess versus splenic lymphoma: risk factors and radiological distinguishing features.

Feature	Splenic Abscess	Splenic Lymphoma
Risk Factors	Immunosuppression, diabetes mellitus, endocarditis, intravenous drug abuse, chemotherapy, trauma.[7]	Immunodeficiency, chronic infections (HCV, EBV), autoimmune disorders.[9]
Key CT Imaging Features	Solitary or multiple hypodense lesions with thick irregular rim enhancement, central liquefaction, surrounding inflammatory fat stranding, and occasionally intralesional gas.[7,8]	Multiple hypoenhancing nodules, diffuse splenic infiltration or a hypovascular mass with splenomegaly. Lesions usually lack thick rim enhancement, liquefaction or gas.[6,8,10] Associated homogeneous abdominal lymphadenopathy without central necrosis, particularly para-aortic or retroperitoneal nodes, strongly favours lymphoma.[10,11]
When should 'splenic abscess' be questioned? Red flags suggesting lymphoma		
• Persistent fever despite antibiotic • Repeatedly negative microbiological investigations • Multiple splenic lesions with splenomegaly, without microbiological confirmation • Homogeneous non-necrotic abdominal lymphadenopathy • New pancytopenia/ cytopenia • Low procalcitonin (when clinically applicable) • Lack of radiological improvement after antibiotic treatment		

splenic involvement in Hodgkin lymphoma may result in disease upstaging and consequently influence treatment decisions.[4] Malignant lymphoma with prominent splenic involvement and no peripheral lymphadenopathy is rare, with a reported incidence of approximately 0.5%.[6]

Although contrast-enhanced CT is the preferred imaging modality for evaluating focal splenic lesions, hypodense splenic lesions are not specific for infection. Splenic abscess is usually associated with identifiable predisposing conditions (**Table 1**) along with supportive microbiological evidence.[7,8] Our patient had none of these risk factors. Repeated blood cultures and targeted serology remained negative. Therefore, splenic abscess should not be diagnosed on imaging findings alone when the clinical profile and microbiological investigations are not supportive. Instead, the differential diagnosis should include lymphoma, metastatic disease, splenic infarction, tuberculosis, fungal infection, and other granulomatous diseases.[8]

Radiological features of splenic lymphoma and diagnostic pitfalls: The most common CT manifestation of splenic lymphoma is a solitary hypoenhancing splenic mass, reported in up to 75% of cases.[6] In our patient, CT demonstrated multiple small hypodense splenic lesions with homogeneous, non-necrotic abdominal lymphadenopathy; these findings were initially interpreted as splenic microabscesses. Although this imaging appearance is less characteristic of splenic lymphoma, radiological interpretation should always be integrated with the overall clinical context. Homogeneous lymphadenopathy without central necrosis is more suggestive of lymphoma than suppurative infection, especially when accompanied by repeatedly negative microbiological investigations. The principal CT imaging features differentiating splenic abscess from splenic lymphoma are summarized in **Table 1**.

Comparison with previously reported cases. A review of the literature identified only two reported cases of lymphoma with a miliary splenic distribution on imaging, both of which were diffuse large B-cell lymphoma (DLBCL).[12,13] To our knowledge, the present case appears to represent a rare presentation of cHL with miliary splenic abscess-like lesions.[6,10]

More importantly, published reports demonstrate that lymphoma is repeatedly misdiagnosed as splenic abscess, with DLBCL being the predominant histological subtype (**Table 2** and **Supplementary Table S1**). Particularly relevant is the Malaysian case reported by Khoo *et al.*, in which a patient was empirically treated for melioidosis for eight weeks before bone marrow biopsy established the diagnosis of Hodgkin lymphoma.[3] Similar to our case, this highlights how endemicity bias, reliance on non-specific CT findings, and continued escalation of empirical antimicrobial therapy may delay consideration of lymphoma and tissue diagnosis.

Key clinical lessons and Limitations. In retrospect, our patient had several clues arguing against splenic abscess, including the absence of recognised risk factors, repeatedly negative microbiological investigations, non-necrotic abdominal lymphadenopathy, emerging pancytopenia, and persistent fever despite broad empirical antimicrobial therapy. Together, these findings should have prompted earlier tissue diagnosis rather than continued antibiotic

Table 2. Published cases of lymphoma presenting as splenic abscess or with atypical splenic imaging findings.

Case	Age/Sex	Pathology subtype	Imaging finding	Outcome
Splenic-dominant lymphoma cases with a miliary distribution pattern on imaging				
Current case	31/Male	cHL	CT: splenomegaly with multiple small, ill-defined hypodense lesions, multiple abdominal lymphadenopathy	Deceased
1.[12]	88/Female	DLBCL	CT: splenomegaly, multiple ill-defined splenic hypodense foci, and no lymphadenopathy	Not reported
2. [13]	60/Male	DLBCL	CT: multifocal intensely enhancing areas in the splenic parenchyma MRI: splenomegaly with multifocal cystic areas, which showed evidence of variable sized blood products.	Not reported
Other reported cases of splenic-dominant Hodgkin lymphoma (additional cases of NHL are summarized in **Supplementary Table S1**)				
3.[3]	53/M	cHL	CT: splenomegaly with multiple ill-defined splenic collections; no lymphadenopathy	Responded to ABVD chemotherapy

escalation. Although earlier diagnosis may not have altered the outcome, it could have provided an opportunity for treatment before significant deterioration in performance status. Similar diagnostic delays have been reported by Kar *et al.*, in whom many patients with unsuspected Hodgkin lymphoma initially received antibiotics or antituberculosis therapy.[14] The absence of an autopsy remains a limitation of this case.

Key Diagnostic Lessons. This case illustrates how cHL can masquerade as splenic abscess, particularly in regions where endemic infections are common. Although such presentations are uncommon, the more important lesson is to avoid premature diagnostic closure based on imaging alone. Persistent fever despite broad empirical antimicrobial therapy, repeatedly negative microbiological investigations, and emerging cytopenias should prompt early tissue diagnosis from the safest accessible site, allowing earlier recognition of lymphoma and facilitating timely initiation of treatment.

Patient consent for publication. Consent obtained directly from patient's next of kin.

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