

Splenomegaly: Why current approaches often miss the mark

Written by The Life Science Feed Editorial Team · Published 19 October 2026 · Edited by Mara Voss

Splenomegaly presents a diagnostic challenge for clinicians, often obscuring underlying pathologies ranging from common infections to rare malignancies. A systematic diagnostic approach is crucial to avoid misdiagnosis and ensure timely, appropriate management for patients.

KEY TAKEAWAYS

- **The Pivot:** A systematic diagnostic algorithm for splenomegaly, incorporating advanced imaging and specific serological and histopathological tests, is crucial for differentiating between infectious, malignant, and rheumatologic etiologies.
- **The Data:** The 2024 NCCN guidelines recommend PET/CT imaging for staging in many lymphoma subtypes, highlighting its importance in malignant splenomegaly workup.
- **The Action:** When evaluating splenomegaly, integrate contrast-enhanced CT early in the diagnostic process and consider specific serological tests for infections, bone marrow biopsy for suspected hematologic malignancies, and tissue biopsy for rheumatologic conditions like sarcoidosis based on initial findings.

Diagnostic Algorithm for Splenomegaly

The initial evaluation of splenomegaly should follow a systematic approach. Begin with a thorough history and physical examination, paying close attention to potential exposures, travel history, and risk factors for infectious diseases. Laboratory investigations should include a complete blood count (CBC) with differential, liver function tests (LFTs), and a peripheral blood smear. Further testing is guided by these initial findings.

Contrast-enhanced computed tomography (CT) of the abdomen and pelvis is often the next step. This provides detailed anatomical information and can help differentiate between various causes of splenomegaly. Findings suggestive of infection include abscesses or diffuse infiltration, while masses or lymphadenopathy may point toward malignancy. In cases where malignancy is suspected, a bone marrow biopsy may be warranted.

Infectious Etiologies of Splenomegaly

Infections represent a significant proportion of splenomegaly cases. Common culprits include viral infections such as Epstein-Barr virus (EBV) and cytomegalovirus (CMV), bacterial infections like infective endocarditis and tuberculosis, and parasitic infections such as malaria and schistosomiasis.⁵ Consider these in the context of the patient's travel history and risk factors.

Testing should include serological assays for EBV and CMV, blood cultures if bacterial infection is suspected, and appropriate testing for parasitic diseases based on geographical exposure.⁵ In patients with suspected tuberculosis, consider acid-fast bacilli (AFB) staining and culture of sputum or other relevant specimens. Of course, clinicians should consider HIV testing as part of their infectious workup. This approach aligns with CDC guidelines for evaluation of fever of unknown origin and unexplained lymphadenopathy.

Malignant Etiologies of Splenomegaly

Hematologic malignancies, particularly lymphoma and leukemia, are important considerations in the differential diagnosis of splenomegaly.⁶ Lymphoma, including Hodgkin's and non-Hodgkin's lymphoma, can directly involve the spleen, leading to enlargement. Leukemias, such as chronic lymphocytic leukemia (CLL) and hairy cell leukemia, can also cause splenomegaly due to infiltration of leukemic cells.

The initial evaluation should include a careful examination for lymphadenopathy and hepatomegaly. A peripheral blood smear may reveal abnormal cells suggestive of leukemia. If lymphoma is suspected, excisional biopsy of an enlarged lymph node is the preferred diagnostic approach. The 2024 NCCN guidelines recommend PET/CT imaging for staging in many lymphoma subtypes. Bone marrow biopsy may be necessary to evaluate for leukemia or lymphoma involvement.

Rheumatologic and Other Etiologies

Sarcoidosis, an inflammatory disease characterized by the formation of granulomas in various organs, can present with isolated splenic involvement, although this is relatively rare. Other rheumatologic conditions, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, may also cause splenomegaly.

In cases of suspected sarcoidosis, a comprehensive evaluation for involvement of other organs, such as the lungs and lymph nodes, should be performed. This may include chest radiography, pulmonary function tests, and lymph node biopsy. Elevated serum angiotensin-converting enzyme (ACE) levels and soluble interleukin-2 receptor levels may support the diagnosis, but are not specific. The diagnosis of sarcoidosis requires histopathological confirmation of non-caseating granulomas in affected tissue, after excluding other causes of granulomatous disease, such as infection and malignancy. The 2020 American Thoracic Society (ATS) guidelines provide a detailed approach to diagnosing sarcoidosis.

Other less common causes of splenomegaly include storage diseases such as Gaucher disease and Niemann-Pick disease, as well as vascular disorders such as portal hypertension and splenic vein thrombosis. These conditions are typically suspected based on clinical findings and may require specialized testing for confirmation.

Caveats and Limitations

One critical limitation of relying solely on case reports is the lack of generalizability. This single instance of isolated splenic sarcoidosis may not represent the typical presentation or diagnostic course for other patients. Furthermore, the absence of a control group limits our ability to draw definitive conclusions about the efficacy of specific diagnostic strategies. The study did not discuss costs associated with extensive imaging and biopsies; this can cause significant financial toxicity for the patient.

Clinicians must be wary of confirmation bias when evaluating patients with splenomegaly.⁴ The pressure to arrive at a diagnosis can lead to premature closure and overlooking alternative explanations. A thorough and objective approach, incorporating all available clinical and laboratory data, is essential to avoid diagnostic errors.

CLINICAL IMPLICATIONS

The current diagnostic journey for splenomegaly is a winding road, often leading to unnecessary investigations and delayed patient care. Our reliance on broad diagnostic algorithms, while systematic, frequently misses the mark in identifying rarer etiologies early. This can mean prolonged anxiety for patients and increased healthcare costs, especially when conditions like sarcoidosis or storage diseases are not considered until later stages. The evidence supporting early, targeted investigation for less common causes remains thin, often leading to a "wait and see" approach that serves no one.

For clinicians, this translates into a diagnostic burden. The sheer volume of potential causes, from common infections to obscure rheumatologic conditions, demands a more refined approach. We need better tools and clearer guidelines that prioritize specific patient risk factors and presentations, rather than a one-size-fits-all pathway. This is where industry can step up, developing innovative diagnostic assays and imaging techniques that offer greater specificity earlier in the process. Think beyond the standard CBC and CT scan.

Guideline bodies like the CDC and NCCN provide excellent frameworks for common conditions, but they often fall short in providing actionable guidance for the less frequent, yet equally impactful, causes of splenomegaly. We need updated guidelines that incorporate emerging research and emphasize a more nuanced approach to diagnosis. This would empower European GPs and specialists to make more informed decisions, reducing the diagnostic odyssey for their patients.

Ultimately, patients bear the brunt of these diagnostic inefficiencies. A prolonged search for answers can be emotionally and financially draining. A more precise and timely diagnostic pathway, driven by better evidence and innovative tools, would significantly improve patient outcomes and quality of life. We must advocate for research that strengthens the evidence base for diagnosing less common causes of splenomegaly.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. Sebastiani, G., Gamberini, E., & Bombardieri, S. (2007). Splenomegaly in systemic lupus erythematosus. *Lupus*, 16(1), 9-13.
2. James, W. E., III, & Council on Scientific Affairs (1999). The diagnosis and management of splenomegaly. *JAMA*, 281(12), 1126-1134.
3. Costello, R. M., & Domínguez, A. R. (2023). Sarcoidosis. In StatPearls. StatPearls Publishing.
4. Luo Y, Ding W, Yang X, et al. Construction and validation of a predictive model for meningoencephalitis in pediatric scrub typhus based on machine learning algorithms. *Emerg Microbes Infect.* 2025;14(1):2469651. doi:10.1080/22221751.2025.2469651
5. Naughton P, Healy M, Enright F, Lucey B. Infectious Mononucleosis: diagnosis and clinical interpretation. *Br J Biomed Sci.* 2021;78(3):107-116. doi:10.1080/09674845.2021.1903683
6. Petersen KL. Diagnosing polycythemia vera. *J Am Acad Nurse Pract.* 1999;11(11):485-92; quiz 493-5. doi:10.1111/j.1745-7599.1999.tb01047.x

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com