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CASE REPORT

A Fatal Etiology of Splenic Infarction

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare systemic inflammatory disorder that is rapidly progressive and carries a poor prognosis. We present a case of HLH caused by undiagnosed B cell lymphoma, presenting initially with splenic infarction. Both HLH and splenic infarction are secondary conditions with a wide range of underlying etiologies. When either condition is identified, a prompt search for the underlying trigger is needed to prevent devastating consequences. We demonstrate the difficulties and barriers that can delay the diagnosis of HLH, and emphasize the importance of early treatment in improving survival rates.

Keywords: Hemophagocytic lymphohistiocytosis (HLH), Splenic infarct, B cell lymphoma, H-score

1. Background

Hemophagocytic Lymphohistiocytosis (HLH) is a rare condition in which immune dysregulation due to certain triggers leads to a hyperinflammatory state. In the healthy individual, cytotoxic lymphocytes (CTLs) and Natural Killer (NK) cells help regulate the immune system by lysing excess or damaged macrophages.[1] In HLH, dysfunction of immune-regulating cells causes overactivation of macrophages which engulf blood cells (causing cytopenia), leading to a cytokine storm and quickly progressing to multiorgan failure.[1] HLH is most common in the pediatric population, where it can be linked to an underlying genetic disorder.[2] However, it is becoming increasingly recognized in adults, who may account for up to 40% of cases.[2] In adults, HLH is caused by an acquired trigger – infection (e.g., tuberculosis, EBV), malignancy (e.g., lymphoma), or rheumatologic disorder. Adult HLH generally has a dismal prognosis, with mortality rates ranging between 58% and 75%.[3] When malignancy is the trigger, early detection and prompt initiation of both HLH-targeted therapy and chemotherapy are crucial to improve outcomes.[4]

2. Case study

2.1. Presentation

A 76-year-old man with a past medical history of benign prostate hyperplasia, type II diabetes mellitus, obstructive sleep apnea and unintentional weight loss for the last two months, presented to the emergency department (ED) with acute onset left sided flank pain, lightheadedness, and progressive dyspnea on exertion. He saw his primary care provider (PCP) two weeks ago for unintentional significant weight loss over a 2-month period. An outpatient computed tomography (CT) of the abdomen showed a 4 mm hypodense lesion in the pancreas. Follow up magnetic resonance imaging (MRI) was recommended, but due to this left flank pain the patient presented to the ED. He had no fever, chills, hematuria, dysuria, diarrhea, or constipation. He denied any changes in appetite, nausea, vomiting, melena, hematochezia, or hema-

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temesis. He reported no notable enlargement of lymph nodes, spontaneous bruising, or bleeding. He had a 2.5 pack-year smoking history, and no history of alcohol or substance use. He denied any family history of cancer. His home medications included Nifedipine 60 mg, Valsartan-Hydrochlorothiazide 160–12.5 mg, Pravastatin 80 mg, Aspirin 81 mg, Finasteride 5 mg, Tamsulosin 0.4 mg and Metformin 1000 mg. He was up to date on age-appropriate cancer screening, including colonoscopy.

2.2. Assessment

On presentation, his vital signs were as follows: blood pressure 136/52 mm Hg, heart rate 58 beats/min, temperature of 36.3 °C, respiratory rate 18 breaths/min, and oxygen saturation of 96% while breathing ambient air. He was 180.3 cm tall and weighed 166 lbs. Notably, he had been 233 lbs. 1 month ago and 249 lbs. 6 months ago. Physical exam was remarkable for signs of temporal wasting. Abdominal examination was benign with no evidence of tenderness, hepatomegaly, or splenomegaly. There was no appreciable lymphadenopathy in the neck, supraclavicular, axillary or groin areas. Cardiovascular examination showed normal S1 and S2, regular rhythm without any murmurs. He was breathing comfortably without any distress. Musculoskeletal and neurologic examination was unremarkable.

Labs (Table 1) were remarkable for normocytic anemia (Hemoglobin 11.9 g/dL) and thrombocytopenia (PLT 144 K/cu mm). Comprehensive

Table 1. Pertinent laboratory results during first and subsequent hospitalization.

Test	Result: Visit 1	Result: Visit 2	Normal Range
Hematology			
White blood cell count	6.61	7.48	4.5–11.00 K/cu mm
Absolute CD4+ Lymphocytes		545	458-1344 cu/mm
Hemoglobin	11.9	11.8	13.9–16.3 g/dL
Hematocrit	35.8	35.6	41.0–53.0%
Mean Corpuscular Volume	80.3	80.7	80.0–100.0 fL
Platelet count	114	129	150–350 K/cu mm
Iron		88	40-80 ug/dL
Ferritin		17,515	30–400 ng/ml
Transferrin		167	200–400 mg/dL
Total Iron Binding Capacity		209	250-450 ug/dL
Coagulation			
INR	1.07		0.90–1.10
Fibrinogen	623		150–450 mg/dL
Prothrombin time	11.4		9.3–11.7 s
D dimer	1.19		0–0.49 mg/L FEU
Chemistry			
Sodium	137		135–148 mmol/L
Potassium	4.3	3.9	3.5–5.1 mmol/L
Chloride	105	106	96–109 mmol/L
Carbon Dioxide	27	25	21–31 mmol/L
Glucose	126	130	71–99 mg/dL
Urea Nitrogen	15	15	7–22 mg/dL
Creatinine	1.26	1.1	0.6–1.3 mg/dL
Estimated GFR	63	75	>60 ml/min/1.73
Calcium	9.5	9.1	8.4–10.5 mg/dL
Total Protein	7.6	6.5	6.0–8.2 g/dL
Albumin	3.8	3.1	3.5–5.3 g/dL
Total Bilirubin	0.6	0.8	0.0–1.2 mg/dL
Alkaline Phosphatase	77	148	30–120 U/L
Aspartate Amino Transferase	43	146	0–37 U/L
Alanine Amino Transferase	21	157	0–40 U/L
Carbohydrate Ag 19-9	17.4		0.0–36.0 U/ml
CEA	0.9		0.0–3.0 ng/ml
Prostate specific antigen	0.5		0.0–4.0 ng/ml
Microbiology			
COVID-19 NAT, NP swab	Negative	Negative	
T-Spot TB		Positive	
Bacterial Culture (blood)		No growth	
HIV, HTLV-I/HTLV-II assays		Nonreactive	

(*continued on next page*)

Table 1. (continued)

Test	Result: Visit 1	Result: Visit 2	Normal Range
Hepatitis A, B, C Antibody		Nonreactive	
CMV Viral Load		<34.5	<34.5 IU/ml
EBV Quant NAT, Plasma		1080 copies/ml	Detects 500 to 10^9
HSV-1 IgM screen		Negative	
Herpes Simplex Virus 2 IgM		Negative	
Histoplasma Antigen (EIA)		Negative	<19.0 ng/ml
Q Fever Ig G, M		Negative	
Immunology			
Anti-nuclear Antibody (ANA)	No Antibodies		
Cardiolipin Ab, IgA, G, M	<10		0−20 units
Beta-2 Glycoprotein Ig A,G, M	<10		0-20 Std units
Mitochondrial Antibody screen		No Antibodies	
Smooth Muscle Antibodies		No Antibodies	
Rheumatoid Factor		14	0−12 IU/ml

Note: For labs that underwent serial monitoring, the value above represents the initial result obtained during the hospitalization.

metabolic panel revealed slightly elevated aspartate aminotransferase (43 U/L) and creatinine (1.26). International normalized ratio (INR) was elevated to 1.19 mg/L FEU and D-dimer was elevated at 1.19 L/FEU. Contrast CT scan of the chest, abdomen and pelvis revealed multiple acute splenic infarcts (Fig. 1).

The patient was admitted and started on anticoagulation with parenteral heparin infusion for splenic infarction. To evaluate for thromboembolic etiology, a transthoracic echocardiogram (TTE) with agitated saline was obtained which ruled out patent foramen ovale. Telemetry did not note any abnormal rhythm. MRI abdomen was obtained to delineate the previously seen pancreatic lesion, which showed normal pancreas. Screening tests for a hypercoagulable state as well as for malignancy remained unrevealing including negative CEA, CA 19−9, PSA, and cardiolipin antibody tests. Without a clear etiology for the splenic infarcts the patient was discharged on enoxaparin injection bridging to warfarin for a possible thromboembolic source, and he was advised to follow up with his PCP in two days time. At that subsequent PCP visit two days later, the patient reported worsening abdominal pain and was found to have orthostatic hypotension for which he was directed to the ED.

2.3. Diagnosis

In the ED, CT angiography of chest, abdomen and pelvis revealed slight progression of the splenic infarcts and a new left sided pleural effusion. Labs were remarkable for worsening elevation in liver transaminases (AST 146 U/L, ALT 157 U/L). The patient was readmitted. Viral hepatitis serologies and autoimmune workup (ANA, AMA, ASMA) were unremarkable (Table 1). Abdominal ultrasound demonstrated a normal-appearing liver with patent hepatic vasculature. Magnetic resonance

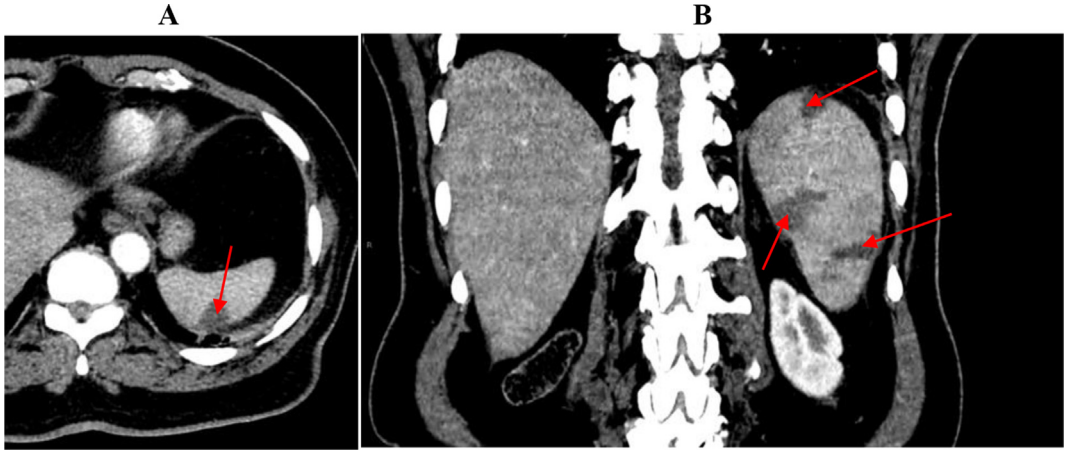

Fig. 1. (A) Axial view of the computed tomography image of the abdomen showing splenic infarction (identified with red arrow). (B) Coronal view of the computed tomography image of the abdomen showing multiple splenic infarcts (identified with red arrows).

cholangiopancreatography ruled out a cholestatic process. Due to worsening anemia, the patient underwent esophagogastroduodenoscopy and colonoscopy to evaluate for bleeding sources, which was also unremarkable. On day 4, the patient experienced fever (38.6 °C). Chest x-ray, urinalysis, and blood cultures did not reveal any infectious source. Additional workup including CMV, Brucella, Q fever serologies, Toxoplasma IgG antibody and urine histoplasma antigen were negative, and a low detectable EBV viral load (1080 copies/ml) was regarded as an incidental finding. T-spot returned positive but without any acute infectious locus. Anticoagulation was discontinued due to anemia and the lack of a thrombotic source of splenic infarct. Further anemia workup showed an elevated ferritin level to 17,515 ng/ml (reference range 30–400 ng/ml).

Due to extreme hyperferritinemia (defined as >10,000 ng/ml), the possibility of Hemophagocytic Lymphohistiocytosis (HLH) was raised.[5] Further supporting this reasoning was the elevation in triglycerides (544 mg/dL). This prompted tests including flow cytometry, interleukin-2 (IL-2), T-cell receptor gene rearrangement and a liver biopsy was planned. Due to clinical stability, empiric HLH-directed therapy was held while monitoring ferritin levels. Liver biopsy was postponed twice due to elevated bleeding risk (elevated INR and thrombocytopenia requiring vitamin K and platelet transfusion respectively). On the day of liver biopsy, his ferritin level had risen to 59,000 ng/ml, platelets had dropped to 49 k/cu mm, and transaminases rose with an AST of 807 U/L and an AST of 435 U/L. A tentative diagnosis of HLH was made. Eventually, liver biopsy was performed on day 12 of the hospitalization. The following day, the liver biopsy report showed B cell lymphoma (Fig. 2), which was thought to be the trigger for HLH.

On day 13, the patient became tachycardic and was found to be more somnolent. He was started on intravenous dexamethasone 20 mg daily for HLH. On day 15, the patient experienced acute hypoxic respiratory failure requiring mechanical ventilation. Within hours, he was in distributive shock refractory to three vasopressors, along with multiorgan failure. In this critical state, he was deemed not a candidate for chemotherapy. He passed away on day 20.

3. Discussion

3.1. Hemophagocytic Lymphohistiocytosis (HLH)

Due to non-specific presenting manifestations, HLH can be an extremely difficult diagnosis to

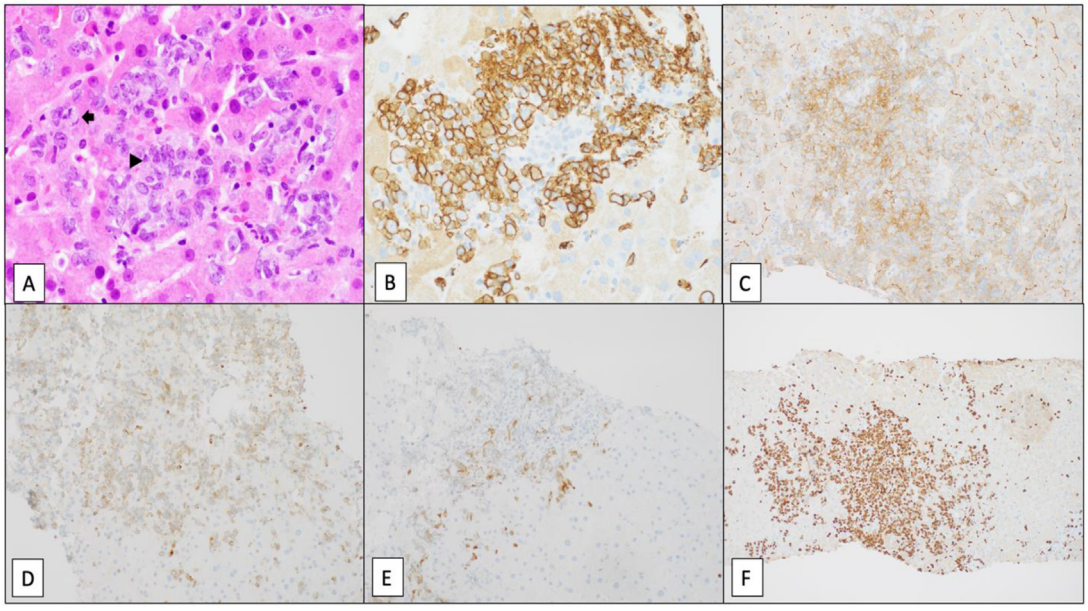

Fig. 2. Histopathological slides of the needle core biopsy of liver. (A) Hematoxylin & Eosin stain (Magnification: 100×) showing abnormal large lymphoid cells in the liver sinusoids (arrow). Mitoses are present (arrowhead). The cells are large and pleomorphic with variably prominent nucleoli. (B) CD20 Immunostaining (Magnification: 100×) showing abnormally large B cells. (C.) CD10 Immunostaining (Magnification: 100×) showing large lymphoma cells are B cells (CD20+), which express CD10 (a germinal center marker), making this a germinal center B-cell lymphoma (Hand classification, Diffuse large B cell lymphoma). (D) The large B cells are weakly positive for BCL2 staining. (E.) B cells are mostly negative for MUM1 staining. (F) Ki67 staining (Magnification 10×) shows high Ki67 proliferative index in the lymphoid cells (low in background liver).

Table 2. Differential diagnosis for splenic infarction.

Malignancy	Hypercoagulable states	Thromboembolic	Pancreatic disorder	Infectious	Others
Leukemia	Sickle cell disease	Atrial Fibrillation	Pancreatitis	Epstein–Barr Virus	Abdominal trauma
Lymphoma	Antiphospholipid antibody syndrome	Prosthetic heart valve	Compressive pancreatic mass	cytomegalovirus	
Myelofibrosis	Lupus	Patent foramen ovale		Babesiosis	
	Protein C/S deficiency	Endocarditis		HIV	
	Polycythemia vera				

clinch. HLH should be considered for unexplained cytopenia, fever, hepatitis or inflammatory CNS disease.[6] As demonstrated in this case, an extremely elevated ferritin should raise suspicion for HLH, as hyperferritinemia is a sensitive (though nonspecific) marker.[6] According to the HLH-2004 guidelines,[7] five of the following must be met to diagnose HLH: fever; splenomegaly; bicytopenia (with at least two of these: Hb < 9 g/dL, platelets <100,000/microL; absolute neutrophil count <1000/microL); hypertriglyceridemia (>265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL); hemophagocytosis in bone marrow, spleen, lymph node, or liver; low/absent NK activity; Ferritin >500 ng/ml; or elevated CD25. The "H-score" offers alternative diagnostic criteria and yields the probability of HLH before histopathologic results are available.[8] At the time of diagnosis our patient met five HLH-2004 criteria (H-score predicting 88–93% probability).

Our patient's underlying B-cell lymphoma was the most attributable cause of HLH, making this a case of Lymphoma-associated hemophagocytic syndrome (LAHS). While his T-spot test was also reported to be positive, no active mycobacterial infection was found. LAHS carries a poor prognosis without treatment of the underlying malignancy.[4] The treatment protocol for HLH involves 8 weeks of induction therapy with Dexamethasone and Etoposide (with or without intrathecal methotrexate and hydrocortisone for CNS involvement).[9] HLH-targeted treatment should commence at any sign of clinical instability. Although LAHS carries a poor prognosis without treatment of the underlying malignancy, timing to initiate chemotherapy in these otherwise sick patients is unclear. Immunochemotherapy with hematopoietic stem-cell transplant is the mainstay of treatment for LAHS.[10] Pasvolsky et al.[4] described four LAHS patients, who were on HLH-directed therapy. Two of them experienced rapid deterioration and death before they could get biopsy making a case to maintain high degree of cancer suspicion in idiopathic HLH cases, treating HLH with steroids as early as possible, avoiding any delays in biopsy and even consideration of early chemotherapy, although evidence is somewhat lacking. Ghose et al.[11] similarly described a case of LAHS where the patient succumbed to complications due to delay in diagnosis and treatment, making a case for early biopsy and malignancy-targeted treatment.

3.2. Splenic infarction

Splenic infarction is a rare phenomenon with broad differential diagnoses (Table 2) and identifying the underlying cause can be a challenge.[12] Many pathophysiological mechanisms have been proposed - occlusion of the splenic artery, hypercoagulable states or thromboembolic events,[13] hypersplenism associated infarction (increased demands of enlarging spleen) and infarction due to abnormally shaped cells causing vascular congestion (e.g. lymphomas).[14]

Once splenic infarction is identified, a search for the underlying diagnosis should commence immediately, as many of the underlying diagnosis are sinister. B-cell lymphoma and HLH have both been associated with splenic infarcts, albeit less commonly.[15,16] As demonstrated in this case, the underlying diagnosis may be delayed while common causes are being ruled out. Anticoagulation is indicated for thromboembolic etiologies and may be considered indefinitely for cryptogenic splenic infarct.[17]

4. Conclusion

HLH diagnosis remains difficult to ascertain, especially without an established trigger. Once HLH is diagnosed, prompt treatment should be initiated to reduce mortality. Simultaneously, a thorough search for the underlying trigger should be conducted. In this case, unexplained weight loss and splenic infarcts raised the concern for lymphoma even in the absence of lymphadenopathy, which was subsequently confirmed by liver biopsy. Malignancy associated HLH is a rapidly progressing, fatal diagnosis that should prompt early HLH and malignancy directed treatment.

Notes on patient consent

The patient has provided an informed consent for publication of this case report.

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Authorship statement

All authors had access to the data and a role in writing this manuscript.

Conflcits of interest

None.

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References

1. Pandey Y, Atwal D, Konda M, et al. Hemophagocytic lymphohistiocytosis in adults. *Baylor Univ Med Cent Proc*. 2020; 33(3):326−330. https://doi.org/10.1080/08998280.2020.1740052.
2. Zhou J, Zhou J, Wu ZQ, Goyal H, Xu HG. A novel prognostic model for adult patients with Hemophagocytic Lymphohistiocytosis. *Orphanet J Rare Dis*. 2020;15(1). https://doi.org/10.1186/s13023-020-01496-4.
3. Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol*. 2015;90(3):220−224. https://doi.org/10.1002/ajh.23911.
4. Pasvolsky O, Zoref-Lorenz A, Abadi U, et al. Hemophagocytic lymphohistiocytosis as a harbinger of aggressive lymphoma: a case series. *Int J Hematol*. 2019. https://doi.org/10.1007/s12185-019-02623-z.
5. Sackett K, Cunderlik M, Sahni N, Killeen AA, Olson APJ. Extreme hyperferritinemia: causes and impact on diagnostic reasoning. *Am J Clin Pathol*. 2016;145(5):646−650. https://doi.org/10.1093/AJCP/AQW053.
6. Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: recommendations from the north American consortium for histiocytosis (NACHO). *Pediatr Blood Cancer*. 2019;66(11). https://doi.org/10.1002/ajh.23911.
7. Henter JI, Horne AC, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124−131. https://doi.org/10.1002/pbc.21039.
8. Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9): 2613−2620. https://doi.org/10.1002/art.38690.
9. Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041−4052. https://doi.org/10.1182/blood-2011-03-278127.
10. Chang Y, Cui M, Fu X, et al. Lymphoma associated hemophagocytic syndrome: a single-center retrospective study. *Oncol Lett*. 2018;16(1):1275−1284. https://doi.org/10.3892/ol.2018.8783.
11. Ghose A, Yellu M, Wise-Draper T, et al. Lymphoma presenting as secondary HLH: a review with a tale of two cases. *Clin Lymphoma, Myeloma & Leukemia*. 2014;14(6):e187−e193. https://doi.org/10.1016/j.clml.2014.06.025.
12. Ami S, Meital A, Ella K, Abraham K. Acute splenic infarction at an academic general hospital over 10 years presentation, etiology, and outcome. *Med Times*. 2015;94(36). https://doi.org/10.1097/MD.0000000000001363.
13. Li Y, George A, Arnaout S, Wang JP, Abraham GM. Splenic infarction: an under-recognized complication of infectious mononucleosis? *Open Forum Infect Dis*. 2018;5(3). https://doi.org/10.1093/ofid/ofy041.
14. Chapman J, Helm TA, Kahwaji CI. *Splenic infarcts. Treasure*. Island, FL: StatPearls Publishing; 2021.
15. Kumar V, Soni P, Dave V, Harris J. Unusual presentation of diffuse large B-cell lymphoma with splenic infarcts. *J Investig Med High Impact Case Reports*. 2017;5(1). https://doi.org/10.1177/2324709617690748.
16. Bonnecaze A, Willeford WG, Lichstein P, Ohar J. *Acute cytomegalovirus (CMV) infection associated with hemophagocytic lymphohistiocytosis (HLH) in an immunocompetent host meeting all eight HLH 2004 diagnostic criteria. Cureus*. March 2017. https://doi.org/10.7759/cureus.1070.
17. O'Donnell M, Shatzel JJ, Olson SR, et al. Arterial thrombosis in unusual sites: a practical review. *Eur J Haematol*. 2018;101(6): 728−736. https://doi.org/10.1111/ejh.13165.