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Splenic Infarction: An Under-recognized Complication of Infectious Mononucleosis?

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Splenic infarction is a rare complication of infectious mononucleosis. We describe 3 cases of splenic infarction attributed to infectious mononucleosis that we encountered within a 2-month period. We underscore the awareness of this potential complication of infectious mononucleosis and discuss the differential diagnosis of splenic infarction, including infectious etiologies. While symptomatic management is usually sufficient for infectious mononucleosis-associated splenic infarction, close monitoring for other complications, including splenic rupture, is mandated.

Keywords. Epstein-Barr virus; infectious mononucleosis; splenic infarction.

While infectious mononucleosis (IM) usually represents a benign clinical process, serious complications can occur. Scant data on the incidence of splenic infarction as a complication of IM exist, with the majority of the literature being individual case reports. We report a cluster of 3 cases of IM complicated by splenic infarction that we saw over a 2-month period. We aim to raise awareness of this potentially under-recognized clinical problem.

CASE 1

A 24-year-old female with Crohn's disease, Hashimoto thyroiditis, and sacroiliitis presented in late summer with a 1-week history of increasingly severe left-sided abdominal pain associated with fever, nausea, loose stools, and fatigue. Review of systems was otherwise negative. She reported no sick contacts, tick bites,

or recent travel. Family history was remarkable for thyroid disease in her mother and brother, but negative for thrombophilic disease. The physical exam was significant for temperature of 38.1°C, submandibular lymphadenopathy, and abdominal tenderness at the left upper quadrant. Blood test results are shown in [Table 1](#). Contrast computed tomography (CT) imaging of the abdomen and pelvis showed splenomegaly of 16.3 cm and multiple wedge-shaped hypodensities throughout the spleen consistent with infarcts ([Figure 1](#)), neither of which was present on an imaging study 1 year before. Blood cultures and transthoracic echocardiogram were negative. Babesia polymerase chain reaction and Lyme antibody screen were negative. The patient was diagnosed with IM complicated by splenic infarction. She received supportive care and was discharged on the fourth hospital day with instructions to avoid contact sports. Approximately 2 months later, she was reassessed for Crohn's disease, at which time MR enterography showed resolving splenomegaly of 11.9 cm with a decrease in the size and extent of splenic infarcts.

CASE 2

A 20-year-old man with no significant past medical history presented with 5 days of neck swelling, soreness, and hives and 1 day of left upper quadrant abdominal pain associated with nausea. Review of systems was otherwise negative. He reported no significant sick contacts, travel, outdoor activities, or trauma. Family history was remarkable for stroke and deep vein thrombosis in his 2 maternal aunts, with no other history of thrombophilic diseases. Physical examination revealed a well-nourished male with resolving hives present on his face and back. The abdomen was soft with mild tenderness without rebound or guarding over the left upper quadrant. The remainder of the exam was unremarkable. Laboratory findings, including hypercoagulable workup, are shown in [Table 1](#). CT scan of the abdomen and pelvis revealed hepatosplenomegaly, multiple hypodensities suggesting splenic infarct, and borderline enlarged portal hepatic and periaortic lymph nodes. Given that no evidence of thrombophilic disease was found, the diagnosis of IM complicated by splenic infarction was made. The patient was managed conservatively with supportive treatment, including intravenous fluids, analgesics, and antihistamines.

CASE 3

A 27-year-old man with no significant prior medical history presented to the emergency department with complaints of left upper quadrant abdominal pain for 1 week. He also had fever, chills, nausea, night sweats, and a sore throat. He denied recent

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Table 1. Laboratory Studies

	Case 1	Case 2	Case 3	Normal Range
WBC	13.3	7.4	13.7	3.9–11.0 × 1000/μL
Lymphocytes	44	1.3	6.0	0.7–4.5 × 1000/μL
Reactive/atypical lymphocytes	8	49	20	0–6%
HgB	11.9	14.7	13.3	12.5–17.0 g/dL
Platelets	236	115	323	150–450 × 1000/μL
AST	36	100	156	0–55 U/L
ALT	20	86	379	0–44 U/L
APTT	25.5	27.1	29.7	25.0–35.0 s
PT	12.1	11	11.3	9.1–12.0 s
INR	1.1	1.1	1.1	2.0–3.5
Heterophile, mononucleosis screen	Positive	Positive	Positive	Negative
Epstein-Barr virus (VCA) antibody IgG	36.8 (positive)	—	—	<18.0
Epstein-Barr virus (VCA) antibody IgM	>160.0 (positive)	—	—	<36.0
Epstein-Barr virus nuclear antigen antibody	Negative	—	—	<18.0
Lupus anticoagulant (dilute Russell's viper venom time)	—	58	476	0–47 s
β-2 Glycoprotein IgM, IgG	Negative	Negative	—	<20 SU
Anticardiolipin IgM	16 (indeterminate)	Negative	15 (indeterminate)	<10 U/mL
Anticardiolipin IgG	Negative	Negative	Negative	<11 U/mL
Phosphatidylserine IgM	29 (equivocal)	—	—	<25 U/mL
Phosphatidylserine IgG	Negative	—	—	<10 U/mL
Protein C activity	—	86	68	73%–180%
Activated protein C resistance	—	2.5	—	2.0–3.5
Free protein S	—	78	—	57%–157%
Total protein S	—	73	—	60%–150%
Functional protein S	—	—	63	63%–140%
Antithrombin III activity	—	116	93	75%–135%
Factor V Leiden mutation	—	Negative	Negative	Negative
Prothrombin gene mutation	—	Negative	Negative	Negative

—, not done. Abbreviations: ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; HgB, hemoglobin; IgA, immunoglobulin A; IgG, immunoglobulin G; INR, international normalized ratio; PT, prothrombin time; SU, standard units; VCA, viral capsid antigen; WBC, white blood count.

travel, tick bites, or sick contacts. Physical examination was remarkable for tachycardia, abdominal tenderness over the left upper quadrant, and mild splenomegaly. Blood work showed a positive heterophile antibody test, leukocytosis with 23% atypical lymphocytes, and transaminitis with AST 279 U/L and ALT 501 U/L. The patient was discharged from the emergency

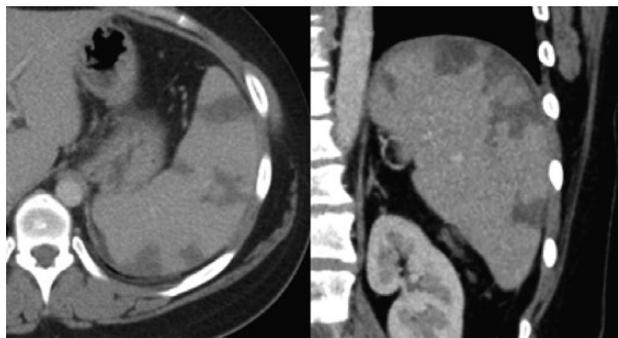


Figure 1. Contrast-enhanced abdominal computed tomography revealed splenomegaly with multiple wedge-shaped hypodensities throughout the spleen consistent with infarcts. Representative axial and coronal images from the patient in Case 1 are shown.

department with analgesics. He was advised to avoid contact sports, physical strain, hepatotoxic medications, and to return in several days for reevaluation. He returned 2 days later with worsening left upper quadrant abdominal pain and a new nonpruritic rash over the low back and lower extremities. He denied fever. A CT scan of abdomen and pelvis showed moderate splenomegaly with multiple peripheral wedge-shaped hypodensities consistent with splenic infarcts. During the hospitalization, laboratory studies and hypercoagulable workup, shown in Table 1, were notable only for a weakly positive anticardiolipin IgM antibody, lupus anticoagulant, and slightly reduced protein C activity; thus his splenic infarction was considered to be a complication of IM. The patient admitted to occasional intravenous drug use, most recently 3 months prior to presentation. Following clinical improvement with symptomatic treatment, he was discharged but lost to follow-up without completion of an infectious endocarditis workup, a preliminary workup having been unrevealing.

DISCUSSION

The clinical course of IM is typically characterized by nonspecific symptoms including fever, sore throat, and lymphadenopathy

followed by spontaneous recovery. Although splenic infarct is reported to be an infrequent complication of IM, quite remarkably, we saw 3 such cases in Worcester, Massachusetts, within a 2-month period. The readily available radiological tools, including CT scan, ultrasonography, and magnetic resonance imaging, contribute significantly in uncovering this potentially under-recognized serious complication of IM. We emphasize a heightened awareness for evaluating for infectious causes of splenic infarct, particularly given the high prevalence of IM. Epstein-Barr virus (EBV) represents the most common cause of infectious mononucleosis. A total of 23 cases of splenic infarction during acute IM due to EBV infection are reported in the medical literature published between 1961 and 2017 [1–4], 20 of which are summarized by Heo et al. [1]. Our cases are similar to these in terms of the median age of 23.5 years (range, 7–57 years; available in 18 cases), mostly occurring in otherwise healthy people without underlying disease, time of symptom onset to diagnosis of infarction of 5 days (range, 1–25 days), presence of splenomegaly, and good clinical outcome [1].

Several mechanisms are proposed for the pathogenesis of splenic infarction during IM. First, arterial blood supply may be insufficient for the increased demand of the hypercellular spleen during acute IM, resulting in local infarct. Second, the presence of a transient hypercoagulable state during IM has been proposed. Transient elevated antiphospholipid antibodies [5], lupus anticoagulant [2], and factor VIII [6] have been documented during the acute stage of IM when complicated by splenic infarction. Notably, anticardiolipin antibodies have been detected in 30%–62% of patients with IM with EBV, with the majority bearing no known clinical significance; such

transient prothrombotic factors tend to disappear in 1–4 years [7]. Third, an increased level of circulating immune complexes due to B cell proliferation, promoting leukocyte aggregation and adhesiveness, has been associated with splenic infarction with EBV [8].

Splenic infarction complicates infections besides EBV, and examples are listed in Table 2. Infectious endocarditis can result in septic emboli to the spleen [9]. At least 11 cases of cytomegalovirus-associated splenic infarction in immunocompetent patients have been reported, and, as with EBV, inadequate blood supply and transient production of antiphospholipid antibodies are postulated as contributors to infarct [10]. Other infections associated with splenic infarct include malaria and babesiosis, which are recognized causes of splenic disease. Forty-four cases of malaria associated with splenic infarcts, many of which involved splenomegaly, were recently reviewed [11]. To date, 4 cases of babesiosis complicated by splenic infarct have been published, for which the mechanism of infarct remains undefined [12–14]. Malaria and babesia can be associated with splenic infarcts even during low parasitemia. A small number of cases of splenic infarction have been associated with parvovirus B19 infection, and very few published reports are available on brucella-associated splenic infarct in the absence of infectious endocarditis. Isolated reports have been made with murine typhus as well. Again, under such circumstances, the reason for infarct is obscure. With regards to noninfectious etiologies, splenic infarction occurs with myeloproliferative disorders, in the presence of thromboembolic or hypercoagulable states including malignancy and antiphospholipid syndrome, and with splenomegaly. Such conditions (adapted from Hunt et al. [15]) are listed in Table 2.

Table 2. Conditions Associated With Splenic Infarct

Infections
Infective endocarditis/septic emboli
Epstein-Barr virus
Cytomegalovirus
Malaria (<i>Plasmodium vivax</i> , <i>Plasmodium falciparum</i>)
Babesiosis (<i>Babesia microti</i>)
Parvovirus B19
Brucellosis (<i>Brucella melitensis</i>)
Murine typhus (<i>Rickettsia typhi</i>)
Noninfectious conditions
Myeloid disorders
Myeloproliferative neoplasm
Myelodysplastic syndrome
Acute leukemia
Thromboembolic events
Cardioembolic
Hypercoagulable states: antiphospholipid syndrome, malignancy
Lymphoma
Hemoglobinopathy
Conditions with marked splenomegaly
Trauma
Wandering spleen

CONCLUSION

IM is a very common condition, whereas splenic infarction occurs relatively infrequently. Splenic infarction may manifest as left upper quadrant abdominal pain during IM. When splenic infarct is observed on imaging studies, infectious etiologies including EBV should be considered. While symptomatic management is usually sufficient for IM-associated splenic infarction, close monitoring for other complications, including splenic rupture, is mandated.

Note

Potential conflicts of interest. The authors declared no potential conflicts of interest with respect to authorship and publication of this article. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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