

Infectious mononucleosis - not always a benign condition: a case report of infectious mononucleosis-associated acute acalculous cholecystitis

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ABSTRACT

Infectious mononucleosis is typically a self-limited viral infection of adolescence and early adulthood that resolves in a period of weeks, causing no major sequelae. We describe a case of a healthy 18-year-old female diagnosed with infectious mononucleosis who also presented with right upper quadrant abdominal pain, moderate transaminitis, and cholestatic biochemistry. An ultrasound revealed acute acalculous cholecystitis, generally a condition seen in the context of critical illness. Further investigating emergency department patients with infectious mononucleosis is often not indicated, but may be important for those who present atypically.

RÉSUMÉ

La mononucléose infectieuse est maladie d'origine virale, en général spontanément résolutive, qui touche surtout les adolescents et les jeunes adultes et qui disparaît d'elle-même au bout de quelques semaines, sans laisser de séquelles importantes. Sera décrit ici le cas d'une jeune fille de 18 ans, antérieurement en bonne santé, chez qui un diagnostic de mononucléose infectieuse a été posé et qui présentait aussi des douleurs abdominales dans le quadrant supérieur droit; à cela s'ajoutaient un taux modéré de transaminases et des résultats d'analyses de sang révélateurs d'une cholestase. L'échographie a mis en évidence une cholécystite alithiasique aiguë, une affection qui s'observe généralement dans les maladies graves. Dans les cas de mononucléose infectieuse examinés au service des urgences, il est souvent non indiqué de poursuivre l'exploration mais, dans les cas atypiques, il peut être important de le faire.

Keywords: acute acalculous cholecystitis, infectious mononucleosis, Epstein-Barr virus, ultrasound, gallbladder, abdominal pain

INTRODUCTION

The Epstein-Barr virus is a human herpesvirus, to which most people are exposed in childhood and acquire active immunity. However, a subset of patients, typically Caucasian adolescents,¹ are infected later in

life through intimate contact with a host and develop infectious mononucleosis. Infectious mononucleosis is characterized by a triad of symptoms: fever, pharyngitis, and lymphadenopathy.

Infectious mononucleosis is almost invariably self limited, and the treatment is conservative. Patients are asymptomatic within 1–2 weeks, except fatigue that can persist for months.² In the emergency department (ED) setting, these patients may have the diagnosis confirmed with a single rapid blood test and are discharged home without advanced blood work or imaging.

An exceedingly rare sequela of infectious mononucleosis is acute acalculous cholecystitis, a condition more typically seen in patients with prolonged admissions in the intensive care unit (ICU). Acute acalculous cholecystitis is an acute inflammatory and necrotic process of the gallbladder in the absence of a gallstone, with high morbidity and mortality.³ It occurs as a consequence of major trauma, malignancy, burns, and sepsis, among other severe causes. Once diagnosed, the treatment of acute acalculous cholecystitis ranges from symptomatic management to antibiotics and surgery.

CASE REPORT

An 18-year-old female presented to the ED with a one-week history of profound fatigue. She also complained of fever, painful swelling in her neck, and reported right upper quadrant abdominal pain. She was otherwise healthy, with no significant past medical history.

Her triage vitals were: heart rate 95 beats/minute, blood pressure 106/71 mm Hg, respiratory rate 20

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breaths/minute, oxygen saturation 98% on room air, and a temperature of 37.8°C (100.4°F). On physical exam, she had marked lymphadenopathy of the head and neck with an erythematous pharynx. Her examination revealed a soft abdomen with significant tenderness in the right upper quadrant and a positive Murphy's sign. She was not jaundiced and had no stigmata of liver disease. Her cardiac and respiratory exams were within normal limits.

Because of her pronounced right upper quadrant abdominal pain, bloodwork was obtained. It revealed leukocytosis, moderate transaminitis, hyperbilirubinemia, elevated alkaline phosphatase, and elevated lipase (see Box 1). A monospot test was positive.

Based on a physical exam and the cholestatic picture in the bloodwork, an abdominal ultrasound was ordered that revealed a distended gallbladder with diffuse wall thickening measuring up to 10 mm. There was a small amount of pericholecystic fluid. The patient had a positive sonographic Murphy's sign. No gallstones or biliary tract dilatations were seen.

A diagnosis of acute acalculous cholecystitis was made. She was admitted under general surgery, observed, and treated symptomatically. With conservative therapy, the patient made a complete recovery and was discharged home two days later with no complications.

DISCUSSION

An adolescent or a young adult patient who presents with the clinical triad of infectious mononucleosis (pharyngitis, fever, and lymphadenopathy) rarely presents a diagnostic dilemma. The diagnosis is confirmed with a rapid test in the heterophile antibody (monospot) assay, which has high sensitivity and specificity (85%

and 100%, respectively).⁴ These patients do well with symptomatic treatment and are not referred or admitted.

However, because they are rare, many of the complications of infectious mononucleosis do not receive much attention despite their severity. Patients are told to avoid contact sports to prevent splenic injury, but, often, the discussion ends there. However, clinicians need to be aware of other non-splenic sequelae. Epstein-Barr virus has been associated with multi-system disease including, but not limited to, multiple sclerosis, myocarditis, myositis, and glomerulonephritis.⁵ Of note, not all cases of infectious mononucleosis are caused by the Epstein-Barr virus, with approximately 10% of cases arising from other viruses such as HIV, cytomegalovirus, and hepatitis B.⁶

The pathophysiology of infectious mononucleosis causing acute acalculous cholecystitis is not fully understood. There are two proposed mechanisms. The first is that cholestasis caused by hepatic or gallbladder pathology leads directly to acute acalculous cholecystitis by the release of proinflammatory cytokines, disrupting bile flow.⁷ However, the second theory is that systemic illness in the absence of cholestasis causes inflammation of the gallbladder (common infections include: cholera, tuberculosis, salmonellosis, brucellosis, and hepatitis A).⁸⁻¹⁰ While Epstein-Barr virus is not a common pathogen causing acute acalculous cholecystitis, it is described.

The infectious theory is more consistent with the literature than the cholestatic theory. According to a systematic review by Kottanattu in 2016, only one of the 37 patients (3%) with Epstein-Barr virus-associated acute acalculous cholecystitis had cholestatic biochemistry. This makes the proposed cholestasis mechanism at least epidemiologically less likely. Further, parallels can be drawn to other disease states: the systemic illness mechanism is in keeping with the proposed pathophysiology of Epstein-Barr virus causing acute pancreatitis, which is also rare but well documented.¹¹

Box 1. Relevant bloodwork

White blood cell count	12.6 × 10 ⁹ /L* (normal = 4–10 × 10 ⁹ /L)	Alkaline phosphatase	258 U/L* (normal = 38–126 U/L)
Platelets	136 × 10 ⁹ /L (normal = 130–400 × 10 ⁹ /L)	Total bilirubin	35 µmol/L* (normal ≤ 26 µmol/L)
AST	461 U/L* (normal = 18–40 U/L)	Lipase	36 U/L (normal ≤ 160 U/L)
ALT	671 U/L* (normal = 17–63 U/L)	Monospot	Positive* (normal = negative)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
*Abnormal values

Acute acalculous cholecystitis secondary to infectious mononucleosis is increasingly being described and is important for the emergency physician to consider.¹²⁻¹⁴ Given the right clinical context (i.e., the infectious mononucleosis triad but with abdominal pain and/or cholestasis), more liberal use of ultrasound should be considered. Furthermore, for patients with right upper quadrant abdominal tenderness in the absence of a cholestatic picture, clinicians should not be falsely reassured that acute acalculous cholecystitis is ruled out. In those cases, an ultrasound should still be considered because cholestasis is not a prerequisite for this condition.

In 2016, Agergaard and Larsen conducted a literature review identifying 26 cases involving infectious mononucleosis-associated acute acalculous cholecystitis.¹⁵ Interestingly, there was a strong sex preponderance, with 25 of the 26 cases being females presenting with abdominal pain. The case presented herein is consistent with that pattern. Similar to the findings of this review, our patient's management and outcome were typical; she did not require antibiotics, corticosteroids, or surgery, and she made a full recovery. It seems the acute acalculous cholecystitis that patients develop from Epstein-Barr virus is far more benign than if it arises from other sources and requires less intervention if any.¹¹

CONCLUSION

Patients diagnosed with infectious mononucleosis should be screened for sequelae of the infection, beginning with a detailed history and physical. For those presenting atypically or with a protracted course, bloodwork and possibly abdominal imaging should be considered. In these patients, the possibility of acute acalculous cholecystitis should be entertained because of its ease of diagnosis and potentially aggressive management requirements. Currently, it is likely underdiagnosed in the ED.

LEARNING POINTS

- 1) Adolescents and young adults with fever, lymphadenopathy, and pharyngitis can be clinically diagnosed with infectious mononucleosis, which is easily confirmed using a monospot test.
- 2) Patients with atypical presentations of infectious mononucleosis should be thoroughly evaluated for several rare complications including acute acalculous cholecystitis especially young females with abdominal pain.
- 3) Infectious mononucleosis-associated acute acalculous cholecystitis often requires supportive management, though in select cases, antibiotics and surgery may be indicated.
- 4) Emergency physicians should be aware of this entity. It is likely underdiagnosed. Despite often not requiring active management, these cases should be identified promptly to monitor for severe complications such as gallbladder perforation and sepsis.

REFERENCES

1. Nye FJ. Social class and infectious mononucleosis. *J Hyg (Lond)* 1973;71(1):145-9.
2. Rea TD, Russo JE, Katon W, Ashley RL, Buchwald DS. Prospective study of the natural history of infectious mononucleosis caused by Epstein-Barr virus. *J Am Board Fam Pract* 2001;14(4):234.
3. DuPriest RW Jr, Khaneja SC, Cowley RA. Acute cholecystitis complicating trauma. *Ann Surg* 1979;189(1):84-9.
4. Linderholm M, Boman J, Juto P, Linde A. Comparative evaluation of nine kits for rapid diagnosis of infectious mononucleosis and Epstein-Barr virus-specific serology. *J Clin Microbiol* 1994;32(1):259.
5. Jenson HB. Acute complications of Epstein-Barr virus infectious mononucleosis. *Curr Opin Pediatr* 2000;12:263-8.
6. Evans AS. Infectious mononucleosis and related syndromes. *Am J Med Sci* 1978;276(3):325.
7. Shaukat A, Tsai HT, Rutherford R, Anania FA. Epstein-Barr virus induced hepatitis: an important cause of cholestasis. *Hepatol Res* 2005;33:24-6.
8. Barie PS, Eachempati SR. Acute acalculous cholecystitis. *Curr Gastroenterol Rep* 2003;5(4):302-9.
9. Lagona E, Sharifi F, Voutsioti A, et al. Epstein-Barr virus infectious mononucleosis associated with acute acalculous cholecystitis. *Infection* 2007;35(2):118-9.
10. Gora-Gebka M, Liberek A, Bako W, et al. Acute acalculous cholecystitis of viral etiology - a rare condition in children? *J Pediatr Surg* 2008;43(1):25-7.
11. Kottanattu L, Lava SA, Helbling R, et al. Pancreatitis and cholecystitis in primary acute symptomatic Epstein-Barr virus infection - Systematic review of the literature. *J Clin Virol* 2016;82:51-5.
12. Beltrame V, Andres A, Tona F, Sperti C. Epstein-Barr virus - associated acute acalculous cholecystitis in an adult. *Am J Case Rep* 2012;13:153-6.
13. Dylewski J. Acute acalculous cholecystitis caused by Epstein-Barr virus infection. *Clin Microbiol Newsl* 2012;34:7-8.
14. Iaria C, Arena L, Di Maio G, et al. Acute acalculous cholecystitis during the course of primary Epstein-Barr virus infection: a new case and a review of the literature. *Int J Infect Dis* 2008;12(4):391-5.
15. Agergaard J, Larsen CS. Acute acalculous cholecystitis in a patient with primary Epstein-Barr virus infection: A case report and literature review. *Int J Infect Dis* 2015;35:67-72.