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ACUTE CHOLECYSTITIS CAUSED BY GRANULOMATOSIS WITH POLYANGIITIS - A RARE CASE

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АКУТНИ ХОЛЕЦИСТИТИС УЗРОКОВАН ГРАНУЛОМАТОЗОМ СА ПОЛИАНГИИТИСОМ - ПРИКАЗ РЕТКОГ СЛУЧАЈА

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ABSTRACT

Granulomatosis with polyangiitis (GPA) most commonly affects the kidneys and lungs, while the involvement of other organs is rare. We present a case of vasculitic changes in the gallbladder as the initial manifestation of GPA. A 65-year-old woman was admitted with fever and generalized weakness. Physical examination revealed signs of dehydration, mild hypotension and tachycardia without abdominal tenderness or a positive Murphy's sign. Laboratory evaluation revealed normocytic anemia and elevated markers of inflammation. Urinalysis revealed proteinuria and hematuria, but cultures and imaging were unremarkable. Despite empirical intravenous antibiotic therapy, the symptoms persisted. A subsequent computed tomography (CT) scan revealed calculous cholecystitis, leading to laparoscopic cholecystectomy. Histopathology of the gallbladder demonstrated small-vessel vasculitis. Further work-up revealed positive proteinase 3-anti-neutrophil cytoplasmic antibodies (PR3-ANCA) and declining renal function, consistent with a diagnosis of GPA. The patient was treated with glucocorticoids and intravenous cyclophosphamide, resulting in clinical and laboratory improvement. This case highlights the importance of considering systemic vasculitis in patients with persistent fever and non-specific systemic symptoms, especially when conventional causes are excluded. Gallbladder vasculitis, though extremely rare, can be the initial presentation of GPA.

Key words: *anti-neutrophil cytoplasmic antibody-associated vasculitis; gallbladder; granulomatosis with polyangiitis.*

САЖЕТАК

Код грануломатозе с полиангитисом (GPA) најчешће су захваћени бубрези и плућа, док су други органи ређе захваћени. Приказаћемо васкулитисне промене на жучној кеси као иницијалну презентацију GPA. Жена старости 65 година примљена је у болницу с тегобама у виду температуре и генерализоване слабости. По пријему је физикалним прегледом уочено да је болесница дехидрирана, хипотензивна и тахикардна. Прегледом абдомена не палпирају се резистенције у абдомену, а Марфијев знак је негативан. У иницијалној лабораторији се уочава нормоцитна анемија и повишени маркери инфламације. У урину се уочава протеинурија и хематурија, а културе и радиолошки налази били су без особености. Упркос емпиријској антибиотској терапији перзистирају симптоми. Начињена је компјутерска томографија (CT) на којој се описује калкулозни холецистити те је начињена лапароскопска холецистектомија. Хистолошком анализом је описан васкулитис малих крвних судова жучне кесе. У даљим лабораторијским испитивањима уочавају се позитивна антинеутрофилна цитоплазматска антитела на протеиназу 3 (PR3-ANCA) и погоршање бубрежне функције, што је у складу с дијагнозом GPA. Започето је лечење кортикостероидима и циклофосфамидом које је довело до клиничког и лабораторијског побољшања. Овај приказ случаја наглашава важност разматрања васкулитиса код болесника са перзистирајућом температуром и неспецифичним системским симптомима, код којих су други уобичајени узрочници искључени. Васкулитис жучне кесе, иако екстремно ретко, може бити иницијална презентација GPA.

Кључне речи: *васкулитис повезан са антинеутрофилним цитоплазматским антителима; жучна кеса; грануломатоза са полиангитисом.*

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) represents a group of small-vessel vasculitides that includes granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA) (1-4). Among them, GPA is the most prevalent subtype, with 85–95% of cases demonstrating positivity for proteinase 3 (PR3)-ANCA antibodies (5).

GPA is characterized by necrotizing granulomatous inflammation and vasculitis primarily affecting small- to medium-sized vessels. It commonly involves the upper and lower respiratory tract and kidneys (1–3). Other organ

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systems may be involved but are less frequently affected. The clinical presentation of GPA is variable and can range from localized to multisystemic disease, often complicating the diagnostic process (6).

The treatment typically consists of glucocorticoids in combination with immunosuppressive agents such as cyclophosphamide or rituximab (1). Gastrointestinal (GI) involvement in GPA is rare, occurring in approximately 5–10% of patients, and it is associated with a poorer prognosis (7, 8). Symptoms can range from mild abdominal discomfort to life-threatening hemorrhage or perforation (9), with abdominal pain being the most common GI manifestation (8).

Gallbladder involvement in systemic vasculitis is extremely uncommon. It may occur as part of a systemic process or as isolated single-organ vasculitis. Gallbladder vasculitis has been reported in 8–40% of patients with polyarteritis nodosa, but in less than 2% of those with other forms of systemic vasculitis (10–12). It is most often diagnosed incidentally following cholecystectomy for presumed acute cholecystitis. Prognostic tools such as the Five Factor Score (FFS) help stratify mortality risk in AAV. Poor prognostic indicators include age >65 years, GI involvement, elevated serum creatinine (>150 μmol/L), cardiomyopathy, and absence of upper respiratory tract symptoms (1).

In cases of isolated gallbladder vasculitis without systemic involvement, a surgery alone may be sufficient. However, if systemic vasculitis is identified, immunosuppressive therapy is required (11). This report presents a rare case of GPA initially manifesting as acute calculous cholecystitis, underscoring the importance of early recognition and treatment to improve patient outcomes.

CASE PRESENTATION

A 65-year-old woman was admitted to the Clinic for Infectious Diseases at the General Hospital Sombor due to persistent fever, generalized weakness, reduced appetite, and mild weight loss. On clinical examination, she appeared dehydrated, mildly hypotensive, and tachycardic. The abdomen was soft and non-tender, with preserved bowel sounds and a negative Murphy's sign.

Initial laboratory tests revealed normocytic anemia (hemoglobin 97 g/L) and elevated inflammatory markers (C-reactive protein 122 mg/L), with preserved renal function and normal liver enzymes and cholestasis parameters. Urinalysis showed proteinuria and hematuria. Blood and urine cultures were negative. Abdominal ultrasound and computed tomography (CT) revealed a folded gallbladder with multiple calcified stones in the fundus.

Empirical triple antibiotic therapy was initiated, but there was no clinical or laboratory improvement. Due to positive fecal occult blood testing, both gastroscopy and colonoscopy were performed. Colonoscopy revealed two polyps, which were removed; histopathological examination showed no significant pathological findings. Gynecologic evaluation and pelvic MRI were recommended, revealing a polypoid endometrial lesion. Fractional curettage and cervical biopsy were performed, with benign histology.

Despite ongoing antibiotic therapy, the patient continued to have fever and developed lower limb weakness, left leg pain, and difficulty bearing weight. Neurological consultation and workup — including electromyography, X-rays of the hip, knee, lumbosacral spine, and brain MRI — resulted in a diagnosis of chronic L5 radiculopathy. Elevated D-dimer prompted a vascular evaluation, and Doppler ultrasound of the lower extremities was normal.

Due to persistent symptoms and rising inflammatory markers (CRP 159 mg/L), the patient was transferred to the Department of Surgery. Repeat abdominal CT showed a folded gallbladder with multiple stones and a thickened, edematous wall. Laparoscopic cholecystectomy was performed. Histopathological examination of the resected gallbladder confirmed acute cholecystitis with features of small-vessel vasculitis.

Postoperatively, the patient developed severe Coombs-positive hemolytic anemia (hemoglobin 44 g/L). High-dose corticosteroid therapy (methylprednisolone 40 mg IV every 12 hours) was initiated, resulting in partial clinical and laboratory improvement (CRP 70 mg/L, ESR 125 mm/h).

The patient was subsequently transferred to the Clinic for Nephrology and Clinical Immunology at the University Clinical Center of Vojvodina. Further workup revealed PR3-ANCA positivity, worsening renal function (urea 32 mmol/L, creatinine 354 μmol/L), persistent proteinuria (24-hour proteinuria: 929 mg), and active urinary sediment with numerous erythrocytes. The diagnosis of granulomatosis with polyangiitis (GPA) was established.

Corticosteroid therapy was adjusted to 1 mg/kg/day (60 mg total daily), followed by a gradual taper. Intravenous cyclophosphamide was initiated (12.5 mg/kg every two weeks for five months, totaling 700 mg per dose). An attempted percutaneous renal biopsy yielded insufficient tissue.

After clinical and laboratory improvement (CRP 3.3 mg/L, ESR 44 mm/h, hemoglobin 94 g/L, creatinine 299 μmol/L), the patient was discharged with instructions for continued outpatient follow-up. At the end of cyclophosphamide therapy, the patient's condition had

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markedly improved, with normalization of inflammatory markers (CRP <1 mg/L, ESR 25 mm/h), hemoglobin increase (104 g/L), and further decline in serum creatinine (161 μmol/L).

DISCUSSION

GPA is a systemic disease with a high mortality rate. Clinical presentation in the form of acute cholecystitis is exceptionally rare. (13). According to our knowledge, there has been only one case of cholecystitis as a manifestation of GPA, along with a few cases of cholecystitis in eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis (14-19). GIT manifestations are most common in polyarteritis nodosa, occurring in 40-60% of cases, and in 5-11% of GPA cases (8, 12). GIT manifestations indicate a poor prognosis and are rarely isolated (8, 15). In one study, 4 out of 5 cases of cholecystitis in systemic vasculitis were due to gallbladder vasculitis, with 2 being related to cholelithiasis (8).

Diagnosis requires clinical evaluation, laboratory testing, radiological and histopathological diagnostics. In this patient, the clinical picture did not correspond to the typical presentation of acute cholecystitis. The classic clinical manifestation of acute cholecystitis includes moderate abdominal pain in the right upper quadrant of the abdomen, nausea, persistent fever and a positive Murphy's sign (20). In single-organ vasculitis, there are no systemic signs, and the most common clinical picture is repeated episodes of abdominal pain and calculous cholecystitis (11). Our patient had persistent fever unresponsive to antibiotic therapy, generalized weakness, decreased appetite, and later, difficulty moving and pain in the left leg. Acute calculous cholecystitis was suspected after radiological diagnostics, where a repeat CT scan described a folded gallbladder with multiple stones and a thickened hypertonic wall. The CT findings in this patient were indicative of a classic chelecystitis pattern, with vasculitis changes being masked by typical calculous features. The radiological findings are inconsistent with a prior study, which indicates that hallmark imaging features like gallbladder thickening are rarely observed in ANCA vasculitis as the inflammation tends to be focal. (14).

After laparoscopic cholecystectomy and the arrival of the histopathological report, vasculitis was first suspected. The differential diagnosis at that time included single-organ vasculitis or systemic vasculitis. Given that the patient had systemic symptoms, hematuria, proteinuria, and later elevated nitrogenous waste levels and positive PR3-ANCA, a diagnosis of GPA was made. Studies show that cholecystitis can be the first sign of systemic vasculitis, which may develop even years later, so in cases of single-organ vasculitis without systemic signs and with negative antibodies, further monitoring for potential development of systemic vasculitis signs is necessary (12).

The diagnosis of ANCA vasculitis is often delayed because symptoms are attributed to malignancies, infections and osteoarthritis, as was the case with this patient, where infection was first suspected, followed by malignancy (21, 22). The other described case of acute cholecystitis in GPA presented with sepsis-like symptoms in an older patient. In that patient, the clinical picture corresponded to sepsis, with tachycardia and hypotension, and without a positive Murphy's sign upon admission. Radiological findings were normal, and cholecystitis was only suspected after persistently elevated inflammatory markers. That patient was treated with corticosteroids with later clinical improvement (14). Due to the suspicion of sepsis, malignancy, and osteoarthritis, our patient had a late diagnosis.

ANCA vasculitis is typically treated with glucocorticoids in combination with immunosuppressive agents such as cyclophosphamide or rituximab (1). In this case the patient was treated with glucocorticoids and intravenous cyclophosphamide, and the patient received six pulse doses of cyclophosphamide resulting in clinical and laboratory improvement. Early diagnosis and treatment of GPA are key to improving long-term patient prognosis and preventing complications (23). Starting therapy should begin as soon as there is a strong suspicion of the disease, as was the case with this patient. Additionally, a kidney biopsy should not delay the start of treatment (21).

The question arises as to whether earlier diagnosis in this case could have avoided surgical treatment. Research shows that in cholecystitis associated with systemic vasculitis medication alone may be sufficient, but only if the absence of gallstones is proven, which was not the case with our patient (8). In this case, calculous cholecystitis was proven to be a manifestation of vasculitis, which is not consistent with previous studies where acalculous cholecystitis is more commonly associated with systemic vasculitis (11, 24, 25). In eosinophilic granulomatosis with polyangiitis, where more cases of cholecystitis have been described compared to GPA, the information is still insufficient to determine whether cholecystectomy is necessary for these patients, and more studies are required (15, 19).

This case underscores the importance of considering granulomatosis with polyangiitis (GPA) in the differential diagnosis of persistent, unexplained fever and systemic symptoms, particularly when standard treatments fail and imaging findings are inconclusive. Although gallbladder involvement is an exceptionally rare manifestation of GPA, histopathological evaluation following cholecystectomy can be pivotal in establishing the diagnosis. Timely recognition and initiation of

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immunosuppressive therapy are essential to prevent irreversible organ damage and improve patient outcomes. Clinicians should remain vigilant for atypical presentations of systemic vasculitis, even in the presence of more common pathologies such as calculous cholecystitis.

ABBREVIATIONS

ANCA - antineutrophil cytoplasmic antibodies;

CT - computed tomography;

GIT - gastrointestinal tract;

GPA - granulomatosis with polyangiitis;

PR3-ANCA - antineutrophil cytoplasmic antibodies to proteinase 3.

REFERENCES

1. Puéchal X. Granulomatosis with polyangiitis (Wegener's). Joint Bone Spine 2020; 87: 359-66.
2. Klapa S, Arnold S, Lamprecht P. Granulomatosis with polyangiitis and microscopic polyangiitis. Laryngorhinootol 2024; 103: 490-9.
3. Greco A, Marinelli C, Fusconi M, et al. Clinic manifestations in granulomatosis with polyangiitis. Int J Immunopathol Pharmacol 2016; 29: 151-9.
4. Ross C, Makhzoum JP, Pagnoux C. Updates in ANCA-associated vasculitis. Eur J Rheumatol 2022; 9: 153-66.
5. Banerjee P, Jain A, Kumar U, et al. Epidemiology and genetics of granulomatosis with polyangiitis. Rheumatol Int 2021; 41: 2069-89.
6. Anderson E, Gakhar N, Stull C, Caplan L. Gastrointestinal and hepatic disease in vasculitis. Rheum Dis Clin North Am 2018; 44: 1-14.
7. Bagai S, Sharma A, Gupta R, et al. Gastrointestinal involvement in granulomatosis with polyangiitis: case report and review. Indian J Nephrol 2019; 29: 415-8.
8. Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides. Medicine (Baltimore) 2005; 84: 115-28.
9. Pérez-Macías JP, Rodarte-Shade M, Garza-García CA, et al. Granulomatosis with polyangiitis with gastrointestinal involvement: a case report. Rev Gastroenterol Mex 2022; 87: 392-4.
10. Kitaguchi D, Kurata M, Shimomura O, et al. Gallbladder bleeding associated with microscopic polyangiitis: a case report. J Surg Case Rep 2017; 2017: rjx159.
11. Hernández-Rodríguez J, Tan CD, Rodríguez ER, Hoffman GS. Single-organ gallbladder vasculitis: characterization and distinction from systemic vasculitis. Medicine (Baltimore) 2014; 93: 405-13.
12. Juliano J, Wilson KD, Gertner E. Vasculitis of the gallbladder: case report and spectrum of disease. J Clin Rheumatol 2009; 15: 75-7.
13. Mohammad AJ, Jacobsson LT, Westman KW, et al. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg–Strauss syndrome and polyarteritis nodosa. Rheumatology (Oxford) 2009; 48: 1560-5.
14. Ohta R, Ikeda H, Kubota S, Sano C. Acute cholecystitis in an elderly patient with antineutrophil cytoplasmic antibody-associated vasculitis: a case report. Cureus 2022; 14: e21877.
15. Seth N, Tran PP. Cholecystitis: a rare presentation for diffuse eosinophilic granulomatosis with polyangiitis. ACG Case Rep J 2023; 10: e01023.
16. Ohnuki Y, Moriya Y, Yutani S, et al. Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) complicated by perforation of the small intestine and cholecystitis. Intern Med 2018; 57: 737-40.
17. Ito H, Mishima Y, Cho T, et al. Eosinophilic cholecystitis associated with eosinophilic granulomatosis with polyangiitis. Case Rep Gastroenterol 2020; 14: 668-74.
18. Ichinose K, Iwanaga N, Okada A, et al. A case of microscopic polyangiitis in an elderly patient presenting predominantly with cholecystitis successfully treated with mizoribine. Mod Rheumatol 2014; 24: 1011-4.
19. Ye L, Lu X, Xue J. Eosinophilic granulomatosis with polyangiitis complicated by cholecystitis: a case report and review of the literature. Clin Rheumatol 2016; 35: 259-63.
20. Gallaher JR, Charles A. Acute cholecystitis: a review. JAMA 2022; 327: 965-75.
21. Kitching AR, Anders HJ, Basu N, et al. ANCA-associated vasculitis. Nat Rev Dis Primers 2020; 6: 71.
22. Bielejewska A, Bociek A, Bociek M, Jaroszyński A. A unique case of ovarian manifestation of systemic vasculitis that mimics ovarian cancer. Sarcoidosis Vasc Diffuse Lung Dis 2020; 37: 179-83.
23. Yaseen K, Mandell BF. ANCA-associated vasculitis (AAV): a review for internists. Postgrad Med 2023; 135: 3-13.
24. Francescutti V, Ellis AK, Bourgeois JM, Ward C. Acute acalculous cholecystitis: an unusual presenting feature of Churg–Strauss vasculitis. Can J Surg 2008; 51: E129-30.
25. Gorgun E, Ozmen V. Acalculous gangrenous cholecystitis in a young adult: a gastrointestinal manifestation of polyarteritis nodosa. Surg Laparosc Endosc Percutan Tech 2002; 12: 359-61.