



# Successful Non-surgical Treatment of an Acute Calculous Cholecystitis in a Myeloma Patient with Covid-19: Case Report

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## Abstract

COVID-19 has a wide spectrum of clinical phenotypes. While fever and cough are the most common symptoms, abdominal pain is rarely reported. We report the first case of COVID-19 pneumonia in an elderly patient with multiple myeloma (MM), complicated by acute calculous cholecystitis (ACC). A 73-year-old gentleman with underlying IgG kappa MM, presented with fever, cough and dyspnoea. His nasopharyngeal swab was positive for SARS-CoV-2. Piperacillin/tazobactam and oral hydroxychloroquine were started in addition to granulocyte colony-stimulating factor (GCSF) support due to neutropenia. Patient deteriorated on day 5, requiring high flow oxygen support. Dexamethasone, low molecular weight heparin prophylaxis and one dose of intravenous immunoglobulin were given. Despite negative swab on day 10, he developed ACC on day 17. With antibiotics and supportive care, patient showed full recovery without any surgical intervention. It remains elusive whether the gallbladder might be vulnerable to COVID-19, necessitating further validation via prospective studies.

**Keywords** COVID-19 · Myeloma · Cholecystitis

## Background

Since its first emergence in late 2019, the novel coronavirus pneumonia, named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO), has been a global pandemic, leading to a high death toll [1]. As COVID-19 has a wide spectrum of clinical phenotypes, it is likely that many patients are undiagnosed. This spectrum ranges from

severe life-threatening respiratory failure requiring ventilator support to a completely asymptomatic disease course, with diversity in clinical manifestations in between. While fever and cough are the most common symptoms, abdominal pain is rarely reported [2]. We report the first case of COVID-19 pneumonia in an elderly patient with multiple myeloma (MM), complicated by acute calculous cholecystitis (ACC).

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## Case Report

A 73-year-old gentleman, an ex-smoker, was diagnosed with symptomatic MM (immunoglobulin Gκ) in January 2019. At that time, a bone marrow aspirate showed 15% clonal plasma cells and multiple osteolytic bone lesions with compression fractures in thoracolumbar regions on radiography. Initial laboratory investigations showed normocytic, normochromic anaemia (haemoglobin 10.1 g/dL) with Rouleaux formation on full blood picture, inverse albumin-to-globulin ratio (globulin 109 g/L), corrected serum calcium of 2.3 mmol/L and lactate dehydrogenase (LDH) of 452 U/L. Serum protein electrophoresis (SPEP) reported IgG Kappa paraproteinemia of 51.2 g/L in the gamma region with immune paresis. The patient received few cycles of induction chemotherapy consisting of thalidomide and dexamethasone; however, it

was complicated by several bouts of pneumonia infection requiring hospitalization. Subsequently, thalidomide was replaced by melphalan from January 2020.

Few months later, the patient complained of fever with chills and rigors, productive cough and dyspnoea for several days. Patient denied any gastrointestinal symptoms with no abdominal pain. Upon assessment, patient appeared tachypnoeic with oxygen saturation of 93% under room air. Lung auscultation noted bilateral coarse crepitation. Chest X-ray showed bilateral lower zone patchy ground glass opacities. Due to resource-restricted setting in a non-COVID hospital, computed tomography (CT) of the thorax was not performed during admission. In this COVID-pandemic era, patient was admitted to isolation ward as per local protocol, and standard COVID-19 workup was performed. Serial laboratory investigation results are shown in Table 1. The first nasopharyngeal swab was negative, but due to high clinical suspicion, a second swab was repeated which turned out to be positive for SARS-CoV-2, detected using qualitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR) assay. No COVID-19 close contacts or travelling history were identified.

As patient's full blood count (Table 1) showed neutropenia and lymphopenia, intravenous (IV) piperacillin/tazobactam and oral hydroxychloroquine were started in addition to granulocyte colony-stimulating factor (G-CSF) support. Patient deteriorated on day 5 of hospitalization (second week since symptoms onset) with respiratory distress and desaturation, requiring high

flow oxygen support (15 L/min). In view of systemic inflammatory response possibly triggered by cytokine, dexamethasone (4 mg) twice daily and low molecular weight heparin (LMWH) prophylaxis were initiated. One dose of intravenous immunoglobulin (IVIg; 0.4 mg/kg) was also given. Patient showed remarkable improvement with oxygen titrating down to nasal prong 2 L/min and cell count recovering.

Patient's swab was negative for SARS-CoV-2 on day 10 of admission. He developed constant pain (pain score 8/10) in the right upper quadrant of the abdomen with positive Murphy's sign and sluggish bowel sound, not resolved with proton pump inhibitor and analgesic on day 17 of hospitalization. ACC was subsequently confirmed by CT of the abdomen which showed markedly distended gallbladder with calculi within, gallbladder wall thickening, peri-cholecystic fat density with no biliary dilatation. IV piperacillin/tazobactam was restarted. All culture and sensitivity (C&S) samples failed to detect any bacteria, mycobacterium or fungal species. Patient showed full recovery without the need of surgical intervention. No recurrence of cholecystitis was noted after 6 months of follow-up.

## Discussion

To the extent of our knowledge, only one case of acute cholecystitis possibly related to COVID-19 was reported [3]. The literature analysing the relationship between gallbladder disease and COVID-19 is scarce. We report the first case of

**Table 1** Patient's laboratory results during hospitalization and post-discharge

Laboratory parameter	Reference range	On admission (Day 1)	Day 5 (desaturation)	Day 10 (swab negative)	Day 17 (ACC)	2-month post-discharge
Hb, g/L	13.0–17.0	8.7	7.9	9.1	9.6	11
WBC, $\times 10^3/\mu\text{L}$	4.0–10.0	0.41	1.21	2.72	5.77	6.6
ALC, $\times 10^3/\mu\text{L}$	1.0–3.0	0.07	0.06	0.24	0.58	2.8
ANC, $\times 10^3/\mu\text{L}$	2.0–7.0	0.27	0.93	1.77	3.96	2.7
Platelet, $\times 10^3/\mu\text{L}$	150–410	34	38	54	146	152
Creat, $\mu\text{mol/L}$	60–120	85	66	89	71	60
AST, U/L	1–37	16	17	47	15	15
ALT, U/L	1–41	4	4	10	24	<4
Albumin, g/L	35–52	32	30	30	32	37
Globulin, g/L	17–35	42	40	38	38	42
D-dimer, $\mu\text{g/mL}$	<0.2	0.85	0.68	0.50	0.77	<0.2
CRP, mg/L	<47.6	705.3	923.4	376.1	166.6	N/A
CK, U/L	39–308	30	35	27	32	N/A
LDH, U/L	125–220	255	308	343	283	318
Calcium, mmol/L	2.2–2.7	2.16	N/A	N/A	2.21	2.18
COVID-19 PCR	Negative	Positive	Positive	Negative	Negative	N/A

ACC acute calculous cholecystitis, Hb haemoglobin, WBC white blood cell, ALC absolute lymphocyte count, ANC absolute neutrophil count, Creat creatinine, AST aspartate aminotransferase, ALT alanine aminotransferase, CRP C-reactive protein, CK creatinine kinase, LDH lactate dehydrogenase, N/A not available, PCR polymerase chain reaction

COVID-19 pneumonia in an MM patient who suffers from ACC after 17 days of hospitalization, highlighting our speculation about this manifestation to be a possible complication of COVID-19. However, the precise mechanism remains elusive, pending further studies that could support this hypothesis. COVID-19 is no longer a virus that only involves respiratory system, but it should be considered as a multi-organ disease [4].

COVID-19 has become common among geriatric population, particularly in those who are immunocompromised like cancer patients [5]. At present, there is only sparse data on MM patients affected with COVID-19 especially in geriatric population [6]. Patients with MM are commonly associated with the acquisition of secondary immunodeficiency, which is attributed, in addition to the disease, to adverse effects of myeloma treatment and repeated infections [7, 8]. Patients with MM are at high risk for mortality from COVID-19 infection, which further complicates the overall management. We postulate that our patient's adaptive immune system is suppressed as commonly found in MM patients, which then leads to low levels of immunoglobulin production, further increasing susceptibility to COVID-19 infection and acute cholecystitis. This might explain the fact that our patient responded well to IVIG treatment with remarkable clinical improvement. The beneficial effect of IVIG therapy in our patient is in accordance with several studies which reported a significant decrease in the occurrence of major and clinically documented infections using an IVIG dosage of 0.25 to 0.4 g/kg body weight [9, 10].

Studies have shown that patients with COVID-19 infection are prone to develop thrombosis, possibly due to the systemic inflammatory response triggered by pro-inflammatory cytokines [11]. Several studies have reported almost 50% rate of thrombotic events among the hospitalized patients with COVID-19 pneumonia [12, 13]. The fact that no thrombosis was observed in our patient treated with prophylactic dose of enoxaparin during hospitalization justifies the rationale to consider prophylactic anticoagulation in this subset of patient population which is in accordance with a published practical review [14].

Hydroxychloroquine was administered in our patient as it was thought to be beneficial in reducing mortality among COVID-19 infected patients in the early pandemic era. Our patient was diagnosed and treated as COVID-19 infection in May 2020, when hydroxychloroquine was still a therapeutic option. Recent literature has shown that hydroxychloroquine produces little or no reduction in the mortality of hospitalized COVID-19 patients. Furthermore, it causes several adverse events [15].

D-dimer greater than 0.5  $\mu\text{g/mL}$  has been shown to be associated with severe infection in patients with COVID-19 [16]. The imbalance of coagulation and

fibrinolysis in the alveoli could result from inflammatory cytokines, leading to activation of the fibrinolysis system, which then increase the D-dimer level [17]. Our patient's D-dimer level (Table 1) decreased from 0.85  $\mu\text{g/mL}$  on admission to less than 0.2  $\mu\text{g/mL}$  8 weeks post-recovery, highlighting the importance of monitoring D-dimer levels throughout the disease course.

ACC occurs in 10 to 20% of untreated patients with gallstone [18]. The bile is relatively sterile in healthy individuals, but gallstone disease might result in bacterial colonization in 20 to 70% of patients [19, 20]. Empiric treatment with piperacillin/tazobactam or a cephalosporin  $\pm$  metronidazole is recommended for moderate and severe acute cholecystitis irrespective of whether there is growth by culture [21]. Despite the fact that surgical intervention remains the treatment of choice for ACC, it has high morbidity and mortality in elderly population [22]. We consider our patient to have a high risk of perioperative complications as he is elderly with immune dysregulation due to underlying myeloma disease and he has concomitant COVID-19 pneumonia and ACC. It is at our discretion that antimicrobial therapy might be the treatment of choice in this challenging scenario.

## Conclusion

Our case highlighted the challenge posed in managing a myeloma patient with COVID-19 infection complicated by ACC. It remains elusive whether the gallbladder might be vulnerable to COVID-19, necessitating further validation via prospective studies.

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**Author Contribution** ASOT was responsible for the study design, data collection and manuscript writing. TSL, LPC and HHC participated in data collection and contributed to case illustration and discussion. LPC and HHC were involved in the manuscript editing and language proof-reading. All authors read and approved the final manuscript.

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## Declarations

**Ethical Approval** This article does contain studies with human participant and was registered via National Medical Research Register Malaysia with a Research ID of NMRR- 20-2194-56866.

**Informed Consent** Informed consent was obtained from the patient.

**Conflict of Interest** The authors declare that they have no conflict of interest.

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