Atypical Hemolytic Uremic Syndrome After Traumatic Rectal Injury: A Case Report

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Case report

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Abstract

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare, progressive, life-threatening condition of thrombotic microangiopathy (TMA) that is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and renal impairment. The mechanisms of aHUS are still unknown. To our knowledge, there is currently no report establishing aHUS after traumatic injury. We herein present a case of aHUS after traumatic injury.

Case presentation: A 55-year-old man with a medical history of percutaneous coronary intervention due to ST elevation myocardial infarction visited the emergency room after a traumatic injury caused by a tree limb. Abdominal computed tomography revealed a rectal wall defect with significant air density in the perirectal space and preperitoneum, implying rectal perforation and, therefore, an emergency operation was performed. As there was an absence of intraperitoneal intestinal perforation, we performed diverting sigmoid loop colostomy. An additional intermittent simple repair was performed due to perianal and anal injuries. One day after the operation, his urine output abruptly decreased and serum creatinine level increased. In addition, his platelet level decreased, and a spiking fever occurred after 2 days. The patient was diagnosed with acute renal failure secondary to aHUS and was treated with fresh frozen plasma replacement. Continuous renal replacement therapy (CRRT) was also started for oliguria and uremic symptoms. The patient received CRRT for 3 days and intermittent hemodialysis thereafter. He received four weekly sessions of hemodialysis for 2 weeks. After hemodialysis and subsequent supportive treatment, his urine output and renal function continuously improved. Similarly, his hemolytic anemia and thrombocytopenia also gradually improved. His dialysis was terminated on day 22 of admission and he was discharged after recovery. His improved state has since been maintained.

Conclusions: This case suggests that a traumatic event can be a triggering factor for aHUS, and it should be considered in patients who have thrombocytopenia and acute renal failure with microangiopathic hemolytic anemia after trauma. Early diagnosis and appropriate management can be critical to achieve favorable outcomes in posttraumatic patients with aHUS.

Background

Atypical hemolytic uremic syndrome (aHUS) is a rare, progressive, life-threatening condition of thrombotic microangiopathy (TMA). This disease is characterized by an abrupt or gradual onset of thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and renal impairment[1–3] and can occur at any age. The mechanisms of aHUS are still unknown. However, this disease has poor prognosis and a higher morbidity and mortality than typical HUS. Thus, untreated aHUS remains a lifelong risk factor for impaired renal function, end-stage renal disease, extrarenal manifestations, and death.[4–7]

The etiology of TMA is important to explain the mechanism of aHUS. TMA is mainly caused by dysregulation of the alternative pathway of the complement system. Aggravating conditions such as pregnancy complications, malignant hypertension, autoimmune diseases, and organ or hematopoietic stem-cell transplantations are associated with the onset of TMA. To the best of our knowledge, there is currently no report establishing aHUS after traumatic injury. Here, we present a case in which the patient developed acute renal failure, thrombocytopenia, and TMA following a traumatic injury. Therefore, the findings suggest the possible occurrence of this disease after a traumatic injury and may contribute to the understanding, diagnosis, treatment, and prognosis of this rare disease. The patient provided and signed informed consent for the publication of this case.

Case Presentation

A 55-year-old man visited the emergency room after a traumatic injury caused by a tree limb. On arrival, he was alert, with a blood pressure of 100/60 mmHg, pulse rate 72/min, respiratory rate 18/min, and body temperature 37.0 °C. He had a

medical history of percutaneous coronary intervention due to ST elevation myocardial infarction 2 years ago. Physical examination revealed a long laceration from the perianal area into the rectal wall. Abdominal computed tomography revealed a rectal wall defect with significant air density in the perirectal space and preperitoneum, implying rectal perforation (Fig. 1). An emergency operation was performed. Diagnostic laparoscopic findings revealed hemorrhagic contusion in the preperitoneal and retroperitoneal space and a small amount of blood in the intraperitoneal space of the pelvic cavity. As there was an absence of intraperitoneal intestinal perforation, we performed diverting sigmoid loop colostomy. An additional intermittent simple repair was performed due to perianal and anal injuries. One day after the operation, his urine output abruptly decreased and serum creatinine level increased. In addition, his platelet level decreased and a spiking fever occurred after 2 days.

Laboratory findings on admission to the emergency room were as follows (Table 1): serum creatinine, 1.1 mg/dL; blood urea nitrogen, 22.1 mg/dL; total bilirubin, 0.42; lactate dehydrogenase, 440 U/L; complete blood count (CBC) showing levels of hemoglobin at 13.4 g/dL, white blood cells (WBC) at 14.8×10^3/μL, and platelets at 203×10^3/μL. Urinalysis revealed clear yellow-colored urine with negative protein, red blood cells, and WBC per high-power field. However, laboratory findings 2 days after the operation suddenly changed as follows (Table 1): serum creatinine, 2.6 mg/dL; blood urea nitrogen, 69.8 mg/dL (Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate [CKD-EPI eGFR] 25.474 mL/min/1.73 m^2); total bilirubin, 2.56 g/dL; direct bilirubin, 0.13 g/dL; lactate dehydrogenase, 1296 U/L; creatinine kinase, 549 U/L; myoglobin, 224.0 ng/mL; troponin I, 0.249 ng/mL; and haptoglobin < 25.80 mg/dL. Arterial blood gases revealed a pH of 7.364, pCO_2 of 32.2 mmHg, pO_2 of 74.5 mmHg, oxygen saturation of 94.6%, and bicarbonate level of 17.9 mmol/L. CBC showed levels of hemoglobin at 10.9 g/dL, WBC at 6.1×10^3/μL, platelets at 45×10^3/μL, and a high reticulocyte count at 1.36%. WBC differential count showed neutrophils at 93.7%, eosinophils at 1.9%, lymphocytes at 4.0%, and monocytes at 0.4%. Both prothrombin time and partial thromboplastin time were 1.01 (international normalized ratio) and 23.9, respectively. The levels of fibrin degradation products, fibrinogen, and D-dimer were 17.5 μg/mL, 469.2 mg/dL, and 3.15 mg/L FEU, respectively. A peripheral blood smear revealed three schistocytes per high-power field (Fig. 2). Serum complement assay showed the C3 level at 78.2 mg/dL and the C4 level at 21.6 mg/dL. Urinalysis revealed dark brown-colored urine with 3 + protein, > 100 red blood cells, and 10–19 WBC per high-power field, along with positive results for hemoglobin. Renal ultrasound showed normal echogenicity in both kidneys with right and left renal size of 9.59 × 4.68 cm and 9.13 × 4.94 cm, respectively.

Table 1
Laboratory findings of the patient during hospitalization

Parameter	Day 1 (admission)	Day 3 (operation)	Day 5 (2 days after operation)	Day 6 (beginning treatment for aHUS)	Day 8	Day 14	Day 22 (termination of dialysis)	Day 50
Hemoglobin (g/dL)	13.4	11.4	10.9	10.8	10.3	10.8	10.1	12.6
Platelet count ($\times 10^3/\mu L$)	203	124	45	56	85	155	318	259
White blood cell count ($\times 10^3/\mu L$)	14.8	4.4	6.1	3.7	3.9	7.1	14.2	7.8
Blood urea nitrogen (mg/dL)	22.1	23.2	69.8	30.3	46.2	47.6	25.2	16.0
Serum creatinine (mg/dL)	1.1	1.1	2.6	1.8	1.2	1.0	0.8	1.0
Total bilirubin	0.42	1.26	2.56	1.37	0.97	0.84	0.92	0.56
Lactate dehydrogenase (U/L)	440	913	1296	782	621	556	540	259
Haptoglobin (mg/dL)			< 25.8					
Complement C3 (mg/dL)			78.2					
Complement C4 (mg/dL)			21.6					
Urinalysis	negative		Protein 3+, RBC > 100, WBC 10–19		Protein -, WBC 0–1 RBC 0–1			
Schistocytes (smear)			3+	2+	negative			

*Hemoglobin (normal range, 12–18 g/dL), platelet count (normal range, $130–450 \times 10^3$ /μL), white blood cell count (normal range, $4.8–10.8 \times 10^3/\mu L$), blood urea nitrogen (normal range, 8–23 mg/dL), creatinine (normal range, 0.5–1.3 mg/dL), total bilirubin (normal range, 0.2–1.3 mg/dL), lactate dehydrogenase (normal range, 218–472 U/L), haptoglobin (normal range, 30–200 mg/dL), C3 (normal range, 90–180 mg/dL), C4 (normal range, 10–30 mg/dL)

*aHUS: atypical hemolytic uremic syndrome, WBC: white blood cells, RBC: red blood cells

The patient was diagnosed with acute renal failure secondary to aHUS and was treated with fresh frozen plasma replacement. Continuous renal replacement therapy (CRRT) was also started for oliguria and uremic symptoms such as nausea, vomiting, and dyspnea. The patient received CRRT for 3 days and intermittent hemodialysis thereafter. He received

four weekly sessions of hemodialysis for 2 weeks. Blood culture and stool culture for *E. coli* O157 were negative. After hemodialysis and subsequent supportive treatment, his urine output and renal function continuously improved. Similarly, his hemolytic anemia and thrombocytopenia also gradually improved. His dialysis was terminated on day 22 of admission. Finally, he was discharged with a creatinine level of 0.7 mg/dL and platelet count of $286 \times 10^3/\mu L$.

At 1-month follow-up after discharge, the patient was in good health with normal CBC and renal function and had undergone colostomy repair. His improved state has since been maintained.

Discussion

aHUS is an extremely rare disease with an incidence estimated to be about 0.23–0.42 cases per million. The pathophysiologic mechanism of this disease is still unclear. However, it is already known that aHUS is developed by induced activation of the uncontrolled alternative complement pathway. In addition, the genetic basis of aHUS has been elucidated. About 40–60% of patients with aHUS were found to have genetic or acquired dysregulation of the alternative complement pathway.[8,9] Although the distinction between cause and trigger is not fully evident, one of the acquired predisposing factors for aHUS is a coexisting disease,[10] which can include autoimmune diseases such as systemic lupus erythematosus, systemic sclerosis, transplantation, cancer, infection, pregnancy, or certain cytotoxic drugs.[11] In the steady state, regulation of the complement pathway has significant functional redundancy but is well tolerated. However, intercurrent infection of some other trigger factors activates the complement pathway through an alternative pathway; particularly, deficiency of a complement regulator can be crucial.[12] Here, to the best of our knowledge, we report the first case of aHUS occurring in a trauma patient, thereby identifying the pathogenesis of aHUS.

Some hypotheses support this result. First, trauma-induced complement-mediated lysis might be one of the predisposing factors of aHUS. Complement-mediated lysis, either as a primary or secondary cause, is one of the main mechanisms underlying hemolysis with schistocytes and fragmented red cell in the peripheral blood in aHUS.[3,13] In a previous study, widespread complement activation after trauma culminated in the dysregulation of complement and excessive complement activation products.[14] Thus, it is possible to hypothesize that the activated complement system after trauma injury may lead to the occurrence of aHUS in this case. Further studies will be needed to identify the causal relationship between complement-mediated lysis and trauma. Second, aHUS may be triggered by a hidden infection. There were several reports about aHUS being triggered by infections, such as cytomegalovirus, influenza virus, parvovirus B19, upper respiratory tract infection, and gastrointestinal infections.[8,15,16] However, in this case, we could not detect any pathogen in the culture exam. Because this patient had mid-rectum laceration with perforation and we already prescribed empirical antibiotics, it may be that coexistence of gastrointestinal infection was not revealed during examination.

aHUS is characterized by clinical manifestations, including MAHA in the presence of fragmented erythrocytes in a peripheral blood smear, thrombocytopenia, and acute kidney injury. In clinical practice, patients with simultaneous acute renal failure and thrombocytopenia are often diagnosed with sepsis. In this case, we suspected this patient of having sepsis and prescribed intravenous antibiotics. However, the response to antibiotics was not sufficient, and we observed aggravated laboratory findings and clinical manifestations. Regardless of maintaining the same antibiotics, the patient improved through the management of aHUS. Thus, it is important to pay attention to these patients as to whether or not they have hemolytic fragmented erythrocytes in the peripheral blood smear.

aHUS is a fatal disease that is associated with approximately 15% mortality in the acute phase and up to 50% mortality in patients with progressive end-stage renal disease. This is especially true for untreated aHUS, which has a greater risk of increasing morbidity and mortality. The standard treatment includes plasma exchange, hemodialysis, and eculizumab. A recent systematic review about aHUS found that there was no significant difference in outcomes between the eculizumab group and the non-eculizumab group.[17] Even though lifelong eculizumab treatment is recommended in some patients with

aHUS, we did not prescribe eculizumab and the patient's condition improved through plasma replacement and hemodialysis with supportive care.

There are several limitations to this report. We could not examine genetic mutations, renal biopsy, or ADAMTS 13 activity in this patient. Since he did not have neurologic symptoms and the clinical manifestations of aHUS progressed rapidly, the patient's clinical manifestations were managed first.

Conclusions

A traumatic event may be considered as a triggering factor for aHUS. We should consider aHUS in patients who have thrombocytopenia and acute renal failure with MAHA after trauma. This case may suggest that early diagnosis and appropriate management can be critical to achieve favorable outcomes in posttraumatic patients with aHUS.

Abbreviations

aHUS: atypical hemolytic uremic syndrome

CBC: complete blood count

CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

CRRT: continuous renal replacement therapy

eGFR: estimated glomerular filtration rate

FDP: fibrin degradation products

MAHA: microangiopathic hemolytic anemia

TMA: thrombotic microangiopathy

WBC: white blood cells

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

The patient provided and signed informed consent for the publication of this case.

Availability of data and materials:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests

Funding:

None.

Authors' contributions:

- Conceived of or designed study: Ji-Hyoun Kang

- Performed research: Yunchul Park

- Analyzed data: Ji-Hyoun Kang

- Contributed new methods or models: Yunchul Park

- Wrote the paper: Yunchul Park

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Not applicable.

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Figures

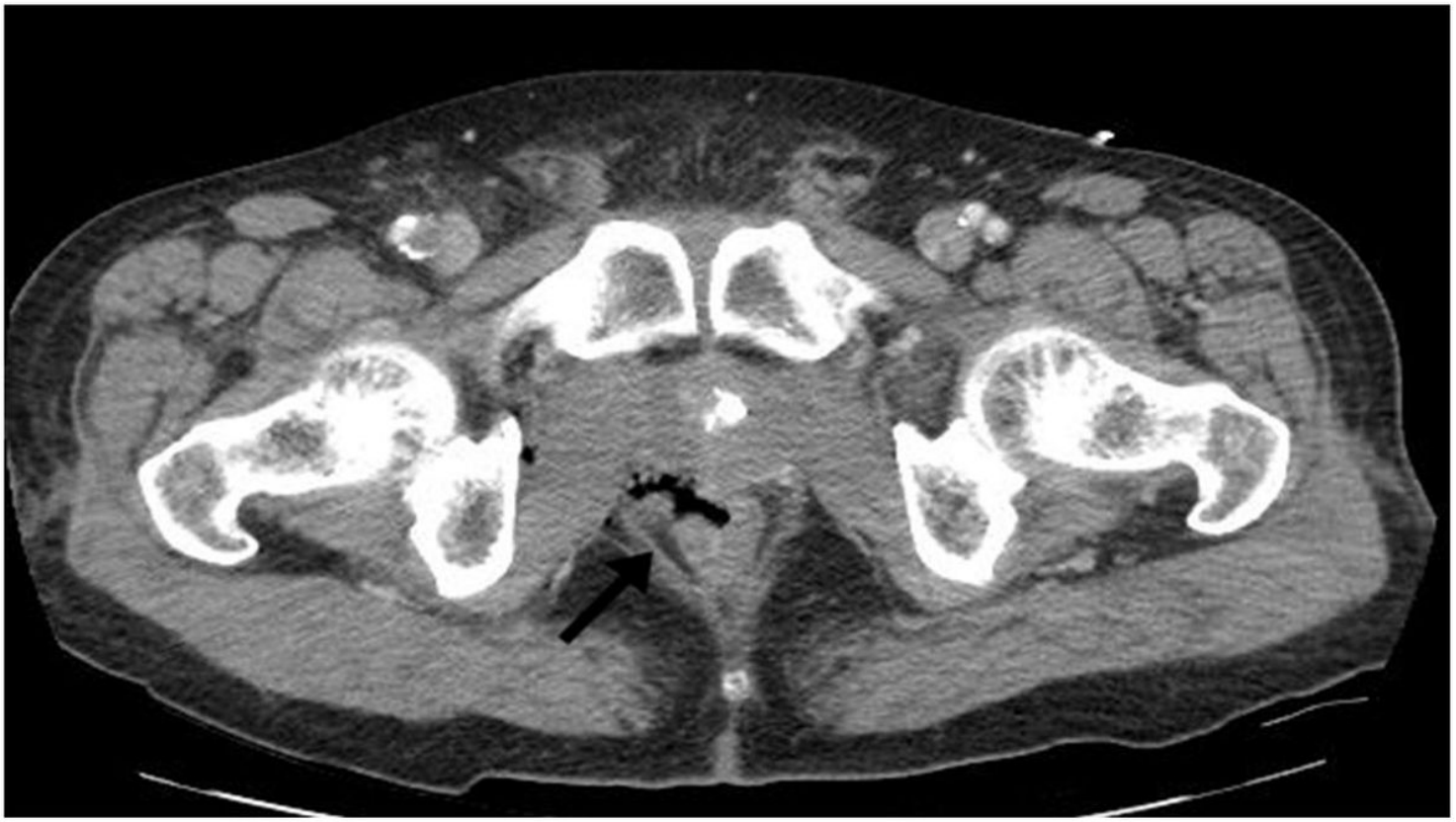
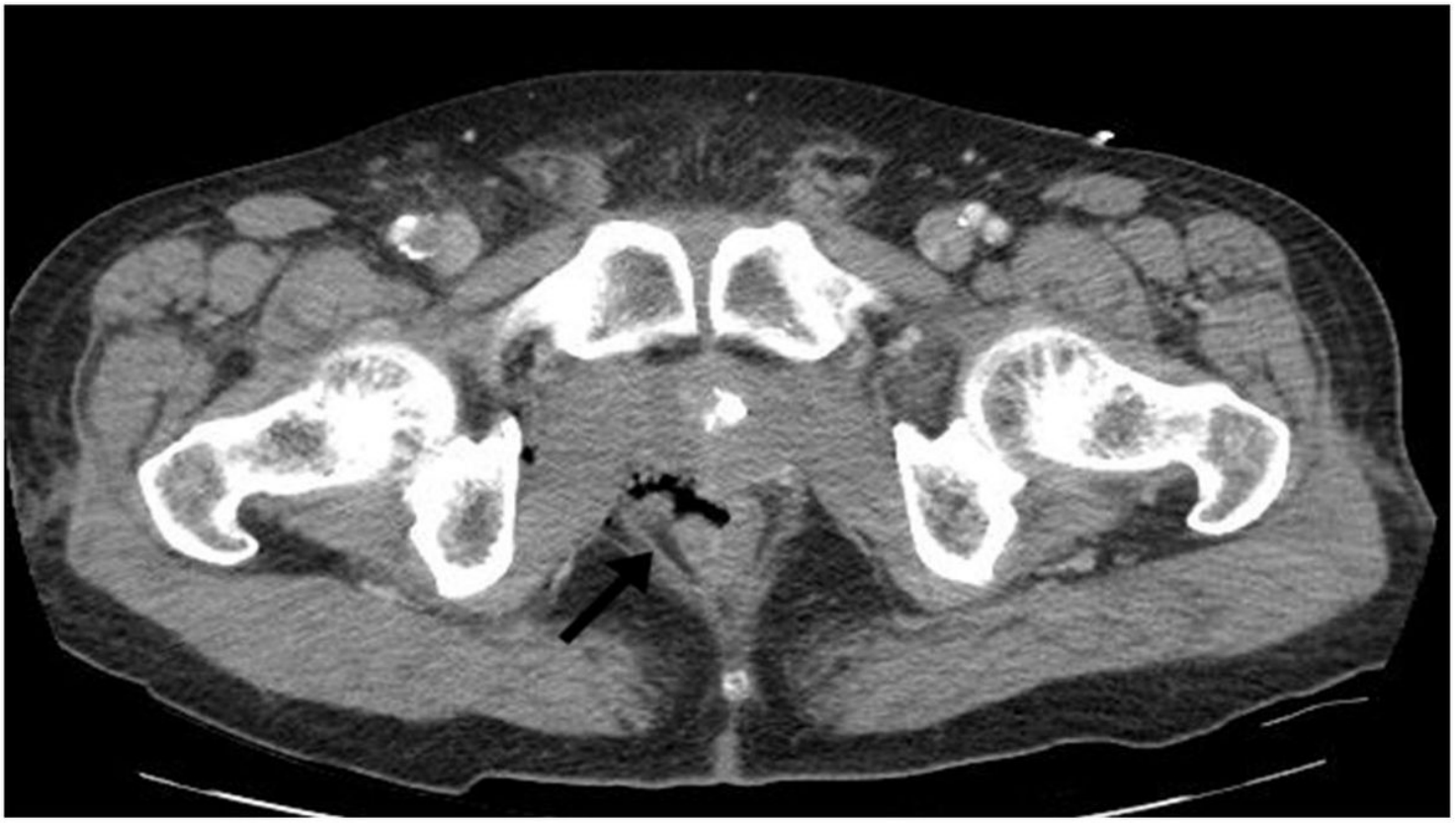


Figure 1

Abdominal computed tomography showing a rectal wall defect and air density in the perirectal space.



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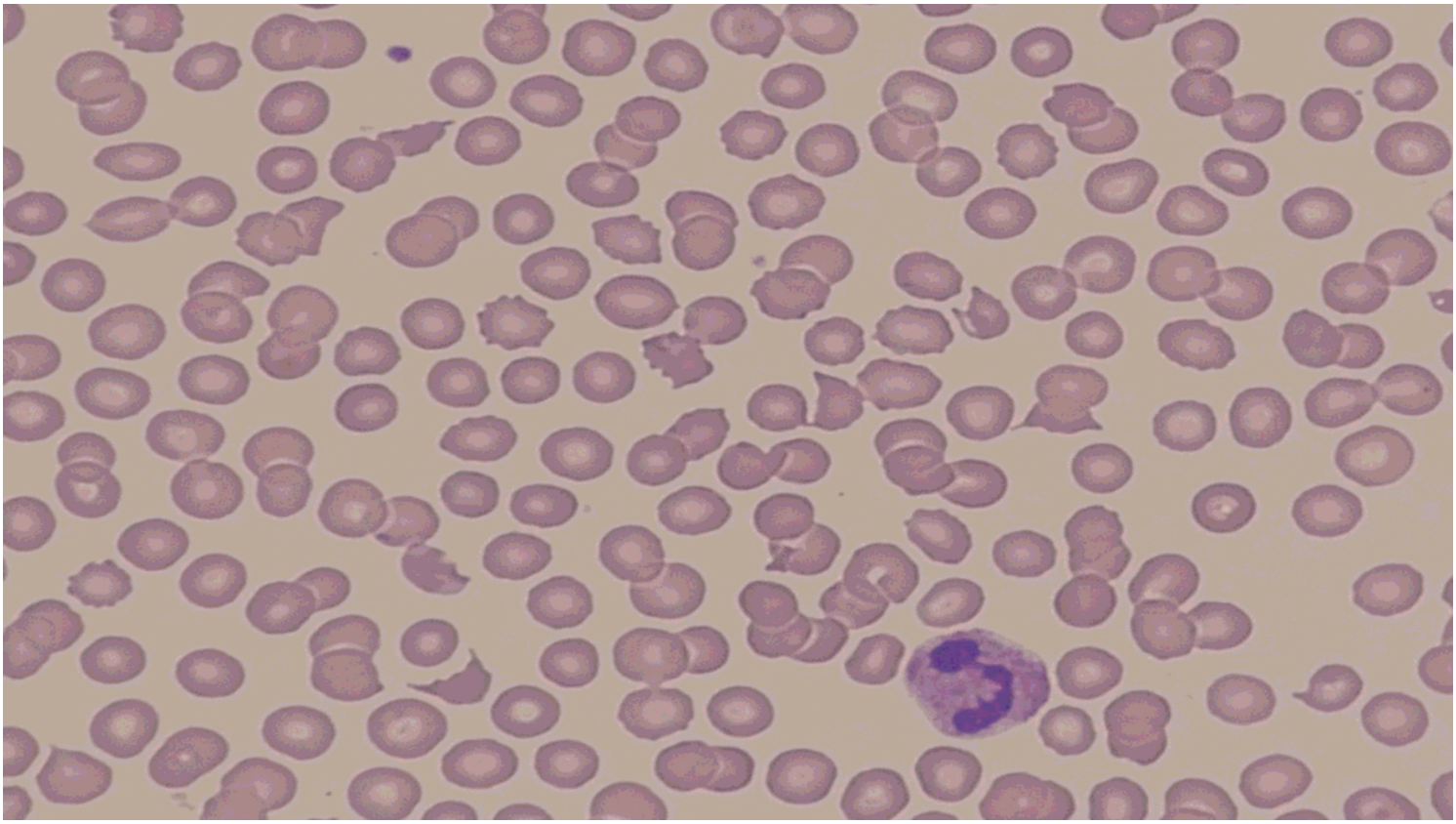
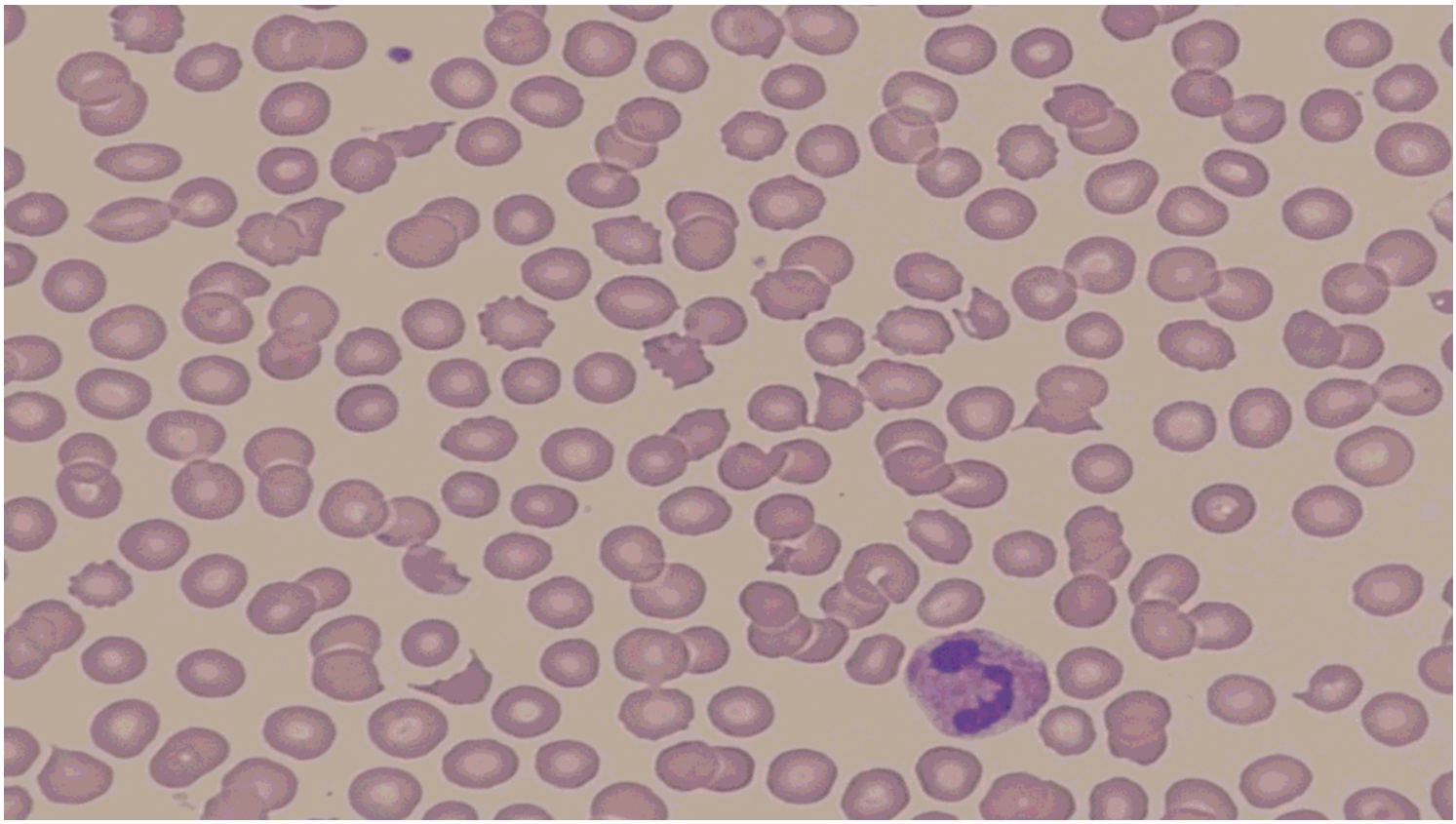


Figure 2

The patient’s peripheral blood smear showing more than three fragmented erythrocytes per high-power field.



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