Rouleaux formation in acute myeloid leukemia: A morphological clue to COVID-19 co-infection

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SUMMARY

Introduction: Acute myeloid leukaemia (AML) is a hematologic malignancy associated with significant immune dysfunction, predisposing patients to opportunistic infections, including SARS-CoV-2. While peripheral blood film evaluation mainly focuses on leukemic morphology, evolving red cell changes may provide important clues to concurrent inflammatory or infectious processes. Rouleaux formation typically reflects elevated plasma proteins or marked systemic inflammation and is rarely observed in AML patients. We describe a case of newly diagnosed AML with the unexpected emergence of rouleaux formation, later identified as a morphological marker of COVID-19 co-infection. Materials & Methods: Clinical, laboratory, and morphological data were collected from a 66-year-old man with newly diagnosed AML. Serial peripheral blood films, complete blood counts, inflammatory markers, and liver and renal biochemical parameters were reviewed. COVID-19 status was confirmed by RT-PCR. Morphological findings were correlated with clinical progression and laboratory indicators of systemic inflammation. Results: Initial blood films showed leukemic blasts without rouleaux formation. Two weeks later, the patient developed fever and tested positive for SARS-CoV-2. Repeat films demonstrated new moderate rouleaux formation (2+), coinciding with markedly elevated CRP, ESR, and ferritin levels. No alternative causes of rouleaux such as paraproteinemia or plasma cell dyscrasia were identified. The rouleaux formation appeared temporally related to the onset of COVID-19–associated inflammation. The patient's condition subsequently deteriorated with gastrointestinal bleeding and required transfer for tertiary care. Conclusion: The sudden appearance of rouleaux formation in AML should prompt evaluation for co-existing pathology, especially infectious or inflammatory triggers such as COVID-19. Peripheral blood film morphology remains a valuable, rapid, and accessible tool for detecting concurrent systemic processes in immunocompromised patients.

INTRODUCTION

AML is a clonal hematopoietic malignancy characterized by the accumulation of immature myeloid blasts in the bone marrow and peripheral blood.[1] Due to both disease-related and therapy-induced immunosuppression, patients with AML are particularly vulnerable to opportunistic infections, including viral infections such as SARS-CoV-2.[2] Although peripheral blood film examination is primarily used to evaluate leukemic morphology, it may also provide important clues to concurrent systemic infections or inflammatory states.

Rouleaux formation is a characteristic stacking of red blood cells resembling coins in a roll. It is commonly associated with elevated plasma protein levels in conditions such as multiple myeloma, chronic inflammatory diseases, autoimmune disorders, and hepatic dysfunction.[3] However, its appearance in AML patients, particularly in the context of acute viral infection, is unusual and may serve as a morphological indicator of co-infection or immune dysregulation. Although SARS-CoV-2 antigen and RT-PCR testing are widely available, immunocompromised patients such as those with acute myeloid leukemia may present with atypical or delayed clinical features of infection. In such settings, unexpected morphological changes on peripheral blood film may serve as an early adjunctive clue prompting further evaluation for intercurrent infection, rather than replacing standard virological testing.

CASE PRESENTATION

A 66-year-old man with a medical history of type 2 diabetes mellitus presented with incidental findings of anemia and thrombocytopenia during routine laboratory evaluation. Initial complete blood count revealed hemoglobin 9.0 g/dL (13.5-17.5 g/dL), white blood cell counts of 20.0×10^9/L (4.0-10.0×10^9/L), and platelet count 16×10^9/L (150-450×10^9/L). Initial peripheral blood film showed 29% blasts with no obvious rouleaux formation (Figure 1). Bone marrow aspiration and biopsy demonstrated 29% myeloid blasts. Flow cytometric immunophenotyping revealed blast cells expressing myeloperoxidase (MPO), CD34, CD117, CD13, HLA-DR, CD36, CD33, and CD123, consistent with a diagnosis of AML according to WHO criteria.[1]

Two weeks following the initial diagnosis and prior to chemotherapy initiation, the patient developed fever (38.5°C) and progressive lethargy. A nasopharyngeal swab tested positive for SARS-CoV-2 RNA by reverse transcription polymerase chain reaction (RT-PCR). Blood cultures and a respiratory viral panel (excluding SARS-CoV-2) were negative, and there were no clinical or laboratory features suggestive of bacterial sepsis or other viral infections at the time rouleaux formation emerged. Repeat peripheral blood film (Figure 2) demonstrated an increased blast count of 68% and the new appearance of moderate rouleaux formation

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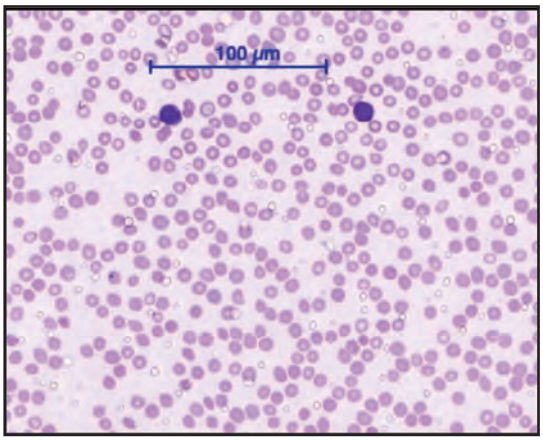

Fig. 1: Peripheral blood film (x40 magnification, Wright stain) at diagnosis, with two blast cells and no obvious rouleaux formation

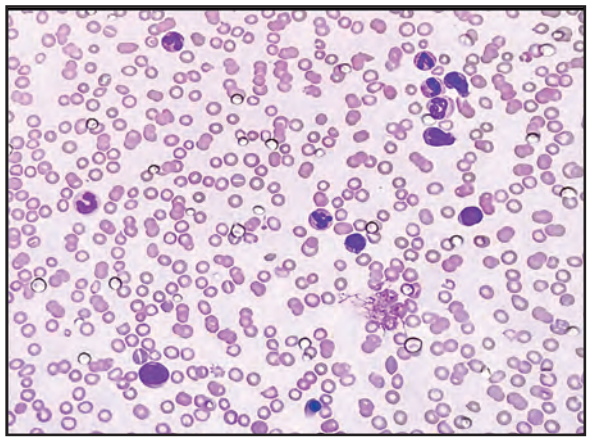

Fig. 2: Peripheral blood film (x40 magnification, Wright stain) after two weeks with prominent rouleaux formation (indicated by the blue arrows) and few blasts

(grade 2+), which was notably absent on initial blood films. Given that rouleaux formation is typically associated with elevated plasma protein concentrations or systemic inflammation, a comprehensive evaluation was undertaken. Inflammatory markers were significantly elevated, with C-reactive protein (CRP) at 62.5 mg/L (reference:<3.0 mg/L) and erythrocyte sedimentation rate (ESR) at 75 mm/hr (reference: <20 mm/hr), consistent with an acute phase response.

Liver function tests showed transient elevation of transaminases (ALT 89 U/L, AST 76 U/L; reference: <40 U/L) and mildly elevated bilirubin (total bilirubin 28 µmol/L; reference: <21 µmol/L). These parameters normalized over subsequent days, suggesting transient hepatic dysfunction secondary to systemic inflammatory response. Renal function, serum calcium, and urea levels remained within normal limits. Serum ferritin was markedly elevated at 569 µg/L (reference: 15-150 µg/L), reflecting both the underlying hematologic malignancy and acute inflammation.

Additional investigations excluded other causes of rouleaux formation. There was no clinical suspicion of monoclonal gammopathy, and serum protein electrophoresis was not performed given the clinical context. No recent administration of intravenous immunoglobulin or medications affecting plasma protein levels was documented. Additional microbiological investigations, including blood cultures and respiratory viral panel (excluding SARS-CoV-2), were negative.

The patient received supportive care for COVID-19 while chemotherapy was deferred pending clinical stabilization. Unfortunately, the patient's condition deteriorated rapidly, with development of hematemesis, abdominal distension, and rectal bleeding. Upper gastrointestinal endoscopy revealed portal hypertensive gastropathy with esophageal varices. The patient was transferred to a tertiary care facility for further management; however, follow-up data was not available due to transfer of care.

DISCUSSION

Rouleaux formation results from decreased erythrocyte surface charge (zeta potential), typically triggered by elevated fibrinogen or immunoglobulins that bridge adjacent red blood cells.[3] In our patient, rouleaux was absent on initial examination but appeared prominently during acute SARS-CoV-2 infection, suggesting an acquired inflammatory process.

COVID-19 is associated with intense systemic inflammation, characterized by marked increases in fibrinogen and other acute-phase proteins, endothelial activation, and cytokine release-conditions that create a biochemical environment conducive to rouleaux formation.[4,5] Alterations in red cell morphology, deformability, and aggregation have been well-documented in COVID-19 patients, particularly those with elevated inflammatory markers or severe disease.[4] In this case, the emergence of moderate rouleaux formation coincided temporally with confirmed SARS-CoV-2 infection and markedly elevated CRP, ESR, and ferritin levels, supporting an inflammatory etiology.

While rouleaux formation has been reported in rare AML-associated contexts such as reactive plasmacytosis, concurrent plasma cell disorders, or marked paraproteinemia, these conditions were not identified in our patient. Importantly, rouleaux was not observed on the initial peripheral blood film at diagnosis and only appeared following the onset of COVID-19 infection. This temporal relationship, together with the exclusion of alternative causes including paraproteinemia, immune-mediated hemolysis, and other documented infections, supports the interpretation that rouleaux formation in this case was more likely related to COVID-19–associated systemic inflammation rather than the underlying leukemia itself.

The management of AML patients with concurrent COVID-19 presents significant clinical challenges. Large registry studies, including data from the EPICOVIDEHA (European Hematology Association COVID-19 and Hematology) database, report high mortality rates among AML patients with concurrent COVID-19. Importantly, delaying chemotherapy during active COVID-19 infection, when

clinically feasible, has been associated with improved survival compared to continuing intensive treatment during active infection.[6] In this context, early recognition of intercurrent infection is critical for patient management.

Although rouleaux formation is a non-specific morphological finding, its sudden appearance in immunocompromised patients may serve as an adjunctive clue to underlying systemic inflammation. In the specific context of COVID-19–associated inflammation, elevated fibrinogen and acute-phase reactants may promote red blood cell aggregation; however, outside this setting, rouleaux formation and its semi-quantitative grading do not reliably correlate with fibrinogen levels or overall inflammatory severity. Therefore, interpretation of rouleaux formation should always be made in conjunction with clinical findings and laboratory markers rather than as a standalone indicator.

Reports describing rouleaux formation in AML patients remain scarce and are largely confined to settings of reactive plasmacytosis, plasma cell dyscrasia, or concurrent inflammatory or autoimmune conditions. Sharma et al. described a case of AML with marked reactive plasmacytosis and prominent rouleaux formation, attributed to elevated serum globulins rather than clonal plasma cell disease.[7] Other reports involving AML occurring alongside plasma cell disorders or therapy-related leukemias have similarly emphasized the importance of distinguishing reactive causes of rouleaux formation from primary hematologic pathology.[8,9] These limited reports reinforce the concept that rouleaux formation in AML typically reflects an accompanying systemic or inflammatory process.

This report is limited by its nature as a single case study, and a causal relationship between SARS-CoV-2 infection and rouleaux formation cannot be definitively established. Nevertheless, the clear temporal association, accompanying inflammatory markers, and exclusion of alternative etiologies support a probable link between COVID-19–associated inflammation and the observed morphological change. This case highlights the continued relevance of peripheral blood film examination as a rapid, accessible adjunct in the holistic assessment of immunocompromised patients.

CONCLUSION

The unexpected appearance of rouleaux formation in patients with AML should prompt evaluation for co-existing pathology, particularly infectious complications. In the context of COVID-19–associated systemic inflammation, this morphological finding may reflect an acute inflammatory response rather than primary leukemia-related pathology. Serial blood film examination remains a valuable adjunctive tool that can provide insights beyond leukemic morphology, when interpreted alongside clinical findings and laboratory markers of inflammation.

CONFLICT OF INTEREST

The authors declare no competing interests.

FUNDING

No funding was received for this study.

ETHICS

Verbal consent was obtained from this patient. The patient described in this manuscript is deceased. As per ethical and publication guidelines, written consent could not be obtained. Institutional ethics approval was not required for this case report.

REFERENCES

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016; 127(20): 2391-405.
2. Wood WA, Neuberg DS, Thompson JC, et al. Outcomes of patients with hematologic malignancies and COVID-19: a report from the ASH Research Collaborative Data Hub. Blood Adv. 2020; 4(23): 5966-75.
3. Bain BJ, Bates I, Laffan MA, Lewis SM. Dacie and Lewis Practical Haematology. 12th ed. Elsevier; 2017.
4. Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med. 2020; 58(7): 1131-4.
5. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol. 2020; 95(7): 834-47.
6. García-Suárez J, de la Cruz J, Cedillo Á, Llamas P, Duarte R, Jiménez-Yuste V, et al. COVID-19 in adult patients with acute myeloid leukemia: a report from the EPICOVIDEHA registry. Blood Adv. 2022; 6(5): 1520-9.
7. Sharma S, Malhan P, Pujani M, Pujani M. Auer rod-like inclusions in reactive plasmacytosis seen with acute myeloid leukemia. J Postgrad Med. 2009; 55(3): 197.
8. Rangan A, Arora B, Rangan P, Dadu T. Florid plasmacytosis in a case of acute myeloid leukemia: A diagnostic dilemma. Indian J Med Paediatr Oncol. 2010; 31(1): 36-8.
9. Rosenthal NS, Farhi DC. Reactive plasmacytosis and lymphocytosis in acute myeloid leukemia. Hematol Pathol. 1994; 8(1-2): 43-51