doi: 10.5146/tjpath.2025.14331

Diagnostic Challenge of a Rare Cause of Anemia After Kidney Transplant: Seronegative Parvovirus B19 Detected by PCR and Bone Marrow Findings

Derya DEMIR[1], Volkan KARAKUS[2], Ayca INCI[3], Muammer AVCI[3], Nazan OZSAN[1], Mine HEKIMGIL[1]

[1]Department of Pathology, Ege University Faculty of Medicine, IZMIR, TÜRKİYE
[2]Division of Hematology, [3]Division of Nephrology, Antalya Training and Research Hospital, Department of Internal Medicine, IZMIR, TÜRKİYE

Turk Patoloji Derg 2025, 41:I-IV

Received: 07.05.2025 **Accepted:** 07.07.2025 **Published Online:** 28.07.2025

ABSTRACT

Objective: Anemia is a common complication in kidney transplant patients, often attributed to viral infections. Our objective was to describe a rare case of severe anemia secondary to Parvovirus B19 infection in a kidney transplant recipient, highlighting diagnostic and therapeutic challenges in the immunosuppressed setting.

Case Report: We present a 43-year-old woman with end-stage renal disease secondary to polycystic kidney disease who received a living-kidney transplant from her husband. Seven months after transplantation, she presented with severe anemia, fatigue, and palpitations. Laboratory findings demonstrated severe normocytic, normochromic anemia (Hb: 5.8 g/dL). Parvovirus B19 serology tests were negative twice, while PCR testing revealed a significant viral load (25×10^6 copies/mL). Bone marrow biopsy findings included giant proerythroblasts with characteristic viral nuclear inclusions. The patient received intravenous immunoglobulin (IVIG, 100 mg/kg/day for 4 days), and mycophenolate mofetil was discontinued. After therapy, hemoglobin levels and viral load improved significantly, leading to successful resolution of anemia.

Conclusion: This case emphasizes the importance of considering Parvovirus B19 in the differential diagnosis of anemia in transplant patients. In immunosuppressed individuals, PCR and bone marrow analysis can be essential for diagnosis, especially when serologic tests are inconclusive. Timely intervention can lead to favorable outcomes.

Keywords: Parvovirus B19, Anemia, Kidney transplantation, Bone marrow biopsy, Immunosuppression

INTRODUCTION

Kidney transplantation is an effective treatment for end-stage renal disease. However, immunosuppressive therapy increases the risk of opportunistic infections, including viral infections that can lead to anemia. Anemia is a frequent complication in kidney transplant recipients and often prompts an extensive diagnostic workup due to its multifactorial etiology, including nutritional deficiencies, graft dysfunction, medications, and viral infections (1). Parvovirus B19 is one such virus known to cause transient aplastic crisis in immunocompromised patients, resulting in severe anemia (2). Among the viral causes, Parvovirus B19 is particularly important due to its tropism for erythroid progenitor cells, where it induces apoptosis via the NS1 protein, leading to pure red cell aplasia (RCA) (1,3). The virus is known to cause transient aplastic crisis in both immunocompetent and immunocompromised individuals, but its diagnosis in transplant recipients remains challenging. Immunosuppressed patients may not mount adequate IgM or IgG responses, making serological assays unreliable (1,4). Therefore, bone marrow examination and polymerase chain reaction (PCR) testing often become critical tools for definitive diagnosis in such cases (1,5).

Although previous reports have described Parvovirus B19-related anemia in transplant settings (6,7), comprehensive cases integrating negative serology, marrow morphology, immunohistochemistry, and PCR confirmation remain rare. In this context, we present a kidney transplant recipient with severe anemia due to Parvovirus B19 infection, where diagnosis was achieved through a multimodal approach and followed by a successful therapeutic response to intravenous immunoglobulin (IVIG) and adjustment of immunosuppressive therapy.

Copyright © 2025 The Author(s). This is an open-access article published by the Federation of Turkish Pathology Societies under the terms of the Creative Commons Attribution License that permits unrestricted use, distribution, and reproduction in any medium or format, provided the original work is properly cited. No use, distribution, or reproduction is permitted that does not comply with these terms.

Correspondence: Derya DEMIR
Department of Pathology, Ege University Faculty of Medicine, IZMIR, TÜRKİYE
E-mail: derya.demir@ege.edu.tr dr.derya.demir@gmail.com

CASE PRESENTATION

A 43-year-old female with polycystic kidney disease underwent peritoneal dialysis for 7 months prior to receiving a living-donor kidney transplant from her husband in June 2021. Antithymocyte globulin was used as induction therapy at a dose of 8.5 mg/kg, followed by maintenance immunosuppressive therapy comprising mycophenolate mofetil (1000 mg twice daily), tacrolimus, and prednisone (5 mg daily). Seven months after transplantation, she presented with complaints of fatigue and palpitations. Kidney function tests were stable, but her hemoglobin level was critically low at 5.8 g/dL. Blood smear and anemia work-up were consistent with normocytic and normochromic anemia with normal morphology and no schistocytes. The results of a comprehensive anemia work-up revealed normal levels of ferritin (1223 µg/L), vitamin B12 (1200 µg/L), folic acid (23 µg/L), LDH (143 U/L), total bilirubin (0.4 mg/dL), and direct bilirubin (0.07 mg/dL).

A bone marrow biopsy was performed (Figure 1A). The bone marrow sample was fixed in 10% neutral buffered formalin, processed into a paraffin-embedded block, and sectioned at 4 µm. Sections were stained with hematoxylin and eosin. Bone marrow biopsy revealed giant proerythroblastic cells with fine granular cytoplasm (Figure 1B, D), prominent viral nuclear inclusions, and a central clear halo (Figure 1C, E, F). Erythroid lineage maturation was impaired, resulting in a decrease or absence of erythroid cells, while myeloid cells and megakaryocytes remained normal (Figure 1B). Immunohistochemistry was performed using a mouse monoclonal anti-Parvovirus B19 antibody (clone R92F6, Cell Marque, Rocklin, CA, USA) at a 1:10 dilution on a Ventana BenchMark ultra autostainer, with DAB chromogen visualization. The diagnosis of Parvovirus B19 infection was confirmed by immunohistochemistry (Figure 1E). Parvovirus B19 serology was performed twice, and both indicated no detectable IgG or IgM antibodies while parvovirus B19 PCR was positive ($25x10^6$ copies/ml). PCR

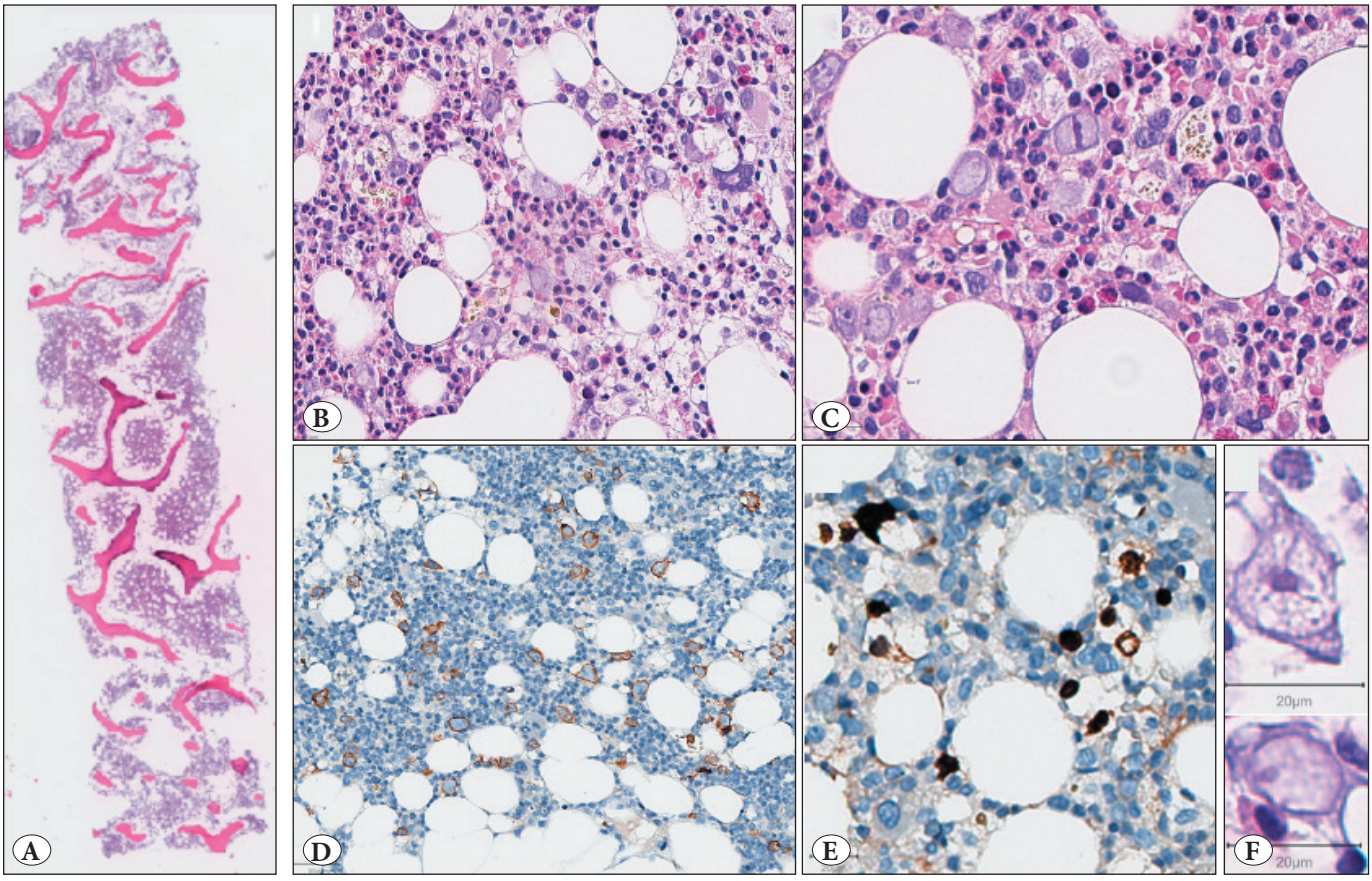

Figure 1: Bone marrow biopsy findings in Parvovirus B19-induced red cell aplasia **(A)** (hematoxylin and eosin (H&E) x 20). Erythroid lineage maturation is impaired, resulting in a decrease or absence of late erythrocytes, while myeloid and megakaryocytes remain normal **(B)** (H&E x200). Giant proerythroblast cells with fine granular cytoplasm **(C)** (H&E x600). Proerythroblast cells are positive with CD71 **(D)** (immunohistochemistry (IHC) x 200). Confirming Parvovirus B19 infection by immunohistochemistry **(E)** (IHC, x300). Prominent viral nuclear inclusions and a central clear halo **(F)** (H&E x600).

for other viruses (CMV, BK virus, and EBV) was negative. The patient was promptly started on IVIG therapy at a dose of 100 mg/kg/day for a total of 4 doses. Mycophenolate mofetil was discontinued to mitigate potential immunosuppression of viral clearance.

Upon discharge, the patient's hemoglobin level increased to 7.1 g/dL, and creatinine remained stable at 1.32 mg/dL (Figure 2). Weekly follow-ups at the post-transplant clinic showed a gradual improvement in hemoglobin levels, reaching 12.5 g/dL after one month. PCR for Parvovirus B19 decreased to 8738 copies/ml (Figure 2). At the last outpatient control, hemoglobin levels had normalized to 14.4 g/dL, and there were no significant changes in creatinine values (Figure 2).

DISCUSSION

The presented case of a 43-year-old woman who developed profound anemia after kidney transplantation highlights the importance of considering viral infections, particularly Parvovirus B19, as a potential cause of anemia in immunosuppressed patients. The absence of evidence for hemolysis, blood loss, or nutritional deficiency, coupled with the detection of giant proerythroblasts and intranuclear inclusions on bone marrow biopsy, strongly suggested a chronic Parvovirus B19 infection that may have been reactivated due to immunosuppression (5). Parvovirus B19 is known to cause transient aplastic crisis, leading to severe anemia in immunocompromised individuals, including kidney transplant recipients (8). Serological examination for Parvovirus B19, particularly the IgM antibody test, may not be reliable in immunosuppressed patients, as they may fail to mount an antibody response during active infection (1,5). In the study by Eid et al.(1), it was shown that a negative Parvovirus B19 IgM serologic test was observed in 29% of the patients. This finding emphasizes the need to use PCR for diagnosis in immunosuppressed patients with a clinical suspicion of Parvovirus B19 infection, as relying solely on serology may delay timely treatment (1,7,9).

Parvovirus B19 targets erythroid precursors, causing RBC aplasia via apoptosis induction in RBC progenitors through the NS1 protein-caspase pathway (3, 10). Broliden et al.(11) have described the pathophysiology and persistence of Parvovirus B19, noting that the NS1 protein not only induces apoptosis but also contributes to persistent infection through immune evasion mechanisms. These insights underscore the need for vigilant long-term monitoring even after apparent clinical recovery. Bone marrow biopsy played a crucial role in establishing the diagnosis in this case, demonstrating giant proerythroblasts and intranuclear inclusions consistent with Parvovirus B19 infection (9). In situations where both serology and PCR tests are negative, but clinical suspicion remains high, a bone marrow biopsy supported by immunohistochemistry can be a valuable tool for confirming the diagnosis (1,5,9).

As previously reported by Agrawal et al.(8) in a case of Parvovirus B19-induced transient aplastic crisis, viral inclusions within proerythroblasts can serve as a critical morphological clue in bone marrow examination, even in immunocompetent hosts (12). The median time to onset of anemia after transplantation in Parvovirus B19 infections

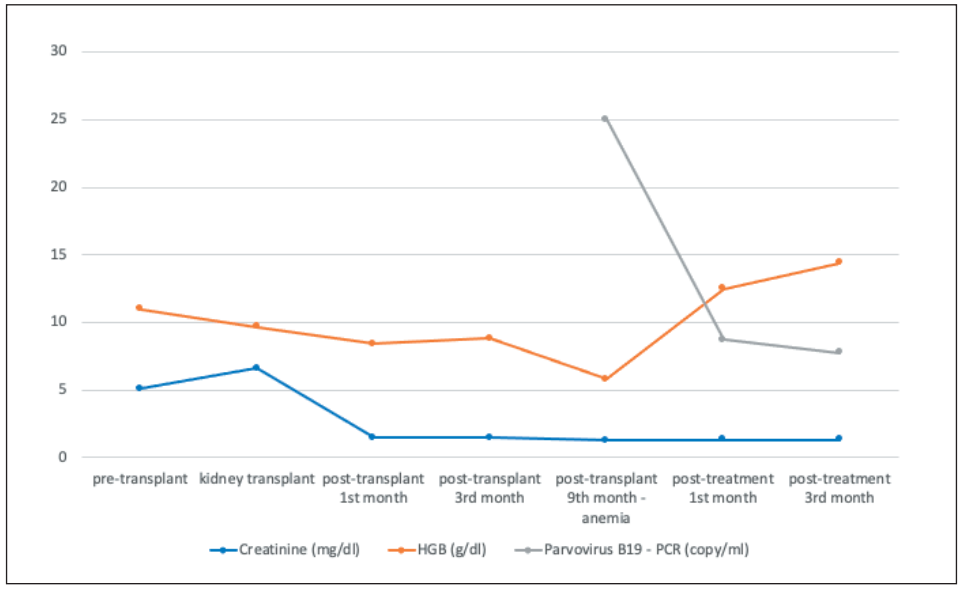

Figure 2: Clinical progression and laboratory parameters.

is reported to be seven weeks highlighting the importance of early recognition and intervention (1,5). Immunosuppression is a major risk factor for Parvovirus B19 infection (6), and this case demonstrated the resolution of anemia following the reduction of immunosuppressive medications, supporting the causal link between immunosuppression and Parvovirus B19 reactivation. Additionally, it was noted that induction therapy with ATG carries a higher risk for Parvovirus B19 infection compared to Basiliximab (13). Understanding these risk factors is crucial in tailoring immunosuppressive regimens for kidney transplant patients to mitigate the risk of opportunistic infections like Parvovirus B19 (14). Treatment strategies for Parvovirus B19 include IVIG therapy and immunosuppression modification. IVIG provides neutralizing antibodies that reduce viral load and resolve anemia (1,9,15). Reducing immunosuppressants, especially mycophenolate mofetil, is crucial for viral clearance (6,7,11). Our management strategy, combining IVIG and immunosuppressive adjustment, resulted in rapid clinical recovery, supporting these findings (6,16). Alves et al. (17) have reviewed multiple cases of Parvovirus B19-related red cell aplasia in transplant patients, providing evidence that combined IVIG and immunosuppression reduction strategies yield high success rates, consistent with our approach. The patient in this case received IVIG therapy, and the discontinuation of mycophenolate mofetil was likely crucial in aiding viral clearance and improving hemoglobin levels (7). Important gaps in the literature include the long-term outcomes of Parvovirus B19 infections post-transplant, standardized guidelines for IVIG dosing and duration, and the potential benefits of routine PCR screening in high-risk patients (6,11,13). There are reported cases of acute anemia relapse due to Parvovirus B19 in kidney transplant recipients, suggesting that some patients may experience recurrent viremia despite initial IVIG therapy. This highlights the potential benefit of periodic PCR screening and extended follow-up in high-risk patients (18). Future studies should address these points to optimize patient management.

In the bone marrow, similar giant proerythroblastic changes and nuclear inclusions can rarely be seen with certain drug effects, other viral infections such as cytomegalovirus or herpesviruses, and in cases of erythroleukemia or congenital dyserythropoietic anemias (19-21). In rare scenarios with marked erythroid precursor proliferation, acute erythroid leukemia may also be a consideration. Correlation with clinical history, specific immunohistochemistry, and PCR confirmation is therefore essential to distinguish Parvovirus B19 from these mimickers. This multidisciplinary approach plays a critical role in distinguishing parvovirus B19 infection from its mimickers and determining the most appropriate treatment strategy for the patient.

Overall, this case report underscores the importance of maintaining a high index of suspicion for Parvovirus B19 infection in kidney transplant patients presenting with anemia during the post-transplant phase. Utilizing PCR for diagnosis, alongside clinical and hematological findings, can lead to timely intervention and improved outcomes. Additionally, individualized immunosuppressive protocols, considering the risk factors for viral infections, can help reduce the occurrence and severity of Parvovirus B19 -related complications. Regular monitoring and close follow-up in the post-transplant period remain essential in optimizing patient care and outcomes. In contrast to previously published reports, our case presents a comprehensive diagnostic triad of bone marrow morphology, immunohistochemistry, and PCR positivity despite double-negative serology, highlighting the diagnostic challenge in immunosuppressed transplant recipients (22). Moreover, our management strategy combining IVIG therapy with temporary discontinuation of mycophenolate mofetil resulted in a rapid clinical recovery, an approach rarely detailed in the existing literature (5,8,15).

CONCLUSION

In conclusion, this case report highlights the importance of considering histopathological clues of Parvovirus B19 viral infection as a potential cause of anemia in transplant patients. Timely identification of Parvovirus B19 infection and appropriate intervention with IVIG therapy can result in a favorable outcome and restoration of hemoglobin levels. Regular monitoring and close follow-up are essential in the post-transplant period to optimize patient outcomes.

Conflict of Interest
The authors have no conflicts of interest to disclose and no funding sources to report.

Ethical Approval
All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Only archival material was used. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Authorship Contributions
Concept: **DD, VK, MH,** Design: **DD, VK, MH,** Data collection and/or processing: **DD, VK, AI, MA, NO, MH,** Analysis and/or interpretation: **DD, VK, AI, MA,** Literature search: **DD, VK, NO, MH,** Writing: **DD, VK, MH,** Approval: **DD, VK, AI, MA, NO, MH.**

REFERENCES

1. Eid AJ, Brown RA, Patel R, Razonable RR. Parvovirus B19 infection after transplantation: a review of 98 cases. Clin Infect Dis. 2006;43(1):40-8. doi: 10.1086/504812. PMID: 16758416.
2. Čapenko S, Kozireva S, Folkmane I, Bernarde K, Rozentāls R, Murovska M. Anemia as a complication of parvovirus b19 infection in renal transplant recipients. Medicina (Kaunas). 2012;48(6):299-304. PMID: 22885363.
3. Moffatt S, Yaegashi N, Tada K, Tanaka N, Sugamura K. Human parvovirus B19 nonstructural (NS1) protein induces apoptosis in erythroid lineage cells. J Virol. 1998;72(4):3018-28. doi: 10.1128/JVI.72.4.3018-3028.1998. PMID: 9525624.
4. Shi Y, Shi X, Wang H, Zhou Z, Zhang L, Chen L. Pure Red Cell Aplasia Secondary to Parvovirus B19 Infection as a Rare Cause of Anemia in a Dialysis Patient. Intern Med. 2024;63(19):2647-2650. doi: 10.2169/internalmedicine.2631-23. PMID: 38369359.
5. Pakkyara A, Jha A, Al Salmi I, Siddiqi WA, Al Rahbi N, Kurkulasurya AP, Mohsin J. Persistent anemia in a kidney transplant recipient with parvovirus B19 infection. Saudi J Kidney Dis Transpl. 2017;28(6):1447-1450. doi: 10.4103/1319-2442.220846. PMID: 29265066.
6. Geetha D, Zachary JB, Baldado HM, Kronz JD, Kraus ES. Pure red cell aplasia caused by Parvovirus B19 infection in solid organ transplant recipients: a case report and review of literature. Clin Transplant. 2000;14(6):586-91. doi: 10.1034/j.1399-0012.2000.140612.x. PMID: 11127313.
7. Sharma N, Bajwa R. Parvovirus Infection-Related Anemia after Kidney Transplantation. Case Rep Transplant. 2020;2020:6437392. doi: 10.1155/2020/6437392. PMID: 3208269.
8. Agrawal M, Paul RT, Pamu P, Avmr N. Parvovirus B19 induced transient aplastic crisis in an immunocompetent child. Turk Patoloji Derg. 2015;31(2):158-60. doi: 10.5146/tjpath.2014.01263. PMID: 24994616.
9. Ma Y, Man J, Niu J, Yang L. Progress of research on human parvovirus B19 infection after renal transplantation. Transplant Rev (Orlando). 2022;36(4):100730. doi: 10.1016/j.trre.2022.100730. PMID: 36368223.
10. Cavallo R, Merlino C, Re D, Bollero C, Bergallo M, Lembo D, Musso T, Leonardi G, Segoloni GP, Ponzi AN. B19 virus infection in renal transplant recipients. J Clin Virol. 2003;26(3):361-8. doi: 10.1016/s1386-6532(02)00104-x. PMID: 12637086.
11. Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. J Intern Med. 2006;260(4):285-304. doi: 10.1111/j.1365-2796.2006.01697.x. PMID: 16961667.
12. Lubomirova M, Bogov B, Filev R, Nikolova R, Kostadinova I, Bekirova E, Tzvetkova G, Hadjiev E. Case Report - Parvovirus B19 Pure Red Cells Aplasia after Kidney Transplantation. Open Access J. Urol. Nephrol. 2023; 8;1-5.
13. Kim JM, Jang HR, Kwon CH, Huh WS, Kim GS, Kim SJ, Joh JW, Oh HY. Rabbit antithymocyte globulin compared with basiliximab in kidney transplantation: a single-center study. Transplant Proc. 2012;44(1):167-70. doi: 10.1016/j.transproceed.2011.12.063. PMID: 22310606.
14. Razonable RR, Eid AJ. Viral infections in transplant recipients. *Minerva Med.* 2009; 100;479-501.
15. Ahmed W, Dogar RUH, Acharya S. Parvovirus B19: A Rare Cause of Post-renal Transplant Anemia. J Coll Physicians Surg Pak. 2017;27(12):785-787. PMID: 29185410.
16. Moudgil A, Shidban H, Nast CC, Bagga A, Aswad S, Graham SL, Mendez R, Jordan SC. Parvovirus B19 infection-related complications in renal transplant recipients: treatment with intravenous immunoglobulin. Transplantation. 1997;64(12):1847-50. doi: 10.1097/00007890-199712270-00037. PMID: 9422430.
17. Alves MT, Vilaça SS, Carvalho Md, Fernandes AP, Dusse LM, Gomes KB. Human parvovirus B19 infection in a renal transplant recipient: a case report. BMC Res Notes. 2013;6:28. doi: 10.1186/1756-0500-6-28. PMID: 23343210.
18. Renoult E, Bachelet C, Krier-Coudert MJ, Diarrassouba A, André JL, Kessler M. Recurrent anemia in kidney transplant recipients with parvovirus B19 infection. Transplant Proc. 2006;38(7):2321-3. doi: 10.1016/j.transproceed.2006.06.116. PMID: 16980079.
19. Carpenter SL, Zimmerman SA, Ware RE. Acute parvovirus B19 infection mimicking congenital dyserythropoietic anemia. J Pediatr Hematol Oncol. 2004 Feb;26(2):133-5. doi: 10.1097/00043426-200402000-00017. PMID: 14767207.
20. Crook TW, Rogers BB, McFarland RD, Kroft SH, Muretto P, Hernandez JA, Latimer MJ, McKenna RW. Unusual bone marrow manifestations of parvovirus B19 infection in immunocompromised patients. Hum Pathol. 2000 Feb;31(2):161-8. doi: 10.1016/s0046-8177(00)80215-4. PMID: 10685629.
21. Reichard KK, Tefferi A, Abdelmagid M, Orazi A, Alexandres C, Haack J, Greipp PT. Pure (acute) erythroid leukemia: morphology, immunophenotype, cytogenetics, mutations, treatment details, and survival data among 41 Mayo Clinic cases. Blood Cancer J. 2022 Nov 2;12(11):147. doi: 10.1038/s41408-022-00746-x. PMID: 36323674; PMCID: PMC9630502.
22. Ersal T, Özkalemkaş F, Özkocaman V, Sezen M, Yalçın C, Orhan B, Candar Ö, Çubukçu S, Koca TG. Two Cases of Kidney Transplant Recipients With Multiple Relapsing Pure Red Cell Aplasia Due to Parvovirus B19 Infection. Exp Clin Transplant. 2024;22(1):75-79. doi: 10.6002/ect.2022.0145. PMID: 36259607.