UDK: 616-056.7-06-008.857-036.81

CASE REPORT

A CRITICAL CARE PERSPECTIVE ON FAMILIAL MEDITERRANEAN FEVER: CASE REPORT

Ognjanova Simjanovska V.[1], Andonovska B.[1], Trajkovska V.[1], Mojsova Mijovska M.[1], Petrusheva Panovska A.[1], Naumovski F.[1]

[1] University Clinic for Traumatology, Orthopedics, Anesthesiology, Resuscitation, Intensive Care and Emergency Center - Skopje, Department of Anesthesiology, Resuscitation and Intensive Care Medicine, "Ss Cyril and Methodius" University, Skopje, Faculty of Medicine

Abstract

Familial Mediterranean Fever (FMF) is a rare autosomal recessive autoinflammatory disorder predominantly affecting individuals of Mediterranean origin. FMF is characterized by recurrent febrile episodes and serositis with amyloidosis being its most severe complication, often leading to end-stage renal disease (ESRD). The progression of FMF to amyloidosis is associated with increased morbidity and mortality requiring early diagnosis and effective management. This case report presents a critically ill patient with FMF, amyloidosis and vasculitis-related complications including massive hemorrhage and multi-organ failure. It highlights these complex conditions, the challenges in ICU management and the necessity of a multidisciplinary approach to optimize patients' outcomes.

Keywords: *amyloidosis; intensive care; Mediterranean fever; rare disease.*

Introduction

Familial Mediterranean Fever (FMF) is an inherited autoinflammatory disorder caused by mutations in the MEFV gene, located on chromosome 16 (16p13). This gene encodes a protein called pyrin, which plays a key role in the regulation of inflammation. Mutations in pyrin result in uncontrolled activation of the inflammatory response which leads to episodic fever, serositis, arthritis and long-term complications such as amyloidosis. Although FMF is rare globally, it's more prevalent in Mediterranean populations particularly among Turkish, Armenian, Arab and Sephardic Jewish communities with an incidence of approximately 1 in 1,000 individuals.(1) The most severe long-term complication of FMF is systemic amyloidosis which results from the deposition of amyloid A protein in various organs, particularly the kidneys. This deposition leads to progressive renal dysfunction and end stage renal disease (ESRD). The life expectancy of patients with FMF-associated amyloidosis is significantly reduced with survival ranging from 24 to 53 months after diagnosis (2). Furthermore, FMF has been linked to vasculitis disorders such as Henoch-Schonlein Purpura (HSP) and Polyarteritis Nodosa (PAN), both of which contribute to vascular inflammation and increased risk of hemorrhagic events. Amyloid deposition in blood

vessel walls weakens the structural integrity of the tunica media and adventitia, leading to luminal stenosis, microaneurysms and a predisposition to vascular rupture and hemorrhage.

Case Presentation

A 49-years-old male with a known history of FMF and ESRD secondary to amyloidosis was admitted to the ICU with hemodynamic instability and altered mental status. He had been receiving regular hemodialysis (3-4 times per week) for renal failure. On admission, his vital signs were as follows: blood pressure 70/40mmHg, heart rate 110bpm and SpO2 86%. The patient was intubated and placed on mechanical ventilation due to respiratory distress and progressive deterioration in mental status.

Management

Day 1-3: The patient presented with septic shock, requiring aggressive fluid resuscitation and vasopressor support. Arterial blood gas analysis revealed severe metabolic acidosis (pH 7.1, HCO3- 12mmol/L, lactate 6mmol/L). Laboratory investigations showed severe anemia (Hb 6.2g/dL), thrombocytopenia (platelets 45,000/μL) and elevated inflammatory markers (CRP 145mg/L). The most concerning feature was massive epistaxis and oropharyngeal hemorrhage, which persisted despite normal coagulation parameters (PT, aPTT and INR within normal limits).
Hemostasis was attempted using a combination of nasal packing, anterior and posterior oropharyngeal tamponade and local application of hemostatic agents. The patient received multiple transfusions, including packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, tranexamic acid and prothrombin complex concentrate. Given the concern for vasculitis-related hemorrhage, he was started on high-dose corticosteroid therapy (methylprednisolone 1g/day for three days).
Day 4-7**:** A contrast-enhanced CT scan was performed, revealing intracerebral hemorrhage (ICH) with surrounding edema, pleural effusion, pulmonary atelectasis and hypoplastic kidneys. Given the extent of bleeding, anticoagulation therapy for dialysis-related thrombotic risk was withheld. The patient's neurological status continued to decline, and neurosurgical consultation advised against surgical intervention due to poor overall prognosis.
Despite intensive medical therapy and collaborative input from rheumatology, nephrology and neurosurgery teams, the patient remained hemodynamically unstable with persistent lactic acidosis and worsening multiorgan failure. The repeated laboratory workup indicated disseminated intravascular coagulation (DIC) further complicating his clinical course.
Day 8: The patient suffered a sudden deterioration with refractory hypotension, bradycardia and pulseless electrical activity (PEA) arrest. Advanced cardiac life support (ACLS) was initiated, but despite prolonged resuscitative efforts return of spontaneous circulation (ROSC) was not achieved. The outcome was negative.

Discussion

FMF has been linked to various vasculitis disorders including Polyarteritis Nodosa (PAN)-like vasculitis. The presence of vasculitis in FMF patients significantly increases the risk of hemorrhagic complications, posing significant challenges in clinical management. PAN is a

necrotizing vasculitis affecting small and medium sized arteries, leading to vascular inflammation, thrombosis and aneurysm formation. In FMF patients PAN-like vasculitis further exacerbates vascular fragility, making them highly susceptible to hemorrhagic events. The underlying inflammatory process disrupts the structural integrity of blood vessels by causing fibrinoid necrosis and fragmentation of the internal elastic lamina. This vascular damage leads to the formation of microaneurysms which are prone to rupture, resulting in both intracerebral and systemic hemorrhages (3).

Amyloid deposition exacerbates this process by infiltrating the vascular walls leading to progressive weakening of the tunica media and adventitia. This deposition compromises vascular compliance increasing the risk of spontaneous hemorrhage even in the absence of trauma or coagulopathy. In severe cases this can lead to life-threatening conditions, such as intracranial hemorrhage, massive gastrointestinal bleeding or diffuse alveolar hemorrhage.

Patients with FMF and PAN-like vasculitis may present with various hemorrhagic manifestations including epistaxis and mucosal bleeding that is persistent nasal and oropharyngeal hemorrhage often requiring aggressive hemostatic interventions. Gastrointestinal hemorrhage like amyloid-related vasculopathy can lead to gastrointestinal bleeding presenting as melena or hematemesis.(4) Intracerebral hemorrhage is one of the most severe manifestations, intracranial bleeding occurs due to the rupture of amyloid-weakened vessels leading to neurological deterioration and high mortality rates. Retroperitoneal and perirenal hematomas can occur due to vascular rupture around the kidneys particularly in patients with amyloidosis related nephropathy.

The management of hemorrhagic complications in FMF patients with PAN-like vasculitis is particularly challenging due to the coexisting risks of thrombosis and bleeding. Hemostatic support in patients with active bleeding requires transfusions of packed red blood cells, fresh frozen plasma and platelets. The use of antifibrinolytic agents such as tranexamic acid should be considered but must be carefully monitored to avoid thrombotic complications (5).

Immunosuppressive therapy like corticosteroids and immunomodulatory drugs are essential for controlling inflammation and preventing further vascular damage. However, high-dose corticosteroids can increase the risk of gastrointestinal bleeding, necessitating gastroprotective measures such as proton pump inhibitors (6). Dialysis considerations in FMF patients with ESRD undergoing hemodialysis are at heightened risk of uremic platelet dysfunction further exacerbating bleeding tendencies. The decision to use anticoagulation during dialysis should be individualized balancing the risks of thrombosis and hemorrhage (7). Multidisciplinary approach is essential to navigate the complex interplay of inflammation, vasculitis and hemorrhagic risks.

Hemorrhagic complications in FMF patients with PAN-like vasculitis are a significant cause of morbidity and mortality driven by vascular inflammation and amyloid deposition. The increased fragility of small and medium sized arteries predisposes these patients to bleeding events including intracranial hemorrhage and gastrointestinal bleeding (8). Given the complexity of these cases early recognition, careful hemostatic management and a multidisciplinary treatment strategy are paramount in improving patients' outcomes. Further research is needed to better understand the mechanisms linking FMF, PAN-like vasculitis and hemorrhagic risk to develop targeted therapies for these high-risk patients.

Renal involvement is the most severe long-term complication, which is due to systemic amyloidosis. FMF-associated amyloidosis leads to progressive renal dysfunction and ultimately end-stage renal disease (ESRD) necessitating long-term dialysis (9). The presence of ESRD not

only worsens patients' outcomes but also contributes to a higher risk of complications including bleeding tendencies due to uremic platelet dysfunction.

Amyloidosis in FMF results from the excessive production and deposition of serum amyloid A (SAA) protein in various organs particularly the kidneys. These deposits progressively damage the glomeruli, impairing renal filtration and leading to proteinuria, nephrotic syndrome and eventually ESRD. Once kidney function deteriorates beyond a critical threshold, patients require renal replacement therapy in the form of hemodialysis or peritoneal dialysis (10).

Patients with ESRD on long-term dialysis face a heightened risk of bleeding due to multiple factors, most notably uremic platelet dysfunction. Uremia is a consequence of renal failure. It alters platelet adhesion, aggregation and secretion, leading to an increased tendency for spontaneous bleeding. This is particularly concerning in FMF patients with concurrent vasculitis where vascular fragility and amyloid deposition already predispose them to hemorrhagic events (11).

Early diagnosis and colchicine therapy for preventing amyloidosis through early and consistent colchicine use, remains the most effective strategy to avoid ESRD. Optimized dialysis management by adjusting dialysis parameters and minimizing the use of anticoagulants during dialysis sessions can help reduce bleeding risk. Use of hemostatic agents in patients with recurrent bleeding, desmopressin (DDAVP) and transfusions may be considered to improve platelet function (12). Regular monitoring for bleeding tendencies with routine laboratory tests including platelet function tests and coagulation profiles, are essential for early detection and intervention.

The management of Familial Mediterranean Fever (FMF) with amyloidosis is complex and requires a collaborative approach among multiple medical specialties. Given the multiorgan involvement of FMF, optimal patient care necessitates coordination between rheumatologists, nephrologists, intensivists, hematologists and neurosurgeons. The complexity of chronic inflammation, renal impairment and vascular complications demands a well-structured multidisciplinary strategy to improve patient's outcome and mitigate complications (13).

FMF is a systemic autoinflammatory disorder, when complicated by amyloidosis significantly impacts multiple organ systems. The deposition of amyloid protein in the kidneys often leads to end-stage renal disease (ESRD) requiring close monitoring by nephrologists. Rheumatologists play a pivotal role in managing the underlying inflammatory process primarily through colchicine therapy which is the first-line treatment to prevent amyloidosis. However, in patients with severe or refractory disease additional immunosuppressive therapies such as corticosteroids are necessary. Intensivists oversee supportive care in cases involving sepsis, hemorrhagic complications or multi-organ failure. Hematologists contribute by managing bleeding disorders associated with uremic platelet dysfunction and amyloid-related vascular fragility, while neurosurgeons may be required in cases of intracranial hemorrhage due to amyloid angiopathy or vasculitis-associated complications.

Immunosuppressive therapy like corticosteroids and biologic agents, is often necessary in FMF patients with severe inflammatory manifestations or vasculitis. Their use must be carefully balanced against the increased risk of infections and hemorrhagic complications in patients undergoing dialysis. High dose of corticosteroids may provide significant anti-inflammatory benefits but can exacerbate the risk of sepsis in immunocompromised individuals. Biologic therapies targeting interleukin-1 (IL-1) and tumor necrosis factor (TNF) pathways offer promising results in controlling inflammation but require vigilant monitoring for opportunistic infections (14).

Early diagnosis, regular monitoring of renal function and colchicine therapy are critical for preventing the progression of amyloidosis and improving long-term prognosis. Future research is necessary to refine therapeutic strategies and improve long-term outcomes for FMF patients with amyloidosis.

Conclusion

We present a rare case of FMF with amyloidosis, complicated by massive hemorrhage, intracerebral bleeding and ESRD. This case highlights the increased risk of vasculitis-associated hemorrhagic events in FMF patients especially those with PAN-like vasculitis. Amyloid deposition in vascular structures leads to fragility and rupture making the management of these patients exceptionally challenging. The relationship between FMF and systemic vasculitis requires further investigation to better understand underlying mechanisms and improve therapeutic strategies. Early colchicine therapy and close monitoring are paramount in reducing FMF complications and improving patients' outcomes.

References:

1. Ozdogan H, Ugurlu S. Familial Mediterranean Fever. Presse Med. 2019 Feb;48(1 Pt 2): e61-e76.
2. Siligato R, Gembillo G, Calabrese V, Conti G, Santoro D. Amyloidosis and Glomerular Diseases in Familial Mediterranean Fever. Medicina (Kaunas). 2021 Oct 1;57(10):1049. doi: 10.3390/medicina57101049.
3. Ozen S, Ben-Chetrit E, Bakkaloglu A,et al. Polyarteritis nodosa in patients with Familial Mediterranean Fever (FMF): a concomitant disease or a feature of FMF? Semin Arthritis Rheum. 2001 Feb;30(4):281-7. doi: 10.1053/sarh.2001.19958.
4. Abbara S, Grateau G, Ducharme-Bénard S, Saadoun D, Georgin-Lavialle S. Association of Vasculitis and Familial Mediterranean Fever. Front Immunol. 2019 Apr 12; 10:763. doi: 10.3389/fimmu.2019.00763.
5. Aksu K, Keser G. Coexistence of vasculitides with familial Mediterranean fever. Rheumatol Int. 2011 Oct;31(10):1263-74. doi: 10.1007/s00296-011-1840-z.
6. Kiraz, S., & Çolak, İ. (2013). The Role of Immunosuppressive Agents in the Treatment of Familial Mediterranean Fever. Current Drug Therapy, 8(1), 25-32. https://doi.org/10.2174/1574885521308010208.
7. Sapan, C. V., & Tüzün, S. (2015). Amyloidosis in Familial Mediterranean Fever. Nephrology Dialysis Transplantation, 30(6), 941-948. https://doi.org/10.1093/ndt/gfv060.
8. Karadag O, Telli TA, Sayinalp N, Ertenli I. P01-003 – Bleeding disorder in FMF. Pediatr Rheumatol Online J. 2013 Nov 8;11(Suppl 1): A7. doi: 10.1186/1546-0096-11-S1-A7.
9. Lachmann HJ. Clinical aspects of familial Mediterranean fever. Nephrol Dial Transplant. 2001.
10. Gül, A., & Özen, S. (2017). Clinical aspects of amyloidosis in familial Mediterranean fever: An overview. Rheumatology, 56(1), 52-58. https://doi.org/10.1093/rheumatology/kew462.
11. Vaziri, N. D., & Rad, N. S. (2012). Uremic platelet dysfunction in end-stage renal disease. Nephron Clinical Practice, 121(1-2), c90-c99. https://doi.org/10.1159/000335290

12. Oner A, Erdoğan O, Demircin G, Bülbül M, Memiş L. Efficacy of colchicine therapy in amyloid nephropathy of familial Mediterranean fever. Pediatr Nephrol. 2003 Jun;18(6):521-6. doi: 10.1007/s00467-003-1129-x. Epub 2003 Apr 16. PMID: 12698329.
13. Tunca, M., & Onen, F. (2009). The management of familial Mediterranean fever. Clinical and Experimental Rheumatology, 27(4), 609-616.
14. Ozen S, Bilginer Y. A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. Nat Rev Rheumatol. 2014 Mar;10(3):135-47. doi: 10.1038/nrrheum.2013.174. Epub 2013 Nov 19. PMID: 24247370.