Supplementary Material

Case Example and Model Responses

Case Presentation

Complaint: Fatigue
Medical History: A 42-year-old male patient was admitted to the nephrology department due to thrombotic microangiopathy (TMA). During the evaluation for secondary causes, colorectal cancer was diagnosed. At presentation, the patient had microangiopathic hemolytic anemia, elevated LDH, thrombocytopenia, and acute kidney injury. Since the cancer was stage I, the patient underwent surgical resection without chemotherapy or radiotherapy and is currently in remission.
During the TMA episode, eculizumab treatment was initiated, after which dialysis was no longer required (December 2024). The patient is currently maintained on eculizumab 1200 mg every two weeks (Soliris). A homozygous c.1159+4A>C variant was detected in the CFH gene; this variant has not been previously reported in the literature or ClinVar. According to ACMG guidelines, it is classified as a variant of uncertain clinical significance (VUS).
CFH deletion/duplication analysis (MLPA): Normal.
Physical Examination: Normal.
Family History: Unremarkable.
Habits: No notable findings.

Current Medications:

- Eculizumab (every two weeks)
- Proton pump inhibitor
- Norvasc 10 mg daily
- Beloc ZOK 50 mg daily
- Colchicum-Dispert 0.5 mg twice daily
- Ecopirin 100 mg daily
- Atorvastatin 20 mg daily

Laboratory Findings (current):

- Creatinine: 1.8 mg/dL
- Hemoglobin: 12.4 g/dL
- Platelets: 233 × 10^3/μL
- LDH: 172 U/L
- Haptoglobin: 1.31 g/L

Abdominal CT Findings:

- Liver size, contours, and parenchyma normal.
- 10 mm gallstone within gallbladder lumen.
- No intra- or extrahepatic bile duct dilatation.
- Pancreas, spleen, and adrenal glands normal.
- Bilateral kidneys normal in size and parenchymal appearance.
- No collecting system dilatation.
- No para-aortic lymphadenopathy.
- Bladder suboptimally filled.
- Prostate gland and seminal vesicles age-appropriate.
- Colocolonic anastomosis line within normal limits, with increased fat attenuation around the site.
- In the mid-rectal region, a 37 mm loculated fluid collection with surrounding fat attenuation observed.
- Abdominal wall shows incision line and diastasis recti appearance.

Clinical Question:
Should additional workup be performed? Do you have any other suggestions regarding treatment?

ChatGPT-4o Response

Assessment Summary:
This is a 42-year-old male with a history of TMA and stage I colorectal cancer (now in remission), currently maintained on eculizumab due to a CFH gene splice variant (c.1159+4A>C) of uncertain significance. The patient experienced TMA with AKI requiring dialysis but improved after eculizumab initiation and is now dialysis-independent. He presents with fatigue. Current labs show stable renal function (Cr 1.8), no active hemolysis (LDH,

haptoglobin, platelets, hemoglobin all normal), and CT shows a new 37 mm loculated fluid collection in the mid-rectal region.

1. Should Additional Workup Be Performed?

Yes.

The rectal collection with increased fat attenuation may represent:

- A presacral abscess or postoperative collection
- Chronic inflammation or low-grade infection

Next steps:

- Pelvic MRI with contrast for further characterization
- Colorectal surgery consultation for potential drainage or biopsy
- Inflammatory markers (CRP, ESR)
- Fatigue workup (TSH, ferritin, B12, vitamin D)
- Consider PNH screening (flow cytometry) if anemia or hemolysis recurs

2. Should Eculizumab Be Continued?

Yes, for now.

Although the CFH variant is classified as a VUS, the patient had severe TMA with renal involvement and clear response to therapy. Until functional testing or a supervised withdrawal trial is performed, continuing eculizumab is reasonable to prevent relapse.

3. Other Recommendations:

- Complement pathway functional assays (C5b-9, sC5b-9, AP activity)
- Genetic counseling for potential variant reclassification
- Trial discontinuation only under close monitoring (weekly labs, rapid access to therapy)
- Review vaccination status (meningococcal, pneumococcal, Hib)
- Ongoing oncologic surveillance via colonoscopy

Conclusion:

Further workup is warranted for the rectal collection and fatigue. Continue eculizumab given

the severe prior TMA and uncertain but possibly pathogenic CFH variant. A personalized, cautious approach is recommended.

Claude 3.7 Sonnet Response

This case involves intersecting issues that make management nuanced.

Additional Workup:
The 37 mm loculated rectal collection requires evaluation.
Recommended steps:

- MRI pelvis for characterization
- Drainage if symptomatic or infected
- Monitor for anastomotic complications

For the TMA/CFH Variant:

- Complement studies (C3, C4, CH50, Factor H/I levels)
- Functional assays if research access available
- Homozygous splice-site variant (c.1159+4A>C) warrants attention despite being a VUS

Eculizumab Continuation – A Balanced Approach:
Arguments for continuation:

- CFH variant may predispose to complement dysregulation
- Good current control on therapy
- Risk of relapse if discontinued

Arguments for cautious discontinuation:

- TMA may have been cancer-associated
- Cancer is now in remission
- No current TMA activity
- Long-term therapy has infection risk and high cost

Suggested strategy:
Gradual interval extension (e.g., every 3–4 weeks) with close monitoring (weekly initially) of Hb, platelets, LDH, haptoglobin, creatinine.

Other Considerations:

- Confirm meningococcal vaccination
- Manage rectal collection
- Genetic counseling for CFH variant
- Multidisciplinary discussion with hematology

Summary:
The patient’s fatigue may relate to chronic inflammation rather than active hemolysis. Careful balance between treatment benefit and risk favors a monitored, stepwise approach.