Pediatric Nephrology (2023) 38:1047–1050
https://doi.org/10.1007/s00467-022-05665-4

CLINICAL QUIZ

Concurrent acute kidney injury and pancreatitis in a female patient: Answers

Darshan B. Patel[1] · Amanda C. Farris[2] · Christian Hanna[3,4] · Faris Hashim[5]

Received: 14 May 2022 / Revised: 25 May 2022 / Accepted: 26 May 2022 / Published online: 27 June 2022

Keywords Child · Acute pancreatitis · Acute kidney injury · Anemia · Thrombocytopenia · Atypical hemolytic uremic syndrome

Answers

1. *What would be your differential diagnosis for acute kidney injury during acute pancreatitis?*

   The differential diagnosis of her acute kidney injury (AKI) includes hypovolemia secondary to decreased kidney perfusion and increased vascular permeability. During pancreatitis, the release of pancreatic amylase from the injured pancreas can lead to increased vascular permeability, and to the hypovolemic state [1]. In addition, intra-abdominal hypertension increases the risk of AKI during acute pancreatitis (AP). Furthermore, inflammatory endotoxins and reactive oxygen species can directly act on the kidney to cause inflammation and a nephrotoxic effect [2].

   In a recent study, the mortality rate among AP hospitalizations with AKI was 2.5%, and AKI almost doubled the risk of mortality among pediatric patients with AP [3].

   AP as a cause of hemolytic uremic syndrome (HUS) is rare and reported in few case reports in both adults and pediatrics [4, 5]. Multiple mechanisms have been suggested, with the most common one that pancreatic inflammation can cause changes in the von Willebrand factor and ADAMTS13 which stimulate spontaneous binding of platelets, leading to platelet aggregation [5, 6].

2. *What additional investigations would you perform?*

   Our patient had sudden onset of microangiopathic hemolytic anemia (hemoglobin < 10 g/dL), thrombocytopenia (platelets < 150,000/mm^3), high serum LDH, and AKI. Those are classical manifestations of HUS. However, she did not have preceding diarrhea which ruled out typical HUS. AP rarely occurs with atypical hemolytic uremic syndrome (aHUS) [7–9]. Since there was no diarrhea or fever, no infectious workup such as a stool PCR was done. She had no neurological symptoms and a normal ADAMTS-13 level, which ruled out thrombotic thrombocytopenic purpura (TTP). Her genetic workup revealed a heterozygous missense mutation (c355G>A, p. Gly119Arg) in exon 3 of the *CFI* gene. This mutation has been published several times in association with aHUS [10, 11]. In addition, she had a heterozygous missense variant (c2669G>T, p. Ser-890lle) in exon 17 of *CFH* (which was determined to be a benign polymorphism since no functional defect was detected) and another heterozygous, missense variant (c3019G>T, p. Val1007Leu) in exon 19 of *CFH* which is also a benign polymorphism. However, this variant mutation has been associated with aHUS in the literature [12]. Our patient had a normal C3 level of 119 (normal range 82–173), we did not get a level of CFI during her

This refers to the article that can be found at https://doi.org/10.1007/s00467-022-05657-4.

✉ Faris Hashim
faris.hashim@bswhealth.org

1 Department of Pediatrics, Texas A&M Health Science Center, Baylor Scott & White McLane Children's Medical Center, Temple, TX, USA

2 Division of Pediatric Hospital Medicine, Baylor Scott & White McLane Children's Medical Center, Temple, TX, USA

3 Division of Pediatric Nephrology and Hypertension, Department of Pediatrics and Adolescent Medicine, Mayo Clinic, Rochester, MN, USA

4 Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN, USA

5 Division of Pediatric Nephrology, Baylor Scott & White McLane Children's Medical Center, Temple, TX, USA

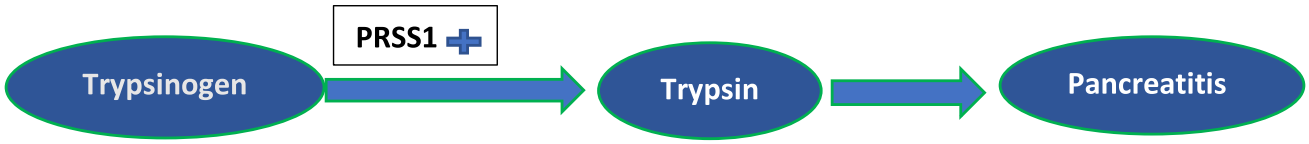

Fig. 1 A gain of function mutation in PRSS1 is associated with premature and continued activation of trypsinogen into trypsin which can cause injury or inflammation of the pancreas

admission. Per literature review, plasma C3 and CFI concentrations decreased in only 30% of patients with *CFI* mutations and a normal level does not rule out the diagnosis of aHUS [12]. The penetrance of the disease is low and only 50% of family members carrying the same complement mutation will have the disease. For that reason, genetic screening is not recommended for parents/siblings and other family members of a patient with a heterozygous complement mutation [12, 13].

3. How would you further manage this patient?

   The clinical presentation and management of aHUS are the same whether the disease is genetic, acquired, or caused by an unknown mechanism [13]. Given that our patient had pancreatitis, IV hydration and gradual return to a regular diet were key to improvement. As the patient's pancreatitis resolved, her AKI then resolved, along with increases in hemoglobin and platelet count. Likewise, the management of HUS is mostly supportive with strict laboratory monitoring to prevent worsening of AKI and systemic complications [13]. These measures include packed cell transfusion for severe anemia (Hb < 8 g/dL), platelet transfusion when the count is < 10,000/mm^3, correction of electrolyte disturbances, and avoidance of nephrotoxic medications. Dialysis is required for patients who develop anuria, significant fluid overload, or become symptomatic with uremia/azotemia. Additionally, outpatient monitoring of kidney and hematologic function should persist on a scheduled basis to monitor for late worsening of anemia or kidney function.

Mutations in many genes have been associated with increased susceptibility for aHUS, these include *CFH*, *CFI*, *MCP*, *C3*, *CFB*, and *THBD* (thrombomodulin). For patients who have a positive genetic mutation, eculizumab should be considered and is often initiated as the first-line agent [14, 15]. Eculizumab binds to complement protein C5, blocking its cleavage and preventing the production of the terminal complement components C5a and the membrane attack complex (MAC) C5b–9. This decreases the activity of the complement cascade and leads to less endothelial damage, thrombosis, and AKI. The earlier eculizumab is started, the greater the chance of hematologic normalization and AKI resolution, along with decreased progression to kidney failure [16, 17]. Plasmapheresis has also been used to treat aHUS and can be an option for those who decline eculizumab or have financial/resource unavailability for eculizumab. It is less effective when compared to eculizumab [17].

Fortunately, our patient got better with resolution of her symptoms and laboratory findings before starting her on medications. She never started on eculizumab as her family declined therapy.

Discussion

A gain of function mutation in *PRSS1* leads to premature activation of the enzyme trypsin which digests the pancreas and increases risk for recurrent pancreatitis (Fig. 1). aHUS is rare and represents a group of patients who do not show infectious diarrhea caused by Shiga toxin-producing *E. coli* O175:H7. Without treatment, it has poor clinical outcomes with high morbidity (50% may develop kidney failure), and mortality (up to 25%) [13].

Heterozygous mutations predispose children to aHUS, but they are often not sufficient to clinically manifest the disease due to poor penetrance and other triggers are often required. Well-known triggers include infections (including recent COVID-19), medications, autoimmune disorders, transplants, pregnancy, and metabolic conditions [14].

In 2011, eculizumab was approved by the FDA as the first terminal complement blocker for patients with aHUS and it showed excellent efficacy and safety in both adult and pediatric populations [15, 16, 18]. It is a humanized monoclonal antibody that specifically binds to the terminal complement protein C5, inhibiting its cleavage into C5a and C5b by C5 convertases and thereby preventing the release of the inflammatory mediator C5a and the formation of the cytolytic pore C5b–9 [17]. Genetic mutation in complement regulatory proteins accounts for 60% of all aHUS cases, with the remaining 40% of cases having no known identifiable causes [13].

Our patient had a pathogenic variant mutation in *CFI* and a benign variant mutation in *CFH*. CFH in conjunction with complement factor I (CFI) competes with complement factor B (CFB) for C3b binding and accelerates C3 convertase decay. The combination of *CFI* and *CFHR-1* or *CFI* and

CFH mutations had more severe outcome than other complement mutations [19–21].

Our case was unique because she had both mutation in *CFI* and *CFH*, which increase her risk for more severe presentation without early treatment. However, she had mild presentation and recovered spontaneously in a few days without starting on eculizumab treatment. (Her parents refused to start her on eculizumab therapy given her mild presentation and rapid recovery before we received the genetic test results.) Currently, our patient is doing clinically well with continued close outpatient monitoring. However, she still has substantial risk of recurrence given her combined genetic defect.

To our knowledge, to date, there are no reported cases with combined *CFI* and *CFH* variant mutations who recovered completely without treatment. Given her genetic results, the likelihood of recurrent aHUS triggered by recurrent AP is high. As all genetic variants in *CFI* may not be associated with a functional defect, and combination with other genetic mutations did not affect the severity of our patient's presentation, we were not able to convince her parents to start on C5 blockade therapy. We believe that understanding the approach to diagnosis and management of aHUS in children is extremely critical as early diagnosis and proper intervention might decrease disease morbidity and mortality.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

References

1. Shi N, Sun GD, Ji YY, Wang Y, Zhu YC, Xie WQ, Li NN, Han QY, Qi ZD, Huang R, Li M, Yang ZY, Zheng JB, Zhang X, Dai QQ, Hou GY, Liu YS, Wang HL, Gao Y (2021) Effects of acute kidney injury on acute pancreatitis patients' survival rate in intensive care unit: a retrospective study. World J Gastroenterol 27:6453–6464. https://doi.org/10.3748/wjg.v27.i38.6453
2. Petejova N, Martinek A (2013) Acute kidney injury following acute pancreatitis: a review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 157:105–113. https://doi.org/10.5507/bp.2013.048
3. Thavamani A, Umapathi KK, Sankararaman S (2021) Prevalence and impact of acute kidney injury in hospitalized pediatric patients with acute pancreatitis. Pediatr Nephrol 36:3785–3788. https://doi.org/10.1007/s00467-021-05106-8
4. Grodinsky S, Telmesani A, Robson WL, Fick G, Scott RB (1990) Gastrointestinal manifestations of hemolytic uremic syndrome: recognition of pancreatitis. J Pediatr Gastroenterol Nutr 11:518–524. https://doi.org/10.1097/00005176-199011000-00013
5. Adragão F, Nabais I, Reis R, Pereira B, Ramos A (2021) Acute pancreatitis as a trigger for thrombotic microangiopathy: a case report. Cureus 13:e20103. https://doi.org/10.7759/cureus.20103
6. Boyer A, Chadda K, Salah A, Bonmarchand G (2004) Thrombotic microangiopathy: an atypical cause of acute renal failure in patients with acute pancreatitis. Intensive Care Med 30:1235–1239
7. Anderson JAM, Simpson PJ, Leber B, Warkentin TE (2007) Acute pancreatitis preceding thrombotic thrombocytopenic purpura. Haematologica 92:e94–e95. https://doi.org/10.3324/haematol.11938
8. Singh NP, Aggarwal NP, Shah HR, Jha LK, Kumar A (2017) Hemolytic-uremic syndrome complicating acute pancreatitis. Indian J Crit Care Med 21:534–536
9. Singh K, Nadeem AJ, Doratotaj B (2017) A rare case of thrombotic microangiopathy triggered by acute pancreatitis. BMJ Case Rep 2017:bcr2016218581. https://doi.org/10.1136/bcr-2016-218581
10. Fakhouri F, Roumenina L, Provot F, Sallée M, Caillard S, Couzi L, Essig M, Ribes D, Dragon-Durey MA, Bridoux F, Rondeau E, Frémeaux-Bacchi V (2010) Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. J Am Soc Nephrol 21:859–867. https://doi.org/10.1681/ASN.2009070706
11. Bresin E, Rurali E, Caprioli J, Sanchez-Corral P, Fremeaux-Bacchi V, Rodriguez de Cordoba S, Pinto S, Goodship TH, Alberti M, Ribes D, Valoti E, Remuzzi G, Noris M, European Working Party on Complement Genetics in Renal Diseases (2013) Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol 24:475–486. https://doi.org/10.1681/ASN.2012090884
12. Sellier-Leclerc AL, Fremeaux-Bacchi V, Dragon-Durey MA, Macher MA, Niaudet P, Guest G, Boudailliez B, Bouissou F, Deschenes G, Gie S, Tsimaratos M, Fischbach M, Morin D, Nivet H, Alberti C, Loirat C, French Society of Pediatric Nephrology (2007) Differential impact of complement mutations on clinical characteristics in atypical hemolytic uremic syndrome. J Am Soc Nephrol 18(8):2392–2400
13. Raina R, Krishnappa V, Blaha T, Kann T, Hein W, Burke L, Bagga A (2019) Atypical hemolytic-uremic syndrome: an update on pathophysiology, diagnosis, and treatment. Ther Apher Dial 23:4–21. https://doi.org/10.1111/1744-9987.12763
14. Noris M, Bresin E, Mele C, et al (2021) Genetic atypical hemolytic-uremic syndrome. 2007 Nov 16 [Updated 2021 Sep 23]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1367/
15. Raina R, Vijayvargiya N, Khooblall A, Melachuri M, Deshpande S, Sharma D, Mathur K, Arora M, Sethi SK, Sandhu S (2021) Pediatric atypical hemolytic uremic syndrome advances. Cells 10:3580
16. Kavanagh D, Goodship TH, Richards A (2013) Atypical hemolytic uremic syndrome. Semin Nephrol 33:508–530. https://doi.org/10.1016/j.semnephrol.2013.08.003
17. Greenbaum LA, Fila M, Ardissino G, Al-Akash SI, Evans J, Henning P, Lieberman KV, Maringhini S, Pape L, Rees L, van de Kar NC, Vande Walle J, Ogawa M, Bedrosian CL, Licht C (2016) Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. Kidney Int 89:701–711
18. Loirat C, Fakhouri F, Ariceta G, Besbas N, Bitzan M, Bjerre A, Coppo R, Emma F, Johnson S, Karpman D, Landau D, Langman CB, Lapeyraque AL, Licht C, Nester C, Pecoraro C, Riedl M, van de Kar NC, Van de Walle J, Vivarelli M, Frémeaux-Bacchi V, HUS International (2016) An international consensus approach

to the management of atypical hemolytic uremic syndrome in children. Pediatr Nephrol 31:15–39
19. Rother RP, Rollins SA, Mojcik CF, Brodsky RA, Bell L (2007) Discovery and development of the complement inhibitor eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Nat Biotechnol 25:1256–1264
20. Bienaime F, Dragon-Durey MA, Regnier CH, Nilsson SC, Kwan WH, Blouin J, Jablonski M, Renault N, Rameix-Welti MA, Loirat C, Sautés-Fridman C, Villoutreix BO, Blom AM, Fremeaux-Bacchi V (2010) Mutations in components of complement influence the outcome of Factor I-associated atypical hemolytic uremic syndrome. Kidney Int 77:339–349. https://doi.org/10.1038/ki.2009.472
21. Fremeaux-Bacchi V, Fakhouri F, Garnier A, Bienaimé F, Dragon-Durey MA, Ngo S, Moulin B, Servais A, Provot F, Rostaing L, Burtey S, Niaudet P, Deschênes G, Lebranchu Y, Zuber J, Loirat C (2013) Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. Clin J Am Soc Nephrol 8:554–562