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CASE REPORT

When the diagnosis is difficult to digest: severe vitamin B_{12} deficiency secondary to pernicious anemia mimicking life-threatening thrombotic thrombocytopenic purpura

Matthew Sochat[1] · Daniela Hermelin[2] · Daniel Chakos[1] · Azam Farooqui[1] · Jason Lunt[3] · Ara Vartanyan[4] · Nishant Poddar[1]

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is an uncommon yet life-threatening condition, usually marked by a classic pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, acute kidney injury (AKI), neurological disturbances, and fevers. Prompt recognition and treatment is essential to reduce morbidity and mortality. The rarity and variability of presentations, however, makes this a difficult diagnosis to make reliably, and in many cases, treatment is initiated empirically before the appropriate diagnostic testing is completed. After TTP and other common causes of thrombotic microangiopathy (TMA) have been excluded, evaluation for causes of "pseudo"-thrombotic microangiopathy ("pseudo"-TMA) should be pursued. Herein, we present a case of a young man with a history of previously treated hepatitis C virus (HCV) infection presenting with a syndrome concerning for TTP: MAHA, thrombocytopenia, and dizziness with gait ataxia. Disseminated intravascular coagulation (DIC) and autoimmune hemolysis were quickly ruled out, and plasma exchange was emergently initiated. Further workup identified an undetectably low vitamin B_{12} level with profound elevations in both homocysteine and methylmalonic acid (MMA) levels. Folate and vitamin B_{12} were replenished, with a rapid resolution of hemolysis and improvement in both the platelet count and hemoglobin that allowed for plasma exchange to be permanently discontinued. Further workup identified positivity of both intrinsic factor and parietal cell autoantibodies, suggesting a diagnosis of pernicious anemia. He was determined to have "pseudo"-TMA secondary to critical vitamin B_{12} deficiency. The patient was safely discharged home with scheduled subcutaneous vitamin B_{12} injections along with outpatient follow-up with both Hematology and Gastroenterology.

Keywords Pernicious anemia · Vitamin B_{12} deficiency · Thrombotic microangiopathy · Microangiopathic hemolytic anemia · Thrombotic thrombocytopenic purpura · Intramedullary hemolysis

Introduction

The syndrome of thrombotic thrombocytopenic purpura (TTP) is classically defined as the pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, acute kidney injury (AKI), and neurological disturbances such as sensory and motor disturbances, and fevers. A form of thrombotic microangiopathy (TMA), TTP is a rare condition; however, and in many cases, patients do not present with all five signs. Making the diagnosis therefore requires a high index of suspicion by the evaluating provider. Definitive diagnosis is made by identifying low levels of the von Willebrand factor (VWF)-cleaving protease ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member #13), which normally cleaves large VWF multimeters within the circulation. Failure to clear these multimeters secondary to

✉ Matthew Sochat
Matthew.Sochat@health.slu.edu

[1] Department of Hematology/Oncology, St. Louis University, 3655 Vista Avenue, St. Louis, MO 63110, USA

[2] Department of Pathology, St. Louis University, 1402 South Grand Blvd, St. Louis, MO 63104, USA

[3] Department of Internal Medicine, St. Louis University, 3635 Vista Avenue, 12th Floor Desloge Towers, St. Louis, MO 63110, USA

[4] School of Medicine, St. Louis University, 1402 South Grand Blvd, St. Louis, MO 63104, USA

ADAMTS13 impairment, with their subsequent accumulation in the microvasculature, leads to the hallmarks of TTP [1].

As most patients who present with suspicion for this syndrome are critically ill at the time of evaluation and have a high probability of rapid decline or mortality, there is often little time to await confirmation of a TTP diagnosis. A reasonably high index of suspicion can usually be achieved by ruling out other TTP mimics whose assessments have rapid turnaround times, such as disseminated intravascular coagulation (DIC) and autoimmune hemolytic anemia (AIHA). Scoring systems such as the PLASMIC score can also assist providers with decision making [2]. Diagnostic uncertainty often remains, however, and empiric initiation of TTP treatment is usually required [3]. In such cases, a low ADAMTS13 assay will confirm the diagnosis. If the level is normal, however, then a search for causes of "pseudo"-thrombotic microangiopathy ("pseudo"-TMA) should be undertaken.

Our patient, a 42-year-old man with a history of previously treated hepatitis C virus (HCV) infection, is one such case of "pseudo"-TMA. His case highlights a very rare case of critical intramedullary hemolysis secondary to vitamin B_{12} deficiency mimicking TTP, and emphasizes many of the numerous diagnostic challenges associated with patients presenting with dangerous TMA syndromes concerning for TTP.

Case report

Our patient, a 42-year-old African American man with a history of genotype 1a HCV infection, for which he had finished a full course of glecaprevir and pibrentasvir 2 weeks prior, presented to our emergency department with several weeks of insidiously worsening dizziness and near falls, generalized weakness, dyspnea on exertion, blurry vision, and malaise. He noted difficulties with his balance while walking. He had lost several pounds unintentionally and noted a decrease in his appetite. Aside from HCV, he had no other past medical problems and was taking no medications since completing his antiviral therapy. He smoked several cigarettes a day but denied other toxic habits and exposures. He had not experienced any unusual bleeding including melena, bloody diarrhea, hematuria, or hematemesis, and did he note any episodes of icterus or jaundice. There was no travel or unusual food intake before presentation. He had never felt like this before, and noted no history of either personal or familial hematological disorders.

He had been seen by his hepatologist 1 week prior for routine follow-up, and at that visit was noted to have a hemoglobin of 8.3 g/dL (reference range 13.5–17.5 g/dL) and platelet count of 201×10^3/uL (reference range 150–400 $\times 10^3$/uL). Concern was raised that he was having gastrointestinal bleeding leading to symptomatic anemia, and outpatient endoscopy was planned in the near future. The symptoms became too much for him to bear, however, prompting him to visit the emergency room before endoscopy could be performed.

On arrival, his vital signs on were stable, and he was afebrile. Physical exam was notable for conjunctival and palmar pallor. No gross blood was seen in his stool or urine, and he had no unusual skin findings such as jaundice, bruising, or petechiae. A neurological examination was nonfocal and his mental status normal, although mild difficulty with ambulation was noted. There was no hepatosplenomegaly. Initial blood count laboratory assessment noted a hemoglobin of 6.0 g/dL, a platelet count of 67×10^3/uL, and a white blood cell (WBC) count of 4.6×10^3/uL (reference range 3.5–10.5 $\times 10^3$/uL); the mean corpuscular volume (MCV) was 83.7 fL (reference range 81.0–97.0 fL) and the red blood cell distribution width coefficient of variation (RDW-CV) was 21.5% (reference range 11.2–14.8%). An automated differential noted increased nucleated red blood cells (8.7/100 WBCs, reference range 0/100 WBCs) and immature granulocytes (3.1% of WBCs, reference range 0–1% of WBCs). The peripheral smear was manually reviewed and further identified 2+ schistocytes and a paucity of platelets without evidence of clumping (Fig. 1).

Electrolyte testing showed a normal creatinine and an elevated total bilirubin of 2.1 mg/dL (reference range 0.2–1.2 mg/dL) with a predominantly indirect bilirubin level of 1.5 mg/dL (reference range 0.2–1.2 mg/dL); the direct bilirubin level was 0.6 mg/dL (reference range 0.0–0.6 mg/dL). Hemolysis assays revealed a lactate dehydrogenase (LDH) of 3646 units/L (reference range 125–243 units/L), an undetectably low haptoglobin level, an elevated D-dimer level of 7.32 mcg/mL (reference range ≤ 0.5 mcg/mL), and a negative direct Coombs assay. DIC testing noted a normal

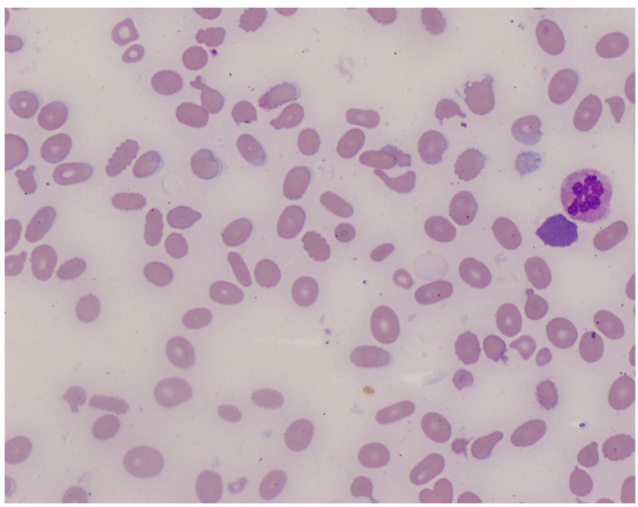

Fig. 1 Prominent hypersegmented neutrophils and thrombocytopenia are seen in the patient's peripheral smear. The marked anisopoikilocytosis induced by the intramedullary hemolysis secondary to vitamin B_{12} deficiency, including the presence of teardrop cells and schistocytes, masks the megaloblastic component evidenced by a small population of large, oval macrocytes. Wright stain, 100× power

fibrinogen level, normal prothrombin time/international normalized ratio (PT/INR), and normal partial thrombin time (PTT). The absolute reticulocyte count was low at 0.02×10^6/uL (reference range $0.02–0.13 \times 10^6$/uL).

This assessment was concerning for a TMA, and a presumed diagnosis that was TTP was made, with MAHA, thrombocytopenia, and dizziness manifesting three of the five hallmarks of the condition. His PLASMIC score was 6, suggesting an intermediate probability of severe ADAMTS13 deficiency. High-dose prednisone (60 mg/day) was started and an ADAMTS13 assay was sent off urgently. He was admitted to the intensive care unit and plasma exchange was initiated after central line placement. With this intervention, a decrease in the LDH to 1482 units/L was noted after two treatments. However, the haptoglobin remained undetectably low and the total bilirubin remained elevated, suggesting ongoing hemolysis and raising the concern for other diagnoses not yet considered. Paroxysmal nocturnal hemoglobinuria testing remained normal, as did glucose-6-phosphate dehydrogenase, nucleotidase-5, and hemoglobin electrophoresis assays. Complement testing was fully normal including C3, C4, and total complement levels. Iron studies demonstrated an elevated ferritin level of 1388 ng/mL (reference range 22–275 ng/mL), a serum iron level of 256 mcg/dL (reference range 50–175 mcg/dL), and a normal transferrin with a saturation of 95% (reference range 16–50%). Vitamin B_{12} testing was also performed, which was undetectably low. The MMA level was elevated at 4529 nmol/L (reference range 0–378 nmol/L), and a homocysteine level returned undetectably high. Folate, zinc, and copper levels were all normal. Three days after admission, the ADAMTS13 activity assay returned at 68% (reference range > 67%), and a VWF multimeter assay noted a normal pattern and distribution of VWF bands.

These laboratory findings raised a suspicion for intramedullary hemolysis secondary to a critical deficiency of vitamin B_{12}, with TTP being ruled out due to the normal ADAMTS13 assay. The normal complement titers made atypical hemolytic uremic syndrome (HUS) less likely. Plasma exchange was stopped after three treatments and the prednisone discontinued, and daily 1000 mcg cyanocobalamin injections were initiated. Several days after starting supplementation, the hemoglobin increased to 9.8 g/dL and the platelet count to 178×10^3/uL. All hemolysis titers, including LDH, haptoglobin, and total bilirubin, normalized rapidly. The absolute reticulocyte count quickly increased to 0.50×10^6/uL. The patient also noted feeling much better, with full resolution of his presenting dizziness, fatigue, and gait balance issues. The peripheral smear was re-reviewed, with a significant decrease in the number of circulating schistocytes being noted and a normalization of the circulating platelet count.

Given the patient's reported weight loss and well-balanced diet, a screen for pernicious anemia was performed. Parietal cell autoantibody titers returned elevated at 38.8 units (reference range 0.0–20 units). Intrinsic factor autoantibody titers were also elevated at 20.9 AU/mL (reference range 0.1.1 AU/mL). He was referred to Gastroenterology and outpatient endoscopy was planned for gastritis surveillance. He was also arranged to have outpatient monthly vitamin B_{12} injection performed indefinitely with his primary care provider. An outpatient Hematology referral was also placed for ongoing monitoring of his blood counts.

Discussion

Our patient presented with a challenging dilemma, with several clinical findings concerning for life-threatening TTP, including an increased number of peripheral smear schistocytes and laboratory serum markers of hemolysis including an elevated total bilirubin, elevated LDH, and undetectably low haptoglobin, all consistent with MAHA. His platelet count had also dropped precipitously over a several week period, and the ataxia was concerning for neurological involvement. DIC and autoimmune hemolysis were ruled out quickly. Plasma exchange was initiated early in his clinical course. Further workup, however, instead identified a profoundly low vitamin B_{12} level with concomitant increases in both homocysteine and MMA levels. Rapid correction of the vitamin B_{12} level normalized the patient's clinical picture, with resolution of presenting symptoms and a normalization of the hemoglobin, platelet count, and hemolysis markers.

Severe vitamin B_{12} deficiency is a known precipitant of "pseudo"-TMA that can mimic TTP. It is also known as cobalamin deficient thrombotic microangiopathy (c.def-TMA) [4, 5]. The pathophysiology is thought to be ineffective erythropoiesis due to impaired deoxyribonucleic acid (DNA) synthesis, which results in early destruction of poorly formed red blood cell and platelet precursors within the bone marrow space. These cells are more prone to lysis due to decreased deformability. This phenomenon, also known as intramedullary hemolysis, results in a severe anemia and thrombocytopenia with schistocyte formation, yet no microthrombi. Associated laboratory findings include profoundly elevated homocysteine and MMA levels, along with positive laboratory assays for hemolysis, all of which were seen in our patient. Assays to rule out other causes of MAHA, such as ADAMTS13 for TTP and complement levels for atypical HUS, are also required. The elevated homocysteine and MMA levels arising from insufficient vitamin B_{12} levels may also precipitate hemolysis by means of direct toxicity to developing red blood cells that are more fragile than usual due to ineffective erythropoiesis [6, 7].

The uncertainty of our patient's presentation and our institution's lack of in-house ADAMTS13 testing prompted us to utilize the PLASMIC score to help guide our decision on whether to initiate plasma exchange. This is a novel validated scoring

system that uses several criteria to determine the probability of the ADAMTS13 titer being ≤ 10% in patients presenting with thrombocytopenia and schistocytes on the peripheral smear concerning for TMA [2]. Fulfilling each criterion awards 1 point, with more points indicating a higher probability of having ADAMTS13 deficiency and therefore classical TTP. Patients are categorized into one of three risk categories: low risk (1–4 points, 4.3% risk of classical TTP), intermediate risk (5–6 points, 56.8% risk of classical TTP), or high risk (7 points, 96.2% risk of classical TTP). The variables assessed include a platelet count < 30×10^3/uL, MCV < 90 fL, INR < 1.5, creatinine < 2.0 mg/dL, evidence of hemolysis (such as an undetectably low haptoglobin or increased indirect bilirubin), no history of active cancer, and no history of prior stem cell or solid organ transplantation. Our patient met six of the seven criteria, not obtaining the 7th point due to a platelet count of 67×10^3/uL on presentation. This categorized him as intermediate risk (56.8%) for a low ADAMTS13 titer. Our patient's intermediate risk score further demonstrates the challenges associated with identifying "pseudo"-TMA in acutely ill patients and highlights the possibility of increased false positive rates when using even this highly sensitive scoring system.

The peripheral smear can also be a helpful tool in such unclear cases. Vitamin B_{12} deficiency usually leads to a macrocytic anemia with marked anisocytosis. Many erythrocytes are oval-shaped macrocytes with mean corpuscular volumes over 100 fL. Because they are thickened and contain an excess of hemoglobin, most macrocytes lack central pallor and are even hyperchromic without an elevated corpuscular hemoglobin concentration. This pathognomonic red blood cell morphology is often masked in the setting of TMA, however. This is due to red blood cell fragments depressing the MCV, as was the case in our patient's initial presentation. Neutrophils are also larger than normal and hypersegmented. Reticulocytopenia is another important feature that helps distinguish between vitamin B_{12} deficiencies and hemolytic anemias; in the latter, an intact marrow responds with a brisk reticulocytosis [8]. Our patient's reticulocytopenia was an early clue to a process other than TTP.

While our patient did not present with fevers and acute kidney injury, this is also the case for many TTP patients; as many as 35% will present without the full pentad, with fevers, neurological symptoms, and/or acute kidney injury often being absent. Often, providers must go by the presence of MAHA and thrombocytopenia alone in their clinical assessment for TTP [1]. Moreover, because there is such a high degree of morbidity and mortality in untreated TTP, awaiting diagnostic certainty can be dangerous for patients and these concerns were raised during our patient's initial assessment. Therefore, providers will often initiate potentially life-saving therapies, including plasma exchange and high-dose systemic corticosteroids, while the workup is underway [1, 3]. In our patient's case, the suboptimal response of the hemolysis parameters to plasma exchange and corticosteroids was a clue to an alternative diagnosis, and this was confirmed when he demonstrated remarkable clinical improvements only after cyanocobalamin injections were administered. In retrospect, we recognize that all three of his presenting findings—MAHA, thrombocytopenia, and ataxia—can all be explained by a severe deficiency of vitamin B_{12}. The hematological disturbances are due to the previously described ineffective erythropoiesis and subsequent intramedullary hemolysis, while the neurological symptoms are associated with vitamin B_{12} deficiency-associated metabolic anomalies in both the central and peripheral nervous systems, including cerebral dysfunction, subacute combined degeneration (SCD), and peripheral neuropathies [9]. This is further supported by the lack of fevers and acute kidney injury in our patient, neither of which is likely to occur secondary to vitamin B_{12} deficiency alone.

It is also interesting to consider the etiology of the vitamin B_{12} deficiency leading to the presentation. While numerous case reports of B_{12}-associated "pseudo"-TMA exist, very few to date have demonstrated pernicious anemia to be the underlying etiology behind the intramedullary hemolysis mimicking TTP [10–13]. This is critical, as 20–50% of adult vitamin B_{12} deficiency cases may be due to underlying pernicious anemia. Moreover, such patients usually require lifelong injections of vitamin B_{12} and cannot reliably be supplemented with oral vitamins [14]. Thus, patients presenting with "pseudo"-TMA secondary to vitamin B_{12} deficiency should be screened for the condition in the right clinical context (such as a history of other autoimmune conditions or concomitant gastrointestinal symptoms, as seen in our patient) and referred for appropriate management by a gastrointestinal specialist, which typically includes interval endoscopy for gastric cancer surveillance [15].

Finally, we considered whether the patient's prior hepatitis C treatment could be related in any way to his clinical picture, given that he concluded treatment 2 weeks prior to presentation. Alpha-interferon therapy for HCV has previously been linked to both exacerbations and new diagnoses of autoimmune gastritis, and the virus itself may sometimes cause autoimmune phenomena such as glomerulonephritis [16–18]. However, our patient never received this therapy and had no prior documented autoimmune syndromes classically associated with HCV. His disease was indolent at diagnosis, and he was successfully treated with glecaprevir and pibrentasvir (Mavyret™), which he tolerated well. This is a novel antiviral drug that is used to definitively treat serotype 1–6 HCV infections [19]. We did a literature review during his hospitalization to determine if any form of hemolysis might be associated with this drug. Common side effects noted were gastrointestinal discomfort, headaches, and fatigue, but no significant mention of any hematological processes was made [20]. The drug was therefore deemed an unlikely precipitant of the patient's presentation as compared to his vitamin B_{12} deficiency.

Conclusion

"Pseudo"-TMA is a rare yet serious presentation of severe vitamin B_{12} deficiency that mimics classical TMA syndromes such as TTP. Our patient presented with life-threatening MAHA, thrombocytopenia, and neurological symptoms (ataxia), which led to a high index of suspicion for TTP, yet ultimately was due to pernicious anemia leading to vitamin B_{12} deficiency with ineffective erythropoiesis and intramedullary hemolysis. While rare, severe vitamin B_{12} deficiency should be a consideration for any patient presenting with TMA, especially if they carry a history of other autoimmune conditions or unexplained gastrointestinal symptoms, as it can be rapidly identified and treated with readily available laboratory assessments and interventions.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. Scully M, Hunt BJ, Benjamin S, Liesner R, Rose P, Peyvandi F, Cheung B, Machin SJ (2012) Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol 158(3):323–335. https://doi.org/10.1111/j.1365-2141.2012.09167.x
2. Bendapudi PK, Li A, Hamdan A, Fry AM, Uhl L, Marques M, Kaufman R, Stowell CP, Dzik WS, Makar RS (2014) Derivation and prospective validation of a predictive score for the rapid diagnosis of thrombotic thrombocytopenic purpura: the Plasmic score. Blood 124(21):231
3. Bommer M, Wölfle-Guter M, Bohl S, Kuchenbauer F (2018) The differential diagnosis and treatment of thrombotic microangiopathies. Dtsch Arztebl Int 115(19):327. https://doi.org/10.3238/arztebl.2018.0327
4. Noël N, Maigné G, Tertian G, Anguel N, Monnet X, Michot JM, Goujard C, Lambotte O (2013) Hemolysis and schistocytosis in the emergency department: consider pseudothrombotic microangiopathy related to vitamin B_{12} deficiency. QJM 106(11):1017–1022. https://doi.org/10.1093/qjmed/hct142
5. Andrès E, Affenberger S, Federici L, Korganow AS (2006) Pseudothrombotic microangiopathy related to cobalamin deficiency. Am J Med 119(12):e3. https://doi.org/10.1016/j.amjmed.2006.02.001
6. Ballas SK, Saidi P, Constantino M (1976) Reduced erythrocytic deformability in megaloblastic anemia. Am J Clin Pathol 66(6):953–957
7. Acharya U, Gau JT, Horvath W, Ventura P, Hsueh CT, Carlsen W (2008) Hemolysis and hyperhomocysteinemia caused by cobalamin deficiency: three case reports and review of the literature. J Hematol Oncol 1(1):26. https://doi.org/10.1186/1756-8722-1-26
8. Aslinia F, Mazza JJ, Yale SH (2006) Megaloblastic anemia and other causes of macrocytosis. Clin Med Res 4(3):236–241
9. Reynolds E (2006) Vitamin B_{12}, folic acid, and the nervous system. Lancet Neurol 5(11):949–960. https://doi.org/10.1016/S1474-4422(06)70598-1
10. Merino A, Cid J (2013) Very unusual presentation of pernicious anemia with schistocytes in peripheral blood. Blood 122(24):3862
11. Aitelli C, Wasson L, Page R (2004) Pernicious anemia: presentations mimicking acute leukemia. South Med J 97(3):295–297. https://doi.org/10.1097/01.SMJ.0000082003.98003.88
12. Hershko C, Ronson A, Souroujon M, Maschler I, Heyd J, Patz J (2006) Variable hematologic presentation of autoimmune gastritis: age-related progression from iron deficiency to cobalamin depletion. Blood 107(4):1673–1679. https://doi.org/10.1182/blood-2005-09-3534
13. Tadakamalla AK, Talluri SK, Besur S (2011) Pseudo-thrombotic thrombocytopenic purpura: a rare presentation of pernicious anemia. N Am J Med Sci 3(10):472–474. https://doi.org/10.4297/najms.2011.3472
14. Andres E, Serraj K (2012) Optimal management of pernicious anemia. J Blood Med 3:97. https://doi.org/10.2147/JBM.S25620
15. PDQ Screening and Prevention Editorial Board (2018) Stomach (Gastric) Cancer Screening (PDQ®): Health Professional Version. PDQ Cancer Information Summaries [Online]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65730/. Accessed 21 Oct 2018
16. Andrès E, Loukili NH, Abdelghani MB, Noel E (2004) Pernicious anemia associated with interferon-α therapy and chronic hepatitis C infection. J Clin Gastroenterol 38(4):382
17. Fabbri C, Jaboli MF, Giovanelli S, Azzaroli F, Pezzoli A, Accogli E, Liva S, Nigro G, Miracolo A, Festi D, Colecchia A (2003) Gastric autoimmune disorders in patients with chronic hepatitis C before, during and after interferon-alpha therapy. World J Gastroenterol: WJG 9(7):1487–1490
18. McMurray RW, Elbourne K (1997) Hepatitis C virus infection and autoimmunity. Semin Arthritis Rheum 26(4):689–701. https://doi.org/10.1016/S0049-0172(97)80005-4
19. Kwo PY, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, Felizarta F, Sulkowski MS, Gane E, Maliakkal B, Overcash JS (2017 Aug 1) Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1–6 without cirrhosis. J Hepatol 67(2):263–271. https://doi.org/10.1016/j.jhep.2017.03.039
20. Pol S, Pockros PJ, Pugatch D, Brau N, Landis C, Elkhashab M, Sasadeusz J, Tran A, Hu Y, Kosloski MP, Mensa F (2017) Safety and efficacy of Glecaprevir/Pibrentasvir in adults with chronic hepatitis C virus infection genotype 1 and 6 and chronic kidney disease: an integrated analysis. Gastroenterology 152(5):S1062–S1063. https://doi.org/10.1056/NEJMoa1704053