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Case Report

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A case of Fisher-Evans syndrome in a patient with type 2 diabetes mellitus after a COVID-19 infection

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Clinical case

Patient A., female, aged 57, was admitted to the hospital with complaints of an increasing general weakness, low-grade fever, discomfort in the right hypochondrium, nausea, lack of appetite, icteric skin and sclera during the last week, the appearance of bruises on the body, hemorrhages that appear after injections or taking blood samples. Patient associated her condition with the COVID-19 infection 2 months before admission.

The next day after admission, multiple hemorrhages appeared on the oral mucosa, blood pressure decreased, body temperature raised. She was consulted by a hepatologist and hematologist. Myelogram showed Fisher-Evans syndrome signs. Treatment started according to the protocol. On the third day, the patient showed a progressive deterioration, which was manifested by an increase in general weakness, motor aphasia, followed by the appearance of generalized tonic-clonic seizures with spontaneous resolution. Despite the intensive therapy, according to the recommendations of the hematologist (plasma and blood transfusion, glucocorticoids pulse-therapy) the patient's condition progressively worsened. In the dynamics, hemoglobin and platelets decreased, signs of cerebral edema developed. On day 4 patient deceased.

Conclusion

Special attention should be paid to the prevention of recurrence of hemolysis and (or) thrombocytolysis in the event of infectious diseases, especially viral ones. The intake of drugs that block platelet function (for example, antiplatelet agents and anticoagulants) should be strictly controlled. In the presence of autoimmune pathology on an outpatient basis, clinical examination of such patients by hematologists, therapists and immunologists is necessary. Further study of the etiology and pathogenesis of the development of FES, observation of patients, identification of possible predictors of the severity of the disease and the development of an optimal therapy strategy are required.

Keywords: Diabetes, COVID-19, Fisher-Evans syndrome

Clinical case

Patient A., female, aged 57, was admitted to the hospital with complaints of an increasing general weakness, low-grade fever, discomfort in the right hypochondrium, nausea, lack of appetite, icteric skin and sclera during the last week, the appearance of bruises on the body, hemorrhages that appear after injections or taking blood samples. Patient associated her condition with the COVID-19 infection 2 months before admission.

Anamnesis: Has had type 2 diabetes for 5 years. Takes Metformin 1000 mg bid, Vildagliptin 50 mg per day. Glycemia within 7.6-9.8 mmol/L. Has artherial hypertension. Had stroke in 2013. Also takes Bisoprolol 2.5 mg, Aspirine 75 mg daily.

Blood group: 0 (I) Rh+.

The next day after admission, multiple hemorrhages appeared on the oral mucosa, blood pressure decreased to 80/50 mm Hg, body temperature raised to 37.2°C. She was consulted by a hepatologist

and hematologist. Due to suspicion of Fisher-Evans syndrome, bone marrow was harvested. Treatment started according to the protocol. On the third day, the patient showed a progressive deterioration, which was manifested by an increase in general weakness, motor aphasia, followed by the appearance of generalized tonic-clonic seizures with spontaneous resolution.

Table 1: Laboratory and instrumental data, reference values are indicated in brackets

CBC	Day 1	Day 3	Day 4
HGB (120 – 140 g/L)	86	77	69
Ht (33 – 44%),	27	22,8	19,9
Erythrocytes (3.9–4.7*10^12/L)	2.8*10^12/L	2.4*10^12/L	2.1*10^12/L
Leucocytes (4.0–9.0*10^9/L)	9.3*10^9/L	10.2*10^9/L	20.5*10^9/L
Platelets (180 – 320*10^/L)	69*10^9/L	48*10^9/L	18*10^9/L
Thrombocrite (0.108–0.282%).	0.27%	0.26%	0.012%
ESR (0 – 15 mm/h)	36	45	54
Leucocytes:			
Stab (1 – 5%)	1	2	4
Segmented (47 – 72)	45	43	82
Eosinophils (1 – 6%)	6	7	--
Monocytes (3 – 11%)	4	5	6
Lymphocytes (19 – 39%)	44	43	8
General urine analysis			
Protein, g/L	0.033	0.066	1.68
Blood biochemistry			
Alkaline phosphatase (30 – 120 U/L)	95	120	
ALT (7 – 31 U/L)	34	36	
AST (7 – 34 U/L)	49	60	
Total bilirubin (5.1–17 μmol/L)	126.4	193.6	
Coagulogram			
Willibrand factor (50 – 150%)	144	---	
Fibrinogen (2 – 4 g/L)	3.9	3.6	
APTT (20`` – 30 ``)	28.4	26.4	
D-dimer (0 – 0,5 mg/L)	1.63		
IL 6 (1 – 7 pg/ml).	4.03		

Myelogram

Bone marrow cells	Reference values	Value
Blasts	0.3-2.8	0.8
Promyelocytes	1.0-4.1	0.4
Myelocytes	6.9-12.12	8.4
Metamyelocytes	8.0-14.9	8.8
Stab	12.8-23.7	**10.0**
Segmented	13.1-24.1	19.2
Eosinophils	0.5-5.8	**0.4**
Lymphocytes	4.3-13.7	**2.0**
Monocytes	0.7-3.1	**0.4**
Plasmacytes	0.1-1.8	0.4
Basophilic normocytes	1.4-4.6	1.6
Polychromatophilic normocytes	8.9-16.9	**33.8**
Oxyphilic normocytes	0.8-5.6	**13.8**
Leuko-erythroblast ratio	2.1-4.5:1	**1:1**
Megakaryocytes	5 - 13	**numerously**

Abdominal ultrasound revealed hepatomegaly (+ 1.5 cm) Fatty liver disease. Chronic pancreatitis. Moderate splenomegaly. Valsava's test is positive. Severe intestinal pneumatosis.

Examined by a cardiologist: Stable exertional angina FC-2. Hypertensive disease stage 3 AH - 0. Risk – 4, very high. Chronic heart failure 1st stage. FC II by NYHA.

Examined by a hematologist: Fisher-Evans syndrome with symptomatic thrombocytopenia and hemolysis.

Despite the intensive therapy, according to the recommendations of the hematologist (plasma and blood transfusion, glucocorticoids pulse-therapy) the patient's condition progressively worsened. In the dynamics of hemoglobin indices with a decrease to 69 g/L, platelets - down to 18*10^9/L, signs of cerebral edema increased. On day 4 patient deseased.

Postmortem diagnosis:

Primary: Fisher-Evans syndrome with symptomatic thrombocytopenia and hemolysis.
Background: type 2 diabetes mellitus.
Complication: Diabetic encephalopathy 3. Diabetic polyneuropathy 2. Diabetic nephropathy CKD C2A3 (GFR 72 mL/min/1.73 m2). Diabetic macroangiopathy.

Concomitant: Atherosclerosis of the vessels of the brain. Condition after stroke (2013). Ischemic heart disease. Exertional angina FC 2. GB 3. AH 0 risk 4. CHF 1 FC II (NYHA). Chronical bronchitis. Chronic gastroduodent. Chronic cholangiohepatitis. Reactive pancreatitis. IBS.

Discussion

Fisher-Evans syndrome (FES) is a rare disorder characterized by immune thrombocytopenia (ITP) and Coombs-positive autoimmune hemolytic anemia (AIHA). At the same time, ITP and AIHA can develop simultaneously or sequentially with an interval from several months to several years.

For the first time, FES was described in children in 1950-1958. However, recent studies show that the syndrome can develop at any age. At the time of diagnosis, the average age is 55±33 years. The disease is the most often seen in female [3].

FES is subdivided into primary (idiopathic) and secondary (symptomatic); the incidence in patients with autoimmune hemolytic anemia is 37–73% [1]. Primary, or idiopathic, FES does not have any connection with other diseases, while secondary FES may be a manifestation of another underlying disease or be concomitant with it. Symptomatic form in 82% of cases was observed in chronic hepatitis, systemic lupus erythematosus, chronic lymphocytic leukemia, lymphomas, rheumatoid arthritis, tuberculosis, autoimmune hepatitis, and diabetes mellitus. All of these pathologies were accompanied by a positive titer of antinuclear antibodies and a change in the level of serum immunoglobulins.

The pathogenesis is based on the increased destruction of erythrocytes and platelets due to the fixation of proteins autoantibodies on their surface. Anti-erythrocyte antibodies are often incomplete agglutinins and belong to different classes of immunoglobulins (G, less often M or A). They specifically bind to antigens of the Rh system; in some cases, they are directed against antigens of other systems. The specificity of antiplatelet immunoglobulin G has not been established, but it has been proven that its content on the surface of erythrocytes is increased in comparison with the normal state [1].

At the time of the development of FES, patient A. had already had

diabetes mellitus, as well as a history of hepatitis. In addition, the patient had coronavirus infection in two months before admission, which could also cause an increase in immunoglobulins and the development of symptoms of thrombotic microangiopathy. But a high risk of cardiovascular and neurological complications in the patient was presumably due to AIHA but not ITP.

Clinical manifestations of FES include the usual symptoms of thrombocytopenia (hemorrhagic rash, bruising, bleeding) and hemolytic anemia (weakness, pallor, drowsiness, jaundice) that the patient had on admission. Symptoms of the disease can develop acutely or gradually [2, 3].

Laboratory presence of the syndrome was confirmed by the detection of hemolytic anemia, thrombocytolysis, reticulocytosis and relative neutropenia in the myelogram [1].

The diagnosis is made on the basis of the clinical picture and the direct Coombs' reaction, which confirms the autoimmune nature of hemolysis. However, in some cases, negative results of the Coombs' test did not exclude the presence of immune hemolysis in the patient, since with increased hemolysis, a significant part of the erythrocytes loaded with antibodies is destroyed.

Also, differential diagnosis was carried out with hemolytic-uremic syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, leukocytosis, clinically manifested diarrhea, vomiting, fever, pallor, acute renal failure, mainly secondary to infections with E. coli, Shigella. Dysentery or Streptococcus pneumoniae.

Due to the lack of data on the dosage of drugs used in the treatment of a previous coronavirus infection in a patient, it is difficult to exclude heparin-induced thrombocytopenia and anemia.

Conclusions

Fisher-Evans syndrome is a chronic relapsing disease, not just a combination of immune cytopenias, but a condition caused by a profound dysregulation of the immune system. Due to the small number of patients with Fisher-Evans syndrome, no randomized trials have been conducted to develop optimal therapy protocols. In most cases, FES is a secondary syndrome and is associated with other autoimmune diseases. All studies conducted to date indicate a poor prognosis of the disease. To date, no literature data and clinical cases with the development of Fisher-Evans syndrome in adult patients who have undergone coronavirus infection have been provided.

Based on this, special attention should be paid to the prevention of recurrence of hemolysis and (or) thrombocytolysis in the event of infectious diseases, especially viral ones. The intake of drugs that block platelet function (for example, antiplatelet agents and anticoagulants) should be strictly controlled.

In the presence of autoimmune pathology on an outpatient basis, clinical examination of such patients by hematologists, therapists and immunologists is necessary.

Further study of the etiology and pathogenesis of the development of FES, observation of patients, identification of possible predictors of the severity of the disease and the development of an optimal therapy strategy are required.

Written consent was obtained from the relatives of the patient for publication.

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