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Fisher-Evans Syndrome. Casereport in Physician's Practice

Abstract

This article presents the clinical features and treatment options for autoimmune thrombocytopenic purpura associated with autoimmune hemolytic anemia — Fisher-Evans syndrome. Patient P., aged 68 years, was admitted to the hospital by an ambulance team with a referral diagnosis of acute pancreatitis. Hemorrhagic and anemic syndromes were the main clinical signs. Physical examination revealed a strip-formed hemorrhagic rash in the area of inguinal folds, the anterior surface of thighs and lower legs. In the course of differential diagnostics, Fisher-Evans syndrome was diagnosed. Initial oral and pulse therapy with prednisolone was not effective. The patient received platelet transfusions regularly. When eltrombopag was included in therapy, there was an improvement in the patient's condition, as well as a tendency to a rising level of platelets. On the 35th day, the patient was discharged from the hospital.

We examined various clinical variants of thrombocytopenia common in real clinical practice.

Keywords: *Fisher-Evans syndrome, clinical features of thrombocytopenia, prednisolone, eltrombopag*

Conflict of interests

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BP — blood pressure, CBC — complete blood count, CT — computed tomography, UA — urinalysis, EGD — esophagogastroduodenoscopy, FCS — fibrocolonoscopy, FES — Fisher-Evans syndrome, GC — glucocorticoids, GED — gastroenterological department, HELLP syndrome –hemolysis, elevated liver enzymes, low platelet count (thrombocytopenia) in the third trimester of pregnancy, ITP — idiopathic thrombocytopenic purpura, NSAIDs — non-steroidal anti-inflammatory drugs, US — ultrasound

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Introduction

Idiopathic thrombocytopenic purpura, or primary immune thrombocytopenia (ITP), is a disease that is an isolated immune-mediated thrombocytopenia (the number of platelets in peripheral blood is less than 100×10^9/L) that occurs and/or persists without any clear reasons, with or without hemorrhagic syndrome of different severity [1]. Typical manifestation of ITP is the development of petechiae or purpura with an underlying health condition a few days or weeks after past infectious diseases.

ITP combined with autoimmune hemolytic anemia is called Fisher-Evans syndrome (FES). The disease was first described in 1947 by J.A. Fisher who suggested the immune genesis of anemia and thrombocytopenia. In 1951, R. Evans examined 24 patients aged 3 to 78 years with isolated AIHA, isolated thrombocytopenia (in some cases neutropenia was also registered) and different variants of their combinations [2].

The incidence of ITP in the world is 1.6-3.9 cases per 100,000 people per year; the prevalence ranges from 4.5 to 20 cases per 100,000 people.. Children are sick more often than adults are, and peak incidence occurs in five years.

Despite the fact that the first cases of the development of FES were described in pediatrics, its manifestation can be observed at any age. According to one study performed in Denmark from 1977 to 2017, the median incidence of FES was 58.5 years [3].

FES is a diagnosis of exclusion because it can be both primary and secondary in relation to other diseases. Its association with the following pathological conditions was described: systemic lupus erythematosus, antiphospholipid syndrome, HIV infection, viral hepatitis, lymphoproliferative diseases, etc. Association of FES with Helicobacter pylori contamination can not be excluded.

The following is a description of the clinical case of patient P., aged 69 years, with primary FES.

Case report

Patient P., until 2018, had a satisfactory state of health. There was a history of compensated hypertensive disease with maximum blood pressure (BP) of 150 and 90 mm Hg, without cardiovascular events; as well as general osteochondritis with back pain; for it, the patient took non-steroidal anti-inflammatory drugs (NSAIDs) systematically for six months. In addition, since 2017 there was noticeable weight loss by 20 kg (from 73 kg to 53 kg).

No significant hereditary or medication history: the patient and her relatives had no allergic or autoimmune diseases, no malignant neoplasms.

In the spring of 2018, patient P. noted the appearance of weakness and shortness of breath with slight physical exertion; as a result, she consulted a therapist at the place of residence.

CBC in the course of outpatient examination revealed decreased hemoglobin to 95 g/L, white blood cells amounted to $5.8*10^9$/L), platelets were not determined. Without testing for serum iron level, an iron supplement was prescribed; the patient took it for 2 months with no effect. Two weeks before hospitalization, dull pains emerged in the epigastric area and left hypochondrium with no definite connection with food intake or physical activity, as well as temperature periodically raising up to 38 °C without chills, which lasted up to 1-2 hours, twice a week, and normalized without any interventions. There were no dyspeptic or dysuric signs. Stool was formed, with no blood admixtures.

P. visited the local clinic at the place of residence wherefrom she was transported by an ambulance team to Buyanov City Clinical Hospital with a referral diagnosis of acute pancreatitis (?). During examination in the emergency room, no data for acute surgical pathology was obtained (the following was performed: plain radiography and ultrasound examination (US) of abdominal organs, complete blood count (CBC) and urinalysis (UA), consultation by surgeon). Due to the unclear cause of abdominal pain, the patient was hospitalized in the Gastroenterological Department (GED).

In the GED, the patient had the same complaints of weakness, fatigue, discomfort in the epigastric area. Her condition was considered as of moderate severity. Body temperature was 36.8 °C. Body mass index — 18.75 kg/m^2. Skin and visible mucosae were pale, with no icteric discolor. Lymph nodes were not enlarged. On the skin, in the area of inguinal folds and on the anterior surface of both thighs, there was a hemorrhagic rash in the form of a strip

4 cm wide; a similar but less intense rash was in the area of the lower legs (Figure 1).

In lungs — vesicular breathing, tachypnea — up to 24 respiratory movements per minute. Heart sounds were weakened, rhythm was regular, tachycardia — heart rate of 100 bpm, hypotension (BP — 90 and 60 mm Hg). The tongue was moist. The abdomen was of normal size, soft, not sharply tender on palpation in the upper part, in the right hypochondrium. The liver and spleen on percussion and palpation are not enlarged.

CBC revealed mild normochromic microcytic anemia (hemoglobin — 94 g/L), leukopenia — 3.3×10^9/L with no WBC differential shift, and severe thrombocytopenia — 14×10^9/L. Blood test showed reticulocytosis (25%); as a result, the hemolytic nature of anemia was suspected and subsequently confirmed with Coombs test.

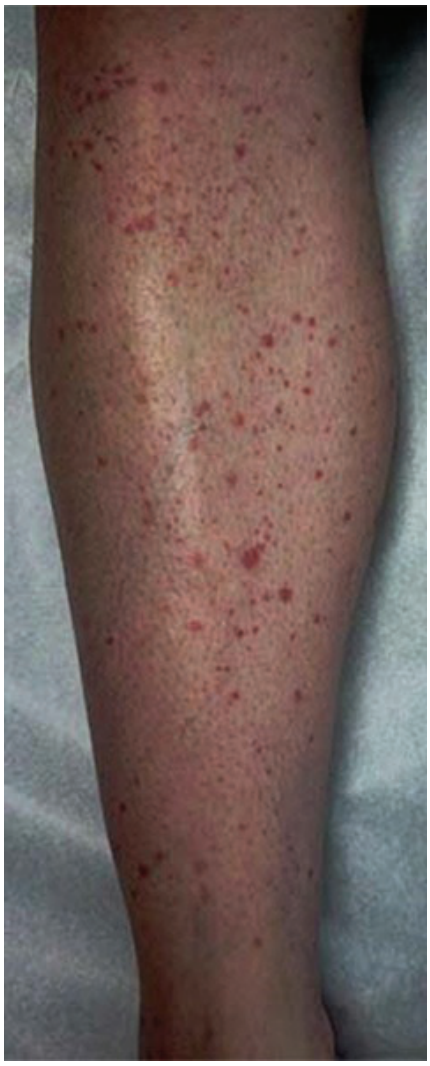

Figure 1. *Petechial rash on the lower extremity of patient P.*

UA results revealed urobilinogen (3.2 μmol/L); qualitative bilirubin determination was negative; protein, glucose — not found.

Blood biochemistry results were the following: alanine (9 IU/L) and aspartate (27 IU/L) aminotransferases, total bilirubin (15 μmol/L), conjugated bilirubin (2 μmol/L), unconjugated bilirubin (13 μmol/L), alkaline phosphatase (108 IU/L), lactate dehydrogenase (230 IU/L), total protein (66 g/L), urea (7 mmol/L), creatinine (92 μmol/L), serum iron (11 μmol/L), glucose (5.2 mmol/L), a-amylase (108 IU/L) — nothing abnormal detected. Coagulogram revealed a more than five-fold increase in D-dimers (3,020 μg/L), other parameters (prothrombin index (100%), thrombin time (17.4 s), fibrinogen (2.2 g/L), international normalized relation (1)) were within the reference range.

During bacteriological tests of body fluids (blood, urine), no microflora growth was obtained.

ECG: normal position of QRS axis, signs of left ventricular hypertrophy, tachycardia — 98 bpm.

Ultrasound of abdominal organs and kidneys revealed no pathological changes in the liver, biliary system, spleen, and kidneys; there was only increased echogenicity of pancreas.

Taking into account the long-term use of NSAIDs and anemia, endoscopic studies were performed.

Results of esophagogastroduodenoscopy (EGD) showed the following: cardiac rosette closes incompletely, superficial gastritis (gastric mucosa is diffusely moderately hyperemic, thinned, vascular pattern is accentuated); no visible changes of esophageal and duodenal mucosa. During fibrocolonoscopy (FCS), all parts of the colon were examined, an endoscope was introduced in the cecum. Mucosa of the colon was pale pink, smooth, vascular pattern without changes, mucosa was segmentally hyperemic only in certain parts of the sigmoid colon, with superficial, contact-bleeding, single erosions of up to 2-3 mm with clearly visible vasculature. No biopsy of intestinal mucosa was performed due to the high risk of bleeding.

The patient was also comprehensively examined in connection with oncologic alarm: computer tomography (CT) of thorax, abdomen and small pelvis revealed no pathological changes.

Sternal puncture was performed to exclude an oncohematological disease. The bone marrow

biopsy specimen was rich in cell elements, there were no blasts, the amount of plasmatic cells was 2%. Megakaryocytes were present in sufficient quantity (0.5%). Impaired platelet release deserved special attention.

Tests for antiphospholipid and lupus antibodies were also performed in order to exclude systemic lupus erythematosus in a patient with fever, hemorrhagic rash and thrombocytopenia; negative results were obtained.

Taking into account severe thrombocytopenia, hemorrhagic presentation and required invasive examination methods (sternal puncture, endoscopy, FCS, blood tests), multiple platelet transfusions were performed (in the amount of 1 dose, daily, during 20 days). The control test 2 hours after transfusion showed that the platelet level increased to $80x10^9$/L, however, the next day it returned to baseline. Changes in blood test parameters are presented in Table 1.

Based on examination results, patient P. was diagnosed with primary FES, glucocorticoid (GC) therapy was started — Metypred 44 mg.

However, on the 14th day of treatment with GC, the aggravation of hemorrhagic syndrome was observed, which was manifested by confluent ecchymoses on the right upper extremity and the abdomen, and hemorrhage in the conjunctiva of the right eye. The patient's condition was considered unstable, in light of which platelet mass transfusion in the same dose was continued, and GC pulse therapy was performed — for three days with intravenous prednisolone at the dose of 300 mg/day.

Due to the lack of positive changes in the patient's condition on the 25th day of hospitalization, a stimulator of thrombocytopoiesis, eltromboрag, was added once to the treatment of P. — at the dose of 50 mg per os (for the period of 25th — 35th day of hospitalization). Gradual dose tapering of GC was started.

The patient was discharged on the 35th day with the final diagnosis of primary, rapidly developed FES (extremely severe thrombocytopenia, mild anemia, minimal leukopenia). Complications: erosive sigmoiditis. Concomitant pathology: hypertensive disease stage 2, grade 2, risk 3 (medical history data). Chronic kidney disease 3a (glomerular filtration rate according to CKD-EPI — 54.73 mL/min/1.73 m^2). Chronic gastritis, cardia insufficiency. General osteochondritis with back pain.

In the course of treatment, P.'s condition stabilized (body temperature remained normal, the area and intensity of hemorrhagic rash decreased, the severity of weakness also decreased), platelets, hemoglobin, WBC with a tendency to increase (Table 1).

Table 1. *Changes in basic laboratory parameters in patient P.*

Parameters, reference range /	23.06.18	25.06.18	26.06.18	09.07.2018	21.07.2018	25.07.18
Hemoglobin (112-153 g/L)	94	93	87	93	105	106
RBC (3.8-5.15*10^{12}/L)	3.60	3.31	3.13	3.39	3.68	3.54
Hematocrit (34.9-45.6%)	28.6	26.9	26.0	28.6	31.4	30.4
Mean Cell Volume (82-98 fL)	79.4	81.0	83.1	84.0	85.3	86.0
Mean Cell Hemoglobin (26.7-33 pg)	26.1	28.2	27.2	27.4	28.5	30.0
Platelets (150-375*10^9/L)	14	10	11	9	16	81
WBC (3.4-10.8*10^9/L)	3.3	3.10	1.90	6.80	4.50	5.40
Iron (9.0-30.4 μmol/L)	-	-	10.5	-	10.4	-
Procalcitonin (0.05-0.50 ng/mL)	-	0.11	-	-	-	-
C-reactive protein (0.1~7.0)	-	17.9	17.7	3.9	1.6	-

The patient was recommended to continue taking eltrombopag at the dose of 50 mg per day with food; Metypred 16 mg (8 mg at 07:00 a.m. and 8 mg at 10:00 a.m.); Omeprazole 20 mg in the evening; Rebamipide 100 mg three times a day; Enalapril 10 mg twice daily. The patent was referred to a hematologist at the place of residence for further management and therapy correction. If any invasive methods of examination and treatment are required, in order to prevent hemorrhagic complications, it will be preferable to perform platelet transfusions for patient P. It is recommended to avoid insolation and taking drugs that block platelet function; to exclude NSAIDs; to avoid contact with patients with viral infections. The decision to conduct vaccine prophylaxis should be made strictly on an individual basis.

Discussion

At the stage of the initial examination of patient P., clinical signs were caused by anemic syndrome. Difficulties in establishing primary diagnosis involved the need for making differential diagnosis between a stable existing chronic disease and a subacute life-threatening pathology. Tachypnea, hypotension, tachycardia with fever required the exclusion of organ dysfunction syndrome. In this regard, the question of the patient's location — in the general ward or in intensive care unit — was solved.

In clinical practice, the SOFA scale is used to assess organ dysfunction syndrome. According to literature, the most important aspect in the treatment of multiple organ failure, including sepsis, is its timely diagnosis. In order to screen for organ dysfunction at the patient's side, Quick SOFA criteria were developed. Our patient had 2 points (systolic BP at admission — 90 mm Hg, RR — 24/min), which also indicated a high probability (80%) of sepsis.

Changes in laboratory parameters (cytopenia and high D-dimers) did not exclude the possibility of generalized response to an unspecified infectious agent. However, the patient had no classic symptoms of inflammation. Instrumental diagnostic methods revealed no infectious focus.

An important aspect in the diagnosis of sepsis is finding biomarkers. The procalcitonin level in P. was 0.11 ng/mL, which, with a high degree of accuracy, indicates the absence of sepsis. Negative results of biological fluids culture were a significant confirmation of this suggestion. Thus, the patient's severe condition was most likely due to a chronic disease.

The differential diagnosis included the following: hemoblastoses, myelodysplastic paraneoplastic syndromes, aplastic anemia. Absence of splenomegaly, normal level of lactate dehydroginase activity made it possible to exclude myelofibrosis, acute leukemia, etc.

No signs of disseminated intravascular coagulation in the presence of hemolytic anemia brought into question such a rare pathology as paroxysmal nocturnal hemoglobinuria in this patient. Taking into account the prevailing hemorrhagic syndrome, we could not exclude platelet pathology as the main factor determining the clinical picture.

Hemorrhagic syndrome can be of various etiology. There can be vasculitis, thrombocytopathy, coagulopathy. The type of bleeding in these cases has a microcirculatory character and occurs with thrombocytopenias and thrombocytopathies, von Willebrand disease, deficiency of prothrombin complex factors (VII, X, V and II), some variants of hypo- and dysfibrinogenemias, moderate overdose of anticoagulants.

It should also be emphasized that thrombocytopenia can both be a primary pathology and proceed with an underlying oncological process. According to the results of thorough instrumental examination (CT of thoracic and abdominal organs, ultrasound of abdomen, kidneys, small pelvis, thyroid gland, EGD, FCS), no signs of tumor process were found.

In the analyzed case, the leading pathological symptom in the clinical picture of patient P. was pancytopenia in combination with hemorrhagic and anemic syndromes. Hyperthermia was apparently non-specific. Taking into account the clinical picture and results of examination in patient P., we diagnosed her with FES.

Thus, differential diagnostics of thrombocytopenia is a very difficult task. Figure 2 shows the most common diseases associated with thrombocytopenia.

We suppose that, first of all, urgent pathology requiring urgent hospitalization should be excluded. Patients with infectious pathology belong to a special category. Burdened epidemiological history, prodromal period, and fever are reliable markers

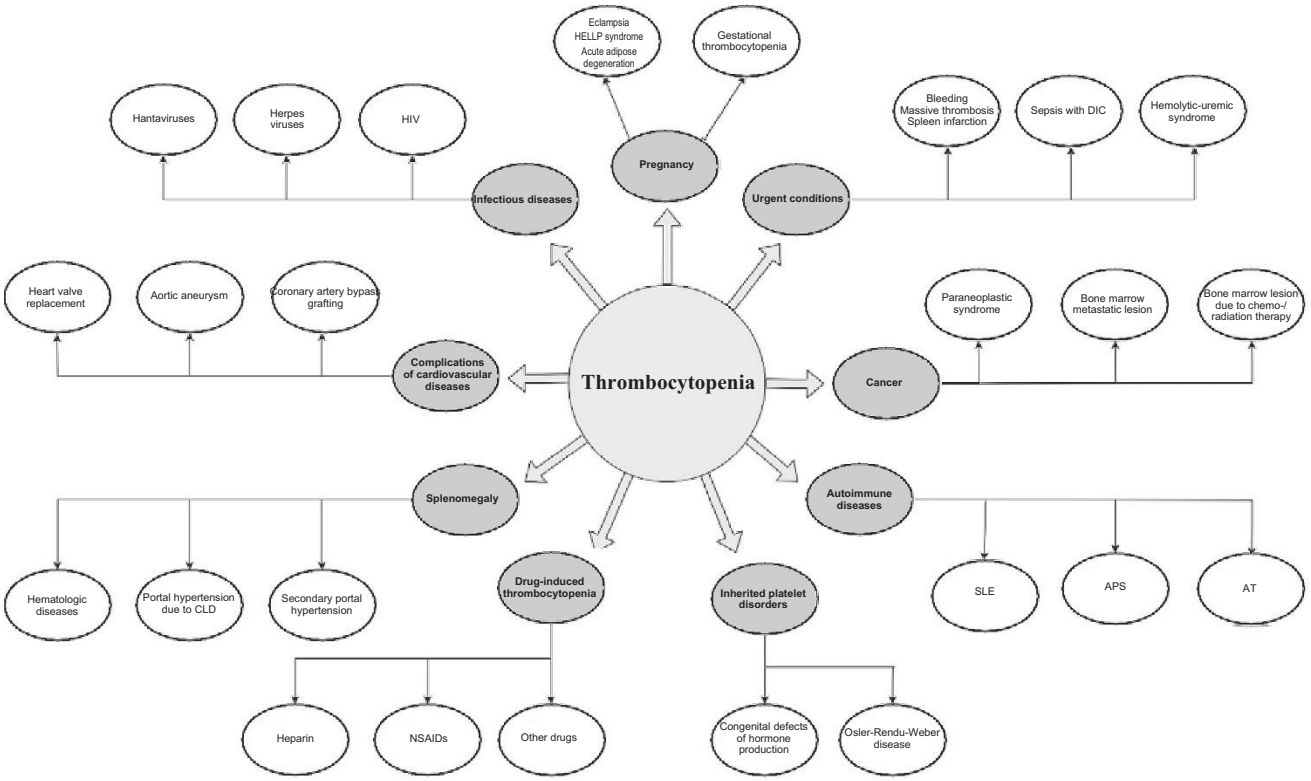

Figure 2. *Thrombocytopenia-associated conditions*

Note: AT — autoimmune thyroiditis, APS — antiphospholipid syndrome, HIV — human immunodeficiency virus, HUS — hemolytic-uremic syndrome, DIC — disseminated intravascular coagulation, NSAIDs — non-steroidal anti-inflammatory drugs, SLE — systemic lupus erythematosus, CLD — chronic liver disease, HELLP syndrome — hemolysis, elevated liver enzymes, low platelet count in the third trimester of pregnancy

for diagnosing this condition. The main cause of thrombocytopenia in the intensive care unit is sepsis complicated by disseminated intravascular coagulation syndrome, most often caused by pneumonia, urosepsis, or soft tissue infection.

Considering special medical and social significance, attention should be paid to women of childbearing age. Gestational thrombocytopenia is the most common cause; it is characterized by spontaneous regression after childbirth and is not associated with adverse outcomes for mother and child. However, we should not forget about such serious conditions as eclampsia/preeclampsia and HELLP syndrome.

In addition to thrombocytopenias typical for gestation, hematological pathology, including ITP, can not be excluded in women.

The exclusion of any technical error in laboratory tests should be considered the second step in the diagnostics of thrombocytopenia; it requires the assessment of morphological characteristics and platelet count according to the Fonio method.

Splenomegaly is typical for the pathology of both the hepatobiliary area due to portal hypertension and hematological pathology. Differential diagnosis is performed taking into account hepatic cell function (prothrombin, total protein and fractions, activity of cytolysis and cholestasis enzymes), the exclusion of secondary portal hypertension. In difficult cases, sternal puncture is performed.

The diagnosis of drug-induced thrombocytopenia is complex. According to some authors, the presence of antiplatelet antibodies is not a reliable marker of this pathology. Only an increase in platelet count after drug withdrawal allows its diagnosis. In addition to common heparin-induced thrombocytopenia, there are many descriptions of cases with decreased platelet count while taking NSAIDs, antiarrhythmic, or antibacterial agents. Drug-induced thrombocytopenia develops more often within 1-5 days of drug administration.

In addition, there are secondary thrombocytopenias in patients with rheumatological and oncological diseases.

It is also not always possible to correct thrombocytopenia in patients with severe cardiovascular diseases, especially after surgical interventions.

Conclusion

FES is a diagnosis of exclusion. However, in addition to difficulties in diagnosing this syndrome, it should be emphasized that in the case of our patient there was resistance to treatment.

According to Russian and foreign publications, GCs (in particular, prednisolone) are the first-line FES therapy, at the dose of 1-2 mg/kg of body weight.

In patient P., 44 mg of Metypred per os and pulse therapy had no expected effect. In more than 70% of adult patients with FES, this tactic is also not effective [1, 5].

Due to the small number of patients, no randomized studies of other therapeutic options for FES were performed, and no therapy algorithm was developed.

Second-line therapy includes rituximab, cyclosporin A, mycophenolate mofetil, vincristine; splenectomy and transplantation of stem hematopoietic cells can be performed [4, 5].

We effectively used a thrombopoietin receptor agonist eltrombopag. This approach was successfully used in patients of different age groups, and it was first used in children with FES.

Using blood components is discussed as a separate issue in the treatment of FES. According to the recommendations of the Russian Society of Hematologists, transfusion of platelet concentrate is not effective. However, with a decrease in platelet count to $50x10^9$ L, the risks of hemorrhagic events appear [1, 5]; in this regard, transfusion of a platelet concentrate in such conditions is necessary, and with the appearance of small-point hemorrhages on the upper part of the body, hemorrhages in conjunctiva and fundus, local bleedings (gastrointestinal tract, uterus, kidneys, bladder), transfusion of platelet concentrate is an urgent, vitally indicated procedure.

Thus, FES is one of the complex diagnostic and therapeutic problems, the awareness of which will allow physicians to help their patients more effectively and in a timely manner. However, in general, the prognosis of FES remains serious due to the recurrent nature of this disease, as well as the development of infectious and hemorrhagic complications during ongoing GC therapy.

Contribution of the authors:

All authors have made a significant contribution to preparation of this article, have read and approved the final version before publication.

A.A. Yakushev: writing, creating figures
L.Yu. Ilchenko: writing and editing the article
I.G. Fedorov: analysis of obtained data
S.S. Shmykova: search for literature
N.V. Ilyin: search for literature
G.G. Totolyan: analysis of obtained data
I.O. Sirenova: editing of the article
I.G. Nikitin: design and approval of the final version of article

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