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Evans Syndrome Associated with Mixed Herpes Encephalitis in A Young Immunocompetent Patient: Illustration of the Difficulty of Therapeutic Management in the Face of this Complex Dysimmune Syndrome and Review of the Literature

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ABSTRACT

Introduction: *Evans syndrome (ES) is a rare disease in which the immune system produces antibodies that mistakenly destroy red blood cells, platelets and neutrophils.*

Observation: *Primary Evans syndrome without cause is very rare and is observed in children; here we describe a case of Evans syndrome associated with mixed herpes viral encephalitis in a young 16-year-old immunocompetent patient whose outcome was fatal. The article presents the therapeutic difficulties specific to this case in our context and also reviews the existing literature on the diagnosis and treatment of this condition.*

Conclusion: *ES is a serious pathology with complex diagnosis and treatment, it requires multidisciplinary care associated with therapeutic education.*

Keywords
Evans syndrome, Encephalitis, Dysimmune syndrome, Internal medicine.

Introduction

Evans syndrome (ES) is a rare autoimmune disease characterized by two or more cytopenias, occurring simultaneously or sequentially, autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP), and in 15% of cases also cases immune neutropenia [1]. Although the syndrome was first considered an "idiopathic" disease and therefore considered a diagnosis of exclusion, approximately half of cases are associated with other pathologies or conditions, including infections (e.g., hepatitis C virus, human immunodeficiency virus, herpes viruses), systemic lupus, common variable immunodeficiency, autoimmune lymphoproliferative syndrome and other lymphoproliferative diseases [1]. ES develops with chronicity and relapses even with controls, and having a poor prognosis [2].

Its management is always a challenge. ES in children may be part of a more complex clinical situation due to primary immunodeficiency disorders (PIDs) that need to be discussed, as the diagnosis of such syndromes can sometimes be suspected in adults [3]. Very few case reports have been published in young patients with severe and fatal forms of Evans syndrome secondary to or associated with infection, particularly in the sub-Saharan region. In this case review, we describe a young 16-year-old HIV immunocompetent patient, suffering from a severe form of Evans syndrome associated with mixed herpetic encephalitis (HSV1 and CMV), and whose final outcome was fatal. The aim of this report is to present to you our experience through this clinical case, the particularity of the clinical-biological evolution and the difficulties in the management of this type of patient in our context.

Observation

We report the case of a 16-year-old patient of Malian nationality; pupil. She was received on January 4, 2023 in the Internal Medicine department of the University Hospital Center Point G in Bamako for weakness of the left upper and lower limbs; and difficulty speaking. The start of the symptoms reported by the family dates back around a week, marked by the sudden onset of muscular weakness in the left upper and lower limbs, without a fall in height or any notion of trauma. To this would be added headaches of sudden onset, of strong intensity, rated 8/10 according to the numerical scale, diffuse, permanent, of unspecified irradiation, without triggering factor or calming factor. These headaches are associated with four episodes of vomiting with a yellowish appearance, spontaneous, not punctuated by meals, occurring at any time of the day, not streaked with blood, not in jet, without notion of photophobia, nor stiffness of the neck, without stopping of matter and gas and not calming the headaches.

This symptomatology evolved in a context of permanent fever, sudden onset, evening-night onset, without chills or excessive sweating, with non-selective anorexia, physical asthenia but no weight loss. All this would be associated with a language disorder concomitant with weakness of the limbs, with difficulty in emitting audible sounds. In addition to the history, the family does not report any abnormalities in other devices. No therapeutic attitude would have been taken, in front of this painting her family consulted the pediatric department of the Gabriel Touré University Hospital Center, who referred her to us for treatment. As antecedents; she has sickle cell form SC, her mother is hypertensive. She is single and not yet sexually active. She would have taken artesunate and ceftriaxone (dosages not specified). She consumes coffee, tea and her diet is mainly based on cereals.

The examination of the general condition revealed a conscious, bedridden, prostrate patient; athletic and feverish to the touch; his Karnofsky index was 50%. Lying blood pressure in the left arm at 140/100 mmHg; tachycardia at 106 bpm; polypnea at 24 cycles per minute; a left axillary temperature of 38.2°C; random capillary blood glucose at entry at 1.90g/L, SpO_2 at 98% in ambient air. His measurements at entry were a weight of 60kg, height of 155cm for a body mass index (BMI) of 24.97kg/m².

The neurological examination revealed a conscious, agitated patient, refusing to cooperate; non-fluent BROCA type 1 aphasia, Glasgow score 10/15, left central facial paralysis, no neck stiffness, Kernig and Brudzinski signs were negative. Left hemiparesis with hypertonia of the left thoracic and pelvic limbs, the Barré maneuver positive in the left thoracic limb and the Mingazzini maneuver positive in the left lower limb. Babinski's sign was negative. The rest of the physical examination noted connective-palmo-plantar pallor, left scleral hemorrhage, petechial purpuric lesions like isolated punctiform macules on the inner surface of the lower lip, confluent punctiform macules at the level of the inner surface of the upper third of the left arm and punctiform macules isolated against a background of erythematous plaques in the left breast (Picture 1); the urine had a port-red appearance in the collection bag of the urinary catheter. The other devices were carefully examined and found no anomalies.

The Paraclinical Assessment Showed

- **Hemogram:** regenerative normocytic normochromic anemia with a hemoglobin level at entry of 8 g/dl, the mean corpuscular volume (MCV) of 81fl; a CCMH at 39 g/dl. Severe erythropenia at 2,250,000/mm³ and a reticulocyte level at 43,300/mm³. Severe thrombocytopenia at 26,000/mm³ and 21,500/mm³ on a citrated tube; leukocytosis at 10500/mm³ with neutrophilia at 6562.5/mm³.

Severe thrombocytopenia on citrated tube contraindicated the performance of a lumbar puncture associated with the analysis of cerebrospinal fluid.

- **Inflammatory assessment:** an inflammatory syndrome with a CRP of 19.8 mg/l; a sedimentation rate of 17mm (h1) and 74mm (h2); hypofibrinogemia at 0.95g/L. Serum protein electrophoresis associated with immunofixation revealed dysglobulinemia (hyperalpha1 and hypobeta 1); but no monoclonal abnormalities.

Picture 1: Photographs of the patient showing petechial purpuric lesions on the inner side of the lower lip and on the left breast, a bilateral scleral hemorrhage – Day 1 (Dr Ibrahima A Dembélé – Dr Stéphane L Djeugoué).

Table 1: Patient's hematological changes.

Date	03-01-2024	04-01-2024	11-01-2024	20-01-2024	09-02-2024
Red cells	2.25×10^9/mm³	2.05×10^9/mm³	1.85×10^9/mm³	1.94×10^9/mm³	0.96×10^9/mm³
Hematocrit	18.2%	18.4%	17.4%	18.2%	9.2%
Hb	8.0g/dL	6.01g/dL	5.4g/dL	7.8g/dL	2.9g/dL
MVC	81fL	90fL	94.1fL	116.3fL	95.8fL
MCHC	39.0g/dL	32.6g/dL	31g/dL	34.5g/dL	31.5g/dL
Reticulocytes	43.300/mm³	352500/mm³			66800/mm³
Platelets	26.000/mm³	21.500/mm³	322.000/mm³	85.000/mm³	42.000/mm³
White cells	10500/mm³	9980/mm³	46890/mm³	12200/mm³	20100/mm³
PN	6562.5/mm³	7740/mm³	16834/mm³	11200/mm³	16280/mm³
PE	210/mm³	31/mm³	47/mm³	0.0/mm³	0.00/mm³
PB	0/mm³	13.6/mm³	94/mm³	0.0/mm³	0.00/mm³
Lymphocytes	3066/mm³	1390/mm³	27993/mm³	700/mm³	2610/mm³
Monocytes	682.5/mm³	68.2/mm³	1922/mm³	200/mm³	1210/mm³

- **Infectious assessment:** the thick blood film was negative, the HbsAg negative, the Ac-antiHbc Ig G positive, the antiHbs Ab not done, HIV1 and 2 serologies; and HCV were negative. HSV1 serologies IgM negative – IgG positive at 479.3 IU/mL (Day 1); Negative HSV2 serology, negative CMV IgM and positive IgG serology (D1) greater than 250 iu/mL. The cytobacteriological and cytological examination of urine were negative. Blood culture on aerobic and anaerobic media is negative. RT-PCR on whole blood negative for Dengue virus.
- **Biochemical assessment:** serum creatinine at 101.9 µmol/l with clearance at 81.35 ml/min. Azotemia at 18.9 mg/L. Hyperkalemia at 6.46mmol/L, hypocalcemia at 1.40 mmol/L, hypomagnesemia at 0.57 mmol/L. the dosage of normal vitamins B9 and B12.
- **Immunological assessment:** anti-nuclear antibodies (ANA-Screen) at 0.00 (negative); negative anti-Sm antibodies. Positive indirect and direct Coombs test (Day 1).

- **Hemolysis assessment:** LDH at 1335 IU/L (45-90 IU/L); haptoglobin at 6 mg/dL (14-258 mg/dL); free bilirubin elevated to 75.8 µmol/L.
- **Hemostasis assessment:** Prothrombin rate at 70.3%, activated partial thromboplastin time at 0.57.
- **Imaging assessment:** the brain scan revealed slight irregular bilateral temporal hypodensities, no abnormality related to a stroke, and bilateral maxillo-ethmoido-frontal chronic rhino-sinusitis.
- **Functional assessment:** The electrocardiogram came back normal without signs of hyperkalemia, and the electroencephalogram was requested but not performed.

In view of all the clinical and paraclinical elements, the diagnosis of Evans syndrome associated with mixed herpes viral encephalitis (HSV1 and CMV) was retained.

Initial treatment with a bolus of methylprednisolone at 20 mg/kg or 1200 mg per day for 3 successive days followed by prednisone at 1 mg/kg or 60 mg per day in the morning; associated with adjuvant measures (gastric protection, deworming with ivermectine, oral calcium and potassium intake). Aciclovir at 15 mg/kg or 900 mg per day in 250 mL of 0.9% saline for 1h30min; paracetamol infusion 1g every 8 hours. A transfusion of 3 bags of platelet pellets, rehydration with 0.9% saline and 10% serum glucose at a rate of 1 liter per 24 hours; Enoxaparin (0.2 ml) 1 injection SC/24 hours. Mobilization 4 times a day in bed, administration of anti-decubitus powder to the support areas, daily supportive psychotherapy and therapeutic education of the patient and those around her.

The evolution after 7 days was marked by an alteration of consciousness with a Glasgow score of 9/15 despite a slight recovery of speech, the patient still febrile (39°C), an attitude of decortication of the 2 associated thoracic limbs. hypotonia of both pelvic limbs; a slight accentuation of purpuric lesions. The control blood count reveals severe anemia at 5.4g/dL, normocytic, regenerative, with reticulocyte level at 352,500/mm^3, severe erythropenia at 1,850,000/mm^3; hyper leukocytosis at 46,890/mm^3 with neutrophilia at 16,834/mm^3 and lymphocytosis at 27,993/mm^3, platelets at 322,000/mm^3. Positive CMV and HSV1 IgG serologies, CRP at 3mg/dl, hypernatremia at 147mmol/L and hyperazotaemia at 12.66mmol/L. Negative indirect Coombs test. We performed a finger smear which revealed erythroblasts with polychromatophilia and numerous polymorphonuclear cells with toxic granulations; the myelogram noted a very rich marrow, with megakaryocytes present at different stages of maturation, hyperplasia of the erythroblastic lineage and an absence of blast cells, concluding in an erythroblastic red marrow. The action taken was to increase the dose of corticosteroid therapy to 2 mg/kg or 120 mg per day in the morning and continue acyclovir and adjuvant measures to corticosteroid therapy; we note that ganciclovir sensitive to CMV was not available in our context.

The patient then progressed well clinically and biologically, with a Glasgow score of 15/15, abduction paralysis of the left eye, mobilization of the 4 limbs despite hypotonia of the 2 lower limbs, disappearance of the purpuric lesions (Picture 2) and the urine becomes clear again. She was discharged after 3 weeks of hospitalization, with discharge treatment of prednisone 120 mg/day combined with adjuvant measures; aciclovir tab of 500 mg, 2 tabs every 8 hours; motor recovery physiotherapy. She returned after 8 days with a picture of hypovolemic shock associated with hypothermia, small port-red urine, bilateral scleral subuterus; The emergency hemogram showed a very severe anemia at 2.9g/dl, normocytic normochromic, regenerative with reticulocyte level at 66,800/mm^3, erythropenia at 96,000/mm^3, thrombocytopenia at 42,000/mm^3. CRP at 250mg/L, CMV and HSV1 – IgG serologies strongly positive at 158.20 iu/mL and 405.9 iu/mL respectively. Hypernatraemia at 147mEq/L, severe renal failure with clearance at 21ml/min associated with hyperazotaemia at 30.7mmol/L and hypercreatininemia at 313.9µmol/L. We concluded that Evans syndrome was complicated by acute adrenal insufficiency. Despite the administration of Gelofusine 4% and methylprednisolone as a bolus of 1200 mg intravenously and hydrocortisone 100 mg intravenously every 6 hours, and the resumption of acyclovir intravenously; the patient died during the night.

Picture 2: Photographs of the patient, we observe a disappearance of purpuric lesions on the inner side of the lower lip and a reduction in purpuric lesions on the left breast after 13 days of corticosteroid therapy (Dr Ibrahima A Dembélé – Dr Stéphane L Djeugoué).

Discussion

We reported a case of Evans syndrome in its severe form associated with mixed herpetic encephalitis with HSV1 and CMV whose final outcome was unfavorable. First described in 1951, Evans syndrome (ES) is characterized by autoimmune bicytopenia, classically autoimmune hemolytic anemia and autoimmune thrombocytopenia which may be concomitant or sequential and may include neutropenia [3]. It is a rare chronic disease with periods of remission and significant morbidity [3]. Evans syndrome is classified as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH) [3]. There is no preferential distribution of Evans syndrome by age, sex or ethnic group. It is a rare chronic disease with periods of remission and significant morbidity [3]. Evans syndrome is classified as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health (NIH) [3]. There is no preferential distribution of Evans syndrome by age, sex or ethnic group.

From the initial series by Robert Evans et al. in 1951 to the very recent studies by Aladjidi et al. and Al Ghaithi et al. in 2015 and 2016, a dozen series include patients with Evans syndrome. Case reports of Evans syndrome in a young patient in sub-Saharan Africa are very rare, hence this presentation. Bruna Paccola Blanco and Marlene Pereira Garanito objectified in their study on Evans syndrome in twenty young patients under 18 years old; the sex ratio was 1.5 (12F/8M), the median age at initial cytopenia was 4.98 years (1.30−12.57), while the median age at diagnosis was 7, 69 years (1.7§08−13.51) [4]. Matthew Dominic McCarthy published an observation of Evans syndrome in a young man in his twenties, presenting rare autoimmune associations and a transplanted liver [5], Juan D and his team reported a case of Evans syndrome Evans in a 32-year-old patient [6].

Etiopathogenesis

Since Evans et al. initial hypothesis of a common mechanism for immunological thrombocytopenias and autoimmune hemolytic anemias, all authors agree on the dysimmune origin of Evans syndrome. Savaşan et al. note the numerous variations in immunoglobulin dosage with hyper- and hypogammaglobulinemia, the frequent exacerbated lymphoproliferation during cytopenic episodes and other autoimmune symptoms in their series and suggest generalized immune dysregulation. Serum protein electrophoresis in our patient revealed dysglobulinemia (hyperalpha1 and hypobeta 1); but no monoclonal abnormalities. In adolescent patients and children, the high frequency of autoimmune, deficiency and lymphoproliferative symptoms observed in children prompts the search for genetic causes [4].

Pathophysiology of cytopenias in Evans syndrome

- **Autoimmune hemolytic anemia**

Immune hemolysis is demonstrated by a positive direct Coombs test, including alloimmune hemolysis (post-transfusion and hemolytic disease of the newborn) and autoimmune hemolytic anemia (AIHA) where the immune hemolysis test direct agglutination (TAD) highlights antibodies directed against erythrocyte membrane antigens [1]. The bone marrow activation necessary for the regeneration of the red lineage can lead to an increase in other blood lines, leukocytes and platelets. The blood smear makes it possible to study the morphology of the red blood cells and shows anisocytosis associated with polychromatophilia due to the presence of reticulocytes [1]. Hemolysis markers (free bilirubin, LDH, haptoglobin) have a high sensitivity, from 80 to 95% [1]. The detection of autoantibodies, most often by positivity of the direct Coombs test, is essential to make the diagnosis. The hemolysis markers were all very high in our patient associated with low haptoglobin; the direct and indirect Coombs test were positive on D1, then negative on D7.

- **Immunological thrombocytopenias/Thrombotic thrombocytopenic purpura (ITP)**

Immunological thrombocytopenias (IT) are peripheral, by destruction of sensitized platelets. The detection of antiplatelet antibodies confirms the diagnosis but is more difficult and often the diagnosis is made by eliminating other causes of thrombocytopenia [7-9]. In our patient, antiplatelet antibodies were requested but were not available in the city's laboratories. The Dixon test is the platelet equivalent of the direct anti-globulin test and can detect antibodies attached to the platelet surface. It is sensitive but not very specific, the test being able to activate platelets and reveal on the surface Ig previously pinocyted by normal megakaryocytes and stored in α granules [1]. The MAIPA (monoclonal antibody immobilization of platelet-antigen assay) has better specificity and at the same time makes it possible to identify the molecular target of the antibody.

- **Autoimmune neutropenia**

Autoimmune neutropenia is defined by the reduction in circulating neutrophils below 1.5.109/L (for people over 1-year-old) associated with the presence of specific autoantibodies [9]. Autoimmune neutropenias can be central or peripheral, depending on the antigenic target and the mechanisms involved.

Etiologies of secondary Evans syndrome

- **Infections**

Many viral infections can cause immunological cytopenias. We classically cite certain viruses from the Herpes viridae group such as EBV and CMV [10]. Very few articles have reported the association of ES with various viral infections, particularly in sub-Saharan Africa (hepatitis C virus (HCV), Epstein Barr virus (EBV), cytomegalovirus (CMV) and varicella-zoster virus (VZV)) which must be excluded even if this situation seems rare. More recently, SARS-CoV-2 has been reported as a potential cause of SE [8]. Due to their potential association with ES, specific viral serological tests and/or blood PCR for EBV and CMV should be considered when the clinical examination is suggestive or in case of atypical lymphocytosis on the blood smear. Additionally, testing for human immunodeficiency virus (HIV), HCV, and hepatitis B virus (HBV) should be performed to prevent reactivation or uncontrolled progression of infection under immunosuppressive therapy [8]. Our patient presented high IgG concentrations successively (after an interval of 7 days during hospitalization and one week after the patient's discharge) for CMV and HSV1; CSF PCR was not performed because the patient's severe thrombocytopenia made lumbar puncture contraindicated. This high concentration of IgG could be explained by herpetic reactivation. HIV, Hepatitis B, C, and erythrovirus B19 serologies were negative in our patient.

- **Hematological malignancies**

In hematological malignancies, autoimmune cytopenias can be added to other symptoms, particularly in chronic lymphocytic hemopathies in adults: malignant non-Hodgkin's lymphomas and Hodgkin's disease, large grain lymphocytic leukemia, chronic lymphocytic leukemia [8]. This is also observed in certain solid cancers, notably of the ovary, colon or pancreas. Our patient did not present with lymphoproliferative syndrome or myeloproliferative syndrome; the myelogram did not reveal any abnormalities of the myeloid or lymphoid lines; the finger smear did not find blasts greater than 20%.

- **Autoimmune disorders**

Some autoimmune diseases are accompanied by cytopenias. These may include systemic diseases such as Sjögren's syndrome, rheumatoid arthritis or anti-phospholipid syndrome, and autoimmune organ diseases such as Graves' disease, ulcerative colitis or primary biliary cholangitis. Autoimmune cytopenias are also an integral part of the 2019 American College of Rheumatology diagnostic criteria for systemic lupus [6]. Anti-nuclear antibodies, anti-native DNA antibodies, anti-Sm antibodies, anti-CCP antibodies and rheumatoid factor were all negative in our case, excluding at this time of diagnosis an autoimmune etiology related to the systemic lupus and rheumatoid arthritis. It should be noted that Evans syndrome very often precedes lupus by a few years before the presence of specific antibodies.

- **Primary immunodeficiencies**

Primary immunodeficiencies (PIDs) are a group of heterogeneous diseases that result from inborn errors of the immune system. These are rare diseases whose description is relatively recent but they represent an area of rapid and spectacular progress [4]. IDPs represent a large and constantly growing group of more than 300 different diseases that consist of a wide range of clinical manifestations in adults and children, such as an increased tendency to infections, autoimmunity, inflammation, allergies and cancers [4]. They are classified into 4 groups: deficiency in number and/or function of the B cell (humoral immune deficiencies), deficiency in number and/or function of the T cell (cellular immune deficiencies and combined immune deficiencies), deficiency in number and/or function or phagocyte function, complement deficiency [4].

Autoimmune and dysimmune manifestations are found in 25% of cases and these patients are at greater risk of long-term complications, with increased morbidity and mortality [8]. They can precede the classic infectious manifestations which usually suggest IDP. It is therefore appropriate to look for IDP in certain autoimmune situations. Autoimmune cytopenias are the manifestations of autoimmunity most frequently encountered during IDPs [11,12]. ITP and/or AHAI precede infectious manifestations in nearly 75% of cases; Evans syndrome has an incidence of 4% in common variable immunodeficiency [12]. Our patient actually presented with mixed herpes viral encephalitis associated with autoimmune cytopenia probably secondary to a primary dysimmune state; genetic testing remains unavailable in our context. The first step in evaluating a possible humoral immunodeficiency is the determination of immunoglobulins IgG, IgA and IgM. The serum level of these immunoglobulins must be quantitative, most often measured by nephelometry; immunoelectrophoresis, which is a semi-quantitative method, is not the technique of choice for evaluating a patient with suspected antibody deficiency [12]. In our patient, immunofixation after serum protein electrophoresis did not reveal any monoclonal gamma globulin abnormalities.

Herpes infection in immunocompetent patients [10,11]

Herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2) belong to the subfamily Alphaherpesvirinae in the genus Simplexvirus; while Cytomegalovirus belongs to the Betaherpesvirinae subfamily. HSV viruses are thus transmitted mainly by direct and close contact via secretions or infected mucous membranes, or skin lesions of a symptomatic or asymptomatic patient excreting the virus.

The pathophysiology of HSV-1 and HSV-2 infections is similar. These are dermo-neurotropic viruses. Primary infection is associated with local viral multiplication associated or not with clinical signs. The virus infects the nerve endings of sensitive neurons. Then a latency phase where the viral genome (DNA) persists in the cell nucleus in circularized form and is not integrated into the cellular genome. From this state of latency, reactivations are possible, causing endogenous reinfections and are associated either with asymptomatic shedding ensuring viral transmission and infection to new hosts, or with clinical signs (recurrences). Viral reactivation can result from certain stimuli: fatigue, stress, sun exposure (UV), menstruation, trauma and immunosuppression. These cycles alternating states of latency and viral reactivations persist throughout the life of the infected individual. In our young patient, it appears to be a herpetic viral reactivation. Asymptomatic reactivations are frequent and almost systematic in all infected individuals, both in individuals presenting clinical recurrences and in individuals who are still asymptomatic. The majority of reactivations are of short duration (<12 hours).

Herpes encephalitis is one of the main serious manifestations of herpes infection. It mainly affects adults with a peak frequency around 40-50 years of age. HSV-1 is the most common etiology of encephalitis. Ours was 16 years old. It is an encephalitis caused by intracerebral multiplication of the virus at the neuron level. It is generally localized in the temporal lobe, often on one side only, in the form of a focus of hemorrhagic necrosis (acute herpetic necrotizing encephalitis). It begins suddenly with fever and various signs of rapidly progressive brain damage: headache, behavioral disorders, aphasia, paralysis, convulsive seizures, most often accompanied by disturbances of consciousness which will worsen until in a coma. In our patient, the initial clinical picture was dominated by fever, then variable left hemiparesis and altered consciousness. Early on, the electroencephalogram is almost always disturbed. Signs of unilateral temporal localization on computed tomography (CT) appear later (however, MRI becomes positive before CT). Our patient was unable to do an electroencephalogram and a brain MRI, however, the brain CT performed showed slight irregular bilateral temporal hypodensities. The spontaneous evolution is catastrophic with a mortality of 70% or very serious neuropsychological after-effects. In our case, the clinical course of the encephalitis before discharge was good despite motor sequelae such as hypotonia predominating in both pelvic limbs upon discharge after her first hospitalization, for which she underwent recovery physiotherapy sessions motor.

Viral encephalitis is always a neurological emergency. The diagnosis of acute infection is based on direct diagnosis; Detection of viral DNA by PCR is the most recommended technique for the diagnosis of neuromeningeal and disseminated infections on CSF

and blood samples. Indirect diagnosis is based on the detection of total anti-HSV antibodies or specific anti-HSV-1 or anti-HSV-2 antibodies. In our observation, severe thrombocytopenia contraindicated the performance of the lumbar puncture, PCR on whole blood was not performed due to financial difficulties; the diagnosis of herpetic encephalitis was made on the basis of the encephalitic and febrile syndromes associated with the very strong positivity of successive HSV1 serologies 7 days apart. In practice, as soon as herpes encephalitis is clinically suspected, it is fundamental to urgently initiate treatment with acyclovir (ACV) intravenously (IV) at a dosage of 10-15 mg/kg/8 hours, without waiting for the results of the virological diagnosis which must then be requested (search for viral DNA in the CSF by PCR). Only early treatment, undertaken as soon as clinical suspicion is detected, offers a chance of survival without after-effects. Any delay in ACV treatment constitutes a "loss of opportunity". Our received this aciclovir protocol early and for a period of 23 days. In immunocompetent individuals, herpes encephalitis generally occurs during viral reactivations. The pathophysiology of this encephalitis remains poorly understood. It seems that certain immune deficiencies of genetic origin could partly explain its occurrence.

Cytomegalovirus infection in immunocompetent patients [13,14]

Cytomegalovirus (CMV) is responsible for a complex pathophysiology, which is still imperfectly understood. Apart from the congenital cytomegalic inclusion disease which gave it its name, it was considered weakly pathogenic for many years. In immunocompetent subjects, CMV infection generally remains asymptomatic. However, in 10% of cases, mainly during a primary infection, clinical manifestations may appear. In adults or older children, the most typical symptomatic form corresponds to an isolated fever or a flu-like syndrome. CMV infection can, however, lead to less frequent clinical manifestations such as anterior uveitis, sometimes recurrent arthralgia and arthritis, ulcerative colitis, pneumonia, aseptic meningitis, Guillain & Barré syndrome, encephalitis and myocarditis. Like HSV, CMV can reactivate in hospitalized non-immunocompromised patients; unlike HSV which only causes lung damage, CMV can cause either isolated blood reactivation (hemolytic anemia, thrombocytopenia), or lung damage.

Biologically, the primary infection is often associated with hepatic cytolysis, mononucleosis syndrome (hyperlymphocytosis with the presence of activated lymphocytes) and sometimes thrombocytopenia. The diagnosis of viral activation is carried out by specific techniques: viral culture and polymerase chain reaction (PCR) on any type of sample and by pp65 antigenemia. Indirect diagnosis is based on the search for IgG or IgM class antibodies in the serum using serological techniques reported in the literature, ELISA or EIA tests. The diagnosis of CMV infection was made in our patient on the basis of the very strong positivity of CMV serology. Three molecules are available for the treatment of CMV infections: ganciclovir strictly intravenously at a dosage of 5 mg/kg per 12 hours for 30-60 min for 14 to 21 days and its prodrug valganciclovir - 900 mg/12 hours in orally for 14-21 days, a monophosphate nucleoside analogue, cidofovir, and an inorganic pyrophosphate analogue, foscarnet (10mg/kg/12h intravenously for 60-90 min with pre-hydration, 14-21 days). Treatments with ganciclovir, valganciclovir or foscarnet were unavailable in our context.

Evans syndrome and viral infections

HSV and CMV are the most common, with 50 to 80% of the adult population being seropositive for HSV and/or CMV [11]. The proposed mechanisms for triggering autoimmunity by viral infections are multiple (molecular mimicry, epitope spreading (promotion of the presentation of self-antigens at inflammatory sites), bystander activation (increased production of cytokines inducing expansion) of T cells previously activated at the inflammatory site), direct lymphocyte activation by lymphotropic viruses, lack of clearance of apoptotic bodies, etc.) [10]. Herpes viridae would be capable of inducing the expression of self-nuclear antigens involved in autoimmune diseases (systemic lupus, RA, APS) and of provoking the synthesis of autoantibodies [11]. The CMV pp65 protein causes the production of antibodies with cross-reaction against nuclear antigens [14]. Anti-pp65 seroprevalence is higher in SLE patients than in patients with other autoimmune diseases and healthy patients [14,15].

Diagnosis of Evans syndrome

The diagnosis of SE is based on the concomitant or sequential diagnosis of AIHA and IPT. AIHA is suspected in cases of anemia associated with reticulocytosis and markers of hemolysis, namely elevated lactate dehydrogenase, low haptoglobin and elevated indirect bilirubin, with a positive direct antiglobulin test (DAT) for IgG with or without complement (C3d) because cold agglutinins are excluded from ES [8]. The biological variations of our patient are presented in table 1. Bruna Paccola Blanco and Marlene Pereira Garanito also demonstrated anemia and very severe thrombocytopenia without neutropenia [4]. ITP remains a suspected diagnosis of exclusion in cases of rapid onset thrombocytopenia not linked to liver diseases (cirrhosis and portal hypertension), splenomegaly (malignant hematological diseases, Gaucher disease), drug-induced thrombocytopenia, bone marrow deficiency (myelodysplastic), neoplasia or hereditary thrombocytopenia [8]. Our patient did not present any of these conditions. Due to the lack of specificity or sensitivity of different tests, the detection and identification of antiplatelet antibodies is still not recommended in routine practice and should be limited to difficult cases [8]. Anti-platelet antibodies were not achievable in our context by city laboratories. Neutropenia is suspected when a neutrophil count < 1.5 G/L, after exclusion of other causes of neutropenia (drug-induced neutropenia; viral infections such as CMV, EBV, HIV, parvovirus B19 and influenza; myelodysplastic syndrome or leukemia) because there is no specific test for its diagnosis. Anti-neutrophil antibodies are quite difficult to determine in clinical practice because the tests have not yet been standardized; in our patient, we did not observe neutropenia but on the other hand during hospitalization, she presented; hyperleukocytosis at 46,890/mm^3 with neutrophilia at 16,834/mm^3 and lymphocytosis

at 27,993/mm^3. The finger smear at the entrance showed numerous polymorphonuclear cells with toxic granulations.

Diagnosis of Evans' Syndrome
- Complete blood count
- Reticulocyte count
- Haptoglobin, LDH, indirect/free bilirubin
- Direct Antiglobulin Test
- Monoclonal Antibody Immobilization Platelet Assay (MAIPA) (not systematic, of potential utility if antiplatelet antibody determination is required)
- Antineutrophil antibodies against CD16/FcγRIII, CD11b, CD35/CR1, CD32/FcγRII (not systematic, of potential utility)
To exclude differential diagnosis and determine the secondary nature of ES
- Blood smear *
- Viral tests (HIV, HCV, HBV, EBV, CMV, parvovirus B19)
- Serum protein electrophoresis, protein immunofixation and immunoglobulin concentrations
- Circulating lymphocyte phenotyping
- Flow cytometry for paroxysmal nocturnal haemoglobinuria clone detection *
- Antinuclear antibodies and anti-dsDNA antibodies
- Lupus anticoagulant assay and antiphospholipid antibodies
- Bone marrow aspiration and karyotyping *
- Bone marrow biopsy
- CT scan of the chest, abdomen and pelvis
- Genetic explorations
*: exams useful to exclude differential diagnosis.

Table 2: Tests recommended during the diagnostic procedure for Evans syndrome [1].

Therapeutic specificity of the management and monitoring of Evans syndrome

- **Therapeutic education**

The management of Evans syndrome remains a challenge. The syndrome is characterized by periods of remission and exacerbation and response to treatment varying even within the same individual. Therapeutic education of the patient and his family must be essential because it is a chronic pathology evolving in outbreaks; as well as the application of hygienic and dietary measures related to corticosteroid therapy; the strict salt-free diet, the sugar-free and low-potassium diet [4,5]. Our patient and her family benefited during her hospitalization and during the various check-ups from therapeutic education on the clinical manifestations of Evans syndrome and encephalitis (notably the probable sequelae), its complications, the aim of the therapeutic; as well as daily supportive psychotherapy.

- **Corticotherapy**

First-line treatment is corticosteroids; prednisone at a dose of 2 mg/kg/day initially for 3-4 weeks then at 1 mg/kg; or methylprednisolone, at a dose of 30 mg/kg/day, for 3 days followed by prednisone [12]. In our observation, the patient initially had a bolus of methylprednisolone for 3 days followed by prednisone at a dose of 1 mg/kg during the first week of hospitalization then at 2 mg/kg throughout her hospitalization (i.e. 23 days) and at 1 mg/kg upon discharge, due to the improvement in his clinical condition, the increase in platelets and his hemoglobin level. This corticosteroid therapy was preceded by deworming and was associated with adjuvant measures. Initial response rates can reach 80%, but the remission rate at one year after corticosteroids is also high [7].

- **IV immunoglobulins**

In ITP, IVIG should be reserved for patients with a low platelet count (<30 G/L) associated with significant bleeding symptoms, best assessed using a bleeding score [6]. IV Ig is generally used at 1 g/kg on day 1 and could be repeated on day 3 if the platelet count remains below 30 G/L [8]. IVIG can be used only as first-line treatment when steroids are contraindicated or ineffective. In addition, in certain cases, they are associated with corticosteroids allowing a more rapid increase in the number of platelets [7]. In the study by Bruna Paccola Blanco and Marlene Pereira Garanito, IV immunoglobulins were used in 84.2% of cases at a dosage of 1-2 g/kg for 2 days [4]. While Juan D. Díaz-García used 1 g of intravenous (IV) methylprednisolone every 24 h for 3 days, treatment continued with 6 g of IV immunoglobulin by pump infusion and hydrocortisone 150 mg-75 mg- 75 mg for 2 days [6]. The unavailability of IV Ig and the financial difficulty in ordering them by the patient's family justified their non-use in our case. Please note that IVIG only represents an emergency treatment which does not modify the natural history of the disease. Only one study reported on IV Ig during isolated AIHA and showed low efficacy (12/37 patients (32%) increased their hemoglobin level by 2 g/dL, and only 15% achieved a response partial defined by hemoglobin 10 g/dL with an increase in hemoglobin 2 g/dL) [5], which excludes their routine use. In addition, they could increase the already high risk of thrombosis during isolated AIHA.

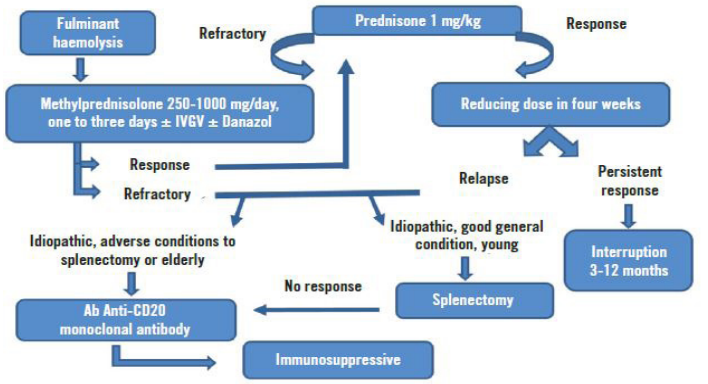

Figure 1: Sequential approach in the management of Evans syndrome [1].

- **Transfusion support**

In cases of severe symptomatic anemia, red blood cell transfusions are necessary. The challenge in the isolated period of AIHA should not rule out alloantibodies which may be masked by autoantibodies, particularly in patients who have already received a transfusion or pregnant women [12]. Autoantibodies generally lead to panagglutination of red blood cells by targeting antigens widely expressed on red blood cells, such as glycophorin, protein band 3, and rhesus. Platelet transfusion is not recommended during isolated ITP and by extension during ES-thrombocytopenia, due to the short half-life of platelets after transfusion and the fact that they do not improve the results in most patients [7]. However, platelet transfusions are necessary in cases of life-threatening hemorrhages, in combination with immunomodulatory drugs, corticosteroids, and IVIG in particular [6]. Our patient received 3 bags of platelet pellets.

- **Rituximab and other immunosuppressants (Second-line therapies)**

Rituximab is the drug of choice in SE. In ES, the initial response rate to rituximab was 82%, which decreased to 64% after one year of follow-up [3]. A study specifically evaluated rituximab in ES associated with systemic lupus in 71 patients, among whom 11 had ES [3], an overall response to rituximab was obtained in 60% of cases, which is lower than those observed in cases of isolated AIHA or isolated ITP associated with lupus, respectively, 87.5 and 91%. A complete response was obtained in 50% of ES compared to 75 and 57% respectively [5]. In the study by Bruna P B and Marlene P G, the main second-line therapy was rituximab with a complete response rate of 71.5% [4]. The good clinico-biological evolution of our patient under heavy corticosteroid therapy during hospitalization combined with the local unavailability of rituximab were the 2 arguments explaining its non-use.

- **Splenectomy**

Splenectomy is a treatment for isolated ITP and isolated AIHA leading to a response rate of 88% (66% complete response) and 70% (40% complete response), respectively [7]. Data regarding splenectomy in ES are derived from small series showing response rates that are quite similar to those observed in isolated AIHA with an initial response rate of 78-85%, with a long-term response rate including between 42 and 62% [7].

- **Anticoagulation**

It is now clearly established that isolated AIHA increases the risk of thrombosis [12], more particularly when the disease is active, with a 7.5-fold increase during the three months following diagnosis [7]. Although there are no clear guidelines regarding anticoagulant prophylaxis during isolated AIHA, experts recommend considering thromboprophylaxis (prophylactic anticoagulation with low molecular weight heparin) for hospitalized patients in the active phase of the disease, taking into account take into account their general risk factors for venous thromboembolism (VTE) events [7]. This recommendation was respected in our patient.

- **Hematopoietic stem cell transplantation**

Autologous hematopoietic stem cell transplantation offers hope to those relapsed cases that do not respond to the above medications and are difficult to treat [12].

- **Treatment of underlying pathology**

Management of patients with ES must take into account the nature and activity of the underlying/associated disorder. For ES associated with SLE or CVID, the initial strategy is similar to that of primary ES, with rituximab being a good second-line corticosteroid-sparing option while splenectomy is not recommended in these settings [2]. Our patient received aciclovir at 15 mg/kg every 8 hours throughout her hospitalization. However, the difficulty that has arisen is that acyclovir is not active on CMV but mainly on HSV. CMV is sensitive to ganciclovir, an anti-viral agent not available in our context. However, after 16 days of acyclovir (associated with strong corticosteroid therapy), the patient's clinical and biological evolution was favorable (apyrexia and improvement of neurological disorders) until her discharge.

- **Evolution and prognosis**

Evans syndrome has a sometimes favorable prognosis with appropriate treatment. The clinical course is complicated and associated with poor outcomes in affected patients. Patients rarely do well with treatment which is often disappointing. Evans syndrome can occasionally be fatal. Hence strict and constant monitoring is very essential. Our patient presented an exacerbation of her hemolysis with resumption of thrombocytopenia and severe anemia 8 days after her discharge (see table 1). Unlike our young patient, Bruna P B and Marlene P G objectified in their study a median of 2.5 episodes of exacerbation of hemolytic anemia and thrombocytopenia, of (2−4.75) and the median time between acute events was 6.62 months (1.58−8.97) [4].

Conclusion

Evans syndrome is a very rare autoimmune disease reflecting a major breakdown in immune self-tolerance. SE can be life-threatening with an overall mortality rate of approximately 20% and it is associated with a high rate of serious infections and thrombosis. The diagnosis of SE can be difficult and requires minimal initial workup to exclude certain other diagnoses of bicytopenia and especially thrombotic microangiopathies. The rate of secondary SE ranges from 20 to 50% in adults and accurately looking for underlying disease at the time of diagnosis is important as it can impact both prognosis and management.

Consent

Written informed consent was obtained from the patient's family to publish this report in accordance with patient consent policies.

Author Contributions

All authors participated in the evaluation and follow-up of the patient, in the writing and correction of the case report. All authors of the manuscript have read and accepted its contents.

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