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POLYCYTHEMIA VERA WITH BUDD-CHIARI SYNDROME – A CASE REPORT

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Abstract: *Polycythaemia vera is a disorder of the hematopoietic stem cell which manifests as the overproduction of normal erythrocytes and variable excess production of WBC and platelets. It is a myeloproliferative disease, grouped with the Philadelphia chromosome-negative disorders and it's very rare among children and teenagers. The thrombotic events are the most common complications due to hyper viscosity of the blood. The authors report the case of a 14-year-old girl who was admitted in hospital for abdominal pain in left quadrant and right hypochondrium. Workout findings reveal hepatosplenomegaly with an infarction of the inferior pole of the spleen and hepatic vein thrombosis (specific with Budd-Chiari syndrome).*

Key words: *polycythaemia vera, children, venous thrombosis, Budd-Chiari syndrome*

1. Introduction

Polycythaemia Vera (PV) is an acquired clonal myeloproliferative stem cell disorder. Because of the uncontrolled red blood cell production, the main feature is an elevated number of erythrocytes. Leucocytosis and thrombocytosis can also be found [15]. PV is rare in children and teenagers. Clonality and the erythropoietin (Epo) independence are the primary aspects of the disease. Even the stem cells colonies do not require Epo, they respond to it, because the receptor (EpoR) is normal, without any functional or quantity defects [2], [4]. The erythropoietin levels in serum are low or normal. Molecular findings over the last decade made a significant approach to the understanding of the mechanisms of this condition. Genome-wide scanning revealed a loss in chromosome 9p. This region is known to contain the gene that encodes the JAK2 tyrosine kinase. This family of kinases is critical for cytokine receptor signalling and for the transmission of the activating signal in Epo-EpoR pathway [1]. The point mutation in exon 14 at codon 617 of JAK2 gene, leads to produce a gain-of-function that affects the kinase, which provides the proliferative advantage that can be seen in polycythaemia Vera [6]. The mutation of the gene itself is not a disease-initiating mutation, but in addition with an

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unidentified mutation or mutations can predispose to the acquisition of the disease. However, higher quantitative levels of JAK2617F allele are correlated with higher values for haematocrit, WBC and LDH. It can also predict patients likely to develop splenomegaly, pruritus, thromboembolic disease and suggested a higher frequency of myelofibrosis [4]. As the prognosis, the disease may follow two phases. The plethoric phase which is characterised by hyperproliferation of the cells with clinical manifestation of thrombosis and haemorrhage (epistaxis, easy bruising, gum bleeding and even GI bleedings) [7]. Following that, the spent phase is known for progressive anaemia, splenomegaly and fibrosis. Patients are at risk to develop leukemic transformation during the entire course of the disease [2]. Except for the potential malignancy, appropriately treated patients are compatible with near normal life. Untreated, half of the patients die within 2 years from the diagnosis, usually from a thrombotic event [13]. Physical findings can include plethora, erythromelalgia, hypertension, an enlarged spleen (75% of the patients) and hepatomegaly (30% of the patients). The WHO 2016 revised diagnosis criteria for PV are described in table 1.

WHO 2016 revised diagnosis criteria for Polycythaemia Vera Table 1

Diagnostic Criteria:
• Major Criteria – Hemoglobin > 16,5 g/dL in men, > 16 g/dL in women; **OR** Hematocrit > 49% in men, > 48% in women; **OR** Increased red cell mass (more than 25% above mean predicted value) – BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including proeminent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic mature megakaryocytes (differences in size) – Presence of JAK2V617F or JAK2 exon 12 mutation • Minor Criteria Subnormal serum erythropoietin level
Diagnosis of polycythemia vera (PV) requires meeting either all three major criteria or the first two major criteria and the minor criterion

Budd-Chiari syndrome is very rare in PV, but very specific to it [10], [14]. Unrecognised splenic or hepatic vein thrombosis can develop into portal hypertension and varices.

Once the disease is suspected, the patient must follow a series of laboratory workout to determine: a CBC count which reveals elevated levels of erythrocytes, 60% of the patients also have elevated level of leukocytes and platelets; coagulation test, leukocyte alkaline phosphatase (LAP), uricemia, levels of Epo and genetic tests for establishing the presence/absence of JAK2 mutations [3], [12]. Ultrasonography, CT exam or MRI of the abdomen achieve important information about the structural state of the liver and spleen, about their size and the presence of arterial or venous thrombosis. The bone marrow and medullar aspirate usually find hypercellularity and hyperplasia of the cell lines or sometimes myelofibrosis (Figure 1).

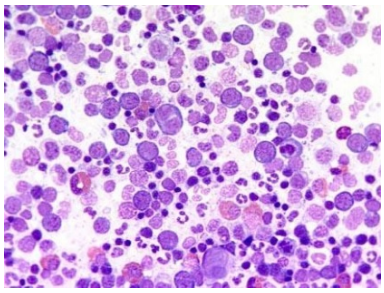

Fig. 1. *Bone marrow 400x*

The goals of the medical treatment of PV are: ameliorate the symptom burden, reducing the risk for thrombosis, prevent bleeding, lower the risk for myelofibrosis and acute myeloid leukaemia [12]. The treatment depends of the phase of the disease. In the plethoric phase, phlebotomy represents the first line for haematocrit level control, patients require a close follow-up for monitoring CBC. Also a low-dose aspirin treatment is started for reducing the risk for thromboembolic events [8], [15]. Chemotherapy cytoreductive therapy, like Hydroxyurea, and biologic response modifiers, like pegylated interferon alfa-2a (Pegasys) are used in high risk cases [16]. As surgical care, splenectomy may be necessary when the dimension of the spleen causes mass effect symptoms and pancytopenia. Even when is correctly treated, polycythaemia Vera has significant morbidity and mortality due to thromboembolic events. Myelofibrosis decreases life expectancy and the transformation to acute leukaemia has a very poor prognosis [11].

2. Case Report

We present a case of a 14-years-old female patient admitted in January 2019 to Clinical Emergency Children's Hospital of Brasov for abdominal pain in left quadrant and right hypochondrium. The symptoms started 3 days before the admission, after she affirmatively consumed fast food for lunch. The child was admitted in Gastroenterology Department.

From family history we mention that the mother was affirmatively admitted in hospital during the third trimester of the pregnancy for a transient ischemic attack. The father and the brother of the patient are healthy, without any chronic disease.

On routine testing, at 9 years old, in December 2014, showed Hb=18.2 g/dl and a haematocrit=61,6% without any complains. She was admitted at 10 years old, in 2015, at Fundeni Clinic Hospital, Bucharest, for persistent polycythaemia found. Medical report describes plethora symptoms (congested conjunctival vessels, purple-reddish face colour, purple coloured fingers and dizziness). The highest haemoglobin (20.6g/dl) and haematocrit (64,2%) values were documented at that time. The other workup performed then revealed leukocytosis, a coagulation profile within normal range, a erythropoietin level below 1 IU/L, bone marrow tap with erythroid hyperplasia. The sonography of the liver and spleen size in the upper normal range. The genetic studies performed then were negative including the sequencing of exons 12, 13 and 14 of JAK2 (also V617F); the panel of translocations associated with AML and ALL were also negative. In the second admission in Fundeni Hospital, a bone marrow biopsy (trephine biopsy) was performed with findings compatible with Polycythemia Vera.

Further investigations were made in Vienna in March 2015. The CBC and blood chemistry showed erythrocytosis, low erythropoietin level in serum, the review of the trephine slides reveal hypercellular

bone marrow compatible with PV and the genetic studies towards mutations associated with PV (JAK2, CALR, cMPL, SH2B3) remained negative.

Nevertheless, the lack of specific mutations in the genes associated with PV, does not exclude this entity. The required two major criteria of hemoglobin >16,5 g/dl in females and hypercellular bone marrow and one minor criteria (suboptimal serum Epo level) according to WHO Diagnostic Criteria (2016) were fulfilled. The recommendations for treatment were phlebotomy targeting a hematocrit below 43%, cytoreductive treatment with Hydroxyurea and low-dose aspirin (75mg/day). In between 2015-2017 the patient didn't follow the treatment and any hematological check-ups, the parents weren't compliant, denying the diagnosis.

In March 2017 the child was admitted in Clinical Emergency Children's Hospital of Brasov in Intensive Care Department for abdominal pain and vomiting. The laboratory findings revealed CBC with erythrocytosis, leukocytosis and thrombocytosis, and a value of 17,9 g/dl for hemoglobin and hematocrit of 54%, and iron deficiency. The ultrasonography of the abdomen describes an enlarged liver and spleen, portal hypertension and moderate ascites. A CT exam of the abdomen was also performed: hepatosplenomegaly with portal edema and parietal edema of the cholecystic (acute cholecystitis). The result raised the suspicion for Budd-Chiari syndrome.

Between the year 2017 and 2019, the patient didn't present for hematological follow-ups, but affirmatively had periodical check-up of the CBC's.

At the time of the admission, in January 2019, she had an altered medical state, weight 62 kg, without any fever, pale with dark circles, erythema of the hands, normal vital signs, normal cardiac and respiratory function, mild distension of the abdomen, painful at palpation and percussion, and enlargement of the liver which was palpable at 7-8 cm below the costal margin and important splenomegaly with a spleen size 14 cm below the costal margin, normal diuresis. The laboratory findings performed at admission showed erythrocytosis and leukocytosis with granulocytosis, hemoglobin at 17,1g/dl, a 54,1% hematocrit, positive markers for inflammation (C reactive protein 2,9 mg/dl), hyperuricemia 7,3 mg/dl, prolonged prothrombine time (PT), cholestasis syndrome. The child was admitted on Gastroenterology Department. During the first day of hospitalization the CBC was repeated, with the same elevated values which led to hematological consult request and the transfer of the child in Hematological Disease Department. Also an ultrasound of the abdomen was requested and the result showed an enlargement of the liver, with a 9 cm AP diameter, enlarged diameter in the portal vein, a spleen with longitudinal axis of 20 cm, with the diameter of the SV of 14 mm and a infracted zone of the inferior pole of the spleen of 5/4 cm. Portal hypertension and medium quantity ascites was also found during the exam.. Further investigation were completed with: low Epo level (1,7 U/l), leucocyte alkaline phosphatases (LAP) index with elevated values, genetic studies with JAK2V617F – negative but with positive mutation in sequence of exon 12. Other test like screening for hepatitis B and C, screening for EBV, CMV, Toxoplasmosis were negative, immune screening negative for ANA and antiDNA antibodies, normal C3, C4, negative screening for thrombophilia.

An angio-MRI was performed during the hospitalization. The results and reveal liver hypertrophy, absence of enhancement of right and middle hepatic veins – chronic occlusion, portosystemic shunts, permeable mesenteric and portal vein, dilated splenic vein, gallbladder with thickened wall, splenic enlargement, with an infarcted zone at the inferior pole (Figure 2), medium quantity of ascites, mostly in the left side.

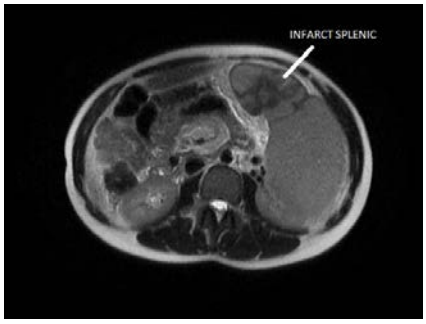

Fig. 2. *Angio-MRI image of the inferior pole infarction*

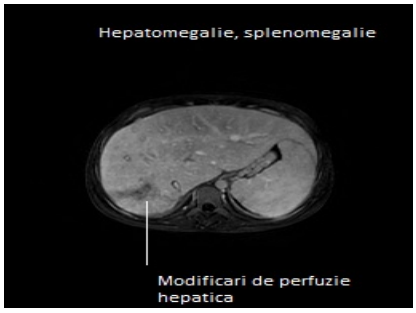

Fig. 3. *Angio-MRI image of the patient liver and spleen in transverse view*

Conclusions: splenomegaly with inferior pole infarction, Budd-Chiari syndrome and ascites (Figure 3).

During the hospitalization the patient received Ceftriaxone 2g/day iv for prophylaxis against infection at the infracted zone of the spleen, cytoreductive treatment with Hydroxyurea 1000mg/day, diuretics , low-dose Aspirin, anticoagulant treatment with LWMH for 12 days (Clexane 0,4ml x 2/day for 9 days), than with oral anticoagulant along with LMWH for 3 days, than only oral anticoagulant medication with Sintrom, K vitamin, IV fluids, gastric protection, hepatic protection, daily phlebotomies, and allopurinol for hyperuricemia. In evolution the patient medical state is improving, the dimension of the liver and spleen are decreasing progressively under cytoreductive treatment. The blood tests reveal that CBC is improving, the inflammation markers are decreasing slowly, the cholestasis syndrome is still persistent (Figures 4, 5).

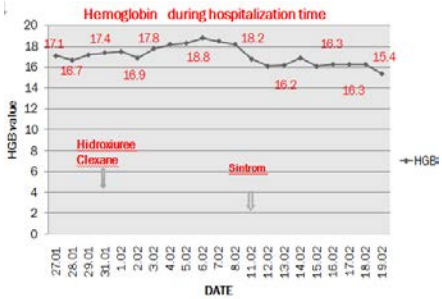

Fig. 4. *Hemoglobin value during the hospitalization*

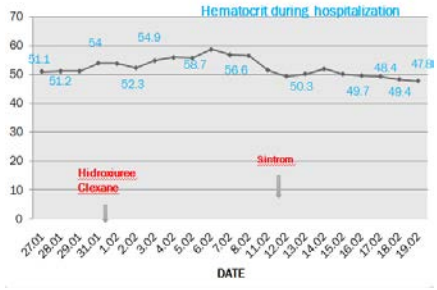

Fig. 5. *Hematocrit values during hospitalization time*

Serried ultrasounds performed during the hole period of hospitalization indicates a progressive decrease in the infracted zone of the spleen, the decrease of the liver AP diameter and disappearance of ascites.

The patient was discharged after 25 days of hospitalisation with recommendation of: cytoreductive treatment with Hydroxyurea, oral anticoagulant, low-dose aspirin, allopurinol, diuretic Spironolactone for another 10 days, hepatic protectors and recommendation of reduced physical activity, avoid abdominal trauma and climbing stairs effort. Periodic re-evaluation of CBC and abdominal ultrasound is in order.

In June 2019 the patient was admitted in the Privational Confraternization Vienna for a more detailed exploration of the suspected hematologic diagnosis of polycythemia Vera, JAK2V617F negative, which was associated with hepatosplenomegaly and hepatic vein thrombosis (Budd-Chiari syndrome). Oral anticoagulant therapy with Sintrom combined with low dose aspirin led to a severe bleeding tendency and hypermenorrhea, and was therefore withdrawn. Final results of the hematologic exploration from June 2019 of the bone marrow biopsy reveal the typical morphology of a myeloproliferative neoplasm with an increased number of megakaryocytes without clustering and without increased content of fibers. There was also no increase of blast cells.

The most important finding was the detection of a very rare pathogenic variant of the JAK2 mutation. In addition, was detected in the stem cell assay an autonomous BFU-E growth, very typical for JAK2 positive myeloproliferative neoplasm. The presence of a mutation in the von-Hippel-Lindau gene could be ruled out by whole exon sequencing.

In the recently analyzed blood from September 2019 there was the typical clinical picture of polycythemia vera with a hematocrit of 46,1 %.

In conclusion the patient suffers from a JAK2 positive myeloproliferative neoplasm, subgroup polycythemia Vera which appears clinically as masked polycythemia Vera (probably due to frequent increased bleeding episodes in form of hypermenorrhea).

As future therapy there is the only option to prevent further thromboembolic complications similar to that in 2017, to use a cytoreductive therapy with pegylated interferon. Therefore, the recommendation is to administer Ropeg-interferon-alfa-2b, 125 µg every two weeks subcutaneously. From this treatment we can expect that the disease activity decreases and with this on the long-term treatment the predisposition for venous thromboembolic events improves. In addition, an anticoagulation treatment with low dose should be administered, Xarelto 15 mg once per day. Since microcirculatory disturbances did not occur during the last years and there is a bleeding tendency, Aspirin 75 mg should be reduced to only 2 to 3 times per week.

3. Discussions

We have reported a case of a 14-year-old female patient, known from last admissions in hospital from 2015 and 2017 with persistent Polycythaemia with fulfilled diagnostic criteria's for PV and Budd-Chiari syndrome in observation.

The main particularity of the case was the age of the patient, who developed the

first symptoms when she was 11-years-old, and came into medical attention after modified routine blood tests.

PV is very rare in children and teenagers, the onset of the disease is typically in fifth or sixth decade, with a peak at the age of 60. Szuber et al., mentioned in a study made at Mayo Clinic that the incidence of the disease in patients aged 40 or younger is less than 12% [13].

Some of the patients are asymptomatic, others may experience nonspecific symptoms like shortness of breath, weakness, dizziness, excessive sweating, neurological symptoms like headache, vertigo, tinnitus, visual disturbances or hypertension, due to erythrocytosis. Erythrocytosis also can increase the risk for thrombosis, myocardial infarction, cerebrovascular accidents and pulmonary embolism [9]. Some of the patients present to the doctor for a complication of PV, as our patient did. A study made by Szuber el al., reveals that almost 33% of the patients present in the plethoric phase, with thrombosis or bleeding. In this study is shown that the incidence of venous thrombosis was higher in patients under the age or 40 or younger [7]. Due to the limited compliance of the family, the patient didn't follow any treatment between the last admission in hospital and the current presentation. The lack of medical attention and specific therapy with the omission of periodic phlebotomies determined all the thrombotic complications. Budd-Chiari syndrome, with prehepatic vein thrombosis, portal hypertension and giant splenomegaly with the infarction of the inferior pole are the consequences of hyper viscosity of the blood determined by elevated levels of haematocrit.

Budd-Chiari syndrome - hepatic vein thrombosis, is rare in polycythaemia Vera but is very specific to it, being the most common underlying disease (it's present in 2-10% of the patients) [10], [14]. A patient who presents with Budd-Chiari syndrome must alert the doctor to consider PV into diagnosis. Once the PV is suspected, a series of laboratory studies must be performed. The CBC usually shows erythrocytosis, like our patient did, initially with elevate levels of leukocytes. Abnormal platelet function can be present, but bleeding time is normal. Coagulation test results usually show prolonged PT (prothrombin time), values found in our patient lab work. Hyperuricemia is present in almost 40% of patients because of the high turnover rate of the bone marrow cells releasing DNA metabolites. Another particularity of the case is the difficulty in setting the diagnostic because of the negative repetitive genetic testing. A gain-function mutation of the gene JAK2 (a cytoplasmatic tyrosine kinase), is found in more than 90% of the adult patients but appears only in 30% of the children with polycythaemia Vera. [5] Our patient has a very rare pathogenic variant of the JAK2 mutation, found as a result of the next generation sequencing analysis. In addition, we could detect in the stem cell assay an autonomous BFU-E growth, very typical for JAK2 positive myeloproliferative neoplasm.

4. Conclusions

The authors present a case of polycythemia vera in a teenager, a very rare clinical entity in children, associated with hepatic vein thrombosis (Budd Chiari syndrome) and splenic vein thrombosis. as a thrombotic complication. This is the first

case of polycythemia vera from Clinical Emergency Children's Hospital of Brasov.

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