Budd-Chiari Syndrome in a Patient with J*AK-2* V617F and Factor V G1691A Mutations

JS Velarde-Félix[1, 2], J Sanchez-Zazueta[2], FP Gonzalez-Ibarra[3], JA González-Valdez[4], B Salcido-Gómez[1], E Gallardo-Angulo[5], J Murillo-Llanes[6]

ABSTRACT

Myeloproliferative neoplasms (MPN) are considered a risk factor for Budd-Chiari syndrome (BCS). The current classification of MPN by the World Health Organization is based on the presence of JAK-2 V617F somatic mutation, which is present in 40 to 60% of patients with BCS. Factor V Leiden mutation is found in around 53% of patients with BCS, representing the most common prothrombotic disease associated with the disorder. We describe a 48-year old woman with a past medical history of deep venous thrombosis in the left upper extremity and one episode in both lower extremities, one episode of transient ischaemic attack and essential thrombocythemia, who presented with jaundice, ascites and hepatomegaly. Budd-Chiari syndrome was diagnosed based on findings on Doppler ultrasound and liver biopsy. Doppler ultrasound showed narrowness of hepatic veins and inferior vena cava in its hepatic portion, diffuse echotexture and portal hypertension. Liver biopsy showed congestion of sinusoids and portal fibrosis. The patient was found to be a heterozygous carrier of Factor V and homozygous wild type G20210A prothrombin mutations. The JAK-2 V617F mutation was detected by allele-specific polymerase chain reaction (AS-PCR). The association of these mutations is rare, with only a few cases reported in the literature. The patient was treated with oral anticoagulation and antiplatelets with good results and proper follow-up. In conclusion, due to the possible coexistence of multiple prothrombotic factors in patients with Budd-Chiari syndrome, the approach to these patients must be focussed on searching for multiple factors and should include the JAK-2 V617F mutation

Keywords: Budd-Chiari syndrome, Factor V G1691A mutation, JAK-2 V617F mutation

Síndrome de Budd-Chiari en un Paciente con Mutaciones *JAK-2* V617F y Factor V G1691A

JS Velarde-Félix[1, 2], J Sanchez-Zazueta[2], FP Gonzalez-Ibarra[3], JA González-Valdez[4], B Salcido-Gómez[2], E Gallardo-Angulo[5], J Murillo-Llanes[6]

RESUMEN

Neoplasias mieloproliferativas (MPN) se consideran un factor de riesgo para el síndrome de Budd-Chiari (BCS). La clasificación actual de MPN por la Organización Mundial de la Salud se basa en la presencia de la mutación somática JAK-2 V617F, que está presente en 40 a 60% de los pacientes con BCS. La mutación del factor V Leiden se encuentra en alrededor del 53% de los pacientes con BCS, representando la enfermedad protrombótica más común asociada con el trastorno. Describimos una mujer de 48 años con antecedentes de trombosis venosa profunda en la extremidad superior izquierda y un episodio en ambos miembros inferiores, un episodio de ataque isquémico transitorio y trombocitemia esencial, que se presentó con ictericia, ascitis y hepatomegalia. El diagnóstico del síndrome de Budd-Chiari se basó en hallazgos de ultrasonido Doppler y la biopsia del hígado. El

From: [1]Centro de Medicina Genómica, Hospital General de Culiacán, "Bernardo J Gastélum", Culiacán, Sinaloa, Mexico, [2]Cuerpo Académico Immunogenética y Evolución, Unidad Académica Escuela de Biología, Universidad Autónoma de Sinaloa, Culiacán, Sinaloa, México, [3]Jersey City Medical Center, Department of Internal Medicine, New Jersey, USA, [4]Departamento de Hematología, CIDOCS, Hospital Civil de Culiacán, Culiacán, Sinaloa, México, [5]Departamento de Gastroenterología, Hospital General de Culiacán, "Bernardo J Gastélum" Culiacán, Sinaloa, México and [6]Departamento de Investigación, Hospital de la Mujer, Culiacán, Sinaloa, México.

Correspondence: Dr FP Gonzalez-Ibarra, Department of Internal Medicine, Jersey City Medical Center, 355 Grand Street, Jersey City, NJ 07302, USA. E-mail: drpavelglez@gmail.com

 DOI: 10.7727/wimj.2013.228

ultrasonido Doppler reveló estrechez de las venas hepáticas y la vena cava inferior en su porción hepática, ecotextura difusa, e hipertensión portal. La biopsia del hígado mostró congestión de los sinusoides y fibrosis portal. Se halló que el paciente era portador heterocigótico del Factor V y mutaciones homocigóticas silvestres de G20210A del gen de la protrombina. La mutación JAK-2 V617F fue detectada mediante reacción en cadena de polimerasa alelo específica (P CR-AS). La asociación de estas mutaciones es rara, con sólo unos pocos casos reportados en la literatura. El paciente fue tratado con anticoagulantes orales y antiplaquetarios, con buenos resultados y un seguimiento adecuado. En conclusión, debido a la posible coexistencia de múltiples factores protrombóticos en pacientes con el síndrome de Budd-Chiari, el acercamiento a estos pacientes debe ser enfocado en la búsqueda de múltiples factores y debe incluir la mutación JAK-2 V617F.

Palabras claves: Síndrome de Budd-Chiari, mutación del Factor V G1691A, mutación *JAK-2* V617F

West Indian Med J 2014; 63 (5): 529

INTRODUCTION

Myeloproliferative neoplasms (MPN) are a set of haematopoietic disorders characterized by overproduction of various cell lines within the bone marrow (1, 2). Myeloproliferative neoplasms are considered important risk factors for Budd-Chiari syndrome (BCS), a thrombotic occlusion of the hepatic veins, usually associated with different genetic and acquired prothrombotic disorders (3). In the current classification of MPN by the World Health Organization, it is recommended to test for the presence of *JAK-2* V617F somatic mutation (4), which is present in 40 to 60% of patients with BCS (5). Furthermore, patients with MPN who are found to be positive for the *JAK-2* V617F mutation usually have a poor clinical progression of the disease, in part due to an increase in the development of multiple forms of thrombosis (6).

Several studies have described a strong association between BCS and various hypercoagulable states (7, 8). According to a recent investigation, Factor V Leiden mutation was found in 53.1% of 64 patients with BCS, representing the most common prothrombotic disorder associated with the disorder, followed by the mutation in the gene of the metilentetrahidrofolate reductase (6).

In the present report, we describe a patient with BCS with the coexistence of *JAK-2* V617F and Factor V Leiden mutations. The association of these mutations is rare, with only a few cases reported in the literature.

CASE REPORT

This is a 48-year old Caucasian woman who was admitted to the Civil Hospital of Culiacan, Mexico, because of vomiting, abdominal pain and fatigue. Past medical history was relevant for an episode of deep venous thrombosis in the left arm and both legs and one episode of transient ischaemic attack two years ago. The patient was taking clopidogrel after the presentation of these clinical events. One year later, she experienced a second episode of deep venous thrombosis in the left upper extremity and she was investigated to rule out a thrombophilic disorder. Laboratory report was: protein C 66% (normal range 70–140), protein S 81% (normal range 70–123), activated protein C resistance 0.62 (normal range 0.86–1.10), lupus anticoagulant negative, antithrombin III 0.35 (normal range 0.19–0.31), antibodies to cardiolipin IgG 11.17 (normal < 23), IgM 5.14 (normal < 11) and homocysteine 8.61 μmol/L (normal range 5–20 μmol/L). Her platelet count was 727 500 mm^3 (average range between 499 000 and 818 000 mm^3).

The patient was found to be a heterozygous carrier of Factor V and homozygous wild type G20210A prothrombin mutations. The *JAK-2* V617F mutation was detected by allele-specific polymerase chain reaction [AS-PCR] (9). All family members were also tested for possible mutations and her father, one sister, one daughter and one son were also carriers of Factor V Leiden, and the rest of the family members were negative for G20210A prothrombin and *JAK-2* V617F mutations.

She had three children and the product of the last pregnancy was lost. She also mentioned irregular use of oral contraceptive pills; the last time was recently for a total of two months before admission, but it was suspended and she was not taking any medications on a daily basis before admission to the hospital.

Physical examination was relevant for the presence of jaundice, ascites and hepatomegaly. Laboratory examinations were relevant for haemoglobin of 14.5 g/dL, leukocytes 9.600 mm^3, prothrombin time (PT) of 19.2 seconds (normal value: 10–12 seconds), partial thrombo-plastin time (PTT) of 29.1 seconds (normal value: 30 to 45 seconds) and platelets of 680 000 mm^3. Therapy with an ursodeoxycholic acid and lactulose was started.

Budd-Chiari syndrome was diagnosed based on findings on Doppler ultrasound and liver biopsy. Doppler ultrasound showed narrowness of the hepatic vein and inferior vena cava in its hepatic portion by extrinsic compression of parenchyma, diffuse echotexture and portal hypertension. Liver biopsy showed congested sinusoids and non-cirrhotic portal fibrosis. Upper endoscopy showed oesophageal varices grade I. Currently, the patient is under anticoagu-

lation therapy and under close follow-up at the haematology and gastroenterology clinic.

DISCUSSION

The importance of the role of different aetiologic and risk factors among patients with Budd-Chiari syndrome has been reported previously in several studies. In this case, the patient presented with two risk factors for Budd-Chiari syndrome: a myeloproliferative disorder (essential thrombocythemia) caused by acquired *JAK-2* V617F mutation, and an inherited disorder of blood clotting caused by Factor V Leiden mutation.

Some authors, based in the World Health Organization criteria for the diagnosis of MPNs, have suggested that essential thrombocythemia is responsible for the hepatic-vein thrombosis (10); in fact, thrombocytosis *per se* can predispose to thrombosis in some patients (11).

In the past, JAK-2 mutation was not considered as a risk factor for systemic thrombosis, in part due to the low prevalence of JAK-2 mutation in patients with thrombosis outside the splanchnic system (12). However, there is increasing data of association of JAK-2 mutation in patients with thrombosis in non-splanchnic sites (13). Recently, a female patient with the JAK-2 mutation and a MPN, who presented with a transient ischaemic attack as the first symptom, was reported (14). Likewise, De Stefano *et al* (15) found a higher relative risk for cerebral vein thrombosis compared with splanchnic veins (2.26 *vs* 1.88) in patients with essential thrombocythemia younger than 60 years (15). Our patient presented with an episode of transient ischaemic attack and thrombosis in the left upper extremity and both legs two years before the diagnosis of BCS was made.

Factor V Leiden mutation is present in a large number of cases of hepatic vein thrombosis, especially in pregnant patients and patients taking oral contraceptive pills (11). Our patient has a history of previous use of oral contraceptives; moreover, the product of her last pregnancy was lost. Although some authors suggest that the Factor V Leiden mutation alone is not sufficient to cause BCS, it does represent a risk factor, with a relative risk of 11 (16) and of 6.6 for venous thromboembolism (17). It is recommended that relatives of these patients should avoid situations that confer a risk for hypercoagulable states and also engage in programmes of periodic medical evaluations.

Family members who are healthy carriers of Leiden mutation become ideal models to monitor the occurrence of *JAK-2* mutation V617F, because apparently the *JAK-2* V617F mutation is practically absent in healthy individuals (18). The genetic factors predisposing to BCS in these at-risk individuals, as well as the genes involved in essential thrombocythemia and its related thrombotic complications should be identified promptly.

The prothrombin G20210A, another thrombophilic mutation, and *JAK-2* V617F mutation are another example of combinations that have been reported in patients with thrombosis (19). In 2008, we reported on a woman with thrombocytosis, detected in a preoperative evaluation, who developed cerebral-vascular disease after the surgery but without liver damage, in whom we found both mutations (20). The prothrombin G20210A mutation was absent in our patient and her relatives.

This case is a good example of the integral management of this disorder. The patient continues with her periodic evaluations and has a good quality of life. We recommend performing an analysis for mutations in thrombophilic genes in those patients with thrombosis at any site with or without JAK-2 mutation. In the diagnostic investigation of our patient, the inherited thrombophilia caused by the Factor V mutation, combined with the component oestrogenic oral contraceptives, are likely precipitated by JAK-2 wild-type mute and later thrombotic events can occur in different sites; however, this hypothesis deserves further investigation.

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