Myeloproliferative Disorders

Myeloproliferative disease in the pathogenesis and survival of Budd-Chiari syndrome

We studied the etiology, diagnosis and natural course of myeloproliferative disease (MPD) in 40 consecutive patients with Budd-Chiari syndrome (BCS). In 38% of the BCS patients with MPD another etiological factor was found. JAK2 mutation was present in 41% of the tested BCS patients. Survival was not significantly affected by the presence of MPD.

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Budd-Chiari syndrome (BCS) is a rare disease primarily caused by thrombosis of the hepatic veins.[1] Myeloproliferative diseases (MPD) are the most important etiological factor.[2] The aim of this study was to evaluate other etiological factors in BCS patients with MPD, to assess the potential added value of the JAK2 mutation in diagnosing MPD and to determine survival of MPD patients with BCS.

All patients referred to our hospital between January 1980 and January 2006 with primary, non-malignant BCS were included in this study. Follow-up was from date of diagnosis until death, study closure, or, in the case of loss to follow-up, the date of the last visit. MPD were classified according to WHO guidelines.[3] Statistical tests were two-tailed with the level of significance set at $p<0.05$. The presence of the JAK2 mutation was determined by polymerase chain reaction in patients from whom DNA was available. Survival was estimated according to the Kaplan-Meier method. Comparison of survival was based on log-rank testing. Forty patients (65% female) with a median age of 28.4 years (range 18.4-53.3) were included. Nine patients had additional portal vein thrombosis. Etiological factors are shown in Table 1. Twenty-nine patients underwent complete diagnostic work-up for MPD. Eleven patients did not undergo a bone marrow biopsy, mostly because of normal blood counts (n=8). Thirteen patients (33%) were considered to have MPD (Table 2): although 11 patients were diagnosed with MPD according to WHO-criteria, two other patients, who were suspected of having MPD, but failed to meet the WHO-criteria, had a JAK2 mutation and were classified as having MPD. Five MPD patients (38%) had additional pro-thrombotic factors. The JAK2 mutation was identified in seven out of 17 tested patients (41%). The median age of patients with and without MPD was 35.7 years and 29.6 years (p=0.10), respectively, and the male:female ratio was 44%:56% versus 59%:41% (p=n.s.). A combination of BCS and portal vein thrombosis was observed in nine patients, all without MPD. The mean follow-up was 7.1±6.9 years. Two patients were lost to follow-up, one in each group. Eleven patients (28%) died during follow-up, of whom two had MPD. Survival rates in MPD patients at 1, 5, and 10 years remained constant at 92% (95% CI, 78%–100%), with the number of patients at risk being 12, 8 and 5, respectively. Survival rates in patients without MPD at 1, 5, and 10 years were 89% (95% CI, 77%–100%), 64% (95% CI, 44%–85%) and 53% (95% CI, 28%–79%), with the number of patients at risk being 24, 11 and 5, respectively. Survival did not differ significantly between the two groups (p=0.18). None of the BCS patients without MPD at diagnosis developed MPD during follow-up. This study showed a prevalence of MPD of 33% in patients with BCS, which is in line with results of earlier studies using only WHO or PVSG criteria for diagnosing MPD.[4,5] Our results showed additional etiological factors in 38% of BCS patients with MPD, highlighting the necessity for extensive screening for pro-thrombotic conditions. Recently, an association between MPD and a mutation of the JAK2 tyrosine kinase (JAK2 V617F) was described.[6] This mutation was shown to occur in 59% of BCS patients and can be used to characterize occult MPD.[7] In our study the prevalence of the JAK2 mutation was 41%. Interestingly, the JAK2 mutation led to the identification of two MPD patients who failed to meet WHO-criteria. This suggests that JAK2 mutation analysis should be included in the work-up for MPD in BCS patients. In this study, the 10-year survival for BCS patients with MPD was 92%. It has been suggested that a shortened survival of MPD patients with additional BCS is primarily related to complications of hepatic dysfunction and portal hypertension. Indeed, the two MPD patients died of causes unrelated to MPD. Survival did not differ significantly between individuals with and without MPD. Additional portal vein thrombosis was only present in patients without MPD. This may account for the slightly lowered survival of these patients compared to MPD patients, since more extensive thrombosis in the splanchnic area is associated with poorer survival.[8] In addition, three patients with and one patient without MPD underwent liver transplantation, which may also have affected survival. In conclusion, we found MPD in 33% of our BCS patients and additional etiological factors in 38% of BCS patients with MPD. Our study confirms the diagnostic importance of determining whether the JAK2 mutation is present in patients with BCS. Survival was not significantly affected by the presence of MPD.

Table 1. Etiological factors in 40 patients with primary, non-malignant Budd-Chiari syndrome[a].

	N	*%*[b]
Myeloproliferative disease	13	33
Coagulation disorder	14	35
Protein C deficiency[c]	2	7
Protein S deficiency[c]	2	7
Factor V Leiden mutation	5	15
Homozygote	2	6
Heterozygote	3	9
Prothrombin gene variant	2	8
Homozygote	0	0
Heterozygote	2	8
Antiphospholipid antibodies[d]	4	11
Anticardiolipin antibodies IgM/IgG	4	11
Lupus anticoagulant	1	3
Plasminogen deficiency	1	3
Others	21	53
Oral contraceptive use	13	52
Paroxysmal nocturnal hemoglobinuria	2	9
Auto-immune[e]	5	13
Ulcerative colitis	1	3
Abdominal surgery	1	3
No underlying disorder	4	10

[a]patients could have more than one etiological factor simultaneously; [b]percentage of tested patients; not all investigations could be performed in the individual patients; [c]patients treated with oral anticoagulants or who had liver failure during the diagnostic work-up were excluded from this analysis; [d]diagnosis of antiphospholipid antibodies was made if lupus anticoagulant or aCL was present and confirmed after 12 weeks; [e]auto-immune diseases: Behcet's disease (n=1), Sjögren's disease (n=1), systemic lupus erythematosus (n=2) and mixed connective tissue disease (n=1).

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Table 2. The diagnostic criteria in the 13 patients with myeloproliferative disease in addition to primary, non malignant Budd-Chiari syndrome.

Patient no.	Sex	Age at diagnosis of BCS	Hb g/dL	Ht %	RBC mass mL/kg	Spleno-megaly	Platelet count 10^9/L	Leukocyte count 10^9/L	Serum epo mU/mL	EEC	JAK2 mutation	Reticulin fibrosis[c]	Iron in marrow	Bone marrow biopsy/ morphology	Additional risk factors[d]
Polycythemia vera															
1[a]	F	49.9	16.3	43	21.1	+	273	25.0	327	-	NA	+	–	Panmyelosis, especially erythroid line, dysplastic megakaryocytes, clustering	None
2	F	46.3	17.4	51	33.9	+	361	10.2	19	NA	+	+	–	Panmyelosis, dysplastic megakaryocytes, clustering	None
3	M	40.2	18.4	54	NA	+	112	16.5	5	NA	NA	+	–	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes, clustering	None
4	F	46.9	12.6	42	39.2[b]	+	418	10.6	NA	NA	+	+	–	Panmyelosis, dysplastic megakaryocytes, clustering	None
5	M	26.0	17.3	41	34.6	+	472	9.7	10	+	+	+	–	Erythroid and megakaryocytic hyperplasia	None
6	M	27.4	17.3	47	41.3	+	328	4.6	12	+	+	–	–	Panmyelosis, dysplastic megakaryocytes dysplastic megakaryocytes, clustering	None
Essential thrombocythemia															
7	F	29.5	14.2	45	29.5	–	520	4.9	NA	+	NA	-	+	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes	OCC
8	F	36.8	9.2	27	NA	–	629	16.0	NA	NA	+	–	–	Megakaryocytic hyperplasia and dysplasia, clustering	Protein C def., OCC
9	F	46.6	11.8	37	26	–	596	3.6	NA	NA	NA	+	–	Megakaryocytic hyperplasia and dysplasia, clustering	None
10	F	35.9	11.0	39	NA	–	497	9.8	23	+	NA	+	–	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes	OCC, SLE
11[e]	F	20.9	11.3	38	NA	–	445	7.3	15	–	+	–	+	Megakaryocytic hyperplasia and dysplasia	OCC
12[e]	M	21.8	15.8	43	26.7	+	450	16	3	–	+	–	+	Megakaryocytic hyperplasia and dysplasia	None
Chronic myeloproliferative disease, unclassifiable															
13	F	36.9	14.4	39	30.0	+	215	23	30	+	NA	–	–	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes, clustering	OCC

[a]Patient 1 was diagnosed with MPD despite an elevated erythropoietin level, as it has been shown that this does not exclude MPD (9). [b]>25% above mean normal predicted value. [c]None of the patients had bone marrow collagen fibrosis. [d]OCC (oral contraceptives), SLE (systemic lupus erythematosus). [e]Patients 11 and 12 were suspected of having MPD based on high platelet counts, the diagnosis was later confirmed by positive JAK2 mutation.

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References

1. Janssen HL, Garcia-Pagan JC, Elias E, Mentha G, Hadengue A, Valla DC. Budd-Chiari syndrome: a review by an expert panel. J Hepatol 2003;38:364-71.
2. Menon KV, Shah V, Kamath PS. The Budd-Chiari syndrome. N Engl J Med 2004;350:578-85.
3. WHO classification of the chronic myeloproliferative diseases (MPD) polycythemia vera, chronic idiopathic myelofibrosis, essential thrombocythemia and MPD unclassifiable. WHO Classification of Tumours. Tumours of Haemtopoiesis and Lymphoid Tissues, IARC; Lyon: 2001. pp. 31-42.
4. Hadengue A, Poliquin M, Vilgrain V, Belghiti J, Degott C, Erlinger S, et al. The changing scene of hepatic vein thrombosis: recognition of asymptomatic cases. Gastroenterology 1994;106:1042-7.
5. Murad SD, Valla DC, de Groen PC, Zeitoun G, Hopmans JA, Haagsma EB, et al. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. Hepatology 2004;39:500-8.
6. Baxter EJ, Scott LM, Campbell PJ, East C, Fourouclas N, Swanton S, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. The Cancer Genome Project. Lancet 2005;365:1054-61.
7. Patel RK, Lea NC, Heneghan MA, Westwood NB, Milojkovic D, Thanigaikumar M, et al. Prevalence of the activating JAK2 tyrosine kinase mutation V617F in the Budd-Chiari syndrome. Gastroenterology 2006;130:2031-8.
8. Murad SD, Valla DC, de Groen PC, Zeitoun G, Haagsma EB, Kuipers EJ, et al. Pathogenesis and treatment of Budd-Chiari syndrome combined with portal vein thrombosis. Am J Gastroenterol 2006;101:83-90.
9. Thurmes PJ, Steensma DP. Elevated serum erythropoietin levels in patients with Budd-Chiari syndrome secondary to polycythemia vera: clinical implications for the role of JAK2 mutation analysis. Eur J Haematol 2006;77:57-60.