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Splenectomy after portal thrombosis in patients with polycythemia vera and essential thrombocythemia

MARIA LUIGIA RANDI, FABRIZIO FABRIS, ELISABETTA RUZZON, ENRICA PACQUOLA, GIUSEPPE CELLA, ANTONIO GIROLAMI

Department of Medical and Surgical Sciences, University of Padua Medical School, Padua, Italy

Correspondence: Dr. Maria Luigia Randi, Dipartimento di Scienze Mediche e Chirurgiche, via Ospedale 105, 35128 Padua, Italy. Phone: international +39.049.8212668. Fax: international +39.049.8212661. E-mail: marialuigia.randi@unipd.it

Background and Objectives. Polycythemia vera (PV) and essential thrombocythemia (ET) are two rare acquired myeloproliferative disorders (MPD) with frequent thrombotic and hemorrhagic complications. The occurrence of thrombosis in unusual sites, e.g. splanchnic vasculature, is a severe complication of these diseases. We describe a single-institution experience in patients with ET and PV, diagnosed in agreement with the *Polycthemia Vera Study Group* criteria, with portal vein thrombosis who did or did not undergo splenectomy.

Design and Methods. The medical records and the follow-up outcome of 16 MPD patients with portal thrombosis who underwent splenectomy (group A1) and 16 who did not (group A2) were evaluated. Their median follow-up was, respectively, 13.45 and 10.49 years. The overall survival of these patients was compared with that of a population of 32 patients with MPD and no portal thrombosis (group B) matched for sex, age, diagnosis and duration of follow-up.

Results. In group A1, 2 patients developed deep vein thrombosis, 1 patient had a surgical hemorrhage and 2 patients died early, one from acute infection, the other from bone marrow aplasia. Among the survivors, one male had a deep vein thrombosis and 1 developed a new portal thrombosis. Four patients died during the follow-up (median 9.48 years, range 3.17-25.1; 1 stroke, 2 gastrointestinal bleedings, 1 leukemic conversion). No difference was observed in the incidence of thrombotic or hemorrhagic complications or in the rate of deaths when group A1 was compared to the other groups. The use of antiplatelets drugs was statistically increased in group A1 after splenectomy, because portal vein thrombosis induced *per se* an increased use of therapeutic agents. No statistical difference was observed in overall survival between the different groups.

Interpretation and Conclusions. 1) Bleeding and thrombosis are the leading causes of morbidity and mortality in ET and PV patients with portal vein thrombosis both with or without splenectomy. 2) Portal vein thrombosis, and sometimes splenectomy, requires increased use of drugs which may enhance the risk of leukemic transformation. In spite of this, the patients who survive the first post-splenectomy period may have a long and safe life.

Key words: splenectomy, polycythemia vera, essential thrombocythemia.

Polycythemia vera (PV) and essential thrombocythemia (ET) are two rare acquired myeloproliferative disorders characterized by overproduction of red blood cells and platelets, respectively. Both diseases may lead into a *spent phase* with myeloid metaplasia, myelofibrosis and splenomegaly.[1,2]

For many years PV and ET can be managed successfully by modalities such as hydroxyurea, phlebotomies and, the more recently introduced, anagrelide and interferon.[3,4] However, thrombotic and hemorrhagic complications are frequent and the occurrence of thrombosis in unusual sites, e.g. splanchnic vasculature[5] or cerebral sinus thrombosis,[6] is a severe complication of these diseases.

Portal district thrombosis has been managed in the past with splenectomy and indeed sometimes splenectomy represents the only palliative measure to improve the patient's condition in the presence of post-polycythemic or post-thrombocythemic myeloid metaplasia. While the effect of therapeutic splenectomy in patients with myelofibrosis has been widely described,[7,8] little is known about splenectomy in ET or PV patients.

In this report, we describe a single-institution experience in patients with ET and PV with portal vein thrombosis who did or did not undergo splenectomy and had a very long follow-up.

Design and Methods

The medical records and the follow-up of patients with PV and ET who had portal thrombosis (group A) during the period 1980 through 1990 were reviewed in 2000. Patients who underwent splenectomy were considered as group A1 while non-splenectomized patients formed group A2. The overall survival of patients of group A was compared with that of a similar population (group B) of patients with ET (15 cases) and PV (17 cases) matched for sex (14 males and 18 females), age (mean 46.75±11.7 years), platelet count at the time of diagnosis (mean 795.66±373.4) and duration of follow-up (median 11.9 years), but who did

not have portal thrombosis. The diagnosis of PV and ET was made in all patients in accordance with the *Polycythemia Vera Study Group* criteria.[9,10]

Statistical analysis

The analysis of variance test was used to compare means for statistical significance. The Kaplan-Maier curve method was used to estimate the probabilities of overall survival as function of time for various groups. The log-rank models were used to assess the significance of the difference between subgroups with 95 percent confidence intervals. The rate of complications in the various groups of patients was compared by the χ^2 test.

Results

Patients and clinical features

Thirty-two patients (15 ET and 17 PV, 14 males and 18 females, mean age 46.7±13.5 years) formed group A (patients with portal thrombosis). All these patients received heparin in the acute phase of thrombosis and then warfarin for at least 6 months. Half of them underwent splenectomy (group A1) and half did not (group A2). Portal hypertension subsequent to portal thrombosis in 5 patients (ET) and acute portal thrombosis in 11 (6 ET and 5 PV) were the indications for splenectomy. The clinical variables of patients of group A are summarized in Table 1. No chromosomal alterations were found in our patients and most of them had a hypercellular bone marrow picture with an increased number of megakaryocytes. Only 4 of the reported patients had mild bone marrow fibrosis. The morbidity and mortality of our patients with myeloproliferative disorders are summarized in Table 2.

Group A1 (patients who had a splenectomy)

Early complications of splenectomy. Two patients (1 with ET and 1 with PV) developed deep vein thrombosis in the perioperative period (within 30 days) and 1 patient with ET had a surgical hemorrhage that required red cell transfusion. Two patients died: one with ET died of acute infection 6 months after surgery and the other, with PV, died of bone marrow aplasia 3 months post-operatively.

Delayed complications of splenectomy. During the post-splenectomy follow-up (median 7.62 years), 1 male with PV had a deep vein thrombosis and 2 ET subjects had hemorrhages (1 purpura and 1 gastrointestinal) 14.5 and 20.1 years after splenectomy, respectively. Four patients died during the follow-up (median 9.48 years, range 3.17-25.1).

The causes of deaths were: 1 stroke, 2 gastrointestinal bleedings (2 ET), and 1 leukemic conversion 13 years after the first diagnosis and 8.8 years after splenectomy. The platelet count of the patients (before 754±267, after 1373±871) increased significantly (p<0.002) after splenectomy.

Table 1. Main clinical data of our patients with portal thrombosis.

	Group A1 splenectomy (16 patients)	*Group A2 no splenectomy (16 patients)*
Age (years)	43.2±13	48±13.3
Diagnosis (ET/PV)	10/6	5/11
Sex (M/F)	6/10	8/8
Palpable spleen size (cm below costal margin, range)	2-4	2-4
Ascites (no. of patients)	2	2
Packed cell volume (%)	42.2±9	43.5±15
White blood cell count (×10⁹/L)	172.6±132.4	154.6±137.1
Platelet count (×10⁹/L)	754±267	676.8±290.2
Circulating blasts (range)	0-2	0-2
Alkaline phosphatase	191±26	174±19
Bone marrow cellularity	(14 cases)	(13 cases)
hypercellular	12	10
hypocellular	1	2
normocellular	1	1
Fibrosis grade on reticulin staining	(12 cases)	(16 cases)
absent	10	14
mild	2	2
Normal cytogenetic results	16	16
Presence of constitutional symptoms (patients, no.)	2	6
Time from diagnosis to splenectomy (years, range)	0-25	–
Hemorrhagic complications (gastrointestinal)	3	7
Major thrombotic complications other than portal thrombosis	2	4
Total follow-up (median years)	13.45	10.49
Total deaths	6	6
Follow-up after splenectomy (median years)	8.59	–

Group A2 (patients without splenectomy)

The mean age at the time of portal thrombosis was slightly higher than in group A1, but the difference was not statistically different. No statistical difference was observed in the platelet count (676.8±290.2) between Group A2 patients and that of group A1 patients before splenectomy.

Therapy. The treatments used for PV and ET are summarized in Table 3. The use of antiplatelets drugs was statistically increased after splenectomy (p=0.014) in group A1, particularly, the use of aspirin associated with myelotoxic drugs (p<0.02) The treatment needs of group A1 patients were similar to those of group A2 patients. In contrast, group A1 patients received fewer drugs before splenectomy than did the patients of group B (p <0.01).

Table 2. Morbidity and mortality after splenectomy in patients with portal thrombosis and in controls.

Events	*Splenectomy Group A1 (16 patients)°*	*Early complications after splenectomy Group A1 (16 patients)°*	*Delayed complication after splenectomy Group A1 (14 patients)°*	*No splenectomy Group A2 (16 patients)°*	*Controls Group B (32 patients)°*
Hemorrhages	**5** (31.25%)	**1** (6.2%)	**4** (28.5%)	**8** (50%)	**7** (21.8%)
Non fatal bleedings	**3** 1 surgical hemorrhage 1 purpura 1 gastro-intestinal	**1** 1 surgical hemorrhage	**2** 1 purpura 1 gastro-intestinal	**8** 6 gastro-intestinal 1 epistaxis 1 purpura	**7** 3 gengival 3 epistaxis 1 gastro-intestinal
Fatal bleedings	**2** 2 gastro-intestinal	0	**2** 2 gastro-intestinal	**0**	**0**
Major infections	**1** 1 pulmonitis	**1** 1 pulmonitis	0	**0**	**0**
Thrombosis	**5** (25%)	**2** (12.5%)	**3** (21.4%)	**5** (31.25%)	**11** (34.3%)
Non-fatal thrombosis	4 1 portal thrombosis 3 deep veins thrombosis	**2** 2 deep veins thrombosis	**2** 1 stroke 1 deep vein thrombosis	**3** 1 pulmonary embolism 1 deep vein thrombosis 1 stroke	**10** 3 stroke 3 myocardial infarction 2 deep vein thrombosis 2 peripheral artery thrombosis
Fatal thrombosis	**1** 1 stroke		**1** 1 stroke	**2** 1 portal thrombosis 1 intestinal infarction	**1** 1 stroke
Major blood disease	**2** 1 bone marrow aplasia 1 acute leukemia	**1** 1 bone marrow aplasia	**1** 1 acute leukemia	**2** 1 acute leukemia 1 bone marrow aplasia	**4** 4 acute leukemias
All deaths	**6** (37.5%)	**2** (12.5%)	**4** (28.5%)	**6** (37.5%)	**7** (21.8%)*

**Some patients died of causes not related to polycythemia vera or essential thrombocytopenia; °The number of patients reported in the table indicate only the patients affected by complications.*

Survival analysis

No statistical difference was observed in the incidence of hemorrhages, infections and thrombosis when group A1 was compared to group A2 and B. No statistical difference was observed in overall survival (Figures 1a and 1b).

Discussion

Splenic-portal-mesenteric thrombosis is a relatively frequent complication in patients with ET and PV.[5] No clear explanation has been given for the occurrence of thrombosis in this unusual site. However, hyperviscosity, at least in PV patients, may play a significant role.[11] The natural history of portal vein thrombosis is unknown, because in all reported cohorts of patients some form of therapy has been administered. The influence of the various medical and surgical interventions remains unknown. Little is known about the outcome of patients with PV and ET with portal vein thrombosis who undergo splenectomy or who do not. In contrast, the effect of therapeutic splenectomy in patients with myelofibrosis with myeloid metaplasia, whether agnogenic, post-thrombocythemic or post-polycythemic, has been well described.[7,8] We report the main features of a large cohort of MPD patients with portal thrombosis. Half of our patients underwent splenectomy and half did not. The long study period of our patients (median follow-up over 10 years) has probably been associated with a change in the profile from the patients seen early in this period to those seen later. The splenectomies reviewed were remote probably because of the low present use of such surgery in patients with known PV or ET. Moreover, it is possible that splenectomized patients had a *different* disease from that of those not operated on: more ET than PV patients have been splenectomized.

Table 3. Main therapeutic options in our patients with MPD.

	Group A1		*Group A2*	*Group B*
	Before splenectomy (16 patients)	*After splenectomy (14 patients°)*	*16 patients*	*32 patients*
No therapy	9 (56%)	4 (28.6%)	4 (25%)	5 (14.3%)#
Aspirin	2 (12.5%)	1 (7.14%)	1 (6.25%)	6 (18.75%)
Myelotoxic drug	3 (18.75%)	1 (7.14%)	5 (31.25%)	4 (12.5%)
Both	2 (12.5%)	10 (71.4%)*	6 (37.5%)	17 (53.1%)
Total treated patients	7 (43.75%)	12 (85.75%)*	12 (75%)	27 (84.37%)#

*°Two patients died within 6 months after splenectomy; *p< 0.002: compared to group A1 before splenectomy; #p=0.01: compared to group A1 before splenectomy.*

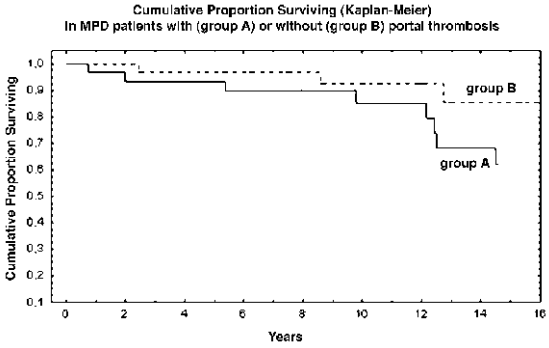

Figure 1a. Overall survival analysis of 32 patients with portal thrombosis (group A) compared to that of 32 MPD patients (group B) matched for sex, age, diagnosis and duration of follow-up but without portal thrombosis.

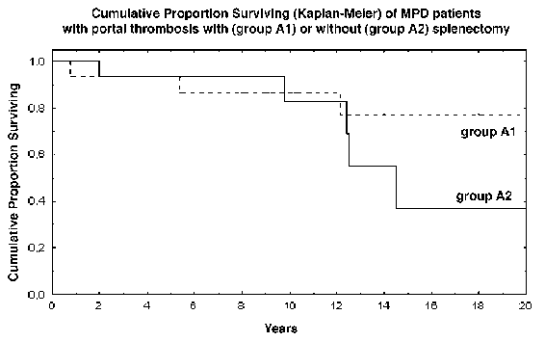

Figure 1b. Overall survival analysis of 16 patients with portal thrombosis and splenectomy (group A1) compared to that of 16 patients without splenectomy (group A2).

The mean platelet count at the time of portal thrombosis was not very high, in accordance with previous data.[12] In contrast, an increased WBC count, probably due to an inflammatory associated condition, was observed.

No significant correlation between the presence of bone marrow fibrosis and bone marrow cellularity and the patients' outcome was observed. All our patients had a normal karyotype and no observations can be made about chromosomal abnormalities.

We are conscious that the number of patients is still too low to draw firm conclusions on outcome; however, no significant difference was observed in the frequency of thrombotic complications between patients who underwent splenectomy and those who did not. In contrast, a higher percentage of patients without splenectomy developed constitutional symptoms or suffered for gastrointestinal bleeding, the most common complication of portal venous thrombosis.[13] The mortality rate was the same in the two groups. The incidence of perioperative mortality and morbidity seems to confirm the incidence observed in myelofibrosis.[7] Not surprisingly, bleeding, thrombosis and infections are the leading causes of early mortality and morbidity. No modification of coagulation tests due to disseminated intravascular coagulation in patients with hemostatic complications was documented.

The most frequent causes of death during the follow-up were hemorrhages and thrombosis, well-recognized problems in PV and ET patients.[14]

However, 2 patients after splenectomy and 2 without splenectomy developed acute non-lymphoid leukemia or bone marrow aplasia. It is interesting to note that all these patients had received multiple cytotoxic drugs that are known to favor leukemic progression.[2,15] In myelofibrosis, splenectomy has been described to have a poor effect on leukemic transformation,[16] attributed to the fact that splenectomized patients are mainly those with a worst prognostic pattern. Our data do not seem to confirm this hypothesis in ET and PV patients.

Despite the relatively high rate of perioperative complications, a substantial number of patients with PV and ET had a long, complication-free follow-up after splenectomy. The benefits of splenectomy on alleviation of symptoms and signs of portal hypertension are due to increased portal flow.[17]

Not surprisingly, after splenectomy, increased use of myelotoxic drugs and phlebotomies was necessary. The use of antiplatelet drugs in patients with portal thrombosis before splenectomy was lower than that in patients of the control group (group B), while it became similar after splenectomy.

This observation is explained by the fact that in most cases (12 out of 16), splenectomy was performed early after the portal thrombosis which was the presenting feature of the myeloproliferative disorder.

It is evident that the absence of a spleen causes an increase in platelet count and physicians caring for such patients prefer to use more drugs. Moreover, it must be considered that the patients who underwent splenectomy had had a major thrombosis (portal thrombosis) which is a known risk factor for a new thrombosis,[18] thus requiring the use of antiplatelet drugs. The survival of MPD patients with or without portal thrombosis does not seem to be different and the use of splenectomy for portal thrombosis does not seem to modify the life expectancy of these patients. However, after 12 years follow-up, patients with portal thrombosis without splenectomy (group A2) seem to have a

worse survival than those of group A1, despite a statistical difference attributable to the small number of patients. In conclusion, this study suggests that the outcome of splenectomy in PV and ET patients performed for thrombosis of the portal vein is usually conditioned by the increased use of cytotoxic drugs, which can increase the risk of leukemic transformation. In spite of this, the patients who survive the first post-splenectomy period may have a long and safe life.

Contributions and Acknowledgments

MLR planned the study and was responsible for writing the paper. FF, GC: clinical diagnosis of the patients. ER, EP: collection and analysis of laboratory data. AG: critical revision of the manuscript. MLR: responsible for all Tables and Figures.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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References

1. Najean Y, Arrago, JP, Rain JD, Dresch C. The "spent" phase of polycythemia vera: hypersplenism in the absence of myelofibrosis. Br J Haematol 1984; 56:163-70.
2. Randi ML, Fabris F, Girolami A. Leukemia and myelodysplasia in patients with essential thrombocythemia treated with cytotoxic agents. Haematologica 1999; 84:1049-50.
3. Murphy S, Peterson P, Iland H, Laszlo J. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. Semin Hematol 1997; 34:29-39.
4. Anonymous. Polycythemia vera: the natural history of 1213 patients followed for 20 years. Gruppo Italiano Studio Policitemia. Ann Intern Med 1995; 123:656-64.
5. Valla D, Benhamou JP. Obstruction of the hepatic veins or suprahepatic inferior vena cava. Dig Dis 1996; 14:99-118.
6. Randi ML, Rossi C, Barbone E, Casonato A, Fabris F, Girolami A. Superior sagittal sinus thrombosis in 5 patients with essential thrombocythemia: a possible disease variant. Rev Iberoam Thromb Hemost 1994; 7:76-8.
7. Tefferi A, Mesa RA, Nagorney DM, Schroeder G, Silverstein MN. Splenectomy in myelofibrosis with myeloid metaplasia: a single-institution experience with 223 patients. Blood 2000; 95:2226-3.
8. Barosi G, Ambrosetti A, Buratti A, Finelli C, Liberato NL, Quaglini S, et al. Splenectomy for patients with myelofibrosis with myeloid metaplasia: pretreatment variables and outcome prediction. Leukemia 1993; 7:200-6.
9. Berlin NI. Diagnosis and classification of the polycythemias. Semin Hematol 1975; 12:339-51.
10. Murphy S, Iland H, Rosenthal D, Laszlo J. Essential thrombocythemia: an interim report from the Polycythemia Vera Study Group. Semin Hematol 1986; 23:177-82.
11. Randi ML, Rossi C, Tison T, Barbone E, Girolami A. Portal thrombosis and myeloproliferative diseases. Int Congress Phlebolymphology 1991; 21.1-21.3[abstract].
12. Valla D, Casadevall N, Huisse MG, Tulliez M, Grange JD, Muller O, et al. Etiology of portal vein thrombosis in adults. A prospective evaluation of primary myeloproliferative disorders. Gastroenterology 1988; 94:1063-9.
13. Condat B, Pessione F, Hillaire S, Denninger MH, Guillin MC, Poliquin M, et al. Current outcome of portal vein thrombosis in adults: risk and benefit of anticoagulant therapy. Gastroenterology 2001; 120:490-7.
14. Randi ML, Stocco F, Rossi C, Tison T, Girolami A. Thrombosis and hemorrhage in thrombocytosis: evaluation of a large cohort of patients (357 cases). J Med 1991; 22:213-33.
15. Higuchi T, Okada S, Mori H, Niikura H, Omine M, Terada H. Leukemic transformation of polycythemia vera and essential thrombocythemia possibly associated with an alkylating agent. Cancer 1995; 75:471-7.
16. Barosi G, Ambrosetti A, Centra A, Falcone A, Finelli C, Foa P, et al. Splenectomy and risk of blast transformation in myelofibrosis with myeloid metaplasia. Italian Cooperative Study Group on Myelofibrosis with Myeloid Metaplasia. Blood 1998; 91:3630-6.
17. van't Riet M, Burger JW, van Muiswinkel JM, Kazemier G, Schipperus MR, Bonjer HJ. Diagnosis and treatment of portal vein thrombosis following splenectomy. Br J Surg 2000; 87:1229-33.
18. Cortelazzo S, Viero P, Finazzi G, D'Emilio A, Rodeghiero F, Barbui T. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Oncol 1990; 8:556-62.

Peer Review Outcomes

Manuscript processing

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What is already known on this topic

Portal vein thrombosis is a rare complication of chronic myeloproliferative disorders, occurring most often in polycythemia vera and essential thrombocytosis. To date, there has been no correlation between the hematocrit, platelet count or platelet function abnormalities and the development of portal vein thrombosis in the setting of a chronic myeloproliferative disorder and also no consensus about the most appropriate therapeutic interventions.

What this study adds

Although retrospective and limited with respect to patient number, this study has the advantages of representing the experience of a single medical institution and a long period of follow-up observation.

Potential implications for clinical practice

This study supports a role for splenectomy in the management of portal hypertension caused by portal vein thrombosis. It also emphasizes that splenectomy alone has no influence on the underlying coagulopathy.

Jerry L. Spivak, Associate Editor (Baltimore, USA)