Pulmonary hypertension in patients with hematological disorders following splenectomy

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Abstract Prevalence of pulmonary arterial hypertension (PAH) was studied by Echocardiography and Doppler in 43 splenectomised patients with various disorders 1–20 years after splenectomy. PAH was detected only in thalassemia major, intermedia, hereditary spherocytosis and myelofibrosis groups comprising a total of 21 patients. Six patients out of 21 was found to have PAH with mean pulmonary arterial pressure of 46.28 ± 28.17 mmHg. Twenty one controls having similar duration and type of disease also were assessed for PAH in this case control study 3/21 had PAH in this control group. The difference in number of patients showing pulmonary hypertension between case and control was not statistically significant (chi-square test $p = 0.29$) though the difference in pulmonary arterial pressure between case and control were significantly different (t-test $p < 0.0029$) with control group showing a mean pulmonary arterial pressure of 25 ± 19 mmHg.

Platelet count in the splenectomised group was significantly higher ($p = 0.0029$) than the controls. Pulmonary thromboembolism was equally high in the PAH patients with and without splenectomy. Patients undergoing splenectomy due to trauma, immune thrombocytopenia, sideroblastic anemia, extra hepatic portal hypertension, autoimmune hemolytic anemia did not show PAH after splenectomy

even years after the procedure PAH following splenectomy is common after certain disorders and control patients with these diseases have tendency to develop PAH even without splenectomy. Pulmonary thromboembolism may be an important pathophysiological mechanism leading to this condition. Patients having hemolytic anemia and myelofibrosis should have regular evaluation of pulmonary arterial pressure whether he/she has been splenectomised or not. This is particularly important as availability of phosphodiesterase inhibitors like sildenafil allows one to manage these cases.

Keywords PAH · Splenectomy · Thalassemia major · Thalassemia intermedia · Myelofibrosis · Pulmonary thromboembolism

Introduction

Splenectomy is widely performed for treating various hematological and non-hematological conditions [1–6]. There are debates as to whether there is increased risk of pulmonary arterial hypertension (PAH) following splenectomy either as a result of increased thromboembolism [7] or due to loss of some other function of spleen other than its filtration function [8].

There are also debates whether the diseases for which splenectomy is done itself predisposes to PAH. PAH again can be caused by several pathophysiologic mechanisms (i) Increased blood flow through the pulmonary circuit (volume overload) (ii) Occlusion of blood vessels (thromboembolic) or (iii) Plexiform arteriopathy as is classically associated with primary pulmonary hypertension.

Conditions for which splenectomy is done may often be associated with anemia and splenectomy itself produce a hypercoagulable state predisposing to pulmonary throm-

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boembolism. In this case control study we matched these clinical conditions which has produced pulmonary hypertension following splenectomy with disease matched controls. In addition there were several other category of patients who underwent splenectomy but did not develop PAH for these patients no control was used.

Materials and methods

Patients

Forty three patients of either sex (25 female and 18 males) underwent splenectomy for various indications 1–20 years back were included in this study. Of these 43 patients, 21 patients were found to have diseases where some of the patients had PAH.

Controls

Twenty one control non-splenectomized subjects were matched with similar spectrum and duration of disease as in the study subjects with diseases associated with PAH.

Institutional ethics committee permitted this study and detailed informed consent was taken from each of the patients after describing them the objective of the study and the procedure to be followed. They all consented for the study.

All the patients and controls were examined clinically, had routine hemogram, blood chemistry, transfusion history, transfusion transmitted viral infection checked. Chest X-ray, ECG was routinely evaluated in all the patients. Autoimmune profile like ANA, dsDNA, rheumatoid factor was checked in all the patients as also the screening coagulation tests comprising of aPTT, PT and TT.

Pulmonary arterial pressure was measured using standard published criteria using echocardiography and Doppler. Techniques measuring the velocity of the regurgitant jet across the tricuspid valve [4, 6]. Those patients who were found to have PAH as defined by a mean pulmonary artery pressure of >25 mmHg at rest underwent ventilation perfusion scan, spiral CT angiography of chest, arterial blood gas analysis and pulmonary function test in addition to regular investigations described above.

Results

Twenty five female and 18 male (21–36 years) were in the patient group. Eleven female and 10 male were in the control group (22–38 years) patients were splenectomised 1–20 years back (Mean $\pm$ 1SD 6.6 years $\pm$ 4.2 years). The mean $\pm$ 1SD duration for splenectomy to detection of pulmonary hypertension was 11.14 $\pm$ 6.49 years which was not very different from the 21 controls with whose disease was detected 3.5–11.5 years earlier.

Pulmonary hypertension was detected in the following group of patients β thalassemia major, intermedia, myelofibrosis, hereditary spherocytosis. Non-splenectomised control of hereditary spherocytosis did not show any evidence of PAH.

In addition to above diagnostic group a large number of patient with immune thrombocytopenic purpura (ITP) [7] who underwent splenectomy did not develop PAH. Similarly few patients of unstable hemoglobin, AIHA, sideroblastic anemia, trauma, extra hepatic portal hypertension and atypical CML did not develop PAH 1–6 years after splenectomy. Mean pulmonary artery pressure (Mean $\pm$ 1 SD) in patients were significantly higher than controls (46 ± 28 vs 25 ± 19 mmHg Student's t-test $p < 0.0029$)

Six out of 21 splenectomised patients and 3 out of 21 cases and duration matched controls developed PAH (χ^2 test $p > 0.05$).

The patients with myelofibrosis in both splenectomised and non-splenectomised group had severe PAH (Mean PAP >45 mmHg) had abnormal chest X-ray and clear cut right ventricular hypertrophy on 12 lead ECG. These patients were clinically symptomatic where as other patients with PAH were clinically asymptomatic. Pulmonary thromboembolism was detected in 3/6 (50%) cases 2/3 (60%) controls. The patients showing thromboembolism were patients of thalassemia syndrome and myelofibrosis. Biochemical autoimmune profiles and screening coagulation tests were normal in all the patients. Platelet count was significantly higher in the cases compared to controls (t-test $p < 0.0029$). The details of the patient and control have been presented in Tables 1–2 and similar distribution of cases and matched controls are shown in Fig. 1a and b.

Discussion

Pulmonary hypertension a hitherto unrecognized complication of splenectomy has its own pathologic import and hematologists have to include this complication also while taking decision to go ahead with the procedure.

The underlying pathogenic mechanism is unclear but it has been hypothesized that because of loss of filtration function of spleen, abnormal erythrocytes may remain in circulation for longer period of time and may trigger platelet activation which could then be trapped in pulmonary vascular bed [8, 9]. Such mechanism could be active in any patient who is splenectomised but would be aggravated in presence of hemolytic disorders [10–12]. There are other possible mechanisms under consideration i.e. splenectomy in portal hypertension may be associated in the hepatoportal shunt and hypoxia which may induce pulmonary hypertension.

In severe anemia higher volume of blood passing through pulmonary circuit may cause pulmonary hypertension. Many conditions associated with antiphospholipid

Table 1 Diagnosis in splenectomised cases and controls with prevalence of pulmonary hypertension each category

Diagnosis	No. splenectomised	No. with PAH	No. of controls	No. with PAH
Thalassemia major	6	2	9	1
Thalassemia intermedia	6	1	5	1
Myelofibrosis	2	1	3	1
Hereditary spherocytosis	7	2	4	0
ITP	9	0	—	—
Unstable hemoglobin	1	0	—	—
Sideroblastic anemia	1	0	—	—
Autoimmune hemolysis	5	0	—	—
Trauma	2	0	—	—
Other myeloproliferative disorders (atypical CML)	3	0	—	—
Portal hypertension	1	0	—	—

Table 2 Comparative data on subjects and matched controls

Parameter	Patient (n = 21)*	Control (n = 21)
Age (yrs)	28 ± 10.2	25 ± 13.2
Hemoglobin (g/dl)	9.13 ± 1.5	8.4 ± 1.6
Platelet count (× 10 ⁹ /L)	4 ± 2.1	2.23 ± 0.8 (p<0.05)
Thrombocytosis (>5 × 10 ⁹ /L)	6/21	3/21 (OR = 2.0, CI 0.8 – 3.5)
Mean pulm arterial pressure (mmHg)	46 ± 28	25 ± 19 (p <0.0029)

* 22 other patients had splenectomy but no PAH. They belonged to different disease categories

Fig. 1a Showing distribution of splenectomised cases **Fig. 1b** Showing distribution of disease and duration of disease matched controls

antibodies may need splenectomy and predispose to pulmonary thromboembolism and pulmonary hypertension. Many so called ITP patients have shown positive antiphospholipid antibodies [13]. However, in our series none of the patients with ITP had shown evidence of PAH after splenectomy. A closer look at the present series of patients show that

except myelofibrosis all other cases of PAH are related to hemolytic anemia or ineffective erythropoiesis.

Hemolysis induces release of cell free hemoglobin and red blood cell arginase resulting in impaired nitric oxide availability and endothelial cell dysfunction as has already proven in sickle cell disease. Splenectomised patients have

higher plasma hemoglobin level than non-splenectomised thalassemia intermedia and higher circulating hemoglobin containing vesicles suggest that worsening of pulmonary hypertension after splenectomy may be due to increased cell free plasma haemoglobin [12]. Moreover, hyper coagulable state in thalassemia is already well established [12, 14].

Pulmonary thromboembolism was also found in a large number of our splenectomised as well non-splenectomised patients with hemolytic anemia this has been demonstrated by other workers too [7, 15].

Hypercoagulable state is known to occur in myeloproliferative disease also. Unexplained PAH has been shown to occur in this disease [16]. One of the most important finding in the present study is that only a few conditions cause pulmonary hypertension following splenectomy and in these condition PAH is also known to occur even without splenectomy. Though we found significantly higher PAH in cases than in controls with similar disease the number of patients in the case and control group with PAH did not reach statistically significant value though there were twice as many cases of PAH amongst splenectomised patients than disease matched controls. Doppler echocardiography with its well established criteria [4, 6, 17] provide a simple and reliable way to asses PAH. Now we know that certain hemoglobinopathies are associated with higher prevalence of PAH and they can be satisfactorily treated with sildenafil [18]. Moreover anti-endothelin compounds like Bosentan may be an additional drug to try and treat this condition early.

Hence it makes sense to regularly monitor these patients with Doppler echocardiography and take a cautious stance before advocating splenectomy in these patients who already have developed PAH associated with hemoglobinopathies. It remains to be seen whether prescribing regular anticoagulation can help some of these patients.

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