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ORIGINAL ARTICLE

# 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 splenectomized patients with various disorders 1–20 years after splenectomy. Pulmonary arterial hypertension was detected only in thalassemia major, intermedia, hereditary sphereocytosis 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 mm of Hg. Twenty-one controls having similar duration and type of disease also were assessed for PAH in this case control study 3/21 had pulmonary arterial hypertension 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 mm Hg.

Platelet count in the splenectomized 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, extrahepatic 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 in 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 splenectomized or not.

This is particularly important as availability of phosphodiesterase inhibitors such as sildenafil allows one to manage these cases.

**Keywords** Pulmonary arterial hypertension (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 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. Pulmonary arterial hypertension 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.

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Conditions for which splenectomy is done may often be associated with anemia and splenectomy itself produce a hypercoagulable state predisposing to pulmonary thromboembolism. 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 (1–20 years back) for various indications were included in this study. Of these 43 patients, 21 patients were found to have pulmonary arterial hypertension.

*Controls* Twenty-one control non-splenectomized subjects were matched with similar spectrum and duration of disease as the study subjects 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 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 splenectomized 1–20 years back (M ± 1SD 6.6 years ± 4.2 years). The mean ± 1SD duration from splenectomy to detection of pulmonary hypertension was 11.14 ± 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, i.e. β thalassemia major, intermedia, myelofibrosis and hereditary sphereocytosis. Non-splenectomized control of hereditary sphereoctyosis 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, extrahepatic portal hypertension and atypical CML did not develop PAH 1–6 years after splenectomy. Mean pulmonary artery pressure (m ± 1SD) in patients were significantly higher than controls (46 ± 28 vs 25 ± 19 mmHg Student's t test $p<0.0029$)

Six out of 21 splenectomized patients and 3 out of 21 cases and duration matched controls developed PAH ($\lambda^2$ test $P>0.05$).

The patients with myelofibrosis in both splenectomoised and non-splenectomized group had severe PAH (mean PAP >45 mm of Hg) 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 cases (50%) and 2/3 controls (60%). 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 $P<0.0029$). Details of the patients and controls have been presented in Table 1, Table 2 and similar distribution of cases and matched controls are shown in Fig. 1.

## Discussion

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

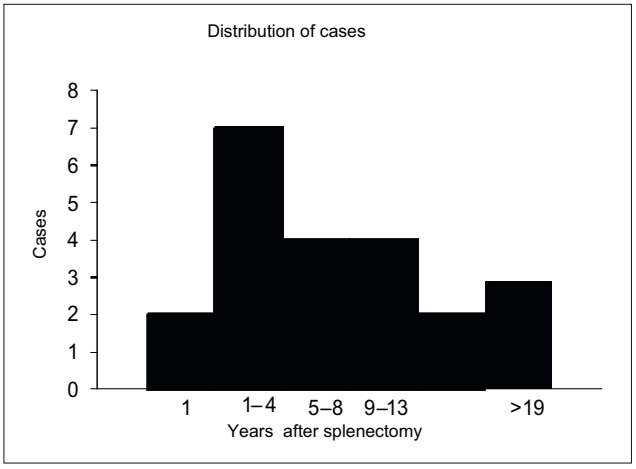


**Fig. 1a** Distribution of splenectomized cases

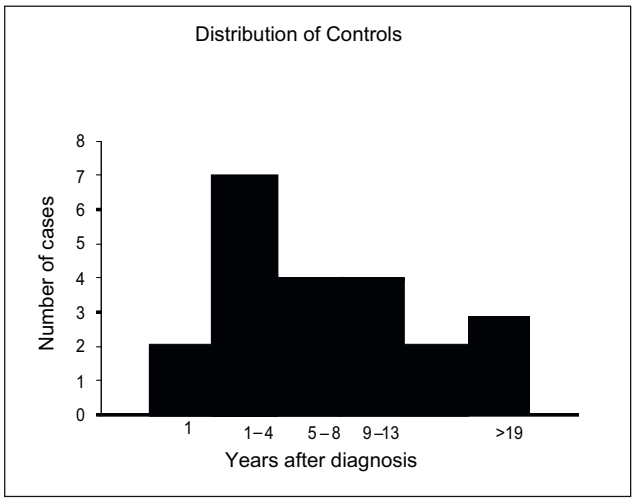


**Fig. 1b** Distribution of disease and duration of disease matched controls

tion function of spleen, abnormal erythrocytes may remain in circulation for a longer period of time and may trigger platelet activation which could then be trapped in the pulmonary vascular bed [8, 9]. Such mechanism could be active in any patient who is splenectomized 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 the pulmonary circuit may cause pulmonary hypertension. Many conditions associated with antiphospholipid antibodies may need splenectomy and predispose to pulmonary thromboembolism and pulmonary hypertension. Many so-called ITP patients have shown the presence of 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

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

| Diagnosis | No. splenectomized | 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 | – | – |

PAH: pulmonary arterial hypertension; ITP: immune thrombocytopenic purpura

**Table 2** Comparative data on subjects and matched controls

| Parameter | Patient (*n*=21)* | Control (*n*=21) |
|---|---|---|
| Age (years) | 28 ± 10.2 | 25 ± 13.2 |
| Hemoglobin (gm/dl) | 9.13 ± 1.5 | 8.4 ± 1.6 |
| Platelet count ( $\times 10^9$/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 pulmonary arterial pressure (mmHs) | 46 ± 28 | 25 ± 19 (P<0.0029) |

*22 other patients had splenectomy but no pulmonary arterial hypertension. They belonged to different disease categories.

The underlying pathogenic mechanism is unclear but it has been hypothesized that because of loss of the filtra-

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

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

Hypercogulable 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 splenectomized 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 antiendothelin compounds such as Bosentan may be an additional drug to try and treat this condition early.

Hence it makes sense to regularly monitor these patience 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 presecribing regular anti coagulation can help some of these patients.

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## References

1. Hoeper MM, Niedermeyer J, Hoffmeyer F, Flemming P, Fabel H (1999) Pulmonary hypertension after splenectomy? Ann Intern Med 16;131:793
2. Grisaru D, Rachmilewitz EA, Mosseri M, Gotsman M, Lafari JS, Okon E, Goldfarb A, Hasin Y (2004) Cunningham and Elliott Vichinsky; cardiopulmonary assessment in beta thalassemia major. ASH Education Programme Book
3. Aessopos A, Farmakis D, Deftereos S, Tsironi M, Tassiopoulos S, Moyssakis I and Karagiorga M (2005) Thalassemia heart disease. a comparative evaluation of thalassemia major and thalassemia intermedia. Chest 127:1523–1530
4. Atichartakarn V, Likittanasombat K, Chuncharunee S, Chandanamattha P, Worapongpaiboon S, Angchaisuksiri P (2003) Pulmonary arterial hypertension in previously splenectomized patients with beta thalassemia disorders. Int J Haematol 78:139–145
5. Aessopos A, Farmakis D, Karagiorga M, Voskaridou E, Loutradi A, Hatziliami A, Joussef J, Rombos J and Loukopuolos D (2001) Cardiac involvement in thalassemia intermedia: a multicentre study. Blood 97: 3411–3416
6. Aessopos A, Farmakis D (2005) Pulmonary hypertension in beta thalassemia. Ann N Y Acad Sci 1054:342–349
7. Jais X, Loos V, Jardim C, Siton O, Parent F, Hamid A, Fadel E, Dartevelle P, Simmonneau G and Humbert M (2005) Splenectomy and chronic thromboembolic pulmonary hypertension. Thorax 60:1031–1034
8. Peacock AJ (2005) Pulmonary hypetension after splenectomy: a consequence of loss of the splenic filter or is there something more? Thorax 60:983–984
9. Kisanuki A, Kietthubthew S, Asada Y, Maruthsuka K, Funahara Y, Sumiyoshi A (1997) Intravenious injectionof sonicated blood induces pulmonary microthromboembolism in rabbits with ligation of the splenic artery. Thromb Res 85: 95–103
10. Chou R, DeLoughery TG (2001) Recurrent thromboembolic diseae following splenectomy for pyruvate kinase deficiency. Am J Haematol 67(3):197–199
11. Jardine DL, Laing AD (2004) Delayed pulmonary hypertension following splenectomy for congenital spherocytosis. Intern Med J 34:214–216
12. Morris Cr. Kuypers FA, Kato GJ, Lavrisha L, Larkin S, Singer T, Vichinsky EP (2005) Hemolysis associated pulmonary hypertension in thalassemia. Ann N Y Acad Sci 1054: 481–485
13. Bidot CJ, Jy W, Horstman LL, Ahn ER, Yamiz M, Ahn YS (2006) Anti phospholipid antibodies (APLA) in immune thrombocytopenic purpura (ITP) and antiphospholipid syndrome (APS). Am J Haematol 81:391–96
14. Eldor and Rachmilewitz EA (2002) The hypercoagulable state in thalassemia. Blood 99:36–43
15. Sonakul D, Fucharoen S (1992) Pulmonary thromboembolism in thalassemic patients. South East Asian J Trop Med Public Health 23:25–28
16. Dingli D, Utz JP, Krowka MJ, Oberg AL, Tefferi A (2001) Unexplained pulmonary hypertension in chronic myeloproliferative disorders. Chest 120:801–808
17. Rubin LJ (1997) Primary pulmonary hypertension. New Engl J Med 336:111–117
18. Michelakis ED, Tymchak W,Noga M, Webster L, Wu XC, Lien D et al. (2003) Long term treatment with oral sildenafil is safe and improves functional capacity and haemodynamics in patients with primary pulmonary hypertension. Circulation 108:2066–2069