Original Article

Pulmonary Arterial Hypertension in β-thalassemia

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Abstract : Background : *Pulmonary arterial hypertension (PHT) is a not uncommon cardiac complication in splenectomized β-thalassemia (β-Thal). Its prevalence in β-Thal and factors associated with it in Thai patients have been unknown.* ***Methods :*** *A cross-sectional study was conducted in β-Thal patients in the Hematology Outpatient Clinic at Ramathibodi hospital during Jan 1999 to Nov 2003. Pulmonary artery systolic pressure (PASP) was determined by doppler echocardiography. PHT was defined as PASP ≥ 40 mmHg. Characteristics of the PHT and non-PHT groups were compared and analyzed.* ***Results :*** *Eighty-eight patients were included: splenectomized 65 (hemoglobin E/β-thalassemia (E/β-Thal) 61, homozygous β-Thal 4) and non-splenectomized 23 (E/β-Thal 22, homozygous β-Thal 1). PHT was detected in 43 (49%) patients (E/β-Thal 42, homozygous β-Thal 1). The PHT group had a higher proportion than the non-PHT group for splenectomy 36 (84%) vs. 7 (16%), p=0.04), and a higher percentage of nucleated red blood cells (nRBCs) to WBC (534/100WBC vs. 228/100WBC, p<0.01). In the splenectomized patients, the percentage of nRBCs was higher in the PHT than the non-PHT group (720/100WBC vs. 404/100WBC, p<0.01), but it was not different in the non-splenectomized patients (11/100WBC vs. 4/100WBC, p=0.38). There were no statistically significant differences in gender, age, post-splenectomy duration, hemoglobin concentration, white blood cell counts, platelet counts, and serum ferritin levels between the PHT and non-PHT group. In a multivariate analysis, features significantly associated with PHT were post splenectomy status (OR 2.83[1.02-7.82]), and nRBCs ≥500/100WBC (OR 3.49[1.24-9.8]).* ***Conclusions :*** *The prevalence of PHT in β-Thal disease in our study was 49%. Factors associated with PHT were post splenectomy status and nRBC ≥500/100WBC.*

Key Words : ● *HbE/β -thalassemia disease* ● *Homozygous β-thalassemia* ● *Pulmonary arterial hypertension (PHT)*

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Pulmonary arterial hypertension (PHT) has been reported as one of the common cardiac complications in β-Thalassemia (β-Thal) patients. Sonakul et al reported thrombi in small pulmonary arteries in splenectomized E/β-Thal (44%).[1] Contributing factors of PHT are increased cardiac output from chronic anemia, increased pulmonary capillary wedge pressure likely from LV diastolic dysfunction from chronic iron overload and increased pulmonary vascular resistance from thrombotic pulmonary arteriopathy.[2,3] Its prevalence in Thailand has not been known. In Greece, PHT developed 10% in thalassemia major, and more than 50% in thalassemia intermedia.[4] Using bedside examination as a search tool, our previous studies suggested that features associated with PHT were female gender, splenectomized β-Thal patients,

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markedly increased levels of peripheral blood nucleated red blood cells, platelet counts and serum ferritin levels.[3] Doppler echocardiography (ECHO) is more sensitive and is a commonly used noninvasive tool to detect PHT nowadays.[4-6] We, therefore, re-studied PHT in β-Thal using ECHO to estimate the prevalence of PHT in β-Thal patients and to determine features associated with PHT in these patients.

Materials and Methods

The total of 88 patients with β-Thal disease, who were treated at the adult (≥ 15 years) hematology outpatient clinic, Ramathibodi Hospital, were evaluated and followed from January 1999 to November 2003. All patients with the diagnosis of E/β-Thal and homozygous β-Thal, established on Hemoglobin (Hb) analysis by high performance liquid chromatography (HPLC). None had clinical evidence of other secondary causes of PHT, eg. HIV infection, collagen vascular diseases, heart and lung diseases, and cirrhosis. The functional class status was classified by the New York Heart Association (NYHA) Classification (Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities, Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion, Class III: patients with marked limitation of activity; they are comfortable only at rest, Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.). The investigation included history taking and clinical examination. Hematologic evaluation consisted of complete blood count, Hb analysis (HPLC), serum ferritin level and liver function test.

Cardiac evaluation consisted of chest radiograph, electrocardiography (ECG) and Doppler echocardiography (ECHO). Pulmonary artery systolic pressure (PASP), was estimated by ECHO, performed in all patients.

Doppler echocardiography was used to obtain Pulmonary artery systolic pressure (PASP) at rest and to evaluate left ventricular (LV) systolic function. PASP was estimated by adding the peak pressure gradient of tricuspid regurgitation and right atrium pressure (estimated from size and collapsibility of inferior vena cava), PHT was defined as PASP ≥ 40 mm Hg at rest[7]. LV systolic function was evaluated from LV ejection fraction.

Statistical analyses were performed with Stata, version 8.0, software (Stata, College Station, TX, USA). Continuous variables were expressed as mean ± SD and median (range). $P<0.05$ was considered statistically significant. The χ^2 test was used to compare category variables between patient groups, student *t* was used to compare continuous variables between patient groups and logistic regression test analysis was used to identify factors associated with PHT.

Results

Patient Characteristics of 88 β-Thal patients are summarized in Table 1. 83 E/β-Thal (61 previously splenectomized) and 5 homozygous β-Thal (4 previously splenectomized) patients were evaluated. PHT, defined as PASP ≥ 40 mm Hg, was detected in 43 (49%) patients, 42 (97.7%) HbE/β-Thal and 1 (2.3%) homozygous β-Thal. There were 19 (44.2%) men and 24 (55.8%) women. The mean age was 33.4 ± 12.2 years. The mean PASP was 55.76 ± 15.33 mm Hg. 36 (83.7%) were previously splenectomized and 7 (16.3%) were non-splenectomized. The mean duration after splenectomy was 17.9 ± 9.7 years. All patients had normal left ventricular ejection fraction (≥60%). The PHT group had a higher proportion than that of the non-PHT group for splenectomy (36 (84%) vs. 7 (16%), p=0.04). There were no statistically significant differences in gender, age, post-splenectomy duration, functional class status, blood pressure and oxygen saturation. Patients with PHT received more blood transfusions during the preceding 12 months than those without PHT (8.09 ± 8.8 vs. 3.96 ± 6.3 units, $p<0.01$). In the PHT group, only 26 of 43 chest radiographs (60.46%) and 10 of 43 ECGs (23.26%) showed evidence of PHT. Iron chelations (desferoxamine) were given to 29 patients.

Table 1. Patient Characteristics (n=88)* PHT (PASP ≥ 40 mm Hg) and Non-PHT group

	Non-PHT	PHT	P-value
No. of patients, (%)	45(51)	43(49)	-
PASP, mm Hg	29.28(± 5.22)	55.76(±15.33)	-
Sex (%)			0.691
male (n=37)	18(40)	19(44.19)	
female (n=51)	27(60)	24(55.81)	
Age, yrs	33.31(±11.70)	33.42(±12.21)	0.964
Age of ECHO, yrs	31.11(±10.66)	31.10(±12.46)	0.996
Splenectomy, n(%)			**0.040**
yes	29(64.44)	36(83.72)	
no	16(35.56)	7(16.28)	
Post splenectomy, yrs	14.63(±9.64)	17.89(±9.74)	0.178
Type of thalassemia, n(%)			0.319
HbE/β°-thal disease	40(88.89)	39(90.70)	
HbE/β^{+}-thal disease	1(2.22)	3(6.98)	
Homozygous β-thalassemia	4(8.89)	1(2.33)	
Functional class status, n(%)			0.569
NYHA class I	5(11.11)	4(9.3)	
II	40(88.89)	38(88.38)	
III	0	1(2.32)	
Systolic blood pressure, mmHg	110(±10.44)	113.27(±13.53)	0.205
Diastolic blood pressure, mmHg	68.82(±8.39)	71.18(±10.44)	0.249
Oxygen saturation,%	95.75(±1.52)	94.21(±5.0)	0.197
Chest radiograph: suggestive of PHT**, n(%)	0	26(60.46)	-
ECG: suggestive of PHT***, n(%)	3(6.67)	10(23.26)	-
LVEF,%	71.67(±6.67)	70.8(±10.45)	0.967
Number of red cell transfusion, U/yr	3.96(±6.3)	8.09(±8.8)	0.003
Desferoxamine use, n(%)	10(22.22)	19(44.19)	**0.028**

*Results are shown in mean and SD (in parenthesis); PHT, pulmonary arterial hypertension.

** Right interlobar pulmonary diameter of grater > 16 mm. and Hilar to thoracic ratio>0.44

***ECG finding suggestive of PHT: right-axis deviation, R/S ratio>1 in lead V1-3, R/S ratio<1 in lead V5 or V6, right atrial enlargement.

PHT patients received desferoxamine more often than non-PHT patients (19 (44.19%) vs.10 (22.22%), p=0.028)

Results of hematologic evaluation are shown in Table 2. The PHT group had a higher percentage of nucleated red blood cells (nRBCs) to white blood cell count (WBC) than the non-PHT group (534/100WBC vs. 228/100WBC, p<0.01). There were no statistically significant differences in the hemoglobin concentration, white blood cell counts, platelet counts, and serum ferritin levels between PHT and non-PHT group. In splenectomized patients, the percentage of nRBCs was higher in the PHT than in non-PHT group (720/100WBC vs. 404/100WBC, p<0.01) (Table 3), but did not differ significantly in non-splenectomized patients (11/100WBC vs. 4/100WBC, p=0.38) (Table 4).

Figure 1 shows the percentage of nRBCs to WBC correlated positively with PASP (correlation coeffecient; r=0.40, p=0.008) in the splenectomized patients, but

Table 2. Hematologic evaluation (n=88)* PHT (PASP ≥ 40 mm Hg) and Non-PHT group

	Non-PHT	PHT	P-value
Hemoglobin (g/dL)	6.95(±1.12)	6.66(±1.06)	0.221
Hematocrit (%)	21.62(± 3.36)	20.56(± 3.12)	0.129
White blood cells x10^3 /mL	10.81(±4.67)	10.35(±4.28)	0.633
Platelets x10^3/mL	601 (129-1,748)	583 (111-1,241)	0.818
Nucleated RBC/100 WBC (%)	228(0-1,370)	534(0-2,021)	**0.0004**
Serum ferritin (mg/L)	2,860(263-8,613)	2,343(366.4-9,858)	0.444

*Result are shown in mean and SD (in parenthesis) and median and range (in parenthesis); PHT, pulmonary arterial hypertension

Table 3. PHT (PASP ≥ 40 mm Hg) and Non-PHT splenectomized b-Thalassemia patients (n=65)

	Non-PHT(n=29)	PHT(n=36)	P-value
Mean PASP, mm Hg	29.03(±5.42)	56.16(±16.30)	
Mean age, yrs	30.27(±10.07)	30.02(±8.9)	0.916
Post splenectomy, yrs	14.63(±9.64)	17.89(±9.74)	0.178
Age at splenectomy, yrs	13.70(±9.58)	10.625(±7.49)	0.150
Hemoglobin (g/dL)	7.0(±1.1)	6.7(±1.09)	0.33
nRBCs/100 WBC	404(45-1,370)	720(165-2,021)	**0.0035**
Platelets x10^3/mL	756(133-1,748)	643(220-1,241)	0.088
Serum ferritin (mg/L)	3,328(306-8,613)	2343(401-9,858)	0.157
Death	1	5	

PHT, pulmonary arterial hypertension

Table 4. PHT (PASP ≥ 40 mm Hg) and Non-PHT non-splenectomized b-Thalassemia patients (n=33)

	Non-PHT(n=16)	PHT(n=7)	P-value
Mean PASP, mm Hg	29.75(±5.0)	53.71(±9.44)	-
Mean age, yrs	37.75(±13.16)	49.14(±14.87)	0.080
Hemoglobin (g/dL)	6.85(1.2)	6.27(0.84)	0.20
NRBC/100 WBC	4(0-84)	11(0-44)	0.381
Serum ferritin (mg/L)	1,580(263-3,500)	2,207(366-3,828)	0.574

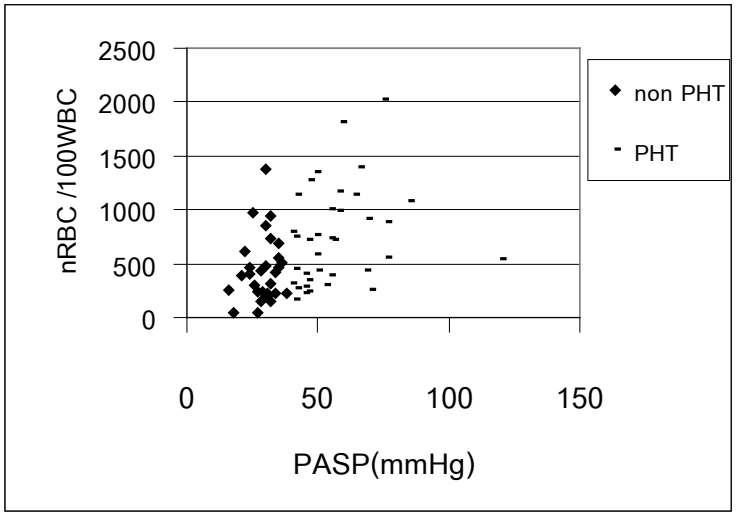
PHT, pulmonary arterial hypertension

there was no correlation in non-splenectomized patients (correlation coeffecient; r=0.18, p=0.40).

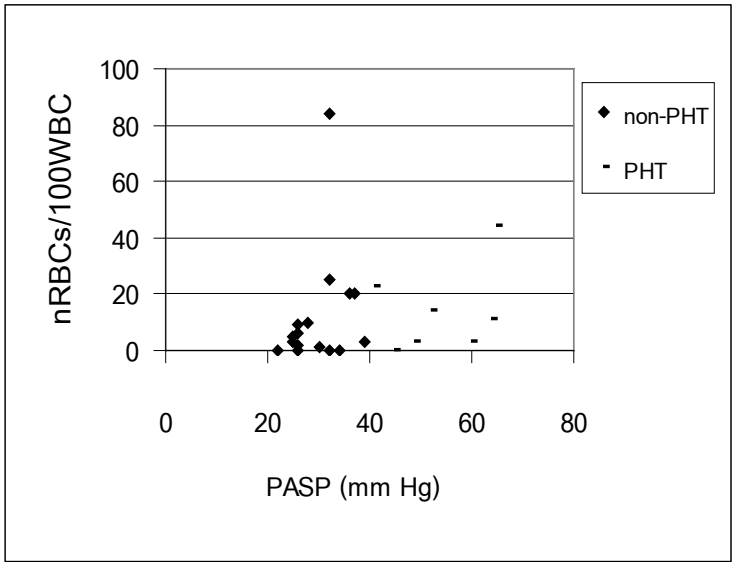
In a multivariate analysis, features significantly associated with PHT were post splenectomy status (OR 2.83[1.02-7.82]), and nRBCs ≥500/100WBC (OR 3.49[1.24-9.8]). Of 43 PHT b-Thal patients, none of them had clinical evidence of acute or chronic deep vein thrombosis (unilateral leg swelling, dilated superficial veins, chronic leg ulcer).

Thirty six of 65 previously splenectomized b-Thal patients had PHT (55%), only 7 of 33 non-splenectomized patients had PHT (33%). Clinical evaluation and mean PASP of splenectomized and non-splenectomized groups were shown in Table 5, splenectomized group had mean PASP and the percentage of nRBCs higher than those of non-splenectomized group (44.06 ± 18.52 vs. 37.04 ± 12.98, p=0.047; and 470/100WBC vs. 5/100WBC, p<0.01,respectively). The splenectomized patients had significantly higher white blood cell counts and platelet counts (11.32 ± 4.47 vs. 8.49 ± 3.8 x 10^3cells/mL, p<0.01; and 720(133-1,748) vs. 210(111-738) x 10^3cells/mL, p<0.01, respectively).

Figure 1. Correlation between nucleated red cells and pulmonary hypertension in splenectomized and non-splenectomized β-Thalassemia



Splenectomized (n=65)



Non-splenectomized (n=23)

The causes of death are shown in Table 6. 6 of 7 deceased β-Thal patients had pulmonary hypertension. The main causes of death were infection and severe pulmonary hypertension with right ventricular failure.

Discussion

The previous study showed that β-Thal patients had a high proportion of PHT. The prevalence of PHT reported in our patients was 49%. This finding was consistent with a recent report, which also found that 50% of patients with β-Thal intermedia with normal left ventricular ejection fraction had significant PHT.[4] In the present study, we have evaluated factors associated with PHT. However, we need a cohort study to identify risk factors and to compare clinical courses between severe and non-severe PHT in β-Thal.

Regular blood transfusions and iron chelation had been reported to prevent PHT in thalassemia major[20], but we found that the patients with PHT received more blood transfusions than the patients without PHT.

Table 5. Splenectomized and nonsplenectomized β-Thalassemia patients (n=88)

	Non-splenectomy	**Splenectomy**	**P-value**
No. of patients (%)	23(26.13)	65(73.86)	-
Mean age, yrs	41.54(±14.41)	30.47(±9.38)	**0.0018**
PHT (%)			**0.040**
yes	7(30.43)	36(55.38)	
no	16(69.56)	29(44.61)	
Mean PASP, mm Hg	37.04(12.98)	44.06(18.52)	**0.047**
Hb, gm/dL	6.67(±1.12)	6.85(±1.09)	0.49
WBCx10^3/mL	8.49(±3.8)	11.32(±4.47)	**0.008**
Platelets x10^3/mL	210(111-738)	720(133-1,748)	**<0.001**
NRBC/100 WBC	5(0-84)	470(45-2,021)	**<0.001**
Serum ferritin (mg/L)	1,757(263-3,828)	2,490(306-9,858)	0.057

PHT, pulmonary arterial hypertension

Table 6. Causes of death in β-thalassemia patients (n=88)

	Non-PHT(n=45)	**PHT(n=43)**	**P-value**
Alive	44(97.78)	37(86.05)	0.055
Death	1(2.22)	6(13.95)	
Death age , yrs	27	29.33(±8.35)	-
PASP, mm Hg	24	60(±15.97)	-
Causes of death			-
-PHT	-	3(50%)	
-PHT+infection	-	2(33.33)	
- infection	1(100)	-	
- other (carcinoma)	-	1(16.67)	

PHT, pulmonary arterial hypertension

This higher level of blood transfusions may imply more severe disease in patients with PHT. Additionally, more desferoxamine used in the PHT group likely reflects more aggressive treatment.

In our study, feature significantly associated with PHT was splenectomized β-Thal. The percentage of nRBCs to WBC correlated positively with PASP in splenectomized patients but there was no correlation in non-splenectomized patients. This finding is consistent with the proposed pathogenesis of other authors.[2,3,15,17] The possible mechanisms leading to PHT after splenectomy may involve nucleated red blood cells, platelets and the coagulation cascade. Eldor et al[21] reported a shorter life span of platelets in both splenectomized and non-splenectomized patients with thalassemia than in non-thalassemic splenectomized patients. There is also evidence of endogenous platelet activation in patients with thalassemia.[2,22] Moreover, thalassemic red blood cells can induce thrombotic complications. These cells have increased membrane expression of anionic phospholipids that accelerate thrombin generation and activate platelets.[17] The mechanisms are likely to be intensified in splenectomized patients with thalassemia, as they have more abnormal red blood cells and red blood cell precursors than their non-splenectomized counterparts.

Markedly increased numbers of nRBCs may facilitate adherence by impending flow in the microcirculation. These

cells would promote local clot formation, particularly in the presence of systemic hypercoagulability. Pathophysiologic changes in post-splenectomy β-Thal leading to PHT are increased circulating PS (phosphatidylserine)-exposed RBCs facilitate coagulation process and activated platelets cause vasculopathy and microthrombi leading to increased pulmonary vascular resistance index and vascular occlusion.[2,3]

PHT is the main feature of cardiac complications in β-Thal. It is the leading cause of death and has been well documented in splenectomized β-Thal. In fact, PHT could not be detected early by ECG or chest radiograph. We, therefore, proposed serial ECHO to estimate PASP in high risk group (post-splenectomy β-Thal with markedly increased number of nRBCs) for early appropriate treatment. Regular blood transfusions and iron chelation to prevent splenomegaly, and consequent splenectomy, may well be the key to preventing PHT in thalassemia.

Conclusions

The prevalence of PHT in β-Thal disease in our study was 49%. Factors associated with PHT were post splenectomy status and nRBC ≥500/100WBC.

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ภาวะความดันในหลอดเลือดแดงปอดสูงในผู้ป่วยโรคเบต้าธาลัสซีเมีย

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หน่วยโลหิตวิทยา[*] และหน่วยระบบหัวใจและหลอดเลือด[**] ภาควิชาอายุรศาสตร์ โรงพยาบาลรามาธิบดี

บทคัดย่อ : *ภาวะความดันในหลอดเลือดแดงปอดสูง (Pulmonary arterial hypertension :PHT) เป็นภาวะแทรกซ้อนที่สำคัญและพบบ่อยของระบบหัวใจในผู้ป่วย β-thalassemia (β-Thal) ความชุกในประเทศไทยและปัจจัยที่มีความสัมพันธ์กับภาวะนี้ยังไม่มีการรายงาน จึงได้ทำการศึกษาภาวะ PHT ในผู้ป่วย β-Thal ที่แผนกผู้ป่วยนอก หน่วยโลหิตวิทยา โรงพยาบาลรามาธิบดี พ.ศ. 2542 ถึง พ.ศ.2546 โดยใช้ Doppler echocardiography ในการวัดค่า pulmonary artery systolic pressure (PASP)* ***ผลการศึกษา :*** *จากผู้ป่วย homozygous β-Thal และ hemoglobin E/β-thalassemia (E/β-Thal) 88 ราย (ตัดม้าม 65 ราย(E/β-Thal 61, homozygous β-Thal 4), ไม่ได้ตัดม้าม 23 ราย (E/β-Thal 22, homozygous β-Thal 1) พบผู้ที่มี PHT (PASP ≥ 40 mm Hg) 43ราย (49%) พบผู้ที่ตัดม้ามในกลุ่ม PHT (36 (84%)) มากกว่ากลุ่มnon-PHT (29 (64%)) แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p=0.04) จำนวน nRBCs ในกลุ่ม PHT (534/100WBC) มากกว่าในกลุ่ม non-PHT (228/100WBC) แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (P<0.01) ในผู้ที่ตัดม้าม จำนวนของ nRBCs ในกลุ่ม PHT (720/100WBC) มีมากกว่าในกลุ่ม non-PHT (404/100 WBC)(p<0.01) แต่ในผู้ที่ไม่ได้ตัดม้ามจำนวนของ nRBCs ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (กลุ่ม PHT 11/100WBC เทียบกับกลุ่ม non-PHT 4/100WBC, p=0.38) ส่วน เพศ ระยะเวลาหลังตัดม้าม ชนิดของ thalassemia ระดับฮีโมโกลบิน จำนวนเม็ดเลือดขาว เกร็ดเลือดและระดับ serum ferritin ไม่มีความแตกต่างระหว่างกลุ่ม PHT และ non-PHT ใน multivariate analysis พบว่าปัจจัยที่มีความสัมพันธ์กับ PHT คือ ภาวะหลังตัดม้าม (OR 2.83 (1.02-7.82)) และจำนวนของ nRBCs ที่ ≥500/ 100 WBC (OR 3.49(1.24-9.8))* ***สรุป :*** *ความชุกของภาวะความดันในหลอดเลือดแดงปอดสูงในผู้ป่วยโรค β-Thal เท่ากับร้อยละ 49 ปัจจัยที่มีความสัมพันธ์กับ PHT คือภาวะหลังตัดม้าม และ จำนวน nRBCs ที่สูงมากกว่า 500/100WBC*

Key Words : ● *HbE/β -thalassemia disease* ● *Homozygous β-thalassemia* ● *Pulmonary arterial hypertension (PHT)*

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