PULMONARY ARTERY OBSTRUCTION IN THALASSAEMIA

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INTRODUCTION

During a review of a large series of autopsies of thalassaemia patients in our hospital a very significant proportion was found to have pulmonary arterial obstructive lesions. A search of previous reports (Cooley *et al.*, 1927; Cooley and Lee, 1933; Whipple and Bradford, 1936; Ellis *et al.*, 1954; Witzleben and Wyatt, 1961; Bhamarapravati *et al.*, 1967; Fessas and Loukopoulos, 1974) on pathology of thalassaemia failed to find an identical feature. This is of great interest in its pathogenesis, clinico-physiological implications and management. Patients with severe thalassaemia often exhibit dyspnoea, orthopnoea, sometimes chest pains, symptoms usually attributable to anaemia and cardiac embarassment, and death from cardiac failure is frequent. With this new finding it remains to be evaluated how much of the above symptoms and cardiac failure are contributed by the frequent pulmonary arterial obstructions in addition to anaemia and iron deposition in the heart.

MATERIALS AND METHODS

Slides of lungs from 43 patients with β-thalassaemia/haemoglobin (Hb) E disease autopsied in the Department of Pathology, Siriraj Hospital, in the years 1967-1979 were reviewed. The tissues were fixed in 10% buffered formalin, sectioned and stained with haematoxylin and eosin. In 25 cases in which tissue blocks were available, Verhoeff's elastic, Masson's trichrome and Gomori's iron staining were performed. Autopsy findings and slides of other organs were also studied.

For comparison, slides of lungs from 28 other patients in the files, matched for age, were examined.

RESULTS

Of the 43 patients, 29 were male and 14 female, ranging in age from 4 to 67 years. Twenty-eight patients had been splenectomised 18 months to 32 years prior to final admission; 4 were recently splenectomised.

In 19 patients (44%) the lungs showed obstructive lesions in the pulmonary arteries, predominantly affecting muscular arteries 100-800 μ in size, though occasional larger arteries were also involved. These consisted of organised, recanalised thromboemboli partly or completely occluding the lumens (Fig. 1 and 2). In older lesions, the organised thrombi formed intra-arterial septa (Fig. 3), polypoid structures projecting from the arterial wall (Fig. 4), or cushion-like patches of intimal fibroblastic proliferation or fibrosis causing eccentric narrowing of the lumens. Elastic staining showed that all lesions were internal to the inner elastica, and that there was often splitting and reduplication of the elastic membrane. Some of the larger arteries showed changes indistinguishable from "primary" pulmonary arteriosclerosis. Recent or partly organised thromboemboli were found in 14 of the patients, in "virgin" arteries or superimposing on organised or recanalised thrombi (Fig. 5). These obstructive lesions varied

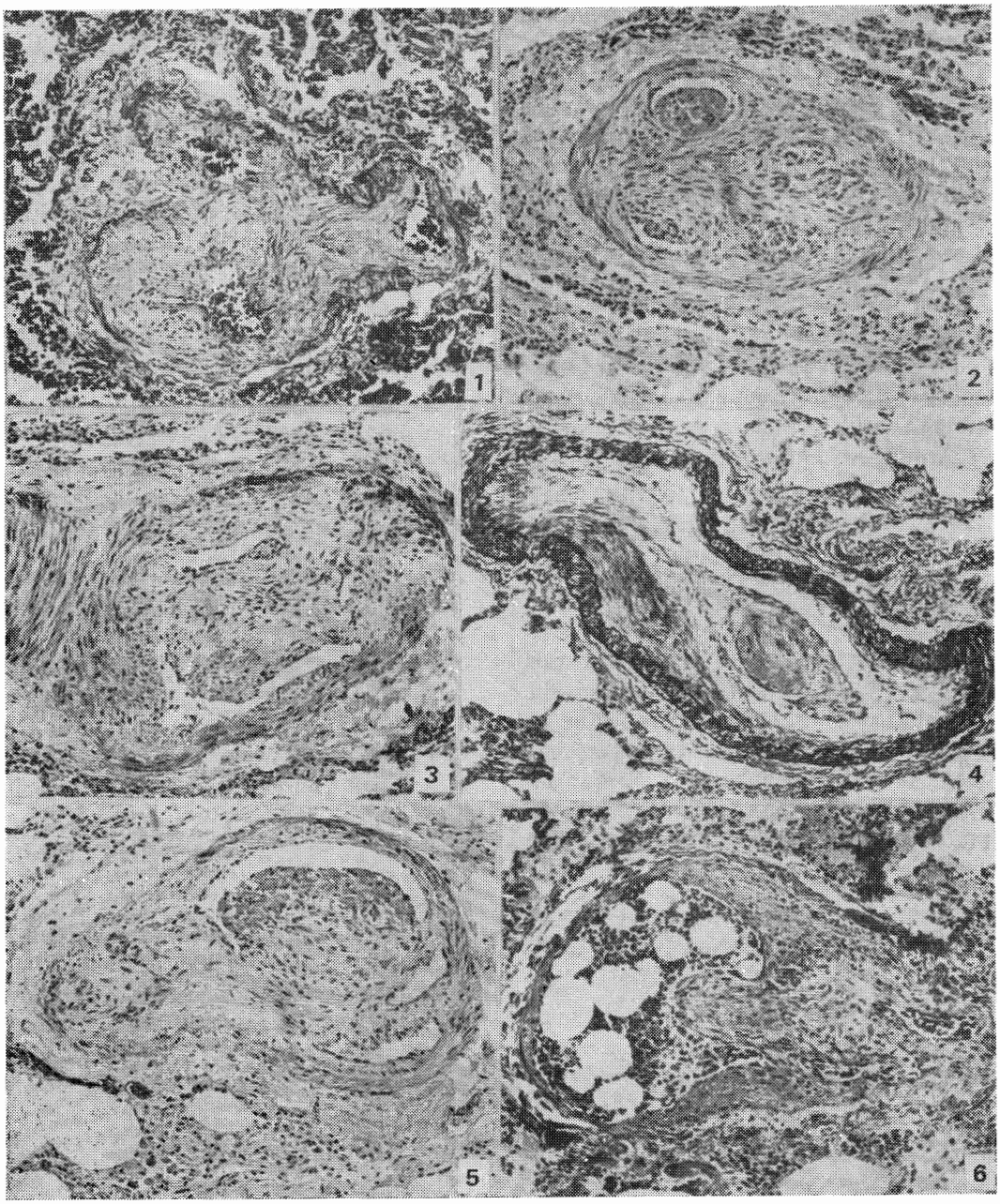

Fig. 1-6— Pulmonary arterial obstructive lesions in patients with β-thalassaemia/Hb E disease. 1. Case 1 showing newly-formed intra-arterial septa. 2. Case 6 showing fenestra due to recanalised thrombus, with recent thrombosis in a new channel. 3. Case 6 showing recently-formed intra-arterial septa. 4. Case 6 showing polypoid structure projecting from arterial wall superimposing on cushion-like intimal fibroblastic proliferation. 5. Case 6 showing polypoid structure with small channels and superimposing recent thrombus. 6. Case 4 showing bone marrow embolus in a recanalised artery with polypoid intimal proliferation. All H & E staining except 4 with elastic Masson, × 100.

in number from 1-2/cm^2 in some patients to 14/cm^2 in others (mean = 6/cm^2); their distribution was irregular, sometimes occurring in clusters suggestive of periodic showers of emboli. Case 4 (Table 1 and Fig. 6) showed bone marrow emboli in several arteries. He did not have bone fracture prior to death nor was cardiac resuscitation performed; his arterial PaO_2 was 46-47 mmHg.

In several patients, arteries uninvolved by the above changes showed concentric intimal proliferation of varying degrees. The tunica media was prominent, but Masson's trichrome staining failed to show actual muscular hypertrophy or fibrosis apart from one case. There was no evidence of arteritis. The arterioles and veins were not affected (Table).

Moderate to marked pulmonary congestion and oedema were observed in all these patients, both on macroscopic and microscopic examinations. However, no old or recent infarct was found. Haemosiderin was present in variable amounts, mostly in macrophages, but bore no relationship to the thromboembolic lesions. In one patient, a 30-year-old male (Case 8), a 2 cm. atheromatous patch was seen in the upper lobar branch of the right pulmonary artery.

In 13 of the patients there was right ventricular or biventricular hypertrophy, often accompanied by moderate to marked right ventricular dilatation, consistent with long-standing pulmonary vascular embarrassment culminating in right heart failure.

Three patients (Case 5,7 and 11) had suffered episodes of chest pains; one of these (Case 7) in addition showed right ventricular hypertrophy and prominent pulmonary conus on chest x-rays. One other patient (Case 9) had severe, clinically inexplicable hypoxaemia with PaO_2 of 46-47 mmHg on his last admission. Though several patients had periodic oedema of the lower extremities, this was regarded as part of cardiac failure, rather than indicative of thrombosis in those regions.

Seventeen of the 19 patients in whom these pulmonary arterial obstructive lesions were found had been splenectomised 5-32 years before death (Table 1). Sixteen patients were male and 3 female. Only one of 18 patients below the age of 20 was affected. In addition to these 19 patients, a 4-year-old splenectomised girl with recent thromboemboli, but with the diagnosis of S.L.E., and a 4-year-old boy with septic thrombi were excluded.

Review of autopsy protocols and examination of slides of other organs from these patients showed no evidence of thromboembolism elsewhere. Unfortunately there was no routine dissection of the leg veins.

Of the control group of 28 patients, 2 showed a few recent or partly organised thromboemboli in pulmonary arteries. One of these was a 10-year-old boy with confluent bronchopneumonia and bronchiectatic cysts. The other was a 37-year-old woman with rheumatic mitral stenosis whose pulmonary arteries showed slight to moderate medial hypertrophy.

DISCUSSION

The findings of pulmonary arterial obstructive lesions in 44% of autopsied thalassaemic patients are striking, a feature not previously known in this disease. Whether this is commonly found only in β-thalassaemia/Hb E disease as in our cases or also in homozygous β-thalassaemia as well remains to be seen.

While it was not possible to distinguish in these cases between thrombosis and embolism, the fact that only pulmonary arteries were affected would seem to support the latter mechanism. No evidence of thromboembolism elsewhere was noticed in these patients. However, routine dissection of the leg veins was not performed. A few other β-thalassae-

Table 1

β-Thalassaemia/haemoglobin E patients with pulmonary vascular obstructive lesions.

Cases	Sex/Age (yr)	Splenectomy (yr)	Causes of death	Recent thromboem-boli	Recanalisation/ intra-arterial septa	Intimal prolifera-tion	Other relevant findings
1. T.W.	M/13	6	peritonitis postcholecy-stectomy	organised	1-2/cm^2	eccentric & concentric	
2. A.P.	M/20	16	*E. coli* septicaemia	recent & organised	1-2/cm^2	eccentric	
3. S.P.	M/21	13	CHF	small	10/cm^2	eccentric	BVH & D
4. Y.P.	M/24	5	CHF	"ordinary" thrombi 3-4/cm^2; bone marrow thrombi 2-3/cm^2	6/cm^2 some only partly organised	often eccentric, almost closing lumens	PaO_2 46-47 mmHg.
5. S.S.	M/25	10+	CHF	O	7/cm^2	eccentric	chest pains RVH
6. V.C.	M/28	10+	pulmonary thrombosis; CHF	organised	14/cm^2	eccentric	RVH & D
7. V.I.	M/28	18	chronic pericarditis; CHF	O	5-6/cm^2	eccentric	RVH & increased pulmonary conus; chest pains; autopsy-RVH & D
8. P.R.	M/30	19	CHF	mostly small, lysed, with in old organised thrombi	9/cm^2 some in very large arteries	eccentric, polypoid prolifera-tion in large arteries	RVH & D
9. Pr.S.	M/32	5	CHF	O	6/cm^2	also larger arteries	BVD
10. S.W.	F/33	12	septicaemia	partly organised in a large vein	2/cm^2, also polypoid structures	eccentric	RVH

Table 1 (Cont'd)

Cases	Sex/Age (yr)	Splenectomy (yr)	Causes of death	Recent thromboem-boli	Recanalisation/ intra-arterial septa	Intimal prolifera-tion	Other relevant findings
11. P.S.	M/34	ND	chronic pericarditis, CHF	few,organised	3/cm^2	eccentric; medial fibrosis	chest pains RVH & D
12. Y.S.	M/43	32	osteomyelites; subdural haemorrhage	O	4/cm^2, old	eccentric	
13.P.L.	M/47	29	haemochrom-tosis infection, Addison's disease	O	6/cm^2, old, some in large arteries	eccentric	
14. T.K.	F/22	10	subacute fibrinous pericarditis with haemo-pericardium	1-2 on old recanalised thromboem-boli	9/cm^2,polypoid structures	eccentric, few concen-tric	RVH & D, mod LVH
15. S.P.	M/22	13	pyogenic liver abscesses with localised peritonitis	O	10-11/cm^2	eccentric	BVH
16. P.B.	M/22	4	acute peri-carditis	1	1-2/cm^2	eccentric	mod BVH
17. S.V.	F/22	17	pulmonary thrombosis	few,partly organised	10-11/cm^2	eccentric, concentric	BVH & D
18. B.K.	M/23	ND	chronic constric-tive peri-carditis with CHF	1 partly organised	3/cm^2	eccentric	D all chambers
19. P.J.	M/28	many	confluent bronchop-neumonia	3 partly organised on old thromboem-boli	3-4/cm^2	eccentric	BVH

CHF = congestive heart failure; BVH & D = biventricular hyperthrophy & dilatation;
RVH = right ventricular hypertrophy; LVH = left ventricular hypertrophy;
D = dilatation; ND = not done.

mia/Hb E patients developed arterial obstruction with gangrene necessitating leg amputation (Wasi's personal observation). The pulmonary arterial obstructive lesions in our patients may have well been due to unrecognised micro-emboli. For unrecognised emboli to the lungs are a frequent known cause of pulmonary vascular disease which may cumulatively lead to cor pulmonale (Owen *et al.*, 1953; Thomas *et al.*, 1956; Cawley and Stofer, 1957; Rosenberg, 1964; Dexter, 1965; Aviado, 1965; Gould, 1965; Wagenvoort and Wagenvoort, 1970; Newfeld *et al.*, 1979). Some authors (Harrison, 1948; Owen *et al.*, 1953; Rosenberg, 1964) have also suggested that, in many cases of "primary pulmonary hypertension" or "idiopathic pulmonary arteriosclerosis", chronic thromboembolism may well have played a part. In experimental animals, pulmonary arteriosclerosis indistinguishable from "primary" pulmonary arteriosclerosis in humans has been produced by intravenous injections of fibrin clots (Heptinstall, 1959; Rosenberg, 1964; Dexter, 1965). The lack of infarction in these patients may have been due to the fact that many emboli may have only partially occluded the vessels, or to bronchial collateral circulation (Aviado, 1965; Dexter, 1965); Dexter estimated that less than 10% of thromboemboli were associated with infarcts.

The adverse effects of these changes on the heart appear to be twofold. First, pulmonary vascular obstruction, if extensive, leads to pulmonary hypertension and increased work load on the right ventricle. Eight of the patients in this series, who had extensive pulmonary vascular lesions, had moderate to marked right ventricular hypertrophy, often accompanied by dilatation. Secondly, hypoxaemia adversely affects both ventricles. In a patient with an already overloaded heart from severe anaemia, sometimes accompanied by pre-existing heart disease, the only manifestation of pulmonary embolism may well be a subtle and non-specific worsening of the patient's cardiac function, often presenting as pulmonary congestion with or without oedema, rather than overt cor pulmonale (Dexter, 1965). The extent of pulmonary vascular damage in the patients in this series appeared to increase with age; in younger patients fewer obstructive lesions were found and were not a direct contributory cause of death, whereas older patients were often the victims of the cumulative effects of chronic, recurrent thromboembolism.

As for the source of unrecognised emboli, Owen (1953), in his study of 12 cases of cor pulmonale from this cause, found the source to be leg veins in 6, the heart in 2, porta-caval shunt in 1; in 3 cases the source was not discovered. Rosenberg (1964) in a study of the aetiology of "primary" pulmonary hypertension cited Rossle who dissected the leg veins in 324 routine autopsies and found thrombi in 27.1%.

Several factors may be responsible for thromboembolism in thalassaemia. The finding of bone marrow emboli in a patient (Case 4, Fig. 6) who had no known fracture and had not received cardiac resuscitation raises a question that the extensively hyperplastic bone marrow in these patients may dislodge small bone marrow emboli which are then trapped in the pulmonary arteries inducing thrombosis on top of them. The fact that bone marrow emboli were observed in only one out of 19 cases makes it unlikely that this is aetiology of the thromboembolism in the majority of cases of thalassaemia.

Perpetual haemolysis in thalassaemia providing abundant thromboplastic material may be another contributing factor. These patients suffer from recurrent infections and there may well be activation of the complement system causing granulocytic aggregation leading to micro-emboli per se or through

endothelial damage from lysosomal release (Craddock *et al.*, 1977; Spaet and Crosby, 1979).

There is a clear association between the observed pulmonary arterial obstructive lesions and splenectomy: of the 19 patients with the pulmonary arterial thrombosis 17 were splenectomised cases. Splenectomy in thalassaemia is known to be followed by increased infections and thrombocytosis both of which can predispose the patients to thromboembolism. Thrombocytosis may lead to circulating platelet aggregates causing neurological dysfunction presumably as a result of obstruction of the cerebral microcirculation (Preston *et al.*, 1979).

The findings of pulmonary arterial thromboembolism are in accordance with our observation that the majority of splenectomised β-thalassaemia/Hb E patients have unexplained low arterial oxygen pressure (Fucharoen, Youngchaiyud and Wasi, to be reported). This newly discovered feature may be an additional factor contributing toward dyspnoea and heart failure in thalassaemia besides anaemia and cardiac iron deposition. If it is proven that the pulmonary arterial thromboembolism is caused by circulating platelet aggregates, preventive measure by administration of drugs reducing platelet aggregation such as aspirin and Persantin should be considered, especially after splenectomy.

SUMMARY

A new feature has been encountered in review of a large series of autopsy materials of β-thalassaemia/Hb E disease. Among 43 patients pulmonary arterial obstructive lesions were found in 19 (44%), of which 17 were splenectomised cases. The pulmonary arterial thromboembolism may have been due to circulating platelet aggregates. This newly discovered pathology may be an additional factor contributing toward dyspnoea and heart failure in thalassaemia besides anaemia and cardiac iron deposition. If it is proven that this pulmonary arterial thromboembolism is indeed due to circulating platelet aggregates, preventive measure by administration of drugs reducing platelet aggregation such as aspirin and Persantin may be indicated, especially after splenectomy.

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