Indian Journal of Pathology: Research and Practice

Hypoploastic Left Heart Syndrome: An Autopsy Study

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Accepted 8 April 2012

Abstract

Background: Hypoplastic left heart syndrome (HLHS) encompasses a spectrum of structural cardiac malformations that are characterized by severe under development of structures in the left heart-aorta complex, including left ventricular cavity. Autopsy reports of this condition occurring in the Indian population are not available. This study was undertaken with the aim of documenting the spectrum of morphological changes of HLHS seen at neonatal autopsy. **Methods**: All autopsies over a period of fifteen years at All India Institute of Medical Sciences were reviewed and all cases of HLHS were included for analysis. The gross anatomical descriptions, histology and gross specimens were reviewed. **Results**: Of 618 neonatal autopsies, 6 were found to have HLHS (0.98%). All the six cases showed hypoplasia of the ascending aorta and left ventricle. On morphology and microscopy, two patterns were seen. Pattern 1, seen in four cases, showed partly stenotic patency of mitral and aortic valves, fibroelastosis of the left ventricular endocardium and mural hypertrophy of left ventricular myocardium. In Pattern 2, seen in two cases, there was complete atresia of mitral valve with slit like left ventricle and normal left ventricular endocardium. On microscopy, Pattern 1 cases showed fibroelastotic thickening and calcification of the endocardium. Myocardium showed hypertrophy and presence of sinusoidal vessels. These findings were absent in Pattern 2. All cases showed atrial septal defect and wide patent ductus arteriosus , which are essential to maintain circulation. **Conclusion:** Hypoplastic left heart syndrome is a complex disorder with a spectrum of malformations. A simplified division into two patterns is useful for autopsy practice and helps in accurate dissection and assessment.

Key words: Hypoplastic left heart syndrome, Endocardial fibroelastosis, Pathology, Autopsy, Congenital heart disease

Introduction

Hypoplastic left heart syndrome (HLHS) was until recently an invariably lethal pathologic condition[1]. HLHS comprises a wide spectrum of cardiac malformations, including hypolasia or atresia of the aortic or mitral valves and hypoplasia of left ventricle and ascending aorta[2-6]. With the advent of the staged Norwood procedure which surgically corrects this condition with dramatic improvement in survival, it is important to accurately diagnose and assess HLHS[1,2,3]. There is little knowledge about the characteristics of HLHS in the Indian setting. With advances in neonatal cardiac surgery and antenatal ultrasonographic detection of cardiac malformations, it has become necessary to accurately document the extent and nature of this rare anomaly in the Indian population, which this study aimed to address by analyzing cases seen at autopsy.

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Methods

Autopsy records of 15 years from January 1988 to December 2003 at the All India Institute of Medical Sciences, New Delhi were examined. All cases with a final anatomical diagnosis of HLHS were included in the study. The gross anatomical descriptions and histological slides were available in all instances. Heart specimens from three autopsies and tissue blocks from four autopsies were available for re-examination.

The chamber size of left and right ventricles [LV and RV respectively) as well as atria, status of the valves (normal, stenosed or atretic), endocardial changes (fibroelastosis), atrial and ventricular septum (nature and extent of defects), ductus arteriosus (closed or patent), caliber of great vessels and their communication with the heart chambers were noted from autopsy records. Where heart specimens were available, they were examined and the features listed above were re-evaluated. Routine Haematoxylin and Eosin sections were available in all and these were re-examined. Where blocks were available, special stains for elastic tissue (Verhoeff Van Gieson) and collagen (Masson's Trichrome) were performed on tissue sections from all chambers of the heart. Histological evidence of hypertrophy was looked for. The LV endocardial thickness of all six cases was measured on microscopy using the stage Vernier scale. LV endocardial thickness of two normal neonatal hearts obtained from other autopsies were measured as control.

Results

In the 15 year time period, 1063 autopsies were performed at AIIMS. Of these 613 (57.7 %) were neonatal autopsies. Six out of 613 neonatal autopsies showed the presence of HLHS yielding a frequency of 0.98% at autopsy.

The details of the gross and microscopic abnormalities are given in Table-1. It can be seen that there was a spectrum of changes in these six autopsies. The heart weight varied from 6 to 25 gms. All six hearts showed hypoplastic ascending aorta with patent ductus arteriosus (PDA) and atrial septal defect. The LV was hypoplastic in all six with reduction in LV chamber size. Cases 1 to 4 showed endocardial fibroelastosis (EFE) of LV. In these, the LV chamber was small but rounded with a thick white and glistening endocardium lining the entire extent (fig -1 and 2). On sectioning, the thickness of LV endocardium greatly exceeded that of the other chambers, including left atrium which normally has the thickest endocardium. On microscopic examination, endocardium of LV showed increased thickness (Fig 3). The endocardial thickness varied from 700 to 1500mm on measurement with the stage vernier. Large foci of calcification were seen in the endocardium at the junction with the myocardium (Fig 3). Special stains for elastic tissue showed marked elastosis (Fig 4). Masson's trichrome stain highlighted the extent of fibrosis within the endocardium (Fig 5). LV endocardial thickness was 100mm in cases 5 and 6 as well as in the two normal hearts. The myocardial wall thickness of LV in cases 1-4 varied from 2 to 6 mm (Table-1). On microscopy, the LV myocardium of Cases 1 to 4 showed features of hypertrophy. In cases 5 and 6, LV wall thickness was not measurable since the chamber was slit like. In the two control cases it was 3mm and 4 mm respectively.

Cases 2 and 3 both showed mitral stenosis along with aortic stenosis. Case 1 showed normal aortic valve with mitral valve stenosis (Fig 6). Case 4 showed normal mitral valve with aortic valve stenosis. Hence cases 1 to 4 had patency of mitral and aortic valves, with either a normal or narrowed lumen. LV was almost slit like in cases 5 and 6 with marked reduction in the chamber size. Both aortic and mitral valves were atretic in both of these and endocardium did not show any EFE (Fig 7 & 8). On microscopic examination there was no hypertrophy of the musculature and blood vessels were not prominent. Case 5 also showed associated multiple congenital malformations including pulmonary

hypoplasia, pulmonary lymphangiectasia, bilobed right lung and facial dysmorphism.

On the basis of our observations, it was possible to divide cases of HLHS into two groups which we have termed as Pattern I and Pattern II . Pattern I, showed EFE with normal to stenosed mitral and aortic valves, chambered but hypoplastic LV, hypoplastic ascending aorta, PDA and patent foramen ovale (Fig 9). In pattern II, complete atresia of aotrtic and mitral valves was present with a slit like hypoplastic LV without EFE, along with hypoplastic ascending aorta, PDA and patent foramen ovale (Fig 10). Cases 1 to 4 fall in Pattern I while cases 5 and 6 belong to Pattern II.

Table 1

Gross and microscopic features seen in six cases of HLHS

Feature	Case1	Case2	Case3	Case4	Case5	Case6
Heart weight gms)	25	25	20	15	6	15
Endocardial thickness (m)	1500	1000	700	800	100	100
Left ventricle wall thickness (mm)	4	6	2	4	NA	NA
ASD (foramen ovale)	Patent	Patent	Patent	Patent	Patent	patent
Left ventricle	Hypo plastic	Hypo plastic	Hypo plastic	Hypo plastic	Slit –like	Slit-like
Ascending aorta	Hypo plastic	Hypo plastic	Hypo plastic	Hypo plastic	Hypo plastic	Hypo plastic
Ductus arteriosus	Patent	Patent	Patent	Patent	Patent	Patent
Mitral valve	Stenosis	Stenosis	Stenosis	Normal	Atresia	Atresia
Aortic valve	Normal	Stenosis	Stenosis	Stenosis	Atresia	Atresia
Fibro-elastosis	Present	Present	Present	Present	Absent	Absent
Pattern						
Associated anomalies						
Pulmonary lymphangiectasias	Absent	Absent	Absent	Absent	Present	Absent
Hypoplastic lungs	Absent	Absent	Absent	Absent	Present	Absent
Bilobed right lung	Absent	Absent	Absent	Absent	Present	Absent
Facial dys-morphism	Absent	Absent	Absent	Absent	Present	Absent

Fig 1. Gross heart specimen of Case 2 viewed from behind showing hypoplastic LV, marked fibroelastosis of LV endocardium (arrow), stenotic aortic valve (arrowhead) and a mildly hypoplastic ascending aorta

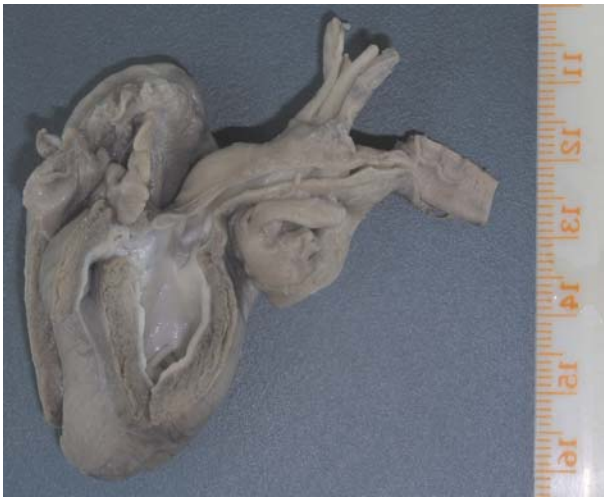


Fig 2. Gross heart specimen of Case 1 viewed from left side showing hypoplastic but properly chambered LV, fibroelastosis of LV endocardium, normal aortic valve without stenosis (arrow) and a very mildly hypoplastic ascending aorta with properly developed lumen

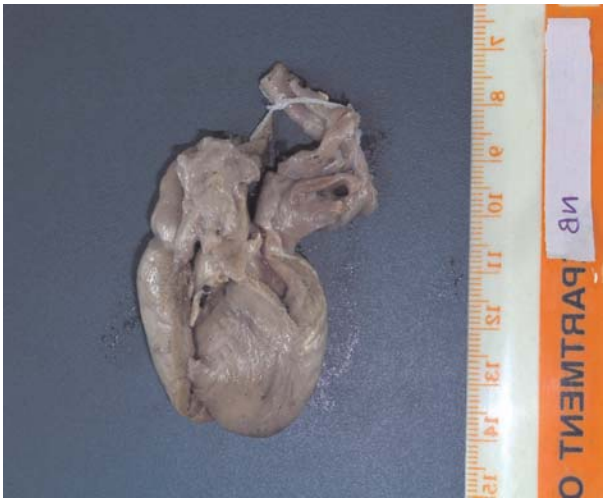


Fig 3. Microphotograph of LV endocardium in Case 2 showing marked increase in thickness with fibrosis and calcification seen near the junction with myocardium. Haematoxylin and Eosin X 100

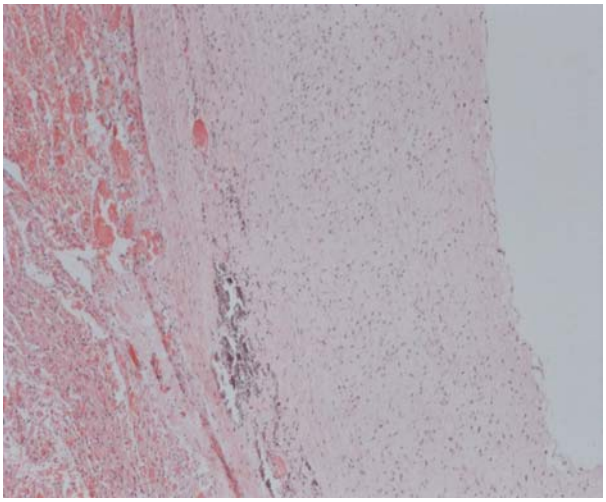


Fig 4. Microphotograph demonstrating the elastotic degeneration of the LV endocardium in Case 3. Elastic fibres are stained black. Verhoeff Van Gieson, X 100

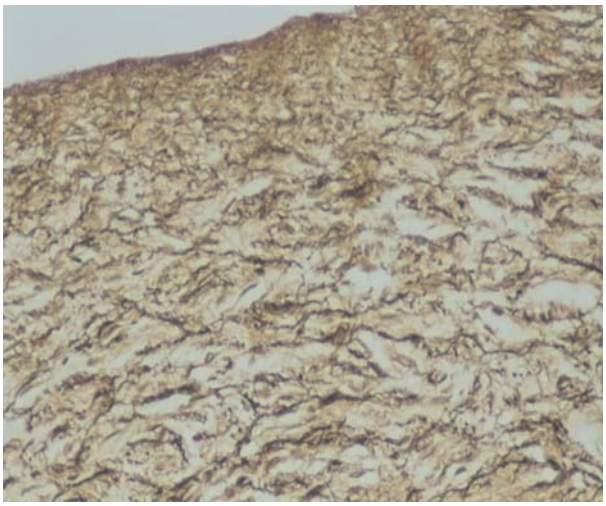


Fig 5. Microphotograph showing fibrosis of the LV endocardium. Collagen is stained blue. Masson Trichrome, X 200

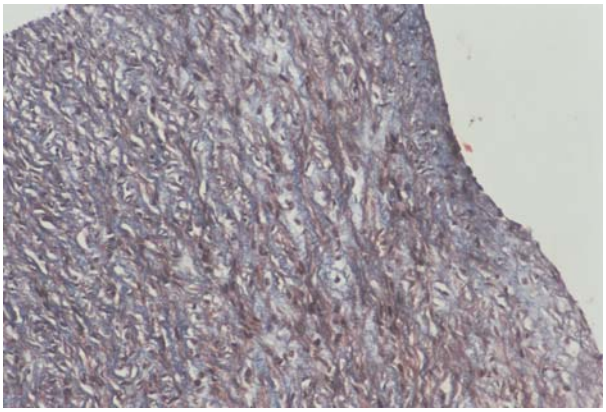


Fig 6. Gross heart specimen of Case 2 viewed from above showing atrium with patent but stenosed mitral valve (arrow)

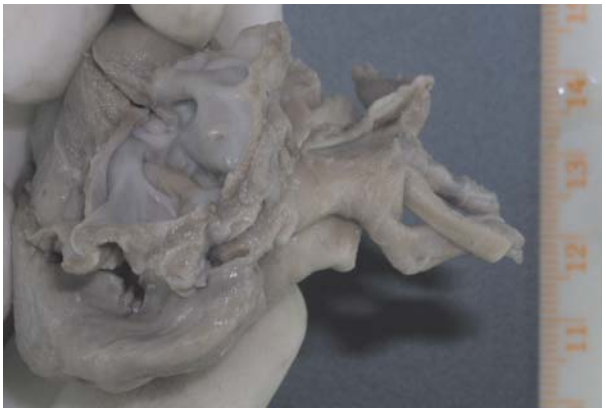


Fig 7. Gross heart specimen of Case 5 showing a markedly hypoplastic LV incorporated within the RV wall, with slit like lumen on opening (white arrow) without communication with the markedly hypoplastic ascending aorta (black arrow) or the left atrium

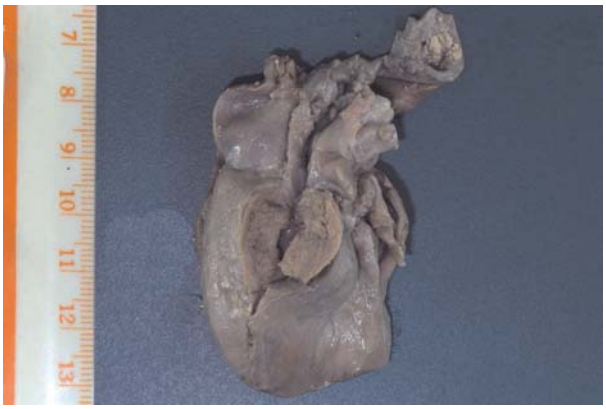


Fig 8. Microphotograph of LV in Case 6 cut obliquely to show the rudimentary lumen lined by thin endocardium without fibroelastosis. Haematoxylin and Eosin X 40

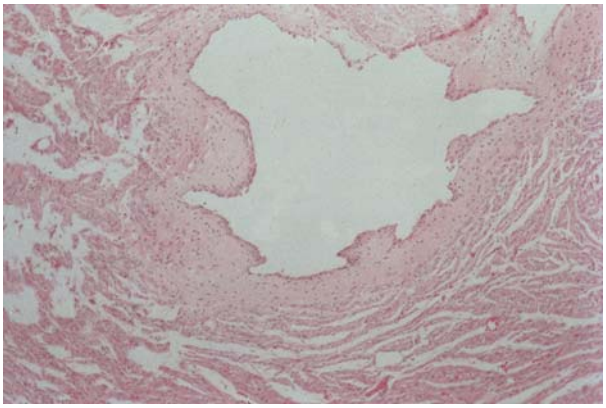


Fig 9. Diagrammatic representation of Pattern 1 HLHS. The LV chamber is developed with normal connections but is hypoplastic with fibroelastosis of endocardium. Mitral and aortic valves are stenosed but patent. Blood flow pattern after birth is illustrated with colour coded arrows

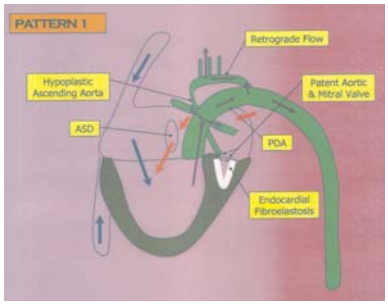
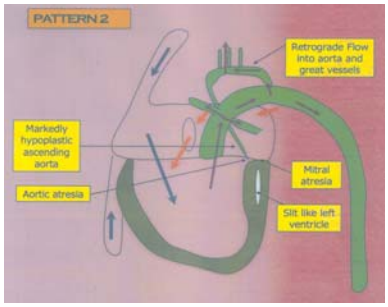


Fig 10. Diagrammatic representation of Pattern 2 HLHS. The LV chamber is a rudimentary slit within RV wall. Left atrium and ascending aorta are not connected to the LV. Flow of blood is however similar to Pattern 1 HLHS



Discussion

The New England Regional Infant Cardiac Program lists HLHS as the commonest form of univentricular cadiac malformation. Along with isolated coarctation and PDA, HLHS is the fourth commonest cardiac malformation to manifest in the 1st year of life behind ventricular septal defect, transposition of great arteries, and tetralogy of fallot[4]. However, univentricular heart malformations are rare in themselves making HLHS a rare disease. HLHS has a reported prevalence of 0.2 per 1,000 live births and is seen twice as frequently in boys[5,6]. HLHS has been described and redefined over the latter half of the 20th century by Lev[7] and by Noonan and Nadas[8] as comprising a wide spectrum of cardiac malformations ranging from hypoplasia to complete atresia of the anatomy of the left side of the heart in patients with normally related great vessels.

The stimulus for normal development of ascending aorta from the aortic sac is the high-pressure systemic blood flow from the LV through the aortic valve[9]**.** When normal flow is impeded by an atretic or stenotic aortic valve, the aortic root and ascending aorta receive low pressure diastolic retrograde flow via the ductus arteriosus and aortic arch[10]. This prevents normal growth and development of ascending aorta, which becomes hypoplastic. While the mal-development of the aortic arch is a secondary event in HLHS, the primary event is the maldevelopment of mitral and aortic valves, which limit blood flow through left heart. Whether this is associated with abnormal LV cardiac muscle development or whether the entire spectrum of anomalies in HLHS represents a field effect disturbing all of these abnormally developed structures is still unclear[10].

Normal intrauterine haemodynamic flow in the fetus is dependent on RV outflow which allows development and maturation of the fetus despite HLHS. However, after birth the shift to LV based systemic circulation is not possible. PDA must be maintained after birth to perfuse the coronary arteries and systemic circulation. In patients with HLHS, flow through the PDA is right to left during ventricular systole, providing flow to the systemic circulation. During ventricular diastole, there is left-to-right flow across the PDA and retrograde flow through the ascending aorta to perfuse the coronary arteries[11]. At the severe end of the spectrum with mitral and aortic atresia, the systemic circulation is completely RV-PDA dependent, with retrograde flow in the aortic arch and the ascending aorta. At the mild end of the spectrum with milder degrees of mitral and aortic stenosis, the descending aortic circulation is RV-PDA dependent while ascending aorta and various portions of the aortic arch and branches are supplied by forward flow from the LV. In very few patients the systemic circulation may be entirely LV dependent in the presence of lesser degree of obstruction through the left heart[1].

Following birth and closure of the PDA, HLHS infants develop metabolic acidosis, decreased systemic perfusion, circulatory collapse, and death. Nowadays the condition is diagnosed in-utero by antenatal ultrasound and patients are offered a choice of medical termination or continuation of pregnancy with two therapeutic options. If pregnancy is allowed to continue, neonates are stabilized with Prostaglandin E 1 after birth, to delay closure of PDA[26]. The two modalities of treatment available are either a heart transplant or surgical correction.

This study highlights the spectrum of malformations which can be seen in HLHS. Cases 5 and 6 represent the severe end of the spectrum of HLHS with slit like hypoplastic LV along with atretic mitral and aortic valves. Cases 1 to 4 represent milder forms with varying degrees of valvular stenosis. Case 5 shows association of HLHS with other congenital malformations. HLHS has been associated with absence of aortic valve leaflets[12], interruption of aortic arch[13], various brain anomalies[14], cor triatum[15], 45 X karyotype[2], pulmonary lymphangiectasia [16] as seen in case 5 of the

present series, abnormalities of the genito-urinary tract[17], Noonan syndrome[18], catch 22 syndrome[19], Holt-Oram syndrome[20] and Edward syndrome[3]. However a consistent genetic abnormality remains to be elucidated and these associations do not throw any light on the genetic events underlying pathogenesis[21].

EFE is considered to be a degenerative change due to endocardial ischaemia and is associated with mitral stenosis in less severe forms of HLHS. Its presence depends on the degree of mitral valve stenosis[22]. With mitral stenosis, the amount of blood entering the LV is inadequate to perfuse the ventricular endocardium. The resulting endocardial ischaemia leads to EFE. In contrast, in mitral atresia, despite LV end-diastolic volume being almost nil, there are enough intramyocardial dilated branches of coronary capillaries which prevent endocardial ischaemia[22]. Although the Norwood procedure does not utilize the LV[23], biventricular procedures have been tried when the LV is better developed. Such patients usually have EFE and it has been observed that EFE is responsible for compromising left ventricular function[24]. Therefore biventricular procedure in such patients, although appearing attractive in theory, is unlikely to be of benefit[24,25].

HLHS is treated by the Norwood procedure, which is a cascade of three open heart surgeries. In 1980, Norwood and associates [23] described a two staged palliative surgical procedure, later modified to the currently used three–stage method of palliation[24]. Stage 1 done at birth is a modified Blalock -Taussig shunt which connects aorta to pulmonary artery, so that RV supplies the systemic circulation. The neo-aorta is constructed from the aortic arch, descending aorta and pulmonary trunk. An unobstructed communication is established between RV and systemic circulation with excision of distal part of PDA. Atrial septum is completely removed for better mixing of oxygenayed and deoxygenated blood. A shunt from the innominate artery to the main pulmonary trunk supplies pulmonary arterial blood flow. Stage 2 is bidirectional cavopulmonary shunt, generally done at 5 to 8 months of age, which connects the superior vena cava directly to pulmonary artery end to end, bypassing ventricles altogether. Since better oxygenation is possible, the aorto pulmonary shunt from innominate artery to main pulmonary artery is removed. This stage partially separates the pulmonary and systemic circulation, relying on venous returns from superior vena cava to directly supply pulmonary circulation. The third stage, known as modified Fontan procedure, is done between 2 to 4 years. It completes the separation of the systemic and pulmonary circulation. A lateral tunnel is created with-in right atrium to direct blood from inferior vena cava to right pulmonary artery. Thus the entire systemic venous return goes to lungs directly without requiring pumping by heart, oxygenated blood returns to the RV through the opened out atrial septum and then systemic arterial circulation is maintained by RV, with no mixing of blood. In patients with less severe aortic stenosis and a nearly-normal sized functioning LV, a two-ventricular procedure can be attempted, using the LV to supply pulmonary circulation. Transplantation has also been used as an alternative[24].

Considerable attention is being paid to the pathology and pathogenesis of this condition in recent years[27-33], although the original study of 101 cases of HLHS remains one of the largest[8]. Changes in the cardiac myosite, fibrous matrix and embryogenetic mechanisms are being investigated, although the pathogenesis remains idiopathic[29-32]. HLHS is ideally described with sequential segmental analysis and standardised nomenclature[1,29].However such methodology is not in common use amongst pathologists in India, from where few reports of the pathology of HLHS are available[27]. The present study illustrates the gross morphologic and histopathologic features of this rare condition, using a simplified classification of this complex entity into two easily recognizable patterns. Such a classification is likely to be of use to practicing

pathologists in India performing neonatal autopsy, for accurate dissection and evaluation of HLHS.

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