

Splenic involvement in a stillborn fetus with tuberous sclerosis and multiple cardiac rhabdomyomas

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Multiple cardiac rhabdomyomas are frequently associated with tuberous sclerosis (TSC). However, splenic involvement in TSC is very rare. Histiocytoid cells in the spleen have been previously reported in only seven neonates and one fetus. We report an unusual case of multiple cardiac rhabdomyomas in a stillborn fetus with TSC who had clusters of histiocytoid cells in the spleen. These large cells had abundant eosinophilic cytoplasm and were positive with CD 68; ultrastructurally, they contained many membrane-bound bodies. It has been suggested that these cells are histiocytes. To the best of our knowledge, the present case is the second stillborn fetus who had splenic involvement with TSC.

Key words: tuberous sclerosis, cardiac rhabdomyoma, spleen, stillborn fetus.

Rhabdomyoma is the most common cardiac tumor in infancy and childhood. It was first described by Von Recklinghausen in 1862. Although it may occur in isolation, cardiac rhabdomyoma is often one of the manifestations of tuberous sclerosis¹⁻³.

Tuberous sclerosis (TSC) is a neurocutaneous syndrome with autosomal dominant inheritance and is characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues. Typical lesions include cortical tubers and subependymal hamartomas in the brain, rhabdomyomas in the heart, angiofibromas and periungual fibromas of the skin and angiomyolipomas in the kidney⁴.

There are few reports of splenic involvement in TSC; two types of the splenic lesions in TSC are known. The first is vascular hamartomas seen in adolescents, and the second is nodules of large cells with abundant eosinophilic cytoplasm in the spleen of neonates⁵⁻¹².

We present a case of multiple cardiac rhabdomyomas in a stillborn fetus with TSC including splenic involvement.

Case Report

The baby was the second stillbirth of an unrelated 21-year-old woman and her 29-year-old husband. The first pregnancy resulted in a

female stillbirth at 26 weeks' gestation on whom autopsy was not performed. This second pregnancy was complicated by ascites. The baby was delivered at 31 weeks' gestation following induction of labor because of intrauterine fetal death.

Autopsy findings:

The female fetus weighed 2215 g, and measured 44 cm crown-heel, 27 cm crown-rump, 5.7 cm foot length, and 30.5 cm head circumference. She was hydropic, having subcutaneous edema, pleural effusions and ascites.

The heart was significantly enlarged by the mass 4x3.5 cm in size, located in the interventricular septum. The free walls of the ventricles were of normal appearance. Multiple tumor nodules composed of large cells with vacuolated cytoplasm and small nuclei were seen throughout the myocardium microscopically (Fig. 1). Some cells exhibited fine cytoplasmic strands giving a spider-like appearance.

The brain weighed 217 g and appeared grossly normal. Twenty-six blocks were taken from the cerebral cortex, and multiple sections were cut and examined from each block. A single nodule was seen in the wall of the lateral ventricle, microscopically. The nodule was composed of large, bizarre giant astrocyte-like cells (Fig. 2). They were positive for glial fibrillary acidic

protein (GFAP) using the streptavidin-biotin peroxidase technique, and were periodic acid-schiff (PAS) positive.

The spleen weighed 4.4 g and was normal on slicing. There were numerous large, mono- or binucleated, bizarre cells with abundant eosinophilic cytoplasm in the red pulp (Fig. 3). They were present alone and in clusters. These

cells were positive for CD 68 and negative for S-100 protein, GFAP and HMB-45. Electron microscopy was performed on formalin-fixed tissue. There were many membrane-bound bodies, some containing electron dense material, in these cells (Fig. 4).

There were no pathological findings in other organs.

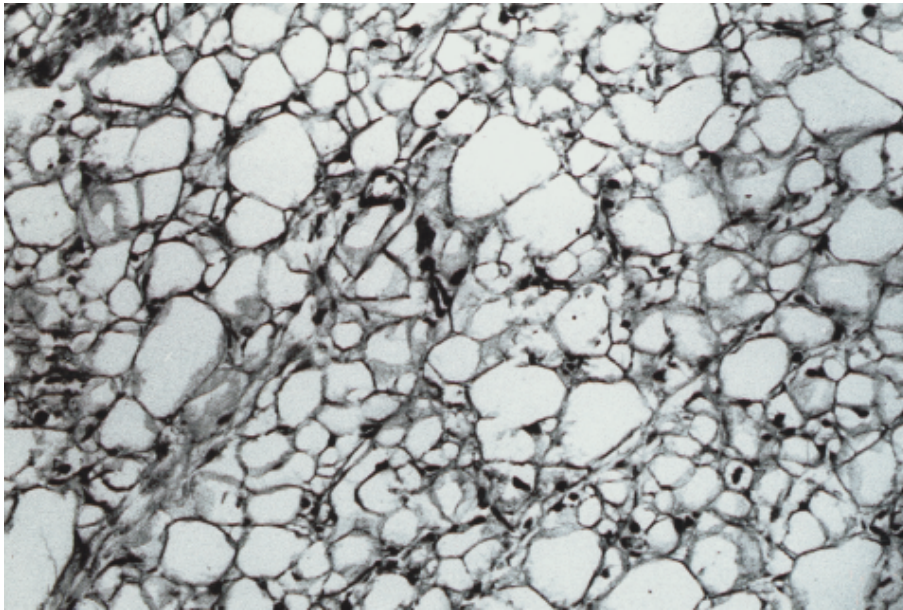


Fig. 1. The large, round and vacuolated cells in the rhabdomyoma (HE X 200).

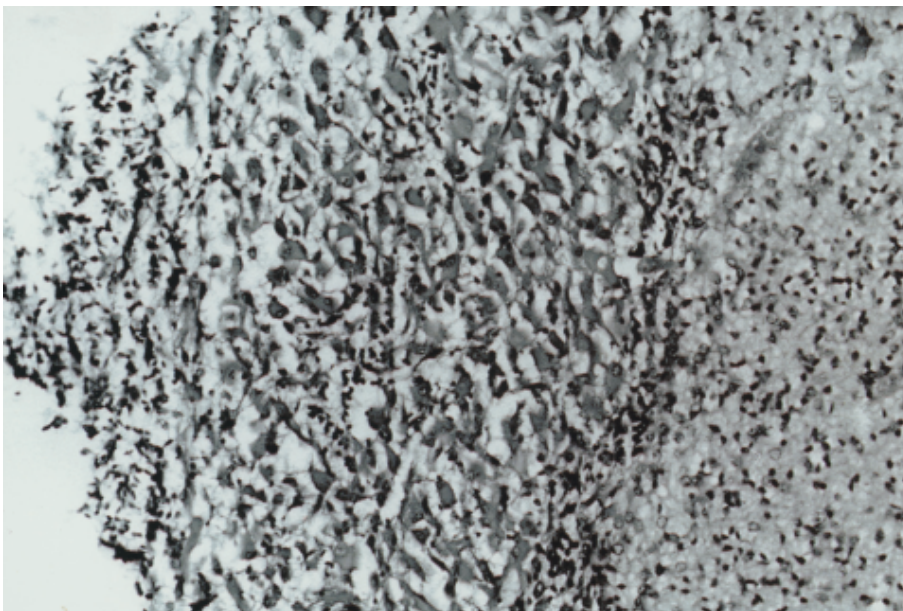


Fig. 2. The nodule composed of large, astrocyte-like cells in the brain (HE X 100).

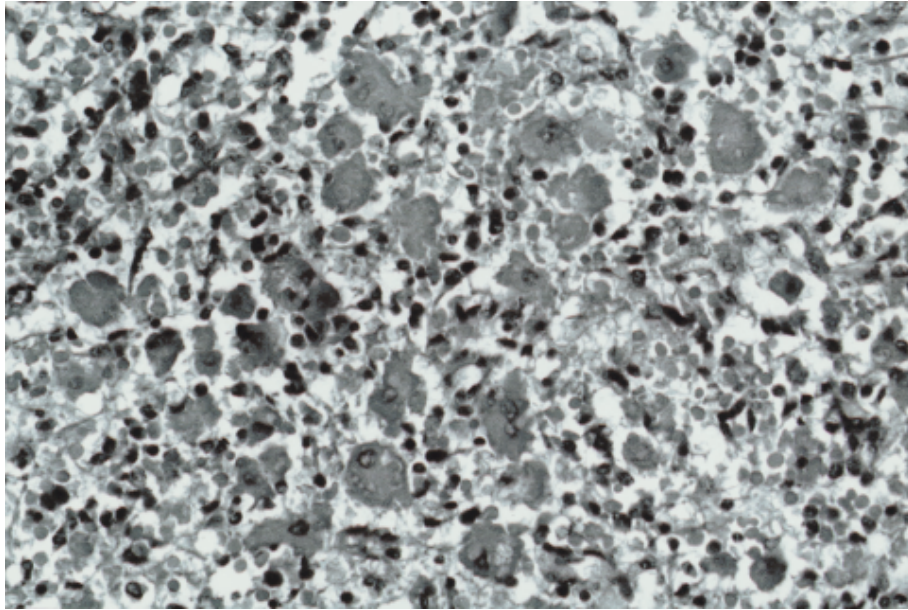


Fig. 3. The large, bizarre cells with abundant eosinophilic cytoplasm in the red pulp of the spleen (HE X 200).

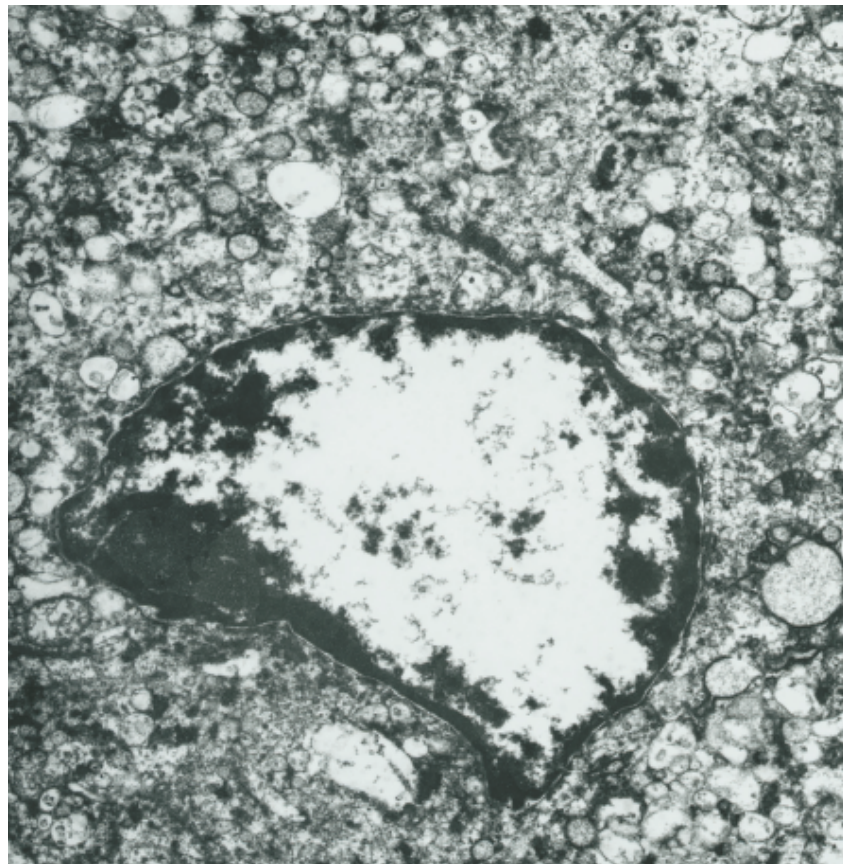


Fig. 4. Membrane-bound bodies, some of them showing electron density (electron micrograph X 1400).

Discussion

Tuberous sclerosis is characterized by multiple hamartomas present in the skin, cerebral cortex, heart, kidney, and eye. TSC gene loci have been identified on chromosomes 9p34 (TSC1) and 16p13 (TSC2). The central nervous system lesions are cortical tubers, white matter heterotopias, subependymal nodules and giant cell astrocytomas^{13,14}. Subependymal nodules, characteristic of the disease, project into the ventricular cavities, usually in the lateral or third ventricles. These nodules grow slowly and may develop into subependymal giant cell astrocytomas⁴.

Rhabdomyomas occur as solitary or multiple white to yellow tan circumscribed nodules within the myocardium or in the subepicardial region, most often within the ventricular myocardium. They may occur in isolation, but are a common manifestation of TSC. Although the coexistence of rhabdomyoma and TSC has been reported in 30-64% of cases, Willis¹⁵ stated that other features of TSC can be found in all cases if the brain and other organs are carefully examined. In this case, after we had detected multiple cardiac rhabdomyomas in the heart, we reviewed the brain histology and a further 26 blocks from the periventricular region in addition to the initial routine brain blocks examined. We found a single subependymal nodule composed of large bizarre giant astrocyte-like cells positive with GFAP and PAS, leading to a diagnosis of TSC.

The large cells with abundant eosinophilic cytoplasm in the spleen have been accepted as a finding in TCS. Morales et al.⁸ postulated that both cerebral and myocardial lesions are based on a common disturbance of carbohydrate metabolism and that the splenic lesions may be the result of excessive storage of accumulated end products derived from the abnormal metabolism of the myocardial and neural cells.

Östör and Fortune⁷ suggested that the giant cells in the brain, the heart and other organs represent the histologic expression of widespread tissue dysplasia. Bender and Yunis¹⁰ noted histiocytoid cells in the spleen in three of five cases with TSC and performed electron microscopy in one of their cases. They suggested that ultrastructurally, the presence of large numbers of moderately electron dense membrane-bound bodies and dilated rough endoplasmic reticulum in these cells may be

related to a secretory capacity, and that the membrane-bound bodies may represent lysosomes. These authors prefer to call the cells "histiocytoid" as they resemble histiocytes more than anything else. In our case, CD 68 positivity in addition to the electron dense membrane-bound cytoplasmic bodies in these cells supported a histiocytic origin for the cells; however, they were HMB-45 negative.

Although hamartomas of the spleen have been reported in adults with TSC^{5,6}, histiocytoid cells in the splenic pulp have only been described in neonates. These splenic lesions have been reported previously in only seven newborns and one fetus⁷⁻¹². To the best of our knowledge, our case is the second report of TSC with multiple cardiac rhabdomyomas and splenic involvement in a stillborn fetus. Despite recognition of splenic involvement in relatively few cases of TSC to date, a further tissue marker is always important for syndrome recognition. Recent parental reluctance in some countries to allow detailed brain examination following perinatal death makes recognition of splenic involvement in TSC even more important.

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