

Tuberous Sclerosis Complex with Diffuse Cytomegalovirus Fetal Infection: Case Report and Review of the Literature

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Citation

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Abstract

We report a case of a stillborn female fetus with combined stigmata of Tuberous Sclerosis Complex (TSC) and cytomegalovirus (CMV) infection. The baby was premature and small for gestational age (1625g). The heart showed multiple cardiac rhabdomyomas. The brain showed cortical tubers and subependymal nodule. Renal cysts are present. Autopsy also revealed multiple organ infected by CMV including lungs, liver and kidneys. The mother was 24 year old. The placental gross findings show multiple hematoma and infarction on maternal side, acute chorionitis with cytomegalovirus infection, chronic deciduitis and focal chronic villitis, might be the cause of the intrauterine demise of the fetus

INTRODUCTION

TSC is a rare, multi-system genetic disease that causes benign tumours to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. A combination of symptoms may include seizures, developmental delay, behavioural problems and skin abnormalities, as well as lung and kidney disease [1-3]. TSC is an autosomal dominant genetic disorder with an incidence of approximately 1 in 5,000 to 10,000 live births [4,5]. However, only one-third of cases are familial [6]. The apparently nonfamilial cases can represent either spontaneous mutations or mosaicism, in which only some germ cells in the affected parent express the mutant gene [6-8]. Some of these parents are asymptomatic, but most have mild abnormalities that can be detected with careful evaluation that is typically performed after TS is diagnosed in the child; the mild phenotype may reflect mosaicism in the somatic cells [8]. Another clue to the presence of mosaicism is when apparently unaffected parents have a second child with TS [6]. TSC lesions are typically hamartomas and rarely malignant. It is a multisystem disorder that can result in significant morbidity and mortality if vital functions are affected. TSC is caused by mutations on either of two separated genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberlin respectively. TSC1 and TSC2, were first identified in genetic linkage analysis of families with TS [9,10]. Both genes were subsequently cloned and the spectrum of mutations in TS patients described [11,12]. A disease-causing mutation can

be identified by mutation analysis in 60 to 80 percent of patients who meet the diagnostic criteria for TS [13,14]. The TSC1 gene, which maps to chromosome 9q34, spans 50 kb of genomic DNA and contains 23 exons [15]. It encodes a protein termed hamartin, which is widely expressed in normal tissues [16]. These proteins act as tumor growth suppressors and regulate cell proliferation and differentiation. The TSC2 gene, which maps to chromosome 16p13.3, spans 45 kb of genomic DNA and contains 42 exons [17]. The gene is ubiquitously expressed in all adult normal tissues, and encodes the tuberlin protein [18].

The prevalence of primary cytomegalovirus (CMV) infection in pregnant women is between 0.7% - 4% and is usually subclinical in more than 90% of cases. CMV transmission to the fetus occurs in 30-40% of cases with a mortality rate of 20-30%. Although the majority of congenital infections are asymptomatic, approximately 5 to 20 percent of infants born to mothers with primary CMV infection will be overtly symptomatic. These children have a mortality rate of nine [19] percent, and severe neurologic morbidity occurs in 80 percent of survivors. Human cytomegalovirus (HCMV) is a ubiquitous virus worldwide that causes a wide variety of clinical manifestations, the most severe occurring in immunocompromised hosts. Seropositivity for this virus increases with age, ranging from 40 to 100 percent depending upon geography and socioeconomic status. Primary infection and reactivation of virus can occur during pregnancy, and both can result in

congenital CMV, the most common congenital viral infection. Risk factors include: socioeconomic background appears to affect the prevalence of CMV infection with seropositivity rates ranging from 50 to 60 percent for American women with middle-class background compared to 70 to 85 percent for those with lower socioeconomic status. Social environment seems to be the most powerful factor predicting both seroprevalence and recurrences during pregnancy. In one study of 1088 consecutive mothers, IgM seropositivity was 3.8 percent in upper and 4.6 percent in lower socioeconomic groups; however there were twice as many recurrent infections in lower socioeconomic groups (3.6 versus 1.7 percent) [20]. Other factors that can influence CMV infection during pregnancy include maternal age, parity and gestational age [21]. Although several studies have suggested that gestational age has no apparent influence on the risk of transmission of CMV in utero [22], an increased risk of transmission was observed in late gestation in one retrospective study (36, 44.9, and 77.6 percent, for the first, second, and third trimesters, respectively) [23]. However, sequelae appear to be more severe when infection is acquired earlier in pregnancy. One cohort study of 3461 multiparous women showed that the presence of preexisting maternal antibody to CMV was protective against congenital CMV infection in the offspring [24]. The only other factor that reduced the risk of acquisition in the newborn was maternal age ≥ 25 years.

CASE REPORT

The patient was a stillborn female fetus, 35 weeks of estimated gestational age. The baby's mother is 24 years old with a diagnosis of IUFD 2/7/2007. She had a history of hypertension of pregnancy, and seizures since 20 years old. On 2/7/2007 the baby was delivered vaginally with a normal appearing. Placenta appears small with a 4 x 5 cm area of necrosis and clot on placenta.

At autopsy, the baby was found to be premature and small for gestational age (1625g). The degree of maceration observed indicated that the baby had been dead in uterus for some time. Microscopically the organs were well developed for the gestational age with marked autolysis.

The mother was 24 year old, her placental gross findings show multiple hematoma and infarction on maternal side; mild acute chorionitis with cytomegalovirus infection, chronic deciduitis and focal chronic villitis might be the cause of the intrauterine demise of the fetus.

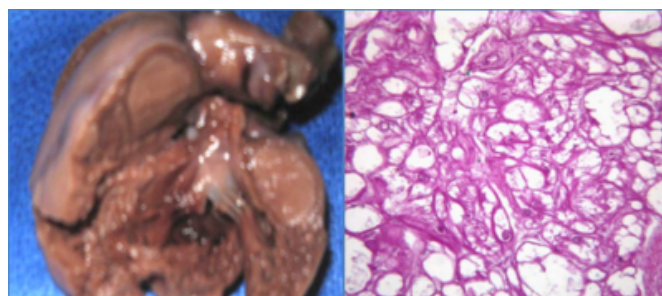
AUTOPSY FINDINGS

At autopsy the stillborn white female fetus showed normal external features with macerated skin. Gross and histological examination of the internal organs showed:

The baby was premature and small for gestational age (35 weeks, 1625 g). Her skin was moderately macerated indicating stillborn in uterus for some time. The internal organs are in right position. Heart weighs 24 grams. The myocardium is red and fleshy. Multiple cardiac rhabdomyomas were present in both ventricles ranging from 0.3 to 1.2 cm in diameter. The cardiac rhabdomyoma shows spider cells (Fig.1). There is moderate bloody effusions are seen in thoracic and pericardiac cavities. Microcysts in the renal cortex of both kidneys were present. The brain weighs 260 grams. Coronal sections of the brain reveal multiples cortical tubers and a white nodule protruding into lateral ventricle (2 cm in diameter). Brain subependymal nodule, multiple cortical and white matter tubers (Fig.2) and marked architectural disorganization with ballooned astrocytes of "Palmini type IIB" cortical dysplasia were seen microscopically. The placenta was small in size (11 x 10 x 1.5 cm) and weighed 186 grams. The main histological findings in the placenta were CMV infection with mild acute chorionitis, chronic deciduitis, focal chronic villitis, and retroplacental hematoma (3 cm in greatest dimension) rimmed by an acute infarction. Disseminated CMV infection in the placenta, both fetal lungs, liver and kidneys were found by H&E and CMV immunostain (Fig.3).

Figure 1

Fig.1 Left panel: Cardiac rhabdomyoma (gross appearance); Right panel:



Cardiac rhabdomyoma, spider-shaped rhabdomyocytes (H&E, 40x; insert 400x)

Figure 2

Fig.2 Subependymal nodule in TSC showing dysplastic disorganized neuroglial architecture (H&E, Left panel: 400x ; Right panel: 40x).

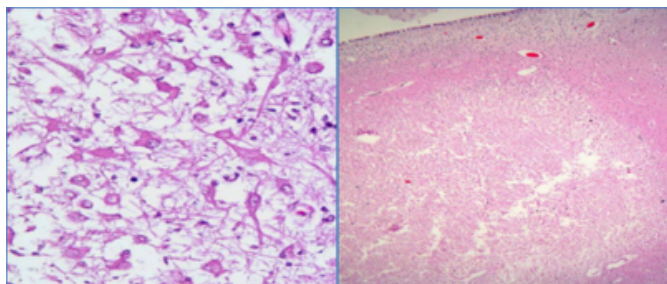
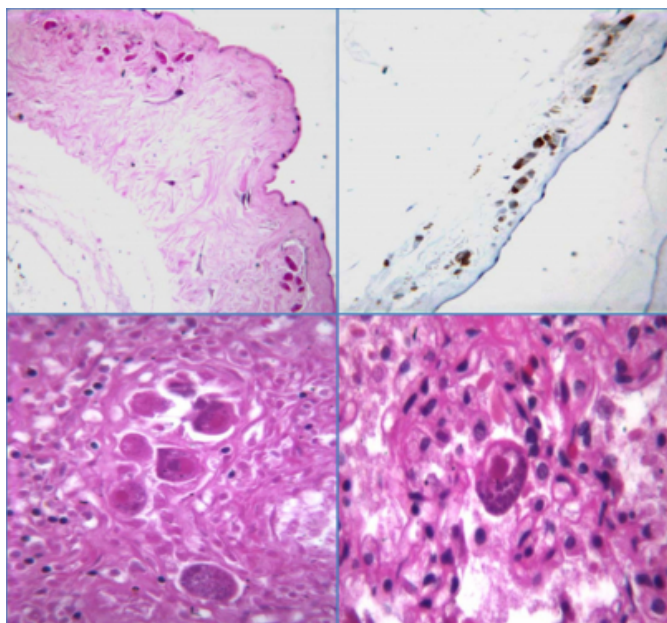


Figure 3

Fig.3 Multiorgan CMV infections. Upper panels: CMV in placental membranes, (upper left: H&E, 100x; upper right: Anti-CMV, 100x); Lower panels: Disseminated CMV fetal infection with nuclear and cytoplasmic inclusions in lower left: liver, and lower right: lung (H&E, 400x).



In summary, disseminated cytomegalovirus infection in lung, liver and kidneys caused the baby's intrauterine demise.

DISCUSSION

Tuberous sclerosis complex is a multisystem disorder which can adversely affect the fetal outcome. The diagnostic criteria for TS, as developed by a consensus conference in 1998, are based upon specific clinical features [25]. According to these criteria, the diagnosis of definite TS requires two major features with one exception noted below, or one major and two minor features. Children with one

major plus one minor feature have probable TS, and those with one major feature or two or more minor features have possible TS.

The following are considered major clinical features of TS:

- Facial angiofibromas or forehead plaques
- Shagreen patch (connective tissue nevus)
- Three or more hypomelanotic macules
- Nontraumatic ungula or periungual fibromas
- Lymphangiomyomatosis (also known as lymphangiomyomatosis)
- Renal angiomyolipoma
- Cardiac rhabdomyoma
- Multiple retinal nodular hamartomas
- Cortical tuber
- Subependymal nodules
- Subependymal giant cell astrocytoma

The following are minor features:

- Confetti skin lesions (multiple 1 to 2 mm hypomelanotic macules)
- Gingival fibromas
- Multiple randomly-distributed pits in dental enamel
- Hamartomatous rectal polyps
- Multiple renal cysts
- Nonrenal hamartomas
- Bone cysts
- Retinal achromic patch
- Cerebral white matter radial migration lines

The presence of seizures is not a diagnostic criterion because of poor specificity for TS [25]. In addition, some women have angiomyolipomas of the kidney associated with pulmonary lymphangiomyomatosis but no other TS-

related features [26]. These patients do not have an increased risk of having an affected child and are therefore not considered to have TS.

Testing of the family members of the affected baby are imperative to differentiate between an inherited versus new occurrence of TSC. Genetic counseling plays an important role in inherited TSC. Prenatal genetic testing with DNA analysis can be performed in families in which a specific mutation in the TSC1 or TSC2 gene has been identified in an affected family member. In families where a specific mutation is not identified but multiple affected individuals are available for testing, it may be possible to perform linkage analysis. There are a number of complications in performing linkage analysis and the results must be interpreted by a geneticist or genetic counselor. For families where a specific TSC mutation is identified, the couple may also be eligible for preimplantation genetic diagnosis. This allows the implantation of embryos through in vitro fertilization, which do not carry the mutation.

Also Screening for primary CMV infection during pregnancy is important to detect subclinical cases which can be associated with a high rate of fetal transmission and high risk of fetal mortality. Some TSC1 and TSC2 gene mutations are de novo, which are probably related with virus of other environmental factors.

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