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Congenital Rubella Syndrome with Necrotizing Panencephalitis (An Autopsy Case)

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= Abstract =An autopsy case of congenital rubella syndrome in a deadborn infant is reported. This case is of particular interest in view of the association of massive necrotizing encephalitis with devastation of the almost entire brain. Necrosis and calcifications were also seen in the retina and the liver.

The rest of the organs showed fairly typical changes of congenital rubella syndrome, such as patent ductus arteriosus, microcephaly and cataract. The skin showed bullous inflammation.

Key words: ***Congenital infection, Encephalitis, Rubella virus, Congenital rubella***

INTRODUCTION

Congenital rubella syndrome is an active contagious disease with multisystem involvement and a wide spectrum of clinical expression.

Although many of the lesions of congenital rubella syndrome, such as patent ductus arteriosus, microphthalmia, resemble true malformations, the neuropathologic abnormalities appear to be resulted primarily from inflammatory vascular disease. However, active encephalitic changes are seldom described in the literature. Recently we have experienced a case of congenital rubella infection with active inflammation in central nervous system and skin.

We report this case to add some unusual new findings of brain involvement in congenital rubella syndrome.

CASE REPORT

This cse was a deadborn baby from a 25 year old primigravid woman. The pregnancy was complicated by an episode of cystitis at 19 weeks of gestation, that was treated with gentamicin for 10 days. At 30 weeks of gestation ultrasonography was done to reveal breech presentation, polyhydramnios and dilated lateral ventricles of the brain. The mother was tested for VDRL, which was negative. The liver function tests were within normal limits. Serum alpha fetoprotein was 9500 ng/ml. The fetus showed signs of severe intrauterine distress, and breech extraction was done. The delivered baby was female and showed no sign of life. Serological tests from the baby for toxoplasma and cytomegalovirus were negative. However, ELISA test of the baby blood for IgM antibody for rubella was positive at the strength of 1:44.

Postmortem examination revealed 1.38 kg baby having extremity skin with multiple excoriations. Internal examination showed hepatosplenomegaly, cardiac and cerebral calcifications. There were bilateral cataracts, patent ductus arteriosus, atrial septal defect and microcephaly. Microscopically massive necrosis, inflammation and mineralization were seen in the brain, liver, adrenal, kidneys, eyeball and pituitary gland.

The most striking feature was massive inflammatory destruction of the brain with almost total loss of parenchyma of the cerebral hemispheres and the brainstem (Fig. 1). Neither toxoplasma cyst nor cytomegalic inclusions were observed. Multiple sections from the cerebral hemispheres showed almost totally devastated cortex and subcortical white matter. The leptomeninges were prominent mainly because of mononuclear cellular infiltrate and edema together with vessels that are showing active vasculitis with concentric infiltration of mononuclear cells chiefly of plasma cells (Fig. 3). Multiple foci of coagulation necrosis were seen in the leptomeninges. The cortex lost its normal architecture. There

Fig 1. A coronal slice of the brain, showing devastated cerebral hemispheres and hydrocephalus ex vacuo. A portion of brainstem and posterior thalamus are also affected.

Fig. 2. A cut surface of the liver after formalin fixation, showing multiple areas of chalky white necrosis and calcification in the right and the left lobes.

was no recognizable neuronal population, and instead massive necrosis and calcification together with mononuclear cell infiltration were seen (Fig. 4). This massive necrosis extended down to subcortical and deep white matter with scattered islands of vessels that were also cuffed with small round cells. Multiple punctuate calcifications were also seen in deep white matter. The sections fromthe basal ganglia and thalamus were also showing massive necrosis with some preservation of blood vessels with inflammatory cells cuffing. Calcifications were again very prominent through out the deep gray matter. The choroid plexus wasinflamed with mononucler cells.

The umbilical cord showed both umbilical arteries and vein that were inflamed in their intima by acute and chronic inflammatory cells with nuclear debris. This inflammatory exudate extended transmurally through the entire thickness of the vessel. The Wharton's jelly was also the site of exudate in small foci. The liver showed scattered round patches of calcification and necrosis that could be seen externally through the hepatic capsule (Fig.2). Extensive extremedullary hemopoiesis was seen in the liver microscopically. Some megakaryocytes were seen. The portal spaces were heavily infiltrated by chronic inflammatory cells as well as hemopoietic cells. Giant cell transformations was not seen. At the line of ossification of the rib bone occasional neutrophils and plasma cells were seen together with increased osteoblastic and osteoclastic activity. The calcification of osteoid was in-

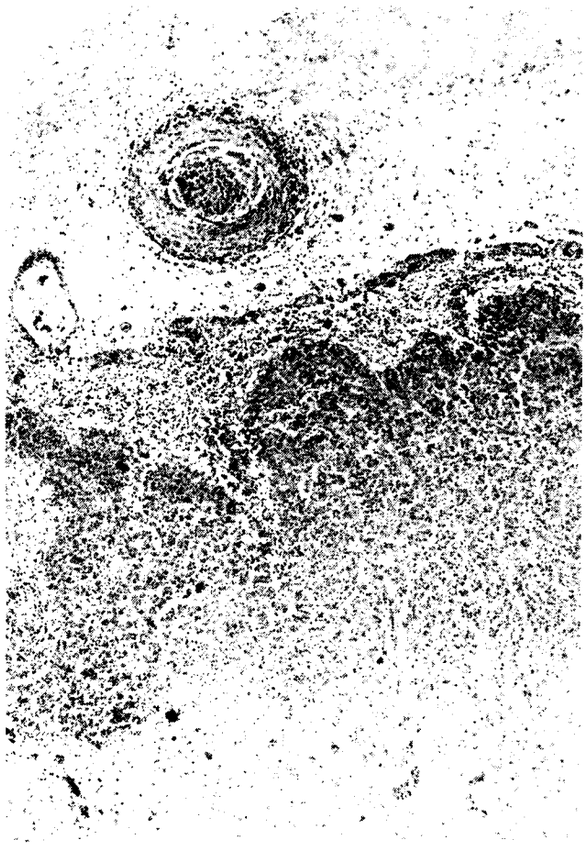

Fig. 3. Photomicrograph of the brain, showing massive necrosis and calcification involving the cortex and the underlying white matter. A vessel in the leptomeninges shows vasculitis and perivascular cuffing. H&E X40

adequate and slight distortion of the columnar orientation of newly formed bone spicules were noted. The bone marrow was normocellular.There

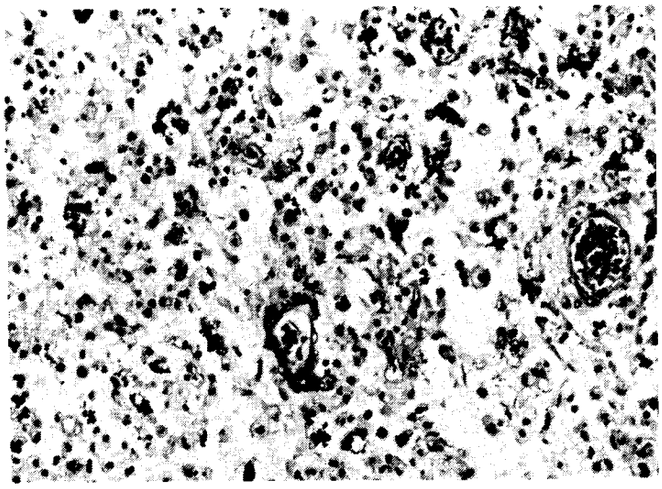

Fig. 4. Higher magnification of Fig. 3, showing almost total loss of the brain parenchyma and infiltration of macrophages, inflammatory cells, capillary proliferation and perivascular or intervening calcium deposits. H&E X2000

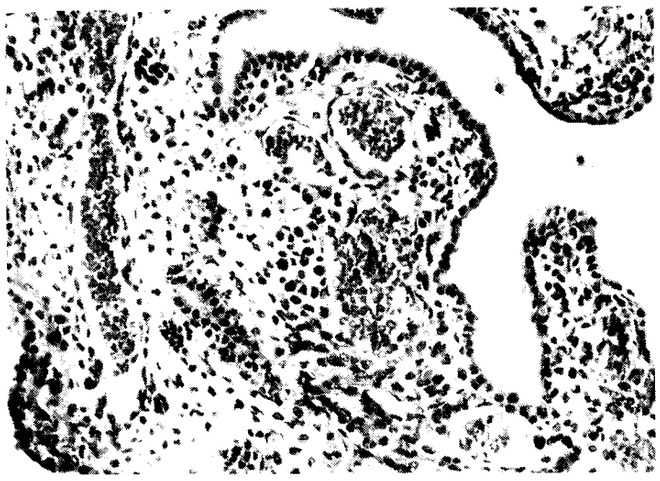

Fig. 5. Photomicrograph of placenta, showing mononuclear cell infiltration in the villous stroma. H&E X2000

Fig. 6. Photomicrograph of the eyeball, showing necrotizing inflammation of the ciliary body and iris. The cornea is also involved by inflammatory cells. H&E X40

was an increased number of plasma cells in marrow spaces as well as periosteum. The megakaryocyte appeared decreased in number. The lung showed obliterative angiopathy particularly in arteries with thickening of the wall, endothelial degeneration and subendothelial proliferation. An interstitial inflammation with mononuclear cells and lymphoplasma cells was also noted. The pituitary showed foci of extramedullary erythropoiesis in the sinusoids of the anterior lobe. Scattered laminated calcium bodies were seen. There was a large area of necrosis and calcification, surrounded by paucity of parenchymal cells and increased number of plasma cells. Pars intermedia was the site of massive erythropoiesis and plasma cell infiltration. There were bullae and acute and chronic inflammatory cell infiltration in dermis. Calcification around the hair shaft was seen in the skin.

The entire eyeball section showed focal small round cell infiltration in the outer layer of the cornea, diffuse small round cell infiltration in the iris and ciliary processes together with spotty calcification (Fig. 6). The necrosis and calcification extended to the retina of the entire eyeball. There was massive infiltration of plasma cells in the choroid. The sclera was relatively spared from the inflammation. The lens was coagulated and lens fibers near the posterior lens capsule showed pyknosis of the nuclei. However, no definite calcification was seen in the lens stroma.

The pancreas, the salivary gland and the thyroid were unremarkable. In the adrenal there were multifocal necrosis and calcifications mainly located in the cortex. Heavy infiltration of mononuclear cells, chiefly plasma cells were also noted. Small islands of extramedullary hemopoiesis were scattered in the fetal zone of the adrenal. The necrotic lesion extended focally into the capsule and periadrenal fat. The kidney section showed normal maturation process with persistent subcapsular nephrogenesis. Scattered collections of extramedullary hemopoiesis of both erythroid and myeloid series were seen. Placenta sections showed preserved membrane and slightly hydropic villi. The chorion and amnion were not inflamed. However, there were several foci of chronic inflammation of the villi, characterized by plasma cell infiltration (Fig. 5). The trophoblastic

epithelium was not specifically altered.

DISCUSSION

The pathogenesis of the malformation in the developing fetus with rubella virus infection probably involves several mechanism. In some cells, infection may lead to destruction, whereas in other the infection may be noncytopathic, with mitotic involution (Singer *et al.* 1967). A theory of clonal noncytopathic infection with mitotic inhibition can account for a number of usual phenomena observed in congenital rubella, such as asymmetrical noninflammatory lesions in some organs, the persistence of inflammatory change despite the presence of transplacental IgG and the fetal production of IgM antibody. Rorke and Spiro (1967), Desmond *et al.* (1967), and Singer *et al.* (1967) have stressed the nature of the vascular changes within the brain in cases of congenital rubella. In some of their cases, vasculitis led to necrosis of the vessel and focal infarction of brain tissue. However, massive destruction of brain to the extent seen in this case was not encountered in the previously reported cases. The other characteristics of the brain and the retinal in this case was massive calcification. These calcium deposits were seen fairly widely. Because there were scattered foci of vasculitis in the leptomeninges and also in the cortical penetrating vessels one should consider that the massive devastation of brain might have resulted from this obstructive vasculopathy.

The reason why this case showed such an active inflammatory process in the central nervous system cannot be easily explained. However, it seemed certain that the lesion seen in the brain was directly related to the rubella virus infection. We have seen similar changes of brain in congenital cytomegalovirus infection (Yu *et al.* 1986) and herpes simplex infection (Suh *et al.* 1987). However, the extent and degree of involvement were much less severe than this case, and there was not active vasculitis as seen in this case. A possibility of toxoplasmosis was also considered in the brain sections. Though the exact nature of the calcium deposits is unknown, the ultrastructural similarities of these lesions to immune complex deposits reported in other conditions (Lampert and Oldstone, 1974) raise the possibility that they may be precipitated globulins.

Despite many clinically or serological suspected cases, congenital rubella syndrome has not been diagnosed with full documentation in Korea. This case appears to be the first autopsy proven congenital rubella syndrome in Korea.

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= 국문초록 =

선천성 풍진 증후군 (1 부검례)

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25세 산모에서 30주의 재태기간후 분만된 사산아에서 부검으로 확인된 선천성 풍진 증후군의 1예를 보고하였다. 본예는 기술된 예들과 비교할 때 중추신경계 소견에서 상당한 차이를 나타내고 있었는데 즉 뇌를 전반적으로 침범하는 극심한 괴사성 염증소견과 석회침착이 있었고 활동성 혈관염을 동반하였다. 유사한 소견이 안구의 망막에서 관찰되었고 피부에서도 심한 염증소견이 관찰되었다.

이상의 소견으로 보아 선천성 풍진은 증례에 따라 상당한 병리학적 차이를 나타냄을 알 수 있었다. 본예는 한국 문헌상 처음 보고되는 선천성 풍진 증후군 부검례이다.