An Autopsy Case of Adrenal Cytomegaly

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Adrenal cytomegaly is a relatively rare phenomenon which refers to the presence of large cells in adrenal cortex of fetus or neonate. Those cells have large hyperchromatic nuclei with inclusion like structures and abundant eosinophilic cytoplasm. This phenomenon was first described by Kampmeier[1], and the term "cytomegaly" was used by Potter[2] at first. On the etiology of this phenomenon, viral infection, precursor of tumor, anomaly, etc. are suggested.

We have experienced a case of bilateral diffuse adrenocortical cytomegaly in a premature neonate during the post-mortem examination and we observed the adrenal cortices on light and electron microscope.

REPORT OF A CASE

A newborn girl, who was the product of 32 weeks of gestation, weighed 1800g. After birth, abdominal distension was noted. The liver edge was palpable 2.5 fingers' breadth below the costal margin at the right mamilary line, and the spleen was also palpable 2 fingers' breadth below the costal margin at the left mamilary line. A soft and smooth mass was palpated 3 fingers' breadth below the lower margin of the liver.

As she had occurred respiratory distress and convulsion from 2 days after birth, the respirator was instituted at 4th day. But she died at 5 days old.

Examination for vanillylmandelic acid in urine was negative. By radiograph for abdomen, a large shadow was shown at right lateral abdomen. The boundary of the shadow to the liver was not clear, and no relation to the kidney by observation of intravenous pyelography. Data of clinical examination were shown in "Table I".

Her mother was 28 years old and not particular in her past history. This pregnancy was complicated with toxemia of pregnancy. At labor hydroamnion (2000ml), too long umbilical cord, adhesion and degeneration of the placenta were noticed.

At autopsy samples of various tissues were fixed in 10% formalin solution. About half a year later, minced samples of adrenal cortices were washed in cacodylate buffer, and these were post-fixed in 1% osmium tetroxide for 2 hours, dehydrated with graded alcohol and embedded in epoxy resin according to the Luft's method.[3] Ultrathin sections cut with an Ivan-Sorvall MT2-B ultra-microtome were double stained with uranyl acetate and lead citrate and examined with a Hitachi HS-8 electron microscope.

Table 1.

Systemic Blood Chemistry (4/XII)
S/P 4.7g/dl B.S. 30mg/dl A/G 0.52 CCFT 0
Alb. 1.6g/dl Glob. 3.1g/dl Chol. E. 0.27△pH
Alk. P. 3.0u/dl Cholest. 134mg/dl Ph.T.T. 8
N.P.N. 32mg/dl Urea N. 16.3mg/dl GPT 4u/dl
LDH 1100u/dl
Peripheral Blood (4/XII)
RBC $437\times10^4/mm^3$ Ht 50.5 %Reticul. 6.9‰
WBC $4900/mm^3$ Myel. 1.5% Metamyel. 1.0%Band 3.0%
Seg. 18.5%Eos. 1.0% Bas. — Lymph. 69.5%Mon. 5.0%

	3/XII	4/XII	5/XII	6/XII	
Bilirubin	7.0	10.5	10.8	14.3	mg/dl

AUTOPSY FINDINGS

Gross Examination

Autopsy was performed about half an hour after death. The patient was 1740g in weight and 40cm in height. In the external examination abdominal distension and slight icteric sclera were found. An appearance of the skull was not remarkable.

Abdominal distension was due to the liver. The liver was congestive and weighed 110g, walnut sized Riedel's lobe was noted at anterior of visceral surface of the right lobe (Fig. 1). This Riedel's lobe was subdivided to a few lobules and on the cut surface small pale patches were recognized.

Adrenals were enlarged and deformed in shape due to hematomas. Left one was 6g in weight, and the right one was 8g. The largest hematoma was a small finger tip sized. On section through the right one, chocolate-like viscous material came out from the hematoma and the other site.

The heart was 13g in weight. Foramen ovale was closed functionally. Botallo's canal did not close yet. The heart had no anomaly.

The lungs were dark reddish and the crepitation decreased. The left one was 11 g in weight and the right was 12 g.

The kidneys were slightly enlarged (left 11 g, right 10 g) but had no other changes morphologically.

In the urinary bladder, mucous membrane was cloudy and submucous hemorrhages appeared.

We could find out neither anomaly nor abnormal findings in the other organs. We could not examine the brain.

Table 2.

	B.W.	Thymus	Heart	Lungs	Spleen
This case	1740g	4g	13g	l=11g, r=12g	5g
8months age[13] female fetus	1718g	5.7g	13g	38g, combined	5.4g

Liver	Kidneys	Adrenals
110g	l=11g, r=10g	l=6g, r=8g
62g	17g, combined	4.8g, combined

Microscopic Findings

Lungs: Neutrophils were seen in the alveolar and bronchiolar spaces here and there, and in almost region the alveloar septa were thickened by congestion and infiltration of neutrophils and mononuclear cells.

Liver: In almost region sinusoids were much dilated by congestion and partially hemorrhages were seen in especially around the central veins. In Riedel's lobe focal edematous fibroses were seen and hemorrhages were more than the other regions.

Adrenals: In the fetal zone of the cortices, giant cells which consisted of large round or ovoid nuclei with prominent chromatin and eosinophilic cytoplasms were diffusely present in both adrenals (Fig. 3). In some of these cells the nuclei contained round or elliptical inclusion like structures stained same as the cytoplasm (Fig. 4). Feulgen's reaction was negative in these structures (Fig. 5). Hemorrhages were present in the fetal zone and medulla, and in some parts cystic hematomas were noted. Small paradrenal nodules were in the peri-adrenal connective tissue. In some parts of adult zone, small cortical cells were hyperplastic.

Pancreas: There was slight fibrosis diffusely. Hyperplasia of the cells in Langerhans' islets was recognized and it was difficult to differentiate the acinic cells from islet cells clearly (Fig. 6).

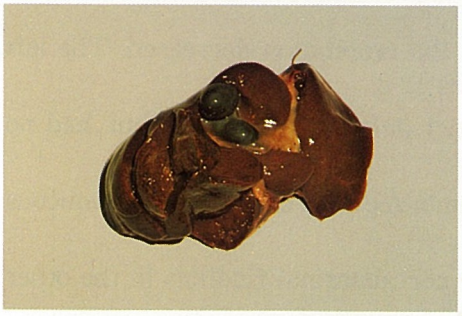

Fig. 1

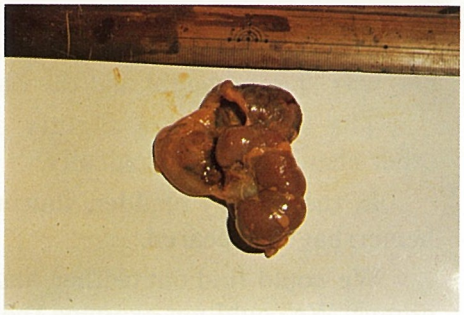

Fig. 2

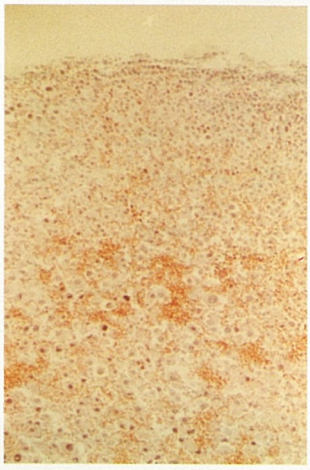

Fig. 3

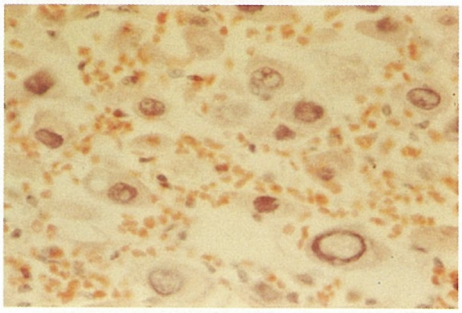

Fig. 4

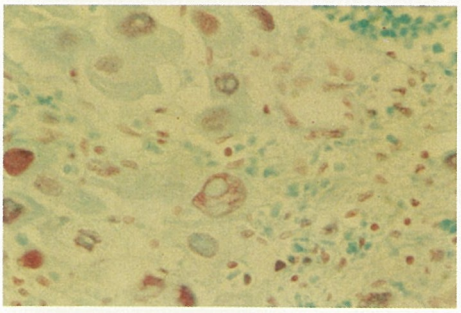

Fig. 5

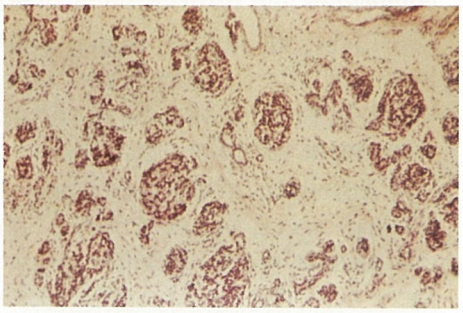

Fig. 6

Fig. 1 Visceral surface of the liver. At lower anterior region of the right lobe, Riedel's lobe is noted.

Fig. 2 Left Kidney and adrenal gland, Adrenal gland is enlarged and deformed.

Fig. 3 Adrenal cortex. Giant cells are seen in fetal zone of adrenal cortex. Among these cells hemorrhages are observed. H.E. stain. lower magnification.

Fig. 4 Giant cells in fetal zone of adrenal cortex. Some of these cells have inclusion like structures in their nuclei. H.E. stain. higher magnification.

Fig. 5 Inclusion like structures in these giant cells are negative for Feulgen's reaction. higher magnification

Fig. 6 Hyperplasia of islet's cells and fibrosis in pancreas. H.E. stain. lower magnification.

The other organs had no serious changes in microscope.

Electron Microscopic Findings of Adrenal Cortex

The giant cells had large and irregular-shaped nuclei that had sometimes intranuclear inclusion like structures. These structures were same as cytoplasm and delimited by the unit membrane. The neurosecretory granules and virus-like particles could not be detected. The fine morphological changes of cytoplasm could not be found clearly (Fig. 7).

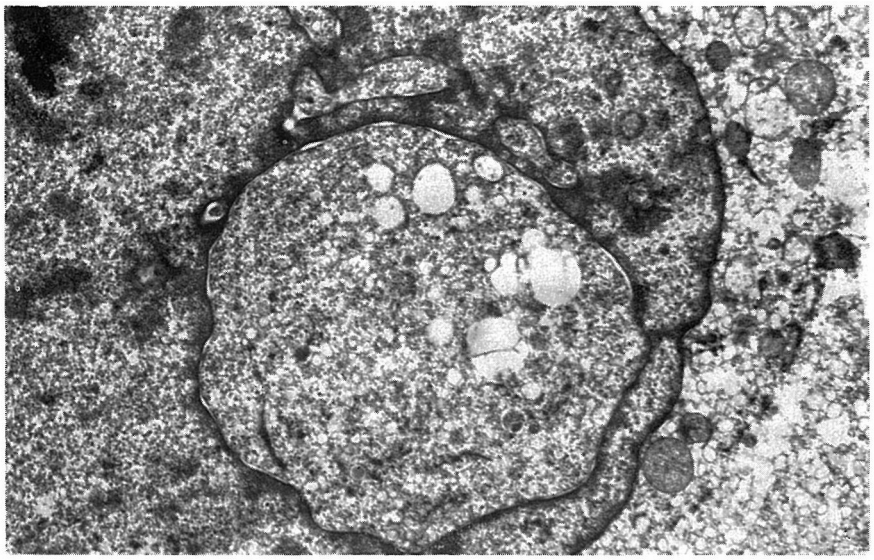

Fig. 7. The intranuclear inclusion like structure is same as cytoplasm and delimited by an unit membrane. ×7700

PATHOLOGICAL DIAGNOSIS

1. Premature neonate (32 weeks of gestation, 1740g)
2. Adrenal cytomegaly
3. Bronchopneumonia
4. Riedel's anomaly lobe of the liver
5. Hyperplasia of islet cells in pancreas
6. Hepatomegaly (110g) and nephromegaly (21g combined)

DISCUSSION

In this case, giant cells appeared diffusely in the fetal zone of bilateral adrenal cortices. On the light microscopy these cells resembled to

the cortical cells in the fetal zone of the fetus in the appearance of prominent eosinophilic cytoplasms and hyperchromatic nuclei. And we could observe the figures of the gradual transition from these giant cells to the physiological cortical cells in the fetal zone. In the electron microscopy, the intranuclear inclusion like structures of the giant cells were same as cytoplasm and delimited by the unit membrane, so these structures were cytoplasmic invagination. The neurosecretory granules could not be found in these cytoplasm.

As mentioned above, we diagnosed the phenomenon in this case as the adrenal cytomegaly which was first described by Kampmeier[1], then reported by Craig & Landing[4], Potter[2] etc.

On the etiology of this phenomenon many hypotheses and opinions have been reported, but it is unkown yet.

Kampmeier[1] inferred that this phenomenon occurred as the fetal development. But these cells are not observed in the physiological fetal adrenals.

Craig & Landing[4] suggested the giant cells in this phenomenon were the precursor of virilizing tumor of adrenal cortex in childhood, because the atypism of the cells was inherent, not a degenerative phenomenon and these 'anaplastic cells' resembled to the virilizing tumor cells. Then Sherman et al[5]. reported a case of a metastasizing adrenal cortical carcinoma with cytomegaly in both primary and metastatic nodules. But in the present case and almost other reports, these characteristic cells are seen diffusely and bilateraly in fetal adrenocortices, so it is difficult to think that these giant cells are neoplastic.

Viral infection also can be considered. Singer et al[6]. reported 3 cases of adrenal cytomegaly in 18 cases of congenital rubella syndrome and they said a viral relationship remained a consideration. But any report could not detect virus like particles untill now and in our case too we could not find out such particles. Viral etiology may not be completely excluded, but the absence of virus like particle in electron microscopy precludes that the viral infection directly leads to the adrenal cytomegaly.

In many cases reported as adrenal cytomegaly, the association with erythroblastosis fetalis is relatively high rate. Eleven of 16 cases in report of Aterman et al[7]. associated with erythroblastosis fetalis, 11 of 37 cases in Craig & Landing's instances and 2 of 23 cases in Oppenheimer's[8]. Aterman et al[7]. suggested that adrenal cytomegaly was a non-specific reactive phenomenon, a response to intense or prolonged stimulation for a variety of reasons, which produced changes in the endcellular structure that manifested themselves as polyploidy, since cytomegaly was not a feature

which was limited to the adrenals nor to fetal age group, and since these cells in this phenomenon might be hyperactive in function, because of their polypoid appearance and intranuclear cytoplasmic invagination[8),9)]. But in almost cases of functioning pituitary adenoma and in over half of the cases of erythroblastosis fetalis this phenomenon did not occur. So occurrence of the adrenal cytomegaly can not be thought simply as a reactive phenomenon.

Since the paper by Beatty & Hawes[10)], the connection between the presence of congenital anomalies and the occurrence of adrenal cytomegaly has been mentioned. In their paper, 9 of 11 cases had coexistant congenital anomaly, and in several, multiple anomalies were noted. Recently this association between adrenal cytomegaly and congenital anomalies has been emphasized by some writers[8),11),12)] on "Beckwith syndrome". The principal features of this syndrome are as follows; hyperplastic fetal visceromegaly, bilateral adrenocortical cytomegaly, pancreatic hyperplasia and dysplasia, omphalocele, macroglossia, and hypoglycemia. In our case Riedel's lobe of the liver, hepatonephromegaly, hyperplasia of islet cells and hypoglycemia were associated with this phenomenon. Therefore this present case is analogous to this Beckwith syndrome. We think the association of congenital anomalies is most important to pathogenesis of this phenomenon.

On the cause of death of this case hypoglycemia is suggested but blood sugar was not examine at shortly before the death and we could not examine the brain, so we can not decide the cause of the death. We think this phenomenon may have not direct relation to death.

The tumor palpated below the liver at physical examination was not neoplasm but Riedel's lobe of the liver.

SUMMARY

We reported a case of adrenal cytomegaly associated with Riedel's lobe of the liver, hepatonephromegaly, hyperplasia of islet cells of the pancreas and hypoglycemia. This case was analogous to the Beckwith syndrome. On the etiology of this phenomenon many hypotheses are contended. We thought the association of congenital anomalies with this phenomenon is important to the pathogenesis of this phenomenon.

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