Noninflammatory Calcification in the Human Adrenal Glands Proper and Accessory, and in Adrenocortical Adenoma

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Noninflammatory massive calcification in the unilateral adrenal gland was confirmed in three cases, and infarction and extensive hemorrhage were prominent in etiology as usual cases in the literature. Infarction was also responsible for localized calcification and ossification in a functioning cortical adenoma which had myelolipomatous lesions as a usual complication. The first description of calcification in the accessory adrenal in the genital region was made of two cases with deposition of numerous calcareous bodies within the fetal zone. The lesions were ascribed to involution of the fetal zone and was regarded to be followed by retrogressive changes of the accessory adrenal gland itself.

Calcification in the adrenal glands has been frequently observed in the cat\(^4\),\(^7\),\(^21\) and in the monkey as well\(^21\), while less frequently in the dog\(^21\). Noninflammatory calcification or ossification is a rare finding in the human adrenal glands. Seligman\(^23\) recorded 4 cases of diffuse calcification in the zona reticularis, of uncertain etiology, out of 1185 autopsies. This incidence is, however, suspected to be exceptionally high as the report of actual cases is only sporadically found in the literature.

The present study deals with noninflammatory massive calcification in the human adrenal glands, focalized calcification in adrenocortical adenoma and deposition of calcareous bodies within the fetal cortex of the accessory adrenal gland.

MATERIALS AND METHODS

Noninflammatory calcification in the adrenal glands proper and accessory was picked up from autopsy materials, and the same lesion in adrenocortical adenoma was detected in surgical materials in the Department of Pathology, Tohoku University School of Medicine.
Unilateral massive calcification of the adrenal gland was confirmed in three cases (0.075%) among 3977 autopsies in recent 17 years (1947-1963). Accessory adrenal glands were studied on 232 cases of fetuses and infants ranged from 4 fetal months to 2 years of age. Every nodule of suspected adrenocortical tissue was obtained by the examination of usual magnifying glass at the time of autopsy and prepared for further histologic examination. Serial sectioning was made and the size of nodules was estimated by measuring the diameters of the largest central cut surface.

Calcification in adrenocortical adenoma was confirmed in one case with adrenogenital syndrome out of 10 cases of surgically resected adrenocortical adenoma with hyperadrenocorticism.

The tissues were fixed in formalin for 2 or more days and then processed by the usual methods for histologic sectioning and staining. Decalcification was done on the cases of massive calcification. According to customary in routine histology the silver method of Kossa was used for the demonstration of calcium phosphate.

RESULTS

Calcification of the Adrenal Glands Proper:

Case 1 (No. 101-51): A 24-year-old male had seminoma of right undescended testicle for two and half years which was followed by metastases to the retroperitoneal lymph-nodes involving the hilar region of the left kidney. Administration of nitrogen mustard-N-oxide, 3550 mg of total dose for two and half months resulted in severe agranulocytosis to death.

Autopsy revealed that the left adrenal gland had distinct atrophy, 3 g in weight, and extensive fibrosis associated with numerous small foci of calcification. The uninvolved cortex was thin showing distinct depletion of lipid. The right adrenal weighed 10.5 g manifesting compensatory hypertrophy of the cortex with notable depletion of lipid.

Histologically the capsule was distinctly thickened and severe cortical lesions with diffuse fibrosis and nodular foci of calcification were observed. Certain lesions of calcification were confirmed to be the sequence of thrombus within the capsular and medullary veins and deposition of small calcareous bodies probably within cortical veins and capillaries was also detected. Nodular lesions of irregular shape located both in the infracapsular and deeper cortical regions were suspected to be the sequence of infarction. The uninvolved cortical tissue was generally composed of compact cells occasionally intermingled with light cells. The medulla was uninvolved and in normal development. Diffuse and nodular hyperplasia of cortical cells, slight in degree, was confirmed in the left.

Case 2 (No. 176-56): A 47-year-old male died of stomach cancer after 6
months of clinical course. Autopsy revealed ulcerative carcinoma of the stomach with severe peritoneal dissemination without distant metastases. The right adrenal gland was extensively involved by massive calcification and only small amount of uninvolved cortical tissue with detectable depletion of lipid was observed in the periphery. The left adrenal gland was slightly hypertrophic and rich in lipid.

Histologically, extensive and advanced fibrosis with severe calcification involved almost entire area of the gland, both cortex and medulla. Formation of bone tissue was detected in certain areas. Calcified thrombus was confirmed within a large capsular artery and the extensive lesions of the gland were regarded as a sequence of massive infarction. The right adrenal had slight hyperplasia of the cortex and medulla associated with several accessory nodules in the capsule.

Case 3 (No. 190–63): A 67-year-old male had epipharyngeal carcinoma on the right side for 3 years, which was followed by severe lumbago 6 months prior to the admission. Laboratory examination revealed osteolytic and osteoplastic changes of the skeleton, severe hypophosphatemia and slight anemia associated with appearance of normoblasts and metamyelocytes in the peripheral blood. Swelling of liver was observed and fever appeared in the final stage.

Autopsy revealed that epipharyngeal carcinoma had extensive and diffuse metastases to bone tissues and resulted in osteosclerotic changes of the sternum, vertebrae and skull. Multiple foci of extramedullary hematopoiesis were detected in the liver and the spleen. Peliosis hepatis with a large liver abscess and acute bronchopneumonia were additional findings.

The right adrenal gland was atrophied and massive calcification of irregular shape, 0.5 cm in diameter, was located in the central region. Histologically, calcification was observed in the butterfly-like contour of massive fibrosis with hemosiderin granules which was suggested a sequence of infarction. The capsular arteries exhibited severe sclerosis.

Multiple healed infarctions were observed in the spleen. The parathyroid glands had slight hyperplasia. No metastatic calcification was detected in the kidneys, gastrointestinal tracts and lungs.

Calcification in Adrenocortical Adenoma:

Case 4: A 21-year-old female complained of amenorrhea and hirsutism. Urinary 17-KS was 68.1–56.1 mg/day and certain other signs of adrenogential syndrome were confirmed. Administration of cortisone, 4,500 mg in total dose, was ineffective and a tumor was detected in the right suprarenal region by X-ray examination. The patient received surgical removal of the tumor at the Department of Urology, Tohoku University Hospital.

Grossly, the tumor was spherical, ca. 5 cm in diameter and brown in color. Histologically it was mainly composed of compact cells rich in densely granular
cytoplasm with scanty lipid droplets. Multiple lesions of ischemic or hemorrhagic necrosis and of fibrosis containing numerous hemosiderin granules were observed. Localized calcification or bony trabeculae with or without myelolipomatous tissue were occasionally found within the above lesions. Obliterative endoarteritis in advanced stages and sclerotic lesions were detected in certain arteries.

**Calcification of the Accessory Adrenal Glands:**

Thirty-two accessory adrenal glands of grossly detectable size were confirmed by microscopic examination in 21 out of 232 autopsy cases. Their locations were as follows: along the spermatic cord 8, attached to the epididymis 2, in the broad ligament 13, adjacent to the ovary 2 and near but detached from the adrenal glands proper 6.

The size of the nodule in histologic slides was ranged from \(0.58 \times 0.38\) mm to \(6.41 \times 3.2\) mm. In relatively large ones the structure of cortical cell cords and of capillary network was in full development with considerable high incidence of pseudolumina formation comparable to the adrenal glands proper. The central vein was observed in cases with the size generally more than 2 mm in diameter. No cases had the medullary tissue. Three cases with small nodule had an underdeveloped structure occasionally composed of undifferentiated cortical cells and small amount of capillaries. Thickening of argyrophilic fibers in the permanent cortex was frequently observed in cases of small nodule. Regressive changes of the fetal zone in various stages were confirmed in 11 cases. The findings were generally comparable to or somewhat retarded from similar events in the fetal zone of the adrenal glands proper in the same patient. However, in exceptional two cases regressive changes of the fetal zone were prevalent in the accessory nodule showing deposition of granular calcareous bodies.

**Case 5:** A six-fetal-month-old stillborn infant, male, had a small accessory adrenocortical nodule attached to the right spermatic cord 2 cm distant from the cauda epididymidis. The nodule \(1.17 \times 1.08\) mm, had the thin permanent cortex in the periphery and the relatively well developed fetal cortex in the center. The fetal cortex was composed of necrotic cortical cells with granular hematoxylin bodies in the cytoplasm, which gave positive reaction by Kossa stain and were interpreted as phosphate lime. The distribution of argyrophilic granules of Kossa stain in the fetal zone was more dense and extensive than that of hematoxylin granules. Other signs of involution such as fibrosis and pigmentation could not be observed in the fetal cortex. The permanent cortex was thin and the cortical cells were arranged in irregular alveoli. The adrenal glands had the well-developed fetal cortex without signs of involution and it is notable that this was the only one case as showing degeneration of the fetal zone in the accessory nodule without any lesion in the adrenal glands themselves.
Case 6: A 5-day-old newborn male, who died of sepsis due to infection through the umbilicus, had three small accessory adrenocortical nodules with quite different findings in histology and in location as well in each other. The first one attached to the left suprarenal vein, 0.97 × 0.64 mm, was composed of masses of small cortical cells similar in appearance and arrangement to those in the permanent cortex. The component of the fetal zone could not be detected. The second one attached to the right spermatic cord, 1.38 × 0.95 mm, showed slight fibrotic changes in general but it was possible to distinguish the inner region with relatively large cells and the outer zone with small cells. The another attached to the left spermatic cord near the epididymis, 1.12 × 0.73 mm, had both permanent and fetal zones. The fetal zone showed advanced signs of involution consisting of diffuse fibrotic lesions with much hemosiderin pigment in the center and deposition of granular hematoxylin bodies in the periphery. Some of the bodies were limited within the necrotic cell as well as in Case 5, and others were deposited as amorphous masses occasionally together with hemosiderin pigment. The lesions were most likely calcification although Kossa stain gave negative reaction. The bundles of argyrophilic and collagenous fibers invaded occasionally into the permanent cortex and divided it into several cortical cell-blocks of irregular sizes. The fetal zone in the adrenal glands proper showed initial signs of involutional degeneration.

DISCUSSION

It is generally accepted that dystrophic calcification appears to be dependent upon a change in the local condition in the tissues. Corticoid-induced suppression of the granulation tissues in the adrenal may be the most prominent in the cause to promote the adrenal calcification. However, the etiology of calcification of the adrenal glands has not been satisfactorily clarified. Seligman and other authors discussed several possible factors and the lesions are generally divided into two groups, of inflammatory and of noninflammatory origin. Among noninflammatory factors infarction has been frequently discussed and diffuse hemorrhage of the fetal cortex at birth as well.

Concerning adrenal calcification due to infarction, Goldstein presented a case and Parker five cases. Arterial infarction would be responsible for the massive calcification in Cases 2 and 3, as calcified thrombus was confirmed within a capsular artery in Case 2 and the extension and contour of the lesion in Case 3 were comparable to those of infarction in origin of capsular arteries (Sasano and Kitagawa). The nature of the lesions in Case 1 consisting of multiple foci of calcification could not be determined, although the calcified mass within the venous system suggested hemorrhage of venous origin.

Focal necrosis with or without hemorrhage probably of vascular origin is
an occasional finding of adrenocortical tumor and its sequent calcification may be induced. In the actual reported cases of adenoma with focal areas of calcification and/or formation of bony trabeculae, the lesions were observed in association with myelolipoma within adrenocortical adenoma (McDonnell\textsuperscript{13}, Patrassi\textsuperscript{14} and Sotti\textsuperscript{25}). Biressi\textsuperscript{1} in 1954 listed 54 cases of myelolipoma among which 7 cases were in association with both calcification and ossification, while 5 cases with ossification and 3 cases with calcification alone. According to Plaut\textsuperscript{18}, some of the cases listed by Biressi were not myelolipoma. However, small foci of calcification and/or ossification are rare, but unavoidable, complications of adrenal myelolipoma as Karsner\textsuperscript{11} pointed out and McDonnell\textsuperscript{13} demonstrated an example (case 3 in his report).

Myelolipoma has been rarely observed within adrenocortical adenoma\textsuperscript{3,5,10,13,25}. The cortical adenoma presented by Sotti\textsuperscript{25} and the heterotopic adrenocortical adenoma in the liver reported by Patrassi\textsuperscript{14} showed formation of bone and bone marrow within the tumor tissue. Formation of bone marrow seems to be an unavoidable complication of calcification or ossification in adrenocortical tumor. The adrenocortical adenoma with localized calcification in the present study (Case 4) also contained myelolipomatous changes contiguous to the area of massive necrosis and fibrosis. These lesions could be ascribed to massive infarction, as sclerotic and oblitative changes were confirmed in certain arteries within and surrounding the adenoma.

Another reliable cause of adrenal calcification is extensive hemorrhage of the fetal zone, which is a sign of regression at or around birth leading to fibrosis and disappearance of the zone. Regression of the fetal zone is also observed in the accessory adrenal gland and is comparable to that in the adrenal glands themselves in the same patient\textsuperscript{6,9}. Calcification should be induced in the accessory adrenal gland as a sequence of regression of the fetal zone. However, reviewing the morphologic features of calcification of the adrenal glands nothing was observed which occurred in the accessory adrenocortical nodule itself, although a few cases with bone marrow formation have been reported\textsuperscript{2,20}. In the present study, regressive changes of the fetal zone in the accessory adrenal locating near the testis were composed of deposition of granular calcareous bodies, without detectable fibrosis in Case 5 and with extensive fibrosis and hemosiderin pigment in Case 6.

In the physiological postnatal development of the adrenal glands, advanced regression leading to disappearance of the fetal cortex is followed by stimulative growth of the permanent cortex. The fetal cortex in the accessory adrenal with calcification had very slight or no significant reduction in volume due to calcification and this would suppress further development of the permanent cortex. Furthermore, thickening of argyrophilic fibers in the permanent cortex was generally predominant in the accessory adrenals particularly in cases with smaller in size compared with the finding in the adrenal glands proper in the same patient.
These findings are significant in considering the fact that the adrenocortical nodule is found frequently in the period of newborn and infant but mostly would be reduced to be an undetectable size in the course of aging.

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Fig. 1. One of the lesions of massive calcification of the left adrenal in Case 1. (Hematoxylin and eosin, ×35)

Fig. 2. A part of diffuse calcification with a focal area of ossification in the right adrenal in Case 2. (Hematoxylin and eosin, ×60)
Fig. 3. Calcified thrombus in a capsular artery in Case 2. (Hematoxylin and eosin, ×100)

Fig. 4. The extension and contour of the calcified lesion in Case 3 suggests the sequence of infarction. (Hematoxylin and eosin ×35)
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Fig. 5. Focal calcification and myelolipomatous tissue in cortical adenoma with adrenogenital syndrome in Case 4. (Hematoxylin and eosin, ×100)

Fig. 6. Deposition of calcareous bodies within the fetal zone of an accessory adrenocortical nodule attached to the right spermatic cord in Case 5. (Hematoxylin and eosin, ×35)
Fig. 7. Calcareous bodies are mainly located within necrotic cells without distinct fibrosis. (Kossa stain, ×100)

Fig. 8. Deposition of calcareous bodies within regressed fetal cortex of an accessory adrenal near the testis in Case 6. (Hematoxylin and eosin, ×100)