Calcium Oxalate Crystals in the Kidney and Thyroid of Leprosy Patients[1]

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The presence of calcium oxalate crystals in the human kidney was reported in 1959 ([15]). This was later followed by many studies in which the same kind of crystals were found in the human thyroid ([17]), retina oculi ([5, 18]), and myocardium ([2]). These calcium oxalate crystals have been thought to have a different pathologic meaning from crystal formation in primary oxalosis. There have been discussions on the relationship between this kind of crystal and malignant tumor ([3]) and uremia ([1, 7]).

In the course of a study of 149 autopsies of leprosy patients performed in two Japanese national leprosaria (Keifu-en Leprosarium and Komyo-en Leprosarium) during 1943-1967, similar calcium oxalate crystals were found in 46 cases of leprosy patients in the kidney and/or thyroid.

Although a group of autopsy cases from the 1960's in this study have shown crystals at a higher rate in the thyroid with distinct correlation with malignant tumors, most of the cases with crystals in the kidney and/or thyroid were not related to uremia. As similar crystals were found frequently in autopsy cases at general hospitals, the presence of these crystals is not a specific finding for leprosy ([10]).

In summarizing the histopathologic findings of 46 cases of leprosy, a hypothesis as to the pathogenesis of the crystals is presented together with a discussion of the pathologic meaning of such crystal deposition in leprosy.

MATERIALS AND METHODS

The autopsy cases were divided into the following three groups:

Group A: 49 leprosy cases autopsied in 1943 and 1944 in Komyo-en Leprosarium in Okayama, Japan.

Group B. 40 leprosy cases autopsied during 1955-1957 in Keifu-en Leprosarium in Kumamoto, Japan.

Group C: 60 leprosy cases autopsied during 1962-1967 in Komo-en Leprosarium in Okayama, Japan.

In each case, paraffin sections of the kidney and thyroid were stained with hematoxylin and eosin. The stained specimens were examined with a polarizing microscope.

X-ray diffraction is the best method for the identification of these crystals. However, the crystals in the tissues were often too scarce for this method; therefore, only one case showing relatively numerous crystals in the kidney could be thus examined. X-ray Geiger counter diffraction (Norelco) identified the crystals of this case as calcium oxalate monohydrate. In addition, histochemical methods ([13]) were applied to four cases, and the results obtained also confirmed the presence of calcium oxalate. It is usually very difficult to find calcium oxalate crystals in tissues with an ordinary light microscope.

RESULTS

Group A. (49 leprosy cases) Crystals found in sections from 10 cases. These cases ranged in age, at the time of death, from 29 to 54, with an average of 41 years. One 42 year old female showed crystals in the kidney. The cause of death in this patient was severe pulmonary tuberculosis. In the other nine cases a small quantity of minute crystals were seen in the thyroid. Most of them died of tuberculosis.

Group B. (40 leprosy cases) Twelve showed the presence of the crystals; in

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three cases in the kidney, in four cases in the thyroid and in five cases both in the kidney and thyroid. The average age was 57 years. Two cases of the first group showed amyloid kidney and one of them also had carcinoma of the uterus. Another also had carcinoma of the liver. Among four cases with the crystals in the thyroid, two had associated carcinoma. In five instances the crystals occurred both in the kidney and thyroid. Of these, two also had tuberculosis and the other three had respectively, hepatoma, chronic pyelonephritis and cresol poisoning by suicide. It was interesting that there were no particular histopathologic findings in the kidney of the suicide case. These 12 cases showed a high incidence of malignant tumor.

Group C. (60 leprosy cases). The crystals were found in the sections of 24. The average age was 63 years. Seven showed the presence of the crystals in the kidney, and three of them had malignant tumors (cholangioma, prostatic carcinoma and malignant lymphoma). The main pathologic findings of the other four cases were pneumonia, nephritis and hepatic cirrhosis. Among 13 with the crystals in the thyroid, malignant tumors were seen in seven. One of them showed dual carcinomas of the urinary bladder and the prostate. In four instances the crystals were found in the kidney and thyroid. Dual carcinomas were found in one of this group showing carcinoma of the stomach and malignant lymphoma. The main findings of the others were bronchopneumonia and pyelonephritis. Pyelonephritis was seen in 13 cases among group C. Tuberculosis was not the cause of death in any instance.

TABLE 1. *Grouping of cases.*

Group (yr.)	No. of cases	Average age (yrs.)
A (1943–1944)	49	41
B (1955–1957)	40	57
C (1962–1967)	60	63

All the results are summarized in Tables 1-4.

Microscopic features of calcium oxalate crystals. Crystals in the kidney. The crystals were almost always present in the convoluted tubules. They were rarely found in the interstitial tissues. There were no associated cellular reactions in the surrounding tissues. Sometimes rather large crystals were found which pressed and broke the epithelium of the convoluted tubules. The crystal was usually round with a diameter of about 50 microns. It was usually colorless

TABLE 2. *Cases showing the crystals in group A.*

No.	Age	Sex	Type	Location of crystals	Renal findings	Cause of death or other main pathologic changes
1	39	M	L	Thyroid	—	—
2	42	F	L	Kidney	—	Tuberculosis of lung and intestine
3	46	M	L	Thyroid	Cellular infiltration (interstitial)	Tuberculosis of lung and intestine
4	32	M	L	Thyroid	"	Laryngeal leprosy
5	29	M	L	Thyroid	"	Tuberculosis of lung and intestine
6	54	M	L	Thyroid	"	Laryngeal leprosy
7	49	M	non-L[a]	Thyroid	"	Pulmonary tuberculosis
8	37	M	non-L[a]	Thyroid	"	Pneumonia
9	?	M	L	Thyroid	"	Pulmonary tuberculosis
10	37	M	non-L[a]	Thyroid	Sclerotic kidney	Pulmonary tuberculosis

[a] Leprosy was divided into two main types, i.e., lepromatous and neuromacular (nonlepromatous), in Japanese leprosaria before World War II.

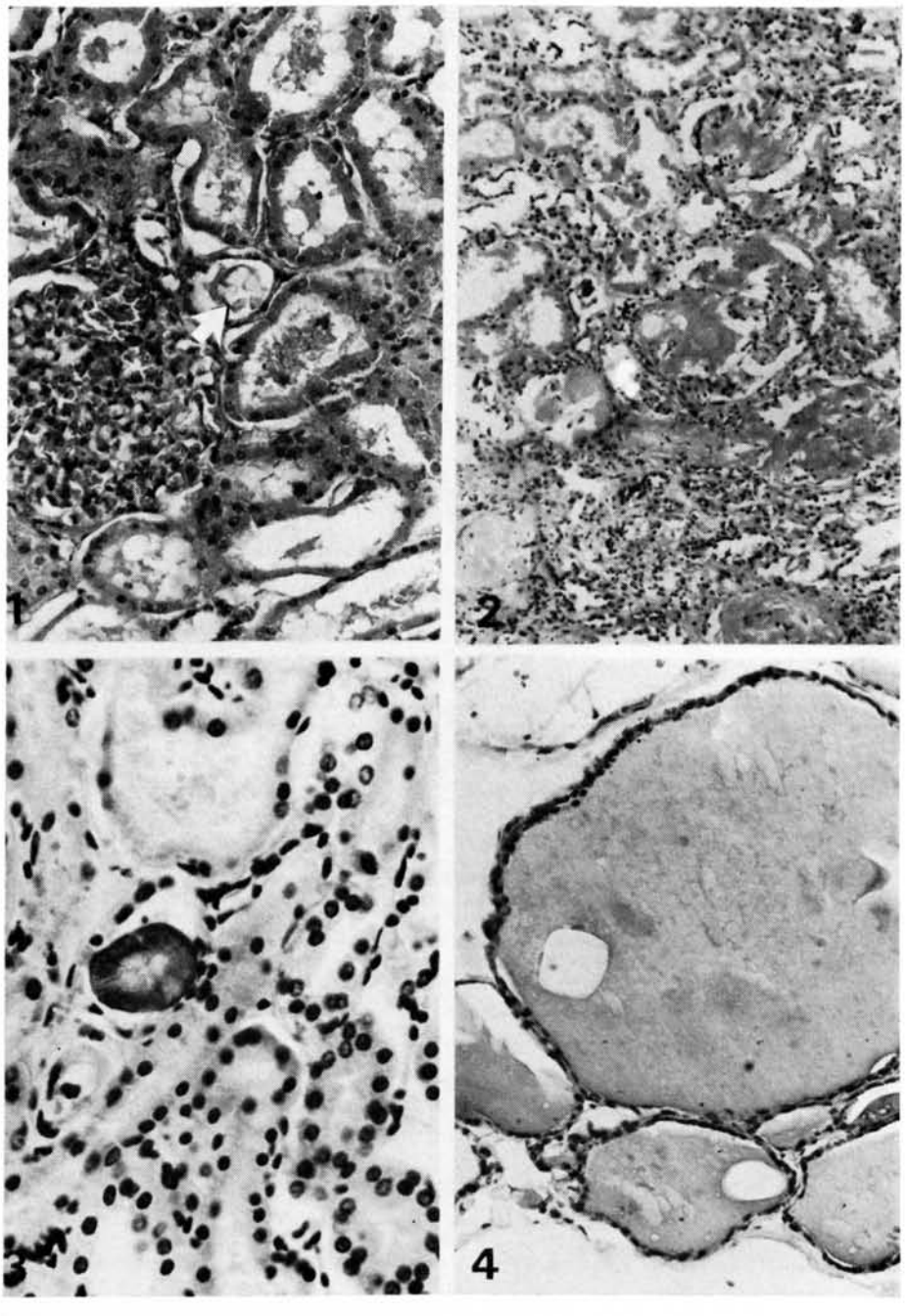

FIG. 1. A crystal in a distal convoluted tubule (arrow) under light microscope. Patient No. 4, Table 3. (Hematoxylin and eosin stain. Magnification X200)

FIG. 2. Amyloid kidney with crystals in a tubule under polarizing microscope. Patient No. 12, Table 3. (Hematoxylin and eosin stain. Magnification X200)

FIG. 3. High magnification of the crystal. Note the radial striations. Patient No. 13, Table 4. (Hematoxylin and eosin stain. Magnification X400)

FIG. 4. A crystal in thyroid follicle. Patient No. 13, Table 4. (Hematoxylin and eosin stain. Magnification X400)

TABLE 3. *Cases showing the crystals in group B.*

No.	Age	Sex	Type[a]	Location of crystals	Renal findings	Cause of death or other main pathologic changes
1	60	M	L	Thyroid	Chronic nephritis Arteriolonephro-sclerosis	—
2	32	M	L	Kidney Thyroid	—	Suicide (cresol poisoning)
3	54	F	non-L	Kidney	Purulent nephritis	Purulent cystitis Carcinoma of uterus
4	39	M	non-L	Kidney Thyroid	—	Carcinoma of liver
5	69	M	non-L	Kidney Thyroid	Amyloid kidney Arterionephro-sclerosis	Pulmonary tuberculosis Liver cirrhosis
6	78	M	non-L	Thyroid	Amyloid kidney Nephrosclerosis	Carcinoma of stomach
7	69	M	non-L	Kidney Thyroid	Chronic pyelone-phritis	Ulcer of stomach
8	53	F	non-L	Kidney	—	Carcinoma of liver Liver cirrhosis
9	70	F	non-L	Thyroid	Pyelonephritis	Cholangiocarcinoma
10	61	M	non-L	Thyroid	—	Pneumonia
11	57	M	L	Kidney Thyroid	Chronic glomerulo-nephritis	Pulmonary tuberculosis
12	38	M	L	Kidney	Amyloid kidney	Pericarditis

[a] The type of leprosy in this table is based on the original description in the protocols of Keifu-en Leprosarium.

and transparent under the light microscope, but sometimes it was yellow or brown. The large ones often showed radial striation, recognizable by light microscopy.

Crystals in the thyroid. Very small crystals were present in the follicles of the thyroid, but they were rarely present in the interstitial tissues. They were colorless and transparent. Their morphology was variable; needle-shaped, sand-like, square, polygonal or irregular. Where they were present, they looked like vacuoles in the follicular colloidal substances by light microscopy.

DISCUSSION

Renal lesion. We considered whether or not the crystals are correlated with the renal changes of patients who suffer from leprosy. It has been reported that this kind of crystals is more frequently found in severe renal lesions. It is generally accepted that the kidney is often affected by bacterial infections but usually not by leprosy itself. Our pathologic examination revealed that nonleprous inflammatory changes of the kidney were present in a considerable number of the autopsied cases, especially in those of group C. Pyelonephritis was the most common([6]). It is not rare that leprosy patients die in uremia. The high incidence of pyelonephritis in group C could have been caused by recurrent bacterial infections. In group A, however, pathologic findings of the kidney were different from that in group C. Earlier reports on autopsies of leprosy patients have agreed as to a high incidence of secondary amyloidosis in the kidney. However, in groups B and C, the incidence of secondary amyloidosis was low. There was no determinable correlation of the appearance of these crystals and leprosy infection of the kidney specifically.

Characteristics of the pathologic changes of each group. Only one case of group A

TABLE 4. *Cases showing the crystals in group C.*

No.	Age	Sex	Type[a]	Location of crystals	Renal findings	Cause of death or other main pathologic changes
1	77	M	T	Thyroid	Chronic pyelonephritis	Carcinoma of pancreas
2	57	M	L	Thyroid	Chronic pyelonephritis Arteriolo-nephrosclerosis	Pneumonia
3	55	M	L	Kidney	Acute glomerulonephritis	Bronchopneumonia
4	46	M	T	Kidney Thyroid	Chronic pyelonephritis	Bronchopneumonia
5	55	M	L	Kidney Thyroid	Chronic pyelonephritis	—
6	64	M	L	Kidney Thyroid	Solitary cyst Chronic pyelonephritis	Malignant lymphoma Carcinoma of stomach
7	74	M	T	Kidney	Chronic pyelonephritis Amyloid deposit	—
8	78	M	T	Kidney	Chronic pyelonephritis	Bronchopneumonia Chronic hepatitis
9	80	F	L	Kidney	Arterionephrosclerosis	Bronchopneumonia Liver cirrhosis
10	40	M	L	Kidney	Nephrosclerosis Hydronephrosis	Malignant lymphoma Liver cirrhosis
11	73	M	T	Thyroid	—	Carcinoma of esophagus
12	63	M	L	Kidney	Renal tubule degeneration Chronic pyelonephritis	Cholangiocarcinoma Hepatic cirrhosis
13	82	M	L	Kidney Thyroid	Benign adenoma	Bronchopneumonia
14	41	M	L	Thyroid	—	Carcinoma of rectum
15	58	M	T	Thyroid	Chronic glomerulonephritis	Carcinoma of stomach Chronic hepatitis
16	57	M	L	Thyroid	—	Carcinoma of pancreas
17	62	F	T	Thyroid	Arterionephrosclerosis	Carcinoma of tongue
18	42	M	L	Thyroid	Pyelonephritis	Death from shock
19	81	F	T	Thyroid	Chronic pyelonephritis Arterionephrosclerosis	Large intestinal ulcer
20	77	M	L	Thyroid	Chronic pyelonephritis	Carcinoma of prostate Carcinoma of urinary bladder
21	74	M	L	Thyroid	—	Bronchopneumonia
22	50	M	L	Thyroid	—	Cerebral hemorrhage
23	73	M	T	Kidney	Chronic pyelonephritis	Hepatic cirrhosis Occult carcinoma of prostate
24	57	M	T	Thyroid	Round cell infiltration	Bronchopneumonia Cerebral hemorrhage

[a] T = tuberculoid; L = lepromatous.

showed the crystals in the kidney. The cause of death in this patient was pulmonary tuberculosis and the structure of the kidney was almost normal. All nine cases with the crystals in the thyroid showed a mild cellular infiltration in the interstitial tissue of the kidney, and five of them died of pulmonary tuberculosis. In group A, malignant tumors were very few in number.

Among the 12 cases of group B showing crystals, carcinoma was found in five. Not all cases showing carcinoma had the crystal in the kidney and/or thyroid. Renal findings in these 12 were mainly nephritis, pyelonephritis and amyloid deposit.

In group C, half of the cases with crystals had pyelonephritis. It is interesting to note the increase in malignant tumors in this group and the complication of more or less serious bronchopneumonia.

Age. The average age of cases with crystals in group A was 41 years. The average age of leprosy patients in Japanese leprosaria has been remarkably lengthened after World War II. The average age of the cases with the crystals in groups B and C was 57 and 63 years respectively. The crystals tend to be found more often in the aged or in cases showing pathologic changes in the kidney, although there were some exceptions.

Causes of crystal formation. Crystals in the thyroid were frequently found in the cases having also malignant tumors especially in group C. When the cause of death was pneumonia or pulmonary tuberculosis, it seems necessary to consider the possible influences of anorexia or respiratory acidosis in explaining the origin of the crystals. We also considered the possible effect of medicine, especially vitamins such as vitamin C ([14]) or vitamin B-6 ([12]) in crystal formation. The history of medical treatment was examined in the protocols of the cases of group C which showed no remarkable renal lesions or malignant tumors in the internal organs. Some of them were not given any vitamin compounds. It was impossible to explain the crystallization of calcium oxalate by the metabolism of vitamins.

It seems likely that destruction of renal tissues might be correlated with the presence of the crystals in the kidney. The most suggestive case in group B was a 32 year old male who committed suicide by taking a large quantity of cresol. Crystals were present both in the kidneys and thyroid of this patient. There were no pathologic changes noticeable in these tissues by light microscopic study, although cresol must have caused dysfunction of renal tubules. This raised the question of how long it takes to crystallize calcium oxalate in the human body. The death of this patient occurred less than a day after taking the cresol. If it is correct to assume that the crystals of the suicide case resulted from renal dysfunction caused by poisoning, then calcium oxalate had to crystallize within a few hours in the kidney and thyroid. The cause of crystallization in this case, however, remains unexplained because we could not confirm the evidence of the renal dysfunction. With respect to the rapidity of crystallization, there has been a suggestive report relating to acute ethylene glycol poisoning ([16]). In this report, calcium oxalate crystals were found in the kidneys and central nervous systems of soldiers who almost all died one or two days after drinking lethal quantities of antifreeze solution of the ethylene glycol type. The same type of crystal was also found in newborn infants with congenital oxalosis ([8]). It might be possible to suppose that calcium oxalate would crystallize in a few hours or days, or at most, within several months.

An 82 year old male patient in group C, who had increased dysacousis ([9]), showed the largest quantity of crystals in the kidney and thyroid. The cause of death was bronchopneumonia. It was this case to which the x-ray diffraction method was applied and the crystals were identified as calcium oxalate monohydrate. The metabolism of oxalate is so complicated that it is difficult to decide the exact process of crystal formation. Special attention was paid to possible disturbances in the metabolism of amino acids such as glycine. The patient had had difficulty in hearing from his youth. This raised the possibility that dysacousis had been correlated with abnormal deposits of oxalate in the neural tissues ([11]).

Crystallization of calcium oxalate is also thought to be closely related to the concentration of oxalate in the serum. Hyperoxalemia would be a preceding condition before producing the crystals in the kidney.

Localization of crystals. The crystals never accompanied pathologic changes of the thyroid, but sometimes accompanied changes in the kidney. This led to the assumption that the cause of crystallization leaves no visible morphologic evidence in the tissues. Our present study was limited to the kidney and the thyroid, because of more frequent localization of the crystals in these organs. The cause of such constant localization of the crystals in certain organs remains unexplained. As for the kidney, it might be supposed that the presence of hyperoxaluria due to some renal dysfunction, for example, poor reabsorption of amino acids through renal tubules might play a role. In some cases such dysfunction would leave no traces in the tissue. In the kidney the crystals were mostly found in the renal tubules of the cortex and rarely in the interstitial tissue. In the case of crytals occurring without reactional cellular infiltration we think that conditions preceding crystallization might have been more harmful than the presence of the crystal itself.

Relation to oxalosis. Oxalosis has been defined as an extra-renal deposit of calcium oxalate crystals. If so, many cases in the present study having crystals might be thought to have had oxalosis ([4]). However, the crystalline calcium oxalate deposition in kidneys and thyroids in these cases seems to have been caused by hyperoxalemia, and for this reason we think it is not suitable to call these cases "oxalosis." The same kind of crystal were found in tissues of nonleprous patients who were autopsied in general hospitals. For this reason, the presence of the crystal seems not to be essentially related to leprosy.

SUMMARY

Polarizing microscopic study of 149 autopsied cases of leprosy patients revealed the presence of crystalline calcium oxalate in the kidneys and thyroid in 46 cases. The presence of the crystal was rare in the kidneys of patients who died in 1943 and 1944. Crystals in the thyroid were frequently found in cases of malignant tumor, especially in the group which died in 1962-1967. The possible relationship of the presence of the crystal to hyperoxalemia, metabolic disturbances of amino acids, oxalosis and medical treatment are discussed. Generally, crystals were found in aged people, in cases with renal lesions, malignant tumor or pulmonary lesions, although there were some exceptions. No definite pathogenic relationship could be made to leprosy.

RESUMEN

Un estudio con microscopio de luz polarizada de 149 casos de autopsia de pacientes con lepra reveló la presencia de oxalato de calcio cristalino en el riñón y tiroides en 46 casos. El cristal se encontró muy pocas veces en los riñones de pacientes que murieron en 1943 y 1944. Los cristales en el tiroides se encontraron frecuentemente en casos de tumores malignos, especialmente en el grupo que murió entre 1962–1967. Se considera la posible relación entre la presencia del cristal e hiperoxalemia, alteraciones metabólicas de amino ácidos, oxalosis y tratamiento médico. En general, los cristales se encontraron en personas de edad, en casos con lesiones renales, tumores malignos o lesiones pulmonares, aunque hubieron algunas excepciones. No se pudo establecer una relación patogénica definitiva con la lepra.

RÉSUMÉ

On a procédé à une étude au microscope polarisant de 149 cas autopsiés de malades de la lèpre. Cette étude a révélé la présence de cristaux d'oxalate de calcium au niveau du rein et de la thyroide chez 46 de ces malades. La présence de cristaux était rare dans les reins des malades décédés en 1943 et 1944. Les cristaux ont été fréquemment observés au niveau de la thyroide dans des cas de tumeurs malignes et particuliérement dans les groupes décédés entre 1962 et 1967. On discute de la relation qui pourrait exister entre la présence de cristaux d'une part, et d'autre part l'hyperoxalémie, les troubles métaboliques des acides aminés, l'oxalose et le traitement médical. En règle générale les cristaux ont été trouvés chez des personnes âgées, de même que chez des cas souffrant de lésions rénales, de tumeurs malignes ou de lésions pulmonaires, encore qu'il y ait eu certaines exceptions. Aucune relation pathogénique nette n'a pu être établie entre ces observations et la lèpre.

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