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Original Articles

Chronic Granulomatous Disease Associated with Peculiar *Aspergillus* Lesions

Patho-Anatomical Report Based on Two Autopsy Cases and a Brief Review of All Autopsy Cases Reported in Japan

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Summary. Chronic granulomatous disease (CGD) is based on the dysfunction of phagocytes and characterized by a comparatively uniform granulomatous lesion caused by organisms which do not produce hydrogen peroxide and which are catalase-positive. This report describes two autopsy cases in children, a nine year-two month-old boy and a ten month-old girl, with the clinical manifestations and autopsy findings of CGD and a brief review of all autopsy cases consistent with CGD reported in Japan.

In these cases, in addition to the usual CGD lesions, there was a markedly different type of granuloma due to *Aspergillus* sp., which consisted of multinuclear giant cells alone, or a caseous center surrounded by giant cells. This peculiar type of aspergillosis may correspond to a primary infection, described as pseudotuberculosis aspergillina. It appears that in some CGD patients, macrophages may function normally and sometimes be more activated by these infections than in the normal body. The histochemical and electron microscopic examination of the present cases and a review of the previous cases suggest that the yellowish brown pigment found seems to resemble a ceroid. It is a product of the degradation of leukocytes and tissue elements with subsequent accumulation in phagocytic histiocytes and is not necessarily peculiar to CGD.

Key words: Chronic granulomatous disease – Pigmented lipid histiocytes – Altered phagocytosis by phagocytes – Aspergillosis – Pseudotuberculosis aspergillina.

Introduction

Chronic granulomatous disease (CGD) is a syndrome characterized by recurrent suppurative infections and granuloma formation of the skin, lung, and reticu-

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loendothelial organs. It was first described independently by Berendes et al. (1957) and by Landing and Shirkey (1957) as a new clinical entity. Since Holmes et al. (1966) demonstrated that CGD was based on a defect in the bactericidal capacity of polymorphonuclear neutrophils in the patients, several types of functional abnormality of leukocytes have been found by many investigators. It is considered at present that the inability of patient's neutrophils to kill some ingested bacteria and fungi derives from defective hydrogen peroxide due to a variety of enzymatic abnormalities (Rutenberg et al., 1977). In addition, the predominant mode of inheritance in the patients was X-linked but recently an autosomal recessive type has been reported (Johnston and Newman, 1977).

Patients with CGD have also been found in Japan (Usui, 1975), but only seven autopsy cases consistent with the diagnosis have been reported thus far (Kobayashi and Konoshita, 1962; Nakayama et al., 1971; Sumiyoshi et al., 1973; Ogawa et al., 1973; Harada et al., 1977; Soejima et al., 1978). This paper presents a study of the pathological examination of two autopsy cases with special attention given to fungal infections, and a brief review of all of the CGD autopsy cases in Japan.

Case Reports

Case 1 (S-3216)

A 9-year, 2-month-old boy. He was born after a normal pregnancy, labour and delivery, weighing 2,900 g. At that time, the father was healthy. However, the mother was found to be a carrier and his sibling, a younger brother, is suffering from the same disease. At the age of 9 months, the patient developed recurrent fever and anaemia. When he was 1 year and 3 months old, he was treated for cervical lymphadenitis and stomatitis. At the age of 1 year and 5 months, he suffered from severe pneumonia with a high fever, and was admitted to Shinshu University Hospital. On admission the intermittent fever persisted, and he had dyspnoea. The breath sounds were diminished. Chest film on admission revealed an abnormal shadow in both lung fields. The leukocyte count was 64,600/mm^3 with a moderate shift to the left. C-reactive protein reaction was five positive. Cultures of blood, urine, gastric juice and material obtained from the pharynx grew no organisms, but he was treated with anti-tuberculous, anti-fungal agents and several other antibiotics with a diagnosis of undetermined pulmonary infection. He was discharged after one year, and did relatively well at home for about two years. At 4 years and 4 months of age, he returned to the hospital because of high fever, cervical lymphadenitis and pneumonia. He was later discharged but was again admitted several times for treatment of suppurative cervical lymphadenitis, liver abscess, perianal abscess and pulmonary infection. When he was 9 years and 2 months of age, an upper-abdominal pain developed and the abdomen became protuberant. He then became unconscious and died. He had suffered from varicella at 1 year and 7 months of age and measles at 4 years and 3 months of age, but both were mild.

Laboratory Studies. Erythrocyte count, 362×10^4/mm^3, leukocyte count, 34,800/mm^3 with 52% segmented neutrophil granulocytes, 23% band forms, 3% monocytes, 22% lymphocytes. Total serum protein was 10.3 g/dl, with 41.7% gamma-globulin. Serum IgG level was 4,800 mg/dl, IgA, 460 mg/dl, IgM, 115 mg/dl, and C-3, 210 mg/dl. Wassermann and tuberculin tests were both negative. Antistreptolysin-0 was negative, RA test was positive, C-reactive protein test was five positive. Cold agglutinin titer was 1:8. Response to DNCB (dinitrochlorobenzene) was slightly reduced. The blastoid transformation ratio of lymphocytes was 65%. Sedimentation rate ranged from 32 to 100 mm in one hour. NBT (nitroblue tetrazolium) test was negative. Electron microscopic examination of his granulocytes after incubation with *Staphylococcus aureus* revealed normal ingestion and a significant reduction of intracellular killing of the bacteria (Fig. 1). Cultures of pus obtained

from each suppurative inflammatory lesion grew *Klebsiella pneumoniae, Serratia marcescens, Staphylococcus aureus* and *Pseudomonas* sp.

Postmortem Examination. He was extremely cachectic, weighing 18.7 kg. Small lymph nodes, up to approximately 1 cm in diameter, were palpable in the cervical, axillary and inguinal regions. A scar of the previous lymph node biopsy was present in the cervical region. Both of the pleural cavities were obliterated by fibrous adhesions. The left lung was relatively firm and showed a few scattered yellowish white nodules surrounded by a hyperaemic area, up to 0.5 cm in diam., on the cut surface. Some of these nodules contained suppurative material in their center. The right lung was basically similar to the left lung, but in the upper and middle lobe, there were a few confluent suppurative lesions approximately 3 cm in diam. (Fig. 2). The liver, weighing 1,250 g, was distinctly enlarged and reddish brown in color, but there were no nodules on gross examination. The spleen, weighing 230 g, was also enlarged and showed numerous grayish white nodules varying in size from a few millimeters to 1 cm in diam. (Fig. 3). Systemic enlargement of lymph nodes was found, and the majority contained focal areas of suppuration. The pancreatico-duodenal, hepatic lymph nodes and thymus (weighing 4.2 g) showed a brownish yellow color. The remaining visceral organs appeared to be normal on gross examination. Cultures obtained from the lung grew *Pseudomonas* sp.

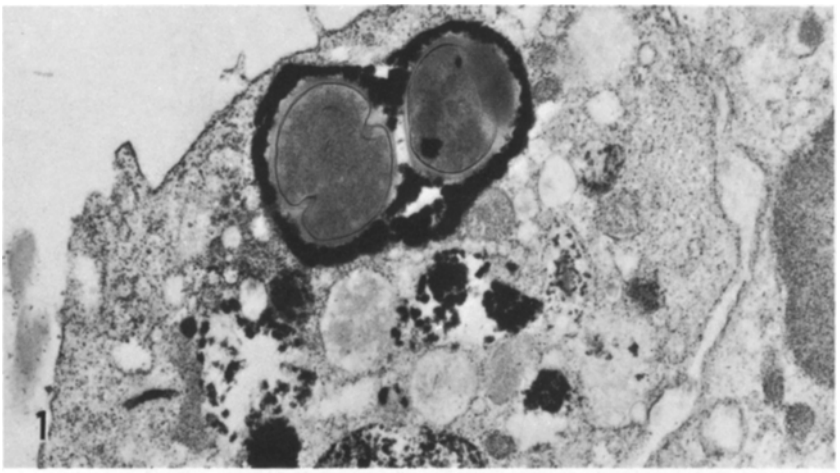
Microscopic examination revealed multiple suppurative granulomata in the lungs, liver, spleen, adrenal glands, bone marrow and various lymph nodes, which consisted of large areas of necrosis and cell debris surrounded by polymorphonuclear neutrophils and large mononuclear cells without multi-nuclear giant cells (Figs. 4 and 5). Specific staining techniques such as Gram, acid-fast and periodic acid-Schiff stains failed to reveal organisms in these lesions.

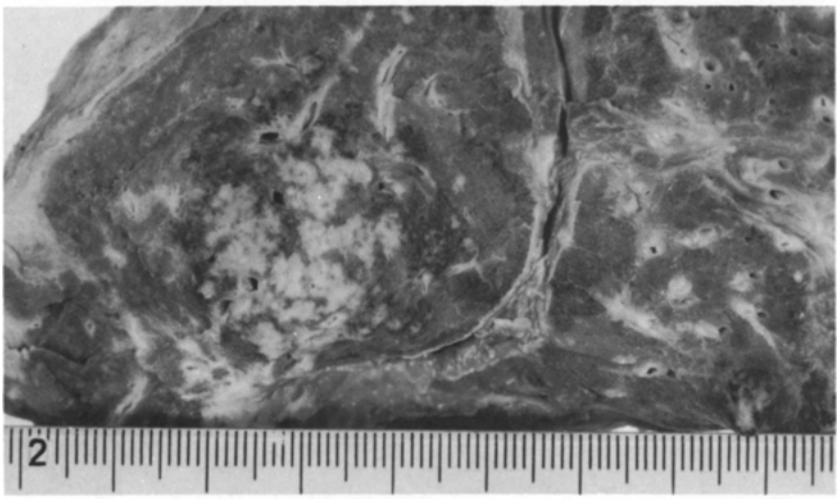
In addition to these lesions, there were scattered minute granulomata present in the lungs, which had a very different appearance. These granulomata consisted of a caseous center and a few multi-nuclear giant cells surrounded by a prominent fibrotic zone (Fig. 6) some of them consisting of a few giant cells only (Fig. 7). These granulomata were related to fungal infection. Most of the giant cells and the caseous center contained a few hyphal elements of unusual shape, which were identified as *Aspergillus* sp. by immunofluorescent techniques (Figs. 8 and 9) (Hotchi, 1967). Pigmented lipid histiocytes (PLH) existed in the various lymph nodes, tonsils, thymus, lungs, liver, spleen, bone marrow and mucosa of the GI-tract. They were most abundant in the thymus, hepatic and pancreatico-duodenal lymph nodes (Figs. 10 and 11) and were also observed at the periphery of the granulomata. Thus although the distribution of PLH seemed to be indefinite in this case it was to some degree, more evident in the regional lymph nodes of those organs in which a large number of granulomatous lesions were present.

Case 2 (S-3016)

A 10-month-old girl. This child was born of an uneventful pregnancy. Beginning at the age of 1 month, erythemas appeared repeatedly on the skin of the face, neck and extremities. She also developed cervical suppurative lymphadenitis with an associated fever, and the lymph nodes were frequently incised. At 7 months of age, she was admitted to Shinshu University Hospital for a further examination of the skin lesions. With a diagnosis of anetodermia erythematosa, she was treated with Cephalexin and cured of these lesions, but during the admission, suffered from acute pyelonephritis and was treated with several antibiotics. She was discharged from the hospital on improvement of the pyelonephritis 1 month after admission. After discharge, she continued to have sporadic episodes of high fever and an abnormal urinalysis. She returned to the hospital 2 months later because she had developed anorexia, vomiting and dyspnoea, and her abdomen protruded. At that time, hepatosplenomegaly existed and the abdomen had become fluctuant. A chest X-ray revealed disseminated miliary shadows throughout the entire lung fields. Several antibiotics and human gamma-globulin were administered, however, her general state became progressively worse and frequent haematemesis appeared. Thirty-eight hours after her readmission, she rapidly became comatose and died.

Laboratory Studies. Erythrocyte count, $305 \times 10^4/mm^3$, leukocyte count, $10{,}200/mm^3$ with 5% metamyelocytes, 56% band forms, 12% segmented neutrophils, 4% monocytes, 23% lymphocytes;





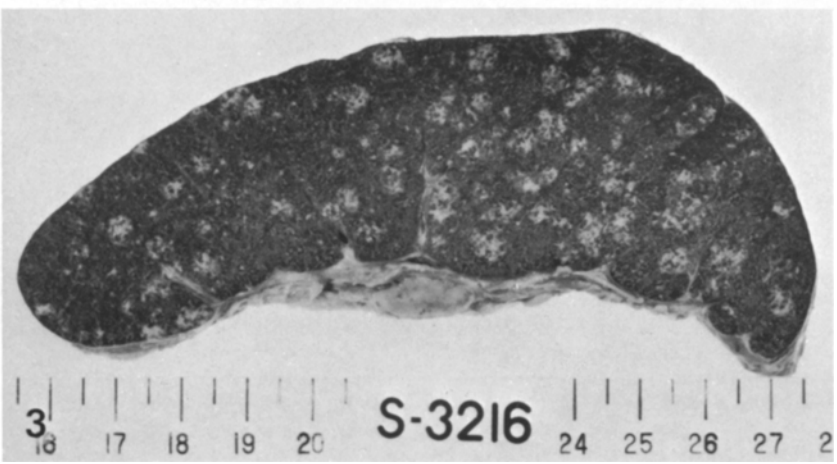


Fig. 1. (Case 1): Electron micrograph of patient's polymorphonuclear leukocyte incubated 1 h with *Staphylococcus aureus*, showing the dark staining acid phosphatase activity surrounding the bacterial bodies in phagosomes. ×15,000 (Courtesy of Dr. A. Komiyama)

Fig. 2. (Case 1): The cut surface of the right lung, showing a confluent lesion of small nodules surrounded by a hyperaemic area

Fig. 3. (Case 1): Multiple nodules existing on the cut surface of the spleen

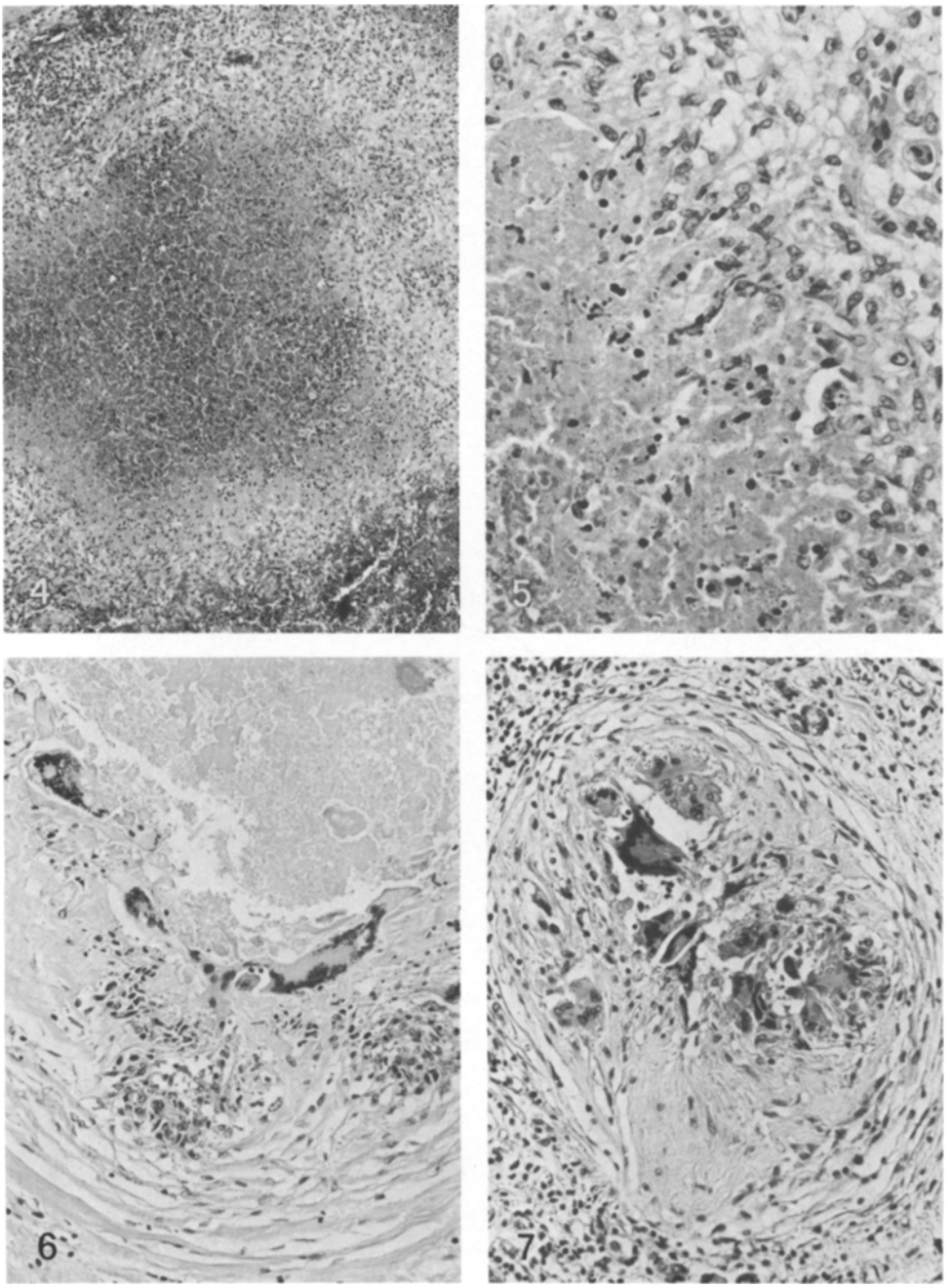
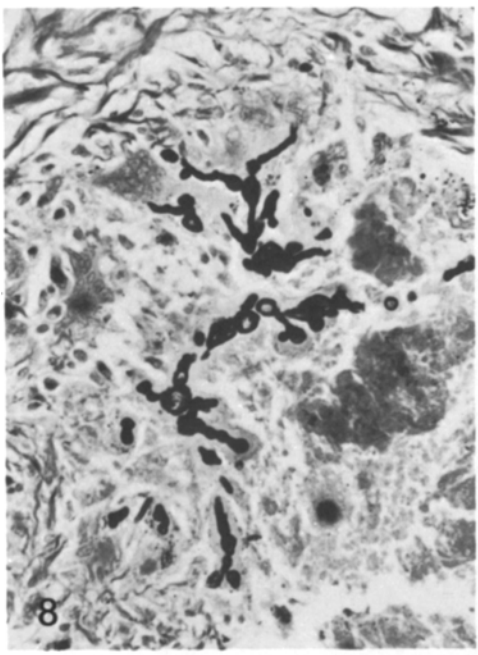


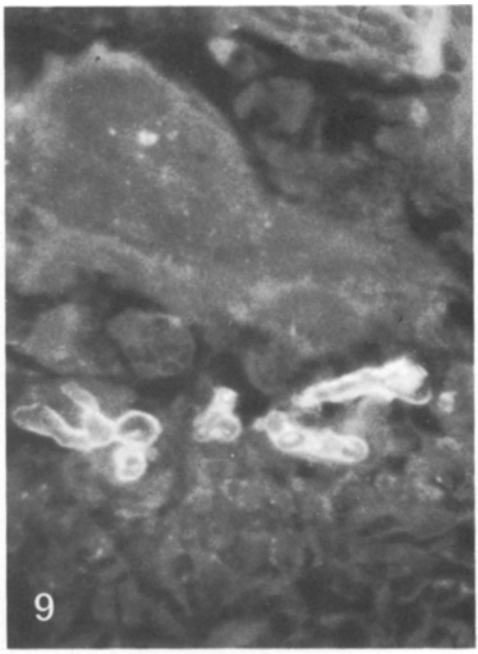
Fig. 4. (Case 1): Typical granuloma of the lung with a large area of necrosis. H.E. ×40

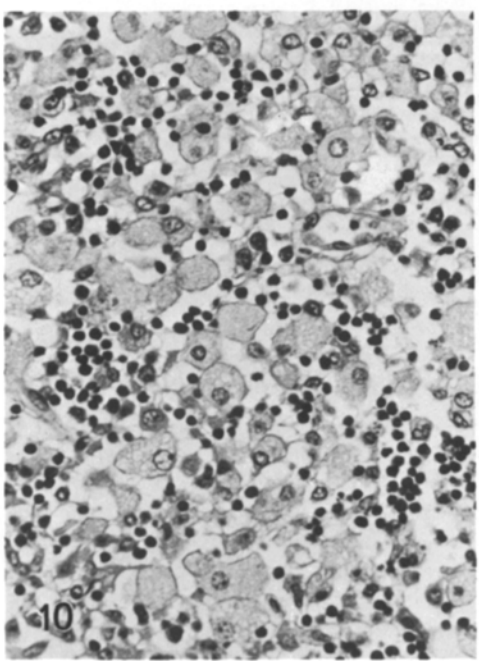
Fig. 5. (Case 1): High magnification of Fig. 4, showing a necrotic area and surrounding large mononuclear cells. H.E. ×200

Fig. 6. (Case 1): Tuberculoid granuloma due to *Aspergillus* sp., showing caseation in the center and a few multinuclear giant cells surrounded by a prominent fibrotic zone, H.E. ×100

Fig. 7. (Case 1): Minute granuloma due to *Aspergillus* sp., consisting of only a few multi-nuclear giant cells and surrounding fibrous tissue. H.E. ×100







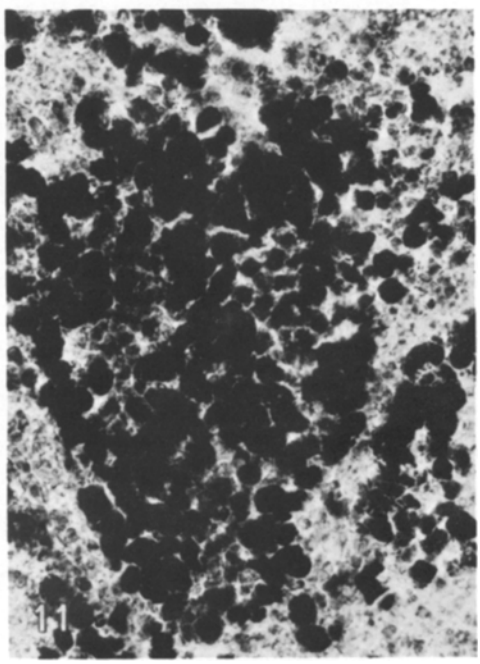
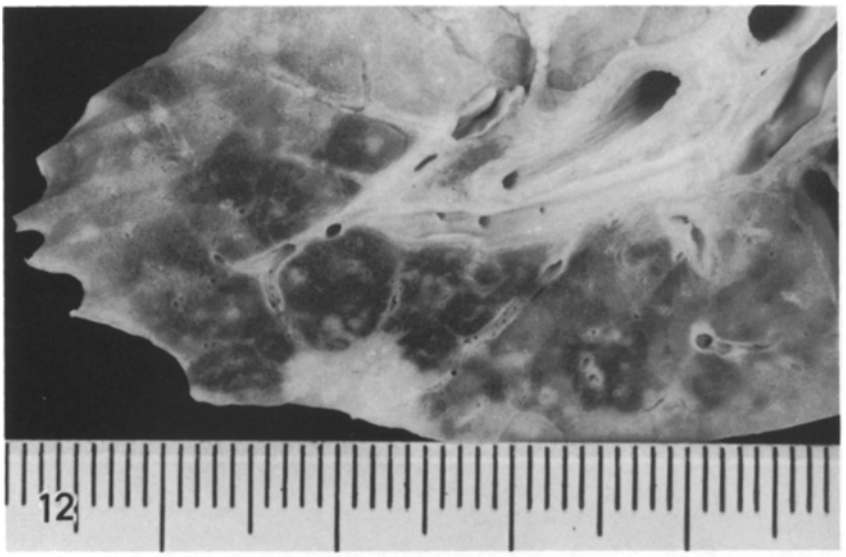


Fig. 8. (Case 1): A few hyphal elements of unusual shape in the *Aspergillus*-granuloma. Grocott's methenamine silver ×200

Fig. 9. (Case 1): Fluorescence of the fungal elements in the granuloma. FITC-labeled anti-A. fumigatus antibody ×400

Fig. 10. (Case 1): Numerous pigmented lipid histiocytes in the hepatic lymph node. H.E. ×200

Fig. 11. (Case 1): Frozen section of the hepatic lymph node, showing numerous sudanophilic pigments in histiocytes. Sudan black B ×100



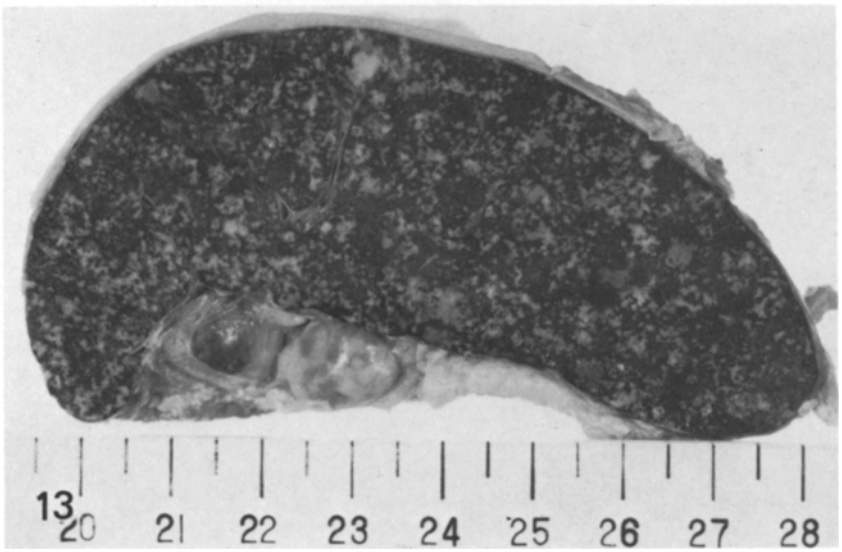
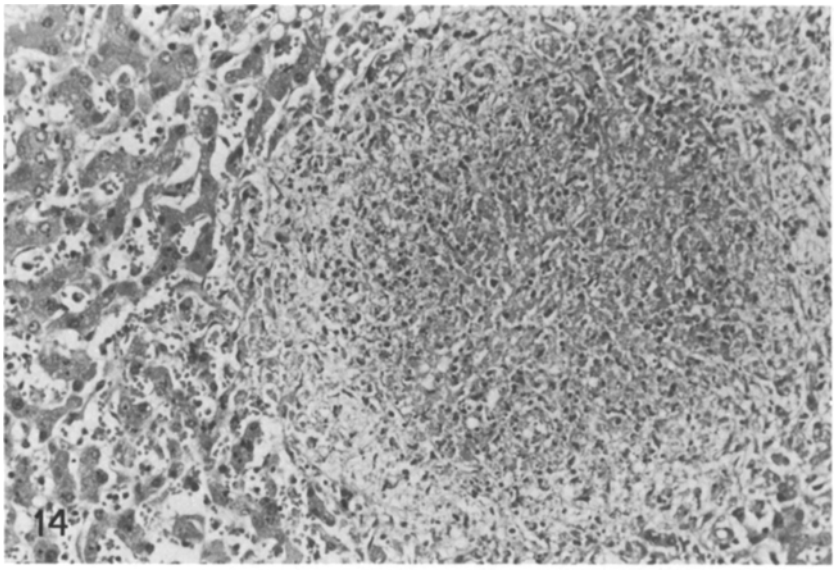


Fig. 12. (Case 2): The cut surface of the left lung, showing scattered round nodules and small consolidated areas

Fig. 13. (Case 2): The cut surface of the spleen, showing fibrous thickening of the capsule and innumerable small nodules

platelet count, $8.8 \times 10^4/mm^3$, bleeding time, 9′30″, coagulation time of blood, 15′. Total serum protein was 7.7 g/dl with 19.6% gamma-globulin. LDH was 2,100 U, GOT, 640 U, GPT, 110 U. Total bilirubin was 8.3 mg/dl. C-reactive protein was five positive. Wassermann and tuberculin tests were both negative. Her sedimentation rate was 57 mm in one hour and 90 mm in two hours. Examinations of leukocyte functions were not performed in this case. Culture obtained from the urine grew *Enterococcus* sp. and the blood cultures grew no organisms.



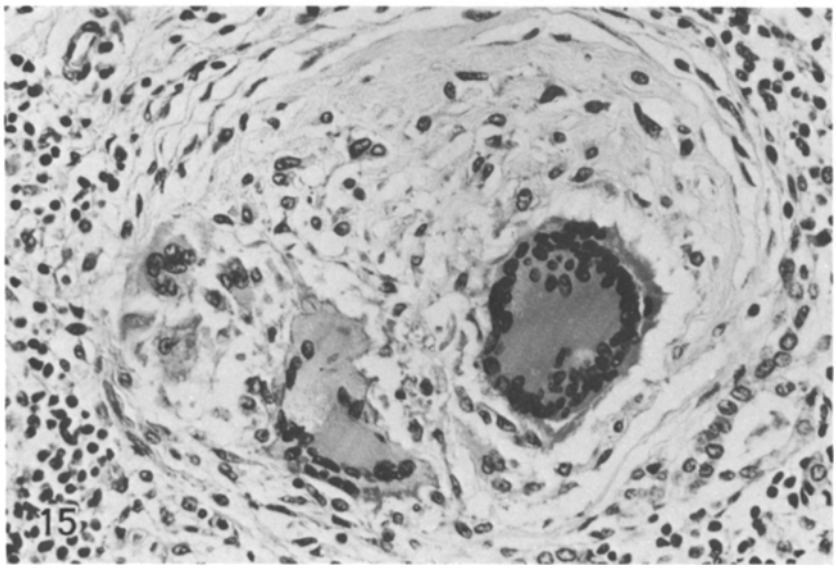


Fig. 14. (Case 2): Typical granuloma of the liver. H.E. $\times 100$

Fig. 15. (Case 2): Minute giant cell granuloma due to *Aspergillus* sp. H.E. $\times 200$

Postmortem Examination. The body was well nourished and the skin was atrophic at the shoulders and all extremities. The external surface of the lungs appeared pale. On the cut surface there were small consolidated areas and scattered nodules (Fig. 12). The liver was grossly enlarged, weighing 610 g. The cut surface of the liver showed a patchy greyish white appearance. The spleen was also enlarged, weighing 50 g. Its capsule was thickened and there were innumerable miliary nodules throughout the cut surface (Fig. 13). The lymph nodes showed a systemic enlargement varying in size up to 1.5 cm in diam. The remaining visceral organs appeared to be grossly normal.

Microscopic examination of the lungs, liver, spleen, kidneys, bone marrow and lymph nodes revealed numerous small granulomatous lesions similar to those found in Case 1 (Fig. 14). In addition, the lower lobe of the right lung showed scattered giant cell granulomata which were sharply circumscribed by fibrous tissue, as in Case 1 (Fig. 15). The hyphal elements of *Aspergillus* sp. existed in most of the giant cells and were identified by immunofluorescent techniques. PLH were also found in the lungs, liver, thymus, bone marrow and lymph nodes, but they were not as numerous as in Case 1. Although examination of leukocyte functions was not performed in this case, both the clinical and pathological findings seemed to be consistent with CGD.

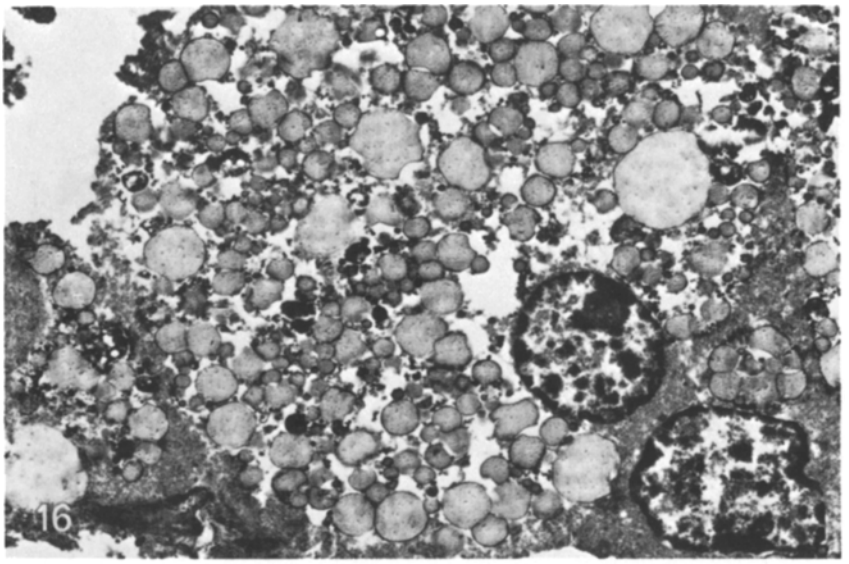
Electron Microscopic and Histochemical Findings of PLH in Both Cases

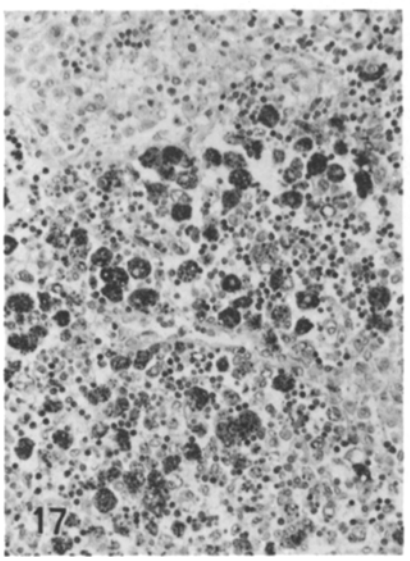
The formalin-fixed lymph nodes obtained from both cases were subjected to an electron microscopic examination. PLH contained a great number of round or ovoid granules in their cytoplasm, which varied widely in size up to 4 μ in diameter, and which were homogenous and of low electron density. A single (limiting) membrane was observed in several portions at the border of the granules (Fig. 16). There were no myelin-like configurations. As summarized in Table 1, the histochemical findings in PLH were almost the same in both cases. The pigment in the PLH was insoluble in ordinary fixatives. It stained

Table 1. Histochemical findings of the pigment in pigmented lipid histiocytes

Staining methods	Result	Staining methods	Result
Methods for fatty substances		Methods for lipofuscin or ceroid	
Sudan III (f. and p.[a])	+	Autofluorescence	+
Sudan IV (f. and p.)	+	Schmorl	±
Sudan black B (f. and p.)	+	Acid-fastness	+
Oil red O (f. and p.)	+	Gomori's chrome alum hematoxylin	−
Nile blue sulfate (f. and p.)	+	0.2% Nile blue sulfate	+
		Leuco-malachite green	+
Methods for cholesterol and cholesterol ester		Miscellaneous	
Liebermann-Schultz	−	Luxol fast blue	+
Modified Romieu	−	Schiff reaction	−
Digitonin	−	PAS (f. and p.[a])	+
		PAS after diastase digestion	+
Methods for fatty acid		PAS after lipase digestion	+
Peracetic acid-Schiff	+	Acetylation PAS	−
Ultraviolet-Schiff	+	Acetylation and deacetylation PAS	+
Holczinger	+	Casella	+
		Alcian blue, pH 2.5	−
Methods for phospholipid		Toluidine blue (pH 2.5, 4.1, 7.0),	
Ciaccio	+	metachromasia	−
Osmium tetroxide alpha		Prussian blue	−
naphthylamine (OTAN)	+	Bleaching method for melanin	−
OTAN after acetone extraction	+	Gmelin	−
OTAN after NaOH hydrolysis	−		
Baker's acid hematein	+		
Okamoto, Shimamoto, Ueda, Kusumoto and Shibata (I, II, III)	+		

[a] f. = frozen section, p. = paraffin section





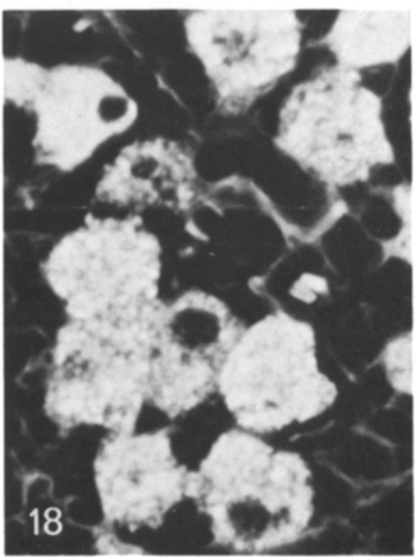


Fig. 16. (Case 1): Electron micrograph of a pigmented lipid histiocyte in the hepatic lymph node, showing numerous round bodies in the cytoplasm. × 1,800

Fig. 17. (Case 1): Paraffin section of the hepatic lymph node, showing sudanophilic pigments in histiocytes. Sudan black B × 100

Fig. 18. (Case 1): Autofluorescence of the pigments in histiocytes in the hepatic lymph node. × 400

positive with Sudan III and other common reagents for the staining of fat in frozen sections and remained sudanophilic even in paraffin sections (Fig. 17). All staining methods for phospholipid resulted in a positive reaction. It failed to show the presence of cholesterol or cholesterol ester. It was positive to the periodic acid-Schiff reaction, and remained so after both diastase and lipase

digestion. In addition, it was acid fast and fluoresced a brilliant yellow green (Fig. 18). Schmorl's ferric-ferricyanide reaction was slightly positive, and Gomori's chrome alum haematoxylin, 0.2% Nile blue sulfate, and leuco-malachite green stains were all positive. Thus, the result indicated that the pigment was an insoluble lipochrome similar to ceroid.

Discussion

Chronic granulomatous disease (CGD) is a rare hereditary syndrome which starts in the early months of life and usually ends in death before adolescence, except in a few cases (Baehner et al., 1968; Moellering and Weinberg, 1970; Rodey et al., 1970; Balfour et al., 1971; Cooper et al., 1972). It was originally termed a fatal granulomatosis of childhood (Berendes et al., 1957) and at present the descriptive term chronic granulomatous disease is used most commonly, even though the disease is based on an abnormality of leukocyte function. The infectious granulomas are produced by a limited number of organisms and their morphological findings are often determined by the causative organism, however, in this syndrome the patients develop a comparatively uniform granulomatous lesion with various organisms which do not normally produce granulomatous infection. Generally, the lesion may consist of a central necrotic area with suppuration, and surrounding mononuclear cell and plasma cell infiltration. Among these cells, giant cells are uncommon. The granulomata vary widely in size, but as indicated in the present cases, their distribution seems to be similar to that of disseminated miliary tuberculosis. Usually in these lesions, there are no organisms which can be identified by routine staining methods (Johnston et al., 1967). In our experimental study, a similar lesion has been produced in the lungs of rabbits treated with cytotoxic agents by inoculating numerous spores of *Rhizopus oryzae* through the trachea (Hotchi and Okada, 1979). This organism is rapidly killed by polymorphonuclear leukocytes in a normal body without any tissue reaction. However, in these animals with a severe leukopaenia or dysfunction of neutrophils, it is likely that macrophages accumulate at the suppurative foci containing the spores of the fungus. These facts have been also reported by Brunn et al. (1976) in an autopsy case of acute disseminated phycomycosis in a less severe form of CGD. Among the organisms cultured from the suppurative foci of patients in the previous reports, *Aspergillus* and *Candida* sp. have been included in some instances (Johnston and Newman, 1977). Holland et al. (1968) reported three cases of fungus infections which consisted of numerous granulomatous lesions originally thought to represent miliary tuberculosis in X-ray findings. Microscopic examination of the lesions revealed a granuloma similar to the lesion described above apart from a few differences in individual characteristics. As a defective candicidal capacity in leukocytes from CGD patients has been reported (Oh et al., 1969), presumably the ability to kill *Aspergillus* sp. might also be impaired. However, Carson et al. (1965) reported two types of granulomas in CGD patients. A part of the descriptions was as follows: "One consists of a caseous center surrounded by a narrow zone of compressed, elongated cells with a deep staining nucleus. Giant cells are extremely rare. The second type of granuloma is apparently related to fungus infection. The wall consists of plump, epitheloid cells

Table 2. All autopsy cases consistent with CGD reported in Japan

No.	Authors	Patient			Hereditary factor	NBT test	Cultured organisms
		Age		Sex			
		yrs	mos				
1.	Kobayashi and Konoshita	3	3	M	+	?	*Candida albicans* *Streptococcus hemolyticus* *Staphylococcus aureus*
2.	Nakayama et al.	2	10	M	+	(−)	*Staphylococcus aureus*
3.	Sumiyoshi et al.	2	4	M	?	?	*Staphylococcus aureus* *Candida albicans*
4.	Sumiyoshi et al.	5	1	M	?	?	*Staphylococcus aureus*
5.	Ogawa et al.	7	1	M	+	(−)	*Staphylococcus aureus*
6.	Harada et al.	2	8	M	?	(−)	
7.	Soejima et al.	1		M	+	(−)	*Streptococcus viridans* *Klebsiella* sp.
8.	Present authors	9	2	M	+	(−)	*Klebsiella pneumoniae* *Serratia marcescens* *Staphylococcus aureus* *Pseudomonas* sp. *Corynebacterium* sp.
9.	Present authors		10	F	?	?	*Enterococcus* sp.

and innumerable giant cells of the foreign body. The center is loose and composed of polymorphonuclear cells and debris. Hyphae are frequently found." In the present cases, as already noted, there was a very different type of granuloma due to *Aspergillus* sp. intermingled with the usual lesions. The granuloma consisted of multi-nuclear giant cells alone or a caseous center surrounded by giant cells. From these findings, it seemed to us that these granulomata were produced by macrophages alone, from their onset. This type of aspergillosis may correspond to the rare primary form described as pseudotuberculosis aspergillina (Reiss, 1954). It has been reported that in CGD patients the polymorphonuclear neutrophils not only show an inability to kill bacteria, but that macrophages also show the same inability (Baehner et al., 1968; Davis et al., 1968; Rodey et al., 1969; Vildé and Vildé, 1976). However, as Mandell and Hook (1969) reported, macrophages from the patient do not have the same defect and are capable of ingesting and killing *Staphylococcus aureus* normally. In some CGD patients, macrophages may function normally and sometimes be more activated by infections than in the normal body. Thus, the fungal lesions will vary widely in microscopic appearance, according to the general condition of the patients.

The histochemical findings concerning PLH in our cases were basically the same as those in previous reports (Bartman et al., 1967; Harada et al., 1977), and the stainings for ceroid showed positive results. Electron microscopically,

Table 2 (continued)

No.	Other conspicuous laboratory findings	Involved organs	Organs with PLH
1.	Leukocytosis, hypergammaglobulinaemia	Lungs, spleen, kidneys, thyroid, skin, intestine, lymph nodes	Spleen?
2.	Leukocytosis, anaemia	Lungs, liver, spleen, diaphragm, peritoneum, lymph nodes	Spleen, lymph nodes
3.	Leukocytosis, hypergammaglobulinaemia	Lungs, liver, heart, pleura, lymph nodes	Liver, spleen, stomach, intestine, tonsils, bone marrow, lymph nodes
4.	Leukocytosis, hypergammaglobulinaemia	Lungs, liver, spleen, kidneys, intestine, lymph nodes	Liver, spleen, thymus, tonsils, stomach, intestine, lymph nodes
5.	Leukocytosis, hypergammaglobulinaemia	Lungs, liver, spleen, lymph nodes	Lungs, liver, spleen, lymph nodes
6.		Lungs, liver, spleen, intestine, bone marrow, skin, lymph nodes	Liver, spleen, thymus, bone marrow, lymph nodes
7.	Leukocytosis, hypergammaglobulinaemia	Lungs, liver, spleen, kidneys, lymph nodes	(−)
8.	Leukocytosis, hypergammaglobulinaemia	Lungs, liver, spleen, adrenal glands, bone marrow, lymph nodes	Lungs, liver, spleen, tonsils, thymus, bone marrow, stomach, intestine, lymph nodes
9.	Leukocytosis	Lungs, liver, spleen, kidneys, bone marrow, lymph nodes	Lungs, liver, thymus, bone marrow, lymph nodes

the granules in PLH were less electron dense and more homogenous than those in previous reports (Bartman et al., 1967; Harada et al., 1977), but the simple structures were quite similar. Therefore, the present study indicates that the pigment is an insoluble lipochrome which consists of a complex of unsaturated fatty acids, phospholipids and glycoproteins as reported by Harada et al. (1977) and it is likely to be most similar to ceroid (Maeda, 1967). From evidence of a bactericidal deficiency in monocytes in the patients, Harada et al. (1977) noted the functional defects in macrophages as a possible cause of PLH. However, as mentioned above, macrophages in the patient do not always show the same defect. In addition, a lipochrome with a staining characteristic similar to PLH has often been observed in macrophages in the regional lymph nodes of organs with a necrotizing malignant tumour. It is therefore likely that the pigmented granulations in the macrophages are not peculiar to CGD and may be products of the degradation of leukocytes and tissue elements with subsequent accumulation in the phagocytic histiocytes.

The nine autopsy cases in Japan are summarized in Table 2. All of them were children under ten years of age. They showed a similar distribution of

lesions and also of PLH except for one case where PLH were absent. Organisms cultured during their clinical course seemed to be almost the same as those in previous reports from other countries (Johnston and Newman, 1977). The leukocyte functions of four patients (3 males and 1 female) have not been examined but they are fully consistent with CGD regarding their clinical course, the laboratory and autopsy findings. The second case in our report may be the first female autopsy case in Japan. In previous papers, CGD has been described as a septic infection based on the dysfunction of phagocytes and characterized by a comparatively uniform granulomatous lesion caused by several low- or non-virulent organisms. However, since the incidence of *Aspergillus* lesions in the present cases differs from the CGD cases previously reported in which *Aspergillus* lesions were absent, it is suggested that in CGD patients, tissue reactions of different type may also develop depending on the influence of various organisms.

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