TECHNICAL REPORT
07 - 59
業 績 報 告 書

AN AUTOPSIED CASE OF LETTERER-SIWE'S DISEASE

LETTERER-SIWE 病の一剖検例

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ATOMIC BOMB CASUALTY COMMISSION
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INTRODUCTION

Letterer-Siwe's disease was first reported as Aleukemische Reticulose by Letterer[1] in 1929, and in 1936 Abt u. Denenholz[2] named it Letterer-Siwe's disease. Approximately 50 cases had been reported until 1954 in Europe and America. but in Japan the case reported by Furuta[3] of Hiroshima ABCC in 1952, was the first, and only about 20 cases[4-22] have been reported to date.

This disease appears to be a reticulo-endotheliosis that arises during infancy and manifests itself clinically by cutaneous eruptions, hepato-splenomegaly, anemia, hemorrhagic diathesis, generalized enlargement of lymphatic glands and osseous changes. The course is rapid and the prognosis is poor, but there are increasing numbers of reports to the effect that the disease responds fairly well to steroid hormone and antibiotics.

This report is a case of Letterer-Siwe's disease that failed to respond significantly to steroids and to antibiotic therapy.

CASE REPORT

The patient was an eleven-month old baby boy whose chief complaints were abdominal distension and weakness.

PAST HISTORY Weight at birth was 3 kg. There was nothing remarkable during pregnancy or at the time of birth. On the third day after birth, he developed severe diarrhea which promptly subsided. He was able to follow things with his eyes, smile and hold his head erect at 3 months. Dentition commenced when he was 8 months old. At that time he could neither sit nor crawl by himself but understood well what his parents said to him.

PRESENT ILLNESS According to the mother, the child's complexion was poor from birth, but was clinically well until 6 months

緒言

Letterer-Siwe病は，最初1929年にLetterer[1]によってAleukemische Reticuloseとして報告され，1936年にAbt u. Denenholz[2]がLetterer-Siwe病と命名した．欧米では1954年までに約50例の報告があるが，本邦では，1952年に広島ＡＢＣＣの古田等[3]が報告した症例を第１例として現在までに約20例[4-22]の報告があるに過ぎない．

本症は乳児期に生ずる細網内皮症であると考えられ，臨床的には皮疹，肝脾腫，貧血，出血傾向，全身淋巴腺腫脹及び骨の変化を来し，その経過は早く予後も不良であるが，本症がステロイドホルモン及び抗生物質にかなり良く反応する旨の報告が多くなっている．

本報告では，ステロイド及び抗生物質に有意に反応しなかったLetterer-Siwe病の１症例について報告する．

症例

患者は生後11箇月の男児で，その主訴は腹部膨隆と衰弱であった．

既往歴：

生下時体重は３kgで，妊娠中或は出産時には特記すべきことはなかった．生後３日目に重症下痢を経過したが，それは間もなく治った．３箇月の時には凝視，微笑及び頸の頭部支持が可能であった．８箇月の時に乳歯の発生をみた．その頃には，坐ったり這ったりすることは出来なかったが，両親の言うことは良くわかった．

現病歴：

母の言によると生来顔色のよくない子供であつたが，生後６箇月までは臨床的には異常がなか

after birth. Watery diarrhea began at about 7 months of age but subsided in about one month after powdered milk was substituted for breast feeding. However, fever of 38°C developed and continued during most of the subsequent course and he became more pale, was fretful, cried almost constantly, and slept very poorly. At about 9 months of age he developed a serous secretion from his external ears and small tissue growths were noted in the external auditory canals. On October 20, radical operation of the right middle ear was performed. The mastoid process was filled with a tumor. The mastoid cells and wall of the external auditory meatus were partially destroyed. The surgical pathology report was "tumor showing acute and chronic inflammation, probably non-chromaffin paraganglioma" ([redacted]). At the same time, he developed generalized enlargement of lymphatic glands, most pronounced in the cervical region. Perspiration, abdominal distension, seborrhea of the head and weakness of his legs developed, and he received transfusions of 50 cc. of blood 12 times. Second biopsies from the right retroauricular incised wound and tumor of left external auditory meatus on November 11, were diagnosed as "reticulo-endotheliosis, compatible with Letterer-Siwe's syndrome" ([redacted]). (Figure 1) Many "boils" appeared over the back of his head, neck, back, buttocks and axillae. At 11 months of age he was given radium irradiation to the cervical lymph nodes for 10 days and the swelling of the nodes decreased. Edema appeared on his face and legs when he was occasionally carried on his mother's back. His appetite remained fairly good but his diet consisted mainly of powdered milk. He was first seen in the clinic in the 5th month of his disease at the age of 11 months.

FINDINGS AT TIME OF HOSPITALIZATION He was very poorly developed and nourished. Body temperature was 37.9°C; pulse, 100; respiration, 40. He was extremely listless with almost no spontaneous activity of his extremities. He cried constantly in a weak, grunting manner. His skin was coarse, dry and loose. Light brown, papular rice

った．生後7箇月頃に水様下痢が約1箇月間続いたが，母乳から粉乳にかえるとこの下痢は治った．しかし，その後38℃の発熱が続き，顔色は一層悪くなり，気嫌が悪く，絶えず泣いていて睡眠は非常に不良であった．生後約9箇月の時に両外耳より漿液性分泌物があり，両外耳道に小さい腫瘤が認められた．10月20日に右中耳の根治手術が行なわれ，乳様突起部には腫瘍がつまっていた．乳様蜂窩及び外耳道壁の一部は破壊されていた．外科的標本の組織学的検査報告は“急性及び慢性炎症を示す腫瘍，恐らく非クロム親和性旁神経節腫”([redacted])であった．同時に全身の淋巴腺腫脹を生じ，それは頸部で最も著明であった．発汗，腹部膨隆，頭部脂漏及び両脚の衰弱があり50ccの輸血を12回受けた．右耳後方の切開痕及び左外耳道の腫瘍の第2回の生検を11月11日に実施し，その結果“Letterer-Siwe 症候群に一致する細網内皮症”([redacted])の診断が下された(図1)．多数の“癤”が後頭部，頸部，背部，臀部及び腋窩部に生じた．生後11箇月に頸部淋巴節に対するラジウム照射を10日間受け，淋巴節腫脹は減少した．時々母に背負われると，顔や両脚に浮腫が現われた．食欲は引続きかなり良好であったが，食餌は主として粉乳であった．生後11箇月の時発病して5箇月目に当所で初診を受けた．

入院時所見：

発育，栄養共に非常に不良である．体温37.9°C；脈搏 100；呼吸40．全く活気がなく，四肢の自発的活動は殆んど認められず，弱々しく泣く．皮膚は粗雑，乾燥，弛緩し，軀幹，両手掌及び両足底部に淡褐色の米粒大の皮疹を散見する．全筋肉は柔軟で緊張を失っている．頭部に脂漏性湿疹があり，大泉門は一横指触れる．著明な可動性無

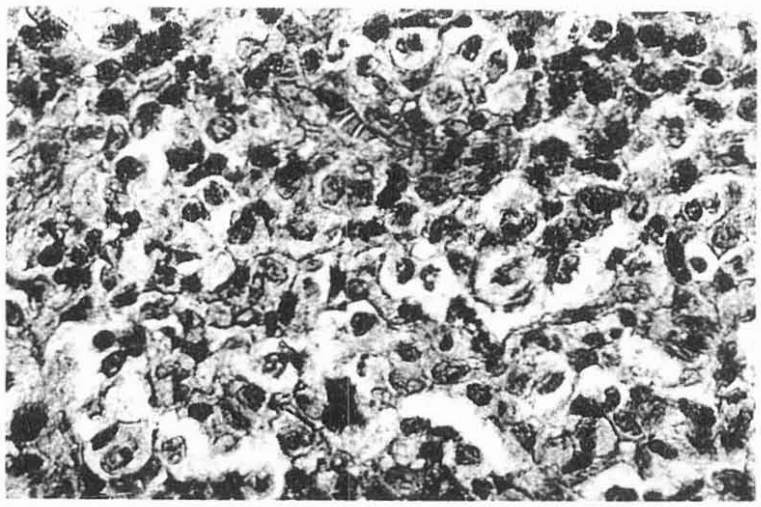

Figure 1 Surgical specimen taken from right retroauricular incised wound

図1 右耳介後部切開創の外科的標本の病理検査 ([redacted]) (x 400)

grain-size skin eruptions were scattered over his body, including the palms of his hands and soles of his feet. All muscles were soft without tension. A seborrheic eruption was noted on his head. The anterior fontanel was palpable at one fingerbreadth. Marked painless, movable enlargement of lymphatic glands were found in the neck, axillary region and inguinal region. The largest nodes in his neck measured 2 x 4 x 4 cm. in size. Both external auditory meatuses were closed by a granulating, inflamed lesion of the external canal which oozed serous fluid. No abnormalities were found in the oral cavity and he had four upper and four lower teeth. Examination of nose, throat, heart, lungs and thorax was normal. Abdominal distension was remarkable with thin dilated veins in the abdominal wall. The navel did not protrude. Circumference of the abdomen was 48.5 cm., but no ascites was detected. Peristaltic sounds were normal. Marked hepatosplenomegaly was evident, with the liver 4 cm. below the costal margin on the right side and the spleen felt 7 cm. below on the left. Several painless, movable masses, the size of soy beans, were palpated on rectal examination and were thought to represent

痛性淋巴腺腫脹が頸部，腋窩部及び鼠径部に見られる．頸部で最大の結節の大きさは２×４×４cmである．両外耳道は肉芽性炎症性外耳道病変によって閉塞され，漿液性分泌物を認める．口腔に異常を認めず，歯牙は上下４本宛である．鼻，咽喉，心臓，肺及び胸廓はいずれも正常である．腹部は著明に膨隆し，腹壁静脈の軽度の怒張がある．臍は突出していない．腹囲は48.5cmであるが，腹水は認められない．蠕動音は正常である．著明な肝脾肥大を認め，肝臓は右季肋下４cm，脾臓は左季肋下７cm触れる．直腸触診により大豆大の可動性無痛性腫瘤を数箇触れ，骨盤淋巴結節腫脹であると思われる．

pelvic lymph node enlargement.

X-RAY FINDINGS P-A lateral of the chest, long bones, and pelvis showed no abnormality except for enlarged thymus. Flat plate of abdomen showed splenomegaly. Skull series and films of the mastoid areas showed actual loss of bone in the region of the squamous portion of the temporal and mastoid areas on both sides.

LABORATORY FINDINGS

Hematology Hgb 4.4 gms. %; RBC 1,600,000 /cu.mm.; hematocrit 16%; MCV 100.0; MCHC 27.5; reticulocytes 20.3%; WBC 6,250/cu. mm., with Segs 83%; Stab forms 1.5%; lymphs 13.5%; monocytes 1.0%; eosinophils 0.5%; myelocytes 0.5%; one normoblast/100 WBC were seen on the smear. Platelets 80,000/cu mm., bleeding time 2-½ min.; coagulation time (Lee-White) 4 min.; prothrombin time 14.6 seconds. Erythrocyte osmotic fragility normal (begin 0.48% saline and complete 0.38% saline). Erythrocyte mechanical fragility 5.55%. Serum Vit. B_{12} 115.5 μμg/ml (normal). Serum iron 48 μg/ml with unsaturated iron binding capacity of 123 μg/ml.

Blood Chemistry NPN 16.2 mg.%; glucose 92 mg.%; total protein 6.2 gm.% with 3.8 gm.% albumin and 2.4 gm.% globulin; serum cholesterol 118.3 mg.%; bilirubin 76 mg.%; serum calcium 10.0 mg.% serum phosphorus 4.09 mg.%; serum alkaline phosphatase 4.89 Shinowara-Jones units.

Urinalysis Negative.

Bacteriology Culture of retroauricular discharge revealed proteus bacilli, staphylococcus aureus, and non-hemolytic streptococci. A urine culture revealed Klebsiella pneumoniae and proteus bacilli in moderate number (7000 colonies/ml). Culture of an infected skin lesion revealed a staphylococcus aureus, coagulase positive. Agglutinins to typhoid, paratyphoid, brucella and proteus were negative. Skin tests to histoplasmin and coccidioidin were negative.

X線検査所見： 背腹方向及び側面方向胸部X線検査，長骨X線検査および骨盤X線検査では胸腺肥大を除いてはいずれも異常を認めない．腹部単純撮影像では脾腫を認める．頭蓋X線検査及び乳様突起部X線検査では，両側頭鱗部及び乳様突起部の骨が欠損しているのを認める．

臨床検査所見

血液学的検査： 血色素量4.4ｇ％;赤血球数1,600,000 /mm³; ヘマトクリット16%; 平均血球容量100.0 μ³ ; 平均血球血色素濃度27.5%; 網状赤血球20.3%; 白血球数6250 / mm³ で分葉核球83%; 桿状核球1.5 %; 淋巴球13.5%; 単球1.0 %; 好酸球0.5 %; 骨髄細胞0.5 %; 塗抹検査で白血球100 につき常赤芽細胞1 を認める．血小板数 80,000 / mm³, 出血時間2.5 分; 凝血時間（Lee-White 法）4分; プロトロンビン時間14.6秒; 赤血球の滲透圧に対する抵抗は正常.（溶血開始は食塩水0.48%, 溶血完結は，食塩水0.38%), 赤血球の機械的作用に対する抵抗は5.55%. 血清ビタミンB_{12}は115.5 μμg/mℓ（正常）．血清鉄は48 μg/ 100 mℓ で不飽和鉄結合能は123 μg/ 100mℓ.

血液化学的検査： 残余窒素16.2mg%; 血糖92mg%; 蛋白総量6.2ｇ %で，アルブミンは3.8ｇ%; グロブリンは2.4ｇ%; 血清コレステロール118.3 mg%; ビリルビン76mg%; 血清カルシューム10.0mg%; 血清燐4.09mg%; 血清アルカリ性フオスフアターゼ4.89 Shinowara-Jones 単位.

検尿： 陰性

細菌学的検査： 耳介後部の分泌物培養検査では変形菌，黄色葡萄状球菌及び非溶血性連鎖状球菌を認める．尿培養検査では中等数の肺炎桿菌及び変形菌を認める（1mℓにつき7000集落）．感染を生じている皮膚病変部の培養検査では，凝血促進酵素陽性の黄色葡萄状球菌を認める．チフス，パラチフス，ブルセラ菌及び変形菌に対する凝集素をいずれも認めない．ヒストプラスミン及びコ

Bone Marrow Marrow was cellular with some increase in erythroid elements (M/E ratio 1.2). Many large cells suggesting reticulum cells were seen in bone marrow aspirate. (Figure 2)

クチジオイディンに対する皮膚検査はいずれも陰性である.

骨髄検査： 骨髄は細胞に富み赤血球系細胞が若干増加している（M/Eは1.2）. 細網細胞を

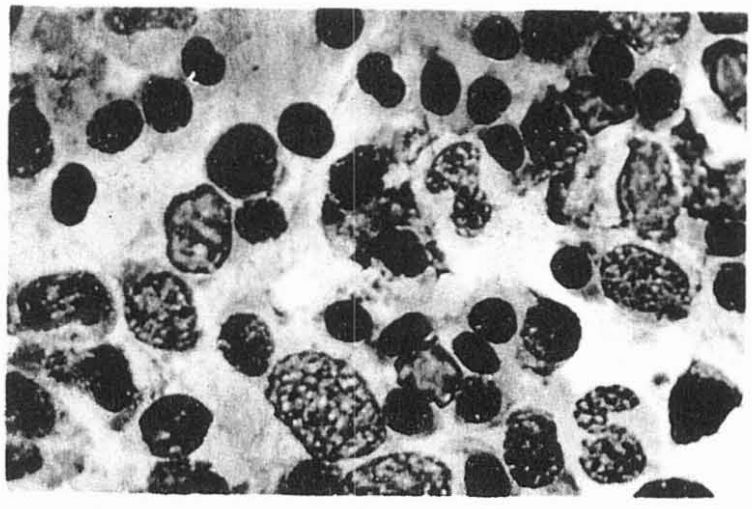

Figure 2 Bone marrow smear (oil immersion) Focus of proliferated reticular cells, mingled with normoblasts (Giemsa stain)

図2 骨髄塗抹像（油浸） 増殖細網細胞巣と常赤芽球を所々認める（ギームザ染色）

CLINICAL COURSE A third surgical biopsy specimen was taken from the skin of the left chest on December 12 and diagnosed as "reticular cell invasion of skin, compatible with Letterer-Siwe's disease" ([redacted]).

During hospitalization, the fever fluctuated between 36.7 and 38.4°C daily. Treatment was started with prednisone, 20 mg/day; intramuscular injection of 200,000 units of penicillin at 12 hour intervals; intramuscular injection of 0.4 gm. of chloromycetin at 8 hour intervals and oral administration of iron preparation three times a day. Calamine lotion was applied to the skin and polymyxin solution was placed into the external auditory meatus after cleansing. During this time, blood transfusions of 150 cc were given twice, resulting in a sudden improvement of the general physical condition. He started to move his hands and legs actively. Enlargement of the cervical lymphatic glands decreased. He seemed generally

思わせる多数の大きい細胞が骨髄穿刺液に認められる.（図2）

経過：

12月12日に左胸部の皮膚について第3回の外科的標本の病理的検査を実施し，“細網細胞の皮膚侵襲があり，これはLetterer-Siwe病に一致する”（[redacted]）と診断した.

入院中36.7°-38.4°Cの間を上下する熱が毎日続いた. 治療としては1日20mgのプレドニソンの投与，20万単位のペニシリンの12時間置きの筋注，クロロマイセチン0.4gの8時間置きの筋注，及び鉄剤の1日3回の径口投与が始められた. 又皮膚にはカラマイン液を塗布し，外耳道には清掃後ポリミキシン液を点滴した. その間150ccの輸血を2回与えたところ，急に全身状態の改善を見て手足を活発に動かすようになり，又頸部淋巴腺腫脹も減じた. 全般的な軽快が認められたように思わ

improved and was discharged after 2 weeks of treatment.

れたので治療2週間後に退院した.

Prednisone, chloromycetin and iron syrup administration was continued after discharge from the hospital, but about 3 weeks after discharge, he developed anorexia, nasal discharge, high fever and generalized hemorrhagic skin eruptions and was re-hospitalized.

退院後プレドニソン，クロロマイセチン及び鉄シロップを投与し続けたが，退院後約3週間してから食思不振，鼻汁，高熱及び全身の出血性皮膚発疹を来し，再入院した.

At the time of the final admission, his face was completely dull and edematous. Rumpel-Leede phenomenon was questionably present. Rice grain-size skin eruptions scattered over the entire body, developed into ecchymoses and the garter marks around the legs became circular ecchymoses. (Figure 3) The spleen had increased in size, 10 cm., but the liver and the cervical lymphatic glands were of the same size as before treatment. The otitis had improved and reddening of the bilateral eardrums was seen. Auscultation revealed no abnormalities of the lung and heart.

再入院時顔貌は全く鈍で浮腫を認めた．ルンペル・レーデ現象は疑陽性であった．全身の米粒大丘疹は溢血斑となっており，靴下用のゴムバンドの痕跡も円形の溢血斑となって脚に認められた.（図3） 脾臓は10cmで増大していたが肝臓及び頸部淋巴腺はいずれも治療を受ける前と大きさは同じであった．中耳炎は軽くなり両鼓膜の発赤が見られた．聴診上肺及び心臓に異常はなかった.

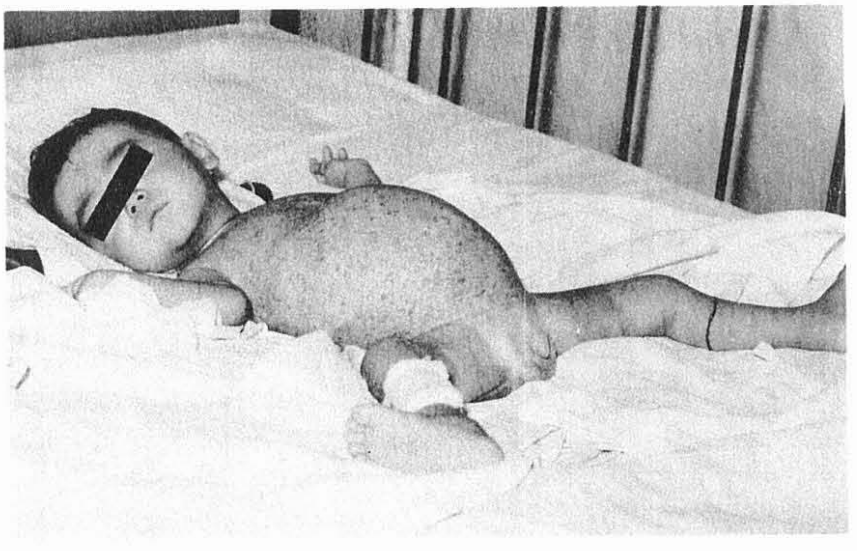

Figure 3 Hemorrhagic skin eruptions

図3 出血性皮疹

Administration of prednisone was again increased to 20 mg/day and 215 mg. intramuscular injection of kanamycin at 12 hour intervals was started, but fever of 40°C continued. Cyanosis of fingers and toes developed; he was placed in an oxygen tent, but he died on the sixth day after hospitalization.

再びプレドニソンを1日20mgに増量し，カナマイシン 215mgを12時間毎に筋注したが40℃の熱が続き手指及び足趾にチアノーゼが生じた．酸素テントを用いたが，入院後6日目に鬼籍に入つた．

AUTOPSY FINDINGS Although a complete autopsy was performed, only pertinent findings are recorded here.

剖検所見：

完全な剖検を行なつたが，ここには関係のある所見のみを記録する．

GROSS FINDINGS The body length was 71 cm. and the weight 7650 gm. Many small, dark red papules up to 0.3 cm. in diameter were scattered on the skin of the chest, abdomen, back and proximal lower extremities.

肉眼的所見： 身長71cm．体重7650 g．胸腹部，背部及び両下肢の上半部の皮膚に多数の暗赤色の直径0.3 cm迄の小隆起が散在している．

The abdominal cavity contained 20 cc. of slightly turbid pale brown fluid. Numerous small dark red papules were present on the intestinal serosa.

腹腔には軽度に混濁した淡褐色の20ccの液をいれる．腸管の漿膜面に多数の小暗赤色斑が散在する．

The lymph nodes were considerably enlarged, measuring up to 6 cm. in greatest dimension, in the cervical and intra-abdominal regions. Some nodes were soft and dark violet with yellow dots. Others were fluctuant, grayish yellow and exuded yellow, pus-like fluid on sectioning.

淋巴節は，相当腫大し，頸部及び腹腔内部においては，最大6 cmに及んでいる．あるものは軟く，暗紫色で，黄色斑点を有する．他のものは波動性，黄灰色で，割面より黄色の膿様物が流出する．

The spleen was greatly enlarged, weighing 380 gm. (40 gm. predicted for age). Its surface was dark red and the organ was firmer than usual. On sectioning there were numerous irregular gray-white nodules slightly larger than Malpighian bodies.

脾臓は380 g （この年令では通常40 g である）で，非常に腫大している．被膜は暗赤色で，硬度は普通より硬い．割面ではマルピギー小体よりやや大きい不整形の灰白色の小結節を多数認める．

The thymus was of normal size and weighed 28 gm. Its capsule was thickened. The organ was divided into lobules by grayish fibrous tissue, the parenchyma being soft and grayish-yellow.

胸腺は正常な大きさで，28 g である．被膜は肥厚し，器官は灰色線維組織によって小葉に分割され，実質は灰黄色にして軟い．

The liver weighed 500 gm. (360 gm. predicted). There was slightly increased consistency and the lobular architecture was accentuated by the presence of a grayish-yellow network. A few intrahepatic bile ducts were slightly dilated.

肝臓は500 g （通常360 g である）．硬度は軽度に増す．割面小葉像は灰黄色の網工により顕著となっている．小数の肝内胆管は軽度に拡大す．

Each lung weighed 100 gm. (60 gm. predicted). Several hemorrhagic spots were present in the pleura. The pulmonary parenchyma was dark red, increased in consistency and contained many small grayish-yellow spots close together.

両肺とも 100 g（通常60 g である）．肺肋膜には数個の出血斑を認む．肺の実質は暗赤色，硬度を増し，多数の黄灰色の小斑点の密集をみる．

The gastrointestinal tract was characterized by the presence of many dark nodules in the tonsils and lower esophagus. Others, similar to the skin papules, were present in the mucosa from the ileum to the rectum in places where lymphoid tissue might be expected.

消化器系では扁桃腺及び食道下部には多数の暗赤色の小結節が認められる．他に回腸以下直腸までの粘膜には，淋巴装置に一致して皮膚に認められたと同様の小隆起が認められる．

Marrow of ribs, sternum and lumbar vertebrae was dark red. In the femur it was pale. No grossly unusual features were noted in the heart, aorta, pancreas, kidneys, pituitary, thyroid or adrenal glands.

肋骨，胸骨及び腰椎の骨髄は暗赤色，大腿骨においては淡赤色である．心臓，大動脈，膵臓，腎臓，脳下垂体，甲状腺及び副腎には肉眼的に著変を認めない．

MICROSCOPIC FINDINGS On microscopic examination there was good correlation between gross alteration and the presence of marked cellular infiltration.

顕微鏡所見： 組織学的な著しい細網細胞の出現と肉眼的変化との間に平行関係を認める．

The skin papules were composed of nodular aggregates of mononuclear cells, accompanied by some hemorrhage, immediately beneath the epidermis. This appearance was similar to that of the surgical specimen. In the lymph nodes, follicles had almost disappeared. Reticular cells with abundant dark, acidophilic or clear cytoplasm, similar to those in the skin, were widely distributed, diffusely or in nodules. The centers of some nodules were necrotic, containing neutrophiles and bacterial foci. Tubercle bacilli were not found histologically or on culture. Microscopically the spleen was similar to the lymph nodes and in the thymus reticular cells without striation were numerous between bundles of connective tissue. (Figure 4)

皮膚の小隆起は表皮直下における単核細胞の集積よりなり，若干の出血を伴う．この様相は外科標本のそれと同様である．淋巴節では，沪胞は殆んど消失している．皮膚に認められると同様の，豊富な，エオジンに濃染する，或は透明な原形質を有する細網細胞が瀰漫性に，或は結節状に広く分布している．ある結節の中央は壊死に陥ちいり，好中球及び細菌病巣を有す．結核菌は組織学的検査においても，培養検査においても認めない．顕微鏡検査では，脾臓の所見は，淋巴節と同様であり，胸腺においては線条のない細網細胞を多数結合織束間に認める．（図4）

The bone marrow changes were somewhat more complex. Small nodular foci of reticular cells were present and erythropoiesis was markedly reduced. Megakaryocytes were also reduced in number and their nuclei were pyknotic. In the lateral portion of the left temporal bone there was

骨髄の変化は更に複雑で細網細胞の結節様病巣を認め，赤血球生成は著しく減退している．骨髄巨核細胞も減少し，その核は濃縮している．左側頭骨の外側部では骨梁は破壊され，細網細胞で置換えられている．外科標本（[redacted]）とは対照的に，好酸球浸潤は殆んどない．

destruction of spicules and replacement by reticular cells. Eosinophilic infiltration was almost absent in contrast to the surgical specimen ([redacted]).

Histochemical studies[35] were also made of the cytoplasm of the reticular cells. There was a moderate amount of red or yellow-red material by Sudan III Stain, but a small amount of purplish pink or pale blue material by Nile Blue Sulfate and black or gray-colored with osmic acid. Using the sulfuric acid method of Okamoto, Shimamoto and Sonoda,[35] cholesterin was not found but cholesterin fat was present. Employing the phosphatid staining method of Okamoto, Shimamoto, Ueda, Kusumoto and Shibata,[35] there was a small amount of blue-violet stained material in reticular cells of the spleen; after acetone washing, this test was still positive. By P.A.S. staining, a small amount of positive substance was present in the same cells in lymph nodes. Material staining with Sudan III after acetone staining was uncommon. These stains suggest the presence of neutral fat, cholesterin fat and a small amount of lipoid, that is, phosphatid and cerebroside.

細網細胞の原形質について組織化学的検査[35]も実施した．これらの細胞の原形質内には，スダンⅢ染色でかなりの量の橙或は赤橙色，ナイルブリュー硫酸塩法で菫紅色或は少量の淡青色，オスミウム酸によって黒色或は少量の灰色に染色する物質を認める．岡本・島本・園田[35]の硫酸法を用いてコレステリンは認められないがコレステリン脂肪が認められる．岡本・島本・上田・楠元・芝田[35]の燐脂質一般染色法によれば脾臓の細網細胞中に少量の青紫色に染色した物質があり，アセトン処置後も尚陽性に見られる．P.A.S.染色によれば，淋巴節の細網細胞内に，少量の陽性物質がある．アセトン処置後のスダンⅢ染色では陽性物質は少ない．これらの染色は中性脂肪，コレステリン脂肪及び少量の類脂質，すなわち燐脂質及び糖脂質が細網細胞中に存在することを暗示する．

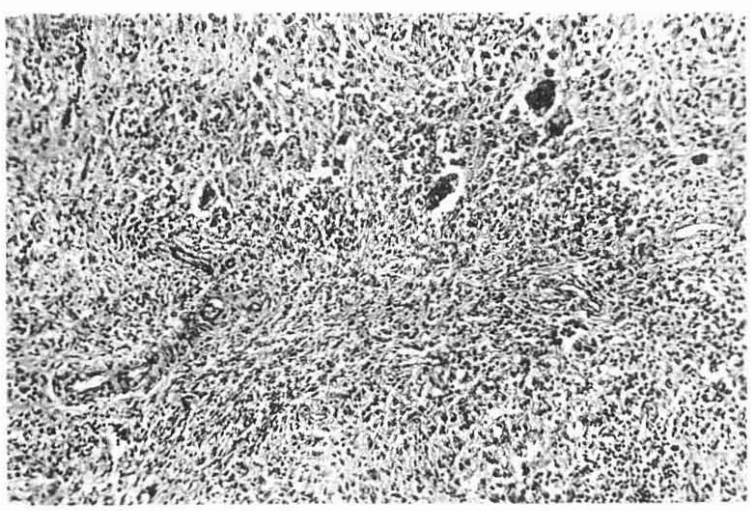

Figure 4 Thymus at autopsy (x 100) Normal architecture of the thymus is completely destroyed. Nodular hyperplasia of reticular cells and new formation of fibrous tissue (The fourth stage) (H.E. stain)

図 4 剖検における胸腺 胸腺の正常な構造は全く破壊されている．細網細胞結節性過形成と線維組織の新生を認める（第4期）（ヘマトキシリン・エオジン染色）

PATHOLOGIC DIAGNOSIS

1. Letterer-Siwe's disease, involving generalized lymph nodes; thymus, diaphragm, spleen, liver, bone marrow, skin, mucosa of gastrointestinal tract, lungs and mediastinal pleura, petrous portion of temporal bone and soft tissue around the external auditory canal.
2. Petechial hemorrhage, pleura, peritoneum, periadrenal fatty tissue and intestinal mucosa.
3. Fatty liver, uniformly peripheral, severe.
4. Intrahepatic biliary obstruction with chronic pericholangitis, probably congenital.
5. Abscess with chronic interstitial inflammation, tail of pancreas.
6. Mild, chronic tracheobronchitis.
7. Decrease of fatty substance of zona fasciculata of adrenal.
8. Fatty degeneration, heart muscle, mild.
9. Mild nephrosis.
10. Ascites.
11. Old operation wound, right retroauricular region.
12. Fresh small hemorrhagic foci, spinal.

DISCUSSION

The eitology of Letterer-Siwe's disease is unknown. Siwe, Coronini and Risak[23]; van Creveld and ter Porten[24]; Green and Farber[25]; and Farber[26] advocated an infectious etiology, and Mizuno,[4] Bierman[27] and Aronson[28] report that antibiotics proved effective. Okada[14] and Arita[9] have reported that this disease is accompanied with otitis media and Sherman,[29] with

病理診断：

1．全身の淋巴腺，胸腺，横隔膜，脾臓，肝臓，骨髄，皮膚，胃腸管粘膜，肺，及び縦隔胸膜，側頭骨の岩様部及び外耳道軟部組織に及んでいる Letterer-Siwe 病

2．肋膜，腹膜，副腎周囲脂肪組織及び腸粘膜の点状出血

3．強度の周辺性脂肪肝

4．おそらく先天的の慢性胆管周囲炎を伴う肝内胆管閉塞

5．膵尾の慢性間質性炎症を伴う膿瘍

6．軽度の慢性気管，気管支炎

7．副腎束状帯の脂肪性物質の減少

8．軽度の心筋脂肪変性

9．軽度のネフローゼ

10．腹水

11．右耳介後部の古い手術創

12．脊髄の新しい小出血巣

考按

Letterer-Siwe 病の原因は不明である．Siwe，Coroniと Risak[23]；van Crevelとter Porten[24]；Green とFarber[25]；Farber[26]等は，感染説を唱え，水野[4]；Bierman[27]，Aronson[28]等は，抗生物質がよく効いたと述べている．岡田[14]や有田[9]は中耳

septicemia; and this case seems to be similar to Okada and Arita's cases. Koch[30] advocated a virus causation because therapeutically, aureomycin reported to be effective for large-sized virus disease, is sometimes effective in Letterer-Siwe's disease whereas penicillin, streptomycin and supronal are not. Although it has been said that this disease is not hereditary, in Bierman's case, the process appeared in monozygotic twins. Sherman[29] and Furuta[3] also reported a congenital case. The disease usually occurs around the age of 1, but Dennis et. al. [31] have reported a case that occurred at the age of 30.

Siwe and Symmer (1951) recognized differences between the three diseases: Hand-Schüller-Christian's disease, eosinophilic granuloma and Letterer-Siwe's disease. These differences were based on the clinical picture, prognosis, and on pathological observations. Wallgren,[32] Farber and Jaffe[33] and Lichtenstein[37] felt that these three diseases had the same etiology and were closely related. They considered the disease to be eosinophilic granuloma when the lesions were localized in the bone, Hand-Schüller-Christian's disease when lipoid is accumulated in the proliferated reticuloendothelium, and Letterer-Siwe's disease when there is no accumulation of lipoid.

Siwe gives the following eight as the characteristic features of Letterer-Siwe's disease:

1. Enlargement of liver and spleen,
2. Purpura,
3. Localized masses in bone,
4. Secondary anemia,
5. Enlargement of lymph nodes,
6. Spleen puncture showing non-lipid containing phagocytes,

炎を，Sherman[29]は敗血症を合併した例を述べている点を考え合せると本症例は岡田や有田の症例に類似しているようである．Koch[30]は治療上ペニシリン，ストレプトマイシン，スプロナールは効果なく，大型のビールス疾患によく効くと云われるオーレオマイシンが時々本症に有効なことより，ビールス説を唱えている．又，本症は遺伝的でないと言われてきたが，Biermanの症例は一卵性双生児の二子に本症が現われている．又，Sherman[29]及び古田等[3]は先天的にきた症例を報告している．好発年令は1才前後であるが，Dennis等[31]は30才の症例を報告している．

SiweとSymmer（1951）は臨床経過，予後及び病理学的に見て，Hand-Schüller-Christian病，好酸球性肉芽腫，Letterer-Siwe病の三者間に相違を認めているのに対し，Wallgren[32]，FarberとJaffe[33]，Lichtenstein[37]等は，これら三者は同一病因により，密接な関係があるとしている．即ち，病変が骨に限局したものが好酸球性肉芽腫であり，増殖した細網内皮細胞にリポイドを蓄積したものが，Hand-Schüller-Christian病であり，リポイドの蓄積のないものがLetterer-Siwe病であると考えた．

SiweはLetterer-Siwe病の特徴として次の8項目を掲げている．

1．肝脾腫
2．紫斑病
3．骨の限局性腫瘤
4．二次的貧血
5．淋巴腺腫脹
6．脾穿刺で類脂肪を持たない貪食細胞を認める

7. Cases occurring mostly among infants, with a course varying from several weeks to several years.

8. Histological findings showing proliferation of large phagocytes without lipoid, with spleen, liver, lymph nodes, bone, lung and skin as major sites of involvement.

Hand-Schüller-Christian's disease presents pituitary symptoms; multiple defects of bones especially in the skull; exophthalmus; diabetes insipidus; disturbance of growth and adiposity. It can be differentiated from Letterer-Siwe's disease by formation of skin granulomata containing histocytes and foam cells, and especially by the chronic course of the disease.

Eosinophilic granuloma is characterized by single or multiple localized bone lesions. has a good prognosis. and can be diagnosed by radiographic appearance of the bone lesions and by exploratory puncture.

Lipoidosis. such as Gaucher's disease and Niemann-Pick's disease. resemble Letterer-Siwe's disease in that they present, with hepatosplenomegaly, enlargement of lymph nodes, and hypersplenism. However, they develop disturbances in growth, in skin coloring, and can be differentiated by demonstrating cells peculiar to them by bone marrow puncture. Differentiation of Letterer-Siwe's disease from disseminated histoplasmosis is difficult. When Letterer-Siwe's disease is present without skin eruptions or bone symptoms, there is difficulty in differentiation unless histoplasma capsulatum can be cultured. Septicemia and syphilis should also be considered in differential diagnosis.

With regard to progress and prognosis, according to Orchard's statistics,[34] the younger the age, the more acute the progress and the higher the death rate. As for treatment, it is reported by many that aureomycin, penicillin, streptomycin, chloromycetin and steroid hormones are

7. 乳幼児に多く，数週から数年の経過を有する

8. 組織学的所見より，リポイドを含まぬ貪喰細胞の増殖があり脾臓，肝臓，淋巴腺，骨，肺，皮膚が主として侵される

Hand-Schüller-Christian 病は骨，特に頭蓋骨の多発性欠損，眼球突出，尿崩症，発育障害，脂肪過多等の下垂体症状を呈し，組織球及び泡沫細胞を含む肉芽腫が皮膚に生じ，特にその慢性経過等によりLetterer-Siwe病と区別される．

好酸球性肉芽腫は単発性或は多発生の限局性骨病変が特徴で，予後良好，骨のX線像と試験穿刺により診断される．

Gaucher 病，Niemann-Pick 病等のリポイド代謝障害は肝脾腫，淋巴腺腫脹，脾臓機能亢進を呈する点でLetterer-Siwe病に類似するが，発育障害，皮膚着色を来し且つ骨髄穿刺により夫々特有な細胞を証明すれば鑑別される．Disseminated histoplasmosisとLetterer-Siwe 病との鑑別が困難で，Letterer-Siwe 病に発疹，骨症状がない場合はhistoplasma capsulatumを培養により証明する以外は鑑別は困難である．その外，敗血症，梅毒等も鑑別すべきである．

経過及び予後については，Orchard の統計[34]によれば，年令が幼若であればある程急性に経過し，死亡率が高いと言っている．治療として一般的にはオーレオマイシン，ペニシリン，ストレプトマイシン，クロロマイセチン，ステロイドホルモン等が効果があると報告している人が多い．治

effective. The variety of treatments offered and the almost uniformly fatal outcome of the disease serve to emphasize the general inefficacy of therapy.

This case certainly did not respond well to treatment, and the progress of the disease was unrelenting.

From the histopathological standpoint, some authors (Rotter, Bungler, Engelbreth-Holm, etc.[36]) have divided Letterer-Siwe's syndrome into four stages as follows:

1. Diffuse or nodular proliferation of reticulo-endothelial cells,
2. Severe eosinophilic and plasmacytic infiltration, often accompanied by lymphocytic and neutrophilic infiltration with lipoid deposition in reticulo-endothelial cells,
3. Xanthoma or lipogranuloma,
4. Granulofibrosis.

In this case, the first and second surgical specimens show proliferation of reticulo-endothelial cells with severe eosinophilic infiltration and are compatible with the second stage. But at the time of autopsy, these inflammatory cells were almost absent and large foam cells were prominent. This is compatible with the third stage. Only in the thymus are collagen fibers and arginaffine fibers moderately produced and this organ is seen to be compatible with the fourth stage. From both clinical and pathological standpoints, however, Letterer-Siwe's disease appears to be the most suitable diagnosis.

SUMMARY

The clinical course and pathological findings of an 11 month old infant with progressive, fatal Letterer-Siwe's disease have been described.

療が多種に亘り，結果が殆んど一様に致命的であることは治療が一般に効果がないことを強調するものである．

本症例は確かに治療により反応を示さず，経過は一途に悪化した．

組織病理学的立場からある著者（ Rotter, Bungler, Engelbreth-Holm 等）[36]は，Letterer-Siwe 症候群を次の4段階に区分している．

1. 細網内皮細胞の瀰漫性又は結節様増殖
2. 細網内皮細胞内リポイド蓄積を伴う淋巴球性，好中球性浸潤を屡々合併する強度の好酸球性，形質細胞性浸潤
3. 黄色腫或は脂肪肉芽腫
4. 肉芽線維化

本症例においては，第1回と第2回の外科的標本の組織検査では，高度の好酸球性浸潤を有する細網内皮細胞の増殖を呈し，第2期に一致する．しかし，剖検時にはこれら炎症性細胞は殆んどなく，大泡沫細胞が顕著であった．これは第3期に一致する．膠原線維，嗜銀線維が中等度に生成されているのは胸腺のみで，この臓器は第4期に一致するものと認められる．しかしながら，臨床的及び病理学的立場から Letterer-Siwe 病と診断するのが至当のようである．

総 括

生後11箇月の男児の進行性 Letterer-Siwe 病の死亡例の臨床経過及び病理学的所見を報告した．

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