DISSEMINATED LUPUS ERYTHEMATOSUS:
REPORT OF A CASE
WITH AUTOPSY FINDINGS

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Disseminated Lupus Erythematosus can no longer be considered a rare
disease in Japan. Approximately 150 cases of this disease have been seen in
the dermatology departments of three major Japanese universities during the
past 20 years(1). Since 1945 the number of cases reported has increased
markedly(2). This increase is probably the result of newer diagnostic criteria,
including the use of new laboratory tests, e.g., the L.E. cell phenomenon which
was first used in 1947.

The protean characteristics of disseminated lupus erythematosus were first
pointed out by Osler(2) and have, of course, been re-emphasized by many later
authors(3, 4).

The purpose of this report is to present a case which demonstrates involve-
ment of nearly all of the systems which can be involved in disseminated lupus
erythematosus, but which had the nephrotic syndrome as the predominant feature.
A secondary purpose is to mention briefly some of the problems produced by
steroid therapy of disseminated lupus erythematosus. In the treatment of this
disease with adrenal steroids it is frequently difficult to distinguish between
symptoms of the disease and effects produced by the drugs.

CASE REPORT

A Japanese woman 31 years of age was admitted to the She complained of

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States Atomic Energy Commission.
of any joint. Because of the continued pain she consulted a physician who made a diagnosis of rheumatoid arthritis. Within a few months the joint symptoms disappeared only to recur as the skin became involved. Thereafter the joint pain waxed and waned, as did the skin disease.

The skin rash began in December 1951 as raised, indurated macules several millimeters in diameter. The eruptions later became erythematous, then desquamated to leave deeply pigmented and pruritic scars. There were several remissions and exacerbations of the arthralgia and skin lesions, but the dermatitis spread with each exacerbation and ultimately involved the face, the neck, the back, the "V" of the chest and the extensor surfaces of the extremities.

In November, 1954 she first noted abdominal swelling. Her private physician performed 25 abdominal paracenteses in the period November, 1954 to May, 1955. During this time her condition continued to deteriorate and the patient began to suffer from anorexia, marked weight loss, shortness of breath, epilation and ankle edema. Menstruation had ceased entirely in late 1954.

Physical examination showed an asthenic, sallow, young woman with marked lassitude and weakness. Body weight was 94 lbs. The blood pressure was 160/70 mm Hg; pulse rate 86 beats per minute; temperature 99.4°F orally; respirations 20 per minute. The skin was pale and atrophic. Skin lesions were distributed over the malar eminences, bridge of the nose, and forehead in a "butterfly pattern." Additional lesions were seen on the chin, "V" of the neck, extensor surfaces of the extremities and the back, especially over the scapular region. (Figs. 1 and 2) The eruptions were deeply pigmented with sharp, slightly raised, reddish margins and measured 2–4 mm in diameter. On the surface of some were thin silvery scales, which when peeled off revealed telangiectases; others revealed central atrophy. Pubic and axillary hair were almost totally absent. The hair was fine and sparse over the scalp. There was periorbital, facial, sacral and ankle edema.

The fundi revealed yellowish-white, hard-appearing exudates surrounding blood vessels, beginning a few millimeters from the circumference of the macula and extending to the periphery. A few small flame-shaped hemorrhages were seen in both fundi especially close to the optic discs.

The chest showed that the diaphragm was elevated and that diaphragmatic excursion was limited. A pleural friction rub was heard in both upper lung fields. The left border of cardiac dullness extended to the midclavicular line in the fifth intercostal space. A soft blowing systolic murmur and a gallop rhythm were heard at the apex and along the left sternal border.

The abdomen was markedly distended and so examination of the abdominal
organs was unsatisfactory. A fluid wave was easily demonstrated.

The extremities revealed fusiform swelling and subluxation of the second interphalangeal joints of the hands.

Laboratory studies of the blood revealed an erythrocyte count of 2.8 million cells per cu mm and 8.8 g of hemoglobin per 100 cc of blood. The leukocyte count was 2,500 cells per cu mm of blood, with a differential count of 50% polymorphonuclear leukocytes, 28.5% lymphocytes, 9.5% monocytes, 10% eosinophils, 0.5% basophils, and 0.5% plasmacytes. A L.E. cell preparation of the peripheral blood was positive. (Fig. 3)

The urine showed a specific gravity of 1.015, a 3 plus reaction for protein by the sulfosalicylic acid method and a negative test for sugar. The urinary sediment contained 8–26 white blood cells, 0–1 hyaline casts, and 0–2 granular casts per high power field.

An Addis count of a 24 hour urine specimen showed a total protein of 9.9 g, RBC 72 million, WBC 194 million, epithelial cells 18 million and hyaline casts 4.7 million per 24 hours. The specific gravity of the 24 hour urine specimen was 1.016.

The total serum protein was 4.24 g with albumin 1.25 g, and globulin 2.99 g per 100 cc of blood. The serum non-protein nitrogen was 24.8 mg and the fasting blood sugar 83.7 mg per 100 cc of blood. Potassium was 4.0 mEq/liter and sodium 142 mEq/liter of blood.

Thymol turbidity was 1.9 units and cephalin flocculation was two plus positive after 48 hours. The bromsulfalein test showed 6.3% of the originally injected dye remaining in the serum at the end of 45 minutes.

An X-ray film of the chest showed the left cardiac border to be slightly prominent. The right dome of the diaphragm was elevated slightly; the lungs appeared normal. An antero-posterior roentgenogram of the abdomen revealed the presence of ascitic fluid. The liver, kidney and spleen shadows were indistinct. X-ray films of the hands showed dimineralization of the ends of the long bones. A 12 lead electrocardiogram was normal.

A diagnosis of disseminated lupus erythematosus was made on the basis of the clinical picture and the presence of L.E. cells in the peripheral blood.

On May 30, 1955, the patient was given 25 mg of Acthar Gel intramuscularly. This dose was gradually increased to 40 mg of Acthar Gel intramuscularly for the next 20 days. The patient’s temperature dropped to 98.6°F 24 hours after initiation of treatment. She developed a mild headache and vague epigastric pains. These complaints lasted throughout this phase of the therapy.

On June 23, 1956 the Acthar Gel was discontinued and the administration
of cortisone was begun. A daily dose of 300 mg was given the patient for 18 days, until there was a sharp increase in body weight, some increase in serum sodium and decrease in serum potassium. (Fig. 4) The dose of the drug was then decreased in a stepwise fashion to 50 mg of cortisone per day, then discontinued. The entire course of therapy extended over a period of 41 days. Orange juice was given daily to counteract the hypokalemic effects of the hormone therapy. One thousand mg of oral Achromycin was given each day. The patient was put on a "low" salt diet and given three tablets of Hexavitamin daily.
During therapy the body weight reached a maximum of 113 lbs., and the NPN rose to 54 mg per 100 cc of blood shortly before medication was ended (cf. above). The total 24 hour urinary protein rose to 25 g per day. Three days after the last dose of cortisone, she developed herpes zoster on the left side of the abdomen. This condition was treated symptomatically and disappeared in two weeks.

A striking remission followed three weeks after cessation of therapy. Body weight decreased to 81 lbs.; edema and ascites were no longer demonstrable. The skin cleared entirely, leaving only areas of light brown pigmentation. The patient no longer complained of joint pains and her appetite improved markedly.

The remission was also reflected in the laboratory tests. One month after completing the cortisone therapy the erythrocyte count was 3.9 million cells per cu mm of blood; the hemoglobin was 11.0 g per 100 cc of blood; the packed cell volume was 39%; the WBC was 5,500 cells per cu mm of blood, with a differential leukocyte count of 52% polymorphonuclear leukocytes, 20% lymphocytes, 14% monocytes, 12% eosinophils and 1% basophils. The L.E. cell phenomenon could not be demonstrated. An Addis count showed a total protein of 2.9 g, RBC 4 million, WBC 69 million, epithelial cells 5 million, and casts 0.5 million per 24 hours. The NPN was 30 mg per 100 cc of blood. The total serum protein was 6.3 g, the albumin being 2.5 g and the globulin 3.8 g per 100 cc of blood. The sodium was 136 mEq/liter and the potassium was 5.0 mEq/liter of blood. (Figs. 4, 5)
In July 1955, after the remission, the patient went home where she resumed work as a book seller. In spite of the remission, laboratory tests such as urinary protein and A/G ratio were still abnormal.

She was readmitted to the ABCC Diagnostic Ward on September 26, 1955 in a state of mental disorientation. Physical examination revealed extensive edema and ascites. Acthar Gel, 40 mg I.M., was started immediately and continued for 10 days. This was followed by 200 mg of oral cortisone daily with a gradual decrease during a 28-day period to 50 mg per day.

In spite of the administration of hormones, the patient's condition continued to deteriorate. She complained of marked weakness, malaise, and anorexia. Her body weight increased to 116 lbs. as the anasarca and ascites became progressively worse. Urinary output decreased to a few cc per day and there was a concomitant rise in NPN (Fig. 4). By November 1, 1955 the NPN was 84 mg per 100 cc of blood.

The patient was now unable to leave her bed because of weakness. She began to vomit frequently and intravenous fluids were administered to compensate both for the insensible loss of fluid and that fluid which was being lost by vomiting. Abdominal paracentesis was performed several times to relieve the intense abdominal pressure.

The patient's condition continued to worsen. The body weight was 117 lbs. By the 16th of January the NPN was 121 mg per 100 cc and the total serum protein was 4.8 g per 100 cc of blood. (Serum albumin 1.3 g, serum globulin 3.3 g) Serum potassium was 4.1 mEq/liter and serum sodium was 166 mEq/liter of blood. The 24 hour urinary output was 20 cc. (Fig. 4) The specific gravity of the urine was 1.014, the protein 3.6 g, the erythrocytes 12.4 million, the leukocytes 138 million, the epithelial cells 9.2 million and casts 1.2 million per 24 hours. The erythrocyte count was 2.1 million per cubic mm of blood; the hemoglobin was 6.1 g per 100 cc of blood. The leukocyte count was 11,000 cells per cc of blood with a leukocyte differential count of 8% neutrophils, 8% lymphocytes, and 3 per cent monocytes. (Fig. 5)

On January 23, 1956, the patient became comatose. Her NPN was 157 mg per 100 cc of blood. Death followed on

**AUTOPSY FINDINGS**

**Gross:** The body was that of a moderately well developed young woman with ascites and marked subcutaneous edema, particularly over the lower extremities.

The pericardial sac contained a few cc of fluid. A firm fibrous adhesion
measuring 2 cm in diameter was found between the visceral and parietal pericardium over the anterior surface of the right ventricle. The heart appeared grossly normal and weighed 270 g.

The right pleural cavity contained 80 cc of fluid and the left pleural cavity contained 30 cc of fluid. On sectioning a moderate amount of fluid escaped from the cut surface of the lungs.

The abdominal cavity contained 3,750 cc of pale yellow, clear fluid containing fibrin and gelatinous masses. The external surface of the liver was finely granular and glistening. On sectioning, each lobule was surrounded by a pale, translucent, irregularly shaped zone. The portal system was widely patent and free of thrombi.

The capsules of the kidneys stripped with ease. The cortical surfaces were finely granular and several flat, depressed areas were noted. There were scattered very pale yellow areas on the purplish external surface and in the cortical substance. The left and right kidney each weighed 175 g.

Histology: Sections taken from the mitral valve of the heart showed small areas of strongly eosinophilic substance suggestive of fibrinoid material. This was associated with permeation of the valve substance by polymorphonuclear leukocytes. The perivascular areas of the papillary muscle showed an increase in collagenous fibrous tissue. Several small foci of polymorphonuclear and mononuclear leukocytes were scattered in the interstitial tissue of the left ventricle and a focal collection of lymphocytes was seen adjacent to a nerve in the epicardial fatty tissue of the left atrium.

Each lobe of the lung showed many of the alveoli to contain polymorphonuclear leukocytes and deposits of stringy eosinophilic material. The lobes of the left lung showed in addition broad deposits of eosinophilic amorphous material mixed with basophilic deposits which frequently were adjacent to the alveolar linings. The alveolar walls and lumina contained leukocytes. The branches of the pulmonary and bronchial arteries were normal. Focal fibrovascular thickening of the pleura was noted in the section from the right middle lobe.

The spleen revealed annular fibrous laminations of the arteriolar adventitia. These laminations were composed of collagenous and reticulum fibers. The lymphoid follicles were small and devoid of germinal centers. Moderate numbers of polymorphonuclear leukocytes and plasma cells were noted within the sinuses and around the trabeculae.

The periportal zones of the liver showed extensive vacuolization of the hepatic cord cells. The vacuoles contained fat as demonstrated by Sudan III
stain. The sections revealed slight sclerosis of arteries and occasionally perivascular fibrosis of the central veins. The bile ducts were prominent but not significantly increased in numbers. There was mild fibrosis of the portal triads associated with prominent infiltrations by lymphocytes and scattered polymorphonuclear leukocytes.

The two supraclavicular and axillary lymph nodes and sections from the paratracheal, mesenteric, paraaortic, iliac and inguinal lymph nodes revealed slight dilatation of the lymphoid sinuses which contained reiculum cells. Several foci of hemorrhage were seen in the left axillary node. The paratracheal node had numerous polymorphonuclear leukocytes and reticulum cells within the sinuses. Lymphoid follicles were absent in all nodes except for the paratracheal node where they were noted in small numbers.

The cortex of each kidney contained large areas composed of fibrosed glomeruli and atrophic tubules in which the interstitial tissue was permeated by lymphocytes and plasma cells. Nearly all the glomeruli were altered to variable degrees. In many, a distinct thickening of the basement membrane by strongly eosinophilic material was seen and hyaline eosinophilic thrombi filled the capillary lumina. These changes involved either portions or the whole of the glomerulus. Occasionally this change was associated with necrosis of cells, and nuclear debris could be seen within the thickened basement membrane. “Hematoxylin bodies” (Fig. 6) were seen in a few glomeruli (12). Where the changes were most marked, a crowding of nuclei around a narrow lumen was seen surrounded by broad eosinophilic bands. Adhesions between the visceral and parietal layers of Bowman’s capsule were common, though variable in extent, (Fig. 6)

Extending from the cortex into the medulla were areas of necrosis in which many of the tubules were filled with polymorphonuclear leukocytes. Similar cells were noted in the peritubular stroma. Scattered throughout were deposits of amorphous basophilic material, intratubularly as well as outside of the tubules, suggestive of deposits of calcium salts. (Fig. 6) A frozen section stained for fat revealed numerous small lipid droplets in the epithelial cells of the preserved tubules but very little in the stroma and no fat in the glomeruli.

The endocrine system showed marked ovarian atrophy and a nodular hyperplasia of the thyroid glands in which many of the nodules contained follicles lined by eosinophilic cells. The adrenal cortex showed very little structural change in spite of the prolonged courses of treatment with cortisone and ACTH. The beta cells of the anterior hypophysis were granulated and free of Crooke’s hyalin changes. The lack of change in these glands may be due
to the fact there was some time interval between cessation of steroid therapy and death. Bennett(13,14) has demonstrated that steroid induced adrenal and pituitary gland changes do regress after stopping the drugs.

A macule from the right leg and one from the left abdominal wall revealed an epidermis composed of only a few layers of squamous cells and a prominent layer of keratin on the surface. The corium was composed of dense fibrous tissue in which scattered skin appendages were seen. They were small and occasionally accompanied by lymphocytes. The pigmentation of the basal layer of the epidermis varied slightly from place to place and pigment granules within phagocytes were occasionally seen in the superficial portion of the corium. One of the sections from the skin over the knee showed a focal collection of large mononuclear cells containing greenish-yellow pigment granules deep in the corium. There was no evidence of fibrinoid necrosis in the sections examined.

COMMENTS

In many respects this case was typical of disseminated lupus erythematosus. The patient was a woman of child-bearing age. Of the nine organs or organ systems which are said to be most frequently involved(3), all were involved to a greater or lesser degree in the case here presented. There were histopathological alterations or clinical signs of involvement of the joints, skin, kidneys, lymphoid tissues, spleen, liver, pleura, lungs, heart, central nervous systems, and gastrointestinal tract.

Joint manifestations, including arthralgia and arthritis, appear in the majority of disseminated lupus cases(3,4). In this case arthralgia was the earliest symptom and led one physician to make an erroneous diagnosis of rheumatoid arthritis. Only later in the course of the disease did the typical “butterfly rash” appear and then suggest the diagnosis of disseminated lupus erythematosus.

The severe and dramatic kidney lesion left only a small fraction of functioning renal tissues. Microscopic sections of the kidney revealed the so-called “wire-loop” lesion and hematoxylin bodies (Fig. 6) which are “pathognomonic” of disseminated lupus erythematosus and present in about 60% of cases(4). The alteration in fluid and electrolyte balance and azotemia caused by the profound kidney damage rendered treatment with ACTH and cortisone difficult, and was ultimately responsible for death.

Small foci of fibrinoid degeneration were found in the posterior mitral leaf of the heart. It is difficult to correlate this with any heart murmurs heard while the patient was alive. The myocarditis demonstrated on the histopathologi-
cal sections of the heart muscle may be responsible for the gallop rhythm occasionally heard. The warty, non-bacterial valvular vegetations described by Libman and Sacks\(^5\) were not observed.

Secondary bacterial infection of the lungs is a very common complication of disseminated lupus erythematosus\(^3\). Sections of lung in this case showed evidence of widespread pneumonitis. This, however, may simply have been a terminal event in a debilitated uremic patient and not the result of the primary disease process. The lung lesion did not resemble Rich’s allergic pneumonitis.

Fibrovascular thickening of the pleura and the fibrous pericardial adhesion showed evidence of involvement of serosal surfaces. The pleural friction rub heard during the first admission of the patient may have been caused by this serositis.

Mental disorientation led to the final admission of the patient. As in this case, central nervous system alterations usually occur only during a serious exacerbation and are a grave prognostic sign\(^3\).

Retinal cytoid bodies are reported to be present in about 25% of disseminated lupus erythematosus cases\(^3,4\). The exudative retinal lesion seen in this case and referred to as “cotton wool” exudates may also be observed in arteriosclerosis, in association with hypertension, renal disease, diabetes, severe anemia, increased intracranial pressure and septicemia\(^3\). These exudates may however have been cytoid bodies\(^4\).

Gastro-intestinal complaints were a prominent part of the patient’s symptoms but histopathological sections failed to show the characteristic fibrinoid degeneration and arteritis frequently causing hemorrhage and ulceration in the gastro-intestinal tract\(^3,4\). It is very possible some of the gastro-intestinal symptoms were due to the therapy.

Clinically, signs and symptoms originating from the liver, spleen, and lymph nodes were overshadowed by the severe damage to the kidneys which produced the “nephrotic syndrome” with anasarca and ascites. The microscopic sections of these organs however showed alterations which, while not specific for disseminated lupus erythematosus, are nevertheless frequently found. The absence of lymphoid follicles in lymph nodes and their numerical reduction in the spleen may very well be effects of ACTH and cortisone treatment.

Because of the uniformly poor prognosis of disseminated lupus erythematosus, vigorous treatment measures were undertaken. The aim in therapy was to produce symptoms of hypercorticism then decrease the dose gradually\(^6,7,9,10\). The severe kidney lesion which existed prior to initiation of ACTH and cortisone therapy made maintenance of a proper electrolyte and fluid balance doubly
difficult. Anasarca and ascites which the patient had on her first admission increased with the administration of these hormones (Fig. 4). However, the serum sodium level, except for one measurement, remained normal. There was a fall in the serum potassium level during cortisone therapy.

Following the first course of treatment there was a dramatic remission. The patient lost her edema and ascites, her hemoglobin increased sharply and the total serum protein became normal in amount but still had a reversal of the albumin, globulin ratio. The patient continued to show abnormal amounts of protein in the urine in spite of the tremendous decrease in the total 24 hour urinary protein excretion values. (Fig. 4) This was perhaps to be expected, as the renal injury observed in patients with acute disseminated lupus is, according to Soffer, persistent(8).

When the patient was readmitted to the ABCC Diagnostic Ward there was evidence of profound kidney damage. As cortisone was administered there was further fluid retention which necessitated repeated paracenteses and removal of fluid from the lower extremities with Southey’s tubs. Since cortisone seemed to be adding to the fluid retention it was stopped to allow the patient some symptomatic relief.

At this time the serum sodium was somewhat low. However the rather sharp drop of the serum potassium would seem to indicate a cortisone effect. Shortly thereafter the urinary output gradually decreased to levels as low as 20 cc per day and the NPN and serum sodium began to rise. At this point it was felt that steroid therapy would be of no further benefit and it was not reinstituted. The patient died in uremia shortly thereafter. In the experience of most investigators the renal lesion of disseminated lupus erythematosus is not reversible with cortisone(9,10).

SUMMARY

A typical case of disseminated lupus erythematosus has been reported. Although many organs were involved, a kidney lesion resulting in the nephrotic syndrome produced the most striking clinical and pathological findings. The relation of the clinical symptoms to the subsequent histopathologic findings has been discussed.

The problems encountered when treating disseminated lupus erythematosus have been outlined.

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Fig. 3  L.E. cell in peripheral blood

Fig. 6  Glomerulus showing hyalin, eosinophilic thickening of the basement membrane in three capillary loops ("wire loop" lesion). Note persistence of lumens and endothelial cells. A hyalin thrombus partly fills the lumen in the upper segment. Two adjacent loops contain "hematoxylin bodies" (arrow). Inflammatory exudate in the stroma and tubules is characteristic of the superimposed pyelonephritis (Periodic acid Schiff technique stain).