LUPUS ERYTHEMATOSUS CELLS IN SYSTEMIC SCLEROSIS

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The lupus erythematosus cell (L.E. cell) phenomenon is usually regarded, if properly interpreted, as being almost specific for systemic lupus erythematosus (Wilkinson and Sacker, 1957). On the other hand, too rigid an outlook may lead to diagnostic errors or retard progress in the understanding of other diseases.

Careful repeated examination of the blood of patients with classical rheumatoid arthritis may reveal the presence of L.E. cells in as many as 27 per cent. of cases (Black, Goldin, Poske, and Malmed, 1960), although most authors report a lower incidence. Dubois (1960) goes so far as to state that systemic lupus erythematosus is a malignant variant of rheumatoid arthritis. Treatment with steroids may increase the incidence of L.E. cells in rheumatoid arthritis (Ishmael, 1955) and L.E. cells have also been found after cortisone withdrawal (Slocumb, 1953). Ogryzlo (1953) reported the presence of L.E. cells in patients suffering from rheumatoid arthritis with visceral involvement, so-called "diffuse systemic rheumatoid disease", and Heaton (1959) found L.E. cells in ten out of 28 patients with Sjögren's syndrome. Lupus erythematosus cells have also been found in cases of polyarteritis nodosa (Lincoln and Ricker, 1954; Ogryzlo, 1956), dermatomyositis (Eaton, 1954; Ogryzlo, 1956), acrosclerosis (Volpé and Hauch, 1955; Arnold and Tilden, 1957), scleroderma (Miller and Horgan, 1960), and thrombohaemolytic thrombocytopenic purpura (Siegel, Friedman, Kessler, and Schwartz, 1957).

The finding of L.E. cells in chronic discoid lupus erythematosus has been reported by Berman, Axelrod, Goodman, and Mc Claughry (1950), Marten and Blackburn (1956), and Weiss and Swift (1955). In a personal series of 132 cases of chronic discoid lupus erythematosus, L.E. cells were found in three patients. However, two of these patients had associated rheumatoid arthritis (one with Sjögren's syndrome). The question arises whether they are really suffering from chronic systemic lupus erythematosus, and they serve to emphasize the close relationship between the discoid and systemic varieties of the disease.

Lupus erythematosus cells have been found in acquired haemolytic anaemia (Dubois, 1952) and the latter is now a well-recognized presentation of systemic lupus erythematosus.

Several drugs have precipitated reactions which have been associated with the finding of L.E. cells. The most interesting is hydralazine (Morrow, Schroeder, and Perry, 1953; Dustan, Taylor, Corcoran, and Page, 1954; Perry and Schroeder, 1954; Rheinhardt and Waldron, 1954; Shackman, Swiller, and Morrison, 1954; Ogryzlo, 1956); this causes a syndrome which is indistinguishable from systemic lupus erythematosus, but remits on stopping the drug. Lupus erythematosus cells have also been found with sensitivity to tetracycline (Domz, McNamara, and Holzapfel, 1959), penicillin (Walsh and Zimmerman, 1953), and phenylbutazone (Ogryzlo, 1956). Gold (1951) has discussed the significance of sulphonamides and penicillin in the pathogenesis of systemic lupus erythematosus.

Lupus erythematosus cells have been found in hepatitis (Joske and King, 1955; Bettley, 1955; Heller, Zimmerman, Rozengvaig, and Singer, 1956), in cirrhosis (Ogryzlo, 1956; Bearn, Kunkel, and Slater, 1956; Wilkinson and Sacker, 1957), and also in small numbers in cases of the so-called "autoclastic" hepatitis which usually occurs in young women (Mackay, Taft, and Cowling, 1959). Bartholomew, Hagedorn, Cain, and Baggenstoss (1958) considered that the women with hepatitis and cirrhosis and L.E. cells in the peripheral blood described by them, were, in fact, suffering from systemic lupus erythematosus with possibly super-added viral hepatitis.

Other conditions in which small numbers of L.E. cells have been found are:
L.E. cells have been described, usually in single cases, include pernicious anaemia and dermatitis herpetiformis (Berman and others, 1950), moniliasis (Gausewitz, Jones, and Worley, 1951), glomerulonephritis (Parellho, 1953), leukaemia (Weiss and Swift, 1955), Hodgkin's disease (Ogryzlo, 1956), and miliary tuberculosis (Jacobs, 1955), although the patient described by Jacobs had also had penicillin, Gantiran, and chloramphenicol. Hauser (1952) described L.E. cells in the Senear-Usher syndrome, but Weiss and Swift (1955) did not find any L.E. cells in five of their cases of this condition.

Butterworth (1953) was able to demonstrate the occasional L.E. cell (less than one in 10,000) in the blood of normal individuals and he was able to enhance the L.E.-cell phenomenon by the addition of desoxyribonuclease. Experimentally, L.E. cells have been demonstrated in artificially-produced cantharides blisters in patients with systemic lupus erythematosus (Watson, O'Leary, and Hargraves, 1951), and by inoculation of the traumatized skin of normal subjects with plasma from patients with lupus erythematosus (Rebuck and Berman, 1950), and cells resembling L.E. cells have been produced by the addition of fungi, particularly of the Aspergillus group, to heparinized bone marrow (Haserick, 1951).

Confusion with nucleophagocytosis may occur. The so-called "tart" cell is a polymorph or monocyte which has ingested a free nucleus. Some nuclear structure remains and this differentiates the "tart" cell from the L.E. cell in which the inclusion is completely homogenous. The presence of "tart" cells is not usually significant, but Weiss and Swift (1955) consider that large numbers of "tart" cells occur only in systemic lupus erythematosus, rheumatoid arthritis, or hydralazine sensitivity. Other phagocytosed materials found in leucocytes are red cells, globules of cryoglobulin (Hutchinson and Howell, 1953; Volpé and Ogryzlo, 1955; Heller, Yakulis, Glick, and Krasnow, 1958; Farmer, Cooper, and Pascuzzi, 1960), which stain bluish-pink, and globules of amyloid (Trubowitz, 1950), which also stain pink and are homogenous. The latter may explain the finding of so-called L.E. cells in cases of multiple myeloma (Hargraves, 1949; Weiss and Swift, 1955).

The case reports of three patients with systemic sclerosis, in whom L.E. cells have been found in the peripheral blood, are presented below.

Case Reports

Case 1, a man aged 51 years, gave a history of Raynaud's phenomenon of the hands for 5 years. Marked telangietasia over the upper half of the body developed about 6 months after the onset of Raynaud's phenomenon. Attacks of supraventricular tachycardia, lasting up to 4 hours several times a day had occurred for 4 years. He had also developed progressive kyphoscoliosis with osteophytic changes in the cervical spine.

Examination.—He appeared apprehensive. He showed striking macular telangiectases over the face, arms, and trunk down to the waist. The skin of the face and hands was shiny and tight, although atrophy was not a marked feature. The fingers were cyanotic and he was unable to flex them fully. There were no abnormal signs in the cardiovascular system apart from cardiac irregularity due to ectopic beats. The blood pressure was 160/110. The resting electrocardiogram showed notching of the P-waves, pathological Q-waves, ST depression, and T-wave abnormalities in the left ventricular leads and ectopic beats. Radiography of the chest showed cardiac enlargement only. Pulmonary function studies showed a diffusing capacity 27 per cent. of normal, indicating a marked degree of alveolar-capillary block. Lupus erythematosus cells were found in the peripheral blood. The Wassermann test, Kahn reaction, Coombs's test, and differential agglutination test were negative. Serum protein levels and electrophoresis, serum glutamic oxalocetic transaminase, liver function tests, blood counts including platelets, serum electrolytes, and examination of the urine were all normal. Cryoglobulins were not detected in the serum. A barium swallow showed typical changes of systemic sclerosis in the oesophagus, which was dilated, atonic, and contained air.

Treatment.—Procaine amide, 250 mg. eight times a day, reduced the frequency and severity of the attacks of paroxysmal tachycardia. Quinidine was less effective. Triamcinolone 4 mg. twice a day was maintained for 2 years, during which time his condition remained unchanged. Lupus erythematosus cells persisted in the peripheral blood.

Result.—In October, 1960, he had an episode of pneumonia which responded to penicillin, and 2 months later he developed cardiac failure with atrial flutter and complete atrio-ventricular block. Death occurred on January 6, 1961.

Autopsy.—The main macroscopic features included congestion of the lungs, liver, spleen, and kidneys; fibrous pericardial adhesions; enlargement and dilatation of the heart, especially the right ventricle; extensive old pleural adhesions; loss of epithelium in the lower oesophagus; petechial haemorrhages in the stomach; congestion of the small intestine.

Microscopic examination showed extensive, but patchy, fibrotic replacement of the myocardium; congestion, oedema, and some bronchopneumonia of the lungs, with fibrosis, mainly in the lower lobes and in places focal, and some thickening of the pulmonary arterioles; congestion of the kidney with hyalinization...
of a few afferent arterioles, normal glomeruli with no evidence of wire-loop lesions; congestion of the spleen, but no onion-skin lesions in the splenic arterioles; slight submucosal fibrosis of the lower oesophagus; atrophy of the circular muscle layer of the jejunum; marked congestion of the liver; sclerodermatous changes in specimens of skin taken from various sites.

Comment.—This man had systemic sclerosis with cutaneous, cardiac, pulmonary, oesophageal, and jejunal involvement. There was no pathological or clinical evidence, apart from the demonstration of L.E. cells, to suggest a diagnosis of systemic lupus erythematosus. He had no fever, anaemia, leucopenia, or thrombocytopenia. The erythrocyte sedimentation rate, serum proteins, and liver function tests were normal. The Wassermann reaction, differential agglutination test, and Coombs’s test were negative.

Case 2, a man aged 56 years, had had severe episodes of Raynaud’s phenomenon in his hands for many years. At the age of 48 he began to have ulcers on the fingers and hands, and a bilateral cervical sympatheticotomy was performed a year later. Subsequently he had intermittent ulceration of the tips of the elbows and on the ears. At the age of 55 he had difficulty in straightening his back and in lifting his hands above his shoulders, together with pains in the joints of the hands, knees, ankles, and feet. He also complained of some dyspnoea on exertion, nausea about 2 hours after meals relieved by vomiting, and symptoms of slight oesophageal regurgitation.

Examination.—He had acrosclerotic changes in the face, hands, and feet, with telangiectases over the face. There was slight limitation of movement at the wrists, elbows, and knees, because of sclerosis of the tissues. Some of the nail-fold capillaries were dilated and similar in appearance to those seen in dermatomyositis. There were congenital polar cataracts in each eye. The blood pressure was 135/85. He was afebrile.

Investigations.—Haemoglobin 70 per cent. White cell count 5,800 per c.mm. with normal differential count. Erythrocyte sedimentation rate 26 mm. in one hour. Total serum proteins 7.1 per cent., albumin 3.0 per cent., globulin 4.1 per cent., albumin/globulin ratio 0.7. L.E. cells present in the peripheral blood. Urine normal. Urea nitrogen 3.3 mg. per 100 ml. Serum calcium 9.9 mg. per 100 ml., phosphorus 3.3 mg. per 100 ml., alkaline phosphatase 7-7 units. Electrocardiogram normal. Radiography of the chest showed early fibrotic changes. Barium studies of the gastrointestinal tract showed dilatation and atony of the second and third parts of the duodenum and upper jejunum, although the oesophagus was normal. Radiographs of the spine showed degeneration of the fifth, sixth, and seventh cervical vertebrae with widespread osteoarthritic changes in the spine, shoulders, and hands.

There was no erosion of the terminal phalanges and no calcinosis either in the fingers or elsewhere.

Comment.—This man had undoubted systemic sclerosis with acrosclerosis of the face, hands, and feet; pulmonary fibrosis, and involvement of the kidneys and gastrointestinal tract. Dilatation and atony of the second and third parts of the duodenum and upper jejunum is a well-recognized feature of systemic sclerosis (Atkinson, Rowell, and Sumerling, 1962). The raised serum globulin, with reversed albumin/globulin ratio, slightly elevated erythrocyte sedimentation rate, and mild anaemia, might suggest the possibility of associated systemic lupus erythematosus. However, all these findings are compatible with a diagnosis of systemic sclerosis alone.

Case 3, a woman aged 45 years, gave a history of having had pneumonia as a child and an episode of juvenile rheumatism at the age of 13. She had had chilblains since childhood and episodes of Raynaud’s phenomenon in the hands for 10 years. In February, 1953, she complained of tiredness and a dragging pain across the chest, together with occasional episodes suggestive of pleuritic pain.

Examination.—There were no abnormal signs. Radiography of the chest showed bilateral apical scarring, but no evidence of active disease. Repeated examinations of sputum were negative for tubercle bacilli. The haemoglobin was 85 per cent., the red cell count 4.3 million per c.mm., and the white cell count 5,000 with normal differential. The erythrocyte sedimentation rate was 45 mm. in one hour. An electrocardiogram showed inversion of T-waves in all leads.

She remained in bed for a week and was off work for 2 months. An electrocardiogram, 3 months later, showed that the T-wave inversion had disappeared, although the erythrocyte sedimentation rate was still 45 mm. in one hour.

In August, 1953, although she was feeling well, the erythrocyte sedimentation rate had risen to 100 mm. in one hour and some fleshy lymph nodes were palpable in the left axilla. Histology of one of these showed only reactive sinus catarh.

Treatment.—She was started on Priscol 25 mg. three times a day for the Raynaud’s phenomenon in October, 1953, and was seen at intervals over the next few years.

Progress.—The only abnormality was a consistently elevated erythrocyte sedimentation rate between 40 and 60 mm. in one hour.

In March, 1955, she had a transient small effusion into the right knee. In 1956 she began to notice difficulty in swallowing and symptoms of mild oesophageal regurgitation.

She remained reasonably well, but when seen in 1959 was found to have developed some atrophy of the face.
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and nostrils. The mouth was small with radial scarring, and there were telangiectases on the face. The fingers were bluish with some scarring at the tips of the fingers, but relatively little atrophy. The left fourth finger tip was gangrenous and this was amputated. Barium studies showed the oesophagus to be dilated and completely inert. A hiatus hernia and oesophageal reflux were present. There was reduced movement in the stomach and a little delay in the duodenal loop. Radiography of the chest showed apical scarring only, and radiography of the hands showed no erosion of the terminal phalanges. The electrocardiogram showed low voltage and flat T-waves. The erythrocyte sedimentation rate was 54 mm. in one hour. The haemoglobin was 77 per cent., and the white cell count 3,400, with normal differential count. The total serum proteins were 8.0 per cent., albumin 3.6 per cent., globulin 4.4 per cent., albumin/globulin ratio 0.8. Serum electrophoresis showed an increase in the gamma globulin fraction. Lupus erythematosus cells were not found in the peripheral blood at this time. Biopsy of one of the inguinal nodes (which were still enlarged) showed only low-grade inflammation.

Treatment.—She was started on prednisolone and discharged on a maintenance dose of 5 mg. twice daily.

Further Progress.—In December, 1959, she developed gangrene of the tip of the left middle finger and this had to be amputated. One of the digital vessels showed complete occlusion of the lumen by dense fibrous tissue and another showed intimal thickening. Bilateral cervical sympathectomy was carried out at the same time.

She has since remained in fairly good health, apart from some difficulty in swallowing and attacks of Raynaud’s phenomenon. In June, 1960, L.E. cells were demonstrated in the peripheral blood for the first time. The erythrocyte sedimentation rate was 19 mm. in one hour, and the differential agglutination test and Wasserman reaction were both negative, but there was still a slight increase in gamma globulin in the serum.

Comment.—This is a most interesting case. In retrospect the illness in 1953, with malaise, possible pleuritic pain, lymphadenopathy, transient electrocardiographic changes, elevated erythrocyte sedimentation rate, anaemia, low normal white cell count, and later joint effusion, are all compatible with a diagnosis of systemic lupus erythematosus. Unfortunately, the blood was not examined for L.E. cells at that time. However, over the next 6 years the patient developed cutaneous, oesophageal, and duodenal changes which are diagnostic of systemic sclerosis. Moreover, histological changes in the digital arteries of an amputated finger were similar to those seen in other cases of systemic sclerosis. The presence of L.E. cells, a persistently elevated erythrocyte sedimentation rate for 7 years, raised gamma globulin, and reversal of the albumin/globulin ratio with anaemia and leucopenia, suggest that systemic lupus erythematosus and systemic sclerosis co-exist.

Discussion
The diagnosis of systemic sclerosis in these cases is not in doubt. In all three, episodes of Raynaud’s phenomenon were followed by typical cutaneous changes of acro sclerotic type, and these were accompanied by involvement of one or more systems of the body. In the first case there was no evidence of systemic lupus erythematosus to account for the presence of L.E. cells, but in the third case, and possibly in the second, systemic lupus erythematosus may co-exist with systemic sclerosis. None of the conditions sometimes associated with the finding of L.E. cells, mentioned earlier, were present.

The incidence of the L.E.-cell phenomenon in systemic sclerosis, or the association of systemic lupus erythematosus, may be commoner than it is realized. The three cases reported here were found in a series of sixteen cases of systemic sclerosis whose peripheral blood was examined for L.E. cells by the method of Zimmer and Hargraves (1952). Of the thirteen patients with a negative phenomenon, ten were females and three were males. In three of the females the gamma globulin was raised, but there was no anaemia, leucopenia, or thrombocytopenia, and the Wasserman reaction, Coombs’s test, differential agglutination test, and flocculation tests were negative. These investigations were all normal in the other patients.

Muehrcke, Kark, Pirani, and Pollak (1957) have also given details of a case in which there were features of both systemic lupus erythematosus and systemic sclerosis.

The patient was a 39-year-old Negro housewife. An initial diagnosis of systemic lupus erythematosus was made because of the intermittent course with fever, a butterfly facial rash typical of lupus erythematosus and confirmed by biopsy, lymphadenopathy, hepatomegaly, and evidence of involvement of joints, pleura, and pericardium. The serum globulin and thymol turbidity were raised and L.E. cells were repeatedly found. A year later she began to develop cutaneous signs of acro scleriosis, confirmed by a second skin biopsy. Later she developed Raynaud’s phenomenon and oesophageal changes typical of systemic sclerosis. Lupus erythematosus cells were still present.

Volpé and Hauch (1955) described the case of a 28-year-old woman with Raynaud’s phenomenon and acro scleriosis, in whom large numbers of L.E. cells were found. They rejected the diagnosis of systemic lupus erythematosus because of the absence of anaemia, leucopenia, and rash. The case was complicated, however, because the patient also had rheumatoid arthritis with nodules and had been given penicillin.

In the case of acro scleriosis reported by Arnold and Tilden (1957), the L.E.-cell phenomenon was
strongly positive on six occasions over a period of 11 months. At autopsy there was no evidence of systemic lupus erythematosus.

The case reported by Miller and Horgan (1960) is interesting in that L.E. cells were found in a patient with true scleroderma which, in almost all cases, is a purely cutaneous disorder.

Pathological evidence of a relationship between systemic lupus erythematosus and systemic sclerosis is shown by the occasional finding of "wire-loop" lesions in the glomeruli of patients with systemic sclerosis (Pollack, 1940; Bevans, 1945; Mathisen and Palmer, 1947; Allen, 1951).

The factor in the gamma globulin fraction of the serum responsible for the production of L.E. cells is one of several anti-nuclear factors present in systemic lupus erythematosus. Bardawil, Toy, Galins, and Bayles (1958) found a serum factor which had a reactive affinity with intranuclear material, probably desoxyribonucleoprotein, of autologous, homologous, and heterologous tissue, in cases of acrosclerosis and scleroderma as well as in systemic lupus erythematosus. Hall, Bardawil, Bayles, Mednis, and Galins (1960) were able to show the presence of an anti-nuclear factor in eight patients with scleroderma (clinical criteria not defined), two of whom had a few L.E. cells.

Although systemic sclerosis and systemic lupus erythematosus may occur in the same patient and small numbers of L.E. cells may be found in some cases of systemic sclerosis, the presence of L.E. cells should never be taken as diagnostic of systemic lupus erythematosus in the absence of any other evidence of the disease. The pathogenesis of systemic lupus erythematosus and systemic sclerosis is still unknown, but the finding of L.E. cells and antinuclear factors in each condition suggests that both may be associated with abnormal immunological responsiveness.

Summary

Lupus erythematosus cells are found occasionally, usually in small numbers, in conditions other than systemic lupus erythematosus. The literature has been reviewed.

Lupus erythematosus cells were found in three out of sixteen cases of systemic sclerosis. In one of these cases there was no other evidence of systemic lupus erythematosus; in the third case and possibly in the second, systemic lupus erythematosus and systemic sclerosis co-existed.

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REFERENCES


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Les cellules de lupus érythémateux dans la sclérose généralisée

RÉSUMÉ
On trouve quelquefois des cellules de lupus érythémateux, habituellement en petite quantité, dans des affections autres que le lupus érythémateux diséminé. On passe en revue la littérature sur ce sujet.
On trouva des cellules de lupus érythémateux dans trois cas sur seize de sclérose généralisée. Dans un de ces cas il n'y eut pas d'autres signes de lupus érythémateux diséminé; dans le troisième cas et possiblement dans le deuxième, le lupus érythémateux généralisé et la sclérose généralisée coexistaient.

Las células de lupus eritematoso en la esclerosis generalizada

SUMARIO
Células de lupus eritematoso, generalmente pocas, se hallan a veces en afecciones otras que el lupus eritematoso diseminado. Se pasa revista a la literatura sobre este sujeto.
Se hallaron células de lupus eritematoso en tres sobre dieciséis casos de esclerosis generalizada. En uno de estos casos no hubo otra evidencia de lupus eritematoso diseminado; en el tercer posiblemente en el segundo, el lupus eritematoso generalizado y la esclerosis generalizada coexistieron.