The Pseudo-L.E. Cell Phenomenon, with Report of a Case

By N. B. Kurnick

It is generally considered that the L.E. cell test is highly specific and may be relied upon for the diagnosis of systemic lupus erythematosus (SLE). However, a number of "false positive" tests have been noted, most often in cases of rheumatoid arthritis and drug hypersensitivity. In a large series of patients with apparently uncomplicated rheumatoid arthritis, Soffer (personal communication) found 5 per cent positive L.E. tests. In another series, as many as 34 per cent of 82 patients with rheumatoid arthritis had positive L.E. cell tests. However, in the latter series, all of the positives apparently occurred among the 46 patients with "atypical" disease (37% positive) and the 9 patients with "severe, nonarticular complications" (100% positive). In our own experience, in each case of long-standing rheumatoid arthritis in which L.E. cells were found, atypical clinical features were present. These included parenchymatous disease (most commonly recurrent pneumonitis and pericarditis), false positive serology, hemolytic anemia, and thrombocytopenia. We would suggest, therefore, that these do not represent false positive L.E. cell tests, but rather cases of SLE in which the presenting symptom for a number of years was arthritis. The arthritis is not infrequently deforming, but almost always to a lesser degree than is encountered in severe rheumatoid arthritis.

We believe that the concept of SLE requires revision. It appears that critical review of the patients with rheumatoid arthritis who have positive L.E. cell tests regularly discloses bizarre findings similar to those encountered in classic acute systemic lupus erythematosus. However, the former patients differ in that the disease is milder, chronic, more frequently remittent, less frequently involves the kidney, and begins later in life. We believe, therefore, that these patients fall into a group which may be termed chronic SLE. Indeed, a new term might profitably be introduced for the entire entity, both acute and chronic, since only the word "systemic" of the three in the present terminology is appropriate. We would propose "diffuse mesenchymopathy," since the disease appears to affect diverse mesenchymal tissues.

The other principal group of reported false positive L.E. cell tests is that of drug hypersensitivity. In many of these, the disease appears not to have followed the usual self-limiting course of drug reactions, but has run a protracted course without complete remission. In our own experience we have seen a number of patients in whom the differential diagnoses included SLE and miliary
tuberculosis. In several of these patients, following repeated negative L.E. cell tests, therapeutic trial with para-aminosalicylic acid resulted in exacerbation of symptoms, at which time L.E. cells were found. Our interpretation of these cases is that they were examples of SLE with negative L.E. cell tests originally. As in many patients with SLE, these individuals were hypersensitive to drugs (notably the sulfonamides), and the induced exacerbation was associated with the emergence of the L.E. cell phenomenon. We have seen a similar phenomenon in a patient whose disease was exacerbated by a therapeutic trial of quinaacrine.

Another group of individuals reveals what we shall term pseudo-L.E. cell tests. We believe that a number of so-called false positive tests may belong to this group. The group may be subdivided further into a group in which the resemblance to the L.E. cell is morphologic only, but the inclusion is chemically different, and another group in which cells are found which are morphologically and chemically indistinguishable from the true L.E. cell, but in which the pathogenesis is obviously different. In the first sub-group of pseudo-L.E. cell phenomena falls the morphologic change occasionally found in amyloidosis in which the inclusion consists of amyloid. This can be distinguished by special staining methods for amyloid, by the negative Feulgen test for deoxyribonucleic acid (DNA), and by the fact that it is present without the incubation required to elicit the L.E. cell phenomenon. Also in this group may be included the induced “L.E.-like” cells of Inderbitzin, in which the inclusion is Feulgen-negative and appears to consist of protein or protein-polyvinyl sulfonate complexes, and the L.E.-like cell induced by fungi.

In the second sub-group of pseudo-L.E. cells, polymorphonuclear neutrophils are found with a homogeneous cytoplasmic inclusion containing depolymerized DNA, just as in the L.E. cell. However, examination of such slides often reveals numerous examples of leukophagocytosis, in which the inclusion is a whole cell or an intact nucleus. It appears from this observation that the occasional “L.E. cell” found in these preparations represents digestion of the phagocytosed nucleus. In the true L.E. cell phenomenon leukophagocytosis is very rarely (if ever) encountered. Some of the reported instances of positive L.E. cell tests in drug reactions appear to fall into this group. Meyler has documented several such instances.

We have discussed the mechanism of the L.E. cell phenomenon elsewhere. In summary, we believe that the abnormal factor in the γ-globulin fraction of serum from an L.E. patient alters the cell membrane so as to permit access of a proteolytic enzyme (in Fraction III) into the cell. This enzyme inactivates the cell’s inhibitor of deoxyribonuclease (DNase). As a consequence, the cell’s DNase causes depolymerization of the nuclear DNA. Phagocytosis follows, rather than precedes, the depolymerization. In the smear of a positive L.E. preparation the following may usually be observed: (1) cells with depolymerized (homogenized) nuclear segments, often still connected with intact segments; (2) completely depolymerized nuclei; (3) extracellular masses of depolymerized DNA no longer recognizable as nuclei morphologically, and finally (4) phagocytosed homogeneous depolymerized DNA varying in size from very small droplets to masses which fill the cytoplasm. This picture is quite different from that of the pseudo phenomenon in which the inclusions are mostly intact nuclei,
while only occasional cells contain a homogenized mass slightly larger than a normal nucleus. No droplets or extra-cellular depolymerized DNA masses are seen. Occasionally, leuko-agglutination, which may resemble “rosettes” superficially, is also encountered in the pseudo-phenomenon. The distinction between leukophagocytosis and the L.E. cell phenomenon has been previously emphasized by Hargraves. We agree with him that the “Tart cell” is not related to the L.E. cell phenomenon, although others have suggested that the Tart cell is a precursor of the L.E. cell.

We believe that the “L.E. cell phenomenon” induced experimentally with antileukocytic sera is an example of this pseudo-L.E. cell phenomenon. In our own experience with antileukocytic sera, the major phenomena are agglutination and phagocytosis. Only an occasional phagocytosed nucleus undergoes depolymerization to give the picture of an L.E. cell. Although some of these authors (notably Miescher; see also Heller and Zimmerman) consider that this is the mechanism of the L.E. cell phenomenon, we cannot agree. It is our opinion that the spontaneous phenomenon of leukophagocytosis is responsible for some reports of false positive tests. A report of such a case follows.

CASE REPORT

The patient, a 46 year old white male automotive engineer, was admitted to the Long Beach Veterans Administration Hospital on 5/25/55. In February 1955, approximately a week after administration of a mercurial prophylactic intraurethrally, the patient developed a rapidly progressive, generalized, pruritic, painful dermatitis. The lesions were at first dry, but following local ointment therapy became edematous, then weeping and exfoliative. In March 1955 he was admitted to another hospital because of marked oliguria. The urine revealed many WBC, RBC, 1+ albumin. Granulocytosis and slight azotemia were reported. In early April he noted dysphagia, peri-orbital and facial edema, pain in the shoulders and arms, and progressive weakness. He was considered to have mercurial intoxication with renal damage and exfoliative dermatitis, and was treated with BAL, cortisone, vitamin B12, intravenous calcium, anti-histaminics and autologous blood intramuscularly. A muscle biopsy was negative. A right mediastinal mass, interpreted as a possible thymoma, did not respond to 890 r x-ray therapy and a prostigmine test for myasthenia gravis was negative. Progressive dysphagia, aphasia, generalized weakness, weight loss (210 to 175 lbs.), and dermatitis prompted his transfer to this institution.

Past history was noncontributory. Family history revealed that his father died of tuberculosis and one brother had had a nephrectomy for tuberculosis. His mother and both daughters suffered from hay fever. The patient had had no known allergic manifestations in the past.

Physical examination on admission revealed a well-oriented, somewhat drowsy, 6'3" well-developed white male who appeared chronically ill. Speech was nasal and slurred and a nasal gastric tube was in place. The skin revealed healed atrophic areas symmetrically distributed over the chest and upper abdomen, scaly vesicular lesions over the right anterior thigh and left knee, several bullae and granulating ulcers over both scapulae. No muscle atrophy was noted, but generalized flabbiness of muscles, particularly of the calves was reported. The remainder of the examination was essentially negative. Blood pressure was 120/70, pulse 100.

Multiple laboratory examinations revealed normal hemograms except for slight anemia.

* In a later paper, however, Delacretaz, Inderbitzin, and Miescher describe a “pseudo-L.E. cell phenomenon” in which the cytoplasmic inclusion retains more or less nuclear structure. They do not discuss its mechanism, but do make clear its distinction from the “specific L.E. cell phenomenon.” They ascribe reports of false positive tests, including by implication their own, to this “pseudo-L.E. cell phenomenon.”
and rapid sedimentation rate; blood chemistry revealed slight hypo-albuminemia, no azotemia or electrolyte imbalance; urinalyses varied from negative to occasional microscopic hematuria. Electroencephalography revealed very low alpha frequency; electrophotography on 9/6/55 was interpreted as consistent with a primary muscle disease such as polymyositis which is now rather far advanced with replacement of a good deal of muscle by fibrous tissue'. Iliac crest bone marrow revealed myeloid hyperplasia. Pulmonary function was slightly impaired. X-ray of the chest revealed the previously noted lobulated anterior mediastinal mass, unchanged from the examination of 2 months previously. Biopsies early in his hospital stay included (1) tongue, which disclosed chronic inflammation in the muscle and dyskeratosis of mucous membrane, (2) right trapezius muscle, which showed degeneration and fibrous replacement of muscle and perivascular inflammatory cuffing compatible with dermatomyositis, (3) bronchial mucosa, which was negative, as were smears of sputum, and (4) skin, interpreted as nonspecific dermatitis.

L.E. cell preparations on 6/2, 6/3 and 6/6 were reported as strongly positive, including numerous rosettes; but several later examinations were negative. The diagnosis of systemic L.E. was, therefore, believed to have been established. On reviewing these slides, however, this author was unable to concur in the interpretation of the "positive" L.E. tests. He noted that "in all slides, many polymorphonuclear neutrophils are seen with cytoplasmic inclusions which show considerable nuclear structure. A rare inclusion is homogeneous. No homogeneous droplets or extra-cellular homogeneous masses are seen." The rosettes appeared to be examples of leukoagglutination. He considered therefore that this was an example of leukophagocytosis, possibly secondary to a neoplastic disease. An L.E. cell test on 6/9 showed only occasional erythrophagocytosis and vacuolated granulocytes. Subsequent tests were entirely negative.

Without specific therapy the patient's dysphagia and dermatitis gradually improved, but his diffuse myalgias and weakness persisted and revealed intermittent maculopapular eruptions over the lower extremities and edema. He developed thickening of the skin of his hands and induration in the subdeltoid area, suggestive of scleroderma.

In July 1955 a 1 cm. firm, fixed subcutaneous nodule was felt in the left upper quadrant of the abdominal wall. Biopsy of this mass disclosed "anaplastic adenocarcinoma, metastatic to skeletal muscle." Since it appeared probable that the primary carcinoma was bronchogenic, in view of the bronchostenosis noted on bronchography (despite the negative bronchial biopsy) and the mediastinal mass, extensive radiotherapy was applied to the chest. The patient developed a lung abscess and deteriorated rapidly thereafter. He expired on 12/18/55.

Post-mortem examination revealed an anaplastic oat cell carcinoma of the right main bronchus, with necrosis and abscess formation, metastases to regional, cervical, axillary and mesenteric lymph nodes, myocardium, left adrenal gland, abdominal wall, duodenal wall, and pancreas, and terminal right suppurative broncho-pneumonia. Skin and muscle areas not invaded by tumor revealed only increased pigmentation, slight fragmentation of collagen, fibrous replacement of muscle. These changes were not considered diagnostic of "collagen disease." Compression of the esophagus by the mediastinal mass was considered to have accounted for the dysphagia. No pathology was noted in the central nervous system.

**DISCUSSION**

This case was presented to illustrate the development of leukophagocytosis with pseudo-L.E. cell formation during the course of carcinomatosis. It appears probable that the dermatomyositis which the patient presented clinically, and which has been reported as a complication of visceral carcinomatosis²¹ was due to the development of antibodies against the neoplasm which cross-react with other tissue antigens. Stefanini²³ has presented evidence of the development of agglutinating auto-antibodies against platelets, erythrocytes, and leukocytes in patients with neoplasia. In the patient described in this report, mesenchymal auto-antibodies active against muscle, connective tissue, and leukocytes appear to have developed. The improvement in the dermatomyositis and the disappear-
ance of the pseudo-L.E. cell phenomenon, as the carcinoma progressed and metastasized, suggest the possibility that the progressively enlarging lesion may have adsorbed the circulating auto-antibodies, thereby lowering the systemic titer.

Our concept of the pathogenesis of systemic lupus erythematosus implicates mesenchymal cell auto-antibodies. However, the mechanism of their action, according to our hypothesis is different from that which may be assumed in this patient. In the latter, a "complete" antibody leading to tissue damage, leukophagocytosis and leuko-agglutination appears to be active. In systemic lupus,
on the other hand, the antibody itself appears to be "incomplete," in the sense that it does not itself directly produce the L.E. cell picture and does not lead to agglutination or phagocytosis.\textsuperscript{15, 16} Whereas patients with systemic lupus erythematosus not infrequently develop a variety of auto-antibodies (anti-thromboplastin,\textsuperscript{2, 23} hemolysins,\textsuperscript{24-26} erythrocyte agglutinins\textsuperscript{27, 28}) the L.E. serum factor apparently acts against the cell membrane only.\textsuperscript{15, 16} Secondary to the change in permeability which results, proteolytic enzymes enter the cell body, destroy the intracellular inhibitor of desoxyribonuclease,\textsuperscript{14} permitting the desoxyribonuclease to depolymerize the nuclear DNA.\textsuperscript{16} This depolymerization antecedes release of the nuclear material and its subsequent phagocytosis.\textsuperscript{2, 16, 29} The sequence of morphologic changes in the L.E. cell phenomenon is readily seen in smears.\textsuperscript{17a, 30} The very different sequence of events in the pseudo-L.E. cell phenomenon described here is also readily inferred from smears, in which the sequential changes in the cytoplasmic inclusions from whole leukocytes to bare nuclei with intact structure, to homogeneous nuclei may be detected (fig. 1). This,
too, is the mechanism of the “Tart cell”, which has been previously described and differentiated from the L.E. cell.\(^1\) Weiss and Swift,\(^18\) however, believe that the “advanced Tart cell”, in which nuclear homogenization has occurred may be equivalent to the L.E. cell phenomenon (although they warn against diagnosis on this basis alone). We do not agree with this interpretation, and believe that the pseudo-L.E. phenomenon must be distinguished from the true reaction. The predominance of leukophagocytosis and/or agglutination is the diagnostic feature in this pseudo-phenomenon. The pseudo-L.E. cell phenomenon does not include extra-cellular homogeneous masses\(^{17a}\) (“globs”\(^{17b}\)) which we consider a \textit{sine qua non} for the true L.E. phenomenon.

We believe that leukophagocytosis, leading to the pseudo-L.E. cell phenomenon probably accounts for some examples of misdiagnosis of systemic lupus (as in the case reported here) and reports of nonspecific positive L.E. cell tests. Leukophagocytosis is also the mechanism of pseudo-L.E. cell production in experiments with induced heterologous leukoantibodies.

**Summary**

An example of leuko-phagocytosis secondary to metastatic bronchogenic carcinoma is presented. The transitory development of leukoagglutination and leukophagocytosis (pseudo-L.E. cell phenomenon) led to the erroneous diagnosis of systemic lupus erythematosus. The differentiation between the L.E. cell phenomenon and the pseudo-phenomenon is discussed.

**Summario in Interlingua**

Es presentate un exemplo de leuco-phagocytose secundari a metastatic carcinoma bronchogene. Le disveloppanimento transitori de leucoagglutination e leucophagocytose (pseudo-phenomeno L.E.) causava le diagnose erronee de systemic lupus erythematos. Es discusice le differentiation inter le phenomeno L.E. e le pseudo-phenomeno.

**Addendum**

After this paper had been submitted for publication, a somewhat similar view was presented by Goukhin, E. N., and Diggs, L. W.: L.E. and L.E.-like cells. South. M. J. \textbf{49}: 560–566, 1956. We are in agreement with their morphological differentiation. However, we do not agree that the “L.E. factor” acts directly on the nucleic acid.\(^{18a}\) We would also emphasize that the development of “L.E. cells” from the “L.E.-like” cells does not signify SLE.

**References**


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