

SEZARY SYNDROME WITH ARTHROPATHY

Report of a Case

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Abstract. A 65-year-old black female with Sezary syndrome had generalized intractable pruritus, erythroderma, alopecia, onychogryphosis, lymphadenopathy and hepatomegaly. Abnormal lymphocytes with large, convoluted and grooved nuclei (Sezary cells) were identified in the skin and peripheral blood. A striking feature of her disease was severe, deforming arthropathy of the hands and knees, a clinical finding which has been described previously in only one patient with Sezary syndrome. At necropsy no associated lymphoma was found.

Key words: Sezary; Erythroderma; Rheumatoid arthritis; Keratoderma

Although the diagnosis of Sezary syndrome has been expanded by some authors to include leukemic and lymphoma patients with an associated erythroderma (4, 6, 11, 18), there is a distinct syndrome which occurs in otherwise healthy individuals characterized by a severe, pruritic erythroderma and infiltration of the skin and peripheral blood by atypical lymphocytes (22, 25). Additional features often present are benign lymphadenopathy, alopecia, onychodystrophy, keratoderma, hyperpigmentation, leukoderma, chronic blepharitis, peripheral and facial edema and recurrent pyoderma (1, 25, 29). The patient described in this report had all of these findings and, in addition, had a severe, deforming arthritis of the hands and knees.

CASE REPORT

A 65-year-old black female was admitted to the hospital complaining of generalized severe pruritus, erythema and thickening of her skin, and stiffness and pain in her hands, wrists, knees and ankles. Her family history was unknown. About 10 years prior to admission the patient first noted progressive alopecia. Subsequently, she developed an ecze-

matous eruption on her hands and forearms which gradually spread until the skin of her entire body was red, thickened, and scaly. During 5 years prior to death, she became incapacitated by increasing stiffness of the joints of the hands, knees, and ankles and by marked thickening of the palmar and plantar skin. She had been seen by many physicians and had received oral corticosteroids, topical corticosteroids, antihistamines, multiple vitamin preparations, and a variety of topical keratolytic and anti-inflammatory agents with no amelioration of symptoms. Her general health, however, remained remarkably good, and she felt well despite her discomfort and grotesque appearance.

Physical examination revealed an elderly lady who incessantly rubbed and scratched her skin. The entire integument was deeply erythematous, hyperpigmented, and lichenified with diffuse branny scaling. Small patches of leukoderma were scattered over the body with a large depigmented area on the vertex of her scalp (Fig. 1). All body hair was absent except for a few tufts remaining on her scalp. She had bilateral, chronic conjunctivitis and blepharitis. There was swelling of the proximal interphalangeal and metacarpophalangeal joints and ulnar deviation and flexion contractures of the digits of both hands (Fig. 2). Her knee joints were swollen and tender. She had severe hyperkeratosis of her palms and soles, and her nails were hypertrophic and gryphotic (Fig. 3). Her lower legs were slightly edematous and had many small infected ulcerations. Multiple large (3-6 cm), rubbery, discrete, non-tender lymph nodes were visible and palpable in the cervical, axillary and inguinal regions. The liver edge was palpable just below the right costal margin, but the spleen was not felt. Examination of the heart and lungs was normal, as was the blood pressure.

Six skin biopsies were obtained during a 4-year-period, and all demonstrated similar features: a thickened parakeratotic stratum corneum, acanthotic epidermis and a dense band-like lymphocytic and monocytic infiltrate in the dermis with no predilection for vascular or adnexal structures. The diagnosis was always chronic non-specific dermatitis. A snap-frozen skin biopsy specimen was examined with fluorescein-tagged antihuman IgG, IgA, IgM, and Beta₂C and showed no specific fluorescence. Electron microscopic examination of two skin biopsies disclosed the presence of atypical lymphocytic cells infiltrating the dermis. These cells had a high

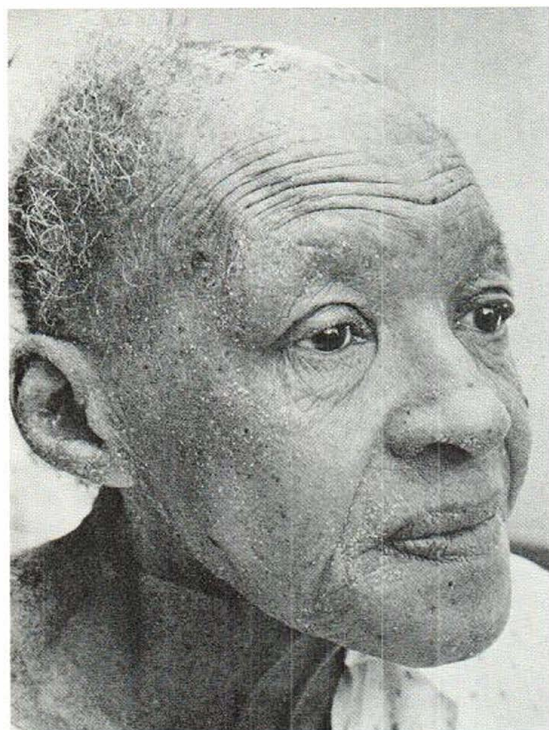


Fig. 1. Diffuse scaling and erythroderma of the face. Note the scarring alopecia.

nucleus/cytoplasm ratio and a distinctive nucleus which was either convoluted or grooved, with multiple indentations (Fig. 4).

One inguinal, two axillary and two cervical lymph nodes were removed during a 5-year period, and the findings in all were consistent with a diagnosis of dermatopathic lymphadenopathy. After each biopsy, the patient developed a

wound infection from *S. aureus* or B-hemolytic streptococci which responded to appropriate antibiotic therapy.

Two bone marrow preparations obtained during her disease course showed normal erythropoiesis and myelopoiesis. The total peripheral white blood count ranged from 3 800 to 8 800 with 4 to 17% eosinophilia. Atypical lymphocytes were noted on the peripheral smear during her final admission. These atypical cells had large, dark, convoluted nuclei and scanty cytoplasm with vacuoles encircling the periphery of the cell. Chromosome studies of peripheral blood leukocytes demonstrated a normal female karyotype and no deletions, aneuploidy or anomalies of cultured cells. In vitro lymphocyte transformation studies showed a response of 40-fold to phytohemagglutinin, four-fold to candida antigen, two-fold to purified protein derivative and no response to streptolysin O.

Rheumatoid factor was consistently present for 4 years. During the final admission latex fixation titer was 1:2,560 and sheep cell agglutination titer 1:2,048. Antinuclear antibody, lupus erythematosus cell preparations, and cryoglobulin determinations were negative. Serum total hemolytic and Beta₂C levels were normal. Joint fluid from the knee had a latex fixation titer of 1:1,200 and a Beta₂C level of 33 mg% (normal 40–60 mg%).[†] Radiographs of the hands demonstrated soft tissue swelling and erosions of the carpal bones, the distal radius and ulnar bones of the right wrist. Protein electrophoresis on six occasions showed a consistently elevated gamma globulin ranging from 4.2 to 6.0 g%. Quantitative immunoglobulin levels were IgG 2 400 mg%, IgA 1 300 mg% and IgM 200 mg%.

The following laboratory determinations were consistently normal: urinalyses, BUN, creatinine, uric acid, alkaline phosphatase, bilirubin, serum glutamic oxaloacetic transaminase, lactic dehydrogenase, fasting blood sugar, cholesterol, calcium, phosphorus, VDRL. Chest films showed fixed fibrotic apical infiltrates. Sputum and lymph node cultures for acid-fast bacilli were negative.

During her last admission the patient was found to be hypothyroid with a T₄ of 1.2 µg/100 ml (normal 5–13.7 µg/100 ml) and hypoadrenal with a plasma cortisol level of 6

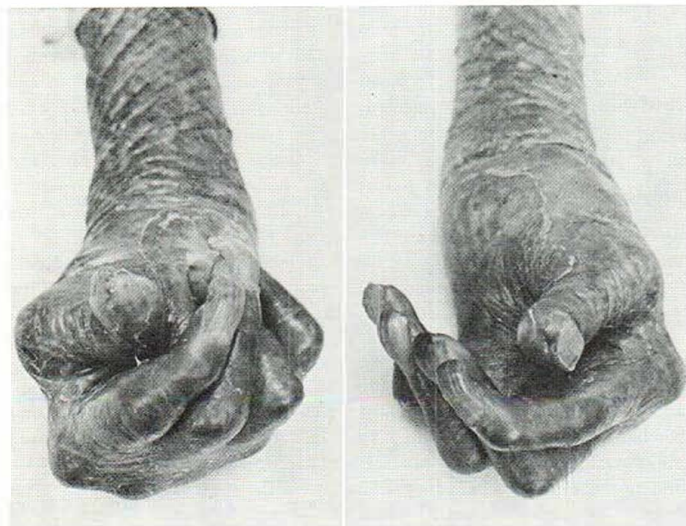


Fig. 2. Severe lichenification, hyperpigmentation and erythroderma of arms and hands. Also shown are palmar hyperkeratosis, onychogryphosis and severe flexion contractures of digits.



Fig. 3. Feet, showing exfoliative erythroderma and onychogryphosis.

$\mu\text{g/ml}$ (normal 10–25 $\mu\text{g/ml}$) and urinary 17-hydroxy-corticoids of 1.2 mg/24 hours (normal 3–11 mg/24 hour). TSH was 2.0 $\mu\text{U/ml}$ (normal up to 10 $\mu\text{U/ml}$) and FSH was 96 mIU/ml (normal 6–48 mIU/ml). Her hospital course was complicated by bacteremic shock which responded to antibiotic therapy, cortisone acetate and adequate thyroid replacement. She was eventually discharged from the hospital to a nursing home. Low-dosage alkylating therapy was being considered pending adequate follow-up care and nursing home cooperation when she suddenly expired during the night.

Necropsy revealed an emaciated elderly female with cutaneous changes as described above. There was moderate generalized atherosclerosis, marked stenosis of the left anterior descending coronary artery, an enlarged heart, a moderate pericardial effusion and chronic inflammation of the pericardium. Multiple foci of pulmonary fibrosis were present. The thyroid gland and adrenal cortices were hypoplastic. There was arterial and arteriolar nephrosclerosis. The liver, spleen and gastro-intestinal tract were normal. The lymph nodes showed dermatopathic lymphadenopathy. Microscopic abnormalities of skin were similar to those seen on skin biopsies. The immediate cause of death was not determined.

DISCUSSION

The Sezary syndrome was first documented in a publication which described 2 patients with generalized erythroderma and abnormal cells in the peripheral blood (22). Nevertheless, specific diagnostic criteria for this disorder were not well established until recently, and other clinical entities were often

classified as, and confused with, the Sezary syndrome. The current upsurge of interest in this syndrome by a number of investigative groups has led to a more precise definition of the clinical and histopathological features and the morphologic, cytogenetic and functional properties of the circulating atypical lymphocyte (27).

The patient described above had the typical clinical and cytologic findings of Sezary syndrome but, in addition, had a severe arthropathy of multiple joints. In a large series of 28 patients reported with Sezary syndrome (28), arthritis was not mentioned and rheumatoid factor and antinuclear antibody determinations were not recorded. There have been only two previous reports of arthritis associated with this syndrome. The patient described by Alderson (1) had ulnar deviation and flexion contractures of both hands very similar to our patient. Rheumatoid factor and antinuclear antibody were not determined, however. The patient discussed by Paradinas (18) probably had less severe involvement since there is no description of joint changes, and both rheumatoid factor and antinuclear antibody titers were negative. Our patient had a striking elevation of rheumatoid factor in her serum throughout her disease course as well as a significant titer in her synovial fluid and a depressed synovial fluid complement level. She had pain on motion, symmetrical joint swelling, soft tissue thickening, roentgenographic changes typical of rheumatoid arthritis and a positive rheumatoid factor, fulfilling five of the criteria of the American Rheumatism Association (31) required for diagnosis of rheumatoid arthritis.

The Sezary cell has been identified as an abnormal thymus-derived lymphocyte. In 1968, Lutzner (13) described its ultrastructural features, emphasizing the characteristic grooved and folded nucleus. In a more recent study (15), two subtypes were delineated—a large cell with a serpentine nucleus and a small cell variant with an indented nucleus. These cells, however, are not pathognomonic for Sezary syndrome since they have also been found in patients with mycosis fungoides and other inflammatory non-lymphomatous skin diseases (10, 12, 14, 17). Sezary-like cells have also been seen in tissue culture explants obtained from normal and mycosis fungoides skin (9). These studies suggest that the Sezary cell may be a reactive cell of lymphocytic origin which is present in small numbers in diverse diseases but which occurs with high frequency in patients with Sezary syndrome.

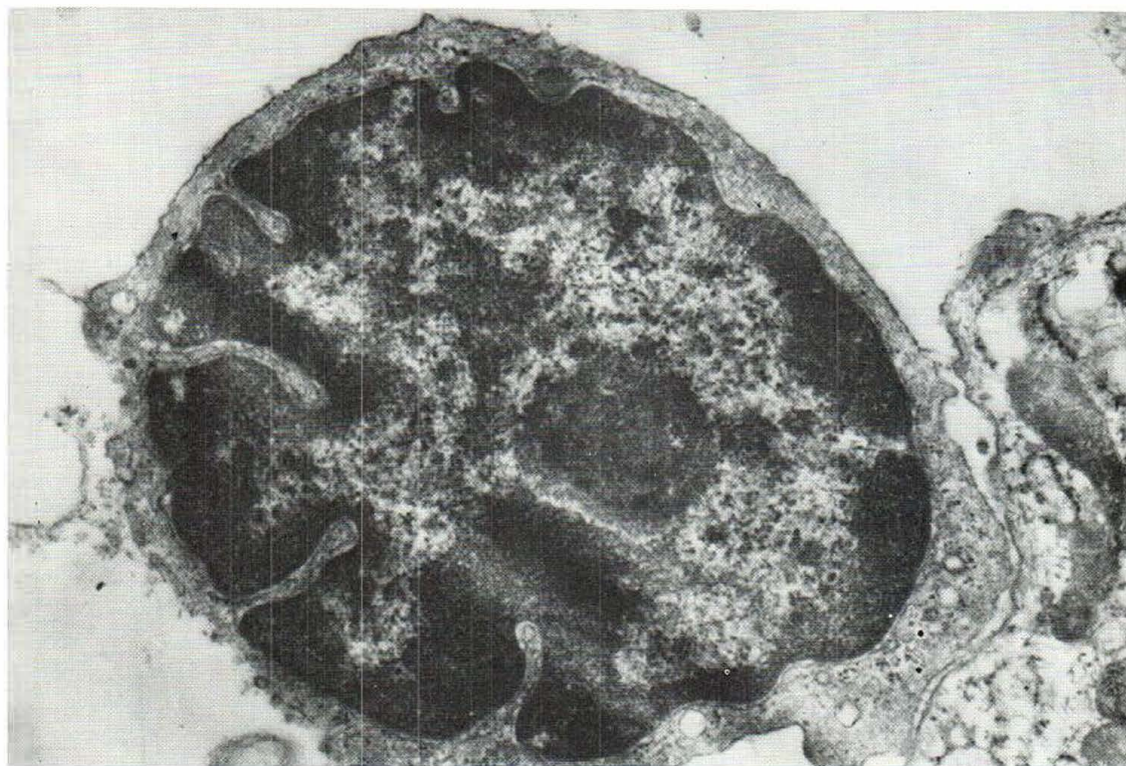


Fig. 4. Abnormal lymphocyte from skin biopsy. Nucleus is large, with multiple indentations. ($\times 10\,100$).

Evidence for thymic derivation of the Sezary cell has come from a variety of sources. Several investigators have now shown that these abnormal cells form rosettes with sheep erythrocytes and lack complement receptor sites and surface immunoglobulins (2, 3, 30). Crossen's study of lymphocytes from one patient with Sezary's syndrome demonstrated a definite mitogenic response to stimulation with phytohemagglutinin (5). Our patient had lymphocytes which responded to PHA, PPD, candida and streptolysin O antigens. All responses were somewhat depressed as compared with controls, however. Cytogenetic studies of peripheral blood lymphocytes were normal in our patient, but some individuals with Sezary syndrome have had distinctive findings. Heteroploid cells (5), increased DNA content, and distinctive chromosomal markers have all been described. Of particular interest is the observation that two types of Sezary cell can also be differentiated on the basis of chromosomal studies: a large cell type with convoluted nucleus and near-tetraploid DNA values and a small cell variant with diploid DNA values (15).

The relationship of Sezary syndrome to malignant lymphoproliferative disorders and mycosis fungoides has been the subject of much debate. Some investigators (29) regard Sezary syndrome as a benign dermal lymphoproliferative disease, which, on occasion, may result in lymphoma. Crossen et al. (5) have suggested that the Sezary cell is potentially neoplastic but is still able to respond to controls. Transformation to a true lymphoma may follow the breakdown of normal control mechanisms. Others view the Sezary syndrome as part of the spectrum of malignant lymphoproliferative disorders (4, 11, 20, 21, 23). Edelson (6), in a study of neoplastic cells obtained from 3 patients with mycosis fungoides and 3 patients with lymphocytic leukemia and exfoliative erythroderma, determined that these cells had membrane properties of thymus-derived lymphocytes. Clearly, in some instances, the Sezary syndrome is closely related to the malignant lymphoproliferative disorders, though in other instances, it appears to be a separate and basically benign disease state.

It is interesting to note the similarities between

Sezary syndrome and Sjögrens syndrome. The latter disease is characterized by a massive mixed T- and B-cell infiltrate in the salivary, lacrimal, nasotracheal and bronchial glands and is associated with autoimmune disorders such as rheumatoid arthritis. In some of these patients, a generalized lymphoproliferative process may occur and assume a variety of clinical forms including pseudolymphoma, reticulum cell sarcoma and Waldenström's macroglobulinemia. Sjögrens syndrome has been called a "pivotal" disease that links the benign lymphoid infiltration of autoimmune disease with the more malignant forms of lymphoproliferation (24).

The association of Sezary syndrome and rheumatoid arthritis may be entirely fortuitous in this patient. On the other hand, proliferation of lymphoid cells is central to the pathogenesis of both autoimmune disease and the lymphoproliferative group of disorders. Benign lymphadenopathy is a frequent finding in rheumatoid arthritis (16), and large numbers of T-cells are present in the synovium and synovial fluid of involved joints (26). Furthermore, rheumatoid arthritis has been reported to improve following the removal of lymphocytes by thoracic duct drainage (19), suggesting that T-cells play a role in the pathogenesis of rheumatoid arthritis. In the immune response, an interaction occurs between T- and B-cells with T-cells amplifying antibody production by release of mediators which maximally stimulate B-cells (7-8). The activated T- and B-cells may account for the massive production of rheumatoid factor in selected patients. The nature of the antigenic stimulus that attracts the T-cell to the tissue site, the skin, is not known, however, in the Sezary patient, the initial rash has been known to follow an allergic contact dermatitis (28). It may be postulated that normal mechanisms regulating the immune process become deranged and permit uncontrolled lymphocytic proliferation and perpetuation of the inflammatory process observed clinically as erythroderma and intractable pruritis characteristic of Sezary syndrome.

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