Lymphedema, Pleural Effusions and Yellow Nails
Associated Immunologic Deficiency*

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Two siblings with congenital lymphedema had recurrent pleural effusions in adult life. The brother also had yellow toenails and thus represents an example of the syndrome of lymphedema, pleural effusions, and yellow nails. An immunologic deficiency state in these patients was suggested by recurrent bronchopulmonary and skin infections, hypogammaglobulinemia, and episodes of lymphopenia. The sister developed Hodgkin's disease terminally, an interesting occurrence in keeping with the increased incidence of lymphatic malignancies in patients with immunologic deficiency.

INTRODUCTION

The association of hereditary lymphedema and pleural effusions was encountered in two siblings studied at the Montefiore Hospital.1 The purpose of this report is to provide additional data on the patients, both of whom have died; the sister (L.F.) with disseminated Hodgkin's disease and the brother (E.F.) with cor pulmonale. The combination of lymphedema, pleural effusion and yellow nails has evolved into a new clinical entity.2,3 There is evidence to suggest that the syndrome may also include an immunologic deficiency state.

CASE REPORTS

Patient E.F. was born in 1914 with edema of both lower extremities. The swelling extended proximally to involve the thighs during childhood, the scrotum after puberty, and finally the abdominal wall and hands. Frequent skin infections accompanied by high fever occurred as often as five times yearly, but responded to treatment with penicillin. The patient's sister (L.F.) with cor pulmonale. The combination of lymphedema, pleural effusion and yellow nails has evolved into a new clinical entity.2,3 There is evidence to suggest that the syndrome may also include an immunologic deficiency state.

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Case reports

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Blood pressure was 124/78; respiratory rate was 24. The patient had a chest deformity with a marked scoliosis and a dorsal kyphosis.

Hematocrit 40 percent, white blood cells 5,100, 78 polymorphonuclear leukocytes, 1 eosinophil, 15 lymphocytes and 6 monocytes. Chest x-ray showed bilateral pleural effusion. Pulmonary function tests revealed a vital capacity of 23 percent of predicted, maximum breathing capacity, 20 percent of predicted. Bronchospirometry showed that the tidal volume of the right lung was only 25 percent of the total tidal volume. The vital capacity of the right lung was only 9 percent of that predicted or 28 percent of the total. Skin testing with purified protein derivative was negative in first and second strengths. Pleural fluid from the right chest contained 3.1 gm percent protein, and from the left chest 3.4 gm percent.

August 3, 1959 a right pleurectomy was performed. The pleural space contained fibrinous, viscid material. The lung was bound to the mediastinum by a thickened membrane. The membrane was incised, and the lung was decorticated by dissection. Microscopic study of the membrane showed a thick layer of fibrocollagenous tissue containing a large amount of amorphous and fibrinous debris with a scattering of lymphocytes and polymorphonuclear leukocytes.

The patient improved slightly following surgery but failed to make any dramatic progress. He was hospitalized for a second time in December, 1961, with left lower lobe pneumonia which responded to treatment with chloram-
Phenicol. At that time the total serum protein was 5.8 gm with albumin 2.9 gm and globulin 2.9 gm. Chest x-ray showed free pleural fluid on the left and loculated fluid on the right. The patient developed right heart failure for which he was again hospitalized at Montefiore in 1962. The hematocrit was 42 percent, white blood cells 10,100, 80 polymorphonuclear leukocytes, 4 eosinophils, 16 lymphocytes. The total protein was 6 gm with an albumin of 2.5 gm and a globulin of 3.5 gm. Serum protein electrophoresis showed a definite decrease in the gamma globulin (Fig 1). At this time chest x-ray study, including decubitus films, showed no free pleural fluid but there was loculated fluid on the right and pleural thickening and loculated fluid on the left.

Thereafter the patient became progressively disabled with dyspnea and right-heart failure. He died during his fourth and final admission to Montefiore Hospital on April 11, 1965.

Autopsy revealed severe pulmonary fibrosis of the right lung and a moderate degree of pulmonary fibrosis of the left lung. There were extensive pleural adhesions bilaterally associated with marked pleural fibrous thickening. The hilar and tracheobronchial lymph nodes were grossly unremarkable. The spleen contained a normal white pulp and abundant plasma cells. The heart weighed 425 gm. There was dilatation and hypertrophy of the right ventricle.

Patient L.F. was born in 1908 with edema of the lower extremities which gradually progressed proximally to involve the thighs, abdominal wall and the hands. The patient enjoyed normal activity and worked as a bookkeeper. Frequent attacks of skin infection, accompanied by fever, were successfully treated with penicillin. At age 39, bilateral pleural effusions were noted on a routine chest roentgenogram. In 1953, an intracapsular cataract extraction was performed on the right eye. In 1960, the patient was hospitalized for the first time at Montefiore with cough, malaise, fever, and dyspnea on exertion. There was no history of diarrhea or bulky bowel movements. Blood count on admission showed hematocrit, 39 percent, white blood cells 3,000, 78 polymorphonuclear leukocytes, 1 stab, 20 lymphocytes and 1 monocyte; 1,150 ml of straw-colored fluid was removed by thoracentesis from the right pleural cavity. The specific gravity was 1,024, protein was 3.5 gm percent. glucose 108 mg percent and cholesterol 63 mg percent. The left pleural cavity yielded 1,000 ml of fluid containing 3.6 gm percent protein. The total serum protein was 5.5 gm; albumin 2.9 gm and globulin 2.6 gm. The patient was treated with bedrest and diuretics. Thoracenteses yielded an additional 1400 ml from the right pleural cavity and 750 ml on the left. Cultures of the fluid showed no growth.

The patient was discharged from the hospital and maintained on diuretic therapy. Bilateral pleural effusions remained. In 1962, during an episode of skin infection, blood count showed hematocrit, 46 percent, white blood cells 2,500, 64 polymorphonuclear leukocytes, 3 stabs, 27 lymphocytes, 3 eosinophils, 1 baso, and 2 monocytes. There was a definite change in the course of the patient's illness during June of 1966 with the onset of increased edema, dyspnea, orthopnea and easy fatigability. The patient was hospitalized for the third time from June 9th to July 18th, 1966, and then for the final time on August 18th, 1966.

Physical examination during the final admission revealed massive edema of the lower extremities with moderate edema of the abdominal wall and upper distal extremities. There were no yellow nails. There was no lymphadenopathy in the neck, axillary or inguinal areas. There was clinical evidence of bilateral pleural effusions. Flexion contractures of both fourth fingers were present. The skin of the lower extremities was roughened and thickened.

Laboratory data on the final admission showed a total protein of 5.5 gm, with 3 gm of albumin and 2.5 gm of globulin. Unfortunately, no electrophoresis was done. Hemoglobin 11.4 gm, white blood cells 7,000, with 76 percent polymorphonuclear leukocytes, 2 stabs, 7 monocytes, 3 eosinophils and 12 lymphocytes. The patient, as in previous admissions, had a relative lymphopenia. The absolute lymphocyte count ranged from 196 to 1,300 per c. Three LE preps were negative. Venereal disease research laboratories test (VDRL) was negative, but the latex fixation was 1 to 2,560 (normal 1 to 80).

X-ray films showed massive bilateral effusions which on thoracentesis had a specific gravity of 1,015, a protein content of 3.5 gm percent and a glucose content of 105 mg percent. All cultures were negative.

The patient had a prolonged final hospitalization and went progressively downhill and died in respiratory difficulty on September 24, 1966.

Autopsy disclosed a malignant lymphoma of the Hodgkin's disease type involving the posterior mediastinum, the lungs, diaphragm, tracheal, hilar, paraaortic, perportal and peripancreatic lymph nodes, the liver, spleen, kidneys and lumbar vertebrae. The posterior mediastinal tumor (Fig 2) formed an extensive fusiform mass entrapping the descending thoracic aorta within it and invading all contiguous structures including both lower lobes of the lungs.

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FIGURE 2. Posterior aspect of the thoracic viscera showing a fusiform mass of a malignant lymphoma of the Hodgkin's disease type in the posterior mediastinum entrapping the entire descending thoracic aorta.

and the diaphragm. The thoracic duct could not be identified and was presumably buried within the tumor tissue. There were 150 ml of cloudy fluid in the right pleural cavity and 200 ml in the left. No thymic tissue was identified. The spleen contained an intact white pulp with germinal center activity and abundant plasma cells.

**DISCUSSION**

**Lymphedema, Pleural Effusion, Yellow Nails Syndrome**

E.F. and L.F. were the first reported cases of a concurrence of hereditary lymphedema and pleural effusion. One of our patients, E.F., also had yellow slowly growing toe nails, an observation not made in the original report. It is apparent that both patients represent examples of a new clinical entity produced by defective lymphatic circulation. Samman and White noted that a group of patients with impaired lower extremity lymphatic drainage had associated abnormalities, in the growth, color and shape of the nails. Initially there is a marked slowing of the rate of nail growth. Then the finger and toenails acquire a pale yellow or slightly greenish color which affects the entire nail plate with occasional sparing of the proximal half. Finally, the nail acquires an excessive horizontal convexity. The lateral edges retract so that they recede from the adjacent soft tissues and the cuticles become deficient. The edema was most prominent in the lower extremities and all four cases studied had abnormal lymphangiograms. Emerson further expanded the syndrome with a report of three examples of chronic pleural effusion due to chronic lymphedema. Two of the three patients had yellow nails. The author's thesis was that the chronic lymphedema, the pleural effusions and the yellow nails were all due to some deficiency in lymphatic drainage. Dilley and others reported five additional cases with varying combinations of primary lymphedema, yellow nails, and pleural effusions.

The lymphedema, pleural effusion, yellow nails syndrome can be extended to include increased susceptibility to skin and respiratory tract infections. The mother of our patients had repeated episodes of erysipelas. She stepped on a nail, infected a toe and died with septicemia. E.F. had skin infections involving the extremities four to five times yearly. Illness was characterized by a red, hot, blotchy cellulitis accompanied by high fever. L.F. had similar episodes. Attacks of erysipelas and cellulitis were also present in the patient reported by Wallace and Zerfas. Patient E.F. had prolonged pleuropulmonary inflammation in 1958 with persistent fever for seven months. At autopsy there was extensive post-inflammatory pulmonary fibrosis. A patient with "yellow nail syndrome" had emphysema at age ten, chronic cough with rales and rhonchi, and roentgen evidence of bronchiectasis. Dilley and associates provided detailed descriptions of three patients. The first had a 20-year history of respiratory tract disease including chronic sinusitis, bronchitis, bronchiectasis and recurrent pneumonitis. A second patient had three episodes of pneumonia.

**Immunologic Deficiency State**

The two Montefiore patients probably had an immunologic deficiency state. Leukopenia and lymphopenia were demonstrated. A striking reduction in gamma globulin was noted in the serum electrophoresis performed on E.F. The high titer of rheumatoid factor in L.F. is an additional clue to the existence of disturbance in the immune mechanism. There is an impressive coincidence of rheumatoid arthritis, rheumatoid agglutinating activity and other autoimmune disorders in patients with immunologic deficiency states. Active rheumatoid arthritis was also present in a patient with lymphedema, pleural effusions, and yellow nails, described by Sharill.

The coexistence of congenital lymphedema and Hodgkin's disease in patient E.F. is of considerable interest. An increased incidence of acquired lymphoreticular malignancies has been observed in association with defective function of the lymphoid system. An important activity of competent lymphoid tissue is the recognition and rejection of aberrant cells which arise by mutation. Where there is a deficiency in the lymphatic homeostatic mechanism, it is theorized that mutant lymphoid cells may survive to initiate a malignant cell population. Another possible consequence is the production of...
LYMPHEDEMA, PLEURAL EFFUSION AND YELLOW NAILS


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DE FABRICA HUMANI CORPORIS

Vesalius (1514–1564) born in Brussels (original name Wesal, after the town of the same name, meaning weasel), came from a family of illustrious physicians. His extensive experience and broad knowledge of the dead body won him the professorship at Padua when he was but twenty-two years of age. Before large audiences he gave three-week courses in human as well as in comparative anatomy. The immortal opus of Vesalius is On the Structure of the Human Body published in 1543. This folio volume is a grand exposition integrating into whole the parts of the human body clearly, concisely and artistically, demonstrating the relation of one part to another, eliminating many of the errors of previous anatomy texts and recording observed facts accurately and in detail. Described for the first time were, among several other items, the mediastinum, the pleura, the pylorus, the ductus venosus and the course of the azygos vein.

Steno, F. (Editor): The Growth of Medicine, C. C Thomas, Springfield, 1967

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