Disseminated Eosinophilic Collagen Disease

By LAWRENCE E. PIERCE, ABDOL H. HOSSEINIAN, and ANTHONY B. CONSTANTINE

In 1956, ENGFEELD AND ZETTERSTROM described disseminated eosinophilic collagen disease (DECD) in two pediatric patients. Only Bousser and Odeburg have reported additional instances of this illness. The clinical symptoms resemble the acute form of dermatomyositis. Initial blood and bone marrow studies are consistent with inflammation but eventually progress to resemble chronic to subacute granulocytic or eosinophilic leukemia. The present case is an example of this condition and illustrates the significant clinicopathologic features separating this entity from previously described collagen diseases and leukemoid reactions.

CASE REPORT

J. P., a 58-year-old, married, white, male machinist was hospitalized in April 1964 because of suspected urinary calculus. Physical examination was normal. His hematocrit was 41 per cent and WBC 8350 per cu. mm. with a normal differential (Table 1). Urologic evaluation was normal except for moderate cystitis.

In May 1965 he noted gradual onset of bilateral and symmetrical swelling, tenderness, and stiffness without redness of all interphalangeal, metacarpophalangeal, wrist and ankle joints. Colchicine was begun without benefit, and a change to oral cortisone afforded similar lack of improvement. Injection of a mercurial diuretic to mobilize pedal edema was associated with bladder neck spasm and he was admitted for the second time. His appearance was still that of a well-developed and well-nourished stocky male. He complained of a gritty sensation in both eyes and examination showed conjunctival hyperemia and granularity. Liver span was 11 cm. and there was 2+ pitting pedal edema. His hematocrit was 39 per cent and WBC 12,200 per cu. mm. with 37 per cent eosinophils. Urinalysis showed 5 to 10 WBC and innumerable red cells per high power field. IVP, cystoscopy, and retrograde pyelography were normal and no diagnosis was established. Following discharge, he was unable to return to work because of persistent weakness. He became anorectic, experienced drenching night sweats, and rapidly lost 20 pounds in weight. His joints continued stiff, and muscular weakness progressed. Dermal pruritus interfered with sleep. He was readmitted in August 1965 for medical evaluation.

He had smoked one pack of cigarettes daily for 50 years and avoided alcoholic spirits. Medications on admission were vitamin B12, oral iron, and a combination tablet of Benemid and colchicine. On examination he was pallid, perspiring, and showed signs of recent weight loss, particularly about the shoulder girdle. BP was 125/80, pulse regular at 90 per minute and oral temperature 102 F. There was no adenopathy, and the heart, ocular fundi and lungs were unremarkable. Neither liver nor spleen was enlarged. No arthritic deformities or nodules were present. He had a fine nonintentional tremor of the extended arm and hand bilaterally and the fingers showed early clubbing. He was unable to make a fist. The fingers

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Table 1.—Patient Hematologic Data

<table>
<thead>
<tr>
<th>Determination</th>
<th>Apr. '64</th>
<th>May '65</th>
<th>Aug. '65</th>
<th>Sept. '65</th>
<th>Jan. '66</th>
<th>Mar. '66</th>
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<tbody>
<tr>
<td>Hct. %</td>
<td>41</td>
<td>39</td>
<td>27</td>
<td>25</td>
<td>24</td>
<td>24</td>
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<tr>
<td>Retic. %</td>
<td></td>
<td>1.4</td>
<td>1.7</td>
<td>3.0</td>
<td>5.4</td>
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<tr>
<td>Platelet per cu. mm. $\times 10^5$</td>
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<td>325</td>
<td>277</td>
<td>170</td>
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<tr>
<td>WBC per cu. mm. (corrected)</td>
<td>8350</td>
<td>12,200</td>
<td>7,200</td>
<td>28,100</td>
<td>82,500</td>
<td>67,000</td>
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<tr>
<td>% polymorph</td>
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<td>31</td>
<td>24</td>
<td>30</td>
<td>21</td>
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<td>9</td>
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<tr>
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<td>6</td>
<td></td>
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<td>3</td>
<td>4</td>
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<tr>
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<td>2</td>
<td>4</td>
<td></td>
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<td>Lymphocyte</td>
<td>28</td>
<td>23</td>
<td>25</td>
<td>18</td>
<td>15</td>
<td>18</td>
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<tr>
<td>Monocyte</td>
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<td>1</td>
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<tr>
<td>Basophil</td>
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<td></td>
<td></td>
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<tr>
<td>Eosinophil</td>
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<td>37</td>
<td>44</td>
<td>26</td>
<td>32</td>
<td>21</td>
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<td>Nucleated RBC per 100 WBC</td>
<td></td>
<td>3</td>
<td>5</td>
<td>6</td>
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</tr>
</tbody>
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were edematous and excessively firm, but the overlying skin was not tightly fixed to the digits. The chest and abdominal skin was doughy and thickened with patches of scaly erythema. The hematocrit was 27 per cent and ranged between 24 and 28.5 per cent during his 3½-week hospitalization. ESR was 68 mm. per hour corrected to 25 mm. Admission WBC was 7200 per cu. mm. with 24 per cent mature eosinophils. This gradually rose to 28,100 per cu. mm. with 26 per cent eosinophils at which time an infrequent metamyelocyte, myelocyte, blast cell, and nucleated red cell began to appear peripherally. Serum iron was 37 µg. per cent and UIBC 145 µg. per cent. Haptoglobin was increased to 175 mg. per cent. Urinalysis: calcium/phosphorus, FBS, BUN, uric acid, bilirubin, stools for blood, ova and parasites, three LE preps, ASO titer, trichinella CF, heterophile, alkaline phosphatase, SCOT and SGPT, rheumatoid factor, urine for cystine, EKG, chest film and IVP were all normal or negative. The C-reactive protein was 4+; 24-hour urinary protein excretion 100 mg.; and serum electrophoresis showed albumin of 2.0 Gm. per cent and globulins of 4.5 Gm. per cent with 2.1 Gm. being gamma globulin. Posterior iliac crest marrow aspirate was hypercellular with marked eosinophilia and granulocytic hyperplasia. The predominant granulocyte was the myelocyte. Erythroid activity was relatively decreased and megakaryocytes normal. There was moderate plasmacytosis and hemosiderosis. The marrow was consistent with chronic inflammation, possibly parasitic, and suggestive of an early myeloproliferative disease. A deltoid skin-muscle biopsy was nondiagnostic, although there was moderate perivascular lymphocytic and plasmacytic infiltration in the corium without vascular necrosis. It was felt the most likely diagnosis was a collagen disease resembling periarteritis or lupus erythematosus and weakly supported by the skin-muscle biopsy; the patient received 250 mg. i.v. Solu-cortef for 3 days with prompt defervescence of fever, return of appetite, a feeling of well-being, and ability to be ambulated. He was maintained on 4.5 mg. dexamethasone and discharged improved.

From September 1965 through January 1966 he was maintained on oral steroids and intermittent ACTH injections, but fatigue, fever, and muscular aching and weakness gradually returned. The liver span enlarged to 15 cm. in January 1966 and the WBC had risen to 51,000 per cu. mm. with 22 per cent eosinophils. An outpatient marrow aspirate and peripheral smear were consistent with chronic myelogenous leukemia (Fig. 1). Leukocyte alkaline phosphatase activity was normal. His gait became unsteady and shuffling with a wider base, but he was able to take daily walks and attempted exercises to maintain muscular tone. The WBC progressively rose to 82,500 per cu. mm. with 32 per cent eosinophils, and increased granulocytic immaturity was apparent in the peripheral blood.
In March 1966 he developed splenic infarction with an overlying refractory *E. coli* pneumonia. A tender 2.5 cm. spleen was palpated. His muscles were tender but flabby in consistency. The admission hematocrit was 24 per cent and WBC 67,000 per cu. mm. with 21 per cent eosinophils. Direct Coombs' test was positive. Marrow aspirate (Fig. 2) was unchanged from 1/28/66 and consistent with chronic myelogenous leukemia with eosinophilia. Three days before death he was begun on 8 mg. oral Myleran daily. ECG showed low vol-
Fig. 2.—Top: Large blast cell and two mature eosinophils in peripheral smear. Bottom: Marrow obtained in March 1966 three days prior to death showing eosinophilic persistence.

Autopsy Findings

The skin was edematous and exfoliative. There were scattered patches of bronchopneumonia maximal in the left lower lobe. The pulmonary artery and its branches were free of
Histologically, both skin (Fig. 3) and lungs were diffusely infiltrated with neutrophils, eosinophils, lymphocytes and plasma cells accompanied by healing and healed vasculitis. The heart was dilated and weighed 480 grams. Ventricular wall measurement, endocardium, and valve leaflets were all normal. The coronary arteries showed patchy atherosclerosis but were widely patent. There were no mural thrombi and the pericardial sac contained 40 cc. sterile fluid. The myocardium was severely infiltrated by mature neutrophils and eosinophils with scarring, muscle fragmentation, and necrosis (Fig. 4). The liver was markedly enlarged (2700 Gm.) and there was severe passive congestion with centrilobular necrosis and healed prearteriolar vasculitis. The spleen weighed 570 Gm. and there were several superficial infarcts measuring from 3 mm. to 1.5 cm. It was heavily infiltrated, as was the liver, by nonleukemic cells. Healed vasculitic changes with thrombosis and recanalization were observed in the pancreas (Fig. 5). Except for minor leukocytic infiltration, the length of the gastrointestinal tract was normal. The kidneys (Fig. 6) were large, pale, and swollen. There was severe interstitial infiltration (eosinophilic and neutrophilic) with patchy arteriolar sclerosis and small areas of infarction. Adrenals were thinned and depleted. Abdominal and mediastinal lymph nodes had marked eosinophilic infiltration but were not enlarged nor otherwise remarkable. Pectoral muscle was focally infiltrated with leukocytes and eosinophils with frequent perivascular accumulations (Fig. 7). Bone marrow was as during life, being hypercellular with granulocytic hyperplasia and immaturity with eosinophilia consistent with chronic myelogenous leukemia. The head was not dissected.

**Discussion**

In reviewing 25 cases of eosinophilic leukemia to 1957 Engfeldt and Zetterstrom emphasized only three terminated in myeloblastic transformation. In nearly every case the maturity of the eosinophils was stressed, whether in the marrow, peripheral blood, or various internal organs at autopsy. Heart failure
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Fig. 4.—Photomicrograph of myocardium showing intense infiltration with neutrophils, eosinophils, and mononuclear cells with muscle fragmentation, necrosis, and scar formation.

Fig. 5.—Photomicrograph of pancreatic vessel showing healed vasculitis and thrombosis with recanalization. Similar changes were observed in the lung, liver, and spleen.
Fig. 6.—Renal autopsy specimen. There is moderate atherosclerosis and marked leukocytic interstitial infiltration.

Fig. 7.—Photomicrograph of pectoral muscle obtained at autopsy. In this section, the leukocytic infiltrate was perivascular; in other sections, it was focal and infiltrative.
was the most common terminal complication. Cardiac muscle was edematous, necrotic and infiltrated by mature neutrophils and eosinophils. The authors proposed that the relatively mature eosinophilia and myocardial failure often reported in eosinophilic leukemia was in fact due to disseminated eosinophilic collagen disease (DECD) and they expressed doubt that eosinophilic leukemia had ever been satisfactorily documented.

In the opinion of Bousser, also, there had been no proved case of eosinophilic leukemia. Rather, he again called attention to the probability that many of the reported cases were, in fact, DECD with leukemoid reactions. He suggested anticoagulants for prevention of the frequent vasculitis, thrombosis, and vessel recanalization encountered at autopsy. The simultaneous occurrence of arteriolar thrombosis and eosinophilia is of interest since recent experimental studies have shown the eosinophilic granule to be a source of pro-fibrinolysin. The eosinophil is presumably attracted to the inflammatory site by fibrin or fibrinogen and plays an active role in wound healing. Since both steroid and the eosinophil may promote healing of vasculitis, it raises the possibility, however remote, that the observed healing is as related to eosinophilia as to steroid administration.

The difficulty in establishing a diagnosis of eosinophilic leukemia and its partial dependence on personal conviction has been stressed since it is difficult to be certain whether eosinophilia is an accompaniment of granulocytic leukemia or the primarily affected leukemic cell line. Preexisting erythrocytosis and Philadelphia chromosome positivity have been observed in eosinophilic leukemia. Although these associations are not uncommon in granulocytic leukemia and might argue for basically abnormal granulocytic proliferation, they may be no less characteristic of the relatively rare eosinophilic variant. Simplified diagnostic criteria of marked peripheral eosinophilia with peripheral and marrow blast cell increase sometime during an illness terminating with myeloblastosis is insufficient to separate eosinophilic leukemia since such a reaction may occur with variable intensity or be leukemoid secondary to carcinoma, infection, myelogenous leukemia, or DECD. Our patient's predominantly muscle and joint symptomatology, normal ocular fundi, atypical eosinophilia, adequate leukocyte alkaline phosphatase activity, and lack of splenomegaly or cachexia made him sufficiently atypical in spite of marrow and peripheral blood leukemic suggestivity that leukemia was only a desperate, late consideration when it was apparent he was dying on treatment if he truly had a collagen disease and a change in emphasis was justified.

The patient experienced penicillin allergy in 1959 manifested as morbilliform rash and edema of the skin and eyelids, and received a mercurial diuretic injection immediately prior to his second hospitalization when eosinophilia was first observed. The importance of drugs as a trigger mechanism is well known in the instance of the hydralazine-lupus erythematosus syndrome wherein a reaction including fibrinoid degenerative changes of the skin and typical wire-loop glomerular lesions may develop. Although reversibility is the rule upon discontinuing the drug, recovery may take several years, and
some studies suggest merely quiescence rather than remission of the syndrome.\textsuperscript{13} It is unknown whether cases of hydralazine-induced lupus are identical to those when no etiologic factor is known, but the drug syndrome has increased the possibility that the unknown cases may also be on a hypersensitivity basis and perpetuated by persistent abnormal antibody production.

The term “collagen disease” is a nonspecific designation not intended to imply a single or even similar etiology, clinical course, or therapeutic response; only that the primary inflammation, degeneration and fibrosis reside in those tissues rich in collagen.\textsuperscript{14} Proximal muscle weakness, joint pain and stiffness, myocardial involvement, nonpitting peripheral edema, hypergammaglobulinemia, and Coombs’ positivity are findings common but not exclusive to collagen disorders and DECD. Distinctive DECD deviations include the lack of renal or gastrointestinal vascular involvement, absence of skeletal muscle necrosis, and the granulocytic leukemoid reaction with eosinophilia. Neither is there evidence of associated malignancy, exotic infection, or parasitosis. There are patients in whom the merging of clinical patterns makes differentiation impossible during life, and in a few undifferentiation persists after careful autopsy.\textsuperscript{15} Continued investigation of perplexing eosinophilic syndromes will perhaps uncover additional substantiating instances of disseminated eosinophilic collagen disease.

**Summary**

A patient with disseminated eosinophilic collagen disease as reported in the Scandinavian and European literature and perhaps described under various titles—such as eosinophilic leukemia, Loeffler’s syndrome, parietal endocarditis,\textsuperscript{16} and allergic granulomatosis\textsuperscript{17}—is presented. The major clinical findings are dermal edema and erythema with pruritus and scaling; skeletal muscle pain, tenderness, and weakness; severe arthralgias and stiffness of small and weightbearing joints; hepatomegaly; and conspicuous lack of adenopathy. Blood examination shows normochromic anemia with intense neutrophilic leukocytosis and eosinophilia. Granulocytic leukemoid features eventually appear resembling chronic to subacute myelogenous or eosinophilic leukemia. Cardiac failure or infection is the usual cause of death. At autopsy there is generalized eosinophilic and neutrophilic with lesser mononuclear infiltrations of many organs, particularly the skin, myocardium, and skeletal muscle. The etiology is unknown. Environmental toxicities and hyperimmunity perhaps to drugs, bacterial products, or sustained autoantigenic stimuli are suggested possible explanations. Corticosteroids afford some symptomatic stabilization but the disease pursues a persistent downhill course.

**Summary in Interlingua**

Es presentate un patiente con disseminate morbo eosinophilic de collageno, un condition reportate in le litteratura scandinave e europee e describite possibilemente sub varie nomines, incluse leucemia eosinophilic, syndrome de Loeffler, endocarditis parietal, e granulomatosis allergic. Le major constatationes clinic es edema e erythema dermal con prurito e
scaliage; myopathias skeletic, hypersensibilitate, e debilitate; sever arthralgias e rigiditate de micre articulationes etiam de articulationes de typo portapesos; hepatomegalia; e un conspicue absentia de adenopathia. Examine hemalogic monstra anemia normochromic con intense leucocytosis neutrophilic e eosinophilia. Characteristicas de leucemia granulocytic se manifesta in le curso del tempore, resimilante chronic o subacute leucemia myelogene o eosinophilic. Insufficientia o infection, cardiac es le causa usual del morte. Al necropsia, generalisate infiltrationes eosinophilic e neutrophilic e, minus extensemente, mononucleari es constatate in numerous organos, particularmente le pelle, le myocardio, e musculo skeletic. Le etiologia es incognoscite. Toxicitate exogene e hyperimmunitate secundari, forsan, a pharmacos, productos bacterial, o continue stimulos auto-antigenic es proponite como explicationes possibile. Corticosteroides provide un certe stabilisation symptomatic, sed le morbo seque inexorabilemente un curso deterioratori.

REFERENCES

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