

The Journal of **Allergy**

VOL. 34, NO. 4

JULY—AUGUST, 1963

ORIGINAL ARTICLES

PLEURAL EFFUSION WITH EOSINOPHILIA

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PLEURAL effusions are common and difficult diagnostic problems. Although many pleural effusions can be shown to be the result of a specific etiologic agent, there is a large group falling into the category of "idiopathic pleural effusion." Of this group, 60 to 80 per cent (depending on age) have been stated to be tuberculous in nature.¹ Roper and Waring in this paper state that 90 per cent of those who develop tuberculosis do so within a period of 3 years after the original pleurisy.

Pleural effusions with eosinophilia are rare and have received but scant attention in the English literature. For these reasons the following case histories are presented.

CASE REPORTS

CASE 1.—A 36-year-old white female physiotherapist was referred to an allergy clinic because of pleural effusion and eosinophilia.

She had been well until early April, 1958, when she had developed moderately severe pain in the left lateral chest. She described the pain as "sticking" in character, worse on sneezing and coughing, and when lying down. The pain was quite intense on arising and diminished during the day, although it never completely disappeared. She had no cough, fever or constitutional symptoms. A roentgenogram made on May 3, 1958, showed the chest to be normal. Symptomatic therapy was administered without benefit. On a repeat chest film of May 13, 1958, a left pleural effusion was demonstrated. A thoracentesis was performed and 300 c.c. of dark amber fluid was obtained. No laboratory examinations were made. A pleural biopsy done at the time of the thoracentesis revealed "chronic inflammation."

On May 23, 1958, thoracentesis was repeated and 100 c.c. of straw-colored fluid was obtained. This material had a specific gravity of 1.016, total protein content of 4.2 Gm.

Received for publication Dec. 17, 1962.

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per cent, and a total white cell count of 5,500 per cu. mm. of which 40 per cent were eosinophils. A second pleural biopsy specimen again showed "nonspecific chronic inflammation."

The patient was afebrile during the entire period of hospitalization and there was progressive clearing of the symptoms and of the effusion. The serologic tests were negative and multiple urinalyses were normal. The whole blood counts were seven, 250-259 and 300 per cu. mm. with 6 to 14 per cent eosinophils. The erythrocyte sedimentation rate (ESR) was 10 to 15 mm. per hour. Total serum protein determinations and electrophoretic pattern were normal. Six lupus erythematosus preparations were negative. Three gastric washings and two 72-hour sputum specimens for acid-fast bacilli were negative by smear, culture, and guinea pig inoculations. Culture, smear, and guinea pig inoculations of pleural fluid were negative for acid-fast bacilli. Cold agglutinins and streptococcus MG agglutinins were negative. A complement fixation test for histoplasmosis was negative.

The patient was discharged July 3, 1958, and did well until Aug. 3, 1958, when, after prolonged water skiing, she had a 48 hour episode of swelling and pain in the proximal interphalangeal and metacarpophalangeal joints of the second to the fifth fingers of both hands. On Sept. 3, 1958, when she was asymptomatic, a differential blood count and a roentgenogram of the chest were normal. Skin tests for the usual allergenic substances were negative. She was found to have a multinodular goiter involving the left lobe of the thyroid which was considered to be a benign, nontoxic nodular goiter. On follow-up in 1962 she was still well.

CASE 2.—A 21-year-old white man was hospitalized on Jan. 10, 1956, because of 4 days of pain which was located in the right chest, low and laterally. At the age of 8 years he had had pneumonia, site unknown, with uneventful recovery. In February, 1955, he had suffered an episode of left lower lobe pneumonia, with a minimal effusion, from which he recovered without residuals. (Further details are unknown.) A roentgenogram made in June, 1955, showed the chest to be normal.

In early January, 1956, having been well to this time, he noted the onset of an upper respiratory tract infection manifested predominantly by rhinorrhea and moderate cough. On Jan. 6, 1956, he experienced pain in the right side of the chest, low and laterally, which was made worse by taking a deep breath. X-ray examination of the chest on Jan. 10, 1956, revealed pleural effusion at the base of the right lung. He had no fever, weight loss, chills, night sweats, or other constitutional symptoms.

The complete physical examination was normal except for the chest where it was noted that there was dullness as well as decreased breath sounds and decreased tactile fremitus at the base of the right lung.

Multiple urinalyses, serologic tests, serum protein determinations, serum electrophoretic pattern, 6 lupus erythematosus preparations, 3 sputa and 3 gastric washings for acid-fast bacilli by culture and guinea pig inoculation, examinations of six stools for ova and parasites, and electrocardiogram were negative or normal. The white blood counts were four, 800-19,000 per cu. mm. with 4 to 14 per cent eosinophils; the sedimentation rate was 0 to 12 mm. per hour, and the hemoglobin was 14-15 Gm. per cent. Purified protein derivative No. 1, coccidioidin, and histoplasmin tests were negative. PPD No. 2 was positive. Thoracentesis yielded 200 c.c. of straw-colored fluid: specific gravity was 1.020, protein content was 4.0 Gm. per cent, and there were 6,200 white blood cells per cu. mm., with 50 per cent eosinophils.

The patient remained afebrile. Serial chest x-ray examinations revealed persistence of pleural reaction at the base of the right lung. A friction rub was heard intermittently over the right lower chest. On Feb. 13, 1956, a biopsy of the right pectoralis muscle was normal.

In March, 1956, the patient was transferred to Fitzsimons General Hospital, Denver, Colorado, where he remained until May 10, 1956. Further studies for acid-fast bacilli were negative and a bronchogram was normal. The white blood cell count was normal with only 2 per cent eosinophils. The chest films showed improvement and the patient was returned to full military duty on May 10, 1956. As of 1961, he was still in good health.

CASE 3.—A 49-year-old white man was seen in an allergy clinic during 1958 because of right-sided pleural effusion and eosinophilia.

The family history was significant only in that one uncle and one brother had asthma. A review of the past history revealed that in 1938 he had had a benign teratoma of the right testicle removed surgically with apparent cure. In 1947, 1950, and 1953, he had had episodes of asthma which accompanied severe upper respiratory infections. In 1953, a duodenal ulcer was demonstrated radiographically at a time when he was having typical ulcer symptoms.

The patient states he was well until March 6, 1958, when he noted loss of appetite, belching, and flatus, although he had noted mild constipation with occasional watery stools for one year. On March 13 and 17 he had noted severe pain in the sternal area and upper abdomen which lasted about 5 minutes. He first sought medical attention on March 19 at which time a chest film revealed left pleural effusion.

The physical examination showed a well-developed, well-nourished white man whose temperature, pulse, and blood pressure were normal. The chest examination demonstrated dullness and diminished breath sounds at the base of the left lung. The general examination was otherwise normal.

Serologic tests and multiple urinalyses were negative or normal. The white blood counts were seven, 400 to 17,750 per cu. mm. with 8 to 38 per cent eosinophils; sedimentation rate was 17 to 38 mm. per hour, and hemoglobin was normal. Total serum protein determinations and electrophoretic pattern were normal. Examinations of six stools for ova and parasites were negative. Three sputum specimens and six gastric washings for culture and guinea pig inoculation were negative for acid-fast bacilli. Three lupus erythematosus preparations were negative. Trichinella, brucellergen, histoplasmin, and coccidioidin skin tests were negative. Positive protein derivative No. 1 was positive.

He was afebrile throughout his hospital stay; there were persistent left pleural effusion and marked eosinophilia in the peripheral blood.

On April 15 thoracentesis was performed and 500 c.c. of straw-colored fluid was obtained which contained 5.7 Gm. per cent protein (3.8 Gm. globulin) and a white blood cell count was 2,530 per cu. mm. of which 66 per cent were eosinophils. Cultures and guinea pig inoculations of this fluid were negative for acid-fast bacilli. Cell blocks for malignant cells were negative.

Repeated chest films revealed persistent left pleural effusion. Sigmoidoscopic examination and barium enema were normal. An upper gastrointestinal x-ray examination revealed a deformity of the duodenum consistent with an old healed ulcer. Bone marrow examination demonstrated no abnormality except for increase in normal eosinophilic elements. Bronchoscopy was normal. Bilateral scalene node biopsies revealed only "reticulum hyperplasia."

On May 12, 1958, an open thoracotomy with pleural biopsy was done. The operator stated, "there was a thick pleural granulomatous process occupying the entire visceral surface of the pleura. There were thickened areas with whitish plaques irregularly distributed over all lobes of the left lung. There were about 700 c.c. of pleural fluid within the left chest." Biopsies were taken of the pleural surface of the lung and of the parietal pleura which revealed "acute and chronic inflammation with necrosis." No granulomata were seen. Tissue stains for acid-fast bacilli revealed no organisms and cultures were sterile.

Subsequent chest films revealed only residual pleural reaction at the base of the left lung. A white blood cell count in October, 1958, was 15,850 cells per cu. mm. with 39 per cent neutrophils, 22 per cent lymphocytes, 33 per cent eosinophils, 3 per cent monocytes, and 3 per cent basophils. Sedimentation rate was 28 mm. per hour; hemoglobin was 14 Gm.

He subsequently developed evidence of diffuse vasculitis with arthritis involving the ankles, knees, and metacarpophalangeal joints of his hands and metatarsophalangeal joints of his feet, as well as congestive failure and Raynaud's phenomenon. Eosinophilic leukocytosis persisted. Foot drop and weakness of the legs and arms ensued, as well as tremor and numbness of the extremities. Steroids were administered with considerable improve-

ment in both symptoms and physical findings. It was the opinion, on clinical evidence, that he had a form of diffuse vasculitis. His condition continues at this time (1962) to be moderately well controlled by steroid therapy.

DISCUSSION

These patients present the problem of "idiopathic pleural effusion." Attempts to make definitive diagnoses at the inception of illness failed. They were ultimately referred to an allergy clinic because of eosinophilia in the hope that some purely allergic factor might be incriminated as the cause of the illnesses. No such factor could be isolated after careful allergy history and multiple scratch and intradermal skin tests, with an array of antigens in each case.

The presence of high concentrations of eosinophils in pleural fluid has been recorded in a number of conditions, such as, tuberculosis,^{2, 3} parasitism,⁴ pneumothorax (spontaneous and induced), carcinoma of the lung,⁵ psittacosis,⁶ eosinophilic granuloma, pulmonary emboli,²² lupus erythematosus,^{7, 8} periarteritis, Loeffler's syndrome,⁹ and in some allergic states.^{10, 11, 12} Differential diagnosis must include all of these. Morelli³ states that in most cases of pleural eosinophilia there is very little evidence of eosinophilia in the peripheral blood. De Marchi's patient¹² showed no peripheral eosinophilia. Tservocenis²¹ further mentions the absence of peripheral eosinophilia. However, other authors^{5, 10, 13, 14, 15} do report modest elevations of peripheral eosinophile counts. Robertson²³ states that if peripheral eosinophilia is present, one should think of Loeffler's syndrome, tropical eosinophilia, polyarteritis nodosa, Hodgkin's disease, or hydatid cyst. If there is no blood eosinophilia, the differential rests between pulmonary infarction, trauma, and pneumonia. Tuberculosis and malignancy are unlikely in the presence of pleural eosinophilia. Ordinarily one does not expect allergic states to cause eosinophilia in excess of 6 to 8 per cent.²⁴ In cases of chronic infection, or conditions as noted above, considerable elevation of eosinophile counts may occur.

The specific problem we wish to mention is that of pleural effusion in which large numbers of eosinophils are present. Each of these patients showed some elevation of the eosinophile count in the peripheral blood.

The first reported case of eosinophilic pleurisy of which we are aware was that of Capellini in 1929.¹⁶ Subsequent reports of this phenomenon have appeared, mostly in the European literature.^{11, 12, 14, 17, 18} Burke and Gupta¹⁹ reported a case in England in 1934 and Zivitz and Oshlag¹³ recorded eosinophilic pleural effusion in a patient with asthma in 1949.

Reports of large series of pleural effusion make no mention of the occurrence of eosinophilia. Leuallen and Carr²⁰ studies 436 cases and made note of not a single instance of high eosinophile count in either the pleural fluid or peripheral blood. Donohoe and his associates,¹⁸ in a review of 132 cases of pleural effusion investigated with pleural biopsy, found only one instance of eosinophilic infiltration in the biopsy material. Roper and Waring¹ in their report in 1955 make no mention of this complication.

The cases reported herein are certainly unusual. Differential diagnosis

included the gamut of possibilities heretofore mentioned and all attempts to make an early definitive diagnosis failed. Multiple examinations of sputum specimens and gastric washings were all negative for acid-fast bacilli, fungi, yeast and tumor cells. Pleural biopsies and muscle biopsies were not diagnostic of any entity. Tuberculin skin tests (PPD) were negative in all strengths in one case, a positive PPD No. 2 was recorded in one and a positive PPD No. 1 in the other. Multiple lupus erythematosus preparations were negative. Multiple chest films failed to reveal the presence of pulmonary infiltrates.

These patients were eventually seen in consultation by an allergist because of the lack of an adequate diagnosis and because the presence of eosinophilia suggested an allergic problem to the referring physician. The complete allergy survey was unrevealing.

At the present time the function of the eosinophil is little understood. No one knows for certain what it does—whether it carries something to an area, or takes it away, whether it is vital in antibody formation or not. We know it is often present in increased numbers in allergic states, but it is also elevated in some nonallergic conditions, such as chronic infection. The patients reported here certainly do not have allergic problems of the usual varieties.

We do not wish to present the view that these cases represent a clinical entity in themselves for they seem to be a phase of some other disease, most likely one of the collagen diseases. We believe that all physicians who treat patients with chest problems should be aware of this entity.

SUMMARY

Three cases of pleural effusion with eosinophilia are presented. The literature on the subject is reviewed. It is our opinion that this group represents an unusual clinical problem and we encourage reports of additional cases. The causes of this finding are multiple, but, in the individual case or "idiopathic" occurrence, one should strongly consider the possibility of collagen disease. Time and observation will be the only final answer to diagnosis. Conservatism and careful follow-up are indicated in the absence of a specific etiological diagnosis.

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