THE ASSOCIATION OF EOSINOPHILIC POLY-ARTERITIS, LIBMAN-SACKS ENDOCARDITIS, AND ASTHMA WITH DIFFUSE COLLAGEN DISEASE

BY

M. GILLESPIE AND A. POTELIAKHOFF

From the Group Laboratory and Department of Medicine, St. Mary Abbots Hospital, London

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In the last decade a considerable number of papers have been written describing fatal illnesses in which the salient clinical features were asthma, eosinophilia, and heart failure. Weir (1939), Harkavy (1941), Chafee, Ross, and Gunn (1942), Miller and Daley (1946), Bergstrand (1946), Smith (1948), and Lennox (1948) have all reported such cases, the clinical course of which differed little from the comparatively common asthma ending in heart failure or occasionally status asthmaticus. The post-mortem findings, however, showed lesions which linked those cases with the so-called collagen diseases or allergic syndromes.

In view of the great interest in collagen diseases at present the following case seems to be worthy of record.

Case History

A married woman, aged 36, was admitted to hospital on October 4, 1950, complaining of a rash of four days' duration.

She had been well until the beginning of her pregnancy in November, 1948, when she developed spasmodic attacks of asthma with bronchitis after she had had some teeth extracted.

She had a normal delivery in another hospital on July 4, 1949, and five days later developed a severe attack of asthma. She remained in hospital for ten weeks, and during this time the leucocyte count was 17,000, of which 2,500 were eosinophils. A radiograph of the chest was normal. Since then she had had recurrent asthmatic attacks lasting from five minutes to two days, with greenish, frothy sputum, occasionally blood-stained. She had frequent night sweats and lost much weight. There was increasing dyspnoea on exertion, and for two weeks before admission she had pains in the back, neck, and arms, with tingling in the hands. On September 30, 1950, she developed a whitlow of the right index finger and bronchitis. Her doctor gave her an injection of procaine penicillin, 600,000 units, and that evening she developed a diffuse purpuric rash.

On admission on October 4 her colour was good and she was not dyspnoeic. A petechial rash covered the trunk and was present in the mucous membranes of eyes and mouth. A few scattered rhonchi were heard in the chest, but there was no expiratory wheeze and no signs of emphysema. The pulse was regular, the heart not clinically enlarged, and there were no murmurs. The systolic blood pressure was 110, the diastolic indefinite. The liver and spleen were not palpable, but there was slight tenderness in the

upper abdomen. There was also some tenderness of the spinal muscles in the mid-dorsal region. The central nervous system showed no obvious abnormality.

During the next few days she had no asthmatic attacks, but there was slight pyrexia, the maximum being 100.4° F., and the pulse varied between 70 and 100.

Investigation of the blood showed mild normocytic anaemia, with a haemoglobin of 11.5 g. % and leucocytosis of 35,000 per c.mm., of which 15,500 were eosinophils. Blood platelets and bleeding and clotting times were normal. The erythrocyte sedimentation rate on October 11 was 38 mm. (Wintrobe, corrected).

The sputum contained many eosinophils but no Charcot Leyden crystals; *Strep. viridans* was grown on culture.

The urine contained a trace of albumin, a few leucocytes and hyaline casts, but was sterile on culture. The stools were positive for occult blood.

A blood culture (penicillinase added) taken on October 9 grew after five days a haemolytic streptococcus belonging to Lancefield's Group D.

X-ray examination of the chest on October 7 showed clear lung fields with a borderline cardiac enlargement. The pear-shaped outline suggested a pericardial effusion.

In view of the purpuric rash an inquiry was made about the various drugs with which the patient had been treated since the onset of asthma. These included ephedrine, "franol," "felsol," and "dormiprin." Iodides had produced a rash and had been discontinued. She had several courses of penicillin injections, the last in January, 1950, eight months before the onset of the present illness. There was no history of any reaction to these injections. A further course of penicillin was given from October 4 to 9.

On October 10 the purpuric rash had begun to fade, but the patient's general condition deteriorated. She complained of abdominal pain and vomited. The liver was palpable. Next day the pain was at the lower end of the sternum, and a pericardial friction rub was heard. There was congestion of the lung bases, but no engorgement of the neck veins or oedema of the ankles. Splinter haemorrhages were found under the nails in both hands. She died suddenly and unexpectedly on the morning of October 12.

Post-mortem Report

The body was that of a small, thin woman, with a fading purpuric rash on the trunk and limbs, splinter haemorrhages under the finger-nails, and a recent infection of the nail-bed of the right index finger.

Chest.—The pharynx, larynx, trachea, and oesophagus were normal. The pericardium was distended with about 500 ml. of clear, deep yellow fluid. The heart (321 g.) was small, and the entire surface covered with small flakes of fibrinous exudate. Apart from some dilatation of the left ventricle with thinning of the wall, the chambers were not enlarged. The endocardium of both auricles showed fairly diffuse thickening with yellowish verrucose vegetations, varying in size from 1 to 5 mm., scattered over the surface. The endocardium of the ventricles showed only slight patchy thickening, but numerous similar vegetations were found on the upper parts of the walls under the cusps of mitral and tricuspid valves, the distribution described by Libman and Sacks (1924). The largest vegetations had formed at the junction of the valve and ventricular wall (Fig. 1). The free margins of the cusps showed no obvious lesion. The pulmonary and aortic valves were normal. Small, pale, sub-endocardial flecks were seen in the inter-ventricular muscle of the left ventricle, and the cut surface of the myocardium showed deep red and yellow mottling. The coronary arteries were patent. The aorta was healthy. Both lungs were slightly adherent at the apices posteriorly, and a small quantity of free fluid was present at the base of each pleural cavity. The lung substance was well aerated. A few small haemorrhagic areas were found in both lower lobes. There were no large infarcts. The bronchi were clear.

FIG. 1.—Right ventricle showing endocardial vegetations, $\times 2$. The reflected tricuspid is seen.

Abdomen.—The liver (1,654 g.) was congested, with subcapsular haemorrhages producing a mottled surface. The spleen (153 g.) was firm and congested, with a few small infarcts. A splenunculus (1.5 cm. diameter) was present. The kidneys (left, 150 ; right, 146 g.) were congested. The capsules stripped easily. There were no definite infarcts. The uterus appeared normal. There was a small cyst of the right ovary. The pancreas was firm and congested. The other organs showed no obvious abnormality.

Head.—The brain (1,206 g.) was congested and oedematous. There were no obvious lesions.

Histology

Heart.—There was diffuse eosinophil infiltration of the myocardium, not only in the fibrous septa but between the muscle fibres. Many of the small arteries were thrombosed (Fig. 2) and surrounded by eosinophils. Focal granulomata with giant cells were also present in the perivascular connective tissue ; in some cases the granulomata were closely associated with, and apparently part of, the arterial wall, with giant cells forming from the intima (compare Fig. 8). Similar small granulomata were found in the muscle of the auricles not obviously connected with vessels, and giant cells appeared to be forming from degenerate muscle cells. In some areas there was marked fibrosis of the myocardium (Fig. 3), with focal degeneration of muscle fibres. There was also considerable infiltration of the endocardium and pericardium with eosinophils and plasma cells. Sub-endocardial areas of necrosis were present, surrounded by well-formed fibrous tissue resembling healing rheumatic nodules. Similar nodules and granulomata were found in the pericardium. Abacterial thrombi, consisting of fibrin and degenerate eosinophils

FIG. 2. — Myocardium showing diffuse eosinophil infiltration with thrombus in an arteriole. H. and E., $\times 90$.

FIG. 3.—Fibrosis of myocardium with eosinophil infiltration. H. and E., $\times 400$.

FIG. 2

FIG. 3

and polymorphs, were adherent to the thickened endocardium. Pyknotic nuclei were numerous in the degenerate muscle fibres and in the pericardial fat, but the haematoxylin-stained bodies described by Gross (1940) and Klemperer, Pollack, and Baehr (1941) in lupus erythematosus could not be found.

Lungs.—Diffuse eosinophil infiltration of alveoli and alveolar walls in the right and left lower lobes had produced focal areas of consolidation. Many of the small arteries were thrombosed, the thrombus containing numerous degenerate eosinophils (Fig. 4). The walls of the vessels showed no obvious change, and the elastic laminae were well preserved. The fibrinoid necrosis present in the splenic arterioles (Fig. 5) could not be found in any of the sections, and the walls of the patent arterioles appeared healthy. Many of the small bronchioles were contracted and plugged with mucus and eosinophils, and there was some hypertrophy of the peribronchial muscle.

Spleen.—The splenic pulp showed diffuse eosinophil infiltration with more marked cellular foci around degenerate or partially degenerate arterial walls. In Fig. 5 a patch of fibrinoid necrosis is shown in the longitudinal section of a small artery. There is a definite break in the wall with protrusion of the fibrinoid material across the lumen of the vessel. A ring of eosinophils surrounds this area. Similar lesions were found throughout the sections and, in some, heavy deposits of fibrin, staining deep blue with Mallory's phosphotungstic acid-haematoxylin, were present. Breaks in the elastic lamina were seen in sections stained by Weigert's method, resembling the lesion of polyarteritis nodosa (Pagel, 1951). Numerous small granulomata, consisting mainly of giant cells, were scattered throughout the pulp (Figs. 6 and 7). Some were paravascular in distribution, others appeared to be forming from vessel walls (Fig. 8). The vascular lesions were quite apart from the macroscopically infarcted areas. There was no increase in the fibrous tissue surrounding the penicillary arteries.

Liver.—There was marked chronic venous congestion, with fibrosis and eosinophil infiltration of the portal tracts. Some of the arterioles showed fibrinoid degeneration of their walls with the formation of a few small granulomata.

Pancreas.—In the connective tissue around the ducts there were small aggregations of giant cells, and some of the small arteries showed fibrinoid changes in their walls with eosinophil infiltration.

Kidneys.—There was diffuse congestion and small, wedge-shaped subcapsular areas of eosinophil infiltration throughout the cortex. These surrounded small thrombosed arteries. Many of the thrombi had become hyalinized and partly retracted from the wall. There was no obvious fibrinoid necrosis of the walls of the thrombosed vessels. The glomeruli were congested, but their capillaries appeared healthy, and no "wire loop" changes could be detected. Apart from slight interstitial fibrosis around the thrombosed arterioles and one definitely infarcted area, the remainder of the kidney tissue appeared normal, the tubular epithelium showing only post-mortem change.

Lymph Nodes.—There was congestion and oedema with diffuse eosinophil and plasma cell infiltration.

Skin.—Small foci of sub-epithelial haemorrhage were present with a few eosinophils, but no obvious lesions of the arterial walls.

Sternal Marrow.—Apart from a great excess of eosinophils and fairly numerous megakaryocytes there was nothing significant in the marrow.

Voluntary Muscle.—The section showed no apparent lesion.

FIG. 4

FIG. 4.—Section of lung showing eosinophil thrombus in arteriole. H. and E., $\times 400$.

FIG. 5

FIG. 5.—Section of spleen showing fibrinoid necrosis of arteriole with surrounding eosinophil infiltration. H. and E., $\times 400$.

FIG. 6.—Section of spleen showing small granulomatous areas. H. and E., $\times 90$.

FIG. 7.—Section of spleen showing giant cell formation in granuloma. H. and E., $\times 400$.

FIG. 6

FIG. 7

FIG. 8.—Section of spleen showing giant cells forming from intima of thrombosed arteriole. H. and E., $\times 400$.

Discussion

The clinical course of this patient was very much the same as that of those previously described. The disease had apparently begun with asthma and bronchitis nearly two years before death. In Bergstrand's four patients asthma had been present from two months to two years. Lennox's patient had a history of asthma for five years and Smith's for about six months.

The purpuric rash and splinter haemorrhages shown by our patient, combined with pyrexia, strongly supported a diagnosis of bacterial endocarditis. The blood culture taken the day before death grew a haemolytic streptococcus Lancefield D after five days' incubation. Since by this time post-mortem examination had shown an endocarditis with vegetations of the typical Libman-Sacks distribution, and histologically the vegetations were abacterial, the streptococcus may be regarded as a contaminant. Haemolytic streptococci of Lancefield Group D are an unusual cause of subacute bacterial endocarditis, and, since the particular strain isolated was sensitive to penicillin, it is unlikely that the finding was of pathological significance. Cultures taken at necropsy grew only a non-haemolytic enterococcus.

The constant leucocytosis which was present, not only during the last part of the illness but also after the patient's confinement a year before, is also suggestive of a bacterial infection. The high proportion of eosinophils, however, which finally reached 16,000 per c.mm., favours the diagnosis of an allergic response to some antigen. Such high eosinophilic counts are unusual in uncomplicated asthma,

but of the papers already quoted Harkavy (1941) and Miller and Daley (1946) reported totals of 25,000 to 30,000 per c.mm. Similar high counts have been found by Lumb (1950) in eosinophilic arteritis, and referred to by Lennox (1948) in a series of cases of eosinophilic endocarditis. Although asthma was not a clinical feature in either of these diseases the histological changes closely resembled those found in the present case.

Histologically the main lesion is a diffuse arteritis with fibrinoid necrosis of the wall affecting the small vessels of the myocardium, spleen, and pancreas, and surrounded by eosinophils (Fig. 5). This is essentially the lesion found by Rich (1942) in serum sickness and sulphonamide sensitivity, and shown by the experiments of Rich and Gregory (1943) to be a manifestation of hypersensitivity in animals. The interstitial myocarditis with infiltration of polymorphs, monocytes, and eosinophils described by Rich (1942) in three of his patients with polyarteritis nodosa is an outstanding feature of the present case (Fig. 2). The pericarditis with plasma cell and eosinophil infiltration, and the endocardial changes with the formation of vegetations, are part of the same process. The extensive myocardial fibrosis appears to be of much longer duration (Fig. 3). As asthma and bronchitis were the first symptoms of the illness it might have been expected that the lung lesions would be more chronic in type, but in all the sections examined the changes appear to be comparatively recent (Fig. 4). This corresponds with the negative x-ray findings throughout the illness and the focal distribution of the lesions in both lower lobes. The changes in the lungs and kidneys suggest an embolic origin from the endocardial vegetations rather than a primary arteriolitis.

The other type of lesion consists of small granulomata found mainly in the spleen and adjacent splenunculus (Figs. 6 and 7). They have been described as "paravascular" by Pagel (1951), but in Fig. 8 giant cells are forming from the intima of a small splenic vessel. Bergstrand (1946) found intimal formation of giant cells, and an illustration in his paper shows similar changes to those in Fig. 8. These focal granulomata are also associated with hypersensitive states and are usually surrounded by eosinophils.

Although there was clinical and histological evidence of hypersensitivity it is difficult to decide the nature of the antigen or antigens responsible. The patient was known to be sensitive to iodine, and polyarteritis nodosa has been described by Rich (1945) following the administration of iodine to a sensitive subject. No iodine, however, had been prescribed since the patient's original allergic reaction. A bacterial antigen cannot be eliminated, since the onset of the illness followed tooth extraction, and exacerbations occurred during the puerperium and following a whitlow. From the history it seemed possible that penicillin was the offending substance, since the final dose apparently precipitated the final allergic response. Unfortunately no satisfactory skin tests were done before the patient died. Gold (1951) reported a case of lupus erythematosus which developed after penicillin injections, and several others which deteriorated following penicillin therapy, but no detailed pathological data were presented.

Further difficulty is encountered when an attempt is made to place this case in any definite disease category. Clinically the illness began with asthma and bronchitis two years before death. Apart from the severe attacks after the birth of her second child, there appears to have been nothing to distinguish the course of the disease from

any other case of asthma until the last few weeks of her life, when the symptoms suggest a widespread disease process affecting the cardiovascular as well as the respiratory system. The pathological findings confirm the widespread nature of the lesions, but do not correspond to any of the established syndromes. There is a diffuse arteritis, but the skin and muscle lesions found in polyarteritis nodosa were not present. The lung changes suggest a severe form of Löffler's (1936) benign eosinophilic alveolitis, and the endocardial changes could be linked with Löffler's endocarditis with eosinophilia. The Libman-Sacks distribution of the endocardial vegetations is usually associated with lupus erythematosus, but other findings in lupus erythematosus, such as the typical rash and the histological changes occurring in the glomerular capillaries and splenic arterioles, were not present. The conception of diffuse disease of fibrous tissue originated by Klinge (1930) in relation to rheumatic fever has been elaborated by many later writers, including Klemperer, Pollack, and Baehr (1941), and many diseases previously considered as entities have been correlated. Whatever the aetiology, in some cases allergic and in others without any obvious allergic basis, the fundamental lesion of fibrinoid necrosis of fibrous connective tissue with surrounding cellular reaction and the formation of granulomata is similar in all diseases of the group. Since the changes found in any one case must therefore depend upon the site of the lesions and the extent to which the organ is affected by the disease process, it is not surprising that clear-cut clinical and pathological differentiation does not always occur. The case described in this paper is an example of the overlapping of the syndromes grouped under the heading of diffuse collagen disease.

Summary

A fatal case, presenting as asthma with high eosinophilia, is described.

The pathological findings include arteriolitis, endocarditis, myocarditis, granulomata, with giant cell formation in the spleen, multiple changes in the lungs, and eosinophil infiltration of all the affected organs.

The post-mortem histological changes are discussed and linked with the allergic group of "collagen" diseases.

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