RHEUMATOID ARTHRITIS AND AMYLOID DISEASE

BY

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This paper is a continuation of that by Lush, Chalmers, and Fletcher in the *Annals of the Rheumatic Diseases* for December 1948, vol. 7, p. 225, and reports a follow-up study of the case therein described.

Progress of the Patient since the Report in December 1948

Just over three hundred days after the onset of the patient's illness and while she was still in the Royal Free Hospital she suddenly developed a rigor just after getting into bed. There were no premonitory symptoms or signs. Her temperature rapidly rose to 104·6° F. and the pulse to 130 per minute. Her only complaints were of pain over the sacrum and in the region of the left knee. Apart from the fever, tachycardia, and collapsed condition, no new physical signs were elicited. The blood pressure was 100/50 mm. Hg. The blood picture was unusual (white cells 9,000 per c.mm. of blood; polymorphs 93 per cent., lymphocytes 7 per cent.), but no explanation for it could be found, and at the next examination it was more normal (white cells 7,700 per c.mm.; polymorphs 38 per cent., lymphocytes 41 per cent., monocytes 13 per cent., eosinophils 5 per cent., basophils 3 per cent.). The urine contained a trace of protein and a few pus cells, but was sterile on culture.

No satisfactory explanation of the cause of this febrile attack was forthcoming. Infection was considered to be a possibility, and in view of her desperate condition it was considered justifiable to give the patient a course of penicillin, although this might obscure the diagnosis; 250,000 units were given twice daily without demonstrable effect. For four days she remained shocked and ran a hectic fever; then her condition slowly and spontaneously subsided. Two weeks after the onset of the episode she said she felt far better in every way than she did before the attack. Her condition never again gave any cause for anxiety, and she was discharged from the hospital shortly afterwards. At that time she was almost free from pain and was able to walk without assistance. The liver and spleen remained slightly enlarged.

Condition after Discharge from Hospital

For subsequent news of her progress we are indebted to the patient herself, to Dr. H. F. G. Hensel of Blandford, Dorset, and to Drs. E. H. Shaw and K. I. Scott of Northampton General Hospital.

On June 14, 1948 (three months after her discharge), Dr. Hensel wrote: "You will be glad to hear that since she came home she has remained free from pain and has put on 9 lb. in weight and is altogether much better. As you suggested, I am giving her 4 c.cm. of Plexan per month. I notice that you suggested also 10 mg. of calcium aurothiomalate weekly. I gave this twice, but

she produced an albuminuria and a metallic taste in the mouth. I tested the urine twice during the week and produced a heavy cloud of albumin each time, so I have had to stop it."

In reply to a later letter, Dr. Hensel wrote as follows on Oct. 21: "Mrs. — recently developed an acute tonsillitis which caused a slight flare up of her arthritis. She responded, however, to intensive penicillin therapy, the liver injections being maintained throughout. Afterwards I suggested a change, and she went away to Oxfordshire where she made wonderful progress. On her return to Dorset she relapsed again, with more swelling of the wrists and fingers and much pain. She assures me that there is no psychological association here and cannot account for the original onset of the trouble here, or of the present slight relapse."

"I have advised her to go back to Oxfordshire and have promised to try and help her husband to get a job and a farm cottage there. She has promised that she will come down to London to report to you when she is due."

Three weeks later, in normal handwriting, the patient herself replied as follows to a request to visit the hospital for a follow-up examination: "I am writing to tell you that I have had an attack of pleurisy and slight effusion, but I saw my doctor yesterday and he thought that I should be able to travel in a fortnight's time."

Patient's Last Illness and Death

The patient recovered sufficiently to travel to Northampton to see her sister, but was almost immediately taken ill with severe pain in the chest. She was admitted to the General Hospital under the care of Dr. E. H. Shaw, whose house physician, Dr. K. I. Scott, wrote:

"This lady was admitted to Hospital on Nov. 20, 1948, with a complaint of severe pains in the chest of six days' duration. Following discharge from the Royal Free Hospital in May of this year she had been feeling very well, although a week or two after discharge she had some pain in the knee joints and hands. In September she moved to Brackley, hoping that the climate would suit her. She did well there but her pain recurred when she returned to Bournemouth six weeks later. She went back to Brackley, and in mid-November developed a pain below the left ribs which was worse on breathing. There was no pain in her chest or shoulder. The pain lasted for fourteen days, during which time she ran a slight temperature. She had no vomiting or headache. A diagnosis of pleurisy was made. She then developed a pain across the front of her chest which went through to the back. She described it as a gripping pain, like indigestion. It was not affected by food, but was eased by taking tablets. The pain lasted for a day or two and made breathing difficult. She had

not lost any weight. The pain continued to recur at intervals of a day or so up to the day of admission. She had no cough and no urinary symptoms. She had noticed no swelling of the abdomen and her bowels were regular. On admission she looked very ill, was pale and sweating. The tongue was furred, the pulse regular, 130 per minute, blood pressure 120/90 mm. Hg., and heart sounds normal. Examination of the chest showed the signs of a pleural effusion at the left base. The abdomen was somewhat distended and she appeared to have marked enlargement of both liver and spleen. A radiograph of the chest confirmed the presence of a large left pleural effusion. The blood urea was 70 mg. and the blood sedimentation rate 105 mm. per hour. Examination of the blood showed 44 per cent. haemoglobin, 2,400,000 red cells per c.mm. of blood, and 9,000 white cells per c.mm. (74 per cent. polymorphs). Blood films showed marked anisocytosis and hypochromasia. Aspiration of the pleural effusion was attempted, but only 7 c.cm. of heavily blood-stained fluid were withdrawn. Sternal puncture showed a normoblastic marrow with no significant changes in cytology. A fractional test meal showed a complete histamine-fast achlorhydria.

A transfusion of 2 pints of blood was given on Nov. 28, 1948, and the haemoglobin rose to 74 per cent. Examination of the chest a fortnight later showed dullness of both lung bases, and 40 c.cm. of blood-stained fluid was withdrawn from the right pleural cavity. On repeated examination of the abdomen it was finally established that what appeared to be splenic enlargement was, in fact, gross enlargement of the liver, which extended to the level of the umbilicus and filled the epigastrium. The patient gradually developed a yellowish-brown pigmentation of the skin. Urine and stools remained normal in colour, and the sclera were not at first affected.

A provisional diagnosis of amyloid disease was made. Investigations of liver function were reported as follows: plasma proteins: albumin 0.9 per cent., globulin 3.9 per cent., total protein 4.8 per cent.; plasma bilirubin 1.5 per cent.; thymol turbidity 9 units; serum alkaline phosphatase 36 units.

The patient's temperature on admission had been 101.4° F., and she was started on a course of penicillin, 500,000 units twice a day. Her temperature settled during the next two days, but after that continued to vary between 97° and 99° F. On Dec. 11, 1948, the patient complained of severe pain centred round the left costal margin in the anterior axillary line. On examination the spleen could not be felt, the liver edge was three fingers' breadth below the right costal margin, and the abdomen was less distended than formerly. Peristalsis was normal, and there was no free fluid. Examination of the urine was negative. Her white cell count was 24,900 per c.mm. of blood with 91 per cent. polymorphs, and serum bilirubin was 2.2 per cent. A radiograph of the chest showed elevation of the right diaphragm, but the lung fields were clearer. During the next few days she continued to have left-sided pain, and her general condition deteriorated. On Dec. 14, 1948, she showed slight jaundice of the sclera. Her temperature continued irregular but not high, and her

pulse remained about 90 to 100 per minute. Her respiration rate remained normal. She had a minor degree of albuminuria, although less than on admission. On the evening of Dec. 15, 1948, she had a very severe attack of pain across the abdomen. The upper abdomen was filled with a smooth, firm, and tender liver. No other abnormality was found in the abdomen. Her condition continued to worsen and she died at 7.30 the following morning. Permission to perform a necropsy was not given."

Discussion

Unless a third concurrent disease was missed, this case must be classified as of fatal rheumatoid arthritis, for there were only sixteen months between the onset of the disease in a previously healthy woman and her death. Amyloidosis was diagnosed seven months after the first symptom of rheumatoid arthritis.

The cause of the pyrexia at various times was never explained, and she exhibited leucocytosis only in the last stages of her illness. The almost complete remission of symptoms, first on treatment with crude liver extract and secondly when she had a change of location is interesting, but its significance is difficult to assess. The most probable cause of the pleural effusions would be cardiac failure due to amyloid involvement of the myocardium, which would also explain the rapid terminal enlargement of the liver. There was evidence of both hepatic and renal failure towards the end, as would be expected in amyloidosis. Perhaps the severe anaemia occurring while the patient was on liver and iron therapy was due to amyloid involvement of the bone marrow. It will be noted that, contrary to expectation, the albuminuria was never very gross. The incredibly low level of the serum albumin cannot readily be explained. The pigmentation of the skin, occurring independently of jaundice or ultra-violet ray therapy, remains yet another mystery.

It is a pleasure to acknowledge our debt to Dr. Hensel for his keen interest in the progress of his case and his helpful reports thereon, and to Drs. Shaw and Scott for their information about the last stages of the disease.

Arthrite Rhumatismale et Maladie Amyloïde

RÉSUMÉ

Dans le numéro de décembre 1948 des *Annals of the Rheumatic Diseases*, 7, 225, Lush, Chalmers, et Fletcher avaient décrit un cas d'arthrite rhumatismale et de maladie amyloïde; maintenant ils donnent la suite de l'étude du cas précédemment décrit allant jusqu'à la mort de la malade.

A moins qu'une troisième maladie ne décelée n'ait été présente, ce cas doit être classé comme un cas mortel d'arthrite rhumatismale, car il ne s'est écoulé que seize mois entre le début de la maladie chez cette femme jusque là bien portante et sa mort. La maladie amyloïde a été diagnostiquée sept mois après l'apparition du premier symptôme d'arthrite rhumatismale.