AMYLOIDOSIS COMPLICATING REITER'S SYNDROME*

BY

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Reiter (1916) described the case of a young army officer who developed urethritis, conjunctivitis, and arthritis after an attack of dysentery. Although Brodie (1818) had described five similar cases, this triad of urethritis, conjunctivitis, and arthritis of non-gonococcal origin has become known as Reiter's syndrome. Since that time a considerable literature has developed about this disease, the manifestations of which are protean (Weinberger, Ropes, Kulka, and Bauer, 1962). However, as far as can be ascertained, there appears to be no previous report of amyloidosis occurring in Reiter's syndrome. This is surprising as there are so many features of similarity between Reiter's syndrome and rheumatoid arthritis, which is one of the commonest causes of secondary amyloidosis. In spite of the similarity between the two diseases, Reiter's syndrome is regarded as an entity.

The case is here reported of a young man with Reiter's syndrome, who had extensive lesions of keratoderma blennorrhagica and who developed amyloidosis, affecting particularly the alimentary tract.

Case Report

A man aged 27 developed a urethral discharge in October, 1961, a few days after sexual intercourse. The discharge cleared in a few days without any specific therapy, but was followed a month later by a poly-arthritis involving the knees, ankles, elbows, and temporomandibular joints. The joints were swollen and tender and the patient felt unwell.

Examination.—In August, 1962, he was admitted to hospital and at that time both knees were painful, hot, and swollen. Movement was restricted by pain and there was marked wasting of the muscles of both thighs. The

movements of the cervical spine were restricted and he had difficulty in opening his mouth. He was pyrexial and anaemic, Hb 76 per cent. (11·2 g. per 100 ml.); erythrocyte sedimentation rate 35 mm./1 hr (Westergren); plasma proteins 6·8 g. (albumin 2·9 g., globulin 3·9 g.); the electrophoretic strip showed an increase in gamma globulins. No L.E.-cells were seen in six specimens. Other negative findings included the Waaler-Rose and the rheumatoid latex-fixation tests, Wassermann reaction, Kahn test, and gonococcal complement-fixation test. Six blood cultures and fluid aspirated from the knee were sterile.

Progress.—In September, 1962, Prednisolone 20 mg. three times a day was started. The pyrexia settled and there was considerable symptomatic improvement. However, on the dose of steroids being reduced, the fever recurred, and there was recrudescence of joint pains. Courses of penicillin and tetracycline had been given before starting steroid therapy and later streptomycin and chlortetracycline were given. In November, 1962, haemorrhagic psoriasiform pustular lesions developed under all the nails of both hands and feet and the nails were gradually shed. Later in the month the eruption affected the soles of the feet (Fig. 1 opposite) and the backs of the hands, and spread to involve the trunk and forehead.

In January, 1963, the patient was pyrexial, thin, depressed, and irritable. The knees, ankles, right wrist, left shoulder, and elbow joints were swollen, and movements at these joints were restricted by pain. There was wasting of the muscles of both arms and legs, with severe wasting of the quadriceps on both sides. A bilateral purulent conjunctivitis was present. There were many small, scaling, discoid lesions on the forehead and on the beard area of the face and several larger lesions on the upper part of the chest. The palms of the hands and the soles of the feet were thickened and the skin was erythematous and scaling. All the nails were dystrophic, being ridged and pitted; some were separated from the nail bed. The liver and spleen were not palpable and no abnormality was found on rectal examination.

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FIG. 1.—Keratoderma blennorrhagica affecting the soles of the feet.

Laboratory Investigations.—On January 17, 1963, the Hb was 93 per cent. (13.6 g. per 100 ml.); WBC 14,000 per c.mm (neutrophils 74 per cent.); erythrocyte sedimentation rate 60 mm./1 hr (Westergren); rheumatoid latex-fixation test negative; plasma proteins 5.8 g. per 100 ml. (albumin 3.8 g., globulin 2.0 g.); the electrophoretic strip was normal.

X-rays of the joints showed no abnormality, apart from some osteoporosis especially around the knee joints. The sacro-iliac joints were normal apart from sacralization of the right transverse process of the fifth lumbar vertebra.

A mid-stream specimen of urine showed an occasional pus cell and an epithelial cell, but culture was sterile.

On February 26, 1963, the patient was again anaemic, Hb 58 per cent. (8.5 g. per 100 ml.), M.C.H.C. 26 per cent., packed cell volume 33 per cent. The erythrocyte sedimentation rate had risen to 125 mm./1 hr (Westergren).

Treatment with oral steroids was maintained, but in addition, 20 units ACTH gel were given on alternate days.

The skin condition improved with daily potassium permanganate baths and Lassar's paste. Several blood transfusions were given in March and May, 1963, the pyrexia settled, and with intensive physiotherapy the arthritis improved. In November, 1963, the pyrexia

returned and was accompanied by malaise, frequent loose stools, a flare-up of the arthritis, and loss of weight. The diarrhoea persisted in spite of an increase in the dose of steroid therapy. Sigmoidoscopy showed a mild proctocolitis and faeces culture on several occasions gave a growth of *Staphylococcus aureus*, but the symptoms did not improve with antibiotic therapy and nightly Predsol retention enemata. A barium enema showed changes consistent with a colitis.

Operation.—The condition of the patient continued to deteriorate in spite of treatment and 3 months later, on February 24, 1964, the serum proteins had fallen to a total of 3.9 g. per 100 ml. (albumin 1.8 g., globulin 2.1 g.). An aspiration bone marrow biopsy showed an increased cellularity, with 5 per cent. plasma cells. Because of the toxæmia and the severe protein loss, total colectomy was performed on February 26, 1964.

Pathological Reports

Macroscopic Appearance.—The specimen consisted of 104 cm. of dilated caecum and colon from a total colectomy, together with 8 cm. of terminal ileum. The mucosal surface of the bowel was smooth, but there was no evidence of active or healed ulceration. In the caecum and ascending colon the wall of the bowel was atrophic. No enlarged lymph nodes were apparent.

Histology.—There was heavy deposition of amyloid in the superficial mucosa of the terminal ileum (Fig. 2), caecum, and colon (Fig. 3). Lesser deposits of amyloid were present in the muscularis mucosa, in the walls of blood vessels of the oedematous submucosa, and in the muscle and serosal coats of the colon. There was lymphocytic and plasma cell infiltration of the deeper layers of the mucosa of the large bowel, but there was no evidence of ulceration or of crypt abscesses. In the atrophic area of the caecum and ascending colon, the glandular pattern had been lost, but the surface was covered by simple columnar epithelium and the muscularis mucosa was intact. There was no evidence of ulcerative colitis.

Death.—Five days after operation, the patient developed a paralytic ileus which did not respond to treatment and he died on 8th March, 1964.

Postmortem Examination*.—This was performed 48 hours after death.

The body was that of a thin, wasted male. There was swelling of both wrists, knees, and left ankle. The skin showed multiple small areas of pigmentation and haemorrhages. The abdomen was distended, the coils of dilated gut being adherent. Both lungs were congested

and there was free fluid in the pleural cavities. There was brown atrophy of the myocardium and the aorta was hypoplastic. The liver was congested and the spleen firm. The kidneys were swollen, but the bladder, prostate and penis appeared healthy. The bone marrow was hyperplastic.

Histology.—The small intestine was severely autolysed but showed subacute inflammation, most marked on the serosal surface. There was no evidence of a vasculitis. The liver showed considerable mid-zonal deposition of amyloid with secondary atrophy of the parenchymal cells (Fig. 4, opposite).

Considerable deposition of amyloid was also seen to be present in the spleen and adrenals. The kidneys showed mild chronic pyelonephritis and very scanty amyloid material in a few glomeruli. There was thickening of the capsule of the wrist joint with proliferation of blood vessels and perivascular round cell infiltration. No villous hypertrophy of the synovial lining was apparent. The penis showed a chronic inflammatory infiltrate consisting mainly of plasma cells and lymphocytes in the submucous connective tissue of the urethra and para-urethral glands (Fig. 5, opposite). The sternal bone marrow was active and showed a slight increase of mature plasma cells.

*Report by kind permission of H.M. Coroner for Southwark.

FIG. 2.—Amyloid in the stroma of one of the villi in the terminal ileum, $\times 585$.

FIG. 3.—Amyloid deposition in the superficial mucosa of the colon. Moderate numbers of plasma cells are present in the deeper mucosa and there is submucosal oedema, $\times 172$.

The conclusion of the *post mortem* examination was that death was due to peritonitis following a total colectomy for a protein-losing enteropathy, the result of secondary amyloidosis of the ileum and colon complicating Reiter's disease.

Discussion

The diagnosis of Reiter's syndrome in this case is established by the triad of urethritis, arthritis, and conjunctivitis, with the skin lesions of keratoderma blennorrhagica, and negative tests for rheumatoid arthritis.

Secondary amyloidosis occurs most commonly in patients suffering from chronic inflammatory diseases of which rheumatoid arthritis is the most

important cause at present in Great Britain. There are many features of similarity between rheumatoid arthritis and Reiter's syndrome (Weinberger, 1962), but in spite of this, amyloidosis complicating Reiter's syndrome appears to be rare.

The mechanism of formation and deposition of amyloid is still uncertain. Two theories are currently popular:

The first is that a circulating soluble glycoprotein is formed by cells of the plasma cell series and this combines with a sulphated mucopolysaccharide produced by endothelial cells to form an insoluble protein-polysaccharide complex, amyloid. This accounts for the characteristic subendothelial distribution of amyloid (Kennedy, 1962).

FIG. 4.—Liver showing midzone deposition of amyloid with atrophy of the adjacent parenchymal cells. $\times 130$.

FIG. 5.—Penile urethra showing severe chronic inflammation with many lymphocytes and plasma cells in the submucosa. $\times 520$.

The second theory, largely dependent on the work of Teilum (1964a, b), suggests a biphasic development of amyloid. The initial phase is associated with proliferation of pyroninophilic reticulo-endothelial cells and plasma cells, and a rise in the serum gamma globulin. These pyroninophilic cells are concerned with immunoglobulin production in response to antigenic stimuli. The second, or amyloid phase, depends on a suppression of the proliferating pyroninophilic cells associated with a decrease in the serum gamma globulin level and the appearance of a glycoprotein staining with periodic acid-Schiff (PAS) within the reticulo-endothelial cells. The failure of immunoglobulin production associated with suppression of the pyroninophilic cells in the presence of persistent stimulation results in the precipitation of amyloid *in situ*. The glycoprotein products are not carried away in the general circulation, but remain as insoluble amyloid aggregates in juxtaposition to the cells. According to this theory, it is not essential to have a raised serum globulin or circulating glycoprotein before amyloid formation, as this is laid down *in situ*. This would explain the occasional case of hypogammaglobulinemia associated with amyloidosis (Teilum, 1964b). In support of this theory is the earlier work of Teilum (1952), showing that cortisone has an enhancing effect in the development of amyloidosis. He considered that this was part of a suppressive effect of cortisone on the pyroninophilic reticulo-endothelial cells (Teilum, 1964a) and confirmed this by showing a similar effect with nitrogen mustard (Teilum, 1954).

Reiter's syndrome is associated with plasma cell proliferation, as is rheumatoid arthritis, but the rarity of amyloidosis in Reiter's disease is of interest. In view of Teilum's work with cortisone and the experimental production of amyloidosis, the possibility is raised that the long-continued corticosteroid therapy in this patient may have contributed to the development of amyloidosis. The fall in the serum gamma globulin level which occurred on steroid therapy would then correspond with the second phase in Teilum's theory. This was followed by

amyloid deposition in the gut, causing a protein-losing enteropathy and a fall in the serum albumin level, possibly accentuated by the liver damage.

Amyloidosis is rarely considered as a cause of persistent diarrhoea, although Casad and Bocian (1965) have recently described a case of amyloidosis simulating acute ulcerative colitis. Once heavy deposits of amyloid have occurred in the gut, it is difficult to see how protein loss can be controlled other than by gut resection of the more severely affected area and control of the underlying inflammatory processes inducing the amyloid deposition.

Summary

A case is described of secondary amyloidosis complicating Reiter's syndrome. Severe amyloid deposition occurred in the colon causing a protein-losing enteropathy, which required total colectomy. The possibility of corticosteroid therapy inducing amyloidosis in this case is discussed.

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Amyloidose compliquant le syndrome de Reiter

RÉSUMÉ

Un cas d'amyloidose secondaire compliquant le syndrome de Reiter est décrit. Un dépôt amyloïde marqué a eu lieu dans le colon causant une entéropathie qui a amené une perte de protéides nécessitant une colectomie totale. La possibilité du traitement corticostéroïde causant l'amyloïdose chez ce malade est discutée.