Amyloidosis—a Complication of Pustular Psoriasis

PETER A. BERGER,* M.B., B.S., M.R.C.P.ED.

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Summary: Two patients with generalized pustular psoriasis developed amyloidosis with a fatal outcome. It is suggested that generalized pustular psoriasis may predispose to the development of secondary amyloidosis either by prolonged stimulation of the reticuloendothelial system or through abnormal immunoglobulin synthesis.

Introduction

This appears to be the first time that pustular psoriasis has been described in direct association with amyloidosis. Although the first patient (Case 1) had an arthritis it was of the psoriatic type. No evidence of active infection, tubercle or otherwise, was found in Case 2. Neither patient had multiple myeloma. In analysing the current views on the causation of pustular psoriasis and amyloidosis certain similarities are seen. Evidence is presented to show why it is thought that pustular psoriasis may result in abnormal stimulation of the reticuloendothelial system. In this respect it probably occupies a position somewhere between a chronic infective condition such as leprosy or osteomyelitis and an abnormal immunological response such as rheumatoid arthritis or multiple myeloma.

Case 1

A 31-year-old man first presented in 1961 to Hairmyres Hospital, Glasgow, with arthralgia of the left hip. He had no evidence of skin disease at that time. The pain became more widespread and he was admitted with a diagnosis of acute rheumatism. During that admission he developed a patch of psoriasis over the sacrum. This spread to involve most of the body and scalp. Several months later he was discharged free of both psoriasis and arthralgia.

Two years later, in October 1963, he was admitted to the Royal Infirmary, Glasgow, with generalized pustular psoriasis of the body and scalp and widespread arthritis. The distribution and x-ray appearance of the affected joints was consistent with psoriatic arthropathy. All fingernails and toenails showed various stages of pitting, thickening, onycholysis, and dystrophy.

Between April 1964 and October 1966 he required four admissions to hospital for a total period of six months. By October 1966 recurrent episodes of extensive pustular psoriasis and gross joint deformity necessitated terminal hospitalization.

From March 1967 onwards he was noted to have persistent proteinuria. Apart from facial telangiectasis no other abnormal physical signs developed and he remained normotensive. His serum protein in 1963 was albumin 3.9 and globulin 3.4 g./100 ml.; in July 1967, albumin 1.0 and globulin 3.2 g./100 ml.; and in November 1967, albumin 0.5 and globulin 4.1 g./100 ml. Rheumatoid arthritis and lupus erythematosus latex, Rose-Waaler, lupus erythematosus cell, and antinuclear factor tests were all negative on six occasions throughout his illness. Apart from the usual topical therapy he received Betnesol (betamethasone 21-disodium phosphate) 1 mg. twice daily for seven days in 1963. Methotrexate was given on two occasions. Four courses of 2.5 mg. daily for six days with an interval of four days between courses were given in 1965. Three weekly intravenous injections of 25 mg. were given in 1966. Later in his illness he also received infusions of blood and Aminosol.

In September 1967 he complained of intermittent diarrhoea. Sigmoidoscopy to 15 cm. showed multiple mucosal petechiae and purpuric lesions. Biopsy of the rectal mucosa unfortunately did

not include the submucosa. Both thioflavine T and Congo red stains failed to show evidence of amyloid. Faecal fat excretion was 3.6 g./day and faecal cultures were negative.

The urinary protein excretion remained about 300 mg./100 ml. and the serum cholesterol 324 mg./100 ml. The creatinine clearance fell from 83 ml./minute in March 1967 to 15 ml./minute in October 1967. Microscopy and culture of the urine proved sterile. An intravenous pyelogram in October showed faint excretion from the right kidney in which no lesion was demonstrable. No excretion was apparent from the left kidney. The diarrhoea persisted. By November intermittent vomiting had begun. His urinary output fell sharply for the first time and he died in uraemia on 16 November 1967. At necropsy, extensive infiltrates of amyloid (confirmed by Congo red and methyl violet stains) were found in both kidneys and adrenal glands, in the liver, and in the small intestine. The immediate cause of death was left renal vein thrombosis. Histological changes in the skin were consistent with psoriasis, and those of the synovium with psoriatic arthropathy.

Case 2

A 51-year-old man from New York had psoriasis for the first time in 1954. For one year before his admission to the Aberdeen Royal Infirmary, in June 1956, he had numerous episodes of pustular psoriasis. These were treated with prednisolone, the dosage varying between 5 and 20 mg./day, and A.C.T.H. 40 units weekly. The pustular psoriasis was widespread, with the trunk and proximal parts of the limbs most severely affected. The fingernails and toenails were dystrophic. There was no lymphadenopathy, splenomegaly, evidence of arthritis, or other abnormal findings. Cultures of the pus were either sterile or grew commensals only. Hoarseness, diarrhoea, and increasing albuminuria accompanied the illness. The stools were frequent, small, and pale but had a normal fat content. Stool culture and barium enema were also within normal limits. Albuminuria was persistent and profuse but there was no evidence of urinary infection. Pyelography showed a large left kidney and in the right renal area a patch of calcification but no kidney. Chest radiography showed some emphysema and apical evidence of healed tuberculosis. Sputum, urine, and gastric washings did not contain acid-fast bacilli.

The diarrhoea worsened, the skin improved, but the patient's general condition deteriorated and he died on 10 September 1956. During his three months in hospital his haemoglobin remained fairly constant at 12.3 g. while his leucocyte count rose from 9,500 to 19,400/cu. mm. The blood urea fell from 67 to 28 mg./100 ml. and 10 days before his death his serum albumin was 1.8 and globulin 2.3 g./100 ml. (high α_2 and low γ -globulin fractions). Throughout his last illness, apart from topical applications, he received a total dose of only 2.4 g. of prednisolone and 1.4 g. of A.C.T.H.

At necropsy a small fibrotic right kidney containing amorphous and calcareous material was found. There was no evidence of an active focus of infection in the lungs or kidneys. Acid-fast bacilli were not seen histologically or on cultures. Extensive amyloid disease with heavy infiltration of the spleen, kidneys, adrenals, and entire intestine was present. Smaller deposits were also found in and around vessels in the thyroid, heart, liver, and testes. There was ulceration of the larynx.

Discussion

Amyloidosis was found in two patients with pustular psoriasis. In neither patient was there any definite evidence of the usual causes of amyloidosis, including tuberculosis and rheumatoid arthritis. The first patient (Case 1) had arthritis.

* Formerly Registrar, Royal Infirmary, Glasgow C.4. Present address: Hitchcock Clinic, Dartmouth Medical School, Hanover, New Hampshire, U.S.A.

Nevertheless, the negative sheep cell agglutination tests, the specific x-ray appearances, and biopsy, together with maximal involvement of the terminal interphalangeal joints, would appear to exclude the diagnosis of rheumatoid arthritis (Baker *et al.*, 1963; Barduagni and Carlesimo, 1967). The second patient (Case 2) had completely inactive renal pathology of long standing confined to the right kidney. He had received small, intermittent doses of systemic corticosteroids over a 12-month period. The evidence does not suggest that these factors were significant in the subsequent development of amyloidosis.

Psoriasis is a very common disorder of the skin, the histological features of which are parakeratosis, elongation of the rete pegs, and microabscesses of Munro. Pustular psoriasis denotes a variant in which macroscopic pustules are prominent, usually as crops of small pustules confined to the palms and soles unaccompanied by fever or systemic disturbance. Less commonly widespread sheets of pustules may occur with associated toxæmia. This generalized form may be fatal. The pustules in both forms are sterile.

Generalized pustular psoriasis is an inflammatory disorder in the sense that it produces redness, pyrexia, pustulation, and leucocytosis. Histologically this variant of psoriasis differs only in the severity and speed of evolution of the classical features. The formation of microabscesses appears to be accelerated, adjacent areas of epidermis become involved, and large subcorneal pustules form. This is accompanied by intense intracellular oedema of the Malpighian layer and the invasion of vast numbers of neutrophil polymorphs.

The cause of psoriasis and its variants remains obscure. An inborn error of metabolism or enzyme deficiency in the keratinocyte, particularly in the formation of nuclear protein, has been suggested. (Roe, 1958; *Transactions of St. John's Hospital Dermatological Society*, 1965). In-vitro immunological studies have been unrewarding (Skog and Linder, 1965; Sönnichsen *et al.*, 1965). The clonal theory of psoriasis suggests that the formation of a forbidden clone may result in the synthesis of an autoantibody that promotes hyperplasia of epidermal basal cells. This is based on an analysis of sex, age, and familial distribution of psoriasis, which indicates that the predisposition is genetically based. After an initiating somatic mutation the growth of a forbidden clone begins. These cells then synthesize a humoral antibody, possibly an α 2-globulin capable of diffusing through a damaged epidermal basement membrane. Psoriasis then becomes a disease of disturbed tolerance auto-immunity (Burch and Rowell, 1965).

More recently it has been reported that, following either the ingestion of salicylates and iodides (Shelley, 1964, 1967) or contact with tar (Ogawa *et al.*, 1969), generalized pustular psoriasis has been evoked. Hypersensitivity in an individual with the psoriatic diathesis has been suggested as a possible explanation for this sequence of events, thus implicating immune mechanisms in the genesis of pustular psoriasis.

Amyloid may be defined as a homogeneous, eosinophilic, hyaline extracellular connective tissue substance having a fibrillar ultrastructure. Various aetiological factors have been suggested, including a disorder of protein metabolism or serum proteins with associated hyperglobulinaemia. More recently an abnormality of the reticuloendothelial system or chronic immunological stimulation with antibody production has been considered (Cohen, 1965).

Teilum (1964), in a series of experiments involving the injection of casein into mice, some with added cortisone and others with nitrogen mustard, concluded that casein acts, as do many other substances that induce amyloid, as a non-specific stimulus, probably of the reticuloendothelial system, possibly mediated immunologically, and influenced by extrinsic and intrinsic factors such as corticosteroids. Dick and Leiter (1935, 1937, 1941) reported on an extensive series of experiments in which various bacteria were injected into rabbits. The overall inci-

dence of amyloid was 57%. In the great majority of amyloid-positive animals no focus of chronic suppuration or inflammation was found to account for the progressive evolution of amyloidosis long after the injections had stopped. Rask-Nielsen *et al.* (1960) studied the induction of amyloid in mice by a transplantable reticulum-cell neoplasm. These authors concluded that amyloid was probably produced as a local cellular reaction of reticuloendothelial cells.

The role of hormonal excess or deficiency in the genesis of experimental amyloidosis has been the subject of conflicting reports in the literature. Teilum (1964) stated that cortisone treatment accelerates the appearance of amyloidosis in casein-treated mice. Christensen and Rask-Nielsen (1962) found that cortisone did not alter the casein-induced or sarcoma-related mouse amyloid. Cohen *et al.* (1962) found that in casein-treated rabbits there was a lower incidence of amyloidosis in the cortisone-treated group, but with increased passage of time the incidence tended to approach that of the controls. The severity of the disease was less in the cortisone-treated rabbits. The clinical literature is equally divided on the advantages and disadvantages of steroid therapy in amyloidosis (Gardner, 1962). When one compares the prevalence of amyloid in the years before and after the introduction of cortisone, or determines how many patients with amyloid had rheumatoid arthritis treated with corticosteroids, then the available data do not support the suggestion that secondary amyloidosis is increased in rheumatoid arthritis as a result of the use of hormone therapy.

Immune mechanisms may be involved in the genesis of amyloid. Amyloidosis is commonly associated with chronic infectious disease—for example, tuberculosis, leprosy, osteomyelitis, and chronic inflammatory diseases such as rheumatoid arthritis and multiple myeloma. The evidence of its association with chronic suppuration in animals has been discussed. Even more impressive is the appearance of amyloid when sterile cultures of dead bacteria were used in its production. Horses given repeated injections of toxoids in the commercial production of antisera are prone to develop amyloid, and many noxious stimuli used in experimental animals will induce its formation. These facts have led many workers to postulate that amyloid is the result of an antigen-antibody reaction. Currently it is thought that both rheumatoid arthritis and multiple myeloma are associated with abnormalities of immunoglobulin synthesis. The common factor in these chronic inflammatory diseases appears to be a massive stimulation of the reticuloendothelial system.

On the basis of these case reports it seems reasonable to suggest that generalized pustular psoriasis may predispose to the development of secondary amyloidosis, either by prolonged stimulation of the reticuloendothelial system or through abnormal immunoglobulin synthesis. Hence it may occupy an intermediate position between a frankly infective condition and abnormal reticuloendothelial stimulation.

Case 1 was under the care of Dr. J. O'D. Alexander and Case 2 was under the care of Dr. Alan Lyell (originally under the care of the late Dr. Maurice Costello, New York, U.S.A.). I wish to thank them for allowing me to publish the case histories of these patients. Also I am indebted to Dr. Alan Lyell and Dr. H. J. Wallace, of St. Thomas's Hospital, London, for their guidance and encouragement in the preparation of this paper. Dr. J. Simpson, of the Glasgow Royal Infirmary, and Dr. S. Mathieson, of the Aberdeen Infirmary, reported on the pathological investigations.

REFERENCES

- Baker, H., Golding, D. N., and Thompson, M. (1963). *British Medical Journal*, 2, 348.
- Barduagni, O., and Carlesimo, O. A. (1967). *Policlinico, Sezione Pratica*, 74, 33.
- Burch, P. R. J., and Rowell, N. R. (1965). *Acta Dermato-venereologica*, 45, 366.
- Christensen, H. E., and Rask-Nielsen, R. (1962). *Journal of the National Cancer Institute*, 28, 1.
- Cohen, A. S. (1965). *International Review of Experimental Pathology*, 4, 159.

- Cohen, A. S., Calkins, E., and Mullinax, P. F. (1962). *Archives of Internal Medicine*, **110**, 569.
- Dick, G. F., and Leiter, L. (1935). *Transactions of the Association of American Physicians*, **50**, 135.
- Dick, G. F., and Leiter, L. (1937). *Transactions of the Association of American Physicians*, **52**, 246.
- Dick, G. F., and Leiter, L. (1941). *American Journal of Pathology*, **17**, 741.
- Gardner, D. L. (1962). *Annals of the Rheumatic Diseases*, **21**, 298.
- Ogawa, M., Clendenning, W. E., and Baughman, R. D. (1969). *Archives of Dermatology*, **99**. In press.
- Rask-Nielsen, R., Christensen, H. E., and Clausen, J. (1960). *Journal of the National Cancer Institute*, **25**, 315.

- Roe, D. A. (1958). *Annals of the New York Academy of Sciences*, **73**, 977.
- Shelley, W. B. (1964). *Journal of the American Medical Association*, **189**, 985.
- Shelley, W. B. (1967). *Journal of the American Medical Association*, **201**, 1009.
- Skog, E., and Linder, O. (1965). *Acta Dermato-venereologica*, **45**, 461.
- Sönnichsen, N., Apostoloff, G., and Nebe, H. (1965). *Dermatologische Wochenschrift*, **151**, 1423.
- Teilum, G. (1964). *Acta Pathologica et Microbiologica Scandinavica*, **61**, 21.
- Transactions of St. John's Hospital Dermatological Society*, 1965, **51**, 106.

Boric Acid Preservation of Urine Samples

I. A. PORTER,* M.D., M.C.PATH. ; J. BRODIE,† M.D., D.P.H., F.C.PATH.

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Summary: Comparison of the results of bacteriological culture and microscopic examination of urine samples transported over a distance by the dip-inoculum transport medium, ice-box, and boric acid preservation with “natural” urine specimens showed that the last, in a final concentration of 1.8%, gives satisfactory preservation.

Introduction

Urine is a good culture medium. Delay in delivery to the laboratory may lead to an increase in bacterial content from an initial number of no significance to a total which may be construed as significant. The midstream specimen, promptly delivered, is acceptable for bacteriological examination provided strict care is taken both in the preparation of the patient and in the collection of the sample. The urine must be delivered to the laboratory within one hour of passing. Refrigeration of the specimen for up to 48 hours before delivery is also acceptable.

It is impossible to meet these requirements when the urine comes from a distance and must be sent, for example, by post. Certain procedures to obviate such difficulties have been evolved—for example, the dip-inoculum transport medium outfit (D.I.T.M.) of Mackey and Sandys (1965) and the dip-slide technique of Naylor and Guttman (1967). Both of these methods allow the bacterial count per ml. of urine to be calculated. The significance of the count is interpreted on the basis of the recommendations of Kass (1956), so that a bacterial content of over 100,000 organisms per ml. is of significance, between 10,000 and 100,000 is of doubtful significance, and under 10,000 is of no significance. Counts within each range given above are abbreviated to S, DS, and NS respectively.

The Laboratory, City Hospital, Aberdeen, receives around 140,000 specimens annually, of which some 17,000 are urines. The majority of specimens cannot be delivered to the laboratory within the optimal time because most users of the service are outside the City of Aberdeen itself. The catchment area comprises Kincardineshire, Aberdeenshire, Banffshire, Moray, and Nairn, and includes the Orkney and Shetland groups of islands. There is a brisk postal service between the laboratory

and its users. The majority of specimens arrive within 24 hours of posting, but delays of two to three days are not uncommon, especially if specimens are taken and dispatched at week-ends. Special provisions are made to minimize deterioration of some types of specimens while in transit—for example, serum-coated swab outfits, use of Stuart's transport medium, etc. A urine sample outfit suitable for all users of the laboratory has been difficult to find. Trials of both the dip-inoculum outfit and ice-box transport have been undertaken.

A new outfit using boric acid as a preservative has been evolved and the comparative results are given and discussed. Results with this outfit have been so encouraging that it is now being issued in the region for all urine samples requiring bacteriological examinations.

Procedures and Results

D.I.T.M. Compared with “Natural” Urine Specimen

With the co-operation of the New Gilbert Bain Hospital, Lerwick, Shetland, arrangements were made to send 100 urines. From each midstream specimen collected, 1 fl. oz. (28 ml.) was dispatched in a sterile universal container. A D.I.T.M. sample was also taken from the same urine at the same time. Both were posted in the same envelope to the laboratory in Aberdeen. Of the specimens, 38 were at least two days old on receipt.

The D.I.T.M. was incubated at 37° C. for 24 hours. The colony count was then taken and the number of organisms per ml. calculated. The “natural” urine on receipt was shaken and sampled with a 4 mm. loop. The loopful was spread evenly on culture media and colony counts were made after 24 hours at 37° C. The average of the counts multiplied by 100 gave the number of organisms per ml.

If it is accepted that the D.I.T.M. result is more accurate than that obtained from the natural urine specimen in these circumstances, then the results compare as set forth in Table I, which shows that 18 of the 100 natural urines gave results which did not correspond with the D.I.T.M. estimations. Of these 18, the number showing more organisms than the D.I.T.M. parallel samples was 13. Of the five urines with lower counts than the corresponding D.I.T.M. samples, three contained *Proteus* spp., one a strain of *Escherichia coli*, and the fifth a coagulase-negative staphylococcus.

* Consultant Bacteriologist.

† Consultant-in-Charge.

The Laboratory, City Hospital, Aberdeen.