Imaging amyloidosis in Still's disease

Attaching radioiodine to a protein found in amyloid showed amyloid in the spleen, adrenal, glands, kidneys, and liver

Still's disease is a chronic multisystem disorder of childhood and adolescence characterised by inflammatory arthritis with constitutional features (fever, rash, and weight loss), often more prominent at the time of onset. The disease usually remits in adult life and thus the overall prognosis remains good. In 10% of cases, however, the illness is complicated by reactive systemic amyloidosis, which reduces the survival to about eight years. We present a patient in whom a new imaging technique was used which allows early recognition and treatment of amyloidosis. We believe that this technique will prove useful in the diagnosis and management of this treatable complication.

History

The patient was a 39 year old man, who had been well until the age of 12, when he had developed swelling and pain in his hands and feet, an erythematous rash, and generalised stiffness. He had been seen at the Medical Research Council's rheumatism unit shortly after the onset and had been noted to have diffuse lymphadenopathy, a palpable liver, and widespread arthritis affecting medium and large joints. Analysis of his urine had yielded normal results. A clinical diagnosis of Still's disease was made, and treatment was started with aspirin at high dose and intensive physiotherapy. His symptoms then deteriorated, and he developed high fevers and pleurisy. Treatment with prednisolone on alternate days induced a good response that was maintained over the next five years, during which time he went through puberty normally.

When he was 17 his corticosteroid dose was gradually stopped, after which he remained well for a further three years. His arthritis then recurred, affecting the hips and sacroiliac joints. Daily aspirin and prednisolone every two days were reintroduced with good effect. Two years later trace proteinuria was noted for the first time, arousing the suspicion of amyloidosis. Two rectal biopsies yielded normal results, and a positive diagnosis was made only after a third biopsy. Treatment with the cytotoxic drug chlorambucil was started, and other than a period of nine months in 1979 during which persistent azoospermia was noted he continued to take chlorambucil until December 1988. Corticosteroids had been stopped in 1982. Inflammatory joint activity had been suppressed effectively during this time, and on several occasions proteinuria was absent. Secondary osteoarthritis, especially of the hip and ankles, recently caused him problems, though he remained ambulant and in full time employment.

Recent investigations showed a normal full blood picture, electrolyte concentrations, liver function, and serum immunoglobulin concentrations. His serum creatinine concentration was 198 μmol/l (normal <120) and C reactive protein concentration 13·1 mg/l (normal <10). Analysis of his urine showed 1+ protein. The results of a serum amyloid P component study for amyloidosis are described below.

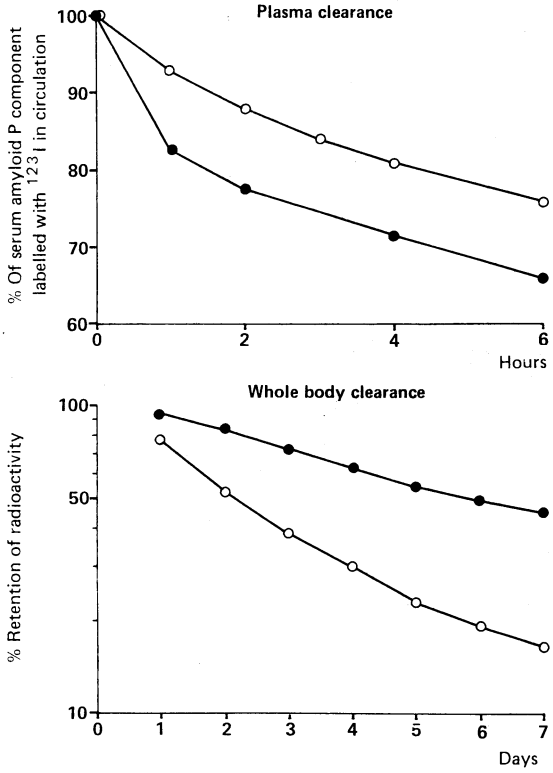

FIG 1—*Clearance profiles after intravenous injection with serum amyloid P labelled with ^{123}I from plasma and whole body, showing mean values for 10 normal volunteers (○) and patient (●). In amyloidosis deviation from normal values is due to sequestration of tracer within amyloid deposits*

Serum amyloid P component isotope study

The basis of this new clinical investigation is the specific molecular affinity of serum amyloid P component, a normal plasma protein, for all types of amyloid fibril, in this case protein AA fibrils derived from the acute phase reactant serum amyloid A.[1] As a result of this interaction native serum amyloid P becomes incorporated as a minor universal constituent of all amyloid deposits, where it is referred to as amyloid P component. In patients with amyloidosis we have shown that radioiodinated pure isologous serum amyloid P introduced into the circulation rapidly leaves the vascular compartment and localises specifically within the amyloid deposits, where it persists. By contrast, in normal subjects serum amyloid P remains within the circulation, from which it is catabolised, and has a biological half life of 24-30 h.

The early clearance of serum amyloid P labelled with iodine-123 is increased in amyloidosis as the tracer localises to the amyloid. Its distribution may then be imaged by scintigraphy, usually performed after 24 hours. As the proportion of serum amyloid P labelled with ^{123}I (up to 95% of the injected dose) that localises to amyloid effectively persists there, whole body retention of radioactivity corrected for decay is also increased and can be conveniently measured as being the inverse of the urinary excretion of radioactive degradation products. These three variables (the early

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Distribution of deposits in organs of 26 patients with reactive systemic amyloidosis on scanning with serum amyloid P component labelled with ^{123}I

Organ	Distribution
Spleen	26
Kidneys	17
Adrenals	7
Liver	7

plasma clearance curve, the scintigrams, and the whole body retention of radioactivity) form a unique profile of each patient with amyloid, which can be repeated at times during their disease. Figures 1, 2, and 3 show the data for this patient.

Comment

Amyloidosis complicates the clinical course of between 5% and 20% of patients with Still's disease. Of the patients reviewed by Schnitzer and Ansell in 1977, those who developed amyloidosis were typically those with polyarticular disease and systemic symptoms at the onset.[2] Patients were usually seronegative for rheumatoid factor and antinuclear factor, and the interval between the onset of Still's disease and the diagnosis of amyloid varied from one to 23 years (mean 9). Proteinuria was the usual feature that prompted investigation for this complication. In this series before the introduction of cytotoxic treatment the death rate was 30% in patients followed up for seven years and 50% in those followed up for 10 years. In 1967 treatment with chlorambucil was introduced and consisted of 2 mg daily, increasing to 4 mg within two months if there were no untoward effects. The dose was later increased to 6 mg if this was needed to control the disease. The platelet count and white cell counts were monitored frequently and the dose adjusted as required. This treatment proved extremely successful with good preservation of renal function, and no deaths were seen in five patients followed up for seven years. Long term survival is now the rule (A Hall and P Woo, personal communication), and many survivors show resolution of some of the clinical features attributable to deposition of amyloid, particularly proteinuria. A major difficulty, however, has been the absence of any means of measuring the amyloid deposits. Questions about, for example, the necessary duration of treatment with its universal complication of sterility and long term risk of carcinogenesis remain unanswered.

We have now studied 35 patients with chronic inflammatory diseases, including patients with Still's disease, rheumatoid arthritis, and ankylosing spondylitis, in whom reactive systemic amyloid was either suspected (15) or histologically proved (20). Positive results were obtained in all patients with proved amyloidosis and in a further six with suspected amyloid, in four of whom rectal biopsy specimens had been negative for amyloid by histological examination. The table shows the distribution of the amyloid deposits in the organs.

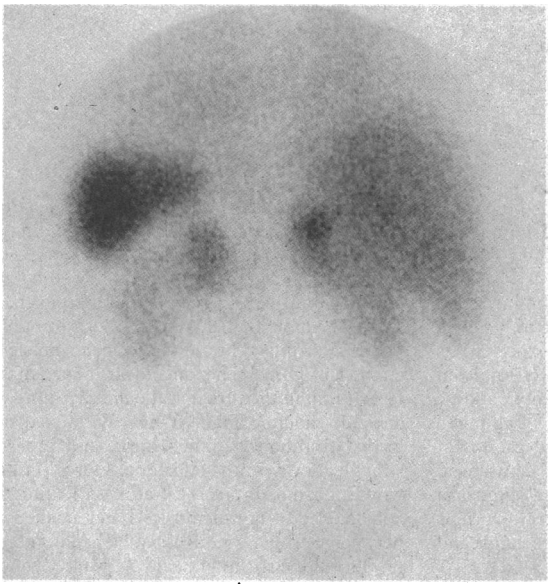

FIG 2—*Posterior abdominal view of scan with serum amyloid P component labelled with ^{123}I showing distinct uptake into spleen and adrenal glands and minor increase of activity in liver and both kidneys, reflecting extent of amyloid deposition in these organs*

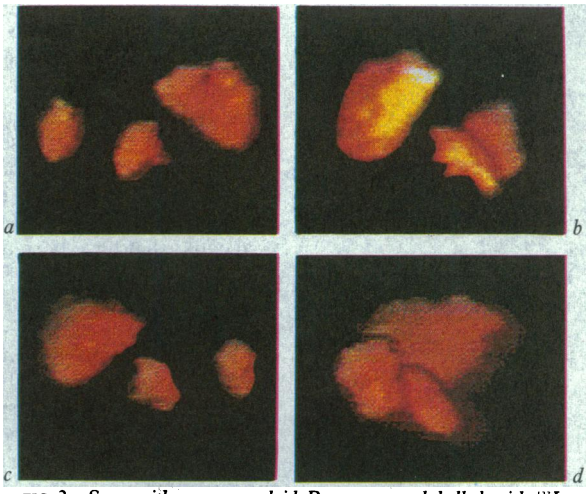

FIG 3—*Scan with serum amyloid P component labelled with ^{123}I. Single photon emission computed tomograms have been reconstructed as rotating three dimensional image. Four enhanced images show spleen and adrenal glands (which seem to be considerably enlarged) at 90° intervals through a single clockwise rotation at (a) 0°, (b) 90°, (c) 180°, and (d) 270°*

In summary, amyloidosis is not only a common complication of the inflammatory arthritides but one that is amenable to treatment. Clinical features of amyloid may be misleading, and splenic, hepatic, and adrenal deposits are common and may contribute to morbidity and mortality. We now have a safe non-invasive method with which to diagnose amyloid and to determine its distribution; it may be possible to use this to assess the benefits of treatment.

Discussion

SRB: We can only be impressed by this useful clinical advance and by the elegant demonstration of affected organs. Now that treatment can be followed up more directly and not just by organ failure, might we document possible regression?

MBP: This is certainly one of our hopes. Still's disease is a serious condition but one that does remit. Children therefore tend to survive into adult life, but some may develop amyloid with its serious consequences. Ansell has shown dramatically the effectiveness of chlorambucil in greatly improving the prognosis, but it is dangerous. The method that we have described will allow more rational use of this treatment. Some of the patients who have died of infection may well have had unsuspected disease in the spleen or adrenal glands, and we hope that this sort of assessment will improve the quality and expectancy of life in these patients. Fundamentally, we have the opportunity to see whether this or any future treatment can make the amyloid regress completely.

TMC: I believe that Dr Woo in the division of molecular rheumatology at Northwick Park Hospital has done studies in which a restriction fragment length polymorphism for serum amyloid P may segregate with and thus predict the development of amyloid.[3] Have you had the opportunity to compare their results on the patients you have studied with this sensitive technique, and, given the complications of treatment, might it become possible to select patients for prophylactic treatment?

MBP: The whole question of restricted fragment length polymorphism is interesting. It is rather distant from the actual coding region for serum amyloid P, and we have no evidence for there being any protein heterogeneity for serum amyloid P in those or any other patients. Two things will help answer this

question: firstly, the sequencing of the coding region, which Dr Woo, who described this restriction fragment length polymorphism, is currently doing and, secondly, establishing the predictive value of restriction fragment length polymorphism in a larger series of patients with Still's disease and more importantly in patients with other forms of amyloid.

Member of audience: Have any of the patients received prednisolone before developing amyloid and if so could that have been a factor in the development of amyloid in the light of the old data that suggest that corticosteroids may sometimes accelerate the deposition of amyloid?

PH: The opposite is more likely to be true as prednisolone can modify the course of the disease and reduce the acute phase response, which we believe is the cause of amyloid A deposition.

MBP: I am glad you raised this point as it illustrates a fundamental and rather distressing fact in medical education that sometimes ideas that are completely wrong and are published on the basis of one or two anecdotal reports become entrenched in everyone's minds. I would like to take this opportunity to try to dispel the concept that corticosteroids are bad for people with amyloid. On the contrary, if you have a patient with an inflammatory primary disease that predisposes to reactive systemic amyloid the best treatment is steroids or some other potent anti-inflammatory drug. There is now good evidence that this improves the prognosis, whether in the context of Still's disease, rheumatoid arthritis, or Crohn's disease. The information that steroids might accelerate the development of amyloid dates from observations made over 30 years ago and I am sure must have been obtained in patients with active infections.

Member of audience: What about in myeloma?

MBP: Myeloma is another story altogether: the amyloid fibril protein is different and, of course, is not the result of inflammation.

OMW: Now that we have stick testing, proteinuria is found in many normal people, and if that is your screen then maybe you should consider using sulphosalicylic acid precipitation or some quantitative measurements.

JW: Infertility is a common complication of cytotoxic chemotherapy, and with chlorambucil it is said that a total dose of 400 mg causes irreversible sterility. Another complication is malignancy. Is there any information regarding these problems in patients with Still's disease?

PH: Malignancies, particularly lymphomas and leukaemias, are occurring, though I cannot be precise as to the exact types and numbers. I think that everyone is aware of this and accepts it as a long term risk when using this type of cytotoxic treatment in rheumatic diseases.

SRB: Is it possible to bank sperm?

PH: On the whole these patients are too young.

JC: Is there any correlation with impaired adrenal function in these patients?

PH: We have not yet shown this by using the short tetracosactrin test as an index of normal adrenal function, though adrenal failure is well known in amyloid.

AJR: Another almost apocryphal clinical observation, first made on the basis of a few patients here, is that proteinuria can go away and yet amyloid deposition remain. Do you believe that this is the case, and have you had the opportunity to correlate changes in proteinuria in any patients with your findings?

MBP: The observation is certainly true; this is commonly happening in association with the decreasing creatinine clearance when sufficient glomeruli are damaged by the amyloid, though obviously it is not a simple relation. We have not studied enough patients serially to answer your second question, though in all those we have studied twice there has been evidence of increasing amyloid deposition over six to 12 months.

PH: We have several patients with proved renal amyloid and clear uptake of serum amyloid P labelled with ^{123}I on the scan in whom there has been no significant proteinuria.

We thank Dr Ann Hall at Wexham Park Hospital for allowing us to report on this patient.

1 Hawkins PN, Myers MJ, Lavender JP, Pepys MB. Diagnostic radionuclide imaging of amyloid: biological targeting by circulating human serum amyloid P component. *Lancet* 1988;i:1413-8.
2 Schnitzer TJ, Ansell BM. Amyloidosis in juvenile chronic polyarthritis. *Arthritis Rheum* 1977;**20**:245-52.
3 Woo P, O'Brien J, Robson M, Ansell B. A genetic marker for systemic amyloid in juvenile arthritis. *Lancet* 1987;ii:767-9.

MATERIA NON MEDICA

Balcony scene

Naturally all the lectures were being given in English, even though we were only a few kilometres from Transylvania. British and Hungarian speakers were alternating at 10 minute intervals, and outside the tall windows the leafy campus was dappled with sunshine.

Hungary's warmth and colour had come as a surprise to us, brainwashed as we were by Le Carré novels into expecting Eastern Europe to be drab, wet, and humourless. The city of Debrecen was full of the unexpected: its church was a stronghold of Calvinism despite being less than 160 km from Russia and only 320 km from the birthplace of the present Pope, and its nightclub boasted stunning showgirls all the way from Havana. Walking to our meeting in the medical school we had passed animated groups of students and now we were finding it increasingly difficult to concentrate on the talk. Through our open first floor windows came the sound of musical instruments and voices, distant at first and then organised into a choir outside our building. The speaker goodnaturedly gave up the struggle and our host headed for the door with an apologetic smile.

"It is graduation day and my students have come to say goodbye. The meeting is adjourned for three minutes."

We crowded on to the balconies. Beneath us were nearly 100 beaming students, dressed informally, some holding balloons and others flowers. They were singing accompanied by a brass section, percussion, and guitar. A Hungarian folk melody was followed by what seemed to be a specially written song, which drew laughter from the staff and uncomprehending smiles from the British. Then the crowd burst into *Gaudeamus Igitur*.

"Extraordinary how potent cheap music is," wrote Noel Coward in another balcony scene, and I learnt later that I was not the only visitor to feel a lump in the throat at the familiar tune with its optimistic lyric in the ancient academic lingua franca. We waved and applauded as the students loaded trombone, French horn, and tuba on to a hospital trolley and straggled away in the sunshine. Our meeting continued and I wondered why English had replaced Latin as the international language of medicine and science, if not of music. Later I asked one of our hosts why, living between Germany and Russia, he had bothered to learn English.

"To tell the truth," he said, "I wanted to find out what the Beatles were saying."—JAMES OWEN DRIFE, *senior lecturer in obstetrics and gynaecology, Leicester*