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PRACTICE

A PATIENT'S JOURNEY

Amyloidosis

After several months of nephrology and respiratory investigation, Malvyn Benjamin was eventually diagnosed with amyloidosis. Here he describes his experience of the condition and its treatment

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

I was diagnosed with amyloidosis in June 2010 at the age of 73. The sequence of events was interesting. I had been attending the hospital for many months, seeing consultants in the nephrology and respiratory departments, unfortunately to no effect.

For several months my ability to walk long distances had been impaired by extreme breathlessness: on a journey of 10 to 15 minutes' duration I would have to stop 20 or 30 times to catch my breath. At one point, after such a walk, I collapsed in a synagogue—which was actually a good place to collapse, as I was surrounded by many doctors.

After routine blood and urine tests at my general practitioner's surgery, my doctor telephoned me to say that she had spotted something and made an urgent appointment at the haematology department in my local hospital.

There, I was put through a battery of tests and was told my results would be sent to the National Amyloidosis Centre for examination. Of course, I had never heard of amyloidosis. Before going to the centre, I had a bone marrow test—not the most pleasant experience—and later, at the centre, I had various other tests, including an electrocardiogram and a full body scan.

When the results of the tests and scan came through I was told by the doctor at the centre that I had amyloidosis and that if I did not receive treatment for it I would not last beyond the end of the year.

My condition involves amyloid deposits in my kidneys, which were working at 20% of the normal rate, and in my heart. The heart wall was thickened and it is this that causes my breathlessness. There are also amyloid deposits in my liver.

When I went back to the haematology department, the consultant prescribed a regimen of pills for me to take. I was taking between 20 and 30 pills a day. My wonderful daughters—I have five—drew up a daily schedule for me with a cabinet into which the pills were placed for me to take daily.

This continued for several months, but it became apparent both to me and to my doctors that the pills were not having the desired effect. Eventually, in October 2010, it was decided that I should have an intensive course of chemotherapy with bortezomib.

I cannot say that I have taken easily to the chemotherapy. I generally feel pretty rotten after it has been administered, and it leaves me totally exhausted. I have lost my appetite and have the greatest difficulty in sleeping. I may sleep for an hour or two but then be awake for the rest of the night. I have become an expert on the BBC World Service, to which I listen while others sleep.

In November 2010 one of my daughters got married. There was considerable doubt among my family and friends as to whether I would actually make it to the wedding. It was agreed that my chemotherapy should be arranged so that I could take a week off for the wedding, but to no avail; in the event, chemotherapy was scheduled for the wedding day. However, I managed to put it off, so I was present when my daughter got married. It was a tremendous lift for me, and this feeling lasted for some time. The lesson I drew from it is that it is always a bonus to have something to aim for outside the medical situation, and the wedding sustained me.

I have now completed five cycles of chemotherapy. I am told there has been a dramatic improvement in my condition, and it has been decided to bring the chemotherapy to an end. Hopefully my amyloidosis will stabilise. If it does not, other options will be considered.

I have every confidence in my haematologist and an absolutely wonderful nurse, and my new nephrologist. I see the haematologist every four or five weeks and the nephrologist every two months. I also have checks every six months at the National Amyloidosis Centre. I guess it will be some time before I cease to have these appointments.

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However, since I stopped chemotherapy, I no longer have to suffer the very unpleasant side effects of diarrhoea and constipation. Indeed, there has been a real improvement in my quality of life so that I am now able to sleep through the night and my appetite has returned. I can walk further than before, and the breathlessness, although still present, is no longer the issue that it was before I was diagnosed and before chemotherapy.

When I was originally diagnosed, my family faced the real possibility of losing their husband and father. Naturally, stress levels increased for all of us. I think we all decided to live each day as it comes, not least because the alternative—to concentrate on my imminent mortality—was not to be contemplated. I myself certainly resolved to put that to the back of my mind.

I am grateful to my general practitioner, who set the process in motion; she is a compassionate and caring doctor. And I consider myself very fortunate, despite all the anguish my condition has caused. Had this happened 15 or 20 years ago I would not have been around to tell the tale. It is also a happy coincidence that the National Amyloidosis Centre is located in my local hospital, the Royal Free Hospital in London.

For all that, I do still harbour a strong resentment that so many health professionals seem completely ignorant of amyloidosis. I accept that it is a relatively rare condition, with only 500-600 new cases diagnosed in the UK each year; however, the disorder is almost certainly underdiagnosed. My concern is that it simply never occurred to the consultants in the nephrology and respiratory departments to consider the possibility of amyloidosis. It just was not on their radar. Indeed the nephrology consultant said he did not understand why my kidney function was declining and said, “I will see you in a year.” My response was that I could be dead in a year! My respiratory consultant suggested I have a lung function test and the result was normal. Once again an alternative cause was never considered.

I am just one patient. Others may have different experiences, but we all have one factor in common: there is no cure for amyloidosis. It is potentially fatal. But research is currently being undertaken to try to find a cure. I hope and pray that it will not be too late for me. In the meantime, however, the doctors manage the condition, so far with a fair degree of success. They are a very devoted and committed group.

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Background and clinical data

Amyloidosis is a multisystem disease, characterised by the misfolding of proteins into highly organised, insoluble amyloid fibrils that deposit in tissues. It is estimated that up to one in 1500 people are affected by amyloidosis in the UK. Without treatment, amyloid fibrils accumulate and lead to organ impairment, failure, and ultimately death. Organ involvement most commonly includes the kidneys, heart, nerves, and soft tissues.

Diagnosis is made by biopsy of the affected organ (for example, kidney) or by a screening biopsy such as a deep rectal biopsy involving submucosa by flexible sigmoidoscopy. Serum amyloid P scintigraphy, which specifically images visceral amyloid deposits, is available at the National Amyloidosis Centre and provides information about the amyloid load throughout the body. Repeating this scintigraphy every six to 12 months is an excellent means of tracking regression (or progression) of amyloidosis post treatment.

There are four main categories for systemic amyloidosis:

- AL (light chain) amyloidosis—associated with a plasma cell dyscrasia or myeloma.This is the most common and lethal form of amyloidosis and requires urgent diagnosis and treatment. Chemotherapy—typically cyclophosphamide and dexamethasone with bortezomib or thalidomide—suppresses production of the amyloidogenic monoclonal serum free light chains. The aim of treatment is to suppress the clone as rapidly and deeply as possible while limiting toxic effects. A 90% or greater suppression of the monoclonal serum free light chain component can result in substantial improvements in organ function and overall survival.
- AA (serum amyloid A protein) amyloidosis—associated with chronic inflammation; for example, rheumatoid arthritis, Crohn's disease, bronchiectasis and inherited fever syndromes such as familial Mediterranean fever.The precursor protein for this amyloid type is serum amyloid A protein, an inflammatory protein similar to C-reactive protein. Chronic raised concentrations of serum amyloid A over many years can result in this type of amyloidosis, typically involving the kidneys, leading to substantial renal impairment or failure with nephrotic syndrome. Treatment is suppression of the underlying cause of inflammation, such as with anti-tumour necrosis factor drugs in rheumatoid arthritis. With adequate control of inflammation (serum amyloid A concentrations persistently <10mg/L), prognosis can be excellent.
- Hereditary amyloidosis—there are several types of hereditary amyloid diseases, and these can mimic systemic AL amyloidosis. A family history can often be absent, and chemotherapy is ineffective. Screening for amyloidogenic genetic mutations, where relevant, is part of the routine assessment at the National Amyloidosis Centre, after patient counselling and consent. Solid organ transplantation can be used in some cases to replace failed organ function.
- Senile systemic amyloidosis—amyloid fibrils from misfolded wild-type ("normal") transthyretin protein deposit in the carpal tunnels and cardiac tissue, leading to a restrictive cardiomyopathy. This condition is most commonly seen in older, white men. Treatment is with diuretics and standard anti-failure medication.

A doctor's perspective

Malvyn has systemic AL amyloidosis, confirmed on serum amyloid P scintigraphy and bone marrow biopsy. His disease led to a substantial restrictive cardiomyopathy, diastolic dysfunction, nephrotic syndrome, and renal impairment. Unfortunately, his story of delayed diagnosis is not uncommon. Presenting symptoms can often be vague—such as lethargy, dyspnoea, fluid retention, dizziness, weight loss, and disturbed bowel function. More suggestive clinical signs can include periorbital bruising ("raccoon eyes") and macroglossia. Any medical professional reviewing a patient with a restrictive cardiomyopathy, significant proteinuria, or a progressive peripheral or autonomic neuropathy should have systemic amyloidosis in their list of differential diagnoses.

Malvyn achieved a 65% clonal response with four cycles of chemotherapy (cyclophosphamide and dexamethasone with thalidomide) but with considerable toxic effects, particularly fluid retention. The decision was made to replace the thalidomide component with bortezomib. Malvyn tolerated the bortezomib well, and his clonal response improved to 85%. This led to an improvement in Malvyn's energy levels, a reduction in proteinuria and dyspnoea, and stabilisation of his renal impairment and cardiomyopathy. Balancing treatment efficacy with toxicity is a constant challenge. However, despite initial significant side effects, Malvyn's treatment has improved both his quality of life and his lifespan. His fighting spirit, his faith, and the support of his family were a huge help. Amyloidosis is still a challenging and incurable disease, but with increasing understanding and treatment options, patients are surviving longer. We are developing new treatments that target amyloid deposits directly at the UCL Centre for Amyloidosis and acute phase proteins in a collaborative programme with GSK. Preliminary clinical trials at the National Amyloidosis Centre will commence shortly.

Simon Gibbs

Useful resources

National Amyloidosis Centre, UK (www.ucl.ac.uk/medicine/amyloidosis/nac)—Any patient with symptoms or signs suggestive of amyloidosis can be discussed with or referred to the National Amyloidosis Centre. Patients undergo serum amyloid P scintigraphy, echocardiography, and relevant blood, urine, and genetic testing as part of their clinical assessment. Further tests such as cardiac magnetic resonance imaging, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy, or nerve function tests are also arranged if required. Any biopsies will undergo confirmatory histological review, including immunospecific staining to confirm amyloid type, and a detailed explanatory diagnostic and management advice report is sent to the referring doctors, the general practitioner, and the patient. Patients are followed up every three to 12 months depending on their individual needs, and a shared model of care with local physicians is encouraged.

Myeloma UK (www.myeloma.org.uk)—registered charity offering a broad and innovative range of services covering every aspect of myeloma including systemic AL amyloidosis, from information and support to improving standards of treatment and care through research, education, campaigning, and raising awareness.