



## **IBMS Sussex Branch: Multiple Myeloma**

Dr Graham Meade recently spoke to the Sussex Branch on the topic of multiple myeloma. He explained that the disease was a tumour of plasma cells. The proliferating cells were monoclonal and tended to form multiple foci in the bone marrow. As the cells were monoclonal they all secreted an antibody that was identical in both type and specificity. In 83% of cases an intact antibody was produced. Free light chains only were secreted in 15% of patients. In the remaining 2% there was no evidence of secretion of immunoglobulin or its components.

A progressive spectrum of disease was observed. The mildest form was called monoclonal gammopathy of uncertain significance (MGUS). This stage could persist for a number of years and was best left untreated with the patient being monitored for signs of disease progression. An intermediate presentation was smouldering or indolent myeloma. Fully active multiple myeloma was subdivided into three stages depending on the severity of the disease.

This illness was associated with old age. The median age at diagnosis was 68 years and it was unusual to see it in individuals under the age of 40. The cause of the disease was unknown and remained speculative. There was a slightly higher incidence among individuals who had been exposed to certain substances such as radiation and petroleum products. The rate of disease in black Americans was twice that observed in the white population, suggesting that there may be genetic factors involved. It accounted for about 13% of all haematological cancers.

A variety of symptoms were observed. Bone pain was due to lesions produced as a result of osteoclast promotion by the tumour cells. Anaemia contributed to fatigability. The calcaemia resulting from bone degradation gave rise to nausea and confusion. Deposition of immunoglobulin fragments in the kidneys impaired renal function. Because of impaired immunity patients were susceptible to recurrent infections. Hyperviscosity could result in confusion and blurred vision. An increased tendency to haemorrhage occurred if haemostasis was affected. Deposition of myeloma cells led to the formation of skin nodules and features of amyloidosis.

There was no cure for multiple myeloma, but treatment was available to prolong the lives of sufferers. Various combinations of systemic chemotherapy had been used along with supportive therapy aimed at relieving the symptoms of the disease. Autologous peripheral stem cell transplant was an important technique used to slow the progress of the disease. However it was not curative so that salvage chemotherapy had to be used to treat subsequent relapses. As time went by the improvement induced by each episode of salvage chemotherapy diminished. Experimental therapies under investigation included thalidomide, vaccination, monoclonal antibodies, and antisense drugs.

Diagnosis required the demonstration of an excess of monoclonal plasma cells in bone marrow along with detection of osteolytic bone lesions. Demonstration of a monoclonal gammopathy in serum or urine was an important laboratory investigation. Serum electrophoresis was sensitive to 2g/L for the detection of the monoclonal antibody and was also used to monitor treatment as the technique could be used quantitatively. Immunofixation and capillary zone electrophoresis were more sensitive (150mg/L and 300mg/L respectively) but were not suitable for quantitative analysis.

Urine could be tested for Bence Jones protein, which was derived from immunoglobulin light chains. After concentrating the urine a hundredfold, analysis was carried out by electrophoresis. Once again immunofixation electrophoresis had a sensitivity advantage. Measurement of Bence Jones protein in urine had been used to monitor the course of disease and its treatment. However their concentration was affected by the action of the kidney as well as the disease itself. Thus the actual concentration was the result of a balance between secretion and resorption.

Dr Meade continued by introducing a nephelometric assay for serum free light chains that he had been developing and then discussed its potential. There were technical difficulties in producing the sheep polyclonal antibody used due to the poor immunogenicity of human light chains. Also it had to be noted that both  $\kappa$  and  $\lambda$  light chains were overproduced in normal plasma cells. The mean serum concentration of  $\kappa$  chains was 8.36 mg/L while that of  $\lambda$  chains was 13.43 mg/L giving a normal mean ratio of 0.63.

The assay clearly had application in those patients whose myeloma produced only free light chains. Moreover measurement of serum free light chains was a better predictor of remission than urine Bence Jones protein determination. In a small series of patients with apparently non-secretory disease, the assay detected an excess of light chains in a significant number. Although elevated levels of free light chains were observed in cases secreting intact immunoglobulin, the concentrations did not correlate well with the level of circulating monoclonal antibody. As a result the assay didn't improve on the standard tests in such cases. However it could be of some benefit in the monitoring of disease status because the half life of free light chains was much less than that of the intact protein. As a result their concentration fell more rapidly after effective therapy.

Light chain amyloidosis was a related syndrome in which precursor protein aggregated to form fibrils in the cytoplasm, predominantly made up of  $\beta$  sheets. In fact approximately 20% of cases occurred in patients with myeloma. Deposits were found in kidney, liver, carpal tunnel, gut and peripheral nerves. The symptoms and outcome of the disease depended on the organ systems in which deposition took place. It was responsible for more than 1 in 1,500 deaths in the UK. In 70% of patients a subtle monoclonal gammopathy could be detected. The median survival from diagnosis was 5 to 15 months. In patients with light chain amyloidosis the serum light chain assay usually gave results outside the normal range and was more sensitive than electrophoresis. Serum free light chain suppression was a good predictor of survival.

Dr Meade concluded by answering a number of questions from the audience. The branch expressed its gratitude to him for travelling down from Birmingham for the evening. The Binding Site, who sponsored the meeting, were also thanked for their support.

**William N Penn**  
**IBMS Sussex Branch**