MYELOMA AND PARAPROTEINAEMIA **MEDICAL APPENDIX**

(including multiple myeloma, Waldenstrom's macroglobulinaemia, heavy-chain disease, solitary plasmacytoma of bone, extramedullary plasmacytoma, plasma cell leukaemia, osteosclerotic myeloma (POEMS syndrome), monoclonal gammopathy of undetermined significance and primary systemic amyloidosis)

DEFINITION

1. These are conditions characterised by the abnormal production, in quality or quantity, of immunoglobulin. (i) (ii) (iii)

2. **Paraproteinaemia** is a term used to describe the presence in the blood of a single immunoglobulin which is derived from the monoclonal proliferation of a single clone of immunoglobulin secreting plasma cells. Paraprotein is detectable on protein electrophoresis. In some cases the cell proliferation is clinically benign. Patients are asymptomatic and there is no evidence of impairment of antibody response or bone marrow function.

3. Paraproteinaemia may be found in healthy subjects as a primary condition or it may be secondary to chronic inflammatory states, liver disease, connective tissue disorders or neoplasms. In most B cell lymphoproliferative disorders, particularly chronic lymphatic leukaemia and diffuse non-Hodgkin's lymphoma, paraproteinaemia may occur. The diagnostic differentiation of benign paraproteinaemia from neoplastic states is based on the absence of radiological evidence of bone marrow disease, a relatively low and constant concentration of serum paraprotein, the absence of urine light chain excretion and normal levels of other serum immunoglobulins.

CLINICAL VARIANTS

(A) **Multiple Myeloma** (myelomatosis, Kathler's disease) is a plasma cell neoplasm. The condition is more common in males and the peak incidence is in the seventh decade. In 10% of cases the diagnosis is made by chance, the patient being asymptomatic or with only vague ill health. The clinical course of myeloma is unpredictable. There is evidence from cell kinetic studies that by the time of diagnosis the disease may have been present for as long as twenty years. It is thought to account for about 1% of all malignancies (iv). An apparent increase in incidence in the last few years probably relates to better diagnosis (v).

CLINICAL MANIFESTATIONS

4. When symptoms do develop they particularly affect the bones or the renal system. 60% of patients present with skeletal pain, vertebral collapse or pathological fracture. Hypercalcaemia associated with bone disease may produce anorexia, depression and vomiting.

5. 50% of patients show evidence of renal impairment at presentation. The classic histology is of hyaline casts in the renal proximal and distal convoluted tubules. There is a foreign body reaction and subsequent tubular atrophy and renal tissue destruction. Resultant renal failure usually progresses slowly.

6. Bleeding may be a feature. This may reflect renal failure or may be due to thrombocytopaenia, impaired platelet function or clotting factors or may be due to hyperviscosity. Anaemia is initially present in two-thirds of patients and eventually is found in almost all.

7. Neurological symptoms range from mental impairment and disturbed vision (usually due to hyperviscosity) to paraplegia resulting from plasmacytoma pressure on the spinal cord. There may be amyloid deposition and associated peripheral neuropathy.

8. Soft tissue myeloma masses occur late in the disease by direct extension from an underlying bone.

9. With a defective antibody response and depression of normal serum immunoglobulin levels myeloma patients are susceptible to recurrent bacterial infections.

10. Asymptomatic patients should not be treated. The two main treatment approaches are a) autologous peripheral blood stem-cell transplantation for patients younger than 70 years and b) for older patients, chemotherapy including melphalan continued for at least a year until the patient is in a plateau state clinically and with stable urine and serum paraprotein.

AETIOLOGY OF MULTIPLE MYELOMA

11. The precise aetiology is unknown but it involves the interaction of the constitution and the environment.

12. Genetic factors are believed to contribute to racial and ethnic variations. This is suggested by the fact that the condition is rare in the Japanese irrespective of where they live or their eating and other habits (vi). In USA it is twice as common in African Americans as in Caucasians. There is some evidence that multiple myeloma may be familial but the precise basis is not clear.

13. Published studies have recorded associations between multiple myeloma and a variety of chemical agents including asbestos, cutting oils, petrochemicals, wood dust and arsenic. Reports have not been consistent and it would be premature to causally link this cancer to any particular chemical agent (vii).

14. The data reporting an increased risk in agricultural communities is more consistent but the significance and basis of this association is unknown.

MULTIPLE MYELOMA AND IONISING RADIATION

15. Based on follow-up of survivors of World War II atomic bombs as well as occupationally and therapeutically exposed groups, myeloma is shown to be causally related to exposure to ionising radiation. (viii) (ix) (x). In relation to the UK atmospheric nuclear test detonations and clear up operations between 1952 and 1958, the UK carried out 21 atmospheric nuclear tests (12 in Australia, 9 at Christmas Island), in the South Pacific. The radiological safety standards at the trials were based on the then consensus of international scientific opinion as formulated by the International Commission on Radiological Protection. A fundamental principle was to keep any exposure as low as possible. Many of the detonations involved high air bursts falling freely. The risk of significant contamination of land occupied by service or civilian participants from these air bursts was avoided by careful selection of weather conditions and environmental monitoring following the tests. The natural background radiation at Christmas Island is very much less than that of average UK locations. Overall it is considered that almost all the British servicemen involved in the UK nuclear tests received little or no additional radiation exposure as a result of participation.

16. As a result of concern amongst some test participants about the effects that participation could have had on health, in 1983 the Ministry of Defence commissioned an independent study by the National Radiological Protection Board (NRPB) to investigate whether the health of participants showed any correlation with radiation exposure. This comprehensive cohort study compared the mortality and cancer incidence in over 20,000 test participants with that of a similar-sized control group of ex-servicemen who had not participated in the test programme.

17. A main conclusion of the first NRPB Report (Darby et al 1988) (xi) was that presence at the nuclear weapons test sites had increased the risk of multiple myeloma compared with service controls. However this was not considered to be due to ionising radiation exposure but because there was a particularly low rate of multiple myeloma in the controls compared with the non-exposed general UK population. Those sub groups who were most highly radiation exposed did not show the highest rates of the condition.

18. The study was extended and the second NRPB Report (Darby et al 1993) (xii) produced an additional 7 years data and concluded that the small hazard of multiple myeloma suggested by the 1988 Report was not supported by the additional data.

19. Following pressure for a further investigation a 3rd NRPB study was commissioned. This study, which extended the follow up period to 1998, was published in February 2003 (Muirhead et al 2003) (xiii). It confirmed the conclusion of the 1993 report that there is no evidence to support a link between participation in the UK test programme and multiple myeloma.

19. The NRPB reports are generally considered reliable by the scientific community. (xiv) (xv). In particular the following points are noted:

- The studies identified the test participants, and followed them up to monitor the occurrence of disease and death in the participant population. It then compared this, over the same time period with the rates in both a service and civilian control population.

- The studies involved 20,000 subjects and an equal number of controls

- The reports describe in detail the efforts made to ensure sample completeness and to control bias.

- The study limitations are discussed by the authors and conclusions are reasoned and restrained.

20. Multiple myeloma is not caused by climatic extremes, trauma, physical or mental stress or lowered resistance arising from hardship or other diseases. Progress is independent of external factors other than medical treatment.

(B) Variant forms of Multiple Myeloma include **smouldering** and **non-secretory multiple myeloma**.

- In the **smouldering** variant there are blood and bone marrow changes only – although patients are at risk of developing frank multiple myeloma.

- In the **non-secretory form** there is no paraprotein in serum or urine.

- **Solitary cell plasmacytoma** is characterised by plasma cell tumour on histology but no clinical evidence of multiple myeloma. Again there is risk of transformation.

- Signs of **osteosclerotic myeloma (POEMS syndrome)** include polyneuropathy (P), organomegaly (O), endocrinopathy (E), M-protein (M), and skin changes (S). Hypercalcaemia and renal insufficiency are rare and patients tend to have normal or high haemoglobin rather than anaemia.

- **Plasma cell leukaemia** can be primary when it occurs de novo (60%) or secondary when a multiple myeloma undergoes leukaemic transformation (40%). Patients are usually younger than for multiple myeloma.

- **Extramedullary plasmacytoma** occurs outside the bone marrow and in 80% of cases in the upper respiratory tract affecting nasal cavity and sinuses, nasopharynx and larynx.

(C) Waldenstrom's Macroglobulinaemia

Less common than multiple myeloma, this disorder is clinically similar to multiple myeloma, lymphoma and chronic lymphatic leukaemia. The most common clinical features are weakness and fatigue but any system can be involved. Diagnosis is again by serum electrophoresis and bone marrow aspiration. As before patients should only be treated when symptomatic – usually by chemotherapy and supportive therapy aimed at correction of anaemia and hyperviscosity.

(D) Heavy Chain Diseases (HCD)

There are 3 variants – gamma, alpha and mu heavy chain disease. The alpha variant is most common, occurring particularly in people from the Mediterranean and Middle East. Presentation, diagnosis and treatment follow the same principles as for multiple myeloma.

(E) Primary Amyloidosis

Amyloid is a substance made up of fibrils compromising various protein and with characteristic microscopic appearance. On the basis of the fibril types various types of amyloidosis are described. These include familial, senile systemic, amyloidosis associated with dialysis as well as primary amyloidosis.

- Paraproteins occur in primary amyloidosis and the cause is unknown. (The clinical features result from the amyloid deposition and so the condition needs to be considered wherever a patient has paraprotein in the urine accompanied by nephrotic syndrome, congestive cardiac failure, sensorimotor peripheral neuropathy, carpal tunnel syndrome, or giant hepatomegaly. 98% of cases have paraprotein in urine or a monoclonal proliferation of plasma cells in the bone marrow).

The median prognosis is 13 months after presentation. Almost half the deaths relate to heart involvement and survival length is dependent on the presenting features. Treatment is with alkylating agents.

CONCLUSION

21. The Paraproteinaemias are a group of conditions characterised by abnormal production of immunoglobulin. There are several clinical variants and some risk of transformation amongst them. Although genetic and environmental factors seem to be involved in their aetiology most cases are of unknown aetiology. Ionising radiation has been causally linked to multiple myeloma. Once diagnosed, prognosis is poor and evidence has not identified environmental factors, other than treatments, which influence the course of the disorders.

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