IgG Monoclonal Gammopathy Associated with Lymphoproliferative Disorders

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SUMMARY

The association of IgG monoclonal gammopathy with lymphocytic lymphoma and chronic lymphocytic leukaemia is reported. Although rare, such immunoglobulin synthesis may have prognostic importance and is of value in monitoring the effect of therapy. The morphological features which should draw attention to this pattern of protein abnormality are briefly reviewed. This finding emphasises the histogenesis of these tumours from the immune system and questions their classification on a purely morphological basis.


The association of a monoclonal gammopathy with neoplastic proliferation of plasma cells is well documented. Furthermore, IgM monoclonal gammopathy is described in patients with lymphoproliferative diseases, and has been the subject of a recent critical study. By way of contrast, the development of IgG monoclonal gammopathy with lymphocytic lymphoma is distinctly uncommon, and in view of this infrequent association, the following 2 cases are reported.

CASE REPORTS

Case 1

A 65-year-old housewife enjoyed good health until 1970 when she developed herpes zoster. The only abnormality at this time was a Westergren erythrocyte sedimentation rate (ESR) of 73 mm in 1 hour, a value which has remained elevated despite her infection having subsided. In June 1972, she was admitted to hospital with pneumonia, and the ESR had risen to 134 mm in 1 hour. She was now reported to have a mild normocytic normocytic anaemia. During November 1972 a normochromic normocytic anaemia of 8 g/100 ml was confirmed, and a leucocytosis of 12 400/μl with 90% lymphocytes and an ESR of 158 mm in the first hour were documented. Protein electrophoresis showed a striking monoclonal increase in gammaglobulin, and aspiration of sternal bone marrow showed the findings of chronic lymphocytic leukaemia. At this stage the patient was referred to Groote Schuur Hospital for further evaluation.

Six months before this admission she started to tire easily and noticed some weakness of her legs and a mild dyspnoea on effort. There was associated nausea, anorexia and the onset of night sweats. One month before hospitalisation hepatosplenomegaly and axillary lymphadenopathy were noticed. The normochromic normocytic anaemia of 8 g/100 ml was confirmed, and a leucocytosis of 12 400/μl with 90% lymphocytes and an ESR of 158 mm in the first hour were documented. Protein electrophoresis showed a striking monoclonal increase in gammaglobulin, and aspiration of sternal bone marrow showed the findings of chronic lymphocytic leukaemia. At this stage the patient was referred to Groote Schuur Hospital for further evaluation.

Physical examination revealed a remarkably fit woman of 65 years of age with a temperature of 39,2°C. There was significant bilateral axillary lymphadenopathy and hepatosplenomegaly. The lymph nodes were rubbery, discrete, non-tender and approximately 2 cm in diameter. Both the liver and the spleen were firm, non-tender, and extended 6 cm below the costal margin. There were no other abnormalities of note in her examination.

Urine was cloudy with mild proteinuria; numerous pus cells and occasional red cells were present. Haemoglobin was 10,9 g/100 ml with normal red cell indices. Total white cell count was 19 800/μl with 42% neutrophils, 55% lymphocytes and 3% monocytes. The platelet count was 112 000/μl, with normal morphology.

Aspiration and trephine biopsy of the bone marrow was obtained from the posterior iliac crest and showed marked increase in cellularity, with reduction of normal haematopoietic tissue by sheets of well-differentiated lymphocytes (H and E × 640).

Fig. 1. Bone marrow showing an area of complete replacement of haematopoietic tissue by sheets of well-differentiated lymphocytes (H and E × 640).
piocytic elements to less than 10% of normal. There was dense infiltration with well-differentiated lymphocytes (Fig. 1). Cytomedical studies demonstrated no PAS-positive globules within the cells, nor any other of the morphological features associated with paraprotein production.

Serum protein was 11.2 g/100 ml, of which 2 g/100 ml was albumin: alpha-globulin 0.5, alpha-globulin 0.9, betaglobulin 1.1, and gammaglobulin 5.4 g/100 ml. Immunoglobulins showed an IgG level of 5 000 mg/100 ml, IgA 229 and IgM 127 mg/100 ml. The remainder of the biochemical, electrocardiographic and skeletal radiological studies were non-contributory.

Treatment was commenced with prednisone and chlorambucil, and a satisfactory clinical and haematological response was obtained with reduction of the paraprotein level. The patient continued on therapy as an outpatient, but died suddenly 8 weeks after commencing treatment, at a time when the immunoglobulin level was beginning to fall. Postmortem examination was not carried out.

Case 2

A 73-year-old man was first seen by his private physician in 1970, complaining of general ill-health. Information is limited, but it appears that he had experienced loss of appetite, loss of weight and weakness. Physical findings were restricted to pallor and a blood pressure of 150/90 mmHg. Blood urea varied between 50 and 175 mg/100 ml, uric acid was greater than 12 mg/100 ml, and monoclonal increase in gammaglobulins was noted.

In 1974 he was admitted to Groote Schuur Hospital with persistent bleeding from a dental socket — the remainder of the history was completely negative. On examination the patient was pale, with a blood pressure of 150/90 mmHg, afebrile, and had evidence of weight loss. No abnormal physical signs were elicited. Blood urea was 200 mg/100 ml. The bleeding from the socket was attributed to a qualitative platelet defect arising in consequence of his uraemia, and the mild degree of anaemia was explained on the basis of chronic renal disease.

The haemoglobin level varied between 8 and 11 g/100 ml, MCH between 31 and 34 pg, and MCV between 94 and 100 fl. Reticulocytes remained below 1%. The white cell count varied around 6 000/μl, with neutrophils between 16% and 51% and mature lymphocytes between 46% and 69%. Red cells showed some anisocytosis, poikilocytosis, and occasional macrocytes were present. The platelet count varied between 60 000 and 80 000/μl. The chronic renal disease was not investigated further in view of the patient's age, but intravenous pyelography and biochemistry, apart from the urea, was normal. Creatinine clearance was 9.35 ml/min, corrected for body surface area of 1.73 m². Of significance was confirmation of total protein level of 9.6 g/100 ml and an IgG monoclonal spike of 5 000 mg/100 ml. Bone marrow (Fig. 2) showed infiltration, with a well-differentiated lymphocytic population interpreted as lymphocytic lymphoma. The lymphoid cells did not show the PAS-positive globules within the cytoplasm, and immunofluorescence studies were, unfortunately, not performed.

The patient was started on chlorambucil and steroids, but died within 3 months with an IgG level of 2 100 mg/100 ml, and with a well-marked decrease in marrow cellularity, though PAS-positive cells could still not be demonstrated.

DISCUSSION

The interest in these cases centres around the unusual association of IgG as opposed to IgM monoclonal gammopathy with lymphoproliferative disorders which, on morphological grounds, are quite distinct from plasma cell neoplasms.

Azar et al.² were able to find 9 cases recorded in the literature between 1937 and 1957 in which patients with malignant lymphoma and lymphatic leukaemia had serum protein abnormalities resembling those found in multiple myeloma. These workers reported a further 13 cases, including one of Hodgkin's disease, but, unfortunately, in none of these individuals was the abnormal immuno­globulin characterised. However, in the light of subsequent experience, it seems likely that most would have been of the IgM class³,⁴,⁵. The association between IgG monoclonal gammopathy and the lymphoproliferative disorders has been recorded on only a few occasions. Okano et al.⁶ described a case of reticulum cell sarcoma associated with IgG monoclonal gammopathy in which the cells had some histochemical and electron microscopic features resembling plasma cells. In a study of 9 patients with malignant lymphomas and paraproteinemia, including one with a clinical picture of Waldenström's macroglobulinaemia, Krauss and Sokal⁷ reported only a single instance of lymphocytic lymphoma with an IgG paraprotein. Additional cases of lymphoma or chronic lymphocytic leukaemia associated with pathological IgG production have been reported.⁸,⁹ The patients of Alami et al.¹⁰ and those of Maldonado and associates¹¹ are interesting in that they exhibited bclonal paraprotein production.

Two cases of IgG production in children with lymphoma have been described.¹²,¹³ A feature of these cases was the
appearance of the paraprotein relatively late in the course of the disease, and in the second case this coincided with the commencement of a prolonged clinical remission. The authors of the latter paper suggest that elimination of neoplastic cells facilitated the emergence of a clone of benign paraprotein-producing lymphocytes. In these patients it could be argued that the monoclonal gammapathy is not an integral part of the malignant process. A similar argument has been advanced by Paulikke and McDonald who were unable to demonstrate immunoglobulin production by the tumour cells in their 2 patients, but were able to show marked immunofluorescence, using appropriate antibodies, of plasma cells and plasmacytoid lymphocytes which were present in excess in tissues not involved by the tumour.

On the other hand, the findings in patients such as those of Okano et al. and the ability of Kim et al. to identify immunoglobulin-producing tumours on morphological grounds alone suggest that at least some of these are directly responsible for the abnormal protein synthesis. The latter workers described those morphological features in lymphoreticular malignancies which should arouse the suspicion of associated monoclonal gammapathy. Three features were found most frequently — a well-differentiated lymphocytic lymphoma of the bone marrow resembling chronic lymphocytic leukaemia but without peripheral lymphocytosis, a lymphocytic lymphoma or chronic lymphocytic leukaemia in which some of the cells showed plasmacytoid features, or thirdly, the presence of intranuclear or intracytoplasmic PAS-positive protein globules. However, this latter feature was found in 3 of their 8 patients with IgM monoclonal gammapathy and in a single patient with IgA monoclonal gammapathy, and then only after a prolonged search in 3 of the 4 cases. None of these patients had IgG monoclonal gammapathy. Four of their 10 patients had infiltration of the bone marrow by lymphocytes without peripheral lymphocytosis. One of our patients showed features of well-differentiated lymphocytic lymphoma, indistinguishable, on marrow examination, from chronic lymphocytic leukaemia but with only minimal peripheral lymphocytosis, a feature which alerted us to the possibility of associated gammapathy; the other patient had typical chronic lymphocytic leukaemia. In neither of these individuals could PAS-positive intranuclear or intracytoplasmic globules be detected, nor were plasmacytoid cells seen.

An interesting study is that of Moore et al., who examined the serum proteins in a consecutive series of patients with lymphoma. Among their 333 patients with diffuse lymphoma they found 5 with monoclonal peaks: 2 with chronic lymphocytic leukaemia, 2 with lymphocytic lymphoma, and 1 with reticulum cell sarcoma. These authors feel that an incidence of 1.5%, which their reported cases represent, is not significantly different from 0.8% found in a population survey by Axelsson et al., and that the relationship between lymphoproliferative disorders and IgG monoclonal gammapathy is a coincidental one. It must be pointed out, however, that the levels of IgG in the patients from both these studies were much lower than those observed in our cases. Among the former, no patients had an IgG level of more than 1500 mg/100 ml, and among the latter the level of 1000 mg/100 ml or less was reported in 84% of the cases, with the highest figure seen being 2 400 mg/100 ml. These findings contrast with our patients' IgG levels of 5 000 and 4 500 mg/100 ml. It may well be that some cases of IgG monoclonal gammapathy are coincidentally associated with lymphoma as postulated by Moore et al., and if this is the situation, it serves to emphasise the great rarity of the true association between these conditions.

There are two practical issues associated with the finding of a monoclonal gammapathy in a patient with lymphoproliferative disorder. Firstly, the abnormal protein may provide an index of tumour mass and activity, as suggested by Moore et al., and by Ward et al., so that response to treatment is accompanied by a fall in the level of paraprotein, while the maintenance of a steady level is a sign that the tumour is unresponsive — an increasing level may accompany deterioration. The second point is the possible prognostic significance of monoclonal protein production. It has been said that this constitutes an adverse prognostic sign, although Hallén et al. felt that the number of cases in his series was too small to establish clearly any prognostic significance of monoclonal protein production. Although the precise interpretation of this association is not yet established, it is noteworthy that both our patients rapidly deteriorated and died, despite therapy which would in the usual way have controlled their disease for a much longer period of time.

These cases are of further interest in the light of changes which are taking place in our understanding of the lymphomas. Previously the classification had been on a purely morphological basis, and such an approach has little, if any, conceptual relevance. Lymphocytic lymphoma is a disease of the immune system, and if we are to take cognisance of our new understanding of B and T cells, then tumours arising from these ought logically to be classified accordingly and appropriate membrane studies carried out and monitored along with the immunoglobulin and light chain production, as an index of the efficacy of therapy.

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REFERENCES