Acta Oncologica Vol. 30 No. 6 1991

FROM THE DEPARTMENT OF HEMATOLOGY AND MEDICAL ONCOLOGY, HOPITAL HOTEL DIEU DE FRANCE, BEIRUT, LEBANON.

FAMILIAL MACROGLOBULINEMIA IN A LEBANESE FAMILY WITH TWO SISTERS PRESENTING WALDENSTRÖM'S DISEASE

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Abstract

We report a non-consanguineous family with ten children, in which two sisters were found to have Waldenström's disease with light chain IgM monoclonal components. Immunoglobulins were examined in four siblings and revealed high serum IgM concentrations with no monoclonal component. This additional case of familial Waldenström's macroglobulinemia stresses the usefulness of screening family members of patients with monoclonal gammopathy since they may be at high risk of developing the disease.

Key words: Waldenström's disease, familial macroglobulinemia.

Familial occurrence of monoclonal gammopathy was described some time ago. Mandema & Wildervanck (1) first reported a documented familial myeloma, and since then reports on at least 42 families have been published, involving siblings in 29 cases (2, 3). More recently, screening the relatives of patients with Waldenström's disease (WD) has revealed the presence of this disease in certain family members, as well as the occurrence of asymptomatic IgM monoclonal gammopathy in others (4–5). Although reports concerning families of patients presenting WD or bearing IgM abnormalities appear to be numerous, the coexistence of WD in two siblings is rare (6–14).

We now report a Lebanese family of 10 members in which two sisters (members 2 and 10 in the Figure) have WD and four other sisters (members 1, 6, 8, 9 in the Figure) have asymptomatic polyclonal IgM hypergammaglobulinemia. Serum proteins were investigated using standard techniques. M-protein was typed by immunoelectropheresis and the amount of polyclonal immunoglobulins was estimated by radial immunodiffusion. The amount of the M component was derived from the total protein content and the densitometric evaluation of the monoclonal band on electrophoresis.

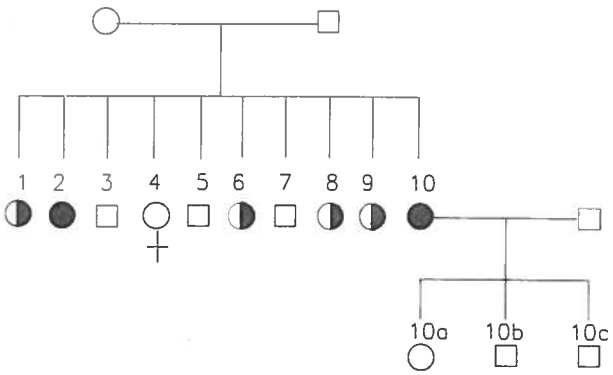

Figure. Pedigree. Family members No. 2 and 10 (●): Waldenström's disease; Members No. 1, 6, 8 and 9 (◑): asymptomatic increase of IgM component; Members No. 10a, 10b and 10c (□): no abnormalities; Members No. 3, 5 and 7 (□): not examined; Member No. 4 (♀): dead of liver cirrhosis.

Case reports

Family member 2. A 64-year-old woman was admitted to the hospital in November 1986, due to anemia, weight loss and diarrhea. On examination no lymphadenopathy was found and the liver was not felt. The spleen was enlarged, descending about 10 cm below the left costal margin. The hematocrit was 26%; white cell count $4.8 \cdot 10^9$/l, with 74% neutrophils, 20% lymphocytes and 6% monocytes. Red-cell aggregation was observed, the platelet count was $220 \cdot 10^9$/l and the erythrocyte sedimentation rate (ESR) 140 mm/h (Westergren). The protein electrophoresis and immunoelectrophoresis showed an IgM kappa monoclonal component at a concentration of 9 g/l (Table). Urine analysis failed to demonstrate Bence Jones proteinuria. Roentgen examina-tions of colon and upper gastrointestinal tract were normal.

Submitted 29 June 1990.
Accepted for publication 25 January 1991.

Table

Serum protein data of the family

Family member No.	Sex/ age/(yrs)	Protein (g/l)	Albumin (g/l)	Gamma-globulins (g/l)	IgA	IgG	IgM	Light chain type
					Normal values (g/l)			
					0.9–4.5	8.0–18	0.6–2.5	
1	F/67	85	36	22	2.85	17.60	3.60	K and L
2	F/64	67	27	24	1.05	6.0	9.0	K
6	F/57	72	31	19	2.30	10.70	3.59	K and L
8	F/53	74	39	13	1.35	10.70	3.60	K and L
9	F/51	67	31	13	3.19	13.10	3.19	K and L
10	F/43	62	29	15	0.85	6.51	3.70	L
10a	F/8	75	41	13	1.62	11.90	2.26	
10b	M/14	76	38	18	2.41	16.30	2.17	
10c	M/16	72	44	13	1.35	10.70	2.08	

F = female, M = male, K = kappa, L = lambda

Ultrasound study of the abdomen showed splenomegaly, slight hepatomegaly, subhepatic enlarged lymph nodes and gallbladder stones. The bone marrow aspirate showed the presence of lymphoplasmocytes and there were no abnormalities on cytogenetic studies. The bone marrow biopsy revealed lymphoid infiltration with a nodular pattern supporting the diagnosis of WD. Chemotherapy was started with a combination of cyclophosphamide, doxorubicin, vincristine and prednisone every 4 weeks for a total of 6 courses, followed by chlorambucil as maintenance therapy. A rapid improvement was noted and 3 months later the patient had normal clinical and blood examination results. When later seen in May 1989, the patient was asymptomatic with normal protein electrophoresis, however, very low amounts of the IgM monoclonal component were detected by immunoelectrophoresis.

Family member 10. A 43-year-old woman was admitted to the hospital in February 1985 due to asthenia, fever and weight loss. Clinical examination revealed moderate hepatosplenomegaly; no lymphadenopathy was found. Routine laboratory tests showed: hematocrit 29%; white cell count $29.9 \cdot 10^9$/l with 25% neutrophils, 44% lymphocytes, 29% lymphoplasmocytes and 2% monocytes. The platelet count was $240 \cdot 10^9$/l and the ESR 60 mm/h. The protein electrophoresis and immunoelectrophoresis showed an IgM lambda monoclonal component at a concentration of 3.7 g/l (Table). The urine was negative for Bence Jones protein. The chest x-ray was normal and no infection was documented explaining the fever. Ultrasound studies of the abdomen showed hepatosplenomegaly and gall bladder stones. A CT scan of the abdomen revealed hepatosplenomegaly with infiltration of the omentum and mesentery but no enlarged lymph nodes were noted. Bone marrow aspirates and biopsy specimens showed minimal lymphoplasmocytic infiltrate with mild myelofibrosis. The patient received various chemotherapy combinations until November 1985 when sections of the bone marrow showed persistent lymphoplasmocytic infiltrates. The disease was classified as low-grade non-Hodgkin's lymphoma of the small lymphocytic plasmocytoid subtype according to the Lennert-Kiel classification. Subsequently, the patient was given various chemotherapy regimens until October 1986 when she presented with acute abdominal pain, fever, chills, agranulocytosis and septicemia. A gangrenous, perforated gallbladder was removed but the patient died a few weeks after surgery. The diagnosis of WD was established post mortem. The patient had been treated by another physician and our data came from her clinical record, tissue sections and blood slides which were reviewed when the diagnosis of WD in her sister was established (family member 2). IgM lambda monoclonal peak and the histologic findings were sufficient to confirm WD.

Family study

Apart from the 2 patients with WD (members 2 and 10), none of the other family members tested had a monoclonal gammopathy (Table). However, a polyclonal increase in IgM level was observed in 4 asymptomatic sisters (members 1, 6, 8 and 9). The 3 brothers (members 3, 5 and 7) refused to give samples for serum studies. One sister (member 4) died at the age of 47 from cirrhosis of the liver. IgG, IgA and IgM levels were normal in the 3 children (members 10a, 10b, 10c) of member 10. The pedigree of this family is shown in the Figure.

Discussion

Familial WD was mentioned for the first time in 1962 (9, 10). Since then, many reports have appeared and immunoglobulin abnormalities, including monoclonal IgM peaks have been described in relatives of patients with WD. Familial multiple myeloma has often been described (1–3) (reports on at least 42 families published), but the coincidence of two or more cases of WD in the same family is rare (6–14). The true existence of asymptomatic benign IgM gammopathies is questionable, due to the tendency of certain cases to progress into WD. This disparity between asymptomatic IgM subjects and those expressing the disease may be due to the time necessary for the transformation to occur. The follow-up of these asymptomatic subjects is often irregular and there are still

no criteria which can predict the transformation of a benign gammopathy into a malignant process.

The present observation adds to the few cases of familial WD reported in the literature. The family studied included 2 sisters with WD having different light chain types and occurring with a 22-month interval. A polyclonal IgM hypergammaglobulinemia was found in another 4 sisters of the same family; in one the IgM level doubled in a few months although she remains asymptomatic (member 8). The significance of these findings is difficult to assess. However, we believe that screening family members of patients presenting WD together with a long follow-up of those in whom immunoglobulins abnormalities have been detected is recommended. This is supported by the occurrence of 3 malignant transformations into WD among 27 patients in Axelsson's series (15) and in 2 siblings of a patient with WD reported by Fine et al. (16), with an asymptomatic period ranging from 7 to 15 years. With the present circumstances in Lebanon, many problems encountered in these cases could not be fully studied. The family member 2 who is still alive has a normal karyotype. The HLA typing has not yet been done. Nevertheless, the data we found in the literature concerning these two points are limited and conflicting (7, 12, 14, 17). Further studies are warranted to clarify the genetic background of this familial predisposition to WD.

ACKNOWLEDGEMENTS

The authors are grateful to Professor M. Seligmann and Dr. F. Danon for performing the analysis of serum samples in the Laboratory of Immunochemistry and Immunopathology, Hôpital St. Louis, Paris and to Professor J. Diebold (Hôpital Hôtel Dieu, Paris) for reviewing bone marrow aspirates and biopsy specimens.

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