# Familial Waldenstrom's Macroglobulinemia

Mary L. McMaster

**The etiology of Waldenstrom's macroglobulinemia (WM) is unknown. A possible role for genetic factors has been suggested by reports of familial clustering of WM. However, it is not yet possible to define the proportion of all WM that occurs in the familial setting. Review of the data on the 12 families published since 1962 suggests that familial WM may differ from sporadic disease in certain respects. Among these families, there is a pronounced occurrence of a variety of immunologic abnormalities in the relatives of WM cases. Notably, the prevalence of IgM monoclonal gammopathy (IgM MG) in first-degree relatives of WM cases was reported to be as high as 6.3%, representing a 10-fold increase relative to general population estimates. IgM MG has been shown to progress to WM at a rate of approximately 1.5% per year in a large case series; whether this rate of progression is altered in familial WM is unknown. Although limited by small numbers and a lack of systematic ascertainment and evaluation, these data are intriguing and provide a compelling basis for further study and systematic investigation of WM in families.**

***Semin Oncol 30:146-152.*** 

THE ETIOLOGY OF Waldenstrom's macroglobulinemia (WM) is unknown. A possible role for genetic factors has been suggested by reports of familial clustering of WM. However, the spectrum of familial WM remains undefined and may include not only families with multiple cases of WM, but also families with a single case of WM accompanied by relatives with IgM monoclonal gammopathy (IgM MG)[1] or related lymphoproliferative disorders (LPD). Because family studies can provide important tools for understanding both genetic and environmental determinants of neoplastic disease, systematic evaluation of WM families would be a useful adjunct to other investigations of WM etiology. Since the definitive spectrum of familial WM has yet to be established, this review will adhere to conservative criteria, considering only families with multiple cases of WM.

## EPIDEMIOLOGY OF WM

Epidemiologic data for WM, particularly pertaining to potential risk factors, are sparse. In the United States, population-based studies have confirmed the rarity of WM.[2,3] Incidence rates are 3.4 per million in males and 1.7 per million in females and increase geometrically with advancing age. Median age at diagnosis is 72 years. WM is substantially more common in white males than in other race/gender groups and is nearly twice as common in whites as in blacks, in contradistinction to multiple myeloma, for which the rate ratio is reversed. Suggestions of a possible occupational or environmental association have been based on a handful of case reports,[4-6] but these have not been corroborated. The sole published case-control study[7] found cases to be better educated, but otherwise found no significant differences in other sociodemographic indicators, specific occupational exposures or employment, tobacco or alcohol use, medication use, or history of prior medical conditions.

## CHARACTERISTICS OF FAMILIAL WM

To date, 12 families containing 31 cases of WM have been reported[1,8-17] (Table 1); these have been characterized with variable detail, making systematic analysis difficult. Numbers are small, but the familial cases differ markedly from sporadic WM in age and gender distribution, being diagnosed at least a decade earlier and much more likely to be male than sporadic cases. The earlier age at diagnosis is unlikely to be explained by ascertainment bias, since it is unchanged when probands are excluded, but numbers are small. Younger age at diagnosis has been recognized as a marker of genetic propensity in other familial cancer syndromes (eg, breast,[18] prostate,[19] colon[20]), although the age disparity is sometimes greater. The gender difference is not readily explained and may reflect small sample size or as yet unrecognized endocrine or genetic factors. The typical reported WM family has only two cases, although up to four

*From the Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD.*

*Address reprint requests to Mary L. McMaster, MD, Executive Plaza South, Room 7010, 6120 Executive Blvd, MSC 7236, Bethesda, MD 20892-7236.*



*0093-7754/03/3002-0028$0.00/0*

*doi:10.1053/sonc.2003.50063*

cases have been identified in selected families. The most commonly reported pedigree configuration is two affected siblings (including one set of monozygotic twins); only three families published exhibit parent to offspring transmission. Whether this represents the true pedigree distribution or a problem of ascertainment is unclear, given the late age of disease onset in combination with the fact that WM was first described in 1944[21] and not universally regarded as a malignancy until 1988.[22]

Bone marrow confirmation was reported in 21 patients; the histological pattern was reportedly discordant (diffuse *v* nodular) in half the families for whom the information was available. Presenting symptoms and signs were reported in about half the families and were generally similar to those found in sporadic WM.[23] A bleeding diathesis (33.3%) or malaise and/or weakness (33.3%) were the most common symptoms, followed by weight loss (22.2%). Anemia (72.2%) was common, and examination revealed hepatosplenomegaly (33.3%), lymphadenopathy (27.8%), retinal dysproteinemic findings (22.2%), and/or peripheral lymphocytosis (16.7%). Nearly all patients (94.4%) had an elevated erythrocyte sedimentation rate (ESR), and Bence-Jones proteinuria was reported in half. When other immunoglobulins were evaluated, most patients (84.2%) had some abnormality (Table 1), usually deficiencies of IgG alone (31.2%) or in combination with IgA (50.0%). There was wide variation in spectrum of autoantibodies examined among the various kindreds. When sought, 41.2% had evidence of autoantibodies, but definite clinical autoimmune disease was rare. Thirteen cases had a pre-existing IgM MG. Most of these were diagnosed with WM within 2 years. However, four patients had a prolonged history of gammopathy documented 3,[14] 7,[15] 10,[16] and 15[15] years prior to diagnosis of WM.

Several studies examined characteristics of the IgM molecule itself. Cases studied in two families shared a human constant region gene allele, inv3. Sixteen cases (69.6%) had kappa light chains, seven (30.4%) had lambda, and light chain typing was discordant in five of eight families. Furthermore, idiotypic determinants were found to be discordant among cases in all five of the families in which this was examined.

As has been historically true for sporadic WM, conventional cytogenetic studies in familial WM have been inconsistent. Cytogenetics were reported specifically in a minority of families, and only one case was found to have a clonal abnormality. Unfortunately, no reported families have yet had cytogenetic analysis using more sensitive molecular techniques. Human leukocyte antigen (HLA) typing was performed in four families and was similarly inconsistent. Several cases were noted to have either A9, B7, or B15 antigens, all of which have been reported to be associated with monoclonal components in some studies[24-26] but not in others.[27,28] Only one family shared a haplotype[14] that cosegregated with B-cell immune response alloantigens Ia 172 and 350, which have been linked to certain autoimmune syndromes,[29] including Hashimoto's thyroiditis.[30] However, in this family, which included individuals with either WM, autoimmune thyroiditis, or serologic autoantibodies, analysis strongly favored linkage to these antigens.

## IMMUNOLOGIC CHARACTERIZATION OF RELATIVES OF FAMILIAL WM PATIENTS

Family studies of WM are replete with evidence of a plethora of immunologic abnormalities in the relatives of WM cases. In 10 of the families, 121 relatives were studied (Table 2). Because of the late age of WM diagnosis, parents were available for study in only two families, including a parent (family no. 7) diagnosed with WM during study evaluation. Moreover, in these 10 families a notable number of cases (n = 8, 29.6%) had no offspring. Family members were evaluated for the presence of immunoglobulin abnormalities in all nine families and for various autoantibodies in six. A conservative estimate of the frequency of IgM MG (range, 3.2% to 6.3%) in first-degree relatives at initial evaluation remains much higher than expected from population estimates. Despite significant geographic variation, the highest population prevalence rates of IgM MG reported to date range from 0.25% (Western France[31]) to 0.64% (Southeast United States[32]). In contrast, no cases of IgG or IgA MG were identified in this series, although it has been reported rarely in relatives of sporadic cases of WM.[33] IgM MG progresses to WM at a rate of 1.5% per year.[34] Whether this risk of progression is altered in WM families is unknown, but it may be substantial, as evidenced by family no. 8, in which two of the three WM cases had originally been diagnosed with IgM MG and progressed over 7 and 15 years of observation.[15] In

**Table 1. Summary of Familial WM Cases and Results of Immunologic and Other Studies**

| | | | | | Clinical Findings | | | | IgM Characteristics | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Family No. | Reference | Case No. | Family Relation | Age (yr) | Symptoms | Signs | ESR | BJP | Light Chain | Idiotypes | AutoAbs (type)* | Other Igs | Cyto† | HLA Typing |
| 1 | Massari[8,11] | 1 (P) | Brother | 61 | Epistaxis, hematomas, melena | Anemia, LN, splenomegaly, retinal | 140 | Yes | κ | Different | No | ↑G ↓A | NR‡ | NR |
| | | 2 | Brother | 61 | Epistaxis, hematomas | Anemia, lymphocytosis, retinal | 140 | Yes | κ | | + (AγG) | ↓G ↓A | NR‡ | NR |
| 2 | Coste,[9] in Seligmann[11] | 1 (P) | Brother | 61 | Gingival bleeding, epistaxis | Anemia, retinal | 138 | Yes | κ | Different | No | NG NA | NR‡ | NR |
| | | 2 | Sister | 54 | NR | NR | NR | NR | κ | | + (AγG) | ↓G ↓A | NR‡ | NR |
| 3 | Jaccottet,[10] in Seligmann[11] | 1 | Father | 74 | Anorexia, malaise | Anemia, ↓ Plt, LN | 124 | No | IgM | NR | NR | NR | NR | NR |
| | | 2 | Son | 49 | Chest pain | Neuropathy, urticaria, leukocytosis | 75 | NR | IgM | — | NR | NR | NR | NR |
| 4 | Drivsholm, in Seligmann[11] | 1 (P) | Brother | NR | NR | NR | | | IgM | NR | NR | NR | NR | NR |
| | | 2 | Brother | NR | NR | NR | NR | NR | IgM | | NR | NR | NR | NR |
| 5 | Youinou[12,35] | 1 (P) | Brother | 61 | NR | NR | 104 | Yes | κ | Different | No (RF) | ↓G/A | + | ND |
| | | 2 | Brother | 68 | NR | NR | 34 | Yes | κ | | No (RF) | ↓G/A | + | A9, B7 |
| | | 3 | Brother | 64 | NR | NR | 23 | Yes | κ | | No (RF) | ↓G NA | + | A9, B7 |
| | | 4 | Brother | 62 | NR | NR | 16 | No | κ | | No (RF) | ↓G ↑A | ND | A9, B7 |
| 6 | Gétaz[13] | 1 | Father | 70 | Malaise, irritability, anorexia, weight loss | Anemia, HSM | 130 | No | IgM | NR | NR | NR | NR | NR |
| | | 2 | Son | 47 | Myalgia, malaise | None | 40 | NR | IgM | | NR | NG NA | NR | NR |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | Blattner[14] | 1 | Father | 84 | NR | NR | NR | NR | κ | NR | No | NR | | NR | A9 B8 DRw3 |
| | | 2 (P) | Son | 53 | NR | NR | NR | NR | λ | | + (ANA) | NR | | NR | A9 B8 DRw3 |
| | | 3 | Son | 43 | NR | NR | NR | NR | λ | | + (ANA) | NR | | NR | A9 B8 DRw3 |
| | | 4 | Daughter | 57 | NR | NR | NR | NR | κ | | No | NR | | NR | A9 B8 DRw3 |
| 8 | Fine[15,36] | 1 (P) | Brother | 61 | Epistaxis | Anemia, LN, HSM, lymphocytosis, retinal | 105 | NR | κ | NR | NR | NR | | NR | NR |
| | | 2 | Brother | 65 | Weakness | Anemia | 120 | NR | λ | | NR | ↓G | | NR | NR |
| | | 3 | Sister | 61 | Weakness, weight loss, abdominal pain, dyspnea | Anemia, HSM | 135 | NR | κ,κ | | NR | ↓G | | NR | NR |
| 9 | Fine[16] | 1 (P) | MZ brother | 75 | None | Anemia | 100 | | κ | Different | NR | ↓G | ↓A | NR | B15 |
| | | 2 | MZ brother | 75 | None | Anemia | 82 | | λ | | NR | NG | NA | NR | B15 |
| 10 | Renier[1] | 1 (P) | Brother | 74 | Epistaxis | Anemia | NR | No | κ | Different | + (AGA) | ↓G | ↓A | NR | No shared haplotype |
| | | 2 | Brother | 75 | None | None | NR | Yes | κ | | No | ↓G | NA | NR | B7, B12 |
| | | 3 | Brother | 68 | Epistaxis | Pancytopenia | NR | Yes | λ | | No | ↓G | ↓A | NR | B7, B12 |
| | | 4 | Brother | 68 | None | LN | NR | Yes | λ | | + (AMA) | NG | ↓A | NR | B7, A9 |
| 11 | DuPont, in Renier[1] | 1 | Mother | 74 | NR | NR | NR | NR | κ | NR | No | Normal | | NR | NR |
| | | 2 | Daughter | 52 | NR | NR | NR | NR | λ | | No | Normal | | NR | NR |
| 12 | Taleb[17] | 1 (P) | Sister | 64 | Weight loss, diarrhea | Anemia, splenomegaly, LN | 140 | No | κ | NR | NR | ↓G | NA | + | NR |
| | | 2 | Sister | 43 | Asthenia, weight loss, fever | Anemia, lymphocytosis, HSM | 60 | No | λ | | NR | ↓G | ↓A | NR | NR |

* Various autoantibodies were sought in different studies, including ANA, AmtA, ASM, AGA, ARA, and AMA.

† Cytogenetic studies: +, indicates procedure performed and results reported.

‡ Seligmann et al[11] reported that "most" of the individuals in their series had cytogenetic studies that were normal; however, specific results were not reported for these individuals.

Abbreviations: ESR, erythrocyte sedimentation rate; BJP, Bence-Jones proteinuria; AutoAbs, autoantibodies; Igs, immunoglobulins; Cyto, cytogenetics; P, proband; LN, lymphadenopathy; Retinal, retinal dysproteinemia; HSM, hepatosplenomegaly; Plt, platelets; AγG, anti–gamma-globulin; RF, rheumatoid factor; ANA, antinuclear antibody; AGA, antigastric antibody; AmtA, antimitochondrial antibody; ASM, anti–smooth muscle antibody; ARA, antireticulin antibody; AMA, antimyelin antibody; G, IgG; A, IgA; M, IgM; NG, normal IgG level; NR, not reported; ND, not determined.

**Table 2. Characteristics of Immunologic Studies in Relatives of Familial WM Cases in Nine Families**

| Family No. | No. of Relatives Studied | Age Range (yr) | AutoAbs* | Immunoglobulins | | | | | Comment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | MC | Increased | (type) | Decreased | (type) | |
| 1 | 1 | 82 | 0 | 1 | 1 | (1 G/A) | 0 | | MC found to be transient on follow-up[8,11] |
| 2 | 17 | 17-69 | 3 AγG<br>1 AγG/RF | 0 | 8 | (2 M, 4 A, 2 G/A/M) | 2 | (2M) | ↑ M/A/G in 17 yo |
| 3 | 3 | NR | NR | 0 | 0 | | 0 | | |
| 5 | 35 | 1-65 | 4 RF<br>1 ANA | 1 | 3 | (2 M, 1 A) | 13 | (13G) | 1 ↑ A in 1 yo;<br>1 ↑ M in 30 yo |
| 7 | 16 | NR | 3 RF<br>2 AMC<br>3 ATM ± ATG | 1† | 0 | | 0 | | |
| 8 | 26 | 1-67 | NR | 1† | 0 | | 13 | (13G) | 1 ↓ G in 1 yo |
| 9 | 6 | NR | NR | 0 | 0 | | 0 | | |
| 10 | 2 | NR | 0 | 0 | 0 | | 0 | | |
| 11 | 12 | 21-63 | 1 ATA<br>1 ANA | 0 | 6 | (1 M, 2 G, 1 A,<br>1 G/A, 1 G/A/M) | 0 | | |
| 12 | 7 | 8-67 | NR | 0 | 4 | (4 M) | 0 | | |

* A variety of autoantibodies were studied in different families. Only those for which any positive titer was discovered are reported here.

† In families no. 7 and 8, monoclonal components were identified in two patients during initial study evaluation and following documentation of familiality (ie, after at least two family members had been diagnosed with WM); both patients were eventually diagnosed with WM.

Abbreviations: AutoAbs, autoantibodies; MC, monoclonal component; AγG, anti–gamma-globulin; RF, rheumatoid factor; AMC, antimyocardial antibody; ATM, antimicrosomal antibody; ATG, antithyroglobulin antibody; G, IgG; A, IgA; M, IgM; yo, years old; NR, not reported.

contrast, the IgM MG was transient in one relative in family no. 1. Overall, 40.5% of relatives had evidence of some immunoglobulin abnormality, including 9.9% with polyclonal IgM elevations (IgM PG). The frequency of IgM PG was highest in siblings (30.0%) and correlated with degree of relationship (14.3% and 7.3% in first- and second-degree relatives, respectively). In addition, 23.4% of tested relatives had autoantibodies, the presence of which was also correlated with degree of relationship (Table 3).

## CONCLUSIONS

An empirical risk study has not been conducted to determine what percentage of WM cases is familial. Thus it is not possible to define the proportion of all WM that occurs in the familial setting, although it appears to be small. Nonetheless, the data provided by these initial family studies are intriguing. For example, these reports, as well as descriptions of familial IgM MG, have provided much of the evidence suggesting a role for an underlying defect in immune regulation as a contributing factor in the development of WM. It is clear, however, that our understanding of WM, both familial and sporadic, remains limited. This series has several limitations, including small numbers of families studied by several different investigators using variable study designs, methodologies, and endpoints, and it is hampered further by wide inconsistencies in data reporting and an overall lack of prospective follow-up. Moreover, the extent to which the published families are representative of familial WM in the general population is not certain. For instance, the male-to-female case ratio in an unpublished series of US families is 1.9 (M.L.M., unpublished observations), which is more consistent than the current series with the gender ratio observed in registry-based sporadic WM cases.[2] To address these limitations, we have undertaken a prospective investigation designed to recruit a large number of WM families from across the United States, employing an array of epidemiologic tools, molecular genetic

**Table 3. Frequency of Immunologic Abnormalities in Relatives of WM Cases in Nine Families**

| Relationship of Studied Family Members to Cases | No. Studied | | | No. Found to Have Any Abnormality | | | |
|---|---|---|---|---|---|---|---|
| | | | | Autoantibody | | Immunoglobulin | |
| | Total | AutoAbs | Igs | n | % | n | % |
| First-degree relative | 63 | 40 | 63 | 12 | 30.0 | 21 | 33.3 |
| Second-degree relative | 41 | 27 | 41 | 6 | 22.2 | 24 | 58.5 |
| Other | 17 | 14 | 17 | 1 | 7.1 | 4 | 23.5 |
| Parents | 1 | 1 | 1 | 0 | 0.0 | 1 | 100.0 |
| Siblings | 20 | 13 | 20 | 5 | 38.5 | 9 | 45.0 |
| Offspring | 42 | 26 | 42 | 7 | 26.9 | 11 | 26.2 |
| Other | 58 | 41 | 58 | 7 | 17.1 | 28 | 48.3 |
| Total | 121 | 81 | 121 | 19 | 23.4 | 49 | 40.5 |

Abbreviations: AutoAbs, autoantibodies; Igs, immunoglobulins.

technologies, and statistical genetic techniques for the systematic evaluation of clinicopathologic, epidemiologic, and laboratory parameters. This study of familial WM may elucidate the genetic and/or environmental determinants of this rare, distinctive disorder.

## REFERENCES


1. Renier G, Ifrah N, Chevailler A, et al: Four brothers with Waldenstrom's macroglobulinemia. Cancer 64:1554-1559, 1989
2. Groves FD, Travis LB, Devesa SS, et al: Waldenström's macroglobulinemia: Incidence patterns in the United States, 1988-1994. Cancer 82:1078-1081, 1998
3. Herrinton LJ, Weiss NS: Incidence of Waldenström's Macroglobulinemia. Blood 82:3148-3150, 1993
4. Williamson LM, Greaves M, Worters JR, et al: Waldenstrom's macroglobulinaemia: Three cases in shoe repairers. BMJ 298:498-499, 1989 (erratum, 298:710, 1989)
5. James JM, Brouet JC, Orvoenfrija E, et al: Waldenstrom's macroglobulinaemia in a bird breeder: A case history with pulmonary involvement and antibody activity of the monoclonal IgM to canary's droppings. Clin Exp Immunol 68:397-401, 1987
6. Tepper A, Moss CE: Waldenstrom's macroglobulinemia: Search for occupational exposure. J Occup Med 36:133-136, 1994
7. Linet MS, Humphrey RL, Mehl ES, et al: A case-control and family study of Waldenstrom's macroglobulinemia. Leukemia 7:1363-1369, 1993
8. Massari R, Fine JM, Metais R: Waldenström's macroglobulinæmia observed in two brothers. Nature 196:176-178, 1962
9. Coste F, Massais P, Menkes C: Un cas de macroglobulinémie. Rev Rhumat 31:37-39, 1964
10. Jaccottet MA, Ramel C: A propos des paraproteinoses atypique. Praxis 54:302-311, 1965
11. Seligmann M, Danon F, Mihaesco C, et al: Immunoglobulin abnormalities in families of patients with Waldenström's macroglobulinemia. Am J Med 43:66-83, 1967
12. Youinou P, Le Goff P, Saleun JP, et al: Familial occurrence of monoclonal gammapathies. Biomedicine 28:226-232, 1978
13. Gétaz EP, Staples WG: Familial Waldenström's macroglobulinaemia: A case report. S Afr Med J 51:891-892, 1977
14. Blattner WA, Garber JE, Mann DL, et al: Waldenstrom's macroglobulinemia and autoimmune disease in a family. Ann Intern Med 93:830-832, 1980
15. Fine JM, Lambin P, Massari M, et al: Malignant evolution of asymptomatic monoclonal IgM after seven and fifteen years in two siblings of a patient with Waldenström's macroglobulinemia. Acta Med Scand 211:237-239, 1982
16. Fine JM, Muller JY, Rochu D, et al: Waldenstrom's macroglobulinemia in monozygotic twins. Acta Med Scand 220:369-373, 1986
17. Taleb N, Tohme A, Abi JD, et al: Familial macroglobulinemia in a Lebanese family with two sisters presenting Waldenstrom's disease. Acta Oncol 30:703-705, 1991
18. Olsen JH, Seersholm N, Boice JD Jr, et al: Cancer risk in close relatives of women with early-onset breast cancer—A population-based incidence study. Br J Cancer 79:673-679, 1999
19. Bratt O, Kristoffersson U, Lundgren R, et al: Familial and hereditary prostate cancer in southern Sweden. A population-based case-control study. Eur J Cancer 35:272-277, 1999
20. Fuchs CS, Giovannucci EL, Colditz GA, et al: A prospective study of family history and the risk of colorectal cancer. N Engl J Med 331:1669-1674, 1994
21. Waldenström J: Incipient myelomatosis or "essential" hyperglobulinemia with fibrinogenopenia—A new syndrome? Acta Med Scand 117:216-247, 1944
22. World Health Organization: International classification of Diseases for Oncology (ed 2). Geneva, Switzerland, World Health Organization, 1990
23. Owen RG, Barrans SL, Richards SJ, et al: Waldenstrom macroglobulinemia—Development of diagnostic criteria and

identification of prognostic factors. Am J Clin Pathol 116:420-428, 2001

24. Smith G, Walford RL, Fishkin B, et al: HL-A phenotypes, immunoglobulins and K and L chains in multiple myeloma. Tissue Antigens 4:374-377, 1974

25. Van Camp BG, Cole J, Peetermans ME: HLA antigens and homogeneous immunoglobulins. Clin Immunol Immunopathol 7:315-318, 1977

26. Saleün JP, Youinou P, Le Goff P, et al: HLA antigens and monoclonal gammapathy. Tissue Antigens 13:233-235, 1979

27. Jeannet M, Magnin C: HL-A antigens in haematological malignant diseases. Eur J Clin Invest 2:39-42, 1971

28. Mason DY, Cullen P: HL-A antigen frequencies in myeloma. Tissue Antigens 5:238-245, 1975

29. Reinertsen JL, Klippel JH, Johnson AH, et al: B-lymphocyte alloantigens associated with systemic lupus erythematosus. N Engl J Med 299:515-518, 1978

30. Chopra IJ, Solomon DH, Chopra U, et al: Abnormalities in thyroid function in relatives of patients with Graves' disease and Hashimoto's thyroiditis: Lack of correlation with inheritance of HLA-B8. J Clin Endocrinol Metab 45:45-54, 1977

31. Saleun JP, Vicariot M, Deroff P, et al: Monoclonal gammopathies in the adult population of Finistere, France. J Clin Pathol 35:63-68, 1982

32. Cohen HJ, Crawford J, Rao MK, et al: Racial differences in the prevalence of monoclonal gammopathy in a community-based sample of the elderly. Am J Med 104:439-444, 1998

33. Fine JM, Lambin P, Valentin L, et al: IgG monoclonal gammapathy in the sister of a patient with Waldenström's macroglobulinaemia. Biomedicine 19:117-121, 1973

34. Kyle RA, Garton JP: The spectrum of IgM monoclonal gammopathy in 430 cases. Mayo Clin Proc 62:719-731, 1987

35. Youinou P, Le Goff P, Saleun JP, et al: Familial monoclonal gammapathy. Preliminary results of a prospective survey. Sem Hop 53:1367-1368, 1977

36. Fine JM, Massari R, Boffa GA, et al: Monoclonal macroglobulinemia of familial nature present in 3 siblings. Transfusion (Paris) 9:333-341, 1966