

Supplement Article

XIII. Waldenström's macroglobulinaemia: an indolent B-cell lymphoma with distinct molecular and clinical features

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Introduction

Waldenström's macroglobulinaemia (WM) is a distinct B-cell lymphoma resulting from the accumulation, predominantly in the bone marrow, of clonally related lymphocytes, lymphoplasmacytic cells and plasma cells that secrete a monoclonal IgM protein [1]. This condition is considered to correspond to the lymphoplasmacytic lymphoma (LPL) as defined by the World Health Organisation classification system [2]. Most cases of LPL are WM, with less than 5% of cases made up of IgA, IgG and non-secreting LPL.

Epidemiology

WM is an uncommon B-cell malignancy with a reported age-adjusted incidence rate of 3.4 per million among men and 1.7 per million among women in the USA, and a geometrical increase with age [3]. The incidence rate for WM is higher among Caucasians, with African descendants representing only 5% of all patients. The incidence of WM may be higher among individuals of Askenazi Jewish decent [4]. Genetic factors appear to be important to the pathogenesis of WM. A common predisposition for WM with other malignancies has been raised [4,5], with numerous reports of familial clustering of individuals with WM alone and with other B-cell lymphoproliferative diseases [6–10].

Biology

Cytogenetics

Chromosome 6q deletions encompassing 6q21–25 have been observed in up to half of WM patients and at a comparable frequency amongst patients with and without a familial history [7,11–13]. The presence of 6q deletions have been suggested to discern patients with WM from those with IgM monoclonal gammopathy of unknown significance

(MGUS) and to have potential prognostic significance including impact on progression free survival following treatment response, although others have reported no prognostic significance to the presence of 6q deletions in WM [11,13,14].

Mutation in MYD88

A highly recurrent somatic mutation (MYD88 L265P) located on 3p22.2 was recently identified in WM patients by paired tumour/normal whole genome sequencing and subsequent confirmation by Sanger and PCR sequencing [15–20]. MYD88 L265P was present as a somatic mutation in 80–100% of WM patients, as well as in non-IgM secreting LPL cases. By comparison, MYD88 L265P was absent in myeloma samples, including IgM myeloma, and was expressed in a small subset of MZL patients who likely were WM patients. The expression of MYD88 L265P in both familial and sporadic WM patients at the same frequency was also shown, denoting that acquisition of MYD88 L265P is a common transforming event for WM regardless of familial predisposition. Of particular interest has been the expression of MYD88 L265P in IgM MGUS [15–17].

The functional significance of MYD88 L265P in WM patients has also been addressed. Knock-down of MYD88 decreased survival of MYD88 L265P expressing WM cells, whereas survival was more enhanced by knock-in of MYD88 L265P versus wild-type MYD88. These observations are of particular relevance to WM because NF- κ B signalling is important for WM growth and survival [21] and highlights the relevance of the MYD88 pathway for novel, targeted therapy of WM.

Nature of the clonal cell

The phenotype of lymphoplasmacytic cells in WM cell suggests that the clone is a post-germinal centre B-cell.

This indication is further strengthened by the results of the analysis of the nature (silent or amino-acid replacing) and distribution (in framework or CDR regions) of somatic mutations in Ig heavy- and light-chain variable regions performed in patients with WM [22,23]. This analysis showed a high rate of replacement mutations, compared with the closest germline genes, clustering in the CDR regions and without intraclonal variation. Subsequent studies showed a strong preferential usage of VH3/JH4 gene families, no intraclonal variation and no evidence for any isotype-switched transcripts [24,25]. These data indicate that WM may originate from an IgM⁺ and/or IgM⁺ IgD⁺ memory B cell. Normal IgM⁺ memory B cells localize in bone marrow, where they mature to IgM-secreting cells [26].

Bone marrow microenvironment

Increased numbers of mast cells are found in the bone marrow of WM patients, wherein they are usually admixed with tumour aggregates [2,27]. The role of mast cells in WM has been investigated in one study wherein co-culture of primary autologous or mast cell lines with WM LPC resulted in dose-dependent WM cell proliferation and/or tumour colony formation, primarily through CD40 ligand (CD40L) signalling. Furthermore, WM cells through elaboration of soluble CD27 (sCD27) induced the upregulation of CD40L on mast cells derived from WM patients and mast cell lines suggesting a microenvironmental support system [27,28].

Clinical features

The excess accumulation of malignant lymphoplasmacytic cells in the bone marrow is the predominant feature of WM. Unlike most other indolent B-cell lymphomas, splenomegaly and lymphadenopathy are present in only a modest fraction of patients (<20%). The morbidity associated with WM is caused by the concurrence of two main

components: tissue infiltration by neoplastic cells and also the physicochemical and immunological properties of the monoclonal IgM (Figure 1). The monoclonal IgM can produce clinical manifestations through several different mechanisms related to its physicochemical properties, non-specific interactions with other proteins, antibody activity and tendency to deposit in tissues [29–31].

Morbidity mediated by the effects of IgM

Hyperviscosity syndrome

Blood hyperviscosity is affected by increased serum IgM levels leading to hyperviscosity related complications [32]. The mechanisms behind the marked increase in the resistance to blood flow, and the resulting impaired transit through the microcirculatory system are rather complex [32–34]. The main determinants are as follows: (1) a high concentration of monoclonal IgMs, which may form aggregates and may bind water through their carbohydrate component, and (2) their interaction with blood cells. Monoclonal IgMs increase red cell aggregation (*rouleaux* formation) and red cell internal viscosity while also reducing deformability. Clinical manifestations are related to circulatory disturbances that can be best appreciated by ophthalmoscopy, which shows distended and tortuous retinal veins, haemorrhages and papilledema [35] (Figure 2). Symptoms usually occur when the monoclonal IgM concentration exceeds 50 g/L or when serum viscosity is >4.0 centipoises (cp), but there is a great individual variability, with some patients showing no evidence of hyperviscosity even at 10 cp [32]. The most common symptoms are oronasal bleeding, visual disturbances due to retinal bleeding and dizziness that may rarely lead to coma.

Cryoglobulinaemia

In up to 20% of WM patients, the monoclonal IgM can behave as a cryoglobulin (type I), but it is symptomatic in 5% or less of the cases [36]. Cryoprecipitation is mainly dependent on the concentration of monoclonal IgM; for this reason, plasmapheresis or plasma exchange are commonly effective in this condition. Symptoms result from impaired blood flow in small vessels and include Raynaud's phenomenon, acrocyanosis and necrosis of the regions most exposed to cold such as the tip of the nose, ears, fingers, and toes, malleolar ulcers, purpura and cold urticaria. Renal manifestations may occur but are infrequent.

Auto-antibody activity

Monoclonal IgM may exert its pathogenic effects through specific recognition of autologous antigens, the most

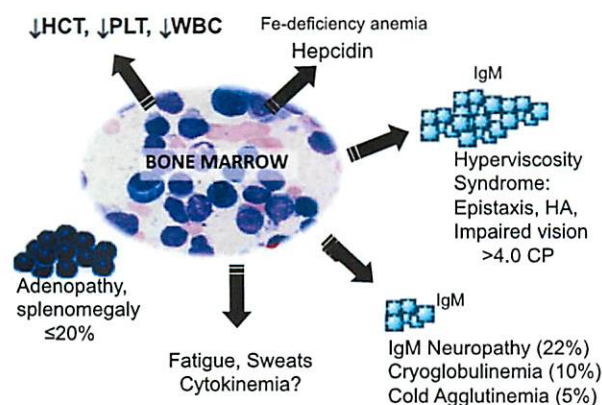


Figure 1. Clinical manifestations of Waldenström's macroglobulinaemia

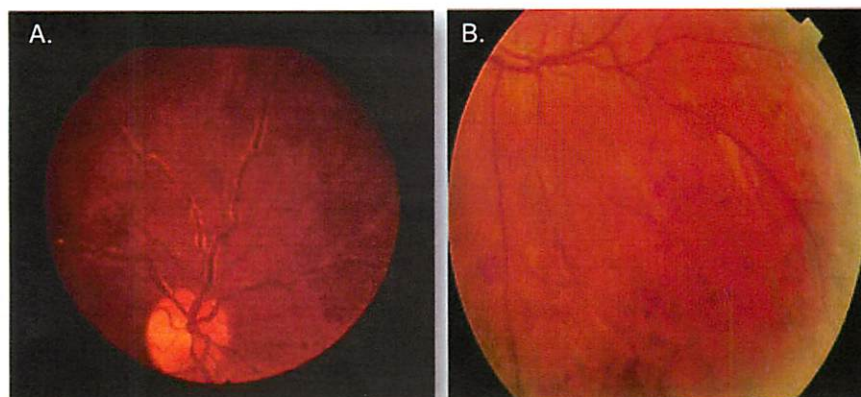


Figure 2. Fundusoscopic examination of patients with Waldenström's macroglobulinaemia demonstrating hyperviscosity related changes including presence of (A) dilated retinal vessels with 'sausaging characteristic', and (B) peripheral haemorrhages. (A) Courtesy of Dr Marvin Stone

notable being nerve constituents, immunoglobulin determinants and red blood cell antigens:

IgM related neuropathy

The presence of peripheral neuropathy has been estimated to range from 5% to 38% in WM patients [37–41]. The nerve damage is mediated by diverse pathogenetic mechanisms: IgM antibody activity towards nerve constituents causing demyelinating polyneuropathies; endoneurial granulofibrillar deposits of IgM without antibody activity, associated with axonal polyneuropathy; occasionally by tubular deposits in the endoneurium associated with IgM cryoglobulin and, rarely, by amyloid deposits or by neoplastic cell infiltration of nerve structures [42]. Half of the patients with IgM neuropathy have a distinctive clinical syndrome that is associated with antibodies against a minor 100-kDa glycoprotein component of nerve, myelin-associated glycoprotein (MAG). Anti-MAG antibodies are generally monoclonal IgMκ and usually also exhibit reactivity with other glycoproteins or glycolipids that share antigenic determinants with MAG [43–45].

Cold agglutinin haemolytic anaemia

Monoclonal IgM may present with cold agglutinin activity; that is, it can recognize specific red cell antigens at temperatures below physiological, producing chronic haemolytic anaemia. This disorder occurs in <10% of WM patients [46] and is associated with cold agglutinin titers >1:1000 in most cases. The monoclonal component is usually an IgMκ and reacts most commonly with I/i antigens, with complement fixation and activation [47,48]. Mild chronic haemolytic anaemia can be exacerbated after cold exposure, but rarely does haemoglobin drop below 70 g/L. The haemolysis is usually extravascular (removal of C3b opsonized cells by the reticuloendothelial system, primarily in

the liver) and rarely intravascular from complement destruction of red blood cell (RBC) membrane. The agglutination of RBCs in the cooler peripheral circulation also causes Raynaud's syndrome, acrocyanosis and livedo reticularis.

Tissue deposition

The monoclonal protein can deposit in several tissues as amorphous aggregates. Linear deposition of monoclonal IgM along the skin basement membrane is associated with bullous skin disease [49]. Amorphous IgM deposits in the dermis determine the so-called IgM storage papules on the extensor surface of the extremities—macroglobulinaemia cutis [50]. Deposition of monoclonal IgM in the lamina propria and/or submucosa of the intestine may be associated with diarrhoea, malabsorption and gastrointestinal bleeding [51,52]. It is well known that kidney involvement is less common and less severe in WM than in multiple myeloma, probably because the amount of light chain excreted in the urine is generally lower in WM than in myeloma and because of the absence of contributing factors, such as hypocalcaemia, although cast nephropathy has also been described in WM [53]. On the other hand, the IgM macromolecule is more susceptible to being trapped in the glomerular loops where ultrafiltration presumably contributes to its precipitation, forming subendothelial deposits of aggregated IgM proteins that occlude the glomerular capillaries [54]. Mild and reversible proteinuria may result, and most patients are asymptomatic. The deposition of monoclonal light chain as fibrillar amyloid deposits (AL amyloidosis) is uncommon in patients with WM [55].

Anaemia related to hepcidin

Hepcidin is a peptide hormone that regulates iron metabolism [56]. Although primarily produced by hepatocytes and

monocytes, WM cells were recently shown to produce hepcidin [57]. Hepcidin exerts its regulatory function by binding to and mediating the internalization and subsequent degradation of the iron export protein ferroportin found on enterocytes, monocytes and macrophages. Upon ligation by hepcidin, ferroportin is internalized, ubiquitinated and degraded. By inhibiting ferroportin, hepcidin prevents gut enterocytes from secreting absorbed iron into the hepatic portal system, thereby limiting iron absorption. Hepcidin levels positively correlated with bone marrow disease involvement and negatively-correlated with haemoglobin among WM patients [57].

Hypogammaglobulinaemia in WM

Deficiencies in the uninvolved immunoglobulins (IgA and IgG or both) are very common in patients with WM and may predispose to recurring sinobronchial infections [58,59]. The presence of IgA or IgG hypogammaglobulinaemia was not associated with WM disease burden, nor was recovery in IgA or IgG observed following successful treatment of patients, including in patients who attained a complete response. These findings suggest either a constitutive defect in B-cell lymphopoiesis or microenvironmental influence versus direct tumour related effects may restrain normal B-cell and immunoglobulin development. Despite investigation of common mutations associated with common variable immunodeficiency syndrome, a syndrome associated with IgA and/or IgG hypogammaglobulinaemia, no systematic mutations were found to suggest a common B-cell defect accounting for these findings in WM patients [58].

In summary, WM, although an indolent B-cell lymphoma, shows distinct molecular, biological and clinical features. Understanding the fundamental differences of WM pathophysiology relative to other B-cell lymphomas can aid clinicians in the diagnostic discrimination and management of patients with WM.

CONFLICT OF INTEREST

The author has no competing interest.

REFERENCES

- Owen RG, Treon SP, Al-Katib A, *et al.* Clinicopathological definition of Waldenström's macroglobulinemia: consensus panel recommendations from the second international workshop on Waldenström's macroglobulinemia. *Semin Oncol* 2003; 30: 110–15.
- World Health Organization. Classification of Tumours of Haematopoietic and Lymphoid Tissues. Swerdlow SH, Campo E, Harris NL, *et al.* (eds). IARC Press: Lyon, 2008.
- Groves FD, Travis LB, Devesa SS, Ries LA, Fraumeni JF Jr. Waldenström's macroglobulinemia: incidence patterns in the United States, 1988–1994. *Cancer* 1998; 82: 1078–81.
- Hanzis C, Ojha RP, Hunter Z, *et al.* Associated malignancies in patients with Waldenström's macroglobulinemia and their kin. *Clin Lymphoma Myeloma Leuk* 2011; 11: 88–92.
- Varettoni M, Tedesci A, Arcaini L, *et al.* Risk of second cancers in Waldenström macroglobulinemia. *Ann Oncol* 2012; 23: 411–415.
- Renier G, Ifrah N, Chevaillier A, *et al.* Four brothers with Waldenström's macroglobulinemia. *Cancer* 1989; 64: 1554–9.
- Treon SP, Hunter ZR, Aggarwal A, *et al.* Characterization of familial Waldenström's macroglobulinemia. *Ann Oncol* 2006; 17: 488–494.
- Kristinsson SY, Björkholm M, Goldin LR, *et al.* Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia patients: a population-based study in Sweden. *Blood* 2008; 112: 3052–3056.
- McMaster ML, Csako G, Giambaresi TR, *et al.* Long-term evaluation of three multiple-case Waldenström's macroglobulinemia families. *Clin Cancer Res* 2007; 13: 5063–5069.
- Ogmundsdottir HM, Sveinsdottir S, Sigfusson A, Skaftadottir I, Jonasson JG, Agnarsson BA. Enhanced B cell survival in familial macroglobulinaemia is associated with increased expression of Bcl-2. *Clin Exp Immunol* 1999; 117: 252–60.
- Schop RF, Kuehl WM, Van Wier SA, Ahmann GJ, Price-Troska T, Bailey RJ, *et al.* Waldenström macroglobulinemia neoplastic cells lack immunoglobulin heavy chain locus translocations but have frequent 6q deletions. *Blood* 2002; 100: 2996–3001.
- Ocio EM, Schop RF, Gonzalez B, *et al.* 6q deletion in Waldenström's macroglobulinemia is associated with features of adverse prognosis. *Br J Haematol* 2007; 136: 80–6.
- Chang H, Qi C, Trieu Y, *et al.* Prognostic relevance of 6q deletion in Waldenström's macroglobulinemia. *Clin Lymph Myeloma* 2009; 9: 36–8.
- Nguyen-Khac F, Lejeune J, Chapiro E, *et al.* Cytogenetic abnormalities in a cohort of 171 patients with Waldenström macroglobulinemia before treatment: clinical and biological correlations. *Blood* 2010; 116: Abstract 801.
- Treon SP, Xu L, Yang G, *et al.* MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N Engl J Med* 2012; 367: 826–33.
- Gachard N, Parrens M, Soubeyan I, *et al.* IGHV gene features and MYD88 L265P mutation separate the three marginal zone lymphoma entities and Waldenström macroglobulinemia/lymphoplasmacytic lymphoma. *Leukemia* 2013; 27: 183–9.
- Xu L, Hunter ZR, Yang G, *et al.* MYD88 L265P in Waldenström macroglobulinemia, immunoglobulin M monoclonal gammopathy and other B-cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. *Blood* 2013; 121: 2051–8.
- Varettoni M, Arcaini L, Zibellini S, *et al.* Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenström's macroglobulinemia and related lymphoid neoplasms. *Blood* 2013; 12: 2522–8.
- Jiménez C, Sebastián E, Del Carmen Chillón M, *et al.* MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenström's macroglobulinemia. *Leukemia*. 2013 Feb 28. doi: 10.1038/leu.2013.62. [Epub ahead of print]
- Poulain S, Roumier C, Decambon A, *et al.* MYD88 L265P mutation in Waldenström's macroglobulinemia. *Blood* 2013; first edition.
- Leleu X, Eeckhoutte J, Jia X, *et al.* Targeting NF-kappaB in Waldenström macroglobulinemia. *Blood* 2008; 111: 5068–77.
- Wagner SD, Martinelli V, Luzzatto L. Similar patterns of V kappa gene usage but different degrees of somatic mutation in

- hairy cell leukemia, prolymphocytic leukemia, Waldenström's macroglobulinemia, and myeloma. *Blood* 1994; 83: 3647–53.
23. Aoki H, Takishita M, Kosaka M, Saito S. Frequent somatic mutations in D and/or JH segments of Ig gene in Waldenström's macroglobulinemia and chronic lymphocytic leukemia (CLL) with Richter's syndrome but not in common CLL. *Blood* 1995; 85: 1913–19.
 24. Shiokawa S, Suehiro Y, Uike N, Muta K, Nishimura J. Sequence and expression analyses of mu and delta transcripts in patients with Waldenström's macroglobulinemia. *Am J Hematol* 2001; 68: 139–43.
 25. Sahota SS, Forconi F, Ottensmeier CH, et al. Typical Waldenström macroglobulinemia is derived from a B-cell arrested after cessation of somatic mutation but prior to isotype switch events. *Blood* 2002; 100: 1505–7.
 26. Paramithiotis E, Cooper MD. Memory B lymphocytes migrate to bone marrow in humans. *Proc Natl Acad Sci USA* 1997; 94: 208–12.
 27. Tournilhac O, Santos DD, Xu L, et al. Mast cells in Waldenström's macroglobulinemia support lymphoplasmacytic cell growth through CD154/CD40 signaling. *Ann Oncol* 2006; 17: 1275–82.
 28. Ho A, Leleu X, Hatjiharissi E, et al. CD27-CD70 interactions in the pathogenesis of Waldenström's macroglobulinemia. *Blood* 2008; 112: 4683–9.
 29. Merlini G, Farhangi M, Osserman EF. Monoclonal immunoglobulins with antibody activity in myeloma, macroglobulinemia and related plasma cell dyscrasias. *Semin Oncol* 1986; 13: 350–65.
 30. Farhangi M, Merlini G. The clinical implications of monoclonal immunoglobulins. *Semin Oncol* 1986; 13: 366–79.
 31. Marmont AM, Merlini G. Monoclonal autoimmunity in hematology. *Haematologica* 1991; 76: 449–59.
 32. Mackenzie MR, Babcock J. Studies of the hyperviscosity syndrome. II. Macroglobulinemia. *J Lab Clin Med* 1975; 85: 227–34.
 33. Gertz MA, Kyle RA. Hyperviscosity syndrome. *J Intens Care Med* 1995; 10: 128–41.
 34. Kwaan HC, Bongu A. The hyperviscosity syndromes. *Semin Thromb Hemost* 1999; 25: 199–208.
 35. Menke MN, Feke GT, McMeel JW, Branagan A, Hunter Z, Treon SP. Hyperviscosity-related retinopathy in Waldenström's macroglobulinemia. *Arch Ophthalmol* 2006; 124: 1601–6.
 36. Merlini G, Baldini L, Broglia C, et al. Prognostic factors in symptomatic Waldenström's macroglobulinemia. *Semin Oncol* 2003; 30: 211–15.
 37. Dellagi K, Dupouey P, Brouet JC, et al. Waldenström's macroglobulinemia and peripheral neuropathy: a clinical and immunologic study of 25 patients. *Blood* 1983; 62: 280–5.
 38. Nobile-Orazio E, Marmiroli P, Baldini L, et al. Peripheral neuropathy in macroglobulinemia: incidence and antigen-specificity of M proteins. *Neurology* 1987; 37: 1506–14.
 39. Nemni R, Gerosa E, Piccolo G, Merlini G. Neuropathies associated with monoclonal gammopathies. *Haematologica* 1994; 79: 557–66.
 40. Ropper AH, Gorson KC. Neuropathies associated with paraproteinemia. *N Engl J Med* 1998; 338: 1601–7.
 41. Treon SP, Hanzis CA, Ioakimidis LI, et al. Clinical characteristics and treatment outcome of disease-related peripheral neuropathy in Waldenström's macroglobulinemia. *Proc Am Soc Clin Oncol* 2010; 28: Abstract 8114.
 42. Nobile-Orazio E, Manfredini E, Carpo M, et al. Frequency and clinical correlates of antineural IgM antibodies in neuropathy associated with IgM monoclonal gammopathy. *Ann Neurol* 1994; 36: 416–24.
 43. Latov N, Braun PE, Gross RB, Sherman WH, Penn AS, Chess L. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. *Proc Natl Acad Sci USA* 1981; 78: 7139–42.
 44. Chassande B, Leger JM, Younes-Chennoufi AB, et al. Peripheral neuropathy associated with IgM monoclonal gammopathy: correlations between M-protein antibody activity and clinical/electrophysiological features in 40 cases. *Muscle Nerve* 1998; 21: 55–62.
 45. Weiss MD, Dalakas MC, Lauter CJ, Willison HJ, Quarles RH. Variability in the binding of anti-MAG and anti-SGPG antibodies to target antigens in demyelinating neuropathy and IgM paraproteinemia. *J Neuroimmunol* 1999; 95: 174–84.
 46. Crisp D, Pruzanski W. B-cell neoplasms with homogeneous cold-reacting antibodies (cold agglutinins). *Am J Med* 1982; 72: 915–22.
 47. Pruzanski W, Shumak KH. Biologic activity of cold-reacting autoantibodies (first of two parts). *N Engl J Med* 1977; 297: 538–42.
 48. Pruzanski W, Shumak KH. Biologic activity of cold-reacting autoantibodies (second of two parts). *N Engl J Med* 1977; 297: 583–9.
 49. Whittaker SJ, Bhogal BS, Black MM. Acquired immunobullous disease: a cutaneous manifestation of IgM macroglobulinaemia. *Br J Dermatol* 1996; 135: 283–6.
 50. Daoud MS, Lust JA, Kyle RA, Pittelkow MR. Monoclonal gammopathies and associated skin disorders. *J Am Acad Dermatol* 1999; 40: 507–35.
 51. Gad A, Willen R, Carlen B, Gyland F, Wickander M. Duodenal involvement in Waldenström's macroglobulinemia. *J Clin Gastroenterol* 1995; 20: 174–6.
 52. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 3-1990. A 66-year-old woman with Waldenström's macroglobulinemia, diarrhea, anemia, and persistent gastrointestinal bleeding. *N Engl J Med* 1990; 322: 183–92.
 53. Isaac J, Herrera GA. Cast nephropathy in a case of Waldenström's macroglobulinemia. *Nephron* 2002; 91: 512–15.
 54. Morel-Maroger L, Basch A, Danon F, Verroust P, Richet G. Pathology of the kidney in Waldenström's macroglobulinemia. Study of sixteen cases. *N Engl J Med* 1970; 283: 123–9.
 55. Gertz MA, Kyle RA, Noel P. Primary systemic amyloidosis: a rare complication of immunoglobulin M monoclonal gammopathies and Waldenström's macroglobulinemia. *J Clin Oncol* 1993; 11: 914–20.
 56. Nemeth E, Tuttle MS, Powelson J, et al. Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. *Science* 2004; 306: 2090–3.
 57. Ciccarelli B, Patterson C, Hunter ZR, et al. Hepcidin is produced by lymphoplasmacytic cells and is associated with anemia in Waldenström's macroglobulinemia. *Clin Lymph Myeloma* 2011; 11: 160–3.
 58. Hunter ZR, Manning RJ, Hanzis C, et al. IgA and IgG hypogammaglobulinemia in Waldenström's macroglobulinemia. *Haematologica* 2010; 95: 470–5.
 59. Treon SP, How I. Treat Waldenström's macroglobulinemia. *Blood* 2009; 114: 2375–85.