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EDITORIAL

A Tribute to Jan Gosta Waldenström

By Robert A. Kyle and Kenneth C. Anderson

ON DECEMBER 1, 1996, the world lost one of this century's giants in hematology. Jan Gosta Waldenström was born the son and grandson of physicians in Stockholm, Sweden, on April 17, 1906. During his long and distinguished career, he made seminal observations in hematology that provided a framework for understanding diseases such as porphyria, hemosiderosis, macroglobulinemia, and the monoclonal gammopathies. After obtaining his M.D. degree at the University of Uppsala, Waldenström studied organic chemistry in the laboratory of Hans Fischer at the Technische Hochschule in Munich. This led to his classical monograph entitled ''Studien Über Porphyrie'' in which he demonstrated the excessive excretion of uroporphyrinogen III in the urine in patients with acute intermittent porphyria (AIP).[1] AIP is characterized by recurrent episodes of abdominal pain, vomiting, constipation, hypertension, tachycardia, and neurologic involvement including muscle weakness, mental changes, and even seizures. Since this early observation, specific inherited deficiencies of enzymes within the heme synthetic pathway have been delineated that allow improved understanding of classification, pathogenesis, and genetic screening. AIP, for example, is characterized as an autosomal dominant condition resulting from decreased levels of porphobilinogen (PBG) deaminase or hydroxymethylbilane (HMB) synthase.[2]

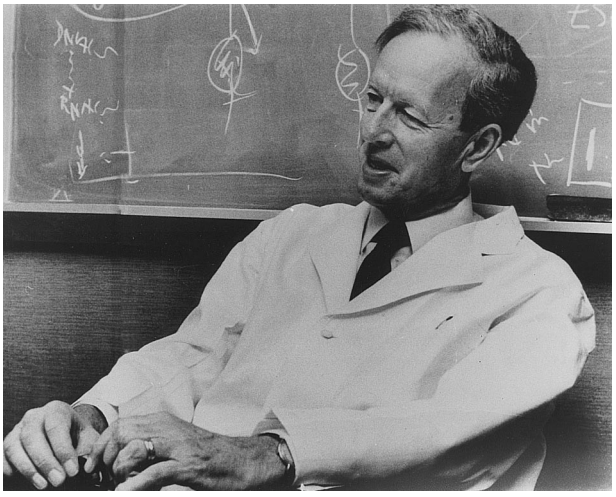

Fig 1. Prof Jan Waldenström at New York Hospital, Cornell University, New York, NY, 1963.

Returning to the University of Uppsala after 1 year in Munich, he studied diseases associated with an elevation of the erythrocyte sedimentation rate (ESR). Waldenström described three patients with an elevated ESR who had hyperproteinemia and petechiae of their lower extremities without evidence of malignancy.[3] Although he coined the term ''purpura hyperglobulinaemica,'' this entity is now recognized as benign hypergammaglobulinemic purpura of Waldenström (BHPW). Subsequent studies have shown that rheumatoid factor was present in all and intermediate complexes ranging from 7 S to 19 S were found on ultracentrifugation.[4] The purpura can be precipitated by increases in hydrostatic pressure. Moreover, we now know that BHPW occurs frequently in autoimmune diseases and rarely with multiple myeloma.

Over the years, Waldenström's clinical insights lead to the recognition of several other disease states. He reported the association of liver cirrhosis and hypergammaglobulinemia, which is now recognized as chronic active hepatitis.[5] He demonstrated frequent iron deficiency in otherwise healthy women[6] and was the first to recognize pulmonary hemosiderosis. Together with colleagues, he noted the skin flushing characteristic of metastatic carcinoid tumors.[7] Importantly, he described an early case of sex-linked hypogammaglobulinemia (Bruton's hypogammaglobulinemia), an area in which rapid progress has recently been achieved. Specifically, the gene for X-linked agammaglobulinemia (XLA) has now been mapped to Xq21.3-q22,[8] and it is hypothesized that the pre-B cells that use the X chromosome with the XLA defective gene fail to develop into mature B cells. Most excitingly, the genetic defect at this locus has been shown to be due to defective gene expression of a B-cell–specific cytoplasmic protein tyrosine kinase, B-cell progenitor kinase, or agammaglobulinemia tyrosine kinase.[9,10]

From the Division of Hematology and Internal Medicine, Mayo Clinic, Rochester, MN; and the Division of Hematologic Malignancies, Dana-Farber Cancer Institute and the Department of Medicine, Harvard Medical School, Boston, MA.

Address reprint requests to Robert A. Kyle, MD, Division of Hematology and Internal Medicine, % Section of Publications, Mayo Clinic, 200 First St, SW, Hilton 920, Rochester, MN 55905.

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Waldenström's multiple contributions to hematology are perhaps overshadowed by his description of macroglobulinemia. In 1944, he described two patients with oronasal bleeding, lymphadenopathy, normochromic anemia, increased ESR, thrombocytopenia, hypoalbuminemia, low serum fibrinogen, and increased numbers of lymphoid cells in the bone marrow.[11] Prolonged bleeding after lymph node biopsy and bone marrow aspiration, lobar pneumonia, and retinal hemorrhages were observed. Importantly, he contrasted this condition with multiple myeloma, because bone pain was not present and bone radiographs were normal. Moreover, excess cells in the bone marrow in these patients were lymphoid, not plasma cells as in his patients with multiple myeloma. In these two patients, he noted the poor quality of the blood and bone marrow smears, presumably from the hyperproteinemia. He modified the Ostwald viscometer and demonstrated a high serum viscosity in both patients. In one patient, the serum gelled at 7°C, indicative of the presence of a cryoglobulin. He noted the euglobulin properties of these proteins, namely precipitation in a solution of low ionic strength. Most importantly, he observed an abnormally large amount of a homogeneous globulin with a sedimentation coefficient of 19 S and 20 S, corresponding to a molecular weight of more than 1,000,000. He postulated that the protein consisted of a giant molecule rather than an aggregation of smaller globulin molecules. His initial description remains to this day characteristic of the clinical presentation and laboratory abnormalities of Waldenström's macroglobulinemia related to excess IgM.[12] Specifically, the oronasal bleeding could have been related to hyperviscosity, observed in 15% of the patients. The bleeding after biopsies could be attributed to IgM interference with platelet function and/or coagulation factors, and the normochromic anemia related to increased plasma volume and reduced erythropoiesis. IgM (type 1) cryoglobulins, which were likely present in one of these original patients, are noted in 15% of the patients with Waldenström's macroglobulinemia. As he hypothesized, the lack of bone disease does distinguish macroglobulinemia from multiple myeloma, because only 2% of the patients with the former and 75% of patients with the latter have manifestations of disease in bone. Finally, phenotypic and functional studies have confirmed Waldenström's morphologic observation that the tumor cells in macroglobulinemia are earlier in B-lineage differentiation than the plasma cell stage in multiple myeloma. Although clinical progress has been slow, recent studies now permit the prognostic classification of affected patients[13,14] and also suggest that fludarabine[15] or 2-chlorodeoxyadenosine (2-CDA)[16] can achieve meaningful responses even in patients who are refractory to other therapies.[17]

Waldenström's most important contribution to medicine was his concept of monoclonal versus polyclonal gammopathies, lucidly presented in the Harvey lecture series in 1961.[18] He described patients with a narrow band of hypergammaglobulinemia as having monoclonal protein. Although many of these patients had multiple myeloma, others had no evidence of malignancy and were described as having ''essential hypergammaglobulinemia'' or benign monoclonal gammopathy. Most physicians now use the term monoclonal gammopathy of undetermined significance (MGUS) because some of these patients will eventually develop multiple myeloma, macroglobulinemia, or a related disorder. However, in our experience, only 24% of the patients observed for a median of 22 years will develop such disorders, whereas the majority of individuals will die of unrelated causes.[19] This highlights the importance of distinguishing patients with MGUS from those with disorders that require therapy. Waldenström further correctly regarded broad band hypergammaglobulinemia as polyclonal protein. This simple distinction is extremely important because patients with a monoclonal gammopathy may either already have or be more likely to develop a neoplastic process, whereas those individuals with polyclonal gammopathy have nonmalignant, primarily inflammatory or reactive causes of their hypergammaglobulinemia.

Jan Gosta Waldenström had a long and distinguished career in academic medicine. He became Professor of Theoretical Medicine at the University of Uppsala in 1947 and 3 years later was appointed Professor of Practical Medicine at the University of Lund and Physician-in-Chief at Malmö General Hospital. He was a member of the National Academy of Science in the United States, the French Academy of Sciences, and was an honorary member of the Royal Society of Medicine, London. He received honorary degrees from the Universities of Oxford, Freiburg, Oslo, Paris, Dublin, Mainz, London, Innsbruck, and Poitiers. Until a hip fracture precluded further travels in 1993, he regularly attended clinical meetings where his comments were uniformly provocative and insightful. He will be sorely missed, but he has left behind a legacy of clinical acumen and dedication to the profession that will serve as an inspiration to future generations of physicians.

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