CURRENT

HEMATOLOGY AND ONCOLOGY

VOLUME 6

Edited by

Virgil F. Fairbanks

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PREFACE

Current Hematology and Oncology, Volume 6, continues our endeavor to place in readers' hands succinct reviews of the most recent and useful information in the fields of hematology and oncology. This volume contains reviews of the recent literature discussing hemolytic anemias (with special reference to paroxysmal nocturnal hemoglobinuria), the continuing explosion of knowledge concerning hemoglobinopathies and thalassemias, the burgeoning literature of cytogenetics in hematology and oncology, and the current literature of myelodysplastic/dysmyelopoietic/preleukemia and myeloproliferative disorders. A chapter on iron addresses important new concepts concerning ferritin and iron overload disorders. We include chapters of special interest about new developments in Gaucher disease and on the effects of biological growth modifiers on neoplasias.

More than 1,200 articles were reviewed by the authors of these eight chapters in preparation of *Current Hematology and Oncology*, Volume 6. Most of these articles were published in the past few years. Thus, we distill the quintessence from the current vintage of the hematology/oncology literature.

Readers who are principally interested in hematologic malignancies will note that no chapters in this volume specifically address lymphomas, leukemias, or plasma cell dyscrasias. Recent literature on these topics was reviewed in *Current Hematology and Oncology*, Volume 5, and new reviews of the hematologic malignancies are being prepared for Volume 7. We believe that most readers will concur that biennial reviews of these topics are an appropriate frequency. However, Chapters 2, 5, 6, and 8 contain important new information concerning various aspects of hematologic malignancies.

I thank the many people who have worked together in the preparation of this volume, particularly the authors of the chapters, their secretaries and ours, the

personnel of Year Book Medical Publishers, Inc., who have completed the preparation of a volume of fine craftsmanship, and the families of editors and authors, for their patience and encouragement.

Virgil F. Fairbanks, M.D.

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CHAPTER 1

Gaucher Disease: New Developments*

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First described over 100 years ago by the French pathologist Phillippe Gaucher, the disease that bears his name is often a devastating burden to the afflicted patient, a frustation to the clinician, and a challenge to the investigator. We and others have nurtured the hope that because of the relative accessibility of the affected tissue, the reticuloendothelial system, this disease may be among the first hereditary abnormalities that will yield to some of the newer biomedical technologies.

Gaucher disease is one of the more common inherited glycolipid storage diseases. The glycolipid that accumulates is glucocerebroside, a normal intermediate in the degradation of globosides and gangliosides, degradation of which occurs largely in cells of the macrophage-monocyte system. Because of this and because glucocerebroside itself is very insoluble, these cells become the primary storage sites, leading to enlargement of the liver and spleen and infiltration of the bone marrow.

There are three types of Gaucher disease. In type I disease, by far the most common, involvement is largely limited to liver, spleen, and marrow. In the much

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more rare types II and III Gaucher disease, there is central nervous system involvement as well.

In this chapter we shall first address some of the clinical and genetic aspects of this disease and then review some of the new understanding of the biochemical pathogenesis of Gaucher disease that has recently emerged.

CLINICAL ASPECTS OF GAUCHER DISEASE

Incidence

Type I Gaucher disease is relatively common among persons of Eastern European Jewish ancestry. Accurate estimates of prevalence are not available. Some patients with the disease are so mildly affected that they do not come to medical attention. Detection of the heterozygous state is not sufficiently accurate to allow for precise calculation of the expected number of births with the disorder. Data that are available suggest that the gene frequency may be approximately 0.027 in the Ashkenazi Jewish population,[1] providing an estimated birth frequency of 1:1400.

The disease is much less prevalent among the non-Jewish population, but in California about one fourth of the patients with Gaucher disease that I see are unaware of any Jewish ancestry.

Genetics

Gaucher disease is an autosomal-recessive disorder. Partial deficiency of glucocerebrosidase can be documented in parents of patients with Gaucher disease and in their children.[2, 3] Heterozygotes manifest no clinical stigmata of the disorder and their marrow contains no Gaucher cells. The frequency of the genes is sufficiently high that it is not entirely unusual to find individuals with Gaucher disease in two and even in three successive generations. Such findings led Groen[4] to suggest that the disease is transmitted in a dominant fashion, but with the advent of biochemical methods that make it possible to identify heterozygotes more detailed investigations of such kindreds have been possible.[3, 5] They show that the apparent dominant transmission is invariably due to mating of heterozygotes with patients with the fully developed disease.

The more common type I Gaucher disease and the more rare neuronopathic type II and type III disease are caused by mutations of the same gene: fusion of cells with two different types of disease does not result in correction of the enzymatic defect.[6, 7] Usually only a single type of Gaucher disease is found in a family, i.e., if one child has type II disease, other affected children in the family will manifest

the same disorder. However, exceptions to this rule have been observed. In one reported kindred,[8] a mother had Gaucher disease that was so mild that it was only biochemically, not clinically, apparent, and was married to a man who was a heterozygote for Gaucher disease. One of their children had type I disease; another, type II disease. It appeared that the mother was a compound heterozygote for two glucocerebrosidase mutations, one of which reacted with the father's mutant gene to cause type I disease and the other type II disease.

Clinical observations have suggested to us that there is considerable genetic heterogeneity even within type I Gaucher disease. The severity of the disease is related inversely to the age of onset, and early onset is more common among non-Jewish patients with Gaucher disease. In a recent study, only four of 13 patients with type I Gaucher disease in whom a diagnosis was established before the age of 10 were Jewish; in the overall series of 45 patients, however, 60% were Jewish.[9] That more severe disease tends to occur in non-Jewish patients with type I Gaucher disease has also been my experience. While other factors cannot be ruled out, it is reasonable to conclude that sporadic mutations involving the glucocerebrosidase gene occurring in the non-Jewish population often have more severe phenotypic effects than the milder form, often observed in the Ashkenazi Jewish population. However, it is necessary to emphasize the marked variability in phenotypic expression even among the Jewish population. What is particularly notable is that there is marked between-family variability in severity in the Jewish population, but in my experience variability in severity of the disease between siblings is relatively small.[10] When Gaucher disease is observed in more than one generation of a Jewish family, there may be a marked difference in severity of disease observed in the parent when compared with that in the child. The child, of course, has received only one of the abnormal alleles from the affected parent, the other abnormal allele being derived from the other (heterozygous) parent. In one such family that we studied, two children were severely affected with Gaucher disease, but a case in a 72-year-old mother was ascertained only because of family studies in which the biochemical defect was discovered.[11]

Such observations are best explained by the existence of more than one "Jewish" Gaucher disease mutation.[10] A reasonable model can be constructed from merely two mutations that would provide three phenotypes, ranging from early-onset, severe form through an intermediate ("compound" heterozygous) to a late-onset, mild form. However, there is no reason that more than two mutations could not exist in this population.

Additional evidence for heterogeneity of the glucocerebrosidase mutation is provided by the use of a recently discovered restriction length polymorphism within or near the glucocerebrosidase gene. Two common genotypes can be identified using the restriction endonuclease Pvu-II. Figure 1 illustrates the restriction pattern observed when the DNA of different individuals is digested with this restriction endonuclease and the fragments containing the coding sequence of a glucocerebrosidase chain are mapped using a labeled probe. As indicated in the figure, we have designated the two genotypes Pv1.1+ and Pv1.1−. Significantly, the inci-

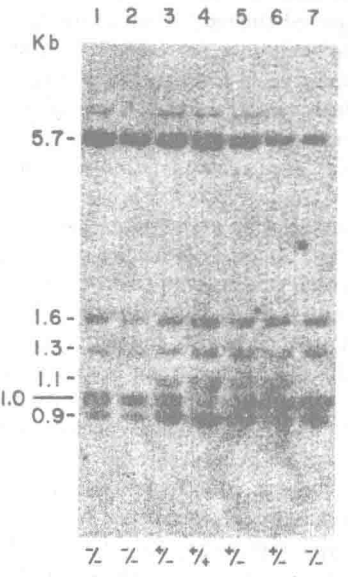

FIG 1.
Southern blots of DNA digested with Pvu II from seven unrelated human subjects. When developed with a glucocerebrosidase cDNA probe, it is apparent that the DNA from some individuals has a 1.1-Kb fragment, which is missing from others. The genotype is given at the bottom of each lane.

dence of this polymorphism seems to be approximately the same in individuals of diverse racial origin. Thus, it is clear that the polymorphism arose early in evolution of humans. In contrast, it is to be presumed that the mutation giving rise to Gaucher disease arose relatively recently. Among Jewish patients genotyped for this restriction polymorphism, 5/8 were found to be heterozygous (Pv1.1+/Pv1.1−) and three were found to be Pv1.1−/Pv1.1−. Thus, Jewish Gaucher disease genes are associated with either of the two restriction length polymorphisms and therefore seem to have arisen quite independently.

Clinical Manifestations

Skeletal

The involvement of bone is the cause of some of the principal clinical manifestations of Gaucher disease. The femur is most often involved,[12] common lesions being osteolysis, sclerosis, and aseptic necrosis with collapse of the femoral head.[13] Involvement of vertebrae and of the humerus is also very common. The orthopedic complications of Gaucher disease have appropriately been classified as: (1) nonspecific bone pain, (2) pseudoosteomyelitis, (3) pyogenic osteomyelitis, (4) joint pain, (5) aseptic necrosis of the femoral head, (6) pathologic fractures,

and (7) spinal malalignment.[13] The mechanism by which Gaucher disease damages bone is not fully understood. Clearly the pathologic findings must be attributed to the infiltration of the medullary space with large numbers of Gaucher cells. Noyes and Smith[14] proposed that pathologic fractures were the result of pressure atrophy of bone and that other damage was due to vascular compromise arising from mechanical obstruction. This, they proposed, led to bone necrosis. However, recent studies[15] utilizing radionuclides were interpreted as indicating that the blood flow to affected regions is increased rather than decreased. Moreover, no obstruction of vascular channels could be seen in biopsied material. A direct effect of Gaucher cells, cells which are of the same cell lineage as osteoclasts, has also been considered. However, histologic material has been interpreted as not showing absorption of bone at Gaucher cell-bone interfaces.[15]

The diagnosis of bone involvement in Gaucher disease is often quite simple. Radiographic changes, including the occurrence of cystic and sclerotic lesions, can readily be appreciated. Radionuclide scans and computed tomography can be useful in evaluating the skeleton of patients.[16] Collapse of the femoral head is not difficult to document. However, one of the most common forms of bone pain in patients with Gaucher disease is not associated with prominent radiologic changes. Such pain, designated by Beighton et al.[13] as "non-specific bone pain," can represent a major problem for these patients, leading, in some cases, to addiction to narcotics.

The management of bone lesions is far from satisfactory, but orthopedic procedures sometimes contribute a great deal to rehabilitation of patients, particularly those with badly damaged hip joints. It is surprising to me that even when the shaft of the femur is fairly extensively involved with Gaucher disease, excellent results are obtained with hip replacement.[12, 17]

Impressive regression of bone lesions has been reported in one patient during treatment with aminohydroxypropylidene biphosphonate, a drug used in Europe for the treatment of Paget's disease.[18] The usefulness of this approach has not yet been verified on additional patients.

Spleen

The spleen is usually severely involved with Gaucher disease, and the thrombocytopenia that commonly occurs is this disease is quite regularly relieved by splenectomy.[19, 20] Yet, there has been considerable controversy and uncertainty about the possible deleterious effects of splenectomy on the course of patients with Gaucher disease.

Once the spleen has been removed, it can no longer serve as a storage site for glucocerebroside, which continues to be formed by the degradation of globosides and gangliosides. It may be presumed that after splenectomy increased amounts of the glycolipid would need to be deposited in other organs, particularly the liver and bone marrow, and it has been suggested that splenectomy is followed by more

rapid progression of bone and liver involvement.[20–23] Since splenectomy is usually performed in an effort to control progressive disease, anecdotal accounts of the worsening of bone lesions following splenectomy could be misleading. Several attempts have been made to resolve the question of whether splenectomy actually causes worsening of bone lesions. In a review of the relationship between bone disease and splenectomy is 239 patients, Lee[37] found that the number of patients who have undergone splenectomy and who do and do not have bone disease is equal. Moreover, the number of patients whose spleen had not been removed when they first developed bone disease exceeded the number who developed bone disease only after the spleen was removed. He concluded that these data supported the concept that bone disease and disease severe enough to require splenectomy were independent. Lee suggested that while bone disease may develop following splenectomy, it probably would have developed whether or not the spleen had been removed. A more recent study[24] drew the opposite conclusion. Eight patients who have undergone splenectomy in the first decade of life were compared with eight patients with disease of similar severity in whom the spleen was not removed until at least the second half of the second decade of life. All patients had early-life onset disease. The measured spleen size in the two groups was essentially equal. The frequency and severity of osteolytic lesions was much greater in the group that had undergone splenectomy in the first decade of life than in the matched controls.

We first introduced partial splenectomy as a treatment for Gaucher's disease in the mid-1970s.[25] Subsequently, other groups have evaluated this approach to Gaucher disease.[26–29] Our rationale for undertaking this procedure was to achieve the beneficial effect of splenectomy on the pancytopenias observed in this disorder while permitting a site of glycolipid accumulation to remain. Others have used this approach to circumvent the lung hazard of fulminating sepsis in patients who undergo splenectomy.[27] The performance of partial splenectomy is not without technical difficulties. Some encouraging results have been reported,[28] however, and the procedure probably deserves further evaluation.

Lung

Pulmonary failure in Gaucher disease is not as rare as the literature on this topic might lead one to believe. It probably exists in two forms. The more common of these may be vascular shunting in the lung, secondary to severe liver disease. I have followed several patients who have been severely incapacitated by this form of respiratory failure. Probably less common, but more frequently reported in the literature, is the direct involvement of the lung by Gaucher disease. By 1977,[30] six cases with direct involvement of the lung had been reported. We are aware of only one additional case that has been reported subsequently.[31] It is not at all clear why extensive accumulation of Gaucher cells occurs in the lungs of such a small subset of patients with apparent non-neuronopathic (type I) disease and it has been suggested that they may represent an additional subtype of the disease.[30] As our

understanding of the molecular biology of this disorder expands, it may become possible to examine this suggestion.

Kidney

Kidney involvement is uncommon in Gaucher disease. Gaucher cells have been found in renal glomeruli, unassociated with renal dysfunction.[31, 32] It is of interest that both reported cases of renal involvement with Gaucher disease were in blacks, a group in which the disease is quite uncommon.

Nervous System

The neurologic involvement that occurs in type II and type III disease has been extensively characterized and will not be discussed here. There are, in addition, a number of reports that imply that neurologic disturbances, particularly seizure disorders, may also occur in type I disease. In none of these cases, however, is it clear that the patient's Gaucher disease actually played a role in the neurologic disorder that was observed. For example, Miller et al.[33] reported that two black siblings with enzymatically proven Gaucher disease manifested abnormalities of mentation and a seizure disorder. Except for the fact that the diffuse neurologic disease observed seemed to be similar to that noted in the juvenile form of Gaucher disease, there was no evidence that the patients' Gaucher disease was related to the neurologic disorder. A Jewish patient with type I Gaucher disease with progressive myoclonic epilepsy was studied by King,[34] but no evidence of a cause-and-effect relationship between the glycolipid storage disease and the seizure disorder was developed. The central nervous system of patients with Gaucher disease may, indeed, be involved histopathologically,[35] without any evidence of neurologic impairment. Occasional Gaucher cells were seen paravascularly in the brain, but no neuronal storage was observed. The amount of glucocerebrosidase accumulating in the brain of such subjects must be quite limited, since lipid analysis failed to disclose the presence of an increased amount of glucocerebroside.[35]

A major unsettled question concerns the occurrence of central nervous system disease in patients with type II and type III Gaucher disease and its apparent absence in type I disease. Only very scant data are available regarding the glucocerebrosidase activity of brain tissue in either of these types of disease. However, brain enzyme activity in the type I patient reported by Soffer et al.[35] and by Glew[36] indicate that glucocerebrosidase deficiency exists in type I as well as in type II disease.

Liver

The liver is always involved in Gaucher disease.[37] The macrophages lining the sinusoids become Gaucher cells. Often, liver involvement is of little clinical con-

sequence to the patient, although abnormalities in biochemical measurement of liver function are the rule.[38] Cirrhosis of the liver is not uncommon, being observed in three of 25 cases in one series,[38] and frank portal hypertension may occur.[39]

Other Organ System Involvement

Anemia and thrombocytopenia are common in patients with Gaucher disease. These changes in the peripheral blood are partly due to bone marrow involvement and partly due to splenic sequestration. The monocytes of patients with Gaucher disease stain positively for tartrate-resistant acid phosphatase, while normal monocytes and monocytes of individuals with monocytosis are negative.[40] The serum of patients with Gaucher disease contains increased levels of acid phosphatase.[41–43] The activity of other acid hydrolases is also increased in the plasma of patients with Gaucher disease,[44] but because acid phosphatase activity is most frequently measured clinically its elevation has been used most frequently for diagnostic purposes. For reasons that are not at all clear the angiotensin-converting enzyme activity of the serum of patients with Gaucher disease is greatly increased.[45, 46]

A variety of clinical abnormalities, not directly related to the main organs of involvement, have been observed in patients with Gaucher disease. It has been suggested that the factor IX deficiency that is often observed in Gaucher disease is an in vitro phenomenon.[47] It is not associated with abnormal bleeding. A patient with decreased factor XI activity has also been described.[48] Although the older literature mentions a number of cutaneous manifestations of Gaucher disease, more recent evaluation of a large number of patients has failed to reveal any characteristic dermatologic stigmata.[49]

Cancer and Gaucher Disease

The incidence of cancer is higher in patients with Gaucher disease than in the general population. In his extensive survey, Lee[37] found 19 cases of malignant tumors among 35 patients with Gaucher disease who died at an average age of 60.

Neoplasms of the lymphoid system seem to be most common. Although disorders of immunoglobulins had been reported only occasionally before 1968, Pratt et al.[50] found that serum samples from ten of 16 patients with known Gaucher disease had immunoglobulin abnormalities. Four of five patients over the age of 60 had monoclonal gammopathies. Although no patients with overt multiple myeloma were found in Pratt's series, Lee[37] encountered three such patients among the 35 who died, and at least three patients with this association have been reported individually.[51–53] Various types of leukemia have also been encountered. Most common seems to be chronic lymphocytic leukemia,[54–58] but chronic gran-

ulocytic leukemia[59] and acute leukemia[60, 61] have also been documented. Hodgkin's disease has also been found in association with Gaucher disease.[62, 63]

The number of patients with benign and with malignant dysfunction of the lymphoid system seems well above the expected frequency, although this has not been verified by careful statistical analysis. A scattering of cases of other malignancies has also been reported. Lee[37] found a variety of tumors, including colon, pancreatic, breast, skin, and larynx. Others have documented the coexistence of Gaucher disease with carcinoma of the breast,[11] dysgerminoma[64] and carcinoma of the sigmoid colon.[54]

Treatment

The treatment of Gaucher disease has been very unsatisfactory. As noted above, measures such as splenectomy and joint replacement may be very beneficial to patients with the disease. Treatment of intercurrent infections, psychologic support, judicious use of analgesics, and maintenance of good nutrition are all helpful, but do not directly affect the disease process.

A number of attempts to treat the disease by organ transplantation have been reported. Both splenic[65] and renal[66] transplantation have been unsuccessful. Replacement of the hematopoietic stem cell, the precursor of the monocyte-macrophage system that is primarily affected in this disorder, can be achieved by bone marrow transplantation. It is of interest in this regard that transplantation of marrow *from* a patient with Gaucher disease *into* one without the disorder caused the disease to appear.[67] Some successful transplants have been documented,[68] but even when regression of the disease did occur, patients have succumbed to the complications of the procedure,[69] and in some instances did not survive long enough for evaluation.[70] The major difficulty in applying this technology to patients with Gaucher disease is that the intrinsic risk of transplantation is very high, even in patients who are in good condition at the time that the procedure is undertaken. Thus, at present one can only justify transplantation of patients with Gaucher disease in those who have very advanced disease; such patients are particularly likely to succumb to complications.

The possibility that enzyme replacement might be useful in the treatment of lysosomal storage diseases was first suggested by de Duve in 1964.[71] With the identification of the enzyme defect in the disorder, it became feasible to purify and infuse glucocerebrosidase into patients with Gaucher disease. This was first done by Brady et al.[72,73] These authors performed liver biopsies before and after infusion of enzyme and concluded that there was a decrease in the amount of stored glycolipid. Because glucocerebroside is very heterogeneously dispersed in the liver of patients with Gaucher disease,[74] it is very difficult to interpret the results of enzyme replacement therapy by this means. We also attempted to treat patients by enzyme infusions, both by injecting purified enzyme directly intrave-