Orthopaedic Manifestations of Gaucher Disease

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Abstract

Gaucher disease is a rare, hereditary disease caused by lack of a lysosomal enzyme. This results in the accumulation of glucocerebroside in the cells of the reticuloendothelial system, including the bone marrow. The orthopaedic manifestations of this disease are important for the orthopaedic surgeon to recognize and understand. Patients with Gaucher disease are at risk for pathologic fracture, abnormal bone remodeling and delayed healing, increased intraoperative bleeding, and infection. Osteomyelitis and avascular necrosis, two common sequelae of the disease, can present in very similar fashions and warrant careful and accurate diagnosis to ensure proper treatment. The impact of Gaucher disease on the musculoskeletal system is reviewed with emphasis on the importance of understanding these effects for the treating orthopaedic surgeon.

Gaucher disease was first reported by French dermatologist, Phillipe Charles Ernest Gaucher, in 1882.1 It is an autosomal recessive disorder resulting in an accumulation of glucocerebroside within cells of the reticuloendothelial system (spleen, liver, and bone marrow) as well as the lymph nodes, tonsils, and thymus.1-3 The aggregation of this substance within the lysosomes of the cells prevents their destruction, and results in their enlargement into “Gaucher cells.”1

Gaucher disease can have a profound impact on the musculoskeletal system. Patients have a decreased rate of new bone production due to impairment of the osteoprogenitor cells of bone. This leads to an alteration in normal bone turnover, which, in turn, can lead to significant osteopenia and risk of pathologic fracture.1,4 Similarly, suppression of osteoclast activity contributes to remodeling difficulties. In Gaucher disease, the classic remodeling defect is the “Erlenmeyer flask,” a deformity of the distal femur (Fig. 1). Patients of all ages can have difficulty with fracture healing.1,5 Chronic vascular insults may lead to osteonecrosis in the proximal and distal femur, proximal tibia, proximal humerus, or in multiple areas.1,6 Increased susceptibility to infection may result in osteomyelitis, septic arthritis, or surgical wound infections.1 This predisposition to infection is particularly important, as osteomyelitis must be differentiated from another feature of Gaucher disease, the painful “bone crisis.”4 Operating surgeons must also recognize the potential for clotting abnormalities and increased bleeding in patients with the disease.1,7 Clinicians must be aware of the possibilities of vertebral collapse, upper limb pain, and foot and ankle complaints.8-10

Pathogenesis

Gaucher disease is an autosomal recessive disorder caused by a mutation on chromosome 1q21.11 This mutation results in a deficiency in glucocerebrosidase, a lysosomal enzyme.3,11 This enzyme typically functions to cleave the glucose residue from ceramide, a by-product of the cell wall destruction that occurs during normal red and white blood cell turnover.1,11 In its absence, glucocerebroside remains intact and accumulates to form the characteristic Gaucher cells of the disease.

There are three recognized forms of Gaucher disease (Table 1). Type 1 is the most common form and is most prevalent in Ashkenazi Jews.1,2 It is a non-neuronopathic form of the disease, which means that its manifestations spare the nervous system. Type 1 Gaucher disease commonly presents with hepatosplenomegaly, anemia, thrombocytopenia, and bone pain or fractures. It may also rarely involve
the cardiopulmonary and renal systems. While type 1 is a chronic disease, patients are expected to have a normal life span. In contrast, type 2 is an acute neuronopathic form of the disease. Severe, progressive neurologic problems predominate the clinical presentation, and death usually occurs by two years of age. There is no ethnic predisposition to this form of the disease. Type 3 is intermediate with the progressive neurologic manifestations starting to appear in the second or third decade. The neurologic problems are far less severe, however, than those seen in type 2 (Table 1).

Orthopaedic Manifestations of Type I Gaucher Disease

The clinical manifestations of type 1 Gaucher disease are variable in magnitude. Many mutations of the glucocerebrosidase enzyme have been identified; however, even siblings and patients with the same mutation may exhibit variable disease severity. Furthermore, the exact nature of the orthopaedic manifestations of the disease is not entirely understood. It is likely the replacement of normal cells by Gaucher cells is a contributing factor; however, the specific mechanism by which this contributes to the pathology seen is not known.

Abnormal Remodeling

A significant number (approximately 80%) of patients with Gaucher disease will develop deformities of the distal femur and proximal tibia. This deformity is caused by a defect in remodeling that is not symptomatic and does not require treatment. The resultant malformation is a classic, typical deformity of the disease and known as the “Erlenmeyer Flask,” due to the remodeling of the normally rounded ends of the bones into a flared, flattened shape (Fig. 1).

Osteopenia

A substantial decrease in bone density and cortical thinning is seen in almost all patients with Gaucher disease. Decreased bone density can be seen in the lumbar spine, femoral neck, trochanter, and distal radius. This is most apparent in patients who have previously undergone splenectomy. The femur is involved more often than the tibia with the epiphyses of the bones usually spared until the disease has advanced through the metaphyses and diaphyses.

Pathologic fractures may occur through compromised bone including femoral neck, thoracolumbar spine, and tibial plateau. Gaucher cell accumulation in bone marrow may cause small areas of bony erosions or large, soft, tumor-like masses, which may also be significant enough to cause pathologic fracture or deformity.

Osteonecrosis

Patients with Gaucher disease are at risk for the development of osteonecrosis, which may present in two forms. The first form, medullary osteonecrosis, is caused by occlusion of

Table 1 Gaucher Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Manifestations</th>
<th>Life Expectancy</th>
<th>Symptoms</th>
<th>Ethnic Predominance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1, Chronic</td>
<td>Bone and hemopoietic</td>
<td>Normal</td>
<td>Bone and joint pain</td>
<td>Ashkenazi Jews</td>
</tr>
<tr>
<td>Type 2, Acute</td>
<td>Neurological bone and hemopoietic</td>
<td>2 years</td>
<td>Progressive neurologic</td>
<td>None</td>
</tr>
<tr>
<td>Type 3, Intermediate</td>
<td>Neurologic, bone and hemopoietic systems</td>
<td>4th and 5th decades</td>
<td>Bone and joint pain, mild neurologic symptoms</td>
<td>None</td>
</tr>
</tbody>
</table>
medullary blood vessels and may be asymptomatic. Subsequent death of the Gaucher cells creates an insoluble calcium soap, which leads to an area of increased medullary density on radiographs. The second form involves corticocancellous structures, with the proximal and distal femur, proximal tibia, and proximal humerus most commonly affected. Risk factors for osteonecrosis in Gaucher disease include male gender, high platelet counts, and osteonecrosis in another location. Additionally, patients who have undergone prior splenectomy have been found to be ten times more likely to have osteonecrosis than patients who have not.

**Osteomyelitis and Bone Crisis**

The acute episode of severe pain that characterizes the bony infarcts seen in Gaucher disease has been called the “Gaucher crisis” because of its similarity to the crisis seen in patients with sickle cell disease. Acute episodes are seen in 10% to 32% of patients, and the clinical presentation is extremely difficult to differentiate from acute osteomyelitis. Patients in an acute crisis may experience localized pain, swelling, and tenderness. They may have systemic signs of infection, including fever, diaphoresis, and tachycardia. Studies, including white blood cell count, erythrocyte sedimentation rate, radiographs, or magnetic resonance imaging (MRI) have not proved useful in differentiating etiologies. It is critical that the distinction be made, however, as osteomyelitis may result from unnecessary surgical drainage or aspiration of a patient in a Gaucher crisis. It is important to recognize osteomyelitis and begin prompt specific treatment to prevent more extensive complications.

A bone scan may be an effective means of differentiating osteomyelitis from a Gaucher crisis. The sensitivity of a bone scan for detecting a Gaucher crisis has been found to be 0.92. In the initial phases of a crisis, the bone scan should show decreased uptake at the involved site. After six weeks, the bone scan may begin to show a ring of increased uptake surrounding an area of decreased uptake. By six months, the bone scan should be normal. Despite the efficacy of bone scans in making this distinction, the diagnosis can still be confusing. Some investigators recommend computed tomography (CT) and MRI as additional sources of information; however, these may also be ambiguous.

**Systemic Manifestations in Type 1 Disease**

Organ enlargement, particularly splenomegaly, is a common feature of the disease. This is related to a vigorous inflammatory response to the enlarged Gaucher cells. The splenomegaly can lead to severe anemia, leukopenia, thrombocytopenia, and life-threatening splenic infarcts. Splenectomy may correct these abnormalities, but otherwise does not improve the course of the disease.

The orthopaedic surgeon must be aware that patients with Gaucher disease have increased susceptibility to infection, and seem particularly predisposed to infection with gram-positive bacteria. This is thought to be due to a decreased ability of macrophage lysosomal enzymes to destroy these organisms. Patients may also exhibit an increased susceptibility to viral infection, and are vulnerable to persistent infection with Epstein-Barr virus.

Another consideration for the orthopaedic surgeon is the association of Gaucher disease with clotting abnormalities. Over 80% of patients with Gaucher disease can have a prolonged prothrombin time. Deficiencies in factor XI are seen most frequently, but abnormalities in factors V, VIII, IX, and XII may also occur. Most of these intrinsic clotting deficiencies are seen in patients who have not had their spleens removed. However, after splenectomy, secondary hepatomegaly with subsequent cirrhosis can contribute further to clotting abnormalities. These can lead to clinically significant increases in operative blood loss. Patients with Gaucher disease were found to lose an average of 1600 ml during routine total hip arthroplasty versus 900 ml in patients without the disease.

Patients may have a benign hypergammaglobulinemia associated with an increased erythrocyte sedimentation rate (ESR). This is important to note, as multiple myeloma is the most frequent neoplasm seen in Gaucher disease. Additionally, the specificity of the ESR in evaluating potential infection may be compromised. Females with Gaucher disease may experience delayed puberty, heavy menstrual bleeding, increased risk of spontaneous abortion, or early postpartum fever and hemorrhage.

**Evaluation of Patients with Gaucher Disease**

Patients with Gaucher disease may present from early childhood to late adulthood. Most cases, however, are seen by the time patients reach adolescence. Patients may complain of easy bruising, chronic fatigue, hepatomegaly, splenomegaly, and bone pain or pathologic fractures. Patients who are diagnosed early (younger than 5 years of age) are frequently not Jewish and typically have a more aggressive disease course. Patients with less severe disease are often diagnosed later in life during evaluations of hematologic or skeletal problems, or may be found to have splenomegaly on routine examination.

Patients with suspected Gaucher disease require a detailed history and complete physical as well as appropriate laboratory evaluations in order to confirm the presence of the disease, define the extent of involvement, and establish a treatment plan. Particular attention should be given to the presence or absence of organomegaly. Family history is relevant and also must be assessed. Once Gaucher disease is suspected, genetic testing with specific identification of the abnormal alleles is indicated to confirm the diagnosis. Bone marrow or liver biopsies, while no longer routinely used to make the diagnosis, would be expected to reveal the presence of Gaucher cells, decreased triglyceride levels, and markedly increased glucocerebrosidase.
and hepatic function tests at baseline and every 12 months in untreated patients. In enzyme-treated patients, these tests should be repeated every three months and at any therapy changes. Imperfectly immunoelectrophoresis, baseline erythrocyte sedimentation rate, angiotension-converting enzyme level, and a complete set of electrolytes should also be examined.

In addition to the standard laboratory studies, other tests can assist in determining and following the extent of bone involvement. These include serum osteocalcin and type I collagen C-terminal telopeptide, both of which have been found to be significantly lower in patients with skeletal involvement.

Initial radiographic evaluation should include plain film radiographs of the chest and CT or MRI of the abdomen to evaluate visceral involvement. Assessment of musculoskeletal involvement should include radiographs of the femora, spine, and symptomatic sites, T1- and T2-weighted MRI of both femora, a technetium-99 bone scan, and bone densitometry. Follow-up radiographic evaluations of skeletal and visceral involvement are suggested every 12 to 24 months in untreated patients, and every 12 months or at therapy changes in patients being treated with enzyme therapy.

T1-weighted MRI is currently the most effective means of evaluating and following skeletal involvement. In addition to detecting bone infarction, avascular necrosis, and pathologic fractures, MRI is helpful in monitoring response to treatment. Bone marrow of a patient with Gaucher disease has a low signal intensity due to a reduction in the fat content of marrow. Enzyme replacement therapy leads to a degradation of Gaucher cell deposits with subsequent reconversion to fatty marrow and production of a high signal intensity on T1-weighted MRI.

Bone marrow fat fraction is another means of evaluating the extent of the disease, as it has been shown to correlate well with disease activity. The fat fraction can be measured using Dixon quantitative chemical shift imaging (Dixon QCSI) or with proton MR spectroscopy. This can be more readily and easily assessed with the vertebra disc ratio (VDR), which examines the ratio between the average T1-weighted gray value of L3 and the L3-L4 intervertebral disc.

Technetium bone scanning is a sensitive technique for determining the presence of bone marrow deposits in Gaucher disease. It has important applications in the differentiation between osteomyelitis and bone crisis. However, it has not proven useful in early identification of patients at risk for skeletal complications of the disease or in monitoring response to enzyme therapy.

**Treatment of Orthopaedic Complications of Type I Gaucher Disease**

**Pathologic Fractures**

Areas of compromised bone due to decreased bone density or osteonecrosis are significant potential sources of pathologic fracture. The management of patients with Gaucher disease and fractures requires special consideration for several reasons. Patients with this disease have delayed fracture healing. In some cases, even in children, healing can take up to two years. Prolonged immobilization and extended periods of non-weightbearing (in some cases up to four months) are necessary to prevent pseudarthrosis or malunion.

Should vertebral compression fractures arise, collapse generally occurs in the thoracolumbar spine and often involves more than one segment. This can be associated with a kyphotic deformity, truncal shortening, and, in some cases, neurologic compromise. Management of kyphotic deformity usually consists of anterior spinal release with fusion and posterior fusion with segmental instrumentation. In cases of neurologic compromise with bone compressing the cord at the apex of the deformity, anterior decompression is required.

When surgical intervention is indicated, a multidisciplinary approach, in which all are alerted to the special needs of the Gaucher patient, is critical. Preoperative optimization with enzyme replacement, autologous blood donation or erythropoietin is essential. Availability of additional blood, platelets, and clotting factors is helpful. The anesthesiologist must be aware of the need to maintain oxygenation to avoid precipitating a bone crisis, and alerted to the potential for increased blood loss due to clotting abnormalities and decreased platelet counts.

The orthopaedic surgeon must be knowledgeable and attentive regarding these issues, and also consider reinforced fixation in potentially compromised bone, increased risk of infection, and potential need to alter standard postoperative thromboembolic prophylaxis due to pre-existing clotting abnormalities.

**Bone Crisis and Osteonecrosis**

Management of bone crisis in the patient with Gaucher disease is largely supportive. Bed rest, analgesics, and non-weightbearing is recommended during the symptomatic stage of the crisis. There is also some evidence that treatment with high dose steroids may be an effective means of decreasing pain during the crisis.

Treatment of subsequent osteonecrosis depends on the location and severity of the disease. In the hip, this includes protected weightbearing, core decompression, bone grafts, or total joint arthroplasty. There is some evidence that children may be effectively treated with bed rest, protected weightbearing, and analgesics during the painful symptomatic stage. Despite radiologic progression of the disease, many of these children remain asymptomatic and are able to perform daily activities. Osteonecrosis of the proximal humerus may cause pain, but less frequently requires surgical intervention.

**Osteomyelitis**

Empiric antibiotic therapy is not recommended in the treatment of osteomyelitis, as patients with Gaucher disease are
prone to infection with unusual organisms. Blood cultures are essential, although these are helpful only if an organism is isolated. While some investigators recommend biopsy to make the diagnosis only in the face of atypical symptoms, others suggest biopsy under strict sterile operating room conditions if any of the diagnostic studies are suggestive of infection. Specific antibiotic therapy can then be directed towards the offending organism.

**Medical Treatment of Type I Gaucher Disease**

Enzyme replacement therapy using recombinant human glucocerebrosidase is the cornerstone of therapy for Gaucher disease. The visceromegaly and hematologic abnormalities usually respond quite well to this treatment within one year. Hepatomegaly has been found to decrease by 30% to 40% and splenomegaly by 50% to 60%. Hemoglobin concentrations and platelet counts can return to normal or nearly normal within 6 to 12 months. The response of the skeletal manifestations of Gaucher disease, however, may respond more slowly and can take up to 4 years to resolve. The major drawback of this treatment has been its cost, which can be $100,000 to $300,000 per year.

Bone marrow transplant has been used in the treatment of Gaucher disease and appears to be effective. The underlying principle is that the transplanted population of normal cells will produce sufficient levels of the enzyme to overcome the deficiency in the affected cells. Difficulties with bone marrow transplant include finding suitable donors and the risk of morbidity to the recipient.

An even newer direction in the treatment of Gaucher disease involves the use of gene therapy. Viral vectors may be used to transfer functional genes into hematopoietic stem cells. Again, the theory is that these repaired stem cells will produce enough enzyme to overcome the deficiencies in compromised cells. While animal studies have been encouraging, a consistent clinical improvement in human patients with the disease has yet to be demonstrated.

**Summary**

The musculoskeletal manifestations of Gaucher disease are important for the orthopaedic surgeon to understand. A previously undiagnosed patient with a mild form of the disease may first present to the surgeon’s office with musculoskeletal complaints, and the orthopaedic surgeon may be called upon to make the diagnosis. Alternatively, a patient with recognized disease may present needing an elective orthopaedic procedure, such as total joint arthroplasty. It is essential that both the systemic and musculoskeletal manifestations of the disease be understood when evaluating and managing these patients. Osteopenia, delayed bone healing, increased propensity for infection, and increased bleeding time must be recognized and accounted for when formulating a treatment plan. This is also important when managing acute complications, such as bone crisis, osteomyelitis, and pathologic fracture. Despite continuing advances in medical therapy, musculoskeletal involvement remains a significant source of difficulty for all of these patients. A thorough understanding of these issues, then, is critical in successfully managing the orthopaedic manifestations of a patient with Gaucher disease.

**References**


