REVIEW

Cytokines in Gaucher disease: Role in the pathogenesis of bone and pulmonary disease

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Abstract Gaucher disease (GD) is the most frequently encountered lysosomal storage disease caused by inborn defects of the membrane-bound lysosomal enzyme, acid β-glucosidase or glucocerebrosidase. This defective activity causes an accumulation of glucocerebroside (glucosyleceramide) in the lysosomes of cells derived from the monocyte/macrophage lineage. Glucocerebroside-engorged cells, termed Gaucher cells, infiltrate various organs, leading to multisystemic abnormalities. The mechanisms by which systemic and organ-specific involvement is propagated or initiated remain unclear. Studies are increasingly recognizing the role of immune dysregulation and inflammation in the pathogenesis of Gaucher disease. Many cytokines have been reported as mediators of tissue damage in Gaucher disease. Bone and lung disease are serious causes of morbidity in non-neuronopathic Gaucher disease. The progress in the understanding of the pathogenesis or relevant mechanism(s) of Gaucher disease is providing insights into additional therapeutic targets, enabling the potential for optimized patient outcomes with the use of adjunctive or supplemental agents.

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Gaucher disease is an autosomal recessive lysosomal storage disorder caused by mutations in the gene encoding acid β-glucosidase (glucocerebrosidase, GCase, EC 3.2.1.45) [1]. Deficient GCase enzymatic activity leads to progressive accumulation of glucocerebroside in the lysosomes of macrophages in various organs. The large macrophages storing glucocerebroside, also called ‘Gaucher cells’, are characterized histologically with a small eccentrically placed nuclei surrounded by a bright cytoplasm with striations or crinkles [2,3].

Macrophages are a heterogeneous group of cells, whose morphology and phenotype differ depending on the tissue/organ and stimuli. They participate in tissue remodeling, host defense, and many disease processes, and can secrete both anti or proinflammatory cytokines [4].

Although an infinite number of potential phenotypes can be suggested, macrophages could be associated with two main types: classical or alternative, depending on the predominant cytokine in the environment, IFN-γ or IL-4/IL-13, respectively. Finally, the stimulus for full activation of classical or alternative macrophages is delivered by a TLR or analogous receptor [5]. Gaucher cells resemble alternative activated macrophages and are characterized by expression of chitotriosidase and CCL18 [6].

The aim of this article is to review the increasingly recognized role of immune dysregulation and inflammation in the pathogenesis of Gaucher disease, with particular emphasis on bone and lung diseases that are serious causes of disease morbidity.

2. Clinical spectrum and types of Gaucher disease

The symptoms associated with GD are due to the progressive accumulation of Gaucher cells in various organs. Thus, GD is a multisystemic disorder with disease manifestation at all ages dependent on the subtype of GD [1].

Three basic clinical forms of GD can be distinguished depending on the degree of neurological involvement; however, recently different forms of GD are considered rather to reflect a continuum ranging from early onset to late onset disease and from severe forms with neurological symptoms to mild forms with solely visceral manifestations [7,8].

GD-1 is the most frequent form and accounts for 94% of all registered GD cases according to the Gaucher Registry [9]. It leads to a chronic course of disease and the organs frequently affected are the spleen, liver, bone marrow and bone and, in severe cases, also the lung and kidney. Hepatosplenomegaly and hematological complications including anemia and thrombocytopenia with bleeding are common in untreated GD-1 [10]. Acute neuronopathic GD (GD-2) manifests in early childhood, neurological deterioration progresses quickly and death generally occurs within the age of 2 years. Subacute neuronopathic GD (GD-3) shows a slower neurological involvement and usually occurs in adolescence, although early onset disease has been reported [1,11,12].

3. Pathophysiology of Gaucher disease

The insufficient catabolism of glucosylceramide [GC] and the engorgement of macrophages by this substrate lead to visceral manifestations of Gaucher disease, but the mechanisms by which systemic and organ-specific involvement are propagated or initiated remain unclear [8,13]. GC has a ceramide backbone with a β-d-glucopyranoside bound at the 1-hydroxyl position. GC is the precursor in the synthesis of 300–400 glycosphingolipids in different mammalian cell types. These include ceramide and its degradation products that regulate cell proliferation, apoptosis, and modulation of cell signaling pathways [14]. These glycosphingolipids also have key roles in diabetes, cancer, kidney, and other common diseases [3]. Disruption of the balance between GC synthesis and degradation in Gaucher disease leads to inflammatory conditions and dysfunctions in different tissues [3,15]. A recent study points to the fundamental role for GBA (glucosidase, β acid) gene in immune regulation, and suggests that GBA mutations in GD may cause widespread immune dysregulation through substrates accumulation [4].

Two major pathophysiological mechanisms that account for macrophage activation have been postulated. Sphingolipids have been implicated in inflammatory and apoptotic processes, and glucosylceramide might have direct activating or enhancing effects on macrophage function [16].

An alternative mechanism by which these proinflammatory and anti-inflammatory pathways could be activated is through abnormal folding of mutant proteins in the endoplasmic reticulum. Such abnormal folding initiates an unfolded protein response that can trigger apoptotic or inflammatory pathways in various tissues [17]. It has been suggested that some mutations in Gaucher disease might lead to proteins that are abnormally folded or maltrafficked [18], however there is no direct evidence of unfolded protein response in Gaucher disease [1,19].
4. Cytokines in Gaucher disease

As indicators of macrophage activation, the levels of interleukin-1β (IL-1β), interleukin-1 receptor antagonist, IL-6, tumor necrosis factor-α (TNF-α), and soluble IL-2 receptor (sIL-2R) are elevated in the serum of Gaucher patients, as are sCD14 and macrophage colony-stimulating factor (MCSF) [20,21]. These changes could potentially explain some of the pathological features, since IL-1β, TNF-α, IL-6 and IL-10 may contribute to osteopenia, IL-1β, TNF-α and IL-6 may contribute to activation of coagulation and hypermetabolism, IL-6 and IL-10 to gammopathies and multiple myeloma [13,21]. Finally, chitotriosidase, a human chitinase produced by activated macrophages, is markedly elevated in Gaucher plasma and is commonly used to examine GD severity and improvement upon treatment [22].

Other cytokines [3] with increased levels in Gaucher disease and possibly implicated in pathophysiology of the disease include IL-8, IL-18, hepatocyte growth factor (HGF), macrophage-inflammatory protein-1 (MIP-1), pulmonary and activation-regulated chemokine (CCL18/PARC), transforming growth factor-beta1 (TGF-β1), chemokine ligand 2 (CCL2), Monocyte chemoattractant protein 1 (MCP1), prostaglandin E2, COX-2 [15].

Pulmonary and activation-regulated chemokine CCL18/PARC has been shown to be a highly specific marker for alternatively activated macrophages and is produced by Gaucher cells [23]. It is constitutively present in human plasma and likely contributes to the physiological homing of lymphocytes and to the generation of primary immune responses [24]. Serum concentrations of CCL18/PARC were found to be correlated reliably with visceral size and hematological parameters, before and during enzyme replacement therapy [25].

A recent murine study [3] suggested a model in which excess GC in antigen presenting cells (APCs), i.e., monocytes (Mφ), and dendritic cells (DCs), and CD4+ T cells, causes their activation and positivity for stimulatory and co-stimulatory molecules (CD40, CD80, CD86, MHCH, CD69, CD40L). These APCs through the CD40 and B7 family molecules and T cells through the CD40L and CD28 molecules interact and trigger enhanced responses of the Th1 and Th17 family cytokines. In addition, with the production of IL17 by the combined activity of APCs and T cells, initial Mφ and DC activation directly triggers a vicious cycle for the release of polymorphonuclear (PMN) attracting chemokines, i.e., KC/CXCL1 and MIP2/CXCL2, which causes the PMN migration into different visceral organs. They concluded that their results highlight the importance of GC accumulation in APC and...
CD4+ T cells in the initiation and propagation of various stimulatory and co-stimulatory molecules as well as enhanced Th1 and Th17 cytokines [3].

Recently, a study in gaucher mice demonstrated elevated levels of the proinflammatory cytokines, IL-1alpha, IL-1beta, IL-6, and TNF-alpha, they were detected in the fetal brains of Gaucher mice. They suggested that accumulated glucocerebroside or glucosylsphingosine, caused by glucocerebrosidase deficiency, may mediate brain inflammation in the Gaucher mouse via the elevation of proinflammatory cytokines [26]. A recent study of the role of neuroinflammation in the pathogenesis of neuronopathic Gaucher disease showed significant changes in levels of inflammatory mediators in the brain of a neuronopathic Gaucher disease mouse model. They suggested that once a critical threshold of glucosylceramide storage is reached in neurons, a signaling cascade is triggered that activates microglia, which in turn releases inflammatory cytokines that amplify the inflammatory response, contributing to neuronal death [27].

5. Cytokines and the bone in Gaucher disease

Bone involvement is a source of significant morbidity among untreated patients with progressive disease and is highly refractory to enzyme replacement therapy [7].

5.1. Spectrum of bone morbidity in Gaucher disease

Among patients with GD, the common manifestations of skeletal involvement include decreased BMD, Erlenmeyer flask deformity, bone cysts and necrosis, increased fracture risk, and, in children, growth retardation [28,29], Figs. 1 and 2. All patients with GD are at risk of bone complications regardless of age of disease onset, the presence and severity of visceral or hematological disease or genotype [30]. Enzyme replacement therapy reduces the episodic frequency of osteonecrosis, and greatly improves the visceral and hematologic manifestations but it cannot reliably restore the bone necrosis nor completely mitigate the risk of infarction crises [6]. The pathological mechanisms of bone alterations in Gaucher disease are still poorly understood and seem to be of complex origin [6,11,31].

5.2. Pathogenesis of bone disease

The pathological cascade starts with the progressive accumulation of glucocerebrosides within the bone marrow cavity leading to a centrifugal expansion of the red bone marrow. The spine, pelvis and the diaphyseal region of the femur and humerus are initially involved. The displacement of inactive yellow marrow by red marrow in the periphery alters vascularity and local pressures possibly leading to thrombosis or infarction by Gaucher cells. Pathologies such as bone crises, avascular necrosis, bone infarcts and localised cortical thinning may be explained in part by these effects [28,29,32]. In addition, accumulation of glucocerebrosides seems to induce macrophage activation which may promote additional inflammatory processes due to the altered expression of different macrophage-derived factors and cytokines [33].

The activity of osteoclasts and osteoblasts is influenced by a variety of hormones including estrogen, testosterone, parathyroid hormone or thyroid hormone. The effects of hormones on the skeleton can be mediated either directly by hormone receptors located on osteoblasts and osteoclasts or indirectly by various other cells of the immune system [11].

Recent work in a murine model of Gaucher disease has demonstrated abnormalities of osteoblast differentiation indicating that bone formation as well as degradation may be affected [7,11], as suggested by bone turnover markers in another study [34].

5.3. Cytokines in the pathogenesis of bone disease

Gaucher disease is associated with release of proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-a), that influence osteoclast and osteoblast activity. In particular, the changes of some cytokines seem to be of relevance to the development of osteoporosis in GD: IL-10 activity may inhibit the osteoblasts activity [35], whereas IL-1β, IL-6 and M-CSF could enhance bone resorption due to increased osteoclast activation and formation [36]. Macrophage inflammatory protein (MIP)-1α and MIP-1β, are elevated in GD, and may mediate increased bone resorption by osteoclasts [37].

CXCL8/IL-8 is reported to be increased 2- to 20-fold in the serum of patients with GD; even after enzyme therapy, being higher in splenectomized patients compared with those with intact spleens [36]. CXCL8/IL-8 is found to be highly expressed in osteoclasts (which originate from macrophage precursors); it stimulates human osteoclastogenesis and bone resorption [31].

In a previous study [31], the serum CCL5/RANTES and monocyte chemoattractant protein 1 (MCP-1) were significantly elevated in GD patients who had osteonecrosis and in the small group of Gaucher patients who had not met therapeutic goals, despite enzyme therapy. CCL5/RANTES and MCP-1 attract and activate monocytes, macrophages and lymphocytes and have been implicated in chronic inflammatory disease. A more recent study [15] described one adult patient with Gaucher disease having the mesenchymal stromal cells from bone marrow with increased expression of CXCL8/IL-8 as well as CCL2/MCP-1.

Studies of CCL18/PARC concentrations in GD found two-fold greater levels in the serum of GD patients who had episodes of bone necrosis [31].

Figure 3 CT chest of a two year old child with type III Gaucher disease (homozygous L444P) showing bilateral interstitial pulmonary infiltrates, with centrilobular and subpleural nodules, interlobular and septal thickening, and prominent pulmonary interstitium [55].
Cathespin K identified as the principal expressed protein of the osteoclast, is highly active in the cleavage of the bone matrix proteins collagen 1 and osteonectin and its role in bone resorption, modeling, and turnover is clearly demonstrated [38]. Cathespin K was reported to be two- to three folds increased in sera from GD-patients as compared to healthy controls, decreasing after ERT. Increased CatK levels may thus be involved in the development of osteoporosis or lytic bone lesions in GD [39].

Normally, the activity of osteoclasts and osteoblasts is regulated by the OPG (osteoprotegerin)/RANK (Receptor Activator of NF-kB)/RANKL (Receptor Activator of NF-kB Ligand) system, which plays a central role in bone metabolism. Interestingly, osteoprotegerin (OPG) levels in GD-patients were comparable to controls [40]. Thus, changes of bone metabolism seem not to be mediated via the OPG/RANKL system [33,40].

Changes in total T-lymphocyte numbers and alterations of CD4+/CD8+ T-lymphocyte ratios may be a further factor, as an overall decrease of T-lymphocytes with lower CD8+ T-lymphocyte numbers has been reported in GD-patients with bone involvement [41]. Mucci et al. (2012) [6] reported that in vitro GCase deficiency, and concomitant glucosylceramide accumulation, generate a state of osteoclastogenesis mediated in part by pro-resorptive cytokines, especially TNF-α; and, T cells are involved in osteoclastogenesis in Gaucher disease chemical model. This cross-talk of immune cell-osteoclast/osteoblast interactions, known as ‘osteoinmunology’, reveals bone metabolism to be a complex network of interacting factors including bone marrow and immune and bone cells [16]. In GD, the complex interactions of cells of the bone marrow with bone, and as two separate compartments closely interacting with each other, may explain some of the changes seen in bone disease with GD [6]. However, the development of different bone pathologies in GD still requires a full explanation, but a complex, multifactorial pathogenesis as pointed out is likely [7].

A study of mesenchymal stromal cells (MSC) obtained from GD patients revealed that, although they have a typical MSC marker phenotype and normal osteocytic and adipocytic differentiation, there was a marked increase in cyclo-oxygenase-2, prostaglandin E2, interleukin-8 and CCL2 production compared with normal controls. These changes suggest a potential role of mesenchymal-derived cells in the genesis of skeletal disease observed in Gaucher disease patients, in addition to the primary macrophage transformation related to lipid storage [15]. Similarly, recent data reported in a chemical model of GD suggest that, in GD, MSCs represent a stem cell population that has altered functions and is likely to be involved in bone pathogenesis [42].

5.4. The impact of therapy on bone manifestations of Gaucher disease

Therapeutic goals in GD include preventing, stabilizing, and reversing the progression of skeletal disease [43]. Accumulated data suggests that earlier treatment initiation decreases skeletal complications and that bone disease may require a longer duration of treatment and higher dose than is necessary for organ involvement and hematopoietic manifestations [1]. When the choices of treatment include multiple enzyme preparations and/or other therapeutic modalities such as small molecules, the decision of therapy should be tailored individually with continuing evaluation [29].

6. Cytokines and the lungs in Gaucher disease

6.1. Spectrum of lung morbidity in Gaucher disease

Lung involvement is not common at presentation of GD and is correlated with severe forms of the disease [44]. Dyspnea, diffuse and/or patchy lung infiltrates, restrictive impairment and low single breath CO diffusing capacity represent the clinical disease profile [45]. Respiratory problems result from infiltration of alveolar, interstitial, perivascular, and peribronchial spaces by lipid-laden macrophages (Gaucher cells) [44]. Patients that are homozygous for 1448G (L444P) mutation may have an additional risk for lung involvement [46].

A large series of type 1 patients noted pulmonary function abnormalities in 68%, but only a fraction of them had overt pulmonary disease [47]. An evaluation of 150 consecutive patients with type 1 Gaucher disease found that less than 5% have evidence of clinical interstitial lung disease (ILD) [48]. In contrast, autopsy reports of almost all patients with type 2 disease reported pulmonary involvement [49].

6.2. Pathogenesis of lung disease

Histopathological features of Gaucher disease are unique in the lungs. Three patterns of pulmonary pathology have been noted: (1) interstitial infiltration by Gaucher cells with fibrosis, as in Fig. 3, (2) alveolar consolidation and filling of alveolar spaces by Gaucher cells, and (3) capillary plugging by Gaucher cells and resultant secondary pulmonary hypertension [50,51]. As a complication of chronic liver disease arteriovenous shunting (hepatopulmonary syndrome) may also be observed [44].

6.3. Cytokines and lung disease

The pulmonary injury in GD may be the result of macrophage activation by the accumulation of the undigested material due to lysosomal enzyme dysfunction and surrounding lung parenchymal damage by proinflammatory cytokines secreted, including IL6, IL10, IL-1β mRNA and TNF-α. These cytokines are increased in relation to disease severity, suggesting an etiological link [52].

6.4. The impact of therapy on lung pathology in Gaucher disease

Enzyme replacement has been shown to be effective for reduction of organomegaly and improvement of hematological parameters, however, pulmonary manifestations display a comparably slower and more heterogeneous response to enzyme treatment [53,54].

7. Conclusions

Although bone disease is common in GD while symptomatic pulmonary involvement is uncommon, both represent a serious morbidity in Gaucher disease, markedly impairing the patient’s quality of life. Cytokines are highly involved in the
pathogenesis of both conditions. The response to enzyme replacement therapy is slow and variable in both bone and pulmonary involvement, so, newer therapeutic options should be offered to these patients. Recognition of the role of cytokines in the pathogenesis of GD bone and lung involvement, suggest the possibility of the future role of adjuvant anti-cytokine therapy to control the disease associated immuno-inflammatory pathology.

Conflicts of interest

The author has no conflicts of interest to declare.

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