Novel Management and Screening Approaches for Haematological Complications of Gaucher’s Disease

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**Purpose:** Gaucher disease (GD) is the most common lysosomal storage disorder. The principal manifestations for its diagnosis and further monitoring include haematological manifestations such as anaemia, thrombocytopenia, spleen enlargement, and bleeding disorders, among others. This review aims to summarise and update the role of haematological complications in GD diagnosis and follow-up, describe their management strategies, and to use these indicators as part of the diagnostic approach.

**Materials and Methods:** A systematic review following the recommendations of PRISMA-P 2020 was carried out. Publications indexed in the databases PubMed, Embase, Science Open, Mendeley, and Web of Science were electronically searched by three independent reviewers, and publications up to June 2021 were accessed. A total of 246 publications were initially listed, of which 129 were included for further review and analysis. Case reports were considered if they were representative of a relevant hematologic complication.

**Results:** From the first review dated in 1974 to the latest publication in 2021, including different populations confirmed that the haematological manifestations such as thrombocytopenia and splenomegaly at diagnosis of GD type 1 are the most frequent features of the disease. The incorporation of haematological parameters to diagnosis strategies increases their cost-effectiveness. Hematologic parameters are part of the scoring system for disease assessment and the evaluation of therapeutic outcomes, providing reliable and accessible data to improve the management of GD. However, cytopaenia, underlying coagulation disorders, and platelet dysfunction need to be addressed, especially during pregnancy or surgery. Long-term haematological complications include the risk of neoplasia and immune impairment, an area of unmet need that is currently under research.

**Conclusion:** Haematological features are key for GD suspicion, diagnosis, and management. Normalization of hematological parameters is achieved with the treatment; however, there are unmet needs such as the underlying inflammatory status and the long-term risk of hematologic neoplasia.

**Keywords:** Gaucher disease, long-term complications, bleeding disorders, haematologic manifestations

**Introduction**
Gaucher disease (GD, OMIM230800) is the most prevalent of the lysosomal storage diseases (LSD). It affects approximately 1 in 40,000–100,000 inhabitants of the general population, but its frequency in Ashkenazi Jews is as high as ~1 in 850.¹⁻⁵ GD is classically described as three types according to neurological involvement. Type 1 GD (non-neuronopathic) is the most common form of presentation.
Type 3 is characterised in turn by three sub-types with different neurological manifestations (epilepsy, ataxia, sac-cadic eye movements, seizures) and other non-neurological features like heart valve infiltration and kyphosis. Type 2 GD is the most severe presentation with acute/subacute neurological impairment early in life (newborns to 1 year old); GD2 patients have a very short lifespan, usually around 2 years of age.3–6

GD is considered the prototype of the LSD, and was the first LSD to have a specific therapy. Among its multi-systemic impairments, it is the LSD with the most implications compromising the haematopoietic system in terms of manifestations at diagnosis, follow-up, and development of complications.1–3

Haematological manifestations are key features for disease suspicion, as cytopenia and spleen enlargement are almost universal in untreated patients. Among the most frequent manifestations at diagnosis, according to International Collaborative Gaucher Group (ICGG) and other registries, are anaemia (29%), thrombocytopenia (62%), splenomegaly (91%), bleeding (20.6%), and bone pain (57.9%).7,8 In our local experience, almost 80% of GD1 cases undergo a bone marrow exam as part of their patient journey for diagnosis, although a bone marrow aspirate is not necessary to make a diagnosis of GD.8

The target cell in this lysosomal disease is a blood cell, the monocyte-macrophage. Monocyte-macrophages originate from the common myeloid progenitor in the bone marrow; they express acid phosphatase, CD68, CD14, and HLA class II. The classical Gaucher cells are macrophages engorged with a PAS+ substrate and a crinkled paper morphology; they can be found in different tissues, but especially in the bone marrow and spleen. Gaucher cells also express CD163, CCL18, and the interleukin-1 receptor antagonist, characteristic of alternatively activated or M2 macrophages. The altered morphology of Gaucher cells is secondary to the defect in the enzymatic activity of the lysosomal hydrolase β-glucocerebrosidase; these cells and mainly all phagocytic cells show an impairment in their multiple functions that leads to multi-systemic repercussions.9,10

The haematopoietic system of an adult person produces more than 400 billion cells daily. With this high turnover, cellular components, especially membrane remnants, are constantly destroyed and phagocytosed by macrophages to be broken down and reused in the manufacture of new cells.9 The accumulation of undegraded phagocytosed material in the cytoplasm of the macrophage due to impaired enzyme function leads to a thickening of the cells, which transform into Gaucher cells and displace the normal cellular network, increasing the size of the spleen and liver (the organs with the highest macrophage content), which also contributes to blood cell sequestration and increased anaemia and/or thrombocytopenia. In the bone marrow, the displacement of haemopoiesis by Gaucher cell accumulation causes anaemia and thrombocytopenia, which often leads to the suspicion of a haematological malignancy. It should be noted that, in several haematological malignancies, macrophages engorged with excess cellular material in the process of destruction are visualised in the bone marrow with a similar appearance to Gaucher cells (they are called pseudo Gaucher cells).11 For that reason, Gaucher cells are not a pathognomonic finding of GD, but usually a finding that leads the diagnostic suspicion.

Other accompanying haematological changes are hyperferritinemia,12,13 polyclonal or monoclonal gammopathy,14 and other immune abnormalities as a decrease in the overall B-cells and an increase in NK and NK/T-cell population in the peripheral blood15 are found with great frequency and contribute to identifying the underlying inflammatory component derived from monocyte-macrophage dysfunction.

Several haemostatic abnormalities have been described in GD, including prolonged prothrombin time (PT) and activated partial thromboplastin time (APTT), indicative of deficiencies in factor X, factor V, and factor XI (more frequent in Ashkenazi Jews). Also have been reported, but with little incidence deficiencies secondary to liver failure and rarely associated with von Willebrand disease.16 Functional platelet defects such as abnormal platelet aggregation or adhesion defects could contribute to bleeding diathesis.17

In this review, a search was performed in the literature, focused on the haematological manifestations and complications with the aim of updating their incidence, describing novel management strategies, and highlighting these strategies as a part of the diagnostic work-up.

Materials and Methods
Systematic Literature Review Objectives
In this study, a systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) guidelines.18
Eligibility Criteria
The inclusion criteria used for the selection of articles were all published original articles or review articles or registry data and guidelines about the diagnosis and follow-up of GD. Reports of single-case studies were considered if they were representative of a relevant hematologic complication.

Search Strategy
PubMed, Embase, Science Open, Mendeley, and Web of Science databases were electronically searched for relevant papers published up to June 2021, without language limitations. English descriptors were adapted according to the database. The following search strategy was entered into the database: (“haematological manifestations” OR “haematological complications” OR “haematological data” OR “screening haematological diagnosis”) AND (“Gaucher disease”).

A secondary manual search of the reference lists of the relevant articles was also carried out. In addition to these database searches, numerous permutations of our search terms (keywords: bone marrow, spleen, cytopaenia, bleeding, B-cell malignancy, gammopathy) were entered into Google Scholar and thoroughly searched for any additional articles not found in the database searches.

Records identified from: PubMed, Embase, Science Open, Mendeley, and Web of Science databases

n=246

Records removed before screening by duplicate or without abstract

n=33

Records screened
n=213

Selected for full review
n=129

General Review n=45
At Diagnosis n=23
Complications n=40
Clinical cases n=21

Records excluded
n=85

Articles that referred only to basic research n=5
Articles that referred only to bone disease n=15
Review articles without reference to hematological data n=42
Case reports n=5
No related to Gaucher Disease n=6
Removed for other reasons n=12

Two independent reviewers developed an Excel database in order to record the studies that met the inclusion criteria, including the abstract, title, date of publication, authors, and journal in order to facilitate the review and selection process.

Results
We reviewed and selected a total of 246 articles, including two online books updated annually. In the first review, the selection was reduced to 213, as shown in the flow chart in Figure 1. We excluded articles that referred only to basic research results without translatability, treatment results referring exclusively to bone disease or analysis of results that did not include haematological alterations or complications, to finally select 129 works that were included in this review.

Haematological Manifestations and Screening Programmes
The reviewed articles, from the first review from 1974 to the latest publication in 2021, included analyses of different populations, all of them with haematological manifestations such as thrombocytopenia and splenomegaly at diagnosis. GD type 1 was the most frequent manifestation of the disease. Anaemia and hepatomegaly were also a constant in the clinical picture. The intensity and variability of these manifestations was very wide due to the
heterogeneity of the disease. Haematological manifestations may present as early as in the first months of life or go unnoticed for decades. Table 1 shows the selected publications in which data on haematological variables are referred to diagnosis in different populations; the majority of the selected articles were reviews.6,19–38

In the last decade, several screening programmes for lysosomal diseases have been developed in different populations using dried blood spots for early detection before symptoms appear. In a New York study, 15 GD cases were diagnosed,39 while none were found in a Mexican study,40 2 GD cases in an Italian study,41 and 5 GD cases in an Illinois study.42 These studies were performed using both enzymatic analysis and multiplexed tandem mass spectrometry.43 In China, using a fluorometric assay, 1 GD case was diagnosed.44 In Taiwan, using mass spectrometry, no cases were diagnosed,45 and in Brazil, using microfluidics, 2 GD cases were identified.46 There is much controversy over the detection of false positives.47 This approach is controversial because the incidence of cases in general population is low (~1/100,000 live births) in different populations and its application is only promoted in those communities with a high incidence of cases, such as in the Ashkenazi Jewish population, where the incidence is 1/850 births. Recently, the use of genetic analysis panels has been explored.48 Active search for patients with subclinical disease by screening for cases with mild to moderate thrombocytopaenia and splenomegaly has provided variable results with generally low identification rates, ie, 4/73,49 55/787,50 7/196,51 and 2/1000.52 Another different approach is the family study, the current recommendation for low-incidence populations includes familial studies after an index case has been identified. In our practice, more than 10% of the GD cases included in the Spanish Registry were diagnosed following this recommendation.53

**GD Biomarkers and Haematological Features**

Biomarkers are useful tools to help in the disease diagnosis and follow-up. GD is the lysosomal disease that has the most validated biomarkers, which offer objective information about the situation of the disease to detect early complications and measure the response to therapy.

Chitotriosidase is an enzyme produced by activated macrophages; its activity correlates with the burden of the disease and is modified with treatment. Therefore, it is a useful tool to monitor the treatment response; however, other systemic inflammatory statuses or acute conditions such as systemic infections or acute GD complications can increase chitotriosidase activity. In addition, about 6% of the Caucasian population has a 24 base pair duplication in homozygosity in the CHIT1 gene encoding the enzyme and lacks chitotriosidase activity.54 The quantification in plasma of the substrate sphingolipid has rapidly become an important biomarker for diagnosis; glucosylsphingosine (Lyso-Gb1) is increased in GD, with rapid reduction after enzymatic therapy because it specifically reflects substrate accumulation in the body. Therefore, some screening studies have already incorporated these two determinations in combination with a minimum clinical haematological feature for suspicion to identify patients affected by GD. A study carried out by Fuller et al confirmed 9 GD patients by increased chitotriosidase activity among 1415 samples.55 Recently, a study by Tang et al determined glucosylsphingosine in dried blood spot (DBS) samples of 142 high-risk patients with splenomegaly and/or thrombocytopaenia and

| Author Year (Reference) | No Cases | Anaemia (%) | Thrombocytopaenia (%) | Hepatomegaly (%) | Splenomegaly (%) |
|-------------------------|----------|-------------|-----------------------|------------------|------------------|
| Medoff and Bayrd 195420 | 29       | 83.0        | 79.0                  | 100              |
| Giraldo P et al 200027  | 155      | 46.0        | 83.5                  | 61.2             | 71.7             |
| Thomas et al 201231     | 45       | 20.0        | 59.0                  | 44.0             | 82.0             |
| Essabar et al 201523    | 11       | 56.0        | 100                   | 100              |
| Mistry et al 201730     | 212      | 46.6        | 81.0                  | 68.0             | 81.0             |
| Weinreb et al 202138    | 310      | 40.6        | 100                   | 40.0             | 90.0             |

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identified 52 GD patients.\textsuperscript{56} Other strategies using algorithms have been tried.\textsuperscript{57–59}

Screening programmes based on haematological indicators or biomarker determinations are shown in Table 2.

### Coagulation Disorders

Bleeding is a frequent manifestation that occurs at different stages of the disease; at diagnosis, it is a symptom usually secondary to thrombocytopenia, but a variety of coagulation factor abnormalities (fibrinogen, factor II, VII, VIII, X, XII), acquired coagulation factor deficiencies including von Willebrand factor (vWF) deficiency and specific inherited coagulation factor deficiencies (factor XI deficiency among Ashkenazi Jews) have been described. In addition, abnormal platelet aggregation and adhesion can be present at diagnosis and may contribute to bleeding diathesis.\textsuperscript{3,16,17,60–69} Table 3 shows the most relevant studies.

It is important to carry out a haemostatic evaluation including platelet count and basic haemostatic tests such as fibrinogen, prothrombin time, activated partial thromboplastin time as well as platelet function tests, especially if the patient is to undergo surgery to compensate for deficiencies.

In special situations, such as pregnancy, these abnormalities are of special importance, requiring the monitoring of haemostatic function and cellular counts to minimise the bleeding risk.\textsuperscript{70–72}

| Author Year (Reference) | Period Study | No Cases Screened | No Cases Identified | Positive Predictive Value (%) | General Prevalence of GD |
|-------------------------|--------------|-------------------|--------------------|-------------------------------|-------------------------|
| Fuller et al 2011\textsuperscript{55} | 2003–2007 | 1415 | 9 |  | Australia (retrospective) |
| Motta et al 2015\textsuperscript{51} | 2010–2013 | 196 | 7 | 18.4 | Italy 1/100,000 |
| Huang et al 2020\textsuperscript{50} | 2016–2019 | 786 | 55 | 37.4 | China 1/80,000 |
| Miyamoto et al 2021\textsuperscript{52} | 2016–2018 | 994 | 12 |  | Japan 1/330,000 |
| Tang et al 2021\textsuperscript{56} |  | 142 | 52 |  | China |

**Table 2 Screening Programmes for Lysosomal Diseases Based on Haematological Data or Biomarkers**

| Author Year (Reference) | No Cases | Decreased Factors | Platelets Dysfunction | Prolongation PT/APPT | Increased D Dimer or Reduction PC/PS |
|-------------------------|----------|-------------------|-----------------------|----------------------|------------------------------------|
| Billett et al 1996\textsuperscript{60} | 9 | II, V, VIII, XI | – | Yes | – |
| Hollak et al 1997\textsuperscript{61} | 30 | II; V; VII; VIII; IX, X, XI, XII | Yes | Yes | Yes |
| Katz et al 1999\textsuperscript{62} | 22 | V, VIII, IX, XI, XII | – | Yes | – |
| Giona et al 2006\textsuperscript{63} | 15 | II, V, VII, VIII, IX, X, XI, XII, vWF | Yes | Yes | – |
| Deghady et al 2006\textsuperscript{64} | 10 | II, V, VII, VIII, IX, X, XI, XII | – | Yes | – |
| Spectre et al 2011\textsuperscript{17} | 48 | – | Yes | – | – |
| Givol et al 2012\textsuperscript{56} | 7 | XI | Yes | No | – |
| Mitrovic et al 2012\textsuperscript{65} | 31 | II, V, VII, VIII, IX, X, XI, XII, vW | Yes | Yes | – |
| Komninaka et al 2020\textsuperscript{67} | 29 | VIII, vWF, ADAMTS13 | Yes | Yes | Yes |

**Table 3 Haemostatic Abnormalities**

**Abbreviations:** PT, prothrombin time; APPT, activated partial thromboplastin time; PC, C protein; PS, S protein; vWF, von Willebrand factor.
Treatment Effect in Haematological Parameters

The goals of treatment focus on three main areas: recovery of hematologic parameters and a reduction in visceral volumes and bone marrow infiltration. Reversal of haematological alterations is one of the main goals of treatment and is achieved in more than 90% of cases with both enzyme replacement therapy and substrate reduction therapy. However, the underlying inflammatory process is not fully reversible with available treatments, and there is speculation about the importance of this situation in the functioning of the immune system and the development of long-term complications of the disease.22

The application of scoring systems and monitoring guides facilitates the traceability of the response and monitoring indicators. Haematological parameters are easily measurable by any specialist.29,73–79 However, there are other haematological alterations that can be observed in the follow-up of patients, such as megaloblastic features of the red blood cells, accompanied or not by folate or vitamin B12 deficiency.80

All the current available therapies have firmly demonstrated an improvement in haematological parameters, and improvement is rapid during the first 6 months, but continues progressively with the majority of patients normalising blood counts in 2–5 years.

Inflammation and Haematological Alterations

The methods to assess the inflammatory status and immunological alterations are not well defined in GD, although there are some determinations that may help to predict immune status and detect haematological complications that may arise in the long term. Hyperferritinaemia and immunologic abnormalities such as polyclonal and monoclonal gammapathy are detected very often both in children and adults.12–15,81 Persistent immune alterations such as changes in T/B-cell populations, polyclonal gammapathy, and the cytokine profile, especially in splenectomised patients, have been related to long-term complications.37,82–84 Also, a general increased incidence of haematological malignancies has been reported in GD patients since the early 1990s.85–87

Hyperferritinaemia and gammapathies also play a role in GD diagnosis, as they may be the reason for consultation with haematology in previously undiagnosed cases.12,13 Isolated cholestasis88 or elevated transaminases and hepatomegaly may be confounding data in the differential diagnosis with other entities.89

Haematological Complications

Long-term complications in GD patients include a high risk of developing haematological malignancies; this risk has been estimated to be between 14.7-fold and 51.1-fold according to data from the International Collaborative Gaucher Group (ICGG) registry.90 There is a predominance of hematologic neoplasms derived from the B lymphoid lineage and linked to the monoclonal hypergammaglobulinemia so frequently detected in these patients.91–98

Nevertheless, there are discrepancies related to the relative risk according to different studies. B-cell and plasma cell malignancies such as multiple myeloma are the most commonly described. The risk of multiple myeloma is 5.9-fold (95% CI 2.8–10.8) according ICGG data.90 In other studies, the relative risk was higher at 25-fold (95% CI 9.17–54.40).91 Table 4 shows the most significant data.

The pathogenesis of these complications has been interpreted as secondary to the chronic immunological disturbances with a predisposition to develop chronic inflammation following chronic B-cell stimulation. An increase in cytokines such as IL-1, IL-6, IL-10, CCL18, and TNF-α has been demonstrated in several experimental studies81,82 as well as the implication of complement factors82 and their relationship with the presence of gammopathies in GD1 patients.99,100 In mouse models of Gaucher’s disease-associated gammapathy, monoclonal immunoglobulin has been shown to be reactive against lyso-glucosylceramide.101,102 The abnormalities in T-cell function could explain the increased incidence of other haematological neoplasias as acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, Hodgkin’s disease, and non-Hodgkin’s lymphoma.103–107 In isolated cases, the diagnosis of GD has been reached through the study of a hematological alteration such as monoclonal gammopathy, suspicion of multiple myeloma due to pathological fracture, or thalassemia suspicion. More than 25 isolated cases of haematological neoplasms have been reported, some of them diagnosed simultaneously with GD.108–111 Most of the cases correspond to B-lineage lymphoid neoplasms, but other sporadic cases of non-neoplastic haematological disorders have been observed112–115 (Table 5). Co-existence of isolated cases of acute myelogenous leukaemia, chronic myelogenous leukaemia, myelodysplastic syndrome, or myeloproliferative neoplasm have also been described.116–123
Undoubtedly, the haematological manifestations at diagnosis of GD type 1, such as thrombocytopaenia and splenomegaly, are key in the diagnosis of the disease. However, the intensity and variability of these manifestations is very wide due to the heterogeneity of the disease and are therefore not specific. In the various screening programmes in which these variables (thrombocytopaenia and splenomegaly) have been used to identify undiagnosed patients, the number of cases detected was low, ie, less than 10% in selected populations and with analyses carried out over long periods of time (between 2 and 4 years).

Newborn screening programmes also have very low success rates for GD, so they do not appear to be cost-effective outside high-risk populations, with too many probands to identify a very small number of subjects, regardless of the used test (enzyme activity by microfluidics or mass spectrometry, combined with biomarkers or mass genetic analysis). Newborn screening programs are also controversial because of the detection of potentially asymptomatic or oligosymptomatic cases or a high number of false positives, which may have ethical repercussions in terms of parental stress, overmedication or others. This type of search is more applicable in populations with a high prevalence of cases or in family studies. Some approaches have also been used to apply models based on algorithms and methods based on a scoring system by Delphi initiatives in children and adults with a predictive value of around 0.80 in a series of already diagnosed patients. It seems more effective to insist on training programmes for specialists, both in paediatrics and among primary care physicians, haematologists, internists, rheumatologists, and undergraduates.

Splenectomised GD patients generally suffer from increased bone and liver deposits and therefore have increased bone complications and increased susceptibility to infection. It is a therapeutic procedure that should be avoided in GD.

Despite the general attention to cytopaenia, we have highlighted the importance of paying attention to the correct assessment of haemostatic parameters. Bleeding is a frequent clinical manifestation in patients with GD and is secondary not only to the thrombocytopaenia that most patients present at diagnosis, but to numerous alterations in coagulation factors, von Willebrand factor, and platelet dysfunction, even with normal platelet counts. It is of special interest to keep these data in mind in risky situations such as pregnancy and delivery, surgical interventions, and dental extractions, and to establish correct preventive measures.

In the follow-up of patients, cell counts are mandatory parameters for periodic assessment, whether the patients are on treatment or not. These are sensitive indicators in the evaluation of the response, but other parameters must also be considered. Vitamin B12 deficiency is present more frequently in patients with GD than in the general population, so in situations of anaemia not resolved by treatment, the morphology of red blood cells must be monitored to rule out

### Table 4: Haematological Complications in GD

| Author Year (Reference) | No Cases | Hyperimmunoglobulin | Haematol Neoplasia | Risk (%) | Others |
|-------------------------|----------|----------------------|--------------------|----------|--------|
| Shiran et al 1993       | 48       | –                    | 5                  | 10.4     | –      |
| Gielchinsky et al 2001  | 89       | –                    | –                  | –        | B12 deficiency (36) |
| Rosenbloom et al 2005   | 2742 (ICGG) | –                  | 10 (MM)            | 5.9      | –      |
| de Fost et al 2005      | 131      | –                    | 5                  | 12.7*    | –      |
| Zimran et al 2005       | 505      | –                    | 8                  | 14.6     | –      |
| Winer et al 2007        | 23 pediatrics | Yes               | –                  | –        | –      |
| Taddei et al 2009       | 403      | –                    | 8                  | 3.45**   | –      |
| Weinreb et al 2013      | 184      | –                    | 8                  | 14.6     | –      |
| Rodic et al 2013        | 27       | Yes                  | 11 (MGUS)          | –        | –      |

Notes: *The relative risk for MM 51.1; **The relative risk for MM 25.0.

Abbreviations: GD1, Type 1 Gaucher disease; ICGG, International Collaborative Gaucher Group; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance.
megaloblastosis, and vitamin B12 and folate levels in the blood must be determined periodically.

Also, in cases with persistent thrombocytopaenia, the association of immune thrombocytopaenia must be ruled out.

Regarding the current concerns about the risk of neoplastic processes, eg, haematological neoplasms, the origin of this association is still under debate. However, the sphingolipid that accumulates most in this disease, ceramide, is involved in the regulation of cellular signal transduction, in cellular oxidative stress, and in cell death. Therefore, the whole cellular regulatory system could be affected, which is a matter of ongoing debate. Moreover, the contribution of the underlying chronic inflammatory state is important in lysosomal diseases, with permanent activation of the immune system as a result of macrophage activation and the secretion of cytokines, causing immune system dysfunction.

The recommendation is to monitor the presence of polyclonal and monoclonal gammopathies in patients by performing an annual proteinogram, quantification of immunoglobulins, ferritin, and C-reactive protein levels, the determination of other parameters such as complement factors and lymphocyte populations may help to understand better the functioning of the immune system, but these tests are expensive and not generally available. Also, there are still not enough data for an appropriate interpretation of their impact or changes with therapy.

Recently, the influence of modifier genes in the appearance of neoplasms in GD has also been considered, but this is probably a casual association as occurs in some patients with BCR/ABL, JAK2, or MSH6 mutations and is due to chance. There is no justification for a systematic panel study of genes related to different neoplasms, except for research purposes.

Conclusion

In this review, an extensive search of the literature was performed. Haematological manifestations are without any doubt a universal feature of GD patients. The variability of their presentation is related to the age of the patient, but mostly with the severity of the disease. Despite the presence of cytopaenia, coagulation complications can also appear in a non-small number of patients and treating physicians need to be aware of it, especially in situations such as pregnancy or surgery. Massive screening strategies are expensive, but programmes that include a minimum of clinical suspicion with haematological parameters are more cost-effective; moreover, awareness strategies among the different medical specialties are a continuous need. There are still unmet needs in the understanding and managing of haematological complications, such as the interpretation and evaluation of the risk for long-term complications or the immune imbalance before and during therapy.

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Table 5 Cases Reported with Co-Existence of GD and Haematological Diseases

| Author Year (Reference) | Haematol Neoplasia | Non-Neoplastic Haematol |
|-------------------------|--------------------|-------------------------|
| Lester et al 1984       | –                  | ITP                     |
| Petrides et al 1998     | CML                | –                       |
| Halioglou et al 1999    | –                  | Budd-Chiari             |
| Webb et al 2011         | Chronic myeloproliferative neoplasia | – |
| Miri-Moghaddam et al 2011 | –                | α-thalassaemia           |
| Ranade et al 2013       | LAL                | –                       |
| Villarrubia et al 2014  | MDS (del5q)        | –                       |
| Kubo et al 2014         | –                  | Epidural haematoma       |
| Noya et al 2018         | CML                | –                       |
| Kose et al 2019         | –                  | Severe neutropaenia      |
| Ruchlemer et al 2020    | MDS & ICUS         | –                       |
| Maity et al 2021        | AML                | –                       |

Abbreviations: GD, Gaucher disease; ITP, immune thrombocytopenia; CML, chronic myeloid leukaemia; LAL, lymphoblastic acute leukaemia; MDS, Myelodysplastic syndrome; ICUS, idiopathic cytopenia of undetermined significance; AML, acute myeloid leukaemia.
Disclosure
Dr Marcio Andrade-Campos report personal fees from Sanofi-Genzyme, personal fees from Takeda-Shire, personal fees from Astra Zeneca, outside the submitted work. The authors report no other conflicts of interest in this work.

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