ORIGINAL ARTICLE

Clinical utility of different bone marrow examination methods in the diagnosis of adults with sporadic Gaucher disease type 1

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KEY WORDS

aspiration biopsy, bone marrow, Gaucher cell, Gaucher disease type 1, trephine biopsy

ABSTRACT

INTRODUCTION In the absence of a known affected family member, frequent symptoms of Gaucher disease (GD), a rare lysosomal storage disorder, such as thrombocytopenia or splenomegaly, often lead to hematological diagnostic workup.

OBJECTIVES The aim of the study was to compare the clinical utility of aspiration biopsy of the bone marrow (ASP) with trephine biopsy (TB) for the diagnosis of GD type 1 (GD1).

PATIENTS AND METHODS Six non-Jewish patients with sporadic GD1 were initially examined with ASP and TB to establish the cause of cytopenia and splenomegaly. In the current study, samples from each patient consisted of 2 bone marrow slides. On each slide, 500 nucleated cells were counted and then averaged. The composition of bone marrow TBs was assessed using digital images analyzed on a computer.

RESULTS Of 6 patients, 5 carried at least 1 N370S allele with a c.1226A>G mutation in the *GBA1* gene. The median number of Gaucher cells identified during cytological assessment of bone marrow smears was 4 (range, 1–18), and the median percentage of Gaucher cells was 0.4% (range, 0.1%–1.8%). The absolute proportion of Gaucher cells in histological samples ranged from 22% to 36% (median value, 28%), and the ratio of Gaucher cell infiltrate to hematopoietic tissue ranged from 34% to 54% (median value, 47%). The median value of the ratio of Gaucher cells to hematopoietic tissue was strikingly lower when using ASP compared with TB ($P = 0.028$).

CONCLUSIONS Our results indicate that ASP is not a reliable diagnostic tool for the detection of GD1. Thus, patients with unclear long-lasting splenomegaly and/or thrombocytopenia, in whom bone marrow aspirate cytology is negative for Gaucher cells, should be routinely referred for an enzymatic assay for GD.

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INTRODUCTION Gaucher disease (GD) is a progressive, multisystem lysosomal storage disorder caused by the deficient activity of the lysosomal enzyme, glucocerebrosidase, resulting from autosomal recessive mutations in the *GBA1* gene (1q21).[1,2] Common symptoms of GD type 1 (GD1), such as thrombocytopenia, anemia, or splenomegaly, often lead to hematological diagnostic workup.[1-5] As part of such workup, routine diagnostic procedures include aspiration biopsy of bone marrow (ASP) and trephine biopsy (TB), for the cytological assessment of bone marrow smears (BM-S) and histological evaluation of bone marrow TBs (BM-TB), respectively.[4,5]

The lipid-laden macrophages, referred to as storage or Gaucher cells, are the pathological hallmark of GD.[3,5,6] These large cells of 20 to 100 μm in diameter with small, usually eccentrically placed nuclei, have slightly basophilic cytoplasm with characteristic crinkles or striations described as having a "wrinkled tissue paper" appearance.[6] Gaucher cell infiltrates can be found in organs and

TABLE 1 Characteristics of patients with Gaucher disease type 1

Pt	Sex/age	*GBA1* gene mutations (mutated alleles)	Age at symptom onset, y	SMG	SPC (age, y)	Bone disease	GBA	Chito
1	F/21	c.798C>G/c.1040T>G (F227L/I308S)	3	NA	5	yes (B)	0.49	9743
2	F/56	c.1226A>G/c.1226A>G (N370S /N370S)	55	yes	no	yes (A)	0.43	1549
3	M/65	c.1226A>G/RecNci c.1448T>C, c.1483G>C, c.1497G>C (N370S /L444P, A456P and V460V)	51	yes	no	yes (A)	0.1	1322
4	M/66	c.721G>A/c.1226A>G (G202R/N370S)	61	yes	no	yes (B)	0.41	2448
5	M/81	c.1226A>G/c.1448T>C (N370S /L444P)	30	NA	32	yes (A)	0.59	2170
6	M/84	c.1226A>G/c.1448T>C (N370S /L444P)	20	NA	22	yes (B)	0.32	2804

Abbreviations: A – radiological signs only, B – symptomatic bone disease, F – female, GBA – activity of glucocerebrosidase in peripheral blood leukocytes (reference range: 2.1–3.8 μkat/kg protein), Chito – activity of plasma chitotriosidase (reference range: <40 nkat/l), NA – not applicable, M – male, Pt – patient, SMG – splenomegaly, SPC – splenectomy

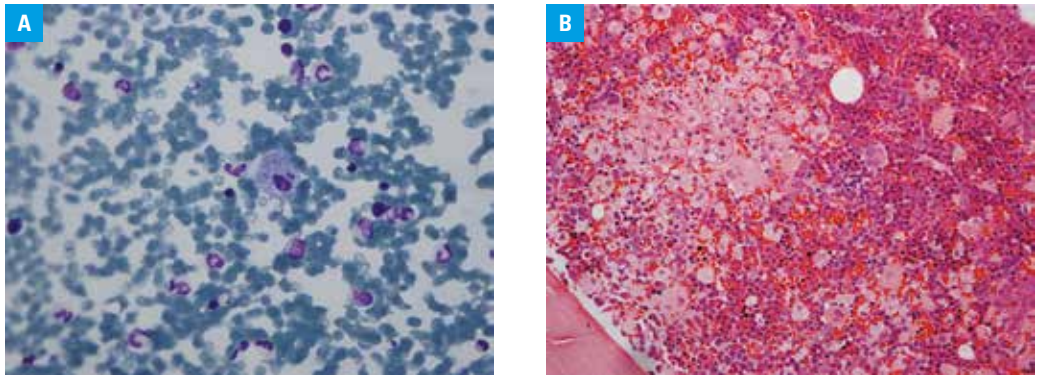

FIGURE Gaucher disease type 1: cytological (**A**) and histological (**B**) images of bone marrow samples obtained by aspiration biopsy of the bone marrow and trephine biopsy; **A** – presence of cells from 2 hematopoietic series, including a centrally placed histiocyte with Gaucher cell morphology (May–Grünwald–Giemsa stain; magnification, ×400); **B** – hypercellular bone marrow with all hematopoietic series present, including prominent histiocytic infiltrates composed of Gaucher cells (hematoxylin and eosin stain; magnification, ×200)

tissues rich in cells of the mononuclear phagocyte system, such as the spleen, liver, and, in particular, the bone marrow.

The results of ASP and/or TB examinations often give the first clue towards GD diagnosis in non-Jewish patients who do not have any previously known GD1-affected family members (ie, sporadic GD1), since they disclose the presence of macrophages having a Gaucher cell appearance.[2,4,5] However, because there are virtually no published studies comparing ASP and TB in the diagnostic workup of GD, little is known about the utility of these 2 methods in the assessment of bone marrow involvement in GD.

The aim of our study was to compare the results of cytological and histological analyses of BM-S and BM-TB, obtained by means of ASP and TB, in adult non-Jewish patients with newly diagnosed GD1.

PATIENTS AND METHODS

There are currently 35 patients diagnosed with GD1 in Sweden.[7] Between 2002 and 2013, 16 adults with GD1 were followed at the Karolinska University Hospital in Stockholm. Of these, 6 non-Jewish patients (2 women and 4 men) with sporadic GD1 who initially underwent diagnostic ASP and TB as part of the evaluation for cytopenia accompanied by splenomegaly were included in this analysis.

Bone marrow samples were collected under local anesthesia from an entry site on the posterior iliac crest of patients in the prone position. The samples were stained with May–Grünwald–Giemsa (BM-S) or hematoxylin and eosin (BM-TB) stains according to routine methods. Stored bone marrow samples were reassessed by a hematopathologist for study purposes.

Differential counts of BM-S were made under ×400 magnification using an Olympus BX 40 microscope. Samples from each patient consisted of 2 slides. On each slide, 500 nucleated cells were counted and then averaged. An assessment of the composition of BM-TB, ie, a relative proportion of the hematopoietic tissue, Gaucher cells, fat tissue, and trabecular bone, was carried out using digital images and the GNU Image Manipulation Program (GIMP2) (freeware available at www.gimp.org).

TABLE 2 Cytological composition of bone marrow smears obtained by aspiration biopsy in patients with Gaucher disease type 1

Pt	Differential count of 1000 nucleated hematopoietic cells calculated in 2 bone marrow smears (2 × 500 cells)											Total
	ErP	Bl	maturing myeloid cells					Mono	Lym	Plasm	Mgk	GCs	
			Pml	My	Neu	Eos	Bas						
1	260	5	9	94	313	12	2	25	279	0	0	1	1000
2	335	15	22	53	428	7	3	71	62	1	0	3	1000
3	154	10	8	35	469	21	11	71	214	0	1	6	1000
4	259	9	17	124	401	32	1	28	114	0	0	15	1000
5	173	8	12	7	560	7	4	62	124	40	0	3	1000
6	355	8	22	71	300	12	0	83	121	10	0	18	1000

Reference values (per 1000 nucleated bone marrow cells) according to Sundström and Öst (1985): erythroblasts, 80–400; myeloblasts, 3–50; promyelocytes, 10–80; myelocytes and metamyelocytes, 106–365; band granulocytes, 50–140; neutrophilic granulocytes, 70–300; eosinophilic granulocytes, 5–40; basophilic granulocytes, 0–7; monocytes, 5–50; lymphocytes, 30–170; plasma cells, 0–20; megakaryocytes, 3–30

Abbreviations: Bas – basophilic granulocytes, Bl – blasts (including myeloblasts, monoblasts, and lymphoblasts), Eos – eosinophilic granulocytes, ErP – erythrocytic precursors, GCs – Gaucher cells, Lym – lymphocytes, Mgk – megakaryocytes, Mono – monocytes, My – myelocytes and metamyelocytes, Neu – neutrophilic granulocytes, Plasm – plasma cells, Pml – promyelocytes, others – see **TABLE 1**

TABLE 3 Histological composition of bone marrow in trephine biopsies in patients with Gaucher disease type 1

Pt	Histological composition of the bone marrow, %				
	HT	GCs	fat tissue	trabecular bone	proportion of GCs to HT
1	39	32	6	23	45
2	46	24	18	12	34
3	38	36	15	11	49
4	31	22	34	13	41
5	29	29	19	23	50
6	23	27	43	7	54

Abbreviations: HT – hematopoietic tissue, others – see **TABLE 2**

TABLE 4 Mean reference values in healthy individuals, according to Burkhardt et al.[9]

Age group, y	Hematopoietic tissue	Fatty tissue	Trabecular bone
20–39	47.5%	27.9%	21.4%
40–59	43.1%;	33.8%	20.5%
60–99	43.8%	37.7%	15.3%

Reference values for the proportion of hematopoietic tissue to fat tissue according to Sundström and Öst[8]: 25%–75% in adults; about 40% in the age group of 30–70 years. The hematopoietic tissue fraction decreases slightly after the age of 70 years.

Digital imaging of BM-S and BM-TB was carried out using the Nikon DX m 1200F digital camera mounted on the Nikon Eclipse E1000 microscope with a ×40 objective for the BM-S and ×2 respective ×20 objectives for the BM-TB.

In all patients, the diagnosis of GD was confirmed by low glucocerebrosidase activity in peripheral blood leukocytes. All patients also demonstrated increased plasma chitotriosidase activity (**TABLE 1**). The activity of both enzymes was assessed by a reference laboratory according to standard practice.[5,7] Next, direct DNA sequencing performed at the Academic Medical Center in Amsterdam, Netherlands, revealed mutations in the *GBA1* gene in all cases. The patients' medical records were reviewed to collect relevant clinical data.

The reference values for cytological and histological composition of bone marrow samples in healthy individuals were obtained from the studies of Burkhardt et al.[8] and Sundström and Öst.[9]

The nonparametric Wilcoxon signed-rank test was used to evaluate statistically significant differences between the results of ASP and TB examinations for the detection of Gaucher cells (the relatively small sample analyzed could not be assumed to be normally distributed). The *P* value was 2-tailed and calculated using Stata 9.2 (StataCorp LP, College Station, TX, USA). A *P* value of less than 0.05 was considered statistically significant.

The study protocol was developed according to the ethical standards of the Declaration of Helsinki and approved by the local ethics committee in Stockholm. All patients provided their informed consent to participate in the study.

RESULTS The median age of the patients was 65 years (range, 21–84 years). Three patients (50%) had undergone splenectomy. All but 1 patient (83%) carried at least 1 N370S allele with the c.1226A>G mutation in the *GBA1* gene. Patient characteristics are presented in **TABLE 1**.

Examples of cytological and histological images of bone marrow samples, obtained by ASP and TB from one of the patients, are shown in the **FIGURE**.

The results of cytological analyses of BM-S including identified Gaucher cells are presented in **TABLE 2**. The median number of Gaucher cells identified in the studied patients was 4 (range 1–18), and the median percentage of Gaucher cells among all nucleated bone marrow cells was 0.4% (range, 0.1%–1.8%).

The proportions of hematopoietic tissue, Gaucher cells, fat tissue, and trabecular bone in BM-TB from the patients are presented in **TABLES 3** and **4**. The Gaucher cell burden in BM-TB ranged from 22% to 36% (median value, 28%) and the ratio of Gaucher cells to hematopoietic tissue ranged from 34% to 54% (median value, 47%). The ratio of Gaucher cells to hematopoietic tissue in ASP

was strikingly lower than that in TB samples. Similar results were observed in all patients studied and the difference between the 2 diagnostic modalities in the whole group was statistically significant (Wilcoxon signed-rank test: $P = 0.028$).

DISCUSSION The diagnosis of inherited metabolic disorders, including GD, may be difficult and prolonged. Thrombocytopenia, anemia, splenomegaly, hepatomegaly, and bone manifestations are the most typical signs of the most prevalent form of GD, GD1.[1-5,10] The presence of central nervous system disease, in addition to the above symptoms, is a hallmark of GD type 2 and type 3.[11]

GD is well known for its striking phenotypic diversity, which can complicate diagnosis.[10-13] Although according to the European Union definition, GD belongs to so called rare diseases (ie, affecting less than 1 persons/2000 inhabitants),[14] the diagnosis of GD1 should be considered in any patient who presents with a long clinical history of splenomegaly and thrombocytopenia, in children with acute or chronic bone pain, growth retardation, and in individuals with nontraumatic avascular necrosis of a large joint at any age.[1,10]

In patients of Ashkenazi Jewish ancestry, the frequency of GD is 1 in 800, while hematologic malignancies are much less frequent (1 in 2500 people).[15] Owing to such a high prevalence of GD among Jewish patients, enzyme assays (ie, glucocerebrosidase activity in peripheral blood leukocytes as well as plasma chitotriosidase activity and/or CCL18/PARC concentration) aimed at GD diagnosis should precede bone marrow examination, unless there is a strong reason to suspect another cause of splenomegaly and thrombocytopenia.[1,2,15]

In the non-Ashkenazi populations, GD is markedly less frequent (1 in 40,000–200,000 people) than hematologic malignancies.[1] In milder forms of GD1, when the clinical picture is scant, and in the absence of any known affected family member, GD remains a diagnostic challenge. It is often not included in the differential diagnosis of thrombocytopenia even by experienced hematologists.[16] However, sooner or later, the presence of the most frequent initial GD1 symptoms, splenomegaly and/or thrombocytopenia, leads to hematological diagnostic workup.[4,5,17,18] In such cases, routine diagnostic procedures include ASP for the cytological assessment of BM-S and TB for the histological evaluation of BM-TB. In many non-Jewish patients with sporadic GD1, the results of bone marrow examinations provide the first clue to diagnosis.

Historically, the diagnosis of GD was usually based on a morphological examination of bone marrow specimens, liver biopsy, or a surgically removed spleen.[5,15] Until 1966, when pseudo-Gaucher cells had been described for the first time in chronic myeloid leukemia, it was believed that the presence of Gaucher cells in the bone marrow was pathognomonic of GD.[19] Later, pseudo-Gaucher cells were also reported in many other diseases, including malignancies, chronic inflammatory disorders, and AIDS. These patients have normal ability to catabolize glucocerebroside but rapid cell turnover causes functional overload of the hydrolyzing enzyme, which leads to formation of pseudo-Gaucher cells.

The absence of Gaucher cells in bone marrow specimens obtained by means of ASP from GD1 patients diagnosed by enzymatic assays has also been reported.[20] However, this finding was not studied further owing to changed diagnostic practices for GD among Jewish patients, which shifted towards the enzymatic and genetic methods. Currently, if GD is suspected based on morphological findings, such as the presence of Gaucher cells in tissue specimens, the gold standard diagnosis requires confirmation by appropriate enzymatic and genetic assays.[1-5,15]

The choice of the bone marrow examination method is often random, influenced by many different factors related both to the patient (eg, concomitant symptoms, comorbidities, local conditions at the examination site, etc) and the physician (eg, local routines, personal experience, etc). TB has been introduced into routine hematological diagnostic workup relatively recently in many countries (approximately the last 20 years), at the time when bone marrow examination was no longer recommended for the sole purpose of GD diagnosis.[21]

The results of the present study indicate a low sensitivity of ASP in detecting Gaucher cells in the bone marrow. Most analyzed patients (4 of 6) had 6 or fewer Gaucher cells among 1000 counted nucleated hematopoietic cells. Of note, routine differential count in BM-S usually includes only 200 nucleated hematopoietic cells. Thus, there is a serious risk of overlooking GD in some patients when using only ASP, and we conclude that ASP is not a reliable diagnostic tool for GD1.

Gaucher cells are often tightly packed in the affected areas of the bone marrow tissue and therefore difficult to aspirate by ASP, which may explain our findings. Additional problems with aspiration of Gaucher cells can result from increased density of reticulin fibers in the bone marrow. The sensitivity of TB for detection of Gaucher cells in the bone marrow is much higher, and the observed detected Gaucher cell burden in the present study was approximately 100-fold higher compared with cytological specimens obtained by ASP. Although histological findings are reliable in the diagnosis of GD1, TB is a more advanced procedure than ASP, and it should be performed by an experienced physician.

When an ASP sample is negative for Gaucher cells (false-negative ASP result) and an enzyme assay for GD is not performed, there is a serious threat that the diagnosis of GD1 may be postponed for many years.[16] Therefore, proper interpretation and recognition of the limitations of ASP results are crucial in avoiding diagnostic delays in patients affected with this treatable condition.

The introduction of enzyme replacement therapy (ERT) for the treatment of GD1 has resulted in a dramatic improvement in the prognosis of the affected patients.[1,22] ERT has the potential to positively affect all domains of GD1 (ie, hematological, visceral, and skeletal).[23,24] Since 1991, GD has become a model for the development of ERT in other lysosomal storage disorders.[25,26]

Conclusions Common initial symptoms of GD1, such as thrombocytopenia or splenomegaly, often result in patient referral to a hematologist for diagnostic workup. To obtain a reliable diagnosis of GD, cytohistological examinations are neither necessary nor sufficient. The gold standard for a definitive diagnosis of GD requires confirmation of reduced enzymatic activity of glucocerebrosidase in leukocytes, cultured fibroblasts, or amniocytes obtained during prenatal diagnosis.[27] Therefore, enzymatic assays should be applied in suspected cases. Measurement of glucocerebrosidase is supplemented by the *GBA1* mutation analysis.[1-3]

However, since GD is a very rare condition and its clinical manifestation may mimic lymphoma or other hematological diseases, bone marrow or liver biopsy is usually performed before the diagnosis of GD is considered, especially in the absence of known affected family members.

To the best of our knowledge, this is the first report comparing clinical utility of ASP with that of TB in the diagnosis of sporadic cases of GD. The results indicate that ASP is not a reliable diagnostic tool for detecting Gaucher cells. Therefore, patients with unclear long-lasting splenomegaly and/or thrombocytopenia and in whom cytological assessment of BM-S provides negative results, should proceed routinely to enzymatic assays for GD.

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Contribution statement MM conceived the idea for the study. MK and AM-K contributed to the design of the research. All authors were involved in data collection. SR and AM-K analyzed the data. MM coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Wartość kliniczna zastosowania różnych metod badania szpiku kostnego w diagnostyce osób dorosłych ze sporadyczną chorobą Gauchera typu 1

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SŁOWA KLUCZOWE

biopsja aspiracyjna, choroba Gauchera typu 1, komórka Gauchera, szpik kostny, trepanobiopsja

STRESZCZENIE

WPROWADZENIE W przypadku niestwierdzenia zachorowania w rodzinie, częste objawy choroby Gauchera (*Gaucher disease* – GD), rzadkiej lizosomalnej choroby spichrzeniowej, takie jak małopłytkowość lub splenomegalia, często prowadzą do wdrożenia diagnostyki hematologicznej.

CELE Celem badania było porównanie użyteczności klinicznej biopsji aspiracyjnej szpiku kostnego (*aspiration biopsy* – ASP) z trepanobiopsją (*trephine biopsy* – TB) w rozpoznawaniu GD typu 1 (GD1).

PACJENCI I METODY Sześciu pacjentów ze sporadyczną GD1 i niebędących pochodzenia żydowskiego, zbadano początkowo przy użyciu rutynowej ASP i TB w celu ustalenia przyczyny małopłytkowości i powiększenia śledziony. W ramach obecnego badania, analizowany materiał od każdego pacjenta składał się z 2 szkiełek z rozmazami szpiku kostnego, gdzie na każdym z nich oceniano 500 komórek jądrzastych, a następnie liczono średnią. Ocenę składu szpiku kostnego uzyskanego metodą TB przeprowadzono komputerowo, analizując obrazy cyfrowe szpiku.

WYNIKI U większości pacjentów (5/6) stwierdzono obecność co najmniej jednego allelu N370S z mutacją c.1226A>G w genie *GBA1*. Średnia liczba komórek Gauchera zidentyfikowanych podczas oceny cytologicznej rozmazów szpiku kostnego wyniosła 4 (zakres 1–18), a średni odsetek komórek Gauchera wyniósł 0,4% (zakres 0,1–1,8%). Całkowity odsetek komórek Gauchera stwierdzanych w preparatach histologicznych wahał się od 22% do 36% (mediana 28%), a stosunek nacieków z komórek Gauchera do tkanki krwiotwórczej mieścił się w zakresie 34–54% (mediana 47%). Wartość mediany stwierdzanego odsetka komórek Gauchera w stosunku do tkanki krwiotwórczej była wyraźnie mniejsza przy użyciu do badania szpiku kostnego ASP w porównaniu z TB ($p = 0,028$).

WNIOSKI Uzyskane wyniki wskazują, że ASP nie jest dostatecznie wiarygodną metodą diagnostyczną wykrywania GD1. Dlatego pacjentów z niejasnym długotrwałym powiększeniem śledziony i/lub małopłytkowością, u których wynik badania cytologicznego na obecność komórek Gauchera materiału uzyskanego za pomocą ASP jest ujemny, powinno się rutynowo kierować do diagnostyki enzymatycznej choroby Gauchera.

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