Refractory wound healing and cytopenias treated with a sodium-glucose cotransporter-2 inhibitor in a patient with glucose-6-phosphatase catalytic subunit 3 deficiency

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INTRODUCTION

Glucose-6-phosphatase catalytic subunit 3 (G6PC3) deficiency, a rare inborn error of immunity leading to impaired hydrolysis of glucose-6 phosphate (G6P), which is the last step of the gluconeogenic and glycogenolytic pathways. Patients present with a variable complex syndrome including cytopenias and severe congenital neutropenia leading to recurrent infections.[1]

It is now well established that neutropenia found in G6PC3 deficiency is due to a cellular detoxification defect caused by the accumulation of 1,5-anhydroglucitol-6 phosphate (1,5-AG6P).[2] Indeed, neutrophils express enzymes that phosphorylate glucose (hexokinases and adenosine diphosphate-glucokinase), allowing the formation of G6P. However, these enzymes also convert 1,5-anhydroglucitol, a blood polyol structurally similar to glucose, into 1,5-AG6P, which inhibits hexokinase and reduces G6P formation. The decrease in G6P production leads to a cellular energy deficit and induces apoptosis,[3] which accounts for the neutropenia. The role of G6PC3 is to dephosphorylate 1,5-AG6P into 1,5-anhydroglucitol, thereby detoxifying the neutrophil and ensuring the production of G6P necessary for cellular metabolism. In patients with G6PC3 deficiency, the accumulation of 1,5-AG6P has been shown to be reduced using an sodium-glucose cotransporter-2 (SGLT2) inhibitor, which has been demonstrated to be effective in treating neutropenia.[4,5] The SGLT2 inhibitor, a transporter in the proximal renal tubule, increases the excretion of blood 1,5-anhydroglucitol, thereby reducing the availability of this substrate to form 1,5-AG6P in the neutrophil. Preserving hexokinase function allows for maintaining adequate cellular metabolism and functions in addition to correcting neutropenia.[6]

We present the case of a 30-year-old woman with severe congenital neutropenia due to G6PC3 deficiency with persistent, nonresponsive wound for 5 years. Because tissue repair partially depends on granulocyte function, we aimed to observe the effect

Abbreviations used:

1,5-AG6P:	1,5-anhydroglucitol-6 phosphate
G6P:	glucose-6 phosphate
G6PC3:	glucose-6-phosphatase catalytic subunit 3
GSD:	glycogen storage disease
PG:	pyoderma gangrenosum
SGLT2:	sodium-glucose cotransporter-2

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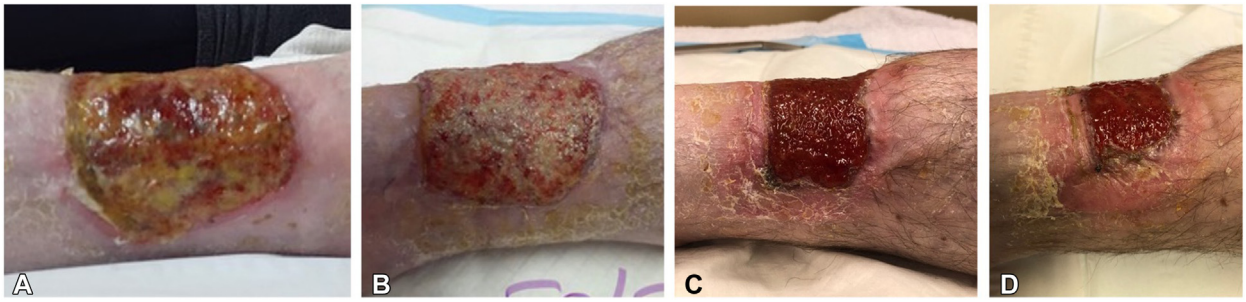

Fig 1. Course of wound healing at (**A**) baseline, and (**B**) after 2 months, (**C**) 10 months, and (**D**) 13 months of empagliflozin treatment.

of an SGLT2 inhibitor on the healing process of a refractory wound in a patient with G6PC3 deficiency. By extension, in glycogen storage disease (GSD)-1b, a deficiency of the G6P transporter that also lead to accumulation of 1,5-AG6P in neutrophils, treatment with empagliflozin, an SGLT2 inhibitor used to treat diabetes, has been shown to correct neutrophil defects and wound healing.[3,7] Thus, we hypothesized that empagliflozin could treat a refractory wound in a patient with G6PC3 deficiency, supported by reports of patients whose neutropenia were corrected by treatment with empagliflozin.[4,5] To our knowledge, this case represents the first instance of employing an SGLT2 inhibitor to not only correct neutropenia but also facilitate the healing of a refractory wound in a patient with G6PC3 deficiency.

CASE PRESENTATION

The patient is a 30-year-old woman followed since childhood for congenital neutropenia then inflammatory colitis in adolescence. As previously reported, our patient's severe congenital neutropenia was caused by compound heterozygous mutations in *G6PC3*[8] and was associated with lymphopenia (0.3-0.6 $\times$ 10^9/L) mainly affecting naive $CD4^+$ T lymphocytes ($CD31^+CD45RA^+CD4^+$: 8%-13%, normal values 27%-60%), and hypergammaglobulinemia (IgG 20.5-31.5 mg/dL, normal values 5.29-15.21 mg/dL). In childhood, she developed skin abscesses at the site of a previous vaccination, chickenpox lesion, and enterocutaneous fistula. After a right hemicolectomy at 13 years of age, her colitis was treated with infliximab and neutropenia with filgrastim.

At 25 years, this patient presented with a skin lesion on the right malleolus following sclerotherapy, which evolved into a refractory wound. Fungal cultures were negative, and a wound biopsy was compatible with pyoderma gangrenosum (PG)-like ulcer. Attempted treatments, included topical clobetasol followed by intralesional triamcinolone acetonid (Kenalog), systemic dapsone (up to 200 mg/d), which increased wound pain and required treatment with prednisone (40 mg/d), and 3 months of unsuccessful treatment with cyclosporine A. The concern that filgrastim may be increasing neutrophilic stimulation of the PG led to increasing treatment intervals to 2 days without any significant improvement of the lesion. A total of 3 follow-up biopsies continued to be consistent with PG and ruled out chronic infection or underlying neoplasia. Multiple bacterial, mycobacterial and fungal cultures were negative.

Given the fact that the patient developed PG while on infliximab, and the persistence of the wound combined with difficulty in weaning the patient off steroids, infliximab was switched to ustekinumab for >1 year, without leading to any significant improvement in wound healing (Fig 1, *A*). Thus, while continuing treatment with ustekinumab, empagliflozin was started at 10 mg daily for 2 months then increased to 25 mg daily for 1 year. After 2 months of treatment, a decrease in inflammation, resorption of fibrinous necrotic tissue and new areas of epidermization were noted (Fig 1, *B*). Thereafter, the wound continued to improve, with a budding appearance, increased areas of epidermization, absence of necrosis, and significant reduction of the wound size from 12.2 $\times$ 8 cm (Fig 1, *C*) to 10.5 $\times$ 5.2 cm (Fig 1, *D*) in the last 4 months of treatment. In parallel, the cytopenias gradually normalized including significant neutrocytosis, allowing for complete discontinuation of filgrastim after 9 months of treatment (Table I). The patient continued to have a normal white blood cell and neutrophil count 9 months after cessation of filgrastim. No major side effects of empagliflozin such as hypoglycemia or urinary tract infections were observed.

DISCUSSION

This case highlights the successful use of empagliflozin in treating a refractory wound and correcting

Table I. Evolution of complete blood counts during treatment with empagliflozin

	Time from start of treatment with empagliflozin (mo)		
Parameter (reference values)	**0 (Baseline)**	**4**	**12**
Treatment with filgrastim	+	+	–
WBC count, × 10^9/L (4.5-10.0)	1.6	24.7	5.6
Hemoglobin, g/L (125-155)	123	133	138
MCV, fL (82.0-98.0)	81.7	83.1	85.1
Platelets, × 10^9/L (130-400)	350	461	465
Neutrophils, × 10^9/L (1.8-7.5)	0.7	21.49	3.3
Lymphocytes, × 10^9/L (1.0-4.0)	0.7	2.22	1.5
Monocytes, × 10^9/L (0.20-1.00)	0.2	0.74	0.38
Eosinophils, × 10^9/L (0.04-0.80)	0	0.25	0.40

fL, Femtoliter; *g/L*, gram/liter; *MCV*, mean corpuscular volume; *WBC*, white blood cell.

cytopenias, including congenital neutropenia, in a patient with G6PC3 deficiency. Moreover, empagliflozin allows for discontinuation of filgrastim treatment and prevents the possible development of secondary myeloproliferation process described in patients with GSD-1b treated with sustained filgrastim therapy.[9,10]

Our observations suggests that altered G6P production in G6PC3 deficiency causes abnormalities that are similar to those reported in GSD-1b. Consistent with the clinical improvements described in patients with GSD-1b treated with empagliflozin,[3,7] wound healing and neutropenia improved dramatically in our patient. Thus, the use of empagliflozin, which has been shown to be effective in treating complications associated with GSD-1b, is also effective, well-tolerated, and could be used in the long-term treatment of patients with G6PC3 deficiency. However, it is important to carefully monitor potential side effects of empagliflozin that was be associated with increased susceptibility to urinary tract infections and hypoglycemia, especially in the context of inborn errors of immunity. It is reassuring that no major side effects have been reported with the use of empagliflozin in patients with GSD-1b.[3] This case underscores the critical role of intact phagocyte functions in tissue repair and highlights the significance of regulating cell metabolism, particularly in G6P formation, for maintaining phagocyte functions. Furthermore, it specifically advocates for the use of empagliflozin in restoring cellular metabolism in G6PC3 deficiency.

Conflicts of interest

None disclosed.

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