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Case Report

Reversible Injection-Site Lipoatrophy Induced by Long-Acting Growth Hormone (Somatrogon) in Pediatric Growth Hormone Deficiency: A Case Series

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What is already known on this topic?
Lipoatrophy is a rare adverse event associated with recombinant growth hormone (GH) therapy. In patients receiving somatrogon, only a single case has been reported to date, and the condition is generally considered uncommon and reversible.

What this study adds?
This report presents the first case series describing somatrogon-associated lipoatrophy. It demonstrates that the condition is fully reversible with appropriate injection-site rotation and highlights the importance of regular inspection and systematic site rotation to prevent recurrence during long-acting GH therapy.

Abstract
Recombinant human growth hormone (GH) has been utilized for nearly four decades in the management of growth hormone deficiency (GHD); however, adherence to daily injections may be suboptimal in children. To overcome this limitation, long-acting GH analogues have been developed. Somatrogon, a once-weekly formulation and the first long-acting GH approved for use in Türkiye, is indicated for children aged ≥3 years with GHD. Clinical trials have demonstrated that adverse events are predominantly mild, with injection-site pain being the most frequently reported. Lipoatrophy associated with somatrogon therapy has been documented only once previously, rendering the present series the first to describe multiple cases. We report three pediatric patients (two males and one female; aged 7.2, 13.2, and 6.9 years, respectively) who developed localized lipoatrophy at upper-arm injection sites during somatrogon therapy. The condition emerged after 9 months in two patients and after 12 months in the third. All had a history of repeated injections at the same anatomical sites. No systemic adverse effects were observed, and growth responses remained appropriate. Treatment was continued while injection sites were rotated to the thighs and abdomen. Complete resolution of lipoatrophy was achieved within three months, with no recurrence during follow-up.
Keywords: Long-acting Growth hormone, Somatrogon, Somatropin, Lipoatrophy

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Introduction

Daily administration of recombinant human growth hormone (rhGH) has been approved and widely utilized worldwide for the treatment of growth hormone deficiency (GHD) (1). Although generally well tolerated, both systemic and local adverse events have been reported with daily rhGH therapy, among which lipoatrophy represents a rare and typically transient complication (2,3). Lipoatrophy is characterized by localized loss of subcutaneous adipose tissue and is thought to result from a combination of local inflammatory responses and the lipolytic effects of GH on adipocytes (4).

To reduce the treatment burden associated with daily injections and to enhance therapeutic adherence and efficacy, several strategies have been explored in the development of long-acting growth hormone (LAGH) analogues. These include depot formulations, polyethylene glycol (PEG)-conjugated molecules, pro-drug formulations, albumin-binding GH variants, and GH fusion proteins (5). In 2009, lipoatrophy was first reported in association with a PEGylated LAGH formulation, highlighting the importance of systematic rotation of injection sites to prevent local adverse effects (6).

Currently, three LAGH preparations have received approval from the U.S. Food and Drug Administration and the European Medicines Agency: somatrogon (a GH fusion protein), somapacitan (an albumin-binding analogue), and lonapegsomatropin (a pro-drug formulation) (7). Recently, a single case report documented localized lipoatrophy developing at repeated somatrogon injection sites (8).

Here, we describe three pediatric patients with GHD who developed localized, reversible lipoatrophy during somatrogon therapy, associated with repeated injections at identical sites. To our knowledge, this represents the first case series reporting multiple instances of somatrogon-associated lipoatrophy.

Case 1

A 5.5-year-old boy, born at term with a birth weight of 3430 g, was evaluated for short stature. At presentation, his weight standard deviation score (SDS) was −1.5, height SDS −2.1, body mass index (BMI) SDS −0.2, and midparental height SDS −1.3. The prepubertal patient had an annual height velocity (HV) of 3.9 cm/year, bone age (BA) of 3.5 years, and insulin-like growth factor-1 (IGF-1) SDS −0.7. Additional laboratory investigations, including thyroid function and celiac screening, yielded normal results. GH stimulation testing with clonidine and L-Dopa demonstrated subnormal peak GH response (clonidine 7.6 ng/mL; L-Dopa 7.1 ng/mL). Pituitary magnetic resonance imaging (MRI) revealed normal findings.

Based on these results, a diagnosis of GH deficiency was established, and somatropin therapy was initiated at 0.025 mg/kg/day. After 1.6 years of treatment, at 7.2 years of age, the patient was transitioned to once-weekly somatrogon (0.66 mg/kg/week) due to the burden of daily injections. At the time of transition, his weight SDS was −1.0, height SDS −1.1, BMI SDS −0.5, HV 8.5 cm/year, and IGF-1 SDS −0.7. The patient and family were instructed to rotate injection sites at each visit.

Despite satisfactory adherence, the patient reported injection-site pain and therefore divided the weekly somatrogon dose into two injections, both administered exclusively into the upper arms. No adverse events were noted during the first 9 months of treatment. At the 9-month

follow-up, marked bilateral upper-arm lipoatrophy was detected, with mid-arm circumference measuring 14 cm (Figure 1A). Growth velocity remained adequate, and the patient was instructed to avoid upper-arm administration and instead rotate injection sites among the thighs and abdomen.

By month 12, the lipoatrophy had completely resolved with mid-arm circumference measuring 18 cm (Figure 1B). Bilateral upper-arm MRI performed at that time confirmed normalization of subcutaneous tissue without residual lipoatrophy. At this visit, HV was 6.1 cm/year. IGF-1 concentrations remained within the age-appropriate reference range throughout follow-up. The patient continues somatrogon therapy with proper site rotation and without recurrence of lipoatrophy.

Case 2

A 6.9-year-old girl, born at term with a birth weight of 2800 g and a karyotype of 46,XX, was evaluated for short stature. At presentation, her weight SDS was −1.5, height SDS −2.4, BMI SDS −0.2, and midparental height SDS −0.8. She was prepubertal, with an annual HV of 3.6 cm/year, BA of 3.5 years, and IGF-1 SDS of −1.6. GH stimulation testing with clonidine and L-Dopa revealed subnormal peak GH response (clonidine 0.9 ng/mL; L-Dopa 2.5 ng/mL). Pituitary MRI demonstrated an ectopic posterior pituitary gland.

Based on these findings, a diagnosis of GH deficiency was established, and once-weekly somatrogon therapy was initiated at a dose of 0.66 mg/kg/week. The patient demonstrated good adherence throughout treatment. Despite repeated counseling to rotate injection sites, she consistently administered injections exclusively into the left upper arm. No adverse events were observed during the initial nine months of therapy.

At the 9-month follow-up, localized lipoatrophy was noted in the left upper arm, with a mid-arm circumference of 6.3 cm on the left and 6.7 cm on the right (Figure 2A). The patient was advised to discontinue injections in the upper arms and to rotate injection sites among the abdomen, thighs, and right upper arm. By month 12, the lipoatrophy had completely resolved with a mid-arm circumference of 6.7 cm (Figure 2B). Follow-up MRI confirmed normalization of subcutaneous tissue without residual defects in either arm.

At that time, her HV was 7.8 cm/year. The patient continues somatrogon therapy with appropriate injection-site rotation and without recurrence of lipoatrophy.

Case 3

A 13.2-year-old boy, born at term with a birth weight of 2700 g, presented with short stature. At baseline, his weight SDS was −1.5, height SDS −2.5, BMI SDS −0.3, and midparental height SDS −2.1. The patient was pubertal, with an annual HV of 3.2 cm/year, BA of 11.5 years, and IGF-1 SDS of −1.7. GH stimulation testing with clonidine and L-Dopa demonstrated subnormal peak GH levels (clonidine 4.6 ng/mL; L-Dopa 2.7 ng/mL). Pituitary MRI showed normal findings.

A diagnosis of GH deficiency was established, and once-weekly somatrogon therapy was initiated at a dose of 0.66 mg/kg/week. Despite good treatment adherence and repeated counseling regarding injection-site rotation, the patient consistently administered injections exclusively into the right upper arm. No adverse events were noted until month 12, when localized lipoatrophy of the right upper arm was observed (mid-arm circumference: right 23 cm, left 24 cm) (Figure 3A). As HV remained appropriate, the patient was instructed to discontinue injections in the upper arm and to rotate sites among the thighs, abdomen, and left upper arm.

At the 15-month follow-up, the lipoatrophy had completely resolved, with both mid-arm circumferences measuring 24 cm (Figure 3B). Forearm MRI at that time confirmed normal subcutaneous tissue without residual abnormalities. The patient's HV was 12.6 cm/year. The patient continues somatrogon therapy with appropriate injection-site rotation and without recurrence of lipoatrophy. The clinical and laboratory characteristics of the three patients who developed lipoatrophy are summarized in Table 1.

Discussion

This is the first pediatric case series describing reversible lipoatrophy associated with somatrogon therapy in children with GHD. All three patients maintained adequate growth velocity and normal IGF-1 SDS throughout treatment, which was administered at standard doses (0.66 mg/kg/week subcutaneously) using the same recombinant LAGH formulation. Lipoatrophy developed after repeated injections exclusively into the upper arms but resolved completely within three months after injection-site rotation, without treatment interruption or dose adjustment, and recovery was confirmed by both clinical and MRI findings. Consistent with previous reports (3,6,8), our findings, suggest that lipoatrophy is unrelated to treatment indication, dosage, or product formulation, but is instead attributable to repeated administration at the same anatomical sites.

Several studies have proposed that excipients contained in LAGH formulations may contribute to the development of lipoatrophy. Although excipients are essential for maintaining biomolecular stability and optimizing delivery, they have also been implicated in adverse reactions, including injection-site reactions, and, rarely anaphylaxis (9). Severe cutaneous hypersensitivity reactions related to metacresol have been reported in patients receiving insulin therapy; however no cases of rhGH-associated lipoatrophy have been directly attributed to this preservative (10, 11). To date, only a single pediatric case of somatrogon-associated lipoatrophy has been reported. In that report, the pathophysiological mechanism was hypothesized to involve both the mild local irritant effects of glycosylated carboxy-terminal peptides (CTP) and the potential cytotoxic effects of metacresol on adipocytes, particularly when injections were repeatedly administered at the same site (8). In our patients, repeated injections into a limited anatomical area—without adequate site rotation—appeared to be the predominant risk factor. Nevertheless, a contributory role of metacresol or glycosylated CTPs cannot be completely excluded.

GH possesses well-established lipolytic properties. It promotes lipolysis both directly, through its actions on adipocytes, and indirectly, by suppressing lipoprotein lipase activity, thereby reducing fatty acid uptake into adipose tissue (6). GH has also been shown to decrease adipocyte number and reduce the size of mature adipocytes, limiting adipose tissue expansion and contributing to an overall reduction in total body fat (4). These mechanisms may account for the development of localized lipoatrophy when injections are repeatedly administered to the same anatomical site, particularly with LAGH formulations that prolong hormone exposure within the subcutaneous tissue.

Reports of GH-related lipoatrophy date back to 1995, when the first mild, localized cases were described (12). Subsequently, in a 9-year-old girl with isolated GH deficiency, severe lipoatrophy involving all four extremities was reported during the sixth year of high-dose rhGH therapy. The absence of anti-GH antibodies and the non-specific histopathological findings in that case indicated a non-immune etiology, implicating the direct lipolytic effects of GH as the likely mechanism (2). Although antibody testing and tissue biopsy were not performed in our patients, the benign clinical course and spontaneous resolution following injection-site rotation similarly suggest a non-immunologic, locally mediated process.

Additional evidence supporting a localized lipolytic effect of GH originates from a phase 2 clinical trial of a long-acting PEG–GH formulation, in which lipoatrophy developed following repeated injections into the same thigh. Although the study was resumed with strict injection-site rotation protocols, subsequent cases—including one in a pediatric participant—prompted permanent discontinuation of the trial, representing the first documented instances of lipoatrophy associated with LAGH therapy (6). Similarly, a 2021 study reported localized lipoatrophy in 14.5% (9/62) of children receiving daily rhGH, again attributed to the local lipolytic effects of GH and repeated injections into restricted anatomical sites (3). Our findings are consistent with these observations, suggesting that limited site rotation likely contributed to the development of localized lipoatrophy, potentially exacerbated by the prolonged subcutaneous GH exposure characteristic of long-acting formulations.

When previous reports are considered, the onset of lipoatrophy has shown notable variability across GH formulations and dosing regimens. In a phase 2 trial of PEG–GH, lipoatrophy developed after the fifth or sixth injection (6); in the single reported pediatric case of somatrogon-associated lipoatrophy, it occurred following the 11th injection (8); in a child receiving high-dose Daily rhGH, it emerged after six years of therapy (2); and among daily rhGH users, the mean time to onset was reported as 19 months (range, 3–37 months) (3). In our patients,

lipoatrophy manifested at months 9 and 12, affecting both unilateral and bilateral injection sites, which is consistent with the temporal pattern described in previous studies.

In contrast to previous reports (3,6), in which recombinant GH therapy was discontinued following the onset of lipoatrophy—with resolution typically occurring within 8 to 12 weeks—our patients continued somatrogon treatment at the same dosage, with injections redirected to alternative sites. In all three cases, complete clinical recovery was achieved within three months, and normalization of subcutaneous tissue was confirmed by MRI.

A limitation of this study is the small number of cases, which restricts the generalizability of the findings. Furthermore, neither skin biopsy nor anti-GH antibody testing was performed; thus, potential immunological mechanisms could not be fully assessed. Although MRI confirmed complete resolution of lipoatrophy, imaging at the time of initial presentation was not available due to technical constraints. While all cases demonstrated full recovery, longer-term follow-up is warranted to determine whether recurrence may occur with continued LAGH therapy.

Conclusion

Although injection-site pain is the most frequently reported adverse event associated with somatrogon, our findings demonstrate that reversible, localized severe lipoatrophy may also occur, most likely due to repeated injections at the same anatomical sites. Awareness of this complication, routine inspection of injection areas, and strict adherence to systematic site rotation are essential to minimize its occurrence and ensure long-term treatment safety. Further studies are warranted to elucidate the true incidence, underlying mechanisms, and optimal prevention strategies for lipoatrophy in children receiving long-acting GH therapy.

Ethics

Informed Consent: Written informed consent was obtained from the patients' parents in their native language (Turkish) for publication of this case report and accompanying clinical images.

Authorship Contributions

Surgical and Medical Practices: Kübra Şen Küçük, Ahmet Anık, Concept: Kübra Şen Küçük, Ahmet Anık, Design: Ahmet Anık, Data Collection or Processing: Kübra Şen Küçük, Ahmet Anık, Analysis or Interpretation: Kübra Şen Küçük, Göksel Tuzcu, Ahmet Anık, Literature Search: Kübra Şen Küçük, Ahmet Anık, Writing: Kübra Şen Küçük, Göksel Tuzcu, Ahmet Anık.

Conflict of interest: None declared.

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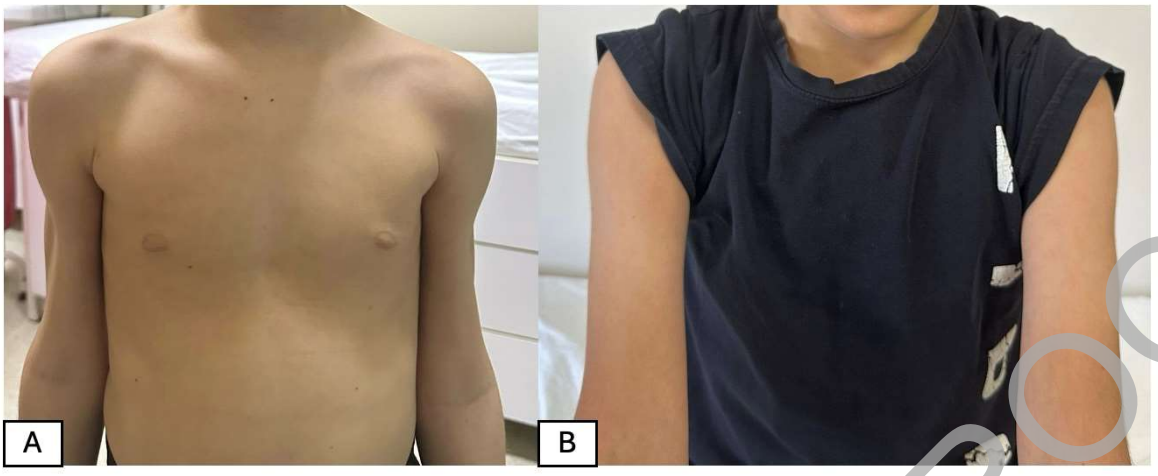

Figure 1. Bilateral upper arm lipoatrophy and resolution in Case 1. A) Bilateral upper arm lipoatrophy observed at month 9 of somatrogon therapy. B) Complete resolution of lipoatrophy after 3 months with proper injection site rotation.

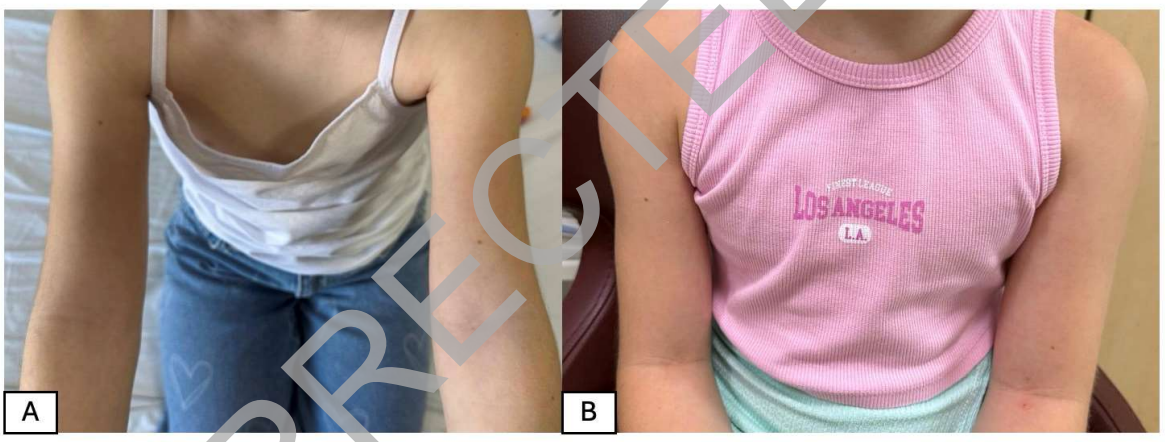

Figure 2. Left upper arm lipoatrophy and resolution in Case 2. A) Localized lipoatrophy of the left upper arm observed at month 9 of somatrogon therapy. B) Complete resolution of lipoatrophy after 3 months with proper rotation of injection sites.

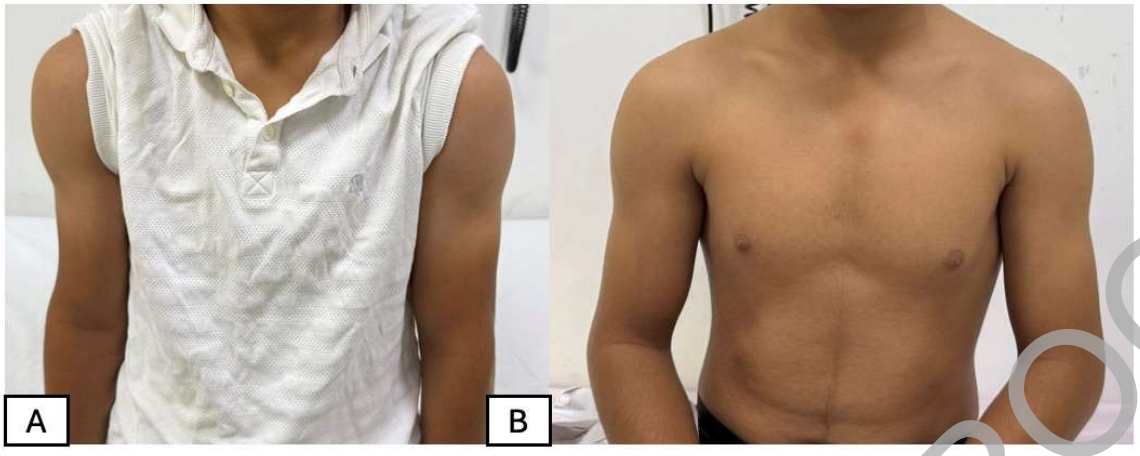

Figure 3. Right upper arm lipoatrophy and resolution in Case 3. A) Localized lipoatrophy of the right upper arm observed at month 12 of somatrogon therapy. B) Complete resolution of lipoatrophy after 3 months with proper rotation of injection sites.

Table 1. Clinical characteristics of three patients who developed lipoatrophy during somatrogon treatment			
	Case 1	**Case 2**	**Case 3**
Age (years) *	7.2	6.9	13.2
Sex	Male	Female	Male
Pubertal Status	Prepubertal	Prepubertal	Pubertal
Height SDS*	-1.1	-2.4	-2.5
Clonidine peak GH response (ng/mL)	7.6	**0.9**	4.6
L-Dopa peak GH response (ng/mL)	**7.1**	**2.5**	**2.7**
Status	Switch[&]	Naive[x]	Naive
IGF-1 SDS*	-0.7	-1.6	-1.7
Dose (mg/kg/week) *	0.66	0.66	0.66
Lipoatrophy Onset (month)	9	9	12
Site of Lipoatrophy (upper arm)	Bilateral	Left	Right
Mid-arm Circumference (cm) (Right/Left)	14/14	6.7/6.3	23/24
Recovery Time (month)	3	3	3
Post-recovery Mid-arm Circumference (cm)	18/18	6.7/6.7	24/24
Treatment Duration (month)	12	12	15
HV (cm/year)[#]	6.1	7.8	12.6
Abbreviations: SDS: Standard deviation score; GH: Growth hormone; IGF-1: Insulin-like growth factor-1; HV: Height velocity. * Values represent data at the initiation of somatrogon treatment. [&] Values represent patients switched from somatropin to somatrogon. [x] values represent patients who initiated somatrogon treatment. [#] Values indicate the change from baseline to the end of treatment.			