

## LETTER TO THE EDITOR

# Lipodystrophy during pegvisomant therapy: a case report and review of the literature

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## INTRODUCTION

Acromegaly is a serious, chronic endocrine disorder characterized by exaggerated growth hormone (GH) secretion and increased levels of insulin-like growth factor-1 (IGF-1). Treatment modalities include somatostatin analogues and pegvisomant and/or radiotherapy following pituitary tumor resection.<sup>1</sup> Pegvisomant is a pegylated analogue of human GH and functions as a GH receptor antagonist. Pegvisomant acts in the periphery and significantly decreases serum IGF-1 levels.<sup>2</sup> Various studies have shown that pegvisomant is safe and well-tolerated and is an effective therapy for acromegaly patients. Possible adverse effects of pegvisomant treatment include self-limited erythematous injection-site reactions, mild liver toxicity, influenza-like syndrome and headache.<sup>3</sup> Here, we describe an acromegalic patient who developed lipohypertrophy following initiation of pegvisomant therapy.

## CASE REPORT

A 61-year-old female patient was diagnosed with acromegaly eight years ago. The diagnosis of acromegaly was confirmed by elevated serum IGF-1 levels accompanied by failure of GH suppression following a 75 g glucose load. The patient displayed a 22x17x16 mm pituitary adenoma, which was operated transsphenoidally two months after diagnosis. After surgery, the patient was treated with long-acting octreotide LAR for persistent symptoms. After 14 months of octreotide therapy, 0.5 mg cabergoline administered 3 days a week was added to the treatment regimen to address unremitting symptoms. The patient underwent a gamma-knife procedure three years after the initial surgery to treat the residual disorder, which was identified by persistently high levels of IGF-I and magnetic resonance imaging (MRI). At the 4<sup>th</sup> year of follow up, the patient displayed an IGF-I level of 485 ng/ml. At this point (December 2009), cabergoline treatment was discontinued and the patient was given subcutaneous injections of 10 mg pegvisomant per day. The patient was advised to alternate the injection areas around the arms, thighs and the abdominal wall. After two months of treatment, the patient found soft, painful swellings on her arms, thighs and the abdominal wall. Clinical examination found a clearly visible thickening of the tissues in these



**Figure 1** - Areas of lipohypertrophy on the anterior abdominal wall.



**Figure 2** - Sagittal T1 weighted MRI of the left arm shows lipomatous hypertrophy (arrows) at the injection site. Note the normal subcutaneous fat (asterisks) where injections were performed.

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**Table 1 - Review of literature**

Literature	Age/gender	Method	Diagnosis	Area	Time after treatment	Result
Maffei et al.	35 / male	USG + MRI	Lipohypertrophy	Abdominal wall	1 month	Avoiding abdominal injection, changing injection site
Salvatore et al.	38 / female	USG + biopsy	Lipoatrophy	Arms	20 months	Changing injection site
Marazuela et al.	33 / female	USG+ biopsy	Lipohypertrophy	Left arm	8 months	Changing injection site
Bonert VS et al.	50 / female					
	6 female 1 male					
	Patient 1	PE	Lipohypertrophy	Thighs, Buttocks	5 months	Discontinuation
	Patient 2	PE	Lipohypertrophy	Abdominal wall, Thighs	1 week	Discontinuation, restart, recurrence
	Patient 3	PE	Lipohypertrophy	Thighs, Arms	3 months	Discontinuation Regression
	Patient 4	PE +MRI	Lipohypertrophy	Abdominal wall	A few weeks	?
	Patient 5	PE	Lipohypertrophy	Abdominal wall, Thighs	1 month	Discontinuation
	Patient 6	PE	Lipohypertrophy	Abdominal wall	4 months	Changing injection site
	Patient 7	PE	Lipohypertrophy	Abdominal wall, Buttocks, Upper arm	3 weeks	Changing injection site

PE: Physical examination

areas (Figure 1). No significant increase was detected in serum IGF-1 levels, indicating that the treatment was effective. Ultrasonography revealed a subcutaneous fat hypertrophy in the extremities. MRI of the left arm confirmed lipomatous hypertrophy at the injection site (Figure 2).

The accuracy of the injection sites and the drug applications were controlled by a dedicated nurse (Somavert education service). The patient was dissatisfied with the lipohypertrophy at the sites of injection, and pegvisomant therapy was therefore discontinued.

## DISCUSSION

Somatostatin analogues and pegvisomant are frequently used in the treatment of acromegaly. Pegvisomant is a pegylated analogue of human GH that blocks hepatic production of IGF-1. The adverse effects of pegvisomant therapy include self-limited erythematous injection-site reactions, mild liver toxicity, influenza-like syndrome, headache, asthenia, diarrhea, arthralgia and hypercholesterolemia.<sup>3</sup>

Lipodystrophy is a disease of the adipose tissue. It can be localized and acquired by administration of particular drugs. If the adipose changes are related to depressed areas of skin, the disease is called lipoatrophy. Lipohypertrophy is an enlargement of fat tissue caused by subcutaneous deposition of adipose and is associated with parenteral drug administration. The pathogenesis of lipohypertrophy is unclear. It is known that growth hormone and IGF-1 both display lipolytic activity. Blockage of growth hormone action through pegvisomant therapy can affect adipose size and increase local adiposity.<sup>4-7</sup> Immunologic factors can also contribute to lipodystrophy. An inflammatory reaction to substitutions of pegvisomant can often cause this disorder.<sup>8</sup> However, a biopsy of a pegvisomant-induced lipohypertrophy from an acromegalic patient showed normal-appearing mature adipocytes with no fat necrosis and no inflammatory cells. Additionally, the biopsy showed no anti-pegvisomant antibodies.<sup>7</sup>

To our knowledge, the literature contains 4 reports describing 11 patients who developed lipodystrophy during pegvisomant therapy<sup>5-8</sup> (Table 1). These reports describe lipohypertrophy in 10 patients and lipoatrophy in 1 patient.

Maffei et al. have reported one male and one female patient who suffered from lipohypertrophy on the abdominal wall, confirmed by ultrasonography and MRI, following 1 month of pegvisomant therapy. These patients were advised to avoid abdominal injections and alternate the injection sites.<sup>5</sup> Salvatore et al. reported pegvisomant-induced lipoatrophy.<sup>6</sup> Marazuela et al. described lipohypertrophy on the left arm of a female patient caused by pegvisomant therapy. This lipohypertrophy resolved once injections at the same site were ceased.<sup>7</sup> Bonert et al. identified seven different cases of lipohypertrophy induced by pegvisomant therapy; two of the patients began rotating the injection site, and four patients discontinued pegvisomant therapy.<sup>8</sup>

It is worth noting that 9 of the 11 patients described in the literature were female. Thus, pegvisomant-induced lipohypertrophy can be referred to as a gender-specific response. In most cases, lipohypertrophy was reversed after the injection site was rotated or treatment was discontinued. It is unknown whether the development of lipohypertrophy is associated with the dose or frequency of injection.<sup>5,7,8</sup> In our patient, pegvisomant therapy was administered together with a low dose of octreotide LAR. The treatment effectively normalized IGF-1 levels, but pegvisomant treatment was stopped due to discomfort caused by lipohypertrophy.

In conclusion, pegvisomant injection appears to have induced lipohypertrophy in our patient following two months of therapy. We recommend injection site rotation to different parts of the body, which should prevent the development of lipohypertrophy. Physicians should be aware of this complication and carefully monitor patients under pegvisomant treatment.

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