Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2013;22:83-85
doi: 10.2478/v10162-012-0041-0

Insulin-induced localized lipoatrophy

Vesna Breznik[1] ✉, Rok Kokol[2], Boštjan Luzar[3], Jovan Miljković[2]

Abstract

Insulin lipoatrophy is a rare immunologic cutaneous complication in diabetes mellitus that presents with localized subcutaneous fat atrophy at the insulin injection site. We report the case of a 62-year-old woman with type 2 diabetes mellitus that developed localized lipoatrophy on the abdomen after 6 years of therapy with the insulin analogues detemir and aspart.

Received: 5 November 2013 | **Returned for modification:** 10 November 2013 | **Accepted:** 13 November 2013

Introduction

Long-term insulin use in diabetes mellitus can be associated with local subcutaneous fat abnormalities known as lipodystrophies. They are characterized by either fat accumulation (lipohypertrophy) or fat loss (lipoatrophy). Lipodystrophies may have a negative cosmetic impact on patients. Injection into lipodystrophied sites can result in erratic absorption of the drug, leading to difficulties in achieving ideal blood glucose control (1, 2).

Insulin lipohypertrophy presents as benign tumor-like swelling of fatty tissue at the injection site and is a result of local anabolic effects of insulin with promotion of fat and protein synthesis. It remains a frequent complication of insulin therapy irrespective of the insulin source (animal, recombinant, or analogue) and the mode of administration (3, 4).

Insulin lipoatrophy is clinically characterized by visible cutaneous depression and palpable atrophy of subcutaneous fat tissue at the injection site. It is thought to be an immune complex–mediated inflammatory lesion associated with all types of insulin (3). In the past it was reported in 10 to 55% of diabetic patients treated with nonpurified bovine/porcine insulin preparations (5). Nowadays with recombinant human insulin and analogues it is a rare complication with an estimated prevalence of 3.6% (6). It mostly develops in lean young female patients with type 1 diabetes mellitus and it sometimes overlaps with other autoimmune diseases. The respective exposition to the analogues lispro, aspart, glargine, and detemir prior to lipoatrophy development varies between 4 weeks and 2 years according to some authors (7). Lipoatrophy can also occur with continuous subcutaneous insulin infusion (CSII, insulin pump) (8), rapidly absorbed insulins, and more than one type of insulin analog in the same patient (9). Repeated use of the same insulin injection site and multiple usage of same pen needle increases the risk of lipoatrophy (3).

Case report

A 62-year-old woman with type 2 diabetes mellitus presented with 4-month history of a 15 × 10 cm depressed area of skin on the abdomen (Fig. 1). For 6 years she had been using long-acting insulin detemir (Levemir, Novo Nordisk) and short-acting insulin aspart (Novorapid, Novo Nordisk), which she applied at various sites on her abdomen. Her history was significant for diabetic retinopathy and nephropathy, obesity, hypertension, hyperlipidemia, and chronic venous insufficiency. Her therapy was enalapril, indapamide, atorvastatin, fenofibrate, acetylsalicylic acid, and diosmin/hesperidin. Her body mass index was 35 kg/m^2. Routine complete blood count and chemistry were normal. HbA1C was 7.6% (normal range 4.0–6.1%). Specific IgE for porcine and human insulin were normal. A biopsy was obtained from the lipoatrophic area. On histology, prominent atrophy of the subcutaneous fatty tissue was seen, associated with disappearance of the subcutaneous fat and its replacement by loose, partially myxoid connective tissue (Fig. 2). Numerous foamy macrophages, including multinucleated giant cells of the Touton and foreign body type, were present surrounding atrophic fat lobules and within connective tissue septa (Fig. 3). Focal areas of hemosiderin deposition and aggregates of lymphocytes were also noted (Fig. 4).

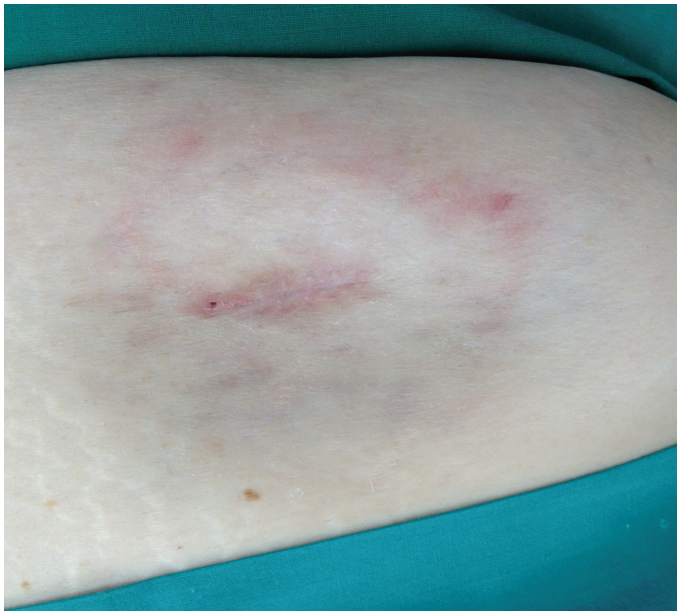

Figure 1 | Lipoatrophic area on the abdomen.

The patient was advised to stop injecting insulin into the lipoatrophic area, to rotate insulin injection sites, and to change the needle every day. She was not interested in therapy for her localized lipoatrophy, which remained unchanged during the following year.

Discussion

The etiology of localized acquired lipoatrophy is heterogeneous. It may result from sequelae of abscess formation, repetitive trauma,

[1]Department of Dermatology, University Medical Centre Maribor, Slovenia. [2]Department of Dermatology, Medical Faculty, University of Maribor, Slovenia. [3]Department of Pathology, Medical Faculty, University of Ljubljana, Slovenia. ✉ **Corresponding author: breznikv@gmail.com**

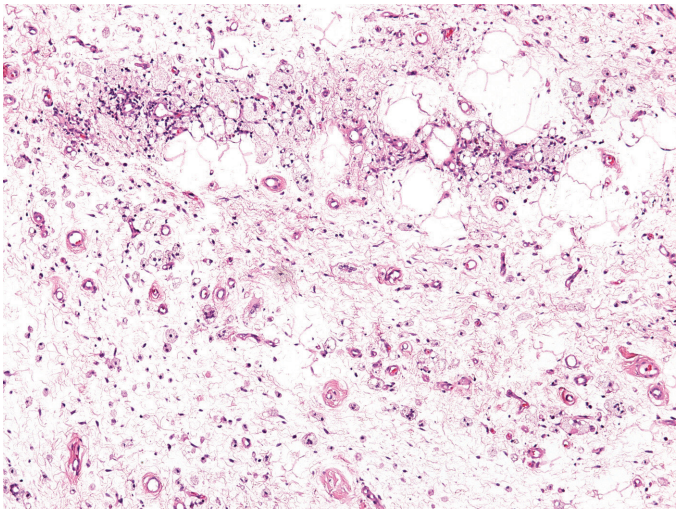

Figure 2 | Prominent atrophy of subcutaneous fat.

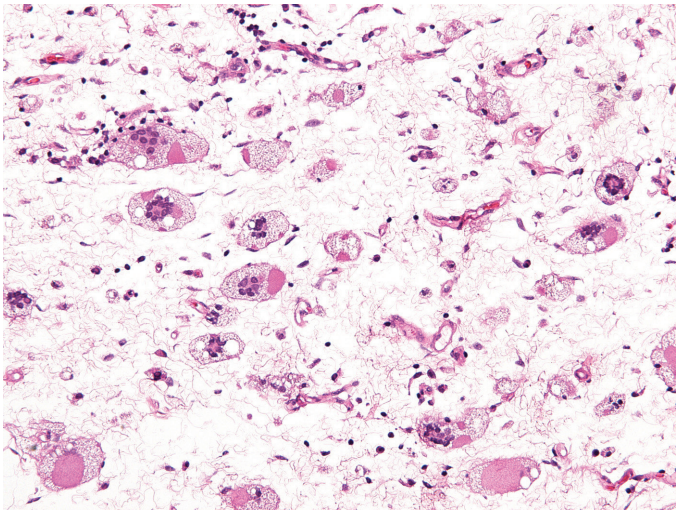

Figure 3 | Numerous multinucleated giant cells in loose myxoid connective tissue at the lipoatrophy site.

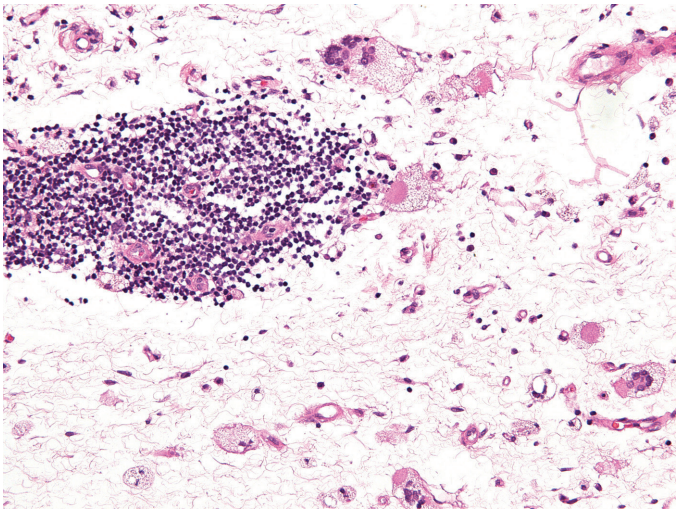

Figure 4 | Focal formation of lymphoid aggregates composed of lymphocytes at the lipoatrophy site.

constant or intermittent pressure (lipoatrophia semicircularis) (10), localized connective tissue diseases such as lupus profundus, morphea, or panniculitic lymphoma, or systemic autoimmune disorders such as systemic lupus erythematosus or dermatomyositis. Iatrogenic causes include complications of injected medications, including insulin (especially the non-human form), corticosteroids, antibiotics, iron, heparin, vaccines, and growth hormone (11). Up to 60% of lipoatrophy may be associated with prior local injections, suggesting a trauma-related phenomenon (12, 13).

We presented a rare case of localized lipoatrophy after repetitive injections of insulin analogues detemir and aspart in an obese adult female patient with type 2 diabetes mellitus. Otherwise it mostly occurs in lean young female patients with type 1 diabetes mellitus in whom insulin lipoatrophy sometimes resolves spontaneously (7). In our patient, the lesion showed no spontaneous resolution in the observing year. In an adult, spontaneous resolution of insulin lipoatrophy is uncommon (8).

The pathogenesis of insulin-induced lipoatrophy remains unclear. It is thought to be a subcutaneous immune complex–mediated inflammation (3, 4, 14). Biopsy samples from lipoatrophic areas associated with the use of various insulins—mostly bovine/porcine—revealed abnormal deposition of immunological components (IgM with C3 fraction) in dermal vessel walls (14). In addition, local release of TNFα and IL-6 from macrophages with dedifferentiation of adipocytes was found (4). Lipophagocytizing macrophages seen on electron microscopy, which were also numerous in the histopathological report of our patient, suggest an initial stimulation by injectable material (12, 15, 16). In a case series of five patients with insulin-induced lipoatrophy, subcutaneous adipose tissue biopsies showed increased numbers of degranulated mast cells, which were tryptase-positive and chymase-positive (3). The exact role of circulating insulin autoantibodies is unclear. Insulin IgE-autoantibodies are involved in immediate hypersensitivity reactions that present with generalized reactions such as urticaria or anaphylaxis or local symptoms in the form of erythema, itching, and swelling rather than lipoatrophy. Insulin IgG-antibodies were measured in six patients with lipotrophy that had been exposed to multiple types of analogues: human and animal insulins. In two cases they were highly elevated, whereas in the other four cases they were only modestly increased. Increase in cross-reactive insulin antibodies with a subsequent fall toward baseline values without any clinical relevance was observed in various studies. Thus, the pathogenetic role of circulating insulin autoantibodies appears questionable (7).

Treatment options for insulin-induced lipoatrophy include subcutaneous co-administration of corticosteroid with insulin (e.g., dexamethasone or betamethasone), low-dose oral corticosteroid (prednisone 5–10 mg daily) (8), changing between different insulin preparations (9), or changing the mode of insulin delivery (the use of CSII). Mast cell stabilizing therapy with topical 4% sodium cromolyn has been reported to reverse early and prevent new lipoatrophic lesions (3). Soft tissue augmentation using a variety of permanent and non-permanent fillers is also an option for cosmetic improvement of localized lipoatrophy (9).

Because the treatment success of lipoatrophy is generally poor, prevention should take first place. Any insulin formulation, including recombinant human insulin and analogues, can cause lipoatrophy, and so it seems to be more a problem of structured diabetes education with daily needle change and rotating of injection site than a matter of insulin preparation (2, 8). Annual examination with inspection and palpation of injection sites is also recommended (2).

Conclusion

In conclusion, the case of our patient presents a rare development of insulin analogue-induced lipoatrophy in an adult female pa-

tient with type 2 diabetes mellitus. Underlying mechanisms of the reaction remain to be determined. It seems that it is a transitory immune reaction, probably provoked by repetitive injection of insulin in the same site with fat necrosis and massive macrophage activation that result in subcutaneous fat atrophy.

References

1. Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. Am J Clin Dermatol. 2003;4:661–7.
2. Mokta JK, Mokta KK, Panda P. Insulin lipodystrophy and lipohypertrophy. Indian J Endocrinol Metab. 2013;17:773-4.
3. Radermecker RP, Pierard GE, Scheen AJ. Lipodystrophy reactions to insulin: effects of continuous insulin infusion and new insulin analogs. Am J Clin Dermatol. 2007;8:21-8.
4. Atlan-Gepner C, Bongrand P, Farnarier C, et al. Insulin-induced lipoatrophy in type 1 diabetes. A possible tumor necrosis factor-alpha-mediated dedifferentiation of adipocytes. Diabetes Care. 1996;19:1283-5.
5. Schernthaner G. Immunogenicity and allergenic potential of animal and human insulins. Diabetes care. 1993;16(Suppl 3):155-65.
6. Sackey AH. Injection-site lipoatrophy. N Engl J Med. 2009;361;e41.
7. Holstein A, Sterge H, Kovacs P. Lipoatrophy associated with the use of insulin analogues: a new case associated with the use of insulin glargine and review of the literature. Expert Opin Drug Saf. 2010;9:225-31.
8. Chantelau EA, Praetor R, Praetor J, Poll LW. Relapsing insulin-induced lipoatrophy, cured by prolonged low-dose oral prednisone: a case report. Diabetology & Metabolic Syndrome. 2011;3:33.
9. Lopez X, Castells M, Ricker A, Velazquez EF, Mun E, Goldfine AB. Human insulin analog-induced lipoatrophy. Diab Care. 2008;31:442-4.
10. DeGroot AC. Is lipoatrophia semicircularis induced by pressure? Br J Dermatol. 1994;131:887-90.
11. Buyukgebiz A, Aydin A, Dunlar B. Localized lipoatrophy due to recombinant growth hormone therapy in a child with 6,7 kilobase gene deletion isolated growth hormone deficiency. J Pediatr Endocrinol Metab. 1999;12:85-7.
12. Dahl PR, Zalla MJ, Winkelmann RK. Localized involutional lipoatrophy: a clinicopathologic study of 16 patients. J Am Acad Dermatol. 1996;35:523-8.
13. Yamamoto T, Yokozeki H, Nishioka K. Localized involutional lipoatrophy: report of six cases. J Dermatol. 2002;29:638-43.
14. Reeves WG, Allen BR, Tattersall RB. Insulin-induced lipoatrophy: evidence for an immune pathogenesis. Brit Med J. 1980;1500-3.
15. Zalla MJ, Winkelmann RK, Gluck OS. Involutional lipoatrophy: macrophage-related involution of fat lobules. Dermatology. 1995;191:149-53.
16. Sasaki T, Kanbara T, Inayama Y. Do mucin-phagocytosing histiocytes in localized lipoatrophy have any primary pathogenic importance? Br J Dermatol. 1999;140:976-8.