Contents lists available at ScienceDirect
Diabetes Research and Clinical Practice
journal homepage: www.elsevier.com/locate/diabres
International Diabetes Federation

Case report

Type III hypersensitivity to insulin leading to leukocytoclastic vasculitis

B. Rachid, M. Rabelo-Santos, E. Mansour, R. de Lima Zollner, L.A. Velloso *

Clinical Immunology, Department of Internal Medicine, University of Campinas, DCM – FCM Unicamp, 13083-970 Campinas, SP, Brazil

ARTICLE INFO

Article history:
Received 8 February 2010
Accepted 20 May 2010

Keywords:
Diabetes
Allergy
Insulin

ABSTRACT

Here, we report the occurrence of leukocytoclastic vasculitis as an outcome of type III allergy to insulin in a patient with type II diabetes mellitus. The diagnosis was made on the basis of anatomo-pathological examination of a skin biopsy.

© 2010 Elsevier Ireland Ltd. All rights reserved.

Allergy is a rare complication of insulin treatment, which has a wide spectrum of clinical manifestations ranging from simple cases of urticaria to life threatening anaphylaxis [1]. With the introduction of human recombinant insulin, the incidence of this disease has dropped considerably [2]. Although most cases of insulin allergy are IgE-mediated, leading to the release of inflammatory and vasoactive intermediaries from mast cells and basophiles, some few examples of type IV reactions have also been reported [1]. However, to our knowledge, only one previous report has described a case of histologically proven type III hypersensitivity to insulin [3]. Here we report another case of type III reaction to insulin with the anatomo-pathological diagnosis of leukocytoclastic vasculitis.

A Caucasian, 38-year-old Brazilian male was diagnosed type 2 diabetes mellitus in 1983. At the diagnosis his body mass index was 31 and an attempt to obtain metabolic control with glibenclamide failed and porcine NPH insulin (Lilly) was introduced. After 4 days, he presented an outbreak of purpuric edematous nodules and plaques accompanied by intense itching in the forearms, legs and abdominal and thoracic wall. The clinical diagnosis of urticaria was made and insulin was interrupted with complete recovery after 10–15 days. With a rigorous dietary control and the use of glibenclamide, the patient remained metabolically controlled for more than 10 years. In 1994, glucose and HbA1c levels were out of control and an attempt to introduce recombinant human NPH insulin (Novo Nordisk) was followed by a more severe outbreak of purpuric edematous nodules and plaques accompanied by intense itching in almost all body surface. Once again, insulin was interrupted and the lesions disappeared after 6–8 weeks with the use of systemic corticosteroids. At this time, metabolic control was obtained with the association of a tight dietary approach and the use of metformin.

In 2008, fasting glucose levels rose to 210–230 mg/dL and HbA1c reached 8.4% (upper normal 6.2%); body mass index was 28 and no clinical and laboratorial signs of vascular, renal or ophthalmologic diseases were observed. Once more, recombinant human NPH insulin (Novo Nordisk) was introduced and after 2 days a severe outbreak of purpuric nodules with itching and some degree of pain developed in the legs, arms and trunk. A skin biopsy was performed in a 4-day-old lesion and showed superficial and deep perivascular and

* *Corresponding author*. Tel.: +55 19 35218022; fax: +55 19 35218950.
E-mail addresses: lavelloso@fcm.unicamp.br, lavelloso.unicamp@gmail.com (L.A. Velloso).
0168-8227/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.diabres.2010.05.019

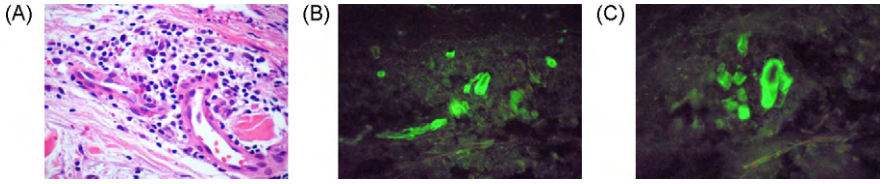

Fig. 1 – (A) Hematoxilin/eosin staining of a skin biopsy fragment depicting the neutrophil and eosinophil rich perivascular infiltrate. (B) Direct immunofluorescence staining for IgG depicting the deposits of IgG in the vascular wall. (C) Direct immunofluorescence staining for C3 depicting the deposits of C3 in the vascular wall. In all, magnification 40×.

interstitial infiltration with neutrophils and eosionophils. Vascular wall disruption with erythrocyte extravasation accompanied by a considerable amount of fibrinoid necrosis and leukocytoclasia determined the diagnosis of leukocytoclastic vasculitis (Fig. 1A). In addition, by direct immunofluorescence, the presence of IgG (Fig. 1B) and C3 (Fig. 1C) supported the diagnosis. Insulin was interrupted and a complete control of the lesions was obtained after 15 days with the association of prednisolone 10 mg once daily and hydroxyzine 25 mg twice a day.

Prick test to human insulin and protamine were negative as well as RAST (IgE) for insulin. In addition, the following laboratory tests were normal: C-reactive protein; sedimentation rate; total serum IgG, IgA, IgM and IgE; cryoglobulins; antinuclear antibody; rheumatoid factor; eosinophil counts; erythrocyte counts; platelet counts; hemoglobin and serum creatinine. Currently the patient is under clinical control with the use of metformin (Merk) and rosiglitazone (GlaxoSmithKline).

Leukocytoclastic vasculitis is a condition commonly seen in a number of systemic diseases such as myeloproliferative disorders, primary biliary cirrhosis, viral infections, bacterial endocarditis among others [4]. In allergy, leukocytoclastic vasculitis develops as a consequence of immunocomplex formation and deposition in the walls of small vessels. In a previous report a patient with type I diabetes mellitus, while in continuous use of insulin, was controlled with the use of immunosuppressive therapy with predinisolone and azathioprine followed by methotrexate [3]. In the patient herein reported, since metabolic control could be achieved with oral glucose reducing agents, short term, low dose corticosteroid therapy was sufficient to promote clinical control. In conclusion, although type III allergy to insulin is an extremely rare condition, it must be included as a differential diagnosis in cases of vasculitis in patients under insulin therapy.

Conflicts of interest

The authors declare that they have no conflict of interest.

REFERENCES

[1] Fernandez L, Duque S, Montalban C, Bartolome B. Allergy to human insulin. Allergy 2003;58:1317.
[2] Heinzerling L, Raile K, Rochlitz H, Zuberbier T, Worm M. Insulin allergy: clinical manifestations and management strategies. Allergy 2008;63:148–55.
[3] Mandrup-Poulsen T, Molvig J, Pildal J, Rasmussen AA, Andersen L, Skov BG, et al. Leukocytoclastic vasculitis induced by subcutaneous injection of human insulin in a patient with type 1 diabetes and essential thrombocytemia. Diabet Care 2002;25:242–3.
[4] Stone JH. Vasculitis: a collection of pearls and myths. Rheum Dis Clin North Am 2007;33:691–739.

Please cite this article in press as: Rachid B, et al. Type III hypersensitivity to insulin leading to leukocytoclastic vasculitis. Diab Res Clin Pract (2010), doi:10.1016/j.diabres.2010.05.019