ASTIM ALLERJİ İMMÜNOLOJİ
ASTHMA ALLERGY IMMUNOLOGY

doi: 10.21911/aai.5027
Asthma Allergy Immunol 2017;15:55-59

CASE REPORT/OLGU SUNUMU

An Unusual Trigger for Cutaneous Mastocytosis: The Insulin Pump

Kutanöz Mastositozun Nadir Bir Tetikleyicisi: İnsülin Pompası

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ABSTRACT

Mastocytosis is a relatively infrequent disorder characterized by mast cell proliferation within primarily the skin, but also various organs such as the bone marrow, liver, spleen, lymph nodes and the gastrointestinal system. Several factors are known to induce symptoms in patients with mastocytosis. A 13-year-old boy with cutaneous mastocytosis and type 1 diabetes mellitus developed multiple itchy papules 2 to 3 days after he started receiving insulin (lispro) pump therapy. Punch biopsy revealed widespread mast cell infiltration on the papillary dermis. We hypothesized that the insulin pump catheter caused a physical stimulus due to local micro-trauma and resulted in the formation of the lesions. We, therefore, discontinued insulin pump treatment and switched to SC insulin therapy. While previous lesions healed successfully, no new lesions occurred. To confirm our hypothesis, we repeated the procedure and observed the occurrence of similar lesions around the insulin pump catheter. Herein, we present for the first time, a patient with type 1 diabetes mellitus and cutaneous mastocytosis who developed exacerbation of lesions during insulin pump therapy.

Key words: Mastocytosis, catheter, trigger

ÖZ

Mastositoz cilt başta olmak üzere kemik iliği, karaciğer, dalak, lenf nodları ve gastrointestinal sistemde mast hücrelerinin klonal artışı karakterize nadir görülen bir hastalıktır. Bazı faktörlerin mastositozlu hastaların semptomlarını tetiklediği bilinmektedir. Bu yazıda, Tip 1 diabetes mellitus (DM) olan hastada, insülin pompa tedavisine bağlı semptomları tetiklenen kutanöz mastositoz olgusu sunulmuştur. Kutanöz mastositoz ve Tip 1 DM tanısı konulan 13 yaşındaki erkek çocukta, insülin pompa ile verilen insülin lispro tedavisinden 2-3 gün sonra meydana gelen çok sayıda kaşıntılı papüler lezyonlar görüldü. Mastositoz olarak değerlendirilen lezyonlardan alınan punch biyopside papiller dermiste yaygın mast hücre infiltrasyonu görüldü. Mevcut bulgulardan yola çıkarak, insülin pompa kateterinin lokal mikro travma ile fiziksel uyaran oluşturduğu ve mastositoz lezyonlarının buna bağlı meydana geldiği düşünüldü. Pompa insülin tedavisi kesilip kateter uygulamasından vazgeçildi. İzleminde yeni lezyon çıkmadığı ve gluteal ve periumblikal bölgedeki lezyonların da hiperpigmentasyon ile düzeldiği görüldü. Doğrulama için yeniden insülin pompa kateteri takılan yerlerde 3 gün sonra aynı lezyonlar tekrarladı. Bu olgu nedeniyle, en az 48 saatlik süre boyunca cilt altında kalan kateterin, mastositozda lezyonları tetikleyebileceğini literatürde ilk defa ortaya koyduk.

Anahtar kelimeler: Mastositoz, kateter, tetikleyici

Received: 23/07/2015 • **Accepted:** 21/12/2015

Geliş Tarihi: 23/07/2015 • **Kabul Tarihi:** 21/12/2015

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INTRODUCTION

Mastocytosis, which is one of the mast cell activation disorders, is a relatively infrequent disorder characterized by excessive proliferation of abnormal mast cells in the skin and in various tissues. The actual prevalence of mastocytosis is unknown, but an estimate from a recent population-based study is approximately 1/10,000 (1,2). Organ systems typically involved are the bone marrow, skin, liver, lymph nodes, and gastrointestinal tract. Mastocytosis is primarily classified as cutaneous and systemic. The diagnosis of cutaneous mastocytosis is established by integrating typical clinical and histological skin lesions in the absence of definitive criteria of systemic involvement. Based on the patterns of skin lesions 3 major clinical manifestations of cutaneous mastocytosis are distinguished: maculopapular type (namely, urticaria pigmentosa), diffuse cutaneous mastocytosis and solitary mastocytoma (2-5).

While adult-onset mastocytosis is associated with multi-organ involvement and follows a persistent course, pediatric mastocytosis is usually a skin-limited disease that spontaneously regresses with age. In children it is usually associated with pruritic, eczematous and vesicular lesions. Several factors are known to trigger symptoms in patients with mastocytosis. While bee sting (Hymenoptera stings), foods and drugs have been shown to provoke anaphylaxis in adults; fever and certain physical factors may cause mast cell degranulation in children. Rubbing, soft tissue trauma and mechanical irritation of skin such as invasive diagnostic procedures leads to release of mast cells mediators, and thus to reddening and urticarial swelling (3,4,6-8).

Type 1 diabetes mellitus (DM) is caused by insulin deficiency following destruction of the insulin-producing pancreatic beta cells and requires insulin treatment and regular monitoring. Multiple daily injection (MDI) regimens attempt to replicate normal insulin secretion through the use of a long-acting insulin analog to replace basal insulin analog to replace basal insulin needs along with bolus injections of rapid-acting insulin analog to cover food intake and to correct elevations in blood glucose levels (9). Continuous subcutaneous insulin infusion involves connection of a catheter on the outside of the body to an insulin pump that is programmed to supply the body's basal needs. Insulin pump therapy uses rapid-acting insulin analogs (insulin lispro, insulin aspart, insulin glulisine) to deliver insulin continuously (24/7). The patient with the pump administers doses to cover meals and correct blood glucose concentrations. A reservoir for the pump is filled with several days' worth of insulin. In conventional pumps, the reservoir attaches to a variable length of tubing, which in turn attaches to a small catheter or steel needle that is inserted into the subcutaneous tissue. The most common sites for insertion include the buttocks, abdomen, upper leg/hip and some children use their arms. Insertion of the infusion set is done by either the child or caregiver and should be done every 2 to 3 days. Insulin pumps cause fewer episodes of hyperglycemia and hypoglycemia than multiple daily injections (9-13).

Herein, we present for the first time, a patient with type 1 diabetes mellitus and cutaneous mastocytosis who developed exacerbation of lesions during insulin pump therapy.

CASE REPORT

A 13-year-old child presented with a childhood history of vesicular lesions on her legs and arms since the age of 6. Lesions used to be itchy and resolved within approximately two months with hyperpigmentation. The patient was diagnosed with cutaneous mastocytosis (urticaria pigmentosia or maculopapular type) following a positive Darier sign and the evaluation of a punch biopsy that revealed widespread mast cell infiltration. There were no associated systemic signs (flashing, hypotension or wheezing) and bone marrow aspiration was negative. Symptoms were well-controlled using antihistamines and no systemic signs were observed during the follow-up period. One and a half year ago the patient was diagnosed with type 1 diabetes mellitus after being hospitalized for diabetic ketoacidosis. During the course of his hospital stay he received subcutaneous (sc) insulin therapy (once daily glargine and 3 times daily lispro) and did not show reactivation of the cutaneous lesions. One month ago he started receiving insulin lispro with pump (Figure 1A-C) and after removing the catheter, within 2 to 3 days, he developed multiple itchy papules of less than 1 cm in diameter. The patient did not have any active skin lesions before insulin pump application. He was referred for consultation to the pediatric allergy and immunology unit.

On physical examination the respiratory rate was 24/min, peak heart rate 94/min and blood pressure 95/60

mmHg. He had multiple papillary lesions bilaterally in the gluteal region and around the umbilicus. Lesions were 4-10 mm in diameter and were not associated with hyperemia (Figure 2A,B).

The results of laboratory studies including complete blood cell count, chemistry panel and liver function tests were unremarkable. Additional examination revealed the following results: serum IgE: 5.0 mg/dL; IgG: 859 mg/dL, IgM: 80.3 mg/dL, IgA: 93.3 mg/dL, anti-HBs (+), C3: 99.5 mg/dL (79-152); C4: 19.7mg/dL (16-38), and serum tryptase 5µg/L. Atopy was evaluated using a skin prick test (SPT) and specific IgE (sIgE) measurements, as well as a core battery of allergens (e.g. dust mite, cockroach, cat, dog, mold, grass, tree, weed, milk, egg, peanut) and a clinic-specific battery of locally relevant allergens (ALK Abelló, Hørsholm, Denmark). SPT and sIgE were negative.

Following the confirmation of the diagnosis with the punch biopsy that revealed widespread mast cell infiltration

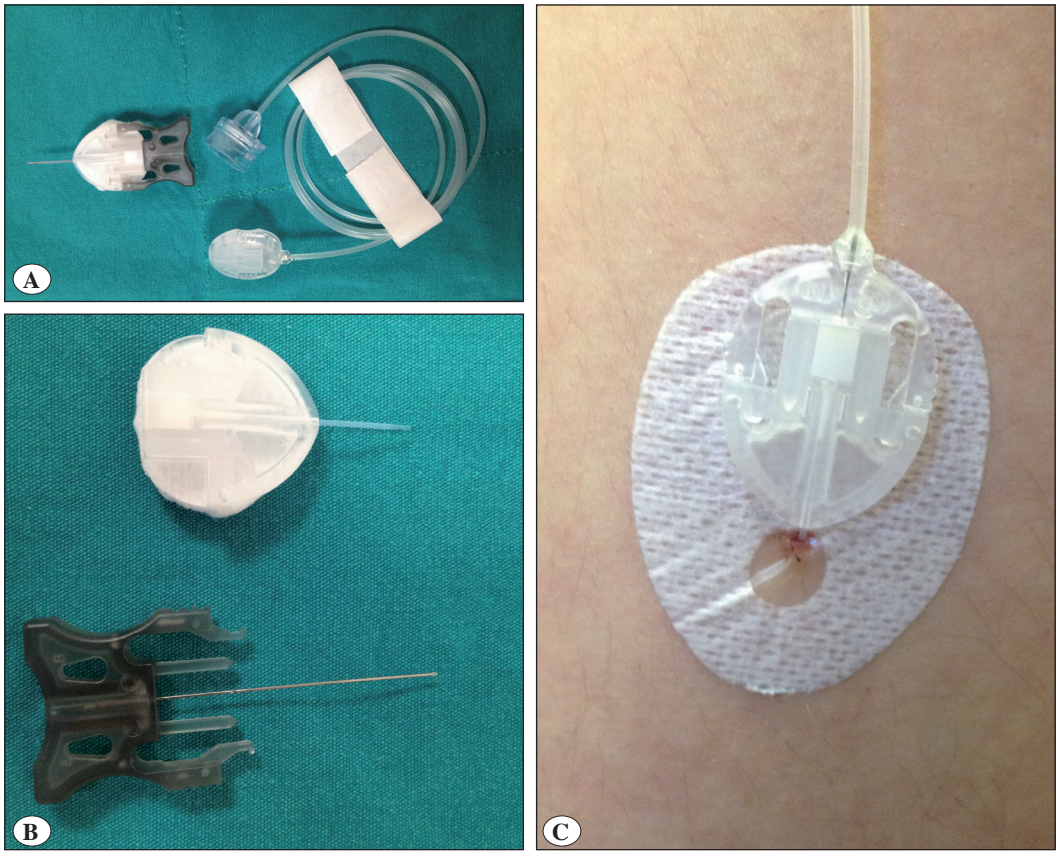

Figure 1. A) The insulin pump and the infusion set. **B)** The needle and the plastic catheter of the insulin pump. **C)** The inserted catheter under the skin.

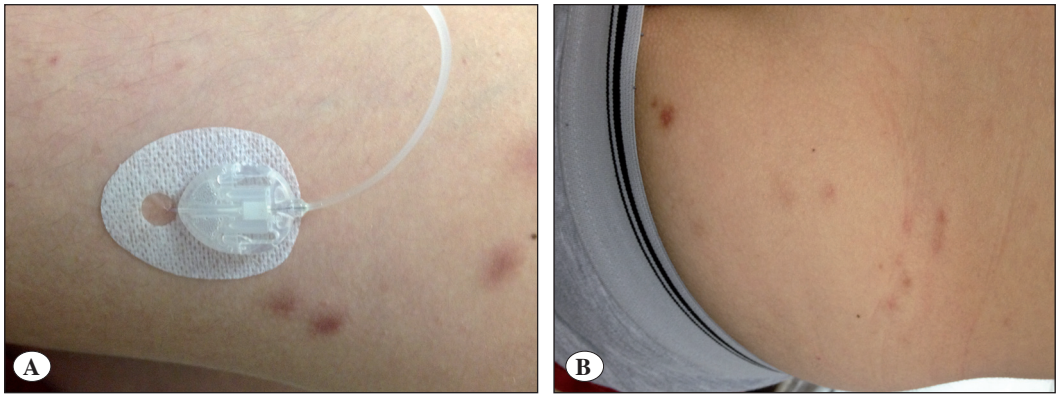

Figure 2. Macular lesions on the gluteal **(A)** and peri-umbilical **(B)** area.

on the papillary dermis (Figure 3A-C), antihistaminic treatment (cetirizine hydrochloride) was initiated. We hypothesized that the insulin pump catheter caused a physical stimulus due to local micro-trauma and resulted in the formation of the lesions. Therefore insulin pump treatment was discontinued and switched to sc insulin therapy (glargine and lispro). No new lesions developed thereafter and previous lesions healed successfully. To confirm our hypothesis, we repeated the procedure and observed the occurrence of similar lesions around the insulin pump catheter.

DISCUSSION

The most common form of mastocytosis in children, i.e. cutaneous mastocytosis, is usually diagnosed in the first years of life and it is commonly characterized by multiple hyperpigmented macular or maculopapular lesions. Patients with cutaneous mastocytosis do not fulfill the criteria for the diagnosis of systemic mastocytosis. The majority of children with cutaneous mastocytosis display spontaneous healing until early adulthood (2,14). Results from the National Institutes of Health (NIH) study revealed that 83% of children with mastocytosis present with pruritus, 65 % with flushing, 53% with vesicles, 41% with abdominal pain, 18 % with bone pain, and 12% with headache (15). Symptoms are triggered by mast cell hyperplasia and degranulation leading to the release of tryptase and histamine. Mast cells are activated through exposure to an antigen that cross-links allergen-specific IgE and many other triggers, including anaphylatoxins, aggregated IgG, certain drugs, venoms, cytokines, neuropeptides, and physical stimuli such as pressure and temperature changes. In children with cutaneous mastocytosis, symptoms are generally triggered by physical irritation, stress, exercise, and fever (2,3,5). In the current case report we observed that a plastic catheter, of approximately 2 cm in length, used for only 48 hrs during insulin pump therapy triggered cutaneous symptoms. We believe that the plastic catheter induced mast cell degranulation and caused cutaneous lesions.

While certain drugs, such as aspirin and non-steroidal anti-inflammatory drugs, opioids, general and local anaesthesia, contrast media, interferon, 2-chlorodeoxiadenosine, hydroxyurea, vaccines and dextrans, have been reported as possible triggers for mastocytosis symptoms, the association of insulin and mastocytosis has not yet been reported before.

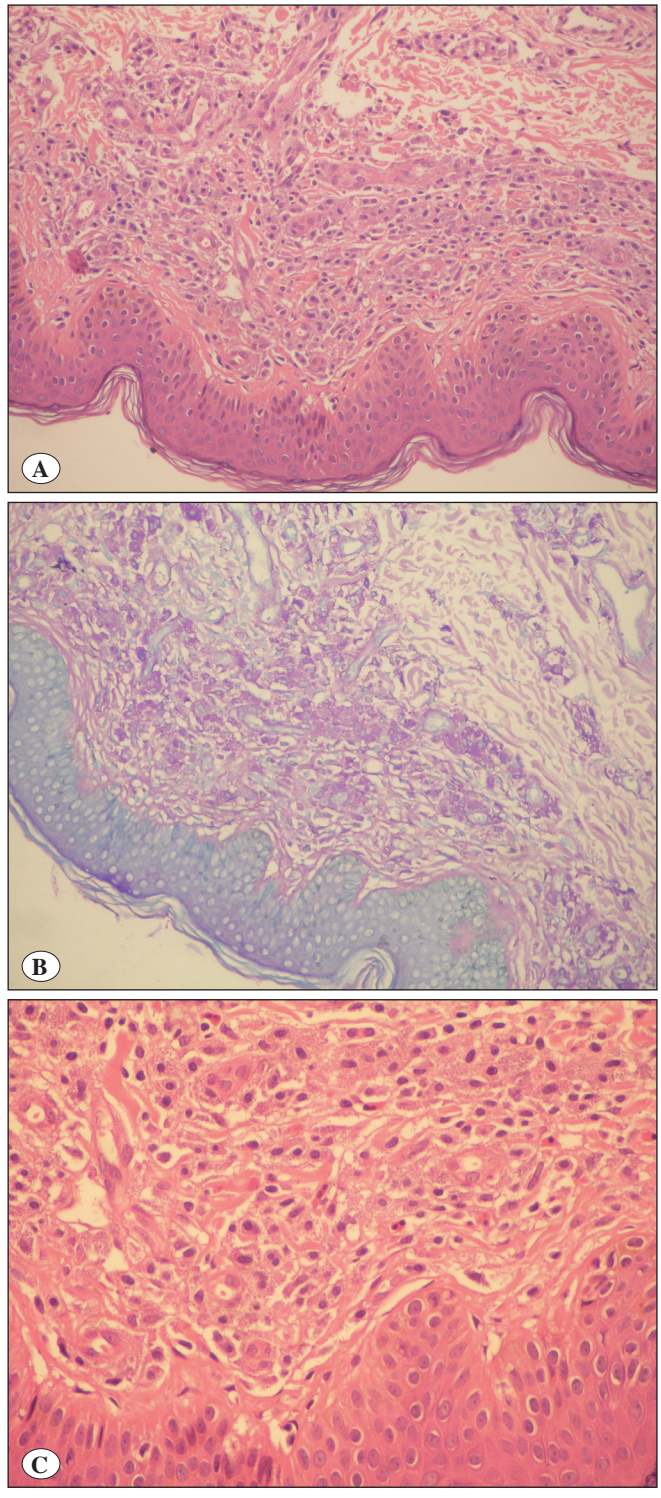

Figure 3. A) Mast cell infiltration in the papillary dermis (H&E x10 HPF). **B)** Mast cells stained with toluidine blue (toluidine blue x10 HPF). **C)** Mast cell proliferation stained with giemsa (giemsa x10 HPF).

Mast cell activation disorders are globally classified as primary, secondary and idiopathic. Primary mastocytosis is further classified into 7 sub-categories by The World Health Organization (WHO). While secondary mastocytosis is associated with IgE mediated or non-IgE mediated allergic disorders, idiopathic cases may be associated with potential underlying causes such as *Helicobacter pylori* infection, irritable bowel syndrome and autoimmune disorders (2,5). To the best of our knowledge, there is no established relationship between type 1 DM and mastocytosis and hence the two disorders should be regarded as two distinct conditions.

Insulin pump therapy has several advantages over multiple daily injections (MDI). Insulin pump therapy is more effective and safer for maintaining glycemic control. It minimizes diabetes-associated complications, provides higher flexibility in daily life, and improves quality of life (13,16,17). Pumps provide an accurate history of insulin use through their menus and often this history can be uploaded and displayed as a graph for purposes of trend analysis. Furthermore, insulin pumps result in fewer episodes of hyperglycemia and hypoglycemia than multiple daily injections (9,10). Taken together, insulin pump therapy is recommended as a treatment modality of choice in selected patients. Yet, we had to discontinue insulin pump therapy in our patient due to the aforementioned reactions observed following its use.

In brief, we have for the first time, reported the occurrence of cutaneous lesions in a patient with cutaneous mastocytosis under insulin pump therapy. Early recognition along with prompt and appropriate intervention may reduce symptoms and prevent the worsening of the condition.

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