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Case report

Vasculitis-like Palpable Purpuric Rush Induced by Decapeptyl in a Pediatric Patient Diagnosed Central Precocious Puberty: A Pediatric Case

Galip N et al. Vasculitis-like Rush Induced by Decapeptyl

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What is already known on this topic?
Drug induced vasculitis is an inflammation of blood vessels caused by pharmaceutical agents and is the most common form of vasculitis. Pathogenesis is not clear yet but many different drugs may cause similar clinical features suggesting a common mechanism. Skin manifestations are most common, following with renal involvement or lung involvement with interstitial pneumonia or acute respiratory distress syndrome. There are several systemic adverse reactions reported due to GRHa treatments including vasculitis-like rushes.

What this study adds?
This case is one of the few pediatric case of CPP experiencing vasculitis-like rushes due to tripotelin (Decapeptyl Depot ®) injection in the literature. It should be kept in mind that in pediatric PCC patients who develop side effects like cutaneous vasculitis, vasculitis-like rushes or other systemic adverse reactions, the treatment may be continued by changing the preparation.

Abstract
Central precocious puberty (CPP) is defined by the appearance of secondary sexual signs in girls younger than 8 years of age or the onset of menarche before the age of 10. Gonadotropin-releasing hormone analogs (GnRHa) are the most effective therapy in CPP. Drug-induced hypersensitivity vasculitis is an inflammation of blood vessels due to the use of several pharmacologic agents. We present the first pediatric case of vasculitis induced by Decapeptyl. 7 years and 3 months old girl admitted to Pediatric Endocrinology outpatient clinic with a complaint of premature breast development. The patient diagnosed CPP with her physical examination and laboratory findings and tripoteline acetate (Decapeptyl®) treatment initiated. She experienced multiple rushes on her body with a mild abdominal pain and high temperature after 8 hours from the second dose of Decapeptyl administration. She hospitalized with the diagnosis of drug-induced vasculitis and single dose of iv metyl-prednisolone 1 mg/kg treatment and oral cetirizine initiated. Her blood and urine analysis revealed no other organ involvement rather than skin. On the third day, all the purpuric lesions started to resolve and completely disappeared on the 6th day. Hereby, we described first pediatric case of CPP experiencing vasculitis due to tripotelin injection. Her treatment for PCC was switched to Depot Leuprolide acetate and she continued her treatment for 2 years uneventfully. It should be kept in mind that in pediatric PCC patients who develop side effects like cutaneous vasculitis, the treatment may be continued by changing the preparation.
Keywords: Drug-induced, central precocious puberty, vasculitis, vasculitis-like rush

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Introduction
Central precocious puberty (CPP) is defined by the appearance of secondary sexual signs in girls younger than 8 years of age or the onset of menarche before the age of 10 and may lead to premature epiphysial fusion with compromise in final adult stature (1) .
CPP occurs 1 in 5000 to 10,000 children and is more common in girls. The idiopathic form of CPP is usually due to the early maturation of the hypothalamic-pituitary-gonadal (HPG) axis without other pathological causes.
Gonadotropin-releasing hormone analogs (GnRHa) , which are able to desensitize the pituitary gland by GnRH release are the most effective therapy in CPP. In the early 1980s, several different formulations of GnRHa were developed with

different durations of action and routes of administration. However, during the past decade, there has been an increase in the number of extended-release formulations of GnRHa. GnRHa have a notable safety profile. The most commonly reported adverse events are injection-site reactions which are typically mild and self-limited.

Drug-induced hypersensitivity vasculitis is an inflammation of blood vessels due to the use of several pharmacologic agents. Decapeptyl is a GnRH analog which is widely used in invitro fertilization processes, sex hormone -dependent malignancies and precocious puberty. Recent studies have been shown immune-modulatory effects of GnRHa and sex steroids; activating role of estrogens in autoimmune disorders by enhancing humoral responses while testosterone enhances suppressor T cells (2, 3). GnRH s also play a role in gender differences in several autoimmune diseases with their immunostimulatory effect. They may also have an influence on the development of autoimmune disorders or worsening of preexisting diseases, however there is no comprehensive studies to prove this information. There are a few case reports about exacerbation of systemic lupus erythematosus related thrombocytopenia and lupus nephritis after GnRHa administration (4, 5), two cases of GnRHa induce vasculitis and one case of polymyositis in a patient treated with leuprolide acetate (6). But all these reports were in adults. The case we present will be the first one in the literature as a vasculitis induced by GnRHa used for the precocious puberty treatment of 7 years old girl.

Case Report

7 years and 3 months old girl admitted to University of Kyrenia, Dr Suat Gunsel Hospital Pediatric Endocrinology outpatient clinic with complaint of premature breast development since 6 months. Informed consent was obtained from her parents. She did not take any medication or had any significant medical history. Her family history revealed only Hashimoto thyroiditis in her father. Physical examination revealed a girl with weight of 24 kg and height of 126 cm with a normal psychomotor development. The patient presented a breast development of Tanner stage 2; with no pubic or axillary hair. Physical examination of other systems revealed normal. Bone Age according to Greulich and Pyle atlas was 9 years old. Pelvic ultrasound revealed an uterine long axis of 27.8 mm, anteroposterior diameter of 15 mm, transverse diameter of 6.1 mm (prepubertal measurements), right ovarian volume 1.3cm^3, left ovarian volume 1.6cm^3 (ovarian volumes were high according to age). Baseline LH was 0.37mIU/ml , FSH was 3.45 mIU/ml , estradiol <10 pg/ml , and prolactin was 6.32 pg/ml. LHRH stimulation test (by chemiluminescence microparticle immunoassay) results were given in Table 1. Her cranial MRI scan was normal. The patient diagnosed central precocious puberty with these findings and tripoteline acetate (Decapeptyl®) treatment initiated with the dose of 3,75mg/25 days. She has not experienced any side effects with the first dose of tripoteline acetate administration. She took the second dose after 25 days from the first dose and she experienced multiple rushes on her body with a mild abdominal pain after 8 hours from administration. Lesions gradually spread towards the upper leg and gluteal region and she was admitted to the emergency unit. Her temperature was 39° C and other vital signs were normal. Physical examination revealed a few maculopapular rushes on her arms and body (Figure 1) and non-blanching purpuric lesions on her legs and gluteal region (Figure 2), conjunctival hyperemia (Figure 3) and abdominal tenderness with palpation. In her blood analysis biochemical parameters were normal and CRP was 0.92 mg/dl. She had mild microcytic anemia with hemoglobin level 11.1 mg/dl with MCV: 58.2 fL. WBC: 8.300/mm3 and PLT count were 498000/mm3. Urine analysis and abdominal ultrasound were normal. The patient was hospitalized mainly for observational purposes. Her temperature fell with single dose paracetamol and did not repeat. Single dose of iv metyl-prednisolone 1mg/kg treatment and oral cetirizine was given in emergency department on her admission. Next day there were no new purpuric lesions and her abdominal pain was gone. Her stool checked for occult blood and was negative in three samples. On the second day of her hospitalization she was discharged from the hospital because her family wanted to continue the treatment at home. Diagnostic skin biopsy recommended but they refused. On the third day all the purpuric lesions started to resolve and there was no lesion on the 6th day. The adverse reaction due to the medication reported to national health authorities and the manufacturer.

Discussion

Medication induced clinical syndromes have been seen for many years and several syndromes are described either self-limiting or life threatening. Some may trigger autoimmune events or may confused with autoimmune diseases. Drug induced vasculitis is an inflammation of blood vessels caused by pharmaceutical agents and is the most common form of vasculitis. Inflammation may be short term (acute) or long-term (chronic) with a few or more organ involvement (7). Systemic form of drug induced vasculitis are rarely seen in patients on long term therapy whereas cutaneous vasculitis is more common(8,9). Drug induced vasculitis usually affect skin and rarely kidneys and lungs(10,11). Pathogenesis is not clear yet but many different drugs may cause similar clinical features suggesting a common mechanism.

A type of anti-neutrophil cytoplasm antibodies (ANCA) associated vasculitis is described in 2000's related to long term use of anti-thyroid medications (12). Since then many other drugs such as antibiotics, anti-tumor necrosis factor alpha agents or psychoactive agents are blamed for ANCA-associated vasculitis (7). Detection of ANCA assays and tissue biopsies are recommended for diagnosis and differential diagnosis of drug-induced vasculitis (13,14).

Usually clinical manifestations of drug induced vasculitis are similar with primary vasculitic syndromes. Skin manifestations are most common, following with renal involvement with varying symptoms like hematuria, proteinuria, or elevated serum creatinine (15).

Some patients may suffer only lung involvement with interstitial pneumonia or acute respiratory distress syndrome (16,17). There are no specific laboratory tests for diagnosis of drug -induced vasculitis, however some laboratory markers may help to distinguish drug induced vasculitis from idiopathic autoimmune diseases such as ANCA, Anti-ds DNA antibodies or Antiphospholipid antibodies. Some laboratory findings may indicate organ involvements, anemia is common whereas acute-phase reactants such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) which are usually elevated are not sensitive or specific for drug-induced vasculitis (13,18). Our case also presented with anemia and slightly elevated CRP level.

Treatment options for drug-induced vasculitis depends on the patients' individualized maintenance. Depending on clinical course and organ involvement of drug-induced vasculitis there is no standard approach for treatment but first step is the discontinuation of medication as we recommended to our patient. Corticosteroids, cyclophosphamide, azathioprine and mycophenolate mofetil are among the available treatment options (19).

In the literature, there are a few case reports defining vasculitis or vasculitis-like rushes following the treatment with GnRHa. First one was reported in 1993 in a 23-year old woman after the first course of Decapeptyl used for in vitro fertilization procedure (20). The patient experienced purpuric papular rushes similarly to our pediatric case and lesions resolved in a few days with oral antihistamine and topical corticosteroid cream (20). Second one was a 67- year old man experiencing fever, rush and arthritis after the second dose of leuprolide (Lucrin) administration for his prostatic cancer and treated with steroids (6). Another case reported in 2010, was a 26-year old woman with a history of previous autoimmune and neuromuscular disease, experiencing polymyositis and vasculitis 5 days after GnRH analogue (Decapeptyl) administration (21).

Kirkgoz et al. recently reported 9 pediatric cases experienced systemic hypersensitivity reactions to GRHa during the treatment of CPP. One of the cases in this report were quite similar to our case with palpable purpuric rushes on her legs who considered as Henoch-Schönlein Purpura (HSP) by her pediatrician. This case also resolved without treatment in 1 week and the patients treatment switched to Leuprolide acetate successfully (22).

Hereby, we described a pediatric case of CPP experiencing vasculitis-like rushes due to tripotelin (Decapeptyl Depot ®) injection. Due to mild clinical course, absence of extracutaneous organ involvement and rapid recovery no further tests or biopsy was required.

However there is a limitation for the article that we could not clarify the histopathological diagnosis with biopsy.

Her treatment for PCC was switched to Depot Leuprolide acetate (Lucrin Depot® 11,25/ 3 months) and she continued her treatment for 2 years uneventfully. This makes us think that apart from the active ingredient of the drug, solvents may also cause such side effects. It should be kept in mind that in pediatric PCC patients who develop side effects like cutaneous vasculitis, the treatment may be continued by changing the preparation.

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Table 1. LHRH stimulation test results

Time (min)	LH mIU/ml	FSH mIU/ml	Estradiol pg/ml
0	0.34	4.33	16
30	5.85	11.94	
60	5.61	13.29	
90	4.56	14.31	17

Figure 1.

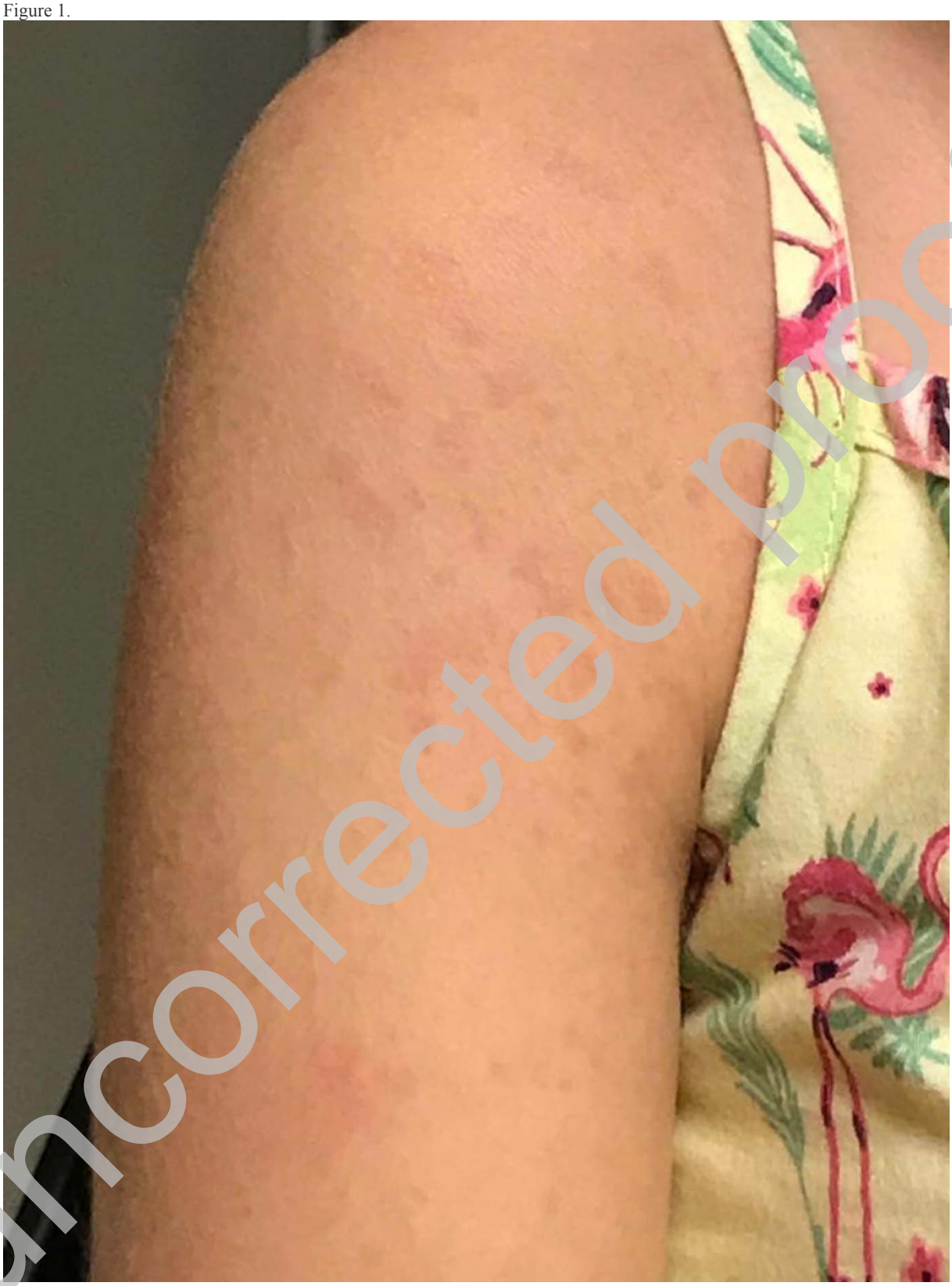

Figure 2.

Figure 3.