CASE REPORT

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Vasculitis-like Palpable Purpuric Rash Induced by Decapeptyl in a Pediatric Patient Diagnosed Central Precocious Puberty

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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 fully undersdtood but many different drugs may cause similar clinical features, suggesting a common mechanism. Skin manifestations are most common, followed by renal involvement or lung involvement usually manifesting as interstitial pneumonia or acute respiratory distress syndrome. There are several systemic adverse reactions reported due to gonadotropin-releasing hormone analogs, including vasculitis-like rashes.

What this study adds?

This is one of the few reported pediatric cases of central precocious puberty (CPP) associated with vasculitis-like rash due to tripotelin (Decapeptyl Depot®) injection. This case will raise awareness of this association so that if pediatric patients with CPP and who develop side-effects such as cutaneous vasculitis, vasculitis-like rashes or other systemic adverse reactions, the management may continue with an alternative preparation.

Abstract

Central precocious puberty (CPP) is defined as the appearance of secondary sexual signs in girls younger than eight years of age or the onset of menarche before the age of 10 years. Gonadotropin-releasing hormone analogs (GnRHa) are the most effective therapy in CPP. Drug-induced hypersensitivity vasculitis is an inflammation of blood vessels, which may be due to the use of a number of pharmacologic agents. This case report describes drug-induced vasculitis in a girl being treated with Decapeptyl. A 7.25 year-old girl was admitted to Pediatric Endocrinology outpatients with premature breast development. She was diagnosed with CPP on the basis of physical examination and laboratory findings and tripoteline acetate (Decapeptyl®) treatment was initiated. She experienced multiple widespread skin rashes and mild abdominal pain with high temperature eight hours after the second dose of Decapeptyl. She was admitted to hospital with the diagnosis of drug-induced vasculitis and a single dose of intravenous methyl-prednisolone (1 mg/kg) and oral cetirizine was given. Her blood and urine analysis revealed no other organ involvement, other than skin. On the third day, the purpuric lesions began to resolve and had completely disappeared by the sixth day. Her treatment for CPP was switched to Depot Leuprolide acetate and she continued her treatment for two years uneventfully. To the best of our knowledge, this is the first report of a child with CPP experiencing drug-induced vasculitis due to tripotelin injection. Effective treatment may be continued by switching to an alternative gonadotropin releasing hormone analog.

Keywords: Drug-induced, central precocious puberty, vasculitis, vasculitis-like rash

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Introduction

Central precocious puberty (CPP) is defined as the appearance of secondary sexual signs in girls younger than eight years of age or the onset of menarche before the age of 10 years. CPP may lead to premature epiphysial fusion with compromise in final adult stature and thus usually requires medical intervention (1).

The incidence of CPP is estimated as 1 in 5000 to 10,000 children and is more common in girls. The idiopathic form of CPP is due to the early maturation of the hypothalamic-pituitary-gonadal axis in the absence of other pathological causes.

Gonadotropin-releasing hormone analogs (GnRHa), which are able to desensitize the pituitary gland to endogenous GnRH 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 good safety profile. The most commonly reported adverse events are injection-site reactions which are typically mild and self-limited (1).

Drug-induced hypersensitivity vasculitis is an inflammation of blood vessels that has been linked to the use of several pharmacologic agents. Decapeptyl is a GnRHa which is widely used in *in vitro* fertilization processes, sex hormone-dependent malignancies and CPP. Recent studies have demonstrated the immune-modulatory effects of GnRHa and sex steroids; estrogens have an activating role in some autoimmune disorders by enhancing humoral responses while testosterone enhances suppressor T cells (2,3). GnRHas also play a role in sex-differences evident in several autoimmune diseases, probably because of their immunostimulatory effect and may also modulate the development of autoimmune disorders or worsening of preexisting diseases. However, this association between GnRH and autoimmunity remains hypothetical due to the lack of conclusive evidence. There are, however, a few case reports of the exacerbation of systemic lupus erythematosus-related thrombocytopenia and lupus nephritis after GnRHa administration (4,5), two cases of GnRHa induced vasculitis and one case of polymyositis in a patient treated with leuprolide acetate (6). All of these reports were in adult patients. We present a case of vasculitis induced by GnRHa treatment for CPP in a seven year old girl, which, to the best of our knowledge is the first published report of pediatric GnRHa-induced vasculitis.

Case Report

A girl, aged 7.4 years, was admitted to the University of Kyrenia, Dr. Suat Günsel Hospital, Pediatric Endocrinology outpatient clinic with a six-month history of premature breast development. She did not take any medication nor have any significant medical history. Her family history revealed only Hashimoto thyroiditis in her father. On physical examination, she had a weight of 24 kg (-0.01) and height of 126 cm (0.52) with normal psychomotor development. Breast development was Tanner stage 2 with no pubic or axillary hair. The rest of the physical examination was unremarkable. Bone age according to Greulich and Pyle atlas was 9 years. Pelvic ultrasound revealed a uterine long axis of 27.8 mm, anteroposterior diameter of 15 mm, transverse diameter of 6.1 mm consistent with prepubertal measurements, while right and left ovarian volumes were 1.3 cm^3 and 1.6 cm^3 which were highfor chronological age. Baseline luteinizing hormone (LH) was 0.37 mIU/mL, follicle stimulating hormone was 3.45 mIU/mL, estradiol < 10 pg/mL and prolactin 6.32 pg/mL. LH releasing hormone stimulation test results, assessed by chemiluminescence microparticle immunoassay, are given in Table 1. Her cranial magnetic resonance imaging scan was normal. On the basis of these findings she was diagnosed with CPP and tripoteline acetate (Decapeptyl®) treatment was initiated at 3.75 mg/25 days. She did not experienced any side effects with the first dose of tripoteline acetate.

After 25 days, she was given the second dose and she experienced multiple rashes on her body with mild abdominal pain starting eight hours after drug 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 rashes on her arms and body (Figure 1)

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

LHRH: luteinizing hormone releasing hormone, FSH: follicle stimulating hormone

and non-blanching purpuric lesions on her legs and gluteal region (Figure 2), conjunctival hyperemia (Figure 3) and abdominal tenderness with palpation. Blood tests showed normal biochemical parameters and C-reactive protein (CRP) was 0.92 mg/dL. She had mild microcytic anemia with hemoglobin level 11.1 mg/dL, mean cell volume 58.2 fL, white cell count 8,300/mm^3 and platelet count 498,000/mm^3. Urine analysis and abdominal ultrasound were normal. The patient was hospitalized in order to continue observation. Her temperature fell with a single dose of paracetamol and did not rise again thereafter. A single dose of intravenous methyl-prednisolone (1 mg/kg) and oral cetirizine were given in the emergency department on admission. On the next day, there were no new purpuric lesions and her abdominal pain had resolved. Her stool was checked for occult blood and was negative in three samples. On the second day of hospitalization she was discharged from the hospital because her family wanted to continue the treatment at home. Diagnostic skin biopsy was recommended but was refused. On the third day, all the purpuric lesions began to resolve and there was no evident lesions by the sixth day. This adverse reaction, apparently due to the tripoteline acetate medication, was reported to the national health authorities and the manufacturer. Informed consent was obtained from her parents. For medical exam and publication.

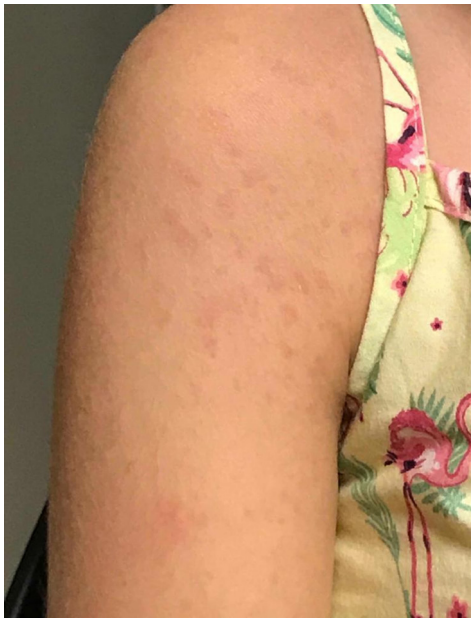

Figure 1. Maculopapular rashes on arms

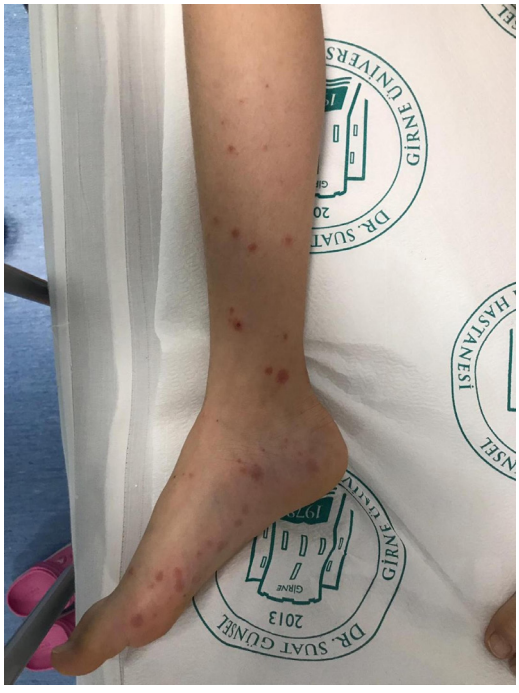

Figure 2. Non-blanching purpuric lesions on her legs

Discussion

Drug-induced clinical syndromes have been recognized for many years and range from self-limiting to life threatening. Some may trigger autoimmune events or may be confused with autoimmune disease. 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 variable non-dermatological organ involvement (7). The systemic form of drug-induced vasculitis is rarely seen in patients on long term therapy, whereas cutaneous vasculitis is more common (8,9).

Drug-induced vasculitis usually affects skin and, rarely, the kidneys and lungs (10,11). Pathogenesis is not clear but

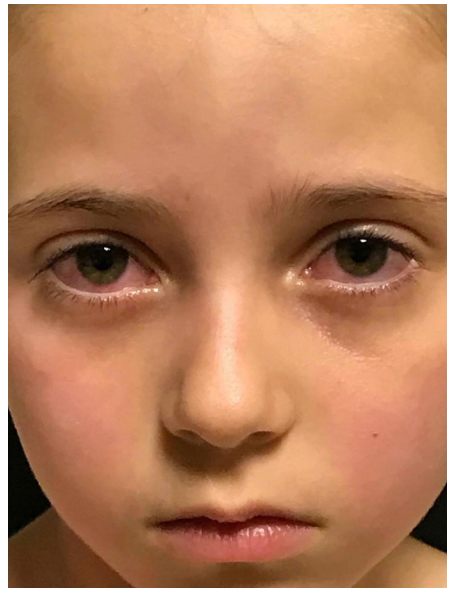

Figure 3. Conjunctival hyperemia

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 have been associated with ANCA-associated vasculitis (7). Tests for ANCA 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 to primary vasculitic syndromes. Skin manifestations are most common, followed by renal involvement with varying symptoms, such as 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, but some laboratory markers may help to distinguish drug induced vasculitis from idiopathic autoimmune diseases. These biomarkers include ANCA, anti-double-stranded DNA antibodies or antiphospholipid antibodies. Some laboratory findings may indicate organ involvement. Anemia is common but acute-phase reactants such as the erythrocyte sedimentation rate or CRP which are usually elevated in autoimmunity, are not sensitive or specific for drug-induced vasculitis (13,18). The presented case presented with anemia and slightly elevated CRP level.

Treatment options for drug-induced vasculitis depends on the patients' individualized maintenance. Clinical course and specific organ involvement in each case of drug-induced vasculitis will determine optimum treatment and there is no standard approach but the first step is the discontinuation of the likely causative medication, as was recommended in this case. Corticosteroids, cyclophosphamide, azathioprine and mycophenolate mofetil are among the available treatment options (19).

There are a few case reports describing vasculitis or vasculitis-like rashes following treatment with GnRHa. The first was reported in 1993 in a 23-year old woman after the first course of Decapeptyl used for *in vitro* fertilization (20). The patient experienced purpuric papular rashes, similarly to those seen in this pediatric case, and lesions resolved in a few days with oral antihistamine and topical corticosteroid cream (20). The second case was a 67-year old man who experienced fever, rash and arthritis after the second dose of leuprolide (Lucrin®) for prostate cancer and was subsequently treated with steroids (6). Another interesting case, reported in 2010, was a 26-year old woman with a history of previous autoimmune and neuromuscular disease, experiencing polymyositis and vasculitis five days after GnRH analogue (Decapeptyl) administration (21).

Kirkgoz et al. (22) recently reported nine pediatric cases experienced systemic hypersensitivity reactions to GnRHa during the treatment of CPP. One of the cases in this report had similarities to the currently presented case with palpable purpuric rash on her legs, which was assumed to be Henoch-Schönlein purpura by her pediatrician. This case also resolved without treatment in one week and the patient was successfully switched to Leuprolide acetate.

Conclusion

In summary, we described a pediatric case of CPP experiencing vasculitis-like rashes due to tripoteline acetate (Decapeptyl Depot®) injection. Due to the mild clinical course, absence of extracutaneous organ involvement and rapid recovery, no further tests or biopsies were performed. However, this represents a limitation of this report as we could not clarify the diagnosis with histopathological confirmation. Her treatment for CPP was switched to Depot Leuprolide acetate (Lucrin Depot® 11.25/3 months) and she continued her treatment successfully for two years. 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 CPP, patients who develop side effects such as cutaneous vasculitis may be successfully treated by changing the GnRHa preparation.

Ethics

Informed Consent: Informed consent was obtained from her parents.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Nilüfer Galip, Nermin Ankay, Rüveyde Bundak, Concept: Nilüfer Galip, Rüveyde Bundak, Design: Nilüfer Galip, Rüveyde Bundak, Data Collection or Processing: Nermin Ankay, Literature Search: Nilüfer Galip, Writing: Nilüfer Galip, Rüveyde Bundak.

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