DOI: 10.59213/TP.2024.117
Trends in Pediatrics 2024;5(1):20-24

Case Report

Sterile abscess formation with two different GnRH analogues: Three case reports

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Cite this article as: Karacan Küçükali G, Özalkak Ş, Peltek Kendirci HN, Bostancı İ, Savaş Erdeve Ş, Çetinkaya S. Sterile abscess formation with two different GnRH analogues: three case reports. Trends in Pediatrics. 2024;5(1):20-24.

ABSTRACT

Gonadotropin-releasing hormone analogues (GnRHa) have been used safely for many years in the treatment of precocious puberty. Although rare, pain, swelling, and erythema at the injection site are known local side effects in patients receiving GnRHa treatment and are temporary. Sterile abscess development is also one of the rare local side effects. Here, we present three cases of treatment failure due to the development of sterile abscesses after GnRHa therapy.

Sterile abscesses developed in three girls who were followed up with a diagnosis of precocious/progressive puberty respectively in 4., 12. and 5. doses of GnRHa treatment. In the first case, a sterile abscess recurred despite the therapy being switched to another preparation. We had to follow up without treatment in three of our cases.

Although sterile abscess is a rare side effect, it is essential as it causes patients to be left untreated. In these cases, the drug's active substance accumulates in the localization at the sterile abscess and cannot be absorbed, so it cannot enter the systemic circulation. Therefore, puberty cannot be suppressed. Also, a remaining scar is annoying for patients and their families.

Keywords: Precocious puberty, GnRH analogues, local reactions, leuprolide acetate, triptorelin, sterile abscess

INTRODUCTION

Central precocious puberty is the onset of puberty with early activation of the hypothalamic-pituitary-gonad axis. GnRH analogues (GnRHa) have been used safely for many years in central precocious puberty treatment.[1] Local reactions with GnRH analogues, such as pain, swelling, redness, and temperature, are seen in 10-15%, and a sterile abscess is seen in 0.6-3%.[2-5] The sterile abscess is an abscess formation that is not caused by pyogenic bacteria.[5] Besides local reactions, treatment ineffectiveness is the main problem in these cases. Here, three patients who developed sterile abscesses during triptorelin (TA) and leuprolide acetate (LA) treatments will be presented in terms of difficulties in treatment and follow-up plans.

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Received: 29.12.2023 **Accepted:** 04.03.2024

CASE REPORT

The patients who were followed up with central precocious puberty between 2018 and 2020 in the Pediatric Endocrine Clinic of our hospital were evaluated for sterile abscesses. Three (1.07 %) of the 278 patients receiving TA or LA had sterile abscesses. None of the cases had a known allergy history. The characteristics of three cases, initiation of treatment, the development process of sterile abscess, and their subsequent management are given below. Anthropometric and laboratory data of the cases are presented in Table 1.

Informed consent was obtained from the parents of the patients for publication of this case series.

Table 1. The clinical and laboratory characteristics of the patients at admission

	1. Patient	2. Patient	3. Patient
Age (years)	$6^{5/12}$ -year-old	$7^{2/12}$-year-old	$8^{7/12}$-year-old
Complaint	Pubic hair	Breast development	Breast development
Weight (kg)/SDS	32 (2.38)	31.1 (1.62)	39 (1.8)
Height (cm)/SDS	130.5 (2.66)	124.3 (0.38)	137 (1.23)
BMI (kg/m^2)/SDS	18.85 (1.48)	20.13 (1.73)	20.7 (1.58)
Breast Tanner stage Pubic Tanner stage	III III Clitoromegaly	III I	III III
Bone Age	11 years	8 years 10 months	11 years
Mother'/Father' height (cm) MPH (cm)/SDS	Height of the parents is unknown (adopted child)	149/170.6 153.3(-1.67)	160/171 159(-0.7)
LABORATORY			
LH (mIU/L)	0.1	<0.07	9.41
FSH (mIU/L)	2	2.41	7.79
E2 (pg/ml)	<12.1	12.9	45.7
Peak LH	24.2	9.27	-
Peak FSH	17.57	14.6	-
Standard dose ACTH stimulation test	Peak cortisol 10µg/dl Peak 17OHP 42.2 ng/ml		
Pelvic USG	Pubertal	Pubertal	Pubertal
Tryptase (µg/l)	-	38.6	3.98
Diagnosis	CAH+ Central puberty precocious	Central puberty precocious	Rapidly progressive puberty
Treatment	Hydrocortisone+ leuprolide acetate	Leuprolide acetate	Leuprolide acetate
Which drug causes sterile abscess	Leuprolide acetate triptorelin	Leuprolide acetate	Leuprolide acetate
Last drug doses	7.5 mg/28 days	3.75 mg/28 days	7.5 mg/28 days
At what dose it developed	4.	12.	5.
Injection site change	Sterile abscess persisted	Sterile abscess persisted	Sterile abscess persisted

SDS: Standard deviation score, BMI: Body mass index, MPH: Mid parental height, USG: ultrasonography, CAH: Congenital adrenal hyperplasia, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, E2: Estradiol, ACTH: Adrenocorticotropic hormone, 17OHP: 17-Hydroxyprogesterone.

Case 1

An "adopted" girl, aged $6^{5/12}$ -years, was admitted to the outpatient clinic with a complaint of pubic hair. The case was diagnosed with non-classical congenital adrenal hyperplasia and central precocious puberty with the clinical and laboratory data presented in Table 1. She was commenced on subcutaneous (sc) leuprolide acetate depot 3.75 mg every 28 days and 12 mg/m^2/d hydrocortisone.

The patient complained only pain at the injection site after the first three doses. Since pubertal suppression could not be achieved at the time of the fourth injection, a GnRH test was performed to ascertain the adequacy of suppression of puberty, and the treatment dose had to be increased by 7.5 mg / 28 days.

Unfortunately, she suffered a local reaction with erythema consistent with an abscess. Since no microorganism was seen in the gram stain and no growth in the culture, a sterile abscess was considered.

Due to the reaction, the treatment was switched to TA. Sterile abscess formation also developed after the injection of TA. The patient was consulted with the allergy department. Sterile abscesses also developed during the test by changing the site in the allergy department. To exclude local reaction at the injection site, medication was applied to the area that had not been injected before, and a sterile abscess developed after the third day. It was planned to switch to a nasal GnRH analogue (nafarelin), but the drug could not be obtained due to the high cost. After the family consultation, the treatment was discontinued in the patient whose bone age was 12.

Case 2

A $7^{2/12}$-year-old girl was admitted to the outpatient clinic with complaints of breast development and was diagnosed with precocious puberty.

LA treatment was started at a dose of 3.75 mg per 28 days subcutaneously. In the first year of treatment, sterile abscess formation developed at the injection site. The allergy department consultation recommended measuring her serum tryptase level because her examination revealed a positive "Darier's sign". It was found to be quite high (38.6 µg/l, n=0-11.4). Repeated tryptase value revealed > 20 g/l, and due to the risk of anaphylaxis, the treatment was discontinued with the family's consent. The case was followed up for mastocytosis.

Table 2. The laboratory results of patients after GnRHa injection

	1. Patient	2. Patient	3. Patient
LH (mIU/mL)	18.9	5.5	6.33
FSH (mIU/mL)	26.6	7.89	10.09
E2 (pg/ml)	48.4	28.2	33.2

LH: Luteinizing hormone, FSH: Follicle stimulating hormone, E2: Estradiol.

Case 3

An $8^{7/12}$-year-old girl was admitted to the outpatient clinic with complaints of breast development. Her signs of puberty started at the age of 8. The patient was diagnosed with rapidly progressive central precocious puberty with the clinical and laboratory data presented in Table 1. LA treatment was started at a dose of 3.75 mg/sc every 28 days. It was learned that the patient had pain after the first injection, and then erythema was added to the pain with subsequent doses. Since LH values were not suppressed in the GnRH analogue test at the time of the fourth injection, the dose was increased (7.5 mg / every 28 days). After the dose increment, sterile abscess formation developed. Switching to TA was planned, but the family refused the treatment.

The laboratory results of patients after GnRHa injection are given in Table 2.

DISCUSSION

GnRHa therapy has been used safely for many years in the treatment of central precocious puberty.[1] It is known that GnRHa treatment may have local side effects.[1] The development of a sterile abscess, one of the local side effects, was first reported in one case by Neely et al.[2] As in our patients, due to the development of sterile abscess with both LA and TA, it is thought that this situation is not against the active ingredient but against the inert polymer (lactic and glycolic acid used as copolymer).[4-6]

The reports of cases developing sterile abscesses with daily leuprolide, which does not contain polymers, are conflicting. It has been reported that the patient who developed a sterile abscess with a three-month depot form containing inert polymer was successfully treated with non-polymer daily applied LA.[6] However, in two cases using depot leuprolide, the treatment was changed to daily administered LA due to local reaction (one

of which was a sterile abscess). While one case was treated successfully, it was reported that the treatment was discontinued in one patient because local erythema developed in the eighth month of the treatment.[2] It has been reported that after the first idiosyncratic reaction against the drug-copolymer combination, a reaction may develop against the drug alone or the copolymer alone.[7] When the first case of Kirkgoz et al. developed urticaria with TA, her treatment was changed to LA. The case developed anaphylaxis in the second year of LA treatment. However, no problem has been reported with the change of treatment in other cases in this series.[8]

Sterile abscess formation was observed in only 1.07 % of the patients who received treatment for early puberty in our clinic. This rate was reported as 0.6% by Lee et al.[5] Before abscess formation is observed in these cases, it is noteworthy that there is pain and swelling at the injection site. Similarly, it is observed that most of the cases reported in the literature have local side effects such as pain, swelling, and erythema before the development of sterile abscess.[4,5,9] It is essential to follow up closely for the development of sterile abscesses in cases with local side effects. A sterile abscess can heal with or without a scar. Scar appearance can cause discomfort in families and patients. For this reason, in cases with local side effects such as pain, swelling, and erythema after injection, it will be beneficial to continue the subsequent injections from the hip rather than the arm, which is a visible place, at least to hide the scar appearance due to the sterile abscess that may occur in the future.

Another problem besides local side effects is treatment failure due to impaired drug absorption. Although changing the preparation seems to be an option, it should be kept in mind that a sterile abscess may develop with the other preparation, as in our first case. In another study evaluating 49 precocious puberty cases, local reaction was observed in two cases, and one of them was stated to be a sterile abscess. It was also emphasized that there was a failure in the suppression of puberty in both cases.[9] Tonini et al. reported that two of the 20 cases (one girl and one boy) developed local reactions, one progressed to sterile abscess, and puberty precocious treatment failed.[3] There are also reported cases in the literature that followed an uneventful treatment process with preparation change.[4,5] As reported by Miller et al., in an 8-year-old patient who received a monthly 15 mg LA treatment, a 50 mg histrelin implant (nonbiodegradable, diffusion-controlled, polymer reservoir containing histrelin acetate) was placed sc on the arm after the development of a sterile abscess.[4] When a reaction was observed with this treatment, the treatment process was completed without any problem with intranasal nafarelin. It has been reported that the development of sterile abscess was observed with LA, TA, and goserelin in a male patient with puberty precocious due to hypothalamic hamartoma when he was two and a half years old. GnRHa treatment was terminated due to treatment failure and was switched to cyproterone acetate.[10] In addition, although it has been reported that local side effects are more common with LA[5], this result is thought to be due to the more common use of LA treatment in recent years.

No evidence that changing the injection site or choosing the subcutaneous/intramuscular (IM) method makes any difference in antigenic terms. Although the injection site was changed in our second case, sterile abscess formation was repeated. Lee et al. reported two cases taking LA (SC), and after the abscess formation, it was switched to TA (IM) with no further reactions. In the same report, the third case developed an abscess under the LA treatment; thereafter, the therapy was switched to the triptorelin acetate depot, which was IM injected in the buttock, but abscess formation was repeated.[5]

Tryptase is a serine protease released from mast cells and a reliable marker of mast cell activation.[11] There is a risk of mastocytosis development in any period of life in cases with serum tryptase > 20 g/l examined at two different times, and the cases should be followed up in this respect.[11] It was planned to follow up on our second case from this point of view and study the c-kit mutation.

CONCLUSION

In conclusion, GnRHa therapy is safe to use in central precocious puberty treatment. However, it should be remembered that local reactions such as sterile abscesses may occur rarely.

Limitations

The limitation of our study is the lack of microscopic examination of abscesses in our cases.

Ethical approval

Ethical approval was not received because it was a retrospective case study. Written informed consents were obtained from parents of the patients.

Author contribution

Surgical and Medical Practices: GKK, ŞÖ, HNPK, İB, ŞSE, SÇ; Concept: GKK,SÇ; Design: GKK, SÇ; Data Collection or Processing: GKK, ŞÖ, HNPK, İB, ŞSE, SÇ ; Analysis or Interpretation: GKK, İB, SÇ; Literature Search: GKK, İB, SÇ; Writing: GKK, İB, SÇ. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

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