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OLGU SUNUMU CASE REPORT

Desensitization to allopurinol in a patient with fixed drug eruption

Allopürinole bağlı fiks ilaç erüpsiyonu gelişen bir hastada desensitizasyon

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ABSTRACT

Allopurinol is the most commonly prescribed urate-lowering drug. Hypersensitivity-type reactions have been reported with its use, and in this case, desensitization is the only viable therapeutic option. Limited availability of equally effective and alternative urate-lowering drugs is an important problem in patients intolerant to allopurinol. Few cases of desensitization to allopurinol because of a fixed drug eruption have been reported in the literature. A 43 years-old male with the diagnosis of polyarticular, tophaceous gout, who had been treated for hyperuricemia for 17 years, was referred to our allergy unit from the rheumatology department with the suspicion of hypersensitivity to allopurinol. An oral provocation test with the full therapeutic dose of allopurinol was performed, and 0.5 to 3 cm hyperpigmented macules developed on his trunk and legs eight hours after provocation. After the established diagnosis of fixed drug eruption due to allopurinol, the drug was reintroduced according to the modified Meyrier regimen. During the follow-up of four months, there was no recurrence of drug eruptions. Desensitization with allopurinol should be considered for effective treatment of gout in such patients.

ÖZET

Allopürinol en sık reçetelenen ürik asit düşürücü ilaçtır. Kullanımı sonucu hipersensitivite reaksiyonları rapor edilmiştir. Allopürinol kullanımı gerekiyorsa, desensitizasyon yapılması önerilir. Hipersensitivite reaksiyonu gelişen hastada, allopürinol kadar etkin ve alternatif tedavi seçeneği kısıtlı olduğu için tedavi de sıkıntılı olmaktadır. Literatürde allopürinole bağlı fiks ilaç erüpsiyonu nedeniyle desensitizasyon uygulanan az sayıda olgu bildirimi vardır. Kırk üç yaşında erkek hasta, 17 yıldır poliartiküler tofüslü gut tanısıyla romatoloji bölümünde takip edilmekteyken, allopürinol hipersensitivitesi düşünülerek tarafımıza yönlendirildi. Allopürinol ile oral provokasyondan sekiz saat sonra gövde ve bacaklarda 0.5-3 cm boyutlarında hiperpigmente maküler erüpsiyonlar gözlendi. Allopürinole bağlı fiks ilaç erüpsiyonu tanısı alan hastaya modifiye Meyrier protokolü ile desensitizasyon uygulandı. Dört aylık takipte fiks ilaç erüpsiyonu gözlenmedi. Sonuç olarak, hipersensitivite reaksiyonu gözlenen hastalarda allopürinol ile desensitizasyon yapılabileceği akılda tutulmalıdır.

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INTRODUCTION

Fixed drug eruption is defined as skin or mucous membrane lesions that recur at the same site when the responsible drug is readministered[1]. We report a case with chronic tophaceous gouty arthritis who had to interrupt allopurinol therapy because of fixed drug eruptions appearing on several previous occasions. Reinstitution of allopurinol was successfully carried out with application of the modified Meyrier regimen[2,3].

CASE REPORT

A 43 years-old male who had been treated for hyperuricemia for 17 years with the diagnosis of polyarticular, tophaceous gout was referred to our allergy unit from the rheumatology department with the suspicion of hypersensitivity to allopurinol. On several previous occasions of allopurinol administration, 0.5 to 3 cm hyperpigmented macules had recurred at the same sites on his trunk and legs in addition to the appearance of new lesions after each administration. The disease remained poorly controlled. He underwent surgical excision of the tophi. Since allopurinol was the required treatment, we decided to carry out a desensitization protocol. The patient provided written informed consent before the procedure.

An oral provocation test with full therapeutic dose of allopurinol was performed to verify it as the responsible drug since he had received concomitant medications previously. Hyperpigmented macules developed on his trunk and legs eight hours after the provocation (Figure 1).

After the established diagnosis of fixed drug eruption due to allopurinol, the drug was reintroduced according to the modified Meyrier regimen[2,3]: 50 mg of allopurinol powder was dissolved in 500 mL of distilled water with 14% sodium bicarbonate. The protocol started with a dose of 10 µg/day and was gradually increased to 300 mg/day over a period of 16 consecutive days. He did not receive prednisone during or after desensitization. The dosage schedule is shown in Table 1. During the follow-up of four months, the patient received 300 mg/day of allopurinol and is well with therapy.

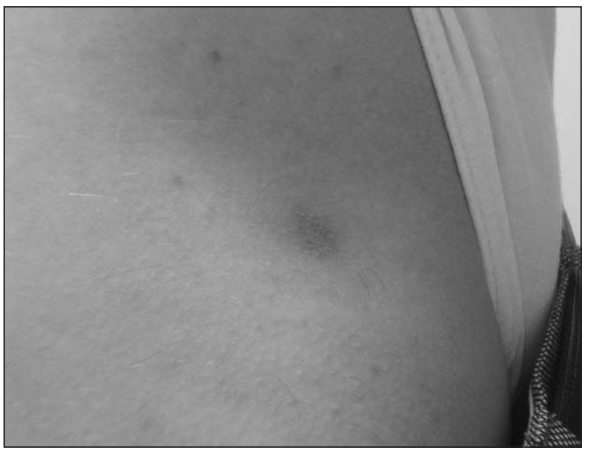

Figure 1. Hyperpigmented macule on abdominal wall after provocation.

DISCUSSION

The mechanism of fixed drug eruptions is not well understood, although it has been reported that the immune system plays a major role. The process may involve an antibody-dependent, cell-mediated cytotoxic response[4]. Lesions may occur on any site on the skin and mucosa and usually heal spontaneously with residual hyperpigmentation after avoidance of the responsible drug[5].

Allopurinol is the most commonly prescribed urate-lowering drug. Although more severe hypersensitivity reactions are rare, up to 2% of

Table 1. Desensitization schedule

Day	Solution	Dose	Day	Solution	Dose	Day	Dose
1	0.1 mL	10 µg	4	1 mL	100 µg	8	50 mg
	0.2 mL	20 µg		2 mL	200 µg	9	75 mg
	0.3 mL	30 µg		4 mL	400 µg	10	100 mg
			5	6 mL	600 µg		
				8 mL	800 µg		
2	0.4 mL	40 µg		10 mL	1 mg	11	125 mg
	0.5 mL	50 µg				12	150 mg
	0.6 mL	60 µg	6	20 mL	2 mg	13	175 mg
				40 mL	4 mg		
				80 mL	8 mg		
3	0.7 mL	70 µg	7	160 mL	16 mg	14	200 mg
	0.8 mL	80 µg		250 mL	25 mg	15	250 mg
	0.9 mL	90 µg		350 mL	35 mg	16	300 mg

patients, particularly those with renal insufficiency, may experience maculopapular skin eruptions that hinder further use. The limited availability of equally effective and alternative urate-lowering drugs is an important problem in patients intolerant to allopurinol. Oxypurinol is an alternative medication in allopurinol-intolerant patients, but the cross-reactivity rate is reported to be as high as 40%[6]. Febuxostat is a novel, potent, non-purine selective xanthine oxidase inhibitor and the first major treatment alternative for gout for more than 40 years and seems to be a promising alternative to allopurinol; however, continued long-term surveillance on its safety and efficacy is required[7]. Our patient remained poorly controlled despite 17 years of rheumatological follow-up and trial of different medications.

Provocation is the only reliable means of finding the causative agent of fixed drug eruptions[5,8]. As our patient had received concomitant medications with allopurinol, an oral provocation test was conducted. Provocation with 300 mg of allopurinol established the diagnosis.

Immunologic desensitization (e.g., to penicillin) and tolerance induction protocols (e.g., to sulfasalazine, ciprofloxacin) have been used for the management of hypersensitivity reactions to drugs[9]. Desensitization inhibits cellular activation mechanisms, and the majority of cases do not experience side effects, but the cellular and molecular inhibitory mechanisms are incompletely understood[10]. The mechanism of desensitization to allopurinol is not well established, but graded reintroduction of the drug induces tolerance.

Previous studies reached a target dose of 100 mg in about four weeks with protocols that utilized a suspension prepared from allopurinol 100 mg tablets[9,11,12]. Fam et al. described 32 patients with cutaneous reactions to allopurinol[9]. Their target dose was 50-100 mg/day, and mean duration of the protocol was 30.5 days in 21 patients and longer in the remaining 7. Desensitization failed in four patients due to unmanageable recurrent rash. Kelso et al. reported a case with multiple medical problems and fixed drug eruption in response to allopurinol[12]. They reached the target dose of 100 mg/day allopurinol in about four weeks with concomitant 10 mg/day prednisone administration. As described previously, our patient received the solution prepared from allopurinol powder, and we reached the target dose of 300 mg/day in 16 days without any cutaneous reac-

tions and with no concomitant corticosteroid administration. The lesions did not recur over the four-month follow-up.

In conclusion, we report successful desensitization to allopurinol in a case with chronic tophaceous gouty arthritis and classic fixed drug eruption in response to allopurinol. He received a modified dose regimen without premedication. Allopurinol has been the mainstay of treatment of hyperuricemia and gout, and in many patients, allopurinol is the only possible treatment. Therefore, desensitization should be considered for effective treatment of gout in such patients.

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