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Ranunculaceae Dermatitis due to Ranunculus Arvensis: Case Series, Literature Review of Reported Cases from Turkey

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Abstract

Magistral drugs prepared with plants in nature have been used all over the world for centuries to treat various diseases. However, besides the benefits expected from plants, unexpected side effects can also be encountered. Irritant contact dermatitis is one of the dermatosis that these plants can cause. Ranunculaceae species are used in conditions such as rheumatic diseases, hemorrhoids, wound healing, abscesses, psoriasis. In the literature, there are reported cases of irritant contact dermatitis depending on various species of the Ranunculaceae family. Here, we present three cases of irritant contact dermatitis, which have been used as an antirheumatic in the traditional treatment and Ranunculaceae family (Buttercup, Mayflower) depending on the topical use of Ranunculus arvensis species and, to make the compilation literature of cases reported from Turkey.

Keywords: *Ranunculaceae Dermatitis, Ranunculus Arvensis, Buttercup, irritant contact dermatitis.*

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Introductıon

Plants can cause allergic reactions on the skin. These reactions occur in various forms. Urticaria (immunological and toxin-mediated), irritant dermatitis (mechanical and chemical), phototoxic dermatitis (phytophotodermatitis), and allergic contact dermatitis are the most common plant reactions [1].

Ranunculaceae, which grows in spring and summer, is a yellow, brightly coloured flower, also known as buttercup or mayflower, that grows wild in many places. It is a plant that believed to have an antirheumatic effect. Acute irritant contact dermatitis may develop in the contact area.

Provided here are three cases where we determined that secondary irritant contact dermatitis developed depending on topical use of Ranunculus arvensis (R. Arvensis). It has also been made a literature compilation of previously reported cases with Ranunculaceae dermatitis from Turkey.

Case serıes

Case 1: Female patient aged 70 was admitted to the outpatient clinic with acute pain, burning and itching sensation, blistering, and burns in both knees. In her anamnesis, it was learned that the patient had gonarthrosis since she did not benefit from the medicines she used for knee pain, she crushed the buttercup that she collected from the field 1 day ago and rubbed it on her knees and applied occlusion, itching and burning started a few hours after the application, followed by redness, blistering and wound development. In her dermatological examination, partly wide erode areas were observed locally, sharply-circumscribed, erythematous, edematous ground with intact bullous lesions in both knees (Figure 1a, b). For treatment, the patient was recommended systemic antibiotic, an oral antihistamine, wet dressing, topical antibiotic, diflucortolone valerate + chlorquinadole cream, prednisolone (40 mg/day, 5 days).

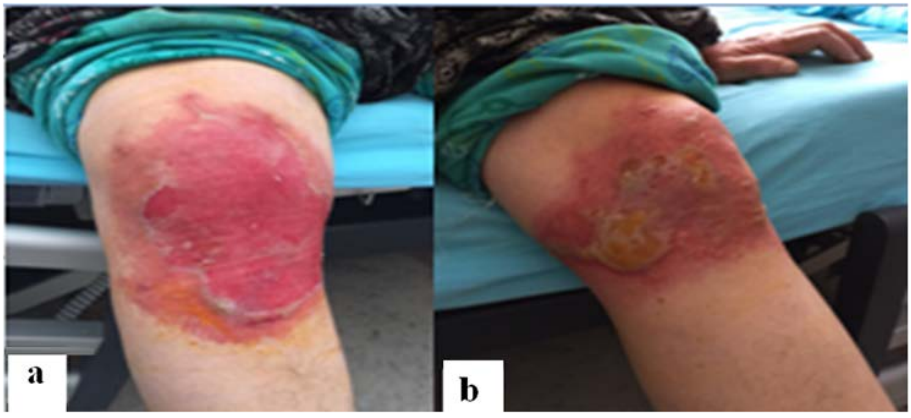

Figure 1(a,b): Case 1; right knee first day (a), left knee first day (b)

Case 2: Female patient aged 55 with rheumatoid arthritis admitted with complaints of severe itching, burning, rubor, and blistering of her knees. It was learned that the patient rubbed the buttercup to his knees and applied occlusion for knee pain, and the lesions developed 8-10 hours after the application. On the 1st day of the application, there was an erythematous, in the edematous ground approximately 10 cm in diameter, stretched bullous lesion with serous content (Figure 2a). On the third day, it was observed that the edema partially regressed and the bullous lesion replaced the superficial erosion on the erythematous purplish ground (Figure 2b). At the end of the 1st week, it was observed that erythema was alleviated and eroded lesions were replaced by dry areas (Figure 2c). In the treatment, the intact bullae in the patient's knee were emptied. Systemic antibiotic, oral antihistamine, wet dressing, topical antibiotic, diflucortolone valerate + chlorquinadole cream, prednisolone (40 mg/day, 5 days) treatment was administered.

Figure 2 (a,b,c): Case 2; left knee first day (a), left knee third day (b), left knee first week (c)

Case 3: Female patient aged 65 who reported that she was close to Case 2 and described a scar on her leg, about one year ago, she applied the buttercup to the area for leg pain by crushing the buttercup. After the application, while the lesions of the patient who developed redness, swelling, blistering and sores, regressed and healed by leaving an atrophic scar in place. The patient, who lived in a settlement close to case 2, reported that the plant she used was the plant used by case 3. In the dermatological examination of the patient, an atrophic scar with a size of 4x2 cm was observed on the right leg, tibialis anterior region (Figure 3).

The patients were asked to bring the plant they used for treatment. The opinion of a scientist of the plant systematist was asked. It was determined that the plant used by the patients was R. arvensis (Figure 4).

Figure 3: Case 3; an atrophic scar on the right leg, tibialis anterior region

Figure 4: Ranunculus arvensis (Buttercup flower)

DISCUSSION

Dermatosis that develops depending on plants is called phytodermatitis. According to the formation mechanism of phytodermatitis, allergic phytodermatitis, photophytodermatitis, irritant contact dermatitis, pharmacological damage, and mechanical damage are discussed in five patterns [2]. Apart from these, pseudophytodermatitis caused by arthropods or insecticides in plants or pseudophytophotodermatitis caused by phototoxic chemicals released in plants in response to infection are also rare presentations [3].

Plants may contain substances that are directly toxic and may cause chemical burn-like reactions. In some plants, toxic substances are released directly to the surface of the plant, while in others they are released only when the plant is cut or crushed [2]. Acids, crystal salts, glycosides, or proteolytic enzymes are responsible for irritant contact dermatitis. Araceae, Amaryllidaceae, Brassicaceae, Euphorbiaceae, Liliaceae, and Ranunculaceae family are the plants that cause irritant contact dermatitis most frequently [2, 3]. Ranunculus and Ceratocephalus species belong to the Ranunculaceae family [4].

In Turkey, especially in elderly patients, traditional treatment methods are frequently used. Ranunculaceae species can be used to relieve rheumatic pain. This plant that grows in high altitude regions is also called Mayflower as it blooms in spring and summer [4,5].

Ranunculaceae species due to their anti-inflammatory characteristics, in addition to rheumatic symptoms such as arthralgia, myalgia, hemorrhoids have become a part of traditional treatment methods in cases such as burns, lacerations, and abrasions [5-11]. Some species in the Ranunculaceae

family have been shown to have antiviral, antibacterial, anti-inflammatory, and antiprotozoal efficacy [12-16]. It also shows an increase in DNA polymerase inhibition and free oxygen radicals and shows antimutagen and antitumoral efficacy [17,18]. In the phytochemical analysis of ranunculus species, flavonoids, saponins, alkaloids, free fatty acids, and organic acids have been encountered [19-23].

Ranunculaceae contains a glycoside called ranunculin. Ranunculin turns into protoanemonin, which is responsible for the actual toxic effect [24]. Protoanemone rapidly polymerizes into the anemone. Since anemonin has no irritating effect, the irritant effect develops in contact with freshly crushed flower petals depending on the protoanemone [24]. Protoanemone breaks disulfide bonds and causes subepidermal separation and leads to chemical irritant contact dermatitis [5,24]. The clinical picture caused by buttercup is frequently in severe vesicle and bulla formation [24-27].

The Ranunculaceae family has about 2200 species [15]. Approximately 84 of these are seen in Turkey [4,28,29]. In Turkey, it grows especially in the Mediterranean, Eastern Anatolia, and Southeastern Anatolia regions [28-31]. The patients in our cases were also living in the Southeastern Anatolia Region (Batman province) of Turkey. When the literature is examined, in the compilation prepared by Akbulut et al. [32] in 2011, it is seen that 25 cases of contact dermatitis related to ranunculaceae species have been reported and so far a total of 51 cases from Turkey have been reported [5, 32-43] (Table 1). The vast majority of the cases have been reported from the Eastern Anatolia region of Turkey. Of the Ranunculacea species, R. arvensis (15 cases) is the most frequently reported species. Apart from R. arvensis, there are cases of irritant contact dermatitis reported with R. illyricus (3 cases), R. kotschyi Boiss (6 cases), R. damascenus, (2 cases) R. constantinopolitus (9 cases), R. scleratus (1 case), C. falcatus (9 cases) and C. testiculatus (1 case).

In reported cases, the onset time and clinic of the lesions vary. Although the clinic of lesions that may occur after contact with the irritant plant for 10 minutes to 48 hours is mostly in bullous form, it can also progress with sharply limited common erythematous non-bullous forms (37, 44-46). Our cases were cases where patients applied freshly crushed R. arvensis plant to the painful joint area and then applied occlusion and stated that lesions developed on the same day. Responsible for the irritant effect of the Ranunculaceae plant, protoanemonin is known to exist only in the form of a fresh green leaf. In contrast to this literature, in three cases reported by Kocak et al., it has been reported that irritant contact dermatitis occurs after boiling and cooling, not fresh crushed form of R. arvensis. For this reason, it has been suggested that the dried or boiled form of the plant is false, and protoanemone has been suggested to be a heat-resistant toxin (42). In most cases, the wet dressing was applied as the first treatment option. As in cases where there is untreated post-

inflammatory hyperpigmentation, there are also cases that can be controlled by systemic steroids, systemic antibiotics and/or surgical methods, with a very severe burn-like picture [24, 33, 37, 46, 47]. A case whose condition has deteriorated and died due to the development of secondary pseudomonas infection has been reported [34]. The severity of clinical findings is thought to vary depending on the Ranunculaceae subspecies, the amount and duration of use of the plant. The vast majority of cases are middle-elderly aged female patients living in rural areas. Since this herb is often used for symptoms of arthralgia and myalgia, the lesions are usually located at the knee and leg. In addition, there are cases that are used in the treatment of palmoplantar psoriasis and have lesions in the hands and feet [43,48]. Our cases, as in most cases in the literature, are middle-elderly aged female patients with rheumatic pain, and their lesions were in the knee and leg areas.

As a result, it is a common situation in Turkey that especially patients who do not get a positive response from medical treatment try to be treated with plants that they have collected from nature. It is observed that especially elderly people living in rural areas are more commonly used in traditional treatment methods with plants. However, it should be noted that the uncontrolled use of these plants, which do not go through experimental stages, therapeutic or toxic dose ranges, and side effects are not known, may lead to serious complications. In order for these herbs, which have been used in traditional treatment for centuries to be useful in complementary medicine, there is a need for further evidence-based research.

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Table 1: Reported cases of Ranunculaceae Dermatitis from Turkey.

Ref.	Age	Sex	Intended use of plant	Administration		Lesion location	Ranunculaceae species	The Geographical region where the case was reported	Treatment	Healing time
				time of the plant	route of the plant					
Yenidunya et al. (1999)[26]	?	F	Arthralgia	Unknown	Fcr+ ocl	Right ankle	C. falcatus	Central Anatolia (Ankara)	Wd	2 weeks
Metin et al. (2000)[33]	45	F	Arthralgia and myalgia	2 days	Fcr+ bo+ dj	Abdomen, right knee, neck	R. damascenus	Eastern Anatolia (Van)	Sab, Oah, Wd, Tab	10 days
Karaca et al. (2005)[47]	47	F	Knee pain	25 min.	Fcr+ ocl	Right knee	C. falcatus	Central Anatolia (Afyon)	Wd, Ts	10 days
Metin et al. (2005)[5]	69	M	Knee pain	2.5 hours	Fcr+ ocl	Left knee	C. falcatus	Eastern Anatolia (Van)	Wd, Tab	2 weeks
	33	F	Foot pain	1.5 hours		Left foot dorsum, ankle				3 weeks
	18	F	Knee pain	1 hour		Right knee				2 weeks
Oztas et al. (2006)[27]	58	F	Knee pain	2 days	Fcr	Both knees	R. illyricus	Central Anatolia (Ankara)	Tab, Oah	a few days
	54	F		1 day					Wd, Tab, Oah	1 week
Emsen (2006)[34]	51	F	Knee pain	48 hours	Fcr+ ocl	Right knee, leg	Ranunculacea family	Eastern Anatolia (Erzurum)	Sab, Wd	Death
Polat et al. (2007)[30]	55	F	Knee pain	1 day	Fcr+ ocl	Knee	R. illyricus	Central Anatolia (Ankara)	Wd, Tab, Oah	3-4 days
Eskitasciogulu et al. (2008)[25]	42	M	Foot pain	8 hours	Fcr+ ocl	Left foot dorsum, ankle	C. testiculatus	Central Anatolia (Kayseri)	Ds+ Dchlor+ gd&p+ skin greft	1 week
	60	F	Knee and foot pain	2 hours		Right foot dorsum, left knee				10 days
	40	F	Foot pain	4 hours		Right foot dorsum, ankle			Ds+ Dchlor+ gd&p	1 week
	65	F	Knee pain	2 hours		Left knee				5 days
	48	F	Knee pain	4 hours		Right knee	C. falcatus		Ds+ Dchlor+ gd&p+ skin greft	2 weeks

Kose et al. (2008)[35]	52-76	6 F, 3M	Arthralgia	12 hours	Fcr	Both knees in 7 patients, one knee in 2 patients	R. constantinopolitanus	Eastern Anatolia (Elazığ) and Mediterranean (Kahramanmaraş)	Tab	10 days
Orak et al. (2009)[36]	64	M	Knee pain	12 hours	Fcr+ ocl	Left thigh distal 1/3	R.arvensis	Eastern Anatolia (Diyarbakır)	Ds, Tab, Sab, analgesic, antipyretic, low molecular weight heparin	3 weeks
Sayhan et al. (2009)[44]	17	M	Back and leg pain	48 hours	Fcr	Back, chest, scrotum, penis	R. arvensis	Unknown	Wd, silver sulfadiazine, collagenase	4 weeks
Calka et al. (2011)[37]	65	M	Knee pain	2 hours	Fcr+ ocl	Right knee	R. kotschyi Boiss	Eastern Anatolia (Van)	Sab , NSAID, eau borique, Ts	Unknown
	73	M	Knee pain	6 hours		Right knee			NSAID, Oah, Eau bor, Ts	
	50	F	Leg pain	2 hours		Both thighs and legs			Ss, NSAID, Oah, Eau bor, Tab	
	51	F	Knee pain	2 hours		Right knee			Ss, Eau bor, Ts, an ointment containing Rivanol	
	66	F	Knee pain	10 minutes		Right knee			NSAID, Oah, Eau de goulard, Ts	
	43	F	Leg pain	1 hour		Right foot and leg			Ss, NSAID, Oah, Eau bor, Ts	
Akbulut et al. (2011)[32]	48	M	Arthralgia	1 hour	Fcr+ ocl	Right-hand thumb	R. arvensis	Eastern Anatolia (Diyarbakır)	Tab	3 weeks
	59	F	Knee pain	1 night		Both knees			Dchlor, silver sulfadiazine	2 weeks
	70	F		2 days						10 days
Albayrak et al. (2011)[38]	60	M	Leg pain	5 hours	Fcr+ ocl	Left thigh distal	R. arvensis	Eastern Anatolia (Erzurum)	Dchlor	1 month
Turan et al. (2012)[39]	81	F	Knee and leg pain	Unknown	Fcr+ ocl	Right leg (cruris)	Ranunculaceae family	Eastern Anatolia (Bitlis)	Ss, Oah, Ts and vaseline	Unknown
Ucmak et al. (2014)[40]	42	M	Knee pain	12 hours	Fcr+ ocl	Right knee	R.arvensis	Eastern Anatolia (Diyarbakır)	Wd, Tab	1 month
	60	M	Leg pain	10 hours		Both leg (cruris)			Topical treatment	2 weeks
Polat	46	M	Psoriasis	3 hours	Fcr+ ocl	Both hands	R. arvensis	Ankara (Central	Deb, Tab, silver sulfadiazine	3 weeks

(2016)[48]								Anatolia)		
Elmas et al. (2015)[41]	57	F	Knee pain	20 min.	Fcr+ ocl	Both knees	R. damascenus	Eastern Anatolia (Erzurum)	Wd, Ta, Oah, Ss	17 days
Degirmenci et al. (2015)[45]	57	F	Knee pain	12 hours	Fcr+ ocl	Left knee	R. scleratus	Marmara region (İstanbul)	Wd	1 week
Kocak et al. (2016)[42]	51	M	Knee pain	12 hours	bo&co + ocl	Right knee	R. arvensis	Eastern Anatolia (Erzurum)	Surgical treatment (flap)	16 days
	52	F		5 hours		Left knee			Wd	5 days
	57	F		10 hours		Right knee				7 days
Benli et al. (2018)[46]	69	F	Knee pain	Unknown	Fcr+ ocl	Both knees	Ranunculaceae family	Central Anatolia (Karabük, Sivas, Ankara)	Wd, Ts	2 weeks
	69	M							Wd, Tab	2 weeks
	71	F							Untreated follow-up	15 days
An et al. (2019)[43]	62	F	Knee pain	6 hours	Fcr+ ocl	Right knee	R. arvensis	Eastern Anatolia (Diyarbakır)	Wd+ Ss+ Tab	
	64	M	Leg pain	8 hours		Right leg			Wd+ Oa+ Ss	
	53	M	Psoriasis	2 hours		Both palms, right foot			Wd+ Ss+ Ta	

Abbreviations: bo, boiling the plant; bo&co, application by boiling and cooling the plant; Dchlor, Dressing with chlorhexidine; Deb, debridement; dj, drinking its juice; Ds, Dressing with saline; Eau bor, Eau borique; Fcr, Apply fresh crushed plant; gd&p, gauze dressing with paraffin; NSAID, nonsteroid anti-inflammatory drug; Oab, Oral antibiotic; Oah, Oral Antihistamine; ocl, occlusion; Sab, Systemic antibiotic; Ss, Systemic steroid; Tab, Topical antibiotic; Ts, Topical steroid; Wd, Wet dressing.