ORIGINAL ARTICLE

Cypress Pollen: An Unexpected Major Sensitizing Agent in Different Regions of Italy

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Abstract

Objectives: In this multicenter survey, we assessed the impact of sensitization to cypress in atopic patients in Italy and determined whether cypress pollen concentration changed over time.
Methods: Allergists were required to collect the results of 100-200 consecutive skin prick tests (SPTs) performed during 2012. Seasonal symptoms were also recorded, as were airborne cypress pollen concentrations (data from the Italian Aerobiology Association) in 1998-2000 and 2010-2012.
Results: We examined 2258 atopic outpatients (56% females; age, 2-84 years) sensitized to at least 1 of the aeroallergens tested (*Dermatophagoides* species, grass, pellitory, olive, cypress, birch, *Alternaria tenuis*, and dog and cat dander). We found that 62.9%, 16.1%, and 32.7% of patients living in central, northern, and southern Italy, respectively, were sensitized to cypress ($P<.0001$). The cypress pollen concentration peak was delayed from February to March in 1998-2000 and 2010-2012 in all 3 regions, with a shift in pollination towards spring. Patients who were monosensitized to cypress reported mainly rhinitis (90.7%-97.6%) and conjunctivitis (38.1%-100%). In polysensitized patients, the prevalence of rhinitis, conjunctivitis, and asthma increased progressively ($P<.0001$) from southern to northern Italy. The same trend was observed for the prevalence of reported winter symptoms typical of cypress allergy (28%-65%).
Conclusions: Today, cypress pollen is the most frequent sensitizing aeroallergen (assessed by SPT) in several areas of central Italy. Variations in the timing of the cypress pollination period may have favored this increased sensitization. Rhinitis and conjunctivitis are the predominant symptoms. The clinical impact of this allergy was poor in southern Italy and increased in central areas before reaching its peak in northern regions.

Key words: Respiratory allergy. Cypress. Cupressaceae. Sensitization. Skin prick tests. Airborne pollen concentration. Prevalence.

■ **Resumen**

Antecedentes: Se trata de una encuesta multicéntrica realizada en Italia para evaluar el impacto de la sensibilización a polen de ciprés en sujetos atópicos y establecer si la concentración de este polen en el aire ha cambiado a lo largo del tiempo.
Métodos: El estudio fue realizado por alergólogos que recopilaron 100-200 sujetos consecutivos con pruebas cutáneas positivas (Prick) realizadas en 2012. Se recogieron los síntomas estacionales, junto con la concentración de polen de ciprés (obtenida por la asociación italiana de aerobiología) en 1998-2000 y 2010-2012.
Resultados: En cuanto a los resultados obtenidos fueron examinados 2258 pacientes atópicos (56% mujeres; edad 2-84), sensibilizados frente al menos uno de los aeroalérgenos testados (*Dermatophagoides*, gramíneas, parietaria, olivo, cipres, abedul, *Alternaria tenuis* y epitelio de gato). El 62.9%, 16.1% y 32.7% de los pacientes que vivían en el centro, norte y sur de Italia, respectivamente, mostraron sensibilización a polen de ciprés ($p<0.0001$). Observamos un pico de concentración de polen de ciprés de febrero a marzo en los años 1998-2000 y 2010-2012, en todas las áreas. Los pacientes monosensibilizados a ciprés mostraron de forma prevalente rinitis (90.7-97.6%) y conjuntivitis (38.1-100%). La prevalencia de rinitis , conjuntivitis y asma se incrementa progresivamente ($p<0.0001$) del sur hacia el norte de Italia en los sujetos polisensibilizados. La misma tendencia se observó en los síntomas invernales típicos de la alergia al ciprés.
Conclusiones: En conclusión, actualmente el polen de ciprés es el aeroalérgeno sensibilizante más frecuente (según resultados de prueba cutánea) en varias áreas de Italia central. Las variaciones del periodo de polinización pueden favorecer el incremento observado en la sensibilización a este polen. Los síntomas predominantes son rinitis y conjuntivitis. El impacto clínico de esta alergia es pobre en áreas del sur de Italia, siendo alto en las áreas del norte.

Palabras clave: Anafilaxia. Hipersensibilidad a medicamentos. Encuesta portuguesa.

Introduction

The prevalence of sensitization to cypress (assessed using skin prick test [SPT]) has increased progressively in the Mediterranean area in the last 20-30 years, particularly in some regions of Italy [1,2]. The possible explanations for this increase include improved diagnostic techniques (better and more routinely used extracts), increased concentrations of airborne pollen (during the pollen season), and widespread use of cypress in parks and gardens [1]. In 2000, an Italian study to detect the prevalence of sensitization to cypress in Italy found that prevalence had increased over the years and that the distribution between northern, central, and southern Italy had changed [3]. Prevalence was higher in central Italy than in southern Italy and very low in northern areas. In the last 6 years, only 2 studies have evaluated the prevalence of sensitization to cypress in 2 restricted areas of Italy (Maremma [Tuscany] and Apulia) [4,5]. Both showed that the prevalence of sensitization to this allergen was greater than that of sensitization to other allergens (grass, pellitory, olive, and other trees). Therefore, we believe that sensitization to cypress has increased in recent years in Italy. We investigated the prevalence of sensitization to cypress detected by SPT in Italy in 2012. We also evaluated the clinical impact of sensitization on symptoms and investigated trends in cypress pollen concentrations since 1998.

Materials and Methods

Data were obtained from 13 outpatient clinics uniformly distributed in different Italian areas. The results of at least 100-200 consecutive positive SPTs performed in 2012 were analyzed. Data were also collected on symptoms and the seasons when the symptoms appeared. All patients underwent SPT because they had reported suspected allergic respiratory and/or ocular symptoms (conjunctivitis, rhinitis, coughing, dyspnea, and wheezing). We analyzed 2258 outpatients (56% females; age, 2-84 years) who were sensitized to at least 1 of the most common aeroallergens tested. The commercial allergen extracts used in the SPTs were provided by ALK Abelló Group. The extracts were from *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae,* grass mix, *Parietaria, Olea europaea, Cupressus sempervirens, Betula pendula, Alternaria tenuis*, and dog-cat dander. SPTs were carried out and interpreted according to international guidelines [6]. All centers followed the same protocol and provided the SPT results obtained. Patients with infectious diseases, malignancies, or dysmetabolic syndrome (eg, diabetes) were excluded, as were pregnant women. Patients with severe cutaneous disorders or a negative skin reaction to histamine and those treated with drugs that might interfere with a cutaneous response were not tested. Reported symptoms (rhinitis, conjunctivitis, cough, and asthma) and the season they appeared or worsened were also recorded. Furthermore, the Italian Aerobiology Association (which coordinates the monitoring of aerobiological and airborne pollen concentration in Italy) provided us with data on airborne cypress pollen concentrations during 1998-2000 and 2010-2012 so that we could determine whether these pollen concentrations had changed over time. For the purpose of this study, all data (sensitizations, symptoms, seasons, and pollen concentrations) were classified based on area of origin (southern, central, and northern Italy). Patients were then classified as cypress-sensitized (polysensitized plus monosensitized), non–cypress-sensitized (sensitized to other allergens), and cypress-monosensitized in order to evaluate whether there were differences in symptoms and their seasonality. A χ^2 test was used to compare sensitizations, symptoms, and seasonality of symptoms.

Table. Symptoms and Seasons When They Appeared, as Reported by Patients Living in Southern, Central, and Northern Italy

	Southern Italy (705 Patients)				Central Italy (782 Patients)				Northern Italy (771 Patients)					
	CS	Non-CS	Mono-CS	P^a	CS	Non-CS	Mono-CS	P^a	CS	Non-CS	Mono-CS	P^a	P^b	P^c
Total	231 (32.8%)	474 (67.2%)	84 (11.9%)	.0001	492 (62.9%)	290 (37.1%)	54 (6.9%)	.0001	123 (16%)	648 (84%)	8 (1%)	.0001	.0001	.0001
Rhinitis	86 (37.2%)	247 (52.1%)	82 (97.6%)	.0002	366 (74.4%)	232 (80%)	49 (90.7%)	.49	118 (95.9%)	457 (70.5%)	8 (100%)	.0001	.0001	.0001
Conjunctivitis	72 (31.1%)	292 (61.6%)	32 (38.1%)	.0001	230 (46.7%)	144 (50%)	28 (68.5%)	.23	92 (74.8%)	364 (56.2%)	8 (100%)	.0001	.0001	.0002
Cough	63 (27.3%)	53 (11.2%)	26 (31%)	.0001	75 (15.2%)	76 (26.2%)	20 (37%)	.0002	8 (6.5%)	30 (4.6%)	0	.37	.0001	.0001
Asthma	29 (12.5%)	51 (10.7%)	11 (13.1%)	.48	111 (22.5%)	83 (28.6)	11 (20.3%)	.18	44 (35.8%)	131 (20.2%)	0	.0002	.0001	.0001
Rhinitis plus asthma	76 (32.9%)	140 (29.5%)	10 (11.9%)	.36	131 (26.6%)	92 (31.7%)	12 (22.2%)	.16	46 (37.4%)	279 (43%)	0	.24	.086	.0001
Perennial symptoms	92 (39.8%)	204 (43%)	15 (17.8%)	.41	197 (40%)	156 (53.8%)	15 (27.7%)	.003	91 (74%)	404 (62.3%)	0	.013	.0001	.0001
Winter symptoms	64 (27.7%)	46 (9.7%)	45 (53.6%)	.0001	178 (36.2%)	45 (15.5%)	30 (55.5%)	.0001	80 (65%)	129 (19.9%)	8 (100%)	.0001	.0001	.0001
Spring symptoms	107 (46.3%)	175 (36.9%)	14 (16.6%)	.016	246 (50%)	149 (51.3%)	14 (25.9%)	.61	83 (67.5%)	269 (41.5%)	8 (100%)	.0001	.0007	.004
Summer/ autumnal symptoms	58 (25.1%)	100 (21.1%)	32 (38%)	.23	90 (18.3%)	61 (21%)	2 (3.7%)	.40	69 (56%)	211 (32.5%)	0	.0001	.0001	.0001

Abbreviations: CS, cypress-sensitized (both polysensitized and monosensitized) patients; Mono-CS, cypress-monosensitized patients; Non-CS, non–cypress-sensitized patients.
Comparisons were made using the χ^2 test.
P^a, statistical analysis results of comparisons between CS and Non-CS subgroups.
P^b, statistical analysis results of comparisons among CS patients from southern, central, and northern Italy.
P^c, statistical analysis results of comparisons among Non-CS patients from southern, central, and northern Italy.

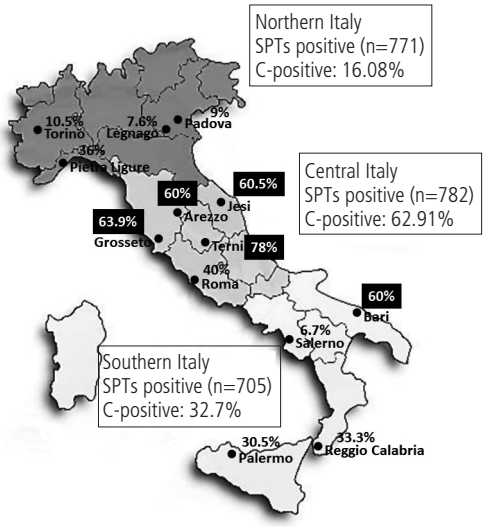

Figure 1. Geographic distribution of the centers showing the percentages of patients with a positive skin prick test result to cypress. In some cities, the prevalence of sensitization to cypress was particularly high. These cities are marked in bold. SPT indicates skin prick test; C indicates cypress.

Results

The results are summarized in the Figures and Table. In most areas of central Italy, cypress is the most common sensitizing allergen—as assessed using SPTs—with a mean prevalence of 62.9% among 782 patients sensitized to at least 1 of the common aeroallergens tested (Figures 1 and 2). In northern Italy, however, sensitization was less prevalent (16.1% of 771 subjects). In southern Italy, prevalence was intermediate (32.7% of 705 subjects) (Figures 1 and 2). Therefore, the mean prevalence was higher in central Italy ($P<.0001$; χ^2 test, Figure 2). Cypress was the main sensitizing allergen in some Italian central areas (Figure 1). The prevalence of grass and olive sensitization was also higher in this region, although sensitization to cat and dog dander was more prevalent in northern Italy (Figure 2). Variations in the mean cypress pollen concentrations were found in the different areas (Figure 3). The pollen concentration peak was clearly delayed from February to March during both study periods (1998-2000 and 2010-2012) in all 3 regions, with a shift in pollination towards spring. Only a small number of sensitized patients (17.2%) were monosensitized, and the largest number were located in southern Italy (Table). Rhinitis was the most frequent symptom reported by monosensitized patients in all 3

regions. Conjunctivitis was also a common symptom, although only in central and northern Italy. In contrast, asthma was less frequent. The distribution of reported symptoms and their seasonality differed both for cypress-sensitized and non–cypress-sensitized patients in all 3 areas (Table). When we compared all cypress-sensitized patients with non–cypress-sensitized patients, we found that rhinitis and conjunctivitis (typical of sensitization to cypress) were less prevalent in southern Italy in the first group ($P<.0001$) and more prevalent in northern Italy ($P<.0001$). In contrast, no differences were found for rhinitis and conjunctivitis in central Italy ($P=.23$). The prevalence of rhinitis and conjunctivitis increased progressively with latitude. In fact, patients from southern Italy had fewer symptoms than patients from central and northern Italy, especially in the case of cypress-sensitized patients ($P<.0001$). Cough was more frequent among cypress-sensitized patients in southern Italy ($P<.0001$) and among non–cypress-sensitized patients in central Italy ($P=.0002$). Furthermore, cough was more common among cypress-sensitized patients in southern Italy than in central Italy and northern Italy ($P<.0001$). No significant differences in the prevalence of asthma were reported between cypress-sensitized and non–cypress-sensitized patients. Comparison by area, on the other hand, revealed that the number of asthmatics increased progressively, with lower values in southern Italy, higher values in central Italy, and the highest values in northern Italy, especially among cypress-sensitized patients. A larger number of cypress-sensitized patients than non–cypress-sensitized patients reported typical winter cypress allergy symptoms in all the areas studied ($P<.0001$). The prevalence of winter and spring symptoms increased progressively with latitude: lower values were found in the south, higher ones in the center, and the highest values in the north, especially in cypress-sensitized patients ($P<.0001$).

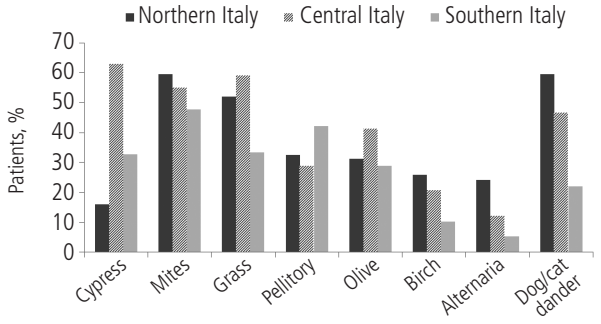

Figure 2. Prevalence of sensitization to various common aeroallergens, according to skin prick test results, in northern, central, and southern Italy. Comparisons between northern, central, and southern areas for each allergen tested ($P<.0001$; χ^2 test).

Discussion

The prevalence of sensitization to cypress pollen was highest in the center of Italy. The next most common sensitization was to *Dermatophagoides* species and grass pollen, which have traditionally been the most common allergens. Using the immunosolid phase allergen chip (ISAC) microarray system, Scala et al [7] found that, of 23 077 unselected consecutive individuals with allergic diseases (mainly from Lazio and Central Italy), 42.7% were sensitized to Cup a 1, 38.7% to Der f 2, and 37.9% to Phl p 1. The prevalence of positive SPT results for the diagnostic panel varied with the region studied: northern, 16.1%; central, 62.9%; and southern, 32.7%. These differences are identical to those recorded over 10 years ago, when the prevalence of sensitization to Cupressaceae (positive skin test results) was 9.2% (north), 28.2% (center), and 20.1% (south) [3]. These results were also confirmed using the ISAC test in a study of 55 000 patients that revealed a greater prevalence of sensitization to cypress in Lazio and Umbria (central Italy) and a lower prevalence of sensitization in Lombardia (northern Italy) [8]. Prevalence has increased progressively and is now significantly higher in all Italian areas than it was 10 years ago [3]. Indeed, in the early 1990s, only 4%-10% of 49 660 patients with pollinosis throughout Italy were sensitized to Fagaceae, Cupressaceae, and *Plantago* [9].

This higher prevalence is generally attributed to increased exposure to pollen over time [1,2,4,5,10]. *Cupressus sempervirens* is particularly widespread in central Italy (especially Tuscany and Umbria) and is mainly used for ornamental purposes. However, no significant differences were observed in airborne cypress pollen concentrations measured in 2 different 3-year periods separated by 10 years between

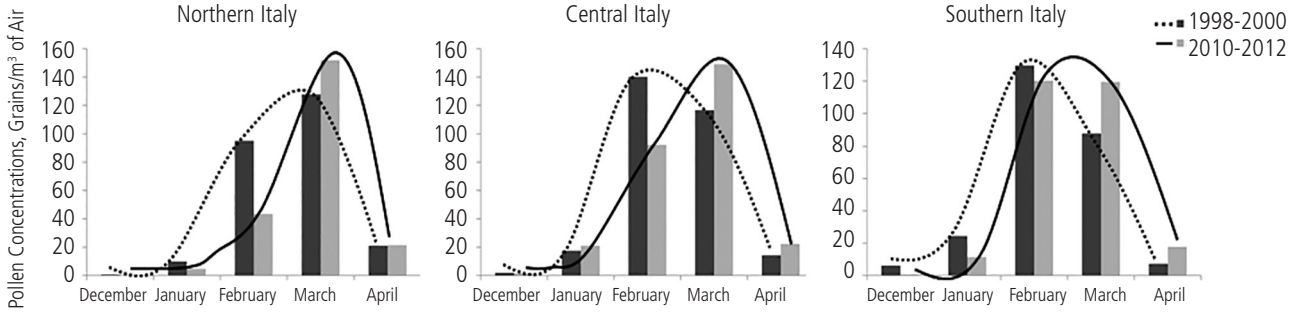

Figure 3. Mean values of airborne cypress pollen concentrations (grains/m^3) measured between December and April of the 3-year periods studied (1998-2000 and 2010-2012) in northern, central, and southern Italy.

northern, central, and southern Italy (Figure 3). Therefore, the increase in airborne pollen concentration alone may not be sufficient to explain this significant increase in cypress sensitization. However, remarkable variations in airborne pollen concentrations can be observed between different sites in the same region; therefore, a mean pollen concentration may not be representative of a specific area. In contrast, our data on airborne pollen concentrations highlighted how cypress flowering is delayed (late winter/early spring) in the second 3-year period compared with the first one. In fact, the peak airborne cypress pollen concentration was observed in February in 1998-2000 and in March in 2010-2012. Moreover, it was associated with a further increase in April. Climate changes in recent years may be responsible for these differences in pollination times and could have favored the increase in sensitization to cypress. Indeed, one study revealed a progressive increase in the duration of pollen seasons (*Parietaria*, olive, cypress) over a 27-year period, with a consequent increase in the percentage of individuals sensitized to the pollens. Again, this increase may have been the result of climate change, in particular, an increase in temperature [10] that was most likely a consequence of increased urban air pollution [11].

The presence of other species belonging to the Cupressaceae family, such as *Juniperus oxycedrus* and *Juniperus communis*, which flower earlier and later, respectively, could further extend the cypress pollen season [4,12]. Moreover, the persistence of old cypress pollen in the environment could prolong exposure, thus favoring sensitization. In fact, the in vivo and in vitro allergenic activity of cypress pollen persists for years after its collection [13].

We found that rhinitis and conjunctivitis were the most prevalent symptoms in monosensitized patients; asthma was less frequent in this group, consistent with the findings of other studies [3,4]. This observation is probably due to the large aerodynamic size of cypress pollen grains (20-30 μm), which do not reach the lower airway, as they become trapped in the nasal or nasopharyngeal mucous membranes, thus causing mainly rhinitis and conjunctivitis [1]. Furthermore, the clinical impact of this sensitization is felt in winter, when cypress blooms, causing typical symptoms in almost all monosensitized patients, whereas polysensitized patients were less affected. In fact, when we analyzed southern, central, and northern Italy separately, 28%, 30%, and 65% of patients sensitized to cypress pollen (and other allergens) reported symptoms during the pollen season, thus confirming that cypress causes typical winter symptoms only in some polysensitized patients, as shown elsewhere [4,14]. In polysensitized patients without typical winter symptoms, cypress sensitization could be the result of—albeit partially—IgE cross-reactivity to proteins/epitopes with structures similar to those of allergens used in other pollen extracts belonging to taxonomically different plants [15]. IgE antibodies against a given allergen may bind to homologous molecules of panallergens (profilin, calcium-binding protein, lipid transfer protein, thaumatin-like protein) in different plant species [16,17]. In fact, in polysensitized patients, the use of allergen extracts to detect pollen sensitization through SPTs often points to cosensitization rather than cross-sensitization due to panallergens. Barber et al [18] found double the number of sensitizations to major allergens identified with SPT in patients who were simultaneously sensitized to polcalcins and profilins. Therefore, only some asymptomatic patients seem not to be sensitized to the main allergens of cypress (eg, Cup a 1), even if they do show cross-reactivity to common or similar panallergens from taxonomically unrelated pollen families. In particular, olive and grass pollens contain allergens—Ole e 2, Phl p 12 (profilin), and Phl p 7 (calcium-binding protein)—that can cross-react with pollens from unrelated species [17,19,20] and probably also with the Cupressaceae family. Some calcium-binding proteins (Cry j 4, Jun o 2, Jun o 4, and Cup a 4), profilins (Cup s 8), and thaumatins (Cup a 3, Cry j 3, Cup s 3, Jun a 3) from Cupressaceae species [8] might have molecular characteristics that are similar to those of other unrelated pollen panallergens, and this may be the reason for cross-reactivity. In fact, Cup a 4 (calcium-binding protein), a recently identified allergen from *Cupressus arizonica*, shows structural similarities to other calcium-binding allergens such as Ole e 3, Ole e 8, and Phl p 7 [21]. Furthermore, there is evidence that sensitization to pollens has become more frequent over time, especially in urban areas [11,22]. Cross-reactivity between panallergens may also have increased over time: in addition to more frequent sensitization to cypress, we found a more significant prevalence of grass and olive sensitization in central Italy than in other areas. Consequently, we hypothesize that there is greater cross-reactivity between these species of plants owing to more frequent sensitization to olive and grass pollen rather than to cypress pollen. This potentially increased cross-reactivity between the various allergenic components of pollen extracts could also be the cause of increased cypress sensitization. However, since cypress extract seems to have a low profilin and polcalcin content [18], cross-reactivity may not be the only explanation for the differences observed.

Variations in prevalence and clinical impact can also be explained by differences in climate between the 3 regions. In fact, on the basis of our results, sensitization to cypress, especially when associated with other types of sensitization, seems to affect symptoms and their seasonality differently in the 3 regions studied. The prevalence of winter and spring symptoms, and of rhinitis and conjunctivitis in particular, increased progressively in southern, central, and northern Italy, especially in cypress-sensitized patients. The same trend was observed for asthma. In contrast, cough was more common among cypress-sensitized patients in southern Italy than in central and northern Italy. Therefore, the clinical impact of sensitization to cypress in polysensitized patients varies with latitude: poor in the south, intermediate in the center, and high in the north. The opposite trend was observed for cough. Differences are observed not only in the prevalence of symptoms, but also in the kind of cypress-induced symptoms at different latitudes, which could in turn be due to differences in the species of cypress planted, rain and wind patterns, humidity and temperature, degree of air pollution, plant distribution, load of other allergens during pollination, and the associations between allergens in the 3 regions (eg, grass in the north and pellitory in the south) [10,11,23]. These differences may also explain the dissimilar prevalence of sensitization in the 3 regions.

In conclusion, today, cypress pollen is the most frequent sensitizing aeroallergen detected using skin prick tests in central Italy. The variations in time of cypress pollination may have favored the increased prevalence of this sensitization. Rhinitis and conjunctivitis are the predominant symptoms, whereas asthma is less frequent. The clinical impact of cypress

on symptoms is lower in polysensitized patients, although it differs with latitude: poor in the south, intermediate in the center, and high in the north. These variations must be taken into account to ensure optimal management of patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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