Prevalence and Clinical Patterns of Ocular Complications Associated With Anti-PD-1/PD-L1 Anticancer Immunotherapy

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• PURPOSE: Immune checkpoint inhibitors (ICI) targeting the programmed cell death protein 1 (PD-1), or its ligand PD-L1, are the mainstay of metastatic cancer treatment. Patients receiving these treatments may develop immune-related adverse events (irAEs). This study aimed to estimate the prevalence and describe the clinical patterns of moderate-to-severe ocular irAEs-associated with anti-PD-(L)1 treatment.

• DESIGN: Prospective case series.

• METHODS: This study included patients recruited via (1) a single-center prospective cohort and (2) a national pharmacovigilance registry between June 2014 and March 2018, and focused on patients with moderate-to-severe ocular irAEs following anti-PD-(L)1. All patients underwent a comprehensive ophthalmologic assessment. The main outcome measure was the prevalence of moderate-to-severe ocular irAEs.

• RESULTS: Of a total of 745 patients included in the prospective cohort, 3 developed moderate-to-severe ocular irAEs, providing a prevalence of 0.4% and an incidence of 0.7 per 1000 patient-months of treatment. An additional 5 cases of moderate-to-severe ocular irAEs were reported through the national registry. From these 8 patients, 5 presented with intraocular inflammation, 2 with ocular surface disease, and 1 with orbital myopathy. Five patients (62.5%) experienced additional extraophthalmologic irAEs. Ocular irAEs led to permanent discontinuation of anti-PD-(L)1 in 4 patients. Treatment by local and/or systemic corticosteroids allowed resolution or control of the ocular symptoms in 7 of 8 patients.

• CONCLUSION: Although uncommon, anti-PD-(L)1-associated ocular complications may be sight-threatening and lead to discontinuation of anti-PD-(L)1 treatments. Patients complaining of eye problems while receiving ICI treatment should immediately be seen by an ophthalmologist. (Am J Ophthalmol 2019;202:109–117. © 2019 Elsevier Inc. All rights reserved.)

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In the last decade, the development of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of various advanced cancers. These drugs block inhibitory receptors of the immune system, thus enabling specific antitumor T cell responses. ICIs include monoclonal antibodies directed against programmed death-1 receptor (PD-1), its ligand (PD-L1), and the cytotoxic T lymphocyte–associated antigen 4 (CTLA-4). Antibodies that interfere with the PD-(L)1 interaction show less toxicity than ipilimumab (CTLA-4-targeting) and are henceforth the most commonly used ICIs, administered either alone or in combination with anti-CTLA-4.[1,2] Though it was initially given for metastatic malignant melanoma (MM) and non–small cell lung carcinoma (NSCLC), indications for anti-PD-(L)1 have recently been extended to treat renal cell carcinoma, head and neck squamous cell carcinoma, and Hodgkin lymphoma.

The PD-1 signaling pathway plays a central role in maintaining peripheral tolerance and downregulating antigen-specific T-cell activation, immunity, and immune-mediated inflammatory disease. When bound by its ligands, PD-L1 and PD-L2, PD-1 inhibits T-cell activation and limits immune effector responses.[3] Tumors can express PD-L1 as one mechanism of inhibiting antitumor T cell–mediated responses in the tumor microenvironment. Blockade of this receptor/ligand interaction with anti-PD-1 monoclonal antibodies, such as pembrolizumab and nivolumab, or anti-PD-L1 atezolizumab, durvalumab, and

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avelumab increases the immune response against tumor cells.

By the same mechanism, anti-PD-(L)1 can override the suppression of self-targeting immune responses to generate immune-related adverse events (irAEs). The most common irAEs affect the skin (pruritus, rash, and vitiligo), the digestive tract (colitis and hepatitis), and endocrine tissues (mainly thyroiditis) in approximately 20% of patients.[1,2] Less frequently, irAEs affect lungs, kidneys, or the nervous system.[2] Ophthalmic irAEs, mainly dry eye disease, were reported in early clinical trials.[4] Since then, few small case series have reported incidence of intraocular or orbital inflammation.[5–20] Yet, the prevalence of these complications among anti PD-(L)1-treated patients has not yet been determined. As ocular irAEs may threaten visual function[20] and lead to severe deterioration of the quality of life of patients, further investigation is warranted, and is described herein. Using a prospective cohort of ICI-treated patients, we determined the prevalence and the incidence of ocular complications following anti-PD-(L)1 treatment. Furthermore, we studied individual cases reported through a national pharmacovigilance registry of ICI-treated patients. We discuss the clinical patterns in our case series and those reported in the literature and the putative underlying pathophysiologic mechanisms.

PATIENTS AND METHODS

THIS NONINTERVENTIONAL STUDY REPORTS THE OCULAR complications associated with anti-PD-1/PD-L1 collected through (1) a single-center prospective cohort and (2) a declarative pharmacovigilance registry, which are merged into the REISAMIC registry (Registre des Effets Indésirables Sévères des Anticorps Monoclonaux Immunomodulateurs en Cancérologie). The study protocol was approved by the Ethics Committee of the French Society of Ophthalmology (IRB 00008855 Société Française d'Ophtalmologie IRB#1).

REISAMIC is a pharmacovigilance registry of irAE in ICI-treated patients, set up at the Gustave Roussy Cancer Centre (Villejuif, France). Only irAE of grade ≥2 (ie, requiring moderate local noninvasive intervention), according to the Common Terminology Criteria for Adverse Events (CTCAE),[21] are included in REISAMIC. REISAMIC is based on (1) a single-center prospective cohort (initiated in June 2014 at Gustave Roussy cancer center) for patients treated in "real-life" situations (ie, following marketing authorization), as part of patient access programs for unlicensed medications or during compassionate use, and (2) a national pharmacovigilance registry of irAEs occurring in ICI-treated patients. A reference network of organ specialists reviews every irAE declared in REISAMIC during bimonthly multidisciplinary meetings.[22] Since 2016 the registry is accessible via a mobile application in order to collect irAE data more efficiently. In the present study, we focused on patients with ocular irAE grade ≥2 following anti-PD-(L)1 immunotherapy to treat malignancy who were included in the REISAMIC registry between June 1, 2014, and March 1, 2018.

• **DATA COLLECTION:** For individual patients, cancer history and disease evolution, treatments received, and all irAEs were recorded. There was no systematic ophthalmologic examination planned in the prospective cohort. Consequently, patients of both the prospective cohort and the declarative registry were referred to the ophthalmology department in any case of ophthalmic complaints. In this case, patients underwent comprehensive ophthalmologic assessment by a trained ophthalmologist that included physical examination, as well as ocular and/or orbital imaging at the discretion of the clinician. Intraocular inflammation was graded according to the Standardization of Uveitis Nomenclature (SUN) criteria.[23] The severity of adverse events was graded according to the CTCAE, version 5.0.[21] Tumoral response to ICI was classified according to revised RECIST guideline (version 1.1).[24] This noninterventional study was conducted in compliance with good clinical practice and the tenets of the Declaration of Helsinki. Constitution of the REISAMIC registry had been authorized by the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés).

• **STATISTICAL ANALYSIS:** Patient anonymity was maintained throughout the data collection and statistical analysis phases. Descriptive statistical analysis was performed with Excel for Macintosh (version 15.16). We estimated the prevalence of ocular complications associated with anti-PD-1/PD-L1 anticancer immunotherapy from the prospective patient cohort of the REISAMIC registry alone. We also estimated the incidence of irAEs per patient-months of anti-PD-(L)1 treatment. The cumulative duration of treatment received by all the patients of the prospective cohort has been calculated as follows: ([date of the last infusion or 03/01/2018] – [date of first infusion])/30.5, where the date 03/01/2018 is the end of the inclusion period and 30.5 is the average number of days per month. Regarding patients who received a single infusion of treatment, and to avoid their de facto exclusion of analysis, we used the value of 0.75 for patients treated with pembrolizumab or atezolizumab (infusion every 3 weeks) or 0.5 for patients treated with nivolumab (infusion every 2 weeks).

RESULTS

• **FREQUENCY OF OCULAR COMPLICATIONS AND SYSTEMIC CHARACTERISTICS OF PATIENTS:** Of a total of 745 patients treated with anti-PD-(L)1 included in the prospective cohort during the study period, 3 were reported as

TABLE 1. Systemic Data of Anti-PD-(L)1-Treated Patients With Immune-Related Adverse Events

Case #	Age/Sex	Cancer	Previous Anticancer Treatments	Anti-PD-(L)1	Systemic Anti-PD-(L)1–Associated Complications	Best Overall Antitumoral Response With ICI
1	77/M	Mesothelioma	Carboplatine, pemetrexed	Nivolumab (combined with ipilimumab)	Peripheral neuropathy, lower limb edema	PR
2	63/F	NSCLC	None	Nivolumab	None	PR
3	**44/F**	**MM**	**Dacarbazine**	**Pembrolizumab**	**Vitiligo, hepatitis**	**SD**
4	**71/F**	**MM**	**Dacarbazine, vemurafenib**	**Pembrolizumab**	**Systemic sarcoidosis**	**PR**
5	56/F	CCRCC	Sunitinib	Nivolumab	None	SD
6	57/F	Parotid adenocarcinoma	Cyclophosphamide, epirubicine, 5-fluorouracil, docetaxel, letrozole, trastuzumab, vinorelbine	Atezolizumab	Lichen planus	SD
7	80/M	NSCLC	None	Pembrolizumab	Myocarditis	CR
8	**70/M**	**Lung adenocarcinoma**	**None**	**Pembrolizumab**	**None**	**PR**

CCRCC = clear cell renal cell carcinoma; CR = complete remission; ICI = immune checkpoint inhibitor; MM = malignant melanoma; NSCLC = non–small cell lung carcinoma; PR = partial remission; SD = stable disease.

Bold entries correspond to the cases from the prospective cohort.

TABLE 2. Anti-PD-(L)1-Associated Ocular Complications

Case #	Number of Infusions Before Onset	Delay of Onset After Infusion (Days)	Ongoing ICI Treatment When the Ocular Complication Occurred (Yes/No)	Ocular Anti-PD-(L)1-Associated Complications	CTCAE Grade	Treatment	Ophthalmologic Follow-up (Months)	Outcome of Ocular irAE	Continuation of ICI Treatment	Reason for ICI Discontinuation	ICI Discontinuation for Ocular Manifestation (Yes/No)
1	2	21	Yes	Bilateral chemosis and nongranulomatous anterior uveitis (1+ cell in both eyes), no posterior synechiae	2	Topical DXM (5 drops/day with tapering over 4 weeks)	3	Resolution	No	Extraocular manifestation (peripheral neuropathy)	No
2	36	14	Yes	Bilateral panuveitis including nongranulomatous anterior chamber inflammation (with cyclitic membrane, Descemet folds, 3+ cell and flare and posterior synechiae OD; 1+ cell and flare OS), 1+ bilateral vitritis, papillitis, choroidal infiltrates	3	Topical DXM (8 drops/day with tapering over 4 weeks OD, 6 drops/day with tapering over 4 weeks OS) + 5 DXM subconjunctival injections OD	1	Controlled	Yes	NA	NA
3	**18**	**3**	**Yes**	**Bilateral nongranulomatous anterior uveitis (1+ cell OU), no posterior synechiae**	**2**	**Topical DXM (6 drops/day with tapering over 4 weeks)**	**2**	**Resolution**	**No**	**Ocular manifestation**	**Yes**
4	**8**	**120**	**No**	**Bilateral nongranulomatous anterior uveitis (1+ cell OU), no posterior synechiae**	**2**	**Topical DXM (6 drops/day with tapering over 4 weeks)**	**7**	**Resolution**	**No**	**Cancer remission**	**No**
5	2	15	Yes	Bilateral panuveitis with nongranulomatous anterior chamber inflammation (2+ cell and flare OU), 1+ bilateral vitritis, bilateral serous retinal detachment, inferomacular retinal pigment epithelial detachment OS	3	Systemic CS (IV methylprednisolone 500 mg/day for 3 days followed by prednisone 1 mg/kg with tapering over 3 months) + topical DXM (6 drops/day with tapering over 4 weeks)	9	Initial improvement with relapse on re-challenge	No	Ocular manifestation	Yes

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TABLE 2. Anti-PD-(L)1-Associated Ocular Complications (*Continued*)

Case #	Number of Infusions Before Onset	Delay of Onset After Infusion (Days)	Ongoing ICI Treatment When the Ocular Complication Occurred (Yes/No)	Ocular Anti-PD-(L)1-Associated Complications	CTCAE Grade	Treatment	Ophthalmologic Follow-up (Months)	Outcome of Ocular irAE	Continuation of ICI Treatment	Reason for ICI Discontinuation	ICI Discontinuation for Ocular Manifestation (Yes/No)
6	10	60	Yes	Bilateral cicatrizing conjunctivitis with bilateral Oxford grade 4 SPK, bilateral inferior fornix shortening + upper and lower tarsal conjunctival fibrosis, Schirmer test <5 mm OU	3	Topical DXM (4 drops/day)/systemic CS (prednisone 15 mg ongoing) + scleral lens	7	Controlled	No	Ocular manifestation	Yes
7	2	1	Yes	Bilateral orbital myositis, with bilateral ptosis and complete left ophthalmoplegia, right limitation of adduction	3	Systemic CS (1 mg/kg) + IVIG (2 g/kg) + methotrexate (15 mg/week)	6	Resolution	No	Ocular and cardiac manifestations	Yes
8	**2**	**1**	**Yes**	**Bilateral severe dry eye disease with Oxford grade 3 SPK, Schirmer test <5 mm, OU**	**2**	**Topical CS (3 drops/day)/punctal plugs**	**6**	**Controlled**	**Yes**	**NA**	**NA**

CS = corticosteroid; CTCAE = Common Terminology Criteria for Adverse Events; DXM = dexamethasone; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; IV = intravenous; IVIG = intravenous immunoglobulins; NA = not applicable; SPK = superficial punctate keratitis.

Bold entries correspond to the cases from the prospective cohort.

having ocular irAEs, providing a prevalence of anti-PD-(L)1-associated moderate-to-severe ocular irAEs of 4 in 1000. Altogether, patients of the prospective cohort were exposed to a total duration of treatment of 4277.4 months. Therefore, the incidence of anti-PD-(L)1-associated moderate-to-severe ocular irAEs was 0.7 per 1000 patient-months.

An additional 5 anti-PD-(L)1-treated patients with moderate-to-severe ocular irAEs were concomitantly declared to the national pharmacovigilance registry and were reviewed by the reference network ophthalmologist (E.B.).

When taking all these 8 cases into account, 6 patients had received anti-PD-1 monotherapy, 2 anti-CTLA-4 therapy (ipilimumab, which had been stopped 5 and 46 months earlier), 1 patient anti-PD-1 as well as anti-CTLA-4 immunotherapy, and 1 patient anti-PD-L1 (atezolizumab). Three patients had non–small cell lung cancer (NSCLC), 2 cutaneous melanoma, 1 adenoid cystic carcinoma of the parotid gland, 1 mesothelioma, and 1 clear cell renal cell carcinoma (Table 1). Five patients experienced an additional extra-ophthalmologic irAE. At the end of the follow-up, all patients were considered to respond to the ICI treatment, with 4 patients being partial responders, 3 presenting with stable disease, and 1 being a complete responder.

Ocular irAEs occurred after the second infusion in half of the patients, but could occur at any time up to the 36th infusion. Ocular irAEs occurred during the treatment or after cessation of the treatment (which could be motivated by cancer remission or serious systemic adverse events). The median time of ocular irAE occurrence was 29 ± 41 days (range: 1–120 days) after an infusion of treatment.

• **OPHTHALMOLOGIC FEATURES:** Ocular irAEs consisted of ocular surface disease (n = 2), intraocular inflammation (n = 5), and orbital inflammation (n = 1). The CTCAE grades of severity were grade 2 (4/8) and grade 3 (4/8). Anti-PD-(L)1 was discontinued in 6 of 8 patients. In these 6 patients, reason for discontinuation was ocular irAEs in 4 patients (in Case #7, discontinuation was motivated by concomitant ocular and systemic adverse events); cancer remission in 1 patient (Case #4), and extraocular irAE in 1 patient (ie, peripheral neuropathy, Case #1). Two patients continued ICI treatment despite ocular complications (Case #2 and Case #8). At the final visit, 4 of 8 patients had complete resolution of ocular irAEs and 4 patients were controlled by treatments. The mean follow-up period was 5.1 months (Table 2). Illustrative case reports and video are provided as Supplemental Material (available at AJO.com).

DISCUSSION

USING A PROSPECTIVE ICI-TREATED PATIENT COHORT, WE were able to robustly determine that the prevalence of moderate-to-severe ocular manifestations associated with anti-PD-(L)1 anticancer immunotherapy was 0.4% and the incidence was 0.7 per 1000 patient-months of treatment. Furthermore, data collected through a national pharmacovigilance registry illustrated distinct clinical patterns, including intraocular inflammation, ocular surface inflammation, and orbital neuromuscular disorders that may occur in anti-PD-(L)1-treated patients.

• **INTRAOCULAR INFLAMMATION:** A few case reports, and short series reported intraocular inflammation associated with anti-PD-(L)1 therapies.[5,7–9,11,13,17,18] The spectrum ranged from anterior uveitis, usually nongranulomatous and of variable severity,[8,11,18] to panuveitis, which may have various nonspecific features including vitritis, retinal vasculitis, papilitis, retinal serous detachment, chorioretinal lesions,[5,7,9,17,25] and even uveal effusion.[20] More generally, uveitis may occur in the context of ICI-associated systemic diseases, such as sarcoidosis[26,27] as in Case #4. Therefore, systemic evaluation may be performed in all patients, both to exclude a differential diagnosis and to look for immune-related systemic conditions.

The prevalence of anti-PD-1-associated symptomatic intraocular inflammation was 0.2% in our current study, which was slightly inferior to that published in a recent systematic review about ocular manifestations of ICIs (0.3%–0.6%).[28] However, this complete review included patients receiving anti-CTLA-4 treatment, known to induce irAEs more frequently.[2] Thomas and associates recently hypothesized that intraocular inflammation from ICIs could stem from reprogramming of the cell death pathway in an immune-privileged tissue.[20] This hypothesis is supported by a case of corneal graft rejection in a patient treated with nivolumab for primary lung cancer.[29] Intraocular inflammation associated with anti-PD-(L)1 can be controlled with topical steroids. However, severe inflammation and posterior segment involvement may require systemic treatment.[9] Diem and associates recently suggested that uveitis secondary to pembrolizumab, as well as other irAES such as vitiligo, could be surrogate markers for a beneficial MM treatment response.[30] Similarly, in our series, we found that the 2 pembrolizumab-treated MM patients presenting with uveitis had positive best overall antitumor responses after treatment.

• **OCULAR SURFACE DISEASES:** Dry eye disease (DED) was the first and initially the most frequently reported ocular side effect in ICI-treated patients. In one of the first phase 1 studies published on anti-PD-(L)1 safety, up to 1% of patients developed dry eye while receiving treatment.[4] Dry eye has also been described as a common complication of all ICI treatments in a recent review.[25] Ocular surface diseases, such as episcleritis and blepharitis, have been included in the detailed recommendations for management of ICI adverse effects by the American Society of Clinical Oncology.[31] The peculiar feature of the patient in Case #8

was (1) the severity of dry eye, which required specific interventions, and (2) the chronology of symptoms that were exacerbated after infusions. For these reasons, we included Case #8 in this study. However, prevalence of anti-PD-(L)1-induced DED may be difficult to assess owing to association with other medications,[32] and owing to difficulties in the reporting criteria for DED.[33] Altogether, these issues may contribute to underreporting of this condition, and more study will be required to determine the connection between ICI and DED. Moreover, anti-PD-(L)1 therapy may induce sicca syndrome as part of a systemic disease like Sjögren syndrome[27,34] or sarcoidosis.[35] Dry eye may also be due to meibomian gland dysfunction arising from anti-PD-1-induced ocular rosacea.[36] Experimental data suggest that downregulation of corneal epithelial PD-(L)1 amplifies DED-associated corneal inflammation and epitheliopathy.[37] Although DED is in most cases not a blinding condition, it can be associated with severe reduction in quality of life.[38] Case #6 developed DED in the context of lichen planus induced by ICIs. Thus, DED in this case was associated with lesions of cicatrizing conjunctivitis, a complication involving the basement membrane of the mucosal epithelia.[39]

• **ORBITAL NEUROMUSCULAR MANIFESTATIONS:** Anti-PD-(L)1 may induce orbital myasthenia gravis and myositis.[40,41] Interestingly, we found 2 reported cases of ophthalmoplegia concomitant with myocarditis associated with anti-PD-1.[14,42] Both cases were treated with intravenous immunoglobulins and high-dose intravenous corticosteroid. Anti–acetylcholine receptor and myositis-associated antibodies were both negative. Magnetic resonance imaging used by Nasr and associates confirmed the diagnosis of myositis of the ocular muscles.[14] Touat and associates reported the clinicopathologic features of 10 patients with myositis during anti-PD-(L)1 therapy.[43] Electrodiagnostic studies highlighted a myopathic process without decrement pattern, while anti–acetylcholine receptor and myositis-associated antibodies were negative. Interestingly, Suzuki and associates recently reported a series of anti-PD-(L)1-treated patients with concomitant myasthenia gravis and myositis. Some patients had positive antiacetylcholine antibodies and concomitant myocarditis.[41] Adverse events including diplopia and/or oculomotor paralysis occurring in patients under ICIs should be considered with the greatest precaution, as these conditions can be associated with life-threatening myocarditis.

• **MANAGEMENT AND EVOLUTION OF OCULAR IMMUNE-RELATED ADVERSE EVENTS:** Most ocular side effects of ICIs are managed with topical or periocular corticosteroids, but advanced cases may require systemic corticosteroids and cessation of checkpoint inhibitor therapy.[25] In this study, most patients were treated with topical corticosteroids (7/8) and/or systemic corticosteroid (3/8), with resolution of the symptoms. Two patients required increasing doses of corticosteroid or immunomodulatory agents because of the severity of the situation. In this study, there were no prospectively defined criteria for stopping ICI treatment in response to ocular complications. Continuation or discontinuation of treatment was evaluated on a case-by-case basis, based on the severity and the response to ophthalmologic treatment. However, detailed recommendations for management of irAEs have been recently published.[31] In summary, for moderate (CTCAE grade 2, such as anterior uveitis) toxicities, ICI should be held until symptoms revert to grade 1 levels or lower and corticosteroids may be offered. For severe (grade 3, such as posterior uveitis) toxicity, patients should receive systemic corticosteroids. Restarting immunotherapy after a grade 3 toxicity requires extreme precaution. These recommendations include specific recommendations for episcleritis, uveitis, and blepharitis but do not address other possible ocular manifestations.

In addition to the variability of the ocular symptoms, the time of onset was variable: symptoms could occur from 1 day after the second infusion, and after the 36th infusion. However, half of the patients developed symptoms after their second cycle (ie, during the early treatment phase).

Limitations of our study included the potential role of other medications in the occurrence of ocular side effects.[44] Anti-CTLA-4 are known to be associated with ocular inflammatory side effects.[6,28] However, only 1 patient had concomitant anti-CTLA-4 treatment, and for patients with previous anti-CTLA-4, the chronology of ocular pathology was in favor of anti-PD-(L)1-induced ocular manifestations. Besides, our series may not encompass the whole spectrum of anti-PD-(L)1-associated ocular complications that are rare and pleomorphic, but provides specific data complementary to those published in a recent comprehensive review on ICI-associated ocular complications.[6,25] Finally, the REISAMIC prospective cohort is based on a declarative process. Some mild ocular manifestations may have been overlooked, as ophthalmologic examination was performed only when a patient complained.

To summarize, based on robust epidemiologic data, the prevalence of moderate-to-severe ocular complications associated with anti-PD-(L)1 can be estimated at 0.4%. Furthermore, anti-PD-(L)1 immunotherapy may be associated with a wide range of orbital/ocular inflammatory complications. The latter may be sight-threatening and/or associated with life-threatening conditions. As ICI treatments are being approved for an increasing number of indications, clinicians should be aware of these complications. Patients complaining of eye problems while receiving ICI treatment should immediately be seen by an ophthalmologist.

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