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Original article

Immune reconstitution inflammatory syndrome in HIV-infected patients with *Pneumocystis jirovecii* pneumonia

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ABSTRACT

Introduction: The incidence of immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients after an episode of *Pneumocystis jirovecii* pneumonia (PJP) seems to be lower than with other opportunistic infections. We conducted an observational study in order to determine the incidence, clinical characteristics and outcome of patients diagnosed with PJP-related IRIS.
Methods: We conducted an observational study of HIV patients diagnosed with PJP-related IRIS from January 2000 to November 2015. We analyzed epidemiological and clinical characteristics as well as laboratory findings. We also carried out a systematic review of published cases.
Results: Six cases of IRIS out of 123 (4.9%) HIV-infected patients with PJP who started ART were diagnosed. All six cases were men with a median age of 34 (IQR: 8) years. The six patients developed paradoxical IRIS. Subjects younger than 40 years old ($p = 0.084$) and with an HIV-RNA viral load >100 000 copies/ml ($p = 0.081$) at diagnosis showed a tendency to develop IRIS. Thirty-seven published cases of PJP-related IRIS were identified. Although 51% of cases involved respiratory failure, no deaths were reported.
Conclusions: PJP-related IRIS is rare condition compared to other opportunistic infections. It can lead to a severe respiratory failure in a significant proportion of cases, although no deaths have been reported.

Síndrome inflamatorio de reconstitución inmune en pacientes con infección por VIH y neumonía por *Pneumocystis jirovecii*

Palabras clave:
Pneumocystis jirovecii
Reconstitución inmune
Virus de la inmunodeficiencia humana

RESUMEN

Introducción: La incidencia del síndrome inflamatorio de reconstitución inmune (SIRI) en pacientes infectados por el virus de la inmunodeficiencia humana (VIH) después de un episodio de neumonía por *Pneumocystis jirovecii* (PJP) parece ser menor que con otras infecciones oportunistas. Hemos realizado un estudio observacional con el objetivo de conocer la incidencia, las características clínicas y la evolución de los pacientes diagnosticados de SIRI asociado con la PJP.
Métodos: Se ha realizado un estudio observacional de pacientes con VIH diagnosticados de SIRI asociado a PJP desde enero del 2000 hasta noviembre de 2015. Fueron analizadas características epidemiológicas y clínicas, así como hallazgos de laboratorio. Asimismo, se ha llevado a cabo una revisión sistemática de los casos publicados previamente.
Resultados: Se identificaron 6 casos de SIRI en 123 pacientes con VIH (4,9%) con PJP que comenzaron TAR. Los 6 casos eran varones con una edad media de 34 (IQR: 8) años. En los 6 casos se trató de una SIRI paradójico. Los sujetos menores de 40 años (p = 0,084) y con VIH-ARN al diagnóstico mayor de 100.000 copias/ml (p = 0,081) mostraron una tendencia a desarrollar SIRI. Se identificaron 37 casos publicados de SIRI relacionado con PJP en la literatura. Aunque el 51% de los casos presentaron insuficiencia respiratoria, no se reportaron muertes.

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Conclusiones: El SIRI asociado con PJP es una entidad infrecuente comparada con el relacionado con otras infecciones oportunistas. Puede provocar insuficiencia respiratoria grave en un porcentaje importante de casos, si bien no se han reportado muertes.

Introduction

Most opportunistic infections experienced a significant decline after the introduction of highly active antiretroviral therapy (ART). However they continue to be present among patients who are unaware of their HIV-infected status or among those subjects who remain unlinked to care or do not take ART properly due to adherence or tolerability issues.[1] In fact, *Pneumocystis jirovecii* pneumonia (PJP) still represents the most common opportunistic infection in patients with AIDS in developed countries.[2,3]

After an episode of PJP, initiation of ART is mandatory as it has been shown in clinical trials and cohort studies. Indeed, early initiation of ART in the first 10–14 days reduced AIDS progression and death in patients with PJP compared with those who started later.[4] Nevertheless the development of an immune reconstitution inflammatory syndrome (IRIS) is a matter of concern when ART is initiated after an opportunistic infection. IRIS has been well described in patients with cytomegalovirus retinitis, cryptococcal meningitis, tuberculosis or progressive multifocal leukoencephalopathy.[5] However the incidence of IRIS remains unclear for other common opportunistic infections such as PJP. Most publications regarding PJP-related IRIS consist in single case-reports or small case series.[6,7] A first attempt to address this issue was performed by Mok et al. who reviewed 17 cases previously published, however in this study data regarding the outcome of the patients were not reported.[7] In any case, the incidence of IRIS after an episode of PJP seems to be lower than with other opportunistic infections. Moreover cases of acute respiratory failure after early introduction of ART in patients treated for PJP have been described.[8]

Because of the scarce data published regarding PJP-related IRIS we performed an observational study in order to determine the incidence, clinical characteristics and outcome of patients diagnosed with PJP-related IRIS. We also carried out a comprehensive review of published cases in the literature.

Patients, material and methods

Study design

This is an observational retrospective study of all HIV adult patients diagnosed with PJP-related IRIS between January 2000 and November 2015 at the University Hospital Vall d'Hebron, in Barcelona, Spain. A cohort study of all cases of PJP in our institution was previously published.[3] Our institution is a 1000-bed tertiary hospital where approximately 2100 HIV-infected are regularly followed in the outpatient clinic. All clinical data of HIV-infected patients are routinely included in a database as a part of a continuous observational study. Data analyzed in the present study have been taken from this database. This study was approved by the Ethics Committee of Vall d'Hebron Research Institute.

Study variables and data collection

For each patient we recorded demographic, clinical, laboratory and radiological data. CD4 lymphocyte count and HIV viral load were recorded at diagnosis of PJP and at diagnosis of IRIS as well as the timing of ART initiation. Development of respiratory failure, need of ICU admission and outcome of PJP and PJP-related IRIS were also recorded.

Definitions

Diagnosis of PJP was performed in patients with suggestive clinical and radiological findings and demonstration by direct immunofluorescence of *P. jirovecii* (PJ) in bronchoalveolar lavage (BAL). In those cases in which fibrobronchoscopy could not be performed, a probable diagnosis of PJP was assumed if all the following conditions were fulfilled: CD4 lymphocyte count <200 cells/μL; clinical and radiological findings suggestive of PJP, no prophylaxis against PJP, good response to specific PJP treatment and exclusion of other pulmonary pathogens, mainly bacterial pneumonia and tuberculosis.

Respiratory failure was defined as oxygen saturation <90% using a pulse oximeter or partial pressure of oxygen <60 mmHg in arterial blood.

PJP IRIS was diagnosed in patients who fulfilled the following criteria: (1) development of inflammatory symptoms after initiation of ART, (2) significant decrease in HIV-RNA level from baseline and an increase in CD4+ cells from baseline and (3) exclusion of a newly diagnosed opportunistic infection or drug toxicity. These criteria have been previously published by other authors.[9]

Treatment

All patients were initially treated with intravenous cotrimoxazol and in those who presented adverse effects treatment was switched to intravenous pentamidine. Metilprednisolone was indicated when the patient developed respiratory failure (pO2< 60 mmHg) with the following dose: 40 mg/12 h during five days, 40 mg per day during five days and after that a progressive reduction in the following weeks until day 21.

Literature review

A search in PubMed database was done using the topics "Immune reconstitution inflammatory syndrome", "Pneumocystis IRIS", "Pneumocystis jirovecii immune reconstitution", "Pneumocystis carinii pneumonia immune reconstitution syndrome", "immune restoration Pneumocystis", "immune reconstitution Pneumocystis carinii pneumonia" and "Pneumocystis carinii pneumonia worsening HAART" in order to find published cases of *P. jirovecii* related IRIS. Results were limited to adult patients (above 18 years old) and to Spanish, English or French literature.

From each case we attempt to obtain the following data: demographic data, CD4 lymphocyte count and HIV-RNA viral load at ART initiation, CD4 lymphocyte count and HIV-RNA viral load at diagnosis of IRIS, use of steroids, clinical and radiological characteristics, antiretroviral therapy, outcome and mortality.

Table 1
Characteristics of patients of Hospital Vall d'Hebron and cases reported in the literature with PJP IRIS.

Ref.	Age	Sex	IRIS subtype	CD4+ count at PJP diagnosis (cells/mm^3)	HIV-RNA at PJP diagnosis (copies/mL)	CD4+ count at IRIS diagnosis (cells/mm^3)	HIV-RNA at IRIS diagnosis (copies/mL)
VH	37	M	Paradoxical	35	250 000	442	80
VH	33	M	Paradoxical	24	1 400 000	98	16 000
VH	34	M	Paradoxical	133	250 000	83	540
VH	24	M	Paradoxical	5	164 000	41	1000
VH	34	M	Paradoxical	82	420 000	290	660
VH	44	M	Paradoxical	50	2 100 000	70	6700
6	37	H	Paradoxical	32	738 000	15	49 700
6	49	H	Paradoxical	145	441 000	63	NR
7	43	M	Paradoxical	7	238 732	27	125
8	37	M	Paradoxical	7	140 000	38	Undetectable
8	47	M	Paradoxical	28	100 000	50	33 000
8	50	F	Paradoxical	230	565 000	564	1386
10	NR	NR	Paradoxical	26[a]	562 000[b]	62[a]	631[b]
10	NR	NR	Paradoxical	26[a]	562 000[b]	62[a]	631[b]
10	NR	NR	Paradoxical	26[a]	562 000[b]	62[a]	631[b]
11	38	M	Paradoxical	4	283 000	125	3620
11	NR	M	Paradoxical	70	NR	182	NR
11	NR	M	Paradoxical	10	NR	30	NR
11	NR	M	Paradoxical	216	NR	340	NR
11	NR	M	Paradoxical	290	NR	430	NR
11	NR	M	Paradoxical	60	NR	130	NR
12	34	M	Paradoxical	46	790 000	435	31 600
13	NR	NR	Paradoxical	NR	NR	NR	NR
13	NR	NR	Paradoxical	NR	NR	NR	NR
14	35	M	Unmasking	20	154 000	510	Undetectable
15	31	M	Paradoxical	332	278 000	537	1840
16	NR	NR	Paradoxical	25	500 000	1238	1238
17	36	M	Paradoxical	150	100 000	250	92
17	54	NR	Unmasking	170	100 000	290	107
18	31	M	Paradoxical	3	170 000	5	75
18	NR	NR	Paradoxical	176	146 000	201	112
18	NR	NR	Paradoxical	86	149 240	61	79
19	34	M	Unmasking	370	750 000	835	28 000
20	40	M	Paradoxical	25	1 250 000	186	1000
20	42	M	Paradoxical	18	51 000	47	501
20	37	M	Paradoxical	76	2 000 000	481	3980
20	45	M	Paradoxical	22	39 800	101	79
21	40	F	Paradoxical	16	5 000 000	359	31 000
22	NR	NR	Paradoxical	6	NR	56	NR
22	NR	NR	Paradoxical	74	NR	162	NR
22	NR	NR	Paradoxical	82	NR	600	NR
23	34	F	Unmasking	270	100 000	510	5322
24	34	M	Paradoxical	79	500 000	292	500
25	34	F	Paradoxical	110	1 323 000 (6.09)	250	427

VH: patients of Hospital Vall d'Hebron; NR: not reported data in the original publication.
[a] Median of the three cases in the original publication.
[b] Mean $\log_{10}$ viral load of the three cases in the original publication.

Statistical analysis

Categorical variables are presented as numbers (proportions) and continuous are expressed as mean and standard deviation or median and interquartile range as appropriate. We carried out an unvaried analysis in order to find differences between patients who developed IRIS and those who did not. The Chi-square test was used to compare categorical variables, and the Mann–Whitney *U* test for continuous variables. All statistical tests were two-tailed and were performed at a level of statistical significance of 0.05. IBM SPSS statistics software for Windows (Version 21.0; IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

From January 2000 to November 2015, 148 HIV infected patients were diagnosed of PJP in our Institution. In 74 (50%) of them the PJP episode was the initial event of HIV infection. Fifteen patients (10.1%) died during the course of PJP before starting ART. Of the 133 subjects who survived, 123 began ART. In this study we focus on these 123 patients with PJP who started ART.

Baseline characteristics of patients at PJP diagnosis

The mean age of the 123 patients was 40.8 (± 9.3) years old. There were 85 (69.1%) men and 38 (30.9%) women. The mean CD4+ lymphocyte count was 48.1/μL (± 59.7). One hundred and eighteen (96.9%) patients had <200 CD4+ lymphocytes/μL at the time of diagnosis and 86 (70.5%) <50 CD4+ lymphocytes/μL. Mean HIV-RNA viral load was 5.78 (± 6.16) $\log_{10}$ copies/mL. Seventy (56.9%) patients had >100 000 RNA copies/mL at diagnosis.

Characteristics of patients with PJP-IRIS

In the following weeks after ART initiation, 6 out of 123 (4.9%) patients presented a PJP associated IRIS. All 6 cases were men with a median age of 34 (IQR: 8) years old. All of them had <200 CD4+ lymphocytes/μL and >100 000 RNA copies/mL at the time of diagnosis of PJP. The 6 patients had been diagnosed by bronchoscopy

Table 2
Clinical data and outcome of patients of Hospital Vall d'Hebron and cases reported in the literature with PJP IRIS.

Ref.	IRIS symptoms	Respiratory failure	ICU	Death	STOP ART	DaysPJP-ART	DaysART-IRIS
VH	Fever	Yes	Yes	No	No	NR	NR
VH	Fever, dry cough	No	No	No	No	35	1
VH	Fever, productive cough, dyspnea	Yes	Yes	No	No	NR	NR
VH	Fever, productive cough.	No	No	No	No	2	19
VH	Fever, dry cough	Yes	Yes (HFNC)	No	No	31	6
VH	Fever, dry cough, dyspnea	Yes	Yes (HFNC)	No	No	22	7
6	Fever, dry cough, dyspnea	Yes	NR (NIV)	No	No	22	6
6	Fever, dyspnea	Yes	Yes (EI)	No	Yes	20	5
7	Fever, dyspnea	Yes	Yes	No	No	22	3
8	Fever, dyspnea	No	No	No	Yes	15	11
8	Fever, dyspnea	Yes	Yes (EI)	No	Yes	1	17
8	Fever, dyspnea	Yes	NR	No	No	19	26
10	Fever, dyspnea	Yes	NR	No	No	15–18[a]	3–17[a]
10	Fever, dyspnea	Yes	NR	No	No	15–18[a]	3–17[a]
10	Fever, dyspnea	Yes	NR	No	No	15–18[a]	3–17[a]
11	Fever, cough, dyspnea	No	No	No	NR	35	14[h]
11	Fever, dyspnea	NR	NR	No	NR	17–24[b]	NR
11	Fever, dyspnea	NR	NR	No	NR	17–24[b]	NR
11	Fever, dyspnea	NR	NR	No	NR	17–24[b]	NR
11	Fever, dyspnea	No	NR	No	NR	17–24[b]	NR
11	Fever, dyspnea	No	NR	No	NR	17–24[b]	NR
12	Fever, dry cough, dyspnea	No	No	No	No	18	14
13[c]	Dry cough	NR	NR	NR	NR	3 years	42
13[c]	Dyspnea	NR	NR	NR	NR	[d]	210
14	Dry cough	No	No	No	No	0[e]	21
15	Fever, dyspnea	NR	NR	No	No	NR	15
16	Fever, dyspnea	NR	NR	NR	NR	NR	NR
17	Fever, dry cough	NR	NR	No	No	35	21
17	Fever, dyspnea	No	No	No	No	0[e]	120
18	Fever, dyspnea	Yes	NR	No	No	13	15
18	NR	Yes	NR	No	NR	23	9
18	NR	Yes	NR	No	NR	4	22
19	Fever, dry cough, dyspnea	NR	NR	No	No	[f]	43
20	Fever, dry cough, dyspnea	NR	NR	NR	NR	9	NR
20	Fever, dry cough, dyspnea	NR	NR	NR	NR	11	NR
20	Fever, dry cough	NR	NR	NR	NR	42	NR
20	Fever, dyspnea	NR	NR	NR	NR	49	NR
21	Dyspnea, dry cough	No	No	No	No	[g]	NR
22	NR	NR	NR	No	NR	170	301
22	NR	NR	NR	No	NR	49	71
22	NR	NR	NR	No	NR	36	5
23	Fever, dry cough	Yes	Yes	No	si	0[e]	8
24	Fever, dyspnea	Yes	No	No	No	NR	9
25	Fever, dry cough, dyspnea	NR	NR	No	NR	NR	25

[a] Range of days of the three cases in original publication.
[b] Range of days of the five cases in original publication.
[c] Only abstract available.
[d] "Immediately after completing the responsive treatment of PCP" in abstract.
[e] Unmasking IRIS, ART is considered to begin on day 0.
[f] "8 weeks" in original publication.
[g] "Shortly before completing treatment for PCP" in original publication.
[h] "two weeks later" in original publication.
ICU: intensive care unit; EI: endotracheal intubation; HFNC: high flow nasal cannula, NIV: non-invasive ventilation; NR: not reported in original publication; STOP ART: interruption of ART because of IRIS symptoms; Days PJP-ART: days between the beginning of PJP treatment and the beginning of ART. Days ART-IRIS: days between the beginning of ART and the beginning of IRIS symptoms.

with microbiological confirmation. The 6 patients developed a paradoxical IRIS. At the moment of IRIS, all 6 patients had completed treatment for PJP and were all receiving secondary prophylaxis with cotrimoxazol. The clinical presentation consisted of reappearance of fever and dyspnea, and worsening of previous bilateral radiological infiltrates in all cases. All but one had been treated with corticosteroids in the previous episode of PJP. Despite CMV was isolated in three of these patients, none of them received specific antiviral therapy with ganciclovir or foscarnet.

ART was begun between days 2 and 35 after the initiation of PJP treatment. Four out of 6 patients developed respiratory failure during IRIS episode and required intensive care unit admission. All 6 patients were treated with steroids and in none of the ART was interrupted. Two of them required noninvasive mechanic ventilation. However, the final outcome was favorable and all 6 patients survived. Tables 1 and 2 show the clinical characteristics and outcome of the patients of the study.

In Table 3 we show a comparison of epidemiological, clinical, and immuno-virological data present at baseline between those patients who developed a PJP associated IRIS and those who did not. In the univariate analysis, we observed a non-significant trend to a higher risk of IRIS in patients <40 years old ($p = 0.084$) and in patients with HIV-RNA viral load >100 000 copies/mL at baseline ($p = 0.081$).

Literature review

We identified a total of 38 PJP-related IRIS cases reported in 19 publications. Demographic data, clinical characteristics, laboratory parameters and outcome were taken from the original

Table 3
Characteristics of patients with PJP depending on the development of IRIS.

	Patients with PJP who developed IRIS ($n=6$)	Patients with PJP who did not developed IRIS ($n=117$)	p
Age <40 years	5 (83.3%)	48/117 (41.0%)	0.084
Male sex	6 (100%)	79/117 (67.5%)	0.176
Previously known HIV infection	3 (50%)	61/117 (52.1%)	1
Previous opportunistic infections	2 (33.3%)	27/117 (23.1%)	0.625
CD4 lymphocytes at baseline <50 cells/μL	4 (66.7%)	82/106 (70.0%)	1
RNA VIH >100 000 copies/mL at baseline	6 (100%)	64/107 (59.8%)	0.081
Use of steroids in the initial episode of PJP	5 (83.3%)	92/117 (78.6%)	1
Respiratory failure in the initial episode of PJP	5 (83.3%)	74/117 (63.2%)	0.419
CMV detection in broncoalveolar lavage in the initial episode of PJP	3/5 (60%)	25/82 (31.2%)	0.323

CMV: citomegalovirus.

Table 4
Comparison between characteristics of patients of Hospital Vall d'Hebron and cases reported in the literature with PJP IRIS.

	VH cases ($n=6$)	Cases reported in literature ($n=38$)	p value
CD4+ count at PJP diagnosis (cells/mm^3) [median, range]	42.5 [128]	53 [367]	NS
CD4+ count at IRIS diagnosis (cells/mm^3) [median, range]	90.5 [401]	184 [1233]	NS
HIV-RNA at PJP diagnosis ($\log_{10}$) [median, range]	5.5 [1.1]	5.47 [4.43]	NS
HIV-RNA at IRIS diagnosis ($\log_{10}$) [median, range]	2.9 [2.3]	2.80 [4.69]	NS
Respiratory failure	4/6 (66.7%)	13/21 (61.9%)	NS
Death	None	None	

VH: Vall d'Hebron; NS: non significant.

publications. All this information, together with our 6 cases, is summarized in Tables 1 and 2.

Considering the 38 cases published in the literature and the 6 diagnosed in our hospital, 5 out of 44 (11.4%) were unmasking IRIS. Seventeen out of the 27 (62.9%) patients in which this information was available developed respiratory failure. Need of intensive care admission was documented in 8 out of these 27 (29.6%) cases. None of the 44 patients died due to IRIS episode. We have compared different data between our patients and those reported in the literature (Table 4) and we have not found significant differences regarding CD4 count and viral load at baseline and IRIS diagnosis. The presentation of patients who developed respiratory failure was similar in both groups.

Discussion

In our study we report 6 cases of PJP related IRIS out of 123 patients with PJP which represents an incidence of 4.9%. This incidence of IRIS after an episode of PJP is similar to the 4% (3 out of 72 patients) in a previous retrospective study and much lower than the incidence of IRIS associated to other common opportunistic infections such as tuberculosis or criptococcosis.[8] In one prospective randomized study that compared early versus deferred antiretroviral therapy after an acute opportunistic infection that included 282 subjects, IRIS was uncommon (7%). Even in those patients with baseline conditions associated with IRIS (low CD4 cell count, ART initiation within first 2 weeks of opportunistic infections diagnosed and good immunovirological response after ART initiation), IRIS incidence remained low.[4] In this study most patients (63%) had PJP and probably this is why the incidence of IRIS was lower than that expected.

The reason why IRIS seems to occur less frequently after an episode of PJP than with other opportunistic infections remains unclear. There are some explanations that can be argued. It is possible that the fungal load after institution of therapy against PJ decreases rapidly and the amount of remaining antigens when ART is initiated is too low to trigger an exuberant immunological response as occurs with other cases of IRIS. According to that, infections caused by microorganisms with a slower decay of the bacterial burden once treatment is established, have been associated with higher rates of IRIS. Indeed, rates of IRIS up to 20–26% have been observed in criptococcal meningitis or tuberculosis infection.[26–28] Therefore, the slower decay of microorganism burden seems to have a role in IRIS occurrence. Previous corticoid treatment has also been proposed as a possible explanation. However, previous publications have found o relation between corticoid treatment during different opportunistic infections and IRIS development.[4,13,22] In our study, only one patient did not received corticoid treatment during previous PJP, so we were not able to asses this issue.

We have made an analysis in order to find factors that could be associated to the development of IRIS. However we have not found any significant variable that could help us to identify those patients with greater risk to develop IRIS, probably because of the small number of subjects with PJP related IRIS reported in our series. The only variables that had a non significant trend to identify these patients were a high viral load at baseline and age <40 years old. The relation between IRIS and age has been described previously.[29] In older patients the loss of the thymic function makes CD4 recovery slower and lower.[29] Conversely in younger subjects a stronger and faster immunological restoration is expected after the initiation of ART which could also play a role in an overexpressed inflammatory response.[11]

From a clinical point of view it is worth to note that most of the patients with PJP related IRIS presented with a severe clinical picture. In our cohort 4 out of 6 patients developed respiratory failure that required intensive care unit admission when IRIS was diagnosed. When we have reviewed together our cases and those previously published in the literature up to 50% of patients had respiratory failure at the moment of IRIS diagnosis. Despite clinical severity at presentation the clinical outcome of these patients was satisfactory and no patient died in our series. Similarly none of the 42 patients previously published in the literature died due to the IRIS episode compared to other opportunistic infections, especially in central nervous system opportunistic infections, in which IRIS is a severe and frequently fatal event.

Our study has some limitations due to its observational design. Moreover the low number of patients with IRIS does not allow identifying risk factors for the development of IRIS in patients with PJP who initiate ART.

In conclusion, although PJP-related IRIS is less frequent than other OI-related IRIS, it usually causes respiratory failure and

further ICU admission. Despite its severity, clinical outcome is usually favorable.

Conflict of interests

The authors confirm they don't have any conflict of interest.

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