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Clinical features and treatment outcomes of pediatric acute promyelocytic leukemia in a Mexican pediatric hospital

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ABSTRACT

Introduction. Acute promyelocytic leukemia (APL) is a distinct type of acute myeloid leukemia (AML) characterized by chromosomal translocations involving the retinoid acid receptor α (RARA) gene on chromosome 17. APL is a relatively rare blood disease that is highly curable with current treatment strategies; however, patient outcomes are heterogeneous in countries with limited resources. Promyelocytic leukemia accounts for 20-25% of all AML cases in Latin American countries. **Material and methods.** We conducted a study from July 2007 to July 2012 and applied the IC-APL2006 protocol. This case study reports the results from eleven patients with AML M3 (five males and six females). In all cases, the diagnoses were made by aspirating bone marrow and evaluating the t(15:17) or t(11:17) transcript. In eight cases, the molecular biology-based diagnostics for the PLM-RARa transcript were positive, and they were negative in two cases. One patient was positive for the PLZF-RARa transcript. **Results.** The mean WBC at the time of diagnosis was 10.1 x 10^9/L, and the mean platelet count was 17.1 x 10^9/L. The mean percentage of abnormal promyelocytes in the bone marrow aspirates was 68%. Of the eleven patients, four presented with disseminated intravascular coagulation. All of the patients began treatment with transretinoic acid (ATRA) (45 mg/m^2/day), which led to 4 cases of ATRA syndrome. There were 2 relapses, and the patient died in one case. The remaining ten patients were alive after the median follow-up period of 33.6 months (range from 11 to 60 months). **Conclusion.** The authors report on a series of cases involving pediatric patients with AML M3 seen at a single institution; the patients were stratified and treated with a standard protocol to obtain satisfactory results. Although the number of patients is limited, the health outcomes are relevant. To our knowledge, this is the first series of pediatric APL patients in Mexico who were treated with the IC-APL2006 protocol.

Hallazgos clínicos y resultados del tratamiento de leucemia promielocítica aguda en un hospital pediátrico de México.

RESUMEN

Introducción. *La leucemia aguda promielocítica (LAP) es un subtipo de leucemia mieloide aguda (LMA) que se caracteriza por alteraciones cromosómicas que involucran al receptor de ácido retinoico α (RARA), cuyo gen se encuentra en el cromosoma 17. La LAP corresponde a 20-25% de todos los casos de LMA en países de América Latina y es altamente curable con estrategias actuales de tratamiento; no obstante, los tratamientos para este grupo de pacientes y los resultados en salud son aún heterogéneos en países con recursos económicos limitados.* ***Material y métodos.*** *Se llevó a cabo un estudio de julio 2007 hasta julio 2012 aplicando el protocolo IC-APL2006. Esta serie de casos reporta los resultados de once pacientes pediátricos con leucemia aguda promielocítica (cinco masculinos y seis femeninos). En todos los casos el diagnóstico fue realizado por aspirado de médula ósea y evaluación de los transcritos de la t(15:17) o t(11:17). En ocho casos, el resultado de biología molecular para el transcrito PLM-RARa fue positivo y en un caso se documentó el transcrito PLZF-RARa. En dos casos ambos transcritos fueron negativos.* ***Resultados.*** *La media de leucocitos al diagnóstico fue de 10.1 x 10^9/L, y la media de plaquetas de 17.1 x 10^9/L. La media del porcentaje de promielocitos anormales en los aspirados de médula ósea fue de 68%. De los once pacientes, cuatro presentaron coagulación intravascular diseminada al diagnóstico. Todos los pacientes iniciaron tratamiento con ácido transretinoico (ATRA) a dosis de 45 mg/m^2/día, y se presentaron cuatro casos de síndrome ATRA. En la serie de casos de este trabajo se presentaron dos recaídas, y uno de estos pacientes falleció. Los diez pacientes restantes se encontraban vivos después de un seguimiento promedio de 33.6 meses (un rango que osciló de 11 a 60 meses).* ***Conclusión.*** *Se reporta una serie de casos que*

involucran pacientes pediátricos con LAP atendidos en una sola institución; los pacientes fueron estratificados y tratados de acuerdo con el protocolo establecido y los resultados obtenidos fueron satisfactorios. Aunque el número de pacientes es limitado, los resultados en salud son relevantes. Ésta es la primera serie de casos que reporta resultados en salud de pacientes pediátricos con LAP en México, tratados con el protocolo IC-APL2006.

Key words. Acute promyelocytic leukemia. Mexican children. Treatment.

Palabras clave. *Leucemia aguda promielocítica. Niños mexicanos. Tratamiento.*

INTRODUCTION

Acute promyelocytic leukemia (APL) is a distinct type of acute myeloid leukemia (AML) that is characterized by chromosomal translocations involving the retinoid acid receptor á (RARA) gene on chromosome 17.

When characterized by immunophenotype, APL cells show CD13 and CD33 expression and also rarely express HLA-DR, CD34, CD10, CD7, CD11b, and CD14.[1]

Chromosomal abnormalities have been identified in leukemic cells from APL patients. The t(15:17) abnormality has been observed in approximately 90% of children with APL, while the t(11:17) abnormality has been observed in approximately 5% of patients.[2]

Only this subtype of AML can be forced into complete remission with ATRA treatment in the majority of patients (90%). This therapy causes the differentiation of promyelocytes but has not been demonstrated to eradicate the leukemic clone unless it is combined with an anthracycline-based chemotherapy treatment.[3] In recent years, the experiences of groups in several countries have shown that combining ATRA and chemotherapy offers improved survival in patients who are newly diagnosed with APL compared to chemotherapy-based treatment alone. Additionally, it has been demonstrated that ATRA and a lower maintenance dose of chemotherapy may reduce the incidence of relapses and result in five-year survival rates of up to 75%.[4,5]

While APL is the most curable subtype of acute myeloid leukemia using current therapy, Latin American countries have reported up to 30% mortality in children and adults with APL, which is caused by early complications associated with the disease or treatment complications.[6]

APL comprises 20-25% of all AML cases in Latin American countries and presents clinical, epidemiological and molecular findings that identify it as a particular entity within AML. APL treatment differs from the other AML subtypes.[6]

To confront the situation of APL treatment in developing countries, the American Society of Hematology has proposed an effort titled the International Consortium on Acute Promyelocytic Leukemia (IC APL).[7] APL specialists from numerous countries have contributed to the IC APL. This protocol is similar to the PETHEMA 2005 protocol but exchanges idarubicin for daunorubicin. There was a remarkable improvement in survival that reached 75% in one year and the disease free survival in the same period was 95%.[8,9]

Herein we report the first study of newly diagnosed pediatric Mexican APL patients, who were enrolled in the IC APL protocol at a third level pediatric hospital in México.

MATERIAL AND METHODS

Enrolled patients and treatment protocol

From July 2007 to July 2012, 57 pediatric patients who were newly diagnosed with AML and previously untreated were seen in a tertiary care hospital (Hospital Infantil de México Federico Gómez). Eleven of these patients (19.2%) were diagnosed with APL. Relatives signed informed consent forms at the start of treatment.

The morphological criteria defining the presence of APL were: APL hypergranular (i.e., if > 20% of the promyelocytes in a bone marrow aspirate were hypergranular) and the presence of Auer rods. The APL variant was identified using the above criteria but with the added condition of fine granularity in the cytoplasm of the promyelocytes.[10]

Bone marrow samples were collected, morphologically evaluated and processed for the PML-RAR alpha rearrangement using reverse transcriptase-polymerase chain reaction (RT-PCR) at the time of diagnosis, after induction, at recovery from the third consolidation cycle and at the end of maintenance.

In cases where the PML-RAR alpha transcript could not be detected, tests for the PZLF-RARa transcript were performed.

Using RT-PCR techniques to identify the PML-RAR alpha fusion transcript has been reported elsewhere.[11]

Briefly, 1 mL of bone marrow was used. After hemolysis of the erythrocytes with red blood cell lysis buffer, RNA extraction was performed using a High Pure RNA Isolation Kit ROCHE®/Germany. The synthesis of cDNA was performed using a First Strand cDNA Synthesis Kit and a thermocycler LightCycler 2.0 ROCHE®/Germany. Detection was performed with real time RT-PCR, using designs by TIBMolBiol® platform Real Time PCR ROCHE Diagnostic®. In addition, we performed the amplification of the gene encoding Glucose 6-phosphate dehydrogenase as a reference transcript; therefore, a ratio could be used to measure positive cases. The method had a sensitivity of 10^1 to 10^6 (Figure 1).

Immunophenotypic analyses were systematically performed at the time of diagnosis and in cases of relapse. The remission induction response was assessed according to the recently revised criteria by Cheson, *et al.*[12]

Molecular remission and relapse were defined as the disappearance and reappearance of positive RT-PCR tests for the PML-RAR alpha fusion transcript.

Relapse risk groups were defined as follows: low-risk patients had a WBC count < 10 x 10^9/L and a platelet count of > 40 x 10^9/L; intermediate-risk patients had a WBC count of < 10 x 10^9/L and a platelet count of < 40 x 10^9/L; and high-risk patients had a WBC count ≥ 10 x 10^9/L.[13] Hematologic toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria, version 2.[14]

The patients had no cardiac contraindications to anthracycline chemotherapy and had serum creatinine levels < 3 times the normal upper limit and serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels < 3 times the upper normal limit.

Coagulopathy, which was defined by hypofibrinogenemia (fibrinogen levels < 150 mg/dL), and prolonged prothrombin and thrombin times, was treated with fresh frozen plasma or fibrinogen. Supportive PLT transfusions were administered in the presence of hemorrhages with or without laboratory signs of severe

Table 1. ASH International Committee Acute Promyelocytic Leukemia Protocol (IC-APL2006).

Remission induction (all patients)	DNR 60 mg/m^2/day (days 2, 4, 6, and 8) ATRA 45 mg/m^2/day (day 1 until CR) Dexamethasone 2.5 mg/m^2/12 h x 15 (if WBC >5 x 10^9/L)		
Consolidation (risk-adapted)	Low-risk (WBC ≤10 x 10^9/L Platelets > 40 x 10^9/L)	Intermediate-risk (WBC ≤10 x 10^9/L Platelets ≤ 40 x 10^9/L)	High risk (WBC > 10 x 10^9/L Platelets ≤ 40 x 10^9/L)
	DNR 25 mg/m^2/day (days 1, 2, 3, 4) ATRA 45 mg/m^2/day x 15	DNR 35 m^2/day (days 1, 2, 3, 4) ATRA 45 mg/m^2/day x 15	DNR 25 mg/m^2/day (days 1, 2, 3, 4) Ara-C 1,000 mg/m^2/day (days 1, 2, 3, 4) ATRA 45 mg/m^2/day x 15
	MTZ 10 mg/m^2/day (days 1,2,3) ATRA 45 mg/m^2/day x 15	MTZ 10 mg/m^2/day (days 1, 2, 3) ATRA 45 mg/m^2/day x 15	MTZ 10 mg/m^2/day (days 1, 2, 3, 4, 5) ATRA 45 mg/m^2/day x 15
	DNR 60 mg/m^2/day (day 1) ATRA 45 mg/m^2/day x 15	DNR 60 mg/m^2/day (days 1, 2) ATRA 45 mg/m^2/day x 15	DNR 60 mg/m^2/day (day 1) Ara-C 150 mg/m^2/8 h (days 1, 2, 3, 4) ATRA 45 mg/m^2/day x 15
Maintenance (all patients)	2 years ATRA 45 mg/m^2/day x 15 (every 3 months) Methotrexate 15 mg/m^2/day (weekly) 6-Mercaptopurine 50 mg/m^2/day		

ATRA: all-trans retinoic acid. DNR: daunorubicin. MTZ: mitoxantrone. Ara-C: cytarabine. CR: complete remission.

coagulopathy or if the PLT count was < 50 x 10^9/L. Blood cell units were transfused to maintain hemoglobin levels > 8 g/dL.

Treatment for ATRA syndrome involved using intravenous dexamethasone at a dose of 10 mg b.i.d. for a minimum of 3 days. The febrile episodes were treated with a cephalosporin and an aminoglycoside.

The treatment protocol consisted of administering ATRA and daunorubicin in the remission induction phase, followed by 3 cycles of chemotherapy in the consolidation phase and two years of maintenance (Table 1).

All patients with newly diagnosed APL entered the study, only one patient was excluded. A 15 year old girl that had already been previously treated with another protocol before the study and was having a relapse during the time this study was being conducted. This patient underwent hematopoietic stem cell transplantation.

RESULTS

The clinical and biological characteristics of the eleven AML M3 patients are summarized in table 2.

The mean patient age at the time of diagnosis was 6.7 years (range 1.4 to 12.7); only one patient was younger than two years of age (Case 2). The clinical features of the disease included fever in most cases (ten patients) and bleeding and coagulopathy in four cases.

On average, WBC counts were 10.1 x 10^9/L, and only four of the eleven patients had WBC counts >10 x 10^9/L WBC at diagnosis (cases two, six, eight and ten). With regard to platelets, the average concentration was 17.1 x 10^9/L, and all of the patients had counts < 40 x 10^9/L.

In all cases, the bone marrow aspirate underwent morphological analysis, and the median percentage of abnormal promyelocytes at diagnosis was 68% with a range between 27-87.2%.

The test for the PML-RAR alpha transcript was positive in seven of eleven cases, while the presence of PLZF-RAR alpha transcript was only documented in one case.

In two cases (cases two and ten), neither of the two abnormal transcripts was detected by RT-PCR analysis, but both patients responded to the ATRA treatment and showed morphological remission. Both patients finished the induction and consolidation therapy and are in maintenance according to the treatment protocol.

ATRA related toxicity is summarized in table 3. ATRA syndrome was identified in four of the eleven

Table 2. Clinical and biological features of the eleven patients.

Patient	Age (years)	Gender	Coagulopathy	WBC x 10^9/L	PLT x 10^9/L	Abnormal promyelocyte on BMA (%)	Transcript	Molecular remission	Morphologic remission	Relapse	Death	Status	Follow-up time since diagnosis (months)
1	10.9	M	No	2.7	17	70	PML RAR α	Yes	Yes	No	No	Under surveillance	36
2	2.4	M	No	23.8	16	86.25	-	-	Yes	No	No	Maintenance	22
3	5.1	M	No	7	11	64.5	PML RAR α	Yes	Yes	No	No	Under surveillance	48
4	7.9	F	No	1.5	7	56.5	PML RAR α	Yes	Yes	No	No	Under surveillance	50
5	7.3	F	Yes	3.6	6	46	PZLF RAR α	Yes	Yes	No	No	Relapse	57
6	1.4	F	No	11	29	27	PML RAR α	Yes	Yes	No	No	Maintenance	8
7	5.7	M	No	2.9	8	87	PML RAR α	Yes	Yes	No	No	Maintenance	19
8	7.7	F	Yes	15.6	36	75.25	PML RAR α	Yes	Yes	No	No	Under surveillance	46
9	7.9	M	No	5.9	19	95	PML RAR α	Yes	Yes	No	No	Maintenance	10
10	4.9	F	Yes	36.3	35	87.25	-	-	Yes	No	No	Maintenance	17
11	12.7	F	Yes	1.8	5	51.5	PML RAR α	Yes	Yes	Yes	Yes	Death in relapse	23

BMA: bone marrow aspiration. WBC: white blood cells.

patients. Nine patients reported severe headache and one of them had a diagnosis of *Pseudotumor cerebri* (case 1), but pleural effusions could not be demonstrated. In only one case a patient reported dyspnea (case 7). Additionally, only one patient complained of severe bone pain (case 10).

All of the patients achieved complete remission and proceeded to consolidation therapy, and all of them underwent the three consolidation courses as scheduled.

Febrile neutropenia occurred in nine children after the first chemotherapy cycle, ten after the second cycle and nine after the third cycle (Table 4).

No deaths occurred during the consolidation therapy.

During the follow-up phase, two patients experienced a relapse (cases five and eleven). The first case occurred in a seven-year-old girl with the PLZF-RAR alpha transcript who had responded to ATRA therapy and had been RT-PCR negative after

Table 3. ATRA-related toxicity and consolidation-related toxicity.

	ATRA related toxicity					Consolidation toxicity (WHO ≥ 2)			
Patients	ATRA syndrome	Severe headache	Pseudotumor cerebri	Pleural effusion	Dyspnea	Severe bone pain	Cycle I infections	Cycle II infections	Cycle III infections
1	Yes	Yes	Yes	No	No	No	No	No	Yes
2	No	Yes	No	No	No	No	Yes	Yes	Yes
3	No	Yes	No	No	No	No	Yes	Yes	Yes
4	No	Yes	No	No	No	No	Yes	Yes	Yes
5	No	No	No	No	No	No	Yes	Yes	Yes
6	No	Yes	No	No	No	No	Yes	Yes	No
7	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
8	No	Yes	No	No	No	No	Yes	Yes	Yes
9	No	No	No	No	No	No	No	Yes	No
10	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes
11	Yes	Yes	No	No	No	No	Yes	Yes	Yes

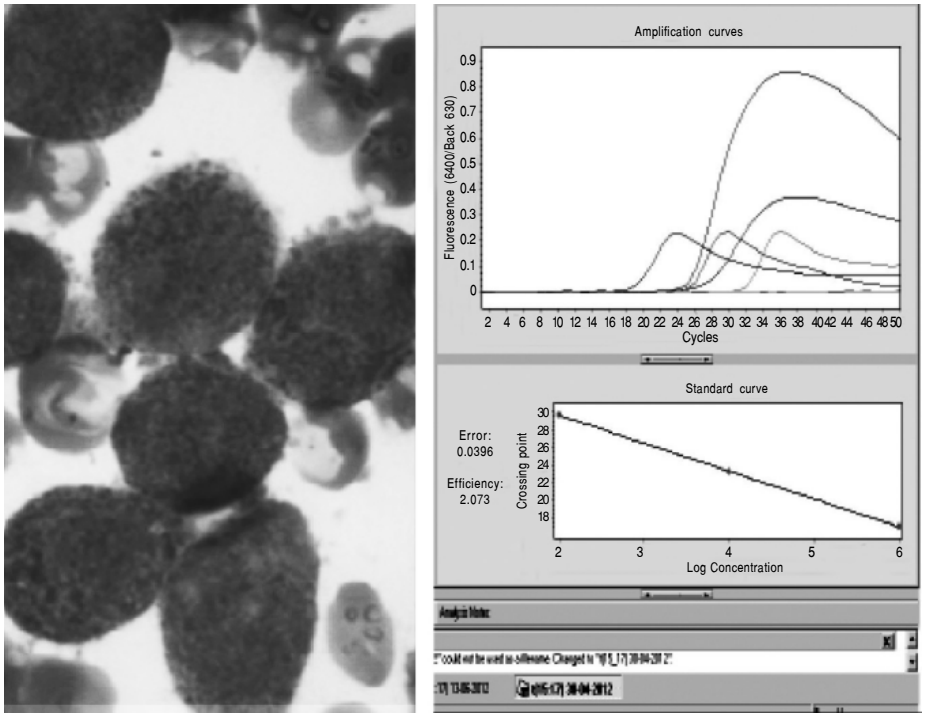

Figure 1. A. Bone marrow aspirate with abnormal promyelocytes. Staining with Wright-Giemsa 100x. ***B.*** *Transcript amplification curve for the t(15:17) transcript. The bottom curve shows the standardization.*

remission induction. She relapsed 16 months after the diagnosis and was examined for bone marrow transplantation. Unfortunately no donor could be found; therefore, we decided to restart chemotherapy. The patient went into remission again and is now under surveillance.

The second relapse occurred in a 12 year-old girl who had attained morphological and molecular remission of the PML-RAR alpha transcript and had finished maintenance but relapsed 25 months after the diagnosis. She presented with coagulopathy and bleeding. ATRA was restarted, but the patient died of a brain hemorrhage 32 days after her relapse was diagnosed, despite the use of transfusion therapy.

The average follow-up period for the 11 patients in the study was 33.6 months. To date, ten of the eleven patients are alive, and only the 2 relapses described above have occurred.

The overall survival of this group was successful (Figure 2) reaching 90 percent with an average follow-up of 33.6 months.

DISCUSSION

APL is a unique type of AML because it involves a translocation that allows for the use of a target therapy. The introduction of ATRA in the 1990s dramatically increased disease free survival.

Recently, the stratification of patients and the standardization of complication management have improved outcomes by reducing mortality in the induction of remission phase of treatment and by decreasing toxicity-related morbidity in low risk cases.

The data on pediatric APL patients in developing countries is limited.

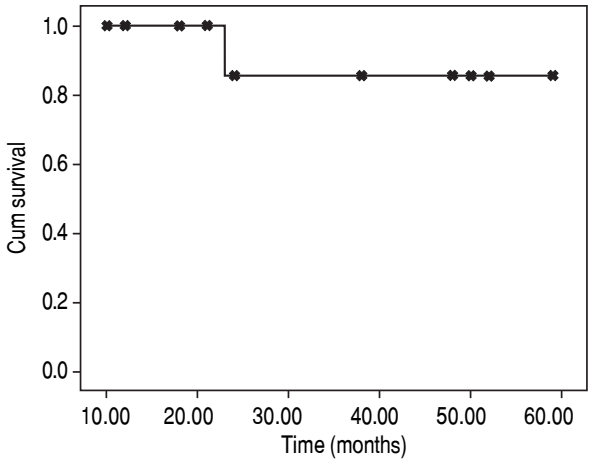

Figure 2. Overall survival curve of the eleven patients in the study. The average follow-up was 33.6 months.

Note that prior to introducing this protocol, patients were treated with short and intense schedules of chemotherapy that included ATRA during the induction phase.

Herein we have described the clinical features and treatment outcomes of pediatric APL patients in Mexico treated under the IC-APL2006 protocol.

The number of APL patients seeking treatment at our tertiary hospital agrees with literature reports from other Latin American countries where the incidence of this condition varies but typically accounts for approximately 20% of all AML patients.

The mean age at diagnosis in our study was consistent with the literature, and there was only one patient younger than 2 years of age.

In our study, male and female children were equally likely to contract the disease. The PML-RAR alpha transcript was found in seven patients, while only one patient was PZFL-RAR alpha positive.

It is known that t(11:17) APL patients fail to respond to ATRA, and indeed primary leukemic cells from these patients do not differentiate when challenged with ATRA. Literature reports have indicated that patients with t(11:17) have a poorer prognosis than patients with the t(15:17) transcript, and these patients fail to achieve remission with conventional chemotherapy or ATRA.[15] Our patient who showed this phenotype (case 5) did show a good response to ATRA but then relapsed, which most likely indicated that some undetected cells stayed in a quiescent state and replicated at the end of the maintenance phase, thereby reactivating the leukemic clone.

The two patients who tested negative for the transcript but whose morphology supported a diagnosis of APL received the IC APL protocol and responded to ATRA. They both finished the induction to remission phase of therapy with morphologic remission and are undergoing maintenance therapy.

Note that all of the patients in the study initially presented with thrombocytopenia ($< 40 \times 10^9$/L), which is a criterion that confers a risk for relapse. Thus there were no low-risk patients in this cohort.

Most of the patients in the study (seven of eleven) had $< 10 \times 10^9$/L WBC in their peripheral blood at diagnosis, thus four patients were treated as high risk patients.

Toxicity related to the induction of remission was characterized by ATRA syndrome in four cases and was treated with dexamethasone. Most patients required hospitalization after the consolidations cycles, but no severe complications were recorded.

Although the median follow-up time for these patients was 33.6 months, this interval was insufficient to allow for a long-term evaluation. Therefore,

it will be necessary to follow these patients to report five-year survival rates.

The aim of this work was to describe the diagnostic features of pediatric APL and the results to date with the IC-APL2006 protocol. The results have been favorable and demonstrated that this subtype of AML is highly curable and even in developing countries, such as Mexico, excellent health outcomes can be achieved if patients are adequately stratified and protocolized. It is important to emphasize that these patients should not be treated similarly to other AML patients because the biology of the disease and targeted therapies are highly specific.

The main limitations of the study are the number of patients, and because the sample size was small, we can show the internal validity of the results, but the results may not be generalized to other hospitals, especially if they do not have the transfusion support or the infrastructure to control infectious events

The authors propose that this work could be the beginning of collaborative work with other hospitals in México to increase the number of patients under this protocol and to improve the survival rates of Mexican children with APL.

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