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Prognostic Factors in Primary Gastric Lymphoma

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Background: There is not a gold standard in the treatment of primary gastric lymphoma (PGL). This study aimed to establish prognostic factors that should be considered for the staging and management of this disease.

Methods: We retrospectively reviewed and analyzed the clinicopathological features of patients treated for PGL in a tertiary referral center in Mexico City in a 10-year period from 1990 through 2000. Staging was performed with the Ann-Arbor system. Overall and disease-free survivals were the primary endpoints.

Results: We identified 41 patients of which 19 (46.3%) were classified as large-cell lymphoma, 16 (39.0%) as low-grade MALT, and 6 (14.6%) patients as lymphoma unspecified. The series included 15 (36.6%) patients with stage IV disease. Twenty patients (48.8%) underwent surgery and 34 (82.1%) received chemotherapy. Twenty-three patients were treated with at least two different types of therapy (56.1%). Actuarial 1 and 5 years survival were 77.8 and 71.2%, respectively. Early stage at presentation, surgery, normal lactic dehydrogenase (LDH) levels and good performance status were associated with longer survival in univariate analysis. Only normal LDH and good performance status retained their significance in multivariate analysis. Regarding disease-free survival in multivariate analysis, only normal LDH was associated with a better prognosis: 131 versus 12 months for LDH <197 and ≥ 197 mg/dl, respectively ($P < 0.0001$).

Conclusions: Optimal treatment of PGL remains controversial. High LDH levels and poor performance status at diagnosis are associated with shorter overall and disease-free survival and should be considered for the staging and management of these patients.

Key Words: Primary gastric lymphoma—Prognostic factors—Overall survival—Disease free survival—Lactic dehydrogenase (LDH).

Primary gastric lymphoma (PGL) although a rare tumor representing only 5% of primary gastric neoplasms, is still the most frequent type of extra nodal malignant lymphoma, accounting for 30–40% of all extra nodal lymphomas and for 4–20% of all non-Hodgkin lymphomas.[1–4] There is not a gold standard in the treatment of PGL and during the past two decades the diagnosis and treatment has changed dramatically.

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Multiple prognostic factors have been analyzed in the literature with inconsistency among series. The objective of this review was to determine factors associated with survival and prognosis in patients with PGL.

PATIENTS AND METHODS

Patients

The study was approved by our Institutional Review Board. We retrospectively reviewed the clinicopathological characteristics of patients with PGL

TABLE 1. *World Health Organization classification of lymphoid neoplasms*

B-cell neoplasms
Precursor B-cell neoplasm
Precursor B-lymohoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
Mature (peripheral) B-cell neoplasms
B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
Lymphoplasmacytic lymphoma
Splenic marginal zone B-cell lymphoma
Hairy cell leukemia
Plasma cell myeloma/plamacytoma
Extranodal marginal zone B-cell lymphoma of MALT type
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/Burkitt cell leukemia
T-cell and NK-cell neoplasms
Precursor T-cell neoplasm
Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)
Mature T-cell neoplasms (peripheral)
T-cell promyelocytic leukemia
T-cell granular lymphocytic leukemia
Aggressive NK-cell leukemia
Adult T-cell lymphoma/Leukemia (HTLV1+)
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic gamma-delta T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides/Sezary syndrome
Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
Peripheral T-cell lymophoma, not otherwise characterized
Angioimmunoblastic T-cell lymphoma
Anaplastic large-cell lymphoma, T/null cell, primary systemic type
Hodgkin's lymphoma
Nodular lymphocyte-predominant Hodgkin's lymphoma
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma

admitted in a tertiary referral care center in Mexico City during a 10-year period from 1990 through 2000. All cases satisfied the criteria for PGL as defined by Lewin et al.[5] and were reviewed by one hematopathologist.

Staging and Diagnostic Procedures

All Hematoxilin and Eosin and immunohistochemical slides were reviewed by one hematopathologist (CLM). Histological subtype classification was performed according to the World Health Organization criteria (Table 1). The stage of the disease was determined according to the Ann Arbor criteria proposed for gastrointestinal lymphoma (Table 2).

TABLE 2. *Classification of PGL according to Ann-Arbor staging system*

I	Involvement of a single lymph node region (I) or a single extralymphatic organ or site (IE)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or of an extralymphatic organ and its adjoining lymph node site (IIE)
III	Involvement of lymph node sites o both sides of the diaphragm (III) or localized involvement of an extralymphatic site (IIIE), spleen (IIIS), or both (IIISE)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement

The staging workup included physical examination, blood cell count, serum chemistry, and chest radiographs for all patients; chest and abdominal CT scans in 39 patients (95.1%). Upper gastrointestinal endoscopy along with biopsy of all suspicious lesions was performed in 40 patients (97.6%).

We defined laboratory studies as low hemoglobin levels if ≤11.9 mg/dl, low albumin < 3.0 g/dl, malnutrition with body mass index ≤19.9, high lactic dehydrogenase (LDH) ≥197 mg/dl, and poor performance status if Karnofsky scale ≤80.

Treatment and Response

Therapeutic modalities were divided into either surgical resection, nonsurgical treatment which included chemotherapy, radiation, antibiotics for *Helicobacter pylori* (*H. pylori*) eradication, and a combination of these modalities. Complete remission was defined as disappearance of all clinical evidence of lymphoma during the last visit to our clinic, and fail to treatment or partial response was defined for all patients alive with disease during the last examination as well as those dead of the disease. Survival was measured from the time of diagnosis.

Prognosis and Statistical Analysis

Statistical analysis was made with SPSS 10.0 Data Analysis Pack¬. Primary endpoints were overall and disease-free survival. Categorical variables were analyzed with the Chi-square method. Survival curves were constructed with the Kaplan–Meier method and compared with the log-rank test. Multivariate analysis was performed with the Cox regression model. Statistical significance was considered at $P < 0.05$.

TABLE 3. *Demographic, clinical, and pathologic characteristics of patients with PGL*

Gender	No. of patients	Percentage
Females	22	53.7
Males	19	46.3
Mean age at presentation 52.6 years (± 17.8)		
Presenting symptom		
Weight loss	37	90.2
Abdominal pain	39	95.1
Gastrointestinal bleeding	17	41.5
B symptoms	15	36.6
Mean duration of symptoms 5.6 months (± 3.7)		
Laboratories at first visit		
Low hemoglobin	21	51.5
Low albumin	17	41.5
Malnutrition	11	26.8
High LDH	13	31.7
Poor performance status	15	36.6
Subtype of primary gastric NHL		
Large cell lymphoma	19	46.3
Low grade MALT	16	39.0
PGL unspecified	6	14.63
Stages at the time of diagnosis Ann Arbor system		
Stage I	11	26.8
Stage II	8	19.5
Stage III	7	17.1
Stage IV	15	36.6

TABLE 4. *Treatment modality*

Modality	No. of patients	Percentage
Single therapy		
Surgery	2	4.9
Chemotherapy	11	26.8
Radiotherapy	1	2.4
H. pylori eradication	1	2.4
Combined therapy		
Surgery + chemotherapy	16	39.1
Chemotherapy + *H. pylori* eradication	5	12.2
Surgery + chemotherapy + radiotherapy	1	2.4
Surgery + chemotherapy + *H. pylori* eradication	1	2.4
No treatment[a]	3	7.3
Total of patients	41	
Procedures performed both single and combined		
Surgery	20	48.8
Chemotherapy	34	82.1
Radiotherapy	2	4.9
H. pylori eradication	7	17.1

[a] Patients where diagnosed and choose not to be treated

RESULTS

Clinical and Histological Features

During the study period, 41 patients were analyzed with a mean age of 52.6 years (±17.8). Twenty-two patients (53.7%) were females. Seven patients (17.1%) had some type of immunosuppression at the time of diagnosis and 13 (31.7%) had a history of any type of cancer in a first relative. The presenting symptoms were weight loss in 37 patients (90.2%), abdominal pain in 39 (95.1%), gastrointestinal bleeding in 17 (41.5%), and either weight loss, fever, or night sweats (B symptoms) in 15 (36.6%) patients. Mean duration of symptoms was 5.6 months (±3.7). Laboratory studies in the first visit to the clinic showed low hemoglobin levels in 21 (51.2%) patients, low serum albumin in 17 (41.5%), malnutrition in 11 (26.8%), high LDH in 13 (31.7%), and poor performance status in 15 (36.6%) (Table 3).

Most frequent pathological subtype of non-Hodgkin gastric lymphoma at the time of diagnosis resulted in 19 (46.34%) patients with large cell lymphoma, 16 (39.0%) low-grade MALT lymphomas, and 6 (14.6%) of unspecified type. Most prevalent stage at the time of diagnosis according to the Ann Arbor system corresponded to stage IV with 15 patients (36.6%), followed by stage I with 11 (26.8%), stage II with 8 (19.5%), and stage III with 7 (17.1%) (Table 3).

Fifteen patients (36.6%) underwent single-modality treatment, being chemotherapy the most frequently used in 11 patients (26.8%). Combined therapy was chosen in 23 (56.1%) patients, and surgery plus chemotherapy accounted for the majority of cases in 16 (39.0%). Surgical treatment either combined or as single therapy was performed in 20 (48.8%) patients, being total gastrectomy the most common type of procedure. The same applies to chemotherapy administered in 34 patients (82.1%) in which cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) was the most used regimen. Two patients (4.9%) received radiotherapy and 7 (17.1%) patients underwent treatment for *H. pylori* eradication (Table 4).

Survival and Prognostic Factors

Actuarial 1 and 5 year survival was 77.8 and 71.17%, respectively, with a mean survival of 138 months (95% CI 108–167). Overall survival showed no mortality in clinical stages I and II. Mean survival for stage I–II was 65 months (95% CI 27–104) and 48 (95% CI 19–76) months for stages III–IV. In patients with stage IV disease the overall mean survival was 16 months. In patients treated with surgery overall mean survival was 168 months (range 136–199) versus 91 months (range 52–130) for those treated with other modalities ($P = 0.04$) (Fig. 1). Regarding performance status and LDH levels,

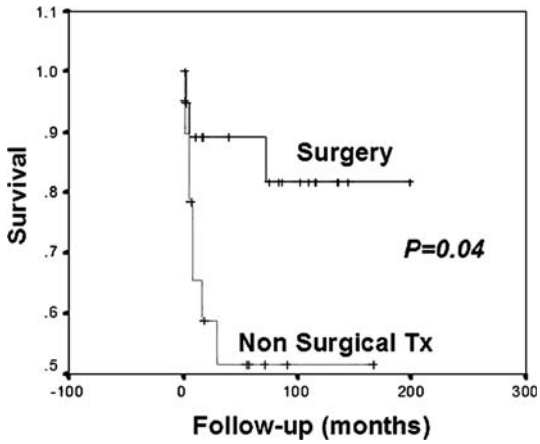

FIG. 1. Effect of surgery on survival.

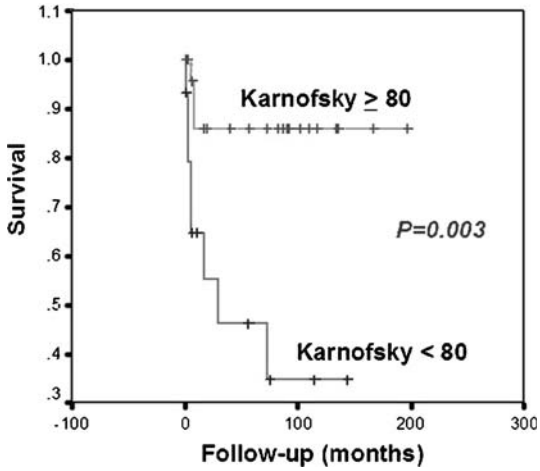

FIG. 2. Survival according performance status.

overall mean survival was 29 months (95% CI 16–99) in patients with poor performance status versus 171 months (range 143–199) if Karnofsky ≥80 ($P = 0.003$) (Fig. 2), and 168 months (95% CI 140–195) if LDH ≤197 mg/dl versus 8 months (range 4–51) if greater than those values ($P = 0.001$) (Fig. 3). Of note, Chi-square analysis comparing LDH levels in clinical stages I, II, III, and IV, showed that only 2 (9%) patients had high LDH levels in stages I, II, and III versus 9 (88.9%) in stage IV ($P = 0.0001$). Univariate and multivariate results for all factors analyzed for overall survival are summarized in Table 5.

Disease free survival at 1 and 5 years were 62.7 and 52.5%, respectively, with a median of 73 months (95% CI 4–142). When chemotherapy was used as a single treatment modality, it resulted in disease free survival of 102 months (95% CI 72–132) versus

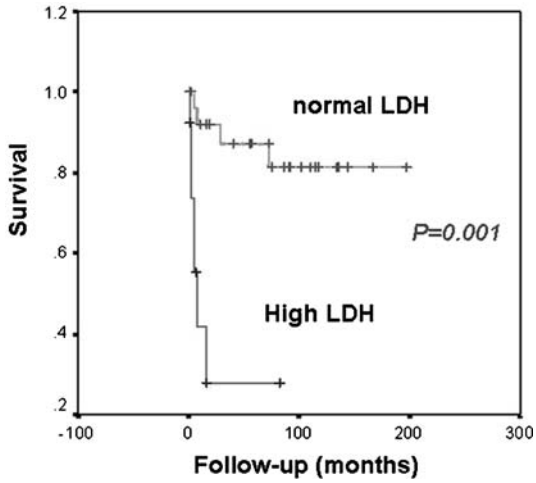

FIG. 3. Survival according LDH serum levels.

18 months (95% CI 0–42) for those without chemotherapy ($P = 0.003$). When analyzing for surgery as single modality treatment, disease free survival resulted in 124 months (95% CI 85–164) versus 53 months (95% CI 24–82) without surgery ($P = 0.02$). Patients treated with surgery plus chemotherapy had a disease free survival of 130 months (95% CI 93–167) versus 34 months (95% CI 16–53) when compared with patients treated with other modalities ($P = 0.0032$). Poor performance status and high LDH levels were the most important prognostic factors for disease free survival resulting in 111 months (95% CI 76–146) for patients with good performance status versus 34 months (95% CI 16–53) if Karnofsky scale ≤80 ($P = 0.048$). Patients with low LDH serum levels had a disease free survival of 131 months (95% CI 98–164) versus 12 months (95% CI 0–24) when LDH ≥197 mg/dl, ($P = 0.0001$). MALT lymphoma showed only a trend for better overall and disease free survival compared with other histological subtypes but it does not reach statistical significance ($P = 0.6$ for overall survival and 0.09 for disease-free survival) (Fig. 4).

DISCUSSION

Primary gastric lymphoma although a rare neoplasm, is the most frequent type of extra-nodal lymphoma. There are at least two definitions of primary gastric non-Hodgkin lymphoma in use. The one by Dawson et al. is restricted to localized diseases (stages IE, IIE). Furthermore Lewin et al. requires that patients exhibit gastrointestinal symptoms or

TABLE 5. *Factors associated with overall survival*

Factor	Mean survival (months)	Univariate-analysis *P* value	Multivariate-analysis *P* value
Gender			
Female	139	0.90	
Male	95		
Family history of malignancy			
Yes	130	0.76	
No	98		
Immunosuppression			
Yes	141	0.67	
No	67		
Malnutrition			
Yes	107	0.51	
No	134		
Poor performance status			
Yes	29	0.003	0.04
No	171		
Anemia			
Yes	102	0.51	
No	127		
High LDH			
Yes	8	0.0001	0.01
No	168		
Stage			
I	All censored	0.002	Not significant
II	All censored		
III	65		
IV	16		
Stage IV			
Yes	16	0.001	Not significant
No	173		
H. pylori			
Yes	144	0.35	
No	131		
MALT type lymphoma			
Yes	125	0.58	
No	132		
Surgery			
Yes	168	0.04	Not significant
No	91		
Chemotherapy			
Yes	139	0.73	
No	62		
Combined treatment			
Yes	161	0.07	
No	52		

predominant lesions in the gastrointestinal tract.[5] Isaacson and Wright introduced the concept of MALT lymphoma in 1983.[2]

Gastric mucosa does not usually have lymphatic tissue. After infection by *H. pylori* and development of chronic gastritis, however, MALT appears in the stomach.[6] Histologically and immunohistochemically MALT lymphomas are of the B-cell non-Hodgkin type. Other forms of gastric lymphomas are non-MALT type and less common may be T cell in origin.[1,4]

Primary gastric lymphomas are divided into low-grade and high-grade, being in the majority of cases either diffuse histiocytic or large cell type. About 40% of PGL are low-grade lesions thought to arise in the

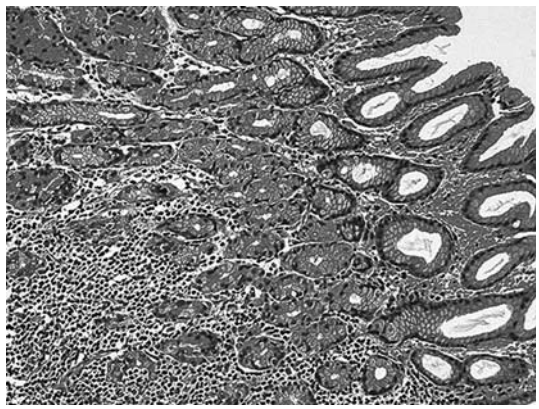

FIG. 4. Hematoxilin and Eosin of a low-grade MALT lymphoma.

mucosa or submucosa from the so-called MALT. Low-grade MALT lymphoma corresponds to the marginal-zone cell lymphoma in the Revised European-American Lymphoma classification. Nearly 60% of gastric lymphomas are high-grade lesions and contain a low-grade MALT component in about one third of cases.[1,5,7,8] Our findings are similar to those reported in the literature with almost 40% of low-grade MALT lymphoma and nearly two thirds of large B-cell lymphoma.

Issacson specified two histological criteria for low-grade MALT lymphoma: (1) replacement of gastric glands by uniform infiltrates comprised of cells resembling follicle center centrocytes, small lymphocytes, or monocytoid B cells; and (2) clear evidence of lymphoid destruction of gastric glands. In addition, polymerase chain reaction can be used to demonstrate monoclonality. Centers vary on the requirements of lympho-epithelial lesions or monoclonality as mandatory for the diagnosis of low-grade MALT lymphoma.[7–9]

The pivotal histological feature of low-grade MALT lymphoma is the presence of diffuse infiltration of small size to medium-size centrocyte-like cells. Histopathologically, high-grade transformation of MALT lymphoma is heralded by the emergence of increased numbers of large lymphoid blasts that eventually form clusters or sheets and may finally grow to confluence effacing the preceding low-grade tumors.[7–9]

Infection with *H. pylori* appears to be a necessary causal factor in the development of MALT lymphomas susceptible to antibiotic treatment. Antigen dependency can be lost in further carcinogenic development and *H. pylori* infection contributes to initiation and promotion of the process. Regression results suggest that more steps are required for the

development of marginal zone B-cell lymphoma than for carcinogenesis of diffuse large B-cell lymphoma.[6] Although 16 patients in our study were diagnosed with low-grade MALT lymphoma, less than half of them received therapy for *H. pylori* eradication. This is due to the recent development and introduction of eradication regimens during the time when those patients were diagnosed.

Multiple factors have been reported to contribute to survival. Female gender, surgical resection, low-grade histology and a good performance status are among the most important ones. In the counterpart, age greater than 60 years, decreased performance status and elevated LDH were associated with a negative outcome.[2,7,10] The extent of tumor resection and lymphadenectomy has also proved to be prognostic. After complete resection, Koch et al. reported survival proportions for disease free and overall survival at 5 years of 91.5% as compared with 68.8% after incomplete resection.[5] It is also well known that a low histopathological grade is associated with a significantly lower incidence of nodal metastasis and less extensive infiltration of the gastric wall despite larger tumor size. Depth of infiltration was found to correlate well with survival.

Kodera et al. reported a 5-year survival rate of >90% attained with surgery alone for MALT lymphoma and for true stage IE lymphoma diagnosed by pathologic examination of up to N2 lymph nodes routinely performed after radical gastrectomy.[3] If surgery is considered, one has to keep in mind that in patients whose lymphoma was not resected radically, prognosis is significantly worse than after conservative treatment only, and that extent of resection can only be judged afterwards.[3,10,11]

In our analysis, variables associated with longer survival were early stage at presentation, surgical treatment, normal LDH levels and good performance status. Only normal levels of LDH and good performance status retained their significance on the multivariate analysis. Histological subtype and chemotherapy administration were not significantly associated with overall survival. Regarding disease-free survival, on univariate analysis the same factors plus chemotherapy administration were associated with favorable prognosis. On multivariate analysis only normal levels of LDH were associated with longer disease-free survival.

Traditionally, surgery was the cornerstone in the treatment of these tumors. Currently, the advent of modern diagnostic methods such as endoscopic ultrasonography, have offered better preoperative diagnostic evaluation and accurate staging in up to 85–90% of the cases.[12] This has great importance since prognosis in stage II1E is as good as in stage IE, whereas prognosis in stage II2E is as bad as in stage IVE.[13] The frequency of lymph node involvement also correlates well with the grade of lymphoma. Depth of infiltration is found to be prognostic with regards survival, since pure MALT lymphoma has an indolent biologic behavior with no serosal involvement and a lower incidence of nodal metastasis, despite larger tumor diameter.[3] In one series of 37 patients, only 15% of low-grade MALT lymphomas spread to lymph nodes while 75–100% of high-grade lymphomas spread to lymph nodes.[7]

Several reports have shown superior outcome when surgical resection is undertaken in the early stages of the disease (I–II1) of MALT type NHL with a 5-year survival rate of 80–93%.[1,3,11] More recently, radical gastrectomy is disputed and considered unnecessary in intent to maintain quality of life, non-surgical treatment such as *H. pylori* eradication, chemotherapy and radiation are becoming increasingly popular even for patients with resectable disease.[4,9]

As treatment strategies continue to evolve, most contemporary treatment algorithms no longer include surgical resection in the primary treatment of gastric lymphoma and reserve surgery for the management of complication or unique cases of locally persistent disease, macroscopic bleeding or perforation.[3,10]

To our knowledge there is only one controlled clinical trial that evaluates the different therapeutic schedules, and prognostic factors in a uniform population. In this study, patients with primary gastric diffuse large cell lymphoma with aggressive histology as well as those with diffuse large cell lymphoma in early stage, achieved good results with surgery plus chemotherapy, but surgery was associated in some of the cases with lethal complications. Thus, these authors recommend chemotherapy as the treatment of choice in this patient setting and conclude that current clinical risk classifications are not useful in defining treatment.[14]

High-grade lymphoma both MALT and non-MALT in origin, should be treated initially with chemotherapy.[15] The same applies to advanced stages of PGL (IIIE, IVE) where tumor behavior is considered to be the same as any other type of advanced non-Hodgkin lymphoma and therefore combined chemotherapy is considered the treatment of choice for locally advanced or disseminated aggressive disease.[1]

Although PGL has been investigated extensively, its optimal histological classification, the most

accurate staging system, and the exact role of the different therapeutic options are still debated.[4] Further randomized prospective studies with a large number of patients are still needed to establish the optimal management for this disease. High LDH levels and poor performance status at the time of diagnosis are associated with shorter overall and disease-free survival and we strongly recommend including them in the staging and management of these patients.

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