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Systemic immunoglobulin light-chain amyloidosis (AL) in Mexico: a single institution, 30-year experience

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Amiloidosis primaria generalizada de cadenas ligeras. Experiencia de 30 años en una sola institución

RESUMEN

Material y métodos. *En un periodo de 30 años en una sola institución se identificaron 23 pacientes con amiloidosis de cadenas ligeras, primaria y generalizada (APG) en un grupo de 1,388 pacientes con neoplasias hematológicas malignas.* ***Resultados.*** *La APG es 14 veces menos frecuente en México que en poblaciones caucásicas y representa 15% de todas las gamopatías monoclonales. La mediana de edad fue de 57 años, con rango de 39 a 98. Once hombres y 12 mujeres. El diagnóstico histológico se hizo en la grasa periumbilical en 39% de los casos, en la médula ósea en 30%, en la biopsia renal en 13%, en el tubo digestivo en 13% y en un ganglio linfático en un caso. Se presentó síndrome nefrótico en 61% de los casos, insuficiencia cardiaca en 35%, neuropatía periférica en 26% y pérdida ponderal grave en 6%. Se identificó anemia en 14% de los casos y la mediana de las cifras de hemoglobina fue de 11 g/dL. Se encontró una paraproteinemia monoclonal en 70% de los casos, con una mediana de 1.2 g/dL (rango de 0.2 a 3.6); hubo siete casos de producción de cadenas ligeras aisladas; en cinco casos no se identificó paraproteinemia. En seis casos había mieloma múltiple asociado. Diecisiete pacientes (74%) fueron seguidos por más de tres meses (90 a 519 días, mediana 210). La supervivencia global (SG) de este grupo fue de 71% a 173 meses, en tanto que la mediana de SG no se ha alcanzado, siendo mayor de 173 meses. Ocho pacientes fueron tratados con melfalán/prednisona y cinco fueron sometidos a trasplante de células hematopoyéticas autólogas.* ***Conclusiones.*** *La APG es menos frecuente en mestizos mexicanos y que probablemente se subdiagnostica; las características clínicas no son diferentes de las descritas en otras poblaciones.*

Palabras clave. *Amiloidosis. México. Tratamiento. Autotrasplante. Prevalencia.*

ABSTRACT

Material and methods. In a 30-year period in a single institution, 23 cases of systemic immunoglobulin light chain amyloidosis (AL) were identified, within a group of 1,388 individuals with some form of a hematological malignancy. **Results.** AL is 14 times less frequent in Mexico than in Caucasians and it represents 15% of all monoclonal gammopathies. Median age was 57 years (range 39-98); there were 11 males and 12 females. The histologic diagnosis was done in the periumbilical fat in 39%, the bone marrow in 30%, the kidney in 13%, the gastrointestinal tract in 13% and in a lymph node in one case. The nephrotic syndrome was present in 61% of cases, heart failure in 35%, sensorimotor peripheral neuropathy in 26% and weight loss in 6%. Anemia was present in 14% of cases at diagnosis; median hemoglobin was 11 g/dL. An abnormal monoclonal spike in the peripheral blood was present in 70% of cases; it had a median of 1.2 g/dL (range 0.2-3.6); there were 7 cases of light-chain only disease and five in whom an abnormal paraproteinemia was not found. Six cases were associated with overt multiple myeloma. Seventeen individuals (74%) were followed for more than 3 months (range 90 to 5190 days, median 210); their overall survival (OS) was 71% at 173 months, whereas the median OS has not been reached, being above 173 months. Eight patients were treated with melphalan/predisone and five were given high dose chemotherapy and an autologous stem cell transplantation; the others were given other treatments. **Conclusions.** AL is less frequent in Mexican mestizos and probably underrecognized; the clinical features of the disease are not significantly different from those informed from other populations.

Key words. Amyloidosis. México. Treatment. Autograft. Prevalence.

INTRODUCTION

The systemic amyloidoses are a group of complex diseases caused by tissue deposition of misfolded proteins that results in progressive organ damage. The most common type, immunoglobulin light chain amyloidosis (AL), is caused by clonal plasma cells that produce misfolded light chains. The amyloidogenic light chain of the monoclonal immunoglobulin becomes water insoluble, precipitates and deposits in the extracellular space resulting in damage of organ function.[1] AL amyloidosis is a plasma cell dyscrasia and can be associated to other monoclonal B-cell diseases. The diagnosis can be challenging, requiring a biopsy and often specialized testing to confirm the subtype of systemic disease.

The monoclonal gammopathies do have a racial distribution.[2-6] In Mexican mestizos, the prevalence of monoclonal gammopathy of undetermined significance (MGUS),[2-4] of multiple myeloma,[5] and of Waldenstrom's macroglobulinemia[6] is substantially lower than in Caucasians.

The prevalence of AL in Mexico is largely unknown. We have retrospectively analyzed here both the prevalence of the disease in México and some of its salient features in a group of 23 Mexican individuals with AL, identified, studied and treated along a 30-year period in a single institution.

MATERIAL AND METHODS

The records of all patients in whom AL was diagnosed at the Centro de Hematología y Medicina Interna de Puebla in Puebla, Mexico, from June 1983 to May 2012, were reviewed. Since its diagnosis remains a tissue diagnosis, a tissue biopsy either of an involved organ or a surrogate site demonstrating amyloid deposition by classic Congo red staining was required to define the condition.[7] Serum and urine protein electrophoresis and immunofixation were done in all patients, whereas the serum free light chain assay was done in patients identified after 2006. Between 1983 and 1993 patients were treated with melphalan and prednisone (M/P),[8] whereas in the last decade individuals were treated with combined chemotherapy,[9] thalidomide/dexametasone (thal/dex),[10] bortezomib or high-dose chemotherapy (melphalan 100 mg/m^2) rescued with autologous peripheral blood stem cell autografting.[1,11-12] The endpoint of the analysis of the response to treatment was death.

RESULTS

Between April 1983 and May 2012, in a group of 14,246 Mexican patients studied prospectively in the Centro de Hematología y Medicina Interna, we identified 1,388 with some form of a hematological malignancy. In this subset of individuals, we found 110 patients with multiple myeloma, 20 patients with Waldenstrom's macroglobulinemia and 17 patients with MGUS; tissue-biopsy proven AL amyloidosis was found in 23 individuals in this period. These data are consistent with previous publications, which indicate that the prevalence of monoclonal gammopathies is lower than that described in white Americans[2-6] and also indicate that the prevalence of AL is 14 times lower in Mexican mestizos than in Caucasians. The figure 1 summarizes the distribution of 170 monoclonal gammopathies in Mexico, compared with that found in the Mayo Clinic in Rochester, Minnesota, in a group of 1,298 cases of monoclonal gammopathies.[13] In this group, there was only one patient younger than 40 years, and 3

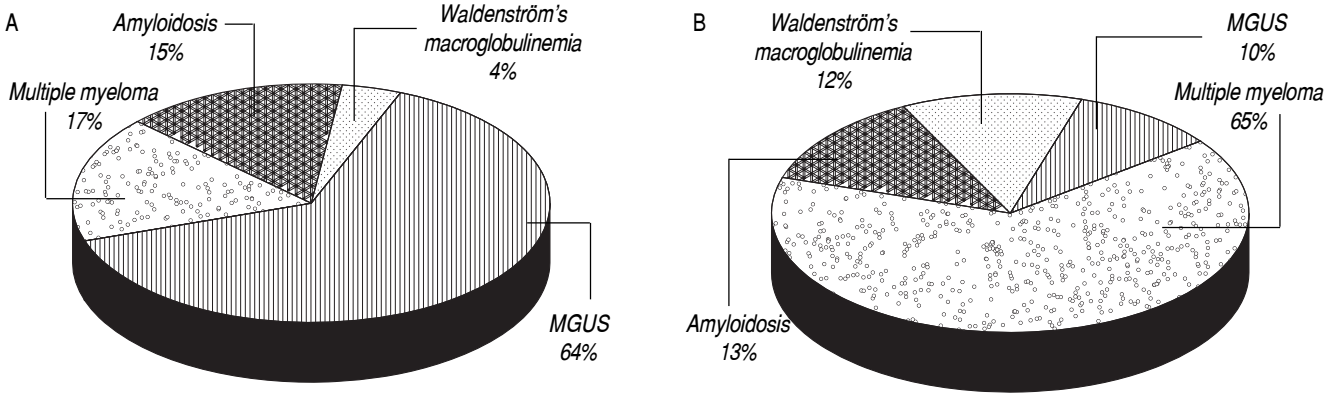

Figure 1. *Distribution of monoclonal gammopathies in 1,298 cases studied at the Mayo Clinic in Rochester, MN, USA (adapted from reference 13) (**A**) and in 170 cases studied at the Clínica Ruiz in Puebla, Mexico (**B**).*

were 70 years or older, the median age being 57 years (range 39-98); there were 11 males and 12 females.

History

Patients presented with the nephrotic syndrome in 61%, fatigue in 57%, cardiac failure in 45%, sensorimotor peripheral neuropathy in 26% and weight loss above 10% in 6%. AL was associated with overt multiple myeloma in six cases (26%).[6] Hepatomegaly was recorded in 22% and macroglosia in 30%.

Diagnostic tests

Anemia at diagnosis was present in 61% of patients; median hemoglobin was 11 g/dL, range 4.8 to 18.2. Table 1 includes the salient hematological data of the patients. The abnormal monoclonal spike had a median of 1.2 g/dL, with a range of 0 to 3.6; the M spike was > 3 g/dL in 3 patients (18%). In all the 23 cases a molecular abnormality of the immunoglobulin chains was disclosed: the abnormal heavy chain was found to be IgG in 8 cases, IgA in one and IgM in one. The most frequent paraproteinemia was IgG (kappa or lambda) (34% of cases), see table 2. In seven cases no abnormal heavy chain was identified, but abnormal light chains were found in the serum and/or urine, consonant with light-chain disease.

Table 1. Some hematological data of the 23 patients with AL.

	Median	Range
Hemoglobin, g/dL	11	4.8 - 18.2
White blood cells x 10^9/L	8.0	2.4 - 18.5
Platelets x 10^9/L	251	35 - 629
Serum monoclonal spike, g/dL	1.2	0 - 3.6
Proteinuria, g/L	5.8	0 - 35.8
Beta 2-microglobulin, mg/L	2.4	0.6 - 36
Serum albumin, g/dL	3.6	0.6 - 6

Table 2. Types of serum monoclonal proteins in the 23 patients with primary systemic amyloidosis.

	Number (%)
IgG kappa	4 (17)
IgG lambda	4 (17)
IgA lambda	1 (4)
IgM lambda	2 (9)
Free kappa only	4 (17)
Free kappa and lambda	3 (13)
None (serum and urine)	5 (22)

In five cases (22%) no abnormal monoclonal protein was detected but tissue light chain deposition was shown by means of immunohistochemistry.

The proteinuria had a range of 0 to 35.8 g/L (median 5.8). In 15 cases (71%) the proteinuria was in the nephotic range, above 3 g/L. Serum albumin levels had a range of 0.6 to 6 g/dL (median 3.6). Beta 2 microglobulin levels ranged from 0.6 to 36 g/L (median 2.4). The table 2 depicts the results of the immunoelectrophoresis and/or immunofixation studies in the serum of the 23 patients. The number of abnormal plasma cells in the bone marrow had a median of 6%, range 0 to 89%. On X ray-films, 12/17 patients (71%) had an abnormal skeletal survey: overt osteolytic lesions in three cases, osteosclerotic lesions in three and only osteoporosis in six cases. Five of 17 individuals were not found to display bone abnormalities disclosed by X-rays at diagnosis. An echocardiogram was done in 14 individuals and a cardiomyopathy was found in twelve (86%), however, the left ventricular ejection fraction (LVEF) had a median of 65% (range 35-77%) and only in one case the LVEF was below 40%.

Treatment

Of the 23 patients, 17 were followed for more than three months (90 to 5,190 days, median 1,830 days. Of these, 8 patients were treated with M/P, 12 were treated with thal/dex and 5 were given an autologous peripheral blood stem cell allograft after being given thal/dex.

Survival

In the subset of 17 individuals who were followed for more than 3 months (90 to 5,190 days, median 1,830): 5 patients are alive, 5 have died and 7 were lost to follow up (FU). Most patients lost to FU had the diagnosis established at our clinic and then followed and/or treated at other medical facilities, mainly for economical reasons. The overall SV of these 17 patients was 71% at 173 months; as a result, the median SV has not been reached, being above 173 months. Probably stemming from the low number of patients included in each treatment category, there were no significant differences observed in survival according to the treatment of the disease (Figure 2).

DISCUSSION

Immunoglobulin light-chain amyloidosis needs to be considered in any patient presenting with cardio-

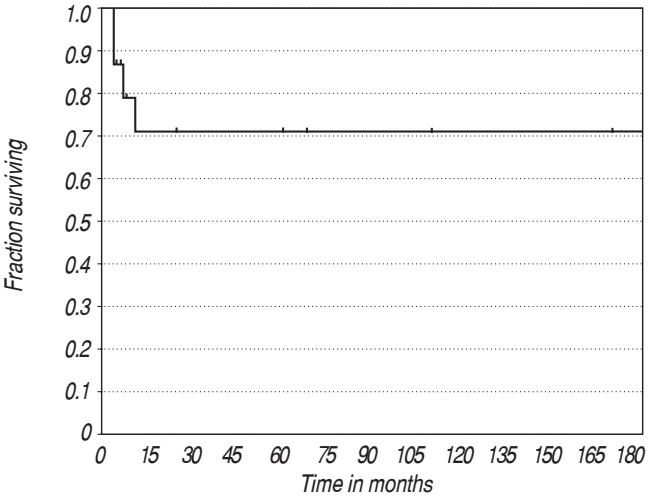

Figure 2. Overall survival of 17 patients with AL which were followed for more than three months in the Clínica Ruiz in Puebla, Mexico. Tick marks denote alive patients when last censored.

myopathy with preserved systolic function, heavy albuminuria, an unexplained sensorimotor peripheral neuropathy, hepatomegaly, atypical MGUS or atypical myeloma;[14-15] accordingly, the suspicion of AL is raised in most instances by the non-hematologist physician, thus leading into an underrecognition of the disease. Different from other hematological diseases which display hematological symptoms such as anemia or bleeding manifestations, AL presents mainly with non-hematological symptoms such as the nephrotic syndrome, cardiac failure, sensorimotor peripheral neuropathy and weight loss. In this study we have found that AL is 14 times less prevalent in Mexican mestizos than in Caucasians; we feel that this striking difference stems in our country from undersuspicion and underrecognition of the condition, despite the fact that the prevalence of other monoclonal gammopathies has been proved to have racial and genetic differences.[2-6] In this single-center experience, AL was found to represent 14% of all the monoclonal gammopathies. This low prevalence of AL is consonant with the low prevalence of some other immunoproliferative disorders in Mexican mestizos as compared with Caucasians, such as Waldenström's macroglobulinemia (11 times less frequent),[6] monoclonal gammopathy of undetermined significance (4 times less frequent)[2-4] and multiple myeloma (2-3 times less frequent).[4-5]

There are few AL publications stemming from our country, some Mexican case reports [15-17] and analysis of the prognostic significance of AL in multiple myeloma,[18] but apparently no papers dealing with the clinical and laboratory features of the disease have been published. The clinical data of these 23 AL patients are not substantially different from those reported previously in the literature.

This study reflects also on the treatment of patients with AL in México and probably in other developing countries: in a private-practice setting, where patients belong to a more privileged group than those in the public health systems, only 17 of the 23 patients could be followed for more than three months after the diagnosis. On the other hand; the high number of patients lost to follow up (7/17 = 41%) mainly for economical reasons is concerning and makes the survival analysis rather questionable. In the subset of 17 individuals who were followed for more than 3 months, the median SV has not been reached, being above 173 months, whereas the overall survival was 71% at 173 months. These figures are better than those published from developed countries,[7] but the comparisons can not be properly done due the high number of patients lost to follow up. On the other hand, other sources of bias could be also considered to explain these results, such as the inclusion of less patients with the nephrotic syndrome or cardiac failure, stemming from referral bias.

Updated staging systems for AL have been described recently, including cardiac biomarkers and serum free light chain measurements.[19] This retrospective study lacks the information of these variables, which should be ideally included in all prospective studies.

All patients with systemic AL require therapy. There is no presymptomatic phase that warrants observation: corticosteroids, alkylating agents, immunomodulatory drugs, and proteasome inhibitors all have shown activity in this disorder, and combinations are currently being explored in clinical trials.[14,20] Limited data has been published on the treatment results in patients with AL. Whenever possible, high-dose melphalan followed by autologous stem cell transplantation (SCT) has been the first treatment option, achieving somehow better results than conventional therapy; treatment with bortezomib/dexamethasone followed by high-dose melphalan and autologous transplantation may be nowadays the treatment of choice in this disease. SCT produces a high response rate but is a viable option in only 20% of patients. It is clear that the adequate dose of melphalan used to autograft AL patients is approximately 50% of that employed to autograft multiple myeloma patients.[1,7,12] In this series, SCT (using melphalan 100 mg/m^2) was given to

five patients; in this small subset of AL patients two are alive (2,057 and 3,439 days after the autograft), two have died and one was lost to FU. Despite advances in the past decade, 30% of patients still die within a year of diagnosis, suggesting that failure to recognize this disorder prior to advanced organ dysfunction remains a major impediment to improving outcomes.

In summary, AL is less frequent in Mexican mestizos than in Caucasians; in addition, this condition is probably underdiagnosed in Mexico since its clinical presentation is proteiform. The clinical findings in Mexican patients with AL are not different from those described in other populations. AL must be considered in any patient presenting with cardiomyopathy with preserved systolic function, heavy albuminuria, an unexplained sensorimotor peripheral neuropathy, hepatomegaly or macroglosia. Its timely identification may lead to better results of the current therapeutic approaches.

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REFERENCES

1- Merlini G, Seldin DC, Gertz MA. Amyloidosis: pathogenesis and new therapeutic options. *J Clin Oncol* 2011; 29(14): 1924-33.
2. Ruiz Delgado GJ, Gomez Rangel D. Gamopatía monoclonal de significado indeterminado en mestizos mexicanos: experiencia de una sola institución. *Gac Med Mex* 2004; 140(4): 375-9.
3. Ruiz-Delgado GJ, Ruiz-Argüelles GJ. Genetic predisposition for monoclonal gammopathy of undetermined significance. *Mayo Clin Proc* 2008; 83: 601-03.
4. Ruiz-Argüelles GJ, Ruiz-Delgado GJ. On the prevalence and genetic predisposition of monoclonal gammopathy of undetermined significance (MGUS). *Int J Hematol* 2012; 96: 144-5.
5. Ruiz-Argüelles GJ, Gomez-Rangel D, Ruiz-Delgado GJ, Aguilar-Romero L. Multiple myeloma in Mexico: a 20-year experience at a single institution. *Arch Med Res* 2004; 35: 163-7.
6. Ruiz-Argüelles GJ, Ramirez-Cisneros FJ, Flores-Martinez J, Cernuda-Graham MC. Waldenstrom's macroglobulinemia is infrequent in Mexican Mestizos: experience of a hematological diseases referral center. *Rev Invest Clin Mex* 2000; 52: 497-9.
7. Cohen AD, Comenzo RL. Systemic light-chain amyloidosis: Advances in diagnosis, prognosis, and therapy. *Hematology Am Soc Hematol Educ Program* 2010; 2010: 287-94.
8. Myeloma Trialist Collaborative Group. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: an overview of 6633 patients from 27 randomized trials. *J Clin Oncol* 1998; 16: 3832-42.
9. Segeren CM, Sonneveld P, van der Holt B, Baars JW, Biesma DH, Cornellissen JJ, Croockewit AJ, et al. Vincristine, doxorubicin and dexamethasone (VAD) administered as rapid intravenous infusion for first-line treatment in untreated multiple myeloma. *Br J Haematol* 1999; 105: 127-30.
10. Rajkumar SV, Hayman S, Gertz MA, Dispenzieri A, Lacy MQ, Greipp PR, Geyer S, et al. Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 2002; 20: 4319-23.
11. Ruiz-Argüelles GJ, Ruiz-Argüelles A, Pérez-Romano B, Marín-López A, Delgado-Lamas JL. Non-cryopreserved peripheral blood stem cells autotransplants for hematological malignancies can be performed entirely on an outpatient basis. *Am J Hematol* 1998; 58: 161-4.
12. López-Otero A, Ruiz-Delgado GJ, Ruiz-Argüelles GJ. A simplified method for stem cell autografting in multiple myeloma: A single institution experience. *Bone Marrow Transplant* 2009; 44: 715-9.
13. Bladé J, Kyle RA. Monoclonal gammopathies of undetermined significance. In: Malpas JS, Bergsagel DE, Kyle RA (eds.). Myeloma Biology and Management. New York: Oxford University Press; 1995.
14. Gertz MA, Dispenzieri A. Immunoglobulin light-chain amyloidosis: Growing recognition, new approaches to therapy and active clinical trials. *Oncology (Williston Park)* 2012; 26: 152-61.
15. Ruiz-Argüelles GJ, García-Herrera JL. Amiloidosis primaria: Desaparición del síndrome nefrótico con melfalán y prednisona. *Rev Mex Patol Clin* 1985; 32: 143-6.
16. Báez-García JJ, Martínez-Hernández Magro P, Iriarte-Gallego G, Báez-Aviña JA. Spontaneous rupture of the spleen secondary to amyloidosis. *Cir Cir* 2010; 78(6): 533-7.
17. López L, González K, Navarrete G, Novales J, Guarneros A, Cortés B, Téllez G. Multiple myeloma and systemic amyloidosis. *Int J Dermatol* 2008; 47(2): 165-7.
18. Vela-Ojeda J, García-Ruiz Esparza MA, Padilla-González Y, Sánchez-Cortés E, García-Chávez J, Montiel-Cervantes L, Reyes-Maldonado E, et al. Multiple myeloma-associated amyloidosis is an independent high-risk prognostic factor. *Ann Hematol* 2009; 88: 59-66.
19. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, Laumann K, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. *J Clin Oncol* 2012; 30(9): 989-95.
20. Dispenzieri A, Gertz MA, Buadi F. What do I need to know about immunoglobulin light chain (AL) amyloidosis? *Blood Rev* 2012. [Epub ahead of print].

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