Geographic Hematology: Some Observations in Mexico

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Keywords

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Abstract

In 1963 Jean Bernard introduced the concept of “geographic hematology” and distinguished 2 branches, i.e., “ethnic hematology,” which deals with differences between populations, and “environmental hematology,” which considers factors such as food habits, infections, and others. Both of these branches have implications in the distribution of hematological diseases worldwide. In comparison with Caucasian populations, in Mexico a significantly higher prevalence of acute lymphoblastic, acute promyelocytic, and acute megakaryoblastic leukemias has been described. The rate of chronic myeloid leukemia seems to be as high as that reported in Caucasian populations, while other myeloproliferative neoplasias are significantly less frequent in Mexico. Significantly lower prevalences of hairy cell leukemia, chronic lymphocytic leukemia, multiple myeloma, and Waldenström’s macroglobulinemia have been reported from Mexico. Regrettably, the influence of drug companies interested in selling their new and expensive drugs has resulted in both overdiagnosis of some diseases and overidentification of the refractory forms of some of these conditions to justify the use of unnecessary drugs.

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Introduction

Over the last years, population studies have reported remarkable differences in the incidence and characteristics of hematological diseases between geographic regions [1–4]. In 1963 Jean Bernard, an icon in the world of hematology, presented the concept of “geographic hematology” and distinguished 2 major branches, i.e., the so called “ethnic hematology,” which deals with differences between populations, and “environmental hematology,” which deals with environmental factors such as food habits, infections, and hematological diseases [5]. It has been shown that Mexico is not the exception and diverse studies have reported differences in rates of distinct hematological diseases when compared to other countries or regions. Non-Hispanic whites have been found to have higher incidence rates of acute myeloid leukemia (AML), chronic myeloid, and chronic lymphocytic leukemia (CLL) than Hispanics, while childhood acute lymphoblastic leukemia (ALL) incidence rates are highest among Hispanics [6]. Certain hematological malignancies have a different prevalence in our country compared to countries with a Caucasian population [7]. Our population has a significantly higher prevalence of M3 and M7 AML and a significantly lower prevalence of hairy cell leukemia, chronic lymphocytic leukemia, multiple myeloma (MM),

and Waldenström's macroglobulinemia (WM) [8–14] (Fig. 1–3).

In this review we remark the salient features in the specific case of Mexico and its differences with other populations and describe the main differences for each disease compared to other geographic regions.

Geographical Differences in Mexico

Acute Lymphoblastic Leukemia

Although the etiology of ALL is unknown, numerous environmental factors, including radiation, chemicals products, and infections, have been associated with the disease. Descriptive epidemiologic studies have reported a higher incidence of ALL in the Latin American population compared to other racial/ethnic groups, leading to a search for possible factors that make the Mexican population more susceptible to developing the disease than others [15]. In Mexico, no large-scale epidemiologic studies have been conducted in this population, but some studies suggest the incidence of ALL in Mexico is among the highest in the world [16–19]. The worldwide incidence of ALL varies from 2.0 to 3.5 cases per 100,000 inhabitants per year, whereas in Mexico the incidence is higher than 6/100,000 inhabitants per year [18, 20]; the explanation for this difference is unknown. Mexican hematologists were the first to prove that malnutrition is an adverse prognostic factor in children with ALL [21], an observation that has been confirmed worldwide [22]. With regard to treatment of ALL, it has been shown that treatment protocols conducted on an outpatient basis are related to results similar to those of other more aggressive protocols endowed with a higher morbimortality but similar long-term results. As an example, we have shown that St. Jude's TOTAL XI-based protocols are as effective as Hyper-CVAD and, since they can be conducted on an outpatient basis, their use in Mexico is more realistic than that of other more complicated ones [23]. The mortality rate of Hyper-CVAD during its administration reaches more than 50% in some institutions, a figure substantially higher than that of the TOTAL XI-based schedules.

Acute Myelogenous Leukemia

In our low-to-middle income population the peak incidence of AML has been observed 10 years earlier than in other countries, with a mean age at diagnosis of 32–43 years [15, 24] compared to a median of 60–70 years in the USA or the UK [25, 26]. As suggested by Jaime-Perez et al. [24], this might be explained by the fact that older pa-

Fig. 1. Proportion of patients with chronic lymphocytic leukemia (CLL) within all the hematological malignancies in Mexican mestizos and Caucasians.

Fig. 2. Proportion of patients with acute promyelocytic leukemia (AML FAB M3) within all myeloblastic leukemias in Mexican mestizos and Caucasians.

Fig. 3. Proportions of monoclonal gammopathies in Mexican mestizos and Caucasians. MGUS, monoclonal gammopathy of undetermined significance.

tients are not referred to seeking care. The median age at diagnosis in Latin American countries or developing countries is very similar to ours. Brazil has reported a median age at diagnosis of 33–44 years [27, 28], and for other low-middle-income countries such as India and Malaysia the median age of patients with AML has been observed to be 40 and 39 years, respectively [29, 30]. The exact cause of this age difference is unclear. Socioeconomic factors including the aging population in developed countries and reduced access to healthcare in elderly patients in developing countries could explain these variations. Other factors such as environmental exposures and diet should be explored. Similar incidences of ALL and AML have been observed in Mexican adults, coinciding with other studies from Latin America and differing from reports from the USA, where AML is more common [15]. Interestingly, the median age of patients with AML is substantially lower in Mexicans than in Caucasians [15].

Particular attention is needed in the case of acute promyelocytic leukemia (APL) in Mexico. APL is the most common subtype of AML in Mexico, with an incidence of 35.5% [8, 15], which is higher than the rate of around 5–13% reported in a Caucasian population [9] (Fig. 2). Latin Americans living in the USA have a greater frequency of APL compared to the non-Latin American Caucasian population (i.e., 24.3 vs. 8.3% and age 31.5 vs. 46 years in Latin Americans vs. non-Latin Americans, respectively, as observed by Douer et al. [31]). This finding has also been observed in other Latin American countries such as Brazil (28.2%) [32, 33], Venezuela (27.8%) [34], and Peru (22%) [35]. The geographic variation suggests a possible genetic predisposition or environmental exposures to specific risk factors. Other factors such as obesity and dietary patterns have been linked to APL [36, 37]. An increased BMI has been independently associated with a higher incidence of APL in Latino patients living in the USA [37]. Seventy percent of the population of Mexico is overweight/obese, and this could partially explain the higher incidence of APL. The distribution of the breakpoint cluster regions of the PML/RAR α fusion gene has been shown to be different in Mexican patients with APL than in Caucasians and similar to those observed in Asians [9]; this observation suggests genetic differences in the features of PML, with a higher predisposition for this disease in Mexico or, alternatively, a protective effect of these differences in Caucasians. As a result of the increased prevalence of APL in Latin America, multicenter studies employing a simplified treatment of the disease have been conducted, with results similar to those ob-

tained in other populations employing more complicated treatment schedules [38]. It is also interesting that the prevalence of acute megakaryoblastic leukemia, the M7 variant of the FAB classification of AML, has also been described as more frequent in Mexicans than in Caucasians [39].

Myeloproliferative Neoplasias

There are data in Mexico indicating that the prevalence of chronic myelogenous leukemia is probably similar to that found in Caucasians [7]. However, we have found that MPN are considerably less frequent in Mexican mestizo populations than in Caucasian populations [35]. Essential thrombocythemia (ET) is the most frequent chronic myeloproliferative neoplasia (MPN) (i.e., 2.53 cases per 100,000 inhabitants per year) in the USA, followed by polycythemia vera [40]. In Mexico in a study of more than 8,000 individuals conducted between 1983 and 2001, chronic myelogenous leukemia was found to be as prevalent as in Caucasian populations, but ET, myelofibrosis, and polycythemia vera were significantly less frequent in Mexicans than in Caucasian populations [7]. It has been speculated that underdiagnosis of this particular group of diseases stemming from the unspecific and low symptoms presented in the burden of MPN may be related to the apparently diminished prevalence of these conditions. Despite the low prevalence of MPN in Mexico, drug companies have pushed the use of novel and expensive drugs such as ruxolitinib in patients in whom it is not clearly indicated.

Chronic Lymphocytic Leukemia

CLL is the most common leukemia in countries with a predominantly Caucasian population [41]; however, it is very rare in Asia and Latin America, including Mexico [13, 42, 43]. In Western countries CLL accounts for approximately 30% of all leukemias, in contrast to less than 7% among Mexican mestizos [4] (Fig. 1). Some minor allele frequency differences have been observed in Mexican mestizos in contrast to the Caucasian population; however, the underlying causes for geographic variations have never been completely clarified [41]. In addition to these possible genetic differences, infectious, occupational, environmental, and genetic factors have all been suggested as other potential contributors [4]. It has also been shown that the clinical course of CLL in Mexico is less aggressive than the course in Caucasian populations [13]. This observation contrasts with the indiscriminate use of novel, expensive drugs in the treatment of refractory forms of CLL in Mexico as a result of pressure from drug

companies to prescribe these novel drugs, which in turn has led to overdiagnosis of both the disease and the refractoriness of the condition; we have seen cases of persons with stage 0 CLL who need no treatment at all and who have been given treatment with ibrutinib or other novel and expensive drugs so that the physicians can be sponsored by drug companies to attend meetings, domestically and abroad. Hairy cell leukemia is infrequent in Mexico and, interestingly, it has been shown to have a geographic distribution [12], being more frequent in the northern states of the country, where inhabitants are more exposed to agricultural pesticides; this possible explanation is purely speculative.

Malignant Monoclonal Gammopathies

MM represents nearly 1% of all cancers and 15% of hematologic malignancies in the world [44, 45]. However, its incidence varies among different regions and ethnic groups. The incidence of MM has been described as higher in blacks than in whites and lower in Asia than in Europe [46]. In general, there is a low prevalence of monoclonal gammopathy in Mexican mestizos compared to Caucasians [47]. In Mexico, the MM incidence represents 4.2% of hematologic malignancies, which is 2–3 times less frequent than in Caucasians [48]. A diminished lower prevalence has also been reported in other monoclonal gammopathies in Mexico, like WM, representing 4.3% of all the malignant monoclonal gammopathies and 0.18% of all hematological malignancies in Mexico, in contrast to 2% in the Caucasian population [14] (Fig. 3).

Monoclonal gammopathy of undetermined significance (MGUS) represents only 2.4% of all monoclonal gammopathies in Mexico, whereas in the Caucasian population MGUS affects about 3% of individuals aged >70 years; this figure is substantially lower in Mexico (i.e., 0.7%) [49]. A genetic basis for these geographic differences is suggested by similar low prevalences in other populations like the Japanese and the Chinese, which also have a low prevalence of MGUS [50]. Regarding systemic light chain amyloidosis, there is scarce information in Mexico. It has been found to be 14 times less prevalent in Mexican mestizos than in Caucasians. This difference could also be explained by underrecognition and low suspicion of the disease. In a multicenter study of the clinical features of MM in Latin America, it was shown that the clinical course of the disease is substantially less aggressive in inhabitants of Latin America than in Caucasians [51]; again this finding contrasts with the irrational use of

novel antimyeloma drugs in Mexico, pushed by the drug companies, leading to indiscriminate use of novel, frequently unnecessary antimyeloma drugs. In our country, autologous stem cell transplant is still the best therapeutic approach for patients with MM and it has the best cost-benefit ratio [52]. We strongly feel that it should be the main therapeutic option for these individuals.

Thalassemia

Thalassemia is considered the most common genetic disorder worldwide and approximately 3% of the world's population carries β -thalassemia genes [53]. Among the different ethnic populations and their geographical regions, there is a huge variation in the spectrum of β -globin gene mutations. In general, each population has its own β -globin gene mutation spectrum [54, 55]. The disease is prevalent in the Mediterranean area, the Middle East, Africa, Southeast Asia, and the Indian subcontinent [55]. The precise prevalence of the carrier state of thalassemia in Mexico is not known but it appears to be not infrequent. Some β -thalassemia gene clusters have been found in the Mexican population, with a prevalence of up to 15% (in some areas these are autochthonous and in others they have been imported from the Mediterranean area) [53, 56]. Information regarding α -thalassemia in Mexico is scarce. α -thalassemia has been found to be responsible for 1% of hypochromic microcytic anemias in Mexico, which represents about half of the rate of β -thalassemia [57].

Non-Hodgkin's Lymphoma and Hodgkin's Lymphoma

Substantial differences in the incidence of non-Hodgkin's lymphoma (NHL) across geographic regions have been reported. These seem to be related to host, racial, and environmental differences [58]. The highest NHL incidence rates are seen in developed countries in North America, Europe, and Oceania. NHL accounts for 4% of cancers in the USA [59]. However, there is data scarcity for less developed countries, and only few reports have addressed the epidemiology of NHL in Mexico and Latin America. One recent analysis of over 19,000 NHL cases revealed wide geographic variation in incidences and mortality rates in Central and South America. The highest incidence rates among males were observed in Uruguay, Colombia, Peru, and Ecuador (i.e., 10.2–10.9%) and among females in Ecuador (i.e., 9.2%) and Peru (i.e., 8.8%), and these values were up to 40% lower than those observed in other countries (England, France, and Nor-

way) and in North American countries for 2003–2007 [60]. A predominance of more aggressive subtypes of NHL has been described in Mexico and other developing countries [61, 62]. Changes in exposure to risk factors, including infectious agents and immunosuppressive drugs, may be related to differences in demographic and geographic distribution patterns. Hodgkin lymphoma (HL) accounts for no more than 0.5% of the total cancer burden worldwide. There is a huge heterogeneity, with notable similarities and differences across patient populations regarding age, gender, and subtype [63]. In developing countries like Mexico, where HL seems to have a higher incidence, HL often presents at earlier ages and with a predominance of the mixed cellularity histologic subtype [64]. In developed countries the predominant histologic subtype is nodular sclerosis (70% of cases); EBV-positive tumors are less frequently found, patients are diagnosed at earlier clinical stages (I–II), and there is a better prognosis for survival [65]. Concerning the therapeutic aspects of these diseases, in Mexico it has not been possible to prove a superiority of the employment of rituximab plus chemotherapy versus only chemotherapy in diffuse large B-cell lymphomas [66].

Aplastic Anemia

Aplastic anemia (AA) has been shown to be more frequent in Mexico than in Caucasian populations [67]. Interestingly, 50% of Mexican patients with AA in anemia have abnormalities in the expression of CD55 and CD59, which suggests that they are hypoplastic variants of paroxysmal nocturnal hemoglobinuria [68]. Most Mexican patients with paroxysmal nocturnal hemoglobinuria have been found to have the hypoplastic variant of the disease [69]. Despite this finding, the indiscriminate use of eculizumab in Mexico has been the result of the efforts of the pharmaceutical industry, when it is known that only the hemolytic variants of the disease respond to this treatment. The most cost-effective treatment in Mexico for patients with AA is intensive immunosuppression [70], whereas bone marrow transplantation should be reserved for those AA patients not responding to immunosuppression [71].

Discussion

The concept of “geographic hematology” emerged in 1963 and opened a new chapter in hematology. This concept is very relevant and in the case of Mexico differences

among the many hematological diseases are considerably significant when compared to other populations. These differences should be taken into account before taking for granted observations in other populations worldwide. Certain geographical variations in the frequency and clinical characteristics of hematological diseases have a different clinical profile and prevalence in Mexico compared to countries with Caucasian populations. The genetic mixture of Mexican mestizos is variable, but it comprises approximately 56% American Indian genes, 40% Caucasian genes, and 4% black genes [72].

In summary the population of Mexico has a significantly higher prevalence of M3 and M7 AML and an incidence of ALL among the highest in the world. There is a significantly lower prevalence of hairy cell leukemia, CLL, MM, and WM. Chronic myeloid leukemia seems to be as frequent as that reported in Caucasian populations, while other MPN are significantly less frequent in Mexicans. Considering the scarcity of well-designed registries and studies in Mexico, the geographical differences in Mexico may have resulted from artifacts in the data. However, there is enough information to affirm that environmental and genetic factors could be affecting. Socio-economic factors including the aging population in developed countries and a reduced access to healthcare for elderly patients in developing countries could also explain some of the geographical variations. Other factors, such as infections, occupational exposure to chemicals, lifestyle factors, diet, and genetic susceptibility, should be explored to better understand the geographic differences in our country and thus establish potential preventive measures and therapeutics. Regrettably, the efforts of the pharmaceutical industry have resulted in changes in the landscape of many hematological diseases in Mexico by pushing the prescription and use of drugs that could be either avoided or replaced by other therapeutic approaches that are more realistic for individuals living in conditions with a restricted economy.

Disclosure Statement

The authors have no conflicts of interest to declare.

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