Etiology and clinico-hematological profile of pancytopenia: experience of a Mexican Tertiary Care Center and review of the literature

César Jonathan Vargas-Carretero a,*, Omar Eduardo Fernandez-Vargas a,b,*, Ana Lucía Ron-Magaña a, José Alejandro Padilla-Ortega a, Carlos Silvestre Ron-Guerrero c and Esperanza Barrera-Chairez a,b

aDepartment of Haematology, Hospital Civil de Guadalajara “Fray Antonio Alcalde”, University of Guadalajara, Guadalajara, Mexico; bDepartment of Physiology, Centro Universitario de Ciencias de la Salud, University of Guadalajara, Guadalajara, Mexico; cDepartment of Haematology, Hospital General ISSSTE “Dr. Aquiles Calles Ramirez”, Tepic, Mexico

ABSTRACT

Background: Pancytopenia is a frequent entity in clinical practice as a feature of a myriad of conditions, ranging from benign to malignant diseases. Since the cause of pancytopenia depends on environmental factors, it is important to know the common etiologies of pancytopenia, however, few studies address this.

Objectives: To identify the etiology of pancytopenia in our population and compare them with what is reported elsewhere.

Methods: We conducted an observational study of patients with pancytopenia in a Mexican Tertiary Care Center. Clinical, hematological and bone marrow studies were performed in all patients.

Results: Of 109 cases included, the mean age at diagnosis was 49.4 years, with a slightly higher female incidence (53.2%). The most common causes of pancytopenia were: MDS (20.2%), megaloblastic anemia (18.3%) and AML (12.8%).

Discussion: We found a complex picture of pancytopenia in Mexico and compared it with what is reported elsewhere in the literature.

Conclusion: The sociocultural context in which the patients develop helps narrowing the possible etiology of pancytopenia, and therefore hasten the diagnostic process. Of all the studies available, bone marrow aspiration seems the most useful.

KEYWORDS
Pancytopenia; hematological malignancies; megaloblastic anemia

Introduction

Pancytopenia is the reduction of all three cellular elements of peripheral blood, leading to anemia, leukopenia and thrombocytopenia, and it is a clinico-hematological entity commonly encountered in clinical practice as a feature of a myriad of diseases, ranging from non-malignant conditions, such as drug-induced pancytopenia, infections or nutritional deficiencies, to malignant neoplasms, either primary hematological malignancies or non-hematological metastatic malignancies. Considering that both treatment and prognosis depend on the cause of pancytopenia, it is essential to reach a definitive diagnosis as soon as possible [1–3].

Since the development of pancytopenia and its primary cause depend, among other things, on environmental factors [4,5], it is important to keep them in mind while studying a patient with pancytopenia; however, there are few reports about its epidemiology, specially in our population. Therefore, we decided to study the etiology of pancytopenia in a tertiary hospital, and then, compare our data with studies of pancytopenia worldwide. In this work, we report the first series of adult patients with pancytopenia in our country.

Methods

Patients admitted to the hospital with pancytopenia defined as Hemoglobin \( \leq 13.5 \) g/dL in males or \( \leq 11.5 \) g/dL in females, leukocytes \( \leq 3.5 \times 10^9/L \) or neutrophils \( \leq 1.5 \times 10^9/L \) and platelets \( \leq 135 \times 10^9/L \) [6], from January 2007 to December 2011, were studied. The inclusion criteria were: (1) age >15 years old, (2) presence of pancytopenia, as defined above, (3) written consent for participation in the study. The exclusion criteria were: (1) patients with previously diagnosed pancytopenia, (2) patients in whom a final diagnosis could not be reached, (3) patients with incomplete medical records, (4) patients with previously known HIV infection. A complete clinical history, medical examination, a full blood count and bone marrow aspiration and/or biopsy were performed at the start of the study. When needed, additional diagnostic studies were performed. All data were analyzed using R Studio and Prism6.

CONTACT Esperanza Barrera-Chairez esperbarrera@hotmail.com

These authors contributed equally to this work.

© 2019 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
Results

Of the 109 patients included, 58 were female (53.2%) and 51 were male (46.8%) with a mean age at diagnosis of 49.4 (16–85) years. Clinically, more than 80% of patients presented with symptoms of anemia, pallor (82.6%) and weakness (81.7%) being the most frequent; and almost half had some kind of bleeding, being ecchymosis (29.4%) and petechiae (17.4%) the most common. Only 23 patients presented with fever and an infection could be documented in 20 cases.

The hematological parameters were a mean hemoglobin of 8.17 g/dL ± 2.03, hematocrit of 23.9% ± 6.3, platelet count of 55,476 × 10^9/L ± 34,282, leukocyte count of 2,4173 × 10^9/L ± 1,3892, neutrophil count of 0.9184 × 10^9/L ± 0.6374 and lymphocyte count of 55.476 × 10^9/L ± 34.282 (Table 1).

The final diagnosis of pancytopenia was made with bone marrow aspirate analysis in 58 cases (53.2%), with bone marrow biopsy in 19 (17.4%) and bone marrow immunophenotyping in 14 patients (12.8%). In the remaining cases, other complementary studies were performed to achieve a diagnosis.

Overall, myelodysplastic syndromes (MDS) were the most common final diagnosis, with 22 patients (20.2%), followed by megaloblastic anemia with 20 (18.3%) and acute myeloblastic leukemia (AML) with 14 patients (12.8%). Other frequent causes were acute lymphoblastic leukemia (ALL) 12 patients (11.1%), hypersplenism 12 (11.1%) and aplastic anemia (AA) with 11 patients (10.1%) (Table 2). Of the patients with megaloblastic anemia, 5 had pernicious anemia with a female to male ratio of 4:1. The cause of hypersplenism was portal hypertension in eight patients (66.6%).

Discussion

Pancytopenia is the clinical triad of anemia, thrombocytopenia and leukopenia, and can be caused by a myriad of conditions. In our population, the clinical presentation of pancytopenia was marked by signs and symptoms of red blood cell and platelet deficiencies, while infections were limited. The most useful single study that aided the diagnostic process, in our series, was the bone marrow aspirate, allowing a final diagnosis in more than half of the patients included. In the rest of the cases, further diagnostic studies such as bone marrow biopsy and immunophenotyping were necessary, reaching a diagnosis in 83.4% of pancytopenia cases. This is similar to what is reported elsewhere [1,7].

We did not find significant differences in age distribution or peripheral blood cell counts that could help discriminate between benign and malignant pathologies, however, for patients with megaloblastic anemia due to either vitamin deficiency or pernicious anemia, we found a male to female ratio of 4:1 for vitamin deficiency megaloblastosis, which reversed to 1:4 for pernicious anemia [8,9]. Additionally, hypersplenism as a cause of pancytopenia was far more common in men than women, with a ratio of 1:5. Nonetheless, portal hypertension was present only in 2/10 female patients.

In our study, the major causes of pancytopenia were myeloid neoplasms (MDS and AML) and vitamin deficiencies. The comparison of these results with what is reported worldwide sets a mixed picture for

### Table 1. Clinical and hematological profile of 109 patients with pancytopenia.

| Age (years) | Sex | Hematological | Clinical presentation |
|-------------|-----|---------------|-----------------------|
| Mean ± SD   |     | Hemoglobin (g/dL) | Pallor |
|             |     | 8.17 ± 2.03 | 49.4 ± 20.7 (16–85) | 90 (82.6) |
|             |     | Hematocrit (%) | Weakness |
|             |     | 23.9 ± 6.3 | 89 (81.7) |
|             |     | Platelet count (1 × 10^9/L) | Dyspnea |
|             |     | 55.476 ± 34.282 | 56 (51.4) |
|             |     | Leukocyte count (1 × 10^9/L) | Bleeding (overall) |
|             |     | 2.4173 ± 1.3892 | 53 (48.6) |
|             |     | Neutrophil count (1 × 10^9/L) | Ecchymosis |
|             |     | 0.9184 ± 0.6374 | 32 (29.4) |
|             |     | Lymphocyte count (1 × 10^9/L) | Petechiae |
|             |     | 1.238 ± 1.244 | 19 (17.4) |
|             |     |               | Epistaxis |
|             |     |               | 14 (12.8) |
|             |     |               | Melena |
|             |     |               | 12 (11) |
|             |     |               | Hematochezia |
|             |     |               | 3 (2.8) |
|             |     |               | Fever |
|             |     |               | 23 (21.1) |
|             |     |               | Weight loss |
|             |     |               | 40 (36.7) |
|             |     |               | Hepatomegaly |
|             |     |               | 13 (11.9) |
|             |     |               | Splenomegaly |
|             |     |               | 19 (17.4) |
|             |     |               | Adenopathies |
|             |     |               | 16 (14.7) |
|             |     |               | Jaundice |
|             |     |               | 10 (9.2) |
|             |     |               | Bone pain |
|             |     |               | 9 (8.3) |
|             |     |               | Headache |
|             |     |               | 19 (17.4) |
|             |     |               | Vertigo |
|             |     |               | 17 (15.6) |

### Table 2. Final diagnosis of adult patients with pancytopenia.

| Diagnosis | Number of patients (%), [F/M] |
|-----------|-------------------------------|
| Benign hematological | |
| Megaloblastic anemia | 20 (18.3), [7/13] |
| Aplastic anemia | 11 (10.1), [8/3] |
| TTP | 2 (1.8), [1/1] |
| ITP | 1 (0.9), [1/0] |
| Hematological malignancies | |
| MDS | 22 (20.2), [14/8] |
| AML | 14 (12.8), [8/6] |
| ALL | 12 (11.1), [5/7] |
| MM | 3 (2.8), [1/2] |
| NHL | 2 (1.8), [1/1] |
| CLL | 1 (0.9), [1/0] |
| Primary myelofibrosis | 1 (0.9), [1/0] |
| Infectious | |
| CMV | 1 (0.9), [1/0] |
| HIV | 1 (0.9), [1/0] |
| Brucellosis | 1 (0.9), [1/0] |
| Other | |
| Hypersplenism | 12 (11.1), [10/2] |
| Drug-related | 4 (3.7), [2/2] |
| Myeloophthisis | 1 (0.9), [1/0] |
| Total | 109 |

ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CLL, chronic lymphocytic leukemia; TTP, immune thrombocytopenic purpura; MDS, myelodysplastic syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; TTP, thrombotic thrombocytopenic purpura.
Table 3. Summary of worldwide studies on pancytopenia.

| Continent | Country | Authors | Year | Population (n) | Most common diagnosis | Second most common | Third most common | Fourth most common |
|-----------|---------|---------|------|-----------------|-----------------------|--------------------|-------------------|-------------------|
| America   | Mexico  | Vargas-Carretero et al. | This study | Adults (109) | MDS (20.2%) | Megaloblastic anemia (18.3%) | AML (12.8%) | ALL (11.1%)/hypersplenism (11.1%) |
|          | USA     | Weinzierl et al. | 2013 | Adults (193) | MDS (28.5%) | AML (20.2%) | AA (7.8%) | Hypersplenism (16.7%) |
|          | Argentina | Mosso et al. | 2007 | Adults (54) | Post-chemotherapy (40.7%) | Hematological malignancies (16.7%) | Megaloblastic anemia (20.1%) | |
| Asia      | Peru    | Ruiz-Franco et al. | 2016 | Adults and children (244) | Megaloblastic anemia (37%) | AA (27%) | Megaloblastic anemia (20.1%) | |
| Asia      | Turkey  | Yokus, et al. | 1990 | Adults (45) | MDS (16.3%) | AML (15.2%) | AA (10.1%) | Lymphoma (8.9%) |
| Asia      | Pakistan | Rehmani et al. | 2016 | Adults and children (250) | Megaloblastic anemia (17%) | AA (20%) | MDS (16%) | AML (12%) |
| Asia      | South Korea | Bae et al. | 2015 | Adults (791) | MDS (16.3%) | AML (15.2%) | AA (10.1%) | Lymphoma (8.9%) |
| Asia      | China   | Azaad et al. | 2015 | Adults (25) | Megaloblastic anemia (28%) | AA (20%) | MDS (16%) | AML (12%) |
| Asia      | India   | Jain et al. | 2013 | Adults and children (111) | Megaloblastic anemia (19.2%) | AA (20.7%) | Megaloblastic anemia (13.2%) | |
| Asia      | Iraq    | Al-Khalisi et al. | 2011 | Adults (105) | AML (30.5%) | AA (17.1%) | Megaloblastic anemia (13.5%) | |
| Asia      | Singapore | Santra et al. | 2010 | Adults and children (285) | Megaloblastic anemia (19.2%) | AA (20.7%) | Megaloblastic anemia (13.5%) | |
| Africa    | Tunisia | Kli et al. | 2016 | Adults (103) | Megaloblastic anemia (35.9%) | Infectious (14.5%) | Hematological malignancies (12.6%) | SLE (10.7%) |
| Africa    | Congo   | Atipo-Tsiba et al. | 2016 | Adults (65) | AML (32.2%) | MDS (13.5%) | AA (17%) | MDS (9.2%) |
| Africa    | Morocco | Nafli et al. | 2012 | Adults (118) | Megaloblastic anemia (49%) | MDS (13.5%) | AA (17%) | MDS (9.2%) |
| Africa    | Ivory Coast | Biley et al. | 2006 | Adults (95) | Megaloblastic anemia (16.7%) | MDS (13.5%) | AA (17%) | MDS (9.2%) |
| Africa    | Djibouti | Lavigne et al. | 2005 | Adults (81) | Megaloblastic anemia (16.7%) | MDS (13.5%) | AA (17%) | MDS (9.2%) |
| Africa    | Zimbabwe | Savage et al. | 1999 | Adults and children (134) | Megaloblastic anemia (16.7%) | MDS (13.5%) | AA (17%) | MDS (9.2%) |

AA, aplastic anemia; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome.
our country, since malignant neoplasms are more common in industrialized and developed nations, while vitamin deficiencies, hypersplenism and infections prevail in developing countries (Table 3). This supports the fact that major causes of pancytopenia are geographically and socio-culturally determined [1–5,7,10–26].

Regarding megaloblastic anemia, both folate but specially vitamin B12 deficiency is more common than previously thought, and several factors could be implicated, including the diminished absorption of B12 in older adults and the fact that depleting this vitamin’s liver deposits is not as lengthy as described before [27,28]. This helps explain how countries like Mexico and Argentina, with an average supply of protein of animal origin of more than 40 g/capita/day still have a high incidence of megaloblastic anemia as a cause of pancytopenia [29], although this was rare for developed nations.

This suggests that B12 deficiency could be the main cause of megaloblastic anemia in developing countries, as supported by a paper published in 2014 in an Indian population in which the authors found that most cases of macrocytic anemia were attributed to B12 deficiency, while almost 50% of cases with either microcytic or normocytic anemia were accompanied with cyanocobalamin deficiency [30]. Additionally, a relative excess of folic acid in comparison to B12 seems to detonate a more severe neurological and psychiatric symptoms, therefore, accurate diagnosis is important [27,30]. Moreover, B12 deficiency could likely be nutritional, since a study [31] demonstrated that only 3.9% of patients with macrocytosis had parietal cell autoantibodies. Nonetheless, a study found no clear correlation between vitamin levels, either folate or cobalamin, and the severity of anemia. This suggests that other factors influence its development and strain the need of performing further research in this topic [32].

With reference to hematological malignancies as a cause of pancytopenia, according to GLOBOCAN [46] of the World Health Organization, there is a higher overall age-standardized rate of cancer in more developed countries versus developing countries. This is true for Hodgkin’s lymphoma (2.1 vs 0.6), multiple myeloma (2.7 vs 0.9), leukemia (7.2 vs 3.8) and non-Hodgkin’s lymphoma (8.6 vs 3.6). This is similar to what we found in our review, since countries with a high gross domestic product (GDP), such as USA and France, where almost 50% of all adult cases with pancytopenia were due to hematological malignancies; furthermore, in our country, hematological malignancies comprised overall more than 40% of all cases of pancytopenia, suggesting possible similarities between these environments. Theories behind these findings include a diminished natural selection, effects of diet, the prevalence of obesity and overfeeding, and more; all which are discussed elsewhere [33–35,37]. Furthermore, although pancytopenia as a presentation of multiple myeloma and both Hodgkin and non-Hodgkin’s lymphoma is not common in developed nations, there were cases both in our series and other developing countries [17,18]. In a report of a Mexican cohort of MM patients, 88% were on ISS stages II or III, suggesting an overall more advanced stage at presentation [38]. Additionally, a study by Perry et al. found that developing regions had a larger rate of high-grade B-cell lymphomas compared to developed countries (59.6% vs 39.2%, respectively) [39]. These disparities may be due to several reasons, including variations in tumor biology, delayed referral or diminished access to health care institutions; to fully explain this difference, further studies are needed.

As expected, malaria was a common cause of pancytopenia only in countries with a high incidence, according to data from the WHO Malaria Observatory and the WHO Malaria report, as are the cases of Yemen and Ivory Coast [36].

There was a higher incidence of pancytopenia due to AA in Asian countries compared to the rest of the world. In our country, AA as a cause of pancytopenia was not common, since it was the final diagnosis in only 11 patients. This is in accord to what is reported internationally, since AA is two to three times more common in Asian populations compared to North America and Europe, with an estimated incidence ranging from 3.9 to 7 per million [40,41]. In this regard, although the reports by the International Agranulocytosis and Aplastic Anemia Study Group did had a higher incidence of AA as a cause of pancytopenia, it is important to take into account that one of their criteria for inclusion was the suspicion of AA as a cause of pancytopenia, therefore, this data should be regarded with caution, especially since other studies from Europe have not arrived to the same results [7,19,41]. The reasons behind this disparity have been discussed elsewhere [42–45].

Overall, the data gathered support a complex picture for pancytopenia in our country, since both benign nutritional deficiencies and malignant hematological neoplasms were common in our population.

**Conclusion**

In studying a patient with pancytopenia, a good clinical correlation is of utmost importance to evaluate each specific case and plan for further evaluations. In this context, the most useful single study is the bone marrow aspirate. Nonetheless, with an extensive differential diagnosis, it is necessary to take into account the environmental factors that might suggest or narrow the possible etiologies to hasten the diagnostic process. It is therefore essential to study not only the patients but their sociocultural context. Taking this
References

[1] Weinzierl EP, Arber DA. Bone marrow evaluation in new-onset pancytopenia. Hum. Pathol. 2013;44:1154–1164.

[2] Jain A, Naniwadekar M. An etiological reappraisal of pancytopenia – largest series reported to date from an single tertiary care teaching hospital. BMC Hematol. 2013;13:10.

[3] Azaad MA, Li Y, Zhang Q, et al. Detection of pancytopenia associated with clinical manifestation and their final diagnosis. OJBD. 2015;05:17–30.

[4] Santra G, Das BK. A cross-sectional study of the clinical profile and aetiological spectrum of pancytopenia in a tertiary care centre. Singapore Med J. 2010;51:806–812.

[5] Lavigne C, Lavigne E, Massenet D, et al. Role of vitamin deficiency in pancytopenia in Djibouti. Findings in a series of 81 consecutive patients. Med Trop (Mars). 2005;65:59–63.

[6] Verburgh E, Achten R, Louw VJ, et al. A new disease categorization of low-grade myelodysplastic syndromes based on the expression of cytopenia and dysplasia in one versus more than one lineage improves on the WHO classification. Leukemia. 2007;21:668–677.

[7] Imbert M, Scoacezy JY, Mary JY, et al. Adult patients presenting with pancytopenia: a reappraisal of underlying pathology and diagnostic procedures in 213 cases. Hematol Pathol. 1989;3:159–167.

[8] Bizzaro N, Antioco A. Diagnosis and classification of pernicious anemia. Autoimmun Rev. 2014;13:565–568.

[9] Balarajyan Y, Ramakrishnan U, Özaltin E, et al. Anaemia in low-income and middle-income countries. Lancet. 2011;378:2123–2135.

[10] Savage DG, Allen RH, Gangaizdo IT, et al. Pancytopenia in Zimbabwe. Am J Med Sci. 1999;317:22–32.

[11] hdr.undp.org. (2016). About Human Development| Human Development Reports [online] [accessed 2016 Dec 22]. Available at http://hdr.undp.org/en/humandev.

[12] Jha A, Sayami G, Adhikari RC, et al. Bone marrow examination in cases of pancytopenia. JNMA J Nepal Med Assoc. 2008;47:12–17.

[13] M M, C A, P S, et al. Impacto clinico de la pancytopenia en pacientes hospitalizados. Rev Méd Univ. 2008;4:1–16.

[14] Biley EE, Koffi KG. Profil épidémiologique, clinique, étiologique et évolutif des pancytopenies fébriles: à propos de 95 cas colligés dans le service d’Hématologie Clinique du CHU de Yopougon. UFR Sci Méd Abidjan. 2006.

[15] Franco O R. Pancytopenia: expresión de la patología hemolítica en un hospital general. Rev Serv Sanid Fuerzas Pulk. 1990;51:25–31.

[16] Retief FP, Heyns AD. Pancytopenia and aplastic anemia: a retrospective study. S Afr Med J. 1976;50:1318–1322.

[17] Al-Khalisi KA, Al-Zubaidy AS, Raima M. Pancytopenia adult patients at Baghdad Teaching Hospital. Iraqi Postgrad Med J. 2017;10:441–448.

[18] Bae M-H, Cho Y-U, Kim B, et al. Pancytopenia or Bicytopenia in a Korean Tertiary Care Center; Etiological profile based on bone marrow examination and suggestion for diagnostic approach. Blood. 2015;126(23):5610.

[19] Keisu M, Ost A. Diagnoses in patients with severe pancytopenia suspected of having aplastic anemia. Eur J Haematol. 1990;45:11–14.

[20] Incidence of aplastic anemia: the relevance of diagnostic criteria. By the International Agranulocytosis and Aplastic Anemia Study. Blood. 1987;70:1718–1721.

[21] Klii R, Chaaben I, Kechida M, et al. Profil étiologique des cytopénies dans un service de médecine interne : à propos de 103 cas. La Rev Méd Int. 2016;37:A145–A142.

[22] AT FO, K I, O T, et al. Aspects Cliniques et étiologiques des Pancytopenies au CHU de Brazzaville. Health Sci Dis. 2016;17:76–79.

[23] Yokus O, Gedik H. Etiological causes of pancytopenia: A report of 137 cases. Avicenna J Med. 2016;6:109–112.

[24] Rehmani TH, Anif M, Haider S, et al. Spectrum of pancytopenia: A tertiary care experience. TJM. 2016;23:620–626.

[25] Nafel H, Tazi I, Sifasalam M, et al. Profil étiologique des pancytopenies chez l’adulte à Marrakech (Maroc). East Med Health J. 2012;8:532–536.

[26] Hamid GA, Shukry SAR. Patterns of pancytopenia in Yemen. Turk J Haematol. 2008;25:71–74.

[27] Allen LH. How common is vitamin B-12 deficiency? Am J Clin Nutr. 2009;89:693S–696S.

[28] Paul L, Selhub J. Interaction between excess folate and low vitamin B12 status. Mol Aspects Med. 2017;53:43–47.

[29] de Benoist B. Conclusions of a WHO Technical Consultation on folate and vitamin B12 deficiencies. Food Nutr Bull. 2008;29:S238–S244.

[30] Food and Agriculture Organization of the United Nations. FAOSTAT statistics database [online] 2016. [accessed 2017 Dec 10]. Available at: http://www.fao.org/faostat/en/#home.

[31] Sukla KK, Nagar R, Raman R. Vitamin-B12 and folate deficiency, major contributing factors for anemia: a population based study. e-SPEN J. 2014;9.e45–e48.

[32] Abdulmena AA, Alsaede AH, Shaik AP, et al. Pernicious anemia in patients with macrocytic anemia and low serum B12. Pak J Med Sci. 2014;30:1218–1222.

[33] Metz J. A high prevalence of biochemical evidence of vitamin B-12 or folate deficiency does not translate into a comparable prevalence of anemia. Food Nutr Bull. 2008;29:574–585.

[34] World Health Organization. World malaria report [online]. 2017 [accessed 2017 Dec 10]. Available at: http://www.who.int/malaria/publications/country-profiles/en/.

[35] Kanavos P. The rising burden of cancer in the developing world. Ann. Oncol. 2006;17(Suppl. 8):viii15–viii23.

[36] You W, Heemega M. Cancer incidence increasing globally: The role of relaxed natural selection. Evol Appl. 2018;11:140–152.

[37] Voskarides K. Combination of 247 genome-wide association studies reveals high cancer risk as a result of evolutionary adaptation. Mol. Biol. Evol. 2018;35:473–485.
[38] Bourlon C, Vargas-Serafin C, Aguayo A, et al. Multiple myeloma. Experience in a Tertiary Referral Center in Mexico City. Blood. 2015;126:5327.

[39] Perry AM, Debold J, Nathwani BN, et al. Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. Hematologica. 2016;10:1244–1250.

[40] Jeong DC, Chung NG, Kang HJ, et al. Epidemiology and clinical long-term outcome of childhood aplastic anemia in Korea for 15 years: retrospective study of the Korean Society of Pediatric Hematology Oncology (KSPHO). J Pediatr Hematol Oncol. 2011;33:172–178.

[41] Issaragrisil S, Kaufman DW, Anderson T, et al. The epidemiology of aplastic anemia in Thailand. Blood. 2006;107:1299–1307.

[42] Montané E, Ibáñez L, Vidal X, et al. Epidemiology of aplastic anemia: a prospective multicenter study. Haematologica. 2008;93:518–523.

[43] Kojima S. Why is the incidence of aplastic anemia higher in Asia? Expert Rev Hematol. 2017;10:277–279.

[44] Young NS, Issaragrisil S, Chieh CW, et al. Aplastic anaemia in the Orient. Br J Haematol. 1986;62:1–6.

[45] Young NS, Kaufman DW. The epidemiology of acquired aplastic anemia. Haematologica. 2008;93:489–492.

[46] Ferlay, J., et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [online] [accessed 2017 Nov 20]. Available at: http://globocan.iarc.fr.