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Coexistence of mycosis fungoides and essential thrombocythemia with JAK2V617F mutation

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Abstract: Background: The coexistence of myeloproliferative neoplasms (MPNs), specifically essential thrombocythemia and lymphoproliferative neoplasms, are a very rare finding with a frequency < 1%. Case report: We present the case of a woman with diagnosis of mycosis fungoides early stage IB, of 5 months of evolution, she received systemic treatment based on methotrexate orally for 4 months; after this, she started with important thrombocythemia reaching up to 1 200 000/mm^3 platelets and leukocytosis ranging from 10000-13000/mL. A study protocol for chronic myeloproliferative disease was performed, reporting 90% cellular bone biopsy, erythroid myeloid ratio 5:1, 25 megakaryocytes per mm^3 , some with hyperlobed nuclei, and giant nuclei. Karyotype: 46XX. PCR without expression of BCR/ABL. JAK 2 positive. The diagnosis of essential thrombocythemia was concluded. Conclusions: There are several hypotheses seeking to elucidate the etiopathogenesis of the coexistence of myeloproliferative and lymphoproliferative neoplasms, some claim that they are precursors of the same multipotential stem cell, while others support that they are the result of a coincidence. More molecular studies are required to elucidate this unknown.

Key words: thrombocythemia; essential; mycosis fungoides; lymphoma; non-Hodgkin

1 Introduction

The coexistence of myeloproliferative neoplasms (MPNs), specifically essential thrombocythemia, and lymphoproliferative neoplasms is a very rare finding, with an incidence typically less than 1% [1]. There are case reports that have attempted to link the two pathologies; in most cases, these involve MPNs with JAK2V617F expression and chronic lymphocytic leukemia (CLL) [2]. As of 2011, 56 cases had been reported, of which 25 involved coexistence of CLL and chronic myeloid leukemia, 18 involved CLL and polycythemia vera, 12 involved CLL and essential thrombocythemia, and only one involved CLL and primary myelofibrosis [3].

A Greek series of nine cases has recently been published; the type of NPMs varies in all patients and lymphoproliferative neoplasms; the JAK2V617F mutation was detected in six patients, one patient had B-cell monoclonal lymphocytosis, three patients had CLL, three patients had non-Hodgkin lymphoma, one patient had multiple myeloma, and another patient had light-chain and heavy-chain deposition disease [4]. There are other reports of sporadic cases documenting the coexistence of chronic MPNs and plasma cell dyscrasias, as well as non-Hodgkin lymphoma [5,6].

Essential thrombocythemia (ET) falls within the group of NMPs; in the United States, there are records of 2.53 per 100,000 inhabitants [7]; however, it is much less common in people of mixed race than in the Caucasian population [8]. It is characterized by a persistent platelet count greater than 450,000/mm^3; other features of the disease include splenomegaly,

thrombosis, hemorrhage, and a risk of progression to leukemia or secondary myelofibrosis [9]. Its diagnostic criteria were recently evaluated in the WHO review on myeloid neoplasms, which was published in 2016 [10].

Mycosis fungoides is the most common cutaneous T-cell lymphoma, with an incidence of 4 cases per 1 million inhabitants [11], and accounts for nearly 1% of all non-Hodgkin lymphomas [12]. Diagnosis is based on clinical and histopathological criteria; at diagnosis, most patients in early stages present with dermal patches or plaques that may mimic eczema, psoriasis, or other benign dermatological lesions; these lesions frequently appear in areas not exposed to the sun, such as the trunk and hips, and may be hyperpigmented or hypopigmented [13].

Several mutations have been observed that are involved in various pathways regulating the cell cycle, apoptosis, chromatin modification, T-cell signaling pathways, the NF-kB pathway, and the JAK-STAT pathways [14].

2 Clinical case

A 65-year-old woman has had chronic obstructive pulmonary disease for four years and is being treated with oxygen and inhalers; the condition is likely secondary to biomass exposure. She first presented with a non-pruritic, scaly erythematous skin lesion in the pelvic area four years ago, which has since increased in number, predominantly on the lower extremities and chest. For the past two months, she has reported a weight loss of six kilograms.

Physical examination reveals erythematous skin lesions, some with scaly plaques, predominantly on the right hip and both legs.

A biopsy of the skin lesion was performed, revealing patchy parakeratosis and a dermis with a superficial, band-like perivascular infiltrate of atypical lymphocytes, some with a cerebellar appearance and sparse, clear, poorly defined cytoplasm; migration of these lymphocytes into the epidermis (epidermotropism) was observed, forming single-file lines in the basal layer at the dermo-epidermal junction and in some intraepidermal clusters (Pautrier microabscesses). Immunohistochemistry showed CD3+, CD4+, CD5+, CD8+, CD20-, Ki-67 5%, and CD30-negative. This is consistent with a cutaneous T-cell lymphoproliferative process, compatible with mycosis fungoides (Figure 1).

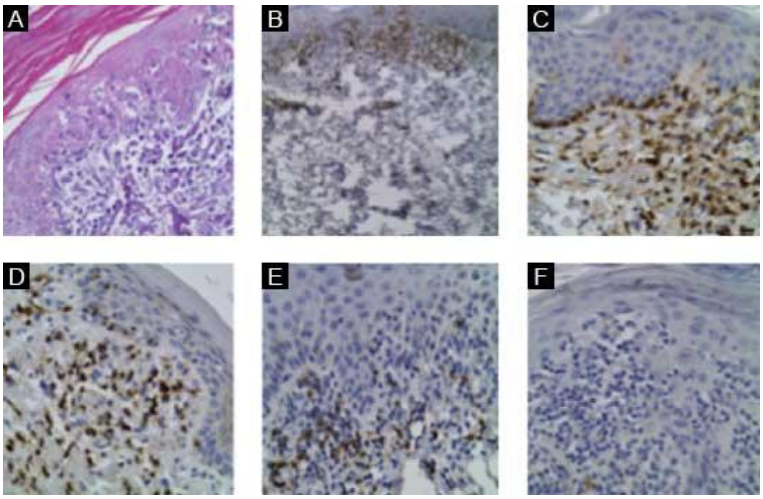

Figure 1. Skin biopsy. A) Hematoxylin and eosin stain, x40: infiltrate of atypical lymphocytes arranged in a band-like pattern in the superficial dermis with epidermotropism. B) CD3+, C) CD4+ in 80%, D) CD5+, E) CD8+ in 20%, F) CD20-

Staging studies were performed, including contrast-enhanced CT scans of the neck, chest, abdomen, and pelvis, as well as a bone biopsy and bone marrow aspiration, concluding a stage IB diagnosis.

The patient received treatment consisting of 12.5 mg of methotrexate orally once weekly, in addition to prednisone (1 mg/kg/day) for one month, with tapering doses. She responded satisfactorily to this regimen, with a reduction of more than

90% in cutaneous lesions and resolution of systemic symptoms three months after starting treatment.

Five months after diagnosis, the patient developed thrombocytosis, with platelet counts reaching 1,200,000/mm³and leukocytosis ranging from 10,000 to 13,000/mL; consequently, a protocol was initiated to rule out chronic myeloproliferative disease. Peripheral blood smears show 10–11 per field, platelet aggregates +++, segmented 78%, lymphocytes 16% (less than 5% cleaved), eosinophils 3%, young granulocytes 1%. The bone marrow aspirate showed +++ cellularity, heterogeneous, with 25–30 megakaryocytes per field. Upon immersion, normoblasts 15%, lymphocytes 12%, mature granulocytes 54%, immature granulocytes 18%, blasts 1% (Figures 2 and 3). The bone biopsy showed 90% cellularity, a myeloid-erythroid ratio of 5:1, 25 megakaryocytes per cubic millimeter, some with hyperlobed nuclei, and giant nuclei (Figure 4). Karyotype: 46XX. PCR showed no BCR/ABL expression. Additionally, a JAK2V617F mutation study was performed using specific probes, yielding a positive result (Figure 5).

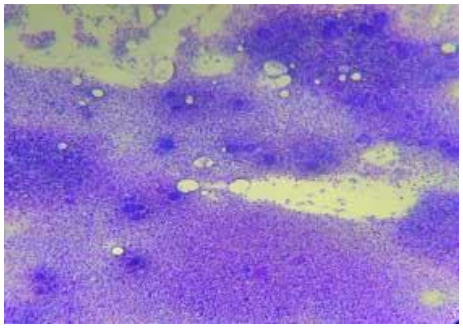

Figure 2. Bone marrow aspirate with Wright stain, 10X magnification, cellularity 25–30 megakaryocytes per field

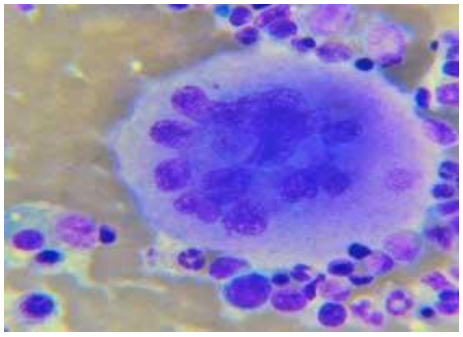

Figure 3. Bone marrow aspirate with Wright stain, 100X magnification, hyperlobed giant megakaryocyte

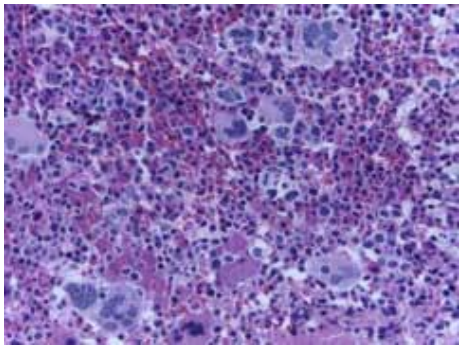

Figure 4. Bone marrow biopsy with hematoxylin-eosin staining, showing 90% cellularity with megakaryocytic hyperplasia. Large, hyperlobed megakaryocytes, with some lobes separated

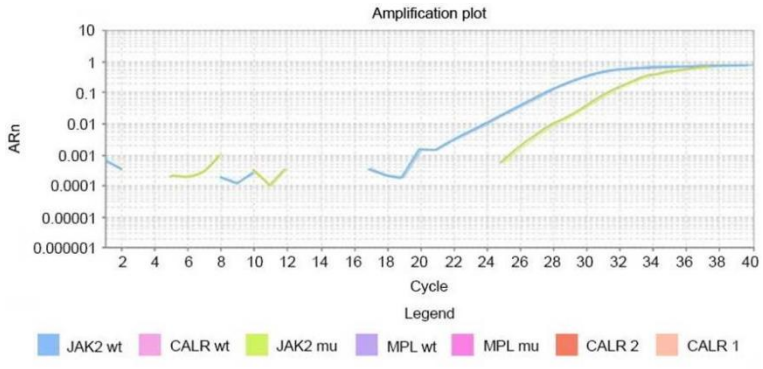

Figure 5. Amplification of the JAK2 gene is detected using specific TaqMan probes

3 Discussion

The coexistence of NMPs and lymphoproliferative neoplasms is uncommon; however, an increasing number of case reports and even case series have been published. It is likely that a relationship exists during their biological development; furthermore, it has been documented that there is up to a threefold increased risk of developing lymphoid neoplasms in a patient with Ph- NMPs harboring a JAK2 gene mutation. And in the specific case of CLL, the risk is 12 times higher [15]. In most reported cases, there is mention of a lymphoproliferative disorder that follows the diagnosis of MPNs some time later, which differs from our case report, where the lymphoproliferative neoplasm preceded the MPN.

There are several theories, and, as mentioned earlier, the JAK gene mutation can be found in both neoplasms.

The JAK (tyrosine kinase) enzyme family includes JAK1, JAK2, JAK3, and TYK2. The JAK2 enzyme is the only one capable of mediating growth signaling for the three myeloid receptors: erythropoietin, granulocyte colony-stimulating factor receptor, and thrombopoietin; These enzymes are essential for growth factor signaling and exert their effect through the phosphorylation of transcription factors called signal transducers and activators of transcription (STAT) in the JAK-STAT pathway. This pathway is one of the main mechanisms by which growth factors and cytokine receptors transduce intracellular signals; this mechanism regulates proliferation, differentiation, migration, apoptosis, and cell survival [16].

The JAK2V617F mutation results from the substitution of two amino acids: valine for phenylalanine at codon 617 of the JAK2 gene, located on chromosome 9. This confers constitutive activation of JAK kinase activity, resulting in uncontrolled cell proliferation [17].

The JAK2V617F mutation arises in a multipotent hematopoietic progenitor cell; it is present in all myeloid lineages and can also be detected in lymphoid cells, primarily B cells, NK cells, and more rarely in T cells [18]. While gain-of-function in the JAK-STAT pathway has also been documented in patients with mycosis fungoides/Sézary syndrome, it occurs more frequently in the tumor stage and only sporadically in the plaque or patch stages; however, further studies are needed to corroborate the association between STAT dysregulation and the presence of mycosis fungoides [19,20]. There are two hypotheses regarding the existence of this rare entity: the first is that these two neoplasms originated from a common progenitor, a theory supported by the presence of the JAK2V617F mutation in both myeloid and lymphoid cells.

Another hypothesis is that they are two independent diseases, originating from different progenitors and with different etiopathogenic pathways. To support this hypothesis, the criterion should be the absence of the JAK2V617F mutation in the lymphoid lineage [2].

There is literature that leans toward a common progenitor with a mutation in the with the addition of subsequent molecular events, precursors of myeloid and lymphoid proliferation, allowing the emergence of two hematologic neoplasms of identical origin but of different lineages [21].

Regarding treatment in patients with essential thrombocythemia, we know that it depends on the thrombotic risk factors the patient has; the IPSET-thrombosis model (International Prognostic Score for Thrombosis in Essential Thrombocythemia) has been used, which incorporates: age over 60 years, previous thrombotic events, and the presence or absence of the JAK2V617F mutation [22], only high-risk patients will require first-line therapy with hydroxyurea, interferon-alpha-2, or anagrelide [23]. Whereas in patients with mycosis fungoides we have more therapeutic options, ranging from topical treatments in early clinical stages to systemic treatments such as methotrexate, vorinostat, interferon, brentuximab, and combination chemotherapies such as EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone), etc.; there is no treatment of choice among these therapies, as the optimal therapy for each patient must be individualized [24].

There is no evidence that any single therapy benefits both of these conditions.

4 Conclusion

Two hematologic neoplasms of myeloid and lymphoid lineage are described in the same patient; there are hypotheses suggesting that these hematologic neoplasms may arise from the same multipotent progenitor cell, while others maintain that it is a coincidence. Further molecular studies are required to resolve this question.

Perhaps, in the future, the documentation of more cases may provide guidance for improved treatment.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] Hauck G, Jonigk D, Kreipe H, Hussein K. Simultaneous and sequential concurrent myeloproliferative and lymphoproliferative neoplasms. Acta Haematol. 2013;129(3):187-96.

[2] Mousinho F, Santos PSE, Azevedo AP, Pereira JM, Lemos R, Matos S, et al. Concomitant myeloproliferative and lymphoproliferative neoplasms, distinct progenitors: A case report and review of the literature. Mol Clin Oncol. 2018;9(3):347-9.

[3] Laurenti L, Tarnani M, Nichele I, Ciolli S, Cortelezzi A, Forconi F, et al. The coexistence of chronic lymphocytic leukemia and myeloproliperative neoplasms: a retrospective multicentric GIMEMA experience. Am J Hematol. 2011;86(12):1007-12.

[4] Bouchla A, Thomopoulos T, Papageorgiou S, Tsirigotis P, Bazani E, Gkirkas K, et al. Coexistence of Myeloid and Lymphoid Neoplasms: A Single-Center Experience. Adv Hematol. 2019;2019:1486476.

[5] Malhotra J, Kremyanskaya M, Schorr E, Hoffman R, Mascarenhas J. Coexistence of myeloproliferative neoplasm and plasma-cell dyscrasia. Clin Lymphoma Myeloma Leuk. 2014;14(1):31-6.

[6] Hernández-Boluda JC, Cervantes F, Alvarez A, López-Guillermo A, Montserrat E. Non-Hodgkin's lymphoma following untreated essential thrombocythemia. Leuk Lymphoma. 2000;36(3-4):421-3.

[7] Mesa RA, Silverstein MN, Jacobsen SJ, Wollan PC, Tefferi A. Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976-1995. Am J Hematol. 1999;61(1):10-5.

[8] Ruiz-Argüelles GJ, López-Martínez B, Lobato-Mendizábal E, Ruiz-Delgado GJ. An addition to geographic hematology: chronic myeloproliferative diseases are infrequent in Mexican Mestizos. Int J Hematol. 2002;75(5):499-502.

[9] Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2019 update on diagnosis, risk-stratification and management. Am J Hematol. 2019;94(1):133-43.

[10] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World

Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.

[11] Wilson LD, Hinds GA, Yu JB. Age, race, sex, stage, and incidence of cutaneous lymphoma. Clin Lymphoma Myeloma Leuk. 2012;12(5):291-6.

[12] González-Ramírez RA, Ocampo-Candiani J, Méndez-Olvera N, Gómez-Flores M. Micosis fungoides: biología y terapéutica. Derma Cosmética y Quirúrgica. 2006;4(4):278-287.

[13] Foss FM, Girardi M. Mycosis Fungoides and Sezary Syndrome. Hematol Oncol Clin North Am. 2017;31(2):297-315.

[14] Berg S, Villasenor-Park J, Haun P, Kim EJ. Multidisciplinary Management of Mycosis Fungoides/Sézary Syndrome. Curr Hematol Malig Rep. 2017;12(3):234-43.

[15] Vannucchi AM, Masala G, Antonioli E, Chiara-Susini M, Guglielmelli P, Pieri L, et al. Increased risk of lymphoid neoplasms in patients with Philadelphia chromosome-negative myeloproliferative neoplasms. Cancer Epidemiol Biomarkers Prev. 2009;18(7):2068-73.

[16] Saeidi K. Myeloproliferative neoplasms: Current molecular biology and genetics. Crit Rev Oncol Hematol. 2016;98:375-89.

[17] Shammo JM, Stein BL. Mutations in MPNs: prognostic implications, window to biology, and impact on treatment decisions. Hematol Am Soc Hematol Educ Program. 2016;2016(1):552-560.

[18] Vainchenker W, Kralovics R. Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. Blood. 2017;129(6):667-79.

[19] Bastidas-Torres AN, Cats D, Mei H, Szuhai K, Willemze R, Vermeer MH, et al. Genomic analysis reveals recurrent deletion of JAK-STAT signaling inhibitors HNRNPK and SOCS1 in mycosis fungoides. Genes Chromosomes Cancer. 2018;57(12):653-64.

[20] Sommer VH, Clemmensen OJ, Nielsen O, Wasik M, Lovato P, Brender C, et al. In vivo activation of STAT3 in cutaneous T-cell lymphoma. Evidence for an antiapoptotic function of STAT3. Leukemia. 2004;18(7):1288-95.

[21] Tabaczewski P, Nadesan S, Lim SH. Zap-70 positive chronic lymphocytic leukemia co-existing with Jak 2 V671F positive essential thrombocythemia: a common defective stem cell? Leuk Res. 2009;33(6):854-5.

[22] Haider M, Gangat N, Lasho T, Abou-Hussein AK, Elala YC, Hanson C, et al. Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients. Am J Hematol. 2016;91(4):390-4.

[23] Tefferi A, Pardanani A. Essential Thrombocythemia. N Engl J Med. 2019;381(22):2135-44.

[24] Foss FM, Girardi M. Mycosis Fungoides and Sezary Syndrome. Hematol Oncol Clin North Am. 2017;31(2):297-315.