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Letter to the Editor

Burkitt Lymphoma as Fourth Neoplasia in a Patient Affected by Cowden Syndrome with a Novel PTEN Germline Pathogenic Variant

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To the editor.

Alterations of the PTEN pathway play a role in the pathogenesis of some aggressive non-Hodgkin B cell lymphomas and other cancers, while germline PTEN mutations predispose to the cancer-associated Cowden syndrome (CS).

Lymphoproliferative neoplasms are not part of the diagnostic criteria for CS, and so far, few cases of lymphomas have been reported in CS patients. We describe the case of a patient with Cowden syndrome sustained by a novel germline pathogenic variant of PTEN, affected, as fourth neoplasia, by Burkitt lymphoma. To the best of our knowledge, this is the first case of Burkitt lymphoma reported in a patient with Cowden Syndrome. Here we describe the case and provide a summary of possible molecular implications of this genetic disorder on the pathogenesis of this peculiar type of lymphoma.

Cowden syndrome is a rare, multisystem disease characterized by hamartomas, macrocephaly, Lhermitte-Duclos disease (a dysplastic gangliocytoma of the cerebellum), mucocutaneous lesions and many types of cancer, mainly involving breast, thyroid, and uterus. Germline pathogenic variants of the phosphatase and tensin homolog (PTEN) gene were detected in about 30% to 35% of patients meeting consensus diagnostic criteria for CS.[1]

PTEN plays a tumor-suppressing function, mainly relying on a protein phosphatase activity and subsequent antagonism of the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway. Besides, PTEN has a critical role in the regulation of genomic instability, DNA repair, stem cell self-renewal, cellular senescence, and cell migration.

The patient we describe was a 57 years old woman who presented to the Emergency Department of our Hospital for worsening fatigue, abdominal pain, and dyspnea. Her past medical history was notable for diagnosis of dysplastic cerebellar gangliocytoma at the age of 46 treated with surgery, multifocal bilateral papillary thyroid carcinoma at the age of 47 treated with thyroidectomy, and ductal infiltrating breast cancer at the age of 51 treated with left quadrantectomy and axillary node biopsy, followed by chemotherapy and radiotherapy. Further, the patient was a carrier of multiple mucocutaneous nodules, bilateral renal cysts, and oral and gastro-duodenal micro-polyposis.

Blood cell counts revealed mild anemia, thrombocytopenia, 1% of blasts, and atypical lymphoid elements. LDH level was elevated. CT scan showed supra- and sub-diaphragmatic lymphadenopathies, splenomegaly, ascites, left hydronephrosis, peritoneal carcinosis, and bilateral adnexal mass (7 cm in the largest diameter on the right and 5 cm on the left). Bone marrow aspirate and biopsy showed massive infiltration of atypical cells with a medium to large size and cytoplasmic vacuoles. This cell population had a mature B cell phenotype in flow cytometry (including bright expression of CD20, positivity for CD10, and clonal restriction for lambda light chain). Immunohistochemical staining of the bone marrow biopsy showed infiltration by a population of blasts that were CD20/PAX-5/BCL-6/CD10 positive and strongly expressed c-MYC, while BCL-2 and MUM-1 expression were negative. The immunohistochemical findings were consistent with the diagnosis of Burkitt lymphoma.

Due to high suspicion of a genetic disorder, the patient underwent genetic counseling leading to the clinical diagnosis of Cowden Syndrome. Consequently, molecular analysis of the *PTEN* gene was performed and a novel variant on exon 5 of *PTEN*, c.335T>G p.(Leu112Arg), was found in a heterozygous state. PTEN gene sequencing was performed by PCR DNA amplification followed by the analysis of the coding sequence and intronic regions of the PTEN gene.

Once the diagnosis of Burkitt lymphoma was established, we began chemoimmunotherapy according

to GMALL-B-ALL/NHL2002 scheme (pre-phase followed by cycle A1) on day 1 from admission. The patient developed infectious complications as neutropenic fever and herpes zoster in thoracic dermatomes. At the time of neutrophil recovery, pulmonary conditions worsened with the need for non-invasive ventilation, but unfortunately, the patient died by multiorgan failure 31 days from diagnosis.

Following family counseling, we found that the 34 years old son of the patient carried the same *PTEN* variant. He presented with macrocephaly (head circumference 59.8 cm, + 2.5 SD; height 174 cm, - 1 SD), multinodular goiter, multiple hyperpigmented cutaneous nodules, and intestinal polyps, with no personal history of malignancies. Cancer surveillance was planned according to the current guidelines.

The described PTEN variant on exon 5 of PTEN, c.335T>G p. (Leu112Arg), is classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) criteria: it is considered of moderate evidence of pathogenicity (PM) since it is located within a critical functional domain in which no benign variants have been previously described (PM1), it is absent in online population databases (PM2), and it affects the same amino acid residue where different pathogenic changes have been observed before (PM5); furthermore, it supports evidence of pathogenicity (PP) because the patient's phenotype is highly specific for the disease (PP4).[2] Identifying this mutation will have important implications for personalized genetic health care. Through phenomic-based research, the spectrum of phenotypes associated with germline PTEN mutations is continually evolving, and these are collectively termed the PTEN hamartoma tumor syndromes (PHTS).

Deregulation of PTEN activity and its functional impact on the PI3K pathway is likely to have contributed to lymphomagenesis in our patient, as there are several lines of evidence for a role of PTEN deregulation in Burkitt and other aggressive lymphomas of germinal center origin. Several mechanisms, as mutation, deletion, transcriptional silencing, or protein instability, have been described to produce a loss of PTEN function in a variety of human cancers, including lymphoproliferative neoplasms.[3]

Although the genetic hallmark of Burkitt lymphoma is the rearrangement of the MYC oncogene to the locus of immunoglobulin (Ig) genes, which results in constitutive MYC overexpression, additional recurrent variants targeting the phosphatidylinositol-3-kinase (PI3K) pathway are frequent. Mutations in genes codifying for TCF3 protein and its negative regulator ID3 have been reported in up to 70% of Burkitt lymphoma bearing pathogenic variants in one or both the genes. TCF3 upregulates components of the B-cell receptor (BCR) pathway leading to activation of the PI3K pathway through 'tonic' non-NF-kB dependent BCR signaling.[4]

It is well established that PTEN loss is inversely correlated with the constitutive activation of the PI3K/AKT signaling pathway. Inhibition of PI3K/AKT with either PTEN re-expression or PI3K inhibition significantly reduced proliferation rate and downregulated MYC expression, suggesting that PTEN loss leads to the upregulation of MYC through the constitutive activation of PI3K/AKT. Signaling through PI3K may also be involved in stabilizing MYC through the regulation of GSK3β activity. The amino-terminus transactivation domain of c-MYC contains two conserved, functionally critical MYC family regions called box 1 and box 2. Box 1 contains phosphorylation sites involved in the proteolysis ofc-MYC by the ubiquitin-proteasome pathway:[5,6] one of these sites is Thr58, and it is a target of glycogen synthase kinase (GSK)3β phosphorylation. The MYC p-Thr58 modification, mediated by GSK3β and required for MYC degradation, can be blocked via PI3K-dependent inhibitory phosphorylation of GSK3β on Ser9. Potentially, constitutive PI3K activation in BL carrying wild type MYC would help promote its stability and may contribute to its tumorigenic effects. The loss-of-function protein encoded by our PTEN variant cannot dephosphorylate PI3K, which consequently, with GS3K beta phosphorylation, will not lead MYC towards proteasomal degradation.[7]

Overexpression of MYC may further contribute to the activation of PI3K through the MYC dependent induction of microRNAs associated with PI3K activation through their inhibitory effect on PTEN, in particular the miR17-92 cluster.[8] MicroRNAs might also contribute to the deregulation of PTEN expression in Burkitt lymphoma.

As the reported PTEN gene variant at exon 5 (c.335T>G) was not previously described, no available studies are helping us to explain why it may have been responsible for the Cowden Syndrome phenotype associated with BL. However, we can hypothesize that the variant found at exon 5 (c.335T>G) resulting in leucine to arginine change at codon 112 may have lead to loss-of-function of the PTEN protein, thus contributing to the hyperactivation of the PI3K-AKT pathway, which is frequent in BL. Indeed, the signaling network in which the PTEN transcript is involved is much more complicated. We know that MYC deregulation in BL contributes to PI3K activation by driving expression of MIR17HG, the precursor RNA for miR-19, an inhibitor of PTEN expression. Perhaps the mRNA that derives from c.335T>G PTEN gene is more sensitive to the inhibition of miR-19, thus contributing to the PI3K-AKT pathway hyperactivation and to the resulting tumoral growth of pathological lymphocytes in the dark areas of the germinal center.

In conclusion, the development of a Burkitt

lymphoma in a patient with Cowden Syndrome and germline PTEN pathogenic variant supports the potential role of PTEN and PI3K pathway in the pathogenesis of Burkitt lymphoma.

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References:

1. Pilarski R, Stephens JA, Noss R, Fisher JL, Prior TW. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet 2011 Aug 1 https://doi.org/10.1136/jmg.2011.088807 PMid:21659347
2. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May 5 https://doi.org/10.1038/gim.2015.30 PMid:25741868 PMCid:PMC4544753
3. Wang X, Huang H, Young KH. The PTEN tumor suppressor gene and its role in lymphoma pathogenesis. Aging (Albany NY) 2015 Dec 10 https://doi.org/10.18632/aging.100855 PMid:26655726 PMCid:PMC4712330
4. Schmitz R, Young RM, Ceribelli M, Jhavar S, Xiao W, Zhang M, et al. Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. Nature 2012 Oct 4
5. Kuttler F, Amé P, Clark H, et al. c-myc box II mutations in Burkitt's lymphoma-derived alleles reduce cell-transformation activity and lower response to broad apoptotic stimuli. Oncogene 2001;20(42): 6084-6094. https://doi.org/10.1038/sj.onc.1204827 PMid:11593416
6. Sears R, Nuckolls F, Haura E, Taya Y, Tamai K, Nevins JR. Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. Genes Dev 2000;14(19):2501-2514. https://doi.org/10.1101/gad.836800 PMid:11018017 PMCid:PMC316970
7. Lindsay C Spender Gareth J Inman. Developments in Burkitt's lymphoma: novel cooperations in oncogenic MYC signaling. Cancer Management and Research 2014
8. Kaymaz Y, Oduor CI, Yu H, Otieno JA, Ong' echa JM, Moormann AM, et al. Comprehensive Transcriptome and Mutational Profiling of Endemic Burkitt Lymphoma Reveals EBV Type-Specific Differences. Mol Cancer Res. 2017 May https://doi.org/10.1158/1541-7786.MCR-16-0305 PMid:28465297