Instituto Nacional de Cancerología

Dual Genetic Anomalies: FIP1L1-PDGFRA–Positive Chronic Eosinophilic Leukemia and 48, XXYY Karyotype in a Female With Mucinous Ovarian Carcinoma

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Context

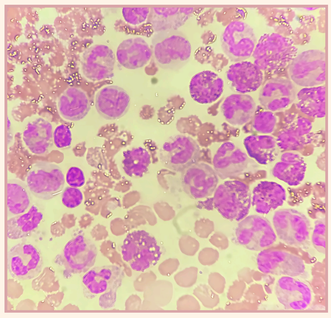
Chronic eosinophilic leukemia is a rare hematological disorder characterized by persistent eosinophilia and organ damage from inflammatory mediators.

The FIP1L1-PDGFRA fusion gene, resulting from a deletion on chromosome 4q12, is present in 5%–15% cases and creates a constitutively active tyrosine kinase that transforms hematopoietic cells.

48,XXYY syndrome is an extremely rare sex chromosome aneuploidy (estimated 1:18,000–40,000 male births) typically associated with male phenotypes, neurocognitive issues, and increased risk of certain health conditions.

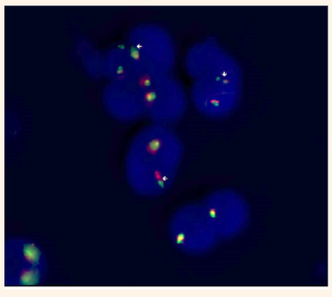
We present an unprecedented case of a phenotypic female with mucinous ovarian carcinoma harboring both genetic anomalies: FIP1L1-PDGFRα fusion and a 48,XXYY karyotype

Case Presentation

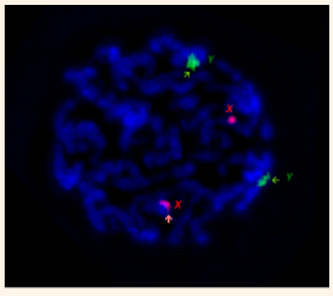


A 23-year-old female diagnosed with stage IIIC mucinous ovarian carcinoma with signet ring cells was referred to hematology for moderate WHO-defined microcytic, hypochromic anemia with hypoproliferative features of mixed etiology (inflammatory and iron deficiency).
The patient presented with fever of undetermined origin, persistent leukocytosis with neutrophilia, and marked hypereosinophilia (eosinophil count, 11–13.5×109/L) for 1 month.
Extensive workup ruled out infection, allergies, lung disease, and autoimmune conditions.
Computed tomography revealed hepatic metastases with elevated liver enzymes, though it remained unclear whether this represented carcinomatous infiltration or eosinophilic involvement.

Bone marrow aspiration demonstrated hypercellularity with myeloid predominance, featuring neutrophils with pseudo–Pelger-Huët anomaly and decreased granulation, increased eosinophils, monocytes, and erythroid precursors.



The photograph shows interphase nuclei obtained from a bone marrow sample in which the FISH hybridization technique (fluorescence in situ hybridization) was applied for the detection of the PDGFRA and FIP1L1 genes. The labeling product shows a positive pattern with abnormality in the copy number of both genes, as three copies of each locus are found. A structural abnormality is also observed when the separate signals corresponding to the PDGFRA and FIP1L1 genes are found, which leads to a translocation pattern. The image describes the interphase nuclei in blue (product of the nuclear marker), the green marks correspond to the region comprising the PDGFRA and FIP1L genes joined by the red-marked region that delimits the CHIC2 gen Interphase fluorescence in situ hybridization (fish) analysis in bone marrow cells using the probe cocktail for the detection of the fip1l1/pdgfra fusion gene (fusion results from an approximately 800 kb interstitial chromosomal deletion that includes the cysteine-rich hydrophobic domain 2 [CHIC2] locus). The result obtained from the analysis indicates that 20% of the cells analyzed carry structural and numerical alterations in the FIP1L1, CHIC2 and PDGFRA genes, 5% carry a single copy of the FIP1L1, CHIC2 and PDGFRA genes (4q12 deletion), 5% of the FIP1L1, CHIC2 and PDGFRA genes (trisomy of chromosome 4) and another 5% show separation of the FIP1L1 gene (suggests translocation, however, the final product is unknown).



FISH analysis was also performed on interphase nuclei of the bone marrow, since we did not obtain an adequate mitotic index for chromosomal assessment, we decided to corroborate the presence of sexual sequences to classify with FISH nomenclature. The result obtained from the labeling of the regions corresponding to the regions of the sexual chromosomes (centomere of the X chromosome with orange mark / heterochromatin of the Y chromosome with green mark) in which it would be expected to find that a Female with normal female cells would observe two unique orange patterns (2O), However, a male pattern characterized as XXYY was observed. This result was analyzed in five thousand cells. We could only corroborate this pattern in peripheral blood and bone marrow but not in tissue.

Conclusion

This presentation is an exceedingly rare convergence of genetic anomalies: a FIP1L1-PDGFRα–positive myeloproliferative neoplasm and 48,XXYY karyotype in a phenotypic female with ovarian carcinoma.
While 48,XXYY typically manifests in males with distinctive physical and cognitive characteristics, only one previous case of this karyotype has been reported in a phenotypic female.
The mechanistic relationship between these genetic findings and the patient's malignancy remains unclear.
We hypothesize that it may involve disruption of shared signaling pathways, particularly MAPK signaling, which is implicated in both FIP1L1-PDGFRα activity and sex phenotype expression in 48,XXYY patients.
This case highlights the clinical implications and importance of comprehensive genetic evaluation in patients with unusual presentations.

References

Cools, J., DeAngelo, D. J., Gotlib, J., Stover, E. H., Legare, R. D., Cortes, J., ... & Gilliland, D. G. (2003). A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. New England Journal of Medicine, 348(13), 1201-1214.
Gotlib, J., Cools, J., Malone, J. M., Schrier, S. L., Gilliland, D. G., & Coutré, S. E. (2004). The FIP1L1-PDGFRα fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. Blood, 103(8), 2879-2891.
Klion, A. D., Robyn, J., Akin, C., Noel, P., Brown, M., Law, M., ... & Fauci, A. S. (2004). Molecular remission and reversal of myelofibrosis in response to imatinib mesylate treatment in patients with the myeloproliferative variant of hypereosinophilic syndrome. Blood, 103(2), 473-478.
Anglesio, M. S., Kommoss, S., Tolcher, M. C., Clarke, B., Galletta, L., Porter, H., ... & Huntsman, D. G. (2013). Molecular characterization of mucinous ovarian tumours supports a stratified treatment approach with HER2 targeting in 19% of carcinomas. Journal of Pathology, 229(1), 111-120.
Lim, D., & Oliva, E. (2013). Precursors and pathogenesis of ovarian carcinoma. Pathology, 45(3), 229-242.

Photographs obtained with Metasystems (IKAROS/ISIS) Zeiss. Cytogenetics and Molecular Biology Laboratory of the Hematological Diagnostic and Support Unit of the Instituto Nacional de Cancerología (Mexico).