EDITORIAL

Updates into the potential association between myeloproliferative neoplasms and inflammatory bowel disease

Adeniyi Abraham Adesola[1], Yongfeng Chen[2], Matei Alexandru Cozma[3,4], Mihnea-Alexandru Găman[3,5,6]

Inflammatory bowel disease (IBD) and myeloproliferative neoplasms (MPNs) are both chronic disorders in whose pathogenesis low-grade chronic inflammation plays a central contribution.[1-3] IBD is characterised by chronic inflammation of the digestive tract, while MPNs are characterized by an overproduction of terminally differentiated myeloid cells.[1,3] IBD may present itself mainly as ulcerative colitis (UC) or Crohn's disease (CD) while the classical Philadelphia-negative MPNs comprise polycythemia vera (PV), essential thrombocythemia (ET) and primary/secondary myelofibrosis (MF).[1,3] A recent cohort study found that subjects with MPNs have a 2.4-fold increased risk of developing IBD compared to individuals without MPNs. The risk of developing IBD was highest within the first year after the diagnosis of MPN and after five years of being diagnosed with an MPN. However, there was a lower risk of developing IBD between the first year and fifth year of being diagnosed with an MPN.[4] These findings suggest that there may be a common underlying mechanism that drives the pathogenesis of both IBD and MPNs. Moreover, alterations of the gut microbiome have been described both in MPNs and IBD, possibly in direct relationship with the high concentrations of pro-inflammatory cytokines measured in these disorders.[1,5]

Another common pathogenetic mechanisms linking IBD and MPNs is autoimmunity. In a study conducted to assess the risk of MPNs in patients with a background of autoimmune diseases, a prior history of autoimmune disease was associated with increased risk of MPNs. CD, but not UC, was specifically associated with a 2-to-3-fold elevated risk for subsequent MPNs.[6] This is similar to findings of Jess et al. who found out that CD patients are at increased risk of lymphoma with no significant risk found in UC.[7] Implicitly, this suggests that individuals living with immune-related diseases are at risk for subsequent MPNs. It has been postulated that a disruption of the JAK2 signalling pathway may be involved in the crosstalk established between CD and MPNs.[8] For example, the detection of the rs10758669 polymorphisms of the JAK2 gene has been demonstrated to elevate the risk of both CD and UC, especially in Caucasian individuals.[9] Moreover, an investigation which aimed to assess the likelihood of cancer in IBD with an onset in the elderly detected no significant risk of colorectal cancer, however, there was an overall increased risk of haematological malignancies, specifically lymphoproliferative and myeloproliferative disorders. Several subjects with UC and CD developed PV, MF, chronic myeloid leukaemia, as well as acute myeloid leukaemia at higher rates versus those predicted for the general population.[10]

Several case reports have documented the coexistence of IBD and MPNs, suggesting a potential link between these two conditions.[11] Literature describes the co-existence of UC and MF, as well as UC and PV complicated by Budd-Chiari syndrome, a thrombotic complication highly suggestive of MPNs.[12,13] Thrombosis is another common feature of both MPNs and IBD which can occur in the context of the prothrombotic status of the disease itself.[14-16] While a causal relationship between the use of biologic therapy and MPN development remains unclear, a case report that documented the emergence of ET after two years of biologic therapy initiation has been published.[17] Moreover, JAK inhibitors have been employed for the management of both IBD and MPNs, e.g., filgotinib and upadacitinib for CD, tofacitinib for UC, ruxolitinib and other JAK inhibitors for MPNs.[18,19] Interestingly, Swei et al. have depicted good results with the administration of ruxolitinib as well in an individual diagnosed with UC.[20] However, the therapeutic potential of this pharmacological agent in IBD is not clear and needs further research.

In conclusion, an association between IBD and MPNs has been hypothesized, underscoring the possibility of shared underlying mechanisms or genetic predispositions. While the exact nature of this intricate relationship remains to be elucidated, the growing body of evidence suggests a potential association. Further research is warranted to understand the pathogenetic crosstalk and explore

[1]College of Medicine, University of Ibadan, Nigeria College Research and Innovation Hub, Ibadan, Nigeria; [2]Department of Basic Medical Sciences, School of Medicine of Taizhou University, Taizhou University, Taizhou, Zhejiang Province, China; [3]Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania; [4]Department of Gastroenterology, Colentina Clinical Hospital, Bucharest, Romania; [5]Department of Hematology, Centre of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest, Romania; [6]Department of Cellular and Molecular Pathology, Stefan S. Nicolau Institute of Virology, Romanian Academy, Bucharest, Romania.

therapeutic strategies that may benefit patients with both IBD and MPNs.

Funding Source: Mihnea-Alexandru Găman was supported by the grant funded by Competitiveness Operational Programme A1.1.4. ID: P_37_798 MYELOALEDIAPROT, Grant Agreement no. 149/26.10.2016 (MySMIS2014+: 106774).

DOI:https://doi.org/https://doi.org/10.47391/JPMA.24-60

References

1. Lee M, Chang EB. Inflammatory Bowel Diseases (IBD) and the Microbiome-Searching the Crime Scene for Clues. Gastroenterology. 2021;160:524-537. doi: 10.1053/j.gastro.2020.09.056.
2. Gaman AM, Moisa C, Diaconu CC, Gaman MA. Crosstalk between Oxidative Stress, Chronic Inflammation and Disease Progression in Essential Thrombocythemia. Rev. Chim. 2019;70:3486–3489. doi: 10.37358/RC.19.10.7581.
3. Gaman MA, Cozma MA, Dobrica EC, Cretoiu SM, Gaman AM, Diaconu CC. Liquid Biopsy and Potential Liquid Biopsy-Based Biomarkers in Philadelphia-Negative Classical Myeloproliferative Neoplasms: A Systematic Review. Life (Basel). 2021;11:677. doi: 10.3390/life 11070677.
4. Bak M, Jess T, Flachs EM, Zwisler AD, Juel K, Frederiksen H. Risk of Inflammatory Bowel Disease in Patients with Chronic Myeloproliferative Neoplasms: A Danish Nationwide Cohort Study. Cancers (Basel). 2020 ;12:2700. doi: 10.3390/cancers12092700.
5. Adesola AA, Chen Y, Găman MA. Gut microbiota and myeloproliferative neoplasms. J Pak Med Assoc. 2023;73:2334-2336. doi: 10.47391/JPMA.23-99.
6. Kristinsson SY, Landgren O, Samuelsson J, Björkholm M, Goldin LR. Autoimmunity and the risk of myeloproliferative neoplasms. Haematologica. 2010;95:1216-20. doi: 10.3324/haematol.2009. 020412.
7. Jess T, Horváth-Puhó E, Fallingborg J, Rasmussen HH, Jacobsen BA. Cancer risk in inflammatory bowel disease according to patient phenotype and treatment: a Danish population-based cohort study. Am J Gastroenterol. 2013 ;108:1869-76. doi: 10.1038/ajg.2013.249.
8. Ferguson LR, Han DY, Fraser AG, Huebner C, Lam WJ, Morgan AR, Duan H, Karunasinghe N. Genetic factors in chronic inflammation: single nucleotide polymorphisms in the STAT-JAK pathway, susceptibility to DNA damage and Crohn's disease in a New Zealand population. Mutat Res. 2010;690:108-15. doi: 10.1016/j.mrfmmm. 2010.01.017.
9. Zhang JX, Song J, Wang J, Dong WG. JAK2 rs10758669 polymorphisms and susceptibility to ulcerative colitis and Crohn's disease: a meta-analysis. Inflammation. 2014;37:793-800. doi: 10.1007/s10753-013-9798-5.
10. Cheddani H, Dauchet L, Fumery M, Charpentier C, Marie Bouvier A, Dupas JL, et.al.. Cancer in Elderly Onset Inflammatory Bowel Disease: A Population-Based Study. Am J Gastroenterol. 2016t;111:1428-1436. doi: 10.1038/ajg.2016.304.
11. Arellano-Rodrigo E, Esteve J, Giné E, Panés J, Cervantes F. Idiopathic myelofibrosis associated with ulcerative colitis. Leuk Lymphoma. 2002 ;43:1481-3. doi: 10.1080/1042819022386590.
12. Vassiliadis T, Mpoumponaris A, Giouleme O, Hatzidakis A, Patsiaoura K, Zezos P,et.al. Late onset ulcerative colitis complicating a patient with Budd-Chiari syndrome: a case report and review of the literature. Eur J Gastroenterol Hepatol. 2009 ;21:109-13. doi: 10.1097/MEG.0b013e32830263cb.
13. Găman MA, Cozma MA, Manan MR, Srichawla BS, Dhali A, Ali S,et.al. Budd-Chiari syndrome in myeloproliferative neoplasms: A review of literature. World J Clin Oncol. 2023;14:99-116. doi: 10.5306/wjco. v14.i3.99.
14. Cheng K, Faye AS. Venous thromboembolism in inflammatory bowel disease. World J Gastroenterol. 2020;26:1231-1241. doi: 10.3748/ wjg.v26.i12.1231.
15. Olivera PA, Zuily S, Kotze PG, Regnault V, Al Awadhi S, Bossuyt P,et.al. International consensus on the prevention of venous and arterial thrombotic events in patients with inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021;18:857-873. doi: 10.1038/s41575-021-00492-8.
16. Moisa C, Gaman MA, Diaconu CC, Gaman AM. Oxidative Stress Levels, JAK2V617F Mutational Status and Thrombotic Complications in Patients with Essential Thrombocythemia. Rev. Chim. 2019;70:2822–2825. doi: 10.37358/RC.19.8.7435.
17. Fischer M, Helper DJ, Chiorean MV. Myeloproliferative disorders in patients with inflammatory bowel disease on anti-TNF-α therapy: report of two cases and review of the literature. Inflamm Bowel Dis. 2011;17:674-5. doi: 10.1002/ibd.21291.
18. Feagan BG, Danese S, Loftus EV Jr, Vermeire S, Schreiber S, Ritter T, et.al. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial. Lancet. 2021;397:2372-2384. doi: 10.1016/ S0140-6736(21)00666-8.
19. Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, et.al. Efficacy of Upadacitinib in a Randomized Trial of Patients With Active Ulcerative Colitis. Gastroenterology. 2020;158:2139-2149.e14. doi: 10.1053/j.gastro.2020.02.030.
20. Swei EC, Fox CM, Bowles DW, Rizeq MN, Onyiah JC. Use of Ruxolitinib for the Simultaneous Treatment of Severe Refractory Ulcerative Colitis and Polycythemia Vera. ACG Case Rep J. 2022;9:e00741. doi: 10.14309/crj.0000000000000741.