Myeloid neoplasms in inflammatory bowel disease: A case series and review of the literature

David M. Mueller [a],[1], Daniel I. Nathan [b],[1], Angela Liu [b], John Mascarenhas [b], Bridget K. Marcellino [b],[*]

[a] *Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, United States*
[b] *Tisch Cancer Institute, Division of Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, United States*

ABSTRACT

Patients with inflammatory bowel disease (IBD) are exposed to chronic systemic inflammation and are at risk for secondary malignancies. Here we review the literature on the risk of myeloid neoplasms (MN) in IBD and present the disease profiles of patients at a single institution with IBD who later developed MN, comparing them to those in the literature. No IBD characteristic was found to associate with MN disease severity, including the previously-identified association between MNs and thiopurine exposure. Of the somatic mutations identified in out cohort's MN, mutations in *TET2* were most prevalent, followed by *FLT3-ITD, BCR-ABL,* and *NPM1* mutations.

1. Introduction and literature review

We reviewed articles indexed in PubMed examining the nature of the relationship between inflammatory bowel disease (IBD) and myeloid neoplasms (MN). IBD is known to be associated with an increased risk of cancer, overall [1]. The general risk of malignancy in IBD is estimated to be 690.2 per 100,000 person-years (an increased incidence rate of 1.29 compared with the non-IBD population), with the risk in Crohn's disease (CD) greater than ulcerative colitis (UC) [1]. Colorectal cancer is the most strongly associated malignancy with IBD. One meta-analysis of IBD cases worldwide between the years 1990 and 2014 calculated the incidence rate of colorectal cancer in CD as 53.3 per 100,000 person-years [2]. Extra-intestinal malignancies such as those of the liver and biliary tract are also commonly encountered, as are lymphomas and MN [1,2]. Advances in colorectal cancer screening with widespread implementation seem to have lessened the incidence burden of colorectal cancer [3]. As a consequence of lower rates of colorectal cancer in the IBD population, lymphoid and myeloid neoplasms have emerged as secondary malignancies of concern.

The true incidence of MN in IBD is unclear. Most studies of malignancies in IBD have identified an increased risk of MN as well as lymphomas, though some have failed to find rates above the general population [1,2,4]. One meta-analysis found the combined incidence of leukemia and multiple myeloma to be 17.1 per 100,000 person-years in IBD (14.1 for CD and 20.3 for UC) [1]. A separate meta-analysis found the incidence of leukemia in IBD to be 1.5 per 100,000 person-years (0.3 in CD and 13 in UC) and the incidence of lymphoma in CD to be 0.8 per 100,000 person-years, which were not considered to be above the general population [2]. Another investigation found that IBD increased relative incident risk of acute myeloid leukemia (AML) by 20 % [4]. Overall, while mixed, most surveys have identified an increased risk of MN with IBD.

Initial investigations implicated prior thiopurine therapy as potentially mediating this association. Thiopurines, specifically azathioprine and 6-mercaptopurine, represent a foundational component of maintenance therapy in IBD as well as in other immune-mediated disorders and in solid organ transplantation. Their widespread use coupled with their mechanism of action involving direct or indirect incorporation into DNA has raised concerns for potential carcinogenicity [5]. One study examined 19,486 patients with IBD from a French cohort, finding an overall non-elevated risk for myeloid neoplasms in the IBD population compared with the general population [6]. However, of the five patients that developed myeloid neoplasms, three had prior and one had ongoing thiopurine exposure. The authors concluded that prior but not current thiopurine exposure was associated with an increased risk of myeloid neoplasms. This is in contrast to a prior investigation of IBD patients in Japan which did not find an association between thiopurine use and risk of hematologic malignancy [7]. A study from Hong Kong found that IBD

patients with a history of thiopurine exposure were at increased risk of malignancy in general, calculating a standardized incidence ratio of 2.37 (95 % CI 1.71–3.18) compared to 1.35 (95 % CI 1.05–1.72) in non-users with IBD [8]. A 2021 study of Veterans Affairs patients with IBD found that thiopurine exposure increased the risk of developing AML and myelodysplastic syndrome (MDS) compared to thiopurine non-exposure with the risk reverting back to baseline after thiopurine discontinuation [9]. The relationship between chronic myeloid leukemia (CML), thiopurines, and IBD has been less studied; one case report examined the role thiopurine therapy may have played in the development of CML in a patient with CD [10]. Several investigations have also found evidence of increased risk of lymphoproliferative disorders with thiopurine therapy in IBD [8,11,12].

Systemic inflammation and certain other chronic systemic disorders have been associated with higher rates of myeloid malignancies. In a Swedish population registry, a history of any infectious disease increased the risk for both AML (odds radio (OR) 1.3, 95 % CI 1.2–1.4) and MDS (OR 1.3, 95 % CI 1.1–1.5) [13]. In the same study, a history of any autoimmune disease likewise increased risks for AML (OR 1.7, 95 % CI 1.5–1.9) and MDS (OR 2.1, 95 % CI 1.7–2.6) [13]. In an analysis of a statewide cancer database in Minnesota, MDS was associated with an increased risk of diagnosis of autoimmune and immune-mediated diseases (adjusted odds ratio (aOR) 1.41, 95 % CI 1.05–1.89, $p = 0.02$) including a trend towards increased risk of inflammatory bowel disease (aOR 1.75, 95 % CI 0.89–3.42, $p = 0.1$) [14]. A separate investigation found autoimmune and immune-mediated diseases to be associated with a higher risk for MN (OR 1.2, 95 % CI 1.0–1.3, $p = 0.021$), including with CD (OR 1.8, 95 % CI 1.1–3.0) [15]. While specific mechanisms are unknown, these data suggest that chronic immune stimulation may be a factor in the comorbidity seen between myeloid neoplasms and inflammatory diseases.

2. Case series

To further explore the relationship between IBD and MN, we conducted a retrospective chart review of patients from the Mount Sinai Health System with IBD who developed MN, specifically AML, CML, and MDS. We collected demographic data and correlated disease characteristics of their IBD with those of their MN. This investigation was reviewed and approved by the local Institutional Review Board and

Program for the Protection of Human Subjects. We queried records between 2007 and 2022 for patients seen in any outpatient setting with ICD-10 diagnoses of either UC or CD and a concurrent diagnosis of MDS, AML, or CML (Fig. 1). Charts with diagnoses of polycythemia vera (PV), essential thrombocythemia (ET), chronic myelomonocytic leukemia (CMML), and myelofibrosis (MF) were not included due to a high frequency of improper ICD-10 coding. Forty-three records bearing these diagnoses were identified, twenty-eight of which contained additional characterizing information (Table 1). The distribution of MNs was similar in the subset of the twenty-eight records with further data. Two records were excluded because the MN diagnosis preceded the diagnosis of IBD. Mutational and chromosomal data from the MN of this population were also collected, when available. Karyotyping and fluorescent in-situ hybridization (FISH) were performed in-house. Details on molecular profiles were obtained from clinical next-generation sequencing (NGS) reports from a commercial laboratory (Neogenomics), when available (see Supplementary Table 1). For some records, mutational data were available through clinic notes but not the original NGS panels. The mean age of IBD diagnosis was 49.0 years (95 % CI 50.5–57.5) and the mean age of MN diagnosis was 61.2 years (95 % CI 55.1–67.2) with a mean latency of 9.4 years (95 % CI 6.8–12.1). The mean age of AML diagnosis in our cohort was 56.0 years (95 % CI 46.6–65.5) and the mean age of MDS diagnosis was 68.7 years (95 % CI 59.7–77.7). The most commonly recorded IBD-directed therapies were 5-ASA, steroids, and anti-TNF monoclonal antibodies (Table 2). Thiopurine use was much less prevalent, found in only seven of the twenty-six records with available treatment information. Neither IBD treatment history, expressed as total number of IBD-directed therapies, nor IBD disease control at time of MN diagnosis were found to significantly associate

Table 1
Number of charts identified by our search criteria, organized by type of MN and IBD. Italicized values represent the number of charts with additional data beyond diagnosis coding.

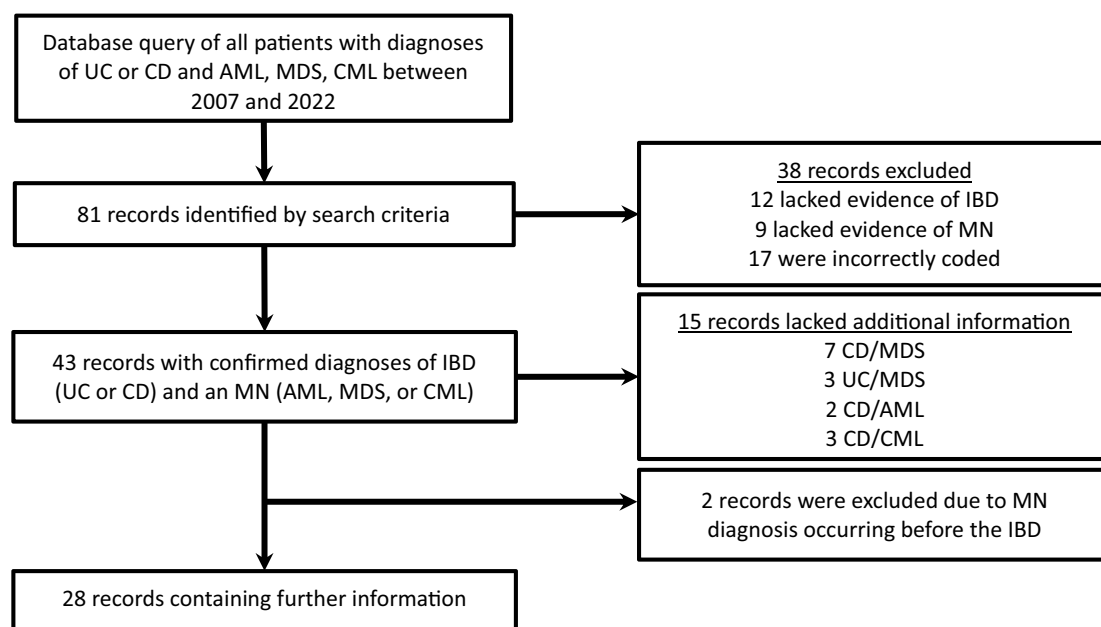|	UC	CD	Total
CML	2 (*2*)	5 (*2*)	7 (*4*)
AML	3 (*3*)	11 (*9*)	14 (*12*)
MDS	8 (*5*)	14 (*7*)	22 (*12*)
Total	13 (*10*)	30 (*18*)	43 (*28*)

Fig. 1. Retrospective study design for identifying patients in the Mount Sinai Health System with diagnoses of IBD and MN. 1B

Table 2

Number of charts with records of specific IBD-directed therapies. 5-ASA includes both oral and rectal formulations. Steroids include both oral and rectal steroids. Anti-TNFα agents include any biologic agents directed against tumor necrosis factor alpha (TNFα). Thiopurines include azathioprine and 6-mercaptopurine. Anti-integrin agents include vedolizumab and natalizumab. Antimetabolites include methotrexate. JAKi refers to JAK inhibitors such as tofacitinib. Anti-IL 12/23 agents include ustekinumab. Calcineurin inhibitors include cyclosporine.

	AML	MDS	CML
5-ASA	9	8	3
Steroids	7	6	3
Anti-TNFα	6	2	2
Thiopurines	4	2	1
Anti-integrin	1	2	1
Antimetabolites	1	1	0
Jak inhibitor	1	0	0
Anti-IL12/23	0	1	0
Calcineurin inhibitor	0	0	1

with any MN type (data not shown, $p > 0.05$ for all tested associations). These characteristics were also not found to associate with any specific driver mutation (Fig. 2). Similarly, the number of prior IBD therapies was not associated with either the complexity of MN karyotype or MN prognostic score at time of MN diagnosis. Overall, no specific MN characteristic was associated with IBD status at MN diagnosis or with prior IBD therapy.

Of the driver mutations detected in our population, variants in *TET2* were found to be most prevalent (6 identified variants), followed by *FLT3-ITD* (5), *BCR-ABL* (4), and *NPM1* (4) (Fig. 2). Mutations in genes known to be associated with MN such as *DNMT3A* (2), *EZH2* (2), *SRSF2*

(2), and *PPM1D* (1) were also observed but were less prevalent (Fig. 2).

Additionally, nine patients had available longitudinal CBC data preceding by years their diagnoses of MN (data not shown). Of these nine, eight had multiple cytopenias over the three years preceding MN diagnosis. Six patients had anemia, four had leukopenia, and four had thrombocytopenia. All cases of anemia were normocytic or macrocytic (mean MCV 93.0, 95 % CI 89.9–96.1) with an elevated RDW.

3. Discussion

This single-center retrospective analysis of IBD patients with MN provides new insights into the relationship between these disorders. Studies to date, including our own, have been limited by size, retrospective nature, and lack of internal control cohorts, but together suggest an underlying mechanism and provide rationale for future prospective work. Potential mechanisms driving the interplay between IBD and MN have been proposed, such as exposure to certain IBD therapies, specifically thiopurines. Existing research into the effect of thiopurine therapy on MN risk in IBD is divided, with some investigations identifying a possible link [5–9]. All prior data are derived from more general retrospective surveys evaluating malignancy risk in IBD. Given this design, all are unable to discern if thiopurine therapy is the cause of increased MN risk versus thiopurine use simply signaling more severe inflammatory disease which causes increased MN risk by other means. Within our cohort, no IBD treatment was found to correlate with risk of MN, including thiopurines. Of the twenty-six records with available data, only seven had a history of treatment with thiopurines. If thiopurine exposure does indeed cause an increased risk of MN, it would only explain at most one quarter of our cases. Whether the remaining
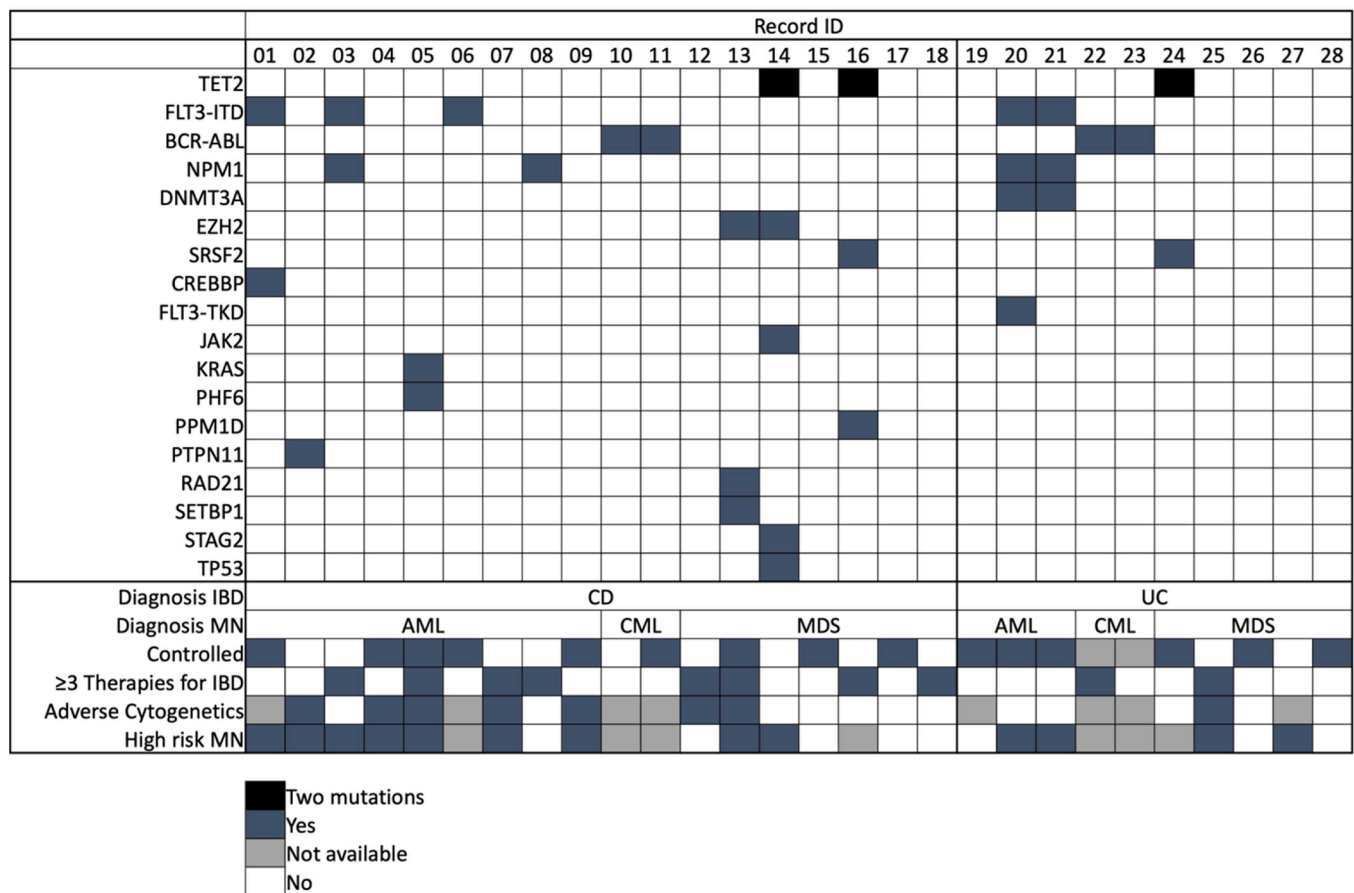

Fig. 2. Graphical representations of mutations for each analyzed record with respective clinical information. Control of IBD was judged at time of diagnosis of MN. Adverse cytogenetics were determined based on karyotype complexity or as defined by European LeukemiaNet (ELN) or International Prognostic Scoring System Revised (IPSS-R) criteria. Higher risk disease includes intermediate or high risk disease as determined by ELN or IPSS-R.

cases without thiopurine exposure are due to a separate source of increased risk or to the expected cases seen in any population due to chance would require a study with an internal control group.

States of generalized inflammation have been hypothesized as contributing to the risk of MN in IBD. Systemic inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, autoimmune hemolysis, scleroderma, polymyalgia rheumatica, and the systemic vasculitides, have all been found to confer an increased risk of MN [15–19]. One theory for this association is that inflammation selects for pre-existing clones in the bone marrow possessing mutations in certain myeloid driver genes, known as clonal hematopoiesis (CH). These clones, through their acquired resistance to inflammation, expand and have the potential to lead to the development of myeloid neoplasms [16]. It has also been theorized that these clones may themselves promote further inflammation [16]. This bidirectional relationship between CH and systemic disease has been found in atherosclerosis, though not yet in autoimmune diseases [20].

It is notable that our population developed AML at a young age relative to the general population (56 vs 68) [21]. This could be consistent with a model of accelerated clonal development through inflammation, but is not exclusive to this model. If this mechanism of systemic inflammation promoting the expansion of pre-existing clones is the cause behind the relationship between IBD and MN, then the distribution of somatic mutations seen in these MN would be expected to be similar to the distribution of mutations seen in clonal disorders such as CH, MDS, and AML. In contrast, if exposure to thiopurine therapy is the cause of increased risk of MN in IBD, it would be expected that mutations such as *PPM1D*, which associate with intrinsic resistance to cytotoxic medications, would be overrepresented.

To date, this is the largest study of somatic mutations in patients with IBD and MN. The distribution of CH mutations in the general population has been well-characterized, with mutations in *DNMT3A* most prevalent followed by mutations in *ASXL1* and *TET2* [22,23]. One investigation into MN in IBD found *DNMT3A* mutations to be most prevalent in this population, followed by *ASXL1* and *JAK2* [24]. Another study evaluating CH in IBD found *DNMT3A* and *PPM1D* mutations to be most prevalent, with *TET2* mutations being relatively uncommon when compared with prior studies of CH in the general population [25]. In contrast, in our population *TET2* mutations were the most prevalent somatic mutation, followed by *FLT3-ITD, BCR-ABL*, and *NPM1* mutations. *DNMT3A* mutations were less commonly observed and *ASXL1* mutations were not encountered at all. The over-representation of mutations in genes such as *NPM1* and *FLT3* in our population compared with CH in IBD is likely due to the fact that our investigation examined patients with clinically diagnosed MN rather than simply CH. Mutations in *NPM1* and *FLT3* are known to be acquired late in the MN transformation process [26–28]. The over-representation of *TET2* mutations and under-representation of *DNMT3A* and *ASXL1* mutations in our population compared with prior studies of CH in the IBD and general population may suggest that clones bearing *TET2* mutations, when compared with other mutations, have different propensities to transform into clinical MN in patients with IBD. The prevalence of *TET2* mutations in our population combined with prior data on the increased incidence of CH in IBD suggests a model of inflammation promoting the expansion of pre-existing clones bearing specific somatic driver mutations, rather than inducing their formation de novo. Consistent with prior studies as well as the rarity of thiopurine use in our population, *PPM1D* and *TP53* mutations were rare, each identified only once.

Our finding of atypical cytopenias preceding MN diagnosis by years is also consistent with a model of evolving clonal fitness (Fig. 3), although this hypothesis cannot be confirmed here due to lack of pre-MN sequencing data and an appropriate control population. Prospective studies involving longitudinal blood counts and sequencing data in the IBD population will be needed to more fully characterize this relationship. This may provide insight into the evolution of clones bearing specific somatic mutations as well as determine the predictive value of
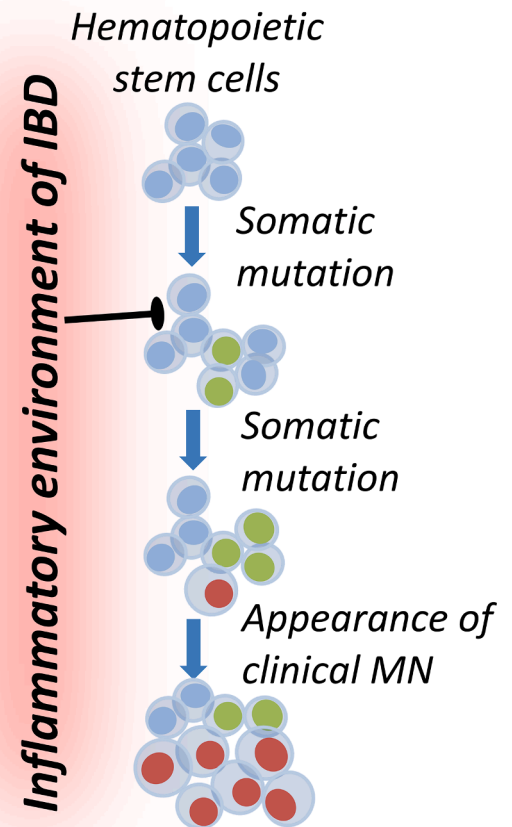

Fig. 3. Theoretical model for how the inflammatory environment of IBD suppresses wild-type hematopoietic stem cells, permitting stem cells that have acquired driver mutations (mutations in *DNMT3A* in this example) to expand as a clone. Blue nuclei represent wild type hematopoietic stem cells, green nuclei represent *DNMT3A*⁻ stem cells, red nuclei represent leukemic cells with mutations in *DNMT3A* and *NPM1*. Transformation to a clinically apparent MN can result as the clone acquires further mutations (*NPM1* in this example) and chromosomal instability.

unexplained cytopenias for MN in the IBD population. Of note, the IBD population routinely has blood count data collected for clinical purposes. This may make preceding cytopenias more apparent than in the general population. For similar reasons, the IBD population may be ideal for testing AML prediction models, given their higher risk of MN and frequent monitoring of blood counts [29].

4. Conclusion

These results from our cohort further characterize the relationship between IBD and MN. Our population developed AML at a young age, relative to the general population. No associations were identified between any IBD and MN characteristic, including treatment history. The somatic mutations identified in our cohort were similar to the distribution seen in a prior survey of CH in UC, as well as MN in general. We also found a signal that atypical cytopenias may precede MN diagnosis in IBD patients. Interestingly, our population was not found to be enriched for prior thiopurine use. Further prospective investigations will be needed to better characterize this relationship between IBD and MN. Overall, given the incompletely understood nature of the risk of MN in

IBD, these findings support timely referrals of IBD patients with unexplained or atypical cytopenias for comprehensive hematologic evaluation.

Funding

CRediT authorship contribution statement

David M. Mueller: Writing – original draft, Visualization, Validation, Investigation. **Daniel I. Nathan:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Angela Liu:** Writing – review & editing, Conceptualization. **John Mascarenhas:** Writing – review & editing, Supervision, Conceptualization. **Bridget K. Marcellino:** Writing – review & editing, Supervision, Project administration, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2024.100458.

References

[1] C.N. Bernstein, et al., Cancer risk in patients with inflammatory bowel disease, Cancer 91 (4) (2001) 854–862.

[2] C.L. Wheat, et al., Worldwide Incidence of Colorectal Cancer, Leukemia, and Lymphoma in Inflammatory Bowel Disease: an Updated Systematic Review and Meta-Analysis, Gastroenterol Res Pract 2016 (2016) 1–18.

[3] N. Narula, et al., Periodic Colonoscopies Are Associated with Improved Survival and Prognosis of Colorectal Cancer in Ulcerative Colitis, Dig. Dis. Sci. 67 (5) (2022) 1850–1857.

[4] J. Askling, Risk of haematopoietic cancer in patients with inflammatory bowel disease, Gut 54 (5) (2005) 617–622.

[5] V.P. Nguyen T, P. O'Neill, et al., Mutagenicity and potential carcinogenicity of thiopurine treatment in patients with inflammatory bowel disease, Cancer Res. 69 (17) (2009) 7004–7012.

[6] A. Lopez, Increased risk of acute myeloid leukemias and myelodysplastic syndromes in patients who received thiopurine treatment for inflammatory bowel disease, Clinical Gastroenterology and Hepatology 12 (8) (2014) 1324–1329.

[7] N. Fukata, et al., Hematologic malignancies in the Japanese patients with inflammatory bowel disease, J. Gastroenterol. 49 (9) (2014) 1299–1306.

[8] K.Y.C. Zheng, et al., Risk of malignancies in patients with inflammatory bowel disease who used thiopurines as compared with other indications: a territory-wide study, Therap Adv. Gastroenterol. 13 (2020) 175628482096727.

[9] P.D. Khan N, C. Trivedi, et al., Incidence of Acute Myeloid Leukemia and Myelodysplastic Syndrome in Patients With Inflammatory Bowel Disease and the Impact of Thiopurines on Their Risk, Am. J. Gastroenterol. 116 (4) (2021) 741–747.

[10] B.C. Zaimi Y, S. Ayadi, et al., Imputability of Azathioprine in the Occurrence of Chronic Myeloid Leukemia in Crohn's Disease: an Exceptional Case Report, Curr. Drug Saf. 18 (4) (2023) 596–598.

[11] D.S. Kotlyar, et al., Risk of Lymphoma in Patients With Inflammatory Bowel Disease Treated With Azathioprine and 6-Mercaptopurine: a Meta-analysis, Clin. Gastroenterol. Hepatology 13 (5) (2015) 847–858, e4.

[12] M. Lemaitre, et al., Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease, JAMA 318 (17) (2017) 1679.

[13] S.Y. Kristinsson, et al., Chronic Immune Stimulation Might Act As a Trigger for the Development of Acute Myeloid Leukemia or Myelodysplastic Syndromes, J. Clin. Oncol. 29 (21) (2011) 2897–2903.

[14] R.M. Linabery AM, M. Richardson, et al., Personal history of autoimmune disease and other medical conditions and risk of myelodysplastic syndromes, Cancer Epidemiol 76 (2022) 102090.

[15] S.Y. Kristinsson, et al., Autoimmunity and the risk of myeloproliferative neoplasms, Haematologica 95 (7) (2010) 1216–1220.

[16] D.A. Hochman MJ, Myelodysplastic syndrome and autoimmune disorders: two sides of the same coin? The Lancet 9 (7) (2022) e523–e534.

[17] D.I. Bekele, Autoimmunity, Clonal Hematopoiesis, and Myeloid Neoplasms, Rheumatic Disease Clinics of North America 46 (3) (2020) 429–444.

[18] L.A. Anderson, et al., Risks of myeloid malignancies in patients with autoimmune conditions, Br. J. Cancer 100 (5) (2009) 822–828.

[19] R.S. Komrokji, et al., Autoimmune diseases and myelodysplastic syndromes, Am. J. Hematol. 91 (5) (2016) E280–E283.

[20] S. Jaiswal, et al., Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease, New England J. Med. 377 (2) (2017) 111–121.

[21] R.M. Shallis, Epidemiology of acute myeloid leukemia: recent progress and enduring challenges, Blood Rev. 36 (2019) 70–87.

[22] G. Genovese, et al., Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence, New England J. Med. 371 (26) (2014) 2477–2487.

[23] S. Jaiswal, et al., Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes, New England J. Med. 371 (26) (2014) 2488–2498.

[24] T.F. Cumbo C, A. Zagaria, et al., Clonal Hematopoiesis at the Crossroads of Inflammatory Bowel Diseases and Hematological Malignancies: a Biological Link? Front Oncol 12 (12) (2022) 873896.

[25] C.R.C. Zhang, et al., Inflammatory cytokines promote clonal hematopoiesis with specific mutations in ulcerative colitis patients, Exp. Hematol. 80 (2019) 36–41, e3.

[26] H.J. Uckelmann, H.E. Takeda R, et al., Mutant NPM1 Directly Regulates Oncogenic Transcription in Acute Myeloid Leukemia, Cancer Discov 13 (3) (2023) 746–765.

[27] N. Daver, et al., Targeting FLT3 mutations in AML: review of current knowledge and evidence, Leukemia 33 (2) (2019) 299–312.

[28] P. Valent, et al., Clonal Hematopoiesis with Oncogenic Potential (CHOP): separation from CHIP and Roads to AML, Int J Mol Sci 20 (3) (2019) 789.

[29] S. Abelson, et al., Prediction of acute myeloid leukaemia risk in healthy individuals, Nat. 559 (7714) (2018) 400–404.