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Original Article

Gastroenteropancreatic Neuroendocrine Neoplasms in Patients with Inflammatory Bowel Disease: An ECCO CONFER Multicentre Case Series

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Abstract

Background: Gastroenteropancreatic neuroendocrine neoplasms [GEP-NENs] have rarely been reported in association with inflammatory bowel diseases [IBDs].

Methods: An ECCO COllaborative Network For Exceptionally Rare case reports project [ECCO-CONFER] collects cases of GEP-NENs diagnosed in patients with IBD.

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Results: GEP-NEN was diagnosed in 100 IBD patients; 61% female, 55% Crohn's disease, median age 48 years (interquartile range [IQR] 38-59]). The most common location was the appendix [39%] followed by the colon [22%]. Comprehensive IBD-related data were available for 50 individuals with a median follow-up of 30 months [IQR 11-70] following NEN diagnosis. Median duration of IBD at NEN diagnosis was 84 months [IQR 10-151], and in 18% of cases NEN and IBD were diagnosed concomitantly. At diagnosis, 20/50 were stage-I [T1N0M0], and 28/50 were graded G1 [ki67 ≤2%]. Incidental diagnosis of NEN and concomitantly IBD diagnosis were associated with an earlier NEN stage [$p = 0.01$ and $p = 0.02$, respectively]. Exposure to immunomodulatory or biologic therapy was not associated with advanced NEN stage or grade. Primary GEP-NEN were more frequently found in the segment affected by IBD [62% vs 38%]. At the last follow-up data, 47/50 patients were alive, and only two deaths were related to NEN.

Conclusions: In the largest case series to date, prognosis of patients with GEP-NEN and IBD seems favourable. Incidental NEN diagnosis correlates with an earlier NEN stage, and IBD-related therapies are probably independent of NEN stage and grade. The association of GEP-NEN location and the segment affected by IBD may suggest a possible role of inflammation in NEN tumorigenesis

Key Words: Inflammatory bowel disease; ulcerative colitis; Crohn's disease; neuroendocrine neoplasms

1. Introduction

Crohn's disease [CD] and ulcerative colitis [UC] are chronic inflammatory bowel diseases [IBDs] whose course may be complicated, among others, by occurrence of neoplasia.[1,2] Several types of neoplasia have been reported in association with IBD in observational studies. These include malignant neoplasia related to chronic inflammation [e.g., colorectal cancer, cholangiocarcinoma, anal cancers, small bowel carcinoma] and those associated with IBD related treatments [e.g., non-melanoma skin cancer, lymphoma, urinary tract cancers, and melanoma].[1]

Neuroendocrine neoplasms [NENs] are a heterogeneous group of tumours deriving from the diffuse endocrine system and represent about 1% of all digestive malignancies.[3] NENs may occur almost anywhere in the body but are most commonly diagnosed in the gastrointestinal tract, the pancreas, and the lungs, with gastroenteropancreatic [GEP] tumours representing 70% of all NENs.[4] Although NENs were historically considered rare, an increasing incidence has been reported worldwide over the past four decades.[5] To date, GEP-NENs have rarely been reported in association with IBD. Data are limited to case reports and retrospective cohort studies, mainly based on histological registries, and lack correlation with IBD's clinical characteristics and course.[6–11]

We aimed to describe a series of patients with IBD and GEP-NENs, and to delineate the association between IBD, GEP-NEN features, and patient outcomes.

2. Materials and Methods

This was a retrospective observational multicentre study that collected cases across the world through the CONFER [COllaborative Network For Exceptionally Rare case reports] project[12] and supported by the European Crohn's and Colitis Organisation [ECCO]. The CONFER project was initiated by ECCO in order to specifically identify and report rare IBD disease associations, which are otherwise seldom reported due to their exceptional rarity. Briefly, the CONFER methodology comprises selecting a topic submitted by ECCO members and worthy of investigation. The steering committee of CONFER chooses the topic, and ECCO launches a call to identify similar cases encountered by IBD physicians worldwide. The call to physicians is made through announcements in the ECCO annual congress, in national IBD meetings across Europe, and during international IBD meetings. In addition, the call for similar cases is disseminated by direct emails to all ECCO members and affiliated physicians, on the ECCO website and through the ECCO eNews.

All adult IBD patients [age >16 years] with a diagnosis of GEP-NEN according to established classifications,[13–16] prior to IBD diagnosis or throughout the course of the disease, were eligible for inclusion in this study. Data were collected using a standardised case report form which was divided into three domains: 1] patient characteristics, including demographic data, past medical history, and IBD-related data; 2] GEP-NEN related data including primary tumour site, stage, grade according to ki-67 proliferative index or mitotic count, immunostaining pattern, and functioning syndrome; 3] GEP-NEN- and IBD-related outcomes. Early stage was defined as absence of lymph node or distant metastasis.

When the NEN was diagnosed after IBD diagnosis, IBD duration was calculated from IBD diagnosis until NEN diagnosis. In all cases, follow-up period was calculated from NEN diagnosis until latest available visit or death. NENs were defined as co-localszed with IBD when the primary tumour site was found within the bowel segment affected by IBD. Patients were categorised as exposed to advanced therapy (i.e., immunomodulators [IMM] and/or biologics) before NEN diagnosis, based on the date of the first prescription and onward. Exposure status to IBD-related therapies and in particular to advanced therapies [exposed vs non-exposed] was described in different NEN subgroups to explore possible correlation between IBD-related therapies and NEN characteristics.

The data were collected and analysed anonymously and handled according to local regulations. Data were analysed for event association with patient- and IBD-related factors.

A general Review Board approval is available for this ECCO project on the ECCO website. Moreover, each participating centre received a local institutional review board approval.

2.1. Statistical analysis

Continuous variables were expressed as mean and standard deviation or median and interquartile range [IQR] as needed, and compared using Student's t test. Categorical variables were expressed as proportions and compared by means of Fisher's exact test and 95% confidence interval. A p-value less than 0.05 was considered statistically significant. For the statistical analysis, we used SAS Software V. 9.4 Packages [Cary, USA].

3. Results

One hundred cases of GEP-NENs diagnosed in patients with IBD (61% female, 55% CD, 41% UC, 4% inflammatory bowel disease unclassified [IBD-U]) were collected from 25 referral centres in 10 different countries [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online]. The vast majority of cases [97%] were reported from

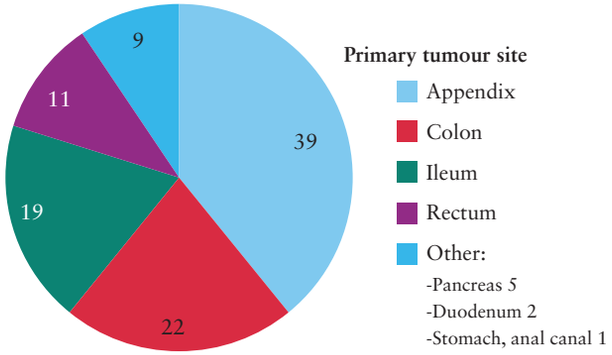

Figure 1. Primary site of neuroendocrine neoplasms among 100 patients with inflammatory bowel diseases.

academic centres. Of these, 51 cases were previously reported within case series[6] and case reports.[11]

Among the entire cohort, median age at GEP-NEN diagnosis was 48 years [IQR 38-59]. The most common location of the primary tumour site was the appendix [39%] followed by the colon [22%], ileum [19%], and rectum [11%] [Figure 1].

GEP-NEN diagnosis was made after a median time of 84 months [IQR 10-151] from IBD diagnosis, and the majority of patients [56%] received NEN diagnosis ≥60 months after diagnosis of IBD. In 18 cases both diagnoses were made concomitantly. None of the patients was diagnosed with GEP-NEN prior to IBD diagnosis.

Clinical characteristics of the entire cohort are reported in Table 1. Comprehensive follow-up data were available for 50 cases and were therefore included in further analysis. Clinical characteristics of these cases are presented in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online. The median follow-up after GEP-NEN diagnosis was 30.5 months [IQR 11.2-70].

In 36/50 cases, GEP-NEN were discovered incidentally either during follow-up imaging or endoscopy [25/50] or within surgical specimens [11/50]. In 14 of the 50 cases, the presence of new symptoms led to NEN diagnosis. Notably, none of the cases were associated with a functional NEN syndrome.

3.1. GEP-NEN stage and grade

At diagnosis, 19/50 [38%] of NENs were at stage I and 13/50 [26%] and 3/50 [6%] were diagnosed at stage III and IV, respectively. Moreover, 28/50 graded G1 [proliferation index ≤3 % or mitotic rate below 2 per 2mm^2]. Complete NEN characteristics are reported in Figure 2.

3.2. GEP-NEN therapy

The majority of patients, that is 45 [90%], underwent surgery with curative intent. Of these, at the end of follow-up 37 [82%] were disease free, seven [16%] had disease progression due to residual or recurrent disease, and one [2%] had stable disease. Of the remaining five patients who did not undergo surgery, one [primary site rectum; G3] was treated with chemotherapy; one [primary site: sigmoid; G3] did not receive any treatment due to rapid disease progression until death; two [primary site: pancreatic T1N0M0] did not receive any treatment and a 'wait and see' strategy was adopted; one [primary site: pancreatic T1N0M0] was treated with somatostatin analogues alone.

Table 1. Clinical characteristics of patients with inflammatory bowel diseases and neuroendocrine neoplasia.

Total patients	***n* = 100**
Age at IBD diagnosis	
Median years [IQR]	39 [29-51]
Age at NEN diagnosis	
Median years [IQR]	48 [38-59]
Gender, *n* [%]	
Female	61 [61]
Ethnicity, *n* [%]	
White	45 [45]
Mixed-ethnic group	2 [2]
Asian	1 [1]
Black/Caribbean/African	1 [1]
Other ethnic group	1 [1]
N/A	50 [50]
CD/UC/IBD-U	55/41/4
Montreal classification, *n*	
A1/A2/A3/N/A	2/27/20/51
L1/L2/L3/L4	13/4/13/25
B1/B2/B3/N/A	11/13/6/24
E1/E2/E3 /N/A	10/7/1/23
Perianal disease, *n* [%]	
Yes	6 [6]
N/A	50 [50]
Extraintestinal manifestations	
None	35 [35]
At least 1	15[15]
N/A	50 [50]
Positive family history of IBD, *n* [%]	4 [4]
Smoking, *n*	
Current/past/never/N/A	7/9/30/54
Previous cancer, *n* [%]	
Yes	2 [4]
Previous drug exposure, *n*	
5-ASA	31
Steroids	32
IMM	20
Biologics	16
Previous IBD-related surgery, *n*	10
IBD activity at NEN diagnosis, *n*	
Active/quiescent/missing	35/14/51

IBD, inflammatory bowel disease; NEN, neuroendocrine neoplasm; CD, Crohn's disease; UC, ulcerative colitis; IQR, interquartile range; A1, >17 years old; A2, 18–40 years old; A3, >40 years old; N/A, not available; L1, ileal; L2, colonic; L3, ileocolonic; L4, upper disease; B1, inflammatory; B2, stricturing; B3, penetrating; E1, ulcerative proctitis; E2, left-sided colitis; E3, pancolitis; 5-ASA, 5-aminosalicylic acid; IMM, immunomodulators; IBD-U: inflammatory bowel disease unclassified.

3.3. Features of IBD

Active IBD at the time of NEN diagnosis, defined by clinically, biochemically, or endoscopically active disease, was documented among 35/50 [70%] of patients.

No difference between CD and UC patients regarding NEN characteristics [tumour grade and stage] and disease course [proportion of patients being disease free, having stable

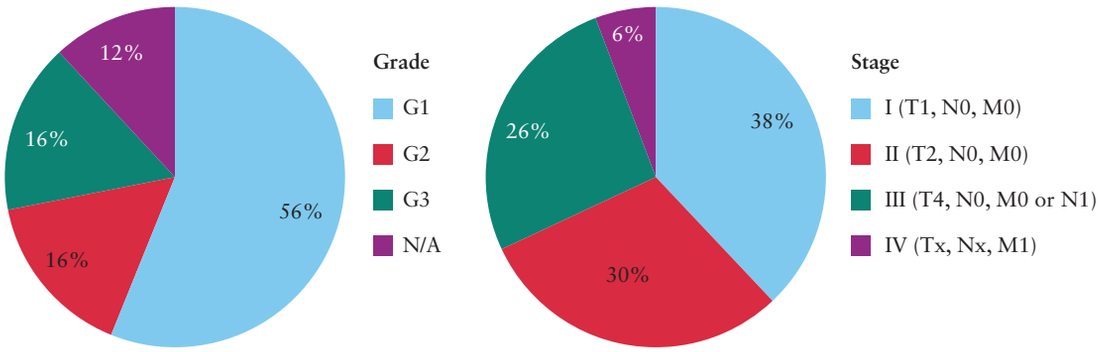

Figure 2. Gastroenteropancreatic neuroendocrine neoplasia-related features.

disease, or with disease progression at the end of follow-up] were found in our series.

A total of 24/50 [48%] patients had been exposed to advanced therapy at the time of NEN diagnosis for a median duration of 20.5 months [IQR 9-74]. Of these 24 patients, four been actively treated with advanced therapy and in all of them treatment was discontinued following NEN diagnosis. Of note, there was no association between exposure to an advanced therapy and advanced NEN stage or grade [$p = 0.14$ and $p = 0.91$, respectively], compared with patients not exposed to an advanced therapy.

Incidental diagnosis of NEN either during follow-up or during surgery, as well as receiving diagnosis of NEN concomitantly with IBD, was significantly associated with an early NEN stage (odds ratio [OR] 0.15, 95% confidence interval [CI] 0.03-0.75 and OR 0.13, 95% CI 0.003-0.97, respectively). In 31/50 [62%] cases, the NEN primary site was found within the bowel segment affected by IBD compared with 19 cases [38%] whose NEN site was not affected.

3.4. Outcome and prognosis

At the latest follow-up date, 47/50 [94%] patients were alive, of whom 31/50 had quiescent IBD and 16/50 had active IBD. Three deaths occurred, of which two were related to NEN. The first patient, a 71-year old man suffering from extensive UC, had a diagnosis of high-grade, poorly differentiated rectal NEN [G3, stage T3N0M0] and died 4 months after NEN diagnosis after failing to response to neoadjuvant chemotherapy. No data about drug exposure and IBD duration were available for this patient. The second patient was a 61-year old man with a history of long-standing extensive UC treated with azathioprine for 7 years, who developed an advanced small cell neuroendocrine carcinoma of the sigmoid colon with metastatic liver disease [G3, T4N1M1]. Death occurred within 2 months from diagnosis due to rapid disease progression.

4. Discussion

GEP-NENs are considered a rare entity, but their incidence is increasing worldwide[5] and they may represent a clinical challenge given their protean behaviour. IBDs are relatively common and GEP-NENs have rarely been reported in association with IBD. The current multicentre case series of GEP-NEN, the largest to date, in patients with IBD, has demonstrated that cases are predominantly diagnosed during the fourth and fifth decade of life, at a median of 7 years from IBD diagnosis, and most commonly within the appendix and along the large bowel. Of note, in two-thirds of the cases GEP-NEN was diagnosed at the bowel segment involved in the underlying IBD. Importantly, we have found more than 70% of GEP-NEN being diagnosed incidentally during IBD follow-up and in early stage. Finally, the vast majority of GEP-NEN cases among patients with IBD carried a favourable prognosis during a median follow-up of over 30 months.

Compared with sporadic NEN not associated with IBD, both age at NEN diagnosis and the primary tumour site seem to be different. In the present case series, the median age at NEN diagnosis was 51 years, more than 7 to 10 years earlier than the age reported in historical cohorts and in population-based registries.[17–20] The younger age at NEN diagnosis in patients with IBD patients can be explained by several factors: 1] the intensive disease monitoring involving endoscopic and imaging studies; 2] patients with IBD more commonly undergo intestinal surgeries and thus incidental findings at a younger age group are more likely to occur; and 3] our cohort include 40% appendiceal NEN, a subtype that may appear at younger age.[21] Alternatively, an expedited pathogenesis related to inflammation might have a role in the development of GEP-NEN tumorigenesis in patients with IBD. Interestingly, an interaction between the neuroendocrine system and the Th17 pathway in human IBD has been described, possibly supporting this hypothesis.[22] Moreover, previous studies demonstrated an inflammation-induced hyperstimulation of enteroendocrine cells which can result in hyperplasia and ultimately neoplastic transformation.[23–26]

As for anatomical distribution of tumours, we found that the most common primary tumour sites were the appendix, the colon, the ileum, and the rectum, overall accounting for about 90% of all cases. Compared with historical cohorts where ileal and rectal NENs account for 40–65% of cases,[17–20] in our series the most frequent primary tumour sites were appendix and colon, together reaching 61%. On one hand, this could reflect a diagnostic bias due to the high prevalence [72%] of incidentally discovered NEN cases, either during follow-up procedures for the underlying IBD [i.e., colonoscopy] or in the surgical specimen at the time of intestinal surgery; on the other hand, this may reflect a peculiarity on NEN associated with IBD. In contrast to our findings, in a previously described case series of four NEN cases identified within 111 CD specimens, no correlation was found between areas involved by inflammation and NEN.[27] This discrepancy may be explained by the significant larger number of patients enrolled in our cohort.

Generally, prognosis of patients with concomitant GEP-NEN and IBD seems favourable and similar to that of NEN

in the general population.[20,28] In fact, after a median follow-up of 30.5 months, 94% of patients were still alive. In a recently published American cohort study of 43 751 patients with GEP-NEN, the overall 3-year survival ranged from 98% for localised disease to ~50% advanced disease with distant metastasis.[20] In our population, with the aforementioned high prevalence of gastrointestinal primary site, the predominant early stage [74% of patients did not present lymph node or distant metastases] and the general favourable grading [72% of cases had G1 or G2] at diagnosis are the clinical factors that most likely contributed to this favourable prognosis.

Noteworthy, we found no cases of functioning NEN in our cohort. This finding is lower than the reported functioning syndrome rate in previous reports on specific subtypes of GEP-NENs, ranging from 3–13% with NEN of the small intestine to up to 30% of patients with pancreatic NEN.[29] The low prevalence of pancreatic and ileal NENs [25% of cases, overall] and the generally early stage at diagnosis found in our series may explain this peculiarity.

We found no association between IBD-related therapies, and particularly conventional immunomodulatory and or biologic therapies, and NEN stage and grade at diagnosis. This observation is reassuring and is in line with previous data reporting no increased cancer risk among patients with IBD treated with biologic therapies.[30–32] However, larger cohorts followed longitudinally for longer periods are needed to rule out possible relationship between these treatments and GEP-NEN long-term course and prognosis.

Finally, as expected, incidental NEN diagnosis either during follow-up or during surgery was correlated to an earlier stage compared with cases diagnosed during investigation of new symptoms. This finding corroborates previous study reporting earlier stage and better prognosis for patients with incidentally discovered pancreatic NEN.[20,33]

However, some limitations need to be pointed out in this study, mostly inherent biases of a retrospective case series design. Data report might be subjected to geographical and selection biases. However, the relatively large number of cases and the participation of 25 centres from 10 different countries could in part overcome this limitation. Due to the relatively small sample size, definitive conclusions on association between IBD-related and NEN-related factors are limited.

In conclusion, the largest case series to date, which included thorough IBD- and NEN-related data with a longitudinal follow-up, showed that prognosis of patients with GEP-NEN and IBD appear largely comparable with that of sporadic NEN cases, when compared with historical case series. Incidental GEP-NEN diagnosis correlates with an earlier NEN stage and IBD-related therapies do not seem to influence NEN stage and grade. The association between GEP-NEN location and the segment affected by IBD may suggest a possible role of inflammation in NEN tumorigenesis. However, larger observational case-control studies are needed to confirm these speculative hypotheses.

Supplementary Data

Supplementary data are available online at *ECCO-JCC* online.

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No sponsors entered in the study design, collection, analysis, and interpretation of the data,or in the writing of the report.

Conflict of Interest

SF has served as speaker, consultant, and advisory member for Janssen Cilag; received consultancy fees and/or educational grants from Takeda, So.Far, Abbvie, Zambon. DP has served as a speaker for Abbvie, Janssen, Takeda, Pfizer. FH has served on advisory boards, or as speaker or consultant for Abbvie, Celgene, Janssen Cilag, MSD, Takeda, Celltrion, Teva, Sandoz, and Dr Falk, and has received unrestricted grants from Dr Falk, Janssen-Cilag, Abbvie. ABGS has served as a speaker or has received research or education funding from Abbvie, Takeda, Janssen, Ferring, Neopharm. MC has served as a speaker for or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma. JPG has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead/Galapagos, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, and Vifor Pharma. TL has received financial support for research from Abbvie, Mylan, MSD, Mundipharma, Biogen, Janssen, Pfizer and Takeda; speaker fees from Ferring, MSD, Abbvie, Janssen, Amgen,FreseniusKabiand Takeda; consultancy fee from Janssen, Galapagos, Amgen, Bristol Myers Squibb Fresenius Kabi and Takeda. CP has received consultancy fees and/or educational grants from Abbvie, MSD, Takeda, Pfizer, Janssen-Cilag, Chiesi, Sofar, Ferring and Zambon. IG has received institutional research grant from Pfizer and research travel grants from the European Crohn's and Colitis Organisation [ECCO] and the International Organization for the Study of Inflammatory Bowel Diseases [IOIBD].

Author Contributions

Substantial contributions to the concept or design of the work: SF, GZ, CP, IG. Contributions to the acquisition, analysis, and interpretation of data for the work: all the authors. Drafting the work or revising it critically for important intellectual content: SF, GZ, IG. Final approval of the version to be published: all the authors approved the final version of the paper. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: SF.

Conference presentation: 16th Congress of ECCO–Inflammatory Bowel Diseases, 2021, e-poster presentation [P124].

References

1. Annese V, Beaugerie L, Egan L, *et al.*; ECCO. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;9:945–65.
2. Beaugerie L, Itzkowitz SH. Cancers complicating inflammatory bowel disease. *N Engl J Med* 2015;373:195.
3. Lepage C, Bouvier AM, Faivre J. Endocrine tumours: epidemiology of malignant digestive neuroendocrine tumours. *Eur J Endocrinol* 2013;168:R77–83.
4. Schimmack S, Svejda B, Lawrence B, Kidd M, Modlin IM. The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. *Langenbecks Arch Surg* 2011;396:273–98.
5. Leoncini E, Boffetta P, Shafir M, Aleksovska K, Boccia S, Rindi G. Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. *Endocrine* 2017;58:368–79.

6. Derikx LA, Vierdag WM, Kievit W, Bosch S, Hoentjen F, Nagtegaal ID. Is the prevalence of colonic neuroendocrine tumors increased in patients with inflammatory bowel disease? *Int J Cancer* 2016;139:535–42.
7. Pellino G, Marcellinaro R, Candilio G, *et al*. The experience of a referral centre and literature overview of GIST and carcinoid tumours in inflammatory bowel diseases. *Int J Surg* 2016;28[Suppl 1]:S133–41.
8. Grassia R, Bodini P, Dizioli P, *et al*. Neuroendocrine carcinomas arising in ulcerative colitis: coincidences or possible correlations? *World J Gastroenterol* 2009;15:4193–5.
9. Sigel JE, Goldblum JR. Neuroendocrine neoplasms arising in inflammatory bowel disease: a report of 14 cases. *Mod Pathol* 1998;11:537–42.
10. Greenstein AJ, Balasubramanian S, Harpaz N, Rizwan M, Sachar DB. Carcinoid tumor and inflammatory bowel disease: a study of eleven cases and review of the literature. *Am J Gastroenterol* 1997;92:682–5.
11. Zerboni G, Capurso G, Pilozzi E, Papi C. Colonic small cell neuroendocrine carcinoma in a patient with long-standing ulcerative colitis treated with azathioprine. *Dig Liver Dis* 2016;48:822–3.
12. Katsanos KH, Domènech E, Rahier JF, *et al*. Making a case for case reports: the ECCO-CONFER viewpoint on investigating rare events in a medical world reigned by group-comparative statistics. *J Crohns Colitis* 2017;11:256–7.
13. Lloyd RV, Osamura RY, Kloppel G, Rosai J, editors. *WHO Classification of Tumours of Endocrine Organs [World Health Organization Classification of Tumors]*. 4th edn. Lyons, France: IARC Press; 2017.
14. Nagtegaal ID, Odze RD, Klimstra D, *et al*.; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020;76:182–8.
15. Rindi G, Klöppel G, Couvelard A, *et al*. TNM staging of midgut and hindgut [neuro]endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007;451:757–62.
16. Rindi G, Klöppel G, Alhman H, *et al*.; all other Frascati Consensus Conference participants; European Neuroendocrine Tumor Society [ENETS]. TNM staging of foregut [neuro]endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006;449:395–401.
17. Maggard MA, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg* 2004;240:117–22.
18. Darbà J, Marsà A. Exploring the current status of neuroendocrine tumours: a population-based analysis of epidemiology, management and use of resources. *BMC Cancer* 2019;19:1226.
19. Caldarella A, Crocetti E, Paci E. Distribution, incidence, and prognosis in neuroendocrine tumors: a population based study from a cancer registry. *Pathol Oncol Res* 2011;17:759–63.
20. Xu Z, Wang L, Dai S, *et al*. Epidemiologic trends of and factors associated with overall survival for patients with gastroenteropancreatic neuroendocrine tumors in the United States. *JAMA Netw Open* 2021;4:e2124750.
21. Katz LH, Levi Z, Twig G, *et al*. Risk factors associated with gastroenteropancreatic neuroendocrine tumors in a cohort of 2.3 million Israeli adolescents. *Int J Cancer* 2018;143:1876–83.
22. Friedrich M, Diegelmann J, Schauber J, Auernhammer CJ, Brand S. Intestinal neuroendocrine cells and goblet cells are mediators of IL-17A-amplified epithelial IL-17C production in human inflammatory bowel disease. *Mucosal Immunol* 2015;8:943–58.
23. Maja CB, Cacev T, Ivkovic TC, Zjacic-Rotkvic V, Kapitanovic S. New insights into the role of chronic inflammation and cytokines in the etiopathogenesis of gastroenteropancreatic neuroendocrine tumors. *Neuroendocrinology* 2014;99:75–84.
24. Le Marc'hadour F, Bost F, Peoc'h M, Roux JJ, Pasquier D, Pasquier B. Carcinoid tumour complicating inflammatory bowel disease. A study of two cases with review of the literature. *Pathol Res Pract* 1994;190:1185–92; discussion 1193–200.
25. Klöppel G, Clemens A. The biological relevance of gastric neuroendocrine tumors. *Yale J Biol Med* 1996;69:69–74.
26. Cadden I, Johnston BT, Turner G, McCance D, Ardill J, McGinty A. An evaluation of cyclooxygenase-2 as a prognostic biomarker in mid-gut carcinoid tumours. *Neuroendocrinology* 2007;86:104–11.
27. West NE, Wise PE, Herline AJ, Muldoon RL, Chopp WV, Schwartz DA. Carcinoid tumors are 15 times more common in patients with Crohn's disease. *Inflamm Bowel Dis* 2007;13:1129–34.
28. Panzuto F, Nasoni S, Falconi M, *et al*. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer* 2005;12:1083–92.
29. Jensen RT, Norton JA, Oberg K. Neuroendocrine tumors. In: Feldman M, Friedman LS, Brandt LJ, editors. *Sleisenger and Fordtran's Gastrointestinal and Liver Diseases*. Philadelphia, PA: Elsevier Saunders; 2015;501–41.
30. Micic D, Komaki Y, Alavanja A, Rubin DT, Sakuraba A. Risk of cancer recurrence among individuals exposed to antitumor necrosis factor therapy: a systematic review and meta-analysis of observational studies. *J Clin Gastroenterol* 2019;53:e1–1.
31. Chen Y, Sun J, Yang Y, Huang Y, Liu G. Malignancy risk of antitumor necrosis factor alpha blockers: an overview of systematic reviews and meta-analyses. *Clin Rheumatol* 2016;35:1–18.
32. Bonovas S, Fiorino G, Allocca M, *et al*. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. *Clin Gastroenterol Hepatol* 2016;14:1385–97.e10.
33. Crippa S, Partelli S, Zamboni G, *et al*. Incidental diagnosis as prognostic factor in different tumor stages of nonfunctioning pancreatic endocrine tumors. *Surgery* 2014;155:145–53.