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

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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) collecting cases of GEP-NENs diagnosed in patients with IBD.

Results. GEP-NEN was diagnosed in 100 IBD patients [61% female, 55% Crohn's disease, median age 48 years (IQR 38-59)]. The most common location was the appendix (39%) followed by the colon (22%).

Comprehensive IBD-related data was 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 graded G1 (ki67≤2%).

Incidental diagnosis of NEN and concomitantly with 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 favorable. 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 tumourigenesis

Keywords: Inflammatory Bowel Disease, Ulcerative Colitis, Crohn's Disease, Neuroendocrine Neoplasms

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Material. Raw data that support the findings of the study are available from the corresponding author, upon reasonable request.

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 last 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.

Materials and Methods

This was a retrospective observational multicenter 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 is 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 and 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 last available visit or death. NENs were defined as co-localized with IBD when primary tumour site was found within the bowel segment affected by IBD. Patients were categorized 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 center received a local Institutional Review Board approval.

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 the Fisher's exact test and 95% confidence interval was calculated. 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].

Results

One hundred cases of GEP-NENs diagnosed in patients with IBD (61% female, 55% CD, 41% UC, 4% IBD-U) were collected from 25 referral centres in 10 different countries (Supplementary Figure 1). The vast majority of cases (97%) were reported from academic centres. Of these, 51 cases were previously reported within case-series [6] and case-report [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, of whom 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 was available for 50 cases and were therefore included in further analysis. Clinical characteristics of these cases are

presented in supplementary table 1**.** 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 specimen (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.

GEP-NEN stage and grade

At diagnosis, 19/50 (38%) of NENs were at stage I while 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**.

GEP-NEN therapy

Majority of patients, 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 cases that did not undergone 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.

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 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 exposure 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 (OR 0.15, 95% CI 0.03-0.75 and OR 0.13, 95% CI 0.003 -

0.97, respectively). In 31/50 (62%) cases NEN primary site was found within the bowel segment affected by IBD compared to 19 cases (38%) whose NEN site was not affected.

Outcome and prognosis

At the last follow-up date, 47/50 (94%) patients were alive. Of whom, 31/50 had quiescent IBD, while 16/50 had active IBD. Three deaths occurred, of which, two were related to NEN. The first patient, a 71-years-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-years 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.

Discussion

GEP-NENs are considered a rare entity but their incidence is increasing worldwide [17] 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 multi-center case-series of GEP-NEN, the largest to date, in patients with IBD, has demonstrated that cases are predominantly diagnosed during the 4th and the 5th decade of life, at 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 that 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 carries a favorable prognosis during a median follow-up of over 30 months.

Compared to sporadic NEN not associated to IBD, both age at NEN diagnosis and the primary tumour site seems 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 [18-21]. 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 thus incidental findings at a younger age group are more likely to occur; 3. Our cohort include 40% appendiceal NEN, a subtype that may appear at younger age [22]. Alternatively, an expedited pathogenesis related to inflammation might have a role in the development of GEP-NEN tumourigenesis 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 [23]. Moreover, previous studies demonstrated an inflammation induced hyperstimulation of enteroendocrine cells that can result in hyperplasia and ultimately neoplastic transformation [24-27].

As for anatomic distribution of tumors, 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 to historical cohorts where ileal and rectal NENs account for 40-65% of cases [18-21], 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 on the surgical specimen at the time of intestinal surgery; on the other hand, this may reflect

a peculiarity on NEN associated to 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 [28]. 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 favorable and similar with that of NEN in the general population [21, 29]. 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 localized disease to ~50% advanced disease with distant metastasis [21]. In our population, 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 favorable grading (72% of case had G1 or G2) at diagnosis are the clinical factors that most likely contributed to this favorable 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 [30]. 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 [31-33]. 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 to cases diagnosed during investigation of new symptoms. This finding corroborates previous study reporting a lower stage and better prognosis for patients with incidentally discovered pancreatic NEN [21, 34].

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 centers 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 that 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 to 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 tumourigenesis. However, larger observational case-control studies are needed to confirm these speculative hypotheses.

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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 Mixed-ethnic group Asian Black/Caribbean/African Other Ethnic Group N/A	 45 (45) 2 (2) 1 (1) 1 (1) 1 (1) 50 (50)
CD/UC/IBD-U	55/41/4
Montreal classification, n A1/A2/A3/N/A L1/L2/L3/L4 B1/B2/B3/N/A E1/E2/E3 /N/A	 2/27/20/51 13/4/13/25 11/13/6/24 10/7/1/23
Perianal disease n (%) Yes N/A	 6 (6) 50 (50)
Extra-intestinal manifestations None At least 1 N/A	 35 (35) 15(15) 50 (50)
Positive family history of IBD, n (%)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

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

Figure 1

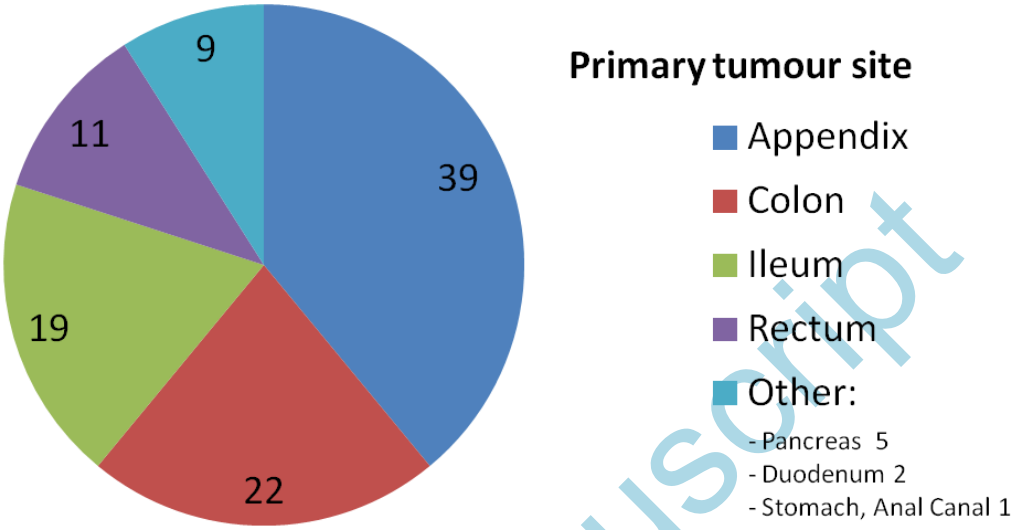

Figure 2