Crohn’s Disease and Intestinal Cancers

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Crohn's Disease (CD) is a chronic, relapsing–remitting disease, which can affect the entire gastrointestinal tract with transmural inflammation. It is characterized by a progressive course with damage accumulation and onset of complications. CD patients have an increased risk of both intestinal and extra-intestinal cancers compared to the general population and chronic inflammation has been identified as the main risk factor for cancerization.

Crohn’s disease colorectal cancer small bowel cancer anal cancer IBD

1. Colorectal Cancer

1.1. Epidemiology

The connection between IBD and CRC was identified in the first decades of the last century, after the report by Crohn and Rosenberg [1]. The modern management of CD, based on strict endoscopic surveillance, a patient-tailored medical treatment and a more aggressive surgical approach, has progressively brought to a slight decrease in CRC onset in CD patients [2][3]. For instance, Canavan et al. and Von Roon et al. reported a pooled SIR of 2.5 (95% CI 1.3–4.7) and 2.4 (95% CI 1.56–4.36), respectively [4][5], while a lower value was shown by Jess et al. and Lutgens et al., with an SIR of 1.9 (95% CI 1.4–2.5) and 1.7 (95% CI 1.01–2.5), respectively [6][7].

In comparison to the general population, CD-related CRC usually appears at an earlier age (40–50 years vs. 60 years) [8], with a higher incidence in case of CD onset before 15 years of age [9]. It generally presents as a mucinous or signet-ring histotype with a higher histological grade and it is frequently associated to synchronous or metachronous lesions [10].

Although CD patients are evidently more prone to develop CRC as compared to the general population, a recent meta-analysis [11] and a case-control study [12] showed similar overall survivals when CD-related and sporadic CRCs were compared. More specifically, Olén et al. reported a mortality of 0.47 and 0.31 per 1000 person-years for CD-related and sporadic CRC, respectively, during their study period of almost 50 years [13]. However, the sub-analysis of patients suitable for current surveillance programs revealed an increased mortality rate in case of CD onset before 40 years of age, colonic involvement and coexisting primary sclerosing cholangitis (PSC) [13].

1.2. Pathogenesis and Risk Factors

Several studies showed different etiopathological mechanisms for sporadic and IBD-related colonic neoplasms. Sporadic CRC arises from premalignant adenomatous polyps as a result of the well-known adenoma–carcinoma

sequence with a well-established pattern of genetic mutations. Conversely, in IBD-related CRCs, a key role is played by the chronic inflammatory damage associated to an altered microbiota [14][15][16]. In genetically susceptible patients [17], these factors may lead to the inflammation–dysplasia–carcinoma sequence instead of the classic adenoma–carcinoma sequence [18][19][20].

With regard to the risk factors for CRC or dysplasia onset in patients affected by CD, the duration, severity and extent of the colonic inflammation have been recognized as the main predisposing features [21][2][22]. Indeed, patients with eight or more years of CD-related colitis are more prone to CRC development, highlighting the need for an ad hoc surveillance program, especially after this time elapse [13][20][23]. In addition, the early onset of CD, in particular before 15 years of age, and the detection of new colonic strictures in longstanding colitis have been recognized as further risk factors [9][24]. Although the exact connection is still not completely clear, concomitant diagnosis of PSC, a family history of CRC and the penetrating pattern of CD have been identified as playing an additional key role in the onset of CD-related CRCs [25][26].

2. Small Bowel Cancer

2.1. Epidemiology

Small bowel carcinoma (SBC) can be considered a rare complication of CD, with an estimated cumulative risk of 2.2% after a 25-year clinical history of regional ileitis [27]. As compared to the general population, CD is associated with nearly a 10-fold increased risk of SBC, with a similar incidence between males and females, but a significantly higher rate in patients aged 60 years old or over [28]. In terms of the time elapse of the major incidence, the first year after CD diagnosis relates to a 100-fold increased probability of SBC development. Conversely, a significant drop to a five-fold higher risk is reported from the second year after diagnosis onwards [28]. In terms of tumor location, CD-related SBC more frequently arises in the ileum, as compared to sporadic SBC that is more evenly distributed between the jejunum and ileum [29]. When adequately and promptly diagnosed, CD-related SBC has shown a 5-year survival rate between 35% and 43% [29][30][31]. This data did not significantly differ from the sporadic manifestation of SBC [30][31]. Moreover, a survival analysis stratified by stage showed similar rates for stages I–IV of CD-SBC as compared to the sporadic SBC [29][32].

2.2. Pathogenesis and Risk Factors

Few retrospectives series specifically analyzed the correlation between CD and SBC. A chronic penetrating disease, immunomodulators and steroids exposure, stricturoplasties and small bowel by-pass loops are currently recognized as risk factors [33]. Moreover, Lashner et al., in a case–control study, found 6-mercaptopurine use and proximal small bowel disease as significantly associated to SBC in patients with CD [34]. Conversely, the results published in 2004 by Solem et al. did not recognize any specific risk factor, although the use of salicylates was identified as protective against SBC onset [35]. In a larger cohort multicenter study, the surgical resection of the tract of ileum affected by CD as well as the prescription of salicylates for more than two years resulted in markedly reducing the risk of SBC development [36].

Although no studies specifically analyzed the physio pathology of the correlation between CD-induced inflammation and higher risk of SBC onset, the current hypothesis is based on the potential evolution from inflammation to dysplasia. Indeed, epithelial dysplasia was found in the proximity of SBC in 7 out of 8 patients in a pathological study presented by Sigel et al. [37]. A further confirmation of this finding was also given by Svrcek et al., who demonstrated a dysplastic lesion adjacent to CD-associated SBC, with several molecular similarities to colitis-associated colorectal cancer [38]. Based on these data, although no effective screening methods for SBC are currently present, the findings of preneoplastic changes could hypothetically guide the decision-making in CD patients.

Similarly, the protective effect of salicylates is not yet fully understood. Indeed, salicylates prescription could reflect a milder disease activity and, thus, would not have a preventive role per se. On the other hand, salicylates (especially for formulation with release in the small bowel) may reduce the local inflammatory response, leading to a decreased risk of SBC [36]. Conversely, the association between immunosuppressive drugs and increased risk of SBS might be attributable to the higher inflammatory burden that characterize CD patients who require advanced therapies.

3. Anal Cancer

3.1. Epidemiology

The risk of anal cancer is increased in patients with CD, mainly in the form of fistula-associated anal carcinoma (carcinoma arising from perianal fistula) [4][6]. Once thought to be rare, anal carcinoma in CD is gaining a growing attention due to increasing reports in the literature [39][40][41][42][43][44][45][46][47]. On the other hand, it is difficult to define its exact incidence because of the lack of population-based studies. As a consequence, there is no unanimous consensus on its diagnosis, surveillance and overall management.

A large case–control study by Beaugerie et al. [16] reported an incidence of 0.38 and 0.26 per 1000 patients/year for adenocarcinoma (ADC) and squamous cell carcinoma (SCC), respectively, after prospectively monitoring more than 2900 patients with a history of active or previous anal/perianal CD. Moreover, a long-standing perianal fistulas history (>10 years) seems the main risk factor for the onset of anal malignancies in CD, as confirmed by other studies [48][49][50].

Similar results were shown by a systematic review, reporting ADC as the most frequently reported histotype among patients with anal fistulizing CD, followed by SCC [51].

Patients with fistula-associated carcinoma in CD have a poor prognosis, with a 5-year survival rate of 37% compared with 60% in the general population [52].

In a systematic review analyzing 65 ADC cases, 30 patients died after a median follow up of 20.5 months, with an overall survival rate at 1, 3 and 5 years of 88%, 54% and 26%, respectively [43]. Prognosis for SCC is dismal as

well. A literature review [45] analyzed 17 patients with a 3.5-year median follow up: 8 patients died of primary cancer (47%), 7 of which in the first year, while the median survival among the survivor was 5 years (0.25–25 years range).

The reason behind this poor prognosis seems to be the delay of diagnosis due to the similarity of the symptoms with the ones of severe perianal disease, such as pain, recurrent abscesses and intractable fistulas. Accordingly, any change in the severity of symptoms, such as a new onset of incontinence, new or different pain, bloody mucus discharge and obstruction, should be considered as a warning sign for the possible onset of cancer.

3.2. Pathogenesis and Risk Factors

The pathogenesis of fistula-associated anal carcinoma in CD likely follows the same paradigm of longstanding colitis, triggered by chronic inflammation and mucosal hyperplasia followed by dysplasia and carcinoma [44]. It is not clear if ADC arises from the epithelial lining of the fistula or from rectal-type mucosa cells migrating to the perianal fistula [50]. Regarding SCC, the same authors reported the presence of high-risk human papilloma virus (HPV) in all the patients with SCC and IBD, confirming the link between HPV infection history and perianal fistula-associated SCC also in IBD patients [50].

The impact of immunosuppressant and biologic drugs on anal cancer onset in CD still remains unclear: on one hand, the reduction of inflammatory activity could lower the cancer incidence; on the other hand, a suppressed immune system could also lead to increasing the risk of carcinoma [50][51][53][54], but these results were not supported by subsequent studies [49][55][56][57]. Further studies are needed to clarify these aspects.

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