Increased risk of colonic neoplasia in patients with sporadic duodenal adenoma

Augmentation du risque de néoplasies coliques en cas d’adénome duodénal sporadique

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Summary

Background. — Recent studies have shown an increased risk of colorectal neoplasia in patients with duodenal neoplasia. The aim of this retrospective case-control study was to confirm this risk.

Patients and methods. — Rate of colorectal neoplasia in 29 patients with one or more duodenal adenomas were compared with controls matched for gender and age, but without duodenal adenomas (one case to two controls). Patients with neoplasia of the ampulla, familial adenomatous polyposis or other known hereditary conditions of the digestive tract were excluded. Indications for upper and lower gastrointestinal endoscopy in controls were abdominal pain or changes in bowel habits. Controls with anemia or digestive bleeding were not included. Neoplastic lesions found at colonoscopy were classified as adenomas, advanced adenomas (size ≥ 10 mm, villous component, high-grade dysplasia), cancers and advanced neoplasia (cancers and advanced adenomas). Comparison between groups was by Fisher’s exact test or Student’s \( t \) test. Odds-ratios (OR) and 95% confidence intervals were calculated, if the difference was significant.

Results. — Mean age of the 29 cases (seven women, 22 men) was 63.2 years and that of the 58 controls (14 women, 44 men) was 62.5 years. First-degree family history of colorectal cancer was present in four cases (13.8%) and eight controls (13.8%) (NS). Colonoscopy showed at least one adenoma in 15 cases (51.7%) and 11 controls (19%) (\( P = 0.0027; \) OR 1.87, 1.0–3.49), advanced adenomas in four cases (13.8%) and three controls (5.2%) (NS), and colonic adenocarcinoma in three cases (10.3%) and no controls (0%) (\( P = 0.03 \)). Advanced neoplasia was present in seven cases (24.1%) and three controls (5.2%) (\( P = 0.014; \) OR 2.86, 0.96–8.52). Results were not significantly modified after the exclusion of patients with a family history of colorectal cancer.

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Conclusion. — Although lacking in statistical power, these results confirm that patients with sporadic duodenal adenoma are at high risk of colonic adenoma and advanced neoplasia, warranting systematic colonoscopy.

Résumé

Introduction. — Des études récentes ont montré une augmentation importante du risque de néoplasie colorectale chez les malades ayant un adénome duodénal. Le but de cette étude cas témoins rétrospective était de confirmer ce risque.

Patients et méthodes. — Les résultats de la coloscopie réalisée dans un centre hospitalier universitaire chez 29 patients ayant un ou plusieurs adénomes duodénaux sporadiques ont été comparés à ceux d’un groupe témoin indemne d’adénomes duodénaux, apparié sur le sexe et l’âge dans un rapport 1:2. Les patients avec néoplasie ampullaire, polypos adénomateuse familiale ou autre maladie héréditaire connue du tube digestif ont été exclus. Les témoins avaient eu une exploration endoscopique haute et basse pour explorer des douleurs abdominales ou des troubles du transit; ceux ayant une anémie ou une hémorragie digestive étaient exclus. Les lésions néoplasiques trouvées à la coloscopie ont été classées en adénomes, adénomes avancés (taille ≥ 10 mm, contingent villoux ou dysplasie de haut grade), cancers et néoplasies avancées (regroupement des cancers et des adénomes avancés). La comparaison entre les groupes a été faite à l’aide du test exact de Fisher ou le t-test. Les odds-ratios (OR) et les intervalles de confiance à 95 % ont été calculés en cas de différence significative.

Résultats. — L’âge moyen des 29 cas (sept femmes et 22 hommes) était de 63,2 ans et celui des 58 témoins (14 femmes et 44 hommes) de 62,5 ans. Des antécédents familiaux de cancer colorectal au premier degré étaient présents chez quatre cas (13,8 %) et huit témoins (13,8 %) (p = NS). La coloscopie montrait un ou plusieurs adénomes chez 15 cas (51,7 %) et 11 témoins (19 %) (p = 0,0027) (OR 1,87 [1,0—3,49]), des adénomes avancés chez quatre cas (13,8 %) et trois témoins (5,2 %) (p = NS), un adénocarcinome colique chez trois cas (10,3 %) et chez aucun témoin (0 %) (p = 0,03). Une néoplasie avancée était présente chez sept cas (24,1 %) et trois témoins (5,2 %) (p = 0,014) (OR 2,86 [0,96—8,52]). Les résultats n’étaient pas significativement modifiés après exclusion des patients ayant des antécédents familiaux de cancer colorectal.

Conclusion. — Malgré le manque de puissance de cette étude, ces résultats confirment que les patients ayant un adénome duodénal sporadique constituent un groupe à risque élevé d’adénomes et de néoplasies avancées, justifiant la réalisation d’une coloscopie.

Introduction

The prevalence of duodenal adenoma is low, estimated to be 1 to 3 per 1000 in endoscopy series [1]. These adenomas are commonly associated with familial adenomatous polyposis (FAP), a disease transmitted by autosomal-dominant inheritance with an estimated prevalence of 1 per 13,000 to 1 per 18,000 births [2]. In this context, the cumulative risk of duodenal adenoma at 70 years is 90%, and 50% for stage IV adenomas according to the Spiegelman classification [3]. The association with neoplasia of the duodenum is also described with attenuated MYH-associated polyposis (autosomal-recessive FAP due to mutations in the MUTYH gene) [4,5], hereditary non-polyposis colorectal cancer (HNPCC) [6] and other familial polyposis syndromes [7].

The risk of colonic cancer in patients with sporadic extrapapillary duodenal adenoma is found.

Patients and methods

This was a retrospective case-control study conducted at the Reims University Hospital Center. The cases included all patients who presented with one or more pathology-proven sporadic adenomas of the duodenum discovered during upper gastrointestinal endoscopy performed over a 10-year period (1997—2007). Patients with a personal or family history of FAP or HNPCC syndrome, von Recklinghausen’s disease and adenoma located in the ampulla were excluded. Patients also had to have undergone a complete colonoscopy for inclusion. The following data were also recorded:

- gender;
- age;
- indication for upper gastrointestinal endoscopy;
• localization, size and pathological findings of the duodenal lesion;
• indications for and results of the colonoscopy;
• time interval between the upper gastrointestinal endoscopy and colonoscopy.

The data collected for the study cases were compared with those recorded for gender — and age — (± 5 years) matched controls (two controls for each case). The controls had also undergone gastrointestinal endoscopy during the same time period, but were free of duodenal adenoma. Upper and lower gastrointestinal endoscopy had been performed in controls because of abdominal pain or changes in bowel habits. Controls with anemia or signs of gastrointestinal- nal bleeding were excluded. A history of colorectal cancer in first-degree relatives was noted in both cases and controls.

The number, size and localization of resected polyps were recorded during the colonoscopy, and the Vienna classification was used to report the pathological findings [12]. When several lesions were identified during colonoscopy, the most severe pathological finding was retained for the present analysis. Advanced adenoma was defined as a lesion that measured 10 mm or more, presented with high-grade dysplasia or a villous component, or had an association of these criteria. Advanced neoplasia was defined as the presence of cancer or an advanced adenoma.

Statistical analysis

The clinical, endoscopic and pathological variables included:
• number (n);
• corresponding percentage (%) for discrete variables;
• mean (m) and standard deviation (S.D.) or median (md) and range for non-date variables.

Data items were compared using Fisher’s exact test for discrete variables and Student’s t test for non-discrete variables.

Conditional logistic regression adapted for case-control studies with two matched controls per case was applied. The significance threshold was set at $P < 0.05$. Odds-ratios (OR) and 95% confidence intervals (95CI) were determined for significant differences. The same analysis was applied after excluding from each group the patients with a family history of colorectal cancer.

Duodenal adenomas

Mean size of the neoplastic duodenal lesions was 6.9 mm (S.D. 9.1, range 2—50 mm). In six cases (20.7%), the duodenal adenoma measured greater or equal to 10 mm. All lesions were adenomas, classified as low-grade dysplasia in 28 cases (96.5%) and high-grade dysplasia in one case (3.5%). The adenoma was villous in two cases (6.9%) and tubular in 27 cases (93.1%).

Colonoscopy results

Colonoscopy was performed over the same time period as the upper gastrointestinal procedure in 20 patients (69%), and had been carried out before the discovery of the duodenal adenoma in three cases (mean 2.3 years, range 2—3 years). In six cases (21%), it had been done following the discovery of a duodenal adenoma during an initial upper procedure.

At least one colorectal neoplastic lesion was reported in 18 cases (62.1%) (Table 1). The lesion was unique in five cases (27.8%), while eight patients (44.4%) had two synchronous lesions and five (17.2%) had at least three synchronous colorectal lesions (3—6 lesions). These lesions were located in the left colon or rectosigmoid colon in four cases, in the right or transverse colon in five cases and in multiple locations in nine cases.

Mean and median sizes of the colorectal lesions were 8.9 mm and 5 mm, respectively (S.D. 13.1 mm, range 2—50 mm). Fifteen cases (51.7%) had at least one adenoma, classified as low-grade dysplasia in 13 and high-grade dysplasia in two. Among the 13 patients with low-grade dysplasia, two had advanced adenoma (one patient had a villous component and the other had a lesion measuring greater than 10 mm).

Overall, an advanced adenoma was found in four out of 18 cases (13.8%). Colonoscopy revealed adenocarcinoma in three cases (10.3%). In these three patients, colonoscopy was performed during the same time period as the upper gastrointestinal procedure because of either abdominal pain or anemia. Seven patients (24.1%) presented with advanced neoplasia. However, colonoscopy results did not differ as a function of the indication: four of six patients (67%) underwent colonoscopy after an upper procedure had revealed duodenal adenoma, and 14 of 23 adenoma cases (61%) had undergone colonoscopy for other reasons. The rate of colorectal neoplasia was 67% in those with associated anemia vs 61.5% in the others (not significant).

In the control group, 11 (19%) had a colorectal lesion, and all lesions were adenomatous (Table 1). Among these 11 patients, three (5.2%) had an advanced adenoma (size ≥ 10 mm). However, high-grade dysplasia or cancer was never seen. Mean and median sizes of the colorectal
lesions were 6.4 mm and 5 mm, respectively (S.D. 2.8, range 2–15 mm). Two controls (3.45%) had at least three polyps at colonoscopy (range 3–4).

The rate of colorectal neoplasia was significantly higher in the cases than in the controls (Table 1). The relative risk of colorectal neoplasia was 2.27 (95CI: 1.2–4.3, \( P = 0.0001 \)). The relative risks of adenoma and advanced neoplasia were 1.87 and 2.86, respectively, but included 1.0 in the confidence interval. These results were not significantly altered after exclusion of patients with a family history of colorectal cancer.

**Discussion**

This study confirms the association between sporadic duodenal adenoma and colorectal neoplasia. The prevalence of colorectal neoplasia was significantly higher in patients with sporadic duodenal adenoma than in the asymptomatic controls free of duodenal adenoma, but matched for age and gender (62.1% vs 18.6%, \( P = 0.0001 \)). The OR for colorectal neoplasia was an estimated 2.27 (1.2–4.3). Colonic adenomas were also more frequent in patients with duodenal adenoma (51.7% vs 19%, \( P = 0.0027 \); OR 1.87 [1.0–3.49]), but the interval of confidence including 1.0 was not significant, probably because of the lack of statistical power related to sample size. This lack of power has also been noted in other studies of the same topic (Table 2). In the French series [10], the OR for advanced colorectal cancer was 8.9 (2.1–53.3), but there were no significant differences in the prevalences of colonic adenoma between patients with and without duodenal adenoma (31.4% vs 24.3%, respectively). In the two other published studies [9,11], the OR for colorectal neoplasia was significantly different between cases and controls (2.5 and 3.6, respectively), but with no difference for colonic adenomas (36% and 35%, respectively). Duodenal adenomas are rare, except in patients with a genetic predisposition. The inclusion of a larger number of patients may be achieved by a prospective multicenter study, although such a review would be difficult to carry out.

In our present series, the duodenal lesions observed were often small – 79.3% were less than 10 mm – with low-grade dysplasia (96.5%), and no cases of duodenal cancer were observed. In the three other series [9–11], the duodenal lesions were often greater than 10 mm (51.4%, 50% and 45% of lesions, respectively) and often with high-grade dysplasia or cancer (36%, 4% and 17%, respectively).

In the only other study reporting a time interval between the upper and lower colonoscopies [10], 43% of the lower procedures were performed during the same time period as the upper procedures compared with 69% in our present series. Also, the results did not change when patients with a family history of colorectal cancer were excluded from the analyses to limit bias.

The main selection bias in the present study was the inclusion of patients with anemia or overt signs of digestive bleeding into our case group. Although these patients accounted for 10.3% of our cases, they did not have a higher rate of colorectal neoplasia than the other patients with duodenal adenoma (67% vs 61.5%, respectively).

The prevalence of colonic neoplastic lesions in the controls was similar to that found in asymptomatic populations in the 50–66 year age range [13]. For this reason, we consider our control group to be closely similar to the general population in this age range. In that study [13], the prevalence of advanced colorectal cancer was 5.9% vs 5.2% in

### Table 1 Colonscopy data.

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 29)</th>
<th>Controls (n = 58)</th>
<th>( P )</th>
<th>Odds-ratio (95CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomas, n (%)</td>
<td>15 (51.7)</td>
<td>11 (19)</td>
<td>0.0027</td>
<td>1.87 (1.0–3.49)</td>
</tr>
<tr>
<td>Advanced neoplasia, n (%)</td>
<td>7 (24.1)</td>
<td>3 (5.2)</td>
<td>0.014</td>
<td>2.86 (0.96–8.52)</td>
</tr>
<tr>
<td>Advanced adenoma, n (%)</td>
<td>4 (13.8)</td>
<td>3 (5.2)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>Adenocarcinoma, n (%)</td>
<td>3 (10.3)</td>
<td>0</td>
<td>0.03</td>
<td>Not valid</td>
</tr>
<tr>
<td>All neoplasia, n (%)</td>
<td>18 (62.1)</td>
<td>11 (18.6)</td>
<td>0.0001</td>
<td>2.27 (1.2–4.3)</td>
</tr>
</tbody>
</table>

95CI: 95% confidence interval; NS: not significant. \( a \) Fisher’s exact test.

### Table 2 Risk of colorectal adenomas, advanced adenomas, neoplasia and advanced neoplasia in patients with sporadic duodenal adenoma: results of published case-control studies.

<table>
<thead>
<tr>
<th></th>
<th>Adenomas</th>
<th>Advanced adenomas</th>
<th>Neoplasia</th>
<th>Advanced neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray et al. [9]</td>
<td>36%</td>
<td>18%</td>
<td>56%</td>
<td>38%</td>
</tr>
<tr>
<td>Pequin et al. [10]</td>
<td>NS</td>
<td>NS</td>
<td>OR 2.5 (1.1–5.4)</td>
<td>OR 2.7 (1.0–5.2)</td>
</tr>
<tr>
<td>Ramsoekh et al. [11]</td>
<td>35%</td>
<td>18%</td>
<td>OR 10.1 (1.8–100.1)</td>
<td>NS</td>
</tr>
<tr>
<td>The present series</td>
<td>51.7%</td>
<td>13.8%</td>
<td>OR 7.8 (2.1–29.4)</td>
<td>OR 3.6 (1.7–7.4)</td>
</tr>
</tbody>
</table>

OR: odds-ratios vs controls, followed by 95% confidence interval in parentheses; NS: not significant.
our controls. In another study focused on asymptomatic subjects aged 50—59 years [14], their prevalence of colorectal adenoma was 16% vs 19% in our control group, and the prevalence for advanced neoplasia was 4% vs 5.2% in our series.

Three or more colonic adenomas were found in 17.2% of cases vs 3.45% of controls. Thus, we hypothesize that these patients had a genetic predisposition for colorectal adenoma. The idea of a weakly expressed MYH-associated adenomatous polyposis should be tested. This is an attenuated polyposis wherein patients present with 15—100 colorectal adenomas with associated duodenal polyposis [15]. None of our patients had that many duodenal or colonic adenomas. The pathogenesis of multiple colonic adenomas (5—15 lesions) remains poorly understood, and it is not known whether the MUTYH gene could be favoring their development. As for the associated duodenal involvement, further objective evaluation is needed. A complementary study is currently underway to identify any immunohistochemical differences between the so-called sporadic duodenal adenoma and those that develop within the context of a known genetic predisposition such as FAP.

In conclusion, considering the high risk of colorectal neoplasia, it would be reasonable to recommend colonoscopy screening for all patients with sporadic duodenal adenoma.

References