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BRIEF ARTICLE

Papillary thyroid cancer and inflammatory bowel disease: Is there a relationship?

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Abstract

AIM: To formally study age of diagnosis of papillary thyroid cancer (PTC) in inflammatory bowel disease (IBD) patients and evaluate the prevalence of PTC in IBD patients compared to a control population.

METHODS: We were interested in testing the hypothesis that patients with IBD are more likely to be diagnosed with PTC than a control population. A retrospective cohort analysis was performed using the University of Pennsylvania Health System's electronic database. Outpatients from 1998-2009 were included in the search, and patients in the cohort were selected based on ICD-9 codes. Inclusion criteria included the diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) and the concurrent diagnosis of thyroid cancer in comparison to a control population. Using these methods 912 patients with CD and 1774 with UC were compared to 1638 diverticulitis and 19 447 asthma controls. Statistics were performed using corrected chi-square analysis. The primary outcome for this study was the diagnosis of PTC. Approval to conduct this study was obtained by the Institutional Review Board at the University of Pennsylvania.

RESULTS: The mean age was 47.5 years (range: 18-102 years) and 66% patients were female. An analysis of variance model was used to compare the age of PTC diagnosis between the CD, UC, asthma and diverticulitis groups, and a statistically significant difference in age at PTC diagnosis was noted across all groups (F = 6.35, df = 3, P = 0.0006). The age of PTC diagnosis in CD patients was statistically significantly lower than UC, asthma, and diverticulitis patients (average PTC diagnosis age for CD 25, UC 49, asthma 45, diverticulitis 63). After covarying for sex and age in 2009, the difference in age at PTC diagnosis remained statistically significant (F = 4.13, df = 3, P = 0.0089). A total of 86 patients were diagnosed with PTC. Nine patients (0.5%) with UC were diagnosed with PTC. Patients with UC were not shown to be more likely to develop PTC [odds ratio (OR): 1.544, 95%CI 0.767-3.108] compared to asthma controls. Four patients (0.4%) with CD were diagnosed with PTC. Patients with CD were not shown to be more likely to develop PTC (OR: 1.334, 95%CI 0.485-3.672) compared to a control population with asthma. Nine patients (0.5%) with a history of diverticulitis were diagnosed with PTC. Pa-

tients with diverticulitis were not shown to be more likely to develop PTC (OR: 1.673, 95%CI 0.831-3.368) compared to asthma controls. Patients with CD or UC were not less likely to develop PTC compared to those with diverticulitis (CD OR: 0.80, 95%CI 0.25-2.60; UC OR: 0.92, 95%CI 0.37-2.33). None of the patients used immunosuppressant medications prior to the diagnosis of PTC (azathioprine, 6-mercaptopurine, and methotrexate).

CONCLUSION: There is a significant difference in age of diagnosis of PTC in patients with CD compared to patients with UC and the control populations studied.

Key words: Papillary thyroid cancer; Inflammatory bowel disease; Crohn disease; Ulcerative colitis

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INTRODUCTION

Inflammatory bowel diseases (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC), are idiopathic chronic inflammatory disorders resulting from defects in the barrier function of the intestinal epithelium and inappropriate activation of the mucosal immune system. IBD is also associated with several other extra-intestinal disease states, including ankylosing spondylitis, arthritis, pyoderma gangrenosum, and uveitis[1]. Less is known about the association of IBD with diseases of the thyroid.

Early studies have suggested a relationship between thyroid abnormalities and IBD[2]. For example, CD has been associated with Graves' disease and Hashimoto' s thyroiditis[3]. However, the association with IBD and thyroid cancer has been less critically analyzed. Thyroid cancer is the most common endocrine cancer, with over 80% of all cases consisting of the papillary type. It is more common in women than in men (3:1 ratio) and is more common in whites than in African-Americans. The mean age of diagnosis is 40 years old[4]. There are several case reports of thyroid cancer in patients with IBD, two of them involving UC[5,6]. Moss *et al*[7] described five cases of papillary thyroid cancer (PTC) in patients with preexisting CD. Despite these anecdotal published findings, there have been no formal studies evaluating the relationship that exists between PTC and IBD in a population cohort study.

It is uncertain whether PTC in patients with IBD is due to an association or coincidence. Knowledge of a relationship is important in order to determine the factors that link IBD and PTC. Exposure to radiation and multivitamin intake are both considered risk factors for PTC, both of which are common in patients with IBD due to diagnostic studies and malnutrition respectively[8]. However, a recent study by Peloquin *et al*[9] concluded that the radiation exposure in an IBD population was equivalent to the average annual background radiation dose from naturally occurring sources in the United States, while a smaller subset of patients had substantially higher doses. In addition, immunosuppressants such as azathioprine and 6-mercaptopurine are commonly taken by patients with IBD to induce remission and can increase the risk of malignancy, specifically lymphoproliferative disorders[10,11]. Whether these medications increase the risk of thyroid cancer is unknown.

It is already established that an inappropriate inflammatory response results in IBD. Defects in genes involving the innate immune system and activation of inflammatory cytokines such as NOD2, autophagy-related 16-like 1, and interleukin-23 lead to intestinal inflammation[12,13]. Similarly, lymphocytic infiltration is seen in PTC, suggesting that immunologic factors may contribute to neoplastic development[14]. Thus, the inflammatory modulators involved in the pathogenesis of IBD may have an effect on PTC development.

This study addressed an important question regarding the epidemiology of IBD and PTC. The specific aim of this study was to identify any relationships between the two diseases and to determine whether patients with IBD have a higher prevalence of PTC than a control population. Knowledge of an association if present has potential to impact the management of patients with IBD, which may warrant screening for thyroid cancer through regular thyroid examinations.

MATERIALS AND METHODS

Definition of the cohort

A retrospective cohort study from within the University of Pennsylvania Health System was performed using the data from the electronic health system database (EPIC Hyperspace Summer 2009 IU 6, EPIC Systems Corporation, Verona, Wisconsin, United States). Patients who were seen as outpatients in our health system from 1998 to 2009 were included in the search. Patients with CD and UC were identified based on ICD-9 codes (ICD-9 codes for CD: 555, 550.0, 555.1, 555.9; codes for UC: 556, 556.0, 556.1, 556.2, 556.3, 556.5, 556.6, 556.8, 556.9).

Inclusion criteria included the diagnosis of CD or UC and the concurrent diagnosis of thyroid cancer. The latter diagnosis was identified using the ICD-9 code for thyroid cancer: 193. The papillary type of thyroid cancer was verified using biopsy reports or the patients' medical records. Patients who met inclusion criteria were included in the final analysis and were compared to patients with inflammatory controls with diverticulitis and asthma. Controls were identified based on a search of our electronic database using ICD-9 codes (ICD-9 code

Table 1 Concomitant diagnosis of papillary thyroid cancer

Diagnosis	No. of patients diagnosed with PTC	Unadjusted OR (95%CI) compared to asthma controls	OR (95%CI) compared to asthma controls, adjusted for sex and age in 2009
CD	4	1.334 (0.485-3.672)	1.510 (0.548-4.162)
UC	9	1.544 (0.767-3.108)	1.679 (0.832-3.389)
Diverticulitis	9	1.673 (0.831-3.368)	1.338 (0.644-2.779)
Asthma	64	NA	NA

OR: Odds ratio; PTC: Papillary thyroid cancer; NA: Not available.

for diverticulitis: 562.11, 562.13; code for asthma: 493). Approval was obtained from the Institutional Review Board at the University of Pennsylvania to perform our study.

Definition of outcome

The primary outcome for this study was a diagnosis of PTC. We did not limit our outcome definition to an incident diagnosis of PTC following a diagnosis of IBD. We were interested in testing the hypothesis that patients with IBD are more likely to be diagnosed with PTC than a control population, not that IBD in and of itself predisposes patients to PTC. As such, we searched for any diagnosis of PTC at any time in the patients' records.

Statistical analysis

All analyses were performed separately for patients with CD and UC, and then as a combined IBD group. Analyses began with descriptive statistics. Continuous variables were reported as means ± SD. Categorical variables were reported as counts and percentages. Since age was approximately normally distributed, we used analysis of variance to test for differences in the mean age at diagnosis of PTC[15]. Statistical analysis was performed at the University of Pennsylvania, Philadelphia, PA using SAS software version 9.2 (SAS Institute, Cary, NC).

To estimate the association between PTC and IBD in this cross-sectional study, we calculated the odds ratio (OR) and 95%CI using logistic regression. We considered a finding to be statistically significance when $P < 0.05$.

Sample size and power calculations

A two group continuity corrected χ^2 test with a 0.050 two-sided significance level had 80% power to detect the difference between a proportion of 0.3% in the asthma group and a proportion of 0.8% in the UC group (OR of 2.41) when the sample sizes are 19 447 and 1774, respectively (a total sample size of 21 221). A two group continuity corrected χ^2 test with a 0.050 two-sided significance level had 80% power to detect the difference between a proportion of 0.3% in the asthma group and a proportion of 1.0% in the UC group (OR of 3.02) when the sample sizes are 19 447 and 912, respectively (a total sample size of 20 359).

RESULTS

Our retrospective analysis yielded a total of 2686 patients who were diagnosed with either CD or UC. A total of 912 patients with CD and 1774 patients with UC met inclusion criteria and were included in our analysis. These patients were compared to 1638 diverticulitis and 19447 asthma controls.

The overall mean age was 47.5 years (range: 18-102 years) and 66% patients were female. Using an analysis of variance model to compare the age of thyroid diagnosis between the CD, UC, asthma and diverticulitis groups, a statistically significant difference in age at PTC diagnosis was noted across all groups ($F = 6.35$, df = 3, $P = 0.0006$). Of note, the age of PTC diagnosis in CD patients was statistically significantly lower than UC, asthma, and diverticulitis patients (average PTC diagnosis age for CD: 25 years, UC 49 years, asthma: 45 years, diverticulitis: 63 years). After covarying for sex and age in 2009, the difference in age at PTC diagnosis remained statistically significant ($F = 4.13$, df = 3, $P = 0.0089$).

A total of 86 patients were diagnosed with PTC. Nine patients (0.5%) with UC were diagnosed with PTC. Patients with UC were not shown to be more likely to develop PTC (OR: 1.544, 95%CI 0.767-3.108) compared to asthma controls. Four patients (0.4%) with CD were diagnosed with PTC. Patients with CD were not shown to be more likely to develop PTC (OR: 1.334, 95%CI 0.485-3.672) compared to a control population with asthma. Nine patients (0.5%) with a history of diverticulitis were diagnosed with PTC. Patients with diverticulitis were not shown to be more likely to develop PTC (OR: 1.673, 95%CI 0.831-3.368) compared to asthma controls (Table 1).

Patients with CD or UC were not less likely to develop PTC compared to those with diverticulitis (CD OR: 0.80, 95%CI 0.25-2.60; UC OR: 0.92, 95%CI 0.37-2.33). None of the patients used immunosuppressant medications prior to the diagnosis of PTC (azathioprine, 6-mercaptopurine, and methotrexate).

DISCUSSION

The results of our present study highlights a statistically significant difference in age of diagnosis of PTC in patients with CD compared to patients with UC and the control populations studied. Patients with CD are diagnosed with PTC at a much younger age, possibly due to a unique pathogenetic mechanism of disease occurring in this subset of patients. It is established that CD results from a variety of factors, including genetic, environmental and immunological factors. An inappropriate inflammatory reaction is a key factor in the pathogenesis of CD. Similarly, PTC involves an inflammatory reaction, in particular, a lymphocytic infiltration of thyroid tissue[14]. Thus, overlapping immunologic factors/pathways may connect these two diseases together. The inflammatory modulators involved in the pathogenesis of IBD

may have an effect on PTC development or PTC may predispose patients to developing IBD.

In addition there have been specific genetic mutations described to be present in patients with CD. The initial frameshift mutation described was in the *NOD-2* gene in 2001[16]. Data from epidemiological studies, based on concordance data in family studies via linkage analysis to genomewide association studies, highlight evidence for over 30 distinct genomic loci involved in the genetic susceptibility to CD. These loci encode genes involved in a number of homeostatic mechanisms: innate pattern recognition receptors, the differentiation of Th17-lymphocytes, autophagy, maintenance of epithelial barrier integrity, and the orchestration of the secondary immune response[17] It is perceived that recognition of these loci will help to improve our understanding of the pathophysiology of CD.

Similarly, there have been several genetic mutations described in patients with PTC, the most common involving the RET/papillary thyroid carcinomas 1 (PTC1) and RET/PTC3 rearrangements which account for more than 90% of all genetic rearrangements found in PTC, and have been found in 30%-40% of adult patients with sporadic PTC in the United States, Italy, and Canada[18]. Other genetic mutations include the neurotrophic tyrosine kinase, receptor, type 1 (NTRK1) rearrangement, Ras kinases and Raf kinases[19-23]. In addition, recent literature has incited the presence of 7 gene regions to be associated with PTC[24]. These results suggest a possible role of genes involved in maintenance of genomic integrity in relation to risk of PTC.

Several studies determined significantly higher oncogenic rearrangements of RET and NTRK1 proto-oncogenes in patients with PTC that occurred primarily in children and young adults. An analysis of 92 patients with PTC determined that patients age 4-30 years had significantly higher frequency of *RET* or *NTRK1* gene compared to those 31-80 years (57% *vs* 32%, $P = 0.019$). Further, among patients ages 4-19 years, 67% of them displayed RET gene rearrangement[25]. Studies by Jhiang *et al*[26] and Soares *et al*[27] found that patients displaying RET rearrangement in their PTC had significantly lower mean age at diagnosis than those whose PTC did not present this rearrangement (32 years *vs* 50 years, $P < 0.05$ and 28 years *vs* 45 years, $P = 0.005$, respectively)[26,27]. An assessment of spontaneous PTC in 33 young patients ages 6-21 years showed that the RET/PTC1 rearrangement was common in the sporadic form of children with PTC (53%), with the RET/PTC3 mutation more commonly seen among children with PTC secondary to radiation exposure (67%-76%) as reported in prior studies[28-31].

One limitation to this study is the small number of patients who were found to have PTC. With so few patients with both diagnoses, it was difficult to elucidate a temporal relationship between the two diseases. Some patients were diagnosed with PTC followed by a CD diagnosis, and vice versa. A larger study would help establish whether there is a diagnosis pattern. The findings on prevalence do not suggest a higher prevalence of PTC in patients with IBD compared to the control populations studied. We cannot exclude the potential for a type Ⅱ error given that our study was underpowered. A study using a much larger cohort of patients would be better-powered and would more likely lead to statistically significant results and better define a lack of relationship between the two diseases.

There were several other limitations to this study. We did not test for confounding; we did not examine other thyroid conditions including Graves disease, Hashimoto's thyroiditis, goiter, and non-papillary type thyroid cancer as potential confounder variables. The other limitation of our study is that some relevant clinical information from the past medical history of patients may not have been included in the electronic database and thus may have been potentially omitted. This is a common limitation of retrospective studies.

In summary, the results of our study suggest that patients with CD who are also diagnosed with PTC are diagnosed at a much younger age than patients with UC and other controls. This is important for cancer detection in CD patients. Currently age, gender, radiation exposure, and a low iodine diet are the only known clinical risk factors for PTC; further studies are needed to establish whether patients with CD are at increased risk of developing PTC. If there is an increased risk, then more stringent methods of cancer screening may be warranted for CD patients, including initiating screening at a younger age.

COMMENTS

Background

Inflammatory bowel diseases (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC), are idiopathic chronic inflammatory disorders resulting from defects in the barrier function of the intestinal epithelium and inappropriate activation of the mucosal immune system. Early studies have suggested a relationship between thyroid abnormalities and IBD. For example, CD has been associated with Graves' disease and Hashimoto's thyroiditis. However, the association with IBD and thyroid cancer has been less critically analyzed. The aim of this study was to formerly study the age of diagnosis of papillary thyroid cancer (PTC) in IBD patients and evaluate the prevalence of PTC in IBD patients compared to a control population.

Research frontiers

This study addressed an important question regarding the epidemiology of IBD and PTC. The results suggest that CD patients are diagnosed with PTC at a much younger age, possibly due to a unique pathogenetic mechanism of disease occurs in this subset of patients.

Innovations and breakthroughs

The researchers drew a conclusion that there is a significant difference in age of diagnosis of PTC in patients with CD compared to patients with UC and the control populations studied. Patients with CD are diagnosed with PTC at a much younger age, possibly due to a unique pathogenetic mechanism of disease occurs in this subset of patients. It is established that CD results from a variety of factors, including genetic, environmental and immunological factors. An inappropriate inflammatory reaction is a key factor in the pathogenesis of CD. Similarly, PTC involves an inflammatory reaction, in particular, a lymphocytic infiltration of thyroid tissue. Thus, overlapping immunologic factors/pathways may connect these two diseases together. The inflammatory modulators involved in the pathogenesis of IBD may have an effect on PTC development or PTC may predispose patients to developing IBD.

Applications

This study answers important questions regarding the epidemiology of PTC and IBD, and also addresses the topic of cancer detection in CD patients. Currently age, gender, radiation exposure, and a low iodine diet are the only known clinical risk factors for PTC; further studies are needed to establish whether patients with CD are at increased risk of developing PTC. If there is an increased risk, then more stringent methods of cancer screening may be warranted for CD patients, including initiating screening at a younger age.

Peer review

The paper evaluated on a retrospective cohort study prevalence of PTC in IBD patients compared to a control population. This is a very interesting subject and there are many lacunae in the literature.

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