

## Amyloid Goiter Complicated with Inflammatory Bowel Disease: Literature Review

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### Abstract

Amyloid goiter (AG) is an uncommon complication of inflammatory bowel disease (IBD). Here a literature review of cases of AG developed as a complication in IBD patients was conducted. Among 13 reviewed cases (12 of Crohn's disease and one of ulcerative colitis), AG was diagnosed between the ages of 26 and 58 years. Among these cases, thyroid function was investigated in 12, of which eight showed thyroid function within the normal range, three demonstrated hypothyroidism, and one showed subclinical hypothyroidism. There were no obvious correlations between the development of AG and activity or flare up of IBD. Six of the thirteen cases were complicated with renal failure or nephrotic syndrome due to renal amyloidosis, and one death occurred because of renal failure associated with renal amyloidosis. However, the number of reported concomitant cases of AG and IBD is limited. It may be necessary to accumulate data regarding such concomitant cases to understand these conditions.

**Keywords:** Amyloid goiter; Amyloidosis; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

### Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two most common forms of inflammatory bowel disease (IBD). Both are chronic recurrent conditions characterized by intestinal inflammation that appears to result from a combination of multiple environmental and/or immunological factors [1]. CD can affect any part of the gastrointestinal tract, whereas UC is characterized by inflammation confined to the large intestine [1]. Microscopically, CD affects the entire bowel wall, whereas UC is restricted to the epithelial lining of the gut [1].

Secondary amyloidosis is a well-known complication of CD, as previous studies reported an incidence of 0.5-9.0% of such cases [2-4], while the prevalence of amyloidosis is reportedly less in UC patients. Amyloid goiter (AG), which is characterized by thyroid enlargement caused by extensive amyloid deposition in the thyroid gland [5-7], is an uncommon complication of IBD. To date, there have been few systematic literature reviews of AG complicated with IBD. Here a literature review to assess the prevalence and characteristics of cases of AG complicated with IBD was conducted.

### Methods

We reviewed the available literature regarding AG complicated with IBD and summarized the findings of all relevant reports. Relevant articles in both English and Spanish were retrieved from the PubMed database. Moreover, relevant articles including proceedings in Japanese were retrieved from the Japana Centra Revuo Medicina (Igakku Chuo Zasshi) database.

### Amyloidosis in IBD patients

Amyloidosis is characterized by the deposition of fibrillary proteins that accumulate in various organs [7,8] and is classified as primary or secondary. Secondary amyloidosis results from a various diseases, including chronic infections such as tuberculosis and chronic inflammation such as what occurs in rheumatoid arthritis, ankylosing spondylitis, and CD [4,6,8-10]. Amyloid A (AA) production in secondary amyloidosis occurs by the increased synthesis of serum AA, which is an acute phase protein produced in the liver in response to inflammation [4,8]. Amyloidosis can manifest in patients of any age, even in children [10]. Although IBD is not typically complicated with amyloidosis, the majority of such patients with secondary amyloidosis also have CD [2].

Greenstein et al. [5] reported 16 cases (0.52%; 15 of CD and one of UC) among 3,050 IBD cases with a prevalence of amyloidosis of 0.88% (15/1709) in CD patients and 0.07% (1/1341) in UC patients. They also reported that only one case (0.03% of all IBD patients and 0.06% of all CD patients) had AG. Moreover, they reviewed 25 IBD cases (22 of CD and three of UC) complicated with amyloidosis and reported the following findings: (1) CD occurred predominantly in males (72.7%, 16/22); (2) amyloid disease was diagnosed at a mean age of 40 years, and the mean duration of the disease was 15 years (range, 1-42 years) after the onset of CD; (3) renal disturbances occurred in 84% (21/25) of IBD patients; and (4) most deaths were associated with renal complications [5]. These findings were in accordance with those of other reports, suggesting that the most common clinical form of amyloidosis is renal amyloidosis and that renal amyloidosis may progress to nephrotic syndrome or renal failure [8].

Some reports have described the resolution of AA amyloidosis after the resection of diseased bowel in IBD [4]. However, it remains controversial whether surgery is an effective treatment for IBD-related amyloidosis due to the risk of intra- or postoperative mortality [8].

## Amyloid Goiter

Focal amyloid deposition in the thyroid gland is common among primary or secondary amyloidosis patients, although the condition is generally undetectable clinically [3,10]. In autopsy studies, amyloid deposition in the thyroid gland is detected in 80% of cases with secondary amyloidosis and 50% of those with primary amyloidosis [3,9]. However, AG is observed in only 0.04% of cases with primary amyloidosis [7].

AG is a relatively uncommon condition characterized by clinically apparent thyroid gland enlargement caused by massive amyloidosis due to non-medullary carcinoma [6,10]. In most cases, AG is associated with amyloid deposition in other organs during the course of systemic amyloidosis and is characterized by the glandular deposition of amyloid AA [10]. Although AG may be associated with either primary or secondary amyloidosis, it most commonly occurs in conjunction with secondary amyloidosis.

AG is clinically characterized by the rapid growth of the thyroid gland, resulting in the development of pressure symptoms [6]. Although thyroid function in AG patients is usually within the normal range, hyper- and hypothyroidism are sometimes encountered [2,6,7,10]. However, Kimura et al. [11] reported that nine of ten (90%) AG patients had abnormal thyroid function, including low triiodothyronine (T3) syndrome, and that five patients had hypothyroidism, one had hyperthyroidism, one had transient hypothyroidism, and two had low T3 syndrome.

### AG in UC patients

Although cases of CD complicated with AG have been sporadically reported, the complications of AG in UC seem to be extremely rare. To

the best of our knowledge, there are no reports of such concomitant cases in English literature. However, one such case was discussed in a Japanese proceeding that involved a 35-year-old female with UC and renal amyloidosis (chronic renal failure on hemodialysis) who developed AG with a slight tendency of hypothyroidism that was diagnosed by fine-needle aspiration biopsy (FNAB) [12]. However, the flare of UC was not detected when she developed AG.

### Characteristics of AG in CD patients

Our literature review identified 12 reports (seven in English, one in Spanish, and four in Japanese) of CD complicated with AG, which are summarized in Table 1 [2,3,5,7,13-19]. The cases of CD with focal amyloid deposition and without goiter were excluded. Among these 12 reported cases, seven occurred in males and four in females, while the sex of one patient was unclear [18]. In these cases, AG was diagnosed between the ages of 26 and 58 years. The major clinical symptoms were the development of a painful neck mass and associated swelling. With regard to thyroid function in the 11 cases, excluding the one case in which it was not mentioned [5], thyroid function in eight cases was within the normal range [2,3,7,13,14,17-19], two cases were diagnosed with hypothyroidism [3,16], and one was diagnosed with subclinical hypothyroidism [15]. These AG cases were diagnosed by histopathological findings and/or Congo red staining after thyroidectomy or FNAB.

Case (year)	Sex	Age at diagnosis of CD (years)	Age at diagnosis of AG (years)	Thyroid function	Flare up of CD	Complications	Reference
1(1992)	F	13	33?	?	?	Chronic renal failure	[5]
2(1995)	M	25	26	Within the normal range	Yes	Subacute thyroiditis-like symptoms	[13]
3(1999)	M	15	26	Within the normal range	No		[2]
4(2000)	M	16	27	Within the normal range	?	Chronic renal failure	[14]
5(2007)	M	?	38	Subclinical hypothyroidism	No	Chronic renal failure	[15]
6(2008)	F	25	30<	Hypothyroidism	?		[16]
7(2009)	F	40?	47	Within the normal range	?	Nephrotic syndrome	[17]
8(2010)	?	?	?	Within the normal range	?		[18]
9(2012)	M	< 21	44	Within the normal range	?		[3]
10(2012)	F	34	46	Slight hypothyroidism	No	Nephrotic syndrome	[3]
11(2014)	M	58?	58	Within the normal range	?		[7]
12(2015)	M	50	56	Within the normal range	No	Subacute thyroiditis and subsequent subacute thyroiditis-like symptoms	[19]

**Table 1:** Characteristics of amyloid goiter in patients with Crohn's disease. CD: Crohn's Disease; AG: Amyloid Goiter; F: Female; M: Male.

Among 12 cases, one reported case suggested that the development of goiter is associated with the activity of CD [13]. However, four cases were reported that showed no correlations between the development of goiter and activity or flare up of CD [2,3,15,19], although these correlations were not mentioned in the remaining seven cases.

Among these 12 cases, three were complicated with chronic renal failure due to renal amyloidosis [5,14,15] and another two were complicated with nephrotic syndrome due to renal amyloidosis [3,17]. One death occurred due to renal failure associated with renal amyloidosis [5].

### Subacute thyroiditis in IBD patients with AG

Among the identified cases of IBD with AG, one was diagnosed with repeated subacute thyroiditis (SAT) and subsequent SAT-like symptoms occurred in one CD patient complicated with AG [19]. Kawashima et al. [19] reported a middle-aged man with AG and CD who developed thyrotoxicosis caused by SAT after the administration of the anti-tumor necrosis factor (TNF)- $\alpha$  inhibitor, infliximab, and subsequent SAT-like symptoms developed after the administration of another TNF- $\alpha$  inhibitor, adalimumab (suspected drug-induced thyroiditis). SAT development in IBD patients is reportedly extremely rare, although Horai et al. [20] reported a female patient who was diagnosed SAT and Takayasu's arteritis more than 20 years after the diagnosis of UC, suggesting that genetic factors may be associated with such an occurrence. Moreover, Kaku et al. [13] reported a young man with CD and AG who developed SAT-like symptoms complicated with AG. Ikenoue et al. [21] reported recurrent SAT-like symptoms in two cases of IBD (one with CD and another with suspected indeterminate colitis) complicated with thyroid amyloidosis. Therefore, AG should be considered in IBD patients with recurrent SAT or SAT-like symptoms.

### Conclusion

A total of 13 cases of IBD complicated with AG were reviewed (12 of CD and one of UC). To discriminate goiter development in IBD (particularly CD) patients, AG should be considered in cases with the rapid development of painful neck masses, onset of repeated SAT or SAT-like symptoms, or presence of renal amyloidosis. However, the number of concomitant cases reported has been limited, and it may be necessary to accumulate these data to understand these conditions.

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