

# Eosinophilic Cholecystitis Occurred in a Patient With Refractory Eosinophilic Airway Inflammation: A Case Report

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## Abstract

**Background:** Eosinophilic cholecystitis (EC) is a rare condition that presents in a manner comparable to acute cholecystitis. The diagnosis is based on classical symptoms of cholecystitis with excessive eosinophilic infiltration within the gallbladder. EC has been reported alone or in combination with manifestations, such as eosinophilic gastrointestinal tract inflammation. However, association with airway inflammation in patients with EC is rare.

**Case Presentation:** We report the case of a 65-year-old man who had refractory eosinophilic chronic rhinosinusitis with bronchial asthma. A second endoscopic sinus surgery (ESS) was performed as treatment for recurrent nasal polyps. EC occurred while inhaled corticosteroids were reduced after ESS. Pathologic examination of the excised gallbladder demonstrated submucosal infiltration with a number of eosinophils. Furthermore, immunohistostaining revealed many galectin-10-positive cells in both the gallbladder mucosa and the paranasal sinus mucosa. Galectin-10 is a major constituent of human eosinophils, also known as the Charcot–Leyden crystal protein, which has been linked with eosinophilic inflammation. Interestingly, nasal polyps were reduced without any additional treatments 1 month after the cholecystectomy.

**Conclusions:** We experienced a rare case wherein EC onset occurred in a patient with refractory eosinophilic airway inflammation during inhaled corticosteroid tapering. Galectin-10 might help diagnose rare cases of eosinophilic inflammation in multiple organs.

## Keywords

asthma, eosinophilic cholecystitis, eosinophilic chronic rhinosinusitis, galectin-10, eosinophilic inflammation

## Background

Eosinophilic cholecystitis (EC) is an uncommon condition that was first described in 1949.<sup>1</sup> The diagnosis of EC is based on classical symptoms of cholecystitis with the presence of >90% eosinophilic infiltration within the gallbladder. Only 64 reports of EC were found based on an online search using PubMed from 1950 to 2017 and Japana Centra Revuo Medicina Web from 1983 to 2017. Most cases of EC are accidentally found due to the pathological diagnosis after cholecystectomy. In a previous report of 625 cases of surgically removed gallbladders, 16 (2.6%) had eosinophilic infiltration, and only 3 (0.05%) fell into EC criteria.<sup>2</sup> It has been reported that EC is not limited to the bladder and can be involved in eosinophilic gastrointestinal tract inflammation, such as eosinophilic cholangiopathy, eosinophilic gastroenteritis,

eosinophilic granulomatous hepatitis, and eosinophilic ascites.<sup>3</sup> In addition, EC can be complicated by eosinophilic granulomatosis with polyangiitis (EGPA) closely associated with airway inflammation. However, EC

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concomitant with only airway inflammation, such as asthma and eosinophilic chronic rhinosinusitis (ECRS), but not EGPA is unusual. ECRS is known as a refractory eosinophilic airway inflammatory disease closely related to bronchial asthma.<sup>4</sup> We experienced a case wherein EC may have been associated with ECRS with asthma, and the existence of eosinophilic inflammation could be confirmed both in the nasal polyp mucosa and in the gallbladder wall mucosa.

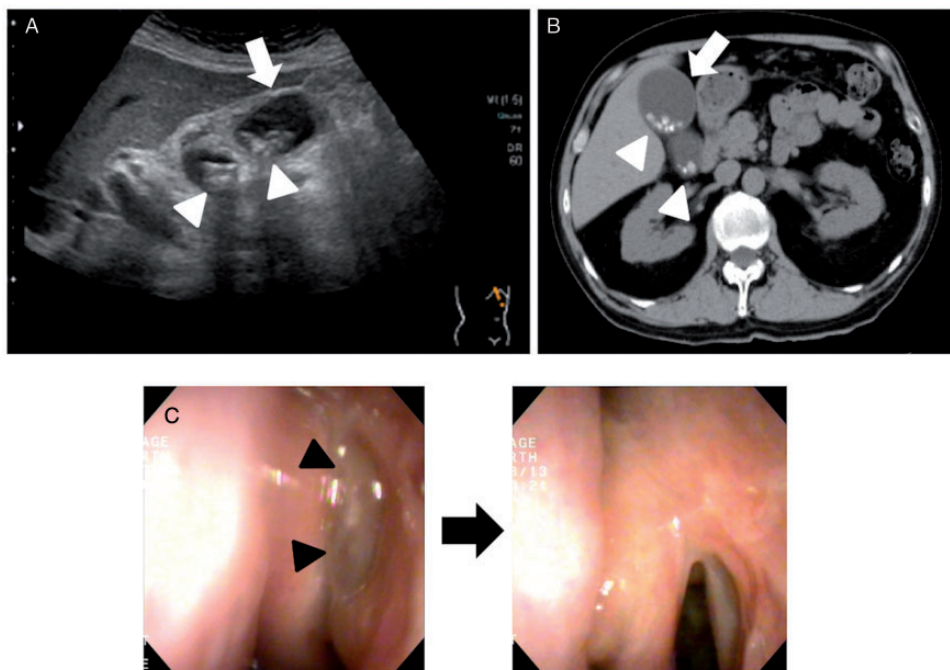
### Case Presentation

A 65-year-old man with poorly controlled ECRS with bronchial asthma had recurrent paranasal sinus polyps, although he underwent endoscopic sinus surgery (ESS) at the age of 58. A second ESS was performed for his refractory ECRS. In addition, inhaled corticosteroid (ICS) exhalation through the nose (ETN) treatment, which provides better control for both asthma and nasal symptoms,<sup>5,6</sup> was initiated instead of conventional ICS exhalation through the mouth treatment. To prevent recurrence of ECRS and reduce asthma symptoms, the doses of ICS were increased to up to 1800  $\mu\text{g}$ . Thirty months after the second ESS, cholecystitis occurred concomitantly with the recurrence of nasal polyps while the doses of ICS were decreased to 1400  $\mu\text{g}$ , 2 months before the onset of biliary colic. After confirmation of the diagnosis with an abdominal ultrasound and a computed tomography scan (Figure 1(A) and (B)),

a cholecystectomy was performed. Pathologic examination of the excised gallbladder demonstrated submucosal infiltration with a number of eosinophils, consistent with EC criteria. There were no histological findings indicating angitis. The laboratory tests at the onset of biliary colic showed a white blood cell count of 6300 cells per  $\mu\text{L}$  with mild eosinophilia (7.7%, 485 per  $\mu\text{L}$ ). Serum total bilirubin was 0.7 mg/dL (normal, 0.2–1.1 mg/dL), aspartate aminotransferase was 32 U/L (normal, 10–40 U/L), alanine aminotransferase was 28 U/L (normal, 5–45 U/L), and alkaline phosphatase was 216 U/L (normal, 110–360 U/L). Thus, no elevation of hepatic functional enzymes was observed when cholecystitis occurred without any signs of inflammation. In addition, serum IgE was 135 IU/mL (normal, 0–320 IU/mL). We confirmed that nasal polyps were concomitantly reduced (from 6 to 4 in polyp score)<sup>7</sup> with decreased blood eosinophils without any additional treatments 1 month after the cholecystectomy (Figure 1(C)) and were recurrence-free with no increase in blood eosinophils for at least 24 months (Figure 2).

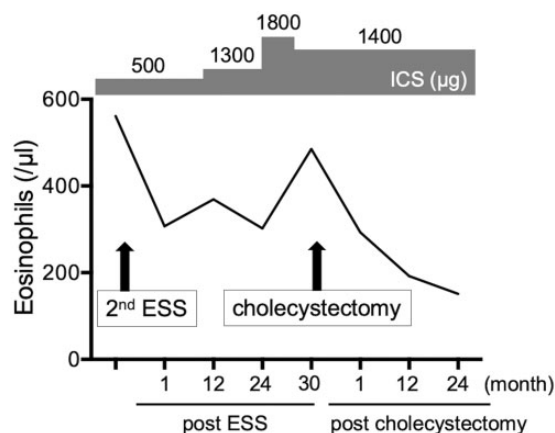
### Discussion and Conclusions

In the present study, EC is a part of eosinophilic inflammation that occurred in the same patient. Till date, there are no reports that describe the relationship between EC and ECRS. The reduction of chemokines and activators against eosinophils via the control of local eosinophilic inflammation (cholecystectomy) could be one of reasons



**Figure 1.** Abdominal ultrasound (A) and computed tomography (B) at the onset of eosinophilic cholecystitis, demonstrating thickening of the gallbladder wall (white arrow) and cholecystolith (white arrowheads). Endoscopic findings of the left nasal cavity before (left panel) and 1 month after (right panel) cholecystectomy (C). Black arrowheads indicate nasal polyps in the superior meatus.

why the nasal polyps shrunk after cholecystectomy. We previously showed that activated eosinophils release eosinophil chemokines, such as CCL4, and enhance their accumulation into local sites.<sup>8</sup> As we can confirm the reduction of blood eosinophils after removal of nasal polyps which include plenty of activated eosinophils,

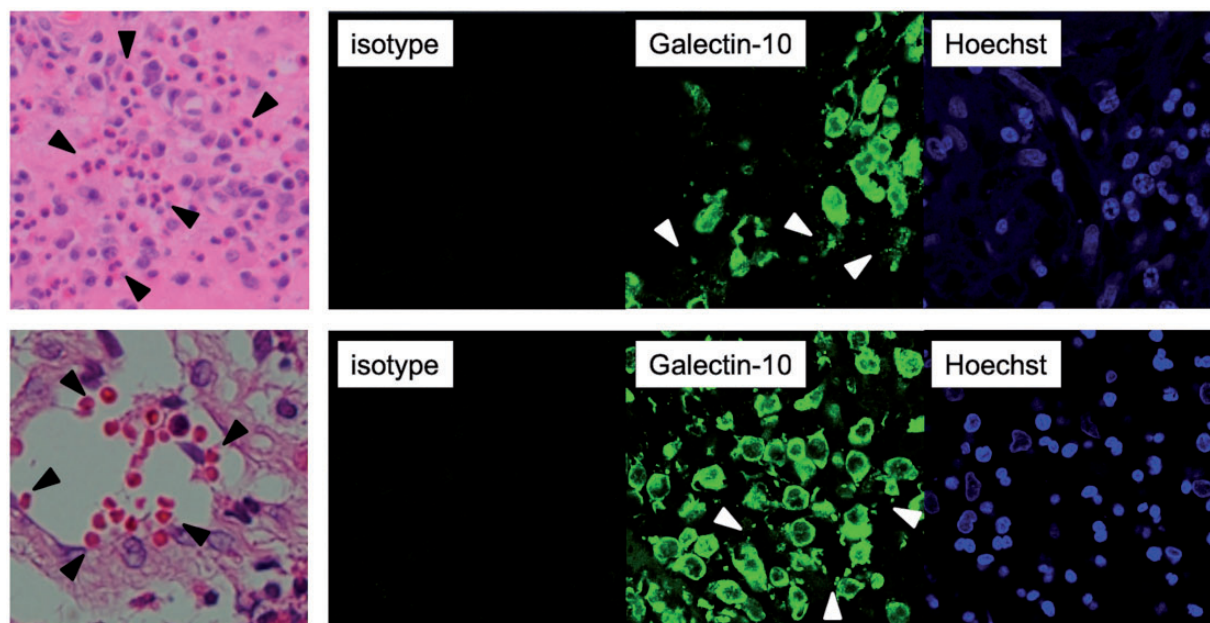


**Figure 2.** Dynamics of eosinophil counts. Values indicate peripheral blood eosinophil counts at each point as follows; before second ESS; 1, 12, and 24 months after second ESS; onset of eosinophilic cholecystitis; and 1, 12, and 24 months after cholecystectomy. Values of inhaled corticosteroid indicate fluticasone propionate equivalent daily doses ( $\mu\text{g}$ ). ESS, endoscopic sinus surgery; ICS, inhaled corticosteroid.

blood eosinophils were reduced after cholecystectomy also in this case (Figure 2).

To further confirm the association between EC and ECRS as eosinophilic inflammation, we focused on a protein called galectin-10, which is a major constituent of human eosinophils. Galectin-10 is also known as the Charcot–Leyden crystal protein and characteristically forms bipyrimalid hexagonal crystals. This glycan-binding protein is associated with eosinophilic inflammation.<sup>9–12</sup> We found many galectin-10-positive cells in both the gallbladder mucosa and in the paranasal sinus mucosa (Figure 3). Although the function of galectin-10 remains largely unknown and it is unclear whether galectin-10 causes eosinophilic inflammation, several studies have demonstrated its association with eosinophilic inflammatory diseases, such as asthma and allergic rhinitis,<sup>13,14</sup> and also EC and ECRS,<sup>10,15</sup> suggesting that at least galectin-10 might be a proof for eosinophilic inflammatory disease.

Galectin-10 positively correlates the percentages of eosinophils or eosinophil extracellular trap cell death (EETosis) which promotes inflammation via the release of free extracellular granules and the development of filamentous chromatin structures.<sup>11</sup> In addition, recent studies have revealed that EETosis mediates Charcot–Leyden crystal formation<sup>10</sup> and that galectin-10 crystal enhances Th2 immune responses.<sup>11</sup> Interestingly, extracellular granular structures were also stained by galectin-10, indicating that galectin-10 could induce activated



**Figure 3.** Histological findings of nasal mucosa (upper panels) and gallbladder mucosa (lower panels), showing infiltration of eosinophils (hematoxylin and eosin staining;  $400\times$  magnification, black arrowheads in left panels) and galectin-10-positive cells (immunohistostaining;  $630\times$  magnification, right panels). White arrowheads indicate extracellular granular structures. Galectin-10 was stained as previously described.<sup>10</sup>

eosinophilic inflammation at local sites.<sup>10</sup> Taken together, the reduction of activated eosinophils could cause less release of eosinophilic chemokines and galectin-10, resulting in decreased eosinophil accumulation into nasal inflammatory sites and nasal polyps.

We have reported that treatment with ICS-ETN is effective for ECRS with bronchial asthma.<sup>5,6</sup> Furthermore, in this case, ICS-ETN treatment provided good control for ECRS with asthma. When the doses of ICS are increased, slight systemic effect of corticosteroid could be induced. Therefore, the reduction of ICS dose might cause EC concomitantly with the recurrence of nasal polyps. In contrast, the increase of ICS dose or addition of systemic corticosteroid might protect against the onset of EC. We kept eosinophilic inflammation in control with high doses of ICS-ETN after cholecystectomy.

When EC is suspected, it is necessary to confirm the existence of eosinophilic inflammation and the spread of inflammation to the gastrointestinal tract and/or airway. Treatment with corticosteroids can be effective in cases wherein EC is not limited within the bladder and affects the gastrointestinal tract, including the bile duct.<sup>16</sup> In this study, eosinophilic inflammation in gastrointestinal tract was not observed; however, eosinophilic inflammation with galectin-10-positive extracellular granular structures was associated with the airway over the bladder, indicating that treatment with corticosteroids or biological drugs against IL-5 may be preferred over surgical management. Although it is difficult to detect eosinophils at the inflammatory site in some cases, the detection of galectin-10 may provide us proof of spatio-temporally spread of eosinophilic inflammation. Galectin-10 is also detectable in biological fluids from the inflammatory sites, such as sputum and nasal secretion.<sup>14,17,18</sup> Recent studies have revealed that galectin-10 levels in the sputum were significantly increased in asthmatics with strong correlation to the levels in sputum eosinophils.<sup>14,18</sup> We also found that galectin-10 levels in nasal mucin from ECRS patients were much higher than those in serum (data not shown), suggesting that galectin-10 in the biological fluids obtained from local sites could be a useful marker of activated eosinophilic inflammation.

We present a rare case wherein EC spatiotemporally occurred in a patient with refractory eosinophilic airway inflammation during inhaled corticosteroid tapering. Galectin-10 may help the diagnosis of rare cases with eosinophilic inflammation in multiple organs.

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### Author Contributions

Y. K., A. K., and H. I. were involved in the conception and design of this case report. Y. K., Y. Y., and M. A. were involved in collection of the clinical data. S. U. performed the histological examination. T. K. and Y. K. were involved in drafting the manuscript for important intellectual content. All authors contributed to revisions and approved the final draft.

### Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.


### Ethical Approval

This study was approved by our institutional review board (KanIRin1313).

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### Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

### Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

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