



Case Report

# Improvement of Eosinophilic Rhinosinusitis Headache after Endoscopic Modified Lothrop Procedure: Case Report and Literature Review

**Tessei Kuruma\*, Mariko Arimoto, Kinga Yo, Yuka Kawade, Yutaka Kondo, Yasue Uchida, Tetsuya Ogawa, Yasushi Fujimoto**

Department of Otorhinolaryngology, Head and Neck Surgery, Aichi Medical University, Aichi, Japan

**\*Corresponding author:** Tessei Kuruma, Department of Otorhinolaryngology, Head and Neck Surgery, Aichi Medical University, 1-1 Yazakokarimata, Nagakute-shi, Aichi 480-1195, Japan

**Citation:** Kuruma T, Arimoto M, Yo K, Kawade Y, Kondo Y, et al. (2022) Improvement of Eosinophilic Rhinosinusitis Headache after Endoscopic Modified Lothrop Procedure: Case Report and Literature Review. J Surg 7: 1507. DOI: 10.29011/2575-9760.001507

**Received Date:** 20 May, 2022; **Accepted Date:** 23 May, 2022; **Published Date:** 26 May, 2022

## Abstract

The main symptoms of eosinophilic chronic rhinosinusitis are olfactory disturbances, nasal obstruction and posterior rhinorrhea. chronic rhinosinusitis cases, only few reports have described an association between eosinophilic chronic rhinosinusitis and headache or its improvement with treatment. We experienced a case of a 43-year-old female patient with eosinophilic chronic rhinosinusitis with recurrent severe frontal headache after endoscopic sinus surgery that was relieved after an endoscopic Among modified Lothrop procedure. In refractory eosinophilic chronic rhinosinusitis, there is severe infiltration of eosinophils around the frontal sinus, as well as polyp formation. We believe that endoscopic modified Lothrop procedure, in which the bilateral frontal sinuses are opened widely as a single cavity, is very useful not only for treatment of the headache, but also for the other symptoms associated with refractory eosinophilic chronic rhinosinusitis, such as posterior rhinorrhea, nasal obstruction, olfactory disturbance, etc.

**Keywords:** Endoscopic modified Lothrop procedure; Endoscopic sinus surgery; Eosinophilic chronic rhinosinusitis; Headache

**Abbreviations :** ECRS: Eosinophilic Chronic Rhinosinusitis; CRSwNP: CRS with Nasal Polyps; CRSsNP: CRS without Nasal Polyps; ESS: Endoscopic Sinus Surgery; EMLP: Endoscopic Modified Lothrop Procedure

## Introduction

Classically, primary Chronic Rhinosinusitis (CRS) is divided into two major subtypes based on its phenotypic appearance: CRS with Nasal Polyps (CRSwNP) and CRS without Nasal Polyps (CRSsNP) [1,2]. CRS is also subtyped as Eosinophilic CRS

(ECRS) and Non-ECRS (NECRS) according to the presence or absence of predominant tissue eosinophilic infiltration. ECRS is considered a special subtype of CRS [3-5] and also a subtype of recalcitrant CRS, which usually has worse disease severity [6-9] and poorer treatment outcomes [8,10,11] compared to NECRS. Half of the cases of CRSwNPs in Japan have been reported to be ECRS [5,12]. Two major CRS guidelines include presence of facial pain and headache as part of the clinical diagnostic criteria for CRS [13,14]. However, the association between headache and CRS continues to be controversial, such that the EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) guidelines highlight literature demonstrating that only a minority of subjects with CRS experience headache [14] Further, a European position paper on sinusitis and nasal polyps, published

in 2012, suggested that rhinosinusitis rarely causes headaches, except when it is associated with acute bacterial infections [2]. The subjective assessment of CRS is based on symptoms such as nasal blockage, nasal discharge, facial pain (pressure), and loss of smell. Nevertheless, headache is a common complaint among many patients diagnosed with CRS [15], and headache has been variously reported to improve after surgery [16] or to remain stable [17]. Nguyen et al. found that in patients with nasal polyps requiring surgery, one-half of the patients reported moderate/severe facial pain/headache before surgery, with improvement of these symptoms after surgery [18].

The main symptoms of ECRS, on the other hand, are olfactory disturbances, nasal obstruction and posterior rhinorrhea. However, among CRS cases, only few reports have described an association between ECRS cases and headache or its improvement with treatment. The Endoscopic Modified Lothrop Procedure (EMLP) is a surgical technique in which the bottom and septum of the bilateral frontal sinuses are removed to create a single cavity, which is opened widely into the nasal cavity. We report a case of ECRS with the chief complaint of headache, in which the EMLP was performed after Endoscopic Sinus Surgery (ESS), with subsequent improvement of the headache.

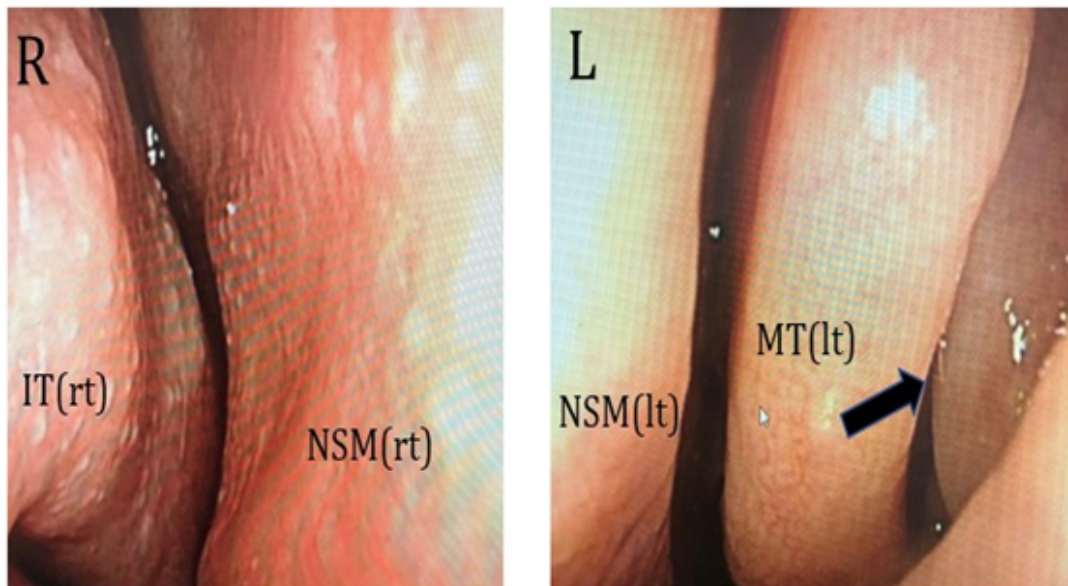
Case Presentation

The patient was a 43-year-old woman with asthma symptoms for the past 7 years, for which she was using inhaled steroids. She was also on antidepressants for depression since an unknown period of time. Three months prior to her first visit to our clinic, she had a severe headache, for which she had visited a neurology clinic and had received migraine medication (eletriptan hydrobromide, sodium valproate, rizatriptan benzoate), although her headache symptoms did not improve. The patient was then diagnosed with sinusitis by imaging diagnosis. One month later, her headache attacks began to occur every day. The pain was in the forehead area, initially presenting as a sense of light-headedness that was suddenly replaced by the pain, as if she had been punched. When the headache was severe, it was accompanied by nausea. The headache sometimes woke her up at night. She visited our emergency room several times for headache attacks and was treated with intravenous analgesics. Other than headache, she complained of rhinorrhea, nasal obstruction and olfactory disturbance. At her initial visit to our clinic, she had

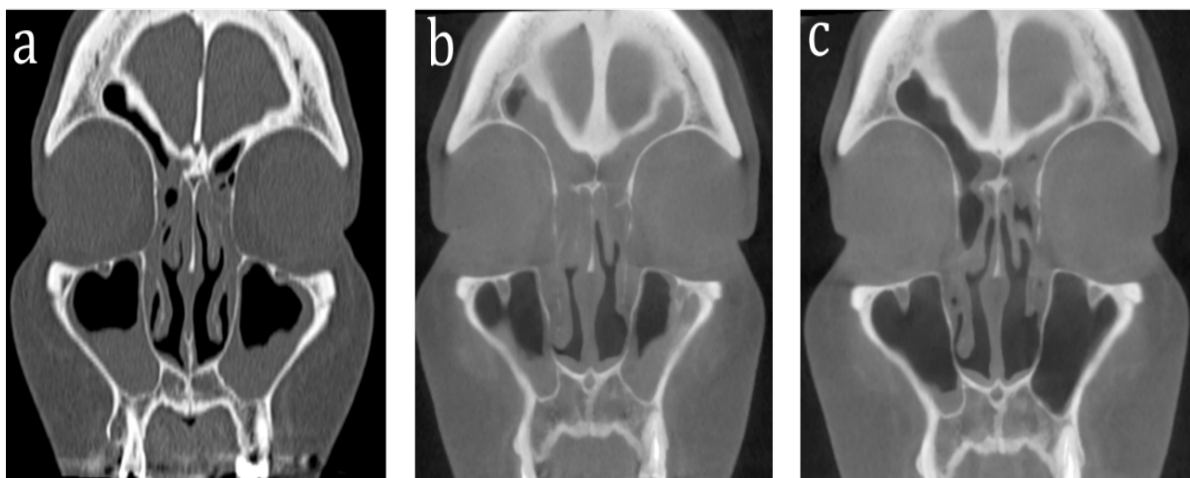
headache as the main symptom and also complained of nasal obstruction, posterior rhinorrhea, decreased sense of smell, and sleep disturbances (Table 1). Endonasal endoscopy revealed rightward curvature of the nasal septum and a small polyp in the left middle nasal canal (Figure 1). Computed Tomography (CT) scan of the sinuses revealed moderate shadows suggestive of pansinusitis, with predominance in the ethmoid sinus (Figure 2a). Hematological evaluation for allergies revealed a total IgE level of 54.0 IU/ml in the non-specific IgE test, the specific IgE antibody test was positive only for cedar pollen antibodies, and her blood eosinophil count was 10.0%. Based on a diagnosis of CRS with polyp, she was prescribed leukotriene antagonists, oral steroids and a nasal steroid spray. Loxoprofen sodium hydrate was also prescribed to treat the headaches, although the frequency and severity of headaches did not improve. To improve the headache, the patient underwent nasal septoplasty, bilateral inferior turbinate surgery, peripheral posterior nasal nerve transection, and bilateral pan-sinus endoscopic surgery under general anesthesia. At the time of surgery, polyp formation around the frontal sinus and frontal recess was mild (Figure 3a). Pathological evaluation of the sinus polyp at the time of surgery showed an average infiltrating eosinophil count (400× magnification) of 45 eosinophils/field in three fields of view.

Symptom	At the first visit	After 1 year of ESS	After 1.5 years of EMLP
Headache	6	4	0
Nasal obstruction	5	2	0
Posterior rhinorrhea	6	1	0
Olfactory disturbance	3	1	1
Sleep disturbance	5	5	1
Mood disturbance	6	2	0

**Table 1:** Changes in subjective symptoms over time according to nasal questionnaire. The nasal symptom questionnaire administered to the patient in this case is shown over time for headache, nasal obstruction, posterior rhinorrhea, olfactory disturbance, sleep disturbance, and mood disturbance. Subjective symptoms were rated on a 6-point scale from no symptoms at all (0) to very severe (6).



**Figure 1:** Nasal endoscopic findings at initial examination. Endonasal endoscopy revealed rightward curvature of the nasal septum(R) and a small polyp(arrow) in the left middle nasal canal(L). IT (rt): right inferior turbinate; NSM (rt): right nasal septal mucosa. NSM (lt): right nasal septal mucosa; MT (lt): left middle turbinate.

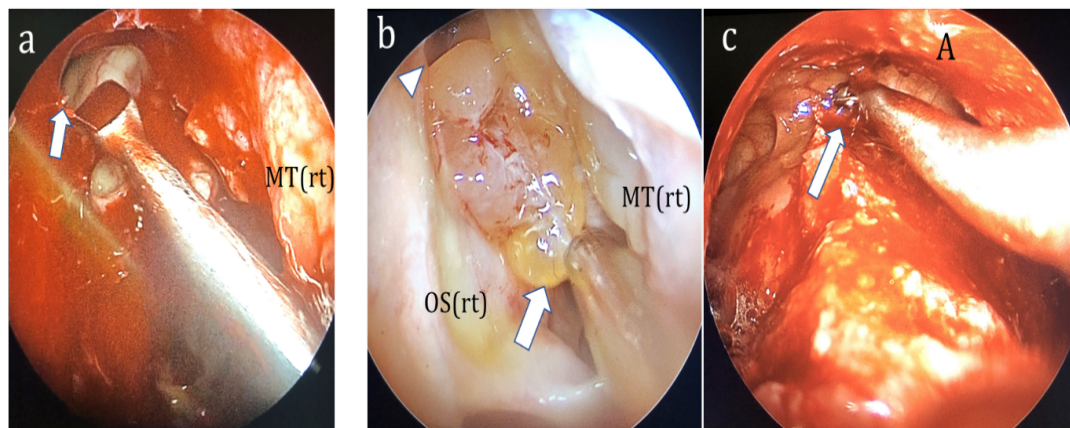


**Figure 2:** Coronal section findings of sinus CT. **a)** Sinus CT findings at initial examination. **b)** Sinus CT findings 1 year after ESS. **c)** Sinus CT findings before EMLP surgery.

After the surgery, the headaches became less severe. One year later, however, she experienced exacerbation of the headaches (Table 1), and a CT scan of the sinuses once again showed re-enhancement of the shadows in both frontal and ethmoid sinuses (Figure 2b). The patient took various headache medications (acetaminophen, loxoprofen sodium hydrate, etc.) and oral steroids, but with no improvement in the headaches. The steroid medication, in particular, could not be taken for a long period of time due to side effects such as edema, fatigue and worsening depression. The patient was also offered the biologic dupilumab, which suppresses the Th2-type inflammatory response, although she did not accept it because she didn't want the needles to stick. CT scan of the sinuses performed at this time showed improvement of the peripheral shadows in the frontal sinus (Figure 2c), but with no change in headache symptoms. Hence, an EMLP was performed to improve the headache.

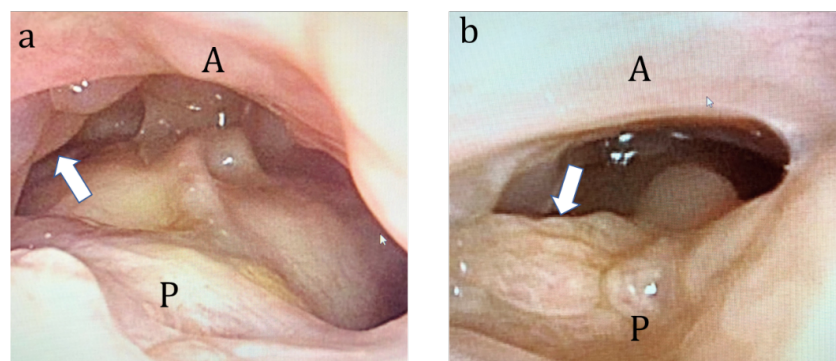


At the time of surgery, the cells and uncinate process around the frontal recess were cleanly opened up after the previous surgery (Figure 3b). Polyps were found around the frontal sinus foramen, which were removed and aspirated with a 4.3-mm Medtronic straight shoot M4 microdebrider (Figure 3b). Next, the EMLP was performed. Intraoperatively, the anteroposterior diameter of the frontal sinus was very narrow. The septum of the frontal sinus was removed at its base, and the bilateral frontal sinuses were merged into a single cavity (Figure 3c). Pathological examination of the polyp in the sinus cavity again showed a large number of infiltrating eosinophils (138 per field of view, 400× magnification), which was an increase in infiltrating eosinophils compared to the previous surgery. The pathology evaluation confirmed that it was an ECRS lesion [5,19,20].



**Figure 3:** Intraoperative findings. **A)** Findings at initial ESS. There is little POLYP formation within the right frontal sinus (arrow). MT (rt): right middle turbinate. **B)** Findings at EMLP (1) A polyp around the right frontal sinus foramen (arrowhead) is excised and aspirated with a microdebrider (arrow). OS (rt): Right orbital side. **(C)** Finding at EMLP (2) The frontal sinus septum is being removed (arrow). A: Anterior wall of frontal sinus.

After EMLP, the patients' headaches quickly disappeared. One and a half years after the surgery, although the polyps in the frontal sinus recurred (Figure 4), there was no recurrence of headache. We asked the patient to answer a questionnaire of subjective symptoms before and one year after surgery to compare her pre- and postoperative condition. In addition to headache, symptoms such as fatigue, posterior rhinorrhea, and decreased sense of smell had also decreased, with particular improvement in her sleep disturbance (Table 1). Her depressive symptoms also decreased along with relief from her various symptoms and she appeared more cheerful. Steroid medication was tapered off over 2 months after the surgery. Currently, she continues only nasal rinsing with saline solution, nasal steroid irrigation, and leukotriene antagonist medication. In particular, the steroid nasal spray is administered daily in the suspended head position, with drops placed in the nose and maintained in that position for 10 minutes. We will continue to treat and monitor her for possible recurrence of ECRS.



**Figure 4:** Postoperative nasal endoscopic findings. **a)** Frontal sinus endoscopic findings 6months after EMLP. **b)** Frontal sinus endoscopic findings 18 months after EMLP. Recurrent polyp in the frontal sinus (Arrow). P: posterior wall of frontal sinus, A: anterior wall of frontal sinus.

## Discussion

In the general population, more than 50% of adults have suffered from headaches in the last year [21], and almost 5% (9% of women) suffer from chronic daily headaches [22]. Headaches can be primary or secondary in origin. Primary headaches are caused by underlying conditions, such as migraine, tension or cluster headaches. Secondary headaches are those resulting from trauma or injury to the head, substance use or misuse, infection and homeostatic disturbances. Additional causes of secondary headache include disorders of the nose and sinuses [23]. Furthermore, sinonasal and migrainous disorders might frequently co-exist as comorbidities; in fact, CRS might increase migraine-associated morbidity and frequency through irritation of trigeminal nerve receptors [24]. There is no way to preoperatively discern whether headache, facial pain and pressure or nasal congestion is a manifestation of migraine or if it is the direct result of sinonasal inflammation.

There was no aura prior to the headache attack. The patient had been treated for migraine headaches before coming to our clinic. However, in clinical practice, migraine headaches might not respond to various medications. Hence, it was very difficult to determine whether the headache in this case was caused by CRS or by an exacerbation of migraine due to CRS. Pain and headache are strong motivating forces for patients to undergo ESS [18], yet little evidence exists regarding the impact of comorbid migraine on Quality of Life (QOL) gains after ESS. In a previous prospective cohort study, Adam et al. classified 229 CRS patients into two groups: 46 CRS patients with a history of migraine and 183 CRS patients with no migraine history, to investigate whether the two groups had comparable improvements in QOL after ESS [25]. Based on their results, they concluded that ESS provided comparable improvement in both patients with and without migraine [25].

On the other hand, Kaymakçı et al. reported that of 26 cases of sinus headache among 113 patients with chronic sinusitis, nine patients (34.6%) had complete resolution of their headache, and five patients (19.2%) had temporary improvement of their headache after ESS [26]. The patients who did not improve were diagnosed with migraine after consultation with a neurologist, and reported that their headache was relieved with conservative treatment.

Although surgery is rarely performed to improve headache in patients with ECRS, we believe that surgery should be performed aggressively in cases of refractory CRS with headache symptoms, as in this case. Even if surgery is not effective for headache, conservative treatment might be more effective after surgery, as reported by Kaymakçı et al [26]. ECRS is not caused by a sinus ventilation defect, but by inflammation of the sinus mucosa. A large number of eosinophils are present in polyps, and viscous mucin, as

well as fungi, staphylococcal enterotoxins and biofilm are present in the sinuses [27]. The vicious cycle caused by the presence of these factors usually cannot be broken. In mild cases of ECRS, the usual ESS can be expected to improve the condition, but in severe cases, polyps and mucin recur immediately after the usual ESS. In severe cases of ECRS, EMLP is an additional treatment option [27,28]. Wormald et al. reported that the Draf type III drillout technique (EMLP) was effective in improving long-term outcomes and reducing the risk of reoperation in patients with nasal polyposis complicated by asthma or aspirin intolerance [29]. In cases of ECRS, the sinus cavity should be monolobulated to the maximum extent possible, and the edematous mucosa should be removed while preserving the ostium.

Nakayama et al. stated that the presence of residual frontal sinus cells is an independent risk factor for postoperative frontal sinus opacification, as are the well-recognized risk factors of nasal polyps, peripheral eosinophil counts and CT scores [30]. However, in the present case, all cells around the frontal recess were opened at the first ESS.

On the other hand, Takeno et al. suggested that strong eosinophilic infiltration of the frontal sinus mucosa is observed in ECRS. They postulated that the strong inflammation of the frontal sinus mucosa might be due to local cytokine bias, in addition to anatomic impairment of ventilation and drainage of secretions. They also examined the expression of eosinophil-related cytokines in the nasal sinus mucosa and reported that the frontal sinuses of patients with eosinophilic sinusitis showed a profile similar to that of the ethmoidal sinus mucosa, along with increased expression of IL-5 and other cytokines [31]. In fact, in a significant number of cases after ESS surgery for ECRS in an outpatient setting, findings of polyps filling the frontal sinus foramen are observed, even though there is usually no recurrence of polyps in the ethmoid sinus. In this case, the second surgery revealed an increase in polyps around the base of the frontal sinus and within the frontal sinus. We believe that EMLP is not an excessive procedure, but a very effective procedure in cases of ECRS with strong intra-frontal sinus involvement.

Shen et al. reported that significant eosinophilia was associated with increased surgical failure, such as frontal sinus closure, and this association was even stronger in the CRS sub-cohort [32]. In our patient, the frontal sinus foramen has not closed even now, one and a half years after EMLP, although microscopic observation showed very strong eosinophilic infiltration of the mucosa of the frontal sinus, suggesting that we need to be careful about frontal sinus closure due to the regrowth of polyps. When EMLP surgery is performed, the prior Functional ESS (FESS) already opens the frontal sinuses, making it easy to understand the orientation of the sinuses, and, thus decreasing operation time. Furthermore, there are no particular postoperative problems in

terms of cosmesis or function. In patients with a narrow anterior-posterior diameter of the frontal sinus, as in this case, since it is easy to assume that the sinus might become obstructed after a normal FESS, EMLP surgery should be considered right from the outset when the ECRS lesion worsens.

Oral steroids are very effective against ECRS. However, in some patients, oral steroids might cause multiple specific side effects, such as hyperactivity, insomnia, swelling of the face, mood swings, weight gain, decreased bone mineral density and anxiety, and hence, might not be tolerated by patients with side effects. Steroid nasal sprays are an essential postoperative treatment for eosinophilic sinusitis, but might be ineffective if the sprayed drug does not reach the entire sinus cavity. A previous double-blind study reported that washing the nasal cavity with the same amount of steroid dissolved in the washing solution was more effective than a mometasone spray [33]. In our case, local steroid treatment after surgery was not administered in a spray form, but rather a nasal steroid solution was dripped into the nose in the suspended head position and maintained in that position for 10 minutes. It is possible that after the EMLP was performed and the bilateral frontal sinuses were mono-cavitated, the dripped steroids remained in the frontal sinuses for a while, from where they effectively reached each sinus. In our patient, the steroid medication was discontinued two months after surgery. Thereafter, with a continued nasal drip of betamethasone sodium phosphate solution, leukotriene receptor antagonist medication and nasal washing, there has been no recurrence of polyps in the frontal sinus, and both the frequency and severity of headaches have improved.

Unfortunately, little is known about the underlying mechanisms that cause the pain associated with CRS, although several mechanisms have been postulated that might contribute to some degree to the development of CRS headache [34]. In this case, the OMC (ostioameatal complex) was opened at the previous surgery. However, since the nasofrontal floor itself was very narrow, negative pressure within the frontal sinus might have caused the pain. Local inflammatory mediators in the sinuses might locally excite nerves within the sinus mucosa with direct pain. For example, maxillary rhinosinusitis can cause radiating toothache due to irritation of the trigeminal nerve [35]. In addition, inflammatory mediators can be transmitted from the immune system to the brain via afferent autonomic neurotransmission, and directly across the blood-brain barrier and/or through periventricular organs [36]. Kato stated that it is clear that type 2 cytokines, especially IL-5 and IL-13, but possibly also IL-4, play important roles mediating inflammation in ECRS and nasal polyp development [37]. The effects of these inflammatory cytokines on the central nervous system are related to both pain, as well as other health-related factors associated with chronic inflammation and ill health, such as sleep disturbances and mood disturbances [38]. In addition to headache, our patient also showed significant

improvement in sleep disturbances and depression after EMLP.

## Conclusion

We experienced a case of a 43-year-old female patient with ECRS who had recurrent severe frontal headache after ESS that was relieved after EMLP surgery. ECRS is a disease that tends to recur even after surgery. Although headache is not a common symptom of ECRS, headache interfered with our patient's daily life and was likely associated with the development of insomnia and depression. In refractory ECRS, there is a strong infiltration of eosinophils around the frontal sinus along with polyp formation. Therefore, it has been suggested that EMLP surgery might be effective in patients with refractory ECRS by widening the opening of the frontal sinus, and that local steroid administration might also be effective. We believe that EMLP surgery is a very useful procedure not only for headache, but also for other symptoms (posterior rhinorrhea, nasal obstruction, decreased sense of smell, etc.) associated with refractory ECRS.

## References

1. Fokkens W, Lund V, Mullol J, European position paper on rhinosinusitis and nasal polyps group (2007) European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 20: 1-136.
2. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, et al. (2012) European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl* 23:3 p preceding table of contents 1-298.
3. Ouyang Y, Fan E, Li Y, Wang X, Zhang L (2013) Clinical characteristics and expression of thymic stromal lymphopoietin in eosinophilic and non-eosinophilic chronic rhinosinusitis. *ORL J Otorhinolaryngol Relat Spec* 75: 37-45.
4. Sakuma Y, Ishitoya J, Komatsu M, Shiono O, Hiramata M, et al (2011) New clinical diagnostic criteria for eosinophilic chronic rhinosinusitis. *Auris Nasus Larynx* 38: 583-588.
5. Ishitoya J, Sakuma Y, Tsukuda M (2010) Eosinophilic chronic rhinosinusitis in Japan. *Allergol Int* 59: 239-245.
6. Snidvongs K, Chin D, Sacks R, Earls P, Harvey RJ (2013) Eosinophilic rhinosinusitis is not a disease of ostioameatal occlusion. *Laryngoscope* 123: 1070-1074.
7. Kountakis SE, Arango P, Bradley D, Wade ZK, Borish L (2004) Molecular and cellular staging for the severity of chronic rhinosinusitis. *Laryngoscope* 114: 1895-1905.
8. Ferguson BJ (2004) Categorization of eosinophilic chronic rhinosinusitis. *Curr Opin Otolaryngol Head Neck Surg* 12: 237-242.
9. Soler ZM, Sauer DA, Mace J, Smith TL (2009) Relationship between clinical measures and histopathologic findings in chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 141: 454-461.
10. Haruna S, Shimada C, Ozawa M, Fukami S, Moriyama H (2009) A study of poor responders for long-term, low-dose macrolide administration for chronic sinusitis. *Rhinology* 47: 66-71.
11. Soler ZM, Sauer D, Mace J, Smith TL (2010) Impact of mucosal eosinophilia and nasal polyposis on quality-of-life outcomes after sinus surgery. *Otolaryngol Head Neck Surg* 142: 64-71.



12. Kimura N, Nishioka K, Nishizaki K, Ogawa T, Naitou Y, et al. (1997) Clinical effect of low-dose, long-term roxithromycin chemotherapy in patients with chronic sinusitis. *Acta Med Okayama* 51: 33-37.
13. Benninger MS, Ferguson BJ, Hadley JA, Hamilos DL, Jacobs M, et al. (2003) Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg* 129: S1-S2.
14. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, et al. (2012) EPOS 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 50: 1-12.
15. Lanza DC, Kennedy DW (1997) Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 117: S1-7.
16. Chester AC, Antisdel JL, Sindwani R (2009) Symptom-specific outcomes of endoscopic sinus surgery: a systematic review. *Otolaryngol Head Neck Surg* 140: 633-639.
17. Soler ZM, Mace J, Smith TL (2008) Symptom-based presentation of chronic rhinosinusitis and symptom-specific outcomes after endoscopic sinus surgery. *Am J Rhinol* 22: 297-301.
18. Nguyen DT, Felix-Ravelo M, Arous F, Nguyen-Thi PL, Jankowski R (2015) Facial pain/headache before and after surgery in patients with nasal polyposis. *Acta Otolaryngol* 135: 1045-1050.
19. Nakayama T, Yoshikawa M, Asaka D, Okushi T, Matsuwaki Y, et al. (2011) Mucosal eosinophilia and recurrence of nasal polyps - new classification of chronic rhinosinusitis. *Rhinology* 49: 392-396.
20. Okano M, Kariya S, Ohta N, Imoto Y, Fujieda S, et al. (2015) Association and management of eosinophilic inflammation in upper and lower airways. *Allergol Int* 64: 131-138.
21. Paparella MM, Berlinger NT, Oda M, el-Fiky F (1973) Otolological manifestations of leukemia. *Laryngoscope* 83: 1510-1526.
22. Shanbrom E, Finch SC (1958) The auditory manifestations of leukemia. *Yale J Biol Med* 31: 144-156.
23. Joseph DE, Durosini MA (2008) Neurological complications of chronic myeloid leukemia: any cure? *Niger J Clin Pract* 11: 246-249.
24. De Corso E, Kar M, Cantone E, Lucidi D, Settini S, et al (2018) Facial pain: sinus or not? *Acta Otorhinolaryngol Ital* 38: 485-496.
25. DeConde AS, Mace JC, Smith TL (2014) The impact of comorbid migraine on quality-of-life outcomes after endoscopic sinus surgery. *Laryngoscope* 124: 1750-1755.
26. Kaymakçı M, Gür OE, Pay G (2014) Prevalence and etiological causes of sinus headache in 113 consecutive patients with chronic rhinosinusitis. *Eastern J Med* 19: 90-93.
27. Bassiouni A, Naidoo Y, Wormald PJ (2012) When FESS fails: the inflammatory load hypothesis in refractory chronic rhinosinusitis. *Laryngoscope* 122: 460-466.
28. Grayson JW, Cavada M, Harvey RJ (2019) Clinically relevant phenotypes in chronic rhinosinusitis. *J Otolaryngol Head Neck Surg* 48: 23.
29. Bassiouni A, Wormald PJ (2013) Role of frontal sinus surgery in nasal polyp recurrence. *Laryngoscope* 123: 36-41.
30. Nakayama T, Asaka D, Kuboki A, Okushi T, Kojima H (2018) Impact of residual frontal recess cells on frontal sinusitis after endoscopic sinus surgery. *Eur Arch Otorhinolaryngol* 275: 1795-1801.
31. Takeno S, Kubota K (2015) Frontal sinus disease in eosinophilic chronic rhinosinusitis. *Journal of Japan Society of Immunology & Allergy in Otolaryngology* 33: 221-224.
32. Shen J, Chan N, Wrobel BB (2018) The endoscopic modified lothrop procedure: Review of single institution experience and long-term outcomes. *Laryngoscope Investig Otolaryngol* 3: 105-109.
33. Harvey RJ, Snidvongs K, Kalish LH, Oakley GM, Sacks R (2018) Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. *Int Forum Allergy Rhinol* 8: 461-470.
34. Whittet HB (1992) Infraorbital nerve dehiscence: the anatomic cause of maxillary sinus "vacuum headache"? *Otolaryngol Head Neck Surg* 107: 21-28.
35. Eccles R (2011) Mechanisms of the symptoms of rhinosinusitis. *Rhinology* 49: 131-138.
36. Alt JA, Smith TL (2013) Chronic rhinosinusitis and sleep: a contemporary review. *Int Forum Allergy Rhinol* 3: 941-949.
37. Kato A (2015) Immunopathology of chronic rhinosinusitis. *Allergol Int* 64: 121-130.
38. DeConde AS, Mace JC, Ashby S, Smith TL, Orlandi RR, et al. (2015) Characterization of facial pain associated with chronic rhinosinusitis using validated pain evaluation instruments. *Int Forum Allergy Rhinol* 5: 682-690.