Case Report

J Korean Soc Radiol 2022;83(4):910-917
https://doi.org/10.3348/jksr.2021.0107
eISSN 2951-0805

# Immunoglobulin G4-Related Disease Involving Various Head and Neck Regions: A Case Report

## 두경부에 국한된 표현형으로 발생한 면역글로불린 G4와 연관된 질환: 증례 보고

Jun Yong Im, MD, Miok Sunwoo, MD*

Department of Radiology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

Immunoglobulin G4 (IgG4) related disease (IgG4-RD) is currently considered an immune-mediated condition and is recognized as a disorder group with common pathological, hematological, and clinical characteristics. This disease may involve diverse organs of the head and neck, and include mainly the lacrimal gland, orbit, thyroid gland, pituitary gland, and the meninges. Here, we report a case of IgG4-RD in a 65-year-old female showing head- and neck-limited but synchronously and mainly manifesting as otalgia and facial neuritis.

**Index terms** Immunoglobulin G4-Related Disease; Facial Nerve Disease; Magnetic Resonance Imaging; Multidetector Computed Tomography; Head

**Received** June 4, 2021
**Revised** August 18, 2021
**Accepted** September 24, 2021

***Corresponding author**
Miok Sunwoo, MD
Department of Radiology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158 Paryong-ro, Masanhoewon-gu, Changwon 51353, Korea.

Tel 82-55-233-5602
Fax 82-55-233-5604
E-mail sunwooeh@gmail.com



**ORCID iDs**
Jun Yong Im
https://orcid.org/0000-0003-3913-9336
Miok Sunwoo
https://orcid.org/0000-0002-8486-4230

## INTRODUCTION

Immunoglobulin G4 related disease (IgG4-RD) is a fibroinflammatory condition characterized by tumefactive lesions, being composed of IgG4-positive plasma cells, lymphoplamacytic infiltrates (rich in storiform fibrosis) and elevated serum IgG4 concentration (1, 2).

However, IgG4-RD of the head and neck is relatively uncommon. The IgG4-RD of the head and neck, excluding lacrimal gland, accounts for 19% of the total IgG4-RD (3). Therefore, the radiological findings of IgG4-RD of the head and neck are expected to be diverse and non-specific based on the diversity of involved organs and different severity in each organ involvement.

Here, we report the first case of an IgG4-RD with head and neck limited type manifesting synchronously as bilateral acute otomastoiditis, nasopharyngitis with cervical lymph-

adenopathy, facial neuritis and hypertrophic pachymeningitis (HP) in a 65-year-old female.

## CASE REPORT

A 65-year-old female presented with one-month history of bilateral hearing loss and ear fullness. On otoscopic examination, bilateral ear effusions without perforation of tympanic membrane were seen and presumed to represent acute otitis media. She was given empirical antibiotics (levofloxacin hydrate, 400 mg/day, for 7 days) and anti-inflammatory drug (dexibuprofen, 600 mg/day, for 7days).

The right facial palsy developed 3 weeks thereafter, when she revisited the emergency department of our institution. Temporal bone CT scan demonstrated effusions in the bilateral middle ear and mastoid air cells, and mucosal thickening of the external auditory canal. Because her symptoms did not improve and she rather developed otalgia, ventilation tube (VT) insertion was performed in order to control middle ear effusion. Culture for her ear discharge was negative for the growth of any organism. Even though steroid pulse therapy (methylprednisolone, 1 mg/kg/day, for 9 days) was given, there was no improvement of other symptoms and signs except hearing loss.

One month after, the patient revisited out-patient otology department complaining of nausea and vomiting, along with progressively worsening facial palsy and hearing impairment. When admitted, VT was working well and via the tube profuse mucoid discharge was coming out. The second culture of the discharge disclosed gram negative bacilli. Until then, she had neither fever nor abnormal white blood cell count; and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found to be normal. Initial temporal bone MRI (TBMR) showed effusion in the mastoid air cells and middle ear cavities, strong enhancement of both the facial nerve and diffuse swelling of the nasopharynx (Fig. 1A). Slightly bulging contour and strong enhancement of the left cavernous sinus were also seen on T1-weighted gadolinium-enhanced images (Fig. 1A). But definite pachymeningeal thickening was not visualized as was parenchymal mass or edema.

Follow-up TBMR and brain MRI were checked for further evaluation of previously known lesions and possible brain abnormality approximately 2 months after the hospitalization. Strong contrast enhancement showed unexpectedly bilaterally extensive mass-like soft-tissue lesions in the parapharyngeal space and the facial nerve. In addition, the internal carotid arteries showed a decrease in luminal diameter associated with the mass effect caused by the parapharyngeal space mass-like lesions (Fig. 1B). Both TBMR and brain MRI demonstrated bilateral irregular and sheet-like pachymeningeal thickening (Fig. 1C). In addition, bilateral patchy hyperintensities without mass effect were observed in the bilateral temporal lobes adjacent to the enhancing pachymenigeal lesions on gadolinium-enhanced fluid attenuated inversion recovery images (Fig. 1C). Enlarged lymph nodes were identified in the upper lateral neck on T1-weighted gadolinium-enhanced images and on neck ultrasonography (Fig. 1D). There was neither hypophysitis nor cervical dural enhancement. At that time, blood tests disclosed elevated level of CRP (> 103 mg/L), and increased serum IgG, IgA and IgM titers.

For diagnosis, we performed both 1) ultrasonography-guided neck node biopsy and 2) intradural biopsy for pachymeningeal lesion by the use of facial nerve decompression. Micro-

scopically, lymph node biopsy specimen disclosed prominent infiltration of IgG4-positive plasma cells; immunohistochemical stain revealed increased CD138, IgG4/IgG ratio of < 40% and IgG4-positive plasma cells up to 50/high-power field (HPF) (Fig. 1E). On the other hand,

**Fig. 1.** IgG4 related disease in head and neck in a 65-year-old female.
**A.** Initial TBMR imaging shows hypointensity on axial T1WI (left top), hyperintensity on axial FLAIR image (right top) and heterogeneous contrast enhancement on axial CE T1WI (left bottom) of bilateral mastoid air-cells. On axial CE T1WI, the contrast enhancement of the bilateral facial nerves (the right facial nerve is not shown here, left bottom) and the bulging contour of the lateral margin with well-contrast enhancement at the left cavernous sinus are seen (arrow, right bottom).
**B.** Follow up TBMR shows extensive hypointensity on axial T1WI (left top), strip like heterogeneous signal intensity on axial PDWI (right top) and extensive contrast enhancement on axial CE T1WI (left bottom) at bilateral tensor veli muscles, levator veli palatini muscles, prestyloid spaces, and carotid spaces. Compression of the internal carotid arteries is also seen on axial CE T1WI (left bottom). Bilateral facial nerve enhancement is more prominent compared to previous TBMR on axial CE T1WI (arrows, right bottom).
**C.** Coronal T2WI shows diffuse pachymeningeal thickening with low signal intensity around the temporal lobes (left top). Coronal CE T1WI reveals homogeneous enhancement of the pachymeninges (right top). Axial FLAIR image shows hyperintensity of both temporal lobes (arrows, left bottom). However, no cerebral masses or enhancing lesions was found on CE T1WI (right bottom).
**D.** Coronal CE T1WI shows bilaterally enlarged cervical lymphadenopathy (left). On neck ultrasonography, enlarged lymph node with hilar echogenicity and hypervascularity is seen (middle). $^{18}$F fluorodeoxyglucose PET/CT scan shows multilevel hypermetabolic lymph nodes at both neck, mediastinum, and abdomen, but there is no evidence of hypermetabolic lesions of the gastrointestinal track and endocrine and exocrine organs (right).
CE = contrast-enhanced, FLAIR = fluid attenuated inversion recovery image, IgG4 = Immunoglobulin G4, PDWI = proton density weighted image, TBMR = temporal bone MR, T1WI = T1-weighted image, T2WI = T2-weighted image

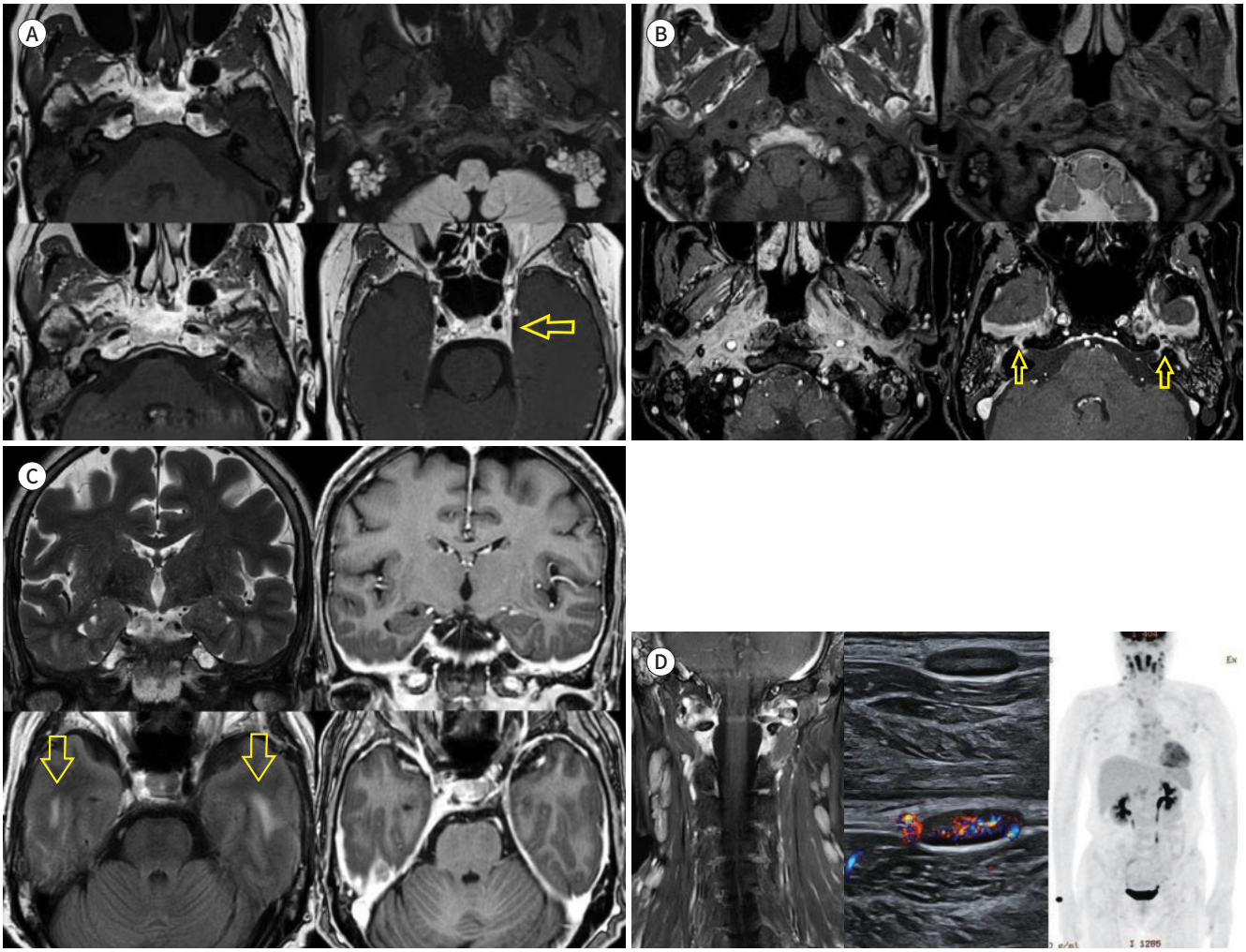
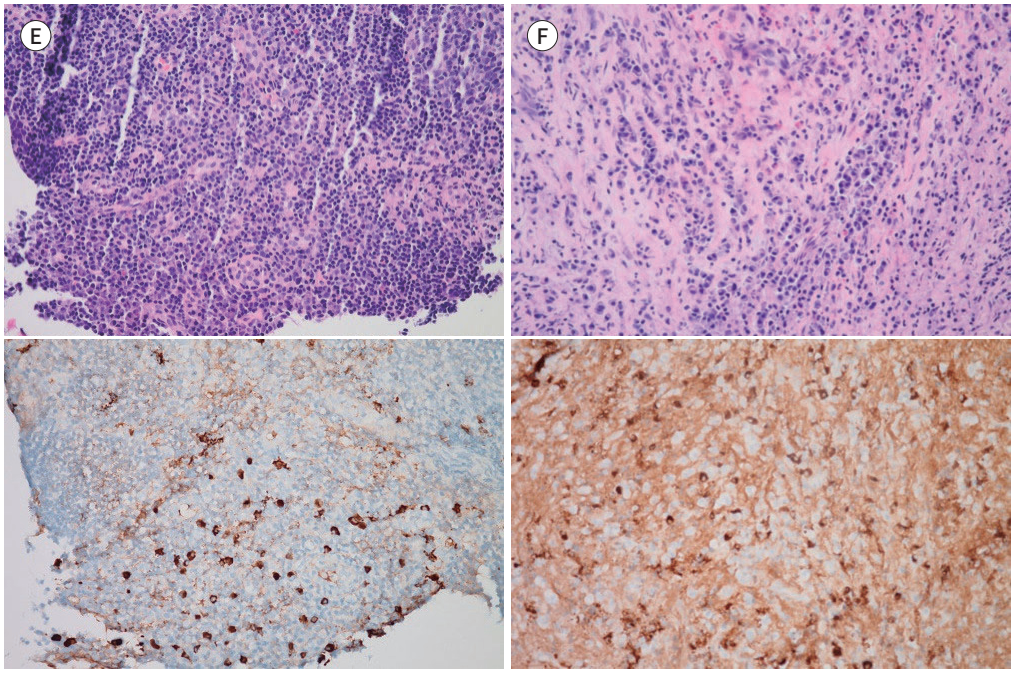


Fig. 1. IgG4 related disease in head and neck in a 65-year-old female.
E. Photomicrograph (top) of the cervical lymph node shows prominently increased infiltration of plasma cells (hematoxylin and eosin stain, × 400). Immunohistochemistry shows IgG and IgG4 (bottom) staining of cervical lymph node (× 400). IgG4: IgG ratio is less than 40% and IgG4 positive plasma cells are up to 50/HPF.
F. Photomicrograph (top) of the pachymeninges shows multifocal lymphoplasmacytic infiltration in the fibrous stroma (hematoxylin and eosin stain, × 400). Immunohistochemistry shows IgG and IgG4 (bottom) staining of pachymeninges (× 400). IgG4: IgG ratio is 50%–60% and IgG4 positive plasma cell are 60–70/HPF.
HPF = high-power field, IgG4 = Immunoglobulin G4




specimens from the dura revealed multifocal lymphoplasmacytic infiltration and increased IgG4-positive plasma cells in the fibrous stroma. On immunohistochemical staining, the IgG4/IgG ratio was 50%–60% and the IgG4 positive plasma cells were up to 60–70/HPF (Fig. 1F).

Fluorine (F)-18 fluorodeoxyglucose (FDG) PET/CT scan showed multi-level hypermetabolic lymph nodes at the bilateral neck, mediastinum and in the abdomen, but no evidence of hypermetabolic lesion in the gastrointestinal tract or in the endocrine and exocrine gland organs (Fig. 1D).

After starting prednisolone (0.6 mg/kg/daily for 4 weeks) therapy with following 6-month tapering plans, her serum IgG level gradually decreased, and hearing impairment and facial nerve palsy improved by degrees.

This case report was approved by the local Institutional Review Board, and the requirement for written informed consent was waived (IRB No. SCMC2021-06-001).

## DISCUSSION

IgG4-RD is a recently recognized fibroinflammatory condition involving multiorgans that is characterized histologically by tumefactive lesions with a dense lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells and storiform fibrosis; and often but not always, is

with elevated serum IgG4 concentrations (1). The histopathological features bear striking similarities across organs, regardless of the site of disease (2). In particular, four clinical phenotypes of IgG4-RD have been defined based on organ involvement: 1) pancreaticobiliary disease, 2) retroperitoneal fibrosis with or without aortitis, 3) head- and neck-limited disease, and 4) Mikulicz's syndrome with systemic involvement (3).

In this presented work, we recently experienced a case in a 56-year-old female patient who initially complained of hearing loss, but was eventually diagnosed with IgG4-RD concurrently with involvement of the cranial nerve, parapharyngeal lymph nodes and pachymeninges.

Until now, the exact prevalence of various organ manifestations of IgG4-RD also remains unclear, but regardless of where it occurs, the typical patient with IgG4-RD is a middle-aged to elderly man (male-to-female ratio of 2 and median age was 53 years) (4).

Head- and neck-limited disease, like our case, neurological symptoms of the intracranial variation of IgG4-RD also depend on the location of the inflammatory process, which is most frequently located at the skull base. Thickening of the dura mater in the area of the anterior fossa skull base, cavernous sinuses area, and superior orbital fissure is frequently connected with the occurrence of pain behind the eyeball, deteriorated vision and disturbances affecting the mobility of the eyeballs. These symptoms are often manifested in the form of Tolosa–Hunt syndrome (5). Our case demonstrated bulging out contoured and well-contrast enhanced cavernous sinus on TBMR without ocular symptom.

When the inflammatory lesions are located in the cerebellar tentorium and the posterior cranial fossa base (mainly in the clivus and foramen magnum area), symptoms and signs of cranial nerve involvement of VI to XII are observed along with cerebellar ataxia. Radiologic imaging is an important part of the diagnostic approach for IgG4-RD in many organs (6).

With the currently reported case, we confronted with broad-spectrum of questions for differential diagnoses, including vasculitic disorders (for example, granulomatosis with polyangiitis [GPA], giant cell arteritis, and Behcet's disease); other immune-mediated conditions (for example, rheumatoid arthritis, sarcoidosis); malignancies (for example, lymphoma); and infections (such as, tuberculosis) (7). There have been no reports so far on the concurrent involvement of extracranial (neuronal and non-neuronal) and intracranial structure upon head- and neck-limited disease. Therefore, we would like to focus on each structural radiologic finding one after another and the descriptions are as follows.

HP-pattern IgG4-RD is characterized by a localized or diffuse thickening of the dura mater, with or without associated inflammation, affecting predominantly the brain and cervical medulla (6). According to a retrospective review, among the 14 cases of HP, there were 4 cases caused by IgG4-RD, 3 associated with GPA, 2 with lymphoma, and 1 each with rheumatoid arthritis, giant cell arteritis, and sarcoidosis. Thus, the case series demonstrate that IgG4-RD may be the most common etiology of noninfectious HP (7).

Meningeal disease can occur either in isolation or in association with other systemic manifestations (e.g., autoimmune pancreatitis, retroperitoneal fibrosis, or orbital pseudotumor) and neurological symptoms typically arise when central nervous system (CNS) structures are compressed by the growing fibrotic mass (8).

On CT scans and MR imaging studies, IgG4-related hypertrophic pachymeningitis may appear either as a linear dural thickening or as a bulging mass; skull bone defect was also iden-

tifed (5). On T2-weighted MR imaging, fibrotic HP is characterized by thickened and relatively hypointense lesions with mass effect to the surrounding organs, and occasionally by scattered foci of hyperintensity suggestive of the presence of inflammation. Gadolinium-enhanced T1-weighted MR imaging studies may offer high spatial resolution and facilitate the identification of active inflammation along the dural edges (7). IgG4-RD seldom, if ever, affects the brain parenchyma but the disease is one of the most common causes of HP. IgG4-RD is also an unheralded cause of hypophysitis. MRI shows sellar enlargement and thickening of the pituitary stalk (6).

IgG4-related lymphadenopathy is noted in approximately 80% of patients with extranodal IgG4-RD (9). On CT and MR images, the involved lymph nodes are difficult to differentiate from other pathologic conditions.

Fatemi and Fang (10) published the first description of IgG4-RD isolated to the pharynx. With literature review, the authors could find additional two cases of IgG4-RD involving the parapharyngeal areas. But we could not be able to find a study dealing with large number of IgG4-RD involving the pharynx or parapharyngeal regions.

Tissue biopsy is the gold standard for the diagnosis of IgG4-RD in most settings (2). Lumbar puncture provides essential information, the primary value of which is the exclusion of CNS infections and malignancies (6).

Additionally, nuclear imaging in the form of PET scans with $^{18}$F fluorodeoxyglucose (FDG) has potential for use in assessing IgG4-RD activity, the degree of active inflammation within the meninges, and in identifying extracranial meningeal involvement, as well as diseases in other organs and was also helpful in monitoring disease activity after treatment (6).

Most clinical manifestations of IgG4-RD respond to glucocorticoids, which are the first-line, standard-of-care approach for most patients. Conventional steroid-sparing agents such as azathioprine, mycophenolate mofetil, and methotrexate, are used as means of achieving additional immunosuppression and sparing patients from the effects of long-term glucocorticoids (6). The most promising steroid-sparing agent (as a B-cell depletion agent), such as Rituximab, was used initially in patients who did not respond to glucocorticoids, conventional steroid-sparing agents, or to both.

By means of MR imaging plus nodal and dural biopsy, we could make a diagnosis of IgG4-RD that was combined with cranial neuropathy, multilevel lymphadenopathy and parapharyngeal soft tissue lesion, and afterwards intracranial involvement (HP). Even though it is well known that IgG4-RD involves multiorgans and despite several reports displayed IgG4-related HP with cranial nerve involvement, we could not find a report demonstrating a pharyngitis case combined with lymphadenopathy, cranial neuropathy and HP. Although in this case, the patient initially presented with hearing loss and following progressive facial nerve palsy and showed nonvisualization of definite intracranial pachymeningitis on first TBMR, we do not exactly know the origin of the disease. According to patient symptoms and serial MR imaging, this case is the first report of IgG4-RD limited to the head- and neck with multiorgan involvements from extracranial to intracranial regions.

In conclusion, even if IgG4-RD is diagnosed through tissue biopsy, our lessons from this case are as follows: CT and MR imaging findings are not specific for the diagnosis of the disease, and the imaging devices are useful for determining and monitoring the extent of the

disease and in demonstrating the effectiveness of treatment.

### Author Contributions

Conceptualization, all authors; data curation, all authors; investigation, all authors; project administration, all authors; supervision, S.M.; visualization, all authors; writing—original draft, I.J.Y.; and writing—review & editing, S.M.

### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

### Funding

None

## REFERENCES

1. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366:539-551
2. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015;385:1460-1471
3. Rampi A, Lanzillotta M, Mancuso G, Vinciguerra A, Dagna L. IgG4-related disease of the oral cavity. Case series from a large single-center cohort of Italian patients. *Int J Environ Res Public Health* 2020;17:8179
4. Levraut M, Cohen M, Bresch S, Giordana C, Burel-Vandenbos F, Mondot L, et al. Immunoglobulin G4-related hypertrophic pachymeningitis: a case-oriented review. *Neurol Neuroimmunol Neuroinflamm* 2019;6:e568
5. Lu LX, Della-Torre E, Stone JH, Clark SW. IgG4-related hypertrophic pachymeningitis: clinical features, diagnostic criteria, and treatment. *JAMA Neurol* 2014;71:785-793
6. De Virgilio A, de Vincentiis M, Inghilleri M, Fabrini G, Conte M, Gallo A, et al. Idiopathic hypertrophic pachymeningitis: an autoimmune IgG4-related disease. *Immunol Res* 2017;65:386-394
7. Wallace ZS, Carruthers MN, Khosroshahi A, Carruthers R, Shinagare S, Stemmer-Rachamimov A, et al. IgG4-related disease and hypertrophic pachymeningitis. *Medicine (Baltimore)* 2013;92:206-216
8. Della-Torre E, Galli L, Franciotta D, Bozzolo EP, Briani C, Furlan R, et al. Diagnostic value of IgG4 Indices in IgG4-related hypertrophic pachymeningitis. *J Neuroimmunol* 2014;266:82-86
9. Pan Z, Zhou J. IgG4-related lymphadenopathy: a potentially under- and over-diagnosed entity. *Int J Clin Exp Pathol* 2017;10:10153-10166
10. Fatemi G, Fang MA. IgG4-related pharyngitis-an addition to the nomenclature of IgG4-related disease: comment on the article by Stone et al. *Arthritis Rheum* 2013;65:2217

# 두경부에 국한된 표현형으로 발생한 면역글로불린 G4와 연관된 질환: 증례 보고

임준용 · 선우미옥*

면역글로불린 G4 (immunoglobulin G4; 이하 IgG4) 관련 질병은 한때는 장기별 별개의 질환으로 진단되었던 질환들을 근래에 공통적인 병리학적, 혈액학적 및 임상적 특징을 가지는 면역 매개 질환을 일컫는다. 이 분류의 질환은 다양한 장기를 침범할 수 있으며, 두경부 역시 침범할 수 있다. 두경부를 침범하였을 경우, 주로 눈물샘, 안와, 갑상선, 뇌하수체 및 뇌수막 등을 주로 침범한다. 이에, 초기 급성중이염과 유양돌기염으로 증상으로 내원한 65세 여자 환자에서 안면신경, 뇌경막, 비인강과 경부임파절에 동시에 발생하여 자기공명영상과 조직검사로 진단된 IgG4 연관 질환에 대하여 증례 보고를 하고자 한다.

성균관대학교 의과대학 삼성창원병원 영상의학과

https://doi.org/10.3348/jksr.2021.0107