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Clinical significance of IgG4 in sinonasal and skull base inflammatory pseudotumor

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Abstract

Introduction Inflammatory pseudotumor (IPT) in the sinonasal cavity and skull base region is benign non-neoplastic inflammatory process. However, IPT can mimic malignant tumor or infectious disease and there are difficulties in confirmation of diagnosis. The aim of study is to evaluate the clinical significance of immunoglobulin G4 (IgG4) in IPT in terms of steroid response and differential diagnosis with other skull base infiltrative lesions.

Methods Medical records were reviewed retrospectively from 1998 to 2016. Subjects diagnosed with IPT by surgical biopsy were enrolled. IgG4 positivity was defined as IgG4/IgG ratio > 0.4. Additionally, IgG4/IgG ratio was calculated in eight skull base osteomyelitis (SBO) patients.

Results Twenty-six IPT patients were included and the average age was 52.3 years, and 57.7% were male and 42.3% were female. Most lesions were involved in the sinuses (88.5%) and the incidence of extension beyond the sinuses itself was as follows: the cheek/hard palate/parapharynx (15.4%), orbit (61.5%), skull base (57.7%), and dura or brain (23.1%). All IPT cases revealed IgG4 + plasma cells and IgG4/IgG ratio over 0.4 was detected in 42.3% (11/26) of cases. In case of SBO, no patients had IgG4/IgG ratio exceed 0.4. Main treatment modality was systemic steroids (61.5%) and other modalities were used: surgery (3.8%), immunosuppressant (7.7%), radiotherapy (30.8%), or a combination of these modalities (15.4%). Steroid responses were not significantly different, but IgG4-positive group tended to have better response to steroid therapy.

Conclusions IgG4-positive and IgG4-negative IPT patients revealed no differences in involvement sites, clinical course, and steroid responses. However, IgG4/IgG ratio and IgG4 + plasma cell count can provide a diagnostic clue for infiltrative skull base lesions such as IPT and a differential diagnosis of SBO.

Keywords Inflammatory pseudotumor · Immunoglobulin G4 · IgG4-related disease · Skull base · Sinonasal lesion

Introduction

Inflammatory pseudotumor (IPT) is a benign idiopathic non-neoplastic inflammatory process. In histopathologic finding, IPT characterized by acute and chronic inflammatory cells (plasma cells and lymphocytes) with fibrosis [1, 2]. IPT can occur in any organ and clinical manifestation is progressive, locally destructive, and usually mimicking malignant tumor or infectious disease [3, 4]. The orbit is the most common location in the head and neck region and IPT can involve the brain, cavernous sinus, nasopharynx, and other specific sites of the skull base [1]. Prevalence of the skull base IPT is unknown but rare and uncommon [5]. Radiographic findings of IPT were ill-defined infiltrative lesions and resembling malignant tumors. It appeared isointense on T1-weighted

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image and hypointense on T2-weighted image though it is not pathognomonic characteristic for IPT [6].

These infiltrative lesions of IPT in the skull base need a differential diagnosis from the following diseases; malignancy, skull base osteomyelitis (SBO), or invasive fungal sinusitis. Radiologic finding alone is difficult to distinguish between these diseases [2, 7]. Thus, endoscopic biopsy and tissue culture are mandatory for confirmation of diagnosis. Once malignant tumors (e.g., nasopharyngeal carcinoma or lymphoma) or fungal infections are excluded, the remaining inflammatory diseases may have similar histopathological characteristics as aggregation of heterogeneous inflammatory cells.

Similar to IPT, immunoglobulin G4 (IgG4)-related disease is fibro-inflammatory condition characterized by tumefactive lesions in multiple sites. It has a characteristic histopathological appearance (dense lymphoplasmacytic infiltrate, storiform fibrosis, and obliterative phlebitis) and often elevates serum IgG4 concentrations [8, 9]. Fibrosis and infiltration of lymphocytes and plasma cells were a common feature of IPT and IgG4-related disease. Recent studies that reviewed 40 papers including 83 IPTs demonstrated that 50 cases were classified as highly suggestive IgG4-related disease and 24 as probable IgG4-related disease [10]. Another systematic review article reported that 11 of 13 patients (84.6%) tested for the presence of IgG4 resulted positive for the antibody in sinonasal and ventral skull base IPT [5]. Previous studies suggest that IgG4-related IPTs may form part of the spectrum of systemic IgG4-related sclerosing disease [9]. Although the relationship between IPT and IgG4-related disease has not been established and the diagnostic value of IgG4 in IPT remains unclear. There are no site-specific diagnostic criteria proposed for IgG4-related sinonasal or skull base inflammation.

The present study aimed to describe the clinical characteristics of IPT in sinonasal and skull base and to recognize the clinical significance of IgG4 in IPT focused on steroid response and a difference with SBO.

Materials and methods

Study subjects

Medical records of 26 consecutive patients were reviewed retrospectively from October 1998 to November 2016 in a tertiary referral hospital. Subjects were enrolled who were diagnosed with IPT histopathologically. If there was no IgG4 result in the previous report in IPT patients, IgG4 and IgG staining were performed. Anatomical location, symptoms, histopathology, radiologic findings, treatment, clinical course, and steroid response were evaluated. This study protocol was approved by Institutional Review Board of Samsung Medical Center (IRB No. SMC 2017-02-135) and the informed consents were waived.

Evaluation of disease activity

Clinical course was presented as asymptomatic, improved symptom, stable, aggravated or recurred. Steroid response was graded as good, partial, or poor [10]:

1. *Good* complete remission or significant reduction in lesion size and relief of symptoms (pain or nerve palsies).
2. *Partial* partially reduced or persistent lesion size and improvement of pain only.
3. *Poor* aggravated or recurred lesion and no symptom relief.

The IgG4-related disease responder index (RI) was measured after treatment and sinonasal and skull base lesions were treated as one organ [11, 12]. RI was scored as follows: the absence of disease (RI score 0); disease has improved but still persists (RI score 1); disease has persistent and unchanged (RI score 2); new or recurrent disease (RI score 3); and disease has worsened (RI score 4).

IgG4/IgG-positive cell quantitation

We measured IgG4/IgG ratio within pathologic specimens using the following methods. Immunohistochemical (IHC) staining was performed on formalin-fixed and paraffin-embedded tissue sections. After deparaffinization, sections were incubated with antibodies to IgG (Dako, 1:40,000 dilution) and IgG4 (Cell Marque, 1:50 dilution). The number of plasma cells staining for IgG and IgG4 was evaluated in 3 different high-power fields (HPF) and the average number was used for calculating IgG4/IgG ratio. IgG4 positive defined as IgG4/IgG ratio over 0.4 based on the pathologic consensus statement [8]. Patients were classified as IgG4-positive and IgG4-negative groups based on the IgG4/IgG ratio. Additionally, SBO cases who tested IgG and IgG4 stain were used only for comparing IgG4/IgG ratios and those were calculated in eight SBO patients.

Statistical analysis

Statistical analyses used in this study include the Mann–Whitney *U* with two-tailed test. Tests for statistical differences for binary classification were analyzed using the Fisher's exact test. A *P* value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using Stata software v14.0 (StataCorp LP, College Station, TX, USA).

Results

A representative case (Case No. 14 of IgG4-negative case)

A 49-year-old male was referred to this tertiary hospital with the nasopharyngeal infiltrative lesion. His first present symptoms were headache and nausea and he visited a university hospital 2 months ago. A magnetic resonance image (MRI) was performed and the MRI showed infiltrative lesion on the left nasopharynx and it was extended to the clivus and petrous apex (Fig. 1a, b). After two-time endoscopic biopsy, he could not have adequate diagnosis. The pathologic report was chronic inflammation with necrosis and coagulase-negative staphylococcus was identified. He had treatment with antibiotics and inflammatory markers were decreased. However, he experienced loss of sensation on the left tongue and voice change, also otalgia was newly developed. He revealed tongue deviation to the left side and vocal cord palsy on the left. After he referred to our hospital, he underwent the third endoscopic biopsy on the left nasopharynx. The histopathologic report was chronic inflammation with fibrosis and necrosis and no microorganisms (bacteria or fungus) were detected (Fig. 2a). We checked IgG and IgG4 for differential diagnosis of IPT of IgG4-related disease. IgG was positive in up to 500 plasma cells/HPF and IgG4 was positive in up to 120 plasma cells/HPF, the IgG4/IgG ratio was 0.24 (Figs. 2b and 2c). The ratio was not above 0.4 whereas the count of IgG4 + plasma cells was higher than usual findings, we decided to administer corticosteroid. After steroid treatment (prednisolone 0.6 mg/kg), his chief complaint (severe headache) were subsided dramatically and inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) were decreased. After 3 months of steroid treatment, he has been prescribed azathioprine and tapering steroid and his symptoms are stable. The lesion completely disappeared on MRI taken 2 years after treatment (Fig. 3).

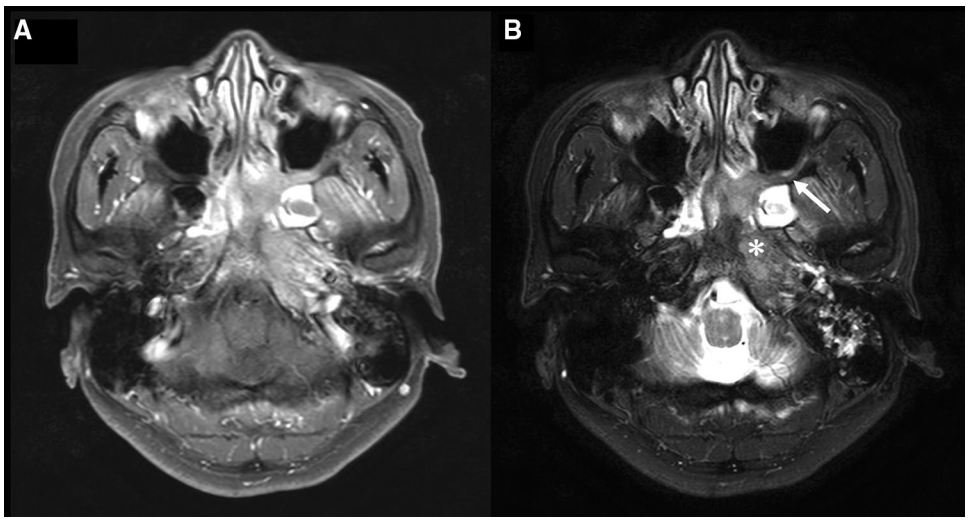

Fig. 1 Case No. 14. **a** T1-weighted MRI image with contrast enhancement. Infiltrative lesion involves the left nasopharynx, petrous apex, and clivus. **b** T2-weighted MRI image. The lesion invaded into the infratemporal fossa via pterygomaxillary fissure (white arrow) and involved the left clivus and petrous apex (star)

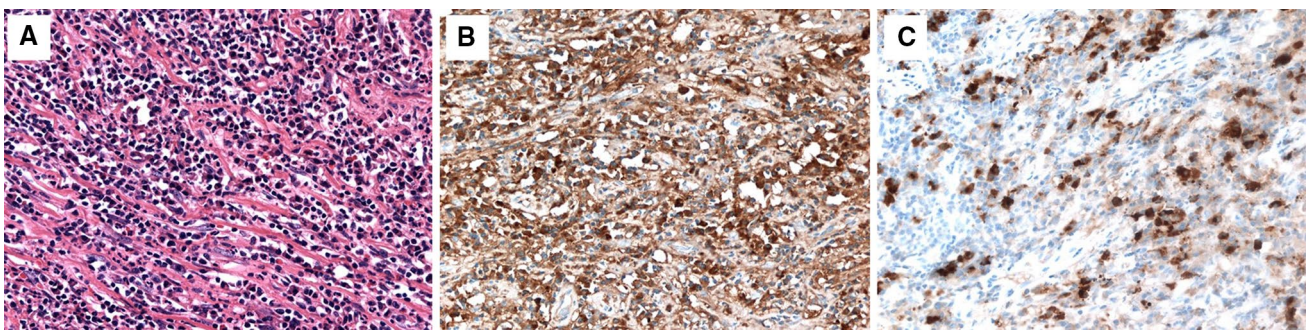

Fig. 2 Case No. 14. **a** Histopathologic finding of endoscopic biopsy specimen was chronic inflammation with fibrosis and necrosis. **b** IgG + plasma cells (500/HPF). **c** IgG4 + plasma cells (120 /HPF). IgG4/IgG ratio: 0.24

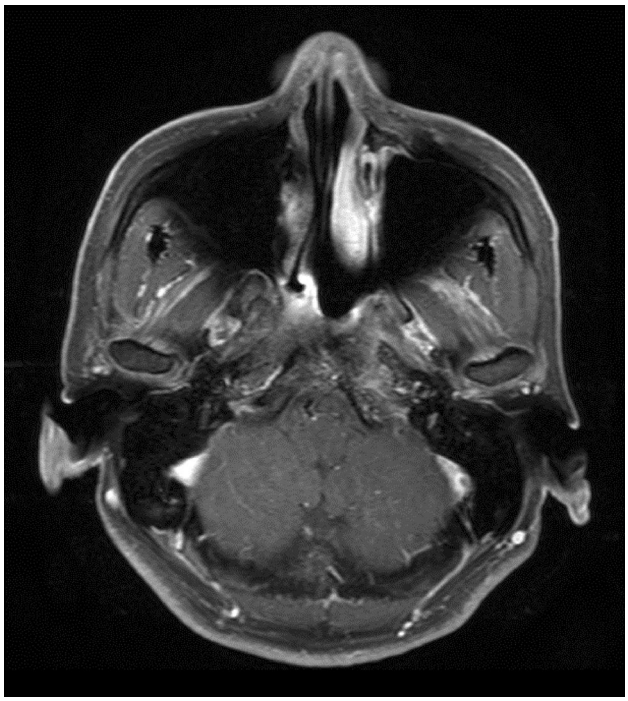

Fig. 3 Case No. 14. The lesion completely disappeared on T1-weighted MRI image with contrast enhancement taken 2 years after treatment

Clinical characteristics of IPT patients

Twenty-six IPT patients were included in this study and 11 cases (42.3%) were IgG4-positive (IgG4/IgG ratio > 0.4) and 15 cases (57.7%) were IgG4-negative (0 < IgG4/IgG ratio ≤ 0.4) on IHC staining. All IPT cases revealed IgG4 + plasma cells with various numbers (range 1–300/HPF; mean, 57.5/HPF). Histopathologic findings of all cases exhibited chronic inflammation, fibrosis, and lymphoplasmacytic infiltration. Radiological examination including computed tomography and MRI showed enhancing infiltrative soft-tissue lesions in the various anatomical sites. Reported radiologic differential diagnosis were pseudotumor, lymphoma, granulomatous disease, invasive fungal infection, or osteomyelitis. The average age was 52.3 years (SD 16.1 years; range 7.2–79.3 years). Patients were male in 15 cases (57.7%) and female in 11 cases (42.3%). Mean follow-up period after endoscopic biopsy was 41.5 months (SD 56.4 months; range of 1–223 months). Eight patients (27.6%) underwent the second biopsy due to inadequate diagnosis.

Demographic data showed no significant differences between IgG4-positive and IgG4-negative groups (Table 1). Most lesions were involved the nasal sinuses (88.5%) and four cases (15.4%) were extended to anterior cheek, hard palate, or parapharyngeal space without orbital or skull base invasion. Sixteen cases (61.5%) were involved the orbit or lacrimal gland. The others (15 cases, 57.7%) mainly located in the skull base including the cavernous sinus, Meckel's cave, infratemporal fossa, petrous apex, or carotid space. Among them, six cases (23.1%) had dura or brain invasion. Detailed sub-sites, symptoms, treatment modalities, and clinical courses of two groups are described in Tables 2 and 3. Involvement sites revealed no statistical differences between IgG4-positive and IgG4-negative cases ($P = 0.399$). Most common manifestations were headache and eye symptoms (diplopia, eyelid swelling, and proptosis, etc.). Some patients presented with nerve palsies including the optic nerve, trigeminal nerve, facial nerve, and vagus nerve.

Treatment and clinical course

Treatment was performed including surgery (3.8%), steroid (61.5%), immunosuppressant (7.7%), radiotherapy (30.8%), or a combination of these modalities (15.4%). Combination therapies were included steroid treatment plus radiotherapy (four cases) or chemoradiation (three cases), or immunosuppressant (two cases). Overall response to a treatment was not different between IgG4-positive and IgG4-negative group. In both groups, more than half of patients (57.7%) were asymptomatic or improved symptoms after treatment. One IgG4-positive patient had aggravation due to sarcoma change of lesion. Three cases recurred after remission (one IgG4-positive and two IgG4-negative). Steroid treatment was mainstay for IPT treatment and the majority of patients in this study (80.8%) were treated with intravenous or oral steroids. Steroid responses were reported in 21 patients (9 IgG4-positive and 12 IgG4-negative). Although steroid response was not different between two groups, almost IgG4-positive patients (8/9, 88.9%) revealed good or partial response except one sarcoma case. Three IgG4-negative patients (3/12, 25%) had poor response to steroid treatment. IgG-positive group showed tendency of better response to steroid treatment than IgG4-negative group (88.9% vs. 75%), but there was no statistically significant difference ($P = 0.856$). Mean RI score was 1.6 in IgG4-positive patients and 1.3 in IgG4-negative patients, respectively. It had no significant differences between two groups ($P = 0.548$).

Three IgG4-negative cases including representative case had treated with antibiotics initially or combining with steroids because IPT and SBO were not distinguished. All three patients experienced aggravation or no improvement of symptoms during antibiotics treatment. After pathologically confirmed as IPT, these patients prescribed steroids only and diseases were controlled. Two patients underwent subsequent therapy with immunosuppressants which were considered as second-line therapy and steroid-sparing treatment. One patient was prescribed rituximab (monoclonal antibody against the CD20) [13] and the other prescribed azathioprine [14] as described above (Case No. 14).

Table 1 Clinical characteristics between IgG4-positive and IgG4-negative patients

Variable	IgG4 positive ($N=11$)	IgG4 negative ($N=15$)	Total ($N=26$)	P value
Age, years (mean ± SD)	45.9 ± 17.8	56.9 ± 13.4	52.3 ± 16.1	0.073
Gender, male	6 (54.5%)	9 (60%)	15 (57.7%)	1.000
Follow-up period, months	46.5 ± 45.3	37.8 ± 64.6	41.5 ± 56.4	0.275
Involvement sites				0.436
Sinus	11 (100%)	12 (80%)	23 (88.5%)	
Orbit	9 (81.8%)	7 (46.7%)	16 (61.5%)	
Nasopharynx	2 (18.2%)	7 (46.7%)	9 (34.6%)	
Skull base	6 (54.5%)	9 (60%)	15 (57.7%)	
Treatment[a]				0.927
Steroid	9 (81.2%)	12 (80%)	21 (80.8%)	
Radiotherapy	5 (45.5%)	7 (46.7%)	12 (46.2%)	
Chemotherapy	2 (18.2%)	2 (16.7%)	4 (15.4%)	
Immunosuppressant	1 (9.1%)	1 (6.7%)	2 (7.7%)	
Surgery	0	1 (6.7%)	1 (3.8%)	
Clinical course				0.701
Asymptomatic	2 (18.2%)	2 (13.3%)	4 (15.4%)	
Improved symptoms	5 (45.4%)	6 (40%)	11 (42.3%)	
Stable symptoms	2 (18.2%)	5 (33.3%)	7 (26.9%)	
Recurred/aggravated	2 (18.2%)	2 (13.3%)	4 (15.4%)	
Steroid response	($N=9$)	($N=12$)		0.856
Good	4 (44.4%)	4 (33.3%)	8 (40%)	
Partial	4 (44.4%)	5 (41.7%)	9 (45%)	
Poor	1 (11.1%)	3 (25%)	3 (15%)	
Responder index (mean ± SD)	1.6 ± 1.1	1.3 ± 1.0	1.5 ± 1.0	0.548
Score 0	1 (9.1%)	3 (20%)	4 (15.4%)	
Score 1	5 (45.4%)	6 (40%)	11 (42.3%)	
Score 2	3 (27.3%)	4 (26.7)	7 (26.9%)	
Score 3	1 (9.1%)	2 (13.3%)	3 (11.5%)	
Score 4	1 (9.1%)	0	1 (3.9%)	

[a]Multimodal treatments counted separately

All IPT patients, not patients with SBO, were stained with IgG4 antibodies and they exhibited abundant IgG + plasma cells, and IgG4/IgG ratio over 0.4 was detected in 42.3% cases. Whereas, in the case of SBO, half of them (4 out of 8 cases) had IgG4 + plasma cells (1, 2, 6, and 15/HPF) but IgG4/IgG ratios were below 0.4 and no patients showed IgG4 positivity (Table 4). Differential diagnosis of infiltrative sinonasal and skull base lesions includes IPT and SBO which were confirmed by endoscopic biopsy as an inflammatory lesion, among them, IgG4-positivity might be favored IgG4-related disease in IPT (Fig. 4).

Discussion

In this retrospective review of 26 IPT patients, all cases showed various numbers of IgG4 + plasma cells and 42.3% of sinonasal and skull base IPT revealed IgG4-positive as definition by IgG4/IgG ratio > 0.4. Even though there is no generally accepted criteria for IgG4 positivity in the sinonasal lesion, we adapted IgG4/IgG ratio > 0.4 as a positive criteria according to the previous reported consensus statement [8]. Skull base involvement was 16 cases (57.7%) among all IPT cases and 6 cases (23.1%) were involved dura and brain. Between IgG4-positive and IgG4-negative IPT patients, there were no significant differences in demographic characteristics, involvement sites, clinical course, and steroid response.

IPT has been considered to be complex and variable in histopathologic findings [4]. Some biopsy specimens were typically identified as myofibroblastic spindle cell infiltration. However, in the other, IPTs were presented with a proliferation of histiocytes and/or dendritic cells [15]. Another histopathologic classification of IPT was trichotomous system which was comprised of myofibroblastic type, plasma cell rich type, and fibrohistiocytic type [10]. Among these three patterns, plasma cell rich type resembles IgG4-related disease [9].

Table 2 Clinical features of IgG4-positive (IgG4/IgG ratio > 0.4) cases

No	Sex	Age	Side	Anatomical location	Symptoms	Treatment	Clinical course
1	M	60	Bilateral	Lacrimal gland, sinus	Diplopia, eyelid swelling	Steroid	Asymptomatic
2	M	77	Right	Sinus, nasopharynx, orbit, petrous apex, infratemporal fossa, cavernous sinus	Visual loss	Steroid	Stable
3	M	7	Right	Maxillary sinus, orbit, orbital fissure, pterygopalatine fossa, cavernous sinus, dura	Ptosis, diplopia, headache	Steroid	Improved
4	F	45	Bilateral	Lacrimal gland, sinus	Eyelid swelling	Steroid	Recurred
5	F	46	Left	Orbit and sinus	Orbital pain	Steroid	Improved
6	M	55	Bilateral	Sinus, orbit, infratemporal fossa, masticatory space, cavernous sinus	Eyelid swelling	Steroid	Improved
7	M	48	Bilateral	Sinus, orbit, nasopharynx, pterygopalatine fossa, orbital fissure, cavernous sinus	Eyelid swelling	RT	Stable
8	F	42	Left	Maxillary sinus, anterior cheek	Cheek pain	Steroid + RT	Improved
9	F	34	Right	Maxillary sinus, orbit, pterygopalatine fossa, cavernous sinus, infratemporal fossa, dura	Facial pain	Steroid + RT + CTx	Asymptomatic
10	M	33	Right	Maxillary sinus, pterygopalatine fossa, cavernous sinus, Meckel's cave, masticatory space	Cheek hypoesthesia	CCRT (d/t sarcoma change)	Aggravated
11	M	56	Bilateral	Lacrimal gland, sinus	Eyelid swelling	Steroid + rituximab	Improved

CCRT concurrent chemoradiation therapy, *CTx* chemotherapy, *IgG4* immunoglobulin G4, *RT* radiotherapy

Table 3 Clinical features of IgG4-negative (IgG4/IgG ratio ≤ 0.4) cases

No	Sex	Age	Side	Anatomical location	Symptoms	Treatment	Clinical course
1	M	63	Bilateral	Orbit, sinus, nasopharynx, petrous apex, Meckel's cave, dura	Headache	Steroid	Stable
2	M	71	Left	Nasopharynx, parapharyngeal space, clivus, petrous apex, cavernous sinus, middle ear	Otalgia	Steroid	Asymptomatic
3	M	79	Left	Orbit, sinus, pterygopalatine fossa	Proptosis	Steroid	Improved
4	M	61	Bilateral	Sinus, nasopharynx, prevertebral space, jugular fossa, clivus, petrous apex	Visual loss, headache	Steroid	Improved
5	F	43	Right	Nasopharynx, parapharyngeal space	Facial pain	RT	Improved
6	M	67	Bilateral	Orbit, sinus, pterygopalatine fossa, infratemporal fossa, cavernous sinus, dura	Visual loss, proptosis	Steroid	Improved
7	F	61	Left	Sinus, septum, internal carotid artery, cavernous sinus, parapharyngeal space	Headache, VCP, FNP	Steroid + RT	Stable
8	F	44	Right	Maxillary sinus, orbit, anterior cheek, hard palate	Cheek swelling	Steroid + RT + CTx	Recurred
9	F	61	Bilateral	Sinus, nasopharynx, infratemporal fossa, cheek, petrous apex, dura	Diplopia	Steroid + RT	Recurred
10	F	35	Right	Orbit, sinus, septum, cavernous sinus, dura, frontal lobe	Headache, eyelid swelling	RT	Stable
11	F	37	Right	Orbit, sinus	Proptosis	Steroid + RT + CTx	Stable
12	M	56	Right	Maxillary sinus, hard palate	Cheek swelling	Steroid	Improved
13	M	75	Bilateral	Nasopharynx, parapharyngeal, prevertebral, carotid space, petrous apex, clivus	Headache	Steroid + RT	Stable
14	M	49	Left	Nasopharynx, sphenoid sinus, petrous apex, clivus	Headache	Steroid + azathioprine	Improved
15	M	53	Right	Orbit, sinus	Epistaxis	Surgery	Asymptomatic

CTx chemotherapy, *FNP* facial nerve palsy, *IgG4* immunoglobulin G4, *RT* radiotherapy, *VCP* vocal cord palsy

Table 4 Differential diagnosis using IgG4/IgG ratio between inflammatory pseudotumor and skull base osteomyelitis

IgG4/IgG ratio	Inflammatory pseudotumor ($N=26$)	Skull base osteomyelitis ($N=8$)	P value
No IgG4 stain	0	4	0.001*
IgG4 negative ($0 < \text{ratio} \leq 0.4$)	15	4	
IgG4 positive ($\text{ratio} > 0.4$)	11	0	

*Statistically significant using the Fisher's exact test

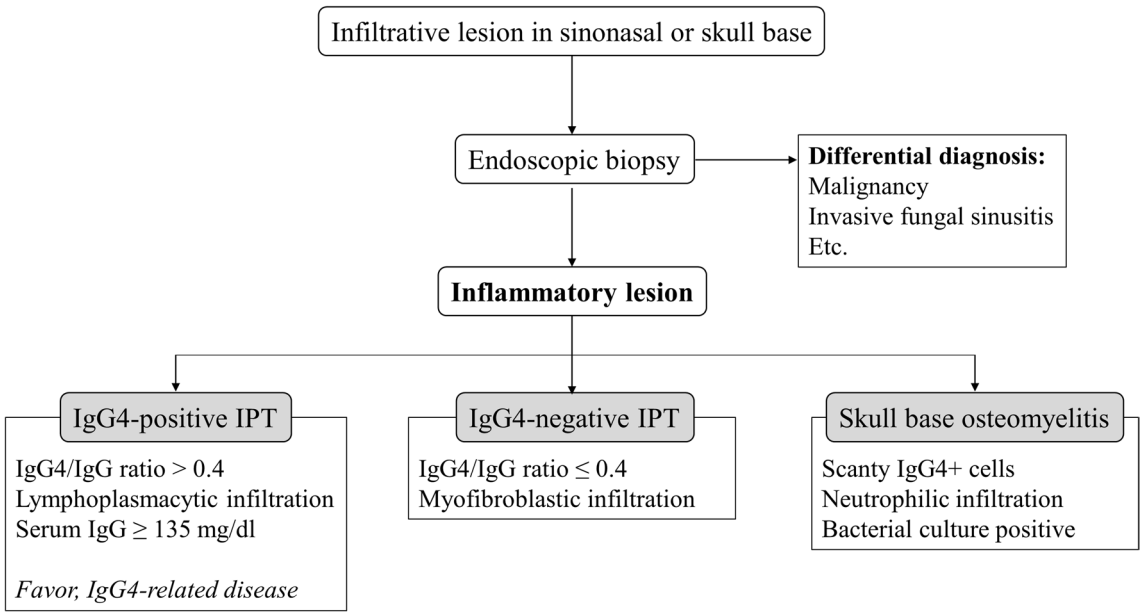

Fig. 4 Diagnostic diagram of infiltrative sinonasal and skull base lesion

Cain et al. reported four cases of the sinonasal cavity and skull base IgG4-related disease [16]. Only one patient met criteria for IgG4-related disease, whereas the others had only 30–50 IgG + plasma cells/HPF in histopathological evaluations. All four cases were treated with steroid and symptoms were resolved. Similarly, in our representative case (Case No. 14 of IgG4-negative case) who did not meet the diagnostic criteria (IgG4/IgG ratio > 0.4), he had abundant IgG4 + plasma cells (120/HPF) and also neutrophilic infiltration. His clinical course improved after steroid treatment, while preceding antibiotics treatment for 2 months did not alleviate his symptoms. Depending on the diagnostic criteria, there are difficulties in diagnosing and treating these patients. Another criteria for IgG4-related disease classified patients into definite, probable, or possible according to serum IgG4 concentrations (≥ 135 mg/dl), histopathological findings of marked lymphocyte and plasmacyte infiltration and fibrosis, and IgG4 + /IgG + cells > 40% and > 10 IgG4 + plasma cells/HPF [17]. Even though the authors recommended that some patients needs organ-specific diagnostic criteria if the patients cannot be diagnosed using this criteria. Therefore, it is necessary to establish suitable criteria applicable to sinonasal or skull base IgG4-related disease.

According to the systematic review of IgG4-related IPT [10], highly suggestive or probable IgG4-related disease (12/14 cases) showed a good response to steroid and insufficient evidence of IgG4-related disease (2/14 cases) had partial or no response. In our study, all IgG4-positive cases had good or partial response to steroid treatment except one sarcoma patient, whereas 25% of IgG4-negative cases showed poor response. Clinically, steroid or antibiotics response of disease can help for differential diagnosis between IPT and SBO. However, systemic steroids can relieve acute symptoms such as pain or swelling in both entities. Therapeutic response to steroid might play a role in differential diagnosis but it is not unique to IPT or IgG4-related disease. If pathogens are not identified from microbiological study in infectious disease especially in SBO, it is difficult to distinguish them from IPT.

Our study is one of the largest case series of IPT in sinonasal and skull base from a single center. However, there are several limitations of our current study. First, there was a large variation in the enrollment period and follow-up

duration. Treatment modalities were diverse according to when the treatment was decided. In the late 1990s and early 2000s, radiation therapy was mainly performed [18] Therefore, many cases underwent radiotherapy with or without steroid treatment. Among them, some cases required additional chemotherapy due to persistent disease. Second, serum IgG4 level can support the diagnosis of IgG4-related disease and some of patients in this study underwent blood test for IgG and IgG subclasses [19]. However, only recent cases had blood test and results were not consistent. Third, it is difficult to know the pure steroid response because of some combination therapies. Most cases underwent treatment with steroid and radiotherapy, simultaneously. It is unclear whether the results were better in steroid plus radiotherapy group than steroid only group. Lastly, additional histopathologic evaluation including immunohistochemistry were not available in this retrospective study. Some cases had immunohistochemical results of lymphoma markers (CD3, CD4, CD56, or CD138) or anaplastic lymphoma kinase, whereas no specific findings were observed.

To obtain information on whether IgG4 positivity may provide differential clues between IPT and SBO, we performed IgG4 test in patients who diagnosed with SBO. As we expected, there was no IgG4-positive case in SBO patients. IPT with IgG4/IgG ratio ≤ 0.4 cases showed various range of the number of IgG4 + plasma cells (range of 1–300/HPF, mean 57.5/HPF). In contrast, SBO cases only have few IgG4 + plasma cells (1, 2, 6, 15/HPF). IgG4/IgG ratio is an important finding for differential diagnosis, but histopathologic evaluation including site-specific positive cell count is needed to better define the diagnosis of IgG4-related IPT. If IgG4/IgG ratio does not reach 0.4, the number of IgG4 + plasma cell may provide the diagnostic clue for IPTs. Subtyping of sinonasal and skull base IPT and diagnostic criteria for IgG4-related IPT in sinonasal and skull base is warranted.

Conclusion

There were no differences in age, gender, involvement sites, clinical course, and steroid response between IgG4-positive and -negative groups in IPT. IgG4/IgG ratio and IgG4 + plasma cell count can provide an important diagnostic clue for IPT when pathologic findings were uncertain in infiltrative sinonasal and skull base lesions such as SBO.

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Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

Ethical approval Obtained.

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