Analysis of the characteristics of rare complications after tympanic injection in south China: a randomized controlled trial

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Abstract

Objectives: To study the complications of intratymapanic dexamethasone for Méniere's disease. Study Design:a randomized controlled trial. Methods:124 patients with Méniere's disease were randomly divided into two groups: Intratympanic dexamethasone(ITD) group (n=62) and Intratympanic lidocaine(ITL) group (n=62). According to the dose of dexamethasone used during treatment, the patients in ITD group were further divided intoITD1(2mg/ml) group (n=31) and ITD2(5mg/ml) group (n=31).The complications in each group were observed and evaluated after 10 times of intratympanic treatment with ear endoscopy. Results:3 patients suffered from the external auditory canal mycosis after ITD therapy. All the 3 patients were in the ITD2 group and the the infectious rate between patients who used 5mg/ml of dexamethasone and those who used 2mg/ml exhibited significant statistical difference. There were 5 cases of tympanic membrane atrophy thinning in ITD group , while no tympanic membrane atrophy thinning was observed in ITL group, the incidence rate between these two groups showed significant statistical difference. In addition, two patients in the ITD group had perforation accompanied by external auditory meatus mycosis, while no tympanic membrane perforation was observed in the ITL group. There was no statistical difference in the incidence of vertigo, pain, tongue numbness, tinnitus and other complications between the two groups. Conclusions: Our study suggests that the occurrence of external auditory canal mycosis and tympanic membrane atrophy thinning were significantly correlated with the use of dexamethasone and the occurrence of external auditory canal mycosis was closely related to the drug concentration, while the occurrence of tympanic membrane atrophy thinning showed not significantly correlated with the drug concentration. Further understanding of the clinical characteristics of complications after ITD will help clinicians select the appropriate concentration of dexamethasone in the therapy and better manage these complications.

Succinct key points

1. External auditory canal mycosis and tympanic membrane atrophy thinning can be observed in some patients after Intratympanic dexamethasone which has rarely been reported before. Herein, we summarized the characteristics of the particular complications we observed in our research center.
2. In our study we have found two steroid-related side effects, including tympanic membrane atrophy thinning and external auditory canal mycosis.
3. The steroid can make the tympanic membrane epithelial layer atrophy .
4. Steroid can lead to immunesuppression, and the higher the concentration, the greater the chance of an opportunistic infection ,then the external auditory canal mycosis may occur.
5. Clinicians can increase their understanding of these complications. Under the premise of ensuring the treatment effect, reducing the concentration of dexamethasone as far as possible can reduce the occurrence of fungal external auditory meatus.

1. Introduction

Intratympanic dexamethasone(ITD) has been reported to be used to treat Méniere's disease, It is widely used in clinical due to its minor systemic side effects, convenient way of administration which dexamethasone can penetrate directly into the inner ear through the round window membrane and effective treatment effect. However, ITD also has adverse reactions that cannot be ignored, such as transient dizziness and vertigo, pain, tongue numbness, bleeding, tinnitus and persistent perforation. In addition, in our research center, external auditory canal mycosis and tympanic membrane atrophy thinning can be observed in some patients after ITD which has rarely been reported before. Herein, we summarized the characteristics of the particular complications we observed in our research center which preferred to reflect the characteristics of patients in southern China due to their origin.

Since 1985, Fradis M et al. used intratympanic lidocaine (ITL) to treat Méniere's disease, with an effective rate of over 67.8%[4]. ITL was also widely carried out in our research center. In order to more accurately evaluate the complication characteristics of Méniere's disease patients treated with ITD, the patients treated with ITL were set as randomized control.

2. Material and methods

2.1 Patient Selection

This study was carried out in removed for blind peer review from April 2019 to March 2020. in order to compare the difference of group ITD and ITL in the patients, the two groups of patients who treated with dexamethasone and lidocaine were included in this study. All the patients were diagnosed with Ménière's disease according to the AAO-HNScriteria:

* i.e.[?]2 episodes of spontaneous paroxysmal vertigo lasting [?] 20 minutes;

* sensorineural hearing loss on [?] 1 audiogram;

* tinnitus or earfullness;

* and other causes ruled out[5].

Exclusion criteria: no external ear, middle ear and other inner ear diseases locally, no systemic disease such as diabetes, hypertension and malignant tumor. This study program has been approved by the ethics committee of removed for blind peer review , and all patients have signed informed consent before treatment.

2.2 Study Design

ITD Group: ITD Group included 62 patients who were all diagnosed with Meniere's disease (83 ears). Meniere's disease is strictly diagnosed according to the symptom complex, including episodic vertigo, aural fullness, tinnitus and hearing loss. All patients had complete audiologic and caloric examination. Then, ITD Group was further divided into ITD1 group and ITD2 group.ITD1 Group: 31 patients (41 ears) were treated with 2mg/ml Dexamethasone. ITD2Group: 31 patients (42 ears) were treated with 5mg/ml Dexamethasone. Injectable dexamethasone was induced in ear drum under the guidance of ear endoscopy. The patient lied on his side with the ears of dexamethasone added upwards to immerse the round window membrane in the solution for an appropriate time. The patient was lied with the ear up for 20 minutes, so that the round window membrane would be bathed in the solution for a proper time. Patients received ITD every three days for a total of ten times.

ITL Group: In order to more accurately evaluate the complication characteristics of Meniere's disease patients treated with ITD, another 62 patients (91 ears) treated with ITL were set as**randomized control** . The method and frequency of tympanic injection were the same as the ITD group.

Throughout the course of treatment, All the patients in both groups received the same regimen of oral medication to improve the inner ear microcirculation and neural function. The medication regimen is as follows: betahistine 12mg tid and mecobalamin 0.5mg tid .

2.3 Methods of follow-up

Before treatment, every patient was given health education, indicating the importance of each follow-up, and the patients enrolled had better compliance with follow-up. Each intratympanic treatment was performed under ear endoscopy, and related complications were recorded in detail. All the operations were performed by the same doctor.

2.4 Statistical methods

The data was analyzed using SPSS software version 22.0.The measurement data were presented as mean+-SD, the Student's t-test or analysis of variance was used for comparison between groups, and the chi-square test was used for comparison of clinical characteristics in the form of discrete variables. p values < 0.05 were considered statistically significant.

3. Result

3.1 The profile of clinical data in each group

A total of 124 patients were enrolled and randomly divided into the ITD group and the ITL group. The ITD group was further randomly divided into the ITD1 (2mg/ml) and ITD2 (5mg/ml) groups. All the patients (174 ears) with Meniere's disease (59 men, 65 women; age range: 21 to 81 years old)were treated with IT. The time between development of otologic complaints and ITD treatment ranged from 6 months to 5 years and 2 months. Prior to the administration of IT, all patients had been treated with other medications. All 124 had been treated with courses (often multiple) of oral medicine. The comparison of the general clinical index of each group before treatment (table 1 and table 2) showed no statistically significant difference ($P > 0.05$), indicating that the two groups had good equilibrium and were comparable.

3.2 Complications

After the patients received different treatments, we counted the incidence of complications in ITD group and ITL group. As showed in table 3, compared with the ITL group, the incidences of external auditory meatus mycosis ($p = 0.029$) and tympanic membrane thinning ($p = 0.018$)were significantly higher in the ITD group which had been further elaborated in section 3.3 and 3.4.In addition, two patients in the ITD group had perforation accompanied by external auditory meatus mycosis, and one of them had recovered from the perforation after active treatment which had been elaborated in section 3.4. .No tympanic membrane perforation was observed in the ITL group. There was no statistical difference in the incidence of vertigo, pain, tongue numbness, tinnitus and other complications between the two groups.

3.3 Tympanic membrane atrophy thinning

Five patients in the ITD group developed tympanic membrane atrophy thinning. However, no tympanic membrane atrophy thinning was observed in ITL group which made a significant difference compared with ITD group ($p = 0.018$). We made a detailed observation of tympanic membrane atrophy thinning through ear endoscopy and found the lesions were all located at the puncture site of the tympanic membrane in the anterior and lower quadrant of the tympanic membrane. Moreover, the tympanic membrane showed increased transparency, more shiny and looked thinner, and local capillary dilatation was visible(Figure 1a showed a patient with tympanic membrane atrophy thinning after ITD , Figure 1b showed the patient's normal tympanic membrane on the right side).Among the 5 patients, 2were in the ITD1 group and the remaining 3 were in the ITD2 group. There was no significant difference in incidence between patients who used 5mg/ml of dexamethasone and those who used 2mg/ml. No perforation of tympanic membrane or fungal or bacterial infection occurred in these cases during treatment.

3.4 External auditory canal mycosis

3 patients suffered from the external auditory canal mycosis after ITD therapy. All the 3 patients were in the ITD2 group (5mg/ml), while no patients in ITD1 group (2mg/ml) suffered from the external auditory canal mycosis which suggested that the occurrence of external auditory canal mycosis might be positively related to the dose of dexamethasone.

One patient experienced the mycosis 12 days after the beginning of ITI. He developed a thick white fungus silk on the left tympanic membrane. We injected triamcinolone acetonide cream into the external auditory canal to eliminate the fungal for 2 week. After treatment, the fungus silk fade away. Then we retreated the patient with ITD therapy. (figure 2a)

The second patient experienced the fungus in the external canal after 21 days with ITI therapy. At first, there was a lot white, brown, yellow fungus folk in the right external canal, 7 days later, he developed right otitis. He was treated with antibiotics, and applied triamcinolone acetonide cream to the external canal. 14 days later, the infection was controlled, but he experienced a perforation of the eardrum after 3 months. He kept on the triamcinolone acetonide cream therapy weekly for 2 weeks, the fungi disappeared but a persistent perforation was remained. (figure 2b)

The third patient suffered from the external auditory canal mycosis at the 18 days after the beginning of ITD. During that time, she received2 times injection in the 7 days when she was treated in the inpatient department. And at the 18 days, she felt obvious itching and a deeply block up in the right ear, and some green secretions came out of the auditory canal. under the endotoscope, we found the mycoses was so thick that covered all the membrane and those secretion appeared white, brown and black in color. There was a needle-like perforation in the anterior-inferior quadrant of membrane after we clean up the secretion and the membrane atrophy thinning was found around the perforation. Then we treated the patient with triamcinolone acetonide cream in the canal for 3 weeks. After treatment, the mycosis disappeared and the perforation was healed. (figure 2c and 2d)

4. Discussion

IT therapy was first reported by Fradis in 1985, then two reports used IT dexamethasone or lidocaine in Meniere disease, and a lot of patients got an improvement in vertigo and tinnitus[4,6]. neither of the two reports mentioned the complications of IT, and both of them thought the IT was safe and effective. However, more and more research found that this technique may cause some adverse side effect in recent years.

4.1 Complications

A lot of studies [7-10]had found that nearly one fifth of the overall study population suffered complications, the majority of these side effects were technique-related, very transient and self-resolving. They included transient dizziness/vertigo postinjection, ear fullness and slight otalgia during injection which can be all caused by the immediate injection technique. But in our study we have found some steroid-related side effects, including tympanic membrane atrophy thinning and external auditory canal mycosis.

4.2 Tympanic membrane atrophy thinning

In our study, tympanic membrane atrophy thinning were observed in 5 ears. The tympanic membrane is composed of three layers: the upper cortex, the fibrous layer and the mucosal layer. Keratinocytes, fibroblasts and the extracellular matrix (ECM) are the main components of the tympanic membrane. The damage of keratinocytes, fibroblasts and ECM will affect the morphology and function of the tympanic membrane. In 1978, Wilson et al.[11]reported that steroid can modify fibroblasts in vitro and inhibit the activity of these cells to varying degrees. Schoepe et al.[12]found that the proliferation and ECM protein synthesis of keratinocytes and fibroblasts were suppressed by steroid. Thereby, the stratum corneum got thinner, followed by an increased transepidermal water loss. Then, the epithelial layer lost its tensile strength and elasticity caused by the water loss and the degraded ECM. So the steroid can make the epithelial layer atrophy and steroid-induced tympanic membrane atrophy is characterized by a profound increase in transparency of skin, a cigarettepaper-like consistency accompanied by an increased fragility, tearing, bruising, thin, shiny, and telangiectatic which is consistent with what we had found in the 5 cases of tympanic membrane atrophy thinning in this study. The membrane presented increased transparency, more shiny, and visually felt thin. It was worth noting that the five patients in our study had no tympanic membrane perforation during the entire observation period, so tympanic membrane atrophy near the injection port was not the result of healing after tympanic membrane perforation.

4.3 External auditory canal mycosis

In addition, we also observed some patients may develop external auditory meatus mycosis in our study. In fact, we didn't find any reports about the mycosis of the external auditory canal after IT. The possible reason is that our vertigo center admits a large number of patients in southern China, including more than 250 meniere's disease patients every year. Due to the large number of patients, some rare complications may be observed in our center.

In our study, the incidence of mycosis of the external auditory canal after dexamethasone injection in the tympanum is higher than that of lidocaine alone, and the most likely risk factor is dexamethasone due to patients who were injected dexamethasone in the tympanic cavity may be at risk for immunosuppression and opportunistic infection. Leav et al.[13]reported a case of invasive pulmonary aspergillosis in a patient with asthma who was treated with high-dose inhaled fluticasone(1760mgdaily) which was significantly higher than the standard dosage in clinical practice (440mg twice daily).This suggests that steroid can lead to immunesuppression, and the higher the concentration, the greater the chance of an opportunistic infection. This is consistent with what we observed in our study, all the patients who were infected by the fungal were treated with 5mg/ml of dexamethasone, while patients treated with 2mg/ml showed no signs of fungal infection. It may suggest that we should reduce the concentration of dexamethasone as much as possible on the premise of ensuring the therapeutic effect.

In addition, the warm and humid environment in southern China is one of the special factor of fungal external auditory meatus. First of all, fungi can easily reproduce in a warm environment. Our hospital is located in the south of China where belongs to a subtropical region, with an average temperature of over 22.5, while the appropriate growth temperature of fungi is between 20-35.Secondly, Guangzhou is close to the ocean and there are no big mountains to prevent the warm and humid air flow coming from the ocean reaching Guangzhou. And this warm and humid environment is very favorable for the growth of fungi[14].

The third factor may be the one that clinicians need to be urgently concerned about is iatrogenic infections, which include the whole treatment process is not standardized or the use of fungus-infected drugs. If the syringe is not properly sterilized during drug extraction, a small amount of fungal spores may be iatrogenic into the eardrum or external auditory canal, which may cause local propagation and spread of the fungus. Treatment with fungus-contaminated steroids is one of the most direct causes of fungal infection. Kauffman CA[15]found that 751 patients were reported with fungal infection and 64died in 2012. In the end, they found that most patients had undergone epidural injection and a few osteoarticular injection with fungus-contaminated methylprednisolone acetate, resulting in a significant number of intracranial and intra-articular infections. Therefore, the government must carry out the most stringent quality control requirements for the production of drugs.

4.4 Conclusions

In this study, we further elaborated on the complications of ITD, mainly including tympanic membrane atrophy thinning and external auditory canal mycosis. By summarizing the characteristics of the above complications, clinicians can increase their understanding of these complications. Under the premise of ensuring the treatment effect, reducing the concentration of dexamethasone as far as possible can reduce the occurrence of fungal external auditory meatus. Mycosis of the external auditory canal is not a stubborn disease and can be cured by active treatment. Given the number of cases in our study is still relatively insufficient, the multi-center and large-sample data are needed to support the conclusion of the study.

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Table 1 Comparison of general clinic opathologic characteristics between ITD group and ITL group

Characteristics	Group ITD	Group ITL	X^2/t	p value
	(n=62)	(n=62)		
Sex (n/%)			X^2=0.130	0.719
Male	30(48.39)	27(43.55)		
Female	32(51.61)	35(56.45)		
Age (y)	45.57±9.23	43.77±11.89	t=1.275	0.762
Side(n/%)			X^2=0.241	0.623
left	37(44.58)	45(49.45)		
right	46(55.42)	46(50.55)		
Decibels(dB)	52.37±14.68	53.77±15.59	t=1.527	0.528
Accompanied Symptoms			X^2=0.315	0.854
Vertigo	26(41.94)	30(48.39)		
Tinnitus	47(75.81)	45(72.58)		
Aural fullness	32(51.61)	34(54.84)		

Table 2 Comparison of general clinicopathologic characteristics between ITD 1 gorup (2mg/ml dexamethasone)and ITD 2 group (5mg/ml dexamethasone)

Characteristics	Group ITD1	Group ITD2	X^2/t	p value

Characteristics	Group ITD1	Group ITD2	X^2/t	p value
	(n=31)	(n=31)		
Sex (n/%)			X^2=0.581	0.446
Male	13(41.94)	17(54.84)		
Female	18(58.06)	14(45.16)		
Age (y)	44.62±12.73	46.35±10.73	t=1.469	0.592
Side(n/%)			X^2=0.118	0.731
left	17(41.46)	20(47.62)		
right	24(58.54)	22(52.38)		
Decibels(dB)	51.38±15.74	52.99±13.69	t=1.109	0.795
Accompanied Symptoms			X^2=0.385	0.825
Vertigo	14(27.45)	12(22.22)		
Tinnitus	22(43.14)	25(46.30)		
Aural fullness	15(29.41)	17(31.48)		

Table 3 comparison of the incidence of complications in ITD group and ITL group

	Group ITD(83 ears)	Group ITL(91 ears)	p
external auditory canal mycosis	3	0	**0.029***
tympanic membrane atrophy thinning	5	0	**0.018***
transient dizziness and vertigo	7	9	0.153
Pain	17	21	0.368
bleeding	7	10	0.289
tongue numbness	8	10	0.227
tinnitus	7	3	0.072
perforation	2	0	**0.035***

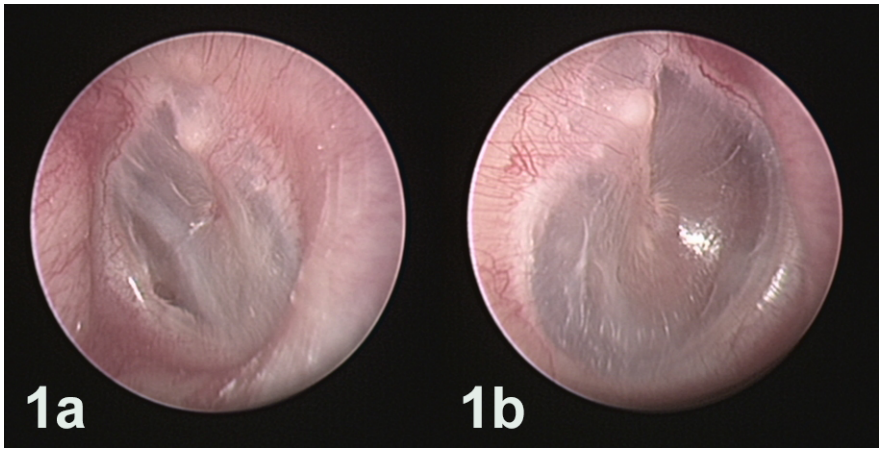


Figure 1 a patient with tympanic membrane atrophy thinning after ITD

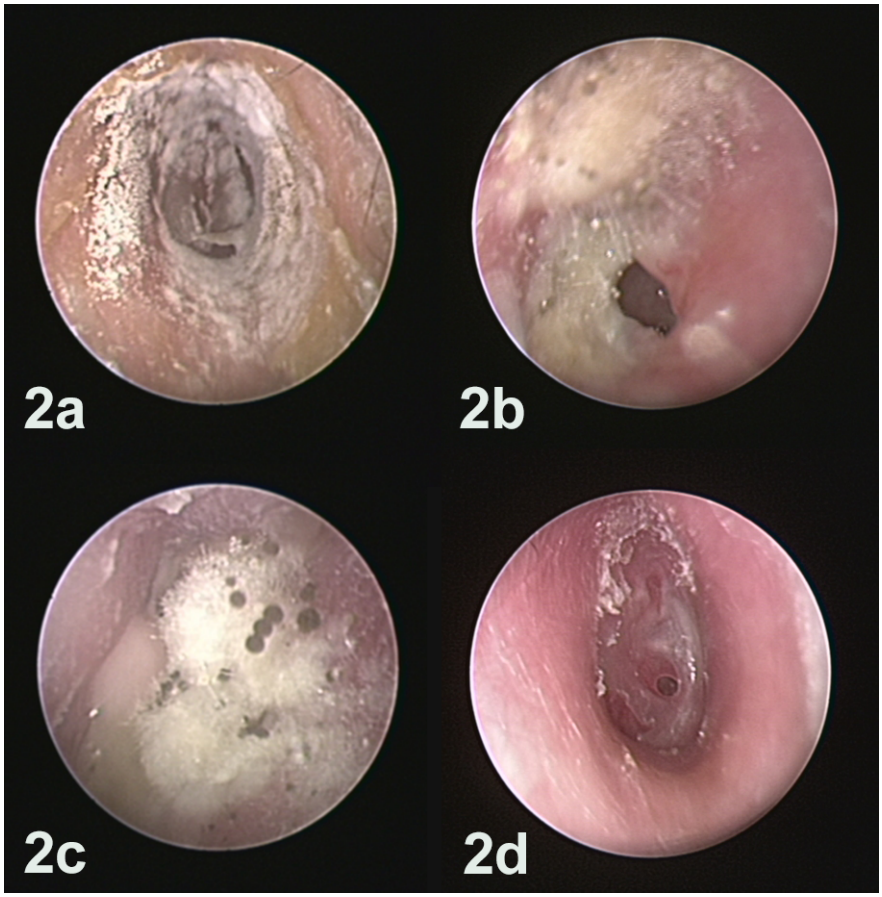
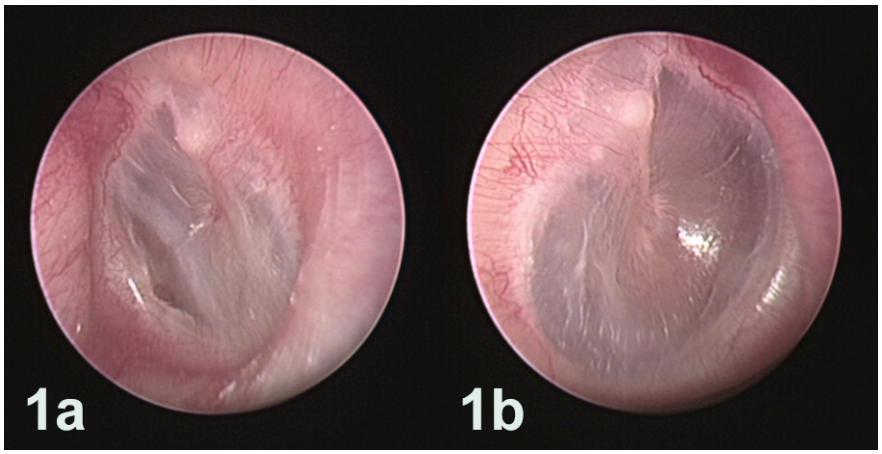
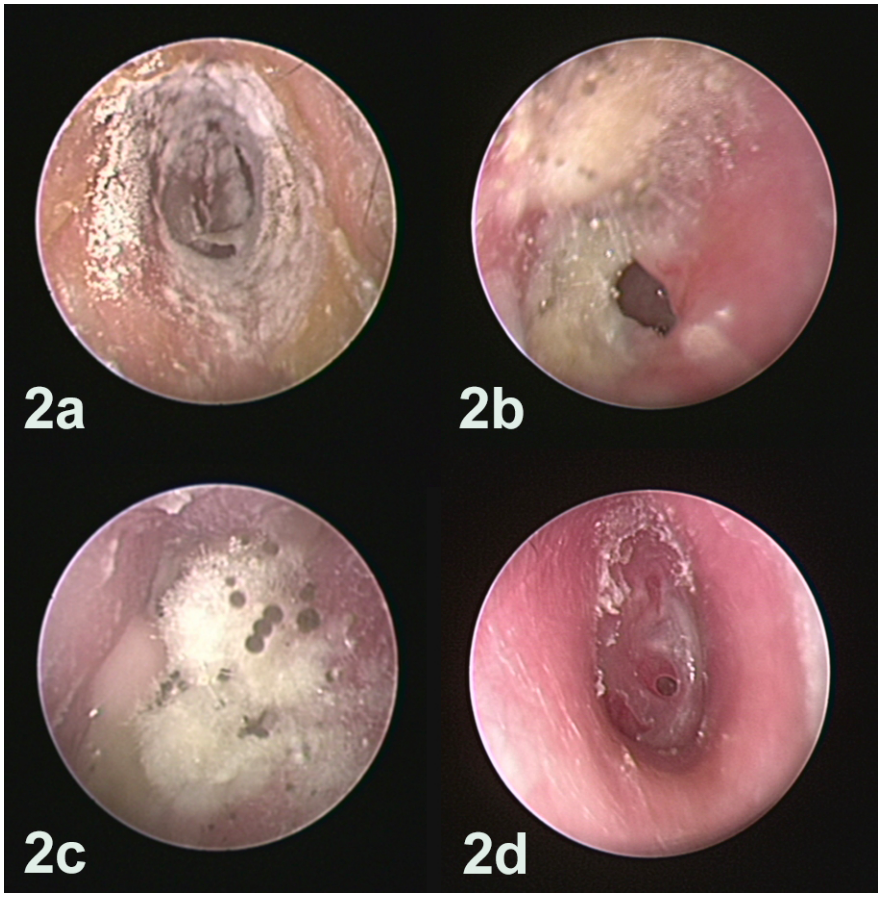


Figure 2 the patients with external auditory canal mycosis after ITD





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