Epithelial pearl formation following tympanic membrane regeneration therapy using an atelocollagen/silicone membrane and basic fibroblast growth factor: Our experience from a retrospective study of one hundred sixteen patients

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Accepted for publication 2 August 2013

Dear Editor,

Tympanic membrane perforation is frequently encountered in outpatient otorhinolaryngology practice. We have introduced a treatment procedure to promote regeneration of the tympanic membrane and closure of perforations using an atelocollagen sponge/silicone membrane combined with human basic fibroblast growth factor that promotes wound healing.[1,2] This report describes epithelial pearl formation following our outpatient-based tympanic membrane regeneration therapy.

Material and methods

Ethical considerations

This treatment procedure was approved by the Ethics Committee of Ehime University Hospital and was applied only to patients who provided written informed consent.

A total of 198 patients presented to the outpatient clinic for tympanic membrane regeneration at the Otorhinolaryngology Department of Ehime University Hospital between July 2009 and December 2011. To clarify the aetiology of tympanic membrane perforation, subjects were selected according to the following criteria: (i) chronic perforation followed for at least 1 year with a duration of perforation prior to treatment longer than 12 months and (ii) without any infection or unhealthy middle ear mucosa cases. We also excluded cases of reoperation due to reperforation after tympanic membrane perforation closure by regeneration therapy.

Tympanic membrane regeneration therapy treatment has been described previously.[2] Briefly, (i) a small cotton ball soaked in anaesthetic solution (4% lidocaine) is placed on the margin of the perforation; (ii) the perforation margin is circumferentially dissected with a sharp pick to expose fresh tissue; (iii) the atelocollagen membrane is trimmed to an appropriate size with scissors; (iv) the silicone membrane should be trimmed into a circle slightly larger than the perforation; (v) using a long needle, 0.1 mL of basic fibroblast growth factor solution is applied onto the atelocollagen.

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Results

A total of 116 patients (35 males and 81 females) were included in this study. Patients ranged in age from 13 to 90 years, with a mean age of 65.0 ± 15.1 years. The numbers of patients with small, medium and large perforations before treatment—defined as those involving one, two and three or more quadrants of the tympanic membrane, respectively—were 53 (46%), 45 (39%) and 18 (16%), respectively.

The causes of perforated tympanic membrane in 116 patients were chronic otitis media in 77 patients (67%), traumatic perforation in 12 patients (10%), perforation following myringotomy or tube placement in 15 patients (13%) and reperforation following tympanoplasty in 12 patients (10%). In the latest evaluation performed 1 year after the operation, 73 patients (62%) achieved complete closure.

Postoperative epithelial pearl formation was observed in 6 of 116 (5%) patients with an average time to onset of 7.3 months (range, 1–19 months) after the operation (Table 1). These patients ranged in age from 13 to 78 years, with a mean age of 61.2 years. The causes of perforated tympanic membrane in these six patients included chronic otitis media in three patients and traumatic perforation in three patients. Epithelial pearl formation occurred in the tympanic membrane in five patients (Figs 1 and 2) and in the ear canal in one patient (Fig. 3). Of the six patients with epithelial pearls in the tympanic membrane, four had a

Table 1. The outcome of postoperative epithelial pearl formation

Patient No./Sex/ Age (years)	Causes of original perforation	Lesion of original perforation	Onset after operation (months)	Residual perforation	Lesion of pearl	Size of pearl (mm)
1./F/65	COM	ASQ + AIQ	19	Small	ASQ	2
2./F/78	COM	AIQ	3	No	AIQ	1
3./F/13	Trauma	AIQ + PIQ	1	No	AIQ	1
4./M/65	COM	Total	2	4 pinholes	AIQ	1
5./F/76	Trauma	AIQ	7	No	AIQ	1
6./F/70	Trauma	ASQ + AIQ + PIQ	12	Pin hole	Ear canal	2
61.2			7.3			

COM, chronic otitis media; ASQ, Anterior Superior Quadrant; AIQ, Anterior Inferior Quadrant; PIQ, Posterior Inferior Quadrant.

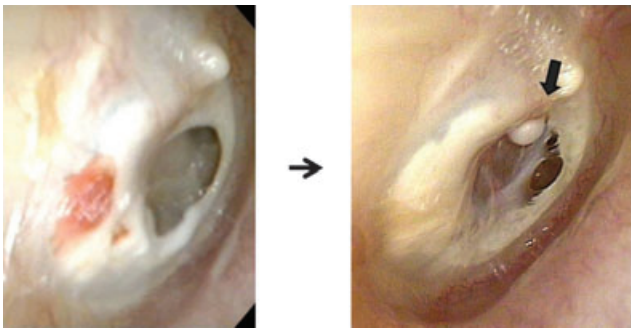

Fig. 1. Patient No.1: Case with a small perforation and postoperative epithelial pearl located in anterior superior quadrant lesion. The arrow indicates 2-mm postoperative epithelial pearl.

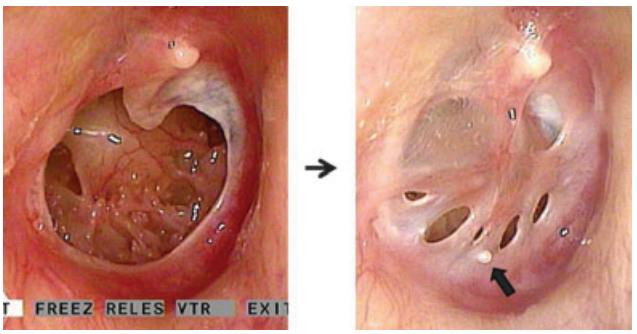

Fig. 2. Patient No.4: Case with multiple pinholes and postoperative epithelial pearl located in anterior inferior quadrant lesion. The arrow indicates 1-mm postoperative epithelial pearl.

lesion in the anterior inferior quadrant (Fig. 2) and one had a lesion in the anterior superior quadrant (Fig. 1). However, the lesions of postoperative epithelial pearls have an obvious relationship to the original lesions of perforation (Table 1). The epithelial pearls were 1 mm or less in diameter in four patients and 2 mm in diameter in one patient (Fig. 1). In the case of epithelial pearl formation in the ear canal, a 2-mm epithelial pearl was found at a projecting portion of the curved ear canal. In all cases, the epithelial pearls were removed with a sharp pick under topical anaesthesia with 4% lidocaine. No lesion recurrence was observed.

Discussion

Synopsis of key/new findings

Here, we described postoperative epithelial pearl formation following tympanic membrane regeneration therapy using an atelocollagen/silicone membrane and basic fibroblast growth factor. The ratio of the incidence of postoperative epithelial pearl formation after this regenerative treatment is equal to that after overlay myringoplasty. Therefore, the incidence of postoperative epithelial pearl formation is not particular to this regenerative treatment.

Strengths of the study

Almost all previous studies evaluated the effects of basic fibroblast growth factor on healing of tympanic membrane perforation. This is the first report of postoperative epithelial pearl formation following tympanic membrane regeneration therapy using an atelocollagen/silicone membrane and basic fibroblast growth factor.

Comparisons with other studies

Basic fibroblast growth factor, a growth factor identified following the discovery of epidermal growth factor, is known to directly promote proliferation of vascular endothelial cells and fibroblasts via its receptor and the formation of well-vascularised granulation tissue *in vivo*.[3] Atelocollagen/silicon membranes are composed of atelo-

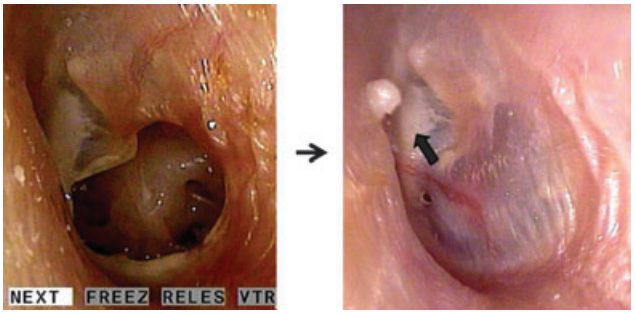

Fig. 3. Patient No.7: Case with a pinhole and postoperative epithelial pearl located in the ear canal. The arrow indicates 2-mm postoperative epithelial pearl.

collagen, a type of non-antigenic collagen made by enzyme treatment, with a silicon membrane attached to the underside of the atelocollagen membrane to help maintain its configuration and moisture. Collagen is highly compatible with surrounding tissue, can serve as a scaffold for new-born cells and tissues and is eventually absorbed; consequently, it is considered to be an excellent synthetic graft material suited for the purpose of perforation closure.[4] Cutting the silicon membrane to fit the shape and size of the tympanic membrane perforation allows the silicon membrane to fit tightly to the tympanic membrane without fibrin glue, while also allowing atelocollagen to be immobilised to the perforation. The addition of basic fibroblast growth factor to atelocollagen is expected to improve the rate of successful closure of perforated tympanic membranes and extend the treatment indications.[1,2,5]

Postoperative epithelial pearl formation was observed in seven patients (6%), six of whom had lesions in the tympanic membrane. Incomplete dissection of the tympanic epithelial layer and the presence of graft tissue, such as fascia, on the remaining keratinised epithelium during the formation of the tympanic membrane may result in the formation of an epithelial pearl between the neotympanic membrane and the original tympanic membrane.[6] An epithelial pearl in the ear canal can also be caused by trauma or may arise iatrogenically from epithelium grafted in the ear canal during middle ear surgery. As no dissection of the ear canal was performed and the lesion formed at a protruding portion of the anterior wall of the curved ear canal in the present cases, the lesions were likely to have resulted from ear canal injury caused by ear operations during the tympanic membrane regeneration therapy.

The obvious relationship between the lesions of postoperative epithelial pearls and the original lesions of perforation suggests that the epithelial pearls arose from the residual epithelium at the dissected perforation margin, although the possibility that pearl formation is caused by regenerative therapy cannot be excluded. As the incidence of postoperative epithelial pearl formation after overlay myringoplasty is 3–7%,[7,8] it is unlikely that the regeneration therapy induced epithelial pearl formation, although it occurs much less often following an underlay technique, with an incidence of 0–0.8%.[7,9]

Clinical applicability of the study

Although basic fibroblast growth factor has not been shown to induce proliferative disorders such as cholesteatoma,[10] attention should also be paid to postoperative complications, such as epidermal pearl formation. In some cases, postoperative epithelial pearl formation had very late onset over 1 year after the operation. These results suggest that long-term observation by fibroscopy is required regardless of the incidence of postoperative epithelial pearl formation.

Conclusion

Our results suggest that attention should also be paid to postoperative epidermal pearl formation. However, the incidence is not particular to this regenerative treatment.

Keypoints

- A total of 116 patients (35 males and 81 females) with tympanic membrane perforation were evaluated after tympanic membrane regeneration therapy.
- Patients ranged in age from 13 to 90 years, with a median of 65.0 ± 15.1 years. Complete closure was achieved in 72 (62%) patients after at least 1 year of postoperative follow-up.
- Postoperative epithelial pearl formation was observed in 6 of 116 (5%) patients, with an average time to onset of 7.3 months.
- Epithelial pearl formation occurred in the tympanic membrane in five patients and in the ear canal in one patient.
- Attention should also be paid to the postoperative incidence of epithelial pearl formation.

Conflict of interest

None of the authors has any commercial associations or sources of support that might pose a conflict of interest.

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Transmastoid repair of meningoencephalic herniation associated with cholesteatoma by canal wall-down procedure: Our experience in eighteen patients

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Accepted for publication 9 August 2013

Dear Editor,

Herniation of meningeal and brain tissue into tympano-mastoid cavities through a bony defect is a rare condition, but it is potentially life threatening due to the risk of intracranial complications and induction of epilepsy. Trauma, neoplasms, inflammatory disorders, arachnoid granulations, congenital anomalies, previous surgical procedures and irradiation are the most common predisposing factors for the condition.[1] In 25% of cases,[2] none of these aforementioned causes can be found and are thus defined as spontaneous or idiopathic. The most frequent localisation of meningoencephalic herniations (MH) in the temporal bone is the epitympanic region followed by the mastoid cavity.[3]

Meningoencephalic herniations requires surgical treatment with the purpose of reducing or resecting the herniation and to repair the bone defect. Different approaches have been proposed: transmastoid approach, middle fossa approach, combined transmastoid/middle fossa approach and obliteration of the middle ear and mastoid.[2]

Objective

To report the efficacy of one stage transmastoid approach with canal wall-down tympanoplasty for meningoencephalic herniations associated with cholesteatomatous chronic otitis media (Fig. 1).

Materials and methods

Patients selection

Inclusion criteria: meningoencephalic herniations associated with cholesteatoma consecutively treated between 2003

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