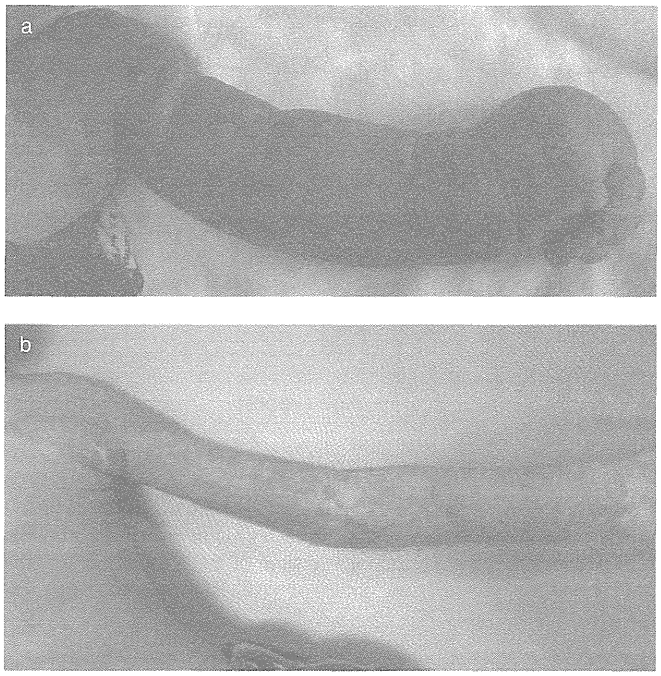

Fig. 4 (a) After six courses of vincristine there was a large, dark-red lesion covering the left arm and upper thorax. (b) After vincristine, actinomycin D and cyclophosphamide therapy, the dark-red lesion of the left arm had largely resolved.

and secondary malignancy, we were initially hesitant to use actinomycin D or cyclophosphamide. Only one case of KHE associated with KMS treated with VAC combination therapy after VCR monotherapy has been reported, but combination VAC chemotherapy was not effective in that report.[12] In addition, no comparative study of VAC combination therapy and VCR monotherapy for KHE associated with KMS has been reported. We decided to treat the present patient with VAC combination therapy because of the persistence of refractory coagulopathy and life-threatening condition.

Gottschling *et al.* reported that cyclophosphamide monotherapy was a safe and effective treatment for patients suffering from life-threatening diffuse hemangiomatosis unresponsive to corticosteroid therapy.[13] Cyclophosphamide monotherapy might have been effective in the present case but the previously reported cases all involved multiple cutaneous and liver hemangiomas, with complications that included high-output failure, and hepatic failure, and did not include KMS.

The present patient was treated with radiation therapy after steroid and interferon therapy. Due to problems with radiation therapy in infants, however, such as cancer or growth disorder, it might be better to treat pediatric patients with VCR or VAC chemotherapy prior to radiation therapy.

Vincristine, actinomycin D and cyclophosphamide therapy resulted in a significant decrease of tumor size, correction of the thrombocytopenia and a complete remission for 6 years in the present patient. The combined therapies of steroids, interferon-α, radiation and embolization were not effective for KHE in this patient. Thus, VAC therapy may provide an alternative therapeutic approach to intractable KMS resistant to conventional combination therapies, even when VCR monotherapy is not effective.

References

1 Enjolras O, Wassef M, Dosquet C *et al.* [Kasabach-Merritt syndrome on a congenital tufted angioma]. *Ann. Dermatol. Venereol.* 1998; **125**: 257–60.
2 Hall GW. Kasabach-Merritt syndrome: Pathogenesis and management. *Br. J. Haematol.* 2001; **112**: 851–62.
3 Moore J, Lee M, Garzon M *et al.* Effective therapy of a vascular tumor of infancy with vincristine. *J. Pediatr. Surg.* 2001; **36**: 1273–6.
4 Taki M, Ohi C, Yamashita A *et al.* Successful treatment with vincristine of an infant with intractable Kasabach-Merritt syndrome. *Pediatr. Int.* 2006; **48**: 82–4.
5 Thomson K, Pinnock R, Teague L, Johnson R, Manikkam N, Drake R. Vincristine for the treatment of Kasabach-Merritt syndrome: Recent New Zealand case experience. *N. Z. Med. J.* 2007; **120**(1249): U2418.
6 Yesudian PD, Klafkowski J, Parslew R, Gould D, Lloyd D, Pizer B. Tufted angioma-associated Kasabach-Merritt syndrome treated with embolization and vincristine. *Plast. Reconstr. Surg.* 2007; **119**: 1392–3.
7 Hu B, Lachman R, Phillips J, Peng SK, Sieger L. Kasabach-Merritt syndrome-associated kaposiform hemangioendothelioma successfully treated with cyclophosphamide, vincristine, and actinomycin D. *J. Pediatr. Hematol. Oncol.* 1998; **20**: 567–9.
8 Vin-Christian K, McCalmont TH, Frieden IJ. Kaposiform hemangioendothelioma. An aggressive, locally invasive vascular tumor that can mimic hemangioma of infancy. *Arch. Dermatol.* 1997; **133**: 1573–8.
9 Haisley-Royster C, Enjolras O, Frieden IJ *et al.* Kasabach-Merritt phenomenon: A retrospective study of treatment with vincristine. *J. Pediatr. Hematol. Oncol.* 2002; **24**: 459–62.
10 Fawcett SL, Grant I, Hall PN, Kelsall AW, Nicholson JC. Vincristine as a treatment for a large haemangioma threatening vital functions. *Br. J. Plast. Surg.* 2004; **57**: 168–71.
11 Perez J, Pardo J, Gomez C. Vincristine: An effective treatment of corticoid-resistant life-threatening infantile hemangiomas. *Acta Oncol.* 2002; **41**: 197–9.
12 Saito M, Gunji Y, Kashii Y *et al.* Refractory kaposiform hemangioendothelioma that expressed vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3: A case report [Case Reports]. *J. Pediatr. Hematol. Oncol.* 2009; **31**: 194–7.
13 Gottschling S, Schneider G, Meyer S, Reinhard H, Dill-Mueller D, Graf N. Two infants with life-threatening diffuse neonatal hemangiomatosis treated with cyclophosphamide. *Pediatr. Blood Cancer* 2006; **46**: 239–42.

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◆特集／血管腫・血管奇形治療マニュアル

PEPARS

リンパ管腫（リンパ管奇形）の診断・治療戦略

藤野明浩*

Key Words：リンパ管腫（lymphangioma），リンパ管奇形（lymphatic malformation），硬化療法（sclerotherapy），OK-432，嚢胞性リンパ管腫（cystic lymphangioma，macrocystic lymphatic malformation），海綿状リンパ管腫（cavernous lymphangioma，microcystic lymphatic malformation）

Abstract　リンパ管腫は主に小児期に発症する腫瘤性病変で，正常組織内に網目状に広がる大小様々なリンパ嚢胞からなる．近年徐々に浸透しつつある脈管病変のISSVA分類においてはリンパ管奇形に分類されている．良性疾患であり，多くは治療にて改善するが，一方で重症・難治性症例が存在し治療に難渋する．診断は主に画像検査によりなされ，治療には主に硬化療法，手術療法が行われる．それぞれに特徴があり，治療を行う際にはその適応，タイミング，治療法の選択，戦略などにつきよく検討することが必要である．

はじめに

リンパ管腫は主に小児期に発症する腫瘤性病変で，正常組織内に網目状に広がる大小様々なリンパ嚢胞からなる．良性疾患であり，多くは治療にて改善するが，一方で重症・難治性症例が存在する．頭頸部に頻発し（40～70％と言われる），外観上の問題を生じるとともに，巨大な患部の感染や腫瘤内出血による炎症や疼痛，気道周辺病変による気道閉塞などに悩まされる症例が約20％存在する[1]．

リンパ管腫はその病変に細胞増殖性など腫瘍の特性は少なく，また先天性に形成されていることが多いため，一種の発生異常による奇形と捉えることが妥当と考えられ，近年ISSVA（International Society of Studying Vascular Anomaly）分類では，リンパ管奇形（lymphatic malformation）と分類されている（表1）．ただし，このリンパ管奇形の分類の中にはいわゆるリンパ管腫を含む多彩なリンパ管疾患が含まれており，病名としてのリンパ管腫と病態を示すリンパ管奇形は現時点では同義とは言えない．筆者らは今後この領域について検討を進め，臨床経過，画像，病理などの観点からリンパ管疾患の細分化を試みたいと考えている．小文においてはこの疾患を表すのにリンパ管腫を用いることとする．

病　因

病因は明らかにされていない．リンパ管腫は，頸部・腋窩など胎生期にリンパ嚢を形成する部からの発生が多いことや胎生期から病変が認められるという臨床的特徴より，胎生のリンパ管形成時期に何らかの異常を生じ嚢胞性病変を形成する，と言われている[2]が定かでない．発生に関して性差や遺伝性は認められていない[3]．

外科的切除の後などに，明らかに後天性に発生したと考えられる症例もある（特に婦人科領域）．

診　断

リンパ管腫はほとんどの場合，画像検査により診断される．超音波，CT，MRI，いずれも有用で

* Akihiro FUJINO，〒160-8582　東京都新宿区信濃町35　慶應義塾大学医学部小児外科，講師

表 1. 血管腫・血管奇形の ISSVA 分類(Cambridge University Press より)

Vascular tumors	Vascular malformations
· Infantile hemangiomas · Congenital hemangiomas (RICH and NICH) · Tufted angioma (with or without Kasabach-Merritt syndrome) · Kaposiform hemangioendothelioma (with or without Kasabach-Merritt syndrome) · Spindle cell hemangioendothelioma · Other, rare hemangioendotheliomas (epithelioid, composite, retiform, polymorphous, Dabska tumor, lymphangioendotheliomatosis, etc.) · Dermatologic acquired vascular tumors (pyogenic granuloma, targetoid hemangioma, glomeruloid hemangioma, microvenular hemangioma, etc.)	**Slow-flow vascular malformations :** · Capillary malformation (CM) Port-wine stain Telangiectasia Angiokeratoma · Venous malformation (VM) Common sporadic VM Bean syndrome Familial cutaneous and mucosal venous malformation (VMCM) Glomuvenous malformation (GVM) (glomangioma) Maffucci syndrome · Lymphatic malformation (LM) **Fast-flow vascular malformations :** · Arterial malformation (AM) · Arteriovenous fistula (AVF) · Arteriovenous malformation (AVM) ***Complex-combined vascular malformations :*** · CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM

C=capillary ; V=venous ; L=lymphatic ; AV=arteriovenous ; M=malformation.
RICH=rapidly involuting congenital hemangioma ; NICH=noninvoluting congenital hemangioma.

あり，臨床症状と併せてリンパ管腫を診断できることが多い．それぞれの画像検査の詳細については成書を参照されたい．

腫瘤性病変の診察時に，経過，視診や触診，発生部位などによってリンパ管腫が疑われた場合，まず行うべきは低侵襲性で簡便な超音波検査である．典型的な嚢胞性のリンパ管腫の場合にはほぼ間違いなく診断できる．しかし海綿状(cavernous，ISSVA 分類では microcystic type)の場合や嚢胞性でも他の類似した病変(嚢胞を有する奇形腫など)と鑑別できない場合もある．腫瘤が深部にある場合や，治療を行う前に全体の広がりを把握するためには超音波に加えて，CT，MRI などを行う．特にヨードアレルギーがなければ造影検査が望ましい．鑑別が困難な低流速血管奇形病変との区別や血管の走行と病変の位置関係などの把握に非常に有益である．

画像検査でリンパ管腫と診断されることが多いが，穿刺液細胞診，穿刺液生化学検査にて嚢胞液がリンパ液であることが確認できればリンパ管腫診断の補助になる．外科的切除を行う場合には，切除標本の組織診断にてリンパ管腫の確定診断がなされる(病理組織診断)．その他に，リンパ液の流れを検査するリンパ管シンチグラフィやリンパ管造影なども必要に応じて行われることがある．

治　療

リンパ管腫に対する治療は，大きく外科的切除，硬化療法，全身療法に分けられる．病変の部位，広がりなどによって，これら単独もしくは組み合わせによって治療戦略が立てられる．

1．治療適応について

治療について考えるにあたり念頭に置くべきことは，リンパ管腫は良性疾患であり，多くの場合は治療にて非常によい結果が得られ，一部の重症・難治性症例においてもこれ自体が悪性腫瘍のように生命を奪うことはないことである．また治療により完全に病変を消失させることは困難であることが多く，外科的切除や硬化療法など一連の治療後も残存病変を伴って日常生活を送っている患者が大勢いる．リンパ管腫の残存病変が悪性転化したという報告は極めて稀であり(別の腫瘍が同じところから発生した報告はある)，必ずしも根治のみを目指す必要はない．

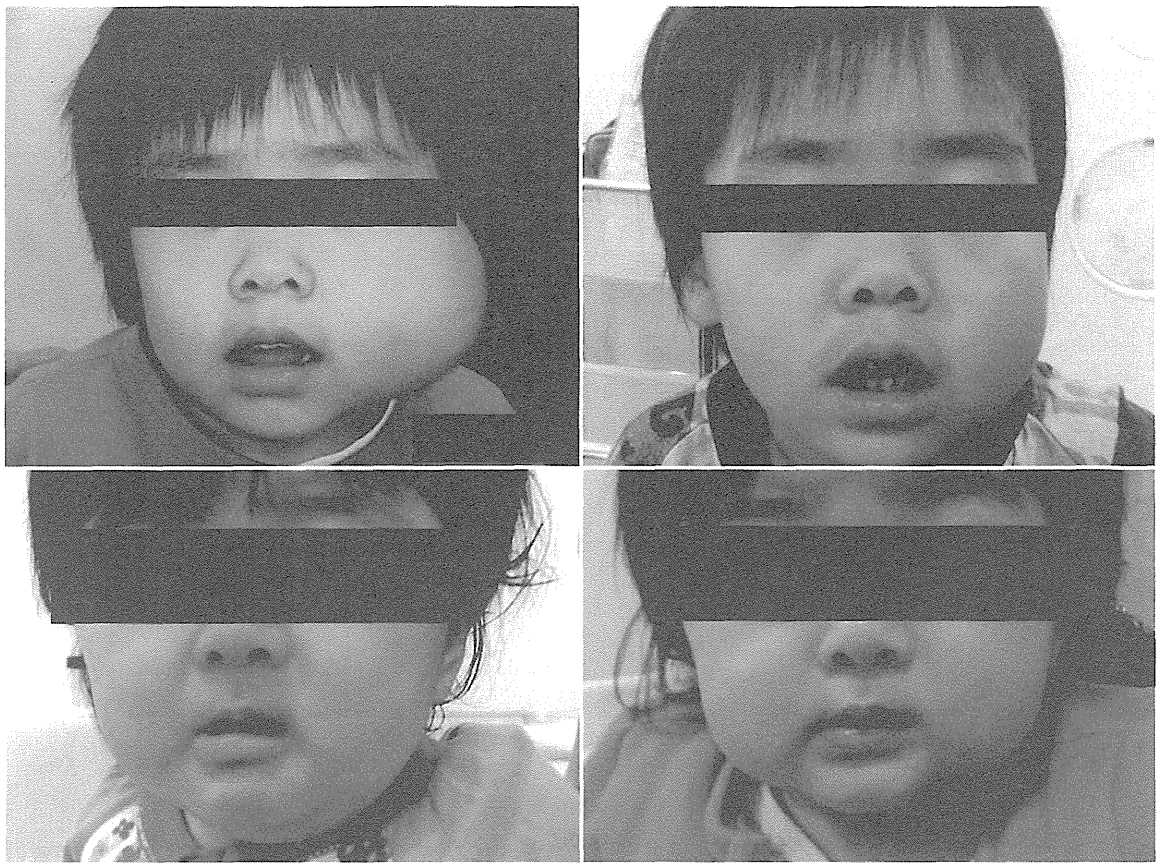


図 1. リンパ管腫硬化療法例
a，b：左頬部リンパ管腫（a：治療前，b：治療後半年）
c，d：左下顎部リンパ管腫（c：治療前，d：治療後2か月）

a | b
c | d

治療が必要となるのは以下の3つのいずれかが理由となり，本人，親がそれを何とかしたいという希望がはっきりある場合に治療へ進むべきである．

リンパ管腫の治療適応となる条件：

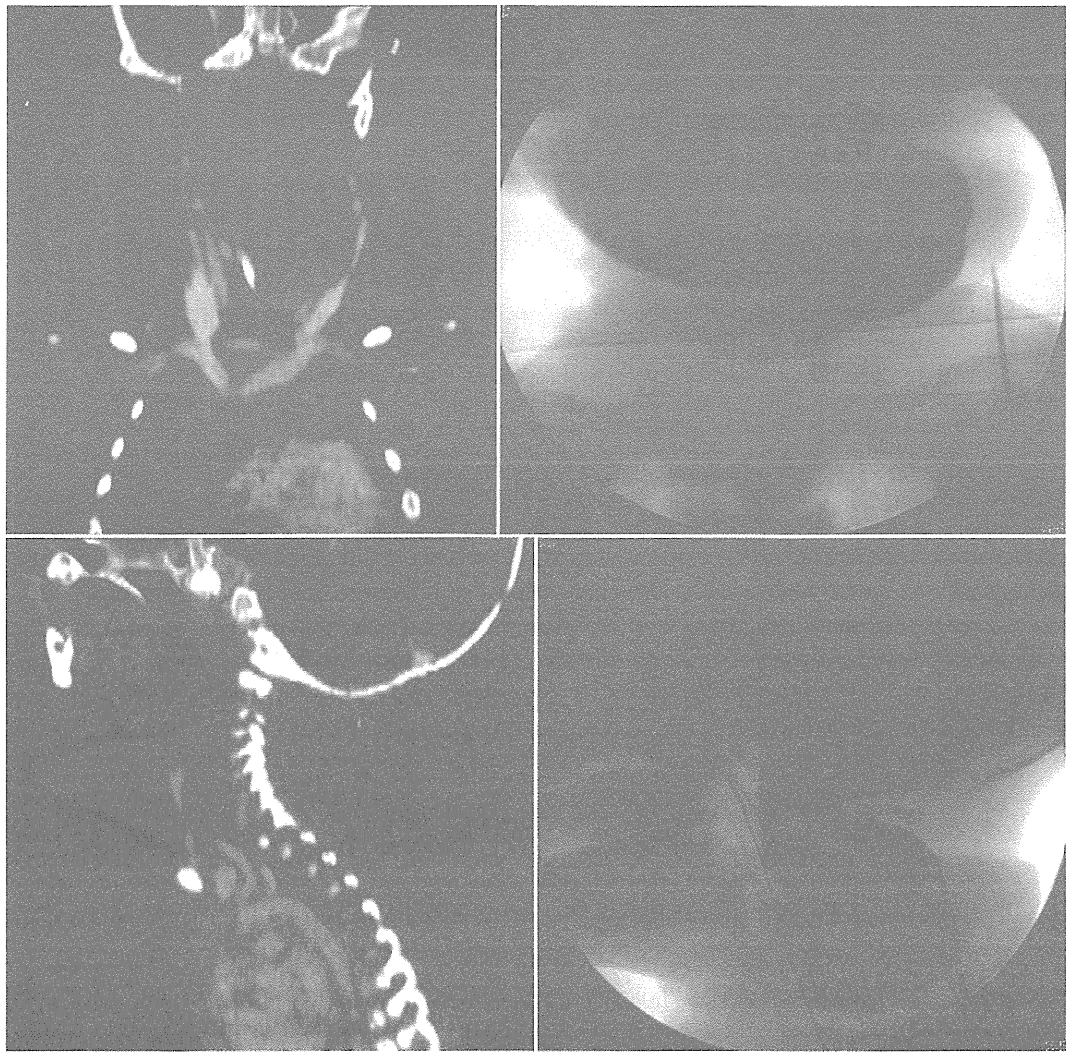
1）腫瘤が外観上問題となる
2）腫瘤が身体機能的問題を生ずる
3）有症状である

顔面や頚部，四肢などに病変があり，目立つため治療を受けるのは当然であるが，病変があってもあまり目立たず，本人も家族も気にならないという場合には治療は必ずしも勧めるべきでない．目立たない部位にあっても，気道の圧排・狭窄があったり，消化管通過障害や，四肢の運動制限などを生じたりする場合には治療適応であろう．また外観上は目立ちもせず，機能的にも問題を生じていなくても，内出血や感染を頻繁に起こし，発熱，疼痛を繰り返し生活に支障をきたすような場合には積極的治療を選択すべきである．治療を決定する際には，病気の予想予後や治療に伴う苦痛，合併症の可能性について十分に情報を提供し，本人・保護者とよく話し合うべきである．

2．硬化療法

リンパ管腫治療において外科的切除と並ぶ治療の柱である．日本では，嚢胞性の場合はまず硬化療法の可能性を最初に考慮することが一般的である．硬化療法では病変を完全に消し去ることはできない．しかしながら，悪性腫瘍でないので十分縮小して満足が得られればそこを終了目標ポイントとしてよいと考えられる．薬剤を病変部に注入すると，その反応でリンパ嚢胞が縮小していく．理想的には嚢胞内リンパ液を吸引し，嚢胞内に薬剤を注入すると最も効果が出ると考えられている．

硬化剤としてはOK-432（ピシバニール®）[4]，ブレオマイシン[5]，無水エタノール，フィブリン糊



a | b
c | d

図 2. 透視併用硬化療法
嚢胞性リンパ管腫に対する硬化療法時には，溶解液に造影剤を混透視を併用すると注入した硬化剤の病変内での拡散を確認できる．
a，c：術前 CT(後咽頭から左頚部に広がる嚢胞性リンパ管腫)
b，d：硬化療法(穿刺による OK-432 注入)時に注入した薬剤の広がりを確認

など，様々な薬剤が用いられてきた．

日本では現在 OK-432 が第 1 選択である．リンパ管腫に対する硬化療法として保険適応がある．発熱，局所の強い炎症反応(発赤，腫脹，疼痛)が生じるが，後遺症を残すことなく多くの場合には最終的に病変部を縮小する(図 1)．嚢胞性リンパ管腫には特に効果的であることが知られている[4)6)~9)]．

A．OK-432 局注硬化療法

OK-432(ピシバニール®)は不活化した溶連菌を抗生剤にて殺傷した後，凍結乾燥させた製剤で強い炎症を惹起し免疫反応を誘導する作用がある．感染性はなく，抗癌剤として使われることもある．

この治療を行う場合，安静・協力を得られない小児においては全身麻酔下で行うことが望ましい．協力を得られる場合は全身麻酔は不要である．

OK-432 は粉末製剤であり，0.1 kE/m*l* に希釈し，嚢胞穿刺により吸引された量と同じ量を投与することが推奨されている(薬剤添付文書参照)．

しかしながら，これに従い巨大嚢胞に対して吸引量と同量を投与すると大量の製剤を投与することとなるが，添付文書指示にも最大 2 kE/回の指

示があり，現実には不可能の場合もある．実際には同容積の薬液を投与しなくても十分な効果が出ることが経験されており，筆者らはむしろ嚢胞容積より少量を投与して，投与後に病変内にOK-432が広がることを期待してよく揉むようにしている．

病変内に投与した硬化剤の広がりを確認するためには，OK-432を希釈する際に少量の等浸透圧性血管造影剤を希釈液に混じて投与する．注入後に揉む操作に従って近接する嚢胞内へ造影剤(硬化剤と同様の動き)が拡散していくのを透視下に確認することができる(図2)．

OK-432の濃度については，1回目の硬化療法時に炎症反応がほとんど認められなかった場合などは濃度を0.3 kE/m*l*程度まで濃くして投与することもある．濃度上昇に応じた効果があるとは言いがたいが，少なくとも副作用の増強は認めていない．

硬化療法後は数時間から数日の間に発熱，局部の発赤・腫脹を認める．一般的に炎症所見が強く認められた方が治療効果は出ると考えられている．

OK-432局注は繰り返すことが可能である．しかし，その治療間隔は各医師の経験により様々であり一定しない．約1週間おいて続けて行うことが良いとされる場合もあるが，一方硬化療法の急性炎症期に引き続いて認められる，病変の縮小が停止し組織の硬結が消失する1～3か月後から次を行うという考え方もある．現時点ではその優劣に関する検討報告はない．

B．その他の硬化療法

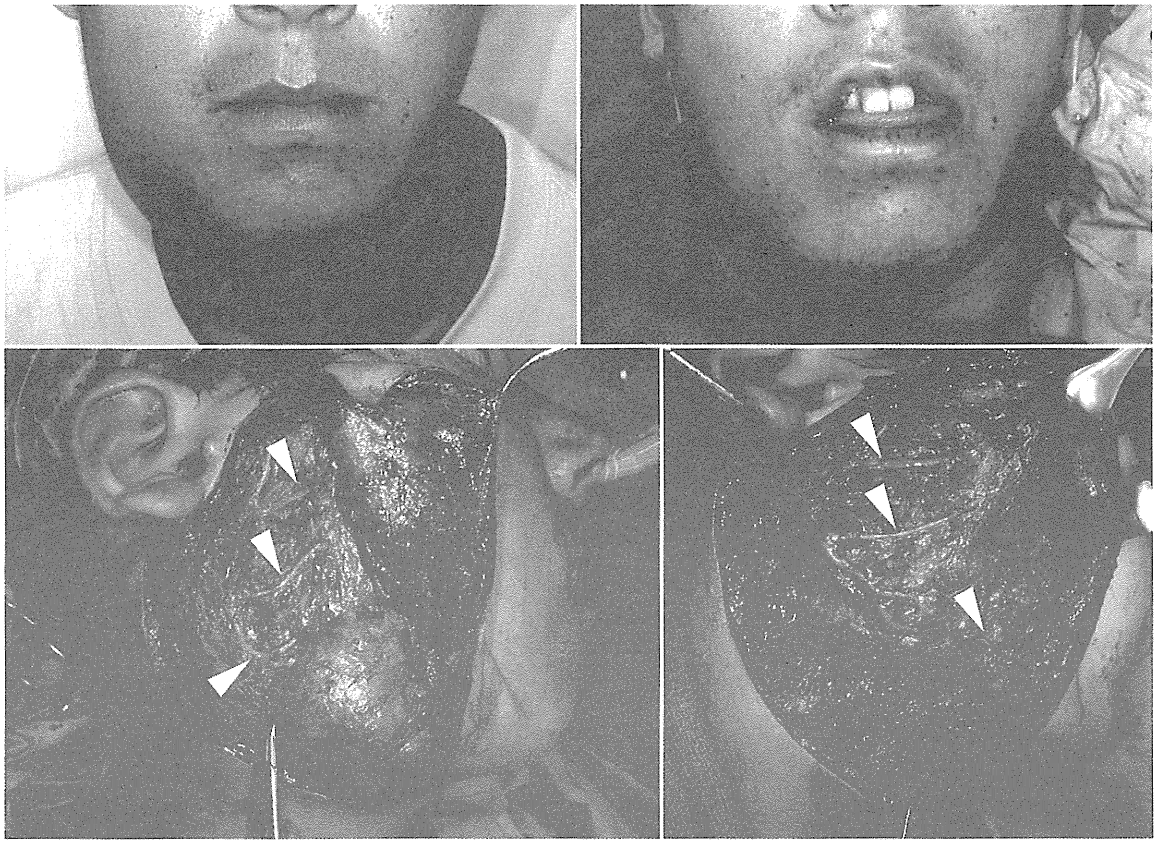
ブレオマイシン：現在世界中で用いられている抗菌性の抗腫瘍剤である．OK-432と同様に嚢胞性リンパ管腫縮小に特に有効であることが認められているが，舌リンパ管腫のように海綿状リンパ管腫に対しても有効との報告がある[10]．用量依存性に肺線維症を起こす可能性があり，第1選択として用いている施設は我が国では少ない[5]が，一方世界では中国，ヨーロッパを中心に使用報告が増えている．

無水エタノール：悪性腫瘍や血管病変に対する硬化療法が先に行われてきたが，接する細胞を瞬時に固定してしまう強力な薬剤であり，リンパ管腫に対しても用いられるようになっている[11]．OK-432のような発熱，発赤などの急性炎症反応を起こさないが，比較的強い疼痛が認められる．ポイントは十分にドレナージが効くことが確認された状況で投与し，一定時間の後排出することである．エタノールは親水性であり，病変部を越えて神経や皮膚など外部の組織を障害する危険性が高い．特にリンパ管腫では大血管のすぐそばに分布していることも多いため，エタノールによる障害が嚢胞内への大出血につながることもある．投与に際してはあらかじめ画像検査を確実に行い，リスクを十分考慮すべきである．無水エタノールを回収できない場合には，生理食塩水を注入しエタノールの濃度を下げることで過度の影響を避けることができる．

筆者らは嚢胞液を可及的に吸引後，エタノール注入し，1分間おいて吸引し，さらに生理食塩水を注入してそれを排出することで一連の手技を終了としている．無水エタノールを注入すると，嚢胞内の浮遊細胞や蛋白成分は直ちに変性を起こし凝集するため，細い針では吸引時につまってしまう．エタノールの回収をしっかりと行うため，我々は21 G針を穿刺に用いている．

フィブリン糊：フィブリン糊(ベリプラスト®，ボルヒール®など)の嚢胞内注入も効果があることが報告されている[12]．特に炎症を起こすことなく嚢胞を縮小する特徴がある．我々も2例の経験があるが，1例で著効し1例では無効であった．文献症例を加えて考察すると，手術や硬化療法の後に行った場合に効果が出ているようであった．我々の2症例もそれに合致した．生物由来製剤である点も踏まえて，現時点では優先して使用すべきではないと考える．

その他にも高張食塩水，高濃度糖水，エタノールアミン製剤など硬化療法に用いられる薬剤は多



a | b
c | d

図 3. 右下顎部リンパ管腫切除術(顔面神経温存)
顔面神経各枝を確実に露出したうえで腫瘤の切除を行った.(国立成育医療研究センター金子剛先生のご厚意により写真をご提供頂いた)
a:術前外観　b:術直後外観　c:腫瘍露出　d:切除後
矢頭:顔面神経各枝

様だが,どれも嚢胞性のリンパ管腫には有効であるものの,海綿状リンパ管腫に確実な効果が得られる薬剤は知られていない.

3.外科的切除

リンパ管腫は手術でリンパ液を含んだ大小の嚢胞を全て取り除くことができれば完治するので,短期間で治療を完了できる[8].体幹や四肢の体表にあり切除が容易な場合には良い適応である.また海綿状リンパ管腫に対しては硬化療法が効かないことが多く,切除術が有効である.気道閉塞をきたすような場合にも早期の解除のため切除を選択せざるを得ないことがある.

手術で切除する際の問題としては,血管・神経・筋肉などが病変部に完全に巻き込まれている時に,完全切除のためにはこれらの正常組織を同時に切除せざるを得ず,機能的・整容的な問題を残すことである.したがって,そういった問題を避けるべく部分切除が選択されることが多い.特に海綿状リンパ管腫の場合には内部にリンパ液を貯めて腫瘤が急速に増大したりすることは少なく,部分切除でも切除しただけの効果が得られることが多い.病変が残っても左右のバランスの改善や突出の改善が得られることは多く,適度な妥協点を手術目的として外科的切除を行うことは妥当である.

リンパ管腫の好発部位は頸部であるが,特に下顎周囲に分布する場合は多く,切除に際しては神経温存が非常に重要となる.頬部から下顎にかけての症例では,多くの場合慎重な手術操作により顔面神経を完全に露出して温存しつつ病変を切除することが可能で,大きな改善が得られる(図3).

また舌も好発部位であり,病変内の出血や口腔

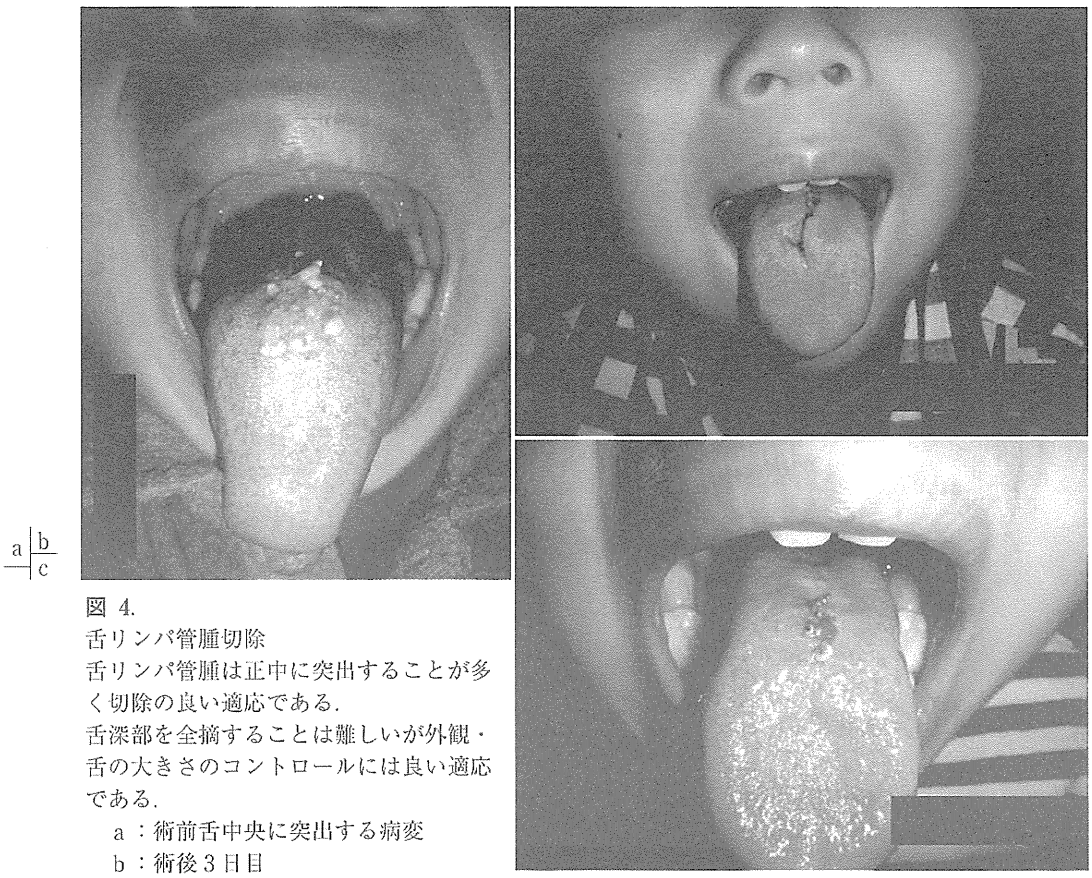


図 4.
舌リンパ管腫切除
舌リンパ管腫は正中に突出することが多く切除の良い適応である.
舌深部を全摘することは難しいが外観・舌の大きさのコントロールには良い適応である.
a：術前舌中央に突出する病変
b：術後3日目
c：術後3週間

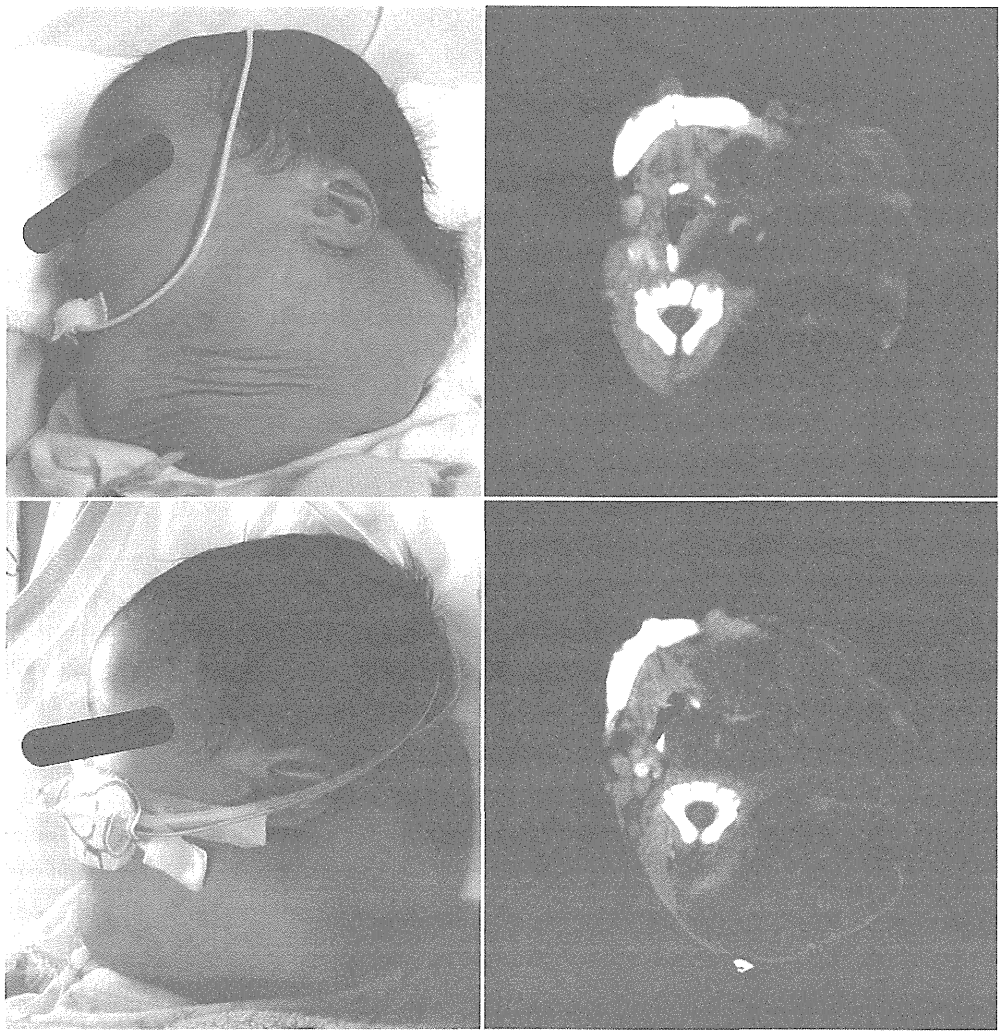
内への出血，疼痛や閉口障害が問題となる．舌病変は正中において表面に突出していることが多く，切除の良い適応である(図4)．

リンパ管腫の特徴として病変部にリンパ液(組織液)が流入するため，部分切除後には，切除断端からのリンパ液流出が長く続くことがある．創部や漏出するリンパ液を伝って細菌が流入し，感染を生ずることもある．これは嚢胞性リンパ管腫の場合に顕著で，海綿状リンパ管腫の方が押さえ込みやすい．持続する場合にはOK-432の局所注入にて炎症を惹起した後に改善する．また断端の結紮処理が困難な場合にはハーモニックスカルペルやリガシュア，エンシールなどの超音波もしくはバイポーラ式凝固切開機器による切開は断端の閉鎖に有用である．

気管切開について：上気道周囲に病変が広がるリンパ管腫では乳児期に気道狭窄症状が重篤な場合には気道閉塞のリスクを避けるために気管切開を造設することが多い．明確な適応基準はないが，筆者らは経験的に咽頭後壁を正中を越えて対側へ病変が広がる症例では，炎症や出血を契機に気道が閉塞するリスクが高いと考えている．このような場合は腫脹を誘発する硬化療法は乳児期には避けるべきである．気道は年齢とともに徐々に強固な組織に成長していくため，気道狭窄症状は年齢とともに出にくくなる傾向が認められる．初期に気管切開を置けば気道閉塞の心配なく治療を進められるが，気切口はリンパ管腫感染の起点にもなり病変への悪影響もあり得るし，チューブトラブルによる突然死も起こり得るため，気管切開の適応を不必要に拡大すべきではない．

4．全身療法

外科的切除や硬化療法による治療効果が十分でない難治性のリンパ管腫に対しては全身療法も試みられている．いずれも即効性は期待できない．インターフェロン(interferon)，抗腫瘍剤のビンクリスチン(vincristine)やステロイドの投与が有効であった症例の報告[13][14]があるが，無効例の報告



a | b
c | d

図 5. 乳児における急速な上気道閉塞例
a，c：外観写真，b，d：造影 CT
a，b：安定時．嚢胞性リンパ管腫で病変の張りは弱い定常状態
c，d：硬化療法後に腫瘤は急速に腫脹し，咽頭後壁から大きく気道を圧排し上気道閉塞をきたした．下顎も大きく右へ変位している．(その後腫脹が改善するまで気管内挿管管理を要した)

もある．ごく最近プロプラノロール(propranolol, βブロッカー)がリンパ管腫症に有効であったとの報告があり[15]，現在リンパ管腫に対する効果についても研究が行われつつある．またサリドマイド(thalidomide)，ラパマイシン(rapamycin)[16]，シルデナフィル(sildenafil)[17]などが国外を中心にリンパ管疾患に対して用いられて効果があったとされる．しかしいずれの治療法も国内外を通じて実際に治療を受けた症例数が不十分で，副作用や効果についての一定の見解はない．使用に際しては適応判断，使用法について細心の注意が必要である．

5．至適治療時期

一般的に，発見時に緊急治療を要することは少ないが，重症の場合や頚部病変の位置によっては新生児・乳児期には気道への影響・内出血による貧血などの理由で早急な治療が必要となることがある．

生後1年ぐらいは特に炎症症状はなく病変が自然縮小・消失していくこともある[18]．

また経過中に内出血や感染などを発症し，これらが誘因となりリンパ管腫が縮小することがあることが知られている．一方で，感染・内出血は疼

痛や外観の変化などを生じ，頻繁に起こると不都合も大きいので，頻繁であればその時に積極的治療の適応となる．

治療の適応は先に述べた3点であり，いずれも許容範囲内であると患者・医療者ともに納得できる軽症の場合は，必ずしも治療の必要はない．乳児期以降は治療適応があれば特に最適年齢はない．病変が大きく規模の大きな治療を行うには，両親の十分な納得を得ている必要があり，時間をかけて治療の必要性を十分理解してもらってから行うべきである．就学前に何とか改善したいという理由も治療時期の選択に影響する．

一般的に乳児期に必ずしも急いで治療を開始する必要はないが，特に頸部に病変がある場合にはCTもしくはMRIにて病変が咽頭後壁部まで広がっていないかどうかを確認しておく必要がある．咽頭後壁に病変が及ぶ場合には，出血や感染などで容易に哺乳困難や上気道閉塞をきたすため，注意が必要である[18]（図5）．外観上の重症性と一致しないこともある．症状が出たら気道確保が必要となり，早期の外科的介入を要することもある．

6．治療の選択

治療を行う際には，症例に応じて最初に硬化療法と外科的治療のどちらを選択すべきかを考えねばならない．嚢胞性リンパ管腫では硬化療法が劇的に効くため，まずは硬化療法を選択することが多い．繰り返しも可能で，腫瘤を徐々に縮小でき，多くの場合満足いく結果が得られる．しかし巨大な病変の場合には，次第に腫瘤に嚢胞成分が少ない海綿状に変化し硬化療法は効果がなくなってくるため，外科的切除へ移行することが多い．嚢胞性リンパ管腫でも明らかに完全切除が可能であり，手術創が苦にならない場合には外科的切除を第一選択とする方が，病悩期間も短く良い点も多い．

軽症の場合にはいずれにしても良い結果が得られることが多いが，上眼瞼，口唇などは病変が小さくても治療が非常に難しい．また巨大病変の場合には最終目標にはある程度の妥協が必要となる．

おわりに

リンパ管腫に対して現時点で得られる治療法には限界があり，必ずしも全ての患者において満足すべきQOLが得られないこともある．外科医は決して冒険しすぎずに，良いバランスを目指して治療を進めるよう心がけるべきである．新たに画期的な治療法が開発されることを期待したい．

文　献

1) 藤野明浩：厚生労働省科学研究費難治性疾患克服研究事業「日本におけるリンパ管腫（特に重症患者長期経過）の実態調査及び治療指針の作成に関する研究」平成23年度　総合研究報告書，2012.
2) Godart, S.：Embryological significance of lymphangioma. Arch Dis Childh. **41**：204-206, 1966.
3) 中條俊夫ほか：嚢胞状リンパ管腫の治療とその成績―273例の分析に基づいた治療方針―．小児外科・内科．**8**：279-285，1976.
4) Ogita, S., et al.：OK-432 therapy in 64 patients with lymphangioma. J Pediatr Surg. **29**：784-785, 1994.
5) 由良次郎ほか：小児の頸部腫瘤，特に嚢腫状リンパ管腫とBleomycinの効果について．小児外科．**16**：925-930，1984.
6) Giguère, C. M., et al.：New treatment options for lymphangioma in infants and children. Ann Otol Rhinol Laryngol. **111**：1066-1075, 2002.
7) 宮坂実木子ほか：画像診断．小児　小児頚部腫瘍・腫瘍類似疾患．頭頚部の診断と治療update．臨床放射線．**53**：1525-1536，2008.
8) 長谷川史郎ほか：小児嚢胞状リンパ管腫　頚部巨大嚢胞状リンパ管腫の治療とその成績．小児外科．**16**：953-959，1984.
9) Fujino, A., et al.：A role of cytokines in OK-432 injection therapy for cystic lymphangioma：an approach to the mechanism. J Pediatr Surg. **38**：1806-1809, 2003.
10) Niramis, R., Watanatittan, S., Rattanasuwan, T.：Treatment of cystic hygroma by intralesional bleomycin injection：experience in 70 patients. Eur J Pediatr Surg. **20**(3)：178-182, 2010.
11) Puig, S., Aref, H., Brunelle, F.：Double-needle sclerotherapy of lymphangiomas and venous angiomas in children：a simple technique to

prevent complications. AJR Am J Roentgenol. **180**(5)：1399-1401, 2003.
12) 羽金和彦ほか：頚部リンパ管腫に対する嚢胞開窓隔壁除去術およびフィブリン糊注入法．小児外科．**33**：238-243，2001.
13) Reinhardt, M. A., et al.：Treatment of childhood lymphangiomas with interferon-alpha. J Pediatr Hematol Oncol. **19**：232-236, 1997.
14) Farmand, M., et al.：A new therapeutic concept for the treatment of cystic hygroma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. **81**：389-395, 1996.
15) Ozeki, M., et al.：Propranolol for intractable diffuse lymphangiomatosis. N Engl J Med. **364**：1380-1382, 2011.
16) Reinglas, J., Ramphal, R., Bromwich, M.：The successful management of diffuse lymphangiomatosis using sirolimus：a case report. Laryngoscope. **121**(9)：1851-1854, 2011.
17) Swetman, G. L., Berk, D. R., Vasanawala, S. S., Feinstein, J. A., Lane, A. T., Bruckner, A. L.：Sildenafil for severe lymphatic malformations. N Engl J Med. **366**(4)：384-386, 2012.
18) Barrand, K. G., Freeman, N. V.：Massive infiltrating cystic hygroma of the neck in infancy. Arch Dis Child. **48**(7)：523-531, 1973.
19) Luzzatto, C., et al.：Further experience with OK-432 for lymphangiomas. Pediatr Surg Int. **21**：969-972, 2005.
20) 小児リンパ管腫に対する最近の治療戦略—第34回九州小児外科研究会アンケート調査による217例の検討—．日小外会誌．**42**：215-221，2006.

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Original contribution

Squamous metaplasia in the cyst epithelium of type 1 congenital pulmonary airway malformation after thoracoamniotic shunt placement

Kentaro Matsuoka MD, PhD[a,*], Satoshi Hayashi MD, PhD[b], Fumihiko Urano MD, PhD[a,c], Lihua J. Zhu PhD[c], Hajime Okita MD, PhD[a], Haruhiko Sago MD, PhD[b], Atsuko Nakazawa MD, PhD[a]

[a]*Department of Pathology, National Center for Child Health and Development, Tokyo 157-8535, Japan*
[b]*Center for Maternal-Fetal and Neonatal Medicine, National Center for Child Health and Development, Tokyo 157-8535, Japan*
[c]*Department of Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01655, USA*

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Cyst epithelium;
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Summary Thoracoamniotic shunting is the treatment of choice for management of the fetus with type 1 congenital pulmonary airway malformation. Thoracoamniotic shunting has been performed to reduce life-threatening risks such as fetal hydrops. However, caution is needed because of possible complications. Here, we report that thoracoamniotic shunting can cause histologic changes in the cyst epithelia. In 5 of 8 patients treated prenatally with thoracoamniotic shunting, squamous metaplasia in the cyst epithelia was seen; whereas squamous metaplasia was not found in 6 patients who were not treated with this procedure. Our results reveal that long-term exposure to the intrauterine environment could possibly lead to the change in the nature of cyst epithelium and consequent squamous metaplasia.

1. Introduction

Congenital pulmonary airway malformation (CPAM), formerly known as *cystic adenomatoid malformation*, of the lung is a rare lung disorder characterized by an increased proliferation and cystic dilation of terminal respiratory bronchioles [1-3]. Although the etiology of CPAM is not clear, it has been suggested that it may be caused by a maturation defect in bronchopulmonary development [4,5]. It has been also shown that the presence of bronchial atresia is strongly associated with CPAM, which supports this concept [6].

Congenital pulmonary airway malformation (ie, cystic adenomatoid malformation) was originally classified into 3 groups based on the relative size of the cysts [3]. Currently, CPAM is classified into 5 types based on the presumed site of development of the malformation. Among these 5 types, type 1 CPAM is the most prevalent one, accounting for approximately 60% to 70% of all CPAM lesions [2,3]. Type 1 CPAM consists of 1 or more air- or air/fluid-filled large cysts. The cyst sizes range from 1 to 10 cm. These cysts are often surrounded by underdeveloped alveolar parenchyma and varying number of smaller cysts. Microscopically, the

* Corresponding author. Department of Pathology, National Center for Child Health and Development, Tokyo 157-8535, Japan.
E-mail address: matsuoka-k@ncchd.go.jp (K. Matsuoka).

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cysts are lined by epithelium that varies from a low cuboidal epithelium to a ciliated pseudostratified columnar epithelium [2,7]. The cyst walls also consist of connective tissue similar to those of bronchi of the patient's uninvolved lung. Cartilage islands may be seen in some cases. It has been reported that tufts of mucigenic cells exist on the surface on large cysts or within the smaller bronchiolar-like structures adjacent to the larger cysts in about 35% of type 1 CPAM cases [2]. Past reports indicate that these cells are involved with the occurrence of bronchioloalveolar carcinoma in both older patients with type 1 CPAM and patients who have had a type 1 CPAM removed in infancy [8-13].

Type 1 CPAM usually causes respiratory distress in the newborn period. Thus, surgical removal of the involved lobe is often required to prevent respiratory distress and allow the other lobes to expand normally. Recent advances in antenatal diagnosis and prenatal ultrasound have allowed us to correctly diagnose and monitor fetuses with type 1 CPAM [14,15]. Fetal interventions are applied to fetuses with life-threatening conditions such as hydrops fetalis or polyhydramnios. Thoracoamniotic (TA) shunting is the treatment of choice for management of the fetus with type 1 CPAM and involves shunt insertion under ultrasound guidance [16-18]. Thoracoamniotic shunting has been performed to reduce life-threatening risks such as polyhydramnios, mediastinal shift, and fetal hydrops [17-19]. However, caution is needed because of possible complications. It has been reported that displacement of the catheter into the amniotic or thoracic cavity, catheter occlusion, premature delivery, and fetal demise can occur [19]. Here, we report that TA shunting can cause histologic changes in the cyst epithelia. In 5 of 8 patients treated prenatally with TA shunting, squamous metaplasia in the cyst epithelia was seen; whereas squamous metaplasia was not found in 6 patients who were not treated with TA shunting. These findings suggest that TA shunting could change the nature of the cyst epithelium as a consequence of long-term exposure to the intrauterine environment.

2. Materials and methods

2.1. Indications for TA shunting in fetal CPAM type 1

In the Department of Maternal-Fetal and Neonatal Medicine at the National Center for Child Health and Development, Tokyo, Japan, the indications for TA shunting in fetal CPAM type 1 include the following:

1. Macrocystic CPAM with large cysts
2. CPAM volume ratio greater than 1.6 [20] or hydrops fetalis
3. Before 34 weeks of gestation

We did not perform TA shunting on patient 1 with hydrop fetalis (Table 1). Instead, we performed thoracocentesis because the cysts were separated by the septum, which implied ineffectiveness of TA shunting.

2.2. Case selection

Between 2004 and 2011, TA shunts were used on 8 of 14 fetuses diagnosed as having type 1 CPAM in the Center for Maternal-Fetal and Neonatal Medicine at the National Center for Child Health and Development, Tokyo, Japan. Shunts were offered in pregnancies complicated by hydrops fetalis, polyhydramnios, or at a significant risk for pulmonary

Table 1 Clinical and microscopic data for type 1 CPAM

	TA shunt	Sex	Age (wk)	Weight (g)	Apgar score	Surgical removal (d)	Follow-up	Additional features
1	(−)	M	35	2800	2.2	0	Death at 2 mo, 17 d	Hydrops fetalis
2	(−)	F	37	2410	8.9	24	Free of disease at 1 y, 3 mo	
3	(−)	M	38	2800	8.9	23	Free of disease at 1 y, 1 mo	
4	(−)	F	39	3250	7.7	0	Free of disease at 7 y and 1 mo; rib deformity	
5	(−)	M	40	3400	7.8	12	Free of disease at 6 y, 8 mo	
6	(−)	M	39	3368	8.9	14	Free of disease at 2 mo	
7	(+)	F	28	1490	ND	0	Death at 1 d	Hydrops fetalis
8	(+)	F	33	3544	1.5	0	Free of disease at 7 mo, 25 d	Hydrops fetalis
9	(+)	F	37	3282	7.9	0	Free of disease at 1 y, 9 mo	Polyhydramnios
10	(+)	F	38	2858	8.9	0	Free of disease at 2 mo, 15 d	Hydrops fetalis
11	(+)	M	38	2722	8.8	0	Free of disease at 1 y, 5 mo; rib deformity	
12	(+)	F	38	2790	8.9	0	Free of disease at 4 y, 9 mo; rib deformity	Hydrops fetalis
13	(+)	F	37	2775	8.8	0	Free of disease at 1 mo	Hydrops fetalis
14	(+)	M	38	3032	8.9	0	Free of disease at 1 mo	Hydrops fetalis

Abbreviations: M, male; F, female; ND, no data.

hypoplasia. All patients underwent surgical resection within 1 month after birth. Patients treated with TA shunting underwent surgical resection at the time of delivery.

2.3. Pathologic examination

All cysts were examined macroscopically and microscopically by pathologists in the Department of Pathology at the National Center for Child Health and Development.

3. Results

Of the 14 fetuses antenatally diagnosed as having type 1 CPAM, 8 were female and 6 were male. Clinical, macroscopic, and histologic data for these 14 cases are summarized in Table 1. Thoracoamniotic shunting was used in 8 cases because of hydrops fetalis, polyhydramnios, or an increased risk of pulmonary hypoplasia (Table 1). Six cases did not undergo TA shunting. Extensive microscopic examination revealed that there existed squamous metaplasia of the cyst epithelia in 5 of 8 patients who underwent TA shunting. In contrast, squamous metaplasia was not found in patients who did not undergo TA shunting (Table 1). We did not find overt inflammation in the cases presented in this study. In some patients who underwent TA shunting, we found slight inflammation at the insertion site.

In case 8, a large complex fetal lung mass was found in the left lower lobe. Because of an increased risk of lung hypoplasia, TA shunt was placed at 26 weeks of gestation. At 1 day of life, the infant underwent lobular resection. The overall size of the mass was 7 × 5 × 1.7 cm. The mass contained several predominant macrocysts (Fig. 1A). Microscopically, the cysts were mainly lined by cuboidal, columnar, and ciliated columnar epithelia, which was consistent with the histology of type 1 CPAM (Fig. 1B). Mucinous epithelium and mucinous hyperplasia were also seen. Further examination revealed that the cyst wall was also lined by squamous metaplastic epithelium (Fig. 1C).

In case 14, a large multilocular cyst of the lung was found in the right middle lobe. The size of the resected lung lobe was 6.5 × 5 × 1.5 cm (Fig. 2A). In this case, the insertion site of the shunt tube could be identified macroscopically. Microscopically, the vernix caseosa was found at the insertion site (Fig. 2B). At the distant area from the insertion site, focal squamous metaplasia was found, suggesting that squamous metaplasia was induced by the cyst content, not by the direct contact with a shunt tube (Fig. 2C).

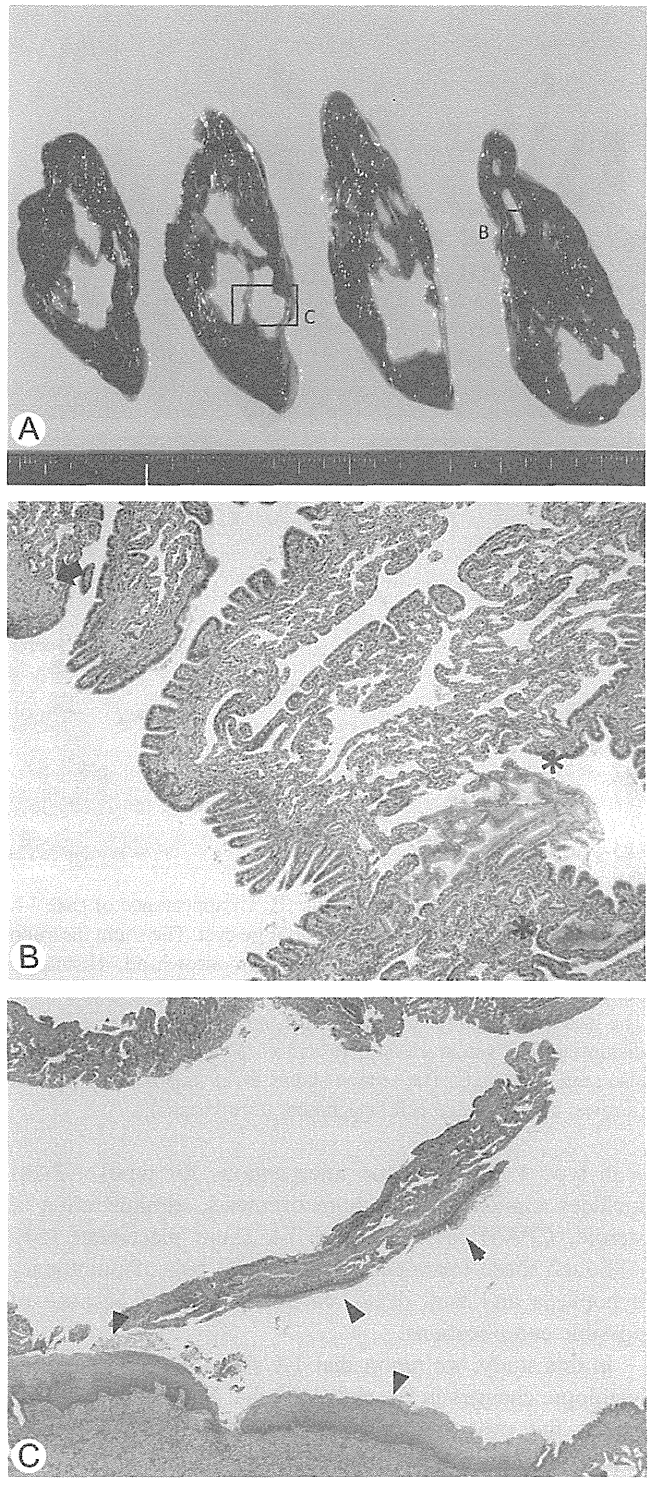

Fig. 1 Gross (A) and microscopic (B, C) appearance of case 8. A, The specimen displays several predominant macrocysts. Histologic sections were made from 2 areas and shown in images B and C. B, The cysts are lined by columnar to pseudostratified columnar epithelia. Mucinous epithelia are seen in the right lower area (asterisks). A small cartilaginous tissue can be found in the left upper area (arrow). C, A histologic section shows focal squamous metaplasia (arrow heads).

4. Discussion

Recent improvements in antenatal diagnosis, prenatal ultrasound, and fetal surgery have allowed us to treat fetuses

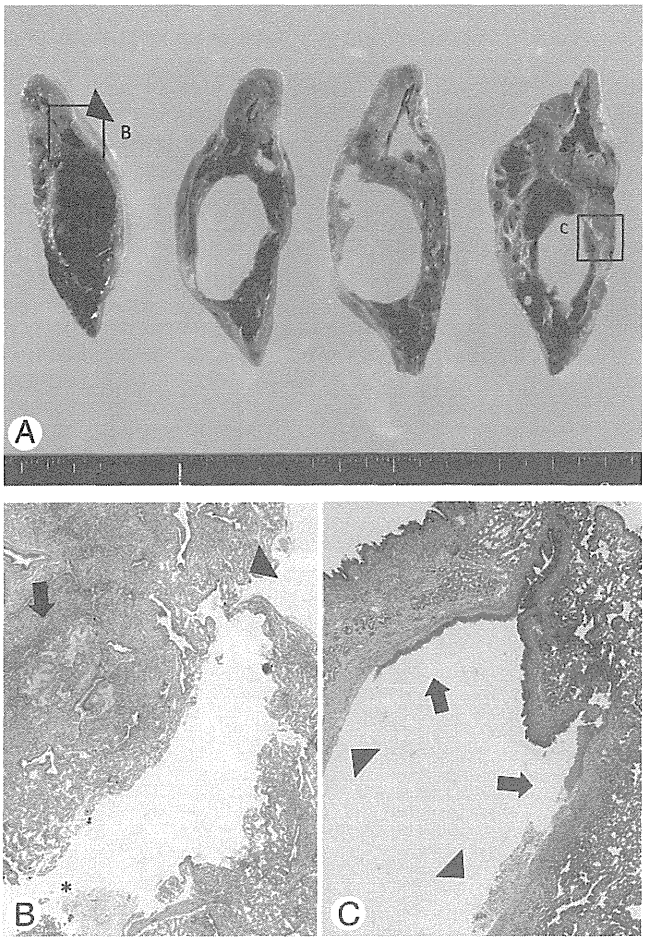

Fig. 2 Gross (A) and microscopic (B, C) appearance of case 14. A, The specimen shows a multilocular large cyst. The shunt insertion site can be identified and pointed by an arrowhead. Histologic sections were made from 2 areas and shown in images B and C. B, The insertion site of the TA shunt tube (arrowhead) shows cyst wall disruption and vernix caseosa (asterisk). Mucinous hyperplasia is also seen (arrow). C, The section shows focal squamous metaplasia (arrows) and epithelial cell detachment (arrowheads).

with type 1 CPAM. Fetal interventions for type1 CPAM includes amnioreduction, thoracocentesis, administration of steroid, CPAM resection, and TA shunt placement [14]. Although these treatments decrease the risk of pulmonary hypoplasia and fetal death, caution is needed because of possible complications.

In this study, we report that TA shunt placement causes histologic changes in the cyst epithelia. Squamous metaplasia in the cyst epithelia was found in fetuses treated prenatally with TA shunting, but not in untreated fetuses, suggesting that TA shunting may change the nature of the cyst epithelium as a consequence of long-term exposure to the intrauterine environment. Supporting this idea is our finding that the increase in mucinous hyperplasia seen in TA shunt population was statistically significant. The Mann-Whitney *U* test was used to test if there was a difference in mucinous hyperplasia between TA shunt population and non–TA shunt population (P =.073). This raises the possibility that residual lung parenchyma could be also affected by the intrauterine environment. Because mucinous hyperplasia has been implicated in the occurrence of bronchioloalveolar carcinoma, this also raises the possibility that there is potential for seeding the thoracic cavity and amniotic cavity with malignant cells through TA shunting. Collectively, squamous metaplasia in the cyst epithelia may be a useful "biomarker" for predicting potential complications and occurrence of bronchioloalveolar carcinoma.

Although TA shunting has lower risks to the fetus and mother as compared to lobectomy, it has been recently reported that fetuses treated with TA shunting could develop postnatal chest wall deformities, suggesting that TA shunt may affect the rib development of patients [21]. Other known risks and complications for TA shunting include catheter displacement, improper function of the catheter, catheter occlusion from thrombus or effusion material, fatal fetal hemorrhage, procedure-related placental abruption, premature rupture of membrane, and preterm labor. These procedure-related complications should be carefully taken into consideration before TA shunting is chosen as a treatment option. In this study, we discovered that TA shunting causes squamous metaplasia of the cyst epithelium. Our findings suggest that histologic changes also should be carefully examined to identify other procedure-related complications.

The cause of squamous metaplasia seen in the cyst epithelium is not clear. It is also possible that long-term exposure to the intrauterine environment led to the change in the nature of cyst epithelium and squamous metaplasia. It has been shown that proinflammatory mediators and meconium in amniotic fluid can cause local inflammation and apoptosis of the lung epithelial cells [22-24]. It has been also reported that the nature of fetal tissue can be changed when it is exposed to the intrauterine environment in long term [25]. Collectively, it is possible that long-term exposure to the intrauterine environment led to the change in the nature of cyst epithelium and consequent columnar to squamous metaplasia.

Our findings raise the possibility that TA shunt placement could cause unexpected changes in the cyst environment, leading to histologic changes in the cyst epithelium. Careful pathologic examination of the cyst is crucial for further understanding of the possible biological effects of TA shunting and prevention of unexpected complications.

References

[1] Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung. Classification and morphologic spectrum. Hum Pathol 1977;8:155-71.
[2] Stocker JT. Cystic lung disease in infants and children. Fetal Pediatr Pathol 2009;28:155-84.
[3] Stocker JT. Congenital pulmonary airway malformation: a new name for and an expanded classification of congenital cystic adenomatous malformation of the lung. Histopathology 2002;41(Suppl. 2):424-31.

[4] Cangiarella J, Greco MA, Askin F, Perlman E, Goswami S, Jagirdar J. Congenital cystic adenomatoid malformation of the lung: insights into the pathogenesis utilizing quantitative analysis of vascular marker CD34 (QBEND-10) and cell proliferation marker MIB-1. Mod Pathol 1995;8:913-8.
[5] Moerman P, Fryns JP, Vandenberghe K, Devlieger H, Lauweryns JM. Pathogenesis of congenital cystic adenomatoid malformation of the lung. Histopathology 1992;21:315-21.
[6] Riedlinger WF, Vargas SO, Jennings RW, et al. Bronchial atresia is common to extralobar sequestration, intralobar sequestration, congenital cystic adenomatoid malformation, and lobar emphysema. Pediatr Dev Pathol 2006;9:361-73.
[7] Lantuejoul S, Nicholson AG, Sartori G, et al. Mucinous cells in type 1 pulmonary congenital cystic adenomatoid malformation as mucinous bronchioloalveolar carcinoma precursors. Am J Surg Pathol 2007;31: 961-9.
[8] Ioachimescu OC, Mehta AC. From cystic pulmonary airway malformation, to bronchioloalveolar carcinoma and adenocarcinoma of the lung. Eur Respir J 2005;26:1181-7.
[9] Sudou M, Sugi K, Murakami T. Bronchioloalveolar carcinoma arising from a congenital cystic adenomatoid malformation in an adolescent: the first case report from the orient. J Thorac Cardiovasc Surg 2003;126:902-3.
[10] MacSweeney F, Papagiannopoulos K, Goldstraw P, Sheppard MN, Corrin B, Nicholson AG. An assessment of the expanded classification of congenital cystic adenomatoid malformations and their relationship to malignant transformation. Am J Surg Pathol 2003;27:1139-46.
[11] Endo C, Imai T, Nakagawa H, Ebina A, Kaimori M. Bronchioloalveolar carcinoma arising in a bronchogenic cyst. Ann Thorac Surg 2000;69:933-5.
[12] Wang NS, Chen MF, Chen FF. The glandular component in congenital cystic adenomatoid malformation of the lung. Respirology 1999;4: 147-53.
[13] Benjamin DR, Cahill JL. Bronchioloalveolar carcinoma of the lung and congenital cystic adenomatoid malformation. Am J Clin Pathol 1991;95:889-92.
[14] Truitt AK, Carr SR, Cassese J, Kurkchubasche AG, Tracy Jr TF, Luks FI. Perinatal management of congenital cystic lung lesions in the age of minimally invasive surgery. J Pediatr Surg 2006;41:893-6.
[15] Olutoye OO, Coleman BG, Hubbard AM, Adzick NS. Prenatal diagnosis and management of congenital lobar emphysema. J Pediatr Surg 2000;35:792-5.
[16] Nicolaides KH, Blott M, Greenough A. Chronic drainage of fetal pulmonary cyst. Lancet 1987;1:618.
[17] Adzick NS, Harrison MR, Flake AW, Howell LJ, Golbus MS, Filly RA. Fetal surgery for cystic adenomatoid malformation of the lung. J Pediatr Surg 1993;28:806-12.
[18] Clark SL, Vitale DJ, Minton SD, Stoddard RA, Sabey PL. Successful fetal therapy for cystic adenomatoid malformation associated with second-trimester hydrops. Am J Obstet Gynecol 1987;157:294-5.
[19] Wilson RD, Baxter JK, Johnson MP, et al. Thoracoamniotic shunts: fetal treatment of pleural effusions and congenital cystic adenomatoid malformations. Fetal Diagn Ther 2004;19:413-20.
[20] Crombleholme TM, Coleman B, Hedrick H, et al. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. J Pediatr Surg 2002;37: 331-8.
[21] Merchant AM, Peranteau W, Wilson RD, et al. Postnatal chest wall deformities after fetal thoracoamniotic shunting for congenital cystic adenomatoid malformation. Fetal Diagn Ther 2007;22:435-9.
[22] Jeng MJ, Soong WJ, Lee YS, et al. Meconium exposure dependent cell death and apoptosis in human alveolar epithelial cells. Pediatr Pulmonol 2010;45:816-23.
[23] Speer CP. Chorioamnionitis, postnatal factors and proinflammatory response in the pathogenetic sequence of bronchopulmonary dysplasia. Neonatology 2009;95:353-61.
[24] de Beaufort AJ. Early human development at the perinatal interface: meconium stained amniotic fluid (MSAF) and meconium aspiration syndrome (MAS). Early Hum Dev 2009;85:605.
[25] Meuli M, Meuli-Simmen C, Hutchins GM, et al. In utero surgery rescues neurological function at birth in sheep with spina bifida. Nat Med 1995;1:342-7.

ORIGINAL ARTICLE

Thoracoamniotic shunting for fetal pleural effusions using a double-basket shunt

Yuichiro Takahashi[1], Ichiro Kawabata[1], Masahiro Sumie[2], Masahiko Nakata[2], Keisuke Ishii[3], Takeshi Murakoshi[3], Shinji Katsuragi[4], Tomoaki Ikeda[4], Mari Saito[5], Hiroshi Kawamoto[5], Satoshi Hayashi[6] and Haruhiko Sago[6]*

[1]Department of Fetal-Maternal Medicine, Nagara Medical Center, Gifu, Japan
[2]Perinatal Care Center, Yamaguchi University Hospital, Ube, Japan
[3]Maternal and Perinatal Care Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan
[4]The Department of Perinatology, National Cerebral Cardiovascular Center, Osaka, Japan
[5]Clinical Research Center, National Center for Child Health and Development, Tokyo, Japan
[6]Center for Maternal-Fetal and Neonatal Medicine, National Center for Child Health and Development, Tokyo, Japan
*Correspondence to: Haruhiko Sago. E-mail: sagou-h@ncchd.go.jp

ABSTRACT

Objective To describe the safety and efficacy of thoracoamniotic shunting for fetal pleural effusion using a double-basket catheter with a very small diameter (1.47 mm).

Method In this 2-year multicenter, prospective single-arm clinical study registered with the University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN00001095); shunting was performed between 18w0d and 33w6d of gestation with this catheter in cases of fetal pleural effusions reaccumulating after thoracocentesis. The primary endpoint measures were maternal and fetal adverse effects and survival in the neonatal period.

Results A total of 24 cases were included, of which 17 had hydrops (71%). The median gestational ages at shunting and delivery were 27.4 and 34.8 weeks, respectively. There were no fetal deaths, lung injuries, or severe maternal complications. Preterm rupture of the membranes occurred in 7/24 (29%) cases at a median of 62 days after the shunting. Preterm rupture of the membranes within 28 days of the procedure occurred in 1/24 (4%) cases. Catheter displacement towards the fetal thoracic cavity occurred in 4/42 (10%) cases. The overall survival rate was 79% (19/24), whereas it was 71% (12/17) in the cases with hydrops.

Conclusion Drainage of fetal pleural effusions with a double-basket shunt is safe and effective, and the shunt could be an alternative device.

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Conflicts of interest: None declared

INTRODUCTION

The prognosis of untreated isolated fetal pleural effusion associated with hydrops is still poor[1–3]; the estimated survival rate of such cases is only around 22–53%.[3] Fetal interventions in cases of recurrent pleural effusion, such as single or serial thoracocentesis, primary thoracoamniotic shunting (TAS), or TAS after initial thoracocentesis, have also been shown to yield similar outcomes.[4] In one review, spontaneous recovery was reported in 22% of cases.[2] Reaccumulation of pleural effusion after thoracocentesis might be considered as a more pragmatic indication for fetal intervention. In 1990, a 'double-basket shunt ' (Hakko Co., Nagano, Japan, Figure 1) was developed in Japan and because it has been frequently used for TAS in that country. There are only sporadic case reports on this device, whereas larger series are lacking.[5–7] Herein, we report on a prospective multicenter study on TAS for fetal pleural effusion using this double-basket shunt.

MATERIALS AND METHODS

Study design

This was a 2-year prospective multicenter single-arm clinical study registered with University hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN00001095), which is a study conducted with the aim of determining the safety and efficacy of TAS using the double-basket catheter. Five fetal medicine units in Japan participated: the National Center for Child Health and Development (Tokyo), Nagara Medical Center (Gifu), Yamaguchi University Hospital

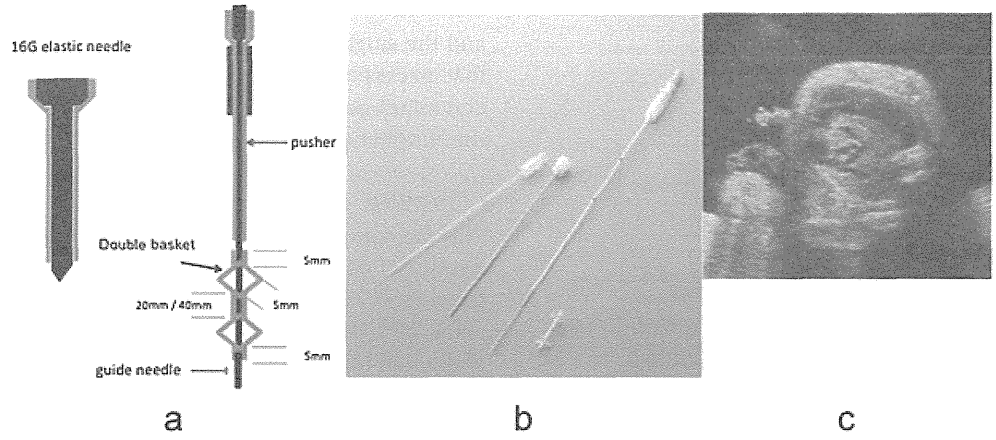

Figure 1 The double-basket catheter. (a) Schema of the double-basket catheter developed by Hakko, Japan; (b) A picture of the trocar and the inner cannula; (c) An ultrasonographic image obtained just after the shunting operation

(Ube), Seirei Hamamatsu General Hospital (Hmamatsu), and the National Cerebral Cardiovascular Center (Osaka). Data were gathered by an independent data-coordinating center at the Japan Clinical Research Support Unit. The study was conducted with the approval of the institutional review board at each center. All patients provided written informed consent.

Pregnant women aged 16–45 years old with a singleton pregnancy between 18w0d and 33w6d were asked to participate. Further inclusion criteria were fetal unilateral or bilateral pleural effusion (effusion area occupying more than half of the fetal chest area) of the fetus that was either isolated (fetal chylothorax) or associated with pulmonary sequestration[7] and showed reaccumulation to the previous level within 7 days after the initial thoracocentesis. The exclusion criteria were major fetal anomalies that could independently affect the chances of neonatal survival. Fetal karyotyping was offered, but was not essential for study entry. Minor fetal anomalies, for example, cleft lip, ventricular septal defect, or polydactyly, were not counted as exclusion criteria. The other exclusion criteria were hydrops because of other causes such as fetal arrhythmias, viral infections (cytomegalovirus, parvovirusB19), and blood-type incompatibility, women with severe maternal complications, such as pregnancy-induced hypertension, mirror syndrome[8–10] associated with hydrops fetalis, or placental thickness >6 cm, cases with a shortened cervix (<10 mm), genital bleeding, or preterm rupture of the membranes (PROM) before the procedure, and cases with a previous history of amniocentesis or amnioreduction. Hydrops fetalis was defined as the presence of skin edema at the head (>5 mm) or accumulation of fluid other cavities (such as ascites or pericardial effusion) in addition to the pleural effusion.

Interventions

We performed TAS within 7 days after the initial thoracocentesis. If the effusion was bilateral, we attempted to insert the TAS catheter on both sides, unless there were obvious technical restrictions. The number of attempts was empirically set at a maximum of three times for each side. The procedure was conducted after administration of a tocolytic drug (ritodorine chloride 50 μg/min i.v.), and the preferred anesthetic technique was local anesthesia. If necessary, a maternal sedative (diazepam i.v. or pentazocine hydrochloride i.m.) was given. In the presence of excessive fetal movements, maternal general anesthesia ($n=2$) or fetal muscular injection of vecuronium bromide ($n=4$) was used. A 16G puncture cannula with a sharp trocar (inner/outer diameter 1.66/2.14 mm; EV16GX 250 mm/150 mm, Hakko Co., Nagano, Japan) was inserted through the maternal abdominal and uterine wall and through the fetal chest wall into the effusion under ultrasound guidance. The preferential insertion site was the lateral chest wall, and the tip of the needle was kept about 10 mm from the fetal chest wall. After confirming flow of the fluid via the cannula, the double-basket catheter was advanced with a pusher through the trocar about 15 mm beyond the tip, until opening of the distal basket could be confirmed by ultrasound. Thereafter, the cannula was withdrawn over the pusher so that the proximal basket would open (shunt tube inner diameter 0.9 mm, outer diameter 1.47 mm; Hakko Co.). Finally, the pusher and cannula were removed (Figure 1). A prophylactic antibiotic (cefazolin 1 g i.v. at the time of the procedure) was also administered.

Follow-up ultrasound and Doppler examination was performed at 1, 3, and 7 days and weekly thereafter until delivery. Standard antenatal corticosteroid therapy (betamethasone 12 mg i.m. twice with a 24-h interval between the two injections) was provided for preterm delivery before 34 weeks of gestation,[11] with the delivery timing decided on the basis of obstetrical indications.

Endpoints and sample size

The primary endpoint measures were maternal and fetal adverse effects (AEs) and the survival rate in the neonatal period (28 days of life). In the cases with hydrops, improvement of the fetal skin edema at the final assessment just before delivery {classified as either (1) complete remission (disappearance of the edema), (2) partial remission [edema decreased, but still persisting to some degree, (3) no change, or (4) progression]}, and other perinatal outcomes. The anticipated survival rate was assumed to be 70% empirically, and with a sample size of 20 patients, and the lower 90% confidence limit would be above 50%.[12]

RESULTS

A total of 24 women were enrolled between April 2008 and March 2010 (24 months). The characteristics of the 24 cases are summarized in Figure 2, and details of the individual cases are

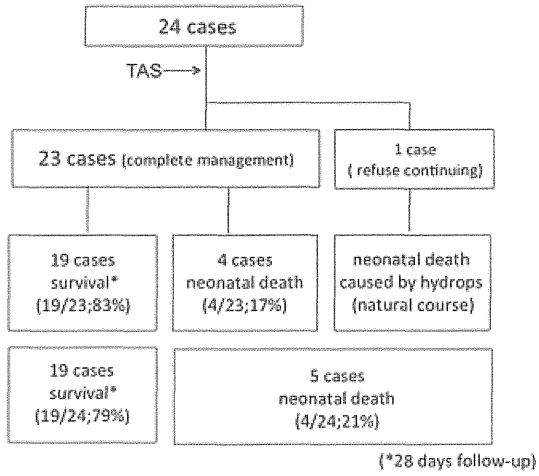

Figure 2 Chart of prospective registered study. TAS, thoracoamniotic shunting

presented in Table 1. The median gestational age at TAS was 27.4 weeks (interquartile range 26.2–31.2). Hydrops was observed in 71% of the cases. Umbilical arterial Doppler revealed abnormalities in 2/24 cases (8%), and none had abnormal ductus venosus. Ten had bilateral pleural effusions (Table 2), and a bilateral shunt was placed in six of these cases. In the remaining four cases of bilateral and 14 cases of unilateral effusion, a shunt could be placed successfully. There were 42 candidate cavities, and the procedure was finally successfully performed in 39 (93%). In one patient, chromosome 6 monosomy was detected after the first shunt, not associated with any visible morphological abnormalities. The family did not desire a second shunt operation (Table 1), as the first did not improve the fetal condition completely, and the patient discontinued the management.

The overall survival rate at 28 days of life was 79% (90% confidence interval, 61.1–91.4%). The median gestational age at delivery was 34.8 weeks (interquartile range). For the fetuses with hydrops, the neonatal survival rate was 71% (90% confidence interval, 47.8–87.6%; $n=12$). Complete remission occurred in 7/16 (42.8%) cases, and partial remission in 4/16 (25%) cases (Table 3).

The catheter-related outcomes and complications are shown in Table 4. There were 34 candidate cavities (unilateral 14, bilateral 10×2) and a total of 42 sessions, including reinterventions. When we analyzed the time-lag for the reintervention (at least 2 days after first shunt), the rate per patient was 8/24 (33%). Catheter displacement into the thoracic cavity occurred in 4/42 sessions. In all of these cases, it was successfully removed by surgery after birth. The two catheters that did not function in utero were found after birth to have fibrin obstruction. The PROM rate within 28 days after the TAS was 4.2% (1/24). There were no cases of intrauterine infection or abruptio placentae. There were three cases of Mirror's syndrome, presenting after shunting at 28, 31, and 30 weeks gestation (Cases 4, 8, and 21 in Table 1), that necessitated immediate delivery and maternal intensive care for lung edema ($n=3$), and maternal pleural effusion ($n=3$); however, all recovered without sequelae. However, neonatal death occurred in two of the three cases of Mirror's syndrome, and the single surviving case showed severe pleural effusion that necessitated prolonged intensive care in the neonatal and infant period, after the diagnosis of congenital aplasia of the lymphatic vessels was made (Case 8).

COMMENT

This was a prospective trial of TAS for fetal pleural effusion using a very thin double-basket shunt. The overall survival rate of the fetuses was 79%, and the survival rate in those with hydrops was about 71%. The reported survival rate of the fetuses with pleural effusion in the absence of fetal intervention is 59%, and that in the fetuses with hydrops is 35%.[13–15] Fetal therapy using the double-basket shunt for pleural effusions seems to be as effective as that reported for other shunts.

The most striking observation of the present study was that there were no fetal deaths. Reported fetal death rates from other series are 20/125 (16%),[13] 8/21(38%),[14] and 9/54 (16%);[15] however, no detailed case profiles have been reported that could allow a reasonable discussion. One retrospective report indicated a PROM rate of 15% (7/27).[15] In our series, the PROM rate was 1/24 within 28 days (4.2%) of the TAS, and the overall PROM rate was 7/24 (29%). Interestingly, the median gestational week at delivery was 34 weeks in both our study and the aforementioned review.[3]

The risk associated with a catheter has been reported to be correlated with the size of the catheter.[3,13,16] The trocar for inserting the double-basket shunt has an inner diameter of 1.66 mm and outer diameter 2.14 mm (16G). The shunting catheter itself has an inner diameter of 0.9 mm and outer diameter of 1.47 mm, which is the thinnest available for fetal shunting at the moment present. However, the reintervention rate in our study was high (23% per procedures and 33% time-lag reintervention per cases). Shunt failure can be caused by obstruction or displacement, potentially caused by the softness of the catheter. However, in four of the five neonatal death cases, we performed once for each cavity (Table 1). Therefore, the reintervention itself did not seem to be related with a poor neonatal prognosis. There were four cases of catheter displacement into the fetal chest cavity, and the catheter could be removed surgically without any adverse outcomes in all cases. In summary, use of this thin polyethylene shunt could be associated with a higher rate of failure, even though the catheter seemed atraumatic. The most widely used catheter is the silicone double pigtail catheter (Rocket of London Ltd, Watford, UK; inner diameter 2.1 mm, outer diameter 3.0 mm).[16–18] Other devices, such as the Harrison shunt (Cook Urological, Spencer, Ind., USA; inner and outer diameter 0.97 mm and 1.67 mm) and the 4F-angiographic single pigtail catheter (Cordis, Johnson & Johnson, The Netherlands) have been also used.[19] When the outcomes were compared, there were no significant differences in the survival rates (around 62–66% 14 vs. 70% in the hydropic fetuses in our series). The reintervention rate in our series was 23–33% and in those reported series were specifically mentioned 3/9 (33%) and 8% (4/49), respectively.[20,21] The reported rate of intrathoracic displacement is 20% (3/15)[19] as compared with the rate of 10% (4/42) in our series.

Complete remission of skin edema occurred in 7/16 fetuses (44%) and partial remission in 4/16 (25%) fetuses. Remission

Table 1 Profiles of all registered cases of thoracoamniotic shunting

NO	GA registration (week)	Indication	Total trials (N)	Final success (N)	Time-lag trials (times)	Preope edema	Preope ascites	Postope pl. effusion	Postope edema	Postope ascites	GA delivery (week)	Prognosis 28 days	Note
1	30	L	1	1	0	+	+	CR	CR	CR	40	Alive	
2	28	bil	2	2	1	–	–	NC	–	–	35	Alive	
3	32	bil	2	2	0	+	–	NC	Progress	–	35	Died	Severe PPHN
4	26	L	1	1	0	+	+	CR	PR	NC	28	Died	Mirror, respiratory failure
5	20	L	1	1	0	+	+	CR	CR	CR	37	Alive	
6	32	R	1	1	0	+	+	PR	PR	CR	35	Alive	
7	27	L	2	2	0	–	–	CR	–	–	34	Alive	
8	27	L	2	2	1	+	–	CR	NC	–	30	Alive	Mirror, aplasia of lymphatic vessels
9	23	R	1	1	0	+	–	Progress	Progress	Progress	36	Died	Refused therapy, 6 monosomy
10	27	bil	3	2	1	+	+	PR	CR	CR	38	Alive	
11	26	R	1	1	0	+	+	CR	CR	CR	37	Alive	
12	26	bil	4	4	2	–	+	PR	–	PR	33	Died	Severe PPHN
13	26	L	2	2	1	–	–	CR	–	–	38	Alive	
14	29	L	1	1	0	–	–	PR	–	–	31	Alive	
15	31	bil	2	2	0	+	+	PR	CR	CR	34	Alive	
16	31	bil	2	2	1	+	–	PR	PR	–	33	Alive	
17	21	L	3	3	2	+	+	Progress	CR	NC	31	Alive	
18	29	bil	1	1	0	+	+	PR	CR	CR	33	Alive	
19	32	bil	2	2	0	+	+	PR	PR	CR	34	Alive	
20	26	R	1	1	0	–	–	CR	–	–	39	Alive	
21	28	bil	1	1	0	+	–	Progress	Progress	Progress	31	Died	PROM, mirror, severe hydrops
22	25	L	4	2	2	–	–	–	–	–	28	Alive	
23	32	bil	1	1	0	+	+	Progress	NC	PR	34	Alive	
24	22	L	1	1	0	–	–	PR	–	–	36	Alive	

final success; final number of trials of succeeded thoracoamniotic shunting; NC, no change; CR, complete remission; PR, partial remission; L, left; R, right; bil, bilateral; PPHN, persistent pulmonary hypertension of neonate; PROM, preterm rupture of the membrane.