壊的大量化学療法後の骨髄救済療法として発展してきた。免疫細胞療法と異なり *in vitro* での細胞処理がほとんど不要なため，悪性腫瘍に対する細胞療法の原点でありなおかつ理想の姿でもある。ドナーを必要とする同種造血幹細胞移植は，1990年代から顆粒球コロニー刺激因子（granulocyte colony-stimulating factor，G-CSF）の臨床応用開始を契機として，しだいに骨髄移植から末梢血幹細胞移植（peripheral blood stem cell transplantation，PBSCT）へと移行した。その後，免疫抑制主体の骨髄非破壊的前処置化学療法を用いた同種PBSCTが，poor riskの造血器腫瘍患者に対する安全な幹細胞移植としてのみでなく，同種抗原を標的として移植片対腫瘍効果（graft versus tumor effect，GVT）を誘導する免疫細胞療法としての性格を有していることが明らかにされた。1998年ごろから，腎癌に対する高い奏効率がChildらを中心に報告されたが[25]，その後の諸家の報告では奏効率の再現性に乏しく，メラノーマや他癌腫に対する効果も乏しいようである[26]。難治性の固形癌に対する新しい免疫細胞療法としての期待が大きかったが，非血縁ドナーの利用，ドナー由来のDCワクチン療法の併用など治療戦略の見直しが迫られている[27-29]。また，前処置化学療法とPBSCTを伴わず，HLA一致同胞をドナーとして誘導した抗原特異的T細胞のみを養子移入する同種T細胞療法も，治療後に抗原特異的免疫応答の増強が誘導されることが明らかにされており，今後の展開が注目される[30,31]。

2. 集学的免疫細胞療法

最近Rosenbergらは，転移性メラノーマに対して化学療法とAITの組み合わせによる，たいへん有望な集学的治療プロトコールの開発を報告している[32]。$CD4^+CD25^+$の表面抗原を有する抑制性T細胞（regulatory T cell，Treg）はDC，細胞傷害性T細胞（cytotoxic T lymphocyte，CTL），ヘルパーT細胞（T helper，Th）などのあらゆる抗腫瘍エフェクターを抑制するT細胞であるが[33-37]，彼らはこのTregを効率的に骨髄非破壊的前処置化学療法で血中から除去した後に，*in vitro* で大量に増殖させたTILを養子移入するプロトコールを確立した。対象症例35例中腫瘍が半分以上に縮小した部分寛解（partial response，PR）が18例でそのうち4例が完全寛解（complete response，CR）であったと報告している。利用しているTILはクローンではなくヘテロな腫瘍特異性をもったキラー細胞集団であり，有効症例の何例かの患者血中には治療終了後数か月にわたり，末梢血リンパ球の70%以上を移入した抗腫瘍性T細胞集団が占めている。化学療法によるTregの制御の後にヘテロなTILを大量に養子移入するこのプロトコールは，二つの予備臨床試験を経て綿密に設計されており[38,39]，明確な理論構築の後に期待された抗腫瘍効果を実現している[32]。

その他，進行胃癌に対して自己PBSCTによる骨髄救済処置を伴う大量化学療法後にPBSC由来DCを用いたワクチン療法を連続して施行する試みや[40]，HER2を共通の標的として抗体療法とCTL療法を併用することによる効果増強の試みなども報告されている[41]。

これら免疫細胞療法の効果を相殺するのではなく，増強するための化学療法や分子標的治療薬の至適併用療法が，集学的免疫細胞療法として今後の臨床研究の一翼を担うであろう。

III. 本邦における免疫細胞療法の問題点と完全閉鎖系体外循環による免疫細胞療法の構築

われわれは，難治性消化器癌を主たる対象疾患とし，1980年代後半からIL-2を用いたAITの臨床応用を[4]，そして1998年から単球由来DCと腫瘍抗原ペプチドを用いたDCワクチン療法の臨床応用を開始した[9,13,40]。これら *in vitro* での細胞処理を伴う免疫細胞療法の本邦での基盤整備は未だ不十分で，明確なGMP基準が開示されていない。また基盤整備が進んだとしても，繰り返し述べてきたように細胞培養のための施設，薬剤経費が莫大であるため，多くの患者に還元できる医療として定着させるには困難が多い。なおかつ培養過程における微生物汚染の危険性を避けて通れない。治療に用いる細胞の培養・処理は，医師や研究者が片手間にすべき仕事ではなく，専門の技師や依頼を受けた企業の担当者が厳密な清潔環境（GMP基準）の管理下で扱うべき業務であり，今後はそのような方向へ進まなければならない。

表 1　癌の免疫学的逃避機構

1. Alteration of MHC class I and tumor antigen expression
2. Dysregulated expression of adhesion/accessory molecules by tumor and/or antigen-presenting cells
3. Secretion of immunosuppressive soluble factors either by tumor cells or infiltrating T cells or both
4. Induction of immune unresponsiveness via anergy induction or clonal deletion of responding T cells
5. Induction of suppressor cells
6. Changes in T-cell signal transduction molecules
7. Tumor utilization of products of stimulated leukocytes, ie immunostimulation of cancer

（文献[44]より改変後引用）

また，癌の免疫細胞療法の開発研究を進めていく上において，本邦と欧米との背景の違いとして最も認識すべきことは，人種差による罹患癌腫の構成比率の違いである。白人において皮膚癌は最も罹患頻度の高い癌腫であり，メラノーマはその中核をなす。しかし本邦においてはその発生頻度は低い（人口10万人当たり年間約1.5人の発生）。ヒト癌腫のなかで最も免疫原性が高く，免疫療法に反応しやすいメラノーマが罹患患者数の多い欧米で，新たなる免疫細胞療法開発のモデルかつ標的疾患として莫大な研究費が投入されることは妥当であるが，本邦においては疑問である。消化器癌や肺癌にメラノーマに対するのと同じ免疫療法を施行しても，その多くは報われないことを歴史は如実に示してきた。したがって，本邦においてはメラノーマにとらわれない免疫療法技術の開発姿勢も大事である。

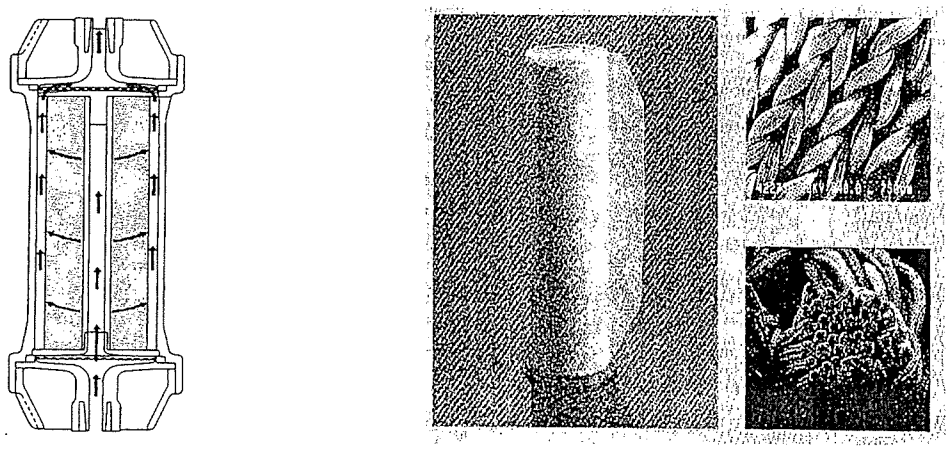
以上述べたような本邦における癌の免疫細胞療法に関する諸問題を鑑み，現在われわれが取り組んでいる *ex vivo* での細胞処理を必要としない完全閉鎖系体外循環治療による免疫細胞療法の開発研究について概説する。

免疫細胞療法，特に能動免疫療法から癌が逃れ治療が奏効しない機序は“免疫学的逃避機構”と称され，様々な要因から成り立っている[42]。表1にその代表的なものを列挙したが，腫瘍の増殖・進展に伴い担癌患者の血中に著しく増加してくる癌細胞由来あるいは宿主免疫担当細胞由来の種々の免疫抑制性の液性因子は，その制御が困難で細胞性免疫能の低下を引き起こし，その結果腫瘍の増殖はいっそう助長される。われわれが化学療法不応性の進行消化器癌，肺癌を対象として行ったDCとCEA由来ペプチドを用いたワクチン療法の臨床試験においても，治療後に血清CEA値が一度も低下せず病状の悪化を来した無効症例10例においては，血清CEA値の低下を来した有効症例8例に比し，治療開始時の末梢血リンパ球PHA幼若化能が有意に減弱しており，血清免疫抑制性酸性蛋白（immunosuppressive acid protein, IAP）が高い傾向を認めた（表2）。すなわち，能動免疫療法であるDCワクチンが有効に作動するには，宿主の基礎免疫能が温存されていることが必須条件であり，DCの成熟化などの改良を行ってもその克服が難しいことを明らかにした[43-45]。この結果を背景に2002年から進行癌患者の血中に増加する免疫抑制物質の除去を目的とした体外循環治療用カラムの開発研究を開始した。すなわち，免疫抑制物質吸着性極細繊維カラムを用いた，血漿交換を伴わない，安全で，簡便で，繰り返し施行可能な癌体外循環治療技術の開発研究である（図1）。

免疫抑制性の液性因子として，IAPやトランスフォーミング増殖因子β（transforming growth factor-β, TGF-β），IL-6，血管内皮細胞増殖因子（vascular endothelial growth factor, VEGF）などがあるが，とりわけTGF-βは免疫抑制の元凶となる中心的存在である[46]。われわれはポリスチレン系極細繊維に種々のアミノ基を付加してスクリーニングすることにより，TGF-β吸着剤を同定し，同吸着剤がVEGF，IL-6の吸

表 2 CEA-DC ペプチドワクチン療法の臨床試験における血清 CEA 値の治療後推移からみた有効症例と無効症例の治療開始時の免疫能の比較

		有効症例（n=8）		無効症例（n=10）
末梢血リンパ球数（/μl）		1,372	NS	1,162
末梢血リンパ球/好中球比		0.46	NS	0.44
末梢血リンパ球サブセット				
CD3（%）		63.5		68.5
CD16（%）		20.9	NS	21.7
CD4/CD8 比		2.21		2.05
末梢血リンパ球 PHA 幼若化能	（cpm）	86,320±27,637		71,985±25,265
	（SI）	148.5±73.4	p<0.01	71.4±27.3
血清 IAP 値（μg/ml）		584.4±279.2	NS	726.5±305.5



進行固形腫瘍患者を対象として
①免疫細胞療法との連動による効果増強
②化学療法との併用による効果増強 ⟶ 難治性癌（膵癌，スキルス胃癌など）を対象とした癌治療用医療機材としての承認をめざす
③末期癌患者の悪液質（QOL）改善
④患者血清の*ex vivo*処理による細胞培養用自己血清の調製

図 1 免疫細胞療法から体外循環治療へ—免疫抑制物質吸着繊維カラムの開発目的と用途—
免疫抑制物質（TGF-β，VEGF，IL-6，IAP など）吸着性極細繊維カラムを用いた，血漿交換を伴わない，安全で，簡便で，繰り返し施行可能な癌体外循環治療技術の開発

着効率にも優れることを明らかにした。また，この吸着剤を充填したミニカラムで担癌ラットを1回体外循環治療するだけで，腫瘍の増殖抑制と生存期間の延長効果が得られることも明らかにしている。

本体外循環治療カラムの実際の臨床上の用途としては図1に示したごとく種々考えられるが，当初の開発目的としての免疫細胞療法との連動，そして特に TGF-β が病態の進展に強く関与するスキルス胃癌や膵癌などの難治性癌を対象とし，化学療法との併用による癌治療用医療機材としての承認をめざしている。

1970～1980 年代にかけて，同じく血中の免疫抑制因子の除去を目的として国内外で血漿交換療法が盛んに試みられ一定の成果が報告されたが[47,48]，われわれが開発中のカラムは，血漿交換に伴う種々の副作用を回避し癌治療において初めて血液吸着療法の形での治療体系を確立していくことに特色と独創性がある。また新たなる創薬を必要とせず，繊維加工技術のみで癌治療用医療機材を開発して

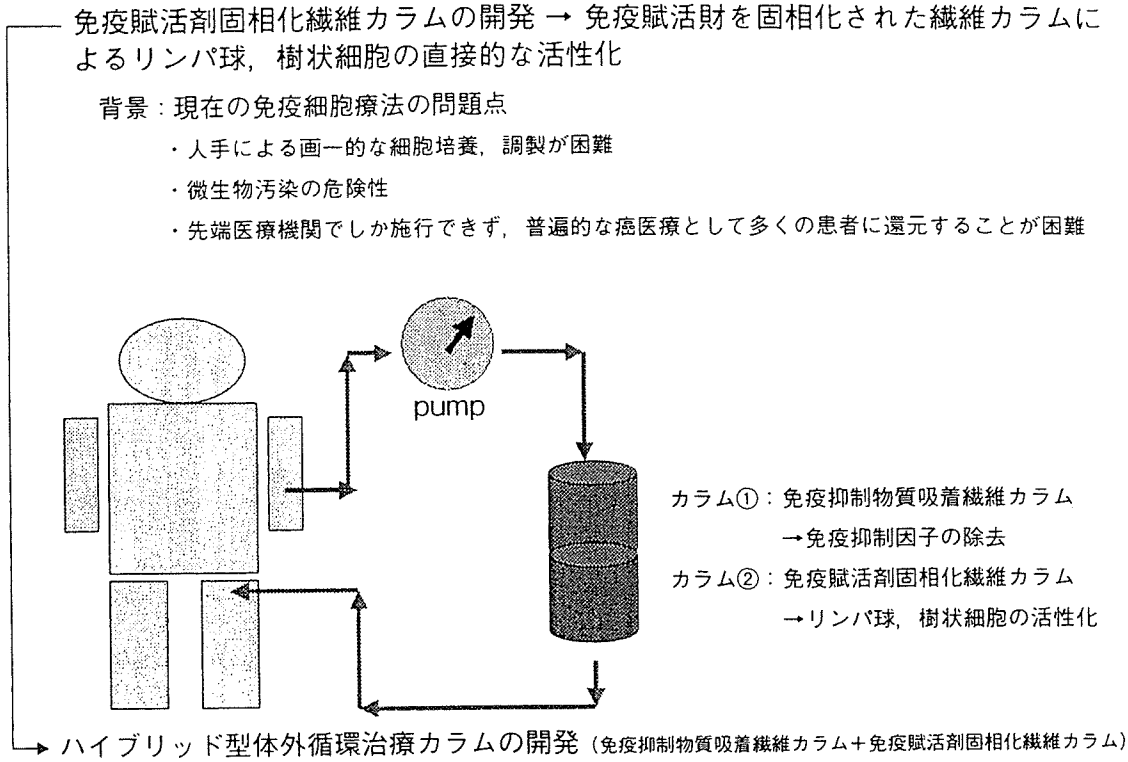


図 2　癌治療用ハイブリッド型体外循環繊維カラムの開発

いくために，承認へ向けた時間の短縮が期待される。

最後に，*in vitro* での細胞処理を伴う現在の免疫細胞療法の多くの問題点を解決するため，2004年からある種の免疫賦活剤を固相化した極細繊維カラムの開発研究を開始している。流血中のリンパ球やDCなどの免疫担当細胞を *ex vivo* に取りだすことなく，体外循環で直に活性化することが目標である。最終的には先の免疫抑制物質吸着繊維カラムと融合させて，完全閉鎖系体外循環による癌免疫細胞療法を構築していきたいと考えている（図2）。

おわりに

ヒト樹状細胞の *in vitro* 誘導と数々の腫瘍拒絶抗原の解明を契機に，受動免疫療法から能動免疫療法へと大きくシフトした固形癌の免疫細胞療法は，再び大きな転換期を迎えつつある。免疫療法としてのsurrogate endpointを充足すれば評価される時代はすでに終わっており，化学療法と共通したprimary endpointである確たる腫瘍の縮小効果と生存期間の延長効果が求められる時代である[49,50]。

化学療法剤の開発研究も，従来のcytotoxic drugからmolecular targeting drug（分子標的治療薬）への開発へと明らかに移行しつつある。これは免疫細胞療法における過去の非特異的から近年の腫瘍特異的治療法の開発の流れと同一であり，将来は免疫療法と化学療法の明瞭な区分がなくなり“癌分子標的治療”という名の下に集約される可能性がある。いずれにしても，今後の癌治療に普遍性，安全性，経済性とともに患者のQOLを重視した簡便性が従来よりいっそう強く求められていくのは間違いない。免疫細胞療法がtranslational researchの枠から抜けだし真の癌治療として今後市民権を得ていくには，少なくとも現在開発されている数々の分子標的治療薬に匹敵する治療成績を，客観的評価に耐え得る臨床試験で証明していかなくてはならない。その道のりは相当険しいと予想されるが，今後の研究の進捗に期待したい。

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と寺本和雄氏との共同研究である。

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担癌ラットにおける免疫抑制物質吸着繊維カラムの細胞性免疫能増強効果

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The Effects of Direct Hemoperfusion Using the Filtration Column Filled with the Adsorption Fiber for Immunosuppressive Substances on Cell-Mediated Immunity in Tumor-Bearing Rats: Arihiro Iwamoto[*1], Yuji Ueda[*1], Kazuo Teramoto[*2], Masaaki Shimagaki[*2], Yoshiki Yamamoto[*1], Tsuyoshi Itoh[*1], Takeshi Shimizu[*1], Atsushi Shiozaki[*1], Hidemasa Tamai[*1] and Hisakazu Yamagishi[*1] ([*1]*Dept. of Surgery, Division of Digestive Surgery, Kyoto Prefectural University of Medicine*, [*2]*Specialty Material Research Labs. Toray Industries, Inc. Shiga Plant*)

Summary

The patients with advanced cancer often lose their anti-tumor immune responses due to the increase of some immunosuppressive substances in the blood, such as cytokines and proteins derived from cancer cells or immune cells. We developed the adsorption fiber in transforming growth factor (TGF)-β for the treatment to remove immunosuppressive substances and investigated the effects of direct hemoperfusion using the filtration column filled with this adsorption fiber in tumor-bearing rats. On day 0, KDH-8 tumor cells (1×10^6 cells/rat) were implanted subcutaneously into the back of WKAH/Hkm rats. On day 21 after tumor implantation, the rats underwent the direct hemoperfusion with this filtration column for 60 minutes. On day 28, the rats were sacrificed and the natural killer (NK) activities of their spleen cells were examined. As a result, the rats that underwent this treatment showed a significant increase in their NK activities compared with those of rats who underwent direct hemoperfusion with an empty column or had no treatment. Therefore, we indicated the possibility of a new immunotherapy technique against cancer using a direct hemoperfusion column filled with an adsorption fiber for immunosuppressive substances. Key words: Direct hemoperfusion, Natural killer activity, Cancer immunotherapy, TGF-β

要旨 癌の進行とともに血中には種々の特異的・非特異的免疫抑制物質が増加し，抗腫瘍細胞性免疫能は抑制される。今回，免疫抑制物質吸着繊維カラム（吸着材としてアミノ基含有多孔質極細繊維を使用）を考案し，これを用いた体外循環による，担癌ラットの細胞性免疫増強効果を検討した。免疫抑制物質吸着繊維カラムを回路内に組み込み60分間の体外循環治療を施行し，脾細胞のnatural killer（NK）活性の検討を行った。免疫抑制物質吸着繊維カラムによる体外循環群は空カラム体外循環群，非循環群に比べ有意なNK活性の増強を認めた。担癌宿主血中の免疫抑制物質を除去するこの体外循環治療は，新たな癌免疫療法となる可能性が示唆された。

はじめに

担癌患者の血中には癌の発展に伴い種々の特異的・非特異的免疫抑制物質が増加し，それに伴い抗腫瘍細胞性免疫能は低下する[1]。これらの免疫抑制物質を十分に除去した後に細胞免疫療法あるいは化学療法を行えば，治療効果を増強することが期待できる[2]。1970年代から80年代にかけて進行癌患者に対し血漿交換による免疫抑制物質除去療法が試みられた。その結果一定の治療効果が示されたが，血漿置換液として大量に使用される血液製剤に起因する感染症リスク，有用な血漿成分の破棄，医療コストなど種々の問題から，本療法は癌治療として普及には至らなかった[3]。近年，癌の伸展に伴う免疫抑制動態の詳細が明らかになり，癌患者の血中に増加してくるtransforming growth factor (TGF)-β[4,5], interleukin (IL)-6, vascular endotherial growth factor (VEGF) などのサ

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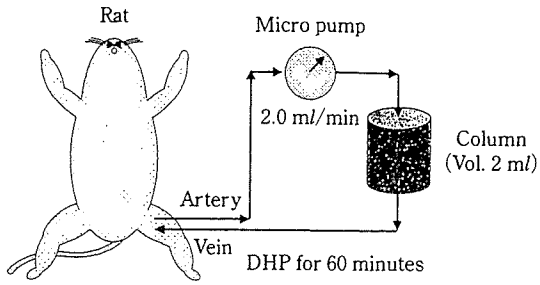

図 1 担癌ラット体外循環治療

イトカインは直に癌の伸展に関与するのみならず，細胞性免疫能を抑制することによりさらに癌の伸展を助長する。また，これらのサイトカインは進行癌患者に悪液質をもたらし化学療法の副作用増強にも関与する。今回われわれは，免疫抑制物質の制御を目的として，免疫抑制物質吸着繊維カラムを用いた血漿交換を伴わない癌体外循環治療を考案し，担癌ラットモデルでその細胞性免疫能の増強効果について検討した。

I. 材料と方法

1. 担癌ラットモデル

10～12 週齢の雄 WKAH/Hkm ラット背部皮下に 2×10^6 個の 4-ジメチルアミノアゾベンゼン誘発肝癌 KDH-8 細胞（TGF-β 産生腫瘍）を接種し，担癌ラットを作製した。

2. 体外循環治療

吸着材として TGF-β の吸着除去に優れたアミノ基含有多孔質極細繊維状吸着材を充填した容量 2 cc のミニカラムを作製し[6]，担癌 3 週目に全身麻酔下にラットの大腿動脈脱血，大腿静脈返血によるミニカラムを回路内に組み込んだ体外循環を毎分 2 m*l*/min の循環速度で 60 分間施行した（図 1）。

3. Natural killer（NK）活性の測定

免疫抑制物質吸着繊維カラムによる体外循環群，非循環群，空カラム体外循環群の 3 群の担癌ラット脾細胞を用いた NK 活性の比較検討を行った。NK 活性は YAC-1 標的細胞の細胞死をユーロピウム遊離法で測定した[7]。

4. 腫瘍増殖とラット生存期間の検討

担癌 2 週目のラットに 2. と同様の体外循環を施行し，その後の腫瘍容積と生存期間を計測した。

II. 結 果

1. NK 活性増強効果

4 時間の短時間 assay，16 時間の長時間 assay ともに体外循環治療群が非循環群，空カラム循環群に比べ NK 活性値の有意な上昇（$p<0.05$）を認めた（図 2，3）。

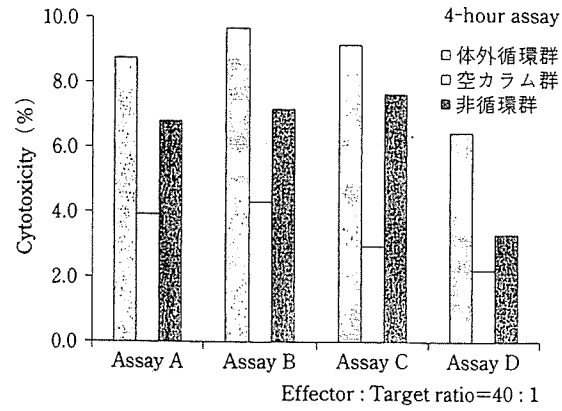

図 2 体外循環による NK 活性増強効果（1）

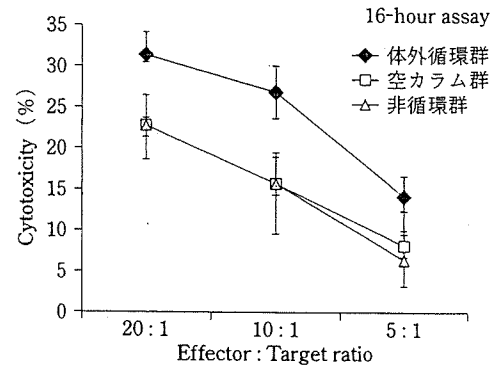

図 3 体外循環による NK 活性増強効果（2）

2. 腫瘍増殖抑制効果と生存期間延長効果

免疫抑制物質吸着繊維カラムを用いた体外循環群では腫瘍の縮小を認めたラットもあり，有意な腫瘍増殖抑制（$p<0.05$）と生存期間の延長（$p<0.05$）を認めた（データ非提示）。

III. 考 察

TGF-β は抗腫瘍免疫誘導のあらゆる段階，機構を阻害することが明らかにされている[1]。われわれは新たなる創薬を伴わず，繊維加工技術のみで TGF-β 吸着繊維を開発したが[6]，本体外循環治療は NK 活性を中心とした細胞性免疫能の増強効果を介して，抗腫瘍効果を発現する可能性が示唆された。将来の臨床応用を前提とし，本治療技術は血漿交換療法と異なり，安全に，安価に，繰り返し施行可能なことが利点である。今後，外科治療，化学療法，細胞免疫療法との組み合わせにより，進行，再発癌に対するより有効な集学的治療システムを構築できる可能性がある。

本論文の要旨は第 26 回癌免疫外科研究会において発表された。

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Case Report

Complication of Jejunal Pouch Interposition after Proximal Gastrectomy: Case Report

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KEY WORDS:
Jejunal pouch; Proximal gastrectomy; Complication; Pouch stasis

SUMMARY
Interposition of a jejunal pouch after proximal gastrectomy is a popular reconstruction method in Japan, because it produces a good quality of life soon after surgery. Many reports have described its usefulness. However, there are few reports describing its complications. We report here for the first time a case of pouch stasis needing surgery.
A 23-year-old man underwent proximal gastrectomy with interposed jejunal pouch for traumatic strangulated diaphragmatic hernia. Three years later, he complained of persistent vomiting. Since surgery, he had eaten as much as other young people. An upper gastrointestinal series showed dilatation of the jejunal pouch and stasis of contrast medium. Since conservative therapy was not effective, surgery was performed. In the operative findings, the jejunal pouch was extremely dilated, the remaining stomach had become atrophic, and moreover, the anastomosis was severely distorted. It was considered that frequent excessive ingestion caused irreversible dilatation of the jejunal pouch, resulting in pouch stasis. Even though the jejunal pouch is interposed for reconstruction, it is very important to give nutritional guidance to patients, especially young patients, to prevent pouch stasis caused by excessive food ingestion.

INTRODUCTION

Recently, jejunal pouch interposition has been in general use for reconstruction after proximal gastrectomy in Japan. It has been reported that this method prevents postoperative reflux esophagitis and allows adequate food ingestion soon after surgery leading to the best possible quality of life (1-3). Therefore, we have also performed proximal gastrectomy interposing a jejunal pouch between the esophagus and the gastric remnant for early gastric cancer and other benign diseases in the upper part of the stomach.

However, the complications of this reconstruction have been reported in only a few papers, describing the development of an ulcer in the jejunal pouch (4,5). Although pouchitis and pouch stasis have been reported in the ileal pouch-anal anastomosis (6), no case in the jejunal pouch for gastric substitute after proximal gastrectomy has ever been reported. There are no reports about the long-term follow-up of jejunal pouch interposition after proximal gastrectomy. Therefore, it is still not clear whether this method is free of serious problems and provides a better quality of life than other methods.

We report here for the first time a patient, who suffered from pouch stasis due to extreme dilatation of the jejunal pouch and required surgery. We also discuss the complications of jejunal pouch for gastric substitute after proximal gastrectomy.

CASE REPORT

A 23-year-old man was admitted to Wakayama Medical University Hospital in May 2001 with persistent vomiting and body weight loss. Three years before admission, he underwent proximal gastrectomy and reconstruction of an interposed jejunal pouch for traumatic strangulated diaphragmatic hernia. At that time, the operation procedure was as follows: after proximal gastrectomy preserving pyloric branches of the vagal nerve, the jejunum was divided 15cm distal to the ligament of Treitz and a 30-cm-long jejunal segment with vascular pedicles was prepared as a substitute for the pouch and brought up posterior to the transverse colon. Sacrifice of the mesenteric arcade was kept to a minimum in order to preserve the autonomic nerve and blood flow in the mesentery. Two cut edges of this segment were placed against the side of the gastric remnant. From the cut edges, a liner stapling device was inserted in order to construct the U-shaped jejunal pouch by side-to-side jejunostomy. An end-to-end anastomosis was made between the upper edge of the jejunal pouch and the esophagus using a circular stapling device. Then, an end-to-end anastomosis was made between the lower edge of the jejunal pouch and the remnant stomach. Our method is almost identical to others which have been reported (2,3).

There were no complications in the postoperative course, and he could eat as much as other young people soon after surgery. After he had been followed up for 6 months without any complications, he did not consult our hospital.

In January 2001, he complained of persistent vom-

Hepato-Gastroenterology 2004; 51:916-918

iting and body weight loss (14kg/5 months). Blood examinations showed hyponatremia (132mEq/L) and hypochloremia (97mEq/L) due to persistent vomiting and low serum levels of albumin (3.4g/dL), triglyceride (38mg/dL) and cholesterol (97mg/dL) due to hyponutrition. An upper gastrointestinal series showed extreme dilatation of the jejunal pouch and stasis of the contrast medium in the pouch **(Figure 1a, b)**. Gastrointestinal endoscopy showed that the jejunal pouch was extremely dilated and the anastomosis bent sharply, and therefore, it was impossible to examine the remnant stomach **(Figure 2a, b)**.

Since conservative therapy was not effective, surgery was performed. The jejunal pouch was hypotonic and remarkably dilated. The remnant stomach was atrophic and the anastomosis was obviously bent. The jejunal pouch and the remnant stomach were resected **(Figure 3a, b)**, followed by Roux-en-Y double tract reconstruction (7,8). Pathological findings showed that the autonomic nerves were not degenerated and that the muscle layer had become hypertrophic associated with the dilatation.

Two months after the operation, he had gained 13kg in weight and all data of the laboratory investigations were normalized, although frequent meals per day were needed.

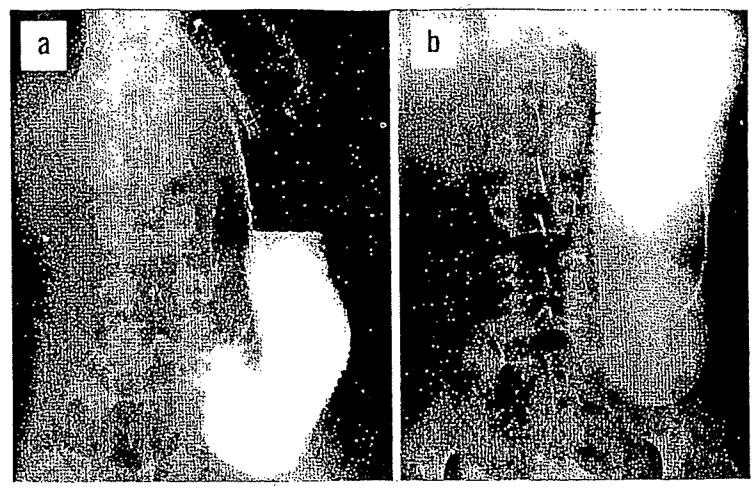

FIGURE 1 Radiograph of the jejunal pouch on admission showing **(a)** immediately after the intake of water-soluble contrast medium, and **(b)** 150 minutes later.

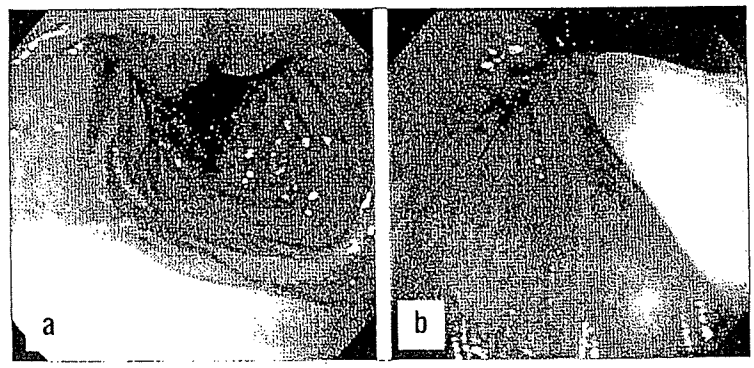

FIGURE 2 Endoscopic findings showing **(a)** the dilated jejunal pouch and **(b)** bending of the anastomosis (arrow).

DISCUSSION

The most popular methods of reconstruction after proximal gastrectomy were previously esophagogastrostomy (Mikulics) or jejunal interposition (Merendino). However, the postoperative course of these reconstruction methods was not favorable, due to the problems such as reflux esophagitis, inadequate food ingestion at any one time and difficulty in endoscopically examining the remnant stomach.

In 1993, Kameyama reported a new method of reconstruction, interposed jejunal pouch, to resolve these problems (9). Since then, several modified methods have been reported (1-3,10) and this method has been evaluated as superior to esophagogastrostomy or single jejunal interposition because of reducing postoperative disturbance such as alkaline reflux esophagitis and inadequate food ingestion, and it has become the most popular method for reconstruction after proximal gastrectomy in Japan. However, there have been two reports mentioning complications with interposed jejunal pouch (4,5). They reported the presence of a marginal ulcer at the interposed jejunal pouch and discussed the possibility of hypergastrinemia after proximal gastrectomy as the cause. However, there have been no studies with long-term follow-up after jejunal pouch interposition, and therefore, it is still to be clarified whether this reconstruction procedure is really superior for proximal gastrectomy.

Our report is the first case of extreme dilatation of the interposed jejunal pouch after proximal gastrectomy resulting in passage disturbance. The length of the jejunal pouch is related to the passage status of food (11), and long pouch reconstruction after total gastrectomy tends to increase reflux and delay emptying time. However, a 15-cm-long pouch, which was made in this case, seems to be standard according to other reports (1-5,9,10). Preserving the pyloric branch of the vagal nerve is important to maintain adequate passage of the food from the remnant stomach to the duodenum (2). Since lymph node dissection was not performed at all in this case because of benign disease, the hepatic branch and celiac branches were completely preserved. In fact, a smooth passage was observed by examining a postoperative barium meal after the first operation.

The problem in this case was that we could not continue to advise the patient about appropriate food ingestion because he stopped attending the hospital 6 months after surgery and, being young, he tended to ingest excessively at one time. We considered that frequent overingestion caused irreversible dilatation of the jejunal pouch resulting in passage disturbance and, finally, the anastomosis was distorted between the dilated jejunal pouch and the remnant stomach. The advantage that interposed jejunal pouch enables the patients to ingest sufficiently at one time soon after surgery became an unexpected pitfall in this case.

This is not a rare situation. Once patients are away from the influence of doctors, they can ingest as much as they want, which could result in a similar outcome

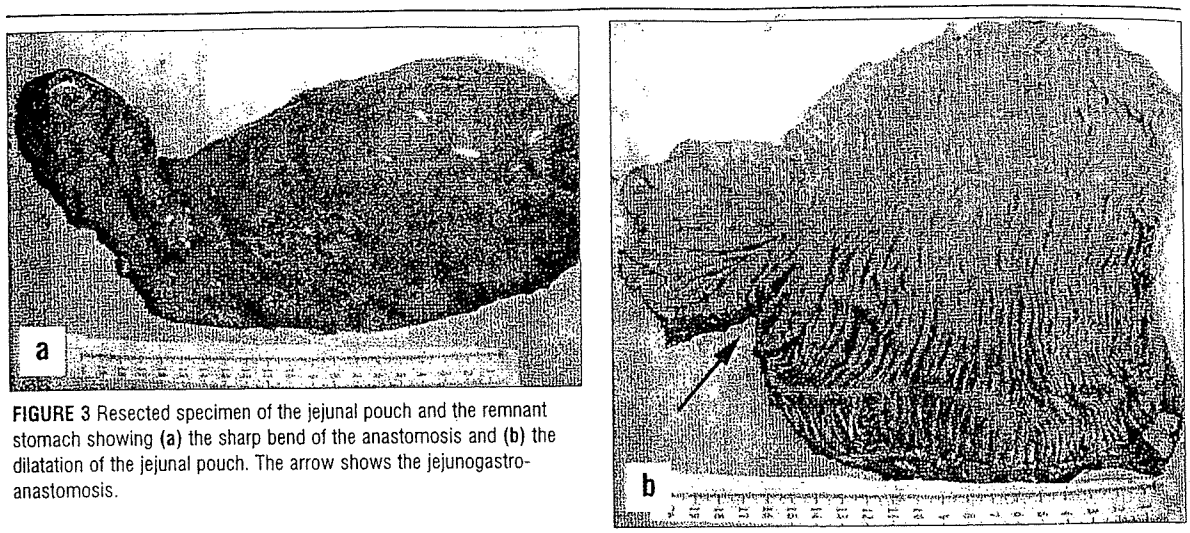

FIGURE 3 Resected specimen of the jejunal pouch and the remnant stomach showing **(a)** the sharp bend of the anastomosis and **(b)** the dilatation of the jejunal pouch. The arrow shows the jejunogastro-anastomosis.

to this case. Therefore, long-term follow-up is necessary, advising patients to avoid excessive ingestion.

In conclusion, the interposed jejunal pouch seems to be superior to other methods of reconstruction after proximal gastrectomy in terms of nutritional benefits and reducing number of meals per day. However, it is very important to give nutritional guidance to patients, especially to the young, for a long time after surgery to prevent pouch stasis caused by excessive food ingestion. A long-term follow-up study is necessary to evaluate whether jejunal interposition is really superior to other methods after proximal gastrectomy.

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Case Report

Virus-associated Hemophagocytic Syndrome and Hemorrhagic Jejunal Ulcer caused by Cytomegalovirus Infection in a Non-compromised Host; A Case Report of Unusual Entity

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SUMMARY
A 76-year-old man was admitted to our hospital with abdominal pain, nausea, and vomiting. The patient was diagnosed as ileus by abdominal radiography, which showed an enlarged bowel and an air-fluid level. Computed tomography of the abdomen showed a thickened intestinal wall. His general status suddenly worsened, and he was placed on a respirator and catecholamines to prevent acute respiratory distress syndrome, septic shock, and disseminated intravascular coagulation. He had continuous fresh anal bleeding. Total colonoscopy showed bloody stool originating from the ileum. Emergency operation was performed for hemorrhagic shock under general anesthesia. Intraoperative jejunal endoscopy revealed deep linear ulcers with bleeding in the jejunum, and 30cm of the jejunum was resected. Histopathologic examination revealed cytomegalic cells with intranuclear inclusion bodies in the tissues surrounding the ulcers, and it was diagnosed as cytomegaloviral enterocolitis with hemophagocytic syndrome in a non-compromised adult.

KEY WORDS:
Cytomegalovirus; Jejunal ulcer; Gastrointestinal hemorrhage; Virus-associated hemophagocytic syndrome; Disseminated intravascular coagulation

ABBREVIATIONS:
Acute Respiratory Distress Syndrome (ARDS); Disseminated Intravascular Coagulation (DIC); Cytomegalovirus (CMV); Virus-Associated Hemophagocytic Syndrome (VAHS); Gastrointestinal (GI)

INTRODUCTION

Cytomegalovirus (CMV) infection and gastrointestinal CMV disease is well recognized in severely immunocompromised patients with acquired immunodeficiency syndrome (AIDS), organ transplants, and malignant disease (1-4). Gastrointestinal lesions may present as either part of a systemic, or as a localized infection (5,6). It is difficult to treat the CMV infection, and the prognosis is usually poor in immunocompromised patients (1,7). On the other hand, healthy persons generally have an acquired permanent immunity against CMV. However, there have been some reports of severe CMV infection even in healthy adults (8,9). Virus-associated hemophagocytic syndrome (VAHS) is a reactive disorder of the phagocytic system, characterized by marked hemophagocytosis (10). There has been one previous case report of VAHS associated with CMV enterocolitis in a healthy adult (11). The patient was treated with steroids and anti-viral drugs.

We herein report a non-compromised case with VAHS and severe enterocolitis, which caused a hemorrhagic jejunal ulcer by CMV, requiring emergency operation.

CASE REPORT

A 76-year-old man was admitted to Wakayama Medical University Hospital with abdominal pain nausea, and vomiting. He had undergone distal gastrectomy with Billroth I reconstruction for early gastric cancer, and Y-graft replacement for abdominal aortic aneurysm 8 years earlier. He has not utilized immunosuppressive anticancer drugs, had no signs of recurrence, and had a good quality of life with social activities.

He had a low-grade fever, epigastrial tenderness, and was admitted on April 2nd, 2000. Blood pressure was 151/60 mmHg and the pulse was 120/min. Several laboratory findings were as follows; white blood cell count 1,000/mm^3, platelet 104,000/mm^3, C-reactive protein 8.0mg/dL, creatinine kinase 824 IU/L, amylase 1,160 IU/L, creatinine 3.1mg/dL, and urea nitrate 40mg/dL.

He was diagnosed as ileus and the abdominal radiography showed an enlarged bowel and an air-fluid level. Two hours after admission, his vital status suddenly worsened. Respiration ceased, and systolic blood pressure was 40 mmHg in spite of administration of cathecolamins. Therefore, we performed extended intensive care with respirator support and hemodynamic drugs for acute respiratory distress syndrome (ARDS), septic shock, acute pancreatitis, and disseminated intravascular coagulation (DIC).

Computed tomography of the abdomen showed a thickened intestinal wall. The intestinal mucosa was enhanced by contrast media, suggesting enterocolitis without ischemia rather than strangulating obstructions (**Figure 1**).

His general condition improved with intensive care,

Hepato-Gastroenterology 2004; 51:491-493

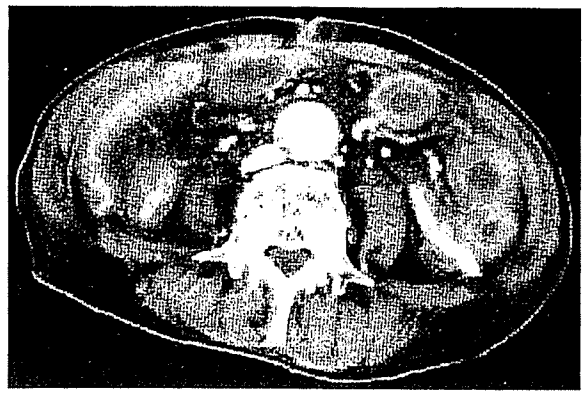


FIGURE 1 The computed tomography on admission.
The computed tomography on admission showed the thickness of the intestinal wall, however, the blood supply to the mucosa was normal.

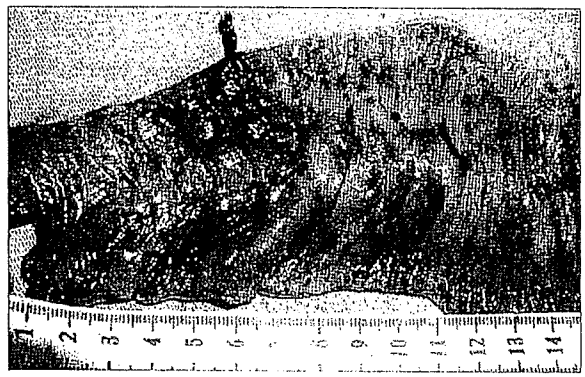


FIGURE 2 Jejunal ulcer.
The deep linear ulcers with bleeding in the jejunum.

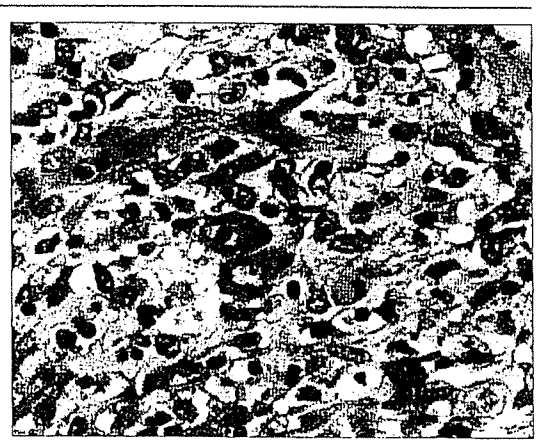
and the ileus was cured by conservative treatment. However, he had continuous fresh anal bleeding from the 17th hospital day of admission. Upper gastrointestinal endoscopy showed normal findings. Total colonoscopy showed the entire colon was filled with bloody stool, supplied from the ileum. As his general condition was poor, we chose interventional treatment. However, angiography revealed no apparent hemorrhagic lesion.

Emergency operation was performed for hemorrhagic shock under general anesthesia. Laparotomy revealed a small amount of clear ascites. Macroscopically, the serosa and the mesenterium were normal and the hemorrhagic lesion was not identified. Intraoperative jejunal endoscopy inserted from the ileum revealed deep linear ulcers with bleeding in the jejunum. Thirty centimeters of the ileum was resected and we performed end-to-end jejunal anastomosis **(Figure 2)**.

Histopathologic examination revealed cytomegalic cells with intranuclear inclusion bodies in the tissue surrounding the ulcers. Immunopathological study with CMV antibody confirmed the presence of CMV infection **(Figure 3)**. The serum antibody to CMV was serologically examined as follows; anti CMV-IgG was 432.8 GI compared to 46.4 GI on the third hospital day, and anti CMV-IgM was 1.9 MI.

The gastrointestinal bleeding improved without antiviral agents including ganciclovir. He had respiratory distress syndrome after the operation and required a respirator for one month. Then, he was discharged and was able to resume social activities.

FIGURE 3
Histological examination.
Cytomegalic cells with intranuclear inclusion bodies were found in the tissue around the ulcers.



DISCUSSION

CMV is a member of the herpes virus family, and from 40 to 100 percent of adults acquire antibody to CMV (12). Primary CMV infection in immunocompetent individuals is usually asymptomatic or nonspecific, similar to many acute viral infections. After initial infection, the virus resides in multiple cellular reservoirs and begins a lifelong latent phase (13).

In immunocompromised individuals, however, CMV is a common pathogen and frequently becomes serious. Gastrointestinal CMV disease either part of a systemic, or localized infection is often seen in severely immunocompromised patients including AIDS, organ transplant recipients, malignancies, immunosuppressive therapy, and sometimes in inflammatory bowel disease (1,14). Clinically apparent CMV disease is most often caused by reactivation with compromising of T lymphocyte-mediated immunity (15) but may also be caused by primary infection by transmission of CMV positive organs or blood to CMV negative recipients (2,16). There are also some reports of severe CMV infection in healthy adults with no identifiable immunosuppression (8,9). Indeed, the present case had been healthy before this episode, and showed no symptoms of immunosuppressive diseases including AIDS, malignancies, and inflammatory bowel disease.

Symptoms of gastrointestinal CMV disease include abdominal pain, diarrhea, vomiting, nausea, and gastrointestinal (GI) hemorrhage (3). Any part of the alimentary tract can be affected (1). Serious cases may cause ileus, perforation and major GI hemorrhage (3,15,17). Its endoscopic features are nonspecific and highly variable, ranging from the presence of multiple deep linear ulcers to diffuse erosions and erythema (5,14,18). Pseudomembranes are also reported as rare endoscopic findings of CMV enterocolitis (4). In the present case, there was a jejunal ulcer caused by CMV, but no colic CMV lesions were observed. Jejunal CMV lesion is rare compared with colic, esophageal, or stomach lesions (9).

The pathogenesis of CMV-associated ulcerations is a complex process involving vascular endothelial CMV infection with subsequent ischemic mucosal injury (7).

Occlusion is caused by invasion of the infected endothelium into the lumen of capillaries and venules. Unfortunately, endoscopic findings, serologic analysis, and radiologic findings, including angiography are not conclusive tools for final diagnosis, and histological examination or viral culture is required.

The present case was diagnosed as CMV enterocolitis by histological examination of ulcerated lesions. Moreover, viral culture and DNA analysis was useful for the differential diagnosis (19-22).

It is suggested that he had VAHS developed by CMV. VAHS is a reactive disorder of the phagocytic system, characterized by marked hemophagocytosis (23). Proliferation of histiocytes is caused by hypercytokinemia, particularly Interleukin (IL)-2, interferon (IFN)-γ, and IL-6 which is activated by viral infection (10,24,25). Epstein-Barr virus is most common in VAHS, however, there are some reports of VAHS developed by CMV infection. Since CMV enterocolitis was not expected before the pathological examination of the resected lesion, we have insufficient data to fulfill the criteria of VAHS, but no other etiology was apparent to explain his course. There was one previous case report of CMV enterocolitis associated with VAHS in a healthy adult (11). The patient was successfully treated for DIC, pancytopenia, and enterocolitis, with antiviral agents and steroids. In our case, although there was no evidence of immunosuppression on admission, it is considered that he had systemic CMV disease, including severe enterocolitis and VAHS. He recovered after the operation without treatment with antiviral agents.

It was emphasized that CMV is a causative virus of gastrointestinal hemorrhage and VAHS, and the outcome of CMV enterocolitis and VAHS has been reported to be better in patients with no obvious evidence of immunocompromised state (10,26). The mortality rate of CMV disease is much higher in immunocompromised hosts. In our case, systemic CMV infection and VAHS in an immunocompetent individual caused severe symptoms. The therapy for CMV infection and VAHS requires further investigation.

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Original Paper

Timing of Laparoscopic Cholecystectomy for Acute Cholecystitis with Cholecystolithiasis

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KEY WORDS:
Early laparoscopic cholecystectomy; Acute cholecystitis; Hospital stay; Conversion rates; Endoscopic retrograde cholangiography (ERC)

ABBREVIATIONS:
Laparoscopic Cholecystectomy (LC); Computed Tomography (CT); Ultrasonography (US); Endoscopic Retrograde Cholangiography (ERC); Magnetic Resonance Cholangiography (MRC); C Reactive Protein (CRP); Glutamate Pyruvic Transaminase (GPT); Total Bilirubin (T-Bil); Percutaneous Transhepatic Gallbladder Drainage (PTGBD)

ABSTRACT

Background/Aims: Laparoscopic cholecystectomy is now used in the treatment of acute cholecystitis. The aim of this study is to define the optimal timing for laparoscopic cholecystectomy treated with cholecystolithiasis in patients with acute cholecystitis.

Methodology: A retrospective analysis of 73 patients with acute cholecystolithiasis who were treated by either early laparoscopic cholecystectomy within 72 hours after initial onset or initial conservative treatment followed by delayed laparoscopic cholecystectomy 4 days later.

Results: There were 31 patients in the early group and 42 in the delayed group. There was no significant difference in the rate of conversion from laparoscopic to open surgery (6.4% *vs.* 20.0%), postoperative complications. However the early group had significantly shorter operation time (103 *vs.* 135 min, $p<0.01$) and shorter postoperative hospital stay (6.2 *vs.* 9.6 days, $p<0.01$).

Conclusions: We advocate early laparoscopic cholecystectomy within 72 hours of onset of symptoms to decrease conversion rates from laparoscopic to open surgery. This decreased conversion rate results in decreasing the length of operation time and postoperative and total hospital stay.

INTRODUCTION

Laparoscopic cholecystectomy (LC) has increasingly been accepted as the procedure of choice for the standard treatment of symptomatic cholecystolithiasis, gallbladder polyps, adenomyomatosis and chronic cholecystitis since its introduction in 1989 (1). A successful LC is associated with a less painful postoperative course, a lower analgesic requirement, a shorter hospital stay, and less cosmetic disfigurement (2). Recently, LC is increasingly being used as well for the treatment of acute cholecystitis (2). In the early reports, LC was considered to be a contraindication for acute cholecystitis (2), however, with increasing experience in laparoscopic surgery many surgeons have reported that LC has been used for acute cholecystitis (3). In an attempt to perform LC in acute cholecystitis, it remains controversial whether early LC should be selected or whether delayed LC should be selected after the acute inflammation has subsided. The potential advantage of early LC during the period of acute phase is associated with an earlier recovery and shorter hospital stay (4,5). On the other hand, initial conservative treatment (delayed LC) may lead to a technically easier and lower conversion rate (6). In the present study, we retrospectively compared the early and delayed laparoscopic treatment of patients with acute cholecystitis. Our assessment of the results of attempted LC for acute cholecystitis paid particular attention to the interval from the onset of symptoms to the time of operation.

METHODOLOGY

Over a 10-year period (1991-2000), 702 cholecystectomies were performed in the Second Department of Surgery at the Wakayama Medical University. Six hundred and twenty-five patients (89%) were operated laparoscopically and 77 patients (11%) by the open method. The study included 73 patients with acute cholecystitis; the diagnosis of acute cholecystitis was based on the combination of a compatible clinical sign (right upper quadrant pain and tenderness, temperature greater than 37.5°C, white blood cell count greater than 12,000/μL) and ultrasonographic evidence (presence of gallstones or debris in a thickened and edematous gallbladder, positive sonographic Murphy sign and pericholecystic fluid collections (9).

Patients were excluded from this study if they had: 1) previous upper abdominal surgery; 2) coexisting choledocholithiasis; 3) the gallbladder with perforated or penetrated other organs; or 4) performed percutaneous transhepatic gallbladder drainage (PTGBD). In the early group (n=31), LC was performed within 72 hours, whereas in the delayed group (n=42), LC was performed after conservative treatment with intravenous fluid and antibiotics for over 5 days. In both the early and delayed group, LC was performed by one surgeon (K.U) who has performed more than 500 laparoscopic cholecystectomies.

All patients were routinely examined by computed tomography (CT) and ultrasonography (US) preoperatively. We routinely performed endoscopic retrograde

Hepato-Gastroenterology 2004; 51:346-348

cholangiography (ERC) or magnetic resonance cholangiography (MRC) for all the patients with acute cholecystitis in the preoperative period to exclude choledocholithiasis and to show the biliary tract anatomy. Laboratory data were studied on admission and after LC; in particular, WBC, C reactive protein (CRP), glutamate pyruvic transaminase (GPT), and total bilirubin (T-Bil). Data were collected retrospectively and included operative findings, conversion to open cholecystectomy, operating time, length of postoperative stay and postoperative complications.

All the data are shown as mean ±standard deviation. Statistical analysis was performed with the chi-square test and Student's *t*-test. Probability differences of 0.05 or less were considered significant.

RESULTS

In the early group (31 patients), there were 17 males and 14 females with a mean age of 52.8 years (range 32-72). Of the 42 patients in the delayed group, there were 22 males and 20 females with a mean age of 62.8 years (range 29-74) **(Table 1)**. There was no significant difference between the gender ratio and the age of patients in both groups. In laboratory findings on admission, the values of WBC were equivalent in the two groups **(Table 1)**.

One of 31 patients (3.2%) in the early group and eight of 42 patients (19.0%) in the delayed group required conversion to open surgery ($p<0.05$) **(Table 2)**. Technical difficulties including inflammatory adhesion and uncontrolled bleeding were the main reasons for conversion. The mean duration of surgery in patients in the early group was 103±23 minutes *versus* 135±42 minutes in the delayed group ($p<0.01$). If converted patients were excluded, mean operation time in the early group was 101±20 min compared with 120±31 min in the delayed group ($p<0.01$). **Table 2** shows intraoperative accidents or complications with LC for patients with acute cholecystitis. There were no major complications during the operation such as the injury of biliary tract or other organs. There were 11 patients (35.5%) in the early group and 17 patients (40.5%) in the delayed group with intraperitoneal spillage of bile. Intraoperative blood loss was 93±56mL in the group and 138±72mL in the delayed group ($p<0.01$) and there were no cases with blood infusion.

Table 3 compares the postoperative course and outcome of the two groups. There were no major complications in the study population. Ten complications occurred in 10 patients (32.3%) in the early group, whereas 13 complications occurred in 12 patients (28.6%) in the delayed group. There was no statistically significant difference between the two groups. Common complications included disturbance of liver function, prolonged fever up (over 37.5°C, during 3 days after operation) and wound infection.

Mean preoperative hospital stay was 2.2 and 13.9 days in the early and the delayed groups, respectively ($p<0.01$) **(Table 4)**. Postoperative hospital stay was 6.2 *versus* 9.6 days in the two groups ($p<0.01$). Total hospital stay in the early group was 8.3 days and in the delayed group 22.3 days ($p<0.01$).

DISCUSSION

Laparoscopic cholecystectomy (LC) is first introduced for elective treatment of cholecystolithiasis, and acute cholecystitis is increasingly managed by LC (6,7). Acute cholecystitis had been considered to be a contraindication for LC in the past and there have been many reports advocating LC for acute cholecystitis (8-10), because the conversion to open surgery is more frequent in acute than chronic cholecystitis and the edematous and inflammatory process found at acute cholecystitis changes the vascular and biliary anatomy, sometimes leading to more complications (7). The conversion rate of LC for acute cholecystitis

TABLE 1 Background of Patients with Acute Cholecystitis

	Early group	Delayed group
No. of patients	31	42
Age Mean ±SD	52.8±15.9	56.8±18.9
(range)	(32-71)	(29-74)
Gender male/female	17/14	22/20
Data of admission WBC (/μL)	14,230±1,250	14,540±1,820

TABLE 2 Intraoperative Course of LC

	Early group (n=31)	Delayed group (n=42)
Surgical duration (min)	103±23*	135±42
Cases requiring conversion	1**	8
Surgical duration exclusion conversion cases (min)	101±20* (n=30)	120±31 (n=34)
Injury of biliary tract	0	0
Injury of other organs	0	0
Spillage of bile	11	17
Blood loss (mL)	93±56*	138±72
Blood transfusion	0	0

*Student's *t* test, $p<0.01$.
**χ^2 test, $p<0.005$.

TABLE 3 Morbidity and Mortality after LC

	Early group (n=31)	Delayed group (n=42)
Death	0	0
Bile leak	0	0
Intra-abdominal abscess	0	0
Intra-abdominal bleeding	0	0
Disorder of liver function	2	4
Prolonged fever*	6	6
Wound infection	2	3
Patients with complications (rate)	10 (32.3%)	12 (28.6%)

*over 37.5°C, during 3 days after surgery.

TABLE 4 Perioperative Hospital Stay

	Early group (n=31)	Delayed group (n=42)
Preoperative hospital stay (days)	2.2±0.6*	13.9±7.5
Postoperative hospital stay (days)	6.2±2.7*	9.6±3.2
Total hospital stay (days)	8.3±3.2*	22.3±11.9

*Student's *t* test, $p<0.01$.

has been reported to range from 6% to 38% (4-6), which is significantly higher than the less than 5% rate reported for chronic cholecystitis (7). However, some authors have reported that early LC for the treatment of acute cholecystitis has no adverse effect on complication and conversion rates (8). In the prelaparoscopic era, prospective randomized studies demonstrated that the outcome for patients undergoing early open cholecystectomy within 7 days of the onset of symptoms was superior to delayed interval surgery (11,12). Garber *et al.* recommended LC within 5 days of the onset of symptoms because of a low incidence of positive bile cultures, a negligible percentage of postoperative complications and mortality, and a short hospitalization associated with lower costs (13). Pessaux *et al.* recommend LC for acute cholecystitis within 3 days of admission because it effectively reduces the length of hospital stay (14).

In the present study, we have retrospectively analyzed 73 patients who were operated laparoscopically for acute cholecystitis. Based on the operation timing the patients were divided into two groups. The early group comprised 31 patients who underwent LC within 3 days of onset of symptoms and the delayed group consisted of 42 patients who underwent LC after more than 4 days following onset of symptoms. The conversion rate from laparoscopic to open cholecystectomy was 12.3% in 73 patients with acute cholecystitis. The conversion rate for the early group was 6.5% as compared to 16.7% for the delayed group. Conversion was significantly less frequent in patients undergoing LC within 3 days of admission (early group) compared to those undergoing surgery beyond 4 days (delayed group). The average operation time for the early group was shorter than the delayed group. Ten patients (32.3%) had postoperative minor complications; however, there were no cases of major complications including injury to the biliary system and no perioperative death. The average intraoperative blood loss in the early group was little compared with the delayed group and the average postoperative hospital stay in the early group was shorter in the delayed group. This study shows that laparoscopic cholecystectomy can be performed safely in patients with acute cholecystitis and suggests that early timing of LC within 3 days of onset of symptoms tends to reduce the conversion rate and length of procedure, as well as the total and the postoperative hospital stay. In our expression, in the early phase of acute inflammation, adhesions are easily separated, and there is usually an edematous plane around the gallbladder to facilitate dissection. After a period of conservative treatment, the inflammation and edema are replaced by fibrotic adhesions between the gallbladder and surrounding structures, which occasionally render laparoscopic dissection extremely difficult.

Some authors reported that unsuspected choledocholithiasis was detected in 4-7% in patients with acute cholecystitis (15-17). Intraoperative cholangiography is controversial because it cannot always be performed routinely without risk of biliary injury under acute processes. We performed endoscopic retrograde cholangiography (ERC) or magnetic resonance cholangiography (MRC) for all patients with acute cholecystitis at the preoperative period of LC to exclude choledocholithiasis and to show the biliary tract anatomy without intraoperative cholangiography. Indeed, there were no patients with choledocholithiasis in the present study.

In conclusion, this study supports the view that early LC within 72 hours of onset of symptoms is safer and more feasible in the treatment of acute cholecystitis. Furthermore, the early procedure provides the economic advantage of a markedly reduced postoperative and total hospital stay.

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ORIGINAL ARTICLE

Clinicopathological Features of Malignant Intraductal Papillary Mucinous Tumors of the Pancreas

The Differential Diagnosis From Benign Entities

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Background: The accurate differential diagnosis of malignant intraductal papillary mucinous tumors (IPMTs) of the pancreas from benign IPMTs remains unclear.

Hypothesis: Predictive factors for differentiating malignant IPMTs from benign IPMTs can be documented.

Design: Retrospective study (1999-2003).

Setting: Wakayama Medical University Hospital, Wakayama, Japan.

Patients: Twenty-seven consecutive patients with IPMTs (11 with adenoma, 3 with dysplasia, 5 with adenocarcinoma, and 8 with invasive adenocarcinoma) who underwent surgery were retrospectively analyzed in terms of clinicopathological features.

Main Outcome Measure: Clinical data, preoperative imaging findings, cytology, and tumor marker level, including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA19-9), in serum and pure pancreatic juice.

Results: In preoperative imaging findings, the mean tumor size for the malignant IPMT group (81±18 mm) was significantly larger than that for the benign IPMT group (31±4 mm) ($P=.002$). The mean mural nodule size for the malignant IPMT group (9.8±4.4 mm) was significantly larger than that for the benign IPMT group (3.3±5.7 mm) ($P=.002$). The CEA levels in pure pancreatic juice in the malignant IPMT group (3051±7556 ng/mL) were significantly higher than in the benign IPMT group (41±80 ng/mL) ($P=.003$), although no significant differences in cytologic analyses and CA19-9 levels in pure pancreatic juice were found between the 2 groups.

Conclusion: Our findings suggest that tumor size larger than 30 mm, mural nodule size larger than 5 mm, and CEA levels higher than 110 ng/mL in pure pancreatic juice were predictive factors for diagnosis of malignant IPMTs.

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SELECTION OF A SURGICAL PROcedure for treating intraductal papillary mucinous tumors (IPMTs) still remains controversial, because IPMTs show a wide spectrum of histological characteristics, ranging from hyperplasia to invasive carcinoma.[1-3] IPMTs are believed to have a favorable prognosis compared with ductal cell carcinoma.[3-5] However, IPMTs have a poor prognosis when invasive carcinoma derived from IPMTs has developed.[5-8] The biologic behavior of IPMTs remains unclear. Previous studies have been performed to differentiate malignant IPMTs from benign IPMTs by retrospective investigations of clinical data, imaging findings,[1,9-15] cytologic analyses in pure pancreatic juice,[16] or molecular analysis.[17] Consequently, no consensus concerning early diagnosis of malignant IPMTs has been attained as yet. Moreover, a simultaneous analysis of these factors has not been performed, to our knowledge. We simultaneously retrospectively analyzed clinical data, imaging findings, cytologic analyses, and tumor markers in pure pancreatic juice. The aim of the present study was to determine preoperative factors that are predictive for the early diagnosis of malignant IPMTs.

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METHODS

From January 1, 1999, to May 31, 2003, 27 patients with IPMTs were treated at Wakayama Medical University Hospital, Wakayama, Japan. Clinicopathologic data were reviewed to determine the age, sex, symptoms, and presence of other pancreatic disease. All patients underwent ultrasonography (US), computed tomography (CT), endoscopic US, and endoscopic retrograde pancreatography (ERP) for