厚生労働科学研究費補助金

医療技術実用化総合研究事業

顆粒球コロニー刺激因子(G-CSF)による急性心筋梗塞治療の効果と安全性に関する臨床研究

(H20-トランス--一般-005)

平成 20年度～21年度　総合研究報告書

研究代表者　高野 博之

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顆粒球コロニー刺激因子(G-CSF)による急性心筋梗塞治療の効果と安全性に関する臨床研究

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研究要旨　虚血性心疾患による心不全の病態に心臓リモデリングが重要な役割をはたしている。これまで世界中の研究グループが心臓リモデリングの治療法を検討してきたが、現存の薬物療法では心臓リモデリングおよび心不全を十分抑制することはできない。我が国でも虚血性心疾患の患者数は増加傾向にあることから、強力に心不全の進展を抑制できる新しい抗リモデリング薬の開発が待たれる。申請者のグループは造血性サイトカインである顆粒球コロニー刺激因子 (granulocyte colony-stimulating factor; G-CSF) が白血球数の増加作用だけでなく臓器保護作用、血管新生作用、抗アポトーシス作用なども有することを明らかにし、急性心筋梗塞後の心臓において血管新生や心筋細胞と血管細胞のアポトーシスを抑制することにより心臓リモデリングを強力に抑制することを報告した。また、心臓に対する G-CSF の分子機序を世界で初めて報告した。

急性心筋梗塞後の心不全に対するG-CSF治療を臨床応用させるためには、申請者らがおこなってきた基礎研究の結果をもとに最も効果的なプロトコールで大規模臨床研究をおこないG-CSFの安全性と効果を確認する必要がある。本研究では100症例の急性心筋梗塞患者を対象に6ヵ月後の心臓の機能やサイズを比較検討する。登録開始から解析終了までの期間は2年間を予定している。本研究で目指している治療法は特殊な設備や技術を必要とせず、投与方法も血管への注射ですむため一般病院でも実施が可能である。このような利点から治療を受けられる患者数も膨大なものになると予想される。本研究の成果は、市場における心不全治療薬の製品戦略にも大きな変革をもたらし医療経済にも好影響を及ぼすと期待される。

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A. 研究目的

さまざまな心血管疾患が心不全に進展する際に心臓リモデリングが重要な役割をはたしている。神経液性因子のレニン- アンジオテンシン系やカテコラミンが一部関与していることから、これらの作用を抑制する薬物が心不全の治療薬として用いられているがその効果は十分ではない。より効果的な新規の抗リモデリング薬を開発することは今後、心不全患者数の増加が予想される我が国において急務の課題である。これまで申請者らはマウスやブタを用いた動物実験で、造血性サイトカインである顆粒球コロニー刺激因子 (granulocyte colony-stimulating factor; G-CSF) が急性心筋梗塞後の心臓において血管新生や心筋細胞と血管細胞のアポトーシスを抑制することにより心臓リモデリングを強力に抑制することを明らかにした (Ohtsuka M, et al. FASEB J. 2004; Iwanaga K, et al. Biochem Biophys Res Commun. 2004)。その分子機序として G-CSF は心筋細胞に存在する G-CSF 受容体を介して直接作用し保護効果をもたらすことを世界で初めて報告した (Takano H, et al. Nat Med. 2005)。

申請者は、実際に急性心筋梗塞患者を対象にG-CSFの安全性と効果を確認してきたが40例という少数例での解析結果であり (Takano H, et al. Int. J. Cardiol. 2007)、臨床応用させるためには大規模臨床研究により安全性と効果を再検討する必要がある。海外でも臨床研究がおこなわれているが、治療プロトコールが異なるため結果については一定の見解に至っていない (Takano H, et al. Trends. Pharmacol. Sci. 2007)。申請者らの基礎研究と臨床研究の結果からは、急性心筋梗塞発症後からG-CSF治療を開始するまでの時間と心機能の改善度には逆相関が認められたが、海外での臨床研究ではG-CSF.開始までの時間に注意が払われていない。海外の臨床研究の結果を検討してみると、興味深い事にpositiveな結果が得られた研究ではG-CSF開始までの時間が比較的早く、一方、negativeな結果が得られた研究では開始時間が遅い傾向にある。本研究では100症例の急性心筋梗塞患者を対象に6ヵ月後の心臓の機能やサイズを比較検討する。登録開始から解析終了までの期間は2年間を予定している。

B. 研究方法

1. 被験者を選ぶ方針および目標数

被験者は、千葉県救急医療センターに入院中の急性心筋梗塞患者で、発症後 12 時間以内にインターベンション治療を施行し再開通が得られた患者。80 歳未満の男性および女性。目標症例数は 100 例（G-CSF 群：50 例、コントロール群：50 例)。ただし、以下の項目に該当する場合は適応から除外する。インターベンション治療終了後も心電図の変化を伴う胸痛が持続する場合。急性冠閉塞の可能性がある場合。心原性ショックの場合。問診にて悪性新生物を合併している（または治療中である）ことが確認された場合。問診にて糖尿病性網膜症を治療中であることが確認された場合。問診にて重篤な薬剤アレルギーの既往が確認された場合。インフォームドコンセントが得られない場合。本研究は千葉大学医学部附属病院未来開拓センターを中心に実施し、研究プロトコールは臨床試験部で厳格に検証をおこない医師主導の臨床研究を成功させることを目指す。

2. 研究方法

(1) 実施方法

①投与方法

急性心筋梗塞発症後、24 時間以内に 1 回目の G-CSF を静脈注射する（この日を day1 とする)。1 回の投与量は 10 μg/kg とする。1 日 1 回、計 5 日間（day1 から day5 まで）連続投与する。計 5 回終了する前に白血球数が 40,000/μl を越えた場合は、その時点で G-CSF の投与は中止とする（臨床研究としては継続)。

②前処置および併用薬の有無

a) 前処置は特に必要としない。
b) ヘパリンを急性心筋梗塞発症後、3 日目まで使用（1 日 15,000 U div)。
c) 併用薬として、ACE 阻害薬（レニベース)、バイアスピリンまたは小児用バファリン、パナルジンを服用する。
d) ACE 阻害薬と ARB の併用はしない（レニベースが忍容性の問題で使えない場合はディオバンのみ使用する)。量は設定せず血圧値に応じて増減。
e) 硝酸薬、Ca 拮抗薬、β遮断薬、スピロノラクトン、スタチンに関しては特に制限を設けず、必要に応じ使用する。他の薬剤についても特に制限は設けない。

③臨床検査項目および観察項目

a) 血液、尿検査-血液検査一般、特に血算、血小板凝集能、CK(CK-MB)、LDH、肝機能、腎機能など。
CK の採血時期はピークまでは 3 時間おきに施行。WBC 数および分画は入院時から day7 まで毎朝測定する。$CD34^+$細胞数は day1 と day5 の朝に測定する。
b) 冠動脈造影検査-入院時（インターベンション治療時）と 6 ヵ月後に施行。
c) MRI 検査と RI 検査を急性心筋梗塞発症 5-7 日後と 6 ヵ月後に施行。
d) 心エコー検査。

④有効性評価項目

a) 1 次エンドポイント（主要評価項目）
梗塞後の心臓リモデリングの抑制- MRI 検査、左室造影検査にて評価。
b) 2 次エンドポイント
・梗塞領域の縮小-RI 検査による定量的評価。
・心血管イベント (MACE) の減少-心臓死、非致死的心筋梗塞、不安定狭心症、心不全による入院、致死的不整脈。

(2) 研究デザイン

無作為割付臨床試験：最小化法を用いた無作為割付により、2 群（G-CSF 群とコントロール群）に分ける。薬剤の投与は二重盲検法 (double-blind method) により実施する。

（倫理面への配慮）

本研究は千葉大学医学部附属病院未来開拓センターを中心に実施し、研究プロトコールは臨床試験部で厳格に検証をおこない、医師主導の臨床研究を成功させることを目指す。

(1) 予想される結果および危険

これまでの基礎研究の結果から、人においても G-CSF の投与により心筋梗塞後の心臓リモデリングの抑制効果が期待される。G-CSF 製剤はすでに臨床の場で使用されており、これまでに蓄積されたデータから副作用に関する頻度は低いと思われる。危険性も極めて低いと考えられるが、治療中および治療後は G-CSF による副作用の早期発見に努める。また重篤な副作用が発生した場合は、その被験者に対する G-CSF の投与は直ちに中止し、副作用に対する治療に努める。

(2) 個人情報の保護

本研究の成果は医学雑誌や学会などを通じて公表されるが、その際に患者の名前や身元が明らかになることはなく被験者のプライバシーは保護される。

(3) インフォームド・コンセントのための手続きおよび方法

インフォームド・コンセントのための手続きとして、まず文書ならびに口頭で説明を行い、十分理解を得た上で、文書による同意を得る。

C. 研究結果

当初の研究計画では、平成 20 年度中に臨床研究開始前の準備を全て終了させて患者登録を開始する予定であった。しかし、以下の挙げる理由により若干の遅れが生じている。進捗状況として平成 20 年度は実施施設の倫理審査委員会に臨床試験計画書を提出し承認された。また、申請者が所属する千葉大学の利益相反委員会に書類を提出し利益相反がないことの承認を得た。登録患者をG-CSF群とコントロール群の2群にランダムに割り当てるソフトを作成しPCにインストールした。試験実施担当者と数回にわたり本研究の打ち合わせをおこなった。本研究で使用するG-CSFと生理食塩水を購入し実施施設に納品した。平成20年度中には目標症例数の1/3 位の登録を予想していたが、倫理審査委員会および利益相反委員会の実施が遅れてしまい承認までに時間がかかった事、実施施設での検査機器（心臓の評価に使用するRI機器）の修理・点検が1ヶ月ほどあったため承認後から試験開始までに間があいてしまった事、などの理由により平成 21 年度より症例登録が開始された。まだ目標の 100 例に達しておらず現在も患者の登録を継続して行っている。

D. 考察

急性心筋梗塞に対するインターベンション治療法の進歩により急性期の死亡率は減少したが、一方で心筋梗塞後に生じる心臓リモデリングにより心不全を発症する患者が増加傾向にある。心臓リモデリングに対する現存の薬物療法は効果が不十分であり、心不全患者は入退院を繰り返すことが多いため医療経済的にも今後の重要課題となることが予想される。

G-CSFの臓器保護・再生作用を利用した治療法は簡便でかつ侵襲が少なく現実的に実行可能である。本研究で目指している治療法は特殊な設備や技術を必要とせず、投与方法も血管への注射ですむため一般病院でも実施が可能である。我が国でも急性心筋梗塞患者数は増加しており、G-CSF治療を受けられる患者数は膨大なものになると予想される。G-CSFは救命された心筋梗塞患者の心不全発症を予防し、その後のQOLの改善をもたらす新規の治療法となるものと思われる。本研究の成果は、国民の医療や福祉の向上のみならず、市場における心不全治療薬の製品戦略にも大きな変革をもたらし医療行政や経済にも好影響を及ぼすと期待される。

E. 結論

本研究を遂行することにより、G-CSFが急性心筋梗塞後の心不全抑制薬として実用化できるか明らかになる。

F. 健康危険情報

特になし。

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H. 知的財産権の出願登録状況

なし。

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Utsumi T, et al.	Abdominal aortic pseudoaneurysm caused by prolonged methicillin-resistant *Staphylococcus aureus* sepsis.	Int J Cardiol	128	294-5	2008
Fujita T, et al.	Takayasu Arteritis evaluated by multi-slice computed tomography in an old man.	Int J Cardiol	125	286-7	2008
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Letter to the Editor

Abdominal aortic pseudoaneurysm caused by prolonged methicillin-resistant *Staphylococcus aureus* sepsis

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Abstract

The mechanism of pseudoaneurysm formation caused by prolonged sepsis is thought to be related to the vascular endothelium being directly invaded and broken by bacteria. Moreover, matrix metalloproteinases (MMPs) which are up-regulated by chronic inflammation have been reported to be implicated in the pathogenesis of aneurysm development through increased proteolysis of extracellular matrix proteins. An effective treatment for infected pseudoaneurysm remains unsettled. Surgery is generally performed, however, because the patients in most of these cases are in very poor physical condition, the operation is associated with high morbidity and mortality. A more successful alternative is endovascular treatment. Recent reports indicate low morbidity and mortality rates with this treatment. If the patient in this case had been in better condition, we could have selected endovascular stent-grafting for her treatment.

Keywords: Pseudoaneurysm; Multi-slice CT; Matrix metalloproteinases

1. Case report

In October 2006, a 77-year-old woman underwent pancreatoduodenectomy for a malignant pancreatic tumor. On the 8th postoperative day, her temperature was 39.3 °C. At that time, laboratory tests showed a white cell count of $1.82 \times 10^4/\mu l$ and a C-reactive protein (CRP) of 5.6 mg/dl. The central venous catheter tip and blood cultures were positive for methicillin-resistant *Staphylococcus aureus* (MRSA). In view of antibiotic sensitivity test results, arbekacin (ABK) was the most sensitive to MRSA and the treatment with ABK was started. On the 13th postoperative day, she suddenly complained of right inguinal pain and lumbar pain. Abdominal and pelvic X-ray revealed no abnormal findings. A 64-slice computed tomography (CT) resulted in the same (Fig. 1A and B). However, the patient continued to complain of the lumbar pain. A second series of blood cultures made after 15 days of the treatment with ABK were still positive for MRSA. Therefore, ABK treatment was changed into vancomycin (VCM). On the 31st postoperative day, the 64-slice CT for the second time showed that a 2.1-cm false aneurysm of abdominal aortaproximal to the divergence of common iliac artery (Fig. 1C and D). We consulted cardiac surgeons about indication of the surgery, however, surgery was ruled out owing to her greatly weaken condition. Although medication was continued, patient's hypotension and MRSA sepsis were not controlled. On the 72nd postoperative day, she died of progressive renal failure.

2. Discussion

Pseudoaneurysm is usually known to be caused by trauma [1] and surgical treatment [2] but rarely MRSA infection.

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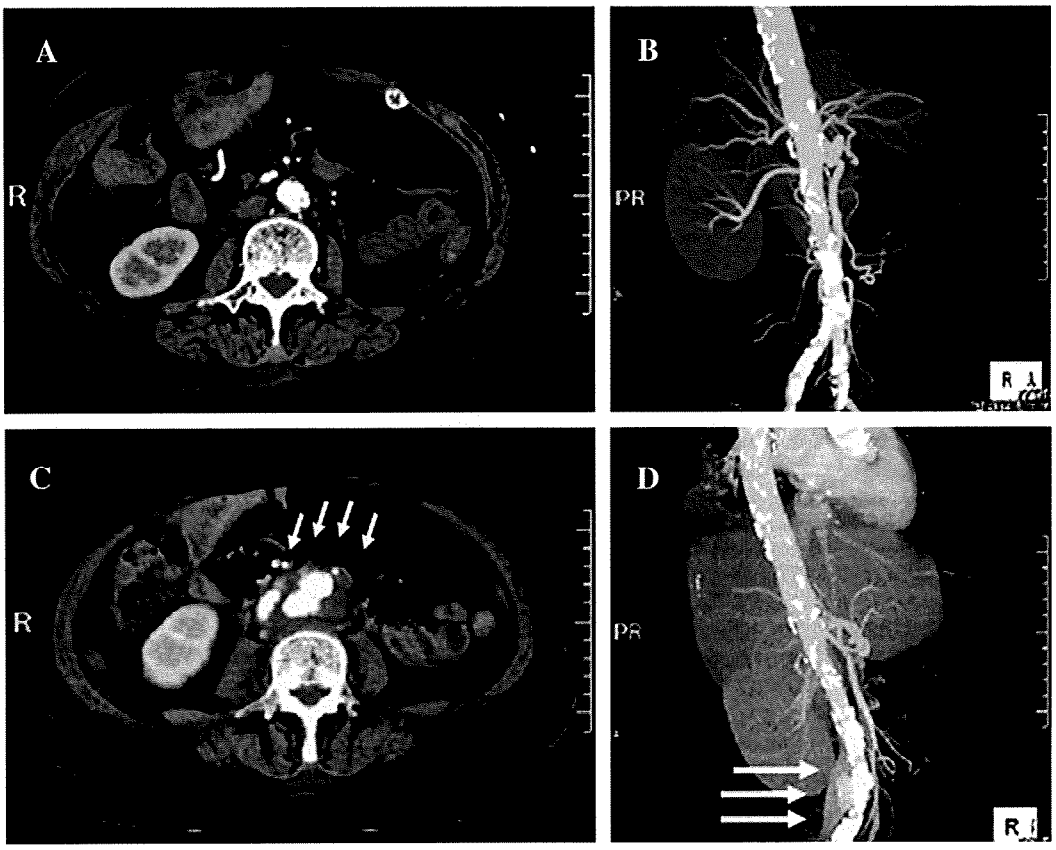

Fig. 1. Multi-slice CT changes shown in abdominal aortic pseudoaneurysm. A 64-slice CT revealed no abnormal findings (A, B). On the 31st postoperative day, the 64-slice CT for the second time showed that a 2.1-cm false aneurysm of abdominal aorta proximal to the divergence of common iliac artery (arrows) (C, D).

This case was thought to have been caused by prolonged MRSA sepsis based on the comparison between CT findings for the first time (Fig. 1A and B) with for second time (Fig. 1C and D). Additionally, it was hardly possible that abdominal aorta had been injured by the surgical procedure in view of its site.

If we suspect pseudoaneurysm with infection, multi-slice CT may be a useful tool in detecting unexpected lesion in a non-invasive manner [3,4]. In fact, CT angiography was very helpful in detecting the pseudoaneurysm and we should further use multi-slice CT.

The mechanism of pseudoaneurysm formation caused by prolonged sepsis is thought to be related to the vascular endothelium being directly invaded and broken by bacteria. Moreover, matrix metalloproteinases (MMPs) which are up-regulated by chronic inflammation have been reported to be implicated in the pathogenesis of aneurysm development through increased proteolysis of extracellular matrix proteins [5].

An effective treatment for infected pseudoaneurysm remains unsettled. Surgery is generally performed, however, because the patients in most of these cases are in very poor physical condition, the operation is associated with high morbidity and mortality [6]. A more successful alternative is endovascular treatment. Recent reports indicate low morbidity and mortality rates with this treatment [6]. If the patient in this case had been in better condition, we could have selected endovascular stent-grafting for her treatment.

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Letter to the Editor

Takayasu arteritis evaluated by multi-slice computed tomography in an old man

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Abstract

In the case of patients with Takayasu arteritis (TA), they consult a doctor for the first time when they have a slight fever, shoulder pain, chest pain, back pain, or headache, or when they are pointed out to have high CRP or anemia by chance in medical check-up. In TA, they are usually young women. In our case, the very old patient had bilateral massive pleural effusion and aortic aneurysm with a 64-slice computed tomography (CT). TA commonly affects primarily large elastic arteries such as the aorta and its main branches. Steroid was very effective for suppression of inflammatory symptom being dose-dependent. His pleural effusion had been decreasing without reducing the size of aortic aneurysm. Multi-slice CT was a very useful tool to detect unexpected lesion in Takayasu arteritis in a non-invasive manner.

Keywords: Takayasu arteritis; Multi-slice CT; Matrix metalloproteinases

1. Case report

In August 2007, a 94-year-old man was admitted to the hospital with low appetite, left shoulder pain and slight fever rising. He had hypertension, but his eye ground findings were not particular. He didn't show extremities claudication, bruit, blood pressure asymmetries and pulse asymmetries. White blood cell counts, liver and renal function were normal. He had inflammatory anemia (Hb 8.8 g/dl, UIBC 81 μg/dl, TIBC 95 μg/dl) and high C-reactive protein (CRP) (9.4 mg/dl). His antinuclear antibody was positive (320 times) and his complement activity was low in blood serum. On the other hand, bacterial culture and other evidence for secondary vasculitis due to other inflammatory indicators (p-ANCA, c-ANCA) were negative. Ultrasonic echocardiography showed only mild left ventricular hypertrophy due to hypertension. It did not show aortic regurgitation and normal left ventricular wall motion. A 64-slice computed tomography (CT) showed bilateral massive pleural effusion and aortic aneurysm with mural thrombus (arrow in Fig. 1A) and wall thickening in aortic arch (arrowhead in Fig. 1B). But we had detected no stenosis on the three branches of aortic arch and no abdominal aortic aneurysm. We had thought that he had inflammatory aortic aneurysm (vasculitis syndrome) and we made a diagnosis of a part of aortic arch syndrome (Takayasu arteritis: TA) with diagnostic criteria by the Ministry of Health and Welfare in Japan. We administrated predonisolone (PSL) 20 mg/day which decreased the fever and CRP decreased from 14.1 to 1.1 for 20 days. His pleural effusion had been decreasing without reducing the size of aortic aneurysm and we controlled PSL 20 mg. Steroid was very effective for suppression of inflammatory symptom being dose-dependent.

2. Discussion

In case of patients with aortic arch syndrome, they consult a doctor for the first time when they have a slight fever,

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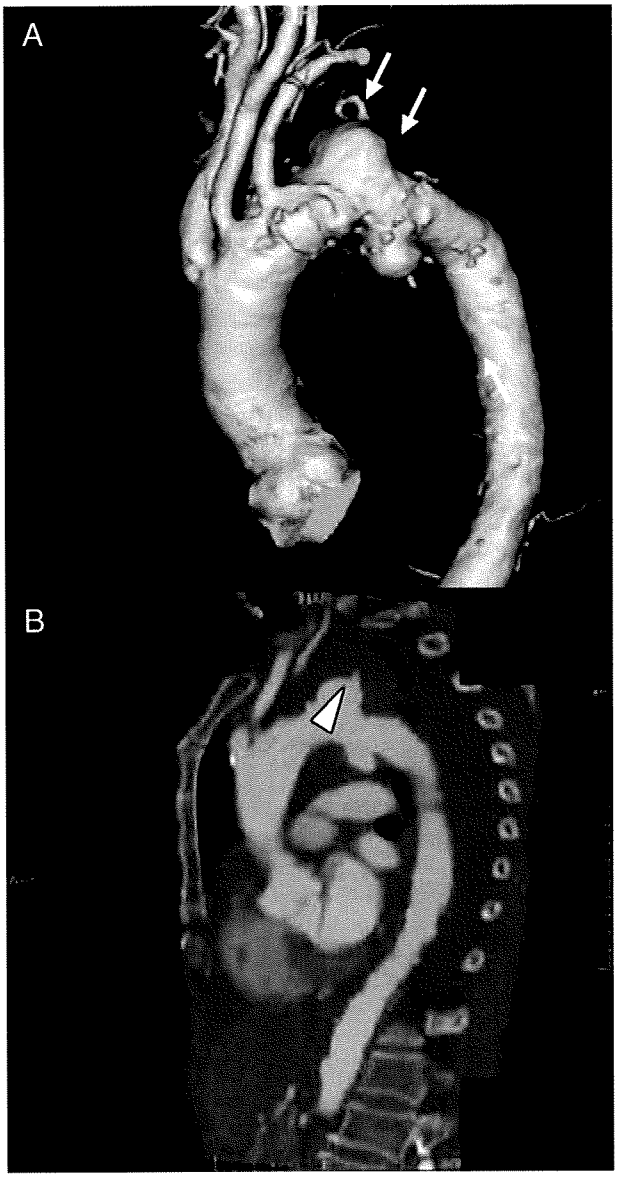

Fig. 1. (A) A 64-slice computed tomography (CT) showed massive aortic aneurysm (arrows), and (B) wall thickening in aortic arch (arrowhead).

shoulder pain, chest pain, back pain, or headache, or when they are pointed out to have high CRP or anemia by chance in medical check-up. In TA, women aged 20–30 years old are usually affected [1], and an old man in this case is very unique.

TA commonly affects primarily large elastic arteries such as the aorta and its main branches. We differentiated it from typical atherosclerosis, a disease much more likely to affect the lower extremity large vessels than the arms and the abdominal aorta than the aortic arch and root. Aneurysms are the most common and clinically most significant in the aortic root, where they can lead to valvular regurgitation. The earliest histological change appears to be a granulomatous inflammation in the adventia and outer layers of the affected arteries, followed by gradual progression to a panarteritis with inflammatory mononuclear cell infiltration. Inflammation and subsequent neointimal proliferation (intimal thickening) result in stenotic or occlusive lesions, whereas destruction of the elastica and muscularis may form dilatation or aneurysms [2]. In this process, proteases secreted from infiltrated cells are thought to play some role in the destruction of elastic fibers. Recently there was a report that matrix metalloproteinases (MMPs) are involved with inflammatory processes [3].

If they don't have appropriate therapy by steroid and inflammatory symptom is not well controlled, ischemic symptom, hypertension, and cardiac failure appear with progression of the disease. Multi-slice CT was a very useful tool to detect unexpected lesion in Takayasu arteritis in a non-invasive manner [4,5].

Because our patient was an old man, we did not expect that he had Takayasu arteritis. Since CT angiography was very helpful in detecting the aortic arch syndrome, we should further use multi-slice CT.

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Letter to the Editor

Active myocarditis in a patient with chronic active Epstein–Barr virus infection

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Abstract

Chronic active Epstein–Barr virus (CAEBV) infection is characterized by chronic or recurrent infectious mononucleosis-like symptoms and the prognosis of CAEBV infection is quite poor. The incidence of myocarditis as a complication of EBV infection is not so high and it is unusual that heart failure appears as the initial symptom. However, it is very important to detect and treat chronic active myocarditis in the early phase of CAEBV infection because chronic active myocarditis disorganizes and decreases cardiomyocytes, resulting in the progression to heart failure. We report a case of a 45-year-old man with CAEBV infection for 5 years. Echocardiography revealed moderate left ventricular systolic dysfunction with mild pericardial effusion. Endomyocardial biopsies demonstrated massive lymphocytic infiltration with adjacent myocytolysis and necrosis of cardiomyocytes suggesting active myocarditis. Immunohistological analysis of biopsies revealed that the infiltrating cells were mainly T lymphocytes. And some of the infiltrating cells showed a positive signal for the EBV-encoded small nuclear RNA by *in situ* hybridization. Positron emission tomography using ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) performed revealed increased uptake of ^{18}F-FDG of whole left ventricular wall with mild heterogeneity.

Keywords: Biopsy; Epstein–Barr virus; Myocarditis; PET

1. Introduction

Epstein–Barr virus (EBV), a ubiquitous virus classified as a γ-herpesvirus, causes infectious mononucleosis and post-transplant lymphoproliferative disorder. Chronic active EBV (CAEBV) infection is characterized by chronic or recurrent infectious mononucleosis-like symptoms and by an abnormal pattern of anti-EBV antibodies with high titers to virus capsid antigen (VCA) and early antigen (EA), and low titers to Epstein–Barr nuclear antigen (EBNA) [1]. The prognosis of CAEBV infection is quite poor and the major causes of death are liver failure and haemophagocytic syndrome.

2. Case report

A 45-year-old man has had fever of unknown origin and general malaise for 5 years from 2000. He was diagnosed as having CAEBV infection because of his symptoms and the abnormal patterns of anti-EBV antibodies in 2003 and followed up without any medication. He developed fever, dyspnea on exertion, general malaise, and hepatosplenomegaly in April 2005. Antibody titer tests against EBV revealed EBVVCA-IgG ×10,240, EBVEA-IgG ×640, and EBNA ×10. As his symptoms persisted despite treatment with prednisolone, he was admitted to our hospital in September 2005 for evaluation of heart failure and further treatments with chemotherapy. The ECG on admission displayed atrial fibrillation and sporadic ventricular premature contractions. Echocardiography revealed moderate left ventricular (LV)

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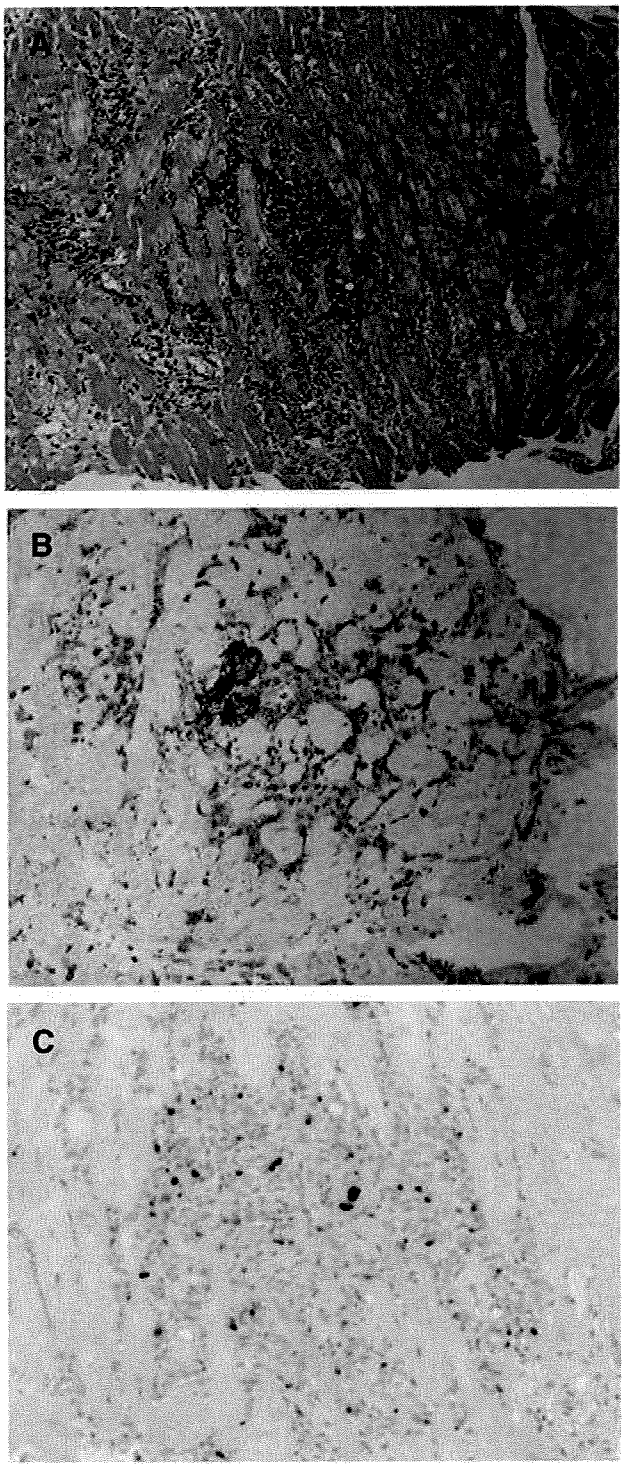

Fig. 1. Histological results of endomyocardial biopsies. A, Histology (hematoxylin and eosin staining) demonstrated active myocarditis with focal lymphocytic infiltration with adjacent myocytolysis (×100). B, Immunohistological staining of CD45RO/UCHL-1^{+} T cells with focal infiltration pattern (×100). C, *In situ* hybridization study for Epstein–Barr virus-encoded small RNA in T cells (×200).

systolic dysfunction with mild pericardial effusion. Endomyocardial biopsies obtained from the LV demonstrated massive lymphocytic infiltration with adjacent myocytolysis and necrosis of cardiomyocytes suggesting active myocarditis (Fig. 1A). Immunohistological analysis of biopsies revealed that the infiltrating cells were mainly T lymphocytes (Fig. 1B). And some of the infiltrating cells showed a positive signal for the EBV-encoded small nuclear RNA by *in situ* hybridization (Fig. 1C). Positron emission tomography (PET) using ^{18}F-fluoro-2-deoxyglucose (^{18}F-FDG) performed after overnight fasting and heparin sodium injection (2000 IU) revealed increased uptake of ^{18}F-FDG of whole LV wall with mild heterogeneity (maximum at lateral wall) (Fig. 2). Since his liver dysfunction got worse in spite of prednisolone, immunochemotherapy with prednisolone, cyclosporin A, and etoposide was started. Although his physical condition and liver dysfunction were temporarily ameliorated, multiple organ failure and disseminated intravascular coagulation were accompanied later and he died 3 months after the admission.

3. Discussion

The patient was thought to have been suffering from CAEBV infection for 5 years. He did not have heart failure at first and the examination for cardiac function was not performed. The incidence of myocarditis as a complication of EBV infection is not so high and it is unusual that heart failure appears as the initial symptom [2,3]. However, chronic active myocarditis disorganizes and decreases cardiomyocytes, resulting in the progression to heart failure. It is very important to detect and treat chronic active myocarditis in the early phase of CAEBV infection. Endomyocardial biopsies are useful but invasive. ^{18}F-FDG PET images can detect myocardial inflammation such as sarcoidosis and myocarditis when obtained at fasting state [4]. Although recent studies demonstrated that contrast-enhanced cardiac magnetic resonance is useful to detect acute myocarditis, late enhancement is mainly related to myocardial necrosis and interstitial edema characterizing the acute phase of inflammatory process [5]. In contrast, non-physiological myocardial uptake of ^{18}F-FDG under the fasting condition may indicate the activity of myocardial inflammation. In the present case, the results of the biopsy specimens and ^{18}F-FDG PET images of the patient revealed myocardial inflammation suggesting the existence of myocarditis. To our knowledge, this is the first report indicating the usefulness of endomyocardial biopsy and ^{18}F-FDG PET in the identification of myocarditis with CAEBV infection.

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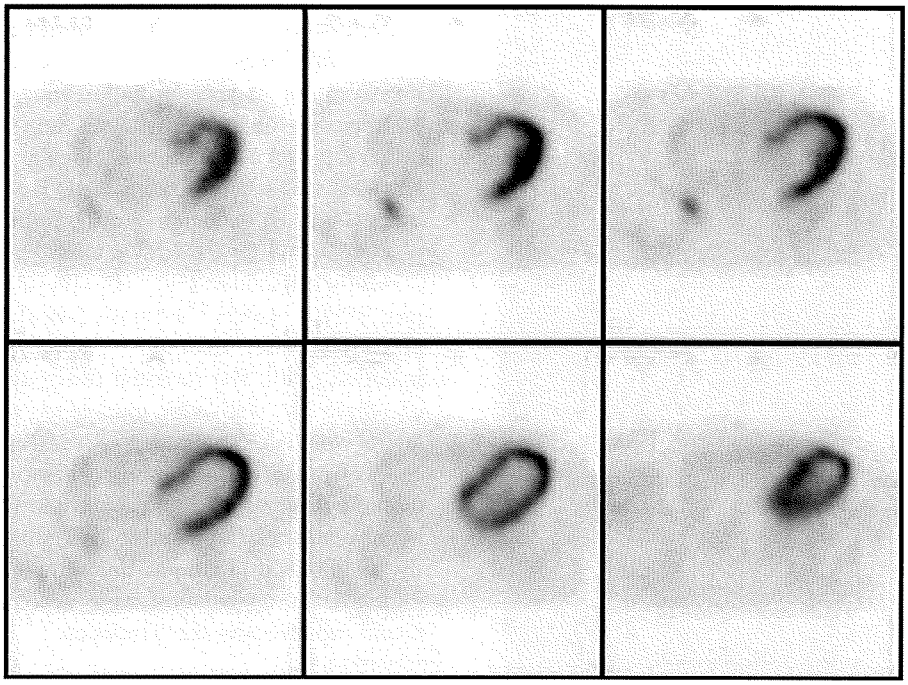

Fig. 2. Transaxial view of cardiac ^{18}F-FDG PET. Diffuse uptake of ^{18}F-FDG of the left ventricle with mild heterogeneity (maximum at lateral wall) was observed even after overnight fasting with heparin sodium injection.

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G-CSF therapy for acute myocardial infarction: Studies of animal experiments give valuable hints to clinical trials

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Abstract

Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine that promotes proliferation and differentiation of neutrophil progenitors. Clinically, hematopoietic stem cells mobilized by G-CSF are widely used for transplantation. G-CSF has been reported to mobilize bone marrow stem cells and regenerate infarcted hearts of mice. Besides mobilization, G-CSF has activated various signaling pathways such as Akt and Janus family kinase-2/signal transducer and activator of transcription-3 through G-CSF receptors in cardiac myocytes and has markedly prevented left ventricular remodeling after acute myocardial infarction by decreasing cardiomyocyte death and increasing the number of vessels. Although several clinical trials have been performed, the efficacy of G-CSF therapy in patients with acute myocardial infarction is still controversial.

Keywords: Angiogenesis; G-CSF; Heart failure; Myocardial infarction; Remodeling

To the Editor,

We are very grateful to Dr Celik et al. [1] for their comments concerning our article [2]. We agree that the clinical consequences of G-CSF therapy and cell therapy on left ventricular (LV) dysfunction and remodeling after acute myocardial infarction (AMI) are yet uncertain. Especially, the efficacy of G-CSF therapy in patients with AMI remains controversial because the protocols are different among the trials. It was reported that the subcutaneous injection of both G-CSF and stem cell factor (SCF) improved cardiac function and reduced mortality after AMI in mice [3]. G-CSF treatment started immediately after AMI (permanent ligation of left coronary artery) was as effective as the treatment started before AMI and that the treatment with G-CSF alone also has beneficial effects by similar degree as the combination treatment of G-CSF and SCF in mice [4]. The number of apoptotic cells was decreased in the border area of the G-CSF-treated hearts after AMI. Although many bone marrow-derived cells were recognized in the border area of the treatment group but not the control group, most of the bone marrow-derived cells were infiltrated blood cells and some cells were endothelial cells [4]. The number of capillaries in the border area after AMI was much greater in the treatment group than in the control group. Beneficial effects of G-CSF were significantly larger when the G-CSF treatment was started earlier after AMI [5]. The treatment started at 3 days after AMI was less effective than that started immediately after AMI and the treatment started at 7 days after AMI had almost no effects [5]. Therefore, we think that the timing of starting G-CSF treatment is very important. Other groups have also reported the beneficial effects of G-CSF on the prevention of LV remodeling and dysfunction after AMI in various animal models [6,7].

Based on the experimental results in animal models, clinical trials evaluating feasibility and safety of G-CSF in patients with AMI have been carried out [2,8–14]. However, the efficacy of G-CSF therapy for patients with AMI is still controversial because the protocols are different among those trials. Unexpectedly, it was reported that high rate of in-stent restenosis in patients with AMI or old MI, who were subjected to subcutaneous injections of G-CSF for 4 days before percutaneous coronary intervention (PCI) [8]. In the study, patients did not receive primary PCI during the golden time of AMI treatment and were treated with G-CSF for 4 days prior to PCI and only a few patients were assessed by coronary angiography at 6-months follow-up [8]. G-CSF treatment for 5 days induced serious adverse events in high-risk patients with severe coronary artery disease in a non-randomized study [9]. Since all 16 patients had Canadian Cardiovascular Society (CCS) functional class 3 or 4 angina despite prior revascularization, there is a possibility that they had many destabilized plaques in their coronary arteries [9]. However, the safety of G-

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CSF treatment for patients with coronary artery disease such as AMI and angina pectoris has been proven by clinical trials performed afterwards [2,10–14]. Occurrence of restenosis was not significantly different between the G-CSF group and the control group and no severe adverse effects were observed in the G-CSF group [2,10–14].

There were some differences in infarct-related artery, TIMI flow grade and the time from AMI to G-CSF administration in the randomized trials [2,10–14]. The rate of left anterior descending coronary artery-related MI was equal between the G-CSF-treated group and the control group, and Thrombosis in Myocardial Infarction (TIMI) flow grade 3 was documented in all patients after PCI in the trials that showed positive results [2,11]. Many investigators thought that G-CSF inhibits LV remodeling and dysfunction after AMI by accelerating cardiac regeneration in the infarcted hearts and did not pay much attention to the timing of G-CSF administration. The trials in which G-CSF treatment was started early after MI seemed to show positive results [2,10,11], whereas the trials in which G-CSF treatment was started late after MI showed negative results [12–14]. Interestingly, our clinical data demonstrated that there were inverse correlations between time from AMI to G-CSF administration and absolute change in LV ejection fraction (ΔLVEF), and between time from PCI to G-CSF administration and ΔLVEF [2,15]. The beneficial effects of G-CSF were significantly reduced when the G-CSF treatment was started late (after 3 days) in AMI mice model as mentioned above [5] and the experimental results are consistent with our clinical data. In most animal studies, the administration of G-CSF was indeed started immediately or within several hours after AMI [4–7]. These results suggest that the timing of the treatment should be very critical to obtain the most beneficial effects of G-CSF, because the cardioprotective effects of G-CSF might be mainly attributable to the direct action on myocardium.

The appropriate protocol should be strictly determined to assess the feasibility and safety of novel therapies such as G-CSF therapy and cell therapy for coronary heart diseases. It has not yet been determined how much dose of G-CSF should be used and when the treatment should be started. And the duration of therapy and the method of administration (e.g. subcutaneous, intravenous or intracoronary) have also yet to be determined. It remains unknown which modality is most appropriate to evaluate the effects of G-CSF and when the evaluation should be performed. Further studies with more rational designs are needed to conclude on the efficacy of G-CSF therapy for AMI. Studies of animal experiments will give valuable hints to clinical trials.

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Peroxisome Proliferator-Activated Receptor γ and Cardiovascular Diseases

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Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily and form heterodimers with retinoid X receptor. Three PPAR isoforms have been isolated and termed α, β (or δ) and γ. Although PPARγ is expressed predominantly in adipose tissue and associated with adipocyte differentiation and glucose homeostasis, PPARγ is also present in a variety of cell types. Synthetic antidiabetic thiazolidinediones (TZDs) are well known as ligands and activators for PPARγ. After it was reported that activation of PPARγ suppressed production of pro-inflammatory cytokines in activated macrophages, medical interest in PPARγ has grown and there has been a huge research effort. PPARγ is currently known to be implicated in various human chronic diseases such as diabetes mellitus, atherosclerosis, rheumatoid arthritis, inflammatory bowel disease, and Alzheimer's disease. Many studies suggest that TZDs not only ameliorate insulin sensitivity, but also have pleiotropic effects on many tissues and cell types. Although activation of PPARγ seems to have beneficial effects on cardiovascular diseases, the mechanisms by which PPARγ ligands prevent their development are not fully understood. Recent data about the actions and its mechanisms of PPARγ-dependent pathway in cardiovascular diseases are discussed here. (*Circ J* 2009; **73:** 214–220)

Key Words: Atherosclerosis; Cardiac hypertrophy; Heart failure; PPARγ; Thiazolidinedione

Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily that heterodimerize with the retinoid X receptor (RXR) and bind to specific response elements termed PPAR responsive elements (PPREs) in target gene promoters. The PPREs are direct repeats of the hexameric consensus sequence AGGTCA, separated by 1 nucleotide. These nuclear receptors are ligand-dependent transcription factors, and activation of target gene transcription depends on the binding of the ligand to the receptor. PPARs have 3 isoforms, α, β (or δ) and γ. PPAR α regulates genes involved in fatty acid oxidation, whereas PPARγ promotes adipocyte differentiation and glucose homeostasis. The main function of PPARβ/δ has yet to be ascertained, but involvement in the regulation of fatty acid oxidation seems likely. PPARα is present mainly in the liver, kidney, and muscle, whereas PPARγ is expressed predominantly in adipose tissue. PPARβ/δ is almost ubiquitously expressed. It was recently demonstrated that PPARγ is also expressed in a variety of cell types. After it was reported that activation of PPARγ suppresses production of inflammatory cytokines in activated macrophages, medical interest in PPARγ has grown, along with a huge research effort.

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PPARγ

Peroxisome is a subcellular organelle that plays a crucial role in cellular metabolism. Peroxisome enzymes are implicated in a broad range of catabolic and anabolic enzymatic pathways, such as fatty acid oxidation, biosynthesis of both glycerolipids and cholesterol, and metabolism of reactive oxygen species. Peroxisome proliferation induced in rodents is associated with cellular responses to a range of chemical compounds. In 1990, Issemann and Green reported that peroxisome proliferators activate a member of the steroid hormone receptor superfamily in mouse liver! This nuclear receptor was named PPAR. Soon after, 3 major types of PPAR (α, β/δ, and γ) were recognized. PPARγ is associated with adipocyte differentiation and glucose homeostasis. PPARγ is expressed in a variety of cell types, including adipocytes, macrophages, vascular smooth muscle cells (VSMCs), endothelial cells (ECs), and cardiomyocytes[2–7] Several lines of evidence have demonstrated the functional significance of PPARγ in atherosclerotic lesions[8,9]

Activity of PPARγ is depressed by phosphorylation of a serine residue (Ser^{112}) in the N-terminal domain, mediated by a member of the mitogen-activated protein (MAP) kinase family, extracellular signal-regulated protein kinase (ERK). In addition, another member of MAP kinase family, c-Jun N-terminal kinase (JNK) also phosphorylates PPARγ at Ser^{82} and reduces the transcriptional activity of PPARγ. The association of PPARγ polymorphism with metabolic syndrome has also been examined![10,11] In the presence of ligand, PPARγ binds to coactivator complexes, resulting in the activation of target genes. In the absence of ligand, PPARγ binds to the promoters of several target genes and associates with a corepressor complex, leading to active repression of target genes. This process is referred to as active repression (**Fig 1**). The corepressor complex constitutes corepressor proteins, such as nuclear receptor corepressor