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陸沿岸部震災被災地域との皮膚科遠隔診療の試み
－陸前高田診療所（岩手県医師会）と岩手医科大学皮膚科との遠隔皮膚科診療－

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The trial of dermatological tele-medicine with Rikuzen-Takata clinic (Iwate medical association) in the Sanriku shore area where is the earthquake disaster stricken area and the dermatology of Iwate Medical University

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要旨

東日本大震災津波により壊滅的な被害を受けた陸前高田地域の皮膚科医は皆無となった。そこで、陸前高田診療所（岩手県医師会）と岩手医科大学皮膚科との遠隔皮膚科診療を試み、遠隔診療が医療過疎の解消の一助となるか検討した。通信方法は専用回線を用い、診療現場に検査機器、ムービーカメラ、照明器具を用い、岩手医科大学には皮膚科専門医が待機するシステムを構築して行った。その結果、1）遠隔医療機器システム立ち上げまでの時間は平均40分であった。2）1人の患者に要する遠隔医療の時間は平均34分であった。患者への説明と同意取得、診断機器や映像機器の切り替えに時間を要した。3）診断一致率は22例中21例が一致（95%）していた。診断確定に苦慮した例の多くは、①頭皮の毛髪間や指間、口腔内、陰部・鼠径部などの皮疹の焦点が合わない、②尋麻疹など淡い紅斑の色調あるいは常色の軽い扁平な盛り上がりが画像で認識しがたい、③アナフィラキシー紫斑病など微小点状出血は映像では不明瞭である、④悪性黒色腫の初期病変や軽症の太田母斑の淡い黒色斑や青色斑は映像で不明瞭である、⑤真菌検査の菌糸の画像が不鮮明である、などであった。これらの問題は診断を補助する機器の充実で改善すると考えられた。4）患者からの遠隔診療に対する評価はVASで66%であった。①大きなモニター画像に映し出され、おどろいた、②診察のスキンシップが感じられない、⑤診療時間が長すぎる、⑥カメラに追い回されている感じがする、などの意見があった。しかし、意見の多くは専門医の診察・判断を仰ぐことができ、安心感を示すものが多くみられた。本研究によって、他科の医師と機器操作に熟練した技術員の存在のもとに皮膚科遠隔医療が可能であることが示唆された。しかし、緊急に改善するべき、①遠隔医療に関する受診者の理解、②運用性に優れたムービーカメラの精度向上、などの問題点が提起された。

キーワード：東日本大震災津波、陸前高田地域、皮膚科遠隔診療、高性能ムービーカメラ、NTT専用回線

1. はじめに

岩手県三陸沿岸地域は以前から医療過疎地域であった。皮膚科診療を行する総合病院が5カ所（うち皮膚科常勤医は1人）、皮膚科開業医診療所が3カ所と皮膚科領域についても医療過疎地域であった。東日本大震災津波により壊滅的な被害を受けた三陸沿岸地域、特に陸前高田地域では開業医1人によって皮膚科診療が行われていたが、震災に被災し大都市に避難したため同地域には皮膚科医は皆無となった。一方、岩手医科大学附属病院は、「岩手県東日本大震災津波復興計画」のなかで、被災した医療過疎地域に対して皮膚科領域も含め医療情報機器等を活用した遠隔医療によって高度な専門医療を提供する役割を求められている。

一方、従来の皮膚科遠隔医療は個別的な支援や簡単な疾患の診断に留まっており、検査や診断・治療など総合的医療の提供はできていない。本研究では三陸沿岸部震災被災地域である陸前高田診療所（岩手県医師会）と岩手医科大学皮膚科との遠隔皮膚科診療を試み、遠隔診療が医療過疎の解消の一助となるかを検討した。

【図1】遠隔医療実証実験プロジェクト概要

2. 目的

本研究では、①被災した医療過疎地域において災害拠点病院である大学病院が皮膚科遠隔医療によって高度医療を安定的に提供するための施設・設備・人員体制・コスト等についての検討と②対面診療と比較した遠隔医療の質についての検討を行う。①においては、専用回線を用い、診療現場に検査機器、ムービーカメラ、照明器具を用い、これらの器材の使用法に熟練した人材がいることでことで、また、岩手医科大学には皮膚科専門医が2名待機するシステムを構築する。②においては、皮膚疾患患者を対象として、陸前高田診療所における皮膚科専門医による対面診療と遠隔診療とを比較検討する【図1】。

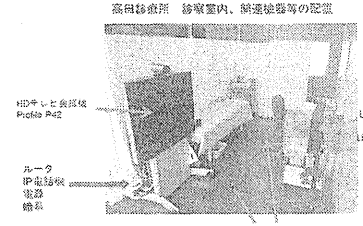
3. 方法

1. 研究倫理および記録保存

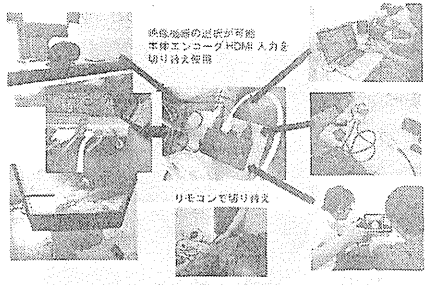
本研究は岩手医科大学倫理委員会の許可を得た。実験は患者のインフォームドコンセントを得て行う。患者情報や画像は匿名化し、個人を特定できないようにする。また、各患者の対面診療の動画は岩手医科大学情報センターにサーバー室を設けて保管した。医療情報は高田診療所の診療録に同診療所医師が記載し、同診療所に保管した。診療録の一部は患者および高田診療所の許可のもと、研究資料として用いた。

2. 利用回線および診療現場の器材

画像および医療情報の更新はNTT専用回線（NTT Business Ether）を使用した。実験に先駆けて、対面診療による問診のためにテレビ電話付き大型モニターを含むテレビ会議支援システム（フルHD（1080P/30fps））【図2】、患部の撮影のため2機の高性能ムービーカメラ、1機の接写カメラ、真菌検査および病理組織検査標本確認のためにオリンパス顕微鏡、患者情報記録のためノートパソコン、FAX機を設置した【図3】。それぞれを接続し、必要に応じてこれらの機器を切り替えて使用した。また、画像の色調を統一化、一定化するためにLED照明システムを使用した。これらのシステムで遠隔診断と医療提供が可能かを評価すると共にシステム設定にかかる時間も計測した。



【図2】高田診療所のシステム機器



【図3】高田診療所カメラの切り替え状況

3. 遠隔対面診療の評価方法

研究の大半は高田診療所に皮膚か専門医が出向き、インフォームドコンセントの取得、患者の問診、診療録記載、処方箋発行、皮膚検査、機器の設定、皮膚病変の撮影、岩手医科大学皮膚科専門医との交信を行い、以下について評価した。平成25年1月末まで計22人の皮膚科患者の診療を行った【図4】。

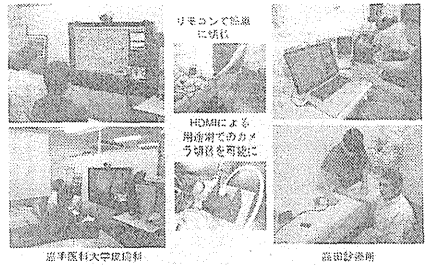
1）患者1人の診察時間

2）診断名：高田診療所と岩手医科大学の皮膚科専門医の診断の一致率

3）皮疹の部位で診断しにくい部位

4）皮疹の形態で診断しにくい皮疹

5）患者満足度（通常の対面診療と比較したVASで表示：100%が通常対面診療と同等、0%が全く対面診療に値しない）



【図4】皮膚科患者画像の送受信状況

4. 結果

1）診療前の遠隔医療機器システム立ち上げまでにかかる時間は平均40分であった。熟練すると短縮可能と考えられた。

2）1人の患者に要する遠隔医療の時間は最短26分、最長52分、平均34分であった。患者への説明と同意取得、診断機器や映像機器の切り替えに時間を要した。

3）診断一致率は22例中21例が一致（95%）していた。診断確定に苦慮した例の多くは、①頭皮の毛髪間や指間、口腔内、陰部・鼠径部などの皮疹の映像の焦点が合わない、②尋麻疹など淡い紅斑の色調あるいは常色の軽い扁平な盛り上がりが画像で認識しがたい、③アナフィラキシー紫斑病など微小点状出血は映像では不明瞭である、④悪性黒色腫の初期病変や軽症の太田母斑の淡い黒色斑や青色斑は映像で不明瞭である、⑤真菌検査の菌糸の画像が不鮮明である、などによるものであった。これらの問題は診断を補助する機器の充実で改善すると考えられた。

4）患者からの遠隔診療に対する評価はVisual Analog Scale（VAS）で66%であった。①大きなモニター画像に映し出され、おどろいた、②診察のスキンシップが感じられない、⑤診療時間が長すぎる、⑥カメラに追い回されている感じがする、などの意見があった。しかし、意見の多くは専門医の診察・判断を仰ぐことができ、安心感を示すものが多くみられた。

5. 考察

本研究の最終目標は遠隔地に皮膚科専門医がいない状況での遠隔診療である。他科の医師と機器操作に熟練した技術員の存在のもとに皮膚科遠隔医療が可能であることが示唆された。しかし、緊急に改善するべき以下の問題点が提起された。①遠隔医療に関する受診者の理解、②他科の医師の皮膚科遠隔医療に対する理解、③カメラ、検査機器、コンピュータの操作に熟練した技術員の存在、④患者誘導や発疹の選択に熟練した看護師の存在、⑤運用性に優れたムービーカメラの精度向上、⑥診断精度向上のための機器（皮膚温検査機、エコー機器など）の必要性、⑦画像および遠隔診療カルテの保存方法の改善、⑧診療費用の配分。

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Annular elastolytic giant cell granuloma developing on lesions of vitiligo

Dear Editor,

A 74-year-old woman presented with a two-year history of reddish annular nodules on the neck, trunk, and forearms. She had a 10-year history of generalized vitiligo that had been untreated. The nodules with elevated borders and central atrophy and hypopigmentation, 0.5–1 cm in diameter, were located on the neck, trunk, and forearms (Fig. 1). These nodules had developed mainly on the preexisting vitiligo lesions. The patient had been taking benidipine hydrochloride for hypertension for the last 14 years. She had no history of diabetes mellitus or sarcoidosis.

A skin biopsy was taken from a nodule on the forearm. Hematoxylin and eosin staining of the specimen showed a granulomatous infiltrate of lymphocytes, histiocytes, and multinucleated giant cells in the upper and middle dermis without palisading (Fig. 2a). Immunohistochemistry showed that the lymphocytes in the inflammatory infiltrate were positive for CD_3. CD_4^+ T-cells predominated over $CD8^+$ T-cells, and the histiocytes and multinucleated giant cells were positive for CD68. Almost all of the epidermal cells were negative for Melan-A (Fig. 2b). Slight mucin deposition was evident. Elastica van Gieson staining showed that elastic fibers were absent from the reticular dermis in the area surrounded by the granulomatous infiltrate (Fig. 2c). Fragmented elastic fibers were present within some of the histiocytes and multinucleated giant cells (Fig. 2d). Ziehl-Neelsen and PAS staining revealed no acid-fast bacilli or fungal organisms. Laboratory examinations, including a full blood cell count, routine biochemistry, fasting blood sugar level, and urinalysis gave normal results. These findings were consistent with

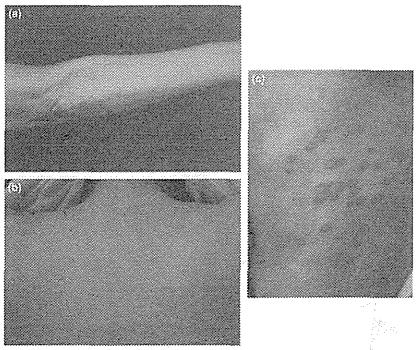

Figure 1 Multiple, erythematous, marginally elevated, annular nodules and round papules, developed mainly on lesions of preexisting vitiligo, distributed on the back (a), forearms (b) and abdomen (c)

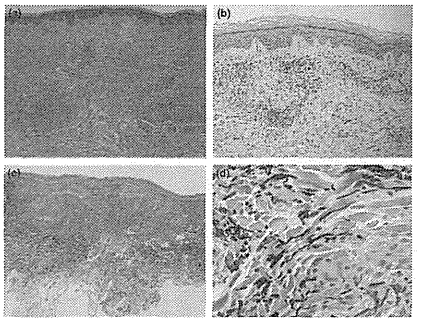

Figure 2 (a) Granulomatous infiltrates of lymphocytes, histiocytes and multinucleated giant cells in the upper and middle dermis without palisading (hematoxylin and eosin, original magnification ×40). (b) Almost all of the epidermal cells were negative for Melan-A (original magnification ×100). (c) Elastica van Gieson staining demonstrates the absence of elastic fibers in the reticular dermis in the area surrounded by the granulomatous infiltrate (original magnification ×40). (d) Fragmented elastic fibers are present within some of the histiocytes and multinucleated giant cells (original magnification ×400)

annular elastolytic giant cell granuloma (AEGCG). Thereafter, the patient was treated with topical corticosteroid (clobetasol propionate). This resulted in gradual flattening of the nodules, some of which finally disappeared.

Annular elastolytic giant cell granuloma is an entity that was proposed originally by Hanke *et al.*[1] for cutaneous annular lesions characterized by elastolysis, elastophagocytosis, and an infiltrate of multinucleated giant cells. The pathogenesis of AEGCG remains unclear. It has been postulated that exposure to the sun or other unknown factors alters the antigenicity of the elastic fibers and induces cell-mediated immune reactions.[2]

Interestingly, in the present case, AEGCG occurred mainly on pre-existing lesions of vitiligo. This anatomical co-localization suggests that the association between the two disorders is not accidental. The pathogenesis of vitiligo is also still unknown, although recently it has been shown that oxidative stress and accumulation of free radicals (FRs) acting as a trigger of melanocyte degeneration in the epidermis of affected skin are involved.[3] Oxidative stress can be induced by an increase in the generation of reactive oxygen species (ROS) and other radicals. Recent studies of vitiligo have shown that FRs are increased and that antioxidant systems are deficient. It has been demonstrated both *in vivo* and *in vitro* that patients with vitiligo accumulate high levels of hydrogen peroxide (H_2O_2), which leads to the destruction of melanocytes in the epidermis.[4] On the other hand, high superoxide dismutase activity in the serum and skin of patients with stable vitiligo has been reported.[5,6] These changes would lead to the accumulation of H_2O_2.

Recent studies of photoaging have revealed that ultraviolet (UV) irradiation induces the formation of ROS in skin tissue. Dermal fibroblasts exposed to ROS show increased expression of mRNA for matrix metalloproteinases (MMP)-1 and MMP-2, which have the ability to degrade collagen and elastic fibers.[7,8] Igawa *et al.*[9] have reported that oral Dapsone, which has an anti-oxidative effect, is effective for treatment of AEGCG. In our present patient, annular nodules were located on covered, as well as sun-exposed areas, and the patient had not been treated with UV irradiation. We postulate that in this case, degradation of dermal elastic fibers in the vitiligo lesions may have triggered the accumulation of lymphocytes and macrophages, elastophagocytosis, and subsequent granuloma formation.

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Conflicts of interest: None declared.

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Spiny keratoderma of the palms in an insulin-treated diabetic patient

Spiny keratoderma is a rare disease characterized by multiple discrete keratotic plugs, resembling a "music box spine", arising from the palms, soles, or both.[1] It was first described in 1971 by Brown[2], who called it punctate keratoderma. These spiny lesions have been described as filiform hyperkeratosis,[3] minute digitate hyperkeratosis,[4] punctate keratoderma,[2] punctate porokeratotic keratoderma[5] and, most recently, spiny keratoderma of the palms and soles.[1] Most of the cases described represent acquired disease, but there are also familial cases. Associations with a systemic disease or malignancy occur in some acquired cases. We present the case of a man with acquired spiny keratoderma who was receiving insulin treatment for type 2 diabetes mellitus.

A 58-year-old Japanese male was referred to us because of multiple asymptomatic, keratotic papules on his fingers and palms. He had a more than 20-year history of diabetes mellitus. He had noted the lesions more than 10 years ago and had started insulin treatment around the same time. Family history was negative for keratoderma, ichthyosis, or other dermatological diseases. He had no history of renal failure or hyperlipidemia and was unaware of any arsenic exposure.

On physical examination, numerous firm keratotic spicules were seen on the volar surface of the palms and fingers (Fig. 1). The lesions were 0.5–1 mm in diameter, 1–2 mm in length, and skin-colored. There were no similar lesions at other sites, including the soles.

Histopathological examination of skin biopsy specimens of the palms showed large columns of keratin arising from the epidermis in an area with a focally decreased granular layer and parakeratosis (Fig. 2). No dyskeratotic or vacuolated keratinocytes were seen in the underlying epidermis. Blood tests and computer tomography scan showed no abnormalities. Results of upper and lower endoscopy did not reveal any malignant neoplasms.

Figure 1 Multiple yellowish filiform keratotic projections on the left palm

in the antimelanogenic action down-regulating the expression of MITF or tyrosinase gene in cAMP-elevated melanocyte cultures and UV-irradiated dorsal skins of guinea pigs (Supplementary Figure S12 online). Finally, this study suggests a potential application of 4H3MC in the treatment of hyperpigmented skin disorders.

Animal experiments were carried out according to the protocols approved by Animal Experimentation Ethics Committee in CBNU institute.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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A Somatic Mutation of the *KEAP1* Gene in Malignant Melanoma Is Involved in Aberrant NRF2 Activation and an Increase in Intrinsic Drug Resistance

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TO THE EDITOR

Among the several characteristics of malignant melanoma, insensitivity to anti-cancer agents is a frequent clinical problem in the treatment of patients (Grossman and Altieri, 2001). In fact, the most commonly used chemotherapy agents cisplatin and dacarbazine for malignant melanoma elicit a response rate of only 10% (Flaherty, 2010).

The small-molecule inhibitor of BRAF, vemurafenib (also known as PLX4032), elicits potent tumor regression in patients with BRAF-positive stage IV melanoma (Huang *et al.*, 2012), and its use is expected in patients harboring the $BRAF^{V600E}$ mutation (Tsai *et al.*, 2008). However, vemurafenib is not effective against melanomas with wild-type BRAF protein (Joseph *et al.*, 2010).

Acral lentiginous melanoma (ALM) is one of the subtypes of cutaneous melanoma most frequent in colored races (Bradford *et al.*, 2009). In fact, only about 10% of ALM cases harbor the $BRAF^{V600E}$ mutation, compared with over 60% of cases of superficial spreading melanoma (SSM), which is most frequent in Caucasian populations (Saldanha *et al.*, 2006). Because these melanomas are insensitive to BRAF inhibitors (Joseph *et al.*, 2010), a search for molecular targets that would enhance sensitivity to standard treatment with cisplatin or dacarbazine would seem justified.

To address the genes responsible for drug resistance in melanoma, whole-exome sequencing was performed. We identified a single-nucleotide deletion in codon 507 from exon 4 of the *KEAP1* gene, common to MM-RU and PM-WK, as a candidate gene for drug resistance (Figure 1a). The KEAP1 protein produced by this mutant allele partially lacks the DGR/Kelch domain that is important for interacting with NRF2, a key transcriptional regulator of oxidative stress such as that resulting from reactive oxygen species (ROS; Figure 1b). Under normal conditions, NRF2 is kept transcriptionally inactive through binding to the DGR domains of KEAP1 and constitutively degraded by the ubiquitin proteasome system (Sekhar *et al.*, 2002). In contrast, in the cell lines harboring the *KEAP1* frameshift mutation (KEAP1-FSM), constitutive NRF2 stabilization, nuclear localization (Supplementary Figure S1 online), and target-gene activation were observed (Supplementary Figure S2 online). We also observed strong expression of the NRF2 protein in HMVI cells, which do not harbor *KEAP1* mutation, suggesting that another signaling pathway, such as the PI3K pathway, may regulate the constitutive expression of NRF2 in HMVI cells (Mitsuishi *et al.*, 2012).

Thus far, several somatic mutations of *KEAP1* that affect its NRF2-inhibitory activity have been identified in patients with cancers of the lungs, gallbladder, and liver (Taguchi *et al.*, 2011). Aberrant activation of NRF2 induced by *KEAP1* gene mutation in gallbladder cancer has been reported to lead to 5-fluorouracil (5-FU) resistance (Shibata *et al.*, 2008). However, the relationship between the KEAP1-NRF2 pathway and drug resistance in malignant melanoma still remains to be elucidated.

Cisplatin (*cis*-diamminedichloro-platinum (II), CDDP) and dacarbazine (5-(3, 3-dimethyl-1-triazenyl) imidazole-4-carboxamide, DTIC) have been shown to increase oxidative stress by raising the levels of intracellular ROS such as H_2O_2 (Zhang *et al.*, 2010; Deavall *et al.*, 2012). Therefore, we investigated whether NRF2 is involved in sensitivity to these drugs. The ratio of reduced-to-oxidized glutathione (GSH/GSSG) was decreased by treatment with CDDP or DTIC in si*NRF2*-transfected PM-WK cells (Figure 1c and d). Furthermore, intracellular ROS levels were increased by treatment with CDDP or DTIC in si*NRF2*-transfected cells, suggesting that the H_2O_2 detoxification pathway is active in these cell lines (Figure 1e; Supplementary Figure S3a online). Notably, knockdown of *NRF2* by small interfering RNA in PM-WK and MM-RU cells significantly enhanced their sensitivity to apoptosis by CDDP or DTIC (Figure 1f; Supplementary Figures S3b and S4 online). Conversely, the over-expression of NRF2 or activation of NRF2 by sulforaphane in G-361 cells reduced their sensitivity to CDDP or DTIC (Supplementary Figure S5 online). Moreover, the NRF2-positive cell lines tended to show higher IC_{50} values compared with NRF2-negative cell lines (Supplementary Figure S6 online). Taken together, the data indicate that, in addition to the mechanisms of drug resistance in melanoma, such as drug trapping by melanosomes and elevated expression of ATP-dependent transporters (Gottesman *et al.*, 2002; Chen *et al.*, 2006), aberrantly expressed NRF2 is one of the causes of resistance to CDDP and DTIC.

Next, we examined *KEAP1* gene mutation and NRF2 expression in specimens of primary melanoma. The histological types, patient genders and ages, and the stages of the primary melanomas we examined are shown in Supplementary Table online. Ten (48%), eight (38%), two (10%), and one (4%) of the 21 cases were ALM, NM, LMM, and SSM, respectively. We performed direct sequencing of *KEAP1* gene exon 4 using the genomic DNAs extracted from these paraffin-embedded specimens. In two of the 21 cases (~10%), we identified a homozygous single-nucleotide deletion that was the same as that identified in melanoma cell lines (#02-2078, 1518delC) and a heterozygous single-nucleotide deletion in a neighboring position (#03-8008, 1519delG) (Supplementary Table online). The stop codon appeared 23 nucleotides after the 1519delG mutation and also produced the same type of truncated KEAP1 protein as that resulting from 1518delC mutation. Immunohistochemical staining revealed that NRF2 was positive in specimens #02-2078 and #03-8008 (Figure 2b and d, respectively), which were ALM specimens harboring KEAP1-FSM mutation, whereas NRF2 was negative in specimens #09-7356 and #07-7252, which were ALM specimen without KEAP1 mutation (Figure 2, Supplementary Table online). We also performed direct sequencing of *BRAF* gene exon 15 using DNAs from #02-2078, #03-8008, #08-6115, and #09-7356, but the typical $BRAF^{V600E}$ mutation was not identified (Supplementary Table online). Taking these results together, it appears that the loss of function of KEAP1 caused by single-nucleotide deletions is indeed correlated with aberrant NRF2 expression in primary melanoma.

Missense mutations of the *KEAP1* gene have been identified in various cancers. Interestingly, the *KEAP1*-FSMs are most frequently identified in the DGR domain (65%), which is important for interaction with NRF2 (Taguchi *et al.*, 2011). Our results also indicate that the DGR domain of the *KEAP1* gene may be a "hot-spot" for FSM that causes aberrant activation of NRF2 and causes melanomas to become more resistant to CDDP or DTIC.

In conclusion, our present results and available data fully support the possibility that decreased expression or inhibition of NRF2 may provide an avenue for treatment of patients with malignant melanoma, by improving the rate of response to the standard chemotherapy agents, namely, cisplatin and dacarbazine.

CONFLICT OF INTEREST
The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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Abbreviations: ALM, acral lentiginous melanoma; CDDP, cis-diamminedichloro-platinum (II); DTIC, 5-(3, 3-dimethyl-1-triazenyl) imidazole-4-carboxamide; FSM, frameshift mutant; ROS, reactive oxygen species; SSM, superficial spreading melanoma

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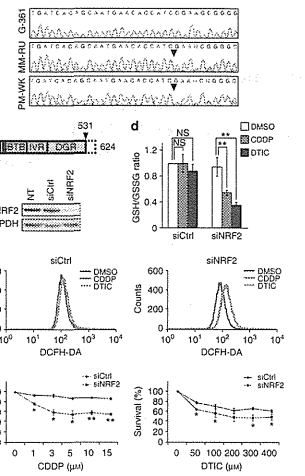

Figure 1. NRF2 contributes to chemoresistance in KEAP1-FSM cells. (**a**) Representative electrophoretograms of *KEAP1* gene exon 4 by capillary sequencing in melanoma cell lines. Arrowheads indicate the single-nucleotide deletion at codon 507 (1518delC). (**b**) Schematic representation of the *KEAP1* protein. Arrowheads indicate the appearance of a stop codon. (**c**) Expression of NRF2 protein in siCtrl- or siNRF2-transfected PM-WK cells. (**d**) Quantification of the ratio of reduced-to-oxidized glutathione (GSH/GSSG) or (**e**) intracellular reactive oxygen species levels after treatment with vehicle, CDDP, or DTIC in siCtrl- or siNRF2-transfected PM-WK cells. (**f**) Cell viability at 24 hours after treatment with vehicle, CDDP, or DTIC in siCtrl- or si*NRF2*-transfected PM-WK cells. NS, no significant difference; $^*P<0.05$ and $^{**}P<0.01$ versus control by *t*-test. CDDP, *cis*-diamminedichloro-platinum (II); DTIC, 5-(3, 3-dimethyl-1-triazenyl) imidazole-4-carboxamide.

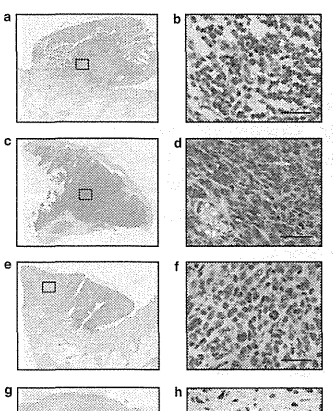

Figure 2. Aberrant NRF2 protein accumulation in primary melanomas harboring *KEAP1* frameshift mutation (FSM). Immunohistochemical analysis of endogenous NRF2 protein expression in melanomas harboring the *KEAP1* FSM (**a** and **b**, #02-2078; **c** and **d**, #03-8008) and with wild-type *KEAP1* (**e** and **f**, #09-7356; **g** and **h**, #07-7252). Cells were stained with NRF2 antibody. High-magnification images correspond to the respective boxed areas in the loupe images. Bar = 100 μm.

The New Aryl Hydrocarbon Receptor Antagonist E/Z-2-Benzylindene-5,6-Dimethoxy-3,3-Dimethylindan-1-One Protects against UVB-Induced Signal Transduction

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TO THE EDITOR

The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that mediates the toxicity of 2,3,7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD), polycyclic aromatic hydrocarbons, and related environmental contaminants (Abel and Haarmann-Stemmann, 2010). The unligated AhR is trapped in a cytosolic multiprotein complex, which rapidly dissociates upon ligand binding. Subsequently, the AhR shuttles into the nucleus, dimerizes with ARNT, and binds to xenobiotic-responsive elements (XREs) in the promoter of target genes, e.g., encoding cytochrome P450 (CYP) 1 monooxygenases, to enforce transcription (Abel and Haarmann-Stemmann, 2010). Furthermore, AhR-triggered activation of c-src tyrosine kinase stimulates EGFR and downstream mitogen-activated protein kinase signaling, resulting in the induction of XRE-independent genes, such as cyclooxygenase-2 (COX-2; Abel and Haarmann-Stemmann, 2010). We have previously shown that the AhR in keratinocytes is not only activated by anthropogenic chemicals but also by UVB irradiation, which leads to the intracellular formation of the tryptophan photoproduct and high-affinity AhR ligand 6-formylindolo[3,2-*b*]carbazole (FICZ; Rannug *et al.*, 1995; Fritsche *et al.*, 2007). Indeed, UVB exposure enhances AhR/XRE binding (Supplementary Figure 1 online) and accompanied CYP1A1/1B1 expression (Katiyar *et al.*, 2000), as well as XRE-independent COX-2 expression (Fritsche *et al.*, 2007).

Because (i) overexpression of a constitutively active AhR causes inflammatory skin lesions (Tauchi *et al.*, 2005), (ii) an increase in CYP activity leads to reactive oxygen species formation (Puntarulo and Cederbaum, 1998), (iii) CYP1 enzymes are critical for chemical-induced skin carcinogenesis (Shimizu *et al.*, 2000), and (iv) COX-2 is involved in UV-induced inflammation and carcinogenesis (Elmets *et al.*, 2010), it was postulated that a transient inhibition of AhR may protect human skin against the detrimental effects of UVB irradiation (Agostinis *et al.*, 2007; Haarmann-Stemmann *et al.*, 2012). Moreover, we have shown that the expression of matrix metalloproteinase-1 (MMP-1), which is critically involved in extrinsic skin aging, is upregulated in an AhR-dependent manner in tobacco smoke extract–exposed keratinocytes (Ono *et al.*, 2013). Therefore, we decided to develop an AHR antagonist that is suitable for topical UV-protection. We screened a library of compounds that possess the structural prerequisites to

Abbreviations: AhR, aryl hydrocarbon receptor; BDDI, E/Z-2-benzylidene-5,6-dimethoxy-3,3-dimethylindan-1-one; COX-2, cyclooxygenase-2; CYP, cytochrome P450; EROD, 7-O-ethoxyresorufin-deethylase; FICZ, 6-formylindolo[3,2-b]carbazole; MMP-1, matrix metalloproteinase-1; MNF, 3′-methoxy-4′-nitroflavone; NHEK, normal human epidermal keratinocyte; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; XRE, xenobiotic-responsive element

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Case Study

Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL) with Hemophagocytosis (HPS) : Successful Treatment Using High-Dose Chemotherapy (BFM-NHL & ALL-90) and Autologous Peripheral Blood Stem Cell Transplantation

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Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of non-Hodgkin lymphoma, in which lymphoma cells infiltrate preferentially into subcutaneous adipose tissue. Although various treatment trials for SPTCL have been attempted, no standardized therapy has been established. Here, we report a case of α/β^+ T-cell-phenotype SPTCL (SPTCL-AB) with hemophagocytosis (HPS) in a 14-year-old girl, who presented with low-grade fever, general fatigue and chest swelling. Laboratory examinations revealed leukocytopenia, and bone marrow aspiration cytology showed HPS. The diagnosis of SPTCL-AB was made by biopsy on the basis of thickened subcutaneous tissue in the chest wall. Following high-dose chemotherapy (HDT) of BFM-NHL & ALL-90, autologous peripheral blood stem cell transplantation (auto-PBSCT) was performed. The patient responded to the treatment and has remained asymptomatic for 2 years. Our results suggest that a combination of HDT of BFM-NHL & ALL-90 and auto-SCT treatment is effective for SPTCL associated with HPS. [*J Clin Exp Hematop 53(2) : 135-140, 2013*]

Keywords: SPTCL, hemophagocytosis, BFM-NHL & ALL-90, auto-PBSCT

INTRODUCTION

In 1991, the distinct clinicopathological features of a T-cell lymphoma in which the lymphoma cells preferentially invade the subcutaneous tissue were described by Gonzalez *et al.*[1] Under the term subcutaneous panniculitis-like T-cell lymphoma (SPTCL), this new condition was established as a distinct disease entity in the World Health Organization (WHO) classification.[2] Because of its peculiar pathological features, SPTCL may be initially misdiagnosed as Weber-Christian disease, a benign inflammatory panniculitis and a granulomatous disease.[3,4] Recent studies have disclosed that cases with an α/β^+ T-cell phenotype (SPTCL-AB) and a γ/δ^+ T-cell phenotype (SPTCL-GD) can be distinguished within the group of SPTCL.[5] SPTCL-ABs have a $CD4^-$, $CD8^+$, $CD56^-$ phenotype, and SPTCL-GDs have a $CD4^-$, $CD8^-$ phenotype with frequent expression of CD56. Compared with SPTCL-ABs, SPTCL-GDs have a poor prognosis.[6,7] On the basis of these observations, the term SPTCL is used only for SPTCL-ABs, and SPTCL-GDs are included within the cutaneous γ/δ^+ T-cell lymphomas.[6,8] Although SPTCL-AB patients without hemophagocytic syndrome (HPS) have a favorable prognosis, the clinical course of cases associated with HPS is generally aggressive, and a delay in diagnosis or treatment may result in a fatal outcome. There have been few reports of successful treatment of SPTCL-AB patients with HPS, and no therapeutic regimen has been established.

Here, we report a case of SPTCL-AB with HPS that was treated successfully with a combination of high-dose chemotherapy (HDT) of Berlin-Frankfurt-Münster-non-Hodgkin lymphoma-90 (BFM-NHL-90) and autologous peripheral blood stem cell transplantation (auto-PBSCT).

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CASE REPORT

A previously healthy 14-year-old Japanese girl visited a physician because of a 1-month history of chest swelling. She also had a 3-month history of general fatigue and low-grade fever. Initial laboratory examinations revealed a white blood cell count of 2.82 × $10^3/\mu L$, hemoglobin of 11.6 g/dL, hematocrit of 33.8 g/dL and platelet count of 16.4 × $10^4/\mu L$. Histopathologic examination of a biopsy specimen of subcutaneous adipose tissue from the chest wall revealed diffuse infiltration of medium-sized lymphocytes. Under a diagnosis of panniculitis due to lupus profundus, administration of low-dose prednisolone (PSL) was started. Several weeks later, the chest swelling expanded gradually. She was therefore referred and admitted to our hospital for further evaluation and treatment.

On physical examination, a massive tumor was evident in her chest subcutaneous tissue (Fig. 1). The findings from laboratory examinations were as follows : aspartate aminotransferase 27 IU/L (normal : 10-40 IU/L), alanine aminotransferase 15 IU/L (normal : 5-35 IU/L), lactic dehydrogenase 235 U/L (normal : 115-359 IU/L), soluble interleukin-2 receptor 641 U/mL (normal : 220-530 U/mL) and ferritin 56 ng/mL. Moreover, previous infection with Epstein-Barr virus was evident. Magnetic resonance imaging revealed noticeable thickening of the subcutaneous tissue, compatible with the region of the massive tumor in the chest (Fig. 2). Histopathology of skin biopsy specimens showed medium-sized lymphocytes diffusely infiltrating into the subcutaneous fat tissue (Fig. 3a). Rimming of the lymphocytes around individual fat cells was observed (Fig. 3b).

Immunohistochemical staining revealed that the infiltrating lymphocytes were $CD3^+$, $CD4^-$, $CD5^+$, $CD8^+$, $CD20^-$, $CD30^-$, $CD45RO^+$, $CD56^-$ and $CD79a^-$ (Fig. 4). They were positive for T-cell receptor-β (Fig. 5a). Cytotoxic molecules such as granzyme B, T-cell intracellular antigen-1 (TIA-1) and perforin were positive (Fig. 5b). Latent membrane protein 1 (LMP-1) and EBER *in situ* hybridization were negative (Fig. 5c & 5d). Bone marrow smears showed hemophagocytosis of red blood cells and neutrophils by histiocytes (Fig. 6).

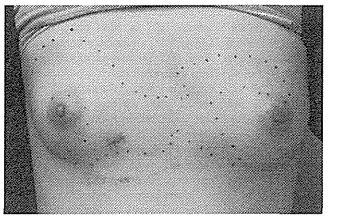

Fig. 1. A massive tumor, indicated by *black dots*, was present in the subcutaneous tissue of the chest.

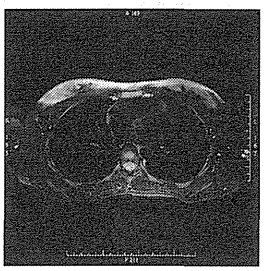

Fig. 2. Magnetic resonance imaging of the chest (T2-weighted). The subcutaneous tumor of the chest wall showed high signal intensity.

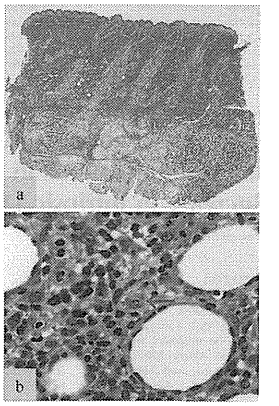

Fig. 3. Histopathology of the skin biopsy specimen (H&E stain). (*3a*) Diffuse cellular infiltration occurred in the subcutaneous fat tissue. (*3b*) Rimming of lymphocytes around fat cells was observed (*arrow*). Bean bag cells, phagocytosing erythrocytes, were found among the lymphocytes. (*3a*) ×10, (*3b*) × 400.

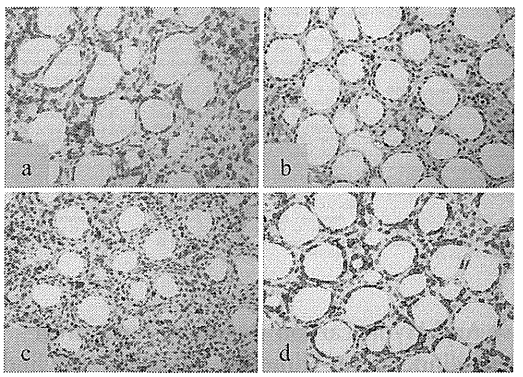

Fig. 4. Immunohistochemistry of CD3 (*4a*), CD4 (*4b*), CD5 (*4c*) and CD8 (*4d*). The infiltrating lymphocytes were positive for CD3, CD5 and CD8, but negative for CD4. ×400.

On the basis of these results, the patient was diagnosed as having SPTCL accompanied by HPS in spite of the low levels of lactic dehydrogenase and ferritin, and was treated with high-dose PSL (75 mg/day internally), starting on day 9 of admission.

Nine days later (on day 17 of admission), despite the PSL therapy, the chest tumor was unchanged in size. Additional HDT of BFM-NHL-90 (protocol I) was therefore applied. After starting the first course of the chemotherapy, the tumor in the chest gradually decreased in size. During the phase of recovery from the chemotherapy, peripheral blood stem cells ($CD34^+$ cells) were harvested. Moreover, chemotherapy of BFM-NHL-90 (Protocol M) was applied as a consolidation therapy. In addition, one course of the BFM-acute lymphoblastic leukemia (ALL)-90 regimen (HR3) was applied for further treatment.

Following pretreatment with the MCVAC (ranimustine, cytarabine, etoposide and cyclophosphamide) regimen, the patient was treated with auto-PBSCT. The clinical course thereafter was uneventful. She has been in complete remission for more than 2 years, and there was no evidence of local recurrence in the chest wall and HPS in the bone marrow at the final follow-up examination.

DISCUSSION

SPTCL is a type of skin lymphoma characterized by the infiltration of subcutaneous tissue by pleomorphic T cells and benign macrophages, mimicking lobular panniculitis. This malignancy typically presents in the form of skin nodules that involve the extremities and can become ulcerated.[9] The clinical course associated with HPS is aggressive, and a delay in diagnosis and treatment may result in a fatal outcome.

Although the mechanism of HPS in SPTCL has not been clarified, the phenomenon of HPS results from overproduction of cytokines, including interferon-γ, interleukin-2 (IL-2), IL-6, IL-12, IL-18 and tumor necrosis factor-α, produced by activated T cells (Th1 cells) and macrophages, which leads to a chain reaction of cytokines.[10-13] Control of HPS in SPTCL-AB patients improves the prognosis.

Various therapies such as radiotherapy, PSL, CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone) (-like) chemotherapy and auto/allo-SCT have been applied for SPTCL-AB.[9] For relapsed or refractory disease, various regimens have been attempted as salvage chemotherapy, including cladribine, DHAP (dexamethasone, cytarabine and cisplatin), ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin), FLAG (fludarabine, cytarabine and granulocyte-colony stimulating factor), mini-BEAM (carmustine, etoposide, cytarabine and melphalan) and VEPPB (vincristine, etoposide, prednisone, pocarbazine and bleomycin).[9] However, no standardized treatment has yet emerged. In SPTCL-AB patients with HPS, a recent report has indicated that CHOP (-like) chemotherapy is not very effective. Auto-SCT or allo-SCT following HDT has been suggested as an important option for patients with refractory or recurrent SPTCL.[4,14]

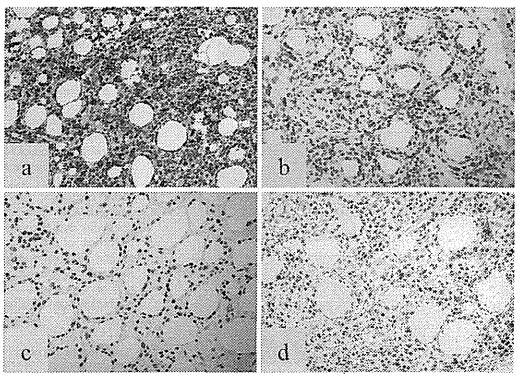

Fig. 5. Immunohistochemistry for T-cell receptor (TCR)-β (*5a*), granzyme B (*5b*), latent membrane protein-1 (LMP-1, *5c*) and Epstein-Barr virus (EVB)-encoded RNA *in situ* hybridization (*5d*). Lymphocytes were positive for TCR-β, and expression of the cytotoxic molecule granzyme B was also found. LMP-1 and EBV were negative. ×200.

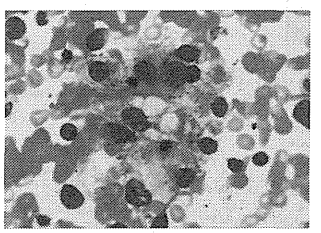

Fig. 6. Hemophagocytosis was seen in a smear of the bone marrow. Giemsa stain, ×1000.

In the present case, high-dose PSL was initially used, but no response was obtained. Therefore, we treated the patient according to the BFM-NHL & ALL-90 protocol.

BFM-NHL-90 is a protocol for pediatric malignant lymphoma and yields a significantly better outcome for non-Hodgkin lymphoma at stage I or II.[15] BFM-NHL-90 is also effective for pediatric anaplastic large-cell lymphoma. BFM-ALL-90 is a superior regimen for high-risk childhood T-cell acute lymphoblastic leukemia.[16]

The present case was treated successfully with a combination of HDT of BFM-NHL & ALL-90 followed by auto-PBSCT, and achieved clinical complete remission (CR). This result suggests that the BFM protocol is applicable and can yield complete remission in cases of SPTCL with HPS. Medhi *et al.* have also reported the value of the BFM-90 protocol for the treatment of patients with SPTCL and HPS.[17]

To date, there have been few reports of effective treatment for SPTCL using HDT following SCT. In almost all of the reported cases, the patients underwent HDT-allo-SCT and its effectiveness was impressive, 92% achieving CR, with a median response duration of ≥ 14 months.[9] In intermediate- and high-grade lymphomas, myeloablative allo-SCT is associated

with a lower relapse rate than auto-SCT for the graft-versus-leukemia effect.[18,19] However, chronic graft-versus-host disease (cGVHD) is a very common complication, with a reported incidence of between 40% and 70%,[20] and is the leading cause of late death in allo-SCT survivors.[20,21]

The median age of patients with SPTCL-AB at diagnosis is 36 years (range : 9-79 years), and about 19% are in the second decade or younger.[8] In children, cGVHD may reduce the quality of life because of the induction of growth irregularity. Mukai *et al.* described a patient with SPTCL and HPS who received HDT of BFM-NHL & ALL-90 and auto-SCT.[4] The present case received a combination of HDT of BFM-NHL & ALL-90 and auto-SCT, and has been in complete remission for more than 2 years. This suggests that auto-SCT might be a feasible option following HDT.

In summary, we have reported a case of SPTCL complicated by HPS, which responded to treatment with HDT of BFM-NHL & ALL-90 and auto-SCT. Although the value of the BFM-NHL & ALL-90 protocol has to be further evaluated in SPTCL cases, our findings suggest that a combination of HDT of BFM-NHL & ALL-90 and auto-SCT is applicable for the treatment of SPTCL with HPS.

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DISCLOSURE/CONFLICT OF INTEREST

The authors state that they have no financial interest in the products mentioned within this article.

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SHORT COMMUNICATION

A Case of Atypical Fibrous Histiocytoma with Positivity for CD163 and CD44

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Atypical fibrous histiocytoma (AFH) is a variant of dermatofibroma (DF) that was first described by Fukamizu et al. (1) in 1983. Histologically AFH is characterized by proliferation of dermal spindle cells composed mainly of atypical histiocytic cells with striking nuclear pleomorphism and atypia, in a background of classic fibrous histiocytoma (2). It is known that many cases of AFH follow a benign course if complete excision is carried out (2, 3). However, because the tumour cells are atypical, AFH must be differentiated from tumours of intermediate malignancy, such as dermatofibrosarcoma protuberans (DFSP) or atypical fibrous xanthoma (AFX), as well as more malignant tumours, such as pleomorphic dermal sarcoma (PDS)/malignant fibrous histiocytoma (MFH).

We report here a case of AFH on the left upper arm of a 63-year-old woman and describe its immunoreactivity in detail. We also discuss the points of histological and immunohistological differentiation between AFH and other cutaneous spindle cell tumours.

CASE REPORT

A 63-year-old woman presented with an 8-month history of a symptomless, slowly growing swelling on the left upper arm. The patient had no unusual medical or family history. Clinical examination revealed an 8-mm black-purplish hard mass with peripheral erythema (Fig. 1A). The tumour had arisen at a site without any known previous history of injury. A haemangioma was clinically suspected, and surgical excision was performed. Microscopic examination revealed a well-defined lesion, located in the dermis and extending to the subcutaneous tissue, with epidermal hyperplasia and a grenz zone (Fig. 1B). The lesion was composed largely of interlacing fascicles of predominant histiocyte-like eosinophilic spindle cells with elongated or plump vesicular nuclei, arranged in a storiform pattern. Abundant pleomorphic giant cells with huge bizarre nuclei (bi-lobed and multi-lobed) and histiocytes with large vesicular nuclei and prominent eosinophilic nucleoli were observed (Fig. 1C). In the peripheral region of the tumour, fibroblast-like spindle cells arranged in a storiform or fascicular pattern with collagen bundles were observed, resembling the classic features of DF. No necrosis was present. Foci of chronic inflammatory cells, including lymphocytes and plasma cells, were also evident. As a typical feature, we noted individual prominent hyalinized collagen bundles surrounded by tumour cells, predominantly in the periphery of the lesion (Fig. 1D). The mitotic count was 3 per 10 high-power fields (HPF).

Immunohistochemical staining revealed diffuse positivity for vimentin, factor XIIIa, CD68, CD163 (Fig. 1E) and CD44 (Fig. 1F). The lesion showed no reactivity for desmin, CD34, AE1/AE3, desmin, S-100 protein, α1-antitrypsin or α1-antichymotrypsin. Ki-67 staining showed less than 5% positive reactivity. Based on these findings, a diagnosis of atypical fibrous histiocytoma was made. As it was suspected that the initial resection may have left some residual tumour cells at depth, expanded excision with a 3-cm margin was performed one month later. At 30 months of follow-up, the patient was asymptomatic with no evidence of tumour recurrence.

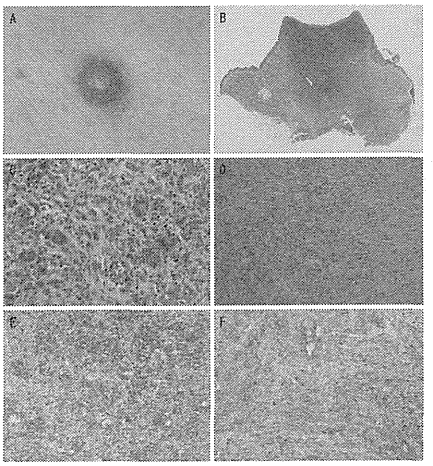

Fig. 1. (A) Macroscopic view of the blackish-purplish skin tumour on the right arm. (B) Dermal-to-subcutaneous tumour with focal extension into the subcutaneous tissue. The epidermis was hyperplastic and a grenz zone was evident (haematoxylin and eosin; HE × 1). (C) The tumour is composed of a proliferation of interlacing fascicles of predominantly histiocyte-like eosinophilic spindle cells with vesicular nuclei. Abundant pleomorphic giant cells with huge bizarre nuclei are present (HE × 100). (D) At the border of the lesion, the cells are interspersed with hyaline collagen bundles (HE × 40). Immunohistochemical studies of the tumour cells. The cells were positive for (E) CD163 and (F) CD44.

DISCUSSION

The distinctive histological features of AFH include a dermal lesion extending into superficial subcutaneous adipose tissue, composed of a population of pleomorphic spindled (fibroblast-like) and polyhedral (histiocyte-like) cells admixed with multinucleated giant cells, and macrophages as well as hemosiderin deposits. Kaddu et al. (2) reported the presence of 1–15 pathologic mitoses per 10 high power field (HPF) (mean 3.4 per 10 HPF) (20/59 cases, 33.9%) and/or geographic-like necrosis (7/59 cases, 11.9%) (2). Many reports have indicated positivity for factor XIIIa (4–6), but negativity has also been reported in some cases (2, 7, 8). Garrido-Ruiz et al. (6) and Wilk et al. (8) reported that AFH was CD34-negative. Although AFH of the skin is considered to be benign, there have been rare cases of multiple recurrence involving metastasis to the lymph nodes and lungs (2, 3, 5). Kaddu et al. (2) reported local recurrence in 3 of 21 cases for which follow-up was possible, and among these cases, distant metastasis occurred in 2. These 3 cases were all incompletely excised. Therefore, complete excision of AFH with a sufficient margin is important.

Histologically, the differential diagnosis of AFH includes DFSP, AFX and PDS/MFH. DFSP commonly occurs on the body trunk or proximal limbs of healthy adults, showing uniform bland spindle cells with spindle-shaped nuclei exhibit a storiform pattern and proliferate from the dermis to the subcutaneous adipose tissue with an unclear boundary, CD34 is diffusely positive, and immunoreactivity for α-SMA and desmin are usually negative (3, 9). In our case, as the tumour cells were notably polymorphic, CD34 was negative, and typical features of DF were observed in the background. AFX commonly occurs in sun-damaged skin of the head and neck in elderly individuals. AFX is similar to AFH in showing proliferation of spindle cells as well as multinucleated giant cells and bizarre cells (2). However, solar elastosis is observed in AFX, and a grenz zone is not evident because the tumour cells proliferate from directly under the skin. Moreover, features of typical DF are not observed (3). PDS/MFH commonly occurs in the limbs of middle-aged individuals, and it is common for the lesion to extend deeply into subcutaneous tissue, thus commonly forming a large tumour. An important point is that the tumour cells with profound atypia proliferate, and immunohistochemically do not demonstrate a specific line of differentiation. α1-antitrypsin and α1-antichymotrypsin are immunohistochemically positive in PDS/MFH (10). In the present case, the tumour cells were negative for both α1-antitrypsin and α1-antichymotrypsin, and atypia of the proliferating cells was not as severe as that in PDS/MFH.

Recent studies have shown that CD163 and CD44 are specific for DF and its variants. CD163, a haemoglobin scavenger receptor expressed by monocytes and tissue macrophages, is reportedly expressed in DF (89%) and cellular fibrous histiocytoma (100%), whereas it is negative in DFSP (83%) (11) and AFX (100%) (12). In addition, CD44 is the cell surface receptor for hyaluronate, and has also been reported to be a useful diagnostic marker of DF (13). In our case, the tumour cells showed strong expression of both CD163 and CD44, thus supporting the contention that AFH is a variant of DF.

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いわて新医療モデルと遠隔医療

小川 彰

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The New Iwate Model of Healthcare and Telemedicine

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1. はじめに

私たちは、厚生労働科学研究費補助金（地域医療基盤開発推進研究事業）「遠隔医療を実施する拠点病院のあり方に関する研究」において、ICTの活用による遠隔医療を核とし、住民、患者の高度医療へのアクセスを保証する一方、クオリティとコストを両立させ、医師不足にも対応した、全国の過疎地、被災地医療のモデルとなりうる「いわて新医療モデル」の確立を目指している。

2. 岩手県の過疎地医療の特殊性

岩手県は面積が北海道に次いで広く、南北約200km、東西約150kmと四国4県に匹敵する総面積中最大の行政区である。盛岡を起点とすると、三陸海岸は約100km離れており、例えば、宮古市に行くまで車で片道約2時間、さらに山田町まで行こうとすれば、片道約3時間かかることになり、ほとんどの沿岸地域まで往復約6時間を要する。この広大な医療圏を、岩手医大にある県内唯一の高度救命救急センターと県立久慈病院と県立大船渡病院にある高次救急センターの3救急センター体制で支えている。

都道府県別にみた医療施設に従事する人口10万あたりの医師数は埼玉県や千葉県が最も少ないが、広い県土を有する東北各県においても医師数は不足している。医療圏の面積当たりの医療供給体制をみると、岩手県の9つの二次医療圏のひとつ、宮古医療圏の面積は、東京都全域の1.2倍、東京都区部の4.3倍であるが、僅か4病院があるのみである。そのひとつが今回津波で被災した県立山田病院であり、総合病院は唯一県立宮古病院のみである。東京都の病院数が658、区部だけでも436あるのに対し、地域によりこれだけの違いがあることを前提に、岩手県の医療を考える必要がある。

岩手県における過疎地医療の特殊性は、広大な県土であり、医師不足県であること、医師の移動に膨大な時間がかかること、しかし大学病院から片道3時間かけて沿岸地域まで行ったとしても多くの患者さんが待っている訳ではないことである。高度医療を効率良く提供するため、大学病院と地域を結んだ遠隔医療の役割が期待されてきた。

3. 岩手県の医療情報ネットワークと遠隔医療

広大な県土を有する岩手県は、医療情報ネットワークの整備に積極的に取り組んできた。行政情報ハイウェイの一部を利用した岩手医療情報ネットワークと小児救急医療遠隔支援システム、インターネットを利用した周産期医療情報ネットワーク等である。しかし、その多くはテレビ会議であり、「がんネット」、「脳卒中ネット」、遠隔手術指導、データベース検索、教育支援など、基本的には全て遠隔教育であり、診療を遠隔医療として行うのは放射線画像診断と遠隔病理診断のみであった。

このなかで周産期医療情報ネットワーク"いーはとーぶ"は、岩手県全域の分娩施設を網羅し、妊婦情報を登録保存していた。津波の被災地ではほとんどの妊婦が母子健康手帳を失ったが、妊婦情報が岩手医科大学にある"いーはとーぶ"のサーバに保存されていたことから、母子健康手帳の再発行が可能となり、その後の妊婦健診の継続な出産につながった。このエピソードは、医療情報の共有、保全が災害時に住民の健康を守る上でいかに重要かを示しており、"いーはとーぶ"の奇跡と呼ばれている。

4. 東日本大震災・津波後の岩手県の医療再生への道

東日本大震災・津波後の医療再生の道は5段階に分けることができる。第1段階はDMAT活動であるが、今回は津波災害であり、多くの場合、津波で生死が決まってしまい、負傷人は少なく、DMATの活動は限定的であった。むしろ第2段階である避難所巡回の医療支援チームの活動が非常に長く必要とされたのがひとつの特徴であった。第3段階は仮設診療所の整備であり、県立山田病院、県立大槌病院、県立高田病院が仮設診療所での診療を再開している。また、陸前高田では、被災した多くの開業医に代わり、岩手県医師会が独自に診療所を作って活動している。

現在進めているのが第4段階、基幹病院の整備である。ここで最も重要なことは、ハードやシステムを単に元に戻す、復旧ではなく、岩手県全域の医療体制を白紙から再構築する、再生するという視点である。広大な県土、過疎地、被災地の3つをキーワードに、住民がいつでもどこでも高度医療を受けることができる、効率のよい、「いわて新医療モデル」を構築することが我々に課せられた使命である。これはさらに第5段階である町の再生に応じた医療体制の整備につながっていく。

過疎地、被災地であっても、住民、患者がいつでもどこでも高度医療を受けることができる「いわて新医療モデル」では次のふたつが重要な柱になると考えている。第1は電子カルテ等のICTを利用することにより、診療所―基幹病院―介護福祉施設―大学病院間で医療情報を共有する遠隔医療システムを構築すること。すなわち、ICTを活用した遠隔医療によって住民が高度の診断や治療方針について専門医療を受けることができる。生活習慣病などの慢性疾患の日常診療を地元で受けることができる。手術や高度医療は大学病院や基幹病院で受けるが、その後は地元に戻って生活することから、大学病院、基幹病院、診療所、福祉施設において医療情報を共有し、住民の健康な生活を支えるシステムである。

第2はテレビ会議システムを利用した外来診療であり、これには専門診療の効力化という極めて重要な視点が必要である。

5. これまでの遠隔医療の問題点

従来の遠隔医療は、ほとんどの場合、医師がいる病院同士をつなぐ「遠隔診療支援」であって、真の遠隔医療ではない。診療として行われている遠隔医療は病病連携としての放射線画像診断と遠隔病理診断であるが、広い県土においては、病診、診診連携にこそ遠隔医療が求められる。また、放射線画像診断と遠隔病理診断は保険適用であるが、医師不在の診療所の看護師と100km、片道3時間離れた岩手医大をつなぐ診療が保険診療になることが本当の意味での遠隔医療であると考えている。本研究でのテーマのひとつが遠隔医療を保険診療にするということであり、陸前高田の診療所における皮膚科診療と県立宮古病院における糖尿病診療をモデル事業として、遠隔診療で、医師がいないところで、看護師と患者さんが向こうにいて、遠く離れた岩手医大の外来に医師がいる。そのような診療が安全なのか、診療として本当に成り立ちうるのかという検証研究を行っている。

もうひとつの課題は電子カルテの標準化がなされていないことである。厚生労働省はSS-MIXさらにSS-MIX2を推奨し、標準化を推進しているが、まだ十分には普及していない。本研究ではSS-MIX、SS-MIX2を中心に、医療連携のために継続すべき情報の範囲について議論を進めていく。

6.「いわて新医療モデル」に向けた岩手県、岩手医科大学の取り組み

岩手県は発災後5か月の平成23年8月に策定した「復興基本計画」の中で、災害に強く、質の高い保健医療の提供体制の整備を謳い、遠隔医療を核とし、沿岸地域の病院や診療所、さらに在宅ケアや訪問介護等を包括するケアシステムとして連動させ、これをドクターヘリの運用等が支えるとした。

ドクターヘリは、既に平成24年5月から運用が開始され、平均ではほぼ1日1回の出動要請がある。岩手医大の矢巾キャンパスにドクターヘリ基地を完成させ、ここに運行管理者、パイロット、整備士、そしてフライトドクター、フライトナースが常駐し、出動要請から5分で上空に舞い上がり、陸路で片道3時間かかるところを25分で行く運用を既に開始している。

さらに、平時には災害医療の検証、教育を行い、災害時には医療体制を速やかに確保するための災害医学講座を新設した。また、災害精神医学講座を設け、岩手こころのケアセンターを岩手医大に、支所を被災地4箇所に開設して活動を開始している。平成25年4月には子どものこころのケアセンターを開設する予定である。

岩手医大の矢巾キャンパスには平成25年4月に、完全免震構造で、独自の非常用発電機能を持ち、全県の医療情報のサーバ機能を有する災害時地域医療支援教育センターを開設する。1階にこころのケアセンターと子どものこころのケアセンターが、2階に災害医学講座が入る。4階には住民、患者の健康情報、カルテ情報を保存し、災害等に対応するため、全県の医療情報を集約するサーバを置く予定である。

ドクターヘリ基地と災害時地域医療支援教育センターが立つ矢巾キャンパスの敷地には5、6年後に1000床規模の病院を建設する予定である。この岩手医大の新病院にはおよそ8000KWの発電機能を併設し、1週間程度のライフライン停止時にも全ての病院機能を稼働できるように整備し、災害に強いモデル災害拠点病院にする方針である。この新病院には岩手県内、東京首都圏の直下型の地震、あるいは東海東南海地震の時にバックアップ病院としての機能を持たせるという意味もある。

地域医療連携、医療情報連携に関わる事業は、厚生労働省、総務省、文部科学省、そして内閣府と様々な行政機関が関与することから、国と県、市町村、医療機関が密接に連携すること、特に岩手医大が各種事業の横糸を紡ぐような役割を果たすことが重要であると考えている。岩手県では医療情報推進連絡協議会が発足され、無駄のない、効果的な医療情報システムの構築に向けて歩み出したところである。

7. まとめ

過疎地、被災地における「いわて新医療モデル」の目的は、ICTを活用した遠隔医療により、「地域」、「病院」、「大学」を連携させる新しい医療情報連携システムを構築し、遠隔医療を「支援」から「医療」へと発展させることである。「いわて新医療モデル」を医師不足にも対応した全国の医療モデルに育てていきたい。

岩手医科大学と県立宮古病院の間の糖尿病遠隔診療支援

高橋 義彦　佐藤 譲

岩手医科大学内科学講座　糖尿病・代謝内科分野

Teleconsultation for the management of diabetes mellitus between Iwate Medical University and Miyako Prefectural Hospital

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要旨

岩手県のなかでも特に三陸沿岸は糖尿病専門医が著しく不足している。同地域の中で、宮古市の基幹病院である岩手県立宮古病院と、岩手医科大学附属病院とをテレビ会議システムで結び、糖尿病遠隔診療支援を行うプロジェクトを立ち上げた。遠隔医療拠点となる岩手医科大学矢巾キャンパスにサーバーを置き、二つの病院の外来の間をVPNによるセキュアなネットワークで結ぶ。そして、WWW連携データベースシステムにより検査結果や指導内容、投薬内容をデータベース化するシステムを構築した。今後比較的病状の安定した患者を対象に参加患者を募り、診療支援を開始したいと考えている。

Keywords : teleconsultation, diabetes mellitus, virtual private network

1. はじめに

日本における糖尿病患者数は年々増加し、糖尿病が強く疑われる人は平成9年度690万人と推計されたものが、平成19年度には890万人となり、さらに糖尿病の可能性を否定できない人を含めると同年度では2210万人が何らかの糖代謝障害を有していると推計されている。糖尿病は全身の血管を障害する代謝症候群であり、細小血管障害としての網膜症、腎症・神経障害のみならず、大血管障害として虚血性心疾患・脳血管障害や末梢動脈疾患の高リスクである。その治療目標は、健康な人と変わらない日常生活の質の維持、および健康な人と変わらない寿命の確保といえる。長期間にわたって良好な代謝管理を行うためには、患者の病態に即した治療が必要であるが、平成25年1月の時点で日本糖尿病学会認定糖尿病専門医は岩手県全体で35名と少なく、広大な面積を有する三陸沿岸については、わずかに3名のみである。また糖尿病合併症治療においても、例えば人口当たり網膜光凝固術施行症例数は三陸沿岸の各地域において県央の半分以下である。そのような状況において、糖尿病専門医が直接現地に赴かずとも、専門的な見地での治療を行うことをめざしたのが今回の糖尿病遠隔診療支援プロジェクトである。

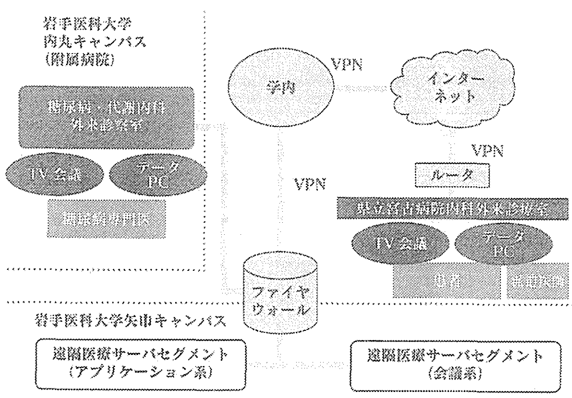
2. 方法

プロジェクトの具体的な内容としては、岩手県立宮古病院内科外来と岩手医科大学糖尿病・代謝内科外来とをVPNで結び、糖尿病専門医が岩手医大側から県立宮古病院へTV会議システムを使ったface to faceの診療支援を行うことと、参加者の診療データを岩手医科大学総合情報センター内にデータベース化し、東日本大震災において問題となった投薬内容などの情報が高度災害対応施設に保存されるシステムを構築していくこととの2点である。問題となったのは、二つの施設の診療システムが異なっていることと、通常の保険診療請求をするためには医師の直接診療が必要となる点であった。このために、宮古病院側にも診療担当医を確保し、TV会議システムを介して閲覧できる検査結果、画面における指導内容、患者との面談後必要と判断した処方の情報をWEB上でデータベースに入力し、それを宮古病院側にリモートプリンティングで出力することとした。そして宮古病院側診療担当医がそれを確認の上、処方や次回診察予約を行うというルールを作成した。また、糖尿病専門医の指導がTV会議システムだけで継続されるのではなく、同じ専門医がTV診療支援と直接診療を交互に行うことや、必要時には岩手医大側医師が宮古病院医師に対して直接診療を依頼できることとし、医療の質や安全を担保するようにデザインした。

平成24年度においては、Cisco社製のTV会議システムを二つの施設に設置するとともに、検査の検査結果、指導内容や投薬内容を登録可能なWEB連携データベースを当大学の総合情報センターが独自に構築。二つの施設からそれぞれデータベースへの入力および内容の閲覧が可能となるようにした【図1】。このためのサーバーは、災害時の医療拠点となる岩手医科大学矢巾キャンパス内に設置した。研究の目標としては、TV会議システムを利用した場合と、専門医の直接診療のみの場合とで、血糖管理状況が異ならないということを目指している。本研究については、すでに当大学倫理委員会の承認を終了している。

3. 結果と考察

現在までのところ、必要機器の設置および通信テストを完了したものの、患者のリクルートを開始したばかりであり、診療支援の開始は未だこれからという段階である。糖尿病管理に関するtelemedicineの手法としては、携帯電話などを用いた、非対面型のteleconsultationと対面型のteleconsultationが国内外で試行されているが、最近のレビューによると、後者すなわちテレビカメラ、ウェブ



【図1】今回構築した糖尿病遠隔診療支援システム

カメラ等を用いたリアルタイムの手法の方が、医療従事者の負担が小さく、コストなどの面で優れているという[1]。血糖管理状況については、teleconsultationが通常診療よりも良いというエビデンスはないが、逆に言えば通常診療に劣らない成績がほとんどである。厚生労働省の統計上、岩手県は高齢者の割合が高く、また糖尿病関連死亡率も高い傾向にある。本プロジェクトが、広大な面積を有する岩手県における糖尿病専門医数の絶対的不足と偏在による医療提供の格差を是正する端緒となれば幸いである。

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遠隔画像診断を発展させた岩手県広域ネットワークによる画像情報連携にむけて

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Prefecture-level wide area network to support imaging diagnosis in the area hit by the earthquake and tsunami

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要旨

震災による被災医療機関の支援として画像診断の遠隔読影に加えて、広域ネットワークによる被災拠点施設との画像情報管理・画像診断支援の推進に努め、最終的には県内陸の中核病院を含めた県全域での画像情報ネットワークの構築を目指す。このような試みは国内での先行例がないが、画像管理などに関わる問題点を抽出しながら構築に進める必要がある。

キーワード：遠隔画像診断、広域ネットワーク、画像情報管理

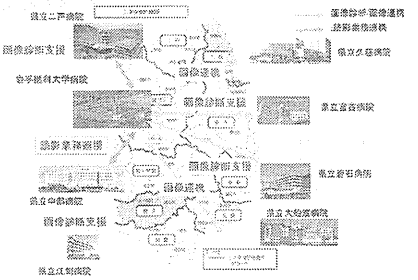
1. 背景

X線撮影やCTといった放射線機器は電源供給に大きく依存しており、災害時には有効に機能しない。さらにデジタル化された画像情報の利用も緊急時の使用には大きな障害が生ずる。MRIもその例外ではなく、超伝導MRI装置では磁場消失給の恐れられることにより希釈材である液体ヘリウムには発失の危険が生じる。装置への問題だけでなく、超伝導の強力なヘリウムの漏出には注意が伴う。また永久磁石装置は、装置の磁場や撮影を続力を保ち続けるため二次災害の危険を持っている。

その一方、1990年代以降推進されてきたDICOM形式による画像データ・フォーマットの共通化や日赤による画像情報システムの設行への動きは、異なる機器や施設で得られた画像情報が共通の基盤で保存や運用することを可能にし、広域ネットワークによる地域レベルでの画像情報の共有化や管理を可能にしてきている。クラウドを利用した画像情報データベースの構築などにより被災の危険の少ない画像情報保存が可能になっている。さらには平成年度で遠隔画像診断の精度に関する評価が行われており、環境整備はすでに進行している[1]。

2. 画像情報ネットワークの現状

岩手県の医師が大きく県内の医療機関が広く分散していることから、岩手医科大学医学部放射線医学講座では画像診断業務の県内病院への支援に関しては、遠隔診断への移行を少しずつ進めてきた。平成25年3月の現状では、県立宮古病院、県立中部病院の読影を岩手医科大学附属病院中央放射線部に置き読影を行っているが、画像情報の共



【図1】ネットワークの現状と将来

有化にまで至っていない。画像情報は紙媒体からのCDやDVDによる運搬に依存している。県立中部病院については、画像情報の物理的な移動による読影支援にとどまっている。

3. 広域ネットワークによる画像診断支援体制の構築に向けて

震災復興事業の目的は被災医療圏における画像診断支援体制の構築にあるが、具体的には以下の2点になる。すなわち、

1）被災地域医療施設（岩手4中核病院）との画像情報ネットワーク構築による画像情報の共有化と読影支援

2）地域連携の推進による内陸の岩手県立の中核病院も含めた県全体の画像診断支援体制の強化と強化

これらの実現は平成25年度から具体的な事業に入ることが予定されるが、その第一の目標は、岩手中央病院との画像情報管理を含めてネットワークの構築と、陸前高生病院を含めた遠隔画像診断の展開整備である。画像レポート管理体制の整備を通じたその情報共有もその一環である【図1】。

画像情報広域ネットワークの構築はアメリカでは多くの例があるが、国内では前単位で存在していない。岩手の県立4病院との画像情報管理の推進と情報の共有化はその手デルになることが期待される。画像診断支援の強化と推進を図り、最初の2病院との間で行い、その後の関連施設との画像情報共有化の推進を同のシステムに組み込むことにより、画像情報および画像診断情報の共有化を進めていく方針である。被災地区への支援の取組みを積極して可能な限りのコンサルテーションの範囲を拡大していくこと、また内陸の中核病院への支援を通じて県内の画像情報の共有化をさらに高めることにより、県下域での画像情報の共有化と画像診断支援体制を構築することが最終目標である。

4. 画像データ管理体制の問題点

現在考えられる画像データ管理体制としては、必要最小限のデータの維持は各病院で行うこと、保存用の画像データを岩手県大データセンターにおくこと、日常診療に利用するための画像データ（レポートを含む）の共有化を病院に進めることを考えている。異なる医療機関にまたがる患者の同一性の検証はデータセンターで十分に注意して病院に進める必要がある。アメリカの社会保険番号のような共通番号のない我が国にあって、異なるシステムでの同一患者の同定においては、氏名と生年月日で絞り込めるが、最終的には人間の判断が必要である。一つの問題としては、過去に手動で入力されたデータには誤入力の可能性が比較的高いことがあり、また医療機関ごとにデータ管理のレベルが異なるため、データの共有化に際しては必要なものから順番に進める必要がある。このようなデータ管理の実際的な運用については経験の不十分な点が大きく、これからの検討に待たれる。

5. 最後に

広域ネットワークによる被災各拠点施設との画像情報管理・画像診断支援の推進により、最終的には県内陸の中核病院を含めた県全域での画像情報ネットワークの構築を目指す。このような試みは、国内での先行例がないが、画像管理などに関わる問題点を抽出しながら構築に進める必要がある。

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Small-cell carcinoma of the breast with squamous differentiation

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Sir: The WHO classifies mammary carcinomas with neuroendocrine (NE) features as a special tumour entity representing <1% of invasive breast carcinomas.[1] *Small-cell carcinoma of the breast is a rare NE subtype that* may show aggressive clinical behaviour, whereas the other, more frequent, breast carcinomas with NE differentiation (cellular mucinous carcinoma and solid papillary carcinoma) are usually of low grade. To our knowledge, there is only one brief description concerning metaplastic change in these NE cancers.[2] Herein, we report an exceptionally rare small-cell mammary carcinoma showing squamous differentiation.

The patient, a 58-year-old postmenopausal Japanese woman, presented with a palpable mass in the upper outer quadrant of the right breast. Her family history included a sister with ovarian cancer. Ultrasonography revealed a well-defined, focally distorted, hypo-echoic right breast tumour. Systemic CT detected no other suspicious lesions. We performed ultrasound-guided, fine needle aspiration of the breast lesion, and the cytological diagnosis was carcinoma.

The cut surface of the mastectomy specimen contained a lobulated grey–whitish tumour, measuring 45 × 40 × 40 mm. Histopathologically, this invasive tumour was composed of solid and/or trabecular growths of densely packed, small to medium-sized carcinoma cells with well-developed vascular stroma (Figure 1A,B). Focal coagulation necrosis and haemorrhage were present. Carcinoma cells were polygonal or occasionally spindle-shaped, with high nuclear/cytoplasmic ratios and ovoid nuclei with finely granular chromatin and absent or inconspicuous nucleoli (Figure 1B). Mitotic figures were numerous [82 per 10 high-power fields (HPFs)]. Squamous differentiation, i.e. formation of nests of polygonal carcinoma cells with abundant, eosinophilic cytoplasm and intercellular bridging with focal keratin pearls, was found (Figure 1C). Mitotic activity was also present in this squamous component, but was lower (12 per 10 HPFs) than that in the small-cell component. Focal lymphatic permeation was detected. An *in-situ* ductal carcinoma component, predominantly showing cribriform architecture, and with comedo necrosis, was observed within and near the tumour mass (Figure 1A,D). No metastases were identified in the 18 excised right axillary lymph nodes.

Immunohistochemically, invasive carcinoma cells were diffusely positive for synaptophysin and CD56 (neural cell adhesion molecule, NCAM) and focally positive for chromogranin A, whereas cells showing squamous metaplasia were negative or weakly positive and *in-situ* cells were negative for these NE markers (Figure 2A). Carcinoma cells were diffusely positive for cytokeratin 7 and negative for cytokeratin 20. High molecular weight cytokeratin (34βE12) was clearly demonstrated only in carcinoma cells with *squamous metaplasia* (Figure 2B). *Gross cystic disease* fluid protein 15 (GCDFP15) was identified in 2% of the invasive carcinoma cells and in 20% of the *in-situ* carcinoma cells (Figure 2C). The tumour was oestrogen receptor-negative in both invasive and *in-situ* areas, whereas weak progesterone receptor reactivity was detected in the invasive carcinoma nuclei (positive cell rate: 1.5%), and the *in-situ* component was progesterone receptor negative. The HER2 score was estimated at 1+, and the *MIB-1* labelling index was 51.4%.

Reverse-transcriptase polymerase chain reaction (RT-PCR) analysis revealed overexpression of chromogranin A mRNA in the invasive cancer tissue.

Postoperatively, the patient received doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) every 4 weeks for four cycles as adjuvant chemotherapy. She remains alive and well, with neither recurrence nor metastasis, 49 months after surgery.

The possibility of metastatic small-cell carcinoma from another site should be ruled out.[1] Imaging and clinical history confirmed that our patient had no lesions in other organs, and an *in-situ* component accompanying the invasive breast cancer was demonstrated histologically. These are regarded as the two most important features for diagnosing primary small-cell mammary carcinoma.[2,3] In addition, GCDFP15 immunoexpression supports a diagnosis of primary NE carcinoma of the breast, despite oestrogen receptor negativity.[4] Furthermore, mammary NE carcinomas are generally cytokeratin 7-positive and cytokeratin 20-negative, whereas pulmonary small-cell carcinoma is negative for both.[1,2]

It has been suggested that mammary NE carcinomas generally result from a divergent differentiation

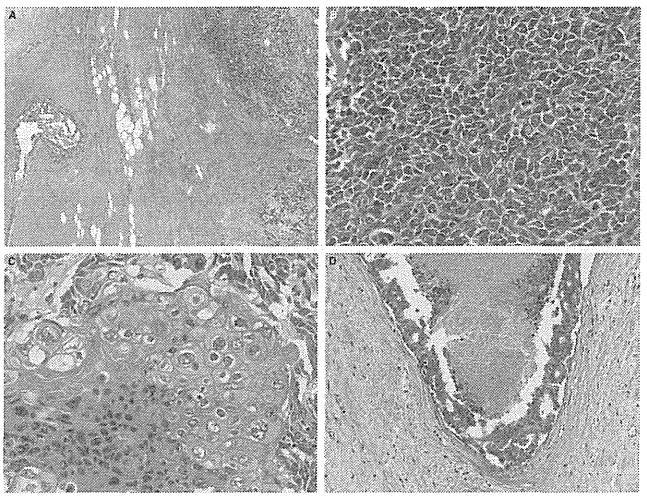

Figure 1. Histological findings of small-cell mammary carcinoma with squamous differentiation. A, Invasive region (right side) and proximally located *in-situ* component (left side). B, Cancer cells showing medullary invasive growth with a capillary network are polygonal or mildly fusiform in shape, and have relatively scant cytoplasm and hyperchromatic nuclei with frequent mitoses. C, Note the nest composed of polygonal cancer cells with abundant, eosinophilic and/or clear cytoplasm, irregularly shaped nuclei, and keratinization. D, *In-situ* component composed of ductal cancer cells arranged in glandular structures, with central necrosis.

event in breast cancer, because normal NE cells are almost never found in the breast,[4,5] whereas we recently described a hyperplastic condition of NE cells that was possibly relevant to the development of some mammary NE carcinomas.[6] In the present case, the *in-situ* ductal carcinoma component had no NE features, immunohistochemically or morphologically, and no normal-like and/or hyperplastic NE cells were detected in background breast tissue. It is thus reasonable to speculate that the breast cancer in this case acquired a small-cell NE nature divergently when *in-situ* cancer cells invaded surrounding stromal tissue or thereafter.

Papotti *et al.* reported that three of four patients with primary small-cell carcinoma of the breast died within 15 months after initial diagnosis, and, accordingly, that this type of tumour could represent an aggressive variant of breast cancer,[3] whereas Shin *et al.* emphasized that an important determinant of the outcome is the disease stage at the time of diagnosis.[2] In addition, invasive breast carcinomas with metaplastic features generally have a poor prognosis.[1] Interestingly, our patient with a highly unusual mammary small-cell carcinoma showing squamous metaplasia has remained alive and well for more than 4 years to date, with the standard treatment for operable infiltrating breast cancers. Despite the local tumour being large and the presence of vascular invasion, there was no evidence of lymph node or distant spread of the cancer (stage IIA), which may account for the patient's survival in this case.

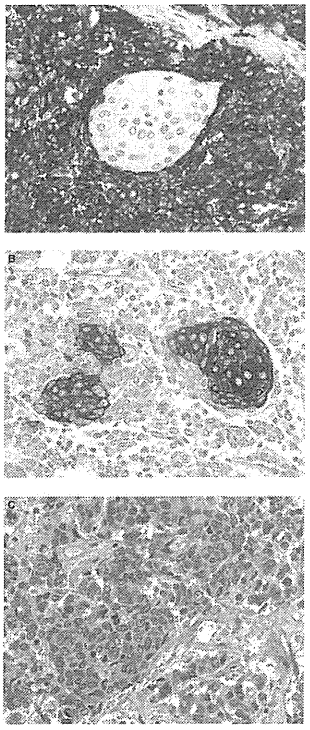

Figure 2. Immunohistochemical findings of small-cell mammary carcinoma with squamous differentiation. A, Synaptophysin immunohistochemistry is diffusely positive in most invasive cancer cells, but the component showing squamous differentiation is negative. B, In contrast, 34βE12 stains only areas showing squamous differentiation. C, Scattered GCDFP15-expressing cancer cells are observed in the invasive lesion.

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岩手県における震災に強い遠隔病理診断システム
―岩手モデルの提案―

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Telepathology in an earthquake disaster
― A proposal for Iwate Model ―

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要旨

東北地方は平成23年3月11日に東日本大震災により未曾有の被害を受けた。それによって被災地の医療は壊滅的な打撃を受け、今後も医療支援が重要となる。今回のような津波と地震による揺れなどによる被害の特徴は、回復不能な被害ということである。これまでの医療支援では到底十分とは言えず、その対応は根本的な発想の転換が必要である。遠隔医療システムは、今回のような被災地支援に有効と思われる。県内の基幹病院を光ファイバーでネットワーク化し、遠隔病理診断に必要な病理診断システム、バーチャルスライド、などを整備することによって効果的、効率的な遠隔病理診断システムの構築が可能になる。今後の遠隔病理診断システムの整備が期待される。

キーワード：バーチャルスライド、遠隔病理診断、病理診断システム、震災

1. はじめに

平成23年3月11日に東北地方は未曾有の災害に直面した。沿岸地方を中心に津波と地震による甚大な被害を受け、多くの人命も失われた。この際、沿岸地方の基幹病院も同様の被害を受け、その機能が低下したことは多くの者が知るところである。一方それに加え交通網の寸断、ガソリンの供給不足からくる交通機関の麻痺も大きな影響を与えた。このような惨禍の中で発災直後より本学は岩手県と連絡を密にして、組織的な医療支援を行ってきた訳であるが、これまでの医療支援のあり方では、今回のような大震災には、十分な医療支援が行えないことも私たちに教えた。

日本は四方を海に囲まれており、地震が起きた場合には、地震による揺れや建物の崩壊による被害のみでなく、津波による被害も念頭に置いて災害時の対応を考えるべきである。今回の震災は、本邦における災害時の対策をいかにして構築すべきについて、大きな教訓を与えた。

最近病理診断の領域を中心に遠隔医療が大きな発展をみせている。ITの進歩により、鮮明な画像や人と人とのコミュニケーションをリアルタイムに行うことが可能になってきた[1-3]。今回のような複合型の震災に対して、遠隔医療のシステムは重要なツールであり、震災時の診療に必要な医療を提供するための有用な役割を担うことになる[4-5]。本稿では病理診断の面から今回のような複合型の被害への対応策について我々の考え方を述べる。

2. 津波による被害の特徴

津波の被害の特徴は、一瞬にして全てを消し去るということである。津波の場合は、被害を受けた後に、診療の回復を回復することは全く不可能である。病理検体標本、ガラス標本、標本ブロック、病理情報（紙情報であれ電子情報になる）、などは完全に喪失することになる。これまで蓄積してきた院内の病理情報は跡も形もなくなる訳で、ある程度の使用可能な状態を残す地震による揺れや建物の倒壊の場合とは大分様相が異なる。

3. 地震による被害

地震による揺れや建物の倒壊によっても病理情報は甚大な被害を受ける。この点では前述の津波による被害と共通する。しかし、基幹病院の多くは耐震や免震の対策を受けており、よほどのことがない限り全倒壊のような被害は想定しにくい。火災による被害は十分考慮すべきであるが、病院のような場所で大きな火災が発生することも考えにくいと思われる。そうなると地震による直接的な病院本体の被害は限定的と思われる。そうは言っても、揺れによる被害は病理情報の散逸化や欠損を生じさせるので、十分な対策が必要であることは言うまでもない。次に忘れてはならないのは、地震による道路の寸断、交通機関の混乱によって交通網の麻痺が生ずることである。人の往来のみでなく、物の行き来も十分に行えなくなる。このことは今回の震災によって津波による被害と共に生じたもう1つの問題点である。

4. 震災に強い病理診断システムの構築

上記の観点から、今回のような津波と地震による揺れの被害から、貴重な病理情報を守るためには、次のような対策を講じる必要がある。まずは、ガラス標本の散逸化、破損のリスクを軽減させる対策である。ガラス標本の作製は、現時点では病理診断にとって必要不可欠であるから、ガラス標本が破損することを完全に予防することは現状では困難である。ガラス標本の情報をデジタル化することにより、

ガラス標本を電子化することが可能になる[1-2]。そうすれば、仮にガラス標本が破損しても、完全な形で病理情報は残せることになる[2-3]。この方法が現時点では最も有効な方法と思われる。また災害時の問題とは異なるが、ガラス標本の保存はどこの病理施設でも頭痛の種である。ガラス標本は、1枚1枚は軽いが、年間何万枚ともなるとその重量は相当に重く、それを何十年も保存することは至難の業である。ガラス標本のデジタル化は、この点にも朗報となることは間違いない。

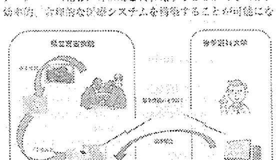
ガラス標本のデジタル化であるが、バーチャルスライド(VS)が最も有効な機器である。いくつかのメーカーから発売されているが、我々が今回採用したのは、ライカ社製のScanscope（最大4Mbps）である。連続枚数は、5枚版と400枚版があるが、スキャン時間は変わらない（通常の送信標本：1cm四方で、約2-3分程度、ファイルサイズはJPEG2000で100-200MB程度）。このVSの優れている点は、顕微鏡的機能も持っていることである。受け手から送り手のVSの台部を操作して、顕微鏡的に使用することも可能である。今回このVSを使用して県内の基幹病院との起動実験を行ったが、結果は良好であった【図1、2】。実際の運用にも支障はないものと思われる。

次に重要な要素となるものが、病理診断情報の共通化・共有化とデータベース化である[1-3]。これらはVS化した場合の基本となるものである。本県では、本学と各県立病院の病理診断システムの共通化・共有化が進んでいるが、沿岸部では、半分の基幹県立病院で本学との共通の病理診断システムが整備されていない。これが未整備のままとなると、本学と各基幹病院との病理情報の共有化も困難になることが予想される。また一方で、病理情報のデータベース化も重要である[5]。病理情報は病院各科にとって欠くことのできない重要な情報を多く含んでいる。病理情報をデータベース化し、各病院と共有化することができれば、効率的、合理的な医療システムを構築することが可能になる。遠隔医療を進めるにあたって病理診断システムの共通化・共有化は根幹となるシステムである。

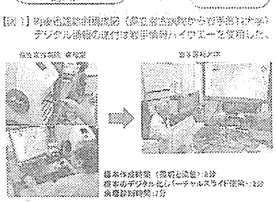
最後に遠隔医療を円滑に行うためには東北地方特有の病理医不足のことは考慮しておく必要がある。いかに優れたシステムであってもそれを動かすのは人間である。システムが有効に作動するのも、しないのも、システムそのものの優劣性はもちろんであるが、それより重要なのは、それを担う人間の育成であることを忘れてはならない[3]。本県における病理医の育成は待ったなしの状況にある。遠隔病理診断システムの整備と同時に病理医の育成事業を同時に行うことが、本システムが成功するかどうかを決めることになろう。

最後における今回の岩手県基幹病院とのVSによる遠隔医療の概略を示す。遠隔医療システムの構築に必要な要素は、主に、VSスキャナー、VS配信サーバー、病理診断システムである【図3】。本学には画像解析ソフトも加わる予定になっているが、これは効率良く病理診断を行うためである。実際には、2名の病理専門医のいる県立中央病院もこのシステムに参加予定になっているが、それによってより効率的、効果的な病理支援が可能になるものと思われる。将来的には、他の基幹病院にも拡張を進められると、まさに全県に跨れる病理遠隔病理診断システムが完成することになるが、今後の検討課題になるものと思われる。

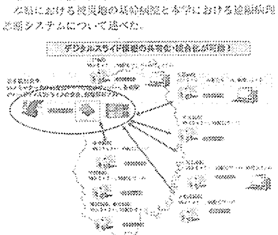
本稿における被災地の基幹病院と本学における遠隔病理診断システムについて述べた。



【図1】遠隔病理診断構成図（県立宮古病院から岩手医科大学）デジタル情報の送付は岩手情報ハイウエーを使用した。



【図2】県立宮古病院における実際の術中迅速診断の様子
標本作製時間は8分、デジタル時間は2分、病理診断時間は2分であった。



【図3】最終的に医療が統合される病理診断システム統合化計画案

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Case Report

Electrical storm after cardiac resynchronization therapy in a patient with nonischemic cardiomyopathy: Signal-averaged vector-projected 187-channel electrocardiogram-based risk stratification for lethal arrhythmia

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ABSTRACT

We describe treatment of atrial flutter and electrical storm presenting as incessant ventricular tachycardia (VT) after implantation of a cardiac resynchronization therapy defibrillator (CRT-D) in a patient with dilated cardiomyopathy. No prior arrhythmic event had occurred. Our treatment strategy, including amiodarone administration, was guided in part by signal-averaged vector-projected 187-channel electrocardiogram (SAVP-ECG)-based risk stratification for ventricular arrhythmia. Corrected recovery time (RTc) dispersion and Tpeak-end dispersion were used to evaluate transmural dispersion of repolarization. RTc and Tpeak-end dispersion increased during the period of electrical storm. Values were improved 2 years after CRT-D implantation, and the amiodarone was discontinued. The VT has not recurred despite discontinuation of the antiarrhythmic agent. SAVP-ECG-based risk stratification for ventricular arrhythmia proved useful for the management of antiarrhythmic therapy.

1. Case report

A 77-year-old man with dilated cardiomyopathy visited our hospital in December 2010 and reported dyspnea on effort. Echocardiography revealed cardiac dyssynchrony with a low ejection fraction of 29%, and the patient was diagnosed with New York Heart Association class III heart failure. The plasma N-terminal pro-B-type natriuretic peptide (NT-pro BNP) level was 3691 pg/mL. The electrocardiogram (ECG) QRS complex (136 ms) was widened to 136 ms, with a left bundle branch block conturation (Fig. 1). The patient was being treated with spironolactone (aldactone), β-blocker (carvedilol), and angiotensin II receptor antagonist (captopril). Implantation of a cardiac resynchronization therapy defibrillator (CRT-D) was scheduled and performed in May 2011, without any complications. After implantation of the right ventricular (RV) lead in the RV apex, coronary venography was performed, and a suitable lateral branch was identified as a candidate vessel for left ventricular (LV) lead implantation. The LV lead was positioned at the midportion of the lateral branch. The LV pacing threshold was 0.5 mV at 0.5 ms without phrenic nerve stimulation. The right atrial (RA) lead was then positioned at the RA appendage. The following device and leads were used: Promote RF generator, Durata 7120Q RV defibrillation lead, QuickFlex 1158T LV lead, and Tendril STS RA lead (St. Jude Medical, St. Paul, Minnesota, USA). The RV pacing threshold was 0.75 V at 0.4 ms, and the RA pacing threshold was 0.5 V at 0.4 ms. The device was programmed with a ventricular tachycardia (VT) zone set to ≥166 bpm (therapies = antitachy pacing (ATP) × 3, shock 10 J, 25 J, 36 J × 4) and a ventricular fibrillation (VF) zone set to ≥230 bpm (therapies = shock 15 J, 36 J × 4).

After CRT-D implantation, the QRS duration decreased to 122 ms (Fig. 2), and the cardiac dyssynchrony improved. However, 5 days after implantation, atrial flutter (AFL) and electrical storm presenting as frequent VT were seen. As shown in Fig. 3A, the VT was initiated by a premature ventricular complex. The CRT-D intracardiac tracing showed both AFL and VT. Appropriate shocks were delivered, and both the AFL and VT were terminated (Fig. 3B); however, incessant VT developed after restoration of sinus rhythm. A total of 9 VT zone shocks were delivered. Biventricular pacing was discontinued, and intravenous administration of amiodarone was initiated to inhibit VT. The VT abated within 1 week, and CRT was restarted. Oral amiodarone was administered to prevent VT recurrence. To determine the risk of ventricular arrhythmia, we evaluated the corrected recovery time (RTc) dispersion and Tpeak-end dispersion on a signal-averaged vector-projected 187-channel electrocardiogram (SAVP-ECG). RTc and Tpeak-end dispersion increased during the period of electrical storm (average, 15 ms and 48 ms, respectively; Fig. 4A). These findings suggest that transmural dispersion of repolarization increased in our patient, leading to ventricular proarrhythmia. Two years after implantation of CRT-D, follow-up SAVP-ECG showed decreased augmentation of RTc dispersion and Tpeak-end dispersion (17 ms and 13 ms, respectively; Fig. 4B). It remains unclear whether this improvement was the result of time or the administration of amiodarone. We halved the dose of amiodarone before withdrawing the drug altogether. No VT recurrence occurred despite discontinuation of the antiarrhythmic agent.

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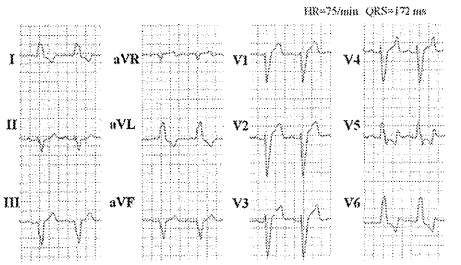

Fig. 1. Twelve-lead electrocardiogram obtained before CRT shows a wide QRS complex with left bundle branch block.

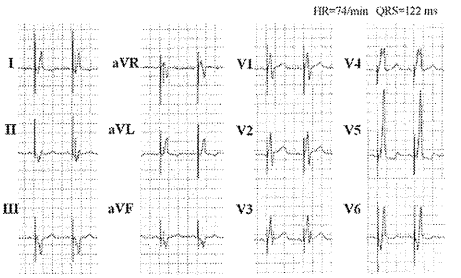

Fig. 2. Twelve-lead electrocardiogram obtained after CRT shows narrowing of the QRS complex compared to that before CRT.

2. Discussion

Proarrhythmic events after CRT have been reported in 5–10% of CRT recipients [1–4]. Gasparini et al. investigated the incidence of electrical storm in patients with heart failure treated with CRT and reported an increased incidence in patients with nonischemic cardiomyopathy in whom a CRT-D was implanted for secondary prevention [5]. In most cases, the arrhythmia can be managed by administration of an antiarrhythmic agent and/or discontinuation of LV pacing within 1 month after implantation of the CRT system. Kantharia et al. reported a case of electrical storm induced by CRT. The VT did not disappear even after extraction of the LV lead, and catheter ablation was performed to control the VT [6]. In another case, VT was induced by biventricular pacing and controlled by triple-site biventricular pacing and atrioventricular node ablation [7]. In contrast, CRT has been reported to suppress arrhythmias in some cases [8–10]. These reports suggest that the suppression is not due to the effects of pacing itself. Rather, reverse remodeling with CRT can decrease the AFL burden and frequency of ventricular arrhythmias.

The mechanism underlying the proarrhythmic effect of CRT is not well understood. One explanation is that transmural dispersion of repolarization increases with LV pacing. Bai et al. studied the effects of LV epicardial pacing and biventricular pacing in a canine model of dilated cardiomyopathy [11] and showed that both LV epicardial pacing and biventricular pacing prolonged the ventricular repolarization time and increased transmural dispersion of repolarization. Prolonged transmural dispersion occurred parallel to augmentation in the Tpeak-end interval. According to Scott et al., CRT with transseptal

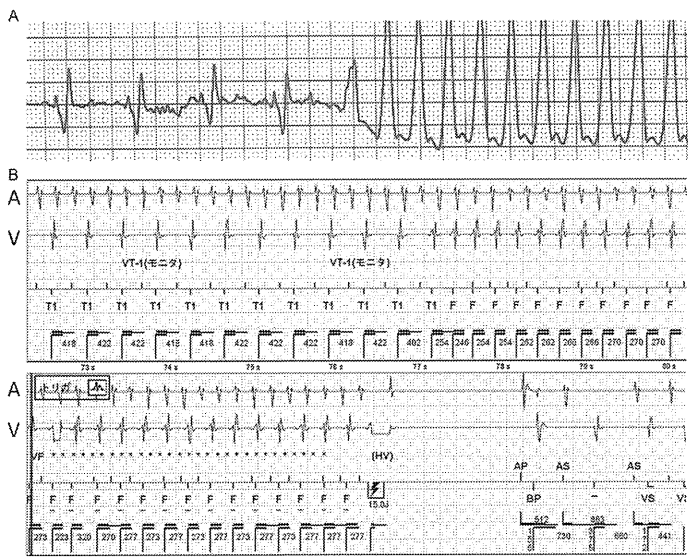

Fig. 3. Cardiac monitor tracing and intracardiac electrocardiogram shows atrial fibrillation and ventricular tachycardia episodes 5 days after CRT-D implantation.

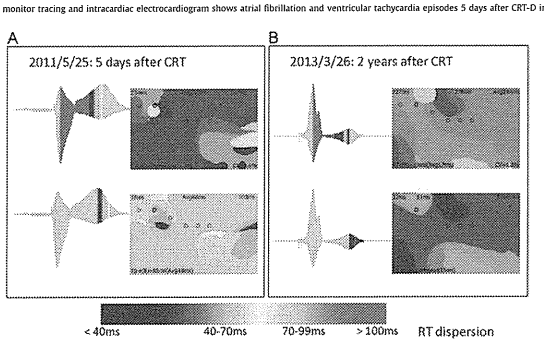

Fig. 4. RTc and Tpeak-end dispersion assessed on SAVP-ECG obtained 5 days and 1 year after CRT implantation. RTc and Tpeak-end dispersion were improved 2 years after CRT implantation.

endocardial LV pacing (in comparison with epicardial LV pacing) reduced QTc and Tpeak-end dispersion, and these authors concluded that transseptal LV pacing may be less arrhythmogenic [12]. Barbhaiya et al. looked at the relationship between ventricular arrhythmia, the QT interval, and Tpeak-end dispersion and found that increases in Tpeak-end dispersion and Tpeak-end/QT ratio were associated with an increased incidence of ventricular arrhythmia in patients with a CRT-D [13]. Another group also reported an association between Tpeak-end dispersion and major arrhythmic events [14].

Nakai et al. showed that RTc and Tpeak-end dispersion can be used to evaluate the spatial distribution of myocardial repolarization [15,16]. We measured RTc and Tpeak-end dispersion in the acute and chronic periods in the case reported herein. Both variables were increased during the acute period after CRT, suggesting that repolarization heterogeneity was augmented before being modified by amiodarone. These changes are consistent with previous reports of prolongation of the Tpeak-end interval with LV pacing. On the follow-up SAVP-ECG, RTc and Tpeak-end dispersion had decreased to within safe ranges. There is no standard index for use of antiarrhythmic agents, and it is difficult to make the decision to stop an antiarrhythmic agent once it is started, even if the patient is free of arrhythmia. In the present case, RTc/Tpeak-end dispersion increased in the acute phase after CRT, suggesting a potential substrate for ventricular arrhythmia, but both measures decreased to within normal range with amiodarone administration and with time. We controlled the dose of amiodarone in response to the low risk for ventricular arrhythmia indicated by the SAVP-ECG. Our experience in this case highlights the importance of risk stratification for lethal arrhythmia after CRT.

3. Conclusion

We treated a patient who experienced electrical storm after CRT-D implantation. Our treatment strategy was guided in part by SAVP-ECG-based risk stratification for ventricular arrhythmia. Our SAVP-ECG findings indicate that the proarrhythmic effect of CRT may be due to repolarization heterogeneity induced by LV pacing. The SAVP-ECG findings allowed us to both administer and withdraw the antiarrhythmic agent effectively; therefore, we suggest use of SAVP-ECG as a risk stratification tool in cases of CRT-induced electrical storm.

Conflict of interest

There is no conflict of interest related to this report.

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スマートフォンを用いた新しい心電図伝送システムとホルター心電図法との比較

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The new ECG telemedicine system using a smart phone; Comparison of Holter ECG

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Abstract：We have developed a new wireless ECG monitoring system (ABS-1) which transmits data via a Bluetooth-equipped smartphone. The quality of ABS-1 ECG was compared against the Holter ECG's in healthy volunteers. At the lowest heart rate of each individual, ABS-1 and Holter devices recorded identical waveforms of ECG. The results suggest that this new Bluetooth wireless ECG monitoring system can become a future compact and inexpensive ECG monitoring tool for health care management at home.

Keywords：ECG, Bluetooth, smartphone

要旨

スマートフォンに標準的に装備されている Bluetooth を使った心電計（ABS-1）を開発した。このABS-1を使ったシステムから得られる心電図の品質を評価するために、ホルター心電計とABS-1を同時に装着して、その波形の比較を行った。本研究の結果、最小心拍数では両者の波形に違いは認められなかった。あたらしい心電図伝送システムは、小型で安価なシステムとして在宅医療や健康管理に活用されることが期待される。

1. はじめに

スマートフォンに標準的に装備される Bluetooth を使った通信機能をもつ小型心電計（ABS-1）を開発した。本システムの臨床的有用性を検討する基礎データとしてホルター心電図検査の波形と心拍数トレンドグラフの追従の検討を行った。また従来から普及しているホルター心電図法やイベントレコーダーと比較した特性について若干の文献的考察を行った。

2. 対象

健常ボランティア6名（男性3名、女性3名、平均52±10歳）

3. 方法

ホルター心電計（テルモ社製 Holtrec）と新しく開発した心電計（ABS-1）のそれぞれの特性について【表1】に示した。ホルター心電計とABS-1を同時に同一被験者に装着し、約2時間の心電図記録を行った。ホルター心電計は2誘導（NASAとCM5）、ABS-1は1誘導（日本光電社製ディスポ電極 T-50）を用いた【図1】。ホルター心電計の心電図データは本体内のフラッシュメモリーに記録され、検査終了後に専用機器（有線クレドール）に

【表1】ホルター心電計（Holtrec）とABS-1の性能比較

	Holtrec	ABS-1
誘導数	2チャンネル	1チャンネル
入力信号電圧範囲（mV）	DC±150、AC±5	DC±6、AC±6
周波数特性（Hz）	0.05～40	0～50
測定精度	10bit、128Hzサンプリング	12bit、200Hzサンプリング
記録媒体	32MBフラッシュメモリ	2GBフラッシュメモリ
通信方式	有線	無線（bluetooth）
記録時間	最長25時間	250時間
満充電での連続稼働時間	不明（25時間保証）	9時間
電源	ボタン形リチウム電池（CR2032）1個、DC3V	充電式リチウム電池　DC3.7V
サイズ、幅×高さ×厚さ mm	50×65×10	40×60×14
質量（電池含む）	30g	35g
EMC規格適合	IEC60601-1-2:1993年	なし

Heart Vessels
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ORIGINAL ARTICLE

Impacts of age on coronary atherosclerosis and vascular response to statin therapy

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Abstract Age is a well-established risk factor for cardiovascular disease. Recent trials using intravascular ultrasound (IVUS) have shown that lipid-lowering therapy with statins halts the progression or induces the regression of coronary artery plaques. However, impacts of age on coronary atherosclerosis and vascular response to statin therapy have not been fully evaluated. The effects of 8-month statin therapy on coronary atherosclerosis were evaluated using virtual histology-IVUS. IVUS data were analyzed from 119 patients who were divided into two groups according to age: elderly patients (≥65 years, $n = 72$) and non-elderly patients (<65 years, $n = 47$). No patients were taking statins or other lipid-lowering therapies at baseline. At baseline, external elastic membrane (EEM) volume (17.27 vs. 14.95 mm^3/mm, $p = 0.02$) and plaque volume (9.49 vs. 8.11 mm^3/mm, $p = 0.03$) in the elderly patients were significantly greater than in the non-elderly patients. The EEM volume (−2.4 %, $p = 0.007$) and plaque volume (−3.1 %, $p = 0.007$) after 8-month of statin therapy had significantly decreased in the non-elderly patients but not in the elderly patients. A significant positive correlation was observed between age and percentage change in plaque volume ($r = 0.265$, $p = 0.004$). A multivariate regression analysis showed that age was a significant predictor of the percentage change in plaque volume during statin therapy ($\beta = 0.223$, $p = 0.02$). Coronary atherosclerosis was more advanced and vascular responses to statin therapy were attenuated in the elderly patients compared to the non-elderly patients.

Keywords Age · Atherosclerosis · Coronary artery disease · Statin · Virtual histology intravascular ultrasound

For the TRUTH Investigators.

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Introduction

Age is a well-established risk factor for cardiovascular disease and silent atherosclerosis. In addition to the high likelihood of other cardiovascular risk factors being present in the elderly, aging process itself induces structural and functional changes in the vascular wall [1]. Plaque burden has reported to increase with advancing age [2–5]. Recent trials using intravascular ultrasound (IVUS) have shown that statins halt the progression or induce the regression of coronary artery plaques [6, 7]. However, impacts of age on coronary artery plaques before and during statin therapy have not been fully evaluated. Therefore, in the present study, we examined the impacts of age on coronary atherosclerosis and vascular response to statin therapy using virtual histology (VH)-IVUS.

Materials and methods

The present study is a post hoc subanalysis of the treatment with statin on atheroma regression evaluated by intravascular ultrasound with virtual histology (TRUTH) study, a prospective, open-labeled, randomized, multicenter trial performed at 11 Japanese centers to evaluate the effects of 8-month treatment with pitavastatin versus pravastatin on coronary atherosclerosis using VH-IVUS [8]. Details of the study design have been reported previously [9]. In brief, 164 patients with angina pectoris were randomized to either pitavastatin (4 mg/day, intensive lipid lowering) or pravastatin (20 mg/day, moderate lipid lowering) therapy after successful percutaneous coronary intervention (PCI) under VH-IVUS guidance. No participants were taking statins or other lipid-lowering therapies at study enrollment. Follow-up IVUS examinations were performed after 8 months of statin therapy. The patients were included in the present study if they had measurable IVUS-detected lesions at both enrollment and the 8-month follow-up. Forty-five patients were excluded because of the following reasons: withdrew consent in three patients, lost to follow-up in seven patients, IVUS images were not obtained or not analyzable in 28 patients, and adverse events in seven patients [8]. In total, 119 patients were divided into two groups according to age: elderly patients (≥65 years, $n = 72$) and non-elderly patients (<65 years, $n = 47$). We compared grayscale and VH-IVUS parameters at baseline and at the 8-month follow-up and compared changes in these parameters between the elderly and non-elderly patients.

The TRUTH trial was conducted in accordance with the Declaration of Helsinki and with the approval of the ethical committees of the 11 participating institutions. Each patient enrolled in the study provided written informed consent.

Details of the IVUS procedure and examination have been previously reported [8]. In brief, after PCI of the culprit lesion, IVUS was used for examining angiographic lesions with <50 % lumen narrowing on the distal and proximal sides of the culprit lesion in the PCI vessel. An IVUS catheter (Eagle Eye Gold, Volcano, San Diego, CA, USA) was used, and a motorized pullback device withdrew the transducer at 0.5 mm/s. During pullback, a grayscale IVUS was recorded, and raw radiofrequency data were captured at the top of the R wave using a commercially available IVUS console (IVG3, Volcano) [10]. After 8 months of statin therapy, the IVUS examination was repeated in the same coronary artery using the same type of IVUS catheter used at baseline.

An independent and experienced investigator (M. T.) performed all baseline and follow-up IVUS core laboratory analyses in a blinded manner. Before the IVUS analysis, the baseline and follow-up IVUS images were reviewed side by side on a display, and the distal and proximal ends of the target segment were identified on the basis of the presence of reproducible anatomic landmarks such as the side branch, vein, and stent edge. Plaques close to the PCI site (within 5 mm) were excluded. Manual contour detection of the lumen and the external elastic membrane (EEM) was performed for each frame. Quantitative IVUS grayscale analysis was performed according to the guidelines of the American College of Cardiology and European Society of Cardiology [11]. All volumetric data were divided by lesion length to obtain a volume index. VH-IVUS data analysis was determined by grayscale border contour calculation, and the relative and absolute amounts of the different coronary artery plaque components were measured using IVUS Lab, version 2.2 (Volcano).

Blood examinations for lipid levels were performed at baseline and at the 8-month follow-up. The serum lipids, apolipoproteins, and high-sensitivity C-reactive protein (hs-CRP) levels were measured at a central clinical laboratory (SRL, Inc., Tokyo, Japan). The serum levels of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA) in conserved frozen samples obtained at baseline and at the 8-month follow-up were measured annually by a central laboratory (BML, Inc., Kawagoe, Japan).

Statistical analyses were performed using StatView, version 5.0 (SAS Institute, Cary, NC, USA). The results were expressed as mean ± SD. Differences in continuous variables between the two groups were compared using an unpaired Student's t test when the variables showed a normal distribution and the Mann–Whitney U test when the variables were not normally distributed. Differences in continuous variables within each group were compared using paired Student's t tests when the variables showed a normal distribution and Wilcoxon's signed-rank sum tests when the variables were not normally distributed. Categorical variables between the two groups were compared using Chi-square tests or Fisher's exact tests. Univariate regression analyses were performed to assess the correlations between the percentage change in plaque volume and several parameters, including nominal variables (gender, coronary artery disease status, hypertension, diabetes mellitus, smoking, and type of statin) and numerical variables [age, estimated glomerular filtration rate (eGFR), percentage change in low-density lipoprotein cholesterol (LDL-C), small, dense low-density lipoprotein (sd-LDL), high-density lipoprotein cholesterol (HDL-C), and hs-CRP, and change in the EPA + DHA/AA ratio). The variables with a p value <0.2 on univariate analysis were entered into multivariate models. Statistical significance was set at $p < 0.05$.

Results

The baseline characteristics of the subjects are listed in Table 1. No significant differences were present in the baseline characteristics between the two groups, except for age (73 vs. 56 years, $p < 0.0001$) and eGFR (60.6 ml/min/1.73 m^2 vs. 70.3 ml/min/1.73 m^2, $p = 0.0004$). The frequency of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker use tended to be higher in the elderly patients (58 vs. 40 %, $p = 0.06$).

The risk factor controls at baseline and at the 8-month follow-up are listed in Table 2. Serum LDL-C levels decreased significantly in both groups, and these levels at the 8-month follow-up were significantly low in the elderly patients compared to those in the non-elderly patients (81 vs. 91 mg/dl, $p = 0.02$). A significant increase in HDL-C levels and decreases in apolipoprotein B, sd-LDL, and hs-CRP levels were observed in both groups. However, apolipoprotein B (70 vs. 79 mg/dl, $p = 0.009$) and sd-LDL levels (17 vs. 21 mg/dl, $p = 0.04$) at the 8-month follow-up were significantly low in the elderly patients. The serum EPA + DHA/AA ratio in the elderly patients tended to decrease at the 8-month follow-up.

Table 1 Baseline characteristics of subjects

	Elderly ($n = 72$)	Non-elderly ($n = 47$)	p value
Age (years)	73 ± 5	56 ± 6	<0.0001
Men	57 (79 %)	42 (89 %)	0.21
Body mass index (kg/m^2)	24.1 ± 3.4	25.0 ± 3.2	0.2
eGFR (ml/min/1.73 m^2)	60.6 ± 14.5	70.3 ± 14.0	0.0004
Treatment allocation			0.25
Pitavastatin	32 (44 %)	26 (55 %)	
Pravastatin	40 (56 %)	21 (45 %)	
Status of coronary artery disease			0.12
Stable angina pectoris	54 (75 %)	29 (62 %)	
Unstable angina pectoris	18 (25 %)	18 (38 %)	
Target coronary artery			0.3
Left anterior descending	38 (53 %)	29 (62 %)	
Left circumflex	2 (3 %)	3 (6 %)	
Right	32 (44 %)	15 (32 %)	
Hypertension	48 (67 %)	27 (57 %)	0.31
Diabetes mellitus	32 (44 %)	18 (38 %)	0.51
ACE-Is or ARBs	42 (58 %)	19 (40 %)	0.06
β blockers	7 (10 %)	6 (13 %)	0.6
Calcium channel blockers	38 (53 %)	22 (47 %)	0.52
Insulin	7 (10 %)	4 (9 %)	>0.99
Thiazolidinedione	5 (7 %)	1 (2 %)	0.4
Follow-up duration (days)	229 ± 35	225 ± 38	0.56

Data are expressed as mean ± SD or as number (percentage)

eGFR estimated glomerular filtration rate, *ACE-Is* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin-receptor blockers

The parameters evaluated using grayscale and VH-IVUS are listed in Table 3. At baseline, EEM volume index (17.27 vs. 14.95 mm^3/mm, $p = 0.02$) and plaque volume index (9.49 vs. 8.11 mm^3/mm, $p = 0.03$) in the elderly patients were significantly greater than in the non-elderly patients. EEM volume index (−2.4 %, $p = 0.007$) and plaque volume index (−3.1 %, $p = 0.007$) had significantly decreased only in the non-elderly patients. Furthermore, the percentage change in plaque volume index was generally different between the two groups (0.0 vs. −3.1 %, $p = 0.07$). In addition, EEM volume index and plaque volume index at the 8-month follow-up were significantly greater in the elderly patients than those in the non-elderly patients. Decreases in the fibro-fatty plaque component, and increases in the calcified and necrotic-core components were observed in both groups, while the fibrous component decreased significantly only in the non-elderly patients. The fibro-fatty component volume index at baseline (1.26 vs. 0.79 mm^3/mm, $p = 0.008$) and at the 8-month follow-up (0.96 vs. 0.62 mm^3/mm, $p = 0.01$) in the elderly patients was significantly greater than in the non-elderly patients.

The percentage change in plaque volume during statin therapy significantly positively correlated with age ($r = 0.265$, $p = 0.004$; Fig. 1; Table 4) and negatively correlated with change in the EPA + DHA/AA ratio ($r = -0.240$, $p = 0.02$; Table 4). A multivariate regression analysis showed that age ($\beta = 0.223$, $p = 0.02$) and change in the EPA + DHA/AA ratio ($\beta = -0.209$, $p = 0.04$) were significant predictors of the percentage change in plaque volume during statin therapy (Table 4).

Table 2 Risk factor control at baseline and at follow-up

	Elderly ($n = 72$)			Non-elderly ($n = 47$)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
TC (mg/dl)	200 ± 35	154 ± 27*	<0.0001	213 ± 37	166 ± 29	<0.0001
% change		−22 ± 13			−21 ± 11	
LDL-C (mg/dl)	128 ± 31	81 ± 22*	<0.0001	138 ± 32	91 ± 28	<0.0001
% change		−35 ± 17			−34 ± 14	
Triglycerides (mg/dl)	120 ± 49*	112 ± 70	0.31	149 ± 82	123 ± 52	0.02
% change		−3 ± 46			−7 ± 39	
HDL-C (mg/dl)	48 ± 10	51 ± 12	0.02	45 ± 12	51 ± 13	0.0003
% change		9 ± 25			15 ± 22	
Apolipoprotein AI (mg/dl)	119 ± 19	132 ± 27	<0.0001	116 ± 22	132 ± 22	<0.0001
% change		12 ± 19			15 ± 16	
Apolipoprotein B (mg/dl)	99 ± 21**	70 ± 16**	<0.0001	111 ± 24	79 ± 18	<0.0001
% change		−28 ± 16			−28 ± 13	
Sd-LDL (mg/dl)	23 ± 12*	17 ± 9*	<0.0001	30 ± 16	21 ± 9	0.0009
% change		−17 ± 41			−17 ± 51	
Hs-CRP (ng/ml)	12,620 ± 36,146	2,652 ± 5,646	0.02	12,189 ± 17,197	2,369 ± 4,429	0.0006
% change		−42 ± 85			−41 ± 118	
EPA/AA	0.49 ± 0.27	0.49 ± 0.30	0.76	0.46 ± 0.27	0.50 ± 0.34	0.24
Change		0.01 ± 0.18			0.04 ± 0.21	
DHA/AA	1.01 ± 0.33	0.92 ± 0.31	0.004	0.94 ± 0.33	0.85 ± 0.35	0.06
Change		−0.09 ± 0.23			−0.08 ± 0.27	
EPA + DHA/AA	1.49 ± 0.55	1.41 ± 0.55	0.08	1.40 ± 0.56	1.36 ± 0.67	0.53
Change		−0.08 ± 0.37			−0.04 ± 0.43	
SBP (mmHg)	137 ± 21	135 ± 23	0.45	131 ± 23	133 ± 21	0.37
% change		0 ± 17			4 ± 16	
DBP (mmHg)	74 ± 10	73 ± 11**	0.5	79 ± 15	80 ± 14	0.59
% change		0 ± 19			3 ± 18	

Data are expressed as mean ± SD

TC total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *sd-LDL* small, dense low-density lipoprotein, *hs-CRP* high-sensitivity C-reactive protein, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *AA* arachidonic acid, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

* $p < 0.05$, ** $p < 0.01$ compared to non-elderly

Discussion

The major findings of the present study were as follows: first, coronary atherosclerosis was more advanced in the elderly patients because EEM and plaque volume at baseline were significantly greater than in the non-elderly patients. Second, we determined that vascular responses to statin therapy were attenuated in the elderly patients on the basis of the significant decreases in EEM and plaque volume were observed only in the non-elderly patients, and

Table 3 Parameters evaluated using grayscale and virtual histology intravascular ultrasound

	Elderly ($n = 72$)			Non-elderly ($n = 47$)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
EEM volume index (mm^3/mm)	17.27 ± 5.49*	17.12 ± 5.55**	0.19	14.95 ± 4.71	14.52 ± 4.54	0.007
% change		−0.9 ± 5.1			−2.4 ± 6.3	
Plaque volume index (mm^3/mm)	9.49 ± 3.63*	9.43 ± 3.52**	0.57	8.11 ± 2.56	7.80 ± 2.40	0.007
% change		0.0 ± 9.1#			−3.1 ± 8.9	
Lumen volume index (mm^3/mm)	7.78 ± 2.53*	7.69 ± 2.63*	0.43	6.83 ± 2.63	6.72 ± 2.61	0.3
% change		−1.0 ± 12.5			−1.0 ± 10.5	
Percent atheroma volume (%)	54.5 ± 7.1	54.8 ± 7.0	0.58	54.7 ± 7.0	54.2 ± 7.0	0.35
Nominal change (%)		0.3 ± 4.5			−0.5 ± 3.6	
Fibrous volume index (mm^3/mm)	3.49 ± 2.01	3.48 ± 1.83**	0.94	3.00 ± 1.48	2.61 ± 1.17	0.0004
Change (mm^3/mm)		−0.01 ± 0.84*			−0.39 ± 0.70	
FF volume index (mm^2/mm)	1.26 ± 1.10**	0.96 ± 0.77*	0.0006	0.79 ± 0.59	0.62 ± 0.63	0.1
Change (mm^3/mm)		−0.30 ± 0.71			−0.17 ± 0.70	
NC volume index (mm^3/mm)	0.75 ± 0.54	0.87 ± 0.56	0.06	0.73 ± 0.59	0.88 ± 0.63	0.1
Change (mm^3/mm)		0.11 ± 0.50			0.15 ± 0.63	
DC volume index (mm^3/mm)	0.47 ± 0.45	0.59 ± 0.54	0.002	0.38 ± 0.36	0.49 ± 0.44	0.01
Change (mm^3/mm)		0.12 ± 0.32			0.11 ± 0.29	
Average length (mm)	25.7 ± 14.9			22.8 ± 15.0		

Data are expressed as mean ± SD

EEM external elastic membrane, *FF* fibro-fatty, *NC* necrotic-core, *DC* dense-calcium

* $p < 0.05$, ** $p < 0.01$ compared to non-elderly. # $p = 0.07$ compared to non-elderly

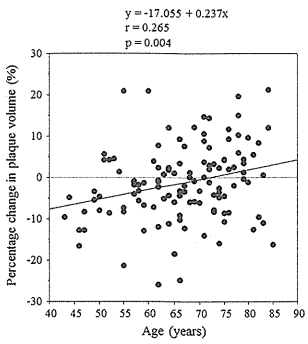

Fig. 1 Correlation between age and percentage change in plaque volume during statin therapy. Age and percentage change in plaque volume during statin therapy showed a significant positive correlation

Table 4 Predictors of percentage change in plaque volume

	Univariate		Multivariate	
	r	p value	β	p value
Age	0.265	0.004	0.223	0.02
Gender	−0.127	0.17	0.012	0.9
Coronary artery disease status	−0.066	0.48		
Hypertension	0.163	0.08	0.063	0.53
Diabetes mellitus	0.137	0.14	0.06	0.54
Smoking	0.088	0.34		
eGFR	−0.035	0.71		
Type of statin	−0.074	0.43		
Percentage change in LDL-C	−0.001	0.99		
Percentage change in sd-LDL	−0.097	0.34		
Percentage change in HDL-C	−0.114	0.22		
Percentage change in hs-CRP	0.056	0.56		
Change in EPA + DHA/AA	−0.24	0.02	−0.209	0.04

Male gender, unstable angina pectoris, hypertension, diabetes mellitus, smoking, and pitavastatin use were assigned a value of 1. Female gender, stable angina pectoris, normal blood pressure, absence of diabetes and smoking, and pravastatin use were assigned a value of 0

eGFR estimated glomerular filtration rate, *LDL-C* low-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *AA* arachidonic acid

the percentage change in plaque volume was different between the elderly and non-elderly patients. Furthermore, age showed a significant positive correlation with the percentage change in plaque volume and a significant predictor associated with the percentage change in plaque volume during statin therapy.

Glagov et al. [12] described vascular remodeling as a compensatory enlargement of the coronary artery in response to an increase in plaque area. In histological studies, expansion in vessel size is associated with an increase in inflammatory cells and proteolytic enzymes [13, 14]. In clinical IVUS studies, expansive remodeling is associated with plaque instability and unstable clinical presentation [15–17]. Consistent with previous findings from human autopsies [2] and IVUS [3–5, 18], our results demonstrated that coronary atherosclerosis was more advanced with expanding remodeling and greater atheroma volume in the elderly patients. Furthermore, a significant negative vessel remodeling and regression in plaque volume during statin therapy were observed only in the non-elderly patients. Thus, atherosclerosis accelerated with age [1], even in patients who received statin therapy.

According to VH-IVUS, the fibro-fatty plaque component is associated with development of acute coronary syndrome [19]. As reported in the main TRUTH trial [8], a decrease in the fibro-fatty plaque component and an increase in the calcified component were observed in both the elderly and non-elderly patients. Consistent with previous studies [20, 21], statins induced significant changes in the composition of coronary atherosclerosis without a significant regression in coronary artery plaques in the elderly patients, which illustrated the potential effects of statin against coronary events even in these high risk patients with elderly. Statin therapy reduces matrix metalloproteinase activity, apoptosis, and macrophages, and increases collagen content [22]. These changes could explain the qualitative changes observed in coronary artery plaque composition without a regression in plaque volume. However, a large amount of atheroma volume, particularly the fibro-fatty plaque component, before and during statin therapy may affect the development of coronary events in the elderly patients. As several studies have reported that statins have no effect on necrotic-core accumulation [8, 23, 24], statin therapy could not halt the progression of the necrotic-core component in this study.

Current lipid-lowering guidelines focus on LDL-C reduction as a principal target for primary and secondary prevention of cardiovascular disease [25]. Indeed, clinical trials using statins have demonstrated reductions in cardiovascular events and atheroma progression [6–8, 26]. However, not only serum LDL-C but also serum HDL-C, the LDL-C/HDL-C ratio, and other parameters are useful markers of atheroma regression and/or inhibition of progression in coronary artery plaques [27–29]. Recently, we reported that >40 % of patients receiving statin therapy continued to demonstrate atheroma progression [30]. Thus, not all patients show reductions in cardiovascular events and regression in coronary atherosclerosis under statin therapy. Bayturan et al. [31] reported that residual risk factors associated with atheroma progression in patients who achieve very low LDL-C levels (<70 mg/dl) included baseline percent atheroma volume, presence of diabetes mellitus, increase in systolic blood pressure, less increase in HDL-C, and a smaller decrease in apolipoprotein B levels. This suggests the need for intensive control of global atherosclerotic risk factors to produce regression in coronary atherosclerosis. However, although serum LDL-C, apolipoprotein B, and sd-LDL levels were significantly lower in the elderly patients, a significant regression in plaque volume was observed only in the non-elderly patients. Considering of change in the EPA + DHA/AA ratio was a significant predictor of the percentage change in plaque volume, the residual risk for cardiovascular events during statin therapy can be explained in part by n-3 to n-6 polyunsaturated fatty acids ratios [32]. More recently, Puri et al. [33] reported that greater baseline atheroma volume was associated with less disease progression while older age was a significant predictor of atheroma progression with potent statin therapy. Although coronary atherosclerosis was more advanced in the elderly patients, statin-induced regression in plaque volume and negative vessel remodeling were attenuated. This suggests that atheroma regression in older individuals in general may be more difficult to achieve.

A meta-analysis demonstrated that effects of statin on major vascular events were similar among patients with age <65, >65 to <75, >75 years [34]. However, a large-scale, prospective, uncontrolled study performed in Japan reported that incidence of cardiovascular events during statin therapy was highest in patients aged >65 years old in the secondary prevention cohort [35]. Therefore, statin therapy may have less impact on the secondary prevention in Japanese patients with elderly.

Study limitations

The present study had several limitations. First, it is a post hoc subanalysis of the TRUTH trial. Second, although we excluded patients with angiographically apparent thrombi, an intramural thrombus might have influenced the study results. Third, IVUS examinations were performed only in the culprit vessel. Mechanical interventions might have affected the atheroma measurements because target segment of interest was located in the proximal site of culprit lesion in some patients and maximum necrotic-core area

has been often located proximal of the most severe stenosis site [36]. Finally, the small number of patients meant that the study's statistical power was insufficient to evaluate differences between the elderly and non-elderly patients. Therefore, a prospective multicenter study involving more patients is required to confirm our conclusions.

Conclusions

Coronary atherosclerosis was more advanced and vascular responses to statin therapy were attenuated in the elderly patients compared to the non-elderly patients.

Conflicts of interest None.

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モバイルネットワーク環境における新生児心臓病の超音波動画像遠隔診断

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Real-Time Mobile Tele-Echocardiography for Neonatal Heart Disease

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要旨

乳児死亡の原因の第1位は先天性心疾患である。出生直後に発症する心疾患の診療では、地域の小児科医と専門医チームをリアルタイムに結ぶ遠隔医療が求められる。複数の医師が、様々なネットワークと解像度の端末を用いて一つの画像検討を同時に行う場合、端末毎に最適な映像データを効率よく送信できなければならない。スケーラブル映像符号化技術（SVC）はインターネット、特にモバイルネットワークのように、不安定で狭帯域な環境であっても、伝送エラーに対する耐性に優れている。また、受信側の帯域変動に合わせた送信データの帯域調節が可能であり、多様な映像品質にも対応できる。私たちはSVCを利用した超音波動画像遠隔診断システムを構築し、新生児先天性心疾患の動画像をVPN接続した3つの回線、①高品質ネットワーク、②インターネット、③モバイルネットワークを用いて送信した。動画像の解像度は960×540、送信帯域は368kbps、768kbps、1Mbps、2Mbpsとした。モバイル接続端末としてiPad及びノートPCを用い、専門医が映像品質を主観的に評価した。その結果、通信回線、送信帯域、受信端末のすべての組み合わせにおいて高い評価が得られ、モバイルネットワーク環境とSVCの有効性が実証された。

遠隔医療において、正しい診断を行い、適切な治療方針を決定するには、超音波動画像のみならず電子カルテ上でアクセス可能な臨床情報をできるだけ多く遠隔地で共有する必要がある。私たちは、HD対応のテレビ会議システムと電子カルテをPC接続ポートを介して一体化するシステムによりこれが可能であることを示した。本システムはVPNの構築によりインターネット上でも安全に利用でき、広域医療連携とコスト削減につながる。運用にあたっては各種ガイドラインの遵守や医療機関間でのルール作りが重要である。

キーワード：乳児死亡、先天性心疾患、超音波検査、モバイルネットワーク、スケーラブル映像符号化技術

1. はじめに

新生児の心臓病は乳児死亡の原因の第1位である。医療過疎地域を含む広域医療圏においても重症の新生児の診療を支援するための、インターネットやモバイルネットワーク環境、スケーラブル映像符号化技術を利用した遠隔医療モデルを提案する。テレビ会議システムと電子カルテを一体化することにより、電子カルテ上にある臨床情報を容易にかつ安全に遠隔地で共有できると考えている。

2. 乳児死亡と心臓病の新生児と遠隔診断

乳児死亡、新生児死亡、早期新生児死亡は、それぞれ生後1年未満、4週未満、1週未満の死亡である。乳児死亡率、新生児死亡率、早期新生児死亡率は、出生数千対のそれぞれの死亡数で表し、平成22年には2.3、1.1、0.8で、世界で最も良好な水準である。しかし、この年出生した1,071,304人のうち2,450人の赤ちゃんが1歳未満で死亡し、その約半数が生後4週未満で、約1/3が生後1週未満で死亡したのである。

乳児死亡の原因の第1位は、新生児にみられる先天性の心臓病、先天性心疾患である。先天性心疾患は新生児の約1%に発生するので、平成22年には約1万人の先天性心疾患をもった赤ちゃんが生まれたと推定される。先天性心疾患のなかで重症なタイプでは、胎児循環と呼ばれる子宮内特有の血流が生存に不可欠である。出生により胎児循環は失われ、成人と同様の循環が始まることから、この病気をもった赤ちゃんでは出生そのものが発症の引き金になり、病状は急激に進行する。早期に診断され、適切な治療が開始されなければ生後まもなく死亡する。

心臓病の新生児を診断し、治療を開始するのは地域の小児科医であり、重症例に対しては循環器小児科医や心臓外科医、麻酔科医などの専門医チームが詳細な診断に基づき、薬物治療やカテーテル治療、手術を行う。広大な岩手県は日本一小児科医が少ない医療過疎地域である。平成22年の15歳未満人口10万人あたりの都道府県別小児科医師数は全国平均150.2人に対し、岩手県は117.1人であり、最多の徳島県の297.9人の半数に満たない。また、東北地方は小児心臓病の専門医も少なく、全国では専門医1人当たり毎年平均約30人の新たに発生する先天性心疾患患者を診るのに対し、東北では約50人を診る計算になる。

医療過疎地域において遠隔診断が小児科医と専門医を結び、生後まもなく発症する先天性心疾患患者のトリアージ、初期治療、搬送を支援できれば、患者や家族の利益は大きく、限られた医療資源の有効利用にもつながる。岩手医大では県内の拠点病院をつなぐテレビ会議システムを用いて、新生児の心臓超音波動画像を受信し、診療支援を行ってきた。しかし、遠隔診断はテレビ会議システムを設置した環境でしか利用できず、専門医が自宅にいる場合や出張中には遠隔診療が困難である。

複数の医師が、モバイルネットワーク環境のように、異なるネットワークと異なる解像度の端末を用いて一つの症例検討を同時に行う場合、端末毎に最適な映像データを効率よく送信できなければならない。先天性心疾患は病態が複雑で微細であり、また、新生児の心拍数は120～180/分と多いため、伝送エラーが起きやすく、モバイルネットワーク環境における動画像遠隔診断が最も困難な対象といえる。

3. スケーラブル映像符号化技術

従来の階層化されないH.264/AVCなどのデータに伝送エラーが生じた場合、フレームのすべてのデータが消失するため、フレームデータを復元できず、画像の乱れ、または直前に受信した画像を表示し続けることによる再生のかくつきが生じる。

これに対して、映像データに基本階層と拡張階層の階層構造を与えるスケーラブル映像符号化技術（SVC）は、データの拡張階層に伝送エラーが生じても、正常に受信した基本階層のデータを利用して画像の乱れを防止する。LTE等により使用可能な帯域が今後増加しても、帯域が保証されていないインターネット、特に通信が不安定なモバイルネットワーク環境では、常に帯域は変動し、混雑によりエラーが発生することは避けられない。SVCはこのエラーへの耐性が強い。また、様々なモバイル端末が増加する環境のなかで、SVCは、送信するデータの帯域を受信側の帯域の変動に合わせて調節することや、フルHDからQVGA等の低画質まで、異なる品質に対応することができる。さらにSVCは従来のシステムに比し、遅延が軽減できる、会議1拠点あたりのコストやネットワークインフラのコストが低廉であるなどの特徴を有している。

4. モバイルネットワーク環境における超音波動画像遠隔診断の実証実験

私たちは、新生児の心臓超音波動画像を符号化パラメータを変化させてSVCで符号化し、ローカル環境、広域ネットワーク環境、モバイルネットワーク環境の3つの環境で映像再生端末に配信し、画質を評価する「心臓超音波画像配信・評価システム」を構築してきた。画質評価は、ITU-T P.910で規定された一重刺激法に従い、学会専属の専門医が、その画像で診断できるか否か、0（不可）から1（優）まで、連続的に評価する主観評価で行い、PSNRによる客観評価も合わせて行った。その結果、1Mbps未満の帯域制限がある場合、解像度640×448の最上位階層の圧縮率を上げるよりも、解像度320×224の階層に下げる方が、高い画質評価が得られることが明らかになった。

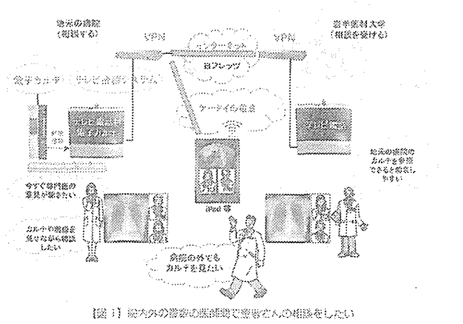
今回の研究では、岩手医大倫理委員会の承認を得て、SVCを実装したテレビ会議システムを用いた映像配信実験を構築した。映像を伝送する回線として、①高品質ネットワーク、②通常のネットワーク（インターネット）、③モバイルネットワーク（インターネット）の3種類を構築した。全ての回線でVPN接続による実験環境を構築し、モバイル接続端末としてiPad及びノートPCを用いた。新生児の心臓超音波動画像を青森県八戸市の医療機関から送信し、岩手医大で受信して、専門医による主観評価を行った。解像度は960×540とし、送信帯域は、368kbps、768kbps、1Mbps、2Mbpsとした。

その結果、専門医の評価値は0.6～0.8であり、受信された動画像は全ての組み合わせにおいて診断可能であると判断された。また、3種類のネットワークでの評価に差がみられなかったことから、配信ネットワークとしてモバイルネットワークが有効利用できると考えられた。SVCがモバイルネットワークという比較的不安定で狭帯域なネットワーク環境において有効であることが実証された。

5. 岩手医大が提案するテレビ会議システムと電子カルテの一体化による医療連携

遠隔診断には、超音波動画像だけではなく、心電図やレントゲン、CT、MRI、PET、シンチ等の画像、血液検査結果等の検体検査、サマリーや処方内容等、患者の病態を正しく把握できる情報を随時参照できることが望ましい。電子カルテ上でアクセス可能な臨床情報をできるだけ多く遠隔地で共有することが、正しい診断と適切な治療方針の決定にとって重要である。

私たちは、HD対応のテレビ会議システムと電子カルテをPC接続ポートを介して一体化することで、それが比較的容易に可能になると考えている【図1】。紹介を受けた患者さんについて岩手医大などの連携先と相談するとき、診察室で使っている電子カルテの端末がそのままテレビ会議システムの端末になる。テレビ会議システムは広域ネットワーク環境のみならずインターネット上でも利用できる。VPNの構築により、セキュリティが確保される。インターネットの利用は、岩手県に限定されない、より広域での医療連携につながり、ランニングコスト上も優れている。SVCの技術を用いることで、モバイルネットワーク環境での利用も可能である。なお、テレビ会議の内容は会議の開始とともに録画によって保存することが可能である。これらの運用にあたっては、厚生労働省「医療情報システムの安全管理に関するガイドライン」等を遵守し、医療機関間で運用のルールを明確にしておくことが重要である。



【図1】院内外の複数の医師間で患者さんの相談をしたい

6. おわりに

遠隔医療は、医療や介護、健康増進に、ICTを役立てることである。それは手段であって、目的ではない。目的はあくまでも住民一人一人が健康に生きることである。手段は多種多様であり、インターネットやモバイルネットワークの利用はその一例にすぎない。現場で最も大切なのは、手段となるものは使い易くなければならないということである。どんなに優れた技術であっても、使いにくいものは結局使われずに廃れていく。遠隔医療が必ずしも広く普及しない理由のひとつは、手段であるはずのものが使いにくく、実際に利用しようとすると、送信者・受信者である医療従事者の負担が大きいことにあるのではないだろうか。私たちはできるだけ使い易い、人にやさしい遠隔医療を目指していきたい。

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Gouty Tophus of the Second Metacarpal Simulating a Malignancy With Pathologic Fracture

To the Editor:

We report on an intraosseous gouty tophus in the second metacarpal causing a pathologic fracture and simulating a malignancy.

A 5-year-old girl with a swollen hand was referred with a diagnosis of a bone tumor. She had been treated for hypoplastic left heart syndrome with protein-loosening enteropathy. She has had 5 surgical interventions, including a fenestrated Fontan procedure. She took many medications, including enalapril maleate. She had generalized edema, hepatosplenomegaly, and ascites. A 2 × 2 cm mass was palpable over the second metacarpal. Slight redness, local heat, and swelling without tenderness were noted. The blood urea nitrogen and uric acid levels were 75.5 mg/dL and 19.1 mg/dL, respectively, much higher than usual, whereas the creatine level was normal, 0.7mg/dL. Total protein was 4.4 g/dL; albumin was 2.8 g/dL; and immunoglobulins were IgG, 128mg/dL; IgA, 30mg/dL and IgM, 56mg/dL, lower than usual. Radiographs showed an ill-marginated lytic and sclerotic legion with a pathologic fracture and periosteal reaction (Fig. 1). Magnetic resonance imaging showed a low–signal-intensity mass on T1-WI and marked high signal intensity on T2-WI surrounding the metacarpus. A needle biopsy was performed. The birefringent crystals suggesting gouty tophus were seen without distinctive inflammatory cellular infiltration histologically. Because of progressively deteriorating renal function, the enalapril maleate was discontinued. Consequently, her renal dysfunction improved, and the uric acid level decreased to 6.4mg/dL. The gouty tophus decreased in size.

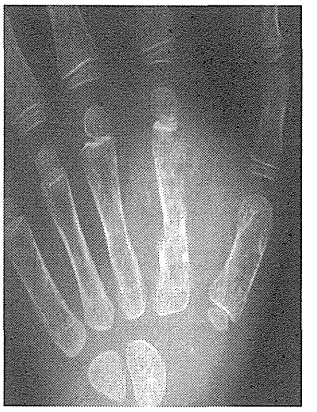

FIGURE 1: Posteroanterior x-ray of the left hand showing a poorly marginated lytic and sclerotic lesion in the second metacarpal associated with periosteal reaction and a pathological fracture.

Enalapril maleate might have caused hyperuricemia and the gouty tophus, which was painless. Hypo-γ-globlinemia might have been responsible for the patient's lack of pain. The immunoglobulin G was strongly absorbed from serum to monosodium urate crystals in gouty tophi.[1] Histological findings did not reveal inflammatory cellular infiltration.

Gouty tophus should be included in the differential diagnosis of the patient considered to have a bone tumor in the hand.

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Letter Regarding "Perilunate Dislocations and Fracture Dislocations"

To the Editor:

We read with great interest the article by Jones and Kakar.[1] It nicely covers the whole spectrum of perilunate dislocations and fracture dislocations. The author did not mention the treatment for dislocations in patients who present late. The treatment mentioned is about the salvage procedure directly. It is mentioned in the literature that open reduction internal fixation in a single stage[2] as well as in a 2-staged procedure[3] is a satisfactory procedure if executed properly in patients who present late. The results of these procedures have been satisfactory.[4] Proximal row carpectomy or wrist arthodesis might not be acceptable to young patients. Because this injury pattern is mainly seen in young individuals, the option of 2-stage reduction should be given to patients. If this method fails, only then should we proceed to a salvage procedure.

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In Reply:

We thank the reader for the insightful comments and for highlighting several papers[1–3] (2 of which were published after our manuscript was submitted) addressing the particularly challenging subset of perilunate injuries presenting to the hand surgeon late. Massoud and Naam also recently reported their experience with open reduction internal fixation of perilunate dislocations and fracture dislocations that were treated 13 to 35 weeks from the time of injury, with good to excellent results in 11 of 19 patients.[4] Although these studies represent relatively small series, they do demonstrate that successful outcomes can be achieved with single-stage or double-stage open reduction internal fixation procedures in the treatment of chronic perilunate injuries. However, the carpus should be easily reducible at the time of surgery, or any form of ligamentous repair can be prone to failure with time. Although these series have not demonstrated loss of intercarpal reduction over time, repair of the intercarpal ligaments can prove challenging secondary to their attenuation and contracture related to the chronicity of the injury. In addition, the articular cartilage must be evaluated at the time of surgery. Kailu et al noted, "With no exception, cases with excellent or good results in this study had satisfactory cartilage condition of the midcarpal joints when evaluated during the operation," and 2 patients with poor outcomes had been noted to have severe scaphoid and lunate cartilage contusion at the time of open reduction.[1] Therefore, in the setting of severe chondral injury, arthritis, or avascular necrosis associated with a

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ORIGINAL ARTICLE
Arrhythmia/Electrophysiology

Genetic Background of Catecholaminergic Polymorphic Ventricular Tachycardia in Japan

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Background: The genetic background of catecholaminergic polymorphic ventricular tachycardia (CPVT) has been extensively investigated for the last decade in Western countries, but it remains unstudied in the Asian population.

Methods and Results: In 50 Japanese probands from unrelated families who satisfied clinical criteria for CPVT, genetic testing was conducted in all exons on 3 CPVT-related genes: *cardiac ryanodine receptor 2* (*RYR2*), *calsequestrin 2* (*CASQ2*) and *inward rectifier potassium channel 2* (*KCNJ2*), and the clinical features between *RYR2*-genotyped and -non-genotyped patient groups were compared. Genetic and clinical evaluation was also done in 46 family members. In the genetic screening, 28 (18 novel) *RYR2* (56.0%), 1 compound heterozygous *CASQ2* (2.0%) and 1 *KCNJ2* (2.0%) mutation carriers were identified. In the *RYR2* mutation-positive group, the frequency of bidirectional ventricular tachycardia and the use of β-blockers were significantly higher than in the mutation-negative group. In contrast, there was no significant difference in supraventricular arrhythmias between the 2 groups. With regard to disease penetrance, the number of family members of *RYR2*-genotyped probands with a clinical diagnosis of CPVT was high.

Conclusions: Thirty gene mutation carriers were found for 3 genes in 50 probands clinically diagnosed as having CPVT. The penetrance of CPVT phenotype was significantly higher in *RYR2* mutation carriers, thus *RYR2* gene screening in CPVT patients would be indispensable to prevent unexpected cardiac sudden death of young family members. (*Circ J* 2013; **77**: 1705–1713)

Key Words: Beta-blockers; Calsequestrin; Catecholaminergic polymorphic ventricular tachycardia; Flecainide; Ryanodine receptor

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a form of inherited cardiac arrhythmia, characterized by polymorphic or bidirectional ventricular tachyarrhythmia (pVT or bVT) induced by physical exercise, emotional stress or catecholamine use.[1–3] CPVT patients have autosomal dominant or recessive traits. The QTc interval is generally within the normal range, but sinus bradycardia and atrial arrhythmias have been associated with CPVT.[3–5]

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The first gene locus mapped to chromosome 1q42–43[2] was an autosomal dominant form of CPVT (CPVT1), and mutations were identified in a gene encoding a cardiac ryanodine receptor (*RYR2*; MIM 180902).[4,6–10] Homozygous or compound heterozygous mutations in calsequestrin 2 (*CASQ2*; MIM 114251) were then reported to cause the second variant of CPVT (CPVT2).[2,11–13] *CASQ2* encodes a Ca-binding protein in the sarcoplasmic reticulum and plays a key role in maintaining cytosolic Ca^{2+} concentration, in collaboration with *RYR2*. In 2009, the third variant of CPVT was reported to result from a mutation in *KCNJ2* (MIM 600681), which encodes Kir2.1, a subunit for inward-rectifier potassium channels.[14] The *KCNJ2* mutation (p.V227F) produced no functional defects on Kir2.1 channels at rest but an unusual latent loss of function regarding the cAMP-dependent protein kinase A (PKA)-dependent phosphorylation of Kir2.1 channel proteins.[14] This in turn leads to the loss of response in Kir2.1 function to β-adrenergic stimulation. More recently, Bhuiyan et al reported a new malignant variant of CPVT in an inbred family with autosomal recessive inheritance. They have mapped this recessive CPVT locus *to chromosome* 7p14–p22.[15] Roux-Buisson et al identified *triadin* (*TRDN*) as a new gene responsible for an autosomal recessive form of CPVT.[16]

To date, there are a substantial number of reports on the genetic background in CPVT cohorts from Western countries,[2,4,6–9,11–13,17,18] but few in Asian populations.[19–21] In the present study, we therefore conducted genetic testing on 3 CPVT-related candidate genes – *RYR2*, *CASQ2*, and *KCNJ2* – in 50 CPVT probands from unrelated Japanese families and their 46 family members and examined their correlation with clinical phenotypes.

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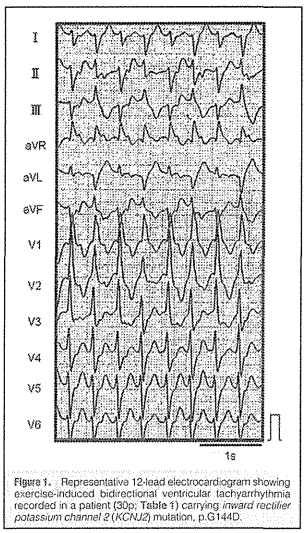

Figure 1. Representative 12-lead electrocardiogram showing exercise-induced bidirectional ventricular tachyarrhythmia recorded in a patient (30p; Table 1) carrying *inward rectifier potassium channel 2* (*KCNJ2*) mutation, p.G144D.

Methods

Subjects

Fifty clinically diagnosed CPVT probands and their 46 family members (total, 96) were included in genetic analysis. The entry criteria were the presence of the following arrhythmias documented on exercise stress testing and/or Holter monitoring electrocardiogram (ECG) in the absence of structural heart abnormalities: bVT (Figure 1); pVT; or ventricular fibrillation (VF). The characteristic QRS morphology of bVT or pVT is a change in QRS axis every other beat, with 2 or more types of patterns, during more than 4 consecutive beats. We also included a 2-year-old boy without typical arrhythmias but whose father was symptomatic and genetically diagnosed as CPVT and who died suddenly in his 30 s (Table 1; 13-p). We excluded patients who suffered bVT or pVT due to prominent electrolyte imbalance, drug treatment, or organic heart disease such as cardiomyopathy, ischemic heart disease, or congenital heart disease. Primary electrical diseases such as long QT syndrome (LQTS) were also excluded. Bradycardia was defined as follows: in children aged <16 years, heart rate below the second percentile of established age- and sex-appropriate norms;[22] in adults, <60 beats/min on resting ECG without intake of β-blocker.

Mutation Analysis

The protocol for genetic analysis was approved by the Institutional Ethics Committee and was performed under its guidance. All subjects gave written informed consent before genetic analysis. Genomic DNA was isolated from peripheral white blood cells. Intronic primers amplifying the *RYR2*, *CASQ2* and *KCNJ2* coding regions were used for polymerase chain reaction (PCR) amplifications as previously reported.[6,7,9,17,23] PCR products were analyzed on direct sequencing. The cDNA sequences of *RYR2*, *CASQ2* and *KCNJ2* were based on the GenBank reference sequence NM_001035.2, NM_001232.3 and NM_000891.2, respectively. Regarding RyR2 mutation-negative probands, we also searched for large genomic rearrangements affecting exon 3 and 97, as reported previously.[4] In addition to these 3 genes, we examined the entire coding sequence for *KCNQ1*, *KCNH2*, *SCN5A*, and *KCNE1–5* to exclude an unexpected presence of compound mutations related to primary electrical diseases.

All novel putative pathogenic variants were examined and confirmed to be absent in 400 chromosomes from 200 Japanese controls.

Statistical Analysis

All continuous variables are reported as mean±SD. Differences between continuous variables were evaluated using unpaired Student's *t*-test, and categorical variables using chi-squared analysis. Statistical significance was set at $P<0.05$.

Results

Genetic Analysis

***RYR2* (CPVT1)** The genetic analysis for *RYR2* identified 26 different missense heterozygous mutation carriers and 2 carriers with large DNA deletions including exon 3 in 50 pro-

Table 1. Characteristics of Genetic Mutation Carriers in CPVT Patients

Family number	Proband or family	Sex	Age at onset (years)	Exercise-related syncope	Required CPR	Cardiac manifestations: HR at rest (beats/min)	QTc (ms)	bVT	pVT	VF	Atrial tachyarrhythmia	Other arrhythmia	β-blockers	Dosage of BBL, mg (mg/kg)
1	p	F	16	+	+	47	424	+	–	–	–	SSS	Bisoprolol	5
	f1	F	–	–	–	44	384	–	–	–	–	SSS	Bisoprolol, Flecainide	NA
	f2	F	–	–	–	85	380	–	–	–	AF	–	–	–
	f3	F	–	–	–	39	381	–	–	–	–	Sinus bradycardia	–	–
	f4	F	–	–	–	81	476	–	–	–	–	–	–	–
	f5	M	–	–	–	76	419	–	–	–	–	–	–	–
2	p	F	1	+	–	53	420	–	+	–	–	C-AVB	Carvedilol	NA
	f	F	–	–	–	52	470	–	–	–	–	–	–	–
3	p	F	19	+	–	41	NA	–	+	–	–	–	Propranolol	90
4	p	M	11	+	–	44	393	+	+	–	–	–	Atenolol	100 (2.22)
5	p	F	7	+	+	76	441	–	–	+	–	–	Propranolol	75 (2.01)
	f	F	–	+	–	NA	NA	–	–	–	–	–	–	–
6	p	M	8	+	+	48	419	–	+	+	–	–	Propranolol	120 (3.20)
7	p	M	13	+	+	84	438	–	–	+	–	–	Atenolol	37.5
	f1	F	–	–	–	52	410	–	–	–	–	–	–	–
	f2	M	–	–	–	75	400	–	–	–	–	–	–	–
8	p	F	12	+	–	56	444	–	+	–	–	–	Atenolol	NA
9	p	M	10	+	–	81	446	+	–	–	–	–	Bisoprolol	2.5
10	p	M	10	+	+	52	440	+	+	+	–	–	Atenolol	50 (0.97)
11	p	F	10	+	–	72	429	+	–	–	AF	–	Atenolol	100 (3.23)
12	p	M	–	–	–	50	394	–	+	–	–	–	Metoprolol	60
13	p	M	–	–	–	84	420	–	–	–	–	–	–	–
14	p	F	14	+	+	56	423	–	+	+	–	–	Atenolol	12.5
15	p	F	8	+	–	58	479	–	+	–	–	–	Propranolol	75
16	p	M	4	+	+	89	400	+	–	–	–	–	Atenolol	50 (2.5)
17	p	F	6	+	–	55	440	+	–	–	–	–	Nadolol	60 (1.51)
18	p	F	6	+	–	67	424	+	+	–	AT	–	Propranolol	120 (5.00)
19	p	M	3	+	–	77	434	+	+	–	–	–	Carteolol	3 (0.20)
	f1	F	–	–	–	NA	NA	–	–	–	–	–	–	–
	f2	M	–	–	–	86	407	–	–	–	–	–	–	–
20	p	M	14	+	+	56	417	–	+	+	–	–	Propranolol	90
21	p	F	7	+	–	56	420	–	+	–	–	–	Propranolol	30 (1.00)
22	p	M	2	+	–	50	423	+	–	–	–	–	Propranolol	NA
23	p	F	15	+	+	60	414	+	+	–	–	–	Metoprolol	120 (2.35)
	f	M	10	+	–	64	428	–	–	–	–	–	Metoprolol	40 (1.03)
24	p	F	2	–	–	47	440	–	+	–	AT	–	Atenolol	NA
25	p	F	6	+	–	86	409	+	+	–	AFl	–	Atenolol	75 (0.86)
26	p	F	9	–	–	NA	NA	–	+	–	–	–	Propranolol	60
	f1	F	–	–	–	NA	NA	–	–	–	–	–	Propranolol	NA
	f2	F	–	–	–	NA	NA	–	–	–	–	–	Propranolol	60
27	p	M	4	+	+	40	396	+	+	+	–	–	Propranolol	60
28	p	F	6	+	–	NA	NA	–	+	–	–	–	Propranolol	NA
29	p	M	4	+	+	75	494	–	+	+	–	–	Propranolol	40 (2.00)
	f1	M	–	–	–	53	372	–	–	–	–	–	–	–
	f2	F	–	–	–	66	403	–	–	–	–	–	–	–
	f3	M	–	–	–	94	385	–	–	–	AT	–	–	–
30	p	F	6	+	–	63	380	+	+	–	–	–	Bisoprolol	NA

(Table 1 continued the next page.)

Other medicine	ICD	Mutation: Gene	Exon	Nucleotide change	Protein change	Previous report	Exercise stress test	Pharmacologic stress test	Family history: Sudden death	Family history: Diagnosed CPVT
–	+	*RYR2*[a]	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Multifocal couplets PVC	–	+	+
–	+	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Bifocal couplets PVC	–	+	+
Verapamil	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Isolated intermittent PVC	–	–	–
–	PM	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	–	–
–	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	–	–
–	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	–	–
–	PM	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	Multifocal couplets PVC	–	+	+
–	–	*RYR2*	3	Deletion	exon3 deletion	Bhuiyan et al[4]	NA	–	+	+
–	–	*RYR2*	8	g506a	R169Q	Hsueh et al[21]	pVT	–	+	–
Flecainide	+	*RYR2*	14	a1221t	R407S	Novel	bVT	–	–	–
–	–	*RYR2*	14	g1259a	R420Q	Medeiros-Domingo et al[18]	VF	–	–	+
–	–	*RYR2*	14	g1259a	R420Q	Medeiros-Domingo et al[18]	Unifocal bigeminal PVC	–	–	–
Verapamil, Flecainide	–	*RYR2*	35	a4652g	N1551S	Novel	pVT	–	+	+
–	–	*RYR2*	43	a6574t	M2192L	Novel	NA	PVC by epinephrine	–	–
–	–	*RYR2*	43	a6574t	M2192L	Novel	NA	–	–	+
–	–	*RYR2*	43	a6574t	M2192L	Novel	Multifocal couplets PVC	–	–	+
–	–	*RYR2*	44	c6737t	S2246L	Priori et al[9]	pVT	–	+	+
–	–	*RYR2*	47	c7160t	A2387V	Novel	Unifocal bigeminal PVC	–	–	+
Flecainide	–	*RYR2*	47	g7199t	G2400T	Novel	pVT	–	–	–
Verapamil, Flecainide	+	*RYR2*	49	a7420g	R2474G	Novel	NA	–	–	–
–	–	*RYR2*	52	g7883a	G2628E	Novel	Multifocal couplets PVC	–	+	–
–	–	*RYR2*	77	a10913	D3638A	Novel	NA	–	+	+
–	–	*RYR2*	86	g11583c	G3861H	Novel	NA	–	–	–
–	–	*RYR2*	86	g11583t	G3861H	Novel	pVT	–	–	–
Verapamil	–	*RYR2*	86	g11628g	D3876E	Novel	NA	–	–	–
–	–	*RYR2*	88	g11836a	G3946S	Priori et al[9]	pVT	–	–	–
Flecainide	–	*RYR2*	88	g11836a	G3946S	Priori et al[9]	pVT	–	–	–
–	–	*RYR2*	90	g12006a, c13175g	M4002I, K4392R	Novel	NA	–	–	–
–	–	*RYR2*	90	c13175g	K4392R	Novel	NA	–	+	+
–	–	*RYR2*	90	c13175g	K4392R	Novel	NA	–	+	+
–	–	*RYR2*	90	c12311t	L4105F	Hasdemir et al[20]	NA	–	–	–
–	–	*RYR2*	90	c12372a	S4124R	Novel	pVT	–	–	–
–	–	*RYR2*	90	a12533g	N4178S	Medeiros-Domingo et al[18]	bVT	–	–	–
Flecainide	+	*RYR2*	94	a13759g	I4587V	Novel	bVT	–	–	+
–	–	*RYR2*	94	a13759g	I4587V	Novel	Multifocal couplets PVC	–	–	+
–	–	*RYR2*	99	a14174g	Y4725C	Novel	NA	pVT by ISP	–	–
Verapamil	–	*RYR2*	99	a14251c	K4750Q	Novel	AFl	–	–	–
Verapamil	–	*RYR2*	100	g14311a	V4771I	Priori et al[9]	bVT	–	–	+
–	–	*RYR2*	100	g14311a	V4771I	Priori et al[9]	pVT	–	–	+
–	–	*RYR2*	100	g14311a	V4771I	Priori et al[9]	pVT	–	–	+
Flecainide	–	*RYR2*	102	c14593g	L4865V	Novel	pVT	–	–	–
Verapamil	+	*RYR2*	103	t14756c	L4919S	Novel	pVT	–	–	–
–	–	*CASQ2*[b]	2, 11	a259t, g1083a	K87X, W361X	Novel	NA	–	–	–
–	–	*CASQ2*	2	a259t	K87X	Novel	NA	–	–	+
–	–	*CASQ2*	11	g1083a	W361X	Novel	NA	–	–	+
–	–	*CASQ2*	11	g1083a	W361X	Novel	NA	–	–	+
Verapamil, Flecainide	–	*KCNJ2*[c]	1	g431a	G144D	Novel	Multifocal couplets PVC	–	–	–

Age at onset, age at which patients experienced the first symptomatic arrhythmic attack or were recorded as having physical stress-induced ventricular tachycardia. [a]NM_001035.2; [b]NM_001232.3; [c]NM_000891.2. AF, atrial fibrillation; AFl, atrial flutter; AT, atrial tachycardia; bVT, bidirectional ventricular tachyarrhythmia; CASQ2, calsequestrin 2; CPR, cardiopulmonary resuscitation; CPVT, catecholaminergic polymorphic ventricular tachycardia; HR, heart rate; ICD, implantable cardioverter-defibrillator; KCNJ2, inward rectifier potassium channel 2; NA, not available; PM, pacemaker; PVC, premature ventricular contraction; pVT, polymorphic ventricular tachyarrhythmia; QTc, corrected QT interval; RYR2, cardiac ryanodine receptor; VF, ventricular fibrillation.