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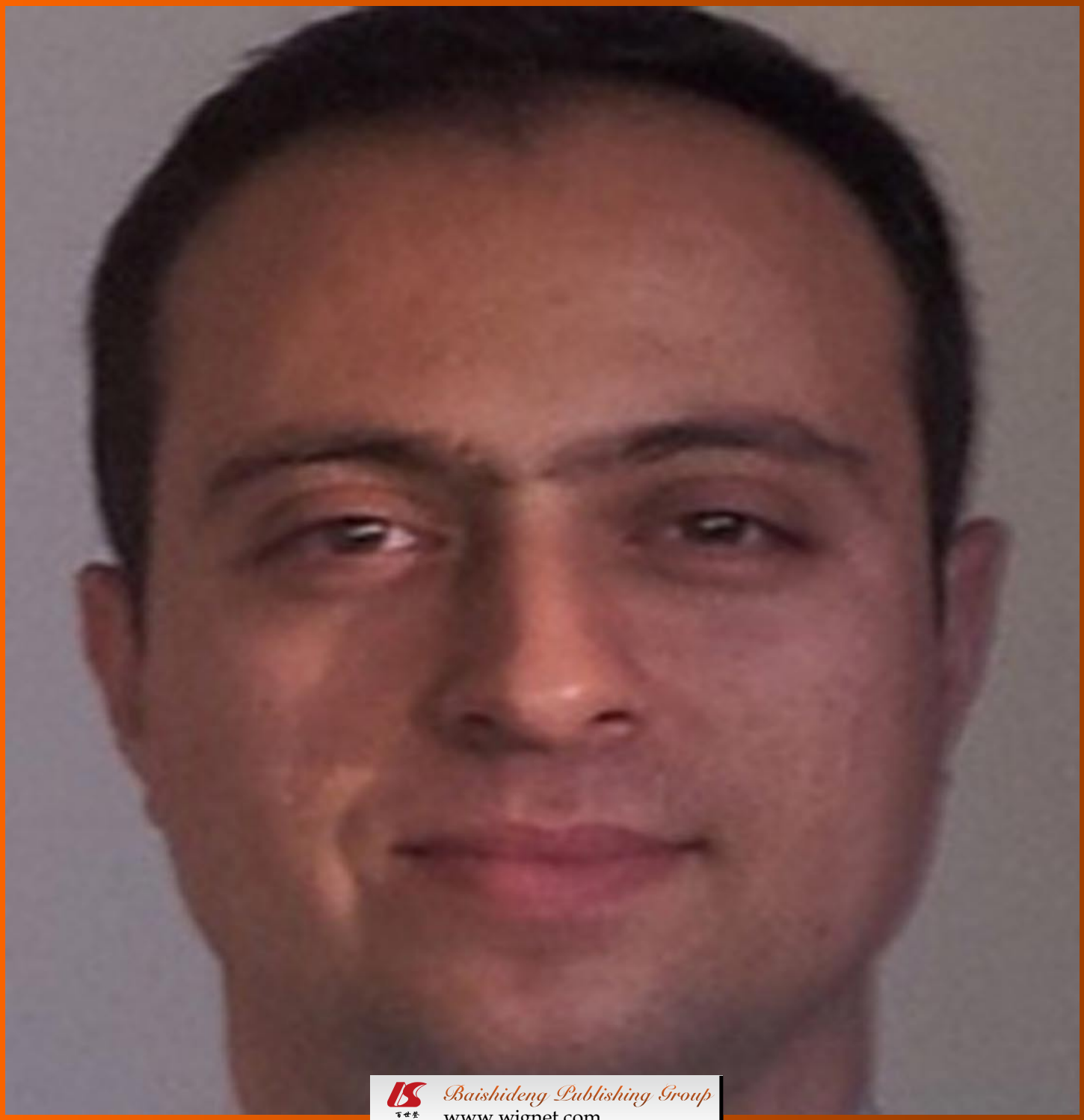

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World Journal of Clinical Cases (*World J Clin Cases*, *WJCC*, online ISSN 2307-8960, DOI: 10.12998) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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BRIEF ARTICLE

Retrospective chart review of skin cancer presence in the wide excisions

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Abstract

AIM: To investigate cancer cell absence or presence in wide excision after biopsy of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) patients.

METHODS: 200 patients (100 BCC and 100 SCC) from the same dermatology clinic, who had positive margin upon biopsy, were selected from a computer generated randomized report. All selected patients had wide excision following biopsy. To determine the correlation of gender, age distribution and cancer absence, BCC and SCC cases were separated based on excision-cancer absent or present after wide excision. χ^2 tests, Fisher's exact tests were used to analyze the ratio of male to female between excision-cancer absent and excision-cancer present patients, while Mann-Whitney *U* test were used to compare the age distribution in the two groups. Statistical analyses were performed using SPSS version 16.0 for Windows.

RESULTS: Our retrospective chart review of the patients showed that cancer cells were absent in 49% of BCC patients (n = 100) and 64% of SCC patients (n = 100) who had previously had positive margins upon biopsy. Gender analysis showed the ratio of male to female (M/F) in the BCC arm was significantly higher compared with the SCC arm in those with excision-cancer absent (2.06 *vs* 0.66; P = 0.004; χ^2 test). But M/F of excision-cancer absent and excision-cancer present in neither BCC nor SCC patients was statistically significant. Age adjustment showed no significant difference between excision-cancer absent and excision-cancer present in BCC and SCC patients. Nevertheless, in excision-cancer absent cases, the age distribution showed that the BCC patients were younger than SCC patients (average age 67 *vs* 74; P < 0.001; Mann-Whitney *U* test). In addition, our data also indicated that in the patient group of 71-80 years old, there were more SCC patients who showed excision-cancer absence (67.6% *vs* 39.4%; P = 0.02; χ^2 test).

CONCLUSION: Our study indicates that approximately 50% or more of BCC and SCC patients with positive margins found on biopsies did not have cancer cells present at the time of wide excisions.

Key words: Biopsy; Histology; Positive margin; Skin cancer; Wide excision

Core tip: Wide excisions are performed for skin cancers when malignant cells extend to the margins of biopsy. It is expected that cancer cells will appear in the excised tissue at the time of wide excision. However, an analysis of wide excision tissue samples from 200 patients revealed that approximately 50% or more basal and squamous cell carcinoma patients with cancer cells that extended to the margins in biopsy did not have

cancer cells present on wide excision. This finding suggests that the wound caused by the biopsy itself may trigger a body response to eliminate cancer cells.

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INTRODUCTION

The incidence and mortality rates of skin cancer are increasing in the United States and many other countries[1]. Of these skin cancers basal cell carcinoma (BCC) is the most common type followed closely by squamous cell carcinoma (SCC)[2]. The incidence of BCC is 200/100000 in men and 100/100000 in women[3]. BCC incidence increases with age; the median age for diagnosis is 68 years old[4]. SCC incidence is 100/100000 in men and 50/100000 in women[3]. Clinically if skin cancer is suspected, a biopsy is taken. The biopsy shows a small sample of the lesion, which can be looked at microscopically by a pathologist. The pathology report will describe the type of cancer and if the cancer extends to the border (positive margin) or is completely excised (negative margin) in the tissue sample[5] (Figure 1). If the lesion is completely removed, no further surgery is needed. For lesions with a positive margin, a wide excision surgery is done to remove the remaining cancer. This wide excision is a common and essential way to treat skin cancer, and incomplete excision may lead to cancer recurrence[6-8]. Theoretically, all the tissue samples from wide excision should contain cancer cells. However, pathological analyses of tissue samples from wide excision in our clinic often only show evidence of scar with no cancer cells remaining. All lesions had photos to ensure the correct lesion was excised. This observation has not been reported. In this study, we systematically analyzed the cancer cells absence or presence in wide excision after biopsy by subtype as well as sex and age from 100 SCC and 100 BCC patients. Our results will provide guidance for future determination of potential mechanism that leads to the disappearance of cancer cells in surrounding tissues of biopsies.

MATERIALS AND METHODS

Patients' data extraction

Chart review of 200 patients (100 BCC and 100 SCC) was obtained from a single dermatology office. The patients were selected from a computer generated randomized report of those who had SCC and a separate list for those who had BCC. Only patients who had a positive margin at the time of biopsy were included. Patients were excluded if pathology was unavailable for either biopsy or wide excision. In cases where patients with more than one biopsy or wide excision, the first lesion from the list was chosen, this was the case unless there was no corresponding wide excision; or location of biopsy and wide excision did not match. There was no exclusion of patients who had SCC and BCC.

Table 1 Patients characteristics

	BCC	SCC	Total patients
No. of cases	100	100	200
Sex			
Male	62	43	105
Female	38	57	95
Male/female	1.63	0.75	1.11[1]
Median age (range)	69 (42-92)	77 (45-95)	73 (42-95)[2]
Biopsy margins positive	100	100	200
Excision-cancer absent	49	64	113[3]

P value (BCC *vs* SCC): [1]$P = 0.007$; [2]$P = 0.003$; [3]$P = 0.032$. BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma.

Statistical analysis

In this chart review, χ^2 tests were used to compare the difference of gender distribution and excision-cancer absent percentage in assigned groups. When the sample size was less than 40, Fisher's exact tests were used instead. All the difference of age distribution was evaluated by Mann-Whitney *U* test. $P < 0.05$ was considered as statistically significant. These statistical analyses were performed using SPSS version 16.0 for Windows.

RESULTS

Clinical characteristics

First, the characteristics of the selected patients were analyzed (Table 1). Among the 200 cases that were reviewed, including 100 BCC and 100 SCC patients, SCC was more common than BCC among female patients (57% *vs* 38%; $P = 0.007$; χ^2 test) while BCC was more common than SCC among male patients (62% *vs* 43%; $P = 0.007$; χ^2 test). Despite a similar age range, the average age of SCC patients were 8 years older than BCC patients (77 years *vs* 69 years old; $P = 0.003$; Mann-Whitney *U* test). All skin cancer patients showed a positive margins upon biopsy. However, cancer cells were found to be absent in excised tissue of 49% of the BCC patients and 64% of the SCC patients. In addition, excision-cancer absent percentage in SCC patients was significantly greater than that in BCC patients (64% *vs* 49%; $P = 0.032$; χ^2 test). Analyses of the excision-cancer absent in the different subtypes of BCC and SCC indicated that there was no statistic significant difference in percentage among the analyzed subtypes of BCC or SCC (Table 2).

Gender distribution of excision-cancer absence with positive margins

To evaluate if cancer cells absence or presence after wide excision was associated with gender, BCC and

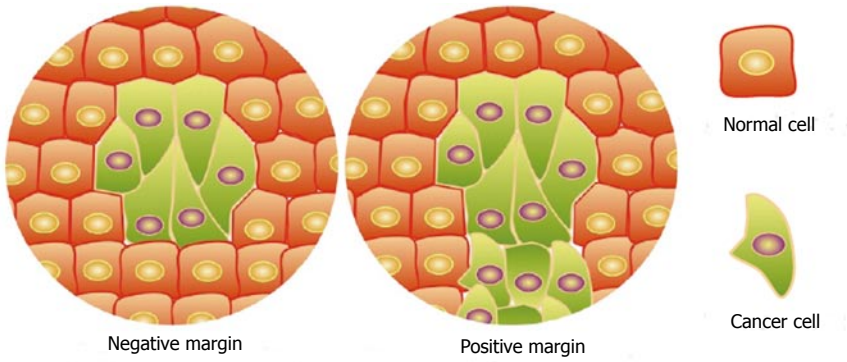

Figure 1 Appearances of negative and positive margins in biopsies.

Table 2 Skin cancer subtype distribution *n* (%)

Subtype		No. of patients	Excision-cancer absent
BCC	Nodular	53	26 (49.1)
	Infiltrative	11	6 (54.5)
	Nodular and superficial	25	15 (60)
	Nodular and infiltrative	10	2 (20)
	Infiltrative and superficial	1	0 (0)
SCC	*In situ*	45	26 (57.8)
	Keratoacanthoma type	12	9 (75)
	Moderately-differentiated	4	3 (75)
	Well-differentiated	16	12 (75)
	Invasive	12	6 (50)
	Other types[1]	11	6 (54.5)

[1]Include following complex subtypes, intraepidermal epithelioma pattern, *in situ*-intraepidermal epithelioma pattern, *in situ* and invasive, *in situ*-well differentiated, moderately to poor differentiated, *in situ* acantholytic and focally invasive, *in situ* and focally superficial invasive, keratinizing well differentiated, and unknown types. BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma.

Table 3 Gender distribution between excision-cancer absent and excision-cancer present cases of basal cell carcinoma and squamous cell carcinoma *n* (%)

		M	F	Total	M/F	*P* value
BCC	Excision-cancer absent	33 (67.3)	16 (32.7)	49	2.06	0.280[1]
	Excision-cancer present	29 (56.9)	22 (43.1)	51	1.32	
SCC	Excision-cancer absent	25 (39.7)	38 (60.3)	63	0.66	0.382[1]
	Excision-cancer present	18 (48.6)	19 (51.4)	37	0.95	
Excision-cancer absent cases	BCC	33 (67.3)	16 (32.7)	49	2.06	0.004[2]
	SCC	25 (39.7)	38 (60.3)	63	0.66	

P value: [1]In BCC or SCC cases, the percentage of male (female) patients in excision-cancer absent *vs* present groups; [2]In excision-cancer absent cases, the percentage of male (female) patients in BCC *vs* SCC. BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma; M: Male; F: Female.

SCC patients were grouped based on excision-cancer absence/presence and then the ratio of male to female was calculated respectively (Table 3). Despite the fact that a higher ratio of male to female was found in excision-cancer absent BCC patients than that in excision-cancer present BCC patients, the difference was not statistically significant (2.06 *vs* 1.32; $P = 0.28$; χ^2 test). A close ratio of male to female SCC patients was observed in excision-cancer absent and present groups (0.66 *vs* 0.95; $P = 0.382$; χ^2 test). However, in excision-cancer absent cases, the ratio of male to female in BCC was significantly higher compared with SCC (2.06 *vs* 0.66; $P = 0.004$; χ^2 test).

Age distribution of excision-cancer absence with positive margins

To evaluate if the malignancy presence after excision was associated with age, BCC and SCC patients were grouped based on cancer presence/absence, and then the median and average ages for the patients in each group were calculated (Table 4). Our data indicated that while there was no statistically significant difference in ages for excision malignancy present and absent patients in both BCC ($P = 0.191$) and SCC ($P = 0.534$), the patients' ages of excision-cancer absent cases for SCC were 8 years older than that for BCC (74 years *vs* 67 years old; $P < 0.001$; Mann-Whitney *U* test), which is similar to the difference between average age of SCC and BCC patients (Table 2). Further evaluation of the percentage of excision-cancer absence in BCC and SCC based on age distributions (< 60, 61-70, 71-80 and > 80 years old) revealed that while the percentage of excision-cancer absence cases among the elderly SCC patients was increased, the percentage among the elderly BCC patients was decreased (Figure 2). Our data indicated that in the patient group of 71-80 years old, SCC showed significantly higher percentage compared with BCC (67.6% *vs* 39.4%; $P = 0.02$; χ^2 test).

DISCUSSION

While currently there are limited reports linking local immune response and cutaneous carcinoma regression after biopsy, it is noteworthy that the local immune cells might contribute to eliminating residual skin cancer cells. For instance, dendritic cells (DCs), the typical antigen-presenting immune cells which consist dermal DCs, Langerhans cells and plasmacytoid DCs, are abundant in both epidermal and dermal tissues and play central role in initiating immune response[9-11].

Despite DCs being present in human carcinomas, the potential to initiate an immune response is largely diminished by tumor environment[12,13]. Tumors suppress the function of DCs significantly by exploiting different cytokines, including interleukin-6 (IL-6), macrophage colony-stimulating factor, IL-10 and IL-13[14-16]. It was reported that the number of Langerhans cells decreased in

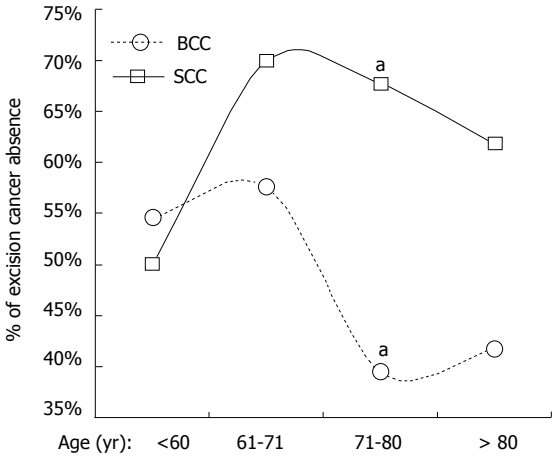

Figure 2 Age distribution and percentage of excision-cancer absence in basal cell carcinoma and squamous cell carcinoma. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) cases were divided into four groups based on age, including cases younger than 60, 61-70, 71-80 and older than 80 years old. The percentage of excision-cancer absence in each group is shown as squares (SCC) and circles (BCC). [a]*P* = 0.02, percentage of excision-cancer absence in BCC *vs* SCC in 71-80 years old group.

SCC, though the mechanism is not fully understood[17-19]. In addition, SCC-associated DCs have much lower potential to stimulate proliferation of T-cells compared with DCs derived from normal tissue[20]. In view of this tumor mediated suppression of DCs, stimulating their function becomes a promising way to fight against skin cancer, as a limited number of DCs are sufficient to induce an immune response[21,22].

During the original biopsy of the SCC or BCC, a substantial part of the cancer tissue, as well as adjacent tumor-associated DCs and macrophages, were removed. This "tissue injury" would cause inflammation, accompanied with both innate and adaptive immune responses in the wound healing process[23-25]. Neutrophils, followed by monocytes, infiltrate the wound where monocytes would differentiate into DCs or macrophages. On the one hand, the immune cells which were either suppressed by the tumor or benefit the tumor growth were removed so that local immune suppression is relieved. Fresh healthy immune cells would then enter the wound area to "clean" the environment. Macrophages are the most abundant cells before fibroblast proliferation, which induced cancer cell apoptosis by producing nitric oxide or inducing nitric oxide production in tumor cells[26-30]. It is possible that the residual cancer cells were killed by these immune responses during the initial wound healing, leading to excision-cancer absence. Further research is needed to understand the underlying mechanism.

In a conclusion, wide excisions from nearly 50% or more BCC and SCC patients with positive margins at biopsy appeared to be absent of cancer cells. The excision-cancer absence is more frequently observed in SCC than BCC patients. No significant correlation between gender and cancer absence is found. However, while the percentage of excision-cancer absence was increased in elder SCC patients, it was decreased in elder BCC patients. These findings might provide evidence for a study on the specific mechanism of cancer cell absence resulting from a biopsy induced immune response.

Table 4 Age distribution between excision-cancer absent and excision-cancer present cases of basal cell carcinoma and squamous cell carcinoma

		Median age (range), yr	Average age, yr	*P* Value
BCC	Excision-cancer absent	66 (45-92)	67	0.191[1]
	Excision-cancer present	72 (42-90)	70	
SCC	Excision-cancer absent	76 (48-95)	74	0.534[1]
	Excision-cancer present	78 (45-91)	75	
Excision-cancer absent	BCC	66 (45-92)	67	< 0.001[2]
	SCC	76 (48-95)	74	

P value: [1]In BCC or SCC cases, age distribution of excision-cancer absent *vs* present cases; [2]In excision-cancer absent cases, age distribution of BCC *vs* SCC. BCC: Basal cell carcinoma; SCC: Squamous cell carcinoma.

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COMMENTS

Background

When examining patients for suspected cancer, biopsies are performed to confirm that the lesion is in fact cancer, which type of cancer, as well as to determine if the cancer is confined to the biopsy or extends to the margins (positive margins). For biopsies which show positive margins, wide excision will be performed. It is expected that cancer cells will appear in the excised tissues of wide excisions. However, clinically this is not always the case.

Research frontiers

As the classic treatment for skin cancer, the wide excision is necessary after the positive margin is confirmed in biopsy. Biopsy is indispensable to define the risk factors of skin cancer. The research hotspot in this field is how to determine the excision margins of different types of skin cancer based on result of biopsy.

Innovations and breakthroughs

This retrospective chart review provided evidences that 49% basal cell carcinoma (BCC) and 64% squamous cell carcinoma (SCC) patients did not have cancer cells left in the original location where the positive margin was reported in biopsy. Although the correlation between excision-cancer absence and gender or age distribution was excluded in both SCC and BCC patients, the analysis revealed that in excision-cancer absent cases, there were more male patients in BCC than that in SCC while SCC patients were older than BCC patients.

Applications

The data provided in this study suggests a potential role of immune response caused by biopsy in removing residual cancer cells. The high percentage of excision-cancer absence might cushion the SCC and BCC patients against the fear of biopsy and promote compliance of them with biopsy demanded by dermatologists.

Terminology

Excision-cancer present SCC or BCC patient means that cancer cells were found in the widely excised tissue which contained positive margin which had been reported previously in biopsy. Excision-cancer absent SCC or BCC means no cancer cells were found in wide excision containing previously defined positive margin.

Peer review

The work is well written and focuses on an interesting aspect of skin cancer surgery.

REFERENCES

1 **Marks R**. An overview of skin cancers. Incidence and causation. *Cancer* 1995; **75**: 607-612 [PMID: 7804986]
2 **Dubas LE**, Ingraffea A. Nonmelanoma skin cancer. *Facial Plast Surg Clin North Am* 2013; **21**: 43-53 [PMID: 23369588 DOI: 10.1016/j.fsc.2012.10.003]
3 **Sterry W**, Paus R, Burgdirf W. Dermatology (Thieme Clinical Companions). 1 ed. New York, NY: Thieme, 2006: 419-433
4 **Bolognia JL**, Jorizzo JL, Schaffer JV, Callen JP, Cerroni L, Heymann WR, Hruza GJ. Dermatology. 3 ed. Philadelphia, PA: Saunders, 2012: Chapter 108
5 **Weinstein MC**, Brodell RT, Bordeaux J, Honda K. The art and science of surgical margins for the dermatopathologist. *Am J Dermatopathol* 2012; **34**: 737-745 [PMID: 23000878 DOI: 10.1097/DAD.0b013e31823347cb]
6 **Tan PY**, Ek E, Su S, Giorlando F, Dieu T. Incomplete excision of squamous cell carcinoma of the skin: a prospective observational study. *Plast Reconstr Surg* 2007; **120**: 910-916 [PMID: 17805118 DOI: 10.1097/01.prs.0000277655.89728.9f]
7 **Pugliano-Mauro M**, Goldman G. Mohs surgery is effective for high-risk cutaneous squamous cell carcinoma. *Dermatol Surg* 2010; **36**: 1544-1553 [PMID: 21053415 DOI: 10.1111/j.1524-4725.2010.01576.x]
8 **Leibovitch I**, Huilgol SC, Richards S, Paver R, Selva D. Scalp tumors treated with Mohs micrographic surgery: clinical features and surgical outcome. *Dermatol Surg* 2006; **32**: 1369-1374 [PMID: 17083590 DOI: 10.1111/j.1524-4725.2006.32308.x]
9 **Valladeau J**, Saeland S. Cutaneous dendritic cells. *Semin Immunol* 2005; **17**: 273-283 [PMID: 15953735 DOI: 10.1016/j.smim.2005.05.009]
10 **Zaba LC**, Krueger JG, Lowes MA. Resident and "inflammatory" dendritic cells in human skin. *J Invest Dermatol* 2009; **129**: 302-308 [PMID: 18685620 DOI: 10.1038/jid.2008.225]
11 **Hunger RE**, Sieling PA, Ochoa MT, Sugaya M, Burdick AE, Rea TH, Brennan PJ, Belisle JT, Blauvelt A, Porcelli SA, Modlin RL. Langerhans cells utilize CD1a and langerin to efficiently present nonpeptide antigens to T cells. *J Clin Invest* 2004; **113**: 701-708 [PMID: 14991068 DOI: 10.1172/JCI19655]
12 **Gabrilovich D**. Mechanisms and functional significance of tumour-induced dendritic-cell defects. *Nat Rev Immunol* 2004; **4**: 941-952 [PMID: 15573129 DOI: 10.1038/nri1498]
13 **Vicari AP**, Caux C, Trinchieri G. Tumour escape from immune surveillance through dendritic cell inactivation. *Semin Cancer Biol* 2002; **12**: 33-42 [PMID: 11926410 DOI: 10.1006/scbi.2001.0400]
14 **Chomarat P**, Banchereau J, Davoust J, Palucka AK. IL-6 switches the differentiation of monocytes from dendritic cells to macrophages. *Nat Immunol* 2000; **1**: 510-514 [PMID: 11101873 DOI: 10.1038/82763]
15 **Steinbrink K**, Wölfl M, Jonuleit H, Knop J, Enk AH. Induction of tolerance by IL-10-treated dendritic cells. *J Immunol* 1997; **159**: 4772-4780 [PMID: 9366401]
16 **Aspord C**, Pedroza-Gonzalez A, Gallegos M, Tindle S, Burton EC, Su D, Marches F, Banchereau J, Palucka AK. Breast cancer instructs dendritic cells to prime interleukin 13-secreting CD4+ T cells that facilitate tumor development. *J Exp Med* 2007; **204**: 1037-1047 [PMID: 17438063 DOI: 10.1084/jem.20061120]
17 **Galan A**, Ko CJ. Langerhans cells in squamous cell carcinoma vs. pseudoepitheliomatous hyperplasia of the skin. *J Cutan Pathol* 2007; **34**: 950-952 [PMID: 18001421 DOI: 10.1111/j.1600-0560.2007.00741.x]
18 **Gibson GE**, O'Grady A, Kay EW, Leader M, Murphy GM. Langerhans cells in benign, premalignant and malignant skin lesions of renal transplant recipients and the effect of retinoid therapy. *J Eur Acad Dermatol Venereol* 1998; **10**: 130-136 [PMID: 9553909]
19 **Gatter KC**, Morris HB, Roach B, Mortimer P, Fleming KA, Mason DY. Langerhans' cells and T cells in human skin tumours: an immunohistological study. *Histopathology* 1984; **8**: 229-244 [PMID: 6233213]
20 **Bluth MJ**, Zaba LC, Moussai D, Suárez-Fariñas M, Kaporis H, Fan L, Pierson KC, White TR, Pitts-Kiefer A, Fuentes-Duculan J, Guttman-Yassky E, Krueger JG, Lowes MA, Carucci JA. Myeloid dendritic cells from human cutaneous squamous cell carcinoma are poor stimulators of T-cell proliferation. *J Invest Dermatol* 2009; **129**: 2451-2462 [PMID: 19387481 DOI: 10.1038/jid.2009.96]
21 **Yanofsky VR**, Mitsui H, Felsen D, Carucci JA. Understanding dendritic cells and their role in cutaneous carcinoma and cancer immunotherapy. *Clin Dev Immunol* 2013; **2013**: 624123 [PMID: 23606870 DOI: 10.1155/2013/624123]
22 **Figdor CG**, de Vries IJ, Lesterhuis WJ, Melief CJ. Dendritic cell immunotherapy: mapping the way. *Nat Med* 2004; **10**: 475-480 [PMID: 15122249 DOI: 10.1038/nm1039]
23 **Tsirogianni AK**, Moutsopoulos NM, Moutsopoulos HM. Wound healing: immunological aspects. *Injury* 2006; **37** Suppl 1: S5-S12 [PMID: 16616753 DOI: 10.1016/j.injury.2006.02.035]
24 **DiPietro LA**. Wound healing: the role of the macrophage and other immune cells. *Shock* 1995; **4**: 233-240 [PMID: 8564549]
25 **Park JE**, Barbul A. Understanding the role of immune regulation in wound healing. *Am J Surg* 2004; **187**: 11S-16S [PMID: 15147986 DOI: 10.1016/S0002-9610(03)00296-4]
26 **Rieder J**, Jahnke R, Schloesser M, Seibel M, Czechowski M, Marth C, Hoffmann G. Nitric oxide-dependent apoptosis in ovarian carcinoma cell lines. *Gynecol Oncol* 2001; **82**: 172-176 [PMID: 11426981 DOI: 10.1006/gyno.2001.6242]
27 **Binder C**, Schulz M, Hiddemann W, Oellerich M. Induction of inducible nitric oxide synthase is an essential part of tumor necrosis factor-alpha-induced apoptosis in MCF-7 and other epithelial tumor cells. *Lab Invest* 1999; **79**: 1703-1712 [PMID: 10616218]
28 **Reveneau S**, Arnould L, Jolimoy G, Hilpert S, Lejeune P, Saint-Giorgio V, Belichard C, Jeannin JF. Nitric oxide synthase in human breast cancer is associated with tumor grade, proliferation rate, and expression of progesterone receptors. *Lab Invest* 1999; **79**: 1215-1225 [PMID: 10532585]
29 **Binder C**, Schulz M, Hiddemann W, Oellerich M. Caspase-activation and induction of inducible nitric oxide-synthase during TNF alpha-triggered apoptosis. *Anticancer Res* 1999; **19**: 1715-1720 [PMID: 10470105]
30 **Kwak JY**, Han MK, Choi KS, Park IH, Park SY, Sohn MH, Kim UH, McGregor JR, Samlowski WE, Yim CY. Cytokines secreted by lymphokine-activated killer cells induce endogenous nitric oxide synthesis and apoptosis in DLD-1 colon cancer cells. *Cell Immunol* 2000; **203**: 84-94 [PMID: 11006006 DOI: 10.1006/cimm.2000.1682]

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CASE REPORT

Multilevel oblique corpectomies as an effective surgical option to treat cervical chordoma in a young girl

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Abstract

Chordomas are malignant tumors arising from notochordal remnants. They are the most frequent tumors of the spine after plasmacytomas. Only 6% of chordomas are localized to the cervical level. In young patients, chordomas are rare and unpredictable. Despite this, the treatment of choice remains the total resection, as much as possible, followed by proton beam radiation. This case was managed using a precarotid and retrocarotid approach at the same time. The tumor was completely resected with the edges free from disease. The cervical spine was stabilized with an anterior plating C2-C4. Eighteen months after surgery the patient is still free from illness. Multilevel oblique corpectomies are an available and safe option for the treatment of upper cervical chordomas.

Key words: Cervical chordoma; Multilevel oblique corpectomy; Surgery; RXT; Retrocarotid approach

Core tip: In young patients, chordomas are rare and unpredictable. Despite this, the treatment of choice remains the total resection, as much as possible, followed by proton beam radiation. When there is a precarotid and retrocarotid extension, the removal by a multilevel oblique corpectomy seems to be a feasible and safe surgical technique.

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INTRODUCTION

Chordomas are malignant tumors arising from notochordal remnants and are the most frequent tumors of the spine after plasmacytomas. Only 6% of chordomas are localized at cervical level[1,2]. The treatment of choice is total resection, or removing as much as possible of the tumor, followed by proton beam radiation. As emphasized in previous studies, total resection and, in particular, *en bloc* removal are not always possible, especially in the upper cervical localization and when the tumor englobes the epidural space (as in our case). This is a consequence both of the fact that the cervical chordoma infiltrates the nearby structures and that the margins of the total resection include unresectable structures. In young patients, chordomas are rare and unpredictable. We describe a rare case of an extensive cervical chordoma in a 14-year-old girl treated simultaneously by a precarotid and retrocarotid approach.

CASE REPORT

A 14-year-old girl was referred to our institution with cervical pain, dysphagia, hyperreflexia and weakness of

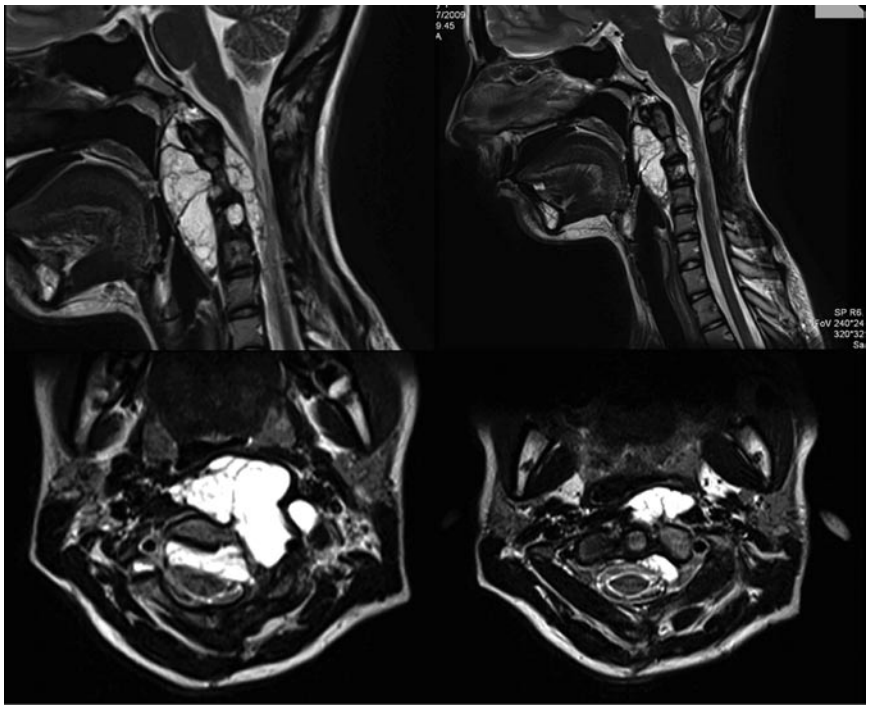

Figure 1 Sagittal and axial T2-weighted magnetic resonance imaging showed diffuse increased signal of a lesion of C2-C3-C4 with important retropharyngeal portion.

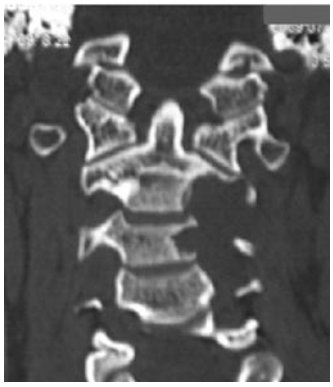

Figure 2 Preoperative coronal computed tomography of the cervical spine demonstrating an osteolytic process involving vertebral body of C2, C3 and C4.

the four limbs for 8 mo. The preoperative magnetic resonance imaging (MRI) showed a lesion of C2-C3-C4 with marked retropharyngeal and epidural space involvement (Figure 1). The tumor extended from the C1 anterior tuberculum as far as the C5 superior plate. Since biopsy had been performed in another institute *via* C2-C3-C4 interhemilaminectomy, the definitive result of the biopsy was not available.

A pre-operative CT showed erosion of the C2-C3-C4 vertebral bodies (Figure 2). An angio-MRI with gadolinium administration pointed out that the left vertebral artery (VA) was encapsulated and displaced without reduction of the vessel diameter. The tumor showed a spare contrast enhancement with gadolinium and in DWI was hyperintense in DWI sequences. Relating to the clinical and radiological features, there were two diagnostic hypotheses, either an epidermoid cyst or chordoma. The tumor was classified IB according to the Enneking classification[3]. It was distributed to layers A-F and sectors 4-7 according to the Weinstein Boriani Biagini Classification[4].

Surgical procedure

Surgical strategy consisted of a precarotid and retrocarotid approach during a single operation. The patient was positioned in the supine position with her head rotated 30° to the right. A presternocleidomastoid longitudinal skin incision was performed starting from left mastoid process. Firstly, the precarotid approach was performed through which the retropharyngeal portion was removed (Figure 3). Infiltrated bone, the portion around VA and the epidural space component were removed *via* the second approach, *via* multilevel oblique corpectomies. During surgery we employed ecodoppler monitoring to control the vertebral artery, as well as the operative microscope and the cavitron ultrasonic surgical aspirator, to remove the epidural component of the tumor. The retropharyngeal component was removed by an *en bloc* excision, while an intralesional excision was performed to remove the residual tumor. The tumor was completely resected together with the disease-free borders. A C2-C3 and C3-C4 discectomy with apposition of synthetic bone was performed to improve and speed up fusion and the cervical spine was stabilized by means of C2-C4 anterior plating.

A post-operative computed tomography (CT)-scan confirmed the correct position of the plate and the screws (Figure 4). The second day after surgery, the patient was free of any neurological deficit and was able to stand up and started to walk. The patient was discharged from hospital the seventh day after surgery. Twenty days after surgery, a post-operative MRI showed total resection of the tumor. A Shantz cervical collar was fitted for 45 d. Forty days after surgery, the patient received postoperative

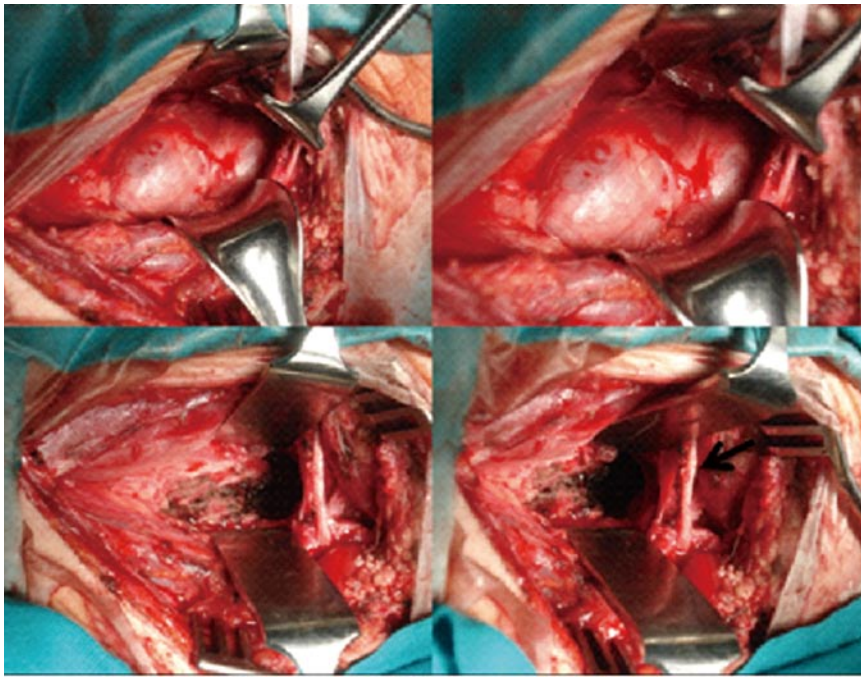

Figure 3 Intraoperative photos shows before (above) and after (below) *en bloc* excision of the retropharyngeal portion. The arrow points to the hypoglossal nerve.

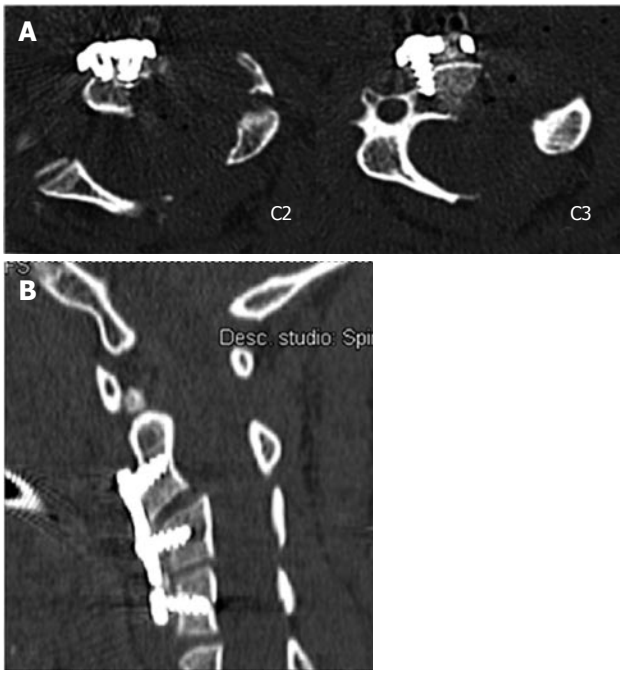

Figure 4 Postoperative axial (A) and sagittal (B) reconstructed computed tomography scans of the cervical spine shows the oblique corpectomies and a fixation with an anterior plating C2-C4.

proton beam radiation therapy. A clinical and radiological control, consisting of cervical MRI with gadolinium, was performed every 6 mo. Twenty days after surgery, the patient returned to school and at present leads a normal life. Fusion was documented at 40 d. No recurrence or metastasis was observed 48 mo after the operation (Figure 5).

DISCUSSION

Chordoma is a low-grade malignant tumor which is rare (incidence of 0.51 cases/million), and is generally slow-growing, radioresistant and has a high tendency of recurrence[4]. Chordomas arise from remnants of the notochord, especially at the two end portions. 32% of chordomas arise from the clivus, 33% from the spinal cord, 29% from the sacrococcygeal region and just 6% from the cervical spine[1]. The treatment of choice is *en bloc* total resection followed by radiation therapy. The chordoma is sensitive to a high dose of "standard" radiation. However, the Bragg peak effect of a proton beam is useful for delivering a high radiation dose without damaging the tissue around the tumor and the spinal cord[1,5]. Total resection and, above all, *en bloc* removal are not always possible, especially in the upper cervical localization and when the tumor englobes the epidural space (as in our case). This is a consequence of the fact that the cervical chordoma infiltrates the nearby structures; moreover, the margins of the total resection include non-resectable structures like the vertebral artery. However, as pointed out by Boriani *et al*[6], "*en bloc* removal of a bone tumor is possible for a tumor arising in the scapula (scapulectomy) and tibia (above knee amputation), but it is absolutely impossible for a spinal tumor. In this sense, even if the spinal cord is sectioned above and below, the epidural space represents a compartment extending from the skull to the coccyx. A trial of aggressive chemotherapy is warranted in patients with metastatic chordomas. In the literature[7-9], two protocols were primarily used, consisting of ifosfamide or imatinib mesylate. Several approaches for treating upper cervical chordoma have been described in the literature: the anterior precarotid cervical approach (bilateral or not); the anterolateral retrocarotid approach; the transoral approach[10]; and anterior fixation or anterior and posterior fixation[11].

In the case described here, an anterior precarotid and an anterolateral retrocarotid (presternocleidomastoid) ap-

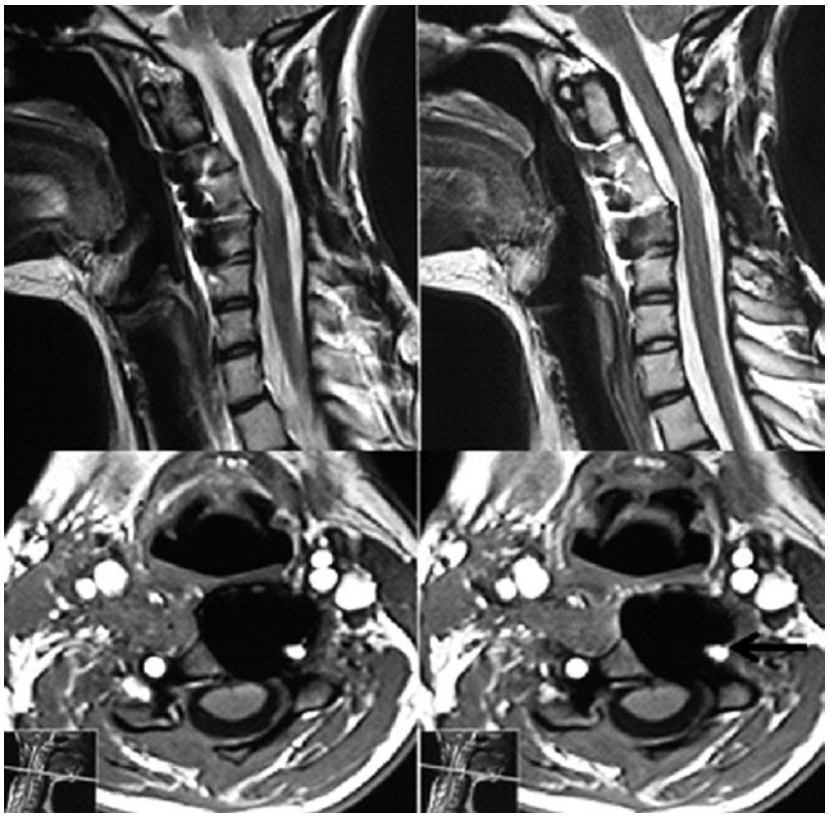

Figure 5 T2 (above) and T1 with gadolinium contrast (below) magnetic resonance imaging shows total resection of the tumor. The arrow underlines the left vertebral artery.

proach were performed at the same time. The advantages of this technique were good control of the left vertebral artery, multilevel oblique corpectomies, removal of the epidural space component of the chordoma and the possibility of anterior plating. It was impossible to perform an *en bloc* excision for the epidural space component because the tumor enclosed the left VA[1]. The procedure that we performed avoided binding of the VA and injuring the cervical roots, with a better outcome in comparison to some recent works[10,12]. Moreover, only anterior fixation was necessary because we performed multilevel oblique corpectomies, thus sparing the posterior structures of the cervical spine. This procedure made it possible to avoid occipitocervical fixation in a 14-year-old girl and the consequent limitations in movement.

In our opinion, a more aggressive strategy (multiple spondylectomy), which has a high morbidity, is justified for the treatment of cervical chordoma because chordomas are tumors whose biological behavior is difficult to predict. Despite this, the most recent publications[1,10-19] have shown that there are no important differences between patients operated on using an aggressive strategy (spondylectomy) and those submitted to corpectomies. So in our opinion, multilevel oblique corpectomies seem to be a feasible and safe surgical technique to treat a cervical chordoma.

COMMENTS

Case characteristics

A 14-year-old girl was referred to our institution with cervical pain, dysphagia, hyperreflexia and weakness of the four limbs for 8 mo.

Imaging diagnosis

The preoperative magnetic resonance imaging showed a lesion of C2-C3-C4 with marked retropharyngeal and epidural space involvement.

Treatment

Surgical strategy consisted of a precarotid and retrocarotid approach during a single operation.

Experiences and lessons

Multilevel oblique corpectomies seems to be a feasible and safe surgical technique to treat a cervical chordoma.

Peer review

This is well written case report presenting a rare condition which is explained well.

REFERENCES

1 **Barrenechea IJ**, Perin NI, Triana A, Lesser J, Costantino P, Sen C. Surgical management of chordomas of the cervical spine. *J Neurosurg Spine* 2007; **6**: 398-406 [PMID: 17542504 DOI: 10.3171/spi.2007.6.5.398]

2 **Currier BL**, Papagelopoulos PJ, Krauss WE, Unni KK, Yaszemski MJ. Total en bloc spondylectomy of C5 vertebra for chordoma. *Spine* (Phila Pa 1976) 2007; **32**: E294-E299 [PMID: 17450062 DOI: 10.1097/01.brs.0000261411.31563.37]

3 **Enneking WF**, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. *Clin Orthop Relat Res* 1980; (153): 106-120 [PMID: 7449206]

4 **Greenberg MS**. Handbook of Neurosurgery. New York: Thieme Medical Publishers, 2006

5 **Noël G**, Feuvret L, Ferrand R, Boisserie G, Mazeron JJ, Habrand JL. Radiotherapeutic factors in the management of cervical-basal chordomas and chondrosarcomas. *Neurosurgery* 2004; **55**: 1252-1260; discussion 1260-1262 [PMID: 15574207]

6 **Boriani S**, Weinstein JN, Biagini R. Primary bone tumors of the spine. Terminology and surgical staging. *Spine* (Phila Pa 1976) 1997; **22**: 1036-1044 [PMID: 9152458 DOI: 10.1097/00007632-199705010-00020]

7 **Chambers PW**, Schwinn CP. Chordoma. A clinicopathologic

study of metastasis. *Am J Clin Pathol* 1979; **72**: 765-776 [PMID: 389031]
8 **Fleming GF**, Heimann PS, Stephens JK, Simon MA, Ferguson MK, Benjamin RS, Samuels BL. Dedifferentiated chordoma. Response to aggressive chemotherapy in two cases. *Cancer* 1993; **72**: 714-718 [PMID: 8334623 DOI: 10.1002/1097-0142(19930801)72]
9 **Casali PG**, Stacchiotti S, Sangalli C, Olmi P, Gronchi A. Chordoma. *Curr Opin Oncol* 2007; **19**: 367-370 [PMID: 17545801]
10 **Jiang L**, Liu ZJ, Liu XG, Ma QJ, Wei F, Lv Y, Dang GT. Upper cervical spine chordoma of C2-C3. *Eur Spine J* 2009; **18**: 293-298; discussion 298-300 [PMID: 19221808 DOI: 10.1007/s00586-009-0907-y]
11 **Leitner Y**, Shabat S, Boriani L, Boriani S. En bloc resection of a C4 chordoma: surgical technique. *Eur Spine J* 2007; **16**: 2238-2242 [PMID: 17713796 DOI: 10.1007/s00586-007-0468-x]
12 **Suchomel P**, Buchvald P, Barsa P, Froehlich R, Choutka O, Krejzar Z, Sourkova P, Endrych L, Dzan L. Single-stage total C-2 intralesional spondylectomy for chordoma with three-column reconstruction. Technical note. *J Neurosurg Spine* 2007; **6**: 611-618 [PMID: 17561755 DOI: 10.3171/spi.2007.6.6.17]
13 **Fujita T**, Kawahara N, Matsumoto T, Tomita K. Chordoma in the cervical spine managed with en bloc excision. *Spine* (Phila Pa 1976) 1999; **24**: 1848-1851 [PMID: 10488517 DOI: 10.1097/00007632-199909010-00016]
14 **George B**, Zerah M, Lot G, Hurth M. Oblique transcorporeal approach to anteriorly located lesions in the cervical spinal canal. *Acta Neurochir (*Wien) 1993; **121**: 187-190 [PMID: 8512017 DOI: 10.1007/BF01809273]
15 **Chibbaro S**, Mirone G, Bresson D, George B. Cervical spine lateral approach for myeloradiculopathy: technique and pitfalls. *Surg Neurol* 2009; **72**: 318-324; discussion 324 [PMID: 19608245 DOI: 10.1016/j.surneu.2009.04.026]
16 **Lim JJ**, Kim SH, Cho KH, Yoon DH, Kim SH. Chordomas involving multiple neuraxial bones. *J Korean Neurosurg Soc* 2009; **45**: 35-38 [PMID: 19242569 DOI: 10.3340/jkns.2009.45.1.35.]
17 **Bruneau M**, Cornelius JF, George B. Microsurgical cervical nerve root decompression by anterolateral approach. *Neurosurgery* 2006; **58**: ONS108-ONS13; discussion ONS108-ONS13 [PMID: 16543867 DOI: 10.1227/01.NEU.0000193521.98836.C5]
18 **Bruneau M**, Cornelius JF, George B. Multilevel oblique corpectomies: surgical indications and technique. *Neurosurgery* 2007; **61**: 106-112; discussion 112 [PMID: 17876240]
19 **Kelley SP**, Ashford RU, Rao AS, Dickson RA. Primary bone tumours of the spine: a 42-year survey from the Leeds Regional Bone Tumour Registry. *Eur Spine J* 2007; **16**: 405-409 [PMID: 16865376 DOI: 10.1007/s00586-006-0188-7]

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CASE REPORT

Can a polymorphism in the thalassemia gene and a heterozygote *CFTR* mutation cause acute pancreatitis?

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Abstract

The case of a 32-year-old black woman of African descent who suffered from repeated episodes of acute pancreatitis, initially triggered when flying on airplanes, is reported. She did not drink alcohol or smoke. Genetic analysis was negative for cationic trypsinogen, serine protease inhibitor Kazal type 1 and chymotrypsin C. However, hemoglobin F was elevated. Sequencing of the thalassemia gene revealed a novel alteration in the 5′ region indicative of a functional abnormality of the molecule. Sequencing the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene revealed a heterozygote sequence variant. The combination of a hemoglobin gene mutation known for thalassemia in conjunction with the hitherto undescribed *CFTR* mutation is suggested to pave the road for initial and repetitive pancreatitis attacks. This will be discussed.

Key words: Acute pancreatitis; Hypoxia; Flying; Thalassemia; Hemoglobin; Cystic fibrosis transmembrane conductance regulator; Hereditary persistence of fetal hemoglobin

Core tip: This is a discussion case with two genetic alterations, one in a pancreatitis-related gene and one in an unrelated gene that might influence the oxygenation in the pancreas.

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INTRODUCTION

Within the group of younger patients suffering from recurrent episodes of acute pancreatitis, those not drinking alcohol impose a special diagnostic challenge. Many of these patients, who were coined to suffer from idiopathic pancreatitis even without a family history, may have mutations in the genes known to be associated with this disease[1]. Among genes identified to convey the risk of developing pancreatitis are cationic trypsinogen (PRSS1)[2], serine protease inhibitor Kazal type 1 (SPINK1)[3], chymotrypsin C (CTRC)[4] and cystic fibrosis transmembrane conductance regulator (CFTR)[5], whereas mutations in the anionic trypsinogen gene[6] appear to be protective. Some who may be negative for genetic factors may have anatomical abnormalities, such as pancreas divisum or other branching disorders[7]. Still then, a small subgroup is left with no identifiable reason. Those may suffer from rare metabolic conditions or syndromes, however, normally present with other symptoms indicative of the underlying disease. Beyond those conditions, there are rather exotic reasons for suffering from acute pancreatitis. We here report on the combination of two hitherto undescribed mutations in both an extrapancreatic and a

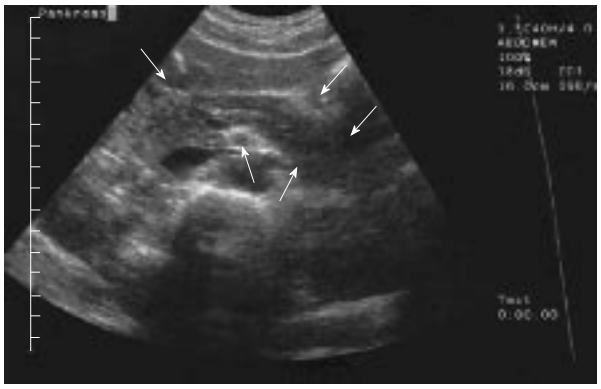

Figure 1 Transabdominal ultrasound depicting a pancreas (arrows) of normal size with slightly enhanced echogenicity.

pancreatic gene that might explain the repetitive attacks of pancreatitis.

CASE REPORT

Previous history

The 31-year-old black woman, who was brought up in Kenya but had been living in Germany for the last 8 years, presented with repeated episodes of acute abdominal pain which started in the middle epigastric region and would eventually radiate into the back, suggestive of acute pancreatitis. These episodes initially occurred after flying on regular commercial aircrafts. She was hospitalized eight years prior to this attack when 23 years old for cystitis and pyelonephritis when a diagnosis of acute pancreatitis was established *via* computer tomography. At that time, she also suffered from iron-deficient anemia [hemoglobin (Hb) 10.7 g/dL, mean corpuscular volume 69.4 μm, iron 28 mg/dL, ferritin 23 ng/mL].

Recent history prior to referral

Abdominal ultrasound and computed axial tomography scan were reported to be normal; endoscopic retrograde cholangiopancreatography showed a slightly irregular main pancreatic duct (grade 0); however, no pancreas divisum and no papillary abnormalities. No overt gallstones, microlithiasis or sludge was present. After the last episode, when the diagnosis of acute pancreatitis was established by laboratory tests (elevated serum amylase and lipase) and abdominal ultrasound (swollen pancreas), the patient was referred to our outpatient pancreas clinic about one week after the last episode.

Current presentation

The patient denied any abdominal pain or discomfort, fever or occasional night sweating. Appetite was normal. Bowel movements were reported to be regular with normal stool consistency and she reported no weight loss. There was no family history of pancreatitis or unclear abdominal pain. The patient denied any alcohol intake, smoking or experience with other drugs. There were no known allergies, prescription medicine or over-the-counter drugs. The patient is a graduate student.

The patient was in no apparent distress. The physical exam was completely normal, vital signs stable and specifically, the abdomen was not tender. Bowel sounds were normal.

Laboratory tests

In the blood, amylase and lipase were elevated (Table 1). All other parameters were within normal limits (Table 1). Infectious pathogens known to be associated with pancreatitis (cytomegalovirus, Epstein-Barr virus, mumps, adenovirus, varicella zoster virus, rubella, human immunodeficiency syndrome, Coxsackie, Legionella, leptospira, echinococcus, filariasis, fasciolosis, toxocara, bilharzia) could be excluded by serology. She did not have and had no history of malaria. Autoantibodies against nuclei, mitochondria and smooth muscle were negative, as were rheumatoid factors. All immunoglobulins, especially total immunoglobulin G (IgG) and IgG4, were within normal limits. Fecal elastase-1 (985 μg/g) and fecal chymotrypsin (14.7 U/g) were well within the normal range.

Imaging

The pancreas appeared almost normal on ultrasound. Notably, the echogenicity was slightly elevated towards a so-called "white pancreas"[8] (Figure 1). There was a normal arterial blood supply to the pancreas. As the patient was slender, the transabdominal ultrasound had a good visibility: no gallstones, sludge or microlithiasis could be detected in the gallbladder or the bile duct all the way down into the pancreas.

Hematological and genetic tests

Since the history of present illness together with the ethnic background of the patient was pressing, we performed further analysis with regard to a possible hemoglobinopathy. The ordinary complete blood count with blood smear was normal.

Hemoglobin F was slightly elevated at 0.92%, suggesting a "hereditary persistence of fetal hemoglobin" (HPFH). Molecular analysis of the hemoglobins resulted in the finding of a heterozygous transition at -158 C → T within the 5' non-coding region of the ^{G}gamma globulin gene (HPFH Swiss)[9,10]. Sequencing of the ^{A}gamma globulin gene did not reveal any abnormalities. Other genetic abnormalities associated with HPFH [HPFH-1 (black), HPFH-2 (Ghana), HPFH-3 (Indian), HPFH-7 (Kenya)] could not be detected. Sequencing of the β-thalassemia gene revealed no abnormalities. Sequencing the *CFTR* gene revealed a heterozygote sequence variant (c.2882T>C; p.M961T (ATG>ACC). Sequencing of *PRSS1*[2], *SPINK1*[3] and *CTRC*[4] did not reveal any additional mutations in these pancreatitis genes.

Further course

During a six year follow-up, the patient did not develop any further episodes of pancreatitis. According to our recommendation, she resisted from flying.

Table 1 Laboratory values upon presentation to the pancreas outpatient clinic

Parameter	Unit	Value	Range
WBC	10E9/L	4.5	3.6-11.0
RBC	10E12/L	4.73	3.8-5.2
Hb	g/dL	14.8	12-16
Hct		43.9	35%-47%
MCV	fL	92.9	80-100
Na	mmol/L	139	135-144
K	mmol/L	4.28	3.5-5.2
Ca	mol/L	2.18	2.25-2.60
Albumin	g/L	36.4	35-52
Blood glucose	mg/dL	74	70-115
Bilirubin (total)	mg/dL	0.31	0.2-1.4
Uric acid	mg/dL	3.2	2.5-5.7
Cholesterol	mg/dL	173	130–260
Triglycerides	mg/dL	36	< 200
BUN	mg/dL	18.8	16.7-45.8
Creatinine	mg/dL	0.7	0.6-1.1
Alkaline phosphatase	U/L	80	55-160
γGT	U/L	9	4-18
GPT/ASAT	U/L	5	5-19
GOT/ALAT	U/L	13	5-15
Cholinesterase	U/L	4238	2800-7400
HbA1C		1.51	1.2-4.6
Zinc	mmol/L	34	16-50
Amylase	U/L	183	25–115
Lipase	U/L	202	114-286
Chymotrypsin	U/g	14.7	> 6
Elastase-1	μg/g	985	> 200
HbF		0.92	< 0.5%
HbA		92.73	87%-94%
HbA2		2.14	1.6%-3.1%
Anomalous Hb		Not detectable	
ALA	μmol/d	24	2-49
Porphobilinogen	μmol/d	6.6	0.5-7.5
Total porphyrines	μg/d	41.7	< 145

WBC: White blood cells; RBC: Red blood cells; Hb: Hemoglobin; Hct: Hematocrit; MCV: Mean corpuscular volume; BUN: Blood urea nitrogen; GOT/ASAT: Glutamic oxaloacetic transaminase; GPT/ALAT: Glutamic pyruvic transaminase; HbA1c: Hemoglobin A1c; ALA: Alpha lipoic acid.

Table 2 Summary of key findings

Etiology	Parameter	Negative/ normal	Positive	Finding
Metabolic parameters	TSH, PTH, α-AT, lipids	X		
Immunological parameters	IgG/IgG4; AMA, ANA, ASMA, RF	X		
Pancreatotrophic virus	Adenovirus, Coxsackie, CMV, EBV, hepatitis, HIV, measles, mumps, Rubella, VZV	X		
Pancreatitis genetics-acinar	PRSS1, CTRC, SPINK1	X		
Pancreatitis genetics-ductal	CFTR		X	c.2882T > C; p.M961T (ATG > ACC)
Hemoglobin	HBs		X	Elevated
HPFH	^{G}gamma-hemoglobin gene		X	-158 C → T (HPFH Swiss)
	^{A}gamma-hemoglobin gene	X		

HIV: Human immunodeficiency syndrome; ANA: Autoantibodies against nuclei; AMA: Autoantibodies against mitochondria; ASMA: Autoantibodies against smooth-muscle; CMV: Cytomegalovirus; EBV: Epstein-Barr virus; VZV: Varicella zoster virus; PTH: Parathyroid hormone; TSH: Thyroid-stimulating hormone; IgG: Immunoglobulin G; RF: Rheumatoid factor; PRSS1: Pancreatitis cationic trypsinogen; SPINK1: Serine protease inhibitor Kazal type 1; CTRC: Chymotrypsin C; CFTR: Cystic fibrosis transmembrane conductance regulator; HBs: Hepatitis B surface; HPFH: Hereditary persistence of fetal hemoglobin.

DISCUSSION

In adolescent and young adult patients presenting with signs of pancreatitis, associations with genetic abnormalities are pressing[1]. Even in sporadic cases, mutations in the genes known to cause hereditary pancreatitis such as PRSS1 have been reported. More recently, mutations in SPINK1 and CTRC have been reported in patients with idiopathic pancreatitis. Those were all normal/negative in this patient. The earlier history of present illness with flying to and from Kenya triggering the episodes of pancreatitis made us suspicious of other mechanisms underlying the etiology of her pancreatitis. The ethnic background led to further analysis of hemoglobinopathies, which revealed elevated hemoglobin F. Elevated fetal hemoglobin is not uncommon: it has been detected in around 10% of teenage high school students[11], a few of them with abnormalities. Amongst these, the ^{G}gamma-globulin gene (HPFH Swiss) alteration is most frequent amongst females, all of them described as of Caucasian origin[11]. Detailed studies of our young black female patient revealed this heterozygous transition at -158 C → T within the 5' non-coding region of the ^{G}gamma-globulin gene (HPFH Swiss) (Table 2). No other abnormalities could be detected. Notably, the patient did not suffer from clinically overt thalassemia, not having the typical mutations in the hemoglobin A (β-chain). Since this particular variant is considered to be minor[12], this could not have been expected. Nevertheless, associations with rather complex hereditary traits have been described in these hemoglobinopathies[13].

Classical thalassemia is reported to be associated with acute pancreatitis; however, the etiology is biliary as gallstones are typical in these patients. Indeed, in a series of 43 juvenile patients with acute pancreatitis, 30 suffered from choledocholithiasis caused by thalassemia[14].

Sequencing the *CFTR* gene revealed a heterozygote sequence variant that has not been described previously (Table 2). The pathophysiological meaning, especially in relation to pancreatitis, is therefore unknown.

Whereas neither of these heterozygote mutations per se might have been sufficient to cause or contribute to pancreatitis, it is suggestive that the minor alterations in two genes, one pancreatic (CFTR) and one extrapancreatic (hemoglobin), might have culminated in a two-step mechanism leading to pancreatitis: impaired hemoglobin,

causing a certain degree of oxygen deficiency which is known to cause pancreatitis, *e.g.*, during iatrogenic ischemia or heart-lung machine usage, imposed on a heterozygote mutation in the *CFTR* gene. This two-hit hypothesis is speculative as we did not investigate the functional changes imposed by such a transition in the non-coding region in the hemoglobulin and the *CFTR* mutation alone or in combination.

There is only one study reporting on a small series of patients with clinically overt thalassemia, gallstones and biliary pancreatitis[14]; however, our patient did not have overt thalassemia or gallstones/sludge or microlithiasis.

The pathological oxygen saturation of hemoglobin in thalassemia has been described[15,16]. Hypoxemia and ischemia have been demonstrated to be able to induce experimental pancreatitis[17]. Microcirculatory disturbances are today considered to play an important role in the exacerbation of acute pancreatitis[18]. Reduced perfusion of the pancreatic gland leading to hypoxia and ischemia is a well-described mechanism causing[19] or worsening pancreatitis[20]. Even in sickle-cell anemia, the acute pancreatitis is considered to be caused by microvascular occlusion[21]. Conversely, hyperbaric oxygen therapy has been demonstrated to ameliorate acute pancreatitis[22]. The combination of an alteration in a gene altering oxygen saturation with a gene altering pancreatic secretion represents the rendezvous of two genes, each in itself not sufficient to induce thalassemia or pancreatitis, an extrapancreatic and an intrapancreatic. This is supported by the finding in our patient during the initial, most severe acute pancreatitis when she was also found to have anemia (Hb 10.7 g/dL). We speculate that such combinations may be responsible for a number of hitherto undefined causes of juvenile pancreatitis. This has been observed in patients with pancreas divisum with CFTR or SPINK1 mutations, also conditions that on their own might not be sufficient to cause pancreatitis[23].

ACKNOWLEDGMENTS

We thank the patient for permission to publish her case and to conduct the genetic analyses. We thank Heiko Witt, Munich and Jonas Rosendahl, Leipzig, for performing the genetic analyses.

COMMENTS

Case characteristics

The case of a 32-year-old black woman of African descent who suffered from repeated episodes of acute pancreatitis, initially triggered when flying on airplanes, is reported.

Laboratory diagnosis

Genetic analysis was negative for cationic trypsinogen, serine protease inhibitor Kazal type-1 and chymotrypsin C. However, hemoglobin F was elevated.

Pathological diagnosis

The combination of a hemoglobin gene mutation known for thalassemia in conjunction with the hitherto undescribed *CFTR* mutation is suggested to pave the road for initial and repetitive pancreatitis attacks.

Treatment

Sequencing of the thalassemia gene revealed a novel alteration in the 5' region indicative of a functional abnormality of the molecule.

Experiences and lessons

Sequencing the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene revealed a heterozygote sequence variant.

Peer review

This is indeed an interesting case that needs to be published to increase awareness of more uncommon causes.

REFERENCES

1 **Witt H**, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. *Gastroenterology* 2007; **132**: 1557-1573 [PMID: 17466744 DOI: 10.1053/j.gastro.2007.03.001]

2 **Whitcomb DC**, Gorry MC, Preston RA, Furey W, Sossenheimer MJ, Ulrich CD, Martin SP, Gates LK, Amann ST, Toskes PP, Liddle R, McGrath K, Uomo G, Post JC, Ehrlich GD. Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. *Nat Genet* 1996; **14**: 141-145 [PMID: 8841182 DOI: 10.1038/ng1096-141]

3 **Witt H**, Luck W, Hennies HC, Classen M, Kage A, Lass U, Landt O, Becker M. Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. *Nat Genet* 2000; **25**: 213-216 [PMID: 10835640 DOI: 10.1038/76088]

4 **Rosendahl J**, Witt H, Szmola R, Bhatia E, Ozsvári B, Landt O, Schulz HU, Gress TM, Pfützer R, Löhr M, Kovacs P, Blüher M, Stumvoll M, Choudhuri G, Hegyi P, te Morsche RH, Drenth JP, Truninger K, Macek M, Puhl G, Witt U, Schmidt H, Büning C, Ockenga J, Kage A, Groneberg DA, Nickel R, Berg T, Wiedenmann B, Bödeker H, Keim V, Mössner J, Teich N, Sahin-Tóth M. Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. *Nat Genet* 2008; **40**: 78-82 [PMID: 18059268 DOI: 10.1038/ng.2007.44]

5 **Malats N**, Casals T, Porta M, Guarner L, Estivill X, Real FX. Cystic fibrosis transmembrane regulator (CFTR) DeltaF508 mutation and 5T allele in patients with chronic pancreatitis and exocrine pancreatic cancer. PANKRAS II Study Group. *Gut* 2001; **48**: 70-74 [PMID: 11115825 DOI: 10.1136/gut.48.1.70]

6 **Witt H**, Sahin-Tóth M, Landt O, Chen JM, Kähne T, Drenth JP, Kukor Z, Szepessy E, Halangk W, Dahm S, Rohde K, Schulz HU, Le Maréchal C, Akar N, Ammann RW, Truninger K, Bargetzi M, Bhatia E, Castellani C, Cavestro GM, Cerny M, Destro-Bisol G, Spedini G, Eiberg H, Jansen JB, Koudova M, Rausova E, Macek M, Malats N, Real FX, Menzel HJ, Moral P, Galavotti R, Pignatti PF, Rickards O, Spicak J, Zarnescu NO, Böck W, Gress TM, Friess H, Ockenga J, Schmidt H, Pfützer R, Löhr M, Simon P, Weiss FU, Lerch MM, Teich N, Keim V, Berg T, Wiedenmann B, Luck W, Groneberg DA, Becker M, Keil T, Kage A, Bernardova J, Braun M, Güldner C, Halangk J, Rosendahl J, Witt U, Treiber M, Nickel R, Férec C. A degradation-sensitive anionic trypsinogen (PRSS2) variant protects against chronic pancreatitis. *Nat Genet* 2006; **38**: 668-673 [PMID: 16699518 DOI: 10.1038/ng1797]

7 **Dinter D**, Löhr JM, Neff KW. Bifid tail of the pancreas: benign bifurcation anomaly. *AJR Am J Roentgenol* 2007; **189**: W251-W253 [PMID: 17954620 DOI: 10.2214/AJR.05.1453]

8 **Schneider K**, Harms K, Fendel H. The increased echogenicity of the pancreas in infants and children: the white pancreas. *Eur J Pediatr* 1987; **146**: 508-511 [PMID: 3315685 DOI: 10.1007/BF00441605]

9 **Dubart A**, Testa U, Musumeci S, Vainchenker W, Beuzard Y, Henri A, Schirilo G, Romeo MA, Russo G, Rochant H, Rosa J. Elevated Hb F associated with beta-thalassaemia trait: haemoglobin synthesis in reticulocytes and in blood BFU-E. *Scand J Haematol* 1980; **25**: 339-346 [PMID: 6163196 DOI: 10.1111/j.1600-0609.1981.tb01412.x]

10 **Indrak K**, Indrakova J, Kutlar F, Pospisilova D, Sulovska I, Baysal E, Huisman TH. Compound heterozygosity for a beta zero-thalassemia (frameshift codons 38/39; -C) and a nondeletional Swiss type of HPFH (A----C at NT -110, G gamma) in a Czechoslovakian family. *Ann Hematol* 1991; **63**: 111-115 [PMID: 1716997 DOI: 10.1007/BF01707283]

11 **Leonova JYe EG**, Smetanina NS, Adekile AD, Efremov GD, Huisman TH. Variability in the fetal hemoglobin level of the normal adult. *Am J Hematol* 1996; **53**: 59-65 [PMID: 8892728]

12 **Kohne E**. Hemoglobinopathies: clinical manifestations, diagnosis, and treatment. *Dtsch Arztebl Int* 2011; **108**: 532-540 [PMID: 21886666]

13 **Losekoot M**, Fodde R, Gerritsen EJ, van de Kuit I, Schreuder A, Giordano PC, Vossen JM, Bernini LF. Interaction of two different disorders in the beta-globin gene cluster associated with an increased hemoglobin F production: a novel deletion type of (G) gamma + ((A) gamma delta beta)(0)-thalassemia and a delta(0)-hereditary persistence of fetal hemoglobin determinant. *Blood* 1991; **77**: 861-867 [PMID: 1704267]

14 **Cosentini A**, Stranieri G, Capillo S, Notarangelo L, Madonna L, Iannini S, Ferro V, Defilippo V, Defilippo RG, Rubino R. Acute pancreatitis in the paediatric age group: a personal experience. *Eur Rev Med Pharmacol Sci* 2005; **9**: 33-40 [PMID: 15850142]

15 **Rachmilewitz EA**, Tamari H, Liff F, Ueda Y, Nagel RL. The interaction of hemoglobin O Arab with Hb S and beta+ thalassemia among Israeli Arabs. *Hum Genet* 1985; **70**: 119-125 [PMID: 3859465 DOI: 10.1007/BF00273069]

16 **Imai K**, Tientadakul P, Opartkiattikul N, Luenee P, Winichagoon P, Svasti J, Fucharoen S. Detection of haemoglobin variants and inference of their functional properties using complete oxygen dissociation curve measurements. *Br J Haematol* 2001; **112**: 483-487 [PMID: 11167851 DOI: 10.1046/j.1365-2141.2001.02598.x]

17 **Su KH**, Cuthbertson C, Christophi C. Review of experimental animal models of acute pancreatitis. *HPB* (Oxford) 2006; **8**: 264-286 [PMID: 18333137 DOI: 10.1080/13651820500467358]

18 **Cuthbertson CM**, Christophi C. Disturbances of the microcirculation in acute pancreatitis. *Br J Surg* 2006; **93**: 518-530 [PMID: 16607683 DOI: 10.1002/bjs.5316]

19 **Sakorafas GH**, Tsiotos GG, Sarr MG. Ischemia/Reperfusion-Induced pancreatitis. *Dig Surg* 2000; **17**: 3-14 [PMID: 10720825 DOI: 10.1159/000018793]

20 **Toyama MT**, Lewis MP, Kusske AM, Reber PU, Ashley SW, Reber HA. Ischaemia-reperfusion mechanisms in acute pancreatitis. *Scand J Gastroenterol Suppl* 1996; **219**: 20-23 [PMID: 8865466 DOI: 10.3109/00365529609104994]

21 **Ahmed S**, Siddiqui AK, Siddiqui RK, Kimpo M, Russo L, Mattana J. Acute pancreatitis during sickle cell vaso-occlusive painful crisis. *Am J Hematol* 2003; **73**: 190-193 [PMID: 12827657 DOI: 10.1002/ajh.10344]

22 **Cuthbertson CM**, Christophi C. Potential effects of hyperbaric oxygen therapy in acute pancreatitis. *ANZ J Surg* 2006; **76**: 625-630 [PMID: 16813630 DOI: 10.1111/j.1445-2197.2006.03793.x]

23 **Bertin C**, Pelletier AL, Vullierme MP, Bienvenu T, Rebours V, Hentic O, Maire F, Hammel P, Vilgrain V, Ruszniewski P, Lévy P. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. *Am J Gastroenterol* 2012; **107**: 311-317 [PMID: 22158025 DOI: 10.1038/ajg.2011.424]

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CASE REPORT

Clinical and radiographic features of Hutchinson-Gilford progeria syndrome: A case report

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Abstract

Hutchinson-Gilford progeria syndrome (HGPS) is a rare dysmorphic syndrome characterized by several features of premature aging with clinical involvement of the skin, bones, and cardiovascular system. HGPS has an estimated incidence of one in four million to one in eight million births. The main clinical features of HGPS include short stature, craniofacial dimorphism, alopecia, bone fragility, and cardiovascular disorders. The most frequent cause of death is myocardial infarction at a mean age of 13 years old. Dental manifestations include delayed development and eruption of teeth, discoloration, crowding and rotation of teeth, and displaced teeth. Cone beam computed tomography images revealed the absence of the sphenoid, frontal, and maxillary sinus, flattening of the condyles and glenoid fossa, and bilateral hypoplasia of the mandibular condyles. The disease is caused by mutations in lamin A/C (*LMNA*). Here, we present a case report of an 11-year-old boy with classical features of HGPS, which was caused by a *de novo* germ-line mutation (C1824T, G608G) in exon 11 of the *LMNA* gene. Some uncommon HGPS-associated features in our patient, such as alterations in the facial sinuses and hypoplasia of the condyles, contributed to the expansion of the phenotypic spectrum of this syndrome from a dentomaxillofacial perspective.

Key words: Cone beam computed tomography; *LMNA* mutation; Craniofacial anomalies; Temporomandibular joint

Core tip: Hutchinson-Gilford progeria syndrome (HGPS) is a rare genetic syndrome characterized by the accelerated appearance of aging in children. We report a case of an 11-year-old boy with HGPS with uncommon HGPS-associated dentomaxillofacial features. Alterations in the facial sinuses and hypoplasia of the condyles were recognized in our patient, expanding the phenotypic spectrum of this syndrome.

Alves DB, Silva JM, Menezes TO, Cavaleiro RS, Tuji FM, Lopes MA, Zaia AA, Coletta RD. Clinical and radiographic features of Hutchinson-Gilford progeria syndrome: A case report. *World J*

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INTRODUCTION

Hutchinson-Gilford progeria syndrome (HGPS; OMIN #176670) is an uncommon genetic disorder characterized by accelerated aging with clinical involvement of the skin, bones, and cardiovascular system[1,2]. The prevalence of HGPS is one in four million to one in eight million live births; males are more frequently affected than females, and the intellect of the affected children is unimpaired[3]. Clinically, individuals with HGPS demonstrate short stature, prominent eyes, micrognathia, craniofacial disproportion, loss of subcutaneous fat, alopecia, beaked nose, coxa valga, pathologic bone fractures, radiolucent terminal phalanges, hearing loss, photophobia, hypertension, hyperlipidemia, atherosclerosis, and cardiovascular disorders. The most frequent cause of death is myocardial infarction at a mean age of 13 years old[4-11]. Oral alterations include high rates of tooth decay, crowding, delayed tooth development and eruption, tooth discoloration, hypodontia, maxillary and mandibular hypoplasia, and small mouth opening[5-7,12,13]. Recognition of dentomaxillofacial features of HGPS may allow oral health problems to be readily identified and aid in implementation of preventative treatment plans to improve quality of life[14,15]. Although HGPS demonstrates both autosomal dominant and autosomal recessive modes of inheritance, most cases are due to sporadic mutations[16]. Mutations in the lamin A/C (*LMNA*) gene are responsible for HGPS[17-19].

Here we report a case of HGPS in an 11-year-old boy with an uncommon phenotype and a *de novo* heterozygous silent mutation at amino acid 608 (G608G) of the *LMNA* gene.

CASE REPORT

An 11-year-old boy with a clinical diagnosis of HGPS was referred to the Clinical Department, School of Dentistry, Federal University of Pará, Brazil for oral health care. He was suffering from angina, peptic ulcer disease, and limited joint mobility. His current medications were pravastatin (5 mg/d) to prevent cardiovascular disease and ranitidine (150 mg/d) for the treatment of the peptic ulcer. The patient had normal neurodevelopment and showed the classical clinical features of HGPS, including short stature, low weight/height ratio, thin and inelastic skin, eyes slightly open when sleeping, photophobia, osteoporosis in the femur region, generalized alopecia, prominent scalp veins, small face with a beaked nose, and high-pitched voice (Figure 1). The patient had no apparent hearing loss. Echocardiogram and electrocardiogram results, blood pressure, pulse, and oxygen saturation were within normal limits. A hand-wrist radiograph showed radiolucencies of the terminal phalanges and the skeletal maturity of a 14-year-old boy with a chronological age of 11 years and 8 mo.

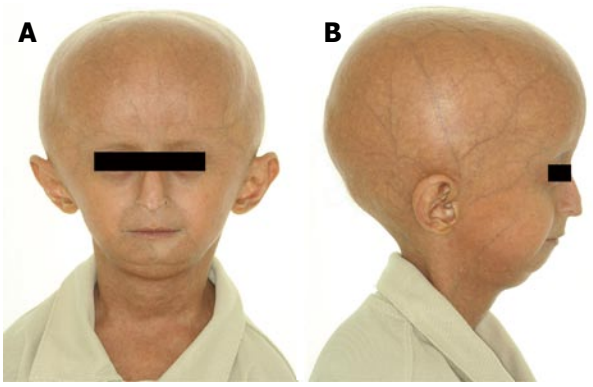

Figure 1 Clinical features of the patient at 11 years of age. A: Facial features were characterized by a deformed head, generalized alopecia, a small face, a beaked nose, and thin and inelastic skin; B: In the lateral view, prominent scalp veins and micrognathia are evident.

His height and weight were 1.1 m and 17.4 kg, respectively, which is well below the 3rd percentile for his age and only 4.4 kg greater than expected for a normal 4.5-year-old boy. Oral examination revealed micrognathia, class II malocclusion, and chronic trimus. Erupted teeth were of normal size, shape and color, but the permanent incisors were lingually erupted. The patient had gingivitis and low salivary flow, but had no dental caries and brushed his teeth while supervised by the mother. An orthopantomographic radiograph showed reduced dimensions of both arches with consequent lack of space for the correct positioning of the permanent teeth, mandible with a steep mandibular angle, eruption of the permanent teeth, and congenitally missing left upper second premolar and both lower second premolars (Figure 2). To better visualize the craniofacial features, cone beam computed tomography (CBCT) was performed. CBCT images revealed the absence of the sphenoid, frontal, and maxillary sinuses (Figure 3A and B), flattening of the condyles and glenoid fossa, and bilateral hypoplasia of the mandibular condyles (Figure 3C). Panoramic and axial images confirmed the dental alterations (Figure 3D-F).

To confirm the clinical diagnosis of HGPS, DNA sequence analysis was performed. The parents gave informed consent before the genetic study began. Mutation analysis of the *LMNA* gene with genomic DNA extracted from oral mucosa cells was performed according to a published protocol[20]. The patient demonstrated a heterozygous C-to-T transition at nucleotide 1824 in exon 11 of *LMNA*, which created a silent point mutation at codon 608 (GGC>GGT, G608G) (Figure 4). A similar mutation was not observed in the patient's parents or sister.

DISCUSSION

This case highlights some common and uncommon dentomaxillofacial features associated with HGPS. Tooth size was essentially normal but the eruption sequence was complicated by both incomplete mandibular and

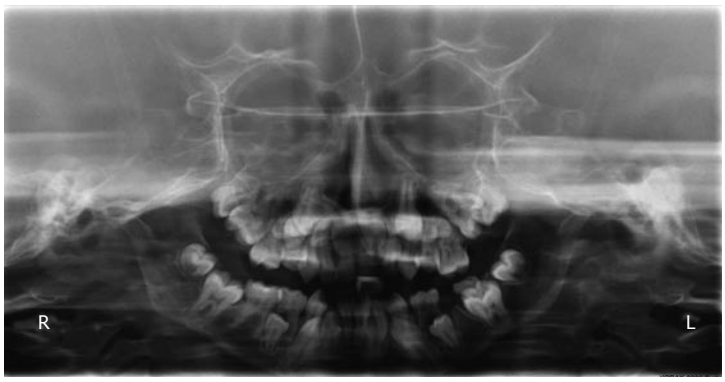

Figure 2 Panoramic radiograph showing delayed eruption of the permanent teeth, hypodontia of the left upper second premolar and both lower second premolars, and temporomandibular joint malformation.

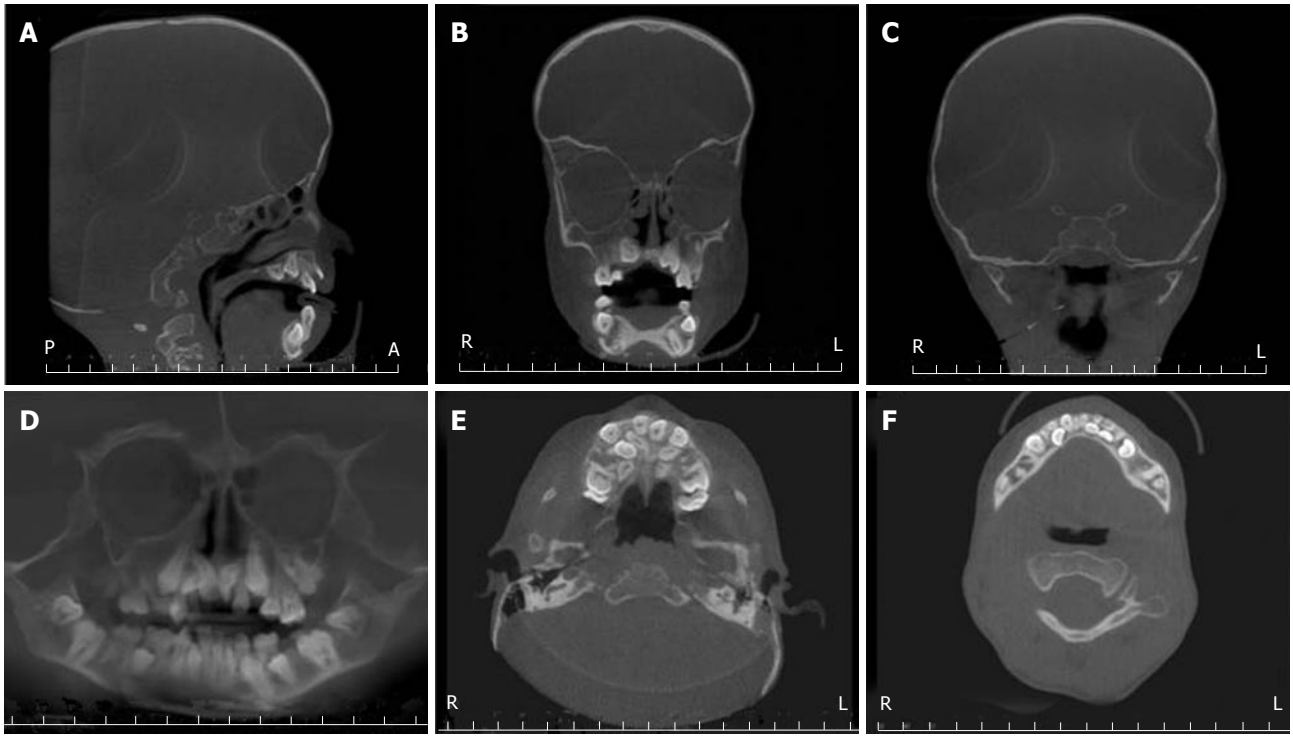

Figure 3 Craniofacial features of the Hutchinson-Gilford progeria syndrome patient detected by cone beam computed tomography. A, B: On sagittal (A) and coronal (B) images, hypoplasia of the sphenoid, frontal and maxillary sinuses was evident; C: This view depicts the temporomandibular joint alteration, which was characterized by flattening of the condyle and glenoid fossa and bilateral hypoplasia of the condyles; D: Panoramic view of the cone beam computed tomography (CBCT) revealing impaction of several permanent molars and hypodontia of the premolars; E, F: Axial slices of the CBCT showed malocclusion and lingual eruption of permanent teeth.

maxillary growth and micrognathia, which contributed to dental impactions. Despite radiographic evidence of normal root development, tooth eruption appeared to be delayed by three years. In addition, the permanent incisors had erupted lingually, and two premolars were absent (hypodontia). Delayed eruption, malocclusion associated with lower anterior dentition crowding, and hypodontia are consistent findings in patients with HGPS, as well as enamel hypoplasia and discoloration[15,20-22]. The permanent teeth in the current case were macroscopically normal in shape and color. Patients who do not present alterations in the joints of the hands can carry out oral hygiene perfectly, but adult supervision is required along with the use of a toothbrush with a small head due to the small oral cavity and limited mouth opening. Interestingly, CBCT images revealed the absence of the sphenoid, frontal and maxillary sinuses, shallow glenoid fossae, and bilateral hypoplasia of the mandibular condyles and articular eminences. After evaluating radiographs of 21 children aged newborn to 14.6 years old, Gordon *et al*[14] concluded that articulation deformities are not a common feature of HGPS. Chen *et al*[11] reported a similar case to ours and highlighted that craniofacial anomalies of HGPS contribute to increased number of caries, severe malocclusion, and problems with swallowing, feeding, and speech. However, Ullrich *et al*[23] evaluated 25 patients with HGPS and identified short mandibular rami in combination with flattened mandibular condyles, shallow glenoid fossae, and hypoplastic or absent articular eminences. The significance of the sinus alterations was unclear; however, patient- and parent-related chronic trismus can occur after a long period of regular dental

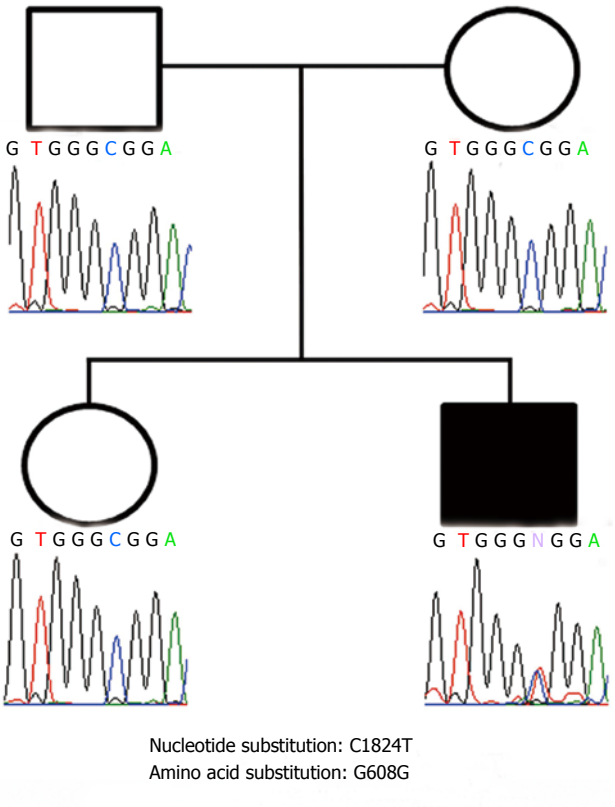

Figure 4 Detection of the *LMNA* mutation in the Hutchinson-Gilford progeria syndrome patient. Shown here are portions of the DNA-sequence electropherogram of the LMNA exon 11 of the affected patient, his parents and older sister. Compared to the normal sequence, the affected patient has a heterozygous C-to-T substitution at nucleotide position 1824 in the *LMNA* gene, which does not change the amino acid (G608G).

treatment. Thus, HGPS patients should be evaluated for temporomandibular joint (TMJ) disorders, and dentists need to be aware of the possible TMJ complications after a long period of regular dental treatment.

Despite the reported clinical characteristics, HGPS may be confused with other syndromes that include some features of premature aging, including neonatal progeroid syndrome (Weidemann-Rautenstrauch syndrome), acrogeria, Cockayne syndrome, Hallermann-Streif syndrome, gerodermia osteodysplastica, Berardinelli-Seip congenital lipodystrophy (congenital generalized lipodystrophy), Petty-Laxova-Weidemann progeroid syndrome, Ehlers-Danlos syndrome, progeroid form, and Werner syndrome[10,21]. Since an overlap in the clinical features of the patients affected by progeroid syndromes is common, the diagnosis of HGPS is based on the recognition of common clinical features and the detection of mutations in the *LMNA* gene and eventually in the *ZMPSTE2* gene, a metallopeptidase involved in processing of lamin A. *LMNA* mutations are present in more than 95% of cases, and genetic testing should start with analysis of the p.G608G mutation at exon 11, in which 62% of the defects reside[12]. DNA sequencing from the patient reported here revealed the p.G608G silent mutation. Although this mutation does not change the encoded amino acid, it results in the activation of a cryptic splice site and causes a truncated lamin A protein (50 amino acids shorter than normal), which is essential for the conversion of normal lamin A from prelamin A[18]. Since HGPS patients develop severe atherosclerosis and death usually occurs as a result of the complications of cardiac or cerebrovascular diseases during adolescence, early diagnosis of HGPS is important. To promote survival of HGPS patients, annual analysis of the vascular status is recommended using baseline electrocardiogram, echocardiogram, and carotid duplex scans to evaluate stenosis and intimal thickness. Additional tests include a skeletal X-ray to evaluate common associated features (*e.g.*, acroosteolysis, clavicular resorption, and coxa valga), dual-energy X-ray absorptiometry to assess bone mineral density, standard goniometry to assess global joint mobility, and nutritional assessment to optimize caloric intake[24].

In summary, we report one patient affected by HGPS who demonstrated unusual features, including the absence of the sphenoid, frontal and maxillary sinuses and bilateral hypoplasia of the mandibular condyles. Proper characterization of the clinical features and genetic defects is of utmost importance for correct diagnosis and timely clinical management. Furthermore, early intervention by a multidisciplinary team can increase the quality of life and survival of HGPS patients.

COMMENTS

Case characteristics

An 11-year-old boy with a diagnosis of Hutchinson-Gilford progeria syndrome (HGPS) presented with a need for oral health care.

Clinical diagnosis

The patient exhibited classical clinical features of HGPS, including short stature, low weight/height ratio, thin and inelastic skin, eyes slightly open when sleeping, photophobia, generalized alopecia, prominent scalp veins, small face with a beaked nose, and high-pitched voice.

Differential diagnosis

Differential diagnosis included neonatal progeroid syndrome (Weidemann-Rautenstrauch syndrome), acrogeria, Cockayne syndrome, Hallermann-Streif syndrome, gerodermia osteodysplastica, Petty-Laxova-Weidemann progeroid syndrome, and Werner syndrome.

Imaging diagnosis

Cone beam computed tomography (CBCT) images revealed absence of the sphenoid, frontal and maxillary sinuses, flattening of the condyles and glenoid fossa, and bilateral hypoplasia of the mandibular condyles.

Pathological diagnosis

DNA sequence analysis and mutation analysis of the lamin A/C (*LMNA*) gene was performed with genomic DNA extracted from oral mucosa cells. The patient demonstrated a heterozygous C-to-T transition at nucleotide 1824 in exon 11 of *LMNA*, which created a silent point mutation at codon 608 (GGC>GGT, G608G).

Treatment

The patient received medical and dental treatment to improve his quality of life.

Related reports

Recognition of dentomaxillofacial features of HGPS may allow for early identification of oral health problems and for the development of preventive treatment plans to improve quality of life.

Term explanation

Hutchinson-Gilford progeria syndrome is an uncommon genetic disorder characterized by accelerated aging with clinical involvement of the skin, bones, and cardiovascular system.

Experiences and lessons

Proper characterization of the clinical features and genetic defects of HGPS is of utmost importance for correct diagnosis and initiation of timely clinical man-

agement; early intervention by a multidisciplinary team can increase the quality of life and survival of these patients.

Peer review

This article reports a case of Hutchinson-Gilford progeria syndrome in an 11-year-old boy with an uncommon phenotype and a *de novo* heterozygous silent mutation at amino acid 608 (G608G) in the *LMNA* gene.

REFERENCES

1 **Badame AJ**. Progeria. *Arch Dermatol* 1989; **125**: 540-544 [PMID: 2649013 DOI: 10.1001/archderm.1989.01670160088018]

2 **Brown WT**, Zebrower M, Kieras FJ. Progeria, a model disease for the study of accelerated aging. *Basic Life Sci* 1985; **35**: 375-396 [PMID: 4062819]

3 **Capell BC**, Collins FS. Human laminopathies: nuclei gone genetically awry. *Nat Rev Genet* 2006; **7**: 940-952 [PMID: 17139325 DOI: 10.1038/nrg1906]

4 **Hennekam RC**. Hutchinson-Gilford progeria syndrome: review of the phenotype. *Am J Med Genet A* 2006; **140**: 2603-2624 [PMID: 16838330 DOI: 10.1002/ajmg.a.31346]

5 **Russo-Menna I**, Arancibias C. The Hutchinson-Gilford Progeria Syndrome: a case report. *Minerva Anestesiol* 2010; **76**: 151-154 [PMID: 20150858]

6 The Progeria Handbook: A Guide for Families and Health Care Providers of Children with Progeria. Accessed January 25, 2011. Available from: URL: http://www.progeriaresearch.org/patient_care.html

7 **Cleveland RH**, Gordon LB, Kleinman ME, Miller DT, Gordon CM, Snyder BD, Nazarian A, Giobbie-Hurder A, Neuberg D, Kieran MW. A prospective study of radiographic manifestations in Hutchinson-Gilford progeria syndrome. *Pediatr Radiol* 2012; **42**: 1089-1098 [PMID: 22752073 DOI: 10.1007/s00247-012-2423-1]

8 **Gordon CM**, Gordon LB, Snyder BD, Nazarian A, Quinn N, Huh S, Giobbie-Hurder A, Neuberg D, Cleveland R, Kleinman M, Miller DT, Kieran MW. Hutchinson-Gilford progeria is a skeletal dysplasia. *J Bone Miner Res* 2011; **26**: 1670-1679 [PMID: 21445982 DOI: 10.1002/jbmr.392]

9 **Zhang H**, Chen X, Guo Y, Liang J, Tang L, Yu H, Yao Z. Hutchinson-Gilford progeria syndrome: report of 2 cases and a novel LMNA mutation of HGPS in China. *J Am Acad Dermatol* 2013; **69**: e175-e176 [PMID: 24034385 DOI: 10.1016/j.jaad.2011.07.002]

10 **Pereira S**, Bourgeois P, Navarro C, Esteves-Vieira V, Cau P, De Sandre-Giovannoli A, Lévy N. HGPS and related premature aging disorders: from genomic identification to the first therapeutic approaches. *Mech Ageing Dev* 2008; **129**: 449-459 [PMID: 18513784 DOI: 10.1016/j.mad.2008.04.003]

11 **Chen CP**, Lin SP, Lin DS, Liu YP, Hsu LJ, Wang W. Clinical imaging findings in a girl with Hutchinson-Gilford progeria syndrome. *Genet Couns* 2012; **23**: 1-7 [PMID: 22611635]

12 **Merideth MA**, Gordon LB, Clauss S, Sachdev V, Smith AC, Perry MB, Brewer CC, Zalewski C, Kim HJ, Solomon B, Brooks BP, Gerber LH, Turner ML, Domingo DL, Hart TC, Graf J, Reynolds JC, Gropman A, Yanovski JA, Gerhard-Herman M, Collins FS, Nabel EG, Cannon RO, Gahl WA, Introne WJ. Phenotype and course of Hutchinson-Gilford progeria syndrome. *N Engl J Med* 2008; **358**: 592-604 [PMID: 18256394 DOI: 10.1056/NEJMoa0706898]

13 **Yu QX**, Zeng LH. Progeria: report of a case and review of the literature. *J Oral Pathol Med* 1991; **20**: 86-88 [PMID: 2016699 DOI: 10.1111/j.1600-0714.1991.tb00895.x]

14 **Gordon LB**, McCarten KM, Giobbie-Hurder A, Machan JT, Campbell SE, Berns SD, Kieran MW. Disease progression in Hutchinson-Gilford progeria syndrome: impact on growth and development. *Pediatrics* 2007; **120**: 824-833 [PMID: 17908770 DOI: 10.1542/peds.2007-1357]

15 **Domingo DL**, Trujillo MI, Council SE, Merideth MA, Gordon LB, Wu T, Introne WJ, Gahl WA, Hart TC. Hutchinson-Gilford progeria syndrome: oral and craniofacial phenotypes. *Oral Dis* 2009; **15**: 187-195 [PMID: 19236595 DOI: 10.1111/j.1601-0825.2009.01521.x]

16 **Mazereeuw-Hautier J**, Wilson LC, Mohammed S, Smallwood D, Shackleton S, Atherton DJ, Harper JI. Hutchinson-Gilford progeria syndrome: clinical findings in three patients carrying the G608G mutation in LMNA and review of the literature. *Br J Dermatol* 2007; **156**: 1308-1314 [PMID: 17459035 DOI: 10.1111/j.1365-2133.2007.07897.x]

17 **Coutinho HD**, Falcão-Silva VS, Gonçalves GF, da Nóbrega RB. Molecular ageing in progeroid syndromes: Hutchinson-Gilford progeria syndrome as a model. *Immun Ageing* 2009; **6**: 4 [PMID: 19379495 DOI: 10.1186/1742-4933-6-4]

18 **Eriksson M**, Brown WT, Gordon LB, Glynn MW, Singer J, Scott L, Erdos MR, Robbins CM, Moses TY, Berglund P, Dutra A, Pak E, Durkin S, Csoka AB, Boehnke M, Glover TW, Collins FS. Recurrent de novo point mutations in lamin A cause Hutchinson-Gilford progeria syndrome. *Nature* 2003; **423**: 293-298 [PMID: 12714972 DOI: 10.1038/nature01629]

19 **De Sandre-Giovannoli A**, Bernard R, Cau P, Navarro C, Amiel J, Boccaccio I, Lyonnet S, Stewart CL, Munnich A, Le Merrer M, Lévy N. Lamin a truncation in Hutchinson-Gilford progeria. *Science* 2003; **300**: 2055 [PMID: 12702809 DOI: 10.1126/science.1084125]

20 **Moulson CL**, Fong LG, Gardner JM, Farber EA, Go G, Passariello A, Grange DK, Young SG, Miner JH. Increased progerin expression associated with unusual LMNA mutations causes severe progeroid syndromes. *Hum Mutat* 2007; **28**: 882-889 [PMID: 17469202 DOI: 10.1002/humu.20536]

21 **Liessmann CD**. Anaesthesia in a child with Hutchinson-Gildford progeria. *Paediatr Anaesth* 2001; **11**: 611-614 [PMID: 11696128 DOI: 10.1046/j.1460-9592.2001.00721.x]

22 **Wesley RK**, Delaney JR, Litt R. Progeria: clinical considerations of an isolated case. *ASDC J Dent Child* 1979; **46**: 487-492 [PMID: 290644]

23 **Ullrich NJ**, Silvera VM, Campbell SE, Gordon LB. Craniofacial abnormalities in Hutchinson-Gilford progeria syndrome. *AJNR Am J Neuroradiol* 2012; **33**: 1512-1518 [PMID: 22460337 DOI: 10.3174/ajnr.A3088]

24 **Gordon LB,** Brown WT, Collins FS. Hutchinson-Gilford progeria syndrome. 2003 Dec 12 [Updated 2011 Jan 6]. In: Pagon RA, Adam MP, Bird TD, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. Available from: URL: http://www.ncbi.nlm.nih.gov/books/NBK1121/

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CASE REPORT

Additional responsibility for physicians caring for cardiac patients: Insight from a case series

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Abstract

Resuscitation measures performed at the scene of the event have the ultimate impact on the outcome of a cardiac arrest. We analysed six case histories of those sudden cardiac arrest patients who were revived in the field and were subsequently admitted to the intensive care unit during a six-month period. All were known cardiac patients and were under the care of healthcare providers. Four of those were discharged home from the hospital and did not suffer any residual damage where as one died of multi-organ failure and the other was declared brain dead. The outcome was good in patients who received early intervention in the form of basic life support. The family members of non-survivors witnessed the cardiac arrest at home but were not familiar with the concept or procedures of basic life support. We propose that physicians who care for cardiac patients should undertake the task of increasing family member awareness and knowledge in the techniques of basic life support.

Key words: Heart disease; Cardiac arrest; Cardiopulmonary resuscitation; Physicians; Family members; Education and training

Core tip: Resuscitation measures performed at the scene of the event have a major impact on the outcome of cardiac arrest. There is no specific strategy in place to motivate family members of cardiac patients to learn life-saving basic life support techniques. We propose that the physicians who care for cardiac patients should undertake the task of increasing family member awareness and knowledge of basic life support.

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INTRODUCTION

Successful revival following sudden cardiac arrest depends on patient characteristics and resuscitation measures[1]. Heart disease is the most common cause of sudden cardiac arrest, and its risk can be reduced by long-term efforts initiated by patients and their healthcare providers. However, "resuscitation measures" performed at the scene of the event have a major impact on the outcome of cardiac arrest[2]. Recently, we reviewed a series of out-of-hospital adult cardiopulmonary resuscitations carried out in the communities served by our regional hospital. An insight of the outcome of that case series is reported.

CASE REPORT

We analysed six case histories of cardiac arrest patients who were revived in the field and were subsequently admitted to the intensive care unit during a six-month period. The patient characteristics and resuscitation measures are shown in Table 1.

In this series, cases 5 and 6 did not survive. Case 5

Table 1 Patient characteristics and resuscitation measures

Case	Age (yr)	Gender	Cardiac disease	Initial diagnosis	BLS/ ACLS	Initial treatment	In-hospital management
1	68	Male	Yes	VFib	Immediate	BLS, ACLS	Ventilation antiarrhythmic inotropes
2	58	Male	Yes	VFib	Immediate	BLS, ACLS	ventilation thrombolytic inotropes
3	79	Male	Yes	PEA	Immediate	BLS, ACLS	ventilation thrombolytic inotropes
4	64	Male	Yes	VFib	Immediate	BLS, ACLS	ventilation antiarrhythmic
5	74	Male	Yes	VFib	Delayed	ACLS	ventilation antiarrhythmic hemofiltration
6	56	Female	Yes	VFib	Delayed	ACLS	ventilation antiarrhythmic therapeutic hypothermia

ACLS: Advanced cardiac life support; BLS: Basic life support; PEA: Pulseless electrical activity; VFib: Ventricular fibrillation.

died of multi-organ failure, and case 6 was declared brain dead. The other four patients were discharged home and did not suffer any residual damage. Though limited in number, this series reveals some patterns with regard to characteristics and resuscitation measure outcome: (1) all were known cardiac patients under the care of healthcare providers; (2) in five of the six patients, cardiac arrest was due to ventricular fibrillation, which is a shockable rhythm and requires the immediate use of a defibrillator, such as automated external defibrillator; (3) the outcome was good in patients who received early intervention in the form of "basic life support" (BLS); and (4) the family members of cases 5 and 6 witnessed the cardiac arrest at home but were not familiar with the concept or procedures of BLS. Two of the four patients who survived suffered from cardiac arrest while they were enjoying in a pub/bar and were able to receive BLS or even defibrillation immediately. One patient who collapsed on his own street was taken care of by paramedical professionals employed at the local hospital who happened to be passing by, and one victim suffered cardiac arrest at a doctor's appointment and was resuscitated by his primary care physician. One of the patients who did not survive was the youngest (56 years old) in this case series but did not receive cardiopulmonary resuscitation until an ambulance arrived twenty minutes later. We asked the families of the survivors about their awareness and ability to provide BLS, and three of the four families acknowledged that they did not know how to implement these measures.

DISCUSSION

Many social organizations actively promote public and community awareness about BLS. Healthcare employees and those that work at public facilities (*e.g.*, airports, restaurants/pubs) are required to complete BLS training. However, there is no specific strategy in place to motivate family members of cardiac patients to learn life-saving BLS techniques[3]. We propose that physicians who care for cardiac patients should undertake the task of increasing family member awareness and knowledge of BLS[4]. Anesthesiologists can motivate families of cardiac patients who undergo anesthesia or intensive care unit admission. This can be accomplished through direct communication with individual families or in the form of combined educational sessions with multiple families[5]. This strategy is especially important in remote areas where ambulance response times are long.

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COMMENTS

Case characteristics

A series of six out-of-hospital sudden witnessed cardiac arrests in cardiac patients.

Clinical diagnosis

Return of spontaneous circulation following sudden cardiac arrest.

Differential diagnosis

Intact cerebral function, cerebral damage, and brain death.

Laboratory diagnosis

Post cardiac arrest.

Imaging diagnosis

Post cardiac arrest in five cases, severe cerebral damage (brain death) in one case.

Pathological diagnosis

Post cardiac arrest.

Experiences and lessons

Family members of cardiac patients should learn life saving basic life support techniques and health care providers involved in their care should motivate family members to learn these techniques.

Peer review

The author who analysed six case histories of cardiac arrest victims proposes that physicians who care for cardiac patients should undertake the task of increasing family member awareness and knowledge of "basic life support". The cases are not rare but the content is worth publishing.

REFERENCES

1 **Bobrow BJ**, Spaite DW, Berg RA, Stolz U, Sanders AB, Kern KB, Vadeboncoeur TF, Clark LL, Gallagher JV, Stapczynski JS, LoVecchio F, Mullins TJ, Humble WO, Ewy GA. Chest compression-only CPR by lay rescuers and survival from out-of-hospital cardiac arrest. *JAMA* 2010; **304**: 1447-1454 [PMID: 20924010 DOI: 10.1001/jama.2010.1392]

2 **Ajmal M**. Incidence of aspiration of gastric contents in out-of-hospital successfully revived adult cardiac arrests - a series of six cases. *Can J Anesth* 2010; **57**: S37

3 **Sayre MR**, Berg RA, Cave DM, Page RL, Potts J, White RD. Hands-only (compression-only) cardiopulmonary resuscita-

tion: a call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest: a science advisory for the public from the American Heart Association Emergency Cardiovascular Care Committee. *Circulation* 2008; **117**: 2162-2167 [PMID: 18378619 DOI: 10.1161/CIRCULATIONAHA.107.189380]

4 **Vukmir RB**. Witnessed arrest, but not delayed bystander cardiopulmonary resuscitation improves prehospital cardiac arrest survival. *Emerg Med J* 2004; **21**: 370-373 [PMID: 15107387 DOI: 10.1136/emj.2003.008383]

5 **Dracup K**, Heaney DM, Taylor SE, Guzy PM, Breu C. Can family members of high-risk cardiac patients learn cardiopulmonary resuscitation? *Arch Intern Med* 1989; **149**: 61-64 [PMID: 2912416 DOI: 10.1001/archinte.1989.00390010079008]

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CASE REPORT

Homozygous factor Ⅴ Leiden mutation in type Ⅳ Ehlers-Danlos patient

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Abstract

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders caused by collagen synthesis defects. Several hemostatic abnormalities have been described in EDS patients that increase the bleeding tendencies of these patients. This case report illustrates a patient with an unusual presentation of a patient with type Ⅳ EDS, platelet δ-storage pool disease and factor Ⅴ Leiden mutation. Young woman having previous bilateral deep vein thrombosis and pulmonary emboli coexisting with ruptured splenic aneurysm and multiple other aneurysms now presented with myocardial infarction. Presence of factor Ⅴ Leiden mutation raises the possibility that the infarct was due to acute coronary thrombosis, although coronary artery aneurysm and dissection with myocardial infarction is known to occur in vascular type EDS. This is the first report in the medical literature of factor Ⅴ Leiden mutation in an EDS patient which made the management of our patient challenging with propensity to both bleeding and clotting.

Key words: Ehlers-Danlos syndrome; Factor V Leiden; Platelets; Coagulopathy

Core tip: Hemostatic abnormalities that have already been described in Ehlers-Danlos syndrome patients include platelet abnormalities (release defects, δ-storage pool disease) as well as clotting factor deficiencies that increase the bleeding tendencies of patients. The coexistence of platelet δ-storage pool disease and factor Ⅴ Leiden mutation in our patient manifested as having aneurysms of the splenic, renal, hepatic, gastric, mesenteric arteries and diffuse aneurysms of the upper and lower extremities as well as bilateral lower extremity deep vein thromboses and pulmonary emboli. This propensity to both bleeding and clotting made the management of our patient challenging on this presentation with acute anterolateral myocardial infarction.

Refaat M, Hotait M, Winston B. Homozygous factor V Leiden mutation in type IV Ehlers-Danlos patient. *World J Clin Cases* 2014; 2(3): 75-77 Available from: URL: http://www.wjgnet.com/2307-8960/full/v2/i3/75.htm DOI: http://dx.doi.org/10.12998/wjcc.v2.i3.75

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a group of heterogeneous heritable diseases that cause hyperextensibility of the skin, hypermobility of the large joints and easy bruising. It is classified in regard to main symptoms, the causative gene and the inheritance pattern. Among the eleven described types of EDS, type Ⅳ EDS known as vascular form, is a rare autosomal dominant inherited disorder with a 100% phenotypic penetrance caused by a mutation of the *COL3A1* gene encoding type Ⅲ collagen. EDS has an estimated prevalence of 1:5000 to 1:250000 births, and among all, vascular type accounts for 5%-10% of cases[1,2]. The vascular type is the most severe because

of vascular system complications as type Ⅲ collagen rich systemic arteries may undergo dissection, aneurysm, or rupture. Vascular rupture or other organ rupture are the presenting signs in 70% of patients with vascular EDS and the mean age for first major arterial or gastrointestinal complication is 23 years[1]. As for the hemostatic abnormalities previously reported in EDS, patients have more tendency to bleed due to platelet abnormalities (release defects, δ-storage pool disease) and clotting factors deficiencies. We report a case of a 40-year-old female with type Ⅳ EDS, platelet δ-storage pool disease and factor V Leiden mutation. Patient who had multiple previous complications including rupture splenic aneurysm and multiple other aneurysms in addition to coexisting bilateral deep vein thrombosis and pulmonary emboli, presented with acute myocardial infarction.

CASE REPORT

The patient is a 40-year-old woman previously diagnosed with Ehlers-Danlos syndrome type Ⅳ and aneurysms of the splenic, renal, hepatic, gastric, and mesenteric arteries as well as diffuse aneurysms of the upper and lower extremities. She was transferred emergently from an outside hospital with nausea, vomiting, chest pain, shortness of breath, productive cough, and fever of two days duration. Her history was significant for coagulopathy associated with platelet storage pool defect, factor V Leiden with large bilateral lower extremity deep vein thromboses and pulmonary emboli, and diet controlled diabetes mellitus. Further history obtained from the patient and medical record revealed a healthy childhood and generally good health in early adulthood. The patient noted that she had always been "double jointed" in her hands. She had excessive bleeding after cesearian section and deep vein thrombosis in her twenties that prompted hematologic evaluation. This revealed a prolonged bleeding time and platelet storage defect, and factor V Leiden homozygous mutation. The patient denied a tobacco smoking history.

At the age of 33 she was hospitalized for abdominal pain and underwent appendectomy for presumed appendicitis. Approximately one month later she presented again with further abdominal pain and was found to have a ruptured splenic artery aneurysm and multiple aneurysms of the hepatic, renal, gastric, and mesenteric arteries. She underwent emergent splenectomy. Extensive vascular adhesions were found on laparotomy at that time. Four days later she developed a left arm compartment syndrome due to an automated sphygmomanometer and underwent emergent vascular reconstruction of her brachial artery. That hospitalization was further complicated by post-op intrabdominal bleeding requiring repeat laparotomy and Jackson-Pratt drainage placement, and hematochezia due to anal fissures. During recovery from these acute events she developed thigh pain and pleuritic chest pain and was found with large bilateral deep vein thromboses and small pulmonary emboli. Surgical pathological examination of the splenic artery aneurysm with molecular and biochemical analysis were diagnostic of Ehlers-Danlos syndrome type Ⅳ.

Initial examination was significant for a woman in moderate distress, pulse of 115 bpm, blood pressure of 80/40 mmHg, respiratory rate of 24 per minute with 96% oxygen saturation on 15 L/min non-rebreather, and temperature of 101.7 F. She had elevated jugular venous pressure to 6 cm above the angle of Louis, and diminished breath sounds in the right lung with right basilar rales. Her cardiac exam revealed no visible heave, a diminished point of maximum intensity, a rapid regular rhythm, and a normal first and second heart sound with no audible S3. She had a holosystolic Ⅱ/Ⅵ murmur loudest at the left sternal border that did not vary with respiration, and she had no pericardial rub. Her extremities were warm, and distal pulses were normal except for a diminished left radial pulse. She had a large surgical scar running the medial length of her left arm from axilla to distal forearm. She had no peripheral edema. Further physical examination was notable for prominent veins of the extremities with a transparent appearance of the skin. Her finger, hand, and wrist joints were hypermobile with passive range of motion.

Electrocardiogram revealed sinus tachycardia with 2 mm ST elevations and Q waves in the antero-lateral leads consistent with acute antero-lateral myocardial infarction. Initial laboratory evaluation was significant for troponin I of 189 ng/mL. Chest X-ray was significant for bilateral hazy infiltrates. The patient was offered emergent cardiac catheterization but declined. She also declined all antiplatelet and anticoagulant medications. Echocardiogram was performed revealing severely decreased systolic function with severe hypokinesis of the anterior wall, septum, apex and inferior wall. The remaining segments were hypokinetic. Right ventricular size and function and estimated pulmonary artery pressures were normal, and mild to moderate mitral regurgitation was present. Her mental status, blood pressure, and chest pain improved with supportive measures including empiric antibiotics for community acquired pneumonia. The patient's recovery from anterolateral myocardial infarction and pneumonia was complicated by parapneumonic effusion. She tolerated percutaneous pleural drainage well and was discharged home.

DISCUSSION

Among the eleven described types of EDS, type Ⅳ EDS, also known as vascular form, is a rare autosomal inherited disorder of connective tissue due to a mutation of the *COL3A1* gene encoding type Ⅲ collagen. It presents a decreased amount of type Ⅲ collagen and therefore an increased vascular friability and fragility. The vascular morbidity this patient has experienced is typical of patients with vascular EDS type Ⅳ who do not express the typical hyperextensible skin and joints[3]. In fact, it is the most severe form and leads to premature death due to hemorrhage from the rupture of the major and visceral arteries. Besides the connective pathology responsible for the bleeding tendency, several hemostatic abnormalities have been described in EDS patients. These include platelet abnormalities (release defects, δ-storage pool

disease) as well as clotting factor Ⅷ, Ⅸ, XI and XIII deficiencies[4-6]. However, cause of the acute anterolateral myocardial infarction remains unclear in this unfortunate young woman with the combination of platelet storage pool defect with coagulopathy and factor Ⅴ Leiden mutation with history of deep vein thromboses and pulmonary emboli. Coronary artery aneurysm and dissection with myocardial infarction is known to occur in vascular type EDS[7-14]. The coexistence of factor Ⅴ Leiden mutation further raises the possibility that the infarct was due to acute coronary thrombosis, although a clear association between MI and factor Ⅴ Leiden in non-smokers has not been established[15]. Coronary artery aneurysm with or without dissection as an anatomic substrate for acute coronary thrombosis in this individual with factor Ⅴ Leiden is one possibility that could tie together her vascular and hematologic abnormalities that resulted in acute anterolateral myocardial infarction. This patient had an unusual combination of pathologies. This rare association of EDS type Ⅳ, platelet δ-storage pool disease and factor Ⅴ mutation is not previously described. As our patient illustrates, this association predisposes to bleeding and clotting tendencies. While there is no therapy for EDS, desmopressin acetate reduces the bleeding time in patients with EDS type Ⅳ and platelet δ-storage pool disease[16].

COMMENTS

Case characteristics

A 40-years-old female diagnosed with Ehlers-Danlos syndrome (EDS) type Ⅳ presented with chest pain, shortness of breath and productive cough.

Clinical diagnosis

Diminished breath sounds in the right lung, holosystolic Ⅱ/Ⅵ murmer loudest at left sternal border and elevated jugular venous pressure to 6 cm above the angle of Louis.

Differential diagnosis

Myocardial infarction, pulmonary embolism, pneumonia.

Laboratory diagnosis

Troponin I 189 ng/mL.

Imaging diagnosis

Electrocardiogram (ECG): 2 mm ST elevations and Q waves in anterolateral leads; chest X-ray: Bilateral hazy infiltrates; echocardiogram: Decreased systolic function with severe hypokinesis of anterior wall, septum, apex and inferior wall.

Pathological diagnosis

ECG and troponin suggestive of anterolateral myocardial infarction.

Treatment

Patient declined both emergent cardiac catheterization and antiplatelet/anticoagulation medications.

Related reports

Patients with type Ⅳ Ehler-Danlos are reported to have increased tendency to bleed rather than having hypercoagulability state.

Experiences and lessons

This case report shows unusual coexistence of platelet storage disease and factor Ⅴ Leiden mutation in EDS, predisposing our patient to bleeding and clotting tendencies.

Peer review

This article reports an interesting factor Ⅴ Leiden mutation in an Ehlers-Danlos patient.

REFERENCES

1 **Beridze N**, Frishman WH. Vascular Ehlers-Danlos syndrome: pathophysiology, diagnosis, and prevention and treatment of its complications. *Cardiol Rev* 2012; **20**: 4-7 [PMID: 22143279 DOI: 10.1097/CRD.0b013e3182342316]

2 **Nakamura M**, Yajima J, Oikawa Y, Ogasawara K, Uejima T, Abe K, Aizawa T. Vascular Ehlers-Danlos syndrome--all three coronary artery spontaneous dissections. *J Cardiol* 2009; **53**: 458-462 [PMID: 19477391 DOI: 10.1016/j.jjcc.2008.09.007]

3 **Oderich GS**, Panneton JM, Bower TC, Lindor NM, Cherry KJ, Noel AA, Kalra M, Sullivan T, Gloviczki P. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30-year experience. *J Vasc Surg* 2005; **42**: 98-106 [PMID: 16012458 DOI: 10.1016/j.jvs.2005.03.053]

4 **Kashiwagi H**, Riddle JM, Abraham JP, Frame B. Functional and ultrastructural abnormalities of platelets in ehlers-danlos syndrome. *Ann Intern Med* 1965; **63**: 249-254 [PMID: 14322851 DOI: 10.7326/0003-4819-63-2-249]

5 **Bertin P**, Treves R, Julia A, Gaillard S, Desproges-Gotteron R. Ehlers-Danlos syndrome, clotting disorders and muscular dystrophy. *Ann Rheum Dis* 1989; **48**: 953-956 [PMID: 2512864 DOI: 10.1136/ard.48.11.953]

6 **Anstey A**, Mayne K, Winter M, Van de Pette J, Pope FM. Platelet and coagulation studies in Ehlers-Danlos syndrome. *Br J Dermatol* 1991; **125**: 155-163 [PMID: 1911298 DOI: 10.1111/j.1365-2133.1991.tb06063.x]

7 **Di Mario C**, Zanchetta M, Maiolino P. Coronary aneurysms in a case of Ehlers-Danlos syndrome. *Jpn Heart J* 1988; **29**: 491-496 [PMID: 3184455 DOI: 10.1536/ihj.29.491]

8 **Eriksen UH**, Aunsholt NA, Nielsen TT. Enormous right coronary arterial aneurysm in a patient with type IV Ehlers-Danlos syndrome. *Int J Cardiol* 1992; **35**: 259-261 [PMID: 1572746 DOI: 10.1016/0167-5273(92)90185-6]

9 **Eltchaninoff H**, Cribier A, Letac B. Multiple spontaneous coronary artery dissections in young woman. *Lancet* 1995; **346**: 310-311 [PMID: 7630265 DOI: 10.1016/S0140-6736(95)92196-6]

10 **Catanese V**, Venot P, Lemesle F, Delille F, Runge I, Kuchly B. Myocardial infarction by spontaneous dissection of coronary arteries in a subject with type IV Ehlers-Danlos syndrome. *Presse Med* 1995; **24**: 1345-1347 [PMID: 7494846]

11 **Athanassiou AM**, Turrentine MA. Myocardial infarction and coronary artery dissection during pregnancy associated with type IV Ehlers-Danlos syndrome. *Am J Perinatol* 1996; **13**: 181-183 [PMID: 8688112 DOI: 10.1055/s-2007-994321]

12 **Zied ME**, Khalil MN, Wilson MF. Assessment of myocardial perfusion by cardiolite stress testing in a young woman with Ehler-Danlos syndrome and coronary dissection. *Am J Med* 1999; **107**: 295-296 [PMID: 10492330 DOI: 10.1016/S0002-9343(99)00180-1]

13 **Trichon BH**, Zidar JP, Bashore TM, Donahue M, Sketch MH. Acute myocardial infarction in a young female. *J Invasive Cardiol* 2001; **13**: 597-59, discussion 597-59, [PMID: 11481510]

14 **Dieter RS**, Murtaugh T, Black J, Russell DC. Coronary arteriomegaly in a patient with Ehlers-Danlos syndrome and multiple aneurysms--a case report. *Angiology* 2003; **54**: 733-736 [PMID: 14666965 DOI: 10.1177/000331970305400616]

15 **Rosendaal FR**, Siscovick DS, Schwartz SM, Beverly RK, Psaty BM, Longstreth WT, Raghunathan TE, Koepsell TD, Reitsma PH. Factor V Leiden (resistance to activated protein C) increases the risk of myocardial infarction in young women. *Blood* 1997; **89**: 2817-2821 [PMID: 9108400]

16 **Español I**, Hernández A, Pujol RM, Urrutia T, Pujol-Moix N. Type IV Ehlers-Danlos syndrome with platelet delta-storage pool disease. *Ann Hematol* 1998; **77**: 47-50 [PMID: 9760152]

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CASE REPORT

Successful recanalization with multimodality endovascular interventional therapy in acute ischemic stroke

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Abstract

Stroke is an important cause of death and disability in adults. However, effective treatments for patients with acute ischemic stroke are limited. Intravenous recombinant tissue plasminogen activator (*iv* rtPA) within 4.5 h after onset has been approved as a standard treatment for patients with acute ischemic stroke. However, due to time constraints, less than one percent of acute ischemic stroke patients in Thailand are able to obtain *iv* rtPA. Although endovascular interventional therapy has not yet been approved as standard treatment in acute ischemic stroke, it is the one of the potentially effective treatment options. There are several reliable methods of endovascular therapy for acute ischemic stroke patients. Endovascular interventional therapy has rarely been done in Thailand. We report seven patients with successful recanalization after endovascular treatment in acute large vessel stroke from a single stroke center in Thailand. Patient screening and selection with multimodal imaging protocol and multimodality methods of endovascular interventional therapy are described.

Key words: Acute ischemic stroke; Intra-arterial thrombolysis; Endovascular therapy; Mechanical thrombectomy

Core tip: We report seven patients with successful recanalization after endovascular treatment in acute large vessel stroke from a single stroke center in Thailand. Patient screening and selection with multimodal imaging protocol and multimodality methods of endovascular interventional therapy are described.

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INTRODUCTION

Stroke is the leading cause of adult disability, particularly in the elderly, and remains the third most common cause of death in the developing world, as well as in Thailand[1,2]. Despite improving the quality of stroke management, morbidity and mortality related to stroke remain significant[3]. Intravenous recombinant tissue plasminogen activator (*iv* rtPA) is a standard treatment for patients with acute ischemic stroke[4]. The NINDS study shows that *iv* rtPA given within 3 h of stroke onset improves the modified Rankin Scale (mRS) at 90 d[5]. The recent

Table 1 Summary of clinical presentation, treatment provided and clinical outcome

	Sex	Age	Location	NIHSS	Onset (h)	AF	*iv* rtPA (mg)	*ia* rtPA(mg)	Solitaire	Penumbra	Carotid stent	Final mRS	Any ICH	sICH
1	F	56	ICA	20	3	-	59	8	Y	-	-	2	N	N
2	F	80	BA	NA	5.5	Y	-	-	-	032″	-	4	N	N
3	M	64	ICA, M1	10	5.5	-	-	-	-	-	Wall stent	1	N	N
4	M	81	BA	30	13	Y	-	-	Y	-	-	0	N	N
5	M	61	M1	9	6	-	-	5	-	-	-	0	Y	N
6	F	87	BA	NA	5	Y	-	5	-	041″	-	4	N	N
7	M	70	M1	NA	5	-	-	5	-	041″	-	2	Y	N

F: Female; M: Male; ICA: Internal carotid artery; BA: Basilar artery; NIHSS: National Institutes of Health Stroke Scale; *iv* rtPA: Intravenous recombinant tissue plasminogen activator; *ia* rtPA: Intra-arterial recombinant tissue plasminogen activator; NA: Not available; Y: Yes; N: Not.

ECASS3 trial expands indication of intravenous rtPA to 4.5 h[6]. Clinical benefit from *iv* rtPA to Thai stroke patients has been shown in studies[7,8]. However, most stroke patients are still not able to get *iv* rtPA due to delayed arrival and tight exclusion criteria[9].

Identification of ischemic penumbra with diffusion-perfusion mismatch by magnetic resonance imaging (MRI) may have a role in patient selection for further treatment in acute ischemic stroke[10,11]. However, the benefit on clinical outcomes of this imaging selection for endovascular treatment in patients with acute ischemic stroke is still controversial[12].

Intra-arterial thrombolysis is a viable option to some patients who arrive after the 3 h[13]. The PROACT Ⅱ trial showed that recanalization rate and functional outcomes are better with intra-arterial thrombolysis[14]. Mechanical thromboembolectomy in acute ischemic stroke has received intense interest in recent years. The multi MERCI trial shows that clot removal with the device, which can be done up to 8 h after stroke onset, raises the recanalization rate up to 60%[15]. The Penumbra Pivotal trial shows that continuous thrombus aspiration with a Penumbra catheter can improve the recanalization rate to more than 80%[16]. The SWIFT trial shows that clot extraction with the Solitaire device in large vessel occlusion, including internal carotid artery (ICA), middle cerebral artery part 1 (M1), middle cerebral artery part 2 (M2) and basilar artery (BA), also provides a recanalization rate of up to 80%[17]. Unfortunately, the two most recent trials published in a landmark journal do not show any benefit in functional outcomes from endovascular treatment in acute ischemic stroke[18,19].

In Thailand, endovascular interventional therapy rarely has been performed in patients with acute ischemic stroke. Intra-arterial recombinant tissue plasminogen activator (*ia* rtPA) is an option in some medical centers. Imaging selection is also optional for decision making in some centers. Recently, Solitaire and Penumbra devices have been available for commercial use. We report our initial experiences with these procedures.

Phyathai 2 is a private hospital located in central of Bangkok. This 200 bed hospital provides 20 intensive care unit beds for medical intensive conditions, including acute ischemic stroke. The medical records of patients who received endovascular interventional therapy for acute large vessel occlusion (ICA, M1, M2 and BA) in Phyathai 2 Hospital during February 2010 to January 2013 were reviewed.

Endovascular interventional therapy protocol

Acute ischemic stroke patients who were not eligible for *iv* rtPA or who still had significant deficits after *iv* rtPA were evaluated by the stroke neurologist (SM). A stroke interventional team (Jongsathapongpan A, Raumthanthong A) was alerted. Multimodal MRI (conventional MRI with MRA and MR perfusion) was done on an emergency basis. If the diffusion-perfusion mismatch was more than 20%, the patient would be transferred to the catheterization lab for endovascular treatment. The anesthesiologist was standing by in the catheterization lab.

The right femoral artery was cannulated with an 8 F sheath. Selective angiography of the carotid or vertebral artery was done with a 5 F Simmon 1 or a 5 F JR4 catheter. The aortic arch angiogram and 4 vessel DSA were not routinely performed. If an occluded artery was confirmed, a 6 F 90 cm sheath was placed as far as a distal cervical ICA or a distal V2 segment. A 018 microcatheter was advanced over the guidewire to the occlusion site. Low dose *ia* rtPA (less than 5 mg) was given. If no clot lysis was seen, continuous clot aspiration using a Penumbra device or clot extraction with a Solitaire device was performed.

CASE REPORT

We identified 7 cases. Age ranged from 56-87 years. National Institutes of Health Stroke Scale (NIHSS) ranged from 9-30. Multimodal MRI was done in 6 of 7 cases (86%). There were 2 patients with ICA occlusion, 2 with middle cerebral artery (MCA) occlusion and 3 with BA occlusion. Carotid stenting was performed in one case. *ia* rtPA, mechanical thrombectomy and combined treatment were done in 4, 5 and 3 cases, respectively. Solitaire and Penumbra devices were used in 2 and 3 cases, respectively. Only 1 patient received intervention after intravenous thrombolysis. Case presentation and treatment are summarized in Table 1.

Case 1

Left distal ICA occlusion opened with *ia* rtPA and

Solitaire device: A 56-year-old female presented with right hemiparesis and aphasia. She arrived at hospital 1 h after onset. Emergency computed tomography (CT) brain showed cord sign in left MCA and distal ICA. Initial NIHSS was 20. Electrocardiography (EKG) showed normal sinus rhythm. Echocardiography showed no intracardiac thrombus. *iv* rtPA was given 90 min after onset. No neurological improvement was noted. Two hours after *iv* rtPA, angiography was done. We found distal ICA occlusion. Balloon inflation with a 2.0 mm × 15 mm coronary balloon was attempted without success. Eight milligrams of *ia* rtPA was infused. No clot lysis was seen. Then, a 4.0 × 15 Solitaire device was deployed 5 h after onset. Immediate angiography showed thrombolysis in cerebral infarction (TICI) 2 flow. The Solitaire was slowly pulled back and a large thrombus was removed. Residual stenosis of mid M1 persisted but it resolved after 1 mg of nimodipine. Final angiography showed TICI 3 in M1 and anterior cerebral artery part 1 (A1). Occlusion of anterior cerebral artery part 2 (A2) was noted. No further intervention was attempted. Six months after the procedure, mRS was 2 (Figure 1A and B).

Case 2

BA occlusion opened with *ia* rtPA and Penumbra device: An 80-year-old female presented with alteration of consciousness. She had hypertension and chronic AF. Warfarin had been discontinued during the last month for unknown reasons. Immediate CT brain showed hyperdense basilar artery. MRI and MRA brain revealed small right cerebellar infarction and occlusion of mid basilar artery. Patent bilateral fetal type posterior cerebral artery was noted. Echocardiography showed no intracardiac thrombus. She was transferred to the catheterization lab 5.5 h after onset. Angiogram showed near occlusion of mid BA. Continuous thrombus aspiration with a 032 Penumbra catheter was done. TICI 3 was seen from proximal to mid basilar artery and bilateral superior cerebellar artery. Occluded distal basilar artery could not be opened. MRI brain on the next day showed bilateral superior cerebellar infarction. No intracranial hemorrhage was seen. After 3 mo mRS was only 4. Four months later, she suffered from a left MCA stroke despite dabigatran maintenance. No thrombolytic drug was given because of late presentation (Figure 1C and D).

Case 3

Tandem ostial left ICA and distal M1 occlusion opened with carotid stent: A 64-year-old male was admitted for prostate surgery. Two days after the operation, he developed a right hemiparesis and dysphasia. Initial NIHSS was 10. MRI and MRA brain showed small left MCA infarction and severe ostial left ICA stenosis. Because of symptom fluctuation, *iv* rtPA was not given. Endovascular treatment was done because of a large diffusion-perfusion mismatch (> 20%). Angiography was done 5.5 h after onset. Critical ostial ICA stenosis and occlusion of supraclinoid ICA were seen. After deployment of a distal protection device, carotid stenting was done using 7.0 mm × 30 mm WALLSTENT™. Angiogram showed good flow of left ICA. Occluded distal M1 was noted. No further intervention was attempted because of good collateral flow. Two days after the procedure, NIHSS was 1 and mRS was 1 (Figure 1E and F).

Case 4

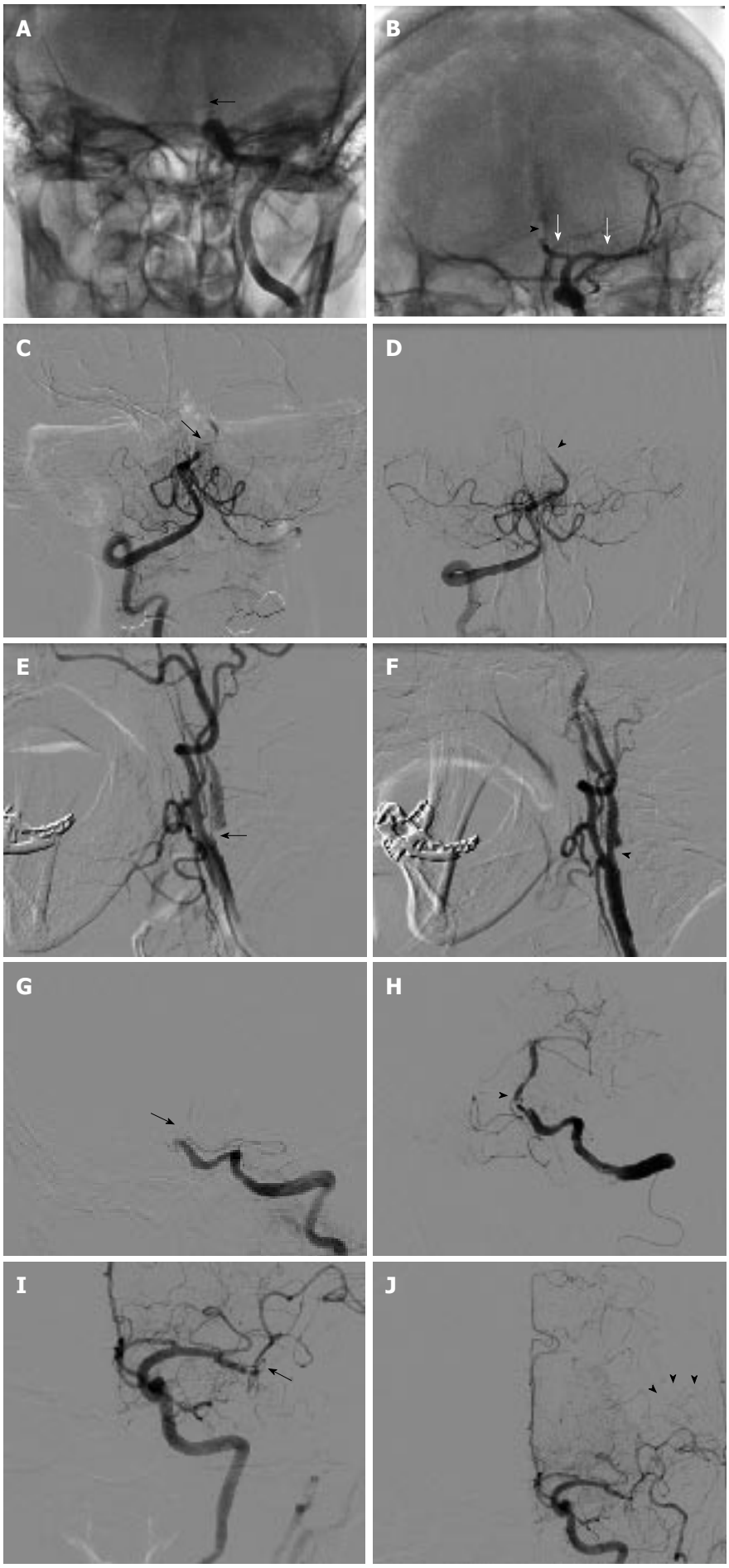
Basilar artery occlusion opened with Solitaire device: An 81-year-old male presented with left hemiparesis. He arrived at hospital 7 h after onset. He had hypertension, dyslipidemia and chronic atrial fibrillation. Echocardiography revealed no intracardiac thrombus. MRI and MRA brain showed small right cerebellar infarction and mid basilar artery occlusion. He was transferred to the catheterization lab 13 h after onset. Angiography showed tortuous left vertebral artery and occluded proximal BA. We failed to advance a 5 F hydrophilic catheter over the left vertebral artery. Then, a homemade 90 cm shortened JR 7 F guiding catheter was placed at the proximal vertebral artery. A 4.0 mm × 15 mm Solitaire was deployed at the basilar artery. After thrombus extraction, TICI 3 flow of basilar was noted. Some residual thrombus remained in the basilar artery. No further intervention was attempted. He regained full consciousness the next day. Final NIHSS was 1 and mRS was 0 (Figure 1G and H).

Case 5

Left distal M1 occlusion opened with *ia* rtPA: A 61-year-old male presented with right arm weakness and dysphasia. He arrived at hospital 1 h after onset. Initial NIHSS was 9. EKG was sinus rhythm. Echocardiography showed no intracardiac thrombus. MRI and MRA brain revealed small infarction in the left MCA area and left distal M1 occlusion. A large diffusion-perfusion mismatch was seen. He was transferred to the catheterization lab 4 h after onset. Angiography showed occlusion of superior M2 and slowed flow in the inferior M2 branch. Good pial collateral flow to the left superior M2 area was seen. Five milligrams of *ia* rtPA was given. TICI 3 flow of M1 and inferior M2 was noted. The superior M2 branch was still occluded. No further intervention was attempted. CT brain on the next day showed small spot hemorrhage in the left temporal lobe and small infarction of the left corona radiata. Right hemiparesis improved after the procedure. Three months later, he had only mild dysphasia and mRS was 0 (Figure 1I and J).

Case 6

BA occlusion opened with *ia* rtPA and Penumbra device: An 87-year-old female patient was referred to our hospital because of loss of consciousness. Initial CT scan showed no significant hypodense area. EKG showed atrial fibrillation. MRI and MRA brain showed left pontine infarction and small bilateral cerebellar infarction. She was transferred to the catheterization lab 5 h after onset.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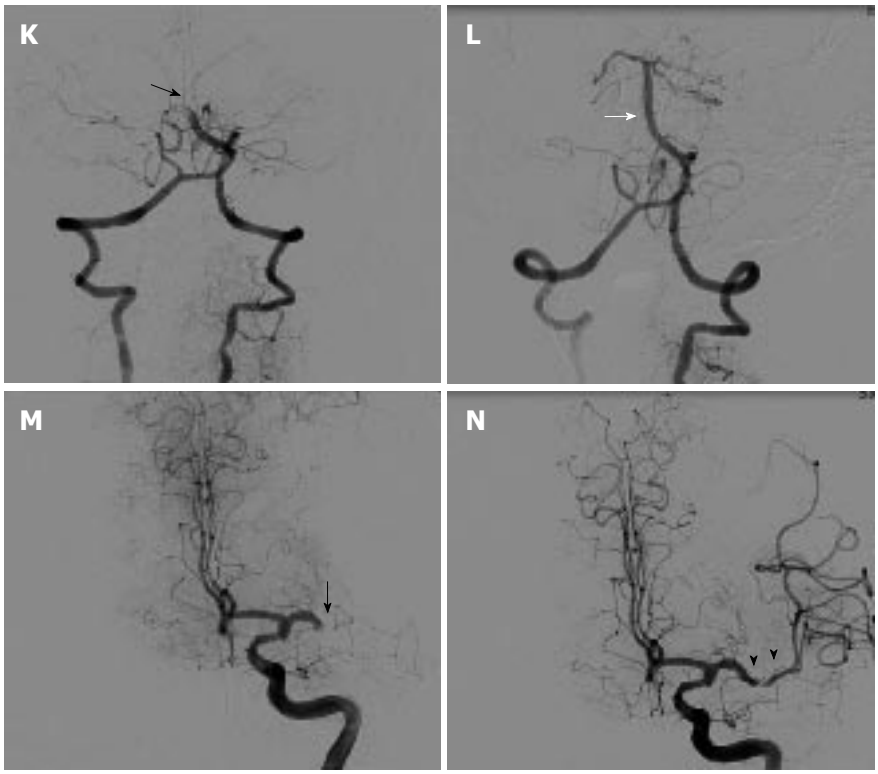

Figure 1 Case angiogram. A: Pre-procedure imaging showed occlusion of distal left internal carotid artery (black arrow); B: Post-procedure imaging showed good flow of middle cerebral artery (MCA) and A1 (white arrow), occlusion of A2 (arrowhead) was noted; C: Pre-procedure imaging showed near total occlusion of mid basilar artery (BA) (black arrow); D: Post-procedure imaging showed improved in mid BA, distal BA (arrowhead) still occluded; E: Pre-procedure imaging showed critical stenosis of ostial left including internal carotid artery (ICA) (black arrow); F: Post-procedure imaging showed mild residual stenosis of proximal ICA after carotid stenting (arrowhead); G: Pre-procedure imaging showed proximal BA occlusion (black arrow); H: Post-procedure imaging showed patent BA with some residual thrombus in proximal part (arrowhead); I: Pre-procedure imaging showed thrombotic occlusion of superior M2 branch and slow flow of inferior M2 branch (black arrow); J: Post-procedure imaging showed good flow of inferior M2 branch, superior M2 branch still occluded and that area was supplied from pial collateral (arrowhead); K: Pre-procedure imaging showed occlusion of distal BA (black arrow); L: Post-procedure imaging showed patent BA (white arrow) and right posterior cerebral artery (PCA), with left PCA still occluded (arrowhead); M: Pre-procedure imaging showed occlusion of distal left M1 (black arrow); N: Post-procedure imaging showed good flow of left MCA (arrowhead) and all branches.

Angiogram showed occlusion of distal BA. *ia* rtPA 5 mg was given without improvement. Four minutes of continuous thrombus aspiration with a Penumbra 041 catheter was done. Complete clot removal was seen. FU CT brain on the next day showed no intracranial hemorrhage but a new right occipital lobe infarction was seen. Despite the good angiographic outcome, she only had mRS 4 on the final visit (Figure 1K and L).

Case 7

Left M1 occlusion opened with *ia* rtPA and Penumbra device: A 70-year-old male patient was referred to our hospital because of stupor, right hemiplegia and aphasia. He had diabetes, hypertension and was post coronary artery bypass surgery. EKG showed normal sinus rhythm. Echocardiography showed no intracardiac thrombus. Initial CT scan showed old cerebral infarction and so *iv* rtPA was not given. MRI and MRA brain showed occlusion of left M1. DWI showed no acute infarction. He was transferred to the catheterization lab 5 h after onset. Angiogram showed occlusion of left distal M1. *ia* rtPA 5 mg was given via a Rebar microcatheter without success. Three minutes of continuous aspiration with Penumbra 041 catheter was done. Complete clot removal was seen. CT brain on the next day showed small subarachnoid hemorrhage in the left sylvian fissure. No new infarction was seen. Three months later, he had only mild weakness of the right arm and mRS was 2 (Figure 1M and N).

DISCUSSION

We described 7 cases of endovascular treatment with successful recanalization in acute ischemic stroke patients. Good outcome, defined by mRS less than 2, were found in 5 of 7 cases (71%). When mechanical thromboembolectomy devices were used, successful recanalization rate and good outcome were found in 80% and 60%, respectively, which are comparable to 81% and 25%, respectively in the PENUMBRA pivotal trial and 61% and 58%, respectively in the SWIFT trials. There was no mortality in our series, compared to 38% in the PENUMBRA pivotal trial and 17% in the SWIFT trial. In our series, intracranial hemorrhage and symptomatic intracranial hemorrhage were found in 28% and 0%, respectively, which is comparable to 28% and 11%, respectively in the

PENUMBRA pivotal trial and 17% and 2%, respectively in the SWIFT trial[16,17]. In our case series, younger (less than 80 years old) patients and good collateral supply were good prognostic indicators. We observed that in patients under 80 years old, all patients had good outcome (4 of 4) and in the presence of collateral supply (case 3 and case 5) a good outcome may be achieved even if the direct flow cannot be restored.

Multimodal MRI is the most reliable study to select the patients[20,21]. Patients with a small infarct core but large diffusion-perfusion mismatch are more likely to have better outcomes[21-23]. There is evidence that multimodal CT is also able to identify the infarct core and penumbra area[21,24]. However, high dose of iodinated contrast usage during CT may be contra-indicated in some patients[25]. Application of the ASPECT score with multimodal CT may be helpful for patient selection and outcome prediction[26,27].

Intra-arterial thrombolysis is one of preferred treatments in some centers[13,28]. Based on the PROACT trial, patency rate (TICI 2, 3) was 66% and mRS less than 2 at the 90th day was 40%, but in our case series, no clot lysis was found in any case[14]. It might be due to the limited dose of rtPA we used (less than 5 mg) and that the waiting time was too short (average 10-20 min). Anyway, we believed that *ia* rtPA still had a role in some patients, such as patients with small thrombus burden and patients with very tortuous neck arteries. However, it is likely that the role of *ia* rtPA will be surpassed by high efficacy mechanical devices in the near future[29].

Recently, mechanical thrombectomy devices in acute stroke have received intense interest[29,30]. High patency rate (61%-86%) and improved clinical outcome were reported in the SWIFT, PENUMBRA and TREVO trials[16,17,31]. However, individual devices may have their own technical issues. A stent based device, using a dragging method, may cause thrombus embolization into new territory. The possible solutions for this problem are to allow the device to "ingest" the thrombus for few minutes, to slowly pull back (1 cm/min) and to add aspiration force through the sheath or guide catheter. The advantage points of stent based devices are small delivery profile and speed of recanalization[32].

Continuous thrombus aspiration using a Penumbra device has one inherited problem, that is "profile"[33]. Because of a larger profile, it may require delivery in triaxial fashion over the guidewire and microcatheter. The strong advantage of a Penumbra device is more complete clot removal and less embolization into new territory[33]. This could benefit the patients with large thrombus burden and in the situation with residual thrombus after the dragging method. The aspiration method, compared to the dragging method, is perceived to result in less vessel trauma. Clinical trials reported no difference in intracranial hemorrhage, compared to the Solitaire device[29,30,33].

We plan to reduce time to recanalization in our center. Focused stroke MRI protocol may shorten it by a few minutes in this critical condition. Using multimodal CT instead of MRI may also be a time saver. An interventionist should be available 24/7. Activation of the interventional team during the imaging study is crucial. Using mechanical thromboembolectomy as a first line treatment, instead of intra-arterial thrombolysis, should be of benefit.

COMMENTS

Case characteristics

The authors report seven patients with successful recanalization after endovascular treatment in acute large vessel stroke from a single stroke center in Thailand.

Clinical diagnosis

There were 2 patients with internal carotid artery occlusion, 2 with middle cerebral artery occlusion and 3 with basilar artery (BA) occlusion.

Imaging diagnosis

Multimodal magnetic resonance imaging was done in 6 of 7 cases (86%).

Treatment

Carotid stenting was performed in one case. Intra-arterial recombinant tissue plasminogen activator, mechanical thrombectomy and combined treatment were done in 4, 5 and 3 cases, respectively. Solitaire and Penumbra devices were used in 2 and 3 cases, respectively.

Related reports

Multimodal magnetic resonance imaging (MRI) is the most reliable study to select the patients.

Experiences and lessons

Focused stroke MRI protocol may reduce time by a few minutes in this critical condition. Using multimodal computer tomography instead of MRI may also be a time saver.

Peer review

The manuscript is a nicely written collection of 7 cases of acute ischemic stroke that were treated with various endovascular techniques. The report is worthy of being published.

REFERENCES

1 **Lopez AD**, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet* 2006; **367**: 1747-1757 [PMID: 16731270 DOI: 10.1016/S0140-6736(06)68770-9]

2 **Hanchaiphiboolkul S**, Poungvarin N, Nidhinandana S, Suwanwela NC, Puthkhao P, Towanabut S, Tantirittisak T, Suwantamee J, Samsen M. Prevalence of stroke and stroke risk factors in Thailand: Thai Epidemiologic Stroke (TES) Study. *J Med Assoc Thai* 2011; **94**: 427-436 [PMID: 21591527]

3 **Poungvarin N**. Burden of stroke in Thailand. *Int J Stroke* 2007; **2**: 127-128 [PMID: 18705969 DOI: 10.1111/j.1747-4949.2007.00104.x]

4 **Adams HP**, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke* 2007; **38**: 1655-1711 [PMID: 17431204]

5 **Tissue plasminogen activator for acute ischemic stroke.** The National Institute of Neurological Disorders and Stroke

rt-PA Stroke Study Group. *N Engl J Med* 1995; **333**: 1581-1587 [PMID: 7477192]
6 **Hacke W**, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359**: 1317-1329 [PMID: 18815396]
7 **Muengtaweepongsa S**, Dharmasaroja P, Kummark U. Outcomes of intravenous thrombolytic therapy for acute ischemic stroke with an integrated acute stroke referral network: initial experience of a community-based hospital in a developing country. *J Stroke Cerebrovasc Dis* 2012; **21**: 42-46 [PMID: 22225863 DOI: 10.1016/j.jstrokecerebrovasdis.2010.03.017]
8 **Suwanwela NC**, Phanthumchinda K, Likitjaroen Y. Thrombolytic therapy in acute ischemic stroke in Asia: The first prospective evaluation. *Clin Neurol Neurosurg* 2006; **108**: 549-552 [PMID: 16289309]
9 **Kasner SE**, Gorelick PB.Prevention and Treatment of Ischemic Stroke: Blue Books of Practical Neurology Series. Oxford: Butterworth-Heinemann, 2004: 267-281
10 **Davis SM**, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gerraty R, Tress BM, Desmond PM. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol* 2008; **7**: 299-309 [PMID: 18296121 DOI: 10.1016/S1474-4422(08)70044-9]
11 **Albers GW**, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol* 2006; **60**: 508-517 [PMID: 17066483 DOI: 10.1002/ana.20976]
12 **Kidwell CS**, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, Feng L, Meyer BC, Olson S, Schwamm LH, Yoo AJ, Marshall RS, Meyers PM, Yavagal DR, Wintermark M, Guzy J, Starkman S, Saver JL. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013; **368**: 914-923 [PMID: 23394476 DOI: 10.1056/NEJMoa1212793]
13 **Nguyen TN**, Babikian VL, Romero R, Pikula A, Kase CS, Jovin TG, Norbash AM. Intra-arterial treatment methods in acute stroke therapy. *Front Neurol* 2011; **2**: 9 [PMID: 21516256]
14 **Furlan A**, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 1999; **282**: 2003-2011 [PMID: 10591382 DOI: 10.1001/jama.282.21.2003]
15 **Smith WS**, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, Lutsep HL, Rymer MM, Higashida RT, Starkman S, Gobin YP, Frei D, Grobelny T, Hellinger F, Huddle D, Kidwell C, Koroshetz W, Marks M, Nesbit G, Silverman IE. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke* 2008; **39**: 1205-1212 [PMID: 18309168 DOI: 10.1161/STROKEAHA.107.497115]
16 **Penumbra Pivotal Stroke Trial I**. The penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 2009; **40**: 2761-2768 [PMID: 19590057 DOI: 10.1161/STROKEAHA.108.544957]
17 **Saver JL**, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, Clark W, Budzik R, Zaidat OO. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012; **380**: 1241-1249 [PMID: 22932715 DOI: 10.1016/S0140-6736(12)61384-1]
18 **Ciccone A**, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, Boccardi E. Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013; **368**: 904-913 [PMID: 23387822 DOI: 10.1056/NEJMoa1213701]
19 **Broderick JP**, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, von Kummer R, Molina CA, Demaerschalk BM, Budzik R, Clark WM, Zaidat OO, Malisch TW, Goyal M, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Martin RH, Foster LD, Tomsick TA. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013; **368**: 893-903 [PMID: 23390923 DOI: 10.1056/NEJMoa1214300]
20 **Chaturvedi S**, Selim M. Multimodal imaging for acute stroke: when is it worth it? *Neurology* 2013; **81**: 608-609 [PMID: 23851961 DOI: 10.1212/WNL.0b013e3182a08f98]
21 **Fisher M**, Albers GW. Advanced imaging to extend the therapeutic time window of acute ischemic stroke. *Ann Neurol* 2013; **73**: 4-9 [PMID: 23378323 DOI: 10.1002/ana.23744]
22 **Lansberg MG**, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, Wilder MJ, Lutsep HL, Czartoski TJ, Bernstein RA, Chang CW, Warach S, Fazekas F, Inoue M, Tipirneni A, Hamilton SA, Zaharchuk G, Marks MP, Bammer R, Albers GW. MRI profile and response to endovascular reperfusion after stroke (DEFUSE 2): a prospective cohort study. *Lancet Neurol* 2012; **11**: 860-867 [PMID: 22954705 DOI: 10.1016/S1474-4422(12)70203-X]
23 **Lemmens R**, Mlynash M, Straka M, Kemp S, Bammer R, Marks MP, Albers GW, Lansberg MG. Comparison of the response to endovascular reperfusion in relation to site of arterial occlusion. *Neurology* 2013; **81**: 614-618 [PMID: 23851962 DOI: 10.1212/WNL.0b013e3182a08f07]
24 **Campbell BC**, Christensen S, Levi CR, Desmond PM, Donnan GA, Davis SM, Parsons MW. Comparison of computed tomography perfusion and magnetic resonance imaging perfusion-diffusion mismatch in ischemic stroke. *Stroke* 2012; **43**: 2648-2653 [PMID: 22858726 DOI: 10.1161/STROKEAHA.112.660548]
25 **Tarlov N**, Nien YL, Zaidat OO, Nguyen TN. Periprocedural management of acute ischemic stroke intervention. *Neurology* 2012; **79**: S182-S191 [PMID: 23008396 DOI: 10.1212/WNL.0b013e31826958d3]
26 **Kent DM**, Hill MD, Ruthazer R, Coutts SB, Demchuk AM, Dzialowski I, Wunderlich O, von Kummer R. "Clinical-CT mismatch" and the response to systemic thrombolytic therapy in acute ischemic stroke. *Stroke* 2005; **36**: 1695-1699 [PMID: 16002756]
27 **Yaghi S**, Bianchi N, Amole A, Hinduja A. ASPECTS is a predictor of favorable CT perfusion in acute ischemic stroke. *J Neuroradiol* 2013; Epub ahead of print [PMID: 24156874]
28 **Kirmani JF**, Alkawi A, Panezai S, Gizzi M. Advances in thrombolytics for treatment of acute ischemic stroke. *Neurology* 2012; **79**: S119-S125 [PMID: 23008386 DOI: 10.1212/WNL.0b013e3182695882]
29 **Taqi MA**, Vora N, Callison RC, Lin R, Wolfe TJ. Past, present, and future of endovascular stroke therapies. *Neurology* 2012; **79**: S213-S220 [PMID: 23008401 DOI: 10.1212/WNL.0b013e31826959e5]
30 **Hennerici MG**, Kern R, Szabo K. Non-pharmacological strategies for the treatment of acute ischaemic stroke. *Lancet Neurol* 2013; **12**: 572-584 [PMID: 23684083]
31 **Nogueira RG**, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, Liebeskind DS, Smith WS. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* 2012; **380**: 1231-1240 [PMID: 22932714 DOI: 10.1016/S0140-6736(12)61299-9]
32 **Novakovic RL**, Toth G, Narayanan S, Zaidat OO. Retrievable stents, "stentrievers," for endovascular acute ischemic stroke

therapy. *Neurology* 2012; **79**: S148-S157 [PMID: 23008390 DOI: 10.1212/WNL.0b013e3182697e9e]
33 **Hussain SI**, Zaidat OO, Fitzsimmons BF. The Penumbra system for mechanical thrombectomy in endovascular acute ischemic stroke therapy. *Neurology* 2012; **79**: S135-S141 [PMID: 23008388 DOI: 10.1212/WNL.0b013e31826958a8]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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