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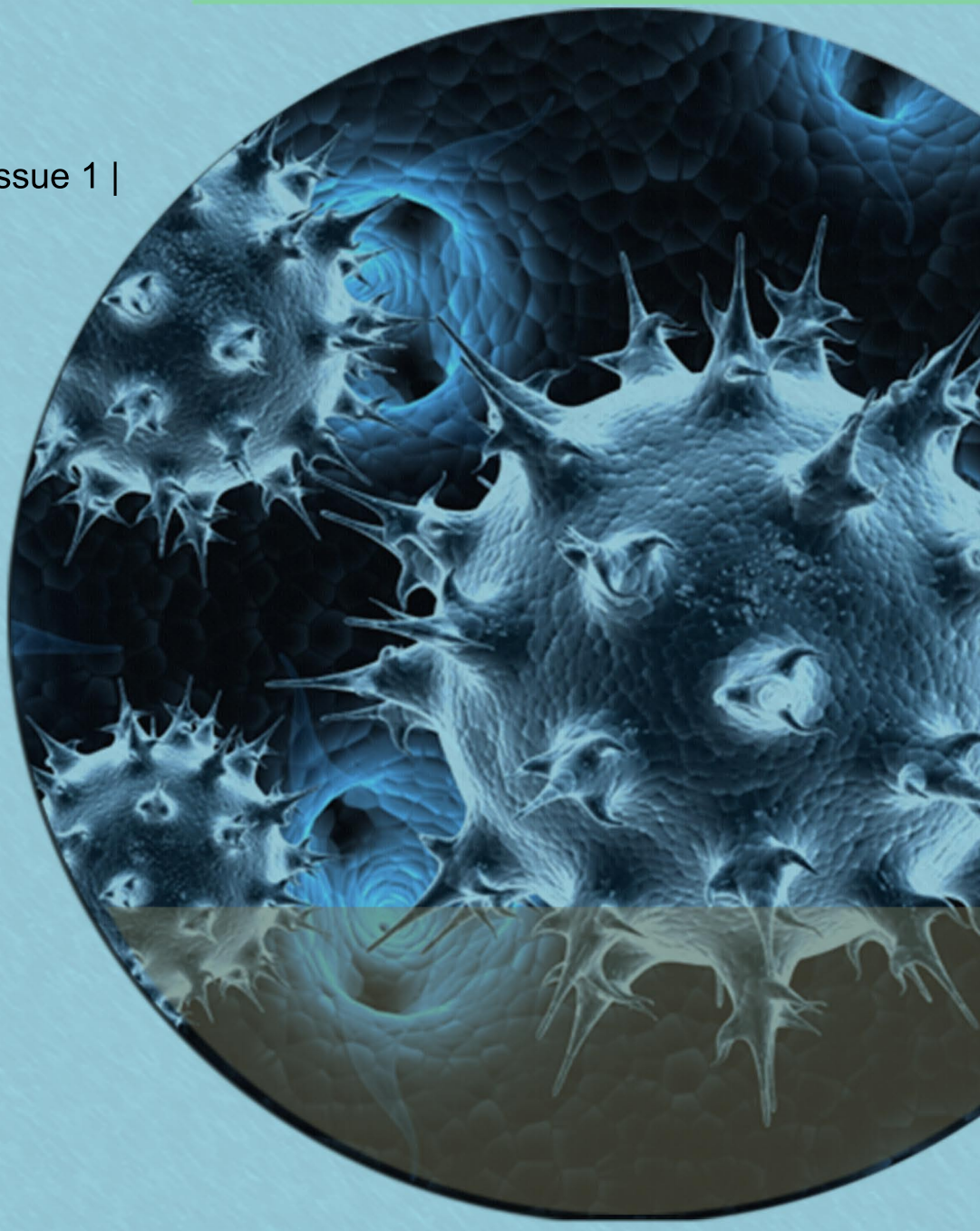

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Case Report

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Successful Treatment of Autoimmune Hemolytic Anemia Concurrent With Gastric Cancer by Rituximab: A Case Report of Evans Syndrome

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ABSTRACT

The concurrence of autoimmune hemolytic anemia (AIHA), thrombocytopenic purpura (Evans syndrome) and solid cancer is rare. In this study, we report a diabetic patient with gastric cancer who developed AIHA and idiopathic thrombocytopenic purpura. Steroid therapy for Evans syndrome restored platelet count; however, no improvement in AIHA was observed. Rituximab administration as a second-line therapy resulted in gradual improvement of anemia. Our observation suggested rituximab as an effective therapy for steroid-resistant AIHA.

KEYWORDS: Evans syndrome; Autoimmune hemolytic anemia; Thrombocytopenia; Rituximab; Gastric cancer.

INTRODUCTION

Evans syndrome is a disorder characterized by combined autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). Although several previous reports were present, Evans syndrome with concurrent malignancy is rare, and cases with concurrent gastric cancer are extremely rare.[1-4] The first-line treatment for AIHA and ITP is steroids, but steroid therapy to diabetic patient is almost contradictory. The second-line treatment is immunosuppressants and/or splenectomy. In recent years, efforts have been made to establish evidence supporting the use of rituximab for steroid-resistant patients.[5,6] In the present case of Evans syndrome with concurrent gastric cancer, steroid therapy improved ITP, but AIHA was steroid resistant. Rituximab was effective for steroid-resistant AIHA in the present case.

CASE REPORT

The single-living patient was a 70-year-old man, 165.8 cm in height, 59.3 kg body weight and BMI 21, who had been followed-up at a local out-patient clinic for type 2 diabetes mellitus for 18 years. Obstructive pulmonary disease and post-operative cervical spine fracture were also his complaints. In December 2010, the patient felt general fatigue which deteriorated. In February 2011, he consulted a local physician for close check-up, and was found to have anemia with a hemoglobin (Hb) concentration of 7.8 g/dl. Upper gastrointestinal endoscopy revealed ulcerated lesions on the lesser curvature near the pyloric region. Biopsy of the lesion revealed funicular and sheet-like proliferative invasion of signet-ring cell-type cancer with the diagnosis of poorly differentiated stage IIc gastric cancer.

The patient refused surgery and selected follow-up observation. In March 2011, further exacerbation of fatigue was observed with a Hb concentration of 4.2 g/dL, and he was admitted to a local clinic on that day. Red blood cell (RBC) transfusion was planned to treat anemia,

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but all erythrocyte concentrates for transfusion were positive on pre-transfusion cross-matching test, rendering transfusion difficult. In addition, elevated lactate dehydrogenase (LDH) and positive Coombs test led to diagnosis of hemolytic anemia, and the patient was transferred to the Department of Hematology at our hospital in March 2011.

Results of laboratory tests upon admission are shown in (Table 1). Blood tests at admission revealed marked anemia and thrombocytopenia. RBC was 103 mil/m^2, Hb at 4.6 g/dL, hematocrit at 12.8%, and platelets (Plts) at 38000 cell/μL. White blood cells at 5750 cell/μL with no abnormalities in the differential white blood cell count, reticulocytes (Ret) increased to 575%. Biochemical testing revealed increased LDH at 831 U/l, total bilirubin at 3.1 mg/dL, in which direct bilirubin at 1.1 mg/dL. In addition, direct/indirect Coombs test and antiplatelet antibody were positive, and Plt-associated IgG level was high. Bone marrow examination revealed a nuclear cell count of 70.4×10^4 /μL and increased erythroblasts (Figure 1). The megakaryocyte count was 104 cell/μl. There were no atypical cells, suggesting malignancy. Evans syndrome was diagnosed based upon the presence of concurrent AIHA and idiopathic thrombocytopenic purpura (ITP). In addition, re-evaluation of gastric cancer was performed using a gastrocamera (OLYMPUS model Q260) and confirmed the ulcerated lesions on the lesser curvature near the pyloric region and the *incisura angularis* of the greater curvature, and the pathological diagnosis was similar to the previous one (Figure 2). Computed tomography performed to deny potential gastric cancer metastasis revealed no metastatic lesions.

WBC 5750 cell/μL (4000-8000)	T-Bil 3.1 mg/dL (0.2-1.2)	IgG 1997 mg/dL (1000-1900)
stab 9%	AST 41 U/L (7-40)	IgA 358 mg/dL (96-430)
seg 32%	ALT 11 U/L (0-35)	IgM 48 mg/dL (48-350)
lympo 37%	ALP 204 U/L (80-300)	HPT 2 (19-170)
mono 12%	LDH 831 U/L(100-225)	DCT/ICT+
eosino 1%	GLU 171 mg/dL (65-110)	CA <4
baso 1%	BUN 15.3 mg/dL (8-20)	PaIgG 22 ng/10 cells(0-25)
myelo 6%	CRN 0.8 mg/dL (0.7-1.3)	Antiplatelet Ab +-(negative)
metamyelo 2%	UA 7.9 mg/dL (3.8-8)	RA 3 IU/ml (0-15)
eryblast 64%	TP 7.0 g/dL (6.5-8.2)	ANA -
RBC 100m/m2 (420-540)	ALB 3.3 g/dL (3.7-5.5)	Anti-DNA Ab <80
Hb 4.6 g/dL (12.5-17.5)	CRP 3.74 mg/dL (0-0.3)	
Ht 13.1% (39-51)	Na 136 mEq/l (135-145)	BM
Plt 38000/μl(130000-330000)	K 3.8 mEq/l (3.4-4.9)	NCC 70.4x104 cell/μl
Ret 565 ‰ (7-23)	Cl 107 mEq/l (98-108)	MgK 104 cell/μL
PT-INR 1.10 (0.9-1.13)	Fe 209 μg/dl (80-200)	No malignancy cell
APTT 26.9 sec (28-40)	UIBC 46 μg/dl (90-275)	
FIB 244.2 mg/dL (150-340)	Ferritin 282 ng/ml (21-282)	Karyotype
FDP 16.3 μg/mL (0-8)	VitB12 9675pg/ml (233-914)	46,XY
AT-3 73.2% (80-120)	Folic acid 1.2ng/ml (3.6-12.9)	
	CEA 4.9 ng/ml (0-5)	
	CA19-9 2.2 U/ml (0-37)	

Table 1: Laboratory data on admission.

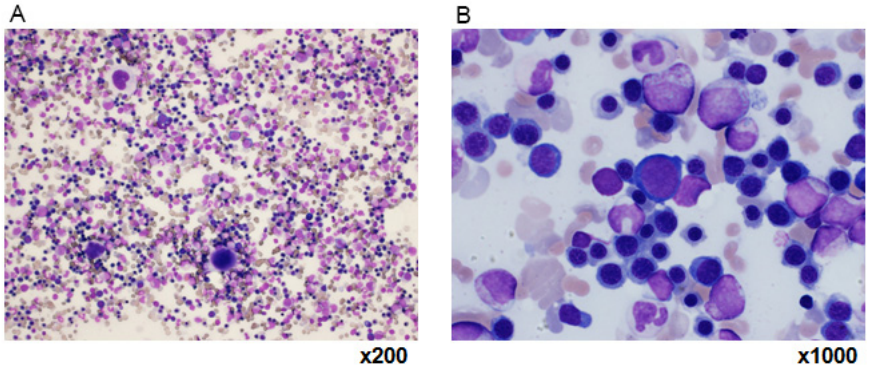

Figure 1: Images A and B of bone marrow examination.

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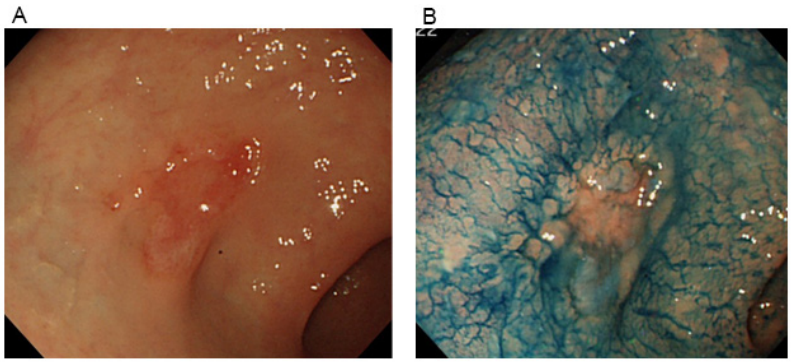

Figure 2: Endoscopic findings of the stomach.

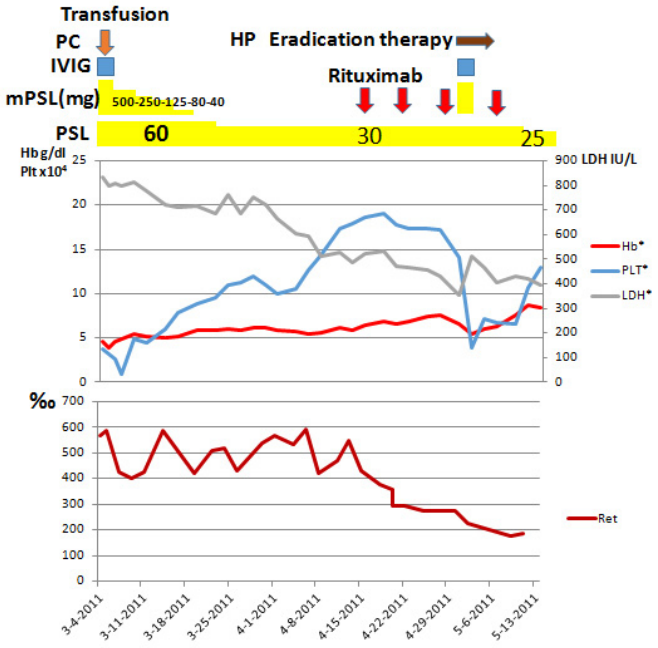

Figure 3: Clinical course.

PROGRESS ON ADMISSION

As summarized in Figure 3, prednisolone (PSL) was administered at a dose of 60 mg/day (1 mg/kg/day) to treat Evans syndrome (Figure 3). Although exacerbation of hemolysis was afraid due to blood typing and cross-matching test, and a compatible blood transfusion was challenging, a total of six units of RBC were transfused, and no clear deterioration of hemolytic findings happened following transfusion. Anemia persisted, however, and signs of cardiac failure developed.

On day 3 of hospitalization, the patient's Platelet count markedly decreased to 9000 cell/μL. Considering the risk of hemorrhage from the gastric cancer, pulse therapy with methylprednisolone (mPSL) was administered on the same day at a dose of 500 mg/day for 3 days. In addition, with 20 units of platelet transfusion and gamma globulin at 5 g/day for 3 days were added to enhance the effect of transfusion. One hour later, the platelet transfusion count increased to 64000 cell/μL and was gradually restored; however, no improvement in anemia was observed. Although insulin had been used for steroid treatment at admission, blood glucose became 545 mg/dL with poor control, so the mPSL dose was gradually decreased after the pulse, and PSL at a dose of 30 mg/day (0.5 mg/kg/day) was continued for an additional 4 weeks.

However, his anemia did not improve, nor did lower Ret and LDH levels. Therefore, the diagnosis of steroid-resistant AIHA was done. As the Plt count improved, surgical resection of the gastric cancer and splenectomy were planned to avoid the risk of intraoperative hemorrhage and to delete the cancer-induced autoantibody to yield paraneoplastic syndrome. However, the patient strongly refused the surgical resection, because one of his relatives had died under the surgery for gastric cancer.

Severe anemia persisted and emergence of cardiac failure deemed it imperative to expeditiously improve the patient's anemia, so rituximab administration was considered. After receiving consent from the patient and his family, rituximab was administered on day 42, total of four times at a

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dose of 375 mg/m^2 once a week. Following rituximab therapy, LDH and Ret count decreased, and anemia gradually improved. As a decrease in Plt count caused by a decrease of steroids was observed, on day 62, repeat mPSL at 500 mg/day and gamma globulin therapy at 5 g/day were administered for 3 days when the Platelet count was 39,000 cell/μL. The patient was positive for *Helicobacter pylori,* for which *pylori* eradication therapy was initiated. Thereafter, the anemia abated, the Platelet count was restored, and the patient discharged. Although the patient's gastric cancer was eligible for surgical treatment, the patient refused any further treatment.

Thereafter, eating disturbances appeared due to the progression of gastric cancer, and the patient underwent surgery at a different hospital. We were notified that there was no recurrence of AIHA or ITP.

DISCUSSION

Evans syndrome is a merger of AIHA and ITP. Both are autoimmune disease, so that the first treatment is a steroid. Treatment guidelines for AIHA recommend steroids at a dose of 1 mg/kg as the first-line therapy. Elderly patients require more scrutiny for potential complications including diabetes and infection. The Patient had diabetes, but early steroid treatment was required for heart failure and bleeding tendency. As he had gastric cancer, microangiopathic hemolytic anemia should be ruled out.[7]

Approximately 40% of patients with AIHA achieve remission in approximately 4 weeks with steroid therapy. In the event of ineffective first-line therapy with steroids, a second-line therapy is initiated; these include, in the absence of an underlying disease, splenectomy or immunosuppressive therapy individually determined based on each patient's condition.

Rituximab, anti-CD20 antibody, selectively targets B lymphocytes and reduces autoantibody production. Recently, numerous reports of cases in which rituximab was used for refractory AIHA have examined its efficacy and safety. Penalver et al[5] treated patients with refractory AIHA with rituximab administered once a week at 375 mg/m^2 for a total of 4 doses and achieved a 77% response rate. Furthermore, Barcellini et al[6] achieved a response rate of 82% with rituximab at a low dose of 100 administered 4 times. Thus, rapid and continuous therapeutic outcomes with rituximab should be anticipated. In patients with an underlying disease such as diabetes who are unsuitable for long-term steroid treatment, rituximab is suggested to be a more effective approach.

Secondary AIHA may develop in the setting of an underlying disease such as connective tissue disorders, particularly systemic lupus erythematosus, lymphproliferative diseases, malignant tumors, certain medications, and infection. The mechanism is suggested to involve alterations in patient RBC antigens resulting in their cross-reactivity with antibodies against foreign antigens and changes in the immune system.

Gastric cancer concurrent with AIHA is rarely observed. Furthermore, only a few reports describe Evans syndrome including both AIHA and ITP.[1] In 2010, a meta-analysis by Joe et al[2] evaluated 52 reported cases of solid cancer concurrent with AIHA between 1945 and 2009. In their report, the most common cancers were pulmonary, renal, and colorectal cancer. There were only a few reports of Evans syndrome with gastric tumor.[4,8] The analysis showed that patients who responded to steroid therapy as first-line treatment subsequently underwent surgical resection. In addition, a subset of patients with steroid-refractory AIHA has been reported to subsequently improve by surgical resection. Furthermore, our literature search revealed only 3 reports of gastric tumor concurrent with Evans syndrome; the types included neuroendocrine tumor, plasmacytoma, and signet ring cell type gastric cancer. Signet ring cell cancer is relatively rare in the stomach, so the association with AIHA is noteworthy.

Surgical resection of gastric cancer would have enabled us to determine whether Evans syndrome was paraneoplastic syndrome of the tumor. However, because the patient refused surgery, it could not be confirmed. The patient received gastrectomy after discharge, and the Evans syndrome has not been recurrent, a possibility of paraneoplastic syndrome could be accepted.

Rituximab therapy, which was initiated as an alternative, resulted in rapid decrease of Ret count and LDH, and early therapeutic effects with only a mild decrease in IgG were observed. Rituximab administration was safe without any major side effects. Currently, although there is insufficient supporting evidence for rituximab therapy in AIHA,[5,9-11] we believe that rituximab is a beneficial therapy for steroid-resistant AIHA, with a favorable safety and efficacy profile.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Research

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Evaluation of Cardio-Ankle Vascular Index and Influencing Factors in Natural Population of She Minority in China

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ABSTRACT

Objective: The present study was designed to investigate the influencing factor of cardio-ankle vascular index (CAVI) in natural population of She minority in China.
Methods: Five hundred and twenty-four subjects were enrolled into our study (male 227 and female 297). Main analyzing indexes included vascular related markers namely of CAVI and carotid artery intima-media thickness (CIMT) and blood markers.
Results: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were high in the entire population (150.08±23.32 mmHg, 91.15±12.42 mmHg). CAVI, left CIMT and right CIMT were normal. Univariate analysis showed CAVI was positively correlated with age, waist hip ratio (WHR), SBP, DBP, pulse pressure (PP), blood urea nitrogen (BUN), serum creatinine (Cr), fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high sensitive C reactive protein (hs-CRP), left CIMT and right CIMT (r=0.570, 0.240, 0.512, 0.372, 0.459, 0.231, 0.095, 0.182, 0.158, 0.164, 0.167, 0.169, 0.395, 0.407, all $p<0.05$). Multivariate linear regression analysis (selected factors including age, heart rate (HR), body mass index (BMI), WHR, SBP, DBP, PP, blood uric acid (UA), BUN, Cr, FPG, TC, TG, high density lipoprotein cholesterol (HDL-C), LDL-C, hs-CRP, left CIMT and right CIMT) showed that age, SBP, FPG, hs-CRP, TG and Cr were the independent related factors of CAVI (adjusted $R^2=0.399$).
Conclusion: Age, systolic blood pressure, fasting plasma glucose, high sensitive C-reactive protein, triglyceride and creatinine levels were independent factors of CAVI in natural populations of She minority in China.

KEYWORDS: She minority; Arterial stiffness; Cardio-ankle vascular index (CAVI).

ABBREVIATIONS: CAVI: Cardio-ankle vascular index; CIMT: Carotid artery intima-media thickness; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; HR: Heart Rate; WHR: Waist Hip Ratio; BMI: Body Mass Index; FPG: Fasting Plasma Glucose; TG: Triglyceride; TC: Total Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; hs-CRP: high sensitive C-reactive protein; BUN: Blood Urea Nitrogen; Cr: Serum Creatinine; UA: Blood uric acid.

INTRODUCTION

Arterial stiffness has been considered as a surrogating indicator of atherosclerosis progression and degree of vascular injury.[1] In addition, arterial stiffness is an independent risk factor and predictor of cardiovascular disease. There were many evaluation methods of arterial stiffness, cardio-ankle vascular index (CAVI) was a new marker reflecting the whole arterial stiffness from aortic to ankle and independently of immediate blood pressure during measurement.[2] Therefore, CAVI was used as a reliable evaluation of early vascular injury. It has been considered as a quantitative assessment of disease progression and therapeutic efficacy.[3,4] Recent

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years, many studies about CAVI found that it was closely related to vascular injuries in patients with hypertension, diabetes mellitus and dyslipidemia, and was regard as a useful tool for screening of vascular health in patients with metabolic syndrome.[3,5-11] Furthermore, the new vascular health classification also included CAVI as an evaluation index of vascular health.[12] However, few study assessed CAVI in a minority population of China. People of the minority lived in a natural mountain area without known vascular related diseases and with little interference from modern society. Therefore, the present study was to evaluate the vascular status using CAVI and assess its influencing factors.

SUBJECTS

A total of 524 subjects from 6 natural minority villages using a cluster sampling method were enrolled into the present study, including male 227 and female 297 with 14-85 years old. Subjects with ankle brachial index equal or below 0.9, serious liver and kidney dysfunction, systematic inflammatory disease, infectious disease and cancer were excluded the study.

The ethics committee of Mindong Hospital in China approved the study. And all participants completed informed consent.

METHODS

The Detection of CAVI

According to the guideline of early vascular detection system (the second report),[1] CAVI was detected by the vascular measurement apparatus VS-1000 (Fukuda Denshi Co. Ltd, Japan) automatically. Subjects were asked to rest for 10 minutes with a supine position. Electrodes were placed on the wrists to collect the ECG waveform, and micro heart sound recorder was placed in the fourth intercostal space of left sternal to capture the heart sounds, and a blood pressure cuff was attached to the double arm and double ankle with appropriate tightness, and then the value of CAVI and blood pressure were measured automatically. In the study, we used the right CAVI to analyze.

The Measurement of CIMT

According to the proposal of series studies on arterial stiffness in China, carotid artery detection for CIMT was conducted by color Doppler ultra sound apparatus (Mylab 70 CV) by a linear probe LA523 and with frequency of 5-13 MHz. It was installed with automatic analysis software of quality intima-media thickness (QIMT). Subjects were detected with a supine position. Bilateral carotid sinus 1.5 cm was the CIMT examination site and the QIMT automatic analysis system will get the value of CIMT during 6 cardiac cycles.

Laboratory Examination

All subjects were drawn the fasting venous blood and using EDTA anticoagulant, and TC, TG, LDL-C, HDL-C, FPG, UA, BUN, Cr and hs-CRP were measured by automatic analyzer.

General Medical History Collection

People were asked to complete a questionnaire for the collection of age, gender, history of diseases (such as hypertension, diabetes mellitus, coronary artery disease, cerebral infarction and peripheral artery disease) and life habits.

STATISTICAL ANALYSIS

SPSS V.20.0 was used as statistical software in the study. Continuous variables were showed as mean±standard deviation ($\bar{x}\pm s$) and categorical variables were showed as percentage and frequency. Pearson correlation analysis was used to quantitatively describe the degree and direction of the relationship between variables. Multiple linear regression analysis was used to screen influencing factors of CAVI. $P<0.05$ (bilateral) was considered of statistical significance.

RESULTS

Eventually 524 subjects were enrolled into our study (male 227 and female 297, age 47.95±13.48 year). From Table 1, we can see that SBP and DBP were high. CAVI and CIMT were both in the mean normal level. Pearson correlation analysis showed CAVI were positively correlated with age, WHR, SBP, DBP, PP, BUN, Cr, FPG, TG, TC, LDL-C, hs-CRP, left CIMT and right CIMT, with age showed the highest correlation. However, it didn't show negative or positive correlation between CAVI and HDL-C (Table 2). In the further linear regression analysis, we included age, HR, BMI, WHR, SBP, DBP, PP, UA, BUN, Cr, FPG, TC, TG, HDL-C, LDL-C, hs-CRP, left CIMT and right CIMT as independent variables and CAVI as dependent variable. The final model indicated age, SBP, FPG, hs-CRP, TG and Cr were independent influencing factors of CAVI (Table 3).

DISCUSSION

In the present study, we found the mean level of both SBP and DBP were high, but the mean CAVI and CIMT were in a normal level in the She minority population in China, which indicated some other factors may influence vascular function and structure. Therefore, further analysis showed age, SBP, FPG, hs-CRP, TG and Cr were independently positively correlated with CAVI in the special population.

CAVI has been put forward as a new evaluation index of vascular health for about ten years. It is independent of immediate blood pressure during measurement and has become a hot field of research.[2] Our previous studies indicated that the influencing factors of CAVI were different for different populations. We compared population between Chinese and Japanese and found that CAVI was both increased by age. However, CAVI level was significantly lower in Chinese than that of Japanese.

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Variables (N=524)	Mean±standard deviation ($\bar{x}$±s)
Age (year)	47.95±13.48
Male/Female	227/297
BUN (mmol/L)	5.09±1.73
Cr (μmol/L)	65.02±18.54
UA (μmol/L)	284.48±83.34
FPG (mmol/L)	5.42±1.35
TC (mmol/L)	5.15±1.37
TG (mmol/L)	1.25±1.04
HDL-C (mmol/L)	1.59±0.49
LDL-C (mmol/L)	2.93±0.89
hsCRP (mg/L)	3.87±6.46
BMI (kg/m^2)	24.1±3.33
HR (beats/minutes)	71.4±13.23
WHR	0.90±0.05
CAVI	7.32±1.30
SBP (mmHg)	150.08±23.32
DBP (mmHg)	91.15±12.42
PP (mmHg)	58.93±15.99
Left CIMT (μm)	557.55±134.15
Right CIMT (μm)	541.01±132.86

Table 1: General clinical characteristics of all subjects.

Variables (N=524)	r	*p*
Age (year)	0.570	<0.05
BMI (kg/m^2)	-0.060	0.183
WHR	0.240	<0.05
HR (beats/minutes)	0.034	0.447
SBP (mmHg)	0.512	<0.05
DBP (mmHg)	0.372	<0.05
PP (mmHg)	0.459	<0.05
BUN (mmol/L)	0.231	<0.05
Cr (μmol/L)	0.095	<0.05
UA (μmol/L)	0.086	0.079
FPG (mmol/L)	0.182	<0.05
TG (mmol/L)	0.158	<0.05
TC (mmol/L)	0.164	<0.05
LDL-C (mmol/L)	0.167	<0.05
HDL-C (mmol/L)	0.025	0.610
hs-CRP (mg/L)	0.169	<0.05
Left CIMT (μm)	0.395	<0.05
Right CIMT (μm)	0.407	<0.05

Table 2: Pearson correlation between CAVI and other variables.

Final entered variables (Adjusted R^2=0.399)	Adjusted β	*p*
Age (year)	0.346	<0.05
SBP (mmHg)	0.202	<0.05
FPG (mmol/L)	0.179	<0.05
hs-CRP (mg/L)	0.157	<0.05
TG (mmol/L)	0.146	<0.05
Cr (μmol/L)	0.138	<0.05

Table 3: Multiple linear regression analysis between CAVI and other variables (adjusted R^2=0.399).

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Age, SBP, FPG, Cr were independent influencing factors of CAVI in Chinese; age, SBP, HDL-C, Cr, BMI, FPG were independent influencing factors of Japanese population.[11] CAVI were both correlated with age, SBP, BMI in healthy women of Chinese and Japanese.[13] In addition, CAVI were independently related to age, BMI, HbA1c, HDL-C in patients with hypertension and diabetes mellitus and community residents.[5,10,14,15] In addition, CAVI level was different between the northern and southern area which was higher in the south region in China.[16] Other studies also indicated CAVI were independently related to Cr and homocysteine.[9,17,18] Study on another minority in China namely Miao minority showed that age, SBP, uric acid, BMI were independent influencing factors of CAVI.[19] Therefore, the above studies informed us that the influencing factors of CAVI were different in different populations. Thus, the present study added some more information on CAVI in a She minority population in China. The results will provide special intervention for different populations and it was also the embodiment of precision medicine.

MERITS AND LIMITATIONS

The subjects enrolled into the study were from natural mountain areas of China. In these areas, people lived with farming works and far away from the cities. People there were influenced little by the modern society and lived with less mental stress. They also ate natural homemade foods. In addition, the participants were almost farmers, thus they knew little about their health or disease condition, therefore few of them were taking drugs which would have little influence on CAVI. Therefore, the results can reflect the natural relationship between CAVI and other markers. In addition, few studies in the China have assessed the influencing factors of She minority. The present study provided a reference for the related factors of CAVI in She minority and some clues for the following-up studies.

However, the above merits may also be the limitations of the study. We could not evaluate the difference between different diseases status in CAVI because of the limited medical knowledge of the local people. Finally, the study was observational and can only provide limited information about CAVI. We have conducted follow-up study for this population and further research results will add more information on CAVI and its influencing factors.

CONCLUSION

The mean level of blood pressure was high but the mean CAVI and CIMT were at the normal level in the natural population of She minority in China. Furthermore, age, systolic blood pressure, fasting plasma glucose, high sensitive C-reactive protein, triglyceride and creatinine levels were independent factors of CAVI in the minority in China. Therefore, in the She minority population, we should focus more on the above influencing factors on CAVI and carry out some early intervention strategies for prevention.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Case Report

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Cerebellar Syndrome as a Presentation of Pulmonary Hypertension

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ABSTRACT

Coincident focal signs and dyspnea can lead to diverse conclusions. However, if they present in the context of a genetic cardiac abnormality a straight forward link can be established. Patent foramen ovale (PFO) can cause a wide range of manifestations. Not always suspected in the Accident and Emergency (A&E) unit, PFO is the most common cardiac abnormality and should be ruled out when systemic embolisms happen in the absence of cardiac arrhythmia or advanced arteriosclerosis. We present a complex case of a lady in which both PFO and an advanced rheumatic condition were the underlying causes of pulmonary hypertension (PH).

KEYWORDS: Cerebellar; Patent foramen ovale; Dyspnea.

INTRODUCTION

A 56-year-old woman with a past history of seronegative rheumatoid arthritis treated with leflunomide came to the Accident and Emergency (A&E) unit complaining of one month of shortness of breath, grade III New-York Heart Association (NYHA), and 48 hours of dysarthria and gait and postural instability causing several falls. Upon physical examination, we found a wide-based gait with negative Romberg test, dysarthria without language impairment and 2 heart murmurs: a systolic one around the tricuspid area and a holosystolic mitral-area localized. Computed-tomography (CT) scan showed a sub-acute infarct in the left superior cerebellar-artery region. Laboratory results revealed an acute respiratory failure and an electrocardiogram (ECG) the following findings (Figure 1).

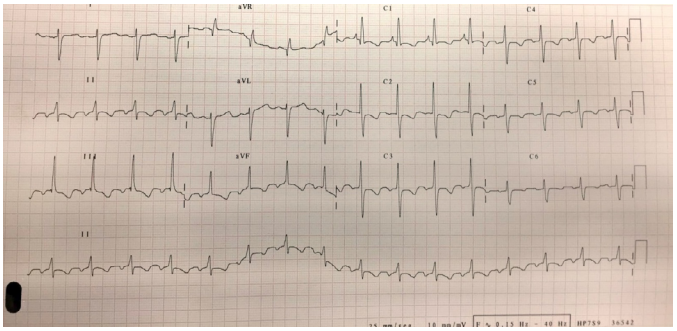

Figure 1: Sinus rhythm with right axis. Criteria of right ventricular hypertrophy and pulmonary hypertension with R-wave bigger than S-wave in V1 and V2 and deep S-wave in V5, V6, I and aVL. P-wave pulmonale. Secondary alterations in repolarization with ST and negative T wave in precordial and inferior leads.

The patient underwent full assessment and an angio-CT scan was performed to rule out pulmonary embolism (PE) and interstitial lung disease (ILD). As well as the angio-CT scan, a supra aortic trunks doppler scan was normal. Transthoracic echocardiogram (TTE), however, estimated a systolic pressure in pulmonary artery of 128 mmHg and the microbubble injection

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technique, the presence of bubbles in the atrium and left ventricle in the 1st 3 beats after opacification of the right cavities. These highly suggestive findings of patent foramen ovale (PFO) were confirmed by the right heart catheterization and defined as a PFO type interatrial communication. A lack of response to the acute vasodilatador test with epoprostenol and a right to left communication with a continuous shunt were observed. We closed the anatomic defect and started her on ambrisentan, tadalafil, aspirin and optimized her underlying rheumatic condition treatment.

DISCUSSION

Pulmonary hypertension (PH) is a disease characterized by elevated pulmonary artery pressure, which often results in right ventricular failure. It may be idiopathic, familial, or associated with multiple other diseases. PH occurs in men and women of any race or age. PH can be a progressive, fatal disease if untreated, although the rate of progression is highly variable.[1] Interestingly, our patient reached an advanced end organ damage stage, but she tailored to her symptoms gradually. After diagnosis, patients with PH should be evaluated in a center with expertise in management of this disease.[2]

Primary or secondary PH classification no longer exists and a new one including 5 groups has been proposed by the World Health Organization (WHO).[3] PH in our case caused right ventricular failure (represented in the TTE and ECG findings) and presented as an acute cerebellar syndrome due to a paradoxical cerebral stroke. Both PFO and aortic regurgitation (AR) were the causes of PH here. As the presence of advanced disease in PH is generally suggested to be less responsive to therapy, we do not expect in our case a great succes.[4] A take-home message are the need of a proactive search of right ventricular overload findings in ECG and the clinical suspicion of PFO as the cause of an unexplained cerebral stroke.

CONCLUSIONS

PFO can cause a wide range of manifestations. Not always suspected in the A&E unit, we need to expand the awareness of this entity to general and junior doctors because the management and prognosis of the patients rely on a prompt and accurate response.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Case Report

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Successful Third Hematopoietic Stem Cell Transplantation for Blast Crisis of Chronic Myeloid Leukemia After Two Times of Graft Failure

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ABSTRACT

Background: Chronic Myeloid Leukemia (CML) is largely treated with BCR-ABL protein targeted drugs called tyrosine kinase inhibitors (TKIs) , imatinib, which have led to dramatical improvement in 2001. Nilotinib and dasatinib were approved as the second new TK inhibitor in 2010, and Radotinib in 2012. However, the only curative treatment for CML is a bone marrow transplant or an allogeneic stem cell transplant.
Case: A 42-year-old man was diagnosed CML in June 2011. He had achieved complete cytogenetic response in 5 months later by nilotinib treatment. It did not lead to major molecular response in the 18th month, and blastic phase of acute promyelocytic leukemia (M3) occurred in the 19th months. Leukemia cells had both promyelocytic leukemia gene/retinoic acid receptor alpha (PML/RARα) and BCR/ABL translocations. A retinoic acid was administered for M3. The dasatinib was administered for the blast crisis, and remission was obtained.
Transplantation: Hematopoietic stem cell transplantation (HSCT) from umbilical cord blood was performed at remission, but it was rejected twice. The third HSCT was succeeded from a sister who had hyperthyroidism.
Conclusion: After 2 times of graft failures, HSCT was succeeded. Long plan of treatment is necessary for middle aged CML patients.

KEYWORDS: Third stem cell transplantation; Graft failure; Chronic myelogenous leukemia; Acute promyelocytic leukemia.

ABBREVIATION: CML: Chronic Myelogenous Leukemia; BCR: Breakpoint cluster region protein; ABL1: Ableson murine leukemia viral oncogene homolog 1; TKI: Tyrosine Kinase Inhibitor; PML: Promyelocytic Leukemia Gene; RARα: Etinoic Acid Receptor α; HSCT: Hematopoietic Stem Cell Transplantation; CD: Cluster of Differentiation; HLA-DR: Human Leukocyte Antigen-Antigen D related; qRT-PCR: quantitative Reverse Transcription Polymerase Chain Reaction; RT-PCR: Reverse Transcription Polymerase Chain Reaction; G-banding: Giemsa banding; SKY FISH: Spectral Karyotyping Fluorescence *in situ* Hybridization; ATRA: All-trans Retinoic Acid; CCyR: Complete Cytogenetic Response; MMR: Major Molecular Response.

INTRODUCTION

Chronic Myelogenous Leukemia (CML) is a myeloproliferative disorder characterized by the existence of Philadelphia chromosome. BCR-ABL protein targeted drugs called tyrosine kinase inhibitors (TKIs) dramatically improved patients' survival in 2010s. These drugs are imatinib, Nilotinib, Dasatinib and Radotinib.

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As a result, hematopoietic stem cell transplantation (HSCT) with allo-HSCT is decreasing.[1] A graft failure is one of the crucial complications in allo-HSCT. If it occurs, the most of the patients run their fatal course. In the present case, promyelocytic blast crisis occurred in the second chronic phase CML and we performed allo-HSCT for three times for graft failures.

CASE REPORT

A 42 year-old male was diagnosed with CML in June 2011 and started the administration of nilotinib of 600 mg/day on June 12, 2011. He was treated by TKI, and a month later, therapeutic effect reached complete hematologic response.Then, 5 months later, it reached complete cytogenetic response although it had never reached major molecular response ever.

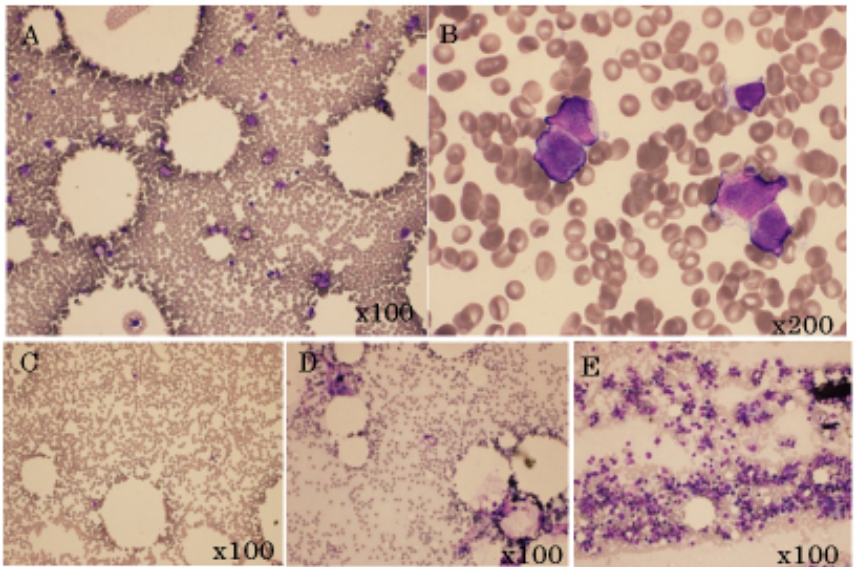
We considered changing nilotinib to dasatinib at the 19th month since it did not reach major molecular response at the 18th month.[2] On January 20, 2013, laboratory data showed pancytopenia; white blood cell count of 1.76×10^9 /L, hemoglobin count of 14.6 g/dL and platelet count of 122.0×10^9 /L. Biochemical testing showed asparatate transaminase (AST) at 33 U/L, alanine aminotransferase (ALT) at 218 U/L, lactate dehydrogenase (LDH) at 148 U/L, total bilirubin (T-Bil) at 2.3 mg/dL and C-Reactive Protein (CRP) at 0.05 mg/dL. Coagulation test showed prothrombin time (PT)-INR at 0.96, activated partial thromboplastin time (APTT) at 27.4 sec, fibrinogen (Fib) at 212 mg/dL, fibrin/fibrinogen degradation product (FDP) 1.6 μg/mL. A smear of bone marrow aspiration showed promyelocytic blastoid cells 31.4% with positive cluster of differentiation 16 (CD16), CD33 and human leukocyte antigen-antigen D related (HLA-DR) staining (Figure 1A and B). RT-PCR showed promyelocytic leukemia gene/retinoic acid receptor alpha (PML/RARα) 47000 copy/μRNA on admission (Table 1). Thus, promyelocytic (M3) blast crisis of CML was diagnosed. Moreover, BCR/ABL was 625 copy/0.5 μRNA and there was no gene mutation of BCR/ABL. Karyotype revealed 46, XY, t(9;22)(q34;q11.2), t(15;17)(q22;q21)9/20 by Giemsa band (G-band) staining and Spectral karyotyping-Fluorescence *in situ* hybridization (SKY-FISH) (Figure 2).

It was positive of BCR/ABL and PML/RARα; therefore, the administration was changed from nirotinib to dasatinib in addition to administer ATRA on January 25, 2013. On March 19, 2013, bone marrow examination revealed to reach complete hematologic remission with negative of BCR/ABL and PML/RARα by fluorescence *in situ* hybridization, but they were positive by the reverse transcription-polymerase chain reaction (RT-PCR).

Hence, this therapeutic effect reached complete cytogenetic response (CCyR) but did not reach major molecular response (MMR). Thus, we diagnosed that his state could achieve second chronic phase. According to the course of treatment until then, we had been considering that it was necessary for him to be performed allogenic hematopoietic stem cell transplantation. Therefore, we began to search for donors immediately.

He had a human leukocyte antigen (HLA) well matched related donor, a sister; however, she had past medical history of hepatitis C and had undergone medical treatment for Graves' disease by methimazole prior to the eligibility test. Based on these factors, we decided she did not suit as his donor, so that we started searching for an unrelated donor. Finally, we selected cord blood for his treatment since there was no well-matched unrelated bone marrow donor in Japan Marrow Donor Program.

Figure 1: Image of Bone Marrow Examination.



The Figure A,C,D and E is x200. The Figure B is x1000. The Figure of A and B Show Promyelocytic Blastoid. The Figure of C and D Show Hypocellular Bone Marrow as Graft Failure. The Figure of E Show the Engraftment.

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Table 1: Hematological Data at the First Admission, Blastic Crisis and Discharge.

	At first	At blast crisis	At discharge
WBC (4000-8000) /μL	**25300**	**1510**	**2480**
stab %	**2.5**	**1**	**1**
seg %	**59.5**	41	40
lymp %	**17.5**	**55**	41
Mono %	6.5	2	**13**
Eosino %	1.5	0	4
Baso %	**3.5**	1	1
Myelo %	**7.5**		
Metamy %	**1.5**		
RBC (420-540) m/mm²	543	416	**277**
Hb (12.5-17.5) g/dL	16.6	13.6	**9.9**
Ht (39-51) %	50.3	40.1	**29.5**
Plt (130000-330000) /μL	284000	136000	147000
Ret (7-23)	22.4	13.6	**35.6**
BM			
NCC /μL	1117000	84000	*105000
MgK /μL	343	12	*50
Promyelocyto(Blastiod) %		**31**	***0.6**
M-bcr/abl mRNA copies/ μgRNA	**27000**	**180000**	*<50
PML/RARα mRNA copies/ μgRNA		**47000**	*<50

In parentheses indicates the normal value.
*is the data of two months before discharge.

Figure 2: karyotype Test. A Chromosomal Abnormality by G-Banding and SKY FISH. Red Circle is an Abnormal Place.

Selected cord blood was from a female, its donor-recipient HLA-allele match was 5/8, nuclear cell count was 3.71×10^6/kg, CD34 positive cell count was 0.756×10^5/kg and blood type was A+ (recipient blood type was B+). HLA antibody was positive yet donor allele type's antibody did not exist. On May 9, 2013, he was hospitalized for allogenic hematopoietic stem cell transplantation.

Stem Cell Transplantation

The conditioning regimen was selected as myeloablative regimen, intravenous busulfan and cyclophosphamide (IV BU/CY) and prevention of graft *vs*. host disease, was used for cyclosporine and short-term methotrexate. Transplantation conditioning was started from 7 day and cord blood (CB) infusion was

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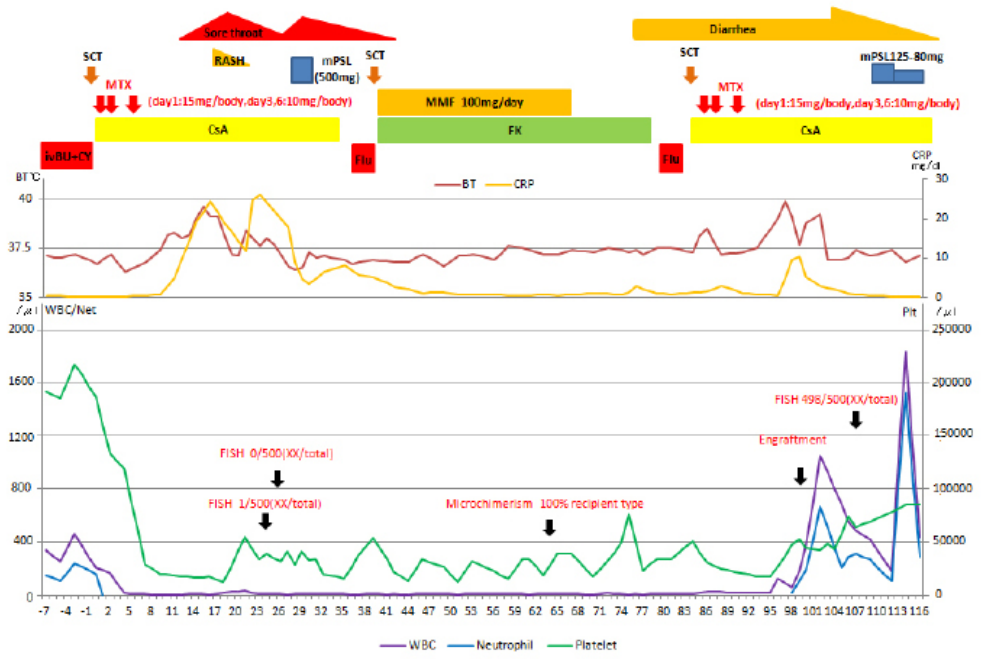

Figure 3: The Figure Explains the Course of Three Bone Marrow Transplantation. Purple, Blue and Green Line Shows WBC, Neutrophil and Platelet. Red and Yellow Line Show Body Temperature and CRP. We Checked The Engraftment by FISH for Heterosexuality and Microchimerism for Same Sex at Black Arrow.

performed on 0 day (Figure 3). It caused myelosuppression and caused a grade 2 fever and a grade 3 sore throat. Rush appeared on the 20% of body surface area mainly on the trunk from day 15 and his white blood cell (WBC) count decreased to 0.18×10^9 /L on 18th day. Therefore, we diagnosed that it was an engraftment syndrome by a febrile neutropenia.

According to his good physical status and no abnormal vital sign, observation on the engraftment syndrome was continued by administration of antimicrobial drug for febrile neutropenia. On the day 21, his fever improved and white blood count became 0.31×10^9 /L and the value of C-reactive protein-improved. However, fever and sore throat was getting worse and a severe neutropenia happened on the day 23 and 25 in which WBC count decreased to 0.09×10^9 /L. A possibility of hemophagocytic syndrome (HPS) was suspected, and bone marrow examination revealed sever hypocellular bone marrow; nuclear cell count was 3.0×10^9 /L without hemophagocytic macrophage (Figure 1C). Ferritin level on the day 25 and 28 were 1190.7 ng/mL and 974.2 ng/mL, respectively. AST, ALT and other hepatic enzymes were within normal levels and no splenomegaly was noticed. Thus, the hemophagocytic lymphohistiocytosis-2004 (HLH) trial criteria were not satisfied.

These conditions seemed to be the secondary graft failure by HPS, so 500 mg methylprednisolone was given for 3 days from the day 28. On the day 30 the severe hypo-cellular bone marrow showed chimaerism of complete recipient pattern.

He was diagnosed with secondary graft failure and the second HSCT was performed. We selected CB from male, and blood type A+. Whose recipient-donor HLA allele match was at 4/8, nuclear cell count was 2.13×10^6/kg, and CD34 positive cell count was 0.495×10^5/kg. Donor allele type's HLA-antibody had not been revealed prior to the second HSCT. We selected non-myeloablative conditioning of fludarabine 30 mg/m^2 for 3 days, because he had an infection as a complication of HSCT. Fujisawa kaihatsu/mycophenolate mofetil (FK/MMF) (MMF 1000 mg/day) was selected for prevention of graft *versus* host disease (GVHD) on the 40th day from the first HSC infusion.

After the second HSCT, his fever and sore throat improved but white blood cell count remained low. Bone marrow examination performed on the day 65 after the second SCT showed a severe hypo-cellular bone marrow in which nuclear cell count was 5000/μL (Figure 1D) and chimaerism was exactly the same as the pattern of the recipient before.

Therefore, we decided that the second HSCT was failed.

On the third HSCT, there was no CB better than the second SCT. Thus, we extended the range of donors to cousins to consider a better possibility of haplo-identical hematopoietic stem cell transplantation. However, there were no haplo-identical donors. We thought there was no superior method to save him besides the transplantation from his sister mentioned earlier who was HLA well matched related donor. We had got sufficient informed consent from him, his family and donor candidate, and she agreed to be a donor.

Her aptitude for SCT was confirmed by hepatitis C vi-

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rus (HCV) infection being below the sensitivity level by qRT-PCR, and the thyroid function was within the normal range. Third HSCT was decided to perform peripheral blood hematopoietic stem cell transplantation, because the recipient had been in continued long-term neutropenia. Conditioning regimen was the same as the second SCT, and prevention of GVHD were done by CyA/ shot-term methotrexate (MTX) (day1:15 mg/body day 3 and 6:10 mg/body). Peripheral blood stem cell harvest was performed to use granulocyte-colony stimulating factor (G-CSF) 10 μg/kg/day. Collected nuclear cell counts (NCCs) was 7.26×10^8/kg and $CD34^+$ cells 2.39×10^6/kg. Stem cell transplantation (SCT) was performed on the day 84 and 85 after operating the 1st SCT. White blood cell count increased from the day 11 and became over 1000/ml on the day 99. He had been having a fever, decreasing percutaneous oxygen saturation and increasing body weight due to edema from the day 98. Those symptoms apparently started progressive from the day 102. Acute GVHD or engraftment syndrome was suspected and 125 mg methylprednisolone (mPSL) was administrated. Diarrhea, fever and respiratory distress were improved after administration of mPSL. Colonoscope was performed for the diagnosis of GVHD, but no pathological finding of GVHD was found. We considered these symptoms were related to the graft failure. Therefore, we decided to decrease the mPSL administration. Bone marrow examination on the day 107 for confirming graft engraftment showed enough hematopoiesis (NCC:73.1×10^4/μL) (Figure 1E). The graft engraftment by *in situ* hybridization was donor type 498/500. Engraftment syndrome was improved so that administration of mPSL was discontinued and CyA was changed intravenous administration to per oral administration (PO) on the day 113. Stage acute GVHD appeared on the skin on the day 155; however, this symptom was successfully controlled by antihistamine and external preparation of steroid.

CyA induced renal dysfunction was improved by decreasing CyA and discontinue on the day 193. PSL 10 mg administration was started from the day 114 because a GVHD still remained. Twelve months later from the third SCT, CML condition retained MMR, HCV level kept below the sensitivity level, thyroid function was normal and thyroid stimulating hormone (TSH) receptor antigen was negative, and he could discharge from the hospital.

DISCUSSION

Graft failure is one of the rare yet crucial complications of allo-SCT. Fatality rate is said to be 40-50% when it occurs. Basically, radical treatment of CML is the only allo-SCT except it caused HPS.[3,12] Therefore, second allo-SCT should be performed as soon as possible after the diagnosis of graft failure. So far, our searched on previous cases which had cured from two times graft failure, found no report of multiple SCT with successful result. Cell number of graft, basic disease, disease stage before SCT, degree of HLA matching, blood type mismatch, cord blood, existing of HLA antibody, prevention of GVHD and conditioning regimen were considered to be the cause of graft failure. Especially, cord blood was known to cause high rate of graft failure, it is recognized at approximately 20% of the cases. Cord blood, HLA antibody, blood type mismatch, conditioning regimen and degree of HLA matching corresponded to our case.

There was no large cohort study describing therapeutic value of cord blood SCT for CML. Currently, there is one retrospective report of 86 cases from Japan Cord Blood bank.[5] The report showed that 2 year predicting event-free-survival (EFS) was 34±6%, leukemia-free-survival (LFS) was 38±6% and overall-survival (OS) was 53±6% after cord blood stem cell transplantation for CML. In addition, with two-year EFS for patients in chronic phase (CP), accelerated phase (AP) and blastic crisis (BC) was 52% (95% CI, 56-90%), 38% (95% CI, 17-84%) and 22% (95% CI, 10-48%) and with two-year OS for patients in CP, AP and BC was 71% (95% CI, 48-100%), 59% (95% CI, 37-94%) and 32% (95% CI, 20-55%), respectively. Cord blood could be acceptable as alternative donor for CML patients who need allo-SCT when well-matched related or unrelated donor was present. Otherwise, this report said that EFS makes a significant difference in nuclear cell count (NCC) and the age of the recipient. Event-free survival (EFS) of the case of NCC above 3.0×10^7/kg was 68% (95% CI, 48-96%) and below it was 20% (95% CI, 12-35%.). Its *p* value was at 0.0005. EFS significantly differed by age; under the age 15 was 74% (95% CI, 48-100%), between the age of 15 and 50 was 33% (95% CI, 22-49%) and overthe age of 50 was 15% (95% CI, 3-72%).

There were 7 cases of graft failure in the report, but the

Table 2: Method of Stem Cell Transplantation of 3 Times.

	1st	2nd	3rd
Donor source	Cord Blood	Cord Blood	Peripheral blood (sibling)
HLA match	5/8	4/8	8/8
Blood type	Major minor mismatch	Match	Match
NCC	3.71×10^6/Kg	2.13×10^6/Kg	7.26×10^7/Kg
CD34+ cell count	0.756×10^6/Kg	0.495×10^6/Kg	2.39×10^6/Kg
Conditioning regime	ivBU(12.8 mg/kg)×4/ CY(120 /m²)x2	Flu(30 mg/m²)X3	Flu(30 mg/m²)X3
GVHD prevention	CsA+Short term MTX	Tac+ MMF	CsA+Short term MTX
Result	Graft failure	Graft Failure	Engraftment

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relationship with NCC and age was not mentioned. In this case, age of our patient had a capability of a risk factor, although cord blood had enough NCC at the first SCT. Nowadays $CD34^+$ cell count showed a better relationship than NCC for graft engraftment. Takahashi et al reported that HLA antibody is related to WBC engraftment but the cases are not effected by that in case cord blood having 0.85×10^5/kg $CD34^+$ cells or more.[1-4] The first and the second SCT had 0.445×105/kg and 0.5×105/kg $CD34^+$ cells so $CD34^+$ cells count was suspected to be the reason of graft failure (Table 2). From the above factors, it is necessary for us to consider $CD34^+$ cells count in case recipient who has HLA antibody.

In recent years, cases of M3 type blast crisis of CML have been reported over 30 cases and 7 cases were treated by TKIs. Some cases showed the effect of chemotherapy, combine all-trans retinoic acid (ATRA) or arsenic trioxide. On the other hand, allo-SCT were performed in 3 cases and these cases showed therapeutic effect ranging from CCyR to MMR. Allo-SCT is considered to be an effective therapy for these cases.

In comparison of myeloablative conditioning regimen, formerly, busulfan and cyclophosphamide (BU-CY) had a weaker immune suppression than cyclophosphamide-total body irradiation (CY-TBI). Employment of BU-CY leads graft failure more frequently in both peroral BU-CY and CY-TBI to CML patients.[6] A retrospective cohort study showed intravenous BU-CY was superior to CY-TBI on OS of CML patients.[7,8] Based on these reports, conditioning regimen of first CBT was not suspected to be a factor of graft failure.[1-3] If the blood concentration of BU is below its effective concentration, frequency of graft failure would increase. Area under the blood concentration-time curve (AUC) of intravenous BU administration is more stable than preoral BU. Almost all cases fit in effective concentration 800-1500 μM-min though approximately 14% of the cases do not fit in.[9,10] There is a possibility that AUC is below the effective concentration because our case did not measure BU AUC.

We had no consensus on the conditioning regimen of re-transplantation for graft failure yet. There is a tendency that fludarabine based nonmyeloablative regimen is selected more. Our case was chosen 3 day fludarabine regimen. Recently, the one-day regimen which is combined fludarabine with alkylating agents, anti-human thymocyte immunoglobulin (ATG) or alemtuzumab has been reported and some cases could have been-treated by this regimen.[4,11]

Second CBT was considered to have an extremely high risk for graft failure since it was cord blood for the second time and its cell count was below 3.0×10^7/kg. Therefore, we had to select a donor as soon as possible. The HLA well-matched relative donor had been infected of hepatitis C and on medication for Grave's disease prior to the transplant, so we had selected her as an urgent donor. As leukocytopenia and neutropenia had continued long term, the patient understood the necessity of the third allo-SCT well. He was enthusiastic for infection prevention so that we could perform the third allo-SCT. Now, he is able to return to his occupation without any infection with hepatitis C. Moreover, his thyroid function is normal. It would be necessary for the patient to be carefully observed for further hepatitis and thyroid function.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Case Report

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Anarchic Deposits: The Intersection of Calciphylaxis and Hemochromatosis, A Case Report

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INTRODUCTION

Calciphylaxis is a rare disease occurring in usually obese women around the age of 40 years subject to hemodialysis. It can be prevented by controlling drug intake and biological markers. However, when installed it is irreversible and lethal. We report the case of a very young woman victim of non-observation with very deleterious consequence of calciphylaxis.

OBSERVATION

We report the case of a 26-year-old woman who was admitted to our hospital because of epistaxis and digital necrosis.

The patient was seen at our hospital 4 times since the age of 10. She had been diagnosed with Fanconi syndrome after a renal biopsy was done in 2001 for hypocalcemia, high PTH level and rachistism. Since then she had a hemodialysis 3 times a week. The patient reported many episodes of epistaxis, menorrhagia which were due to low platelets. Many investigations were done and a fibrotic medulla was diagnosed. Meanwhile, she received many platelet and red blood cells transfusions to recover from her severe anemia. Her last admission to this hospital was in February 2011 for severe hemorrhage after which she continued her medical treatment at a peripheral hospital.

Few months before her actual admission, the patient complained of a progressive dyspnea which was getting worse even on rest. She noted a loss of weight of 10 kg in 9 months and a loss of hearing with otorrhagia. She had as well digital necrosis with rapid progression and firm masses on both her right shoulder and right knee.

On presentation, the patient was very weak with inability to walk and active epistaxis. The distal parts of her 3rd and 4th fingers of her left hand as well as her 2nd, 3rd and 4th fingers of her right hand were necrotic and very painful (Figure 1). She had subcutaneous firm lesions with deformations of her upper limbs' articulations (Figure 2). She had a silver corneal arch with yellow corneal deposits (Figure 1). On auscultation she had normal vesicular murmur and normal cardiac sounds. Her pulses were very weak on both her upper and lower limbs. She had an hepatomegaly and a splenomegaly.

Her usual treatment was Moxonidine, Amlodipine, Ursodeoxycholic acid, Sevelamer, Alfacalcidol, Rabeprazole, Prednisolone, Erythropoetin, Naftidrofuryl, Sulodexide, Aspirine and weekly ferrous IV injections.

At first, we had to manage the epistaxis. The otolaryngology team described an anterior septal necrosis without evidence of telangiectasia and a chronic medial otitis which were the cause of the otorrhagia and epistaxis. A bilateral hemostatic packing with absorbable gela-

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Figure 1: Digital Necrosis on the Left and Silver Corneal Arch on the Right.

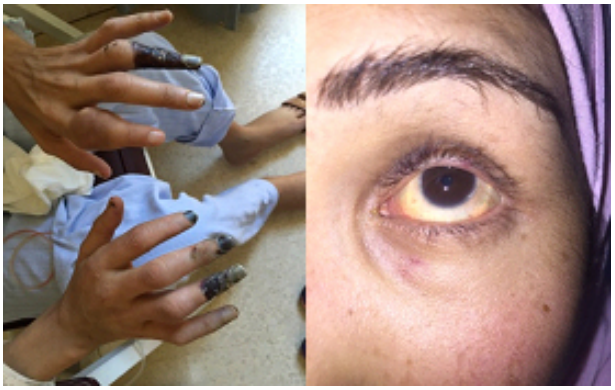
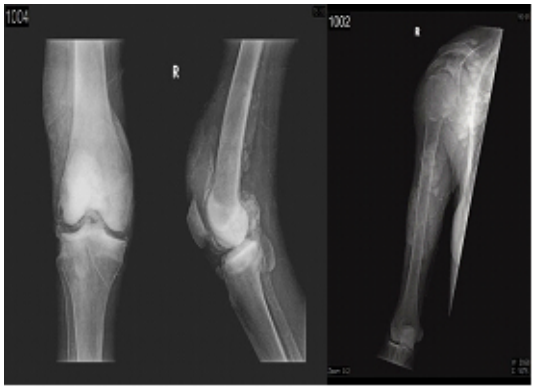


Figure 2: Subcutaneous Calcified Lesions.



tin foam was done and the bleeding stopped 2 days later. The hypothesis of vasculitis was considered. A total body scan was done without evidence of pulmonary vasculitis or adenopathies. The immune assay was negative as well as the purified protein derivative (PPD) skin test (Table 1). A bone marrow biopsy was done to rule out any malignancy in cause of the low platelets; it came back positive for iron deposits and fibrinous changes.

Concerning the digital necrosis, we first did radiography of the hands which showed calcified vessels and calcified subcutaneous lesions (Figure 3).

The arterial doppler of both the upper and the lower limbs showed an occlusion of the left radial artery, weak blood flow at the right cubital artery and bilateral distal arteriopathy in the lower limbs. She received daily doses of Prostavasine with small improvement and decrease of the pain. However, 2 days later she complained of pain again with progression of the digital lesions. The hypothesis of calciphylaxis was considered as we had ischemic lesions with arterial occlusion without signs of vasculitis and subcutaneous calcified lesions. Moreover an echography of her right knee was done and showed an intraarticular echogenic calcific sediment linked to another superficial sediment over the distal quadriceps. A fluid puncture was performed and got back sterile (Figure 4).

Her lab results were accurate with a secondary hyperparathyroidism with a high phosphocalcic product (5,95 $mmol^2/L^2$) (Table 1). The Alfacalcidol was stopped and the Cinacalcet started.

One week after her admission the patient was still unable to walk and was getting weaker. A cardiac ultrasound was then performed. A hypertrophic cardiomyopathy with suspicion of amyloid deposits and a severe diastolic dysfunction were found. An optimal cardiac treatment was impossible due to its side effects which involved more vasoconstriction. A salivary gland biopsy was performed to provide evidence for any amyloid deposits. It came back negative for amyloidosis but with signs of iron deposits. The hypothesis of secondary hemochromatosis was more evident as the results were out. We suggested a cardiac MRI and a hepatic MRI to rule it in; the cardiac MRI was negative for iron deposits but with some imaging limitations (Figure 6) while the hepatic MRI came back positive for iron sediments (Figure 5). We initiated the Deferasirox (Exjade) at that time.

Figure 3: Calcified Vessels, Calcified Lesions of the Left Index.

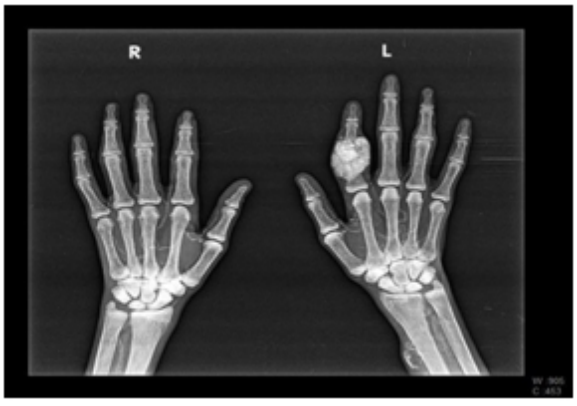


Figure 4: Knee Echography with the Liquid Removed.

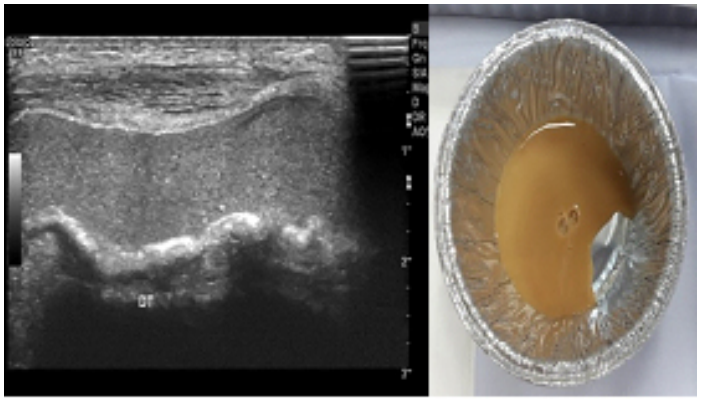


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Table 1: Laboratory Results.

Variable	Reference range, adults	Jan-15	June 2016, before admission	First admission	Second admission
Hematocrit (%)	36-46	35.50	32.50	38.90	36.50
Hemoglobin (g/dl)	12.0-16.0	11.90	10.30	13.20	12.00
White-cell count (per mm3)	4500-11000	7000.00	8100.00	9400.00	6700.00
Differential count (%)					
Neutrophils	40-70	68.00	77.00	79.00	75.00
Lymphocytes	22-44	19.00	16.00	15.00	17.00
Monocytes	4.0-11.0	12.00	6.00	5.00	
Eosinophils	0-8	1.00	1.00	1.00	
Basophils	0-3	0.00	0.00	0.00	
Platelet count (per mm3)	150000-400000	33000.00	25000.00	40000.00	40000.00
Mean corpuscular volume (um3)	80-100	94	97	90	
Erythrocyte count (per mm3)	4000000-5200000	3770000	3360000	4320000	
Erythrocyte sedimentation rate (mm/hr)	0-20			31	
Sodium (mmol/liter)	135-145	141	138	138	139
Potassium (mmol/liter)	3.4-4.8	3.61	3.62	3.5	3.6
Chloride (mmol/liter)	100-108	93	98	97	
Carbon dioxide (mmol/liter)	23-31.9	27	18	19	16
Glucose (mg/dl)	70-110			113.5	
Albumin (g/dl)	3.3-5.0			31	
Calcium (mg/dl)	8.6-10.8		11.86	12	11.4
Phosphore (mg/dl)	2.5-4.5		5.8	5.9	5.4
Urea nitrogen (mg/dl)	8.0-25.0	46.4	46	67	30.5
Creatinine (mg/dl)	0.60-1.50	2.49		6.1	3.1
Alkaline phosphatase (U/liter)	30-100		246	329	489
Aspartate aminotransferase (u/liter)	9.0-32.0	26		31	41
alanine aminotransferase (U/liter)	7.0-30.0	34	20	35	48
Lactate dehydrogenase (U/liter)	110-210				
C-reactive protein (mg/liter)	<8	73.6		22.6	103
Ferritine (ng/ml)	12-150			4720	
Transferrin (mg/dl)	200-350			176	
Total serum iron (µg/dL)	30-170			70.4	
Transferrin saturation (%)	20-50			33.2	
Anti-thrombine III (%)				95	
Lupus-like anticoagulant				(-)	
Proteine C (%)	70-130			120	
Proteine S (%)	55-140			93	
Prothrombin time (sec)	11.0-14.0	14		13.9	
aPTT (sec)	20-40	26		32	
Anti-B2 glycoprotein				(-)	
Ag HBs				(-)	
ANA				(-)	
C3 (mg/100ml)	90-180			122	
C4 (mg/100ml)	10.0-40.0			35.4	
DsDNA				(-)	
Ac HBc				(-)	
Ac HBs				(-)	
Ac HCV				(-)	
Ac HIV				(-)	
p-ANCA				(-)	
c-aNCA				(-)	
TSH (mlU/l)	0.5-5			4.6	
PTH (pg/ml)	<46			514	333
Vit D(25 OH) (ng/ml)	5.0-75			5.3	

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Figure 5: Hepatic MRI T2*.

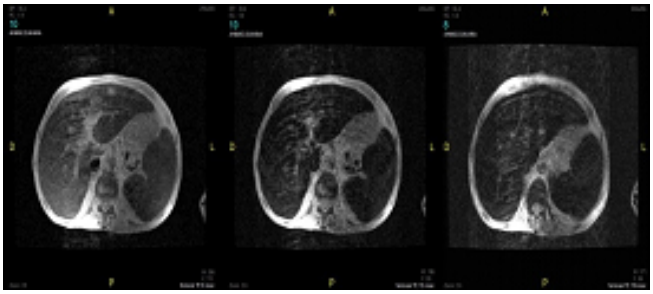
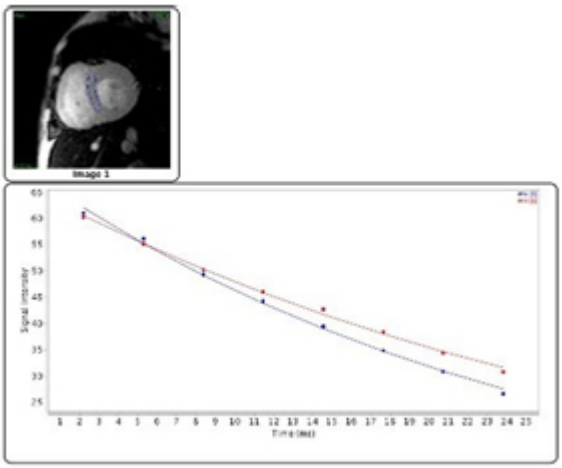


Figure 6: Cardiac MRI- The Mean T2* was 29.9±0.7 ms. It is Superior to the Reference Range of 20 ms set for Machines of 1.5 Tesla.



The patient left home with her new treatments and was denied any blood transfusion. She spent 2 weeks at home and came back with fever and severe weakness. On examination the digital necrosis were surrounded by areas of redness and purulent secretions. The subcutaneous nodules were less firm and some had decreased in size.

An amputation of her fingers previously suggested and rejected by her family was now the only choice. The culture was positive for *E.Coli ESBL* and *E.Cloacae*. Moreover her right knee was red, swollen and warm; another puncture was performed but the culture was sterile. She received 2 weeks of Ertapenem. During her hospital stay we decided to remove her parathyroid glands as the phosphocalcic product was still high even though she was taking the Cinacalcet. An incomplete parathyroidectomy was done because of anesthetic complications. The PTH level fell from 333 pg/ml to 121 pg/ml. Our patient left the hospital and came back one month later.

During this admission, the patient reported pain and severe weakness with insomnia and anorexia. She was given fluids and the parathyroidectomy was completed. She was in a severely depressive mood and decided to go back home as she was not getting any better.

She died 2 hours after she reached her home.

DISCUSSION

Our patient presented unfortunately both calciphylaxis and secondary hemochromatosis.

In fact, calciphylaxis, also called calcific uraemic arteriolopathy, is a rare disease occurring mainly in hemodialysis patients. It is characterized by medial calcification of the small arteries and ischemia of the subcutaneous tissue, often leading to necrosis of subcutaneous fat and skin. It may not be as rare as it seems to be because we believe that the actual incidence is of 1% per year.[1] Consequently the search for risk factors for calciphylaxis is crucial to prevent irreversible lesions. Among the risk factors described in the International Journal of Dermatology in 2007 (Table 2) our patient had too much which confirms the hypothesis of iatrogenicity.

Moreover, this young patient had for many years ferrous injections plus transfusions which concluded to secondary hemochromatosis. One study in 1986 suggested the possibility of iron overload as a challenger for systemic calciphylaxis.[2]

Table 2: Risk Factors for Calciphylaxis.[9]

Medications	Patient factors	Biochemical
Corticosteroids	Renal failure	Hypoalbuminemia
Vitamin D	Female	Hypercalcemia
Calcium salts	Caucasian	hyperphosphatemia
Immunosuppressants	Local trauma	High serum alkaline phosphatase
Iron salts	Obesity	High plasma parathyroid hormone
Insulin injections	Diabetes mellitus	High serum $Ca^{2+} \times PO_4$ product
Calcium-based phosphate binders	Malnutrition hypotension	Protien C and S deficiency Vitamin D excess

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Despite intensive combined therapies, the prognosis of both calciphylaxis and secondary hemochromatosis remains poor especially in the presence of necrotic lesions.

Many studies have emphasized the crucial role of a multidisciplinary therapeutic approach focusing on the correction of the underlying abnormalities of the calcium and phosphorus plasma concentrations in prevention for irreversible necrotic lesions. In fact, parathyroidectomy as well as the use of calcimimetics are actually the most recommended therapies for calciphylaxis. Parathyroidectomy must be done when parathyroid hormone (PTH) is higher than 500 pg/ml and when the $Ca^{2+}xPO_4$ product is refractory to drugs. However, in our patient it was of limited efficacy. Other therapies have been suggested including hyperbaric oxygen,[3] intravenous sodium thiosulphat,[4] steroids[5] and bisphosphonates,[6] but their efficacy is based on scant evidence. On the other hand, calcimimetics increase the sensitivity of the calcium-sensing receptor to calcium decreasing the parathyroid hormone as a consequence. One study reported a very good response to Cinacalect in a patient with calciphylaxis and contraindication for parathyroidectomy,[7] which was not the case in our patient. This observation may be due to the advanced lesions in our patient associated with complete irreversibility.

Secondary hemochromatosis remains difficult to treat as the best treatment is phlebotomy which cannot be done to severe anemic patients who are usually subject to this condition. Iron chelators offer different means of achieving a negative iron balance and tolerable iron concentrations in body tissues. Deferasirox (Exjade) was probably the best choice for our patient because of its excretion in the biliary tract and its oral intake once daily. Moreover, a study published in 2015 reported a significant improvement of iron metabolism in hemodialysis patients with iron overload and an acceptable frequency of adverse effects.[8] Our patient had a good tolerance but she was consistently weak and we did not look for biological improvement of the transferrin saturation. We believe that iron deposits were difficult to remove in the context of severe weakness and calciphylaxis.

CONCLUSION

Our case describes the deleterious effects that some of our practice as doctors can induce. Prevention medicine is not only about vaccinations but also about considering side effects of drugs. Calciphylaxis remains an important diagnosis to consider in patients with renal failure, with the aim of prevention and early therapy to reduce the associated morbidity and mortality. The astute physician should focus on the prevention and reduction of predisposing factors in cohorts at risk. Secondary hemochromatosis is an important side effect of multiple transfusions and ferrous injection. Physicians must limit unneeded therapies.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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