A Case of Malignant Hypertension and Scleroderma after Cosmetic Surgery

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A 44-year-old woman with scleroderma-like skin lesions and malignant hypertension following mammoplasty is reported. Sclerotic change is an unusual finding for ordinary finding progressive systemic sclerosis. On admission, she had severe high-renin hypertension and progressive renal failure, suggesting scleroderma renal crisis. With intensive treatment for hypertension including angiotensin-converting enzyme inhibitor, the blood pressure was well controlled. It was then suggested that she had malignant hypertension due to scleroderma after silicone injection, or the so-called human adjuvant disease after cosmetic surgery.

Key words: Silicone, Adjuvant disease, Mammoplasty, Renal failure

In 1964, Miyoshi et al reported two patients with undifferentiated connective tissue disease who had undergone augmentation mammoplasty using either paraffin or silicone (1). They suggested that this morbidity was the result of prolonged exposure to the injected substances through the adjuvant effect, as the features were similar to those in adjuvant arthritis in rats treated with paraffin (2, 3). Consequently, it has been referred to as human adjuvant disease. There are more than fifty reported cases presenting with connective tissue diseases after cosmetic surgery (4–9). In these cases, scleroderma was the most characteristic feature. Kumagai et al reported that 12 out of 46 patients with connective tissue diseases after cosmetic surgery had scleroderma (5). Although patients with progressive systemic sclerosis (PSS) are often complicated with renal involvement and malignant hypertension (scleroderma renal crisis), very few patients with human adjuvant disease are complicated with malignant hypertension (10).

We recently encountered a patient with malignant hypertension and scleroderma following mammoplasty with direct injection of silicone. This scleroderma renal crisis-like status could be improved by control of the blood pressure with intensive treatment of hypertension.

CASE REPORT

A 44-year-old Japanese woman was admitted to our hospital because of severe hypertension, general malaise, and blurred vision.

There was a history of autoimmune diseases in her family members; her father suffered from rheumatoid arthritis, mother, Hashimoto's disease, and brother, Graves’ disease.

Twenty-five yrs previously, she underwent augmented mammoplasty with silicone injected directly into the bilateral breasts. She had been troubled with Raynaud’s phenomenon for the past three yrs. Two wks before admission, she noticed general malaise after exposure to the sun in August, and visited her family physician. Severe hypertension (blood pressure 220/160 mmHg) and mild hypokalemia (serum potassium 3.4 mEq/l) was noticed. Treatment with diuretics and angiotensin

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converting enzyme (ACE) inhibitor failed to lower her blood pressure. In order to further investigate this refractory hypertension, the patient was admitted to our hospital on September 1, 1988.

Physical examination on admission revealed an exhausted and lethargy patient with severe high blood pressure (230/150 mmHg). Marked differences in blood pressure were not detected among upper and lower extremities. Fundoscopy revealed waxy spots, microhemorrhages and bilateral papilledema, corresponding to Keith-Wegener grade 4. Typical sclerodermaous changes such as thick and tight skin with pigmentation and depigmentation were found in the face, forearms, fingers, and anterior chest. These skin lesions were more prominent in the anterior chest than in the extremities. The masses of injected silicone were palpated in the bilateral breasts. Fine crackles were heard over the bilateral lower lungs. There were 4th sound and a grade 2 holosystolic murmur on the apex. Abdominal bruit was not heard.

Laboratory findings on admission were as follows: Serum creatinine 2.6 mg/dl, blood urea nitrogen 44 mg/dl, serum sodium 133 mEq/l, potassium 3.9 mEq/l, and chloride 92 mEq/l. Red cell count was $365 \times 10^4$/mm$^3$, hemoglobin 10.5 g/dl, and white blood cell count 6,700/mm$^3$ with a normal differential. Serum lactic dehydrogenase and amylase were increased to 919 IU/l (208–398 IU/l) and 772 IU/l (82–243 IU/l), respectively (normal values in parentheses). Plasma renin activity was increased to 40.6 ng/ml/h, and plasma aldosterone concentration to 36.9 ng/dl. Urinalysis showed a 1+ test for protein and the sediment was remarkable. Serological examination revealed an erythrocyte sedimentation rate of 72 mm/h, a positive rate for rheumatoid factor, and serum IgG of 3,416 mg/dl. Antinuclear antibody was positive at 1:320 with nucleolar pattern. Both anti Scl-70 antibody and anticientromere antibody were negative.

Mild cardiomegaly and Kerley's B line were present on chest X-ray. The electrocardiogram showed a normal sinus rhythm of 96 beats/min and left axis deviation. The T wave was inverted in leads V1–V4. Ultrasonic cardiogram revealed mild left ventricular hypertrophy and moderately impaired left ventricular function. Skin biopsy from the forearms and anterior chest wall revealed thickening of collagen bundles in the upper dermis, epidermal hyperplasia with orthokeratosis, and lymphoid and mononuclear cell infiltration of the interstitial subcutaneous tissue. The findings were compatible with PSS (Fig. 1).

The clinical course after admission is shown in Fig. 2. Because the patient had severe hypertension, Keith-Wegener grade 4 changes in the optic fundi, heart failure and rapidly progressive renal failure, the morbidity was diagnosed as malignant hypertension. We immediately started to treat her with an intensive combination therapy of ACE inhibitor (captopril 50 mg/day), calcium antagonist (nifedipine 60 mg/day) and alpha-receptor blocker (prazosin 1.0 mg/day). Subsequently, ACE inhibitor was changed to enalapril 20 mg/day. Then, the blood pressure responded and was decreased to 130–160/80–90 mmHg on day 12. The serum creatinine increased to 6.3 mg/dl on day 16, but declined thereafter gradually. Serum lactic dehydrogenase level was also normalized within two wks and serum amylase decreased gradually. On day 80, she was discharged with a serum creatinine level of 4.5 mg/dl and blood pressure of 146/88.
Malignant Hypertension and Scleroderma

Antihypertensive (mg/day)
ACE Inhibitor
captopril enalapril
nifedipine prazosin

BP (mmHg)
DAILY
80 100 120 140 160 180 200 220

Cr (mg/dl)
DAILY
0 1 2 3 4 5 6

PRA (ng/ml/hr)
DAILY
0 40.6 30.8 24.2

Fig. 2. Clinical course.
ACE, angiotensin converting enzyme; BP, blood pressure;
Cr, serum creatinine; PRA, plasma renin activity

mmHg but without any improvement in her sclero-
derma. Serum lactic dehydrogenase and amylase
levels were 391 IU/I and 285 IU/I, respectively.

Five months later, she was well on a regimen of
lower doses of antihypertensive drugs (enalapril 10
mg/day and nifedipine 20 mg/day) with a blood
pressure of 120/80 mmHg and serum creatinine level
of 2.5 mg/dl.

DISCUSSION

A patient with human adjuvant disease after
mammoplasty, presenting with scleroderma-like skin
lesions and malignant hypertension is reported. This
patient had scleroderma in the fingers, forearms,
anterior chest, and face. It was hidebound and
fibrotic, and not atrophic nor edematous. The skin
changes were more prominent in the anterior chest
than in the extremities. Although patients with
diffuse scleroderma can have widespread hidebound
skin, the distribution of sclerotic changes in the skin
was untypical of PSS. In the serological study, as
well, specific markers of PSS such as anti Scl-70
antibody and anticentromere antibody were
negative. Since the patient received mammoplasty
with silicone injected directly into the breasts 25
yrs ago, the skin lesion is considered to represent
scleroderma following cosmetic surgery, a
characteristic of the so-called human adjuvant
disease (4–9). It is of interest that she had a
positive family history of various autoimmune
diseases; this genetic trend might have been con-
tributory to the development of her scleroderma
following cosmetic surgery.

More than fifty cases of human adjuvant disease
presenting with connective tissue diseases after
cosmetic surgery have been reported; the most
frequent type of the connective tissue disease was
scleroderma. The incidence of scleroderma was
statistically higher in patients receiving cosmetic
surgery, when compared with the expected value for
all women without cosmetic surgery. Consequently,
the adjuvant effect of silicone has been invoked as
the primary factor in the development of sclero-
derma (5). In some cases scleroderma was improved
by removal of the injected material (1, 11). Here no
attempt was made to remove the foreign substance,
because it was injected directly into the breasts.

The possible sequence of events in this patient is
thought to be the following: scleroderma was in-
duced by the adjuvant effect of silicone used at
mammoplasty, resulting in the development of
malignant hypertension possibly by narrowing the
lumen of renal arterioles. In addition, strain and
dehydration served as aggravating factors.

There are very few cases of malignant hyperten-
sion and scleroderma following cosmetic surgery
(10), although patients with PSS often have
malignant hypertension, “scleroderma renal crisis”
(12, 13). The present patient seems to be in a
scleroderma renal crisis-like status, because she had
sclerodermatous skin lesions and severe high-renin
hypertension with progressive renal failure. Her
condition virtually fulfilled the diagnostic criterion
for scleroderma renal crisis advocated by Traub et
al (12) or Steen et al (13). Since neither renal biopsy
nor renal artery angiography was performed because
of severe renal failure and extremely high blood
pressure, we were not able to clarify precisely
whether or not this was in scleroderma renal crisis.

Based on the increased serum lactic dehydro-
genase level on admission, it can not be attributed to microangiopathic hemolytic anemia which is the common characteristic of malignant hypertension, since she had a normal serum bilirubin level and no red cell fragmentation. However, we should consider the involvement of some organs due to the extremely high blood pressure since the serum lactic dehydrogenase level was normalized after the reduction of blood pressure. Furthermore, it should be noted that the serum amylase level on admission was markedly increased. The pancreas is one of the organs most commonly affected with the necrotizing lesions of malignant hypertension (14, 15). The serum concentration of amylase gradually decreased with normalization of blood pressure but the level was still slightly high, possibly due to renal insufficiency.

Generally, patients with PSS and malignant hypertension exhibit an ominous prognosis because of poor control of blood pressure. Recently, several investigators demonstrated that ACE inhibitors could improve or arrest scleroderma renal crisis (16–21). In the present patient with severe high-renin hypertension, the intensive antihypertensive treatment with ACE inhibitor, combined with a calcium antagonist and alpha-receptor blocker, was successful to improve renal failure with the normalization of blood pressure. Thus, ACE inhibitors might be an efficacious adjunct for the therapy of malignant hypertension, since the increased renin-angiotensin system plays an important role in the development of malignant hypertension and the resultant renal failure in scleroderma.

REFERENCES

Dihydroergotamine raises the level of serum growth hormone

To the editor: A patient with a high serum growth hormone (GH) level which seemed to be induced by dihydroergotamine (DHE) is described. DHE acts as a partial alpha-adrenergic agonist as well as a central alpha-adrenergic antagonist (1). It has been widely used to treat migraine and orthostatic hypotension. A central alpha-adrenergic agonist is known as a factor of increasing GH secretion. However, it has not been reported that DHE raises the level of GH.

Report of a case - A 30-year-old male was referred to our hospital because of orthostatic hypotension. The DHE had been administered for about 3 yr. Because he was tall on examination, we measured serum GH level, which showed high serum level (15.0 ng/ml; N< 5.0 ng/ml). However, brain computed tomographic scan could not detect the pituitary tumor or other brain disease. In addition, the level of GH decreased from 17 ng/ml to 0.3 ng/ml after administration of 75 g glucose, which is known as one of the screening tests for acromegaly (2). The serum GH level returned to normal level within 2 days after administration of DHE was discontinued. Therefore, we suspected that DHE raised the serum GH level. To confirm this GH raising effect, we made a DHE loading test. The serum was taken before and after taking 1 mg of DHE. The GH level increased like this: 0' 0.9 ng/ml, 30' 0.6 ng/ml, 60' 1.9 ng/ml, 90' 17.0 ng/ml, 120' 14.0 ng/ml, 150' 11 ng/ml, 180' 3.5 ng/ml. Serum levels of glucose and fatty acids were not changed. From these results, it is clear that DHE affected the serum GH level in our patient.

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Bucillamine may induce Myasthenia Gravis

To the editor: D-penicillamine (D-PC), one of the sulfhydryl compounds, is known to induce myasthenia gravis (MG) in patients with rheumatoid arthritis (RA) (1). Other sulfhydryl compounds, such as pyritinol (2), captopril (3) and tiopronin (4), have also been reported as possible candidates which induce MG in patients with RA. We report here a patient with RA who developed MG during treatment with a new sulfhydryl compound, bucillamine (Rimatil® ). This drug has been used as a disease modifying anti-rheumatic drug in Japan since 1987. This is the first report concerning the possible association of this drug and MG.

The patient was a 36-year-old female with an 8-yr history of RA. From January 21, 1988, she had received D-PC (100 mg/day), and her rheumatic symptoms improved. However, because of the side effect of decreased serum immunoglobulin A, D-PC was discontinued on April 4, 1988. From May 12, 1988, she was given 100 mg/day of bucillamine, and her rheumatic symptoms improved; she received this medication every 2 days from September 1, 1988. In July 1989, she started to feel weakness of extremities. After about 2 wk, she had diplopia, blepharoptosis and weakness of upper limbs which worsened in the evening. She decided to stop taking bucillamine on August 2, 1989 and was admitted to our hospital three days later. She was diagnosed to have MG, based on the clinical symptoms, a 15% decrement in response to repetitive nerve stimulation on the hypothenar muscle, positive tensile tests, and high levels of serum anti-acetylcholine receptor (Ach R) antibodies (89 nmol/l; N < 0.5 nmol/l). Hyperplasia of the thymus was detected on magnetic resonance imaging. Her myasthenic symptoms were improved slightly after discontinuation of bucillamine but she required pyridostigmine bromide (120 mg/day) treatment. Since October 5, 1989, she has undergone plasmapheresis using an IM-T350 immunoabsorbent column 6 times. She showed complete disappearance of myasthenic symptoms after plasmapheresis, and did not need anticholinergic drugs. However she showed myasthenic symptoms again after discharge. So she was treated again by plasmapheresis, steroid pulse therapy and an immunosuppressive agent (Azathioprine). Her clinical symptoms improved but her symptoms and high level of anti-AchR antibody were still present.

It can be suggested that the MG in this patient was associated with the bucillamine treatment, because of the clinical course; the onset of MG occurred during the treatment with bucillamine, and slight, transient improvement of symptoms was seen after discontinuation of the drug.

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