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Case Report

Successful Salvage Therapy of Late-onset Arterial Disorders due to Recurrent Vasospasms Following Free Flap Transfer under the IL-6 and TNF-α Signaling-downregulated Environment: A Case Report

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Abstract

A 77-year-old woman who had been taking iguratimod and sarilumab for rheumatoid arthritis for 3 months had gas gangrene. After hospitalization, she underwent two debridement surgeries, one drainage procedure, and a free latissimus dorsi musculocutaneous flap transfer for the resulting tissue defect on the oral cavity through the temple. Following the free flap surgery, she experienced flap ischemia, possibly caused by the vasospasms of the intraflap and recipient arteries on postoperative days 5 and 6. These immunomodulating drugs might cause vasospasms by downregulating the interleukin-6 and/or tumor necrosis factor-α signaling pathway(s).

Recent developments in antirheumatic drug therapy have increased the chances of performing microvascular surgeries on patients with inhibited immune systems, and this trend will continue or will be reinforced in the future. Close monitoring of the biochemical and clinical status of the microvascular environment is necessary.

Keywords

iguratimod, IL-6, sarilumab, TNF-α, vasospasms

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Introduction

Free flap surgery is routinely performed in patients who receive compound drugs, such as steroids and immunosuppressive agents, i.e., cyclophosphamide and azathioprine that target various immune reactions. Steroids interfere with nuclear transcription control and immunosuppressants inhibit DNA replication, leading to generalized immunosuppression among patients. However, currently, microsurgeons have little experience with free flap surgery under conditions where each cytokine signaling pathway, such as the tumor necrosis factor (TNF)-α pathway or the interleukin (IL)-6/IL-12/IL-17 pathway, is blocked by some biological agent(s).

We report here the case of a patient with rheumatoid arthritis who had been treated with an anti-IL-6 receptor antibody drug and disease-modifying antirheumatic drug (DMARD) and had frequent arterial vasospasms after free flap surgery for severe soft tissue infection.

Case Report

The patient was a 77-year-old woman with a chief complaint of swelling of the left face.

Past history

She was diagnosed with rheumatoid arthritis, takotsubo cardiomyopathy, and dementia. Her regular medications included celecoxib (Celecox®: nonsteroidal anti-inflammatory drug; COX-2-specific inhibitor), eldecalcitol (Edirol®: vitamin D analog), iguratimod (Carelam®: DMARD), and sarilumab (Kevzara®: monoclonal antibody drug against anti-IL-6 receptor α subunit).

Present history of illness

She was diagnosed with rheumatoid arthritis 17 years ago and was originally treated with methotrexate (Rheumatrex®: 5-aminoimidazole-4-carboxamide ribotide transformylase inhibitor). Two years ago before the present hospitalization, methotrexate was discontinued because of pancytopenia and rheumatoid arthritis was treated with celecoxib and igurati-

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mod. One year before hospitalization, the rheumatoid factor levels increased. Therefore, sarilumab was included with her regular medication 3 months before hospitalization. Three days before hospitalization, her left face began swelling. On the day before emergency hospitalization, the swelling worsened and she developed trismus. Because she experienced difficulty in eating, she requested an ambulance and was transported to our hospital.

Physical findings on arrival

Her left face, particularly the left cheek, had swollen, and local heat and tenderness were observed. Friction rub was recognized on the left temporal region. Many of the maxillary teeth appeared to have caries, and foul-smelling pus discharge was noted around the maxillary gingivae.

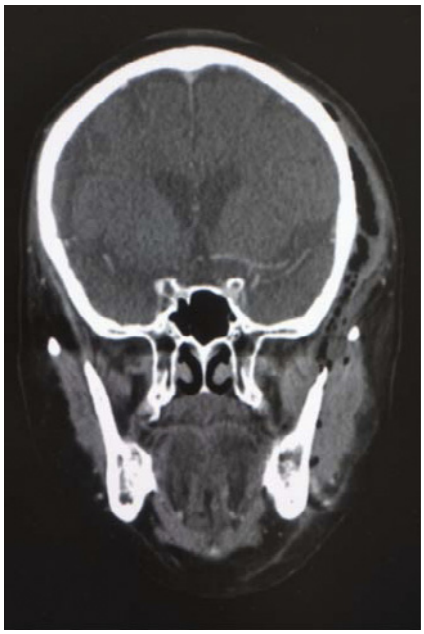

Figure 1. Plain head computed tomography finding on admission.
A radiolucent gas pattern was observed in the soft tissue layer from the left face to the temporal region.

Radiological findings

Computed tomography (CT) revealed radiolucent gas patterns in the soft tissue layer from the left face to the temporal region (**Figure 1**).

The laboratory findings on admission are shown in **Figure 2**.

Bacterial culture findings

The culture of the samples from the necrotic tissue of the temporal muscle revealed *Peptococcus* species 3+, *Prevotella* species 1+, *Acidaminococcus intestini* 1+, and *Staphylococcus caprae* (β-lactamase +) few.

Prognosis

On the basis of the findings of the plain CT and blood tests, we suspected that gas gangrene had developed under the immunosuppressive state, which was potentially caused by IL-6/TNF-α signal transduction blockade. The patient immediately underwent emergency debridement of the left temporal abscess under local anesthesia by emergency physicians. In addition, all drugs used before admission were discontinued on admission.

On day 11 of hospitalization, swelling and redness appeared on the left cheek, suggesting a subcutaneous abscess, and plastic surgeons were consulted for the first time (**Figure 3**). Under local anesthesia, the abscess was incised for drainage, and then, pus discharge was observed. A fistula was found to extend from the mandibular bone to the left temporal region subcutaneously.

After the episodic occurrence of sepsis on day 22 and the

	On admission	7 days before flap surgery	The day before flap surgery	The next day of flap surgery	3 days after flap surgery	6 days after flap surgery	9 days after flap surgery
AST	26	20	16	18	21	25	25
ALT	14	8	5	7	8	10	9
BUN	31	17	16	14	11	10	9
Cre	0.99	0.77	0.71	0.7	0.62	0.66	0.54
Na	137	139	136	140	140	139	134
K	3.8	3.4	3.3	3.6	3.3	3.4	4.1
Cl	102	101	99	105	101	103	99
CRP	32.04	3.05	1.91	7.09	12.74	5.15	5.43
WBC	8600	7600	5800	7600	5600	5600	5400
Hb	13.9	9.4	7.9	7.2	9.8	8.4	8.5
Ht	41.4	28.4	23.4	21.2	29.2	24.9	25.1

2 units of concentrated red cells were transfused

After the first reoperation

Figure 2. Perioperative laboratory data.

recovery from it, a second debridement was performed on day 27 under general anesthesia by an otolaryngologist over a wide range of subcutaneous tissues of the left temporal region and cheek (**Figure 4**). The remaining necrotic tissue of the temporal muscle and the granulation tissue formed on the surface of the medial pterygoid muscle were removed, and consequently, a tissue defect occurred from the left cheek mucosa, through the subcutaneous tissue of the cheek, and up to the temporal region.

On day 67, plastic surgeons performed a free latissimus dorsi musculocutaneous flap transfer surgery for tissue defects (**Figure 5**). A reduced latissimus dorsi muscle flap with the skin island was harvested with thoracodorsal vessels as vascular pedicles, and the serratus anterior branch was ligated. The thoracodorsal vein and artery were anastomosed in an end-to-end manner under a microscope to the facial vein and artery, respectively.

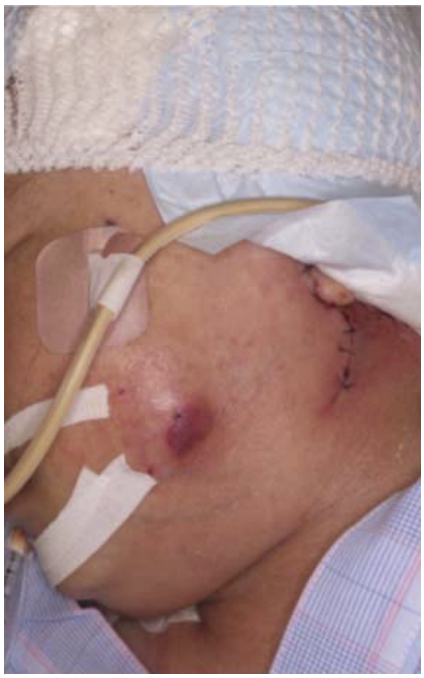

Figure 3. On day 11 after hospitalization, when the plastic surgeons were first consulted with about the patient, subcutaneous abscess was noted on the left cheek.

On postoperative days 5 and 6 after free flap surgery, ischemic signs were observed (**Figure 6**), and in each case, emergency reoperation was performed to rescue the flap. In both cases, no arterial thrombus was found at the vascular anastomosis site and no kinking or twisting of the vascular pedicle was observed. During the reoperation on postoperative day 5, when the arterial anastomosis site was cut off, poor arterial ejection from the recipient artery was observed. This did not improve even with the local administration of papaverine hydrochloride. Therefore, the flap artery was reanastomosed to a more proximal facial artery, where good arterial blood ejection was confirmed. However, the skin flap color tone was still poor and the flush back was weak. Suspecting vasospasms in intraflap arteries, we injected papaverine hydrochloride into the flap through the flap artery, and after several minutes, the color tone of the skin flap recovered rapidly and its flush back improved. During the second reoperation on postoperative day 6, we found poor pulsation of the recipient facial artery on the arterial anastomosis site, which was papaverine hydrochloride-resistant. This time suspecting recipient artery vasospasms, we created a bypass of arterial blood inflow from the left superior thyroid artery to the serratus anterior branch of the thoracodorsal artery using a venous graft. After that, the flap blood flow stabilized and the flap fully survived (**Figure 7**).

The patient was discharged on postoperative day 35 (day 102 after admission) after the skin and mucosal defect wounds were completely cured.

The clinical course until 1 year after discharge was almost uneventful.

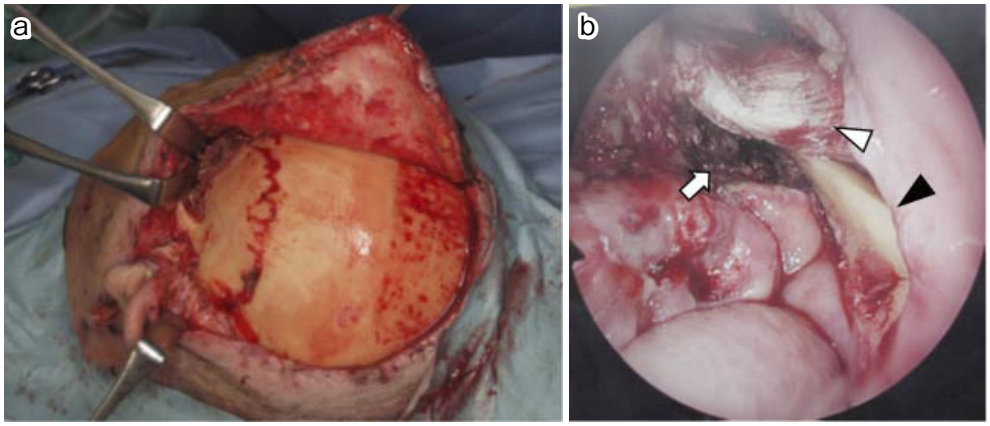

Figure 4. Intraoperative findings at the second debridement surgery. (a) The left temporoparietal region was exposed from the hemicoronal incision. The necrotic left temporal muscle was found under the zygomatic arch. (b) Endoscopic view of the submucosal layer beneath the spontaneously perforated left buccal mucosa observed through the oral aperture. The mandibular bone (▶) and masseter muscle (▷) were exposed, and granulation tissue (⇨) was observed on the medial pterygoid muscle.

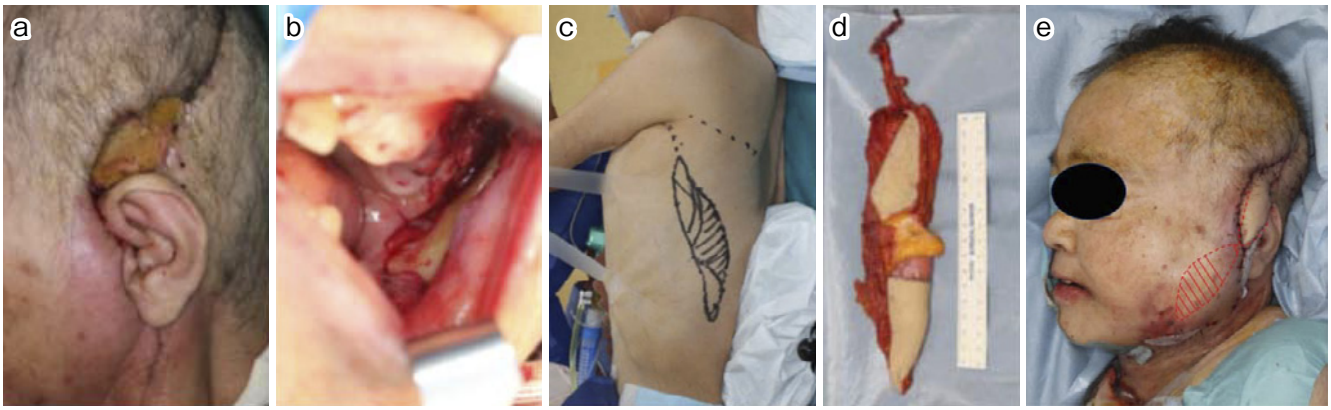

Figure 5. Free latissimus dorsi musculocutaneous flap (muscle-sparing) transfer was performed for the defect wounds on the left temporal region and left buccal mucosa. (a), (b) Skin and mucosal defect. (c), (d) Harvest of the latissimus dorsi musculocutaneous flap. The central portion of the skin island was denuded (black-shaded area on the panel c). (e) The flap was set in the recipient site with its central portion twisted by 180° so that the proximal skin island (red-shaded area) was facing the oral cavity, and the distal skin island (surrounded by dotted line) was facing toward the preauricular to the temporal region.

Discussion

An increasing number of patients with chronic inflammatory diseases, including rheumatoid arthritis, are treated with biological products such as antibody drugs, which intervene in certain immune signal pathway(s), i.e., anti-TNF monoclonal antibody or anti-TNF receptor monoclonal antibody. Although the therapeutic effect of these biological products is generally dominant, their side effects on the cardiovascular system are still not fully understood[1].

In this case, two types of immunomodulating drugs (iguratimod and sarilumab) that inhibit or block the IL-6 signaling pathway were administered for the treatment of rheumatoid arthritis. The product datasheets describe that both drugs have a risk of inducing infection as a side effect. *Peptococcus* species (oral resident bacteria) were bacteriologically detected from a specimen taken from the temporal muscle necrotic tissue. The bacterial species most probably invaded from an oral mucosal wound or periodontal lesions and caused gas gangrene of the left face and temporal region, particularly with the inhibition of the IL-6 immunological signaling pathway.

Although the infection was successfully controlled by discontinuing the immunomodulating drugs, surgical debridement of the infected tissue, and intravenous antibiotic therapy, flap ischemia occurred repeatedly on days 5 and 6 after the free latissimus dorsi musculocutaneous flap was transferred for skin/mucosal defect wounds. Arterial ischemia usually occurs during or shortly after microsurgery, but it occurred late after the surgery in this case. A systematic review by Shen et al.[2] showed that 0% of vascular compromise was successfully salvaged beyond day 5 after the initial free flap surgery. In the present case, we have successfully rescued the transferred flap through two cycles of arterial disorders and salvage interventions.

Late-onset arterial disorders are possibly associated with a decreased circulating blood volume, low blood pressure, high-grade performance status (PS) scale, and arterial vasospasms. In the present case, a decrease in circulating plasma volume was considered less probable because there was little fluctuation in the blood urea nitrogen and blood creatinine values during the perioperative period and vital signs, including blood pressure, were stable. A high-grade PS scale, which represents the patient's low daily functioning ability, could contribute to the postoperative vascular complications. However, at the first reoperation, rapid recovery of the skin flap color tone was observed shortly after the surgeons injected papaverine hydrochloride intra-arterially into the flap. Thus, arterial vasospasms had highly likely occurred in the intraflap arteries. In addition, in both the first and second reoperations, papaverine-resistant arterial vasospasms could have caused facial artery ejection failure, as far as we can retrospectively judge from the intraoperative findings and no history of low blood pressure recorded postoperatively. The mechanisms of arterial vasospasm during free flap surgery have not yet been fully elucidated, and some of them would be resistant to the pharmacological action of papaverine hydrochloride. Therefore, we suspected an unknown side effect of iguratimod and/or sarilumab used for rheumatoid arthritis treatment on the microvascular system in this specific case of unusual postsurgical course, the late-onset, repeated, and partly papaverine-resistant vasospasms. As far as we reviewed literatures, there have been two case reports of reversible cerebral vasoconstriction syndrome (RCVS), vasospastic narrowing of cerebral arteries, which occurred in patients with collagen disease after the IL-6 receptor or TNF-α receptor was pharmacologically blocked[3,4]. Their RCVS onsets were 3 months after the start of tocilizumab, another anti-IL-6 receptor antibody drug, and 4 h after the restart of etanercept, the soluble binding domain of the human TNF receptor, respectively.

The mechanism of action of iguratimod is to suppress or block the activation of the transcription factor nuclear factor κB and resultantly suppress the production of immunoglobulins (IgG and IgM) by B cells and production of inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8, and monocyte

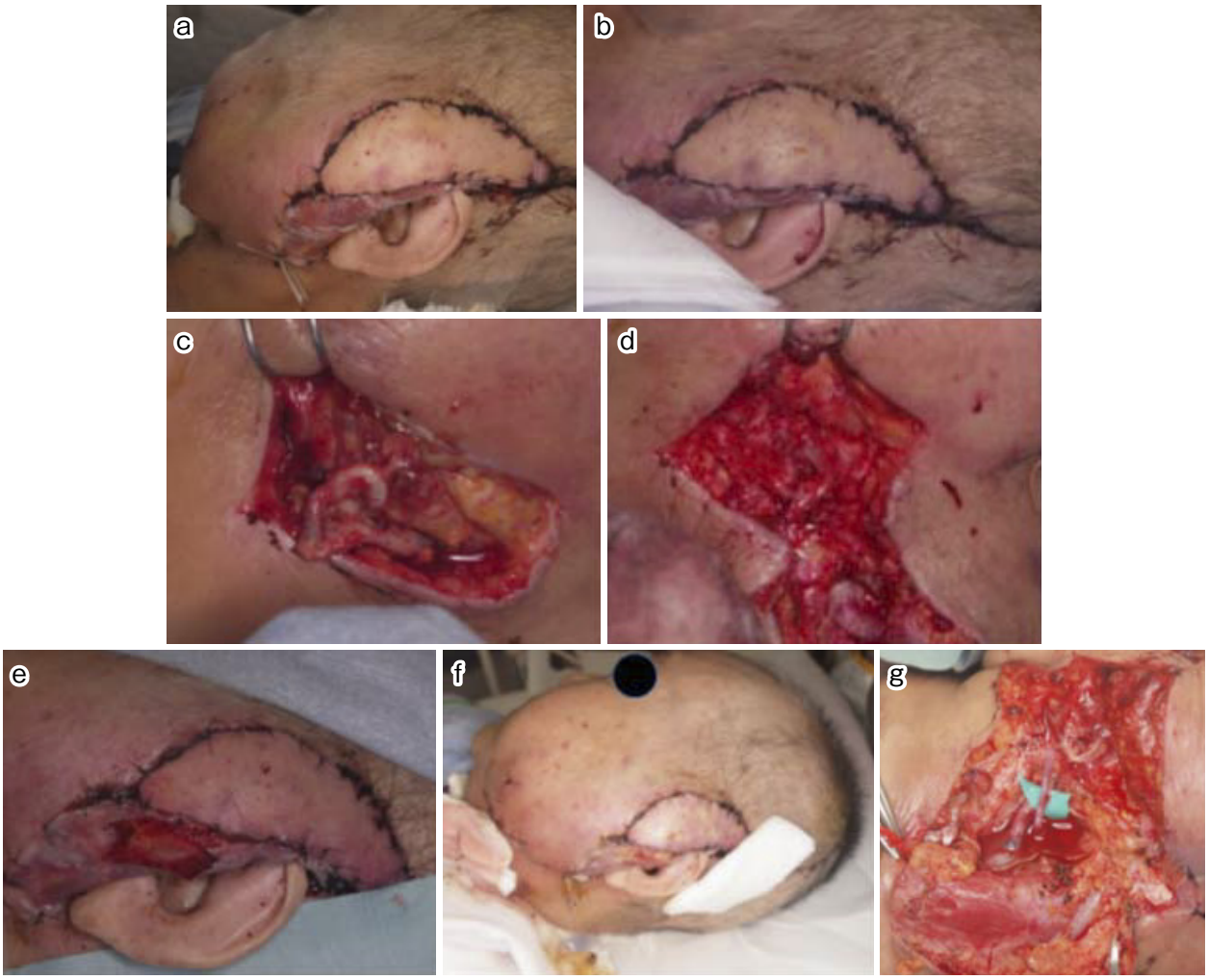

Figure 6. Appearance of the temporal skin island at different time points several days after the free flap transfer and the intraoperative findings at two emergency reoperations. (a) Temporal skin island during the daytime of day 4 after free flap surgery. (b) Temporal skin island on the early morning of day 5 after free flap surgery. (c), (d) Intraoperative findings at the first reoperation (day 5) after free flap surgery. No thrombus was found at the arterial anastomosis site. Blood ejection from the recipient facial artery was poor; thus, the flap artery (thoracodorsal artery) was reanastomosed to the proximal facial artery. (e) Temporal skin island immediately after the first reoperation. (f) Temporal skin island on day 6 after flap surgery and just before the second reoperation. (g) Intraoperative findings at the second reoperation (day 6) after free flap surgery. Again, no thrombus was found at the arterial anastomosis site. Blood ejection from the recipient facial artery was poor, and its pulsation was weak; thus, the serratus anterior muscle branch of the thoracodorsal artery was anastomosed to the superior thyroid artery via a vein graft.

chemoattractant protein-1) by monocytes/macrophages or synovial cells. This cascade of action suppresses the excessive immune response or inflammatory reaction/pain response observed in patients with rheumatoid arthritis. By contrast, sarilumab functions as an anti-IL-6 receptor antibody to block the IL-6 signaling pathway and has similar immune-suppressive effects as iguratimod. Thus, both drugs could cause multiple side effects. However, few studies have currently reported their effects on the microvascular system. According to An et al.[5], IL-6 downregulated the expression of contractile proteins α-smooth muscle actin (α-SMA) and SM22α in vascular smooth muscle cells via ATG4B-mediated autophagy in patients who underwent thoracic aortic dissection. Similarly, another study reported that TNF-α decreased α-SMA and SM22 protein expressions and induced phenotype switching, i.e., dedifferentiation from the contractile phenotype, in rat aortic vascular smooth muscle A7r5 cell line[6]. Thus, IL-6- or TNF-α-induced downregulation of these contractile proteins could be suppressed by blocking IL-6 and/or TNF-α signaling pathways, resulting in the increased production of contractile proteins in vascular smooth muscle cells. Some other reports[7-10] indicated the association of TNF signaling with vasoconstriction/vasodilation, although it remains controversial how TNF stimulation/blockade works on vascular tonus.

In this case, both sarilumab and iguratimod had been discontinued immediately after admission, which was 67 days before the free flap surgery. The half-life of sarilumab is 3.49 ± 1.35 SD days by single-dose treatment of 200 mg, and that of iguratimod is 6.8 ± 0.8 SD h by single-dose treatment of 25 mg. Therefore, the blood concentrations of these two drugs were probably very low at least at the time

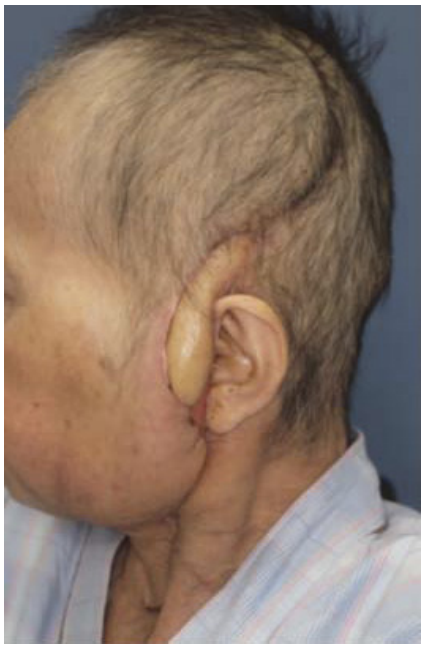

Figure 7. Postoperative view 2.5 months after free flap surgery. The flap fully survived.

of the surgery. However, their effects of modifying the contractile protein profiles on the vascular system are presumably mediated by multistep and accumulative mechanisms requiring a relatively long period, i.e., the process starting from the transcriptional control of genomic genes, through mRNA translation, and leading to the synthesis, accumulation, and phenotypic transformation of contractile proteins within smooth muscle cells. Therefore, the effects of these two drugs were possibly long lasting, being prolonged even approximately 2 months after discontinuation.

In the present case, the recipient facial artery exhibited poor blood ejection, presumably due to vasospasms, but the superior thyroid artery exhibited strong blood ejection, functioning well as a recipient artery at the second reoperation. The site dependence of the vasospasms indicates that its occurrence cannot be explained solely by the systemic pharmacological effects of antirheumatic drugs but also by other factors, including the influence of severe soft tissue infections. The effect of inflammation or infection might have spread to the facial artery but not to the superior thyroid artery. Even if arterial vasospasms occurred under the prolonged effect of antirheumatic drugs, vasospasms could have actually been caused only when there were inflammatory effects as well. In the future, clinical experience of free flap surgery under conditions where some immune signal transduction pathways are modified or blocked must be accumulated.

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Consent to Participate: The patient's family provided written informed consent to participate in this study.
Consent for Publication: The patient's family provided written informed consent to the publication of this study.

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