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1 **First human facial retransplantation: 30-month follow-up**

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39 **ABSTRACT**

40

41 **Background:** Since the first successful face transplant (FT) performed in 2005, the
42 benefits of this procedure on esthetics, functionality, and quality of life are now firmly
43 established. However, despite immunosuppressive treatment, long-term survival of the
44 allograft may be compromised by chronic antibody-mediated rejection (CAMR) leading to
45 irreversible necrosis. In the absence of therapeutic options, this complication was
46 inevitably lethal.

47 **Methods:** Eight years after his first FT for extensive disfigurement from type 1
48 neurofibromatosis and six weeks after complete loss of his graft due to severe CAMR, a
49 patient underwent facial retransplantation. We describe the chronology of immune-related
50 problems that culminated in allograft necrosis and eventually loss of the FT, the
51 desensitization protocol used for this highly sensitized recipient, the surgical technicalities
52 of the procedure, the specific psychological management of this patient, and the follow-up
53 at two years.

54 **Findings:** While the patient had a complicated post-operative course with numerous
55 immunological, infectious, cardiorespiratory, and psychological events, he was discharged
56 after almost one year of hospital stay. He has since been able to reintegrate his community
57 with acceptable restoration of his quality of life.

58 **Interpretation:** This first-in-the-world clinical report is proof-of-concept that the loss of
59 a FT after CAMR can be mitigated successfully by retransplantation combined with an
60 aggressive desensitization process.

61 **Funding:** The Hôpital Européen Georges Pompidou, AP-HP, paid for all costs arising from
62 the surgeries, treatment and relevant investigations.

63 **INTRODUCTION**

64 Vascularized composite allotransplantation (VCA) has emerged as the most advanced
65 reconstruction technique for complex defects such as total hand amputation or massive
66 destruction of the face where no conventional options are available. More than 20 years
67 after the first long-term successful hand transplantation,¹ VCA surgical outcomes are now
68 more predictable and reproducible, and have improved drastically with technological
69 advancements.²

70 However, despite these improvements, the number of complications (metabolic, infectious,
71 and neoplastic) resulting from long-term immunosuppression³ raises many ethical issues⁴
72 and remains the source of much controversy.^{5,6}

73 Immunologically, VCA patients must comply with life-long maintenance
74 immunosuppression, typically using a standard triple drug regimen (i.e.: a calcineurin
75 inhibitor, mycophenolate mofetil (MMF), and steroids). Strict adherence to therapy helps
76 prevent allograft rejection.⁷ Compared to solid organ transplantation, the detection of acute
77 rejection in VCA is arguably easier since skin inflammation represents an early warning,
78 triggering an early therapeutic response.⁸ Surveillance biopsies of VCA skin also allows
79 for the detection of subclinical episodes of acute rejection.

80 Chronic antibody mediated rejection (CAMR) resulting in late allograft loss may occur in
81 all types of solid organ transplantation. In facial transplantation, it has been shown that
82 chronic rejection may result in cellular lichenoid reactions as well as in severe cutaneous
83 fibrosis and chronic scleroderma-like graft versus host disease.⁹ In hand-transplant
84 recipients, severe chronic rejection resulted in amputation, and patients returned to pre-

85 transplant functional status. However, in facial transplant (FT) recipients, VCA loss can
86 result in a major life-threatening defect.¹⁰

87 Herein, we present our experience with a patient who suffered complete loss of his FT due
88 to CAMR eight years after transplantation and who underwent facial retransplantation. To
89 the best of our knowledge, there has been no other case of facial retransplantation reported
90 thus far.

91

92 **CASE REPORT**

93 The patient provided written consent for the publication of this report.

94 A 44-year-old man underwent facial transplantation in 2010 after excision of a massive
95 plexiform neurofibroma (Figure 1, panel A and B). We have previously reported the initial
96 6-year follow-up for this patient (patient #5), among other FT recipients.^{11,12} A progressive
97 humoral rejection was suspected when an increase in plasma levels of donor specific
98 antigen (DSA) was detected 6 years post-transplantation (B51). This immunization against
99 the graft persisted over the next 2 years despite repeated steroid boli and anti-thymocyte
100 globulin infusions (Figure 2). Clinically, the FT became progressively more fibrotic
101 (Figure 1, Panels C) while the patient experienced pain and the loss of facial motion. These
102 symptoms prompted hospital admission on October 25, 2017. Skin biopsies demonstrated
103 diffuse dermal fibrosis, associated with foci of lichenoid interface dermatitis and post-
104 inflammatory pigmentation. The patient was registered on the waiting list for facial
105 retransplantation on October 31, 2017. Over the next two months, the FT underwent
106 progressive and irreversible necrosis (Figure 1, Panel D), which could no longer be left in
107 place due to pain and local sepsis. Eventually, it was excised completely on December 1st,

108 2017. Histologic examination confirmed scleroderma-like chronic rejection (Figure 3). In
109 order to cover the facial skin defect, we first used a dermal matrix (Integra®), but a
110 *Staphylococcus aureus* sepsis forced us to remove it one week later. Facial coverage was
111 subsequently achieved using a split thickness skin graft from the thigh (Figure 1, Panel E).
112 At that time, the immunosuppressive treatment was discontinued since the allograft was no
113 longer present and septic complications represented a major threat. A tracheostomy and a
114 gastrostomy were performed, and the patient was transferred to the intensive care unit
115 (ICU).

116 A preoperative CT angiogram was obtained to evaluate the quality of the recipient's vessels
117 and revealed that the distal external carotid artery (ECA) was stenotic and that no other
118 vein than the internal jugular vein (IJV) could be visualized. We planned to have arterial
119 graft inflow provided by the ECA and venous outflow via the IJV in continuation with the
120 thyrolingual-facial trunk. Cadaveric rehearsals of a modified full-face transplant
121 technique¹³ were organized for the surgeons to practice the various technical steps of the
122 procedure. Of note, the rehearsal was performed mainly for the face procurement
123 (reproducible procedure) but not for the retransplantation itself, due to the impossibility to
124 mimic the dense fibrotic tissue resulting from CAMR.

125 After one month without any proposal, the call for a potential donor was extended from the
126 Greater Paris area to the entire country in order to increase the chances of obtaining a graft.

127 **Facial retransplantation procedure**

128 A facial allograft from a 22-year-old brain-dead donor became available on January 15,
129 2018. The donor and the recipient were matched for blood group (O+) and both tested
130 negative for cytomegalovirus (CMV), Epstein-Barr virus, and toxoplasmosis. However,

131 there were eight full HLA mismatches between recipient and donor, and the pre-transplant
132 panel reactive antibody (PRA) was over 80% attesting to a high level of sensitization. The
133 crossmatch was positive, but we decided to proceed with the surgery because the patient
134 could not remain any longer with this complex maxillo-facial defect.

135 The donor and the recipient were located 390 km apart and two surgical teams worked
136 simultaneously: one prepared the recipient while the other harvested the donor's face. On
137 the recipient, we first removed the skin graft that had been placed as a temporary cover.
138 The facial nerve was tagged at the stylomastoid foramen. The recipient's vessels (ECA and
139 IJV) on both sides were identified and prepared. All remaining scar tissue was excised
140 down to the facial bones and removed. The facial allograft was harvested from the donor
141 prior to the other organs. The face procurement was performed following the same surgical
142 model as for the 1st face transplant, using a pre-established checklist (see Supplementary
143 Material 1 for further details). Briefly, the facial nerve was approached via the transection
144 of the external auditory meatus to reach the nerve trunk, followed by a coronal incision
145 behind the ear and ending at the posterior neck, as reported previously.^{14,15} The facial
146 allograft was then raised along the masseter plane up to the oral mucosa. The graft included
147 the skin, the facial, mental, and infraorbital nerves, the parotid glands, the nose and eyelids.
148 Both ECAs were isolated at their trunk. The veins included the external jugular vein and
149 the thyrolingual-facial trunk, as well as the IJV on both sides. A sural nerve was also
150 harvested from the donor and stored in preservation solution to allow grafting of the facial
151 nerve if necessary. At the end of the harvest procedure, the donor's body was returned to
152 the family with a dedicated tailored resin mask restoring the facial defect.¹⁵

153 To mitigate ischemia-reperfusion injury to the graft, we used a new oxygen carrier
154 (HEMO₂life[®], Hemarina, Morlaix, France) as an additive to standard heparinized Institute
155 Georges Lopez-1¹⁶ storage solution, after obtaining special permission from our national
156 regulatory health authority.¹⁷ The facial allograft was flushed through both ECAs with this
157 solution until blood-free, clear outflow was obtained. The graft was then placed in a
158 conventional portable container at 4°C and transported to the recipient. We anastomosed
159 the donor's face to the corresponding recipient vessels (ECA, IJV) more proximally than
160 for the previous face transplant. The first end-to-end anastomosis between the recipient's
161 left ECA (at its root) and the donor's left ECA was able to perfuse the entire facial allograft.
162 This was followed by an end-to-side anastomosis of the recipient and donor left IJV. The
163 facial nerve was then anastomosed at the level of the trunk. The same procedure was
164 repeated on the right side (Figure 4). The trigeminal nerves (V1, V2, V3) were juxtaposed
165 but not anastomosed, as previously reported.¹⁸ Intra-operatively, the recipient received
166 32 units of packed red blood cell (PRBC), 30 units of fresh frozen plasma, and
167 9 concentrated suspensions of blood platelets. Overall, the durations for recipient
168 preparation, donor harvest, and retransplantation were 9, 6, and 5 hours, respectively. Cold
169 and warm ischemia times were 5 hours and 55 minutes, and 1 hour and 55 minutes,
170 respectively.

171 **Desensitization regimen**

172 Our patient was highly sensitized as a result of his previous facial transplantation and
173 multiple blood transfusions. The desensitization protocol was initiated as soon as the
174 patient's condition was stable (no uncontrolled sepsis) and included (intravenous route)
175 5 doses of anti-thymocyte globulins (75 mg) at POD 3, 4, 5, 6 and 7; 25 doses of

176 methylprednisolone at POD 1 (250 mg), POD 3 (125 mg), POD 4 (125 mg), POD 7-24
177 (20 mg) and POD 25-28 (1 g); 4 doses of anti-CD 20 monoclonal antibodies (mAb)
178 (rituximab) at POD -20 (600 mg), POD 7 (600 mg), POD 14 (500 mg) and POD 21
179 (500 mg); 4 doses of anti-B cell activating factor mAb (belimumab) at POD 1 (520 mg),
180 POD 8 (750 mg), POD 16 (750 mg) and POD 22 (800 mg); 17 sessions of plasma
181 exchanges (PE) at POD -8, -4, -1, 2, 4, 5, 6, 7, 9, 10, 11, 12, 13, 16, 17, 19 and 20; and
182 3 doses of intravenous immunoglobulins (IVIG) (150 mg/kg)¹⁹ at POD 6, 23 and 24,
183 Eculizumab was given at POD 6 (900 mg) (Figure 4). This aggressive desensitization was
184 of paramount importance to reduce the risk of acute rejection. A donor became available
185 two weeks later and desensitization was continued for another two weeks following the
186 facial retransplantation.

187 **Psychological preparation**

188 After the first FT, the patient was followed by a psychiatrist (CL) with a systematic
189 appointment at each visit to the Department of Plastic, Reconstructive and Aesthetic
190 Surgery. Although the first facial transplantation had a positive impact on the patient's
191 mental health,¹² the diagnosis of chronic rejection in 2015 resulted in increased anxiety. At
192 that time, he was encouraged to get familiarized with the practice of mindfulness, in order
193 to strengthen his ability to regulate his emotions in anticipation of the challenges ahead. In
194 September 2017, he experienced recurrent panic attacks and increased concerns about
195 other people staring. He started referring to his FT not as "my face" but as "the graft". He
196 strengthened his practice of mindfulness by attending a group program of mindfulness-
197 based stress reduction supervised by a certified therapist. The possibility to introduce a
198 selective serotonin reuptake inhibitor as prophylaxis against panic attacks was explained

199 to the patient, as was the likelihood of experiencing visual hallucinations in the event of
200 prolonged sensory deprivation (further details in Supplementary Material 2).

201

202 **Immunosuppressive regimen and infection prophylaxis**

203 Immunosuppression induction was achieved using IV antithymocyte globulins
204 1x 25 mg/kg/day for 5 days (Figure 5). Post-retransplantation maintenance regimen
205 included tacrolimus, MMF, and steroids. We aimed at maintaining tacrolimus plasma
206 levels between 10 and 15 ng/mL, MMF area under the curve between 40 and 60 ng/mL,
207 and prednisone was progressively tapered (250 mg on Day 1, 125 mg on Days 2, 3 and 4,
208 20 mg/day for 17 days, and finally 10 mg/day). This triple immunosuppression therapy
209 was never interrupted during the entire follow-up.

210 Despite CMV matching, valganciclovir was administered prophylactically (900 mg per
211 day for six months). The patient also received trimethoprim-sulfamethoxazole (800 mg
212 three times weekly for six months) for prophylaxis against *Pneumocystis carinii*.

213 **Skin Rejection monitoring**

214 Sequential biopsies of VCA skin and mucosa were performed on postoperative day
215 (POD) 2 and were repeated once a week for the first two months, twice a month for the
216 next two months, and then at Month 6, 9, 10, 14, 21 and 23. Although skin biopsies were
217 requested when there was a clinical suspicion of acute rejection, we mostly relied on
218 systematic scheduled biopsies because the donor was a 22-year-old patient with severe
219 facial acne lesions which could be confusing. The grade of rejection was assessed
220 according to the 2007 international BANFF classification.²⁰ DSA plasma levels were
221 monitored every week for two months, and every month thereafter.

222 Post-transplant skin and mucosal biopsies on POD 2 and 7 showed mild lymphocyte
223 infiltration (BANFF Grade 1). Skin biopsies (from the right cervical area) performed on
224 POD 14 showed Grade 2/3 rejection with dermal CD3⁺ lymphocyte infiltrates and
225 interface dermatitis characterized by basal vacuolization and apoptotic keratinocytes.
226 Similar alterations were observed on the mucosal biopsies (from the right internal cheek)
227 (Supplementary Figure 7). The development of skin erythema combined with Grade 2/3
228 rejection on skin biopsies despite steroid boli was attributed to antibody-mediated rejection
229 and treated using one dose of 900 mg eculizumab at POD 6. Since immune
230 histochemistry showed no evidence of C4d deposition on skin biopsies, no further
231 administration of eculizumab was required. On POD 18, due to persistent Grade 2/3
232 rejection, prednisone boli (1 g/day) were administered for four consecutive days. This led
233 to complete resolution of the erythema and subsequent skin biopsies did not demonstrate
234 any sign of rejection (BANFF Grade 0 or 1). Some lymphocyte infiltrates persisted in the
235 mucosa, but no clinical rejection episode has been observed since. Interestingly, the DSA
236 directed against the initial donor decreased abruptly with the desensitization protocol
237 following retransplantation, while DSA directed against the second donor decreased
238 progressively over the first six months in the postoperative period (Figure 2).

239 **Psychological aspects**

240 Prior to retransplantation, the patient developed transient symptoms of delirium, which
241 required low doses of haloperidol. These symptoms of delirium were likely multifactorial,
242 involving drug side effects and transient electrolyte imbalances. The first psychological
243 interview revealed severe anxiety linked to his loss of autonomy, disorientation episodes,
244 uncertainty regarding his medical condition, and impaired ability to communicate

245 following the loss of his first FT. The patient also reported visual hallucinations that he
246 spontaneously attributed to sensory deprivation after removal of the necrotic FT. This
247 hypothesis was indeed supported by the fact that visual hallucinations persisted for days
248 while the other symptoms of delirium (e.g. disorientation, disruption of attention) had
249 disappeared and were not associated with hallucinations in other sensory modalities or
250 delusional adherence to their contents. Haloperidol was switched to olanzapine and
251 sertraline was introduced to alleviate anxiety without increasing the risk of delirium
252 relapses. At that time, the patient actively used mindfulness to maintain his emotional state.
253 Following facial retransplantation, he saw his new face for the first time on POD 10. Just
254 like after the first FT, this was characterized by an immediate sense of ownership (i.e. the
255 patient's feeling that the new face was his own), despite the absence of sensitive feedback
256 at this time. Body image (i.e. the patient's perception of his appearance), which had been
257 severely damaged during the progressive necrosis of the previous transplant, also
258 immediately improved. His sense of identity remained unaffected. Subsequently, a team of
259 psychiatrists and psychologists provided close psychological follow-up. Although the
260 patient experienced transient episodes of discouragement, he never met the criteria for a
261 major depressive episode and has not had issues with compliance thus far. He did
262 experience several panic attacks requiring continued treatment with benzodiazepines and
263 increased sertraline doses. A systematic screening for post-traumatic stress disorder at one-
264 month post-ICU discharge was negative. A dedicated clinical interview at one-month post-
265 ICU discharge did not find diagnostic criteria for a post-traumatic stress disorder. Step
266 down from the ICU to the plastic surgery ward was accompanied by a paradoxical increase
267 in anxiety, however the patient's mental state gradually improved over the next four months

268 with functional improvement and more frequent home leave (see Supplementary
269 Material 2 for further details).

270 **Infectious complications**

271 During the postoperative period, the patient developed several infections. First, at
272 2 months, he contracted a norovirus infection, which led to severe diarrhea and resulted in
273 massive weight loss (-15 kg). A CMV esophagitis resulted in functional achalasia and
274 impaired esophageal emptying. Two episodes of aspiration pneumonia complicated by
275 brief hypoxic cardiac arrest requiring tracheal intubation occurred (at Months 3 and 8) and
276 were treated using systemic antibiotics. Normal oral feeding could be resumed only
277 9 months after retransplantation.

278 **Hospital stay and post-discharge follow-up**

279 The overall length of hospital stay was one full year. Prior to facial retransplantation, the
280 patient had spent three months in the hospital including six weeks in ICU with no face and
281 with very limited ability to communicate. Postoperatively, the patient remained in ICU for
282 two months and spent the next six months in the ward. He was able to resume walking on
283 POD 12 and started to talk and drink by POD 30. The tracheostomy cannula was removed
284 on POD 50. The timeline of significant postoperative events is depicted in Supplementary
285 Figure 8.

286 The patient was eventually discharged home on October 18, 2018 and was followed every
287 other month via the outpatient clinic. Benzodiazepines, and then sertraline, were gradually
288 withdrawn between postoperative months 18 and 24 without any clinically significant
289 relapse of anxiety. Two years after the surgery, the patient was considered in good mental
290 health and was able to carry out his daily living activities unassisted. From the functional

291 perspective, the motor function of the facial nerve allows good eyelid closing and some
292 labial motion on the left side, but there is a complete right facial palsy. Face sensitivity is
293 present on both sides. The facial retransplantation also reduced the patient's concerns about
294 his appearance and restored his quality of life (Figure 6). He was able to resume part-time
295 work as a librarian. No other complication has been reported thus far. A 4-minute video
296 showing the various phases of the disease and of the surgical management, with interviews
297 of the patient summarizes the time-course of this unique facial retransplantation and
298 provides insights on the patient's own appreciation of the result.

299

300 **DISCUSSION**

301 Since the first successful case in 2005, more than 40 FTs have been reported worldwide.²¹
302 Although initial successes have been published in the literature, the description of long-
303 term follow-up has been limited and inconsistently reported. Little is known about the
304 prevalence of CAMR and its consequences among VCA recipients.¹⁰ While CAMR was
305 the underlying cause of FT deterioration in the present case, many questions remain
306 unanswered regarding the pathophysiology of this complication. Although the exact trigger
307 of the rejection process is still largely hypothetical, several factors might have played a
308 role. Transient insufficient plasma level of calcineurin inhibitors²², graft ischemic
309 reperfusion injury, inflammation triggered by regional lipofilling,²³ intercurrent infectious
310 diseases, or skin mechanical trauma²⁴ are all potential contributors to the CAMR observed
311 in our patient. Early detection of this complication might be facilitated in the future using
312 innovative monitoring techniques assessing the graft pedicle. Possible underlying CAMR
313 can be detected early using high-resolution ultrasound²⁵ or MRI²⁶ when intima/media

314 thickening or graft flow reductions, respectively, are measured. CAMR symptoms include
315 progressive skin sclerosis and ultimately necrosis leading to complete loss of the transplant
316 within 12 months.²⁷ At this stage, the patient experiences a decrease in his quality of life
317 and the allograft becomes nonfunctional, which defines end-stage transplant failure in
318 VCA recipients.

319 During the six-week period following explantation of the first FT, the
320 immunosuppressive treatment was withdrawn because we estimated that its risks could
321 exceed the benefits. However, this resulted in a rise in first transplant DSA plasma levels
322 during the interval prior to the retransplantation. We retrospectively hypothesized that
323 maintaining the immune suppressive treatment could have mitigated the intensity of
324 immunization as measured by elevated second FT DSA plasma levels, although we do not
325 know whether life-threatening septic complications could have been facilitated at a time
326 when the patient had no proper cutaneous barrier. The desensitization protocol initiated
327 two weeks before retransplantation reduced DSA plasma levels and no recurrence was
328 observed. We cannot overemphasize the importance of meticulous planning and
329 coordination of all technical, immunological, and psychological aspects of the
330 management. Because this was a second FT, vascular and nervous anastomoses had to be
331 performed more proximally and the dissection for exposure of the recipient's neck vessels
332 was more technically challenging. This was responsible in part for a massive intraoperative
333 blood loss requiring multiple blood products. Allograft ischemia and its potential sequelae
334 were a significant concern in this case due to the distance separating the donor and the
335 recipient. The adjunction of the oxygen carrier HEMO₂life® in the preservation solution
336 was attempted since it had been reported to reduce initial graft dysfunction in kidney

337 transplant patients.²⁸ In all our previous FT cases, the allografts showed some late
338 revascularization areas (video, supplementary material 3) but this phenomenon was not
339 observed in the present case. Whether the oxygen carrier played a role in limiting ischemia-
340 reperfusion injury of the graft remains to be demonstrated. This question deserves to be
341 addressed in future experimentations, as ischemia-reperfusion injuries have been suggested
342 to play a role in the development of CAMR.²⁹ Finally, preparing the patient psychologically
343 to live without a face for weeks was certainly of paramount importance to help him
344 overcome this long and painful process. Pre- and post-operative psychological assessments
345 and management, including handling early psychiatric complication in the ICU (e.g.
346 delirium) and fostering long-term medical adherence through the prevention of depressive
347 episodes certainly played a role in allowing the patient to accept his unprecedented
348 situation and in the overall positive outcomes of his facial retransplantation. This may also
349 have indirectly fostered long-term medical adherence to his immunosuppressive regimen,
350 although longer term follow-up would be required to fully evaluate the psychological
351 consequences of this first-in-the-world experience.

352

353 **CONCLUSION**

354 We have shown that retransplantation is feasible for facial transplants with irreversible
355 necrosis and loss due to CAMR. Although still exceptional for VCA, retransplantation
356 appears as a possible valid treatment option in selected patients. This is especially
357 important for facial transplant patients in whom there is no alternative in case of graft loss.
358 We hope that this demonstration of a possible rescue therapy in case of graft failure will

359 help patients in need of a facial transplant and their caregivers to proceed to transplantation
360 in the future.

361

362 **Declaration of interests**

363 We declare no competing interests

364

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371

372 **Author's contribution**

373 Literature search: LL, AGL

374 Figures: LL, AGL, BC, CL, NO,

375 Data collection: AGL, LL

376 Data analysis: all authors

377 Data interpretation: all authors

378 Study design: LL, AGL

379 Writing: all authors

380 Important intelligent input: all authors

381 Manuscript preparation and corrections: all authors

382

383

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460 **Figure legends**

461 Figure 1. Time-course of the morphological changes in the patient's face: Aspect prior to
462 the first transplantation (A), 1 year post-transplantation (B), 6 years post-
463 transplantation, showing evidence of advanced chronic antibody-mediated
464 rejection (C), 7 years post-transplantation, end-stage deterioration of the facial
465 transplant (D) and after removal of the necrotic facial allograft and replacement by
466 a split thickness skin graft (E)

467 Figure 2. Time-course of donor-specific anti-HLA antibodies plasma levels prior to and
468 following facial retransplantation (Day 0). FVCA: Facial Vascularized Composite
469 Allograft

470 Figure 3. Panel A: Macroscopic, explanted facial allograft with areas of advanced necrosis.
471 Panel B: Skin sample from the explanted face showing diffuse dermal fibrosis
472 expanding into the hypodermis, replacing normal adipose tissue with some residual
473 fat cells and atrophic skeletal muscle fibers (hematoxilin & eosin, x25 original
474 magnification). Panel C: Hyaline fibrosis involving the superficial dermis with
475 numerous melanophages suggestive of post-inflammatory pigmentation
476 (hematoxilin & eosin, x100 original magnification).

477 Figure 4. Timeline depicting the immunological management and immunosuppressive
478 regimens used for the desensitization protocol before and after facial
479 retransplantation (Day 0). Intravenous immunoglobulins (150 mg/kg), belimumab
480 POD 1 (520 mg), POD 8 (750 mg), POD 16 (750 mg), POD 22 (800 mg), rituximab

481 POD -20 (600 mg), POD 7 (600 mg), POD 14 (500 mg), POD 21 (500 mg),
482 eculizumab (900 mg), methylprednisolone (see text for tapering regimen and boli),
483 anti-thymocyte globulins (75mg).

484 Figure 5. Schematic drawings of the recipient's face and vessel anatomy (Panel A), of the
485 internal view of the donor's face harvested (Panel B), and of the main vascular and
486 nervous anastomoses after transplantation (Panel C). On Panel B, numbers indicate
487 the main anatomical structures: 1 = *frontalis musculus*; 2 = *musculus orbicularis*
488 *oculi*; 3 = eyelid; 4 = tear duct; 5 = *musculus zygomaticus minor and major*;
489 6 = buccal mucosa; 7 = *musculus orbicularis oris*; 8 = *musculus risorius*;
490 9 = parotid gland; 10 = submaxillary gland; 11 = external carotid artery; 12 = facial
491 artery; 13 = facial nerve; 14 = common facial nerve; 15 = internal jugular vein;
492 16 = *musculus platysma*.

493 Figure 6. The patient 2 years after facial retransplantation.

494

495 Supplementary Figure 7. Hematoxilin & eosin, x200 original magnification. Panel A: Skin
496 biopsy at Day 14 post-retransplantation showing an interface dermatitis with
497 scattered lymphocytes infiltrating the vacuolized basal layer of the epidermis with
498 apoptotic bodies (arrowheads) suggestive of Grade 3 acute cellular rejection.
499 Panel B: Mucosal biopsy showing interface dermatitis with apoptotic bodies in the
500 basal and upper layers of the mucosal epithelium (arrowheads), suggestive of
501 Grade 3 acute cellular rejection.

502 Supplementary Figure 8. Timeline of selected events that occurred during the 1-year

503 hospital stay (prior to, and after retransplantation). ICU: Intensive Care Unit; ROSC:
504 Return Of Spontaneous Circulation; STSG: Split Thickness Skin Graft.



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