Late Venous Thrombosis in Free Flap Breast Reconstruction: Strategies for Salvage after This Real Entity

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Background: Microvascular free-tissue transfer is a reliable pillar of reconstructive surgery, yet pedicle thrombosis remains a challenge. The authors examined the phenomenon of late venous thrombosis (after postoperative day 3) and detail a method of flap salvage that can be utilized following this microvascular insult.
Methods: A retrospective review was performed of all free flap breast reconstructions performed by the senior author (J.M.S.) from 1991 to 2008, utilizing a prospectively maintained database. All cases of postoperative thromboses were evaluated. Late venous thrombosis was defined as a thrombosis occurring after postoperative day 3.
Results: A total of 1277 free flap breast reconstructions were performed over the 17-year period. Nineteen flaps had venous thromboses (1.5 percent), and 10 of these occurred after postoperative day 3 (average, 5.67 days; range, 4 to 12 days). Operative exploration was employed in seven of 10 cases, with the remaining patients presenting too late or too advanced for operative intervention. Sixty percent of flaps were fully salvaged, and two were partially saved, with some subsequent volume loss. Earlier late venous thrombosis presentation led to better outcomes overall.
Conclusions: Late venous thrombosis is a rare phenomenon that, although occurring late in the postoperative course, is an acute event. Early recognition and urgent treatment are key to flap salvage, with clinical judgment dictating the treatment choice. In the absence of extenuating circumstances, the authors prefer urgent exploration in the operating room, as flap survival following late venous thrombosis is a race against time but with a high probability of salvage if the proper steps are taken. (*Plast. Reconstr. Surg.* 129: 8e, 2012.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Microvascular free tissue transfer is an established, reliable technique in reconstructive surgery, with reported 91 to 99 percent success rates.[1–6] Pedicle thrombosis, however, remains a challenge. Arterial thrombosis typically occurs early in the postoperative course, while venous thrombosis can present with more temporal variability. When thrombosis is detected, surgical reexploration or medical therapy must be initiated without delay.

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Studies have demonstrated that thromboses occur in 3 to 9 percent of free flap breast reconstructions.[7–10] Venous thrombosis is more common than arterial thrombosis, occurring in up to 74 percent of thrombosed flaps,[10] the majority of these complications reportedly occurring within 3 days of the initial operation. To date, no reports have established the incidence of venous thrombosis later in the immediate postoperative period (>3 days).

It has been our experience that a significant proportion of venous thrombotic events occur during this late postoperative period but that salvage following such events is very possible. The purpose of this study was to examine the senior author's (J.M.S.) experience with the phenome-

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non of late venous thrombosis and to detail a method of flap salvage that can be utilized following this subacute, microvascular insult.

PATIENTS AND METHODS

The authors performed a retrospective review of the senior author's experience with postoperative late venous thrombosis, including all patients who underwent free flap breast reconstruction between 1991 and 2008. This phenomenon was defined as a venous thrombosis that occurred later than postoperative day 3. Records were reviewed for any postoperative thrombosis, noting the postoperative day of each event. An analysis was also performed to determine any thrombotic differences between flap types. Data were entered into an Excel workbook, and statistical analysis was performed using Stata 10.0 IC (College Station, Texas).

Free Flap Protocol

Each free flap was treated in an identical fashion. Under loupe magnification, the venous anastomosis was hand sewn or utilized a venous coupling device, while each arterial anastomosis was hand sewn using 8.0 or 9.0 nylon suture. Heparinized saline (100 units/ml) was used to irrigate vessels before and during the anastomosis. An intravenous bolus of heparin was administered only if the vessels appeared to be severely diseased or if there were significant intraoperative anastomotic complications (i.e., recurrent thrombosis despite intraoperative anastomotic revision). In the postoperative setting, flaps were monitored every hour for 48 hours and every 4 hours subsequently until discharge. Each patient received Lovenox (Sanofi-Aventis U.S., Bridgewater, N.J.) or 5000 units of subcutaneous heparin while in the hospital for deep venous thrombosis prophylaxis.

Thrombolytic Protocol: Postoperative Venous Thrombosis

In the rare event that a postoperative venous thrombosis occurs, the patient immediately received a 5000-unit intravenous heparin bolus, and our preference is to return the patient to the operating room as an emergent case. If, upon exploration, it was determined that a venous thrombosis had occurred, the artery was clamped, and the venous anastomosis was resected beyond the thrombosed segment. We then repeated the anastomosis, nearly always utilizing a vein graft (saphenous). When deemed necessary, we found a new recipient vein if the original recipient was not suitable for reanastomosis.

After the reanastomosis, we infused 250,000 units of urokinase or 2 mg of tissue plasminogen activator in 50 cc of sterile water over 30 minutes through a 25-gauge butterfly needle inserted just proximal to the arterial anastomosis (Fig. 1). This was performed in an effort to disrupt any residual clot that may have been lodged in the vessel or in the microvasculature of the free flap. The patient then returned to the intensive care unit for continued monitoring, and a heparin infusion was initiated. In the event that the patient was at home and there was a significant delay in presenting to the hospital after a late event, medical management utilizing a heparin infusion alone may have been implemented. Each event should be examined on a case-by-case basis, and a management decision should be made based on what is best for the patient.

RESULTS

During the 17-year inclusion period, 1277 free flaps for breast reconstruction were performed, with postoperative arterial or venous thrombotic events occurring in 31 flaps (2.4 percent). Of these, 12 events (0.94 percent) were arterial thromboses (1.5 percent), and 19 events were venous in nature. Ten events (0.78 percent) fit the definition for a late venous thrombosis.

These 10 late venous thrombosis events (Table 1) occurred on average 5.67 days after surgery (range, 4 to 12 days). Operative exploration was

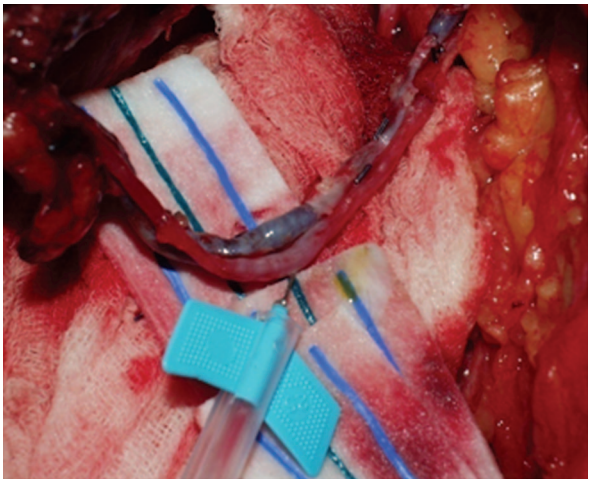

Fig. 1. In the event of a late venous thrombosis, we infused 250,000 units of urokinase or 2 mg of tissue plasminogen activator in 50 cc of sterile water over a 30-minute period through a 25-gauge butterfly needle inserted just proximal to the arterial anastomosis.

Table 1. Patient Course

Patient	Flap Type	POD No.	Treatment	Salvage	Complication
1	msf-TRAM	4	OR: vein graft, tPA	Yes	None
2	IGAP	4	OR: vein graft, UK	Yes	None
3	SGAP	4	OR: vein graft, UK	Yes	None
4	SGAP	4	OR: revision anastomosis, UK	Yes	None
5	SIEA	4	OR: vein graft, UK	No	Flap loss, transfuse 1 unit pRBC
6	DIEP	5	IV heparin	Yes (partial)	Fat necrosis, decreased volume
7	msf-TRAM	6	OR: vein graft, UK	Yes (partial)	Fat necrosis, transfuse 1 unit pRBC
8	msf-TRAM	6	OR: vein graft, tPA	Yes	Fat necrosis
9	IGAP	8	IV heparin	Yes	None
10	msf-TRAM	12	Not treated	No	Flap loss

POD, postoperative day; msf-TRAM, muscle-sparing free transverse rectus abdominis musculocutaneous; OR, operating room; tPA, tissue plasminogen activator; IGAP, inferior gluteal artery perforator; UK, urokinase; SGAP, superior gluteal artery perforator; SIEA, superficial inferior epigastric artery perforator; pRBC, packed red blood cells; DIEP, deep inferior epigastric perforator; IV, intravenous.

employed in seven of 10 cases, with the remaining patients presenting too late for operative intervention. Operative salvage was successful in six of seven cases, although one flap did have volume loss in the subsequent postoperative period. Intraoperative thrombolytics were used in all cases (five urokinase, two tissue plasminogen activator), and six of seven utilized vein grafting after resection of the thrombosis. Of the three nonoperatively managed patients, two were at least partially salvaged, with the one flap loss having presented on postoperative day 12. Only three of these patients had anastomotic issues at the initial procedure that required revision of the anastomosis.

Of the 10 patients who experienced late venous thrombosis, the later the presentation, the more likely the patient was to have flap loss or fat necrosis. Only one of five patients who presented on postoperative day 4 had a serious complication (flap loss), whereas four of five patients presenting after postoperative day 4 had a course resulting in flap loss (one of five) or some degree of fat necrosis (three of five).

An analysis of late venous thrombosis by flap type (Table 2) revealed that late venous thrombosis was more likely to occur in perforator flaps as opposed to the muscle-sparing transverse rectus abdominis myocutaneous (TRAM) flap (1.7 percent versus 0.43 percent; $p = 0.026$). In examining all postoperative venous thrombotic events (early + late; Table 3), we found a similar trend (3.0 percent for perforator flaps versus 0.97 percent for muscle-sparing free TRAM flaps; $p = 0.016$).

Flap loss occurred in four (33 percent) of 12 postoperative arterial thromboses, and four (21 percent) of 19 postoperative early venous thromboses, with two (11 percent) of 19 having partial flap loss. As mentioned, two of 10 of late venous thrombosis events resulted in flap loss, with two of 10 having partial loss.

Table 2. All Postoperative Late Venous Thromboses

Flap	LVT (−)	LVT (+)	*p*
msf-TRAM	934	4	<0.001
DIEP	190	1	
SIEA	98	1	
GAP	45	4	
Total	1267	10	
msf-TRAM	934	4	0.026
Perforator	333	6	

LVT, late venous thromboses; msf-TRAM, muscle-sparing free transverse rectus abdominis musculocutaneous; DIEP, deep inferior epigastric perforator; SIEA, superficial inferior epigastric artery perforator; GAP, gluteal artery perforator.

Table 3. All Postoperative Venous Thromboses

Flap	VT (−)	VT (+)	*p*
msf-TRAM	929	9	<0.001
DIEP	188	3	
SIEA	97	2	
GAP	44	5	
Total	1258	19	
msf-TRAM	929	9	0.016
Perforator	329	10	

VT, venous thromboses; msf-TRAM, muscle-sparing free transverse rectus abdominis musculocutaneous; DIEP, deep inferior epigastric perforator; SIEA, superficial inferior epigastric artery perforator; GAP, gluteal artery perforator.

CASE REPORTS

Patient 8

Patient 8 was a 52-year-old woman who underwent unilateral delayed reconstruction with a muscle-sparing free TRAM flap. There were no intraoperative complications, her postoperative course was routine, and she was discharged on postoperative day 4. On postoperative day 6, she presented with an advanced late venous thrombosis (Fig. 2, *above*). She was immediately explored and found to have the entire internal mammary vein thrombosed. We, therefore, elected to perform a saphenous vein graft from the internal epigastric vein on the flap to the

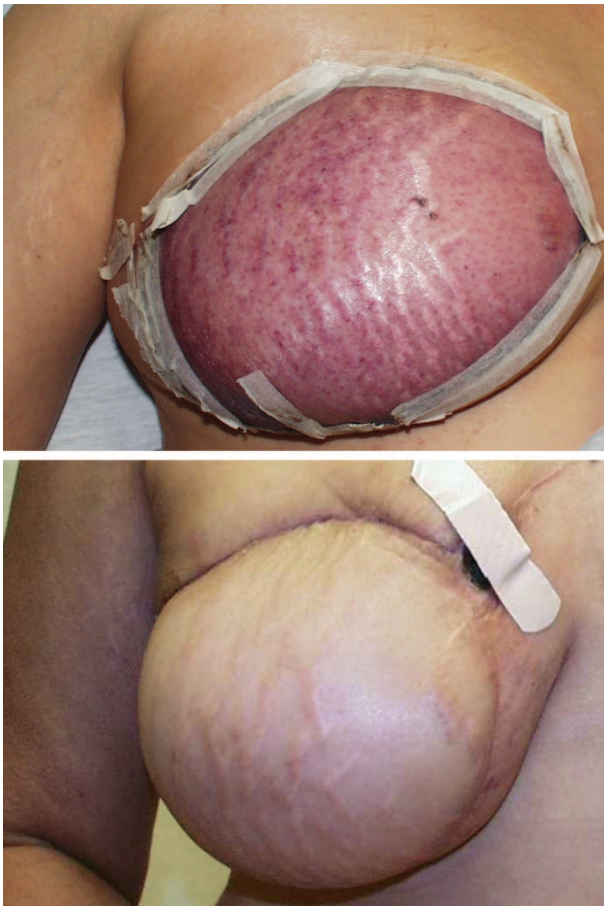

Fig. 2. Patient 8. (*Above*) After a muscle-sparing free TRAM flap, the patient presented on postoperative day 6 with a late venous thrombosis involving the whole inferior mesenteric vein. (*Below*) After a saphenous vein graft to the internal jugular vein, long-term follow-up shows good volume, with some minimal contour irregularities.

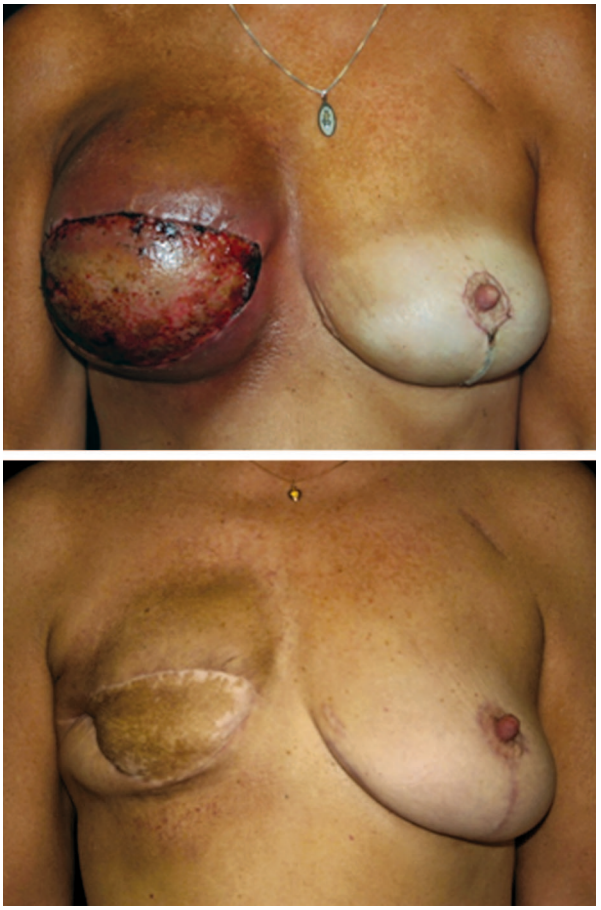

Fig. 3. Patient 6. (*Above*) The patient presented on postoperative day 5 with an advanced late venous thrombosis that had evolved over 24 hours. She was treated conservatively with intravenous heparin. (*Below*) At long-term follow-up, significant volume loss was noted, but partial salvage was achieved even with conservative therapy.

right internal jugular vein through a small transverse incision on the lower neck. We utilized tissue plasminogen activator as our thrombolytic, and after performing this localized infusion with a new venous anastomosis, the flap appeared viable. At long-term follow-up, she had 100 percent flap survival, with some minimal contour deformities (Fig. 2, *below*).

Patient 6

Patient 6 was a 49-year-old woman who underwent unilateral delayed reconstruction with a deep inferior epigastric perforator (DIEP) flap. Her operation was notable for an arterial thrombosis, which was resected, revised, and repaired, with no residual issues. Her hospitalization was uneventful, and she was discharged on postoperative day 4. The next day, she called the office stating that throughout the day her flap had become more swollen and that the skin island had turned purple. She was encouraged to immediately return to the hospital. Upon arrival, it was determined that the changes were advanced and that operative exploration would have yielded little (Fig. 3, *above*). She was admitted, however, and a heparin drip was initiated. With this therapy, the congestion improved, though the flap remained swollen. She ultimately had a partial salvage of the flap, with some volume loss (Fig. 3, *below*).

Patient 9

Patient 9, a 52-year-old woman, had previously undergone bilateral breast reconstruction utilizing DIEP flaps. After the initial reconstruction, she developed a postoperative arterial and venous thrombosis of the left flap on postoperative day 1, which was unable to be salvaged. Approximately 6 months later, she underwent delayed reconstruction with an inferior gluteal artery perforator flap. During the treatment, she developed an arterial thrombosis, which was resected and reconstructed using a reverse saphenous vein graft. It was then decided during her hospitalization that, given the history of multiple thrombotic events in this and the previous reconstruction, conservative management would be the most appropriate course of action should another thrombosis occur. Her postoperative period was uneventful until postoperative day 8, when she presented with a late venous thrombosis (Fig. 4, *above*). She was hospitalized and started on a heparin drip, which resulted in complete salvage of the flap (Fig. 4, *below*). She was then main-

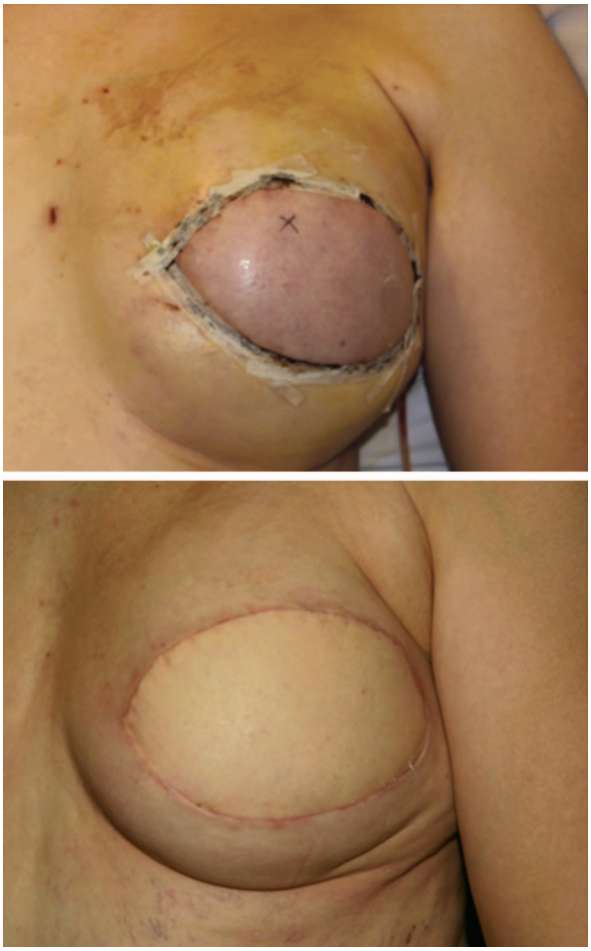

Fig. 4. Patient 9. (*Above*) Six months after a failed DIEP flap (arterial and venous thrombosis), the patient underwent an inferior gluteal artery perforator flap, complicated by a late venous thrombosis on postoperative day 8. (*Below*) Due to her history of multiple thromboses, the patient and senior author had agreed before this complication not to return to the operating room in the event of a subsequent thrombosis. Therefore, conservative management with heparin was initiated, resulting in complete salvage.

tained on warfarin therapy after discharge, and a hematologic workup eventually revealed a hypercoagulable condition with elevated factor VIII.

Patient 5

Patient 5 was a 35-year-old woman, with a family history of a fatal pulmonary embolism in her father, who underwent immediate bilateral superficial inferior epigastric artery flap reconstruction. Her case was complicated by venous thromboses of both flaps, which were corrected intraoperatively. She was then placed on a heparin drip during her inpatient stay. On postoperative day 4, she developed a late venous thrombosis of the left breast that was quickly detected, and she was returned to the operating room. The thrombosis was resected, and an interpositional saphenous vein graft with subsequent urokinase infusion was utilized. After this therapy, it was determined that a thrombosis had formed in the internal mammary artery. This clot was removed and the anastomosis resewn. Upon removing the bulldog clamp, however, there was reperfusion and then a secondary thrombosis. At this point, it was decided that a thrombotic process was occurring in the flap and that more attempts to salvage this flap were not appropriate. The flap was then removed. The patient had no postoperative issues with the right flap, and a hematologic workup revealed no abnormalities.

DISCUSSION

Reported rates of free flap loss continue to decline, with several recent series reporting overall flap survival at 97 to 99 percent.[9–12] Yet even the most methodical surgeon has, to this point, been unable to reduce the risk of flap loss to 0 percent. The most common cause of flap compromise continues to be pedicle thrombosis, which must be addressed in a timely fashion if a flap is to be salvaged. When reexploration is successful, even high rates of thrombotic events can result in low rates of flap loss.

Venous thromboses occur more frequently than arterial thromboses and are therefore a more common cause of flap loss. These occur primarily because of the low-flow venous system being more prone to stasis in a setting of anastomotic imperfections, vessel injury, vasospasm, kinking, or extrinsic compression as a result of a tight closure or poor pedicle orientation.[10,13] When flap loss does occur, it may be related to a delay in treatment of venous thromboses, as the venous system is only monitored clinically while the arterial Doppler signal often continues to be present although significant microvascular changes are occurring throughout the flap. The physical engorgement and microvascular changes can result in an irreversible no-reflow phenomenon.[14,15] When reexplored, however, salvage rates tend to be higher in cases of venous thromboses than in arterial thromboses[10] but still range widely from 30 to 100 percent.[16–19]

Our overall rate of vessel thrombosis was 2.4 percent. Consistent with other reports, venous thrombosis was more common than arterial thrombosis (1.5 versus 0.94 percent). However, whereas most reported venous thromboses occur in the first 2 or 3 days postoperatively,[13] our series demonstrated late venous thrombosis to be more common than early venous thrombosis. Given this finding, we felt it appropriate to emphasize the acute nature of these events even though they occur in a delayed fashion.

Studies have generally demonstrated poor results with salvage attempts of late venous thrombosis events.[7] Although there are undoubtedly additional challenges to these events, we feel that they should be treated as acute thrombotic complications and, when possible, reexplored on an

emergent basis. The late timing presents a challenge in that a patient may already be discharged from the hospital, therefore leading to a further delay in presentation and reexploration, and potentially more advanced or irreversible changes.

As the senior author has observed this phenomenon several times in his practice, all patients are now reexamined and extensively counseled on discharge through written and verbal discussion to be observant with regard to any changes that occur with their free flap reconstruction. They are instructed to call without hesitation should such changes occur and are routinely contacted by our nursing staff within the first few postoperative days. More than half of the late venous thrombosis cases presented after discharge. We do, however, still feel that postoperative day 4 is the most appropriate day for discharge, as this gives adequate time for close observation and medical management. Keeping patients an additional day likely would have only allowed inpatient observation of one additional late venous thrombosis event. Along this line, we do not routinely discharge patients on anticoagulation, as based on this series, we would need to treat over 100 patients to potentially prevent one late venous thrombosis and nearly 500 to potentially prevent one flap loss due to such an event.

We believe that vascular thromboses usually result from a technical problem, and therefore operative management is the rule rather than the exception with regard to treatment. We managed 70 percent of our patients in this fashion, with the other three patients managed medically due to their very late presentation or a previously made decision not to return to the operating room in the event of a thrombotic complication. It is still important to evaluate each patient individually and not simply to reflexively return to the operating room but to assess his or her overall clinical picture. This is certainly an instance in which the art of medicine is evident, as opposed to a hard rule of science.

When operative management was possible, we achieved an 86 percent (six of seven) salvage rate. It is our preference to resect the entire thrombosed segment and to remove any additional vein in which there has been suspected intimal damage (e.g., patient 8). After the vein graft anastomoses are performed, we infuse a thrombolytic substance to disrupt any microemboli that may be within the flap due to the venous congestion and resulting stasis.

As previously described in detail,[17] we prefer to utilize urokinase, if available, as our thrombolytic agent. There is certainly debate surrounding the optimal thrombolytic substance for microsurgical purposes, but in our experience, urokinase has been the best choice. We elect to use this over tissue plasminogen activator because we have, at times, found achieving meticulous hemostasis more difficult following administration of tissue plasminogen activator in comparison with urokinase. This is likely due to the longer half-life of tissue plasminogen activator. Whereas some studies have demonstrated recombinant tissue plasminogen activator to be superior to urokinase in nonmicrosurgery settings,[20,21] others have shown no difference between the two agents.[22,23] Our experience with the two agents has been nearly equivalent with regard to the thrombolytic capability in the microcirculation of flaps. The main difference is cost, as urokinase is significantly more expensive. However, given the increase in systemic bleeding that we have observed with tissue plasminogen activator, we continue to choose urokinase.

Some surgeons advocate infusion of the thrombolytic substance before performing the venous anastomosis to prevent systemic spread.[24] We prefer, however, to perform all anastomoses initially. This allows the thrombolytic to act over the entire circuit of the flap and allows visualization of the new anastomoses for an additional 30 minutes.

The three patients who were medically managed all had factors making operative therapy unlikely to be successful. The patient who presented on postoperative day 5 (patient 6) was placed on anticoagulation as a result of the long delay in the patient returning to the clinic for evaluation, which resulted in what appeared to be advanced or irreversible changes resulting from the thrombosis and the time delay to presentation. The patient presenting on postoperative day 8 (patient 9) had made a joint decision with the physician during her inpatient stay to pursue no further salvage procedures, as previously mentioned. The final patient, who presented on day 12 was given 24 hours of heparin therapy, followed by débridement of the flap, as it was evident that the flap was fully compromised.

Two of three flaps were partially salvaged by medical therapy alone. This was likely due to the presence of effective neovascularization, which has been reported to occur by postoperative day 5.[25] Studies have shown that venous connections occur earlier than the arterial counterpart, appearing as early as postoperative day 2.[26] With this knowledge, it is very plausible that, given the anticoagulation regimen to prevent any additional

thrombosis formation, the venous channels may have been adequate at the point of the late thrombosis to supply adequate drainage for the flap. The patient presenting on postoperative day 12 likely had a significant delay in presenting to the clinic, and although venous channels were potentially adequate to drain the flap, the thrombosis may have developed to the extent that the venous congestion produced irreversible ischemic changes as described by the no-reflow phenomenon.[27] Such patients could be candidates for superselective catheter thrombolysis; however, this is not currently utilized at our institution.

Patient 9 had a history significant for multiple thrombotic complications. She was postoperatively found to have elevated levels of factor VIII, a procoagulant coagulation cascade protein. We routinely refer patients who have multiple thrombotic events for hematologic evaluation following the surgery. As such workups have found several patients to be hypercoagulable, we now perform a more detailed preoperative thrombotic evaluation, including questions about family history of deep venous thromboses or pulmonary embolisms. Patients with a history or family history of thrombotic events often undergo a hematology workup preoperatively.

In patients who present with venous thrombosis before the age of 45, 15 percent will have a deficiency in common, key coagulation cascade proteins.[28] The knowledge of such a deficiency would not preclude us from performing a microvascular procedure; however, it would help us monitor the patient more closely both intraoperatively and postoperatively for any possible thrombotic events.

CONCLUSIONS

Late venous thrombosis is a rare phenomenon that, although occurring late in the postoperative course, is an acute event. Early recognition and urgent treatment are essential to flap salvage, with clinical judgment dictating the treatment choice. In the absence of extenuating circumstances, we prefer urgent exploration in the operating room, as flap survival following late venous thrombosis is a race against time, but with a high probability of flap salvage if the proper steps are taken.

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