Since 2000, nipple-sparing mastectomy (NSM) and immediate breast reconstruction have replaced radical surgical interventions for the treatment of selected patients with breast cancer undergoing prophylactic mastectomy. NSM is technically a difficult procedure. After dissection, the remaining breast skin and nipple-areola complex (NAC) must be thin enough to be free of tumor tissue and thick enough to preserve tissue perfusion. Partial or total NAC necrosis is among the most common complications of NSM and negatively affects cosmetic results.¹

Factor V Leiden (FVL) mutation is the most common cause of hereditary thrombophilia; thrombosis almost always develops in the venous system. The literature includes only a few case series of arterial thrombosis. The present study aimed to describe for the first time a patient with Factor V Leiden mutation that developed nipple-areola complex and skin necrosis, and multiple embolisms in the upper extremity arteries following NSM. (Plast Reconstr Surg Glob Open 2015;3:e529; doi: 10.1097/GOX.0000000000000512; Published online 1 October 2015.)

CLINICAL REPORT

A 61-year-old woman underwent NSM and prophylactic mastectomy of the left breast due to a 5-cm invasive ductal carcinoma in the right breast. During the same surgical session, the right breast was reconstructed using a tissue expander and the left breast was reconstructed using a breast prosthesis. No complications occurred during the intraoperative or postoperative periods, and the patient was discharged 2 days post surgery.

Follow-up 5 days post surgery showed bullae formation in the lateral pillar of the right breast and NAC of the right and left breasts. The bullae were aspirated and the wounds were dressed. The patient presented to the emergency department on postoperative day 7 due to the sensation of cold in the left hand and numbness and cyanosis in the first and second digits. A radial pulse was not present. The patient underwent magnetic pulse resonance angiography,

Summary: Nipple-sparing mastectomy (NSM) and immediate breast reconstruction have replaced radical surgical interventions for the treatment of selected patients with breast cancer undergoing prophylactic mastectomy. NSM is technically a difficult procedure. After dissection, the remaining breast skin and nipple-areola complex (NAC) must be thin enough to be free of tumor tissue and thick enough to preserve tissue perfusion. Factor V Leiden mutation is the most common cause of hereditary thrombophilia; thrombosis almost always develops in the venous system. The literature includes only a few case series of arterial thrombosis. The present study aimed to describe for the first time a patient with Factor V Leiden mutation that developed nipple-areola complex and skin necrosis, and multiple embolisms in the upper extremity arteries following NSM.
which showed thrombus in the subclavian artery and radial artery (Figs. 1, 2). The patient was admitted to the department of vascular surgery for further follow-up.

During 10 days of follow-up in the department of vascular surgery, bullous skin areas developed full-thickness skin necrosis and full-thickness necrosis developed at the incision lines (Fig. 3). The patient responded to medical therapy and circulation in the hand improved; therefore, vascular surgery was not scheduled. Following demarcation of the areas of full-thickness necrosis, the necrotic areas were excised and removed. Hematology consultation due to thrombus formation showed that the patient had an FVL mutation. The patient was then administered low-molecular-weight heparin during and after chemotherapy. Following radiotherapy, the patient was scheduled for implantation of left breast prosthesis and NAC reconstruction of both breasts.

**DISCUSSION**

NAC necrosis is among the most common complications following breast reconstruction. Superficial skin loss can recover spontaneously, whereas full-thickness skin loss can result in infection and prosthesis loss. Smoking, incision type, flap thickness, obesity, and preoperative irradiation are the most common risk factors for loss of breast skin. FVL mutation—an autosomal dominant mutation—is the most common hereditary cause of thrombophilia and accounts for 40–50% of all cases of hereditary hemophilia. The incidence of heterozygous mutation in Caucasians is 5–8% and is associated with a 3- to 7-fold increase in the risk of thrombosis. The incidence of homozygous mutation is 0.18% and is associated with an 80-fold increase in the risk of venous thromboembolism (VTE). FVL mutation was first described by Bertina et al in 1994. As a result of FVL mutation, arginine at amino acid position 506 in the factor V protein is substituted by glutamine. This substitution inactivates activated protein C and decelerates factor V inactivation, which results in a tendency for thrombosis due to over activation of the coagulation cascade (Fig. 4).

Thrombosis is almost always limited to the venous system in individuals harboring FVL mutation and thrombosis is most commonly observed in deep veins.

**Fig. 1.** Magnetic resonance angiography. Arrow shows thrombus in the subclavian artery.

**Fig. 2.** Brachial, ulnar, and radial arteries. * Radial artery cut-off point.

**Fig. 3.** Full-thickness necrosis developed in the lateral pillar of the right breast, NAC of the right and left breasts, and at the incision lines.
Thrombosis in some cases is accompanied by pulmonary embolism. In addition to deep vein thrombosis and pulmonary embolism, cerebral, mesenteric, and portal vein thrombosis have also been reported. There is a debate over arterial thrombosis, and data on thrombosis of the hepatic artery, retinal artery, popliteal artery, and brachial artery are limited to just a few case reports. Studies have reported a weak but controversial association with myocardial infarction, particularly in patients aged <45 years. In patients with heterozygous FVL mutation, environmental factors act in tandem with hereditary factors in the development of thrombosis. Thrombus formation has many triggers, including pregnancy, smoking, use of oral contraceptives, surgery, cancer, and immobilization. The presented patient continued smoking during the early postoperative period, ignoring the recommendation to stop. The presented patient’s history of cancer and surgical trauma—both significant risk factors—in addition to a history of smoking might have triggered arterial thrombosis along with NAC necrosis.

The diagnosis of FVL mutation is established based on genetic testing; however, such testing is not routinely performed in all patients during the preoperative period. Female patients should be asked about problems experienced during pregnancy and history of miscarriage. Late pregnancy loss and pulmonary embolism—with or without deep venous thrombosis in the legs—are the most well-known complications. The presented patient reported 3 late-term pregnancy losses; subsequently, history of pregnancy and miscarriage is investigated extensively in all female patients who present to our outpatient clinic and are scheduled for surgery.

CONCLUSIONS

FVL mutation is the most common cause of thrombophilia. Without external factors (cancer, smoking, trauma, oral contraceptives, etc.), thromboembolic events are rare in FVL heterozygote individuals. Before scheduling patients for a long surgery or cancer surgery, a history of deep vein thrombosis or pulmonary embolism in young patients and miscarriage history in young females may provide clues to the surgeon for conditions as FVL mutation, which cannot be detected by simple laboratory tests during the preoperative period. In the absence of known risk factors, unexplained skin necrosis, and arterial thromboembolism or VTE during the postoperative period should increase the index of suspicion of FVL mutation.

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