It is accepted that immunosuppressant therapy after organ transplantation is associated with an increase risk of neoplasm. Subungual squamous cell carcinoma of the toe is a rare condition and has not previously been reported, to our knowledge, in patients undergoing immunosuppressant therapy. The objective of this case study is to report the clinical and histopathologic findings and the multidisciplinary treatment approach for a case of subungual squamous cell carcinoma of the toe in an organ transplant recipient undergoing immunosuppressant drug therapy. (J Am Podiat Med Assoc 100(4): 304-308, 2010)

It is accepted that the risk of squamous cell carcinoma and other nonmelanoma skin cancers is markedly increased after organ transplantation.\(^1\) With nonmelanoma skin cancer occurring 65 to 250 times more often in transplant recipients than in the general population,\(^2\) long-term implementation of immunosuppression therapy plus the lifetime exposure to sunlight and ultraviolet light may contribute to the higher skin cancer rates.\(^3\) Similar to most cancers, the best outcomes depend on the timing of diagnosis and treatment of the disease. However, owing to the rarity of squamous cell carcinoma in the toenail, it is often overlooked as verruca vulgaris (viral warts), verrucous carcinoma, onychomycosis (fungus), trauma-induced nail dystrophy, chronic paronychia, or epidermoid cysts.\(^4\)\(^-\)\(^7\) This article describes the first reported case, to our knowledge, of invasive squamous cell carcinoma of the great toenail apparatus masquerading as squamous cell carcinoma in situ, or Bowen’s disease, in an organ transplant recipient receiving immunosuppressant therapy.

**Case Report**

A 70-year-old man with a history of cardiac transplantation and immunosuppressant drug therapy presented for Mohs micrographic surgery for squamous cell carcinoma in situ of the left great toe (Fig. 1). The lesion had been present for several weeks and was originally treated with oral terbinafine without improvement. As the lesion persisted, the patient underwent a partial nail avulsion with a 3-mm punch biopsy of the nail bed and lateral perungual skin. A dermatopathologist diagnosed Bowen’s disease based on findings from the punch biopsy specimen (Fig. 2). This punch biopsy specimen was processed as paraffin-embedded permanent sections stained with hematoxylin and eosin. The patient was referred for Mohs micrographic surgery with the referring diagnosis of Bowen’s disease based on the described biopsy findings.

Physical examination revealed 2 × 3-cm dystrophic verrucous plaques covering his entire great toenail, without ulceration or bleeding. Ipsilateral popliteal adenopathy was not appreciated. No other lesions were detected on inspection of the rest of his body. Discussions with his surgical oncology and radiation oncology team concluded that computed tomography for metastasis was not warranted for this localized lesion. Although histologic presentation showed possible viral changes at the granular layer, a human papillomavirus DNA test was not performed.

On the morning of surgery, the entire nail bed was resected (Fig. 3). The diagnosis of invasive squa-
The Mohs surgeon believed that tumor-free margins were unobtainable with Mohs surgery, and the plastic reconstructive surgery service was consulted. Possible reconstruction of the toe extensor mechanisms was also discussed with the podiatric surgery service. However, given the presence of periosteal invasion, consensus was reached to amputate the hallux at the interphalangeal joint. A multispecialty team of physicians followed along with the treatment course of the patient owing to his significant medical history. He was cleared for surgery by his transplant surgeon, his cardiologist, and the department of anesthesiology. His immunosuppressant drug therapy, which included tacrolimus and rapamune for nearly 20 years, was not discontinued. A wide local excision that included amputation of the great toe at the interphalangeal joint level was performed. The pathology service reported invasive squamous cell carcinoma in the periosteum; however, there was no further bone involvement. The patient did well postoperatively, with no local wound problems.

**Discussion**

It is widely accepted that the risk of squamous cell carcinoma is markedly increased after organ transplantation. The development and natural history of nonmelanoma skin cancer seems to be multifactorial; however, it is not well understood. In the United Kingdom, the National Institute on Health and Clinical Excellence published a guidance paper recognizing that organ transplant recipients are at particular risk for squamous cell carcinoma and that the numbers at risk for metastatic disease can be expected to increase as post-transplantation survival rates rise. In general, squamous cell carcinoma is a relatively nonaggressive malignancy, and treatment focuses on excision of the primary tumor. However, those who do develop metastasis have a poor prognosis, with 5-year survival of approximately 25%.

The etiology of subungual squamous cell carcinoma in the toe is unknown, but there are reported possible predisposing factors, including trauma, chronic inflammation, and radiation exposure. Human papillomavirus inoculation has been speculated to play a role in Bowen's disease/squamous cell carcinoma development, especially in immunocompromised patients. However, all cases have been reported with fingernail involvement, and there has never been an association in the toe. There are many reports of organ transplant recipients who are subsequently diagnosed as having...
squamous cell carcinoma, and the most commonly affected regions are the head and neck and the upper extremity. The rarity of this disease, along with its location, encourages us to propose that this is a unique case regarding the organ transplant recipient population.

The present patient had been receiving long-term immunosuppressant drug therapy for more than 20 years. Although most agree that immunosuppressant drug therapy increases the risk of nonmelanoma skin cancer, a recent study has shown that the duration of immunosuppressant drug therapy may have a direct correlation with cancer incidence. Because patients live longer after transplantation owing to advances in medicine and technology, the rate of squamous cell carcinoma is expected to rise as well. However, decreasing the dose of immunosuppressant drug therapy may lead to a decreased risk of nonmelanoma skin cancer.

In many patients, it may not be advisable to decrease the dosage or to discontinue therapy because survival of the transplanted organ may be weighted more

Figure 3. The tumor was resected with Mohs micrographic surgery. A, Preoperative appearance with surgical outlines. B, Postoperative appearance.

Figure 4. Digital slide images captured with a Zeiss Axioskop 40 of the frozen section from the first stage of Mohs surgical excision. A, Low-power (×10) examination shows invasive squamous cell carcinoma involving the central deep resection margin of the nail bed. B, High-power (×40) examination of invasive squamous cell carcinoma reveals marked cellular pleomorphism, hyperchromaticity of nuclei, increased nuclei/cytoplasmic ratios, and mitotic figures (a) and marked cellular pleomorphism (b).
Critically. Therefore, the current recommendation for all organ transplant recipients is to be routinely screened every year, if not more often, for questionable skin lesions.\(^9\), \(^15\) However, as in the present patient, the feet and toenails are commonly overlooked, although some have speculated that predisposing factors for squamous cell carcinoma in the hands are similar to those in the feet.\(^5\), \(^12\), \(^18\) Diagnosis through biopsy was made only after several weeks of treating the lesion as onychomycosis.

The team determined that Mohs micrographic surgery would be attempted to spare the patient’s great toe. As opposed to wide local resections, Mohs micrographic surgery can preserve soft tissue while obtaining clear margins.\(^10\)-\(^24\) After the Mohs surgeon identified positive margins down to the periosteum, a more aggressive approach (ie, amputation) was taken by the plastic surgery service. Although digital amputation or disarticulation to the joint level is commonly used,\(^4\), \(^12\), \(^22\) amputation may have been avoided if detection of the disease and introduction of treatment had been initiated earlier.

The purpose of presenting this case was to report the first unique case of squamous cell carcinoma of the toenail apparatus in an organ transplant recipient and to alert clinicians treating organ transplant recipients to have a heightened suspicion of benign-appearing nail lesions. Since the surgery, the patient has been followed up uneventfully, without recurrence, and he will continue to be screened every 3 months by his oncology team. Several studies\(^1\), \(^3\), \(^15\), \(^23\) recommend routine screening every 3 to 4 months for older patients, those with longer post-transplantation durations, and patients with clinical evidence of previous skin cancers. For any patient with subungual squamous cell carcinoma, recommended therapies vary with each treating clinician; however, most agree that the success of the treatment depends on the extent of the tumor.\(^5\), \(^6\), \(^19\), \(^24\) Timely recognition and treatment of this disease are key to sustaining a higher quality of life for patients. A heightened awareness of the increased risk factors of immunosuppressant drug therapy should keep clinicians suspicious of lesions in the foot and toenail apparatus.

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References


