Blueprint unknown: a case for multidisciplinary management of advanced penile mycosis fungoides

Jonathan S. O'Brien, MD,[1,2] Todd Manning, MD,[1,2] Marlon Perera, MD,[1,2] H. Miles Prince, MD,[3] Nathan Lawrentschuk, MD[1,2,4,5]

[1]Department of Surgery, Austin Health, The University of Melbourne, Victoria, Australia
[2]Young Urology Researchers Organisation (YURO), Melbourne, Australia
[3]Division of Cancer Medicine, Peter MacCallum Cancer Centre and The University of Melbourne, Victoria, Australia
[4]Olivia Newton-John Cancer and Wellness Centre, Austin Health, Heidelberg, Victoria, Australia
[5]Division of Cancer Surgery, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

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A 64-year-old man presented with a 2 week history of progressive phimosis and painful ulcer on his penile meatus. He underwent penile preserving excision, and subsequent pathological examination confirmed T-cell non-Hodgkin lymphoma with immunohistochemical features of large cell transformation of mycosis fungoides. The penis was further treated with local external beam radiotherapy consisting of 27 Gy in 15 fractions and systemic mini-CHOP chemotherapy. An organ-preserving tissue response has since been achieved. This case is the first of its kind in the literature and firmly highlights the role of multidisciplinary management for this rare malignancy.

Key Words: penile lymphoma, mycosis fungoides, penile cancer, radiotherapy, chemotherapy

Introduction

Non-Hodgkin lymphomas (NHL) are a diverse family of hematological malignancies arising from lymphoid cells. These diseases are classified based on their clinical course and histopathological features of T cell or B cell lineages. T-cell lymphomas have a diverse spectrum of clinical behavior ranging from chronic indolent forms to aggressive variants. Most lymphomas proliferate with the lymph nodes or bone marrow, however, primary extra-nodal lymphoma involving the gastrointestinal tract, liver, central nervous system and skin are recognized within the World Health Organization (WHO) classification.[1]

Primary cutaneous lymphomas represent 19% of extra nodal NHL of which approximately three quarters are T-cell malignancies.[1] Mycosis fungoides (MF) is the most commonly observed form of primary cutaneous T-cell lymphomas (CTCL) and is a clonal expansion of memory T-helper cells typically residing in the epidermis. The incidence is increasing with approximately 1,600 new diagnoses in the United States per year.[1] MF typically presents with patch or plaque disease although a minority of patients can develop more advanced-stage disease with tumors, erythroderma, nodal or visceral involvement.

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Address correspondence to Dr. Nathan Lawrentschuk, 5/210 Burgundy Street, Heidelberg, VIC, 3084

The penile lesion biopsy in the case presented here demonstrated large-cell transformation (LCT) of MF. LCT is relatively rare and is pathologically defined by the presence of large lymphocytes comprising at least 25% of the total infiltrate. Although LCT can behave in a variable fashion, it is generally associated with a poor survival and requires a more aggressive therapeutic approach.[2]

Case report

A 64-year-old man with a complex medical history was referred to our tertiary urological service with a 2 week history of progressive phimosis and a painful ulcer on his penile meatus. He presented with multiple comorbidities including a 9 year history of dialysis-dependent renal failure due to focal segmental glomerular sclerosis, ischemic heart disease and MF diagnosed 9 months previously. He had previously received local radiotherapy for cutaneous tumors of MF affecting his left groin and suprapubic region which was being managed with 10 mg of weekly methotrexate.

On examination of the penis, the prepuce was overtly erythematous and the foreskin was tender and non-retractile. An extensive necrotic ulcer was observed extending from the foreskin to the glans penis measuring 14 mm x 12 mm x 8 mm, Figure 1. The extensive inflammatory reaction rendered circumcision impossible and urethroscopy was attempted and found to be impossible beyond 5 mm from the external penile urethra. There was no evidence of palpable lymphadenopathy. His abdomen

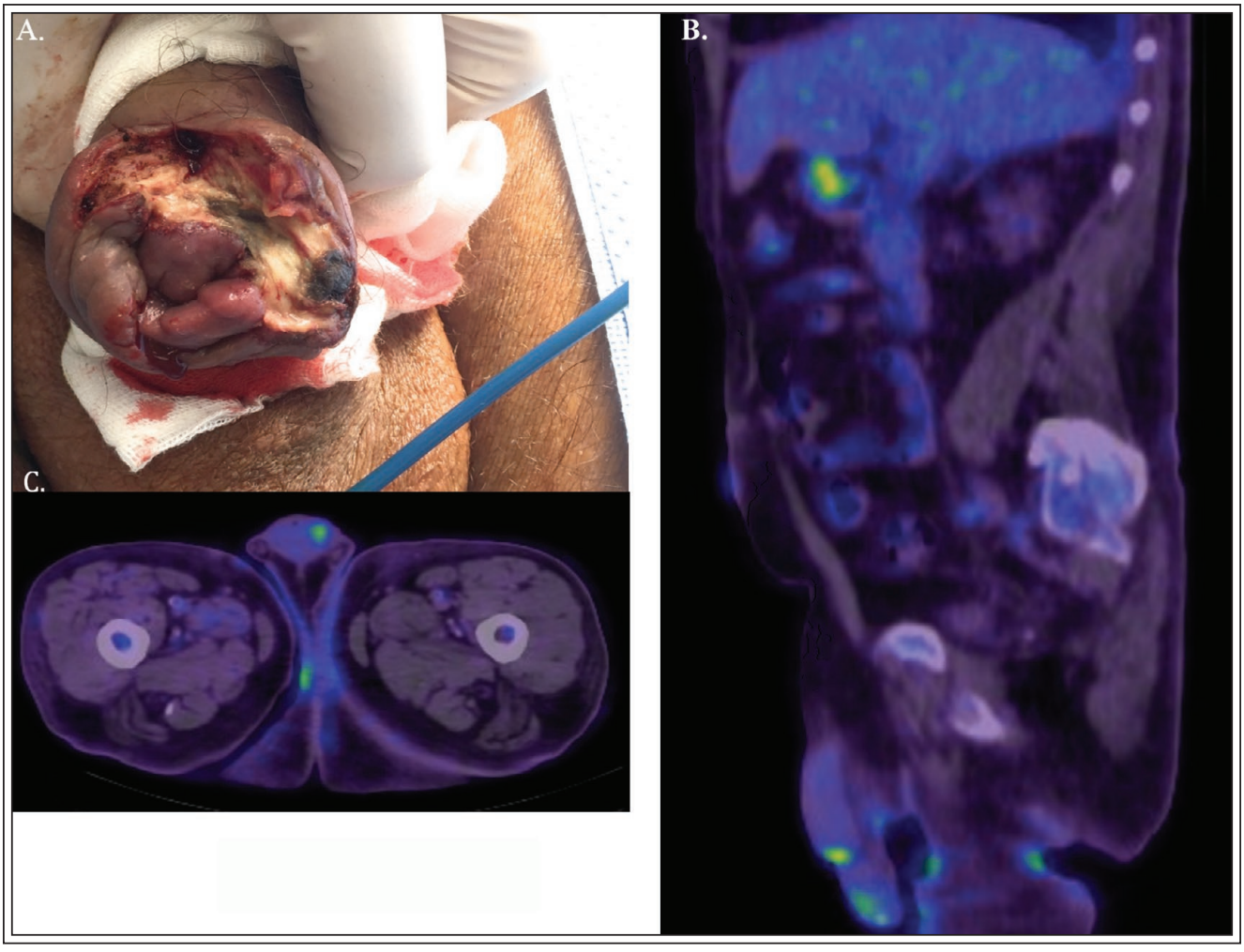

Figure 1. Mycosis fungoides of the penis. **A)** Intraoperative photo depicting the necrotic MF lesion extending from the foreskin to the glans penis measuring 14 mm x 12 mm x 8 mm. PET/CT demonstrating increased 18F-fluorodeoxyglucose (18F-FDG) avidity in the penis in sagittal **B)** and axial **C)** windows.

was unremarkable with no significant hepatomegaly, splenomegaly, palpable kidneys or palpable inguinal lymphadenopathy. Rectal examination revealed a small benign prostate. He was re-staged with PET/CT which demonstrated evidence of disease progression from 3 months previously; multiple ^{18}F-FDG-avid skin and superficial lesions were observed in the chest, abdominal wall and medial aspect of the right upper thigh with no abnormal FDG uptake within lymph nodes or viscera. Full blood examination demonstrated no lymphocytosis nor evidence of circulating lymphoma cells. Biochemistry was within expected limits for a person with well managed end-stage kidney disease.

Concern was raised that the lesions could be penile squamous cell carcinoma (SCC) and biopsies were taken of the ulcerated area for histopathological analysis.

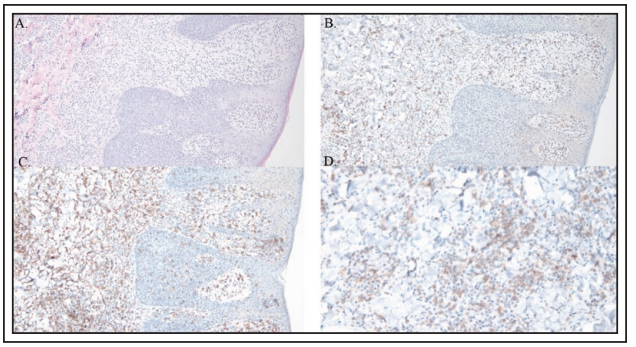

Figure 2. A) Histopathology of penile biopsy showing features of large cell transformation mycosis fungoides. (H&E, x100). **B)** CD30- antibody immunohistochemistry stain, x100. **C)** CD4+ antibody immunohistochemistry stain, x100. **D)** x200.

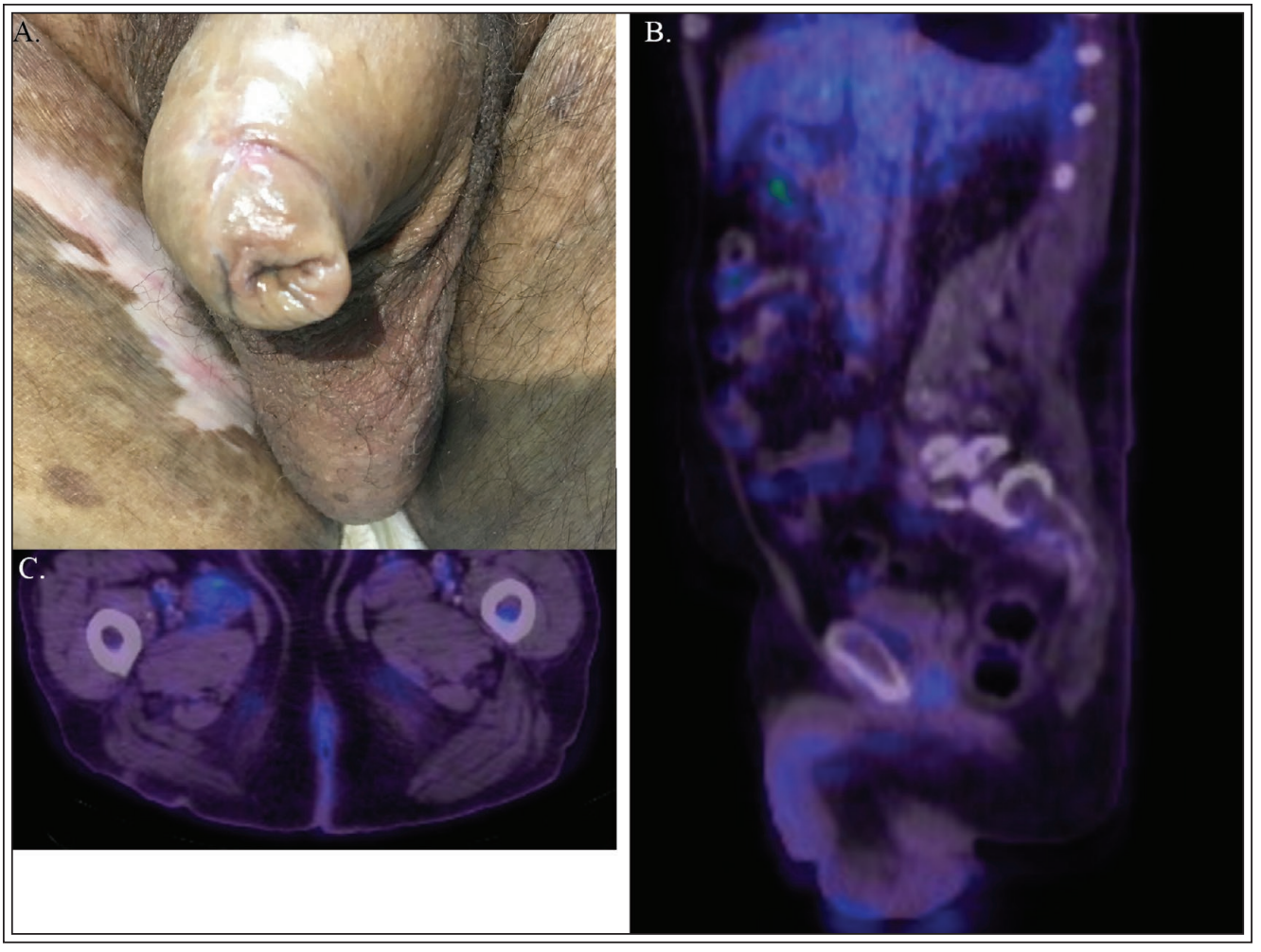

Figure 3. Mycosis fungoides of the penis 6 months post-treatment. **A)** Postoperative depicting a well healed scar on the foreskin measuring approximately 3 cm. PET/CTdemonstrating resolution of disease in the penis in sagittal **B)** and axial **C)** windows.

An extensive excision and glans reconstruction was required to remove the tumor and restore the functional anatomy of the penis. Histopathological analysis of the tissue demonstrated heavy mixed inflammatory T-cell infiltrate consistent with large cell transformation MF, Figure 2. The immunohistochemical profile of the lesion indicated: CD3 (+), CD5 (+), CD4 (+), CD8 (rare, weak staining), CD30 (-), CD20 (-). These investigative results were consistent with a diagnosis of stage IIB (T3, N0, M0, B0) MF.[3]

The extensive debridement of the patient's glans raised concern that further surgery would be required. The patient was also apprehensive about extensive surgical resection. Subsequently, a multidisciplinary discussion was organized to consider the relevant management options. The team decided to increase the dose of methotrexate from 15 mg to 20 mg weekly. External beam radiotherapy to the penis with a planned course of 30 Gy in 20 fractions allotted as three fractions per week was initiated. It was discussed that if penile preserving options failed, a partial or radical penectomy would be offered. The patient was counseled and agreed with the management plan.

After 21 Gy of radiotherapy, the patient experienced a relapse of widespread cutaneous disease. His management was reassessed by the multidisciplinary team and his radiotherapy treatment was curtailed at 27 Gy in 15 fractions to facilitate a more aggressive chemotherapeutic regimen. Three cycles of mini-CHOP were administered a total dose of cyclophosphamide 970 mg, vinicristine 1 mg, doxorubicin 60 mg, predisolone 100 mg, which he tolerated well and has since achieved a remission phase of the disease.

The patient received a routine ^{18}F-FDG PET/CT scan and was clinically reassessed by the urology team 6 months post penile preserving surgery. On examination his penis was non-tender and functionally intact with a non-retractile foreskin. Both the team and the patient were satisfied with cosmetic result which consisted of a 3 cm well healed scar, Figure 3. Because the patient had a long history of phimosis, there was little concern of his non-retractile foreskin and he was discharged from our service.

The positive examination was supported by the PET/CT results which demonstrated a remission of FDG-avid disease in his penis. The report highlighted that the patient has experienced a mixed response to systemic treatment. Previously noted lymphadenopathy and cutaneous lesions had resolved, however, new disease foci were observed developing on the patient's right distal leg right wrist. He continues palliative management for MF under radiation oncology and hematology.

Discussion

MF infiltration of penile tissue is a rare phenomenon. An extensive search of the English literature was conducted and yielded only a single previous case report of a solitary penile MF plaque that was treated with topical imiquimod rather than radiation.[4] Additionally, our case represents the first description of aggressive penile MF with LCT. Our ability to achieve a favorable oncological outcome with penile preserving interventions highlights the importance of a multi-disciplinary approach to treat novel disease presentations.

Penile MF is a diagnostic challenge because clinical presentations can be considerably heterogeneous. Symptoms of penile lymphomas often overlap with more common penile diseases such as Peyronie's disease, lichen sclerosis, syphilis or squamous cell carcinoma. Presentations have included painless, progressive swelling, or ulceration of shaft, glans and penile skin.[5] Pruritus and dysuria precipitated by recurrent balanitis and phimosis of the uncircumcised male foreskin has been reported. Lesions of the penile shaft can obstruct blood vessels on the corpus cavernosum, causing erectile dysfunction. Plaques or ulcers that disrupt phallobase and inguinal lymphatic drainage can give rise to diffuse induration and oedema of preputial tissue. These non-specific symptoms will often have a prolonged indolent course in the early stages of the disease which can delay patient presentation and lengthen time to diagnosis.[6]

Our case presented with a relatively short history of progressive phimosis and a painful ulcer on the penile meatus. Our team was initially concerned that the underlying pathology could be due to penile squamous cell carcinoma, which often has an insidious onset of symptoms. This case highlights the importance of maintaining a measured approach and broad differential diagnosis when managing patients with a complex cutaneous disease such as MF.

Contemporary retrospective series have demonstrated that the median time from symptom onset until diagnosis is 3-4 years in patients with MF.[7] Accurate diagnosis requires a skillful excision or wedge resection of the lesion followed by pathological analysis to differentiate lymphomas from undifferentiated sarcomas or carcinomas. With penile MF the role of urologists is to achieve a comprehensive tissue sample with an attempt at oncological excision whilst also maintaining penile functional anatomy and cosmesis.

Patients with a MF tissue diagnosis require further investigation to assess disease burden and inform

staging. The role of ^{18}F-FDG PET/CT in staging MF is controversial. However, MF lesions are typically ^{18}F-FDG avid, and it has been demonstrated to be useful for defining the extent of extra-cutaneous disease.[8] Our case demonstrated multiple ^{18}F-FDG-avid superficial lesions but no lymphadenopathy or visceral structure involvement. The increased uptake on his penis at the time was not initially reported, but rapidly developed into a symptomatic lesion.

Current International Society for Cutaneous Lymphomas (ISCL)/European Organisation for Research and Treatment of Cancer (EORTC) staging guidelines for MF incorporate extent of skin disease, type of lesion as well as involvement of peripheral blood and extra-cutaneous sites. Our case presented with a locally invasive penile tumor (T3) and limited cutaneous disease (N0, M0, B0), which is consistent stage IIB MF.[3] Furthermore, an inferior outcome for this patient is predicted given the large cell transformation of the lesion.

T-cell lymphomas are among the rarest neoplastic diseases affecting the penis. Management of these diseases remains controversial because of their heterogenous presentation and clinical course. Of the previous six cases in the literature, topical steroids, imiquimod, external beam radiation, systemic chemotherapy, circumcision and surgical excision have been used as intervention strategies with variable degrees of success.[4,9] Despite the lack of standardization, clinical responses were achieved in five out of six cases with an average follow up of 16 months.

The surgical approach for MF is different from other malignancies of the penis. It has been proposed that the absence of lymphoid tissue in the penis suggests that penile lymphomas are a local manifestation of a systemic disease. This has formed the rational for combination therapy because adequate systemic treatment should also address the local disease process.

Achieving clear surgical margins is crucial for achieving oncological control in more common penile neoplasms, however there is a paucity of evidence of whether this is required for penile MF. Teams treating penile lymphoma have reported that achieving tumor-free margins may have a therapeutic role, however its effect on outcomes remains controversial.[5,9] Groups investigating non-urogenital cutaneous lymphomas, have achieved satisfactory results with surgical margins of 5 mm.[10] In the absence of more relevant data, we aimed to preserve normal penile architecture by aiming for a surgical margin of 2 mm combined with adjuvant radiotherapy and chemotherapy.

Cutaneous lymphomas are highly radiosensitive and local radiotherapy is a key palliative therapy for MF. Given this patient's previous response to radiotherapy to lesions on his thigh and back, the MDT planned to administer 30 Gy of local radiotherapy to the penis in 20 fractions. During this time, he was also receiving additional systemic therapy 20 mg of methotrexate weekly. After 21 Gy of radiotherapy, his penile tissue had achieved an adequate response but he experienced progression at other cutaneous sites. Consequently, radiotherapy was curtailed at 27 Gy, and he then received a more aggressive chemotherapy regimen. However, it is important to note that given the relatively brief duration of response, chemotherapy remains a largely palliative option for most patients, including the patient described in this case.

Conclusion

This case emphasizes the clinical heterogeneity of MF and the challenge of coordinating care and escalating therapy in the context of MDT management. Certainly, as the management of penile cancers becomes concentrated in tertiary centers, achieving favorable outcomes requires urologists to maintain vigilance for rare neoplasms and integrate care among relevant subspecialties. This case presents an additional management pathway for a rare disease. Successfully achieving formal tissue diagnosis, excellent local response and limiting extensive surgical debridement in patients diagnosed with CTCL of the penis. □

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