At a 12-week follow-up appointment, a dramatic improvement in the appearance of the cutaneous lesions was noted, with near complete resolution of the patches and plaques and small residual foci at the prior larger nodular areas. The patient continued topical nitrogen mustard with improved improvement over 12 additional weeks (Figure 1B). However, the patient subsequently developed ophthalmic symptoms, including vertical and abduction defects, blurred vision, and peripheral vision loss, attributed to ocular involvement of the NXG. The patient then began dexamethasone 20-mg dose twice a week and cyclophosphamide 300-mg/m² doses on days 1, 8, and 15 of a 28-day cycle. He has shown clinical and laboratory improvement after 6 months.

Discussion | Necrobiotic xanthogranuloma is a chronic granulomatous disorder with the potential to affect multiple organs and is strongly associated with paraproteinemias and lymphoproliferative disease. The typical cutaneous lesions are yellowish-to-orange and erythematous-to-violaceous papules, plaques, and nodules, often with overlying telangiectasias. Scarring and ulceration may also occur in a subset of patients. Ocular lesions are found in the vast majority of patients. For most patients, skin lesions initially start on the trunk or extremities and subsequently involve the periocular area. Most cases are asymptomatic, although pain, and pruritus may occur. Extracutaneous sites may rarely be involved, including the lung, myocardium, larynx, pharynx, skeletal muscle, kidney, intestine, and ovary. Most importantly, approximately 90% of patients with NXG display a paraproteinemia, with IgG-κ monoclonal gammopathy being the most common.

Histopathologically, NXG is characterized by a granulomatous inflammation in the dermis extending into the subcutaneous fat. There are zones of necrobiosis surrounded by granulomas with foreign body-type cells and Touton giant cells. Degenerated collagen is common, and cholesterol clefts within the necrobiosis are characteristic of NXG.

Treatment approaches depend on whether the physician is treating the cutaneous NXG alone or alongside the paraproteinemia component. Successful treatments with corticosteroids (topical, intralesional, and/or systemic), alkylating agents (chlorambucil and cyclophosphamide), interferon alpha, thalidomide, lenalidomide, intravenous immunoglobulin, phototherapy, and plasmapheresis have been reported. Nitrogen mustard is an alkylating antineoplastic agent that has been used to treat cutaneous T-cell lymphoma for over 40 years with a good safety profile. Our patient demonstrated a significant improvement with topical nitrogen mustard, which may be a viable therapeutic option for some cases of NXG.

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Inverse Psoriasiform Eruption During Pembrolizumab Therapy for Metastatic Melanoma

Research in immunotherapy has led to tremendous advancements in the treatment of patients with advanced or metastatic melanoma. The immune checkpoint inhibitors are highly selective agents that exploit key pathways used by malignant cells to evade the host immune response. Pembrolizumab, the first anti–PD-1 humanized antibody approved for cancer therapy, acts by inhibiting the PD-1/PD-1L axis that plays a key role in regulating T-cell activity and helps potentiate the antitumor host immune response. In a randomized clinical trial of patients with advanced melanoma, those randomized to pembrolizumab had a 12-month survival rate of 74%. Despite these groundbreaking therapies, PD-1 inhibitors have been associated with a variety of cutaneous adverse events that can affect morbidity and quality of life. To date, few reports exist characterizing the dermatologic adverse effects of anti–PD-1 therapy. Here we report a case of a patient with metastatic melanoma undergoing pembrolizumab therapy who developed an inverse psoriasiform eruption.

Report of a Case | A woman in her 80s receiving pembrolizumab treatment (2 mg/kg) for metastatic melanoma of the lung and spine presented with a 2-month history of a worsening vaginal and intergluteal pink-red plaque with several erosions and yellow crusting. She developed the eruption between treatment cycles 2 and 3 of pembrolizumab and was hospitalized for what was believed to be a worsening yeast infection, bacterial cellulitis, or even early-stage necrotizing fasciitis.

On admission, she was afebrile with mild leukocytosis and normal pelvis computed tomographic findings. She was started
on treatment with broad-spectrum antibiotics and intravenous fluconazole. Physical examination revealed a well-demarcated, thin, pink-red plaque with a red to violaceous rim extending from her mons pubis to her intergluteal folds, with several 3- to 9-mm erosions (Figure 1). She had mild induration of her right perineal skin but no tenderness, fluctuance, or crepitus. There was desquamating yellow scale-crust. Workup findings were negative for tinea or herpes simplex virus. Wound cultures grew 3+ pansensitive Staphylococcus aureus, and blood cultures were negative.

Punch biopsy specimens taken from her right buttocks showed psoriasiform hyperplasia with mature keratinocytes and focal spongiosis (Figure 2). There was a superficial, mainly lymphocytic inflammatory infiltrate, with scattered eosinophils and dermal edema. Periodic acid–Schiff staining was negative. All oral antifungal agents and antibiotics were stopped, and patient began treatment with clobetasol, 0.05%, and mupirocin ointments with rapid clinical improvement. Subsequent computed tomographic imaging showed an interval decrease in the size of metastatic nodules of the lungs with a stable lytic lesion of the spine. She was subsequently able to resume additional cycles of pembrolizumab.

Discussion | Anti-PD-1 therapy is generally well tolerated, but cutaneous adverse events occur in approximately 18% to 42% of patients.3–5 These cutaneous adverse events have yet to be fully characterized. A recent joint institutional investigation reported maculopapular eruption, pruritus, and hypopigmentation as the top cutaneous adverse reactions within their pembrolizumab-receiving cohort.3 Here we report the first case, to our knowledge, of a psoriasiform eruption in a patient undergoing pembrolizumab treatment for metastatic melanoma.

While the prognostic value of cutaneous reactions from checkpoint inhibitors remains contested and is not as established as in other cancer treatments, it should be noted that this patient’s lung nodules showed interval regression following occurrence of her psoriasiform eruption. Additional studies will help further elucidate the relationship between immune-related cutaneous eruptions and antitumor activity. Furthermore, it is believed that patients who switch from one checkpoint inhibitor to another may develop completely different eruptions.5 Awareness of immune-mediated cutaneous adverse events in patients undergoing cancer treatment will enable earlier diagnosis and management, translating to a better quality of life, with the goal of continuing therapy without disruption. As immunotherapies become the mainstay of treatment for cancer, further studies will be critical for understanding the types and prevalence of cutaneous adverse events.

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6. Shoushtari AN, Postow MA, Horvat TZ, Adel NG, Dang T, Chapman PB. Safety of pembrolizumab (pem) in patients (pts) who stopped ipilimumab (ipi) due to immune-related adverse events. Presented at the ASCO Annual Meeting, May 29 to June 2, 2015; Chicago, IL.

CORRECTION

Author Middle Initial Omitted: In the Clinico-pathological Challenge titled “Painful Perianal Papules in a Middle-Aged Woman,” published online March 23, 2016, there was an omission of the first author’s middle initial. The author’s initial has been added, and the article was corrected online.

NOTABLE NOTES

The Hypertrichosis of Esau

Charles M. Phillips, MD

The story of Jacob and Esau is told in the Old Testament book of Genesis (Genesis 25:19-33:20. NIV). Jacob and Esau were the twin sons of Rebekah and Isaac. The story is one of struggle starting before birth and through their adulthood. Esau, we are told, was the first born and was covered with red hair “like a hairy mantle.” Other translations are “garment,” “fur coat,” while others translate it as “it (hair) was all over his body.”

The diagnosis of hypertrichosis congenita is rare. The differential diagnosis is well elucidated in 2 review articles on the subject.1,2 Hypertrichosis can be divided into localized and generalized variants, and the generalized variants may have associated other findings, such as mental retardation, spina bifida, gingival hyperplasia, and short stature.

Esau had a truly congenital hypertrichosis in that he was born hairy. From the rest of his story it is hard to find any other associated physical findings. He was accomplished and presumably enjoyed good health and mentation; In Genesis 25:27 we learn that Esau became a good hunter and an outdoorsman. Chapter 26, describes a plot that was hatched to steal the blessing from Isaac that would be directed at Isaac’s eldest son, Esau. With the help of his mother, Jacob covered his skin with the hide of a goat to cover the smooth skin on his neck and arms to mimic his hairier brother Esau. His elderly, blind father then mistook Jacob for Esau and bestowed his blessing on the younger brother, Jacob. Despite these setbacks and excessive hairiness, Esau went on to be successful in his own right; he married, led a group of 400 men, and fathered many children and grandchildren. He was so successful that he had to move his family away from Jacob to find enough land to support his flocks.

The hypertrichosis in the story of Esau was congenital and persisted throughout his life. Despite his excessive hair and the betrayal at the hand of his brother Jacob, Esau went on to be a successful patriarch and businessman.

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