BRIEF ARTICLES

Nab-paclitaxel/gemcitabine Induced Acquired Ichthyosis

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ABSTRACT

The ichthyoses are a diverse group of cutaneous disorders characterized by abnormalities in cornification. The majority of ichthyoses are inherited with childhood presentation and new onset ichthyosis in adulthood warrants further medical evaluation. Though most well recognized for its association with Hodgkin's disease, acquired ichthyosis (AI) has been linked to a number of inflammatory, autoimmune, and endocrine processes. However, drug- induced AI is exceedingly rare and remains a poorly understood entity. Here we report a case of a male patient who developed AI while receiving nab-paclitaxel plus gemcitabine for treatment of pancreatic adenocarcinoma.

INTRODUCTION

Acquired ichythyosis (AI) is an uncommon non-inherited cutaneous disorder of abnormal keratinization that is most frequently associated with underlying malignancy. Drug induced AI is uncommon and has been rarely linked to chemotherapeutic agents. Herein, we report the case of a man with pancreatic adenocarcinoma who developed an ichthyosiform eruption upon starting chemotherapy with nab-paclitaxel plus gemcitabine.

CASE REPORT

A 70-year-old male physician with a history of stage II pancreatic adenocarcinoma presented for evaluation of lower extremity swelling and progressive dry, flaky skin. Ten months prior, the patient was first seen for recurrent, self-healing, pruritic erythematous papules. Punch biopsy was performed which showed an atypical cellular infiltrate of scattered large CD30+ cells with clonal T-cell receptor-β gene rearrangement. Though the clinicopathologic diagnosis was most consistent with lymphomatoid papulosis (LyP), imaging was pursued to exclude extracutaneous lymphoproliferative disease. CT scan incidentally detected a mass in the body of the pancreas and biopsy was concordant with pancreatic adenocarcinoma. The patient was otherwise healthy with no medical problems and did not take any medications.

Within the first few weeks of starting chemotherapy with nab-paclitaxel plus gemcitabine, the patient reported new onset lower extremity swelling and skin redness. Lower extremity doppler ultrasound was

negative for deep vein thrombosis (DVT) and the patient denied any previous history of leg swelling. Shortly thereafter he noted progressive non-pruritic, dry, scaly skin, on the legs that was unresponsive to intensive moisturization. After 3 months of medical treatment, pancreatectomy was performed which was followed by adjuvant chemotherapy, again with nab-paclitaxel plus gemcitabine. In the perioperative period during which chemotherapy was held, the patient noted reduced lower extremity swelling and decreased skin dryness on his legs.

At the time of presentation, the patient was in his fourth month of adjuvant chemotherapy. Upon resuming treatment, the patient noted that the leg swelling had returned and his skin had become dry with thick scale. Physical exam was notable for bilateral lower extremity pitting edema and erythema with overlying thick, brown, geometric scales on the anterior tibias (Figure 1). Lower extremity venous ultrasound was again negative for DVT. Clinical presentation, within the context of patient history, was most consistent with drug induced acquired ichthyosis and the patient was started on clobetasol ointment.

DISCUSSION

The ichthyoses are a heterogeneous group of cutaneous disorders that can be acquired or congenital. Ichthyosis vulgaris (IV), the most common inherited ichthyosis, is a benign dermatologic condition due to loss of function mutations in the filaggrin (FLG) gene. FLG protein is critical for normal epidermal homeostasis and proper skin barrier function.[1] IV typically arises in childhood and is characterized by chronic skin scaling, usually affecting the abdomen and extensor surfaces of the extremities.

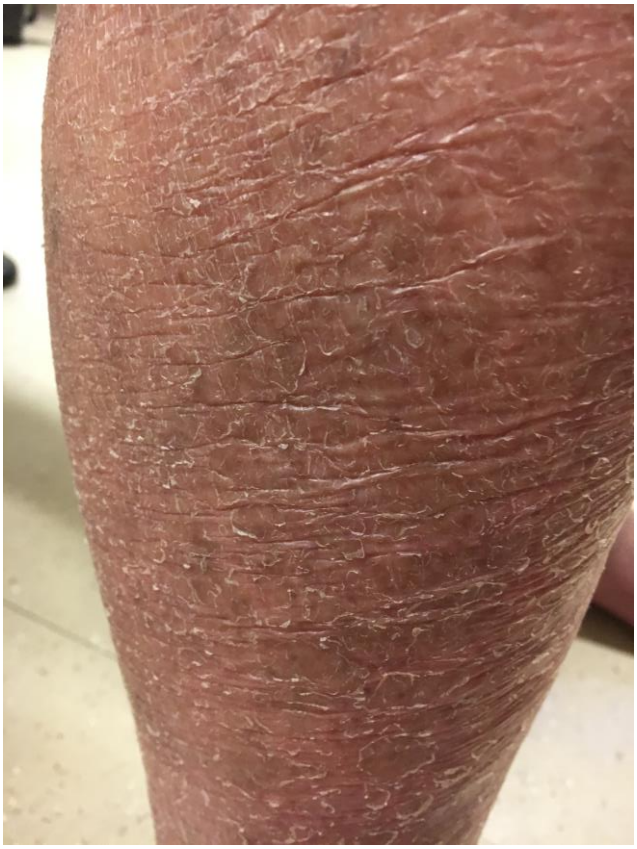

Figure 1: Ichthyosiform plate-like, brown patches with scale on the right anterior lower leg.patient history, was most consistent with drug induced AI and the patient was started on clobetasol ointment.

While physical exam findings of AI can be virtually identical to that of IV, AI develops in adulthood and is frequently associated with underlying systemic disease.[2] AI has been correlated with several conditions including hyperparathyroidism[3], malnutrition[4] and LyP[5]; however, it is most commonly observed as a paraneoplastic syndrome in Hodgkin's disease.[6]

Chemotherapy associated AI has rarely been described with the majority of documented cases confined to one study. Of 74 hospitalized patients evaluated for mucocutaneous complications of chemotherapy, AI was reported in patients treated with doxorubicin (n=11), cytarabine

(n=10), cisplatin (n=4), cyclophosphamide (n=3), etoposide (n=3), vincristine (n=3), gemcitabine (n=2), hydroxyurea (n=2), aminocamptothecin (n=1), mitomycin (n=1), mitoxanthrone (n=1), vinblastine (n=1), bleomycin (n=1), carboplatin (n=1), and docetaxel (n=1).[7] Interpretation of this data is however difficult as no patient received monotherapy and drug regimens were not specified. Other than the aforementioned drugs, ponatinib is the only other chemotherapeutic agent reported in association with AI.[8]

Within the context of this patient, there were several considerations regarding the etiology of AI. Paraneoplastic AI was considered less likely as skin changes most frequently coincide or precede the diagnosis of malignancy and generally improve, not worsen, with treatment.[2] The possibility of AI due to malabsorption was also felt to be unlikely as there was no evidence of such before or after pancreatectomy. The patient's recent diagnosis of LyP was somewhat interesting as LyP has been previously associated with AI.[5] However, given the temporal association of chemotherapy administration and development of AI, we feel this most strongly supports the assumption that AI was chemotherapy-induced.

Since this patient was treated with nab-paclitaxel plus gemcitabine, it is impossible to determine if one or both drugs were contributory. Though uncommon, gemcitabine has been associated with the development of acute lipodermatosclerosis-like or "pseudocellulitis" reactions.[9] The pathophysiology of this reaction is unknown but underlying defects in lymphatic drainage have been suggested as the inciting factor. Subsequent accumulation of fluid in the interstitial space could lead to drug accumulation in subcutaneous tissue and localized dermatologic toxicity due to impaired drug inactivation.[10] Similar to this case, patients typically present with acute onset lower extremity swelling, erythema, and hyperpigmentation over the anterior tibia.[9]

Nab-paclitaxel is an albumin-bound formulation of paclitaxel and belongs to the taxane family of drugs which have been shown to upregulate the production of various cytokines, including tumor necrosis factor-α (TNF-α).[11] Overexpression of TNF-α has been associated with defects in normal skin barrier formation and has been extensively studied in psoriasis.[1] Pathologic expression of TNF-α has been correlated with impaired synthesis of skin barrier proteins including FLG and loricin – both of which are needed for normal formation of the stratum corneum.[1]

We can only speculate about whether gemcitabine, nab-paclitaxel or the combination of both resulted in the development of AI in this patient. It is possible that gemcitabine caused alterations in vascular permeability which altered the inflammatory microenvironement, leading to localized defective tissue repair and keratinocyte dysfunction. With increased fluid extravasation into the subcutaneous tissue, the overlying skin may have been more susceptible to the effects enhanced TNF-α expression, resulting in impaired skin barrier function. Interestingly, it has been shown that patients with pancreatic cancer frequently have increased levels of TNF-α, and thus this may also have played a role.[12] It is presently unclear how gemcitabine, nab-paclitaxel, and systemic cytokine dysregulation may interact to produce AI and additional research is warranted.

Conflict of Interest Disclosures: None.

Funding: None.

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