Toxic epidermal necrolysis caused by etonogestrel implantation: A rare presentation

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The etonogestrel implant (Nexplanon**,** Merck & Co., Inc) is a radiopaque, rod-shaped, subdermal implant used for contraception.[1] The implant contains etonogestrel (68 mg), a synthetic progestin, which provides contraception for up to 3 years.

Adverse effects related to implant insertion include pain, irritation, swelling, bruising, paresthesias, scarring, and keloid formation. Injury to the nerves and blood vessels can also occur during implantation and removal.[1] However, there are no documented reports of etonogestrel implant–induced skin sloughing, skin necrosis, or epidermolysis in the current literature. In this report, we describe a case of toxic epidermal necrolysis (TEN) related to recent etonogestrel implantation.

Abbreviation used:

TEN: toxic epidermal necrolysis

CASE REPORT

A 34-year-old woman presented to the emergency department with a pruritic rash that began the evening prior. The rash began 14 days after etonogestrel implantation, initially presented on the face, and within hours, subsequently spread to involve the scalp, arms, chest, back, and buttocks. The patient also reported painful lips and a sore throat without shortness of breath or wheezing. The patient was febrile (102.9 °F) in the emergency department and was only able to tolerate liquids. Oropharyngeal examination showed swollen lips with crusting. The tongue appeared normal without swelling or discoloration. No lymph nodes were palpated. Skin examination revealed numerous pink papules coalescing into plaques on the face (Fig 1). Scattered papules were observed on the arms, chest, back, and buttocks but spared the legs, palms, and soles. The conjunctivae and vaginal mucosa were unaffected.

The patient's past medical history included hypothyroidism, hypertension, hyperlipidemia, prediabetes, obesity, depression, nonalcoholic fatty liver disease, mild intermittent asthma, atopic dermatitis, and septic arthritis of the ankle 3 years prior. Active medications included levothyroxine (225 μg) and a recently placed etonogestrel implant. No known drug allergies were reported.

The patient was admitted to the medical intensive care unit for further work-up and monitoring. Empiric antibiotics and antihistamines were initiated. Skin punch biopsy of the right upper thigh demonstrated interface dermatitis, consistent with evolving TEN (Fig 2). Other than a positive rapid strep test, comprehensive infectious disease screening was negative for acute or subacute viral infections, including mycoplasma pneumonia. Because the patient's only new medication was the etonogestrel implant, TEN was presumed to be caused by the implant by a diagnosis of exclusion, and the implant was ultimately removed on hospital day 5 (19 days after implant).

After 5 days in the medical intensive care unit, the patient was transferred to our burn center for evaluation and management. We observed a

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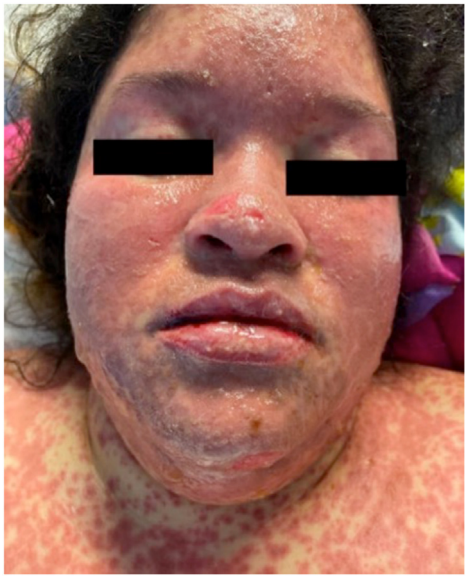

Fig 1. Toxic epidermal necrolysis. Clinical photograph of the patient upon initial presentation demonstrating extensive facial and labial involvement.

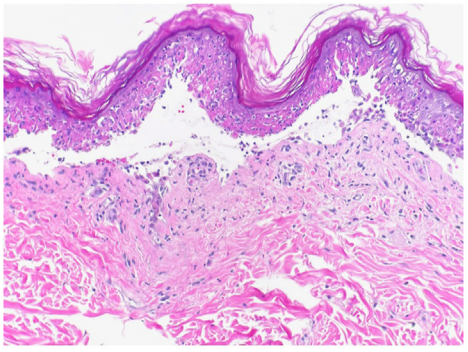

Fig 2. Skin biopsy of the right upper thigh. Skin biopsy demonstrates notable separation of the epidermis from the dermis at the dermoepidermal junction, which contains lymphocytes, vacuolar changes, and occasional necrotic keratinocytes. (Original magnification: ×20.)

full-body eruption of pink and red papules, erythematous plaques on the trunk and extremities, and scattered serous-filled vesicles over the face, back (Fig 3, *A*), upper extremities (Fig 3, *B*), lower extremities, and perineum. Several areas of epidermolysis with a clean, erythematous base were noted (Fig 3, *C*). Mucosal sloughing, hemorrhagic crusting, and desquamation of the lips were also present. The patient was treated supportively with pain control and intravenous IgG (90 g daily at 75 mL/h) for 3 days. The epidermolysis improved gradually with local wound care and whirlpool therapy. The patient began tolerating a regular diet and was discharged 6 days after admission to the burn center following an uncomplicated hospital course.

DISCUSSION

Given our patient's history, presentation, and histological findings, we determined that TEN developed because of the recently placed etonogestrel implant. This diagnosis was reinforced by improving clinical status soon after the implant was removed. The pathogenesis of TEN following etonogestrel implantation in this patient remains unclear, but there are potential hypotheses that should be considered.

The etonogestrel implant is contraindicated in women with active liver disease because of the poor metabolization of progestin.[1] This patient had a history of nonalcoholic fatty liver disease, raising concern for supratherapeutic levels of progestin. Evidence suggests that progesterone-only contraceptives, such as the etonogestrel implant, can trigger or worsen many skin conditions, including acne, hirsutism, rosacea, and alopecia.[2] However, the relationship between progestin and TEN has not been investigated. One case report discusses TEN secondary to levonorgestrel- and ethinyl estradiol–containing contraceptive pill use.[3] Another case report discusses a rare delayed-type (type IV) hypersensitivity reaction to nexplanon manifesting 3 months after implant that was described as red papules surrounding the implant site with progression to erythema and edema of the entire arm.[4] Notably, Stevens-Johnson syndrome/TEN are also considered delayed-type hypersensitivity reactions that may be associated with individual *HLA* and non-*HLA* genes, although many factors contributing to TEN have yet to be identified.[5] Another dermatologic manifestation of progesterone—progestogen hypersensitivity, also known as autoimmune progesterone dermatitis—is a cyclical skin eruption corresponding to the luteal phase of the menstrual cycle.[6] Progestogen hypersensitivity has a variable dermatologic presentation and, therefore, multiple theories underlying its pathogenesis. Although our patient did not have an elevation in eosinophils, mast cells, or basophils, which would be typical of progestogen hypersensitivity, we cannot rule out the possibility that a hypersensitivity to etonogestrel developed in our patient.

The implant itself is composed of ethylene-vinyl acetate, and in addition to etonogestrel, contains barium sulfate (15 mg) and magnesium stearate (0.1 mg). Ethylene-vinyl acetate is a nonabsorbable, inert polymer commonly used in drug delivery systems.[7] No adverse reactions to the material have been reported. Barium sulfate itself is a nonantigenic compound. Etonogestrel implant site reactions, presumed to be caused by barium sulfate, have been reported, although no known reports of systemic

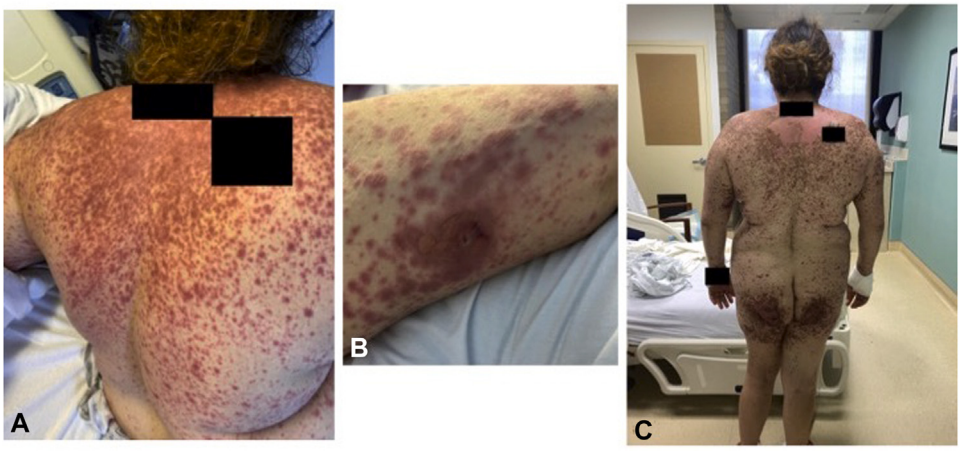

Fig 3. Toxic epidermal necrolysis. Clinical photographs of the patient after transfer to our burn center demonstrating diffuse rashes on the (**A**) back and (**B**) upper extremity and (**C**) desquamation with exposed, erythematous dermis on the upper portion of the back and buttocks.

dermatologic reactions or TEN related to barium sulfate exist.[8,9] Magnesium stearate is a magnesium salt of stearic acid. In addition to its use in the food industry, it is used as an inactive ingredient in pharmaceutical products.[10]

Ultimately, the specific trigger for TEN in this patient remains unclear. The possibilities include therapeutic or supratherapeutic levels of etonogestrel or another compound used in the implant, namely, barium sulfate. Because the ethylene-vinyl acetate and magnesium stearate used in the implant are chemically inactive, it is unlikely that an immunological reaction to either of these compounds occurred.[7,10] Currently, no reports of etonogestrel-induced or barium sulfate—induced TEN exist.

In conclusion, we present a moderately severe form of TEN related to recent etonogestrel implantation. Although the patient's condition resolved without complications, future studies on the potential of the etonogestrel implant to cause TEN should be strongly considered to mitigate the possibility of future events.

Conflicts of interest

None disclosed.

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