compared to an average of 55 cases per year between 2017 and 2021.[2] Epidemiological data indicate that the nation with the largest number of cases was Germany (281), and most of the patients were immigrants from reception centers, particularly males (85%) aged between 5-15 years (62%). Most cases had cutaneous diphtheria with little or no systemic involvement.[2] Therefore, in refugees with chronic skin wounds, even in the absence of systemic symptoms, *C. diphtheriae* should be considered. It is also essential to make a proper differential diagnosis from other diseases such as *Pyoderma gangrenosum*, *Cutaneous leishmaniasis*, cutaneous tuberculosis, ecthyma, tropical ulcer, and fungal ulcer. Although the diagnosis of diphtheria is largely clinical, it is necessary to isolate *C. diphtheriae* from wound and throat swabs. Toxin detection by PCR or Elek immunoprecipitation assay is also required to confirm a toxigenic strain.[4] Countries should follow national guidelines on case management.[4] Most guidelines recommend topical antiseptic and systemic antibiotic therapy with benzylpenicillin (penicillin G) or a macrolide (erythromycin, azithromycin or clarithromycin) for 14 days.[4] It is important to consider that diphtheria resistance to macrolides and Cotrimoxazole is also reported in Europe.[5] This would explain the inadequate response of our patient to the first antibiotic regimen. Antitoxin therapy is generally not necessary in cases of localized skin disease because a very small amount of toxin is released. In addition, it is essential to check the vaccination status of patients and close contacts and provide for missing vaccinations.[4] According to data reported by WHO/UNICEF, Diphtheria vaccination coverage rates in Europe range from 85% to 99% of the population, depending on the state.[2] In 2022, in Morocco, the country of origin of our patient, the vaccination coverage rate was 99% among children aged between 12 and 23 months, according to WHO/UNICEF estimates.[6] Our patient, however, reported that he had not received adequate vaccination in his native country. Before going to Grosseto, he had been living in Udine, in Italy, with other migrants in poor hygienic conditions. One of them had the same painful ankle injury. It was not possible to trace this other case.

As can be seen from this clinical case, poor living conditions with poverty, migration and poor hygienic conditions may favor the occurrence of diphtheria. Given the increase in recorded cases, it is necessary to consider this disease as an important differential diagnosis, especially in the migrant population coming from countries where vaccination rates are lower than the world average. It is crucial to identify possible cases and proceed with proper public health measures and treatment considering the presence of antimicrobial resistance profiles.[2]

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Erythema multiforme major presenting in a teenager with anti-N-Methyl-D-Aspartate receptor encephalitis

Anti-N-Methyl-D-Aspartate receptor (NMDAR) encephalitis, marked by seizures and psychiatric symptoms, is the most common autoimmune encephalitis. Initially linked to ovarian teratomas, it's now recognized in children, often post-infections or idiopathic.[1] Cutaneous manifestations related to this syndrome are rare. Here, we present a pediatric case where it progressed to erythema multiforme (EM), underscoring the intricate relationship between autoimmune responses and skin manifestations. A 15-year-old adolescent male

arrived at the emergency department with a four-day history of confusion, aberrant behavior, speech impediments, and visual hallucinations, preceded by a prodrome of fever. No history of trauma, infection, vaccination, or drug use was reported, and there were no signs of meningism. While brain MRI results were normal, EEG findings indicated a general slowing of background activity. Due to suspected meningoencephalitis, the patient received antibiotics and acyclovir upon admission. Subsequent cerebrospinal fluid (CSF) analysis revealed elevated white blood cell count (60×10^6/L, reference range 0–8 × 10^6/L) with lymphocytic dominance, alongside normal protein, and glucose levels. A CSF culture yielded no growth, while polymerase chain reaction (PCR) testing for herpes virus 1 and 2, JC virus, EBV, VZV, HHV6, CMV as well as enterovirus was negative. Extensive laboratory work-up including sexually transmitted infection testing, bacterial and viral blood cultures and serology, viral direct detection test, and anti-nuclear antibody were noncontributory. Swab tests and serology for SARS-CoV-2 were negative. Notably, serum and CSF analysis confirmed the presence of anti-NMDAR antibodies, leading to a diagnosis of anti-NMDAR encephalitis. Treatment commenced with methylprednisolone (1 g/day) and intravenous immunoglobulins. During steroid therapy, the patient developed a diffuse rash characterized by numerous 2-12 mm erythematous, urticarial, targetoid papules and plaques with central hyperpigmented purple/red duskiness, along with blistering and crusting on the face, trunk, and upper arms. Additionally, hemorrhagic crusting of the lips and ocular hyperemia were present (Figure 1). Ocular and genital area were spared. Histopathology of a skin lesion on the trunk showed acanthosis with orthokeratosis, numerous apoptotic keratinocytes, hydropic degeneration of basal layer with dermo-epidermal detachment and a perivascular and periadnexal infiltrate made of T-lymphocytes with predominance of CD8 and some eosinophils consistent with EM (Figure 2). Therapy was continued with prednisone and mucosal and skin lesions resolved in 10 days leaving hyperpigmented and atrophic lesions. At follow-up, residual neurological symptoms persisted including slurred speech and slight tremors of the hands.

Anti-NMDAR encephalitis is an autoimmune disorder targeting the NR1 subunit of the NMDAR, often manifesting psychiatric symptoms. Prompt treatment yields favorable outcomes in 80% of cases, but mortality rates reach 8-10%, with tumors implicated in 38% of cases, primarily ovarian or testicular teratomas. It can arise idiopathically or post-infection, including severe COVID-19.[1] Cutaneous manifestations are rare. A case study of a 10-year-old with NMDAR encephalitis revealed drug reaction with eosinophilia and systemic symptoms linked to antiepileptic medication.[2] Skin manifestations observed in patients included flushing, pruritus, urticaria pigmentosa, and maculopapular rash, excluding severe conditions like Stevens-Johnson Syndrome.[3] In our case, no tumors, active infections, or drug induction were evident. Treatment with systemic steroids and IVIg, common for anti-NMDAR encephalitis, resolved the skin rash, resembling EM major with slight mucosal involvement.

Research suggests a potential link between NMDAR expression in human skin and cutaneous reactions, as glutamate plays an important role as a signal of cutaneous barrier homeostasis and epidermal hyperplasia induced by barrier disruption, showing the existence of NMDA receptor or a very structurally similar protein in the epidermis.[4] Although the relationship between the expression of the NMDA receptors and skin diseases has not been clarified, some studies have hypothesized neurocutaneous associations are, at least in part, caused by autoantibodies directed at both cutaneous and neurologic tissues.[5]

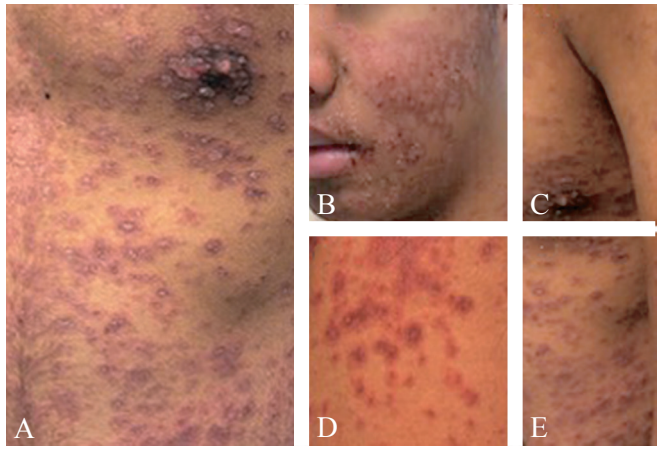

Figure 1.—Clinical images of erythema multiforme major. A) Diffuse rash on the trunk; B) hemorrhagic crusting of the lips; C) erythematous, urticarial, targetoid papules and plaques with blistering; D) Close-up of targetoid, raised papular, vesicular lesions on the back; E) crops of new lesions on the trunk.

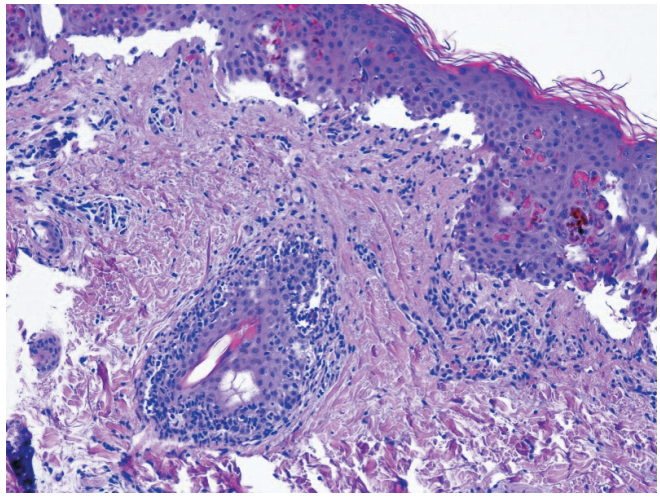

Figure 2.—Histopathology of a skin lesion on the trunk showing acanthosis with orthokeratosis, dermo-epidermal detachment and a perivascular and perifollicular infiltrate, with numerous apoptotic keratinocytes and hydropic degeneration of basal layer, extending to follicular appendages (H-E x10).

This case underscores EM major in a teenager with anti-NMDAR encephalitis, questioning the immunological mechanisms behind anti-NMDAR antibodies, particularly in tumor-unrelated cases.

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Methotrexate and 5-fluorouracil for refractory squamous cell carcinomas in epidermodysplasia verruciformis unresponsive to conventional therapies

Epidermodysplasia verruciformis (EV) is a rare genetic disorder characterized by an abnormal immune response to certain types of human papillomavirus (HPV), particularly HPV types 5 and 8.[1] Patients with EV exhibit widespread wart-like lesions that can resemble pityriasis versicolor or verruca plana. Over time, chronic HPV infection in EV predisposes patients to an increased risk of developing squamous cell carcinomas (SCCs), often in areas exposed to sunlight. The management of SCCs in EV is challenging due to the persistent nature of the lesions and the risk of recurrence requiring innovative therapeutic approaches.[2] Methotrexate (MTX) is a folate antagonist that inhibits DNA synthesis by blocking dihydrofolate reductase, leading to decreased cell proliferation. At low doses, MTX exerts an antiproliferative effect, making it useful in the treatment of rapidly dividing neoplastic cells without significant immunosuppressive effects.[3] 5-Fluorouracil (5-FU) is a pyrimidine antilog that inhibits thymidylate synthase, disrupting DNA synthesis and inducing apoptosis in rapidly dividing cells.[4] When used together, these agents act synergistically to target neoplastic cells, providing a powerful therapeutic option for refractory cases of SCC in EV. Here we report, a case of EV successfully treated, with association of methotrexate at low dose and 5FU. A 23-year-old female with a diagnosis of EV presented with widespread cutaneous lesions, including verrucous plaques on the back, resembling pityriasis versicolor, and erythematous-squamous plaques in the vulvar, gluteal, supraclavicular, and pubic regions. The patient had a history of HPV-associated lesions and had developed multiple cutaneous squamous cell carcinomas. The histological examination carried out on genital areas, confirmed the diagnosis of invasive SCC, with atypical squamous cells infiltrating the dermis, keratin pearls, hyperchromatic nuclei, and evidence of chronic inflammatory infiltrate in the surrounding stroma. The patient refused surgery and wishes to be treated medically. After an informed consent, from September 2018 to February 2021, we started the treatment with acitretin (0.5 mg/kg/day), and after 6 months we already obtained a regression of pityriasiform lesions but did not achieve full resolution. Subsequently, topical imiquimod, applied five times per week for six weeks, was initiated, but it failed to produce a significant clinical response. The patient then underwent a one-month course of topical 5-fluorouracil (5-FU) without achieving any improvement. At this point, we decided to start an off-label treatment approach by combining low-dose methotrexate (MTX) with topical 5-FU. We initiated methotrexate at a dose of 7.5 mg once weekly, in combination with topical 5-FU 4%, applied nightly for 28 days (Figure 1A, B). The rationale behind this combination therapy was based on the antiproliferative action of MTX and the cytotoxic effects of 5-FU, both targeting rapidly dividing neoplastic cells. Following the initiation of combination therapy, the patient developed a marked inflammatory reaction at the sites of application, which is a typical response to 5-FU in the context of successful treatment. Over the course of several weeks, the erythematous-squamous plaques and verrucous lesions gradually regressed, leading to complete resolution of the clinical manifestations. A follow-up histological examination confirmed the absence of dysplastic or malignant cells in previously affected areas. The patient remained free until now of new lesions or recurrence of SCCs during six-month follow-up visits (Figure 1C, D).

EV is a rare genetic condition with a high predisposition to HPV-associated squamous cell carcinomas. Managing these carcinomas is challenging, particularly in patients with refractory lesions. In this case, the combination of low-dose methotrexate and 5-fluorouracil led to a complete resolution of the lesions, where previous therapies, including acitretin, imiquimod, and 5-FU alone, had failed. Methotrexate, at low doses, inhibits dihydrofolate reductase, which prevents the formation of tetrahydrofolate, a precursor required for DNA synthesis. This blockade impairs nucleotide synthesis, specifically inhibiting thymidine production, which is crucial for the rep-