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"It never rains but it pours": Anti-NMDAr encephalitis complicated by staphylococcal-scalded skin syndrome

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Introduction

Anti-NMDAr encephalitis is characterized by the production of antibodies against the NR1 subunit of the NMDA receptor. Patients present with acute or subacute cognitive decline, neuropsychiatric symptoms, new-onset seizures, movement disorders, sleep alterations, and encephalopathy [1]. Approximately 20% of patients develop long-term neurological complications (principally attention, memory, and executive functions deficit) [2], whereas death occurs in 5%-7% of cases. About 10% of patients may relapse within two years from the initial presentation, although with a less severe form of the disease.

The treatment involves supportive therapy, but the prognosis depends on the effectiveness and rapidity of immunotherapy [3]. First-line therapies include steroids, IVIG and PLEX, often combined to save time. The second-line treatment generally consists of rituximab, a monoclonal antibody directed against the CD20 surface antigen. By depleting naïve and memory B cells, it reduces the cells responsible for producing anti-NMDAr antibodies. There are still controversies about the observation time limit after first-line therapy due to the high number of side effects [4]. To prevent these complications, protocols suggest screening all patients for complete blood count, immunoglobulins IgA, IgG, IgM, Quantiferon, HCV, HBsAG, anti-HBV, HCV, VZV before administration of rituximab.

S. aureus is a pathogen capable of causing numerous infections in humans, especially among hospitalized patients, with increased morbidity, mortality, and healthcare costs [5]. It is part of the normal skin microbiota, with 15-40% of the population being asymptomatic carriers in the nostrils [6]. The worst pathological complication of S. aureus is Staphylococcal-Scalded Skin Syndrome (SSSS), characterized by a mortality of 3.6-11% in children and 40-63% in adults [7]. It is caused by the production of exfoliative

toxins by some strains of S. aureus. While a third of the population carries the bacterium on the skin as a commensal, only 5% of S. aureus produces the exotoxins A and B that cause SSSS [8]. After 1-10 days of incubation, the toxins cause skin lesions. The rash typically begins on the face and folds (groin, armpits, neck) with erythema, followed by large, thin-walled vesicles. It is very rare in adulthood, generally affecting immunocompromised people [9]. Successful management of SSSS involves early diagnosis and prompt treatment with an intravenously administered anti-staphylococcal antibiotic. Systemic antibiotic therapy should be introduced at the time of clinical suspicion of SSSS, confirmed by microbiology and histology. Corticosteroids can worsen the disease and are therefore contraindicated [10]. In severe cases, loss of skin barrier function occurs, similar to burn injuries.

Case Report

Here we describe the case of a 30-year-old Malaysian woman affected by NMDA-R encephalitis. Her medical history was unremarkable except for SARS-CoV-2 infection two weeks before admission to the psychiatric department. The onset symptoms included agitation, insomnia, aggressiveness, and visual hallucinations treated with antipsychotic therapy. She progressively developed episodic dystonic posturing, catatonia, mutism, and mild mixed (postural and kinetic) tremor affecting all four extremities. Routine blood tests, brain CT scan, and electroencephalogram were negative for pathological findings.

Three days later, a disorder of consciousness associated with cardiac and respiratory autonomic dysfunction required ICU monitoring with invasive ventilation. Blood tests showed a slight increase in neutrophils, brain MRI was negative, electroencephalogram showed bilateral frontal delta brush activity, and lumbar puncture revealed neutrophilic pleocytosis and positivity for NMDA-R antibodies. Total body CT scan excluded neoplastic masses, further confirmed by transvaginal ultrasound and pelvic MRI. First-line immunotherapy consisted of methylprednisolone (1 g/day for five days), followed by a slow tapering starting from prednisone 50 mg/day orally, without any clear effect. Subtle seizures were controlled by levetiracetam (3000 mg/day) and lacosamide (200 mg/day). A cycle of plasma exchange therapy followed by intravenous immunoglobulin (0.4 g/kg/day) was ineffective. Her cognitive and alertness state worsened. Rituximab was started at 375 mg/m^2 per week. Five days later, we observed the resolution of the comatose state and a clear recovery of neurocognitive functions.

However, the day after the second dose of Rituximab, a diffuse skin rash with thin-walled flaccid blisters appeared on the trunk, limbs, and face, with a positive Nikolsky sign. We immediately discontinued antiseizure drugs and performed HLA-gene analysis to rule out any idiosyncratic reaction, while administering the third dose of anti-CD20 therapy, assuming the rash could be an autoimmune pemphigoid rash. However, anti-skin antibodies were negative, and skin biopsy showed MSSA infection, leading to a diagnosis of Staphylococcal Scalded-Skin Syndrome (SSSS). The latter was treated with Linezolid, and given the severity of the injuries, she received treatment similar to that used for severely burned patients, including resuscitation support, tracheotomy tube preparation, and administration of analgesic and sedative polytherapies for intense pain (remifentanil, propofol, ketamine, dexmedetomidine). Rituximab booster was interrupted.

The patient was discharged after two months of hospitalization with an mRS of 3, which progressively improved to normalization in 3 months, while complete reepithelialization required approximately 6 months. Latest blood examinations showed a normal white blood cell count of 6.3×10^3 u/µL, with no associated abnormalities.

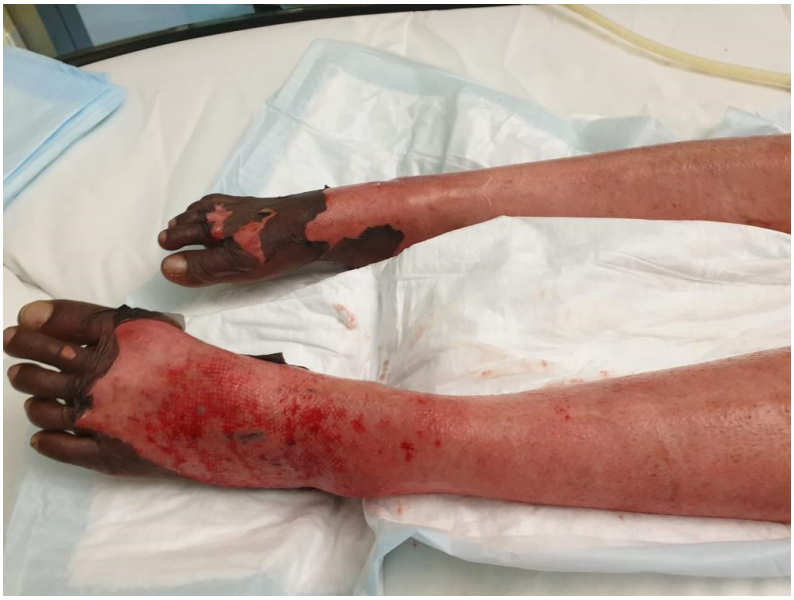

Figure 1: Patient's skin after rupture of skin blisters.

Discussion and Conclusion

Anti-NMDAr encephalitis is a severe condition associated with high mortality and morbidity, requiring timely aggressive immunomodulant therapy and often long-term hospitalization in intensive care units. Early second-line immunotherapy with rituximab is associated with better outcomes and fewer relapses. However, B-cell depletion induced by rituximab therapy may cause secondary immunodeficiency, increasing the risk of opportunistic infections [2]. Literature review in rituximab-treated patients shows a rate of serious infections ranging from 2.2 to 9.8/people/year, including rare Staphylococcus aureus infections. Unfortunately, these infections, although highly predictable and curable if quickly identified, have an intrinsic high mortality, particularly in immunocompromised adult patients.

We reported the case of a young and previously healthy woman who developed anti-NMDAr encephalitis, timely treated with first and second-line immunotherapies. Unfortunately, this treatment was complicated by SSSS, severely delaying her recovery and putting her at risk of death again. Despite the extreme rarity of NMDA encephalitis, the high mortality in adult patients affected by SSSS, coupled with easy therapeutic accessibility, justifies, in our opinion, extending the RTX pre-administration screening to include nasal swabs for Staphylococcus aureus research.

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