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Title: Severe adverse drug reaction in SARS-CoV-2 infection: AGEP induced by ceftriaxone and confirmed by patch test

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Accepted Article

Adverse drug reactions (ADR)s are rarely reported in COVID-19 patients despite the wide range of medications administered to slow the progression of the disease and relieve symptoms caused by SARS-CoV-2. Recently, an overview of cutaneous ADRs by the most frequently used drugs in COVID-19 patients highlighted antimalarials, antivirals, and anti-inflammatory drugs, but not antibiotics.^{1,2} Only rare cases of drug-induced Acute Generalized Exanthematous Pustulosis (AGEP) due to hydroxychloroquine³ and cephalosporins^{4,5} have been reported in COVID-19 patients, but in none of these cases patch test (PT) was performed.

CASE REPORT

During the first wave of COVID-19 in Italy, a 73-year-old woman with no history of drug allergies was admitted on to our COVID-19 Unit with a 2-day history of fever (39°C), vomiting, and oxygen desaturation with breath sounds bilaterally diminished. Chest computed tomography revealed bilateral ground-glass opacities and oxygen and intravenous ceftriaxone (2 gr) was immediately started. After swab for SARS-CoV-2 resulted positive, ceftriaxone was replaced with azithromycin (500 mg/day); hydroxychloroquine (400 mg/day), antiretroviral therapy with darunavir/cobicistat (800/150 mg/day), and enoxaparin (4000 UI/day) were added because of deterioration of clinical conditions. On day 5 azithromycin was stopped. Therapy was implemented with dexamethasone from day 8 to day 10 for progressive respiratory failure; on day 18, hydroxychloroquine and darunavir/cobicistat were also stopped. On day 24 high spiking fever (39.5°C) appeared and the patient received again intravenous ceftriaxone (2 gr). One day later an extensive non-follicular pustular eruption on an erythematous base (60% of body surface area) appeared. Ceftriaxone was immediately stopped and skin biopsy was performed revealing spongiform subcorneal pustules with oedema of papillary dermis; blood tests showed leucocytosis (16,700 per mm³) with absolute neutrophilia (14,910 per mm³). According to clinical and laboratory data, AGEP was diagnosed. The skin eruption in 2 days evolved in flaccid superficial pustules resembling blisters, rapidly denuding the skin superficial of the flaccid pustules affecting 35% of body surface area (Figure 1A,B,C), associated with erosive conjunctival and oral involvement. Due to the worsening of her clinical condition, the patient was transferred to Intensive Care Unit. The research by RT-PCR of SARS-CoV-2 from skin blister fluid was negative. Supportive and intravenous immunoglobulin therapy (2.4 g/kg over 3 days) was administered with gradually improving of skin and mucous lesions. She had a good evolution, respiratory condition recovered and re-epithelialization occurred in 3 weeks without scarring.

According to the initial clinical picture and based on the EUROSCAR scoring system, definite AGEP with final score 9 [morphology 6: pustules (2), erythema (2), distribution (2); course 0: mucosal involvement (-2), acute onset (0), fever (1), neutrophils (1); skin histology 3] in COVID-19 patient was diagnosed.

Three months after complete healing, PT with ceftriaxone sodium 5% and hydroxychloroquine 10%, both in petrolatum, were performed. PT were occluded for 2 days with the Haye's Test Chambers (Haye's Service, Alphen aan den Rijn, The Netherlands) on Soffix tape (Artsana, Grandate, Italy) and readings were performed on day (D)2, D4, and D7.⁵ On D2 and D4 a strong positive reaction (++) to ceftriaxone was documented with infiltrated erythema and pustules (Figure 1, D).⁶ The patient refused PT biopsy.

DISCUSSION

To the best of our knowledge, this is the first case of severe cutaneous ADR in COVID-19 patient confirmed by PT. The diagnostic value and safety of in vivo test to investigate severe T-cell-mediated hypersensitivities is still controversial. In fact, PT has been performed safely in AGEP, DRESS, and SJS/TEN,⁷ while intradermal testing and provocation test in these severe ADRs are contraindicated.⁸ We emphasize that in our patient PT with ceftriaxone showed a pustular reaction pattern, supporting the ability of PT to reproduce the original ADR clinical pattern.

Chronology (fast elicitation in one day after reintroduction), elicitor, neutrophilia, positive pustular patch test, and uncomplicated recovery of the patient pointed to an AGEP. As recently stated by the EAACI position paper classification of cutaneous manifestations of drug hypersensitivity,⁹ the large very superficial detachment observed in our patient resulted from confluent pustules resembling blisters.

The culprit drugs of AGEP are beta-lactam antibiotics, macrolides, diltiazem, terbinafine, and hydroxychloroquine.⁹ In our patient, although the large number of administered drugs, we performed PT with ceftriaxone for short latency time after its second administration and with hydroxychloroquine for its documented role in AGEP.^{3,9} PT confirmed ceftriaxone as culprit, but unfortunately we could not perform ultra-structural studies on ceftriaxone positive PT biopsy to confirm the immunopathogenesis of AGEP, usually classified as type IVd hypersensitivity reaction.¹⁰

In conclusion, given the plethora of used drugs and the lack of approved therapies for COVID-19 patients, our report underlines the necessity to identify culprit drugs in case of ADRs in these patients and confirms the value and safety of patch tests.

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FIGURE 1 (A) Extensive erythematous eruption with (B) flaccid superficial pustules resembling blisters and (C) superficial detachment. (D) Positive patch test (++) with pustular reaction pattern to ceftriaxone (5% in petrolatum, D4)