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A Rash Decision; From Measles Fears to DRESS Syndrome

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Abstract:

Background: Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare but serious condition characterized by a heterogenous rash, eosinophilia, and end organ involvement. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the rarer medications that may induce this severe adverse hypersensitivity reaction.

Case Presentation: We present a case of a 50-year-old male with extensive trauma history complicated by chronic pain and an unvaccinated status who presented with acute onset fevers and dynamic morbilliform rash covering greater than 50 percent of his body surface area (BSA). A clinical diagnosis of NSAID-induced DRESS was made based on the temporal relationship with the patient's ibuprofen use, eosinophilia, and organ involvement. Treatment with systemic corticosteroids (1 mg/kg/day) resulted in significant symptom improvement. The patient was discharged on an oral and topical steroid regimen after nine days of admission, with close outpatient dermatology follow-up.

Conclusion: This case highlights the importance of keeping rare drug-induced hypersensitivity reactions like NSAID-induced DRESS on the differential, particularly in patients with complex medical histories and during a time when there is a rising concern for measles infection, which may initially present with a very similar clinical syndrome.

Keywords:

DRESS; Measles; NSAID; ketorolac

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an idiosyncratic, heterogeneous adverse drug reaction characterized by an extensive skin rash with multi-organ involvement and peripheral eosinophilia. DRESS primarily affects adults and is estimated to occur in up to ~2 per 100,000 patients per year [1]. The mortality rate for patients affected by DRESS can be as high as 10%, making prompt recognition and treatment critical. [2]

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In adults, the vast majority (approximately 75 percent) of DRESS cases are associated with "high-risk drugs" such as aromatic anticonvulsants, such as carbamazepine, phenytoin, and lamotrigine, allopurinol, sulfonamide-containing antimicrobials, anti-tuberculosis agents, mexiletine, minocycline, and vancomycin [3,4,5,6]. Less common culprit drugs for DRESS include antipsychotics, rheumatologic medications such as leflunomide, hydroxychloroquine, bosentan, and solcitinib, IL1 or IL6 inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs).

DRESS is thought to be driven by a T-cell-mediated hypersensitivity reaction following aberrant haptenation of an offending drug. Additionally, evidence has supported the role of latent virus (especially HHV-6) reactivation as a mechanism that helps to sustain the reaction [3,7,8]. DRESS likely represents a complex process between immune responsiveness and predisposing genetic factors (e.g., HLA susceptibilities) [9,10].

The latency period for DRESS is typically between 2-8 weeks after drug initiation or discontinuation [11]. Treatment involves identifying and immediately discontinuing the offending agent. Thereafter, management is centered around high-dose systemic corticosteroids with a slow taper as well as topical steroids, or up to 12 weeks from symptom onset [8].

DRESS itself is rare, and NSAIDs is an even rarer causative agent of this syndrome. Here, we present a case of a patient who presented to the emergency with DRESS induced by ibuprofen use. department

Case Presentation

Case History

A 50-year-old male with an extensive trauma history which includes multiple gunshot wounds leading to complex abdominal wounds and above the knee amputation of the left lower extremity complicated by chronic pain, presented with acute onset pruritic, erythematous rash and fevers. Initially, the patient noticed over the course of two days a new rash localized to his right flank which progressed rapidly to cover his upper and lower extremities, trunk, and neck, sparing the soles of the feet and oral mucosa. He also endorsed mild upper respiratory symptoms of similar duration. Of note, the patient also denied having ever received any vaccinations.

Notably, the patient was initially afebrile but tachycardic to 103. On initial exam, patient was found to have a morbilliform eruption on his trunk, extremities, and flanks with few scattered excoriations as well as scattered annular erythematous plaques with central clearing and erythematous macules and patches on forearms and palms (**Fig. 1**). The patient was found to have an elevated lactate of 2.0 U/L, CRP of 9 mg/dL, and ESR of 18 mm/h. Furthermore, a broad infectious and autoimmune disease work up was pursued. Dermatology was then consulted, and the patient was started on triamcinolone 0.1%, diphenhydramine 25 mg, and a pain regimen which notably included 15 mg of ketorolac every 6 hours.

Initially, the patient's prodrome of upper-respiratory symptoms, and morbilliform rash, and his unvaccinated status led him to be placed under airborne precautions, as the combination of these symptoms was concerning for rubeola (measles) infection.

On day four of his hospitalization, the patient's rash significantly worsened, now covering greater than 50 percent of his body surface area. He developed nausea and emesis and a new eosinophilia to 12 percent. Upon further interview, it was discovered that the patient had recently been unable to obtain prescription opioids for management for his chronic pain and instead three weeks prior to his presentation, started taking over the counter ibuprofen for his pain. According to the patient, he had never used NSAIDs previously and had only relied on opioids and acetaminophen for his pain.

That night, the patient became febrile to 102.7 degrees Fahrenheit, and liver function tests revealed a new transaminitis. With a new worsening rash, end organ involvement and eosinophilia, the decision was made to give intravenous methylprednisolone 1mg/kg (**Fig. 2**). Ketorolac was discontinued based on concerns that NSAIDs were the provoking agents. At this time, the broad infectious and autoimmune workup returned negative: rubeola, rubella, HIV, hepatitis viral panel, parvovirus, respiratory viral panel, ANCA, CMV, EBV, Rubeola, HHV6, RPR, gonorrhea/chlamydia/trichomonas nucleic

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amplification test. After intravenous methylprednisolone, the patient's rash, eosinophilia, and abdominal symptoms improved within 24 hours of administration (**Fig. 3**). His liver function tests fluctuated daily initially, however improved over time as evidenced by most recent measurement (**Fig. 4**).

Treatment Plan

Once a diagnosis of DRESS was made, and the offending agent(s) had been removed, the patient was started on a high-dose corticosteroid (1 mg/kg) with a Dermatology driven taper recommendation. Two days after discharge, the patient followed up at the outpatient dermatology clinic and was found to have recurrent elevated transaminases, AST of 111 U/L and ALT of 165 U/L as well as eosinophilia of 7.4%. The patient's steroid regimen was then increased to 1mg/kg.

Discussion

The patient's presentation was marked by a dynamic morbilliform eruption with febrile illness, eosinophilia, end-organ dysfunction, and first-time NSAID use strongly supporting the diagnosis of NSAID-induced DRESS. The International Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) uses a scoring system to classify potential severe drug reactions. DRESS can be classified as definite (≥5 points), probable (4-5 points), possible (2-3 points), or not DRESS (<2 points) [4]. Our patient scored a 4 on this scale, as he developed fever, rash involving greater than 50 percent of his body surface area with features meeting RegiSCAR criteria, eosinophilia to 12 percent, evidence of end-organ dysfunction (liver injury), and alternative diagnoses excluded (broad infectious and autoimmune workup completed and negative). Notably, a skin biopsy was not obtained in this patient, which could have contributed to strengthening the diagnosis, but was deferred as the patient responded well to systemic steroids, and obtaining a biopsy would not have necessarily changed management for this patient.

The rapidly progressing, dynamic, morbilliform rash that involved greater than 50% of the patient's body surface area approximately three weeks after the initiation of ibuprofen is characteristic of DRESS and is consistent with other published reports. While there have been isolated cases of severe cutaneous adverse reactions linked to NSAIDs such as diclofenac, ibuprofen and celecoxib, these remain relatively rare, particularly compared to more common offenders like anticonvulsants and sulfonamides [3, 12, 13, 14].

Additionally, it is worth discussing that this patient, who is 50 years old was naive to NSAIDs prior to the weeks leading up to this presentation. While a lack of exposure to NSAIDs by the sixth decade of life is uncommon for many patients, the unique clinical context of this case warrants consideration. The patient subjectively stated that he had minimal interaction with the healthcare system or any medications before his recent trauma history, including not receiving vaccinations, having grown up in rural Puerto Rico. His experience of chronic pain from his trauma led him to try ibuprofen for the first time, which became the opportunity for this hypersensitivity reaction.

One of the significant challenges in diagnosing NSAID-induced DRESS is its relative rarity compared to other drug reactions, which can delay recognition and treatment and increase the risk of underdiagnosis and misdiagnosis. Management of DRESS involves immediately discontinuing the offending agent and initiating high-dose corticosteroids and tapering over a long period of time up to 12 weeks, though there remains some variability in duration of steroids in clinical practice. Even when the rash resolves, steroids and surveillance for persistent end-organ injury may be indicated.

In this case, the patient's unvaccinated status and presence of upper respiratory infection symptoms led the team to consider rubeola infection (measles) as a possible diagnosis. The rising incidence of measles outbreaks in nearby regions, along with the patient's history of no childhood vaccinations, made this a reasonable differential [15]. In the context of rising incidence, measles should be ruled out in patients with presentations like that of this patient, if they are of unvaccinated status. However, after obtaining negative serology results, measles was ruled out, further solidifying our diagnosis. Consideration of viral exanthem from a virus other than the rubeola virus as an alternative diagnosis was assessed. Based on his initial presentation with URI symptoms, it is not impossible, although his

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pan-negative viral workup makes much less likely but cannot fully exclude the diagnosis.

A severe drug reaction to NSAIDs significantly limits the pharmacologic agents available to him for the management of chronic pain. In these patients with careful consideration should be given when adjusting cause of the patient's chronic pain, as a drug allergy to NSAIDs would significantly limit the diversity of pharmacologic agents available for him. However, his clinical course more closely parallels DRESS, making NSAID avoidance the likely safest path forward for the patient.

This case underscores the importance of clinical vigilance in recognizing drug-induced hypersensitivity reactions. It also highlights the necessity of maintaining a broad differential diagnosis, especially when dealing with rare adverse drug reactions. Moreover, it serves as a reminder that DRESS can mimic morbilliform rashes that are present in patients with rubeola infection during a time when we are seeing a resurgence of measles.

Conclusion

In this report, we describe the case of a 50-year-old male who developed NSAID-induced DRESS following the initiation of ibuprofen. His clinical symptoms improved significantly with the administration of a high-dose corticosteroid regimen with an extended taper, underscoring the importance of early recognition and appropriate treatment in managing this potentially life-threatening condition. This case also highlights the importance of distinguishing viral exanthem from severe drug reactions. This case further emphasizes the importance of keeping NSAID-induced hypersensitivity reactions and the utility of obtaining a comprehensive medication history in these patients whose drug reaction is on the differential diagnosis. The patient's successful recovery demonstrates a favorable outcome with timely intervention.

FIGURE LEGENDS

Fig. 1 Initial rash presentation. Patient initially presented with morbilliform eruption on his trunk, extremities, and flanks. Scattered excoriations were noted, along with annular erythematous plaques demonstrating central clearing, as well as erythematous macules and patches on forearms and palms. Additional findings include prior traumatic surgical scars on the abdomen, chest, and a left lower extremity amputation.

Fig. 2 Acute worsening of rash. Approximately three days after initiating 15 mg ketorolac q6hrs for pain management, the patient's rash worsened and covered >50% of his total body surface area. Concurrently, he developed new eosinophilia, accompanied by significant nausea and emesis.

Fig. 3 Progression after offending agent removed plus steroids. Following discontinuation of the suspected offending agent (ketorolac) the patient was initiated on 1 mg/kg/day of systemic steroids, which provided significant symptom improvement. This regimen was continued until discharge, with plans for appropriate taper.

Fig. 4 Patient Labs Throughout Admissions. LFTs and %Eosinophils steadily rose in parallel with the patient's worsening rash until ketorolac was discontinued and the patient was started on 1 mg/kg/day of systemic steroids on Day 4.

Fig. 1

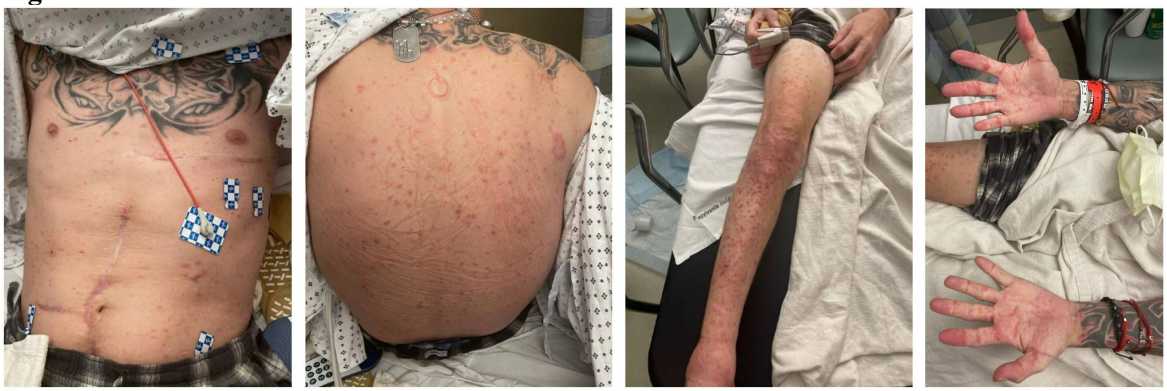

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Fig. 2

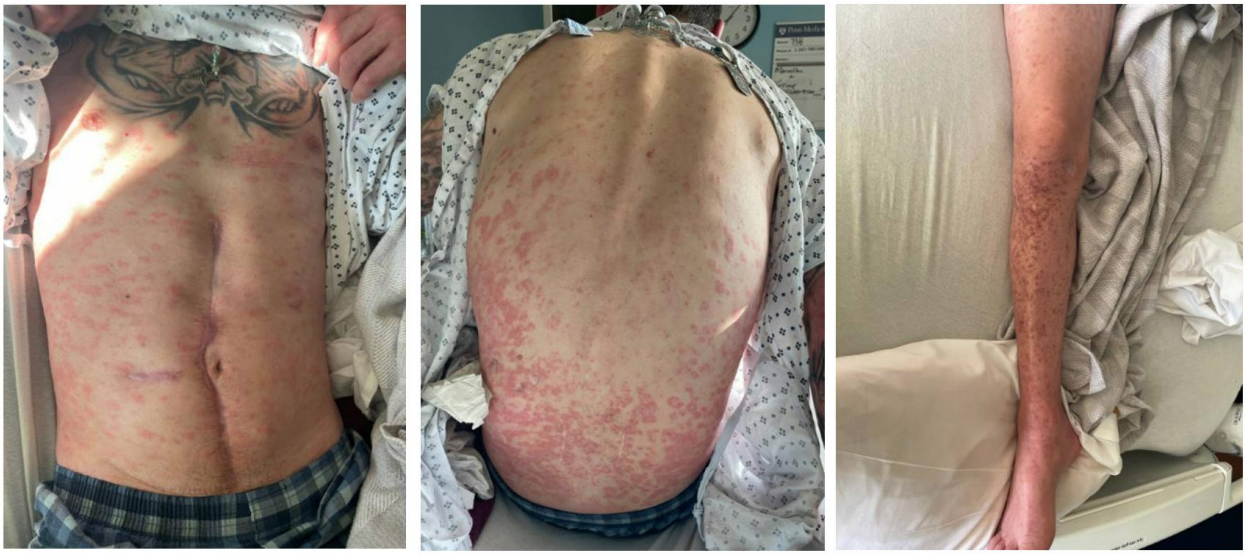

Fig. 3

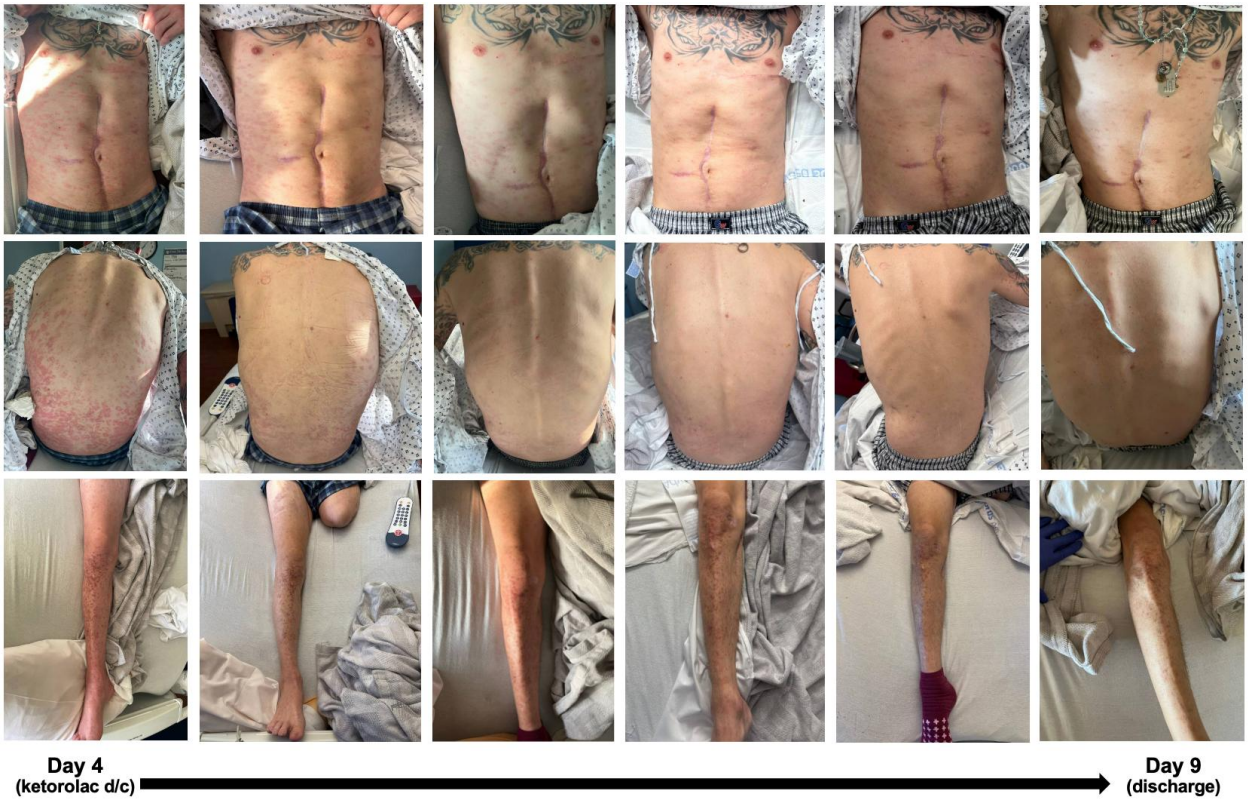

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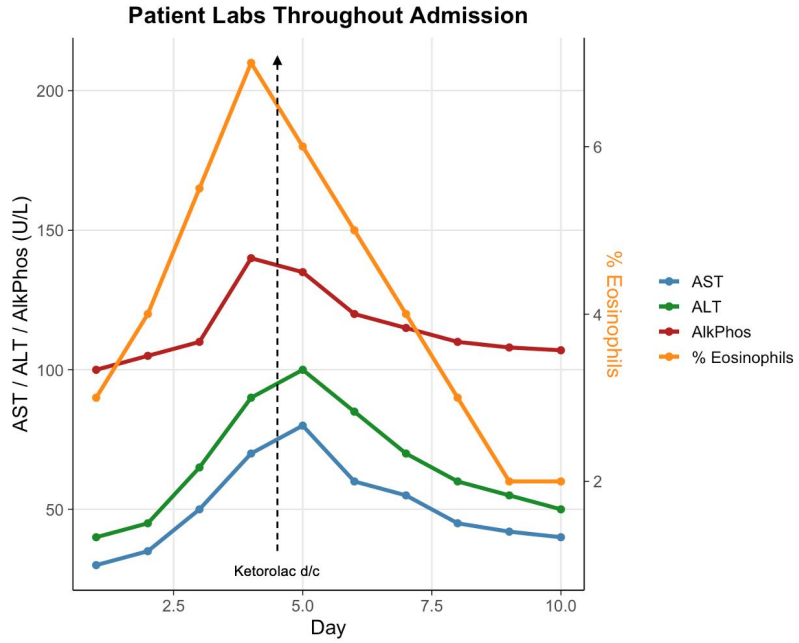
Fig. 4



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