A case of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome complicating airway management

Un cas de syndrome DRESS d'hypersensibilité médicamenteuse (éruption cutanée avec éosinophilie et symptômes systémiques) compliquant la prise en charge des voies aériennes

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Abstract

Purpose Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe multi-system reaction defined by fever, rash, eosinophilia, and internal organ involvement. The condition typically occurs one to eight weeks following exposure to inciting medications. In severe cases, it can develop into multi-organ system failure and death. We present a case of DRESS syndrome with mucosal edema that led to extreme difficulties with airway management.

Clinical features A 65-yr-old male treated for an esophageal perforation with broad-spectrum antibiotics developed fever, eosinophilia, and extensive rash consistent with DRESS syndrome. This condition resulted in a rapid progression to multi-organ system dysfunction, severe hemodynamic instability, and the need for high-dose vasopressors and tracheal intubation. Extensive mucous

membrane involvement led to significant complications with airway management and a nearly impossible tracheal intubation, features in the disease not previously described. With the airway secure, initiation of steroids resulted in regression of the disease within 24 hr, resolution of airway edema, and uneventful tracheal extubation a few days later.

Conclusion We emphasize the need for early identification of DRESS syndrome as well as the possible airway implications associated with this increasingly recognized clinical entity.

Résumé

Objectif Un syndrome DRESS avec éruption cutanée d'hypersensibilité médicamenteuse, éosinophilie et symptômes systémiques est une réaction sévère touchant plusieurs systèmes et est défini par de la fièvre, une éruption cutanée, une éosinophilie et l'implication d'organes internes. Ce syndrome survient habituellement une à huit semaines après l'exposition au médicament causal. Dans les cas graves, il peut évoluer vers une défaillance multi-organes et le décès. Nous présentons un cas de syndrome DRESS avec œdème muqueux qui a débouché sur d'extrêmes difficultés pour le contrôle des voies aériennes.

Caractéristiques cliniques Un homme âgé de 65 ans, traité par antibiotiques à large spectre pour une perforation œsophagienne, a développé une fièvre, une éosinophilie et une éruption cutanée compatibles avec un syndrome DRESS. Cet état a rapidement évolué vers un dysfonctionnement de plusieurs organes, une instabilité hémodynamique sévère et le besoin de recourir à de fortes doses de vasopresseurs et à une intubation trachéale. Une atteinte étendue des muqueuses a conduit à des complications significatives dans le contrôle des

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voies aériennes, rendant presque impossible l'intubation trachéale, des caractéristiques qui n'avaient pas encore été décrites dans le cours de la maladie. Une fois la ventilation assurée, la mise en route d'un traitement par corticostéroïdes a entraîné une régression de la maladie dans les 24 heures, la disparition de l'œdème des voies aériennes et le patient a pu être extubé sans difficulté quelques jours plus tard.

Conclusion Nous insistons sur la nécessité d'identifier précocement le syndrome DRESS ainsi qu'une implication possible des voies respiratoires associée à cette entité clinique identifiée de plus en plus souvent.

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, also named drug-induced hypersensitivity syndrome (DIHS), is a severe multi-system reaction defined by the presence of fever, rash, eosinophilia, atypical lymphocytosis, and internal organ involvement (e.g., hepatitis, myocarditis, or nephritis).¹ This process generally occurs one to eight weeks after exposure to inciting medications, commonly anticonvulsants, antibiotics, and chemotherapeutic agents.² Unique characteristics of the disease in comparison with other drug eruptions include the severity of symptoms, development of end-organ failure, absence of involvement of mucous membranes, and the relatively high mortality risk (8–10%). Treatment is aimed at identifying and withdrawing offending medications, with supportive care for multi-organ dysfunction.³ Although controversial, steroid therapy has been implicated as a therapeutic option in refractory cases.⁴ We present a case of DRESS syndrome that rapidly progressed to severe, life-threatening multi-organ system failure. Further, severe and extensive mucous membrane involvement resulted in significant tracheal edema and stenosis and made airway management difficult. Airway involvement and complications, features not previously identified with DRESS syndrome, have important implications for anesthesiologists and those involved in airway management. Finally, our patient showed a marked improvement concurrent with initiation of systemic steroids.

Case description

Informed consent was obtained to publish this case description of a 65-yr-old male transferred to our institution from an outside facility. The day before his transfer, the patient was diagnosed with an esophageal perforation (related to a recent endoscopic banding procedure of esophageal varices) and an associated large right-sided pleural effusion and consolidation. His medical history was

remarkable for hypertension, hyperlipidemia, non-insulin-dependent diabetes mellitus that was well-controlled on oral hypoglycemics, and chronic alcohol-related liver cirrhosis manifesting as grade I esophageal varices and chronic low-grade ascites. Due to the stability of his clinical condition and the likely subacute nature of his perforation, the patient was managed conservatively with nil per os status, gastric decompression with percutaneous endoscopic gastrostomy tube placement, jejunostomy tube feedings, right-sided chest tube for drainage, and empiric intravenous broad-spectrum antibiotics, including vancomycin, levofloxacin, metronidazole, and fluconazole. He continued to do well until two weeks into the admission when he developed high daily fevers to 39.4°C. Serial blood, urine, sputum, and pleural fluid cultures were negative, and repeat imaging showed complete resolution of his right-sided consolidation and effusion. Concomitantly, he began to develop a diffuse bright increasingly pruritic morbilliform rash involving his arms, trunk, and legs. Given the patient's high fevers, eosinophilia, and generalized rash without a clear infectious source, DIHS, or DRESS syndrome, was determined to be the likely diagnosis according to the dermatology, allergy and immunology, and infectious disease consultants. Antibiotics were thought to be the likely triggering agent. Recommendations by all consulting services included antihistamines, topical steroid cream, and immediate cessation of antibiotics.

Sixteen days following admission, the patient's clinical condition worsened with an acute change in mental status, tachypnea, and tachycardia. Given his deteriorating clinical status, he was transferred to the surgical intensive care unit (SICU). On arrival, the patient was found to have a temperature of 39.4°C, a heart rate of 150 beats·min⁻¹, a blood pressure of 130/70 mmHg, a respiratory rate of 42 breaths·min⁻¹, and an oxygen saturation of 100% with oxygen administered by face tent. He was awake but only intermittently responsive, unable to follow commands, and he complained of severe pruritus. On physical exam, severe audible inspiratory and expiratory stridor was heard; his lungs were clear to auscultation bilaterally, and the previously noted rash was observed. Over the subsequent evening, the patient's skin rash progressed rapidly from morbilliform to near erythrodermic, involving facial erythema, confluent erythema of his back, right mid-back chest erosions and purpura, non-blanching erythema and purpura of his bilateral upper extremities, and bilateral lower extremity coalescing non-blanchable erythematous and violaceous macules. No oral, conjunctival, or mucosal lesions were seen.

Due to the concern for his rapidly deteriorating clinical status, respiratory distress, and audible stridor, the decision was made to secure his airway. A mildly difficult

intubation (by author A.K.) had been reported immediately following initial admission when the patient underwent an esophagoscopy and jejunostomy tube placement. The difficulty was due to an anterior-oriented glottic aperture yielding a grade 2 Cormack & Lehane view that required the use of an Eschmann gum elastic bougie to insert a standard 7.0 cuffed endotracheal tube. Similar difficulty with airway management was anticipated in the SICU given the patient's prior intraoperative tracheal intubation and current stridor; therefore, multiple blades, a fiberoptic bronchoscope, and a standard difficult airway cart containing multiple airway adjuncts were made immediately available. The patient was positioned appropriately and pre-oxygenated. After rapid-sequence induction and muscle relaxation with midazolam, fentanyl, and rocuronium, no view was obtainable with conventional laryngoscopy despite multiple attempts by three experienced operators, including the anesthesiologist who had previously intubated his trachea. This predicament was due to significant tongue and mucosal edema obstructing the anterior-oriented glottis aperture. Adequate mask ventilation was accomplished, but it required an oral airway and a four-handed technique despite the patient's normal body habitus and lack of clinical findings consistent with difficult mask ventilation. Flexible fiberoptic bronchoscopic examination revealed severe supraglottic mucosal edema with all identifiable glottic structures appearing grossly edematous and distorted. An attempt was made to pass a cuffed 6.5 tracheal tube through the glottic aperture with fiberoptic bronchoscopic guidance, but significant resistance was encountered just past the vocal cords. Repeat supraglottic fiberoptic examination revealed severe tracheal edema and herniation of the cuff above the vocal cords. As surgeons were preparing for emergent tracheostomy, the fiberoptic bronchoscope was then used to advance a 5.0 cuffed tracheal tube, and resistance was felt when passing the tube through the glottic aperture. This process involved multiple anesthesiologists simultaneously performing bronchoscopy, tongue retraction, jaw-thrust, laryngoscopy (to facilitate bronchoscopy), and continuous oropharyngeal suctioning.

Following this difficult but successful airway management, the patient continued to deteriorate throughout the following 24 hr. He required escalating doses of vasopressor agents and developed a severe metabolic acidosis with a nadir pH of 6.9. He also developed hemodynamically significant supraventricular arrhythmias requiring synchronized cardioversion and chemical antiarrhythmic stabilization. The leukocyte count increased to a peak leukocytosis of $55 \times 10^9 \cdot \text{L}^{-1}$ with an eosinophilia of 10% and lymphocytosis of 21% with multiple atypical mononuclear forms; serum creatinine reached a maximum of $2.11 \text{ mg} \cdot \text{dL}^{-1}$; the lactate level increased to $21 \text{ mg} \cdot \text{dL}^{-1}$; and liver function tests were three times the

baseline values. Skin biopsies of the rash revealed non-specific inflammatory lesions and no identifiable organisms. Significant discussion ensued regarding the possibility of a repeat infectious source due to the severity of the patient's clinical condition; however, because a repeated infectious workup was negative, including a computerized tomography of the chest, abdomen, and pelvis, and significant eosinophilia was present, the allergy/immunology and infectious disease consultants maintained the clinical diagnosis of DRESS syndrome. Antibiotics were not administered, and the patient was treated with intravenous methylprednisolone 125 mg every six hours.

Over the following 12 hr, the patient made a rapid and profound recovery. His vasopressors were rapidly tapered within 24 hr. His rash resolved progressively; laboratory data showed resolution of his acidosis, normal serum lactate, decreasing serum creatinine, lower white blood cell count, less eosinophilia, and near normalization of liver function tests. Over the following few days, the patient's ventilator support was weaned and a cuff leak was noted when the tracheal tube cuff was deflated. Repeat fiberoptic bronchoscopy showed near complete resolution of glottic, tongue, and oropharyngeal edema. Given the difficulty of his airway management, the patient was taken to the operating room for tracheal extubation in case of failure and need for emergent tracheostomy. His trachea was extubated successfully and uneventfully five days following his admission to the SICU, and he was ultimately transferred to the ward on the following day. The patient was discharged to a rehabilitation facility approximately three weeks later. Of note, he had a mild recurrence of rash and elevation of his serum eosinophils when his steroids were tapered completely; they were reinstituted with plans for progressive taper over six months.

Discussion

The entity named DRESS syndrome or DIHS refers to a specific severe idiosyncratic reaction defined by a widespread and long-lasting papulopustular or erythematous skin eruption. Fever is a common early feature usually preceding a widespread papulopustular skin eruption that occurs within one to eight weeks of exposure to triggering medications and often progresses to exfoliative dermatitis,³ lymphadeopathy, visceral involvement (e.g., hepatitis, myocarditis, or nephritis), and characteristic eosinophilia ($>1.5 \times 10^9 \cdot \text{L}^{-1}$) or mononucleosis. It has been associated most commonly with phenytoin, carbamazepine, and phenobarbital, with an estimated incidence of one reaction per 5,000 to 10,000 exposures; similar reactions have also been described with exposure to vancomycin and levofloxacin.^{2,5-8} The exact mechanism of DRESS

syndrome is unknown, but biologically active metabolites of triggering medications, immunological imbalances, and co-infection with human herpes virus 6 (HHV 6) have all been implicated as playing a central role.^{9,10} Severity is associated with the duration of exposure to the offending agent after the onset of symptoms.³ The clinical heterogeneity of DRESS syndrome symptoms makes the diagnosis difficult; included in the differential are severe bacterial and viral infections (often treated by the same medications implicated in DRESS syndrome), malignancies, autoimmune diseases, and Steven-Johnson syndrome/toxic epidermal necrolysis.¹¹

We present a severe case of DRESS syndrome occurring approximately two weeks after initial exposure to both vancomycin and levofloxacin. Typically, mucous membrane involvement tends to be more indicative of Steven-Johnson syndrome/toxic epidermal necrolysis, which is generally associated with severe mucosal and tracheo-bronchial involvement and rarely associated with eosinophilia and other hematologic dyscrasias. Although this patient had no obesity, obstructive sleep apnea, facial hair, or other indicators predictive of difficult mask ventilation, the requirement for airway adjuncts and a four-handed technique is indicative of the severe progression of DRESS-associated mucosal swelling involving the oropharynx and trachea. Furthermore, although this patient's tracheal intubation was previously performed with mild difficulty, the severe mucous membrane involvement associated with DRESS syndrome resulted in complete distortion of normal laryngoscopic anatomy and almost necessitated an emergent surgical airway. The computerized tomography obtained from the infectious workup showed complete obliteration of air or space between the trachea and endotracheal tube. Some difficulty was anticipated due to the patient's clinical history and the presence of stridor; however, the previously undescribed presence of mucosal edema in DRESS syndrome made conventional airway management a near impossibility.

As DRESS syndrome is an increasingly recognized disease process occurring in a wide variety of clinical settings and presentations, we present a severe rapidly progressive case of mucosal edema resulting in extreme

difficulties with airway management, a problem that is not recognized as typically associated with the condition. We advocate for early recognition, a low threshold for early tracheal intubation in the course of the disease, and a high clinical suspicion for mucosal swelling resulting in difficulty with airway management.

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Competing interests None declared.

References

1. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg* 1996; 15: 250-7.
2. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* 1997; 49: 542-6.
3. Bonnetblanc JM. Drug hypersensitivity syndrome. *Dermatology* 1993; 187: 84-5.
4. Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. *Dermatology* 2003; 206: 353-6.
5. Ahn CM, Moon JH, Moon JG, et al. A case of cephalosporin-induced DRESS (drug rash with eosinophilia and systemic symptoms) syndrome with acute renal failure (Korean). *Korean J Asthma Allergy Clin Immunol* 2005; 25: 69-72.
6. Valencak J, Ortiz-Urda S, Heere-Ress E, Kunstfeld R, Base W. Carbamazepine induced DRESS syndrome with recurrent fever and exanthema. *Int J Dermatol* 2004; 43: 51-4.
7. Kano Y, Shiohara T. The variable clinical picture of drug-induced hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms in relation to the eliciting drug. *Immunol Allergy Clin North Am* 2009; 29: 481-501.
8. Vauthey L, Uckay I, Abrassart S, et al. Vancomycin-induced DRESS syndrome in a female patient. *Pharmacology* 2008; 82: 138-41.
9. Descamps V, Valance A, Edlinger C, et al. Association of human herpesvirus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol* 2001; 137: 301-4.
10. Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? *Arch Dermatol* 2001; 137: 357-64.
11. Benm'rad M, Leclerc-Mercier S, Blanche P, et al. Drug-induced hypersensitivity syndrome: clinical and biologic disease patterns in 24 patients. *Medicine (Baltimore)* 2009; 88: 131-40.