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Single Case

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Associated with *Mycoplasma pneumoniae* Infection

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Keywords

Adverse drug reaction · Drug eruption · Drug reaction with eosinophilia and systemic symptoms (DRESS) · Mycoplasma · Infection · Interferon-γ release test

Abstract

Mycoplasma infection may lower the threshold for drug allergy in particular patients. We present a case of drug reaction with eosinophilia and systemic symptoms (DRESS), with drug etiology and non-drug etiology (Mycoplasma infection). Possible synergism between previously known drug allergy and the acute Mycoplasma infection may have led to DRESS eruption. Interferon-γ release test and TNF-α release test yielded different patterns in the present case, suggesting a different role for each in different drug eruption types.

Case Report

A 19-year-old female with an unremarkable medical history, and known drug allergy to penicillin since infancy, was admitted to our department. She suffered from a severe cutaneous eruption, following treatment with cephalosporin for tonsillitis. Her initial treatment was

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cephalexin (tablet; Cefovit®) 250 mg ×4/day. Two days later, the patient developed mild cutaneous eruption, and the treatment was replaced by cefuroxime (tablet; Zinnat®) 500 mg ×2/day. Under this treatment regimen, her cutaneous eruption was aggravated; thus, the patient was referred to our institution. Physical examination revealed a widespread heterogenic eruption with papular, pustular, erythema target-like lesions and Sweet-like lesions (Fig. 1a, b). Marked facial edema was noted (Fig. 1c). The estimated body surface area involvement was more than 50%. Mild oral erosions were present without any other mucosal involvement. Nikolsky's sign was negative. The patient had a fever of 39°C and bilateral cervical and submandibular lymphadenopathy, larger than 1 cm on palpation. Respiratory auscultation demonstrated bilateral crackles present on both lung bases. A chest X-ray revealed bilateral infiltrates present in both lung bases. Laboratory tests: complete blood count performed upon her admission revealed anemia of 9.3 g/dL, leukocytosis of 30,350 cells/μL, and eosinophilia of 930 cells/μL. The patient had 2% atypical lymphocytes on her peripheral blood smear test. Her creatinine level, liver function tests, and electrolytes were within normal limits, while her albumin level was 2 g/dL. Other ancillary tests revealed hypocomplementemia C3 level of 57 (90–180) and C4 of 4 (10–40). Screening tests for collagen vascular diseases were negative for ANA and RF. Thyroid function tests at baseline were normal. Laboratory investigation screening for viral infections including human herpes virus-6, EBV, CMV, adenovirus, Coxsackie A virus, hepatitis viruses, and varicella zoster virus were all negative. Serologic screening for bacterial infection demonstrated positive IgM and negative IgG for *Mycoplasma pneumoniae*. Sequential Mycoplasma serology test done 10 days from index day revealed seroconversion: positive for IgM and IgG anti-*M. pneumoniae* antibodies. Histopathologic examination supported the diagnosis of drug eruption, demonstrating several necrotic keratinocytes in the epidermis, vacuolar changes with interface dermatitis, and an extensive papillary edema (Fig. 2a, b). Perivascular and interstitial mononuclear infiltrate was present admixed with numerous eosinophils (Fig. 2c). Upon her admission, treatment with cefuroxime (tablet; Zinnat®) was discontinued and switched to intravenous azithromycin. Simultaneous treatment with prednisone 60 mg ×1/day was initiated together with topical corticosteroids. Under this treatment regimen, with gradual tapering down of prednisone, a slow, steady improvement was noticed. Five weeks after initiating this treatment regimen, the patient gained complete resolution. One year following her remission, the patient underwent a patch test for drug series (Cutaneous Adverse Drug Reaction Series CAD-1000), which was negative. In vitro tests for cefuroxime (tablet; Zinnat®), penicillin (tablet; Moxypen©), and cephalexin (tablet; Cefovit®) were performed 1 year following the remission, supporting drug reaction with eosinophilia and systemic symptoms (DRESS) diagnosis (Fig. 3).

Discussion

Our patient presented with two major medical problems that are closely related: on the one hand, acute *M. pneumoniae* infection, a diagnosis that was established clinically ("tonsillitis," systemic symptoms, fever, crackles by auscultation, bilateral lung infiltrate by CXR, and compelling serology tests) and on the other hand, the patient suffered severe drug eruption based on her past medical history (cephalosporin treatments in a patient with penicillin allergy may raise the possibility of cross-reactivity), positive withdrawal test, and positive in vitro tests. Nevertheless, these two problems are probably related. Cutaneous manifestations of Mycoplasma infection include a wide clinical spectrum from exanthematous eruption, erythema multiforme (EM), urticaria, and erythema nodosum to the less common forms of mu-

cositis and Sweet's syndrome [1–3]. *M. pneumoniae*-induced rash and mucositis is a relatively recent entity, usually seen in children and young adults. It is characterized by pronounced mucositis, scant or absent cutaneous involvement and generally good prognosis [4]. The current case is characterized by extensive skin and mild mucous membrane involvement, histologic and in vitro test results, as well as the long course of the disease, making *M. pneumoniae*-induced rash and mucositis diagnosis less favorable. Stevens-Johnson syndrome and toxic epidermal necrolysis are frequently reported to be associated with Mycoplasma infection [5]; nonetheless, drug eruption with systemic symptoms (DRESS) is not commonly reported in association with *M. pneumoniae* infection as demonstrated in the present case [6]. According to the DRESS validation score established by the REGISCAR group [7], our patient has probable DRESS (4-point score) upon her admission: fever, eosinophilia, atypical lymphocytes, extent >50%, rash suggesting DRESS, in the presence of positive serology for Mycoplasma and negative serologies and blood cultures [7]. The association between DRESS and cephalosporins, as in our case, has been given more attention in the last few years [8, 9]. The EM-like morphology in DRESS is associated with more severe liver involvement [10]; interestingly, our patient had entirely normal liver functions; oral erosions are more compatible with the mycoplasma infection EM variant, hinting for a possible EM-DRESS overlap syndrome. However, a short latency period of less than 5 days, which is allegedly non-consistent with DRESS diagnosis, can be explained by previously known sensitivity to penicillin and a possible cross-reaction, suggesting a lowered threshold for drug allergy and cross-reaction in the presence of Mycoplasma infection. Patch tests are not highly sensitive in the case of DRESS eruptions. Thus, negative results do not rule out this option. In vitro tests supported DRESS diagnosis, incriminating cefuroxime (Zinnat®) more strongly than cephalexin (Cefovit®) as the culprit drug. Interestingly, TNF-α release was significantly increased following exposure to penicillin (Mxypen©) and cefuroxime (Zinnat®) but not to cephalexin (Cefovit®), while interferon-γ release test was significantly positive for all three. This observation may hint at the different roles of TNF-α and interferon-γ. Nevertheless, a general conclusion regarding the role of TNF-α in the pathophysiology of DRESS cannot be made on a solid ground based on a single observation.

In conclusion, we presented a case of DRESS, with drug etiology and non-drug etiology (bacterial infection). Each of these can serve as a sole etiology for the cutaneous eruption in the present case, yet possible synergism between the two is reasonable. *M. pneumoniae* infection may lower the threshold for drug allergy in this particular patient with penicillin allergy, triggering a cross-reaction between cephalosporin and penicillin.

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Statement of Ethics

The patient gave written informed consent for the publication of her case (including publication of images). The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

G.S. collected the data and wrote the initial manuscript draft. R.K. collected the data and revised the manuscript. A.H. evaluated and critically revised the manuscript and is the corresponding author. All authors provided critical feedback and contributed to the final version of the manuscript.

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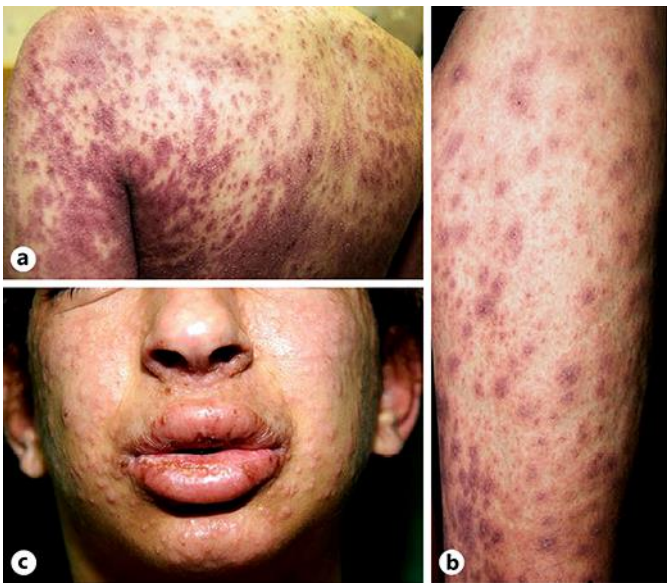

Fig. 1. **a** Papular, pustular, erythema, and target-like lesions over the trunk. **b** Papular, pustular, and target-like lesions over the right thigh. **c** Marked face edema, Sweet-like lesions, and mild oral mucosal involvement.

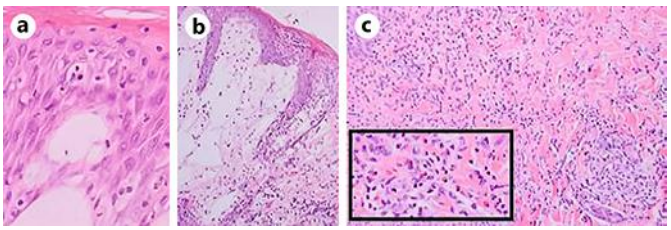

Fig. 2. **a** Necrotic keratinocytes in the epidermis, vacuolar changes, interface dermatitis in the basal layer (H&E, magnification ×360). **b** Extensive papillary edema (H&E, magnification ×360). **c** Perivascular and interstitial mononuclear infiltrate was present admixed with numerous eosinophils (inset) (H&E, magnification ×360).

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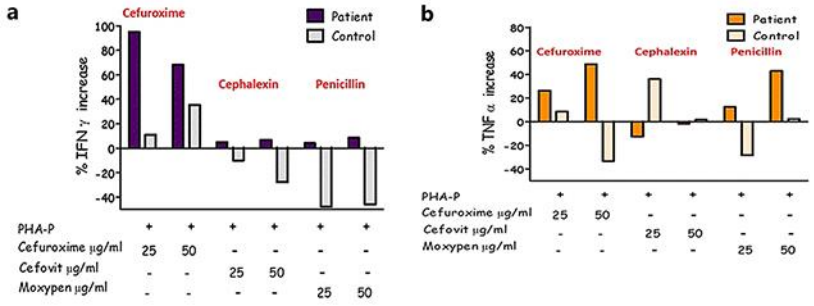

Fig. 3. In vitro tests for cephalexin cefuroxime and penicillin 1 year following the remission. The patient and healthy control subject with no known drug sensitivity: interferon-γ release test (**a**) and TNF-α release test (**b**).