Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) Induced by Meropenem in a Patient Receiving Avelumab and Subsequent Flare-Up

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Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous drug reaction that is potentially lethal owing to visceral organ involvement. Because of the variable clinical picture, the diagnosis has traditionally been based on a validation score (RegiSCAR) [1]. The drugs causing DRESS are mostly antiseizure drugs, certain antibiotics, and xanthine-oxidase inhibitors such as allopurinol. Vancomycin is often the culprit drug in cases with kidney involvement [2]. DRESS has also been reported to be triggered by immune checkpoint inhibitors (ICIs) (eg, CTLA-4-, PD1 and PD-L1-inhibitors) [3]. Avelumab is a PD-L1 inhibitor used to induce an immune response to various types of tumor.

A 46-year-old man with oligodendroglioma (WHO II/III) receiving antiseizure treatment with perampanel, levetiracetam, and lacosamide for 8 months and immune checkpoint blockade with avelumab (AMPLIFY-NEOVAC, Avelumab Mono) for 2 months had revision surgery because of an intracranial abscess followed by antibiotic therapy with vancomycin and meropenem. Three weeks later, he presented with exanthema (approximately 75% body surface area) and fever (Figure). One day after hospitalization, he developed periorbital edema and exfoliative dermatitis (Supplementary Figure 1). The blood work-up on admission showed elevated transaminases (ALT, 206 U/L; AST, 124 U/L), eosinophilia (absolute, 3.21 g/L; relative, 9%), and a normal glomerular filtration rate (89 mL/min). Vancomycin and meropenem were withdrawn, and antibiotic therapy was switched to ceftriaxone. Immunosuppressive therapy with 150 mg prednisolone was started and subsequently tapered. The patient had proteinuria (protein U mg/g creatinine, 561 [normal <150]; albumin U mg/g creatinine, 114.9 [normal <20]). Non–drug-related causes for the skin eruption and fever could not be identified (ANA, 1/400; blood cultures, negative; cranial magnetic resonance imaging, hepatitis serology). The skin biopsy

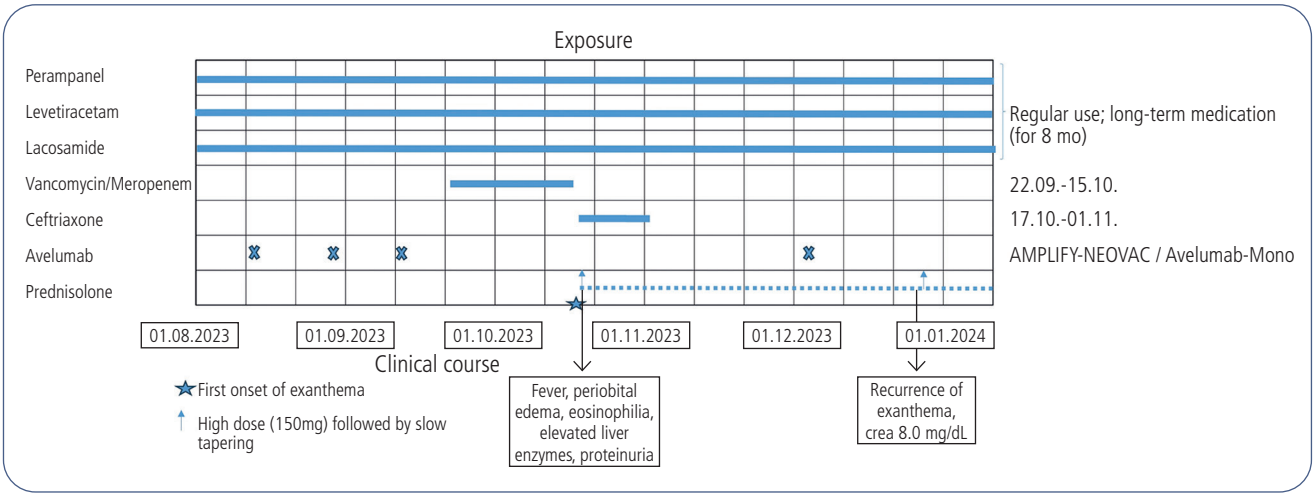

Figure. Medication chart listing the time intervals between intake and initial onset of symptoms to identify the culprit drug and virtually exclude antiseizure drugs as elicitors of the reaction..

revealed superficial perivascular lymphocytic infiltrates and focally localized discrete vacuolization along the basement membrane. Antiseizure therapy was urgently required and continued because of refractory epilepsy. The patient received an allergy passport to avoid meropenem and vancomycin [4] and had completely recovered after 18 days.

One month later, he received another dose of avelumab, which was followed by a mild reoccurrence of the exanthema and elevation of urinary retention parameters (creatinine, 8 mg/dL; uric acid, 10.8 mg/dL; glomerular filtration rate [CKD-EPI, KREA], 7 mL/min). After prednisolone pulse therapy (150 mg/d), all values were in the normal range. The serological examination for a relapse of DRESS was unremarkable (CMV-, EBV-, HHV-6A/B-, HSV-1/2-PCR). Avelumab was discontinued. The skin and blood results were also unremarkable at a check-up 6 weeks later.

The patient gave his written informed consent for his medical data to be published in this case report.

We performed a patch test (10% in petrolatum) 9 months after resolution (Supplementary Figure 2). This yielded negative results for vancomycin but confirmed meropenem allergy with a strongly positive reaction after 72 hours.

DRESS is a severe drug reaction with a mortality of approximately 2% [5]. Its manifestations comprise widespread maculopapulous exanthema, often with facial edema, sometimes leading to erythroderma and exfoliative dermatitis, together with signs of systemic organ involvement (eg, fever, lymphadenopathy, hepatitis, nephritis, carditis) and hematological abnormalities, (eg, eosinophilia, atypical lymphocytes, leukocytosis). We report a patient with multiorgan involvement, extensive skin eruption, and eosinophilia. The diagnosis of DRESS was confirmed based on symptoms and using the RegiSCAR validation score (Supplementary Figure 3).

In affected patients, the culprit drug must be withdrawn immediately. The first suspicion fell on antiseizure drugs, which are the most common elicitors of DRESS. However, in DRESS, the onset of the first symptoms is at 2-12 weeks after intake, usually during the first course of continuous drug use. The prolonged intake in the present case (8 months) before the onset of the reaction makes the antiseizure drugs extremely unlikely as culprits. Therefore, they were continued, as they were necessary and well tolerated.

PD-1 inhibitors have been increasingly associated with severe cutaneous adverse reactions; however, no cases of PD-L1–associated DRESS have been reported in the literature. PD-L1 is a coinhibitory molecule found on antigen-presenting cells. An immune response targeting the structure of the ICI appears unlikely [6]. Furthermore, the case of a patient who tolerated rechallenge with the same ICI has been reported [3]. Blocking the PD-1 pathway can boost T-cell activation, which may at least theoretically enhance T-cell epitope recognition and foster hypersensitivity reactions against other drugs [7,8]. Relapses of DRESS after therapy despite avoidance of the culprit drug are common and can have various causes, such as early withdrawal of immunosuppressive therapy and viral reactivation. Interestingly, in the case we report, further administration of avelumab led to a relapse without intake of the culprit drug, meropenem. This could be explained by the continued presence of meropenem-specific exhausted T-cells 6 weeks after withdrawal followed by regain of function after PD-L1 blockade. It remains unknown whether the patient was subsequently able to tolerate another dose of avelumab and whether DRESS could have been triggered by meropenem without avelumab in the first place.

The patient's history indicated vancomycin and/or meropenem as the culprit drug(s) (Figure). The time interval between vancomycin/meropenem intake and onset of the reaction was typical for DRESS. Vancomycin is a well-known high-risk drug and was much more likely to have caused the reaction than meropenem. It is also known to be associated with frequent kidney involvement, which was recorded in the present case [2]. Patch testing is useful in DRESS, with a sensitivity ranging from 32% to 64% depending on the drug tested [9]. While it confirmed meropenem as the culprit in the case we report, vancomycin cannot be reliably excluded and remains prohibited.

The kidney is the second most frequently affected organ in DRESS [5]. We initially recorded only significant proteinuria. However, urinary values increased considerably during the relapse. Therefore, the diagnostic work-up should always include renal parameters (serological and urinary) to detect critical organ involvement.

In conclusion, this case demonstrates that the elicitor is not always the drug most frequently leading to DRESS. A precise analysis of the medication timeline enabled us to identify the potential culprit drugs and the patient to continue his required antiseizure therapy. The PD-L1 inhibitor avelumab may have contributed to the onset and severity of the reaction. However, the causative drug was meropenem.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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