Iodinated contrast-induced Stevens-Johnson syndrome: A report of a rare complication for a common imaging agent

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ABSTRACT

Steven-Johnson syndrome (SJS) is a rare condition commonly associated with exposure to antibiotics. We have presented the case of a 76-year-old man with end-stage renal disease who had developed SJS after endovascular thrombectomy of hemodialysis access. He had developed epithelial erosions of the mucosal membranes, hemorrhagic bullae to the palmar and plantar surfaces, and erosions of the genitalia. The findings from biopsies of the lip and palm were suggestive of a drug reaction. He developed SJS three times after exposure to iodinated contrast. The one time he did not develop SJS, he had undergone open thrombectomy with no contrast exposure. (J Vasc Surg Cases Innov Tech 2022;8:455-7.)

Keywords: Arteriovenous fistula; Iodinated contrast; Stevens-Johnson syndrome

Stevens-Johnson syndrome (SJS) is a severe mucocutaneous reaction with separation of the epidermis and necrosis commonly associated with adverse reactions to medications.[1] SJS will involve <10% of the body surface area. In contrast, toxic epidermal necrolysis (TEN) will involve >30%.[2] SJS will typically begin with a prodrome of fever and influenza-like symptoms, followed by the occurrence of mucocutaneous lesions. Mucosal involvement will occur in >90% of patients with more than one affected site.[2] Several drugs have been implicated, including allopurinol, lamotrigine, phenytoin, carbamazepine, and others.[3] Rare cases of SJS/TEN induced by vaccinations, herbal medicine, and bone marrow transplantation have been reported.[4-9] Little evidence has shown iodinated contrast as a causal agent of SJS.[10,11] Identification of the agent is crucial to the management of the SJS to allow for removal of the agent and prevention of repeated exposure. We have described a case of SJS that had likely resulted from the use of iodinated contrast, lending support to the idea that iodinated contrast could be a direct cause of SJS.

CASE REPORT

A 76-year-old man with a history of recurrent SJS, end-stage renal disease requiring hemodialysis, atrial fibrillation, and type 2 diabetes mellitus had been admitted for treatment of recurrent dialysis access thrombosis. The dermatology service was consulted because of mucosal eruptions that had developed 2 days after endovascular thrombectomy and were concerning for SJS.

The patient had experienced three separate occasions of SJS with similar presentations, including oral mucosal and lip erosions, hand bulla, and genital erosions. In 2019, the patient was admitted to allow for de-clotting of the access site. During the procedure, he had received iodixanol (Visipaque; GE Healthcare, Chicago, IL), midazolam, fentanyl, heparin, tissue plasminogen activator, and cefazolin. Four days after the procedure, he had developed acrofacial bullae and erosions. It was initially thought that his presentation had resulted from mycoplasma-induced rash and mucositis, although the recent serology findings were not diagnostic for mycoplasma infection (positive mycoplasma IgG; negative IgM). He was treated prophylactically with 100 mg doxycycline twice daily, with rapid improvement of his skin erosions.

In January 2020, he had undergone open construction of new hemodialysis access. However, no contrast agent was administered. Intraoperatively, he had received lidocaine, dexmedetomidine, phenylephrine, propofol, cefazolin, and heparin. The patient was discharged the same day with no signs of cutaneous drug reactions after his surgery.

In December 2020, he had undergone endovascular thrombectomy of hemodialysis access. During the procedure, he had received contrast (not specified at the time), midazolam, fentanyl, heparin, and diphenhydramine. One day after the procedure, he had developed oral mucosal, genital, and palmar erosions and bullae. The herpes simplex virus (HSV) and varicella zoster virus (VZV) cultures and mycoplasma IgG and IgM test results were negative at that time. The findings from punch biopsies of the lip and palm were consistent with a drug reaction favoring SJS. At the time, fentanyl and midazolam were thought to be the causal agents of his SJS.

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Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2468-4287

https://doi.org/10.1016/j.jvscit.2022.06.015

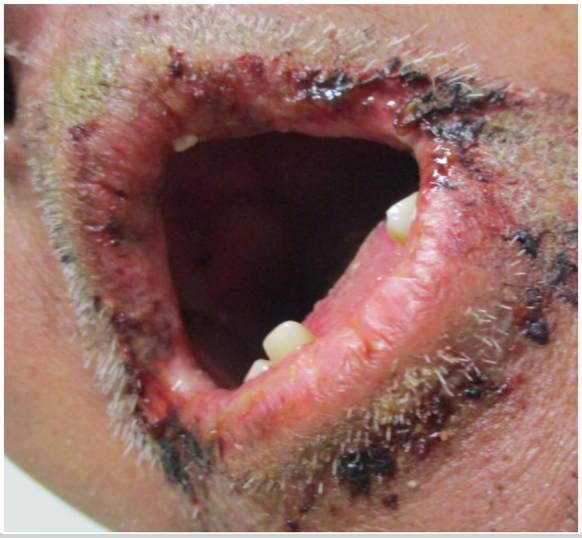

Fig 1. Photograph showing perioral epithelial erosions and crusting of the lips.

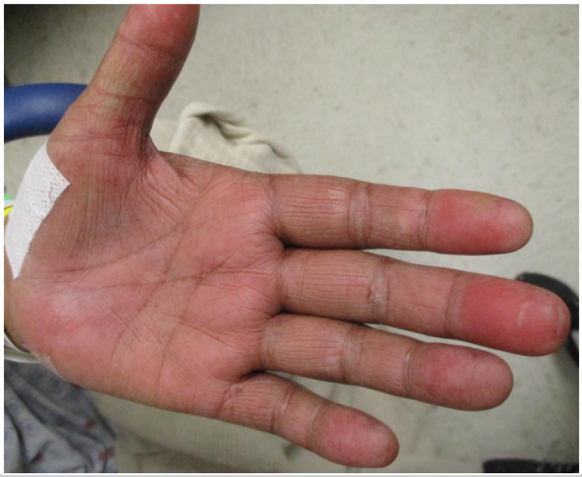

Fig 2. Photograph showing early bullae formations on the palmar surface of the hand that were tender to palpation and later became hemorrhagic (data not shown).

Most recently, on February 7, 2022, he had undergone repeat endovascular thrombectomy of hemodialysis access. During the procedure, he had received iodixanol (Visipaque; GE Healthcare), propofol, phenylephrine, cefazolin, heparin, and tissue plasminogen activator. On February 8, 2022, he had also undergone a computed tomography pulmonary embolism study PE for tachycardia during which he had received another dose of iodixanol. Within 24 hours, he had developed right periorbital erythema with epithelial erosion of the lips, hard palate, tongue, and perioral region (Fig 1). The palmar and plantar surfaces were tender with bullae formation that had later become hemorrhagic (Fig 2). He had also developed pink erosions surrounding the urethral meatus and scrotum, in addition to a "fish-like" hyperpigmented scale over the trunk and extremities. He was not taking any new outpatient medications, and he reported no herbal or other supplements.

The findings from a punch biopsy of the skin of the lower lip had revealed ulcerated epidermis with an overlying heme crust. Superficial perivascular and interstitial lymphocyte predominant inflammatory infiltrate and neutrophils, numerous extravasated erythrocytes, and pigment incontinence/melanophages, with no vasculitis or malignancy. The findings from the punch biopsy of the skin of the palms had revealed orthokeratotic hyperkeratosis overlying some ballooning degeneration of the spinous layer of the epidermis and superficial perivascular and interstitial lymphocyte-predominant inflammatory infiltrate, with no vasculitis or malignancy. According to the pathology report, the findings from both biopsies together were suggestive of a drug reaction favoring the development of SJS. Repeat HSV and VZV cultures and mycoplasma serology test findings were negative.

Because all three occurrences had developed after contrast administration, with the onset of symptoms 1 to 4 days after administration, his SJS was attributed to the contrast material. He received daily etanercept 50 mg subcutaneously after the symptoms developed and was also treated with cyclosporine 3 mg/kg/d divided into two doses until he was fully reepithelialized. The affected areas were treated with clobetasol 0.05% ointment twice daily, with thick hydrophobic ointment and gauze over the genital erosions. He received triamcinolone 0.1% paste for the oral lesions until reepithelialization had occurred and lidocaine suspension for oral pain. The patient made a full recovery, and iodinated contrast was subsequently added to his allergy list. The patient provided written informed consent for the report of his case details and imaging studies.

DISCUSSION

Limited evidence has shown an association between the use of iodinated contrast and the development of SJS and TEN. One review reported 11 cases of iodinated contrast-induced SJS and/or TEN.[10] Of these 11 cases, symptoms had occurred 30 minutes to 3 days after administration, with three of the patients dying. They also reported that several patients had been exposed to contrast several times before they had developed SJS or TEN. More recently, a case was reported that had associated the use of parental and oral contrast as the cause of a patient's SJS or TEN.[11] The patient had received parenteral iopamidol and oral iohexol 4 days before presenting with fevers, chills, extremity blisters, and right eye swelling. Similar to previous case reports, our patient had developed similar symptoms 1 to 4 days after exposure.

The mechanism of SJS and TEN is unclear but most likely results from a delayed T-cell reaction, with additional evidence implicating genetic susceptibilities and cytotoxicity.[1] Thus, any drug likely has the potential to induce SJS and/or TEN. The clinical symptoms will typically improve several days after removal of the causal agent. Other management includes supportive care, including wound care, fluid and electrolyte management, and pain control.[12,13] Consideration must also be

given to the prevention of infection owing to the high risk of infection and sepsis.[14] Emerging evidence has supported the use of immune modulating agents, such as cyclosporine for adjunctive treatment.[15]

Our patient had presented with three events of SJS, all after the administration of iodinated contrast. Other possibilities, such as HSV, VZV, and mycoplasma infections, were ruled out. A diagnosis of generalized bullous fixed drug eruption (GBFDE) could also be considered, given the similarity in presentations.[16,17] However, GBFDE will have mucosal involvement in only 44% to 67% of patients. In contrast, SJS and TEN will almost always have mucosal involvement. Histopathologic examination of GBFDE will show eosinophilic involvement, which is less common in SJS and TEN. Finally, the onset of GBFDE will often be from 30 minutes to 12 hours. Our patient had no eosinophilic presence found on pathologic examination, and the onset was delayed, favoring a diagnosis of SJS.

The Naranjo adverse drug reaction probability scale is a standardized method for assessing the causal agent of an adverse drug reaction.[18] Using this scale, contrast has a score of 7, which is considered "probable" and is higher than that of the other medications at exposure.

In summary, it is likely that our patient's SJS had resulted from the use of iodinated contrast. Because many patients will have been exposed to several medications, a careful review of the patient's history to find patterns is critical to identifying the causal agents. Given the limited case reports and the development of SJS and TEN associated with other common agents, the use of contrast could have been underreported as the underlying cause of SJS and/or TEN. Thus, the use of contrast should be considered for patients with an undetermined cause of SJS and/or TEN.

CONCLUSIONS

We have described the case of a patient who had developed SJS likely from the administration of iodinated contrast. Only a few case reports have suggested such an association; thus, more evidence is needed to determine a direct correlation between the use of iodinated contrast and the development of SJS or TEN.

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Submitted Apr 24, 2022; accepted Jun 21, 2022.