

Type III and Type IV hypersensitivity reactions due to mitomycin C

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A 71-year-old man developed an exfoliative dermatitis of the palms of the hands and soles of the feet, and a generalized itch, during treatment with intravesical instillations of mitomycin C for an undifferentiated carcinoma of the bladder. Patch tests with mitomycin C 0.03%, 0.1% and 0.3% aq. were positive. Because of the serious consequences of this finding, the patient was retested with mitomycin C in pet. (same concentrations), a more stable preparation. This showed clear positive reactions. During this last series of patch tests, he developed palpable purpura on the legs. We postulated that this reaction was an immune-complex-mediated reaction, caused by the 2nd series of patch tests with mitomycin C. To prove this, we performed histopathological and immunofluorescence investigations, and these showed the reaction to be consistent with Henoch-Schönlein-type purpura. We therefore conclude that this patient developed systemic reactions to mitomycin C, characterized by an eczematous dermatitis as well as purpuric reactions. The intravesical instillations with mitomycin C have been stopped. The patient's skin problems (the purpura as well as the eczema) have completely resolved and have not recurred.

Key words: mitomycin C; positive patch tests; bladder cancer; systemic contact dermatitis; immune-complex-mediated reaction (Type III); delayed-type reaction (Type IV); exfoliative dermatitis; Henoch-Schönlein-type purpura. © Munksgaard, 2000.

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Mitomycin C is an antitumor antibiotic used for chemotherapy of superficial bladder cancers by intravesical instillation. Contact allergy to mitomycin C, from intravesical as well as from local application, has been described by several authors (1–8). Mitomycin C, administered intravesically, is absorbed systemically and may lead to systemic contact dermatitis (1).

Case Report

A 71-year-old man had been visiting our outpatient department for many years with psoriasis, which had not troubled him for the last year. He underwent an operation for an undifferentiated bladder carcinoma 10 months prior to presentation, and had received intravesical instillations with mitomycin C (40 mg in 40 ml aq.) 1× monthly since the operation. A few months after starting the instillations, he developed an exfoliative dermatitis of the palms of the hands and soles of the feet, together with a generalized itch. The dermatitis and itch were worse directly after the instillations and subsided with time, until the next

treatment, but never completely went. The symptoms also increased in severity each month. The patient was initially treated with local corticosteroid (clobetasol propionate ointment), but his symptoms did not much improve. He was referred for patch testing to evaluate a possible drug-induced eruption.

Patch tests

Patch tests were performed with the European standard series, an additional standard series and mitomycin C 0.03%, 0.1% and 0.3% aq. (Table 1). Normal patch-test procedures were followed; however, the application time was only 24 h. We were not in a position to perform patch tests in controls. However, the available relevant literature (in which controls are used) indicates that the test concentrations that we used were not irritant.

The results indicated delayed-type allergy to mitomycin C. As this patient had a very strong indication to continue treatment with mitomycin C, and the results were not strongly positive, and mitomycin C in aq. is not a stable solution, it was

Table 1. Results of patch testing with mitomycin C in aq. and pet. at different concentrations

Patch tests	Readings			
	D1	D2	D3	D7
1st series*				
mitomycin C 0.03% aq.	—	—	—	—
mitomycin C 0.1% aq.	—	—	+	?+
mitomycin C 0.3% aq.	—	—	+	?+
2nd series**				
mitomycin C 0.03% pet.	NR	++	++	NR
mitomycin C 0.1% pet.	NR	++	++	NR
mitomycin C 0.3% pet.	NR	++	++	NR

aq. = water; pet. = petrolatum; NR = no reading; D = day.

* Application time 24 h. ** Application time 48 h.

decided to perform patch tests with mitomycin C in pet. as well. Before the 2nd series of patch tests, the patient received a further course of intravesical mitomycin C instillation, together with oral prednisolone 40 mg/day. Despite the prednisolone, he still experienced symptoms of exfoliative dermatitis of the hands and feet and generalized itch. During the instillation with mitomycin C, "red spots" appeared on the legs, which cleared after the instillation was finished. This was something that we were not aware of at the time of the 2nd series of patch tests.

On the 2nd occasion, the patch tests were performed with mitomycin C 0.03%, 0.1% and 0.3%, pet., which showed positive results (Table 1). On D 3 of patch testing, he developed palpable purpura on the legs, similar to the "red spots" that had appeared during the last course of intravesical mitomycin C.

Further investigations

The development of purpura could indicate the occurrence of a Type III allergic reaction coexisting with the already found Type IV reaction. Therefore, a biopsy was taken from a purpuric papule on the leg. Histopathology of this lesion revealed a leucocytoclastic vasculitis. Immunofluorescence investigations showed deposits of IgA in the small vessels of the upper dermis, consistent with a Henoch-Schönlein-type vasculitis (Fig. 1).

Laboratory investigations showed no abnormalities on routine hematology, biochemistry and urine investigations.

Conclusion

The final conclusion was that the patient had developed a systemic contact dermatitis caused by a delayed-type reaction (Type IV) in combination with an immune-complex-mediated reaction (Type III), presenting as purpuric papules.

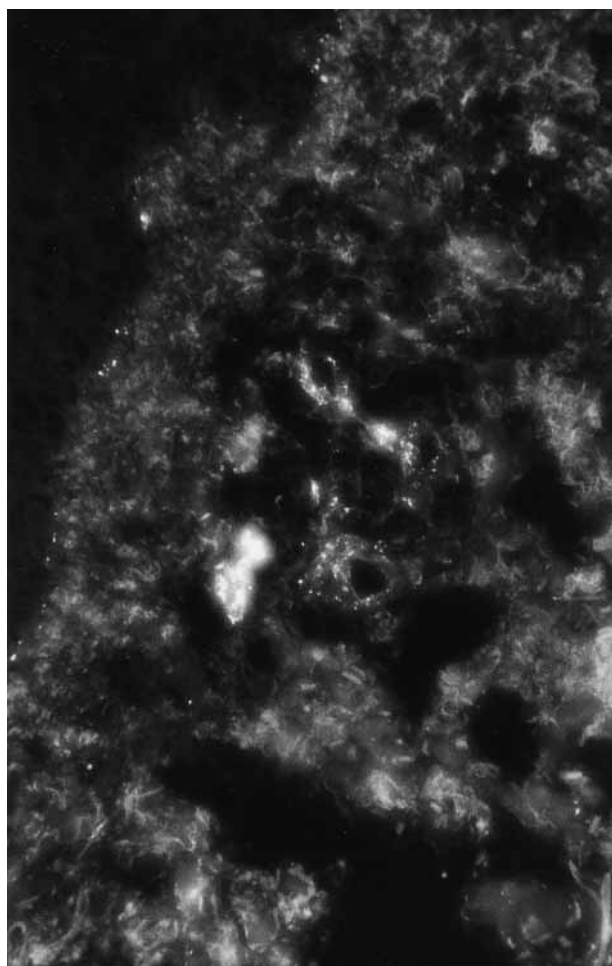


Fig. 1. Granular IgA deposits in the walls of a small subpapillary vessel and of an ascending capillary (400×).

The patient's urologist was consulted and it was decided to stop the mitomycin C instillations and that for the time being no further treatment would be given. The patient's skin symptoms have cleared completely and a recent cystoscopy showed no abnormalities.

Discussion

Mitomycin C is an alkylating antitumor antibiotic (aminoquinone group), derived from *Streptomyces caespitosus*. It selectively inhibits DNA synthesis and is used both intravenously and intravesically (in the latter as treatment for superficial bladder cancers) (9). The most important side-effects from the intravesical instillation are the development of cystitis, either chemical (due to irritation) or eosinophilic (due to allergy) (10), and the induction of skin symptoms. It is estimated that 9% of patients will develop skin problems, consisting of dermatitis of the hands and feet, or a generalized rash (1–8). Investigations by Colver et al. (11) indicated

that this may be caused by an allergic mechanism to mitomycin C. Contact allergy to mitomycin C can develop through direct contact of the skin with the substance, e.g., due to contamination of the skin with mitomycin-containing urine (6, 7), and through systemic absorption of mitomycin via bladder epithelium (1, 8, 11). It has been demonstrated that absorption of mitomycin C through bladder epithelium does occur, and that around 1% of the total administered dose of mitomycin C can be detected in the blood (1, 12).

For patch testing, mitomycin C can be dissolved in aq. or in pet. A disadvantage of the former is that the solution is not very stable and that crystal formation can occur. Thus, fresh preparations should be used, preferably serial dilutions (1, 2). Petrolatum provides a more stable base (1).

Systemic administration of a chemical in a person sensitized to that chemical can lead to systemic contact dermatitis. The occurrence of systemic reactions elicited by patch testing, consisting of severe pruritus and generalized maculopapular lesions, has been described, including to mitomycin C (13). Allergic contact reactions with purpura can also be found in the literature (14–16). Our patient demonstrates that, apart from having a delayed-type contact allergy (Type IV reaction), he also developed palpable purpura on the legs, consistent with purpura of the Henoch-Schönlein type, a Type III allergic reaction. Even a small amount of mitomycin C, applied to the back for patch tests, was enough to elicit this immune-complex-mediated reaction in our patient. It is a difficult decision as to whether mitomycin C therapy should continue in such patients. If only mild adverse reactions occur, therapy can sometimes be continued in combination with steroids, topical or systemic, if necessary, in combination with antihistamines (5, 10). However, as in our patient, this strategy does not always work.

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