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Case Report

Identification of Docetaxel, Cisplatin, and 5-Fluorouracil Regimen Hypersensitivity by *In vitro* T-cell Activation Assay

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Abstract

An *in vitro* T-cell activation assay measuring granulysin and granzyme B has been used to identify the drug hypersensitivity of common causative drugs, but not of chemotherapeutic drugs. Both granulysin and granzyme B are cytotoxic molecules involved in skin eruptions during drug hypersensitivity. Herein, we report the first clinical application of an *in vitro* T-cell activation assay to identify the causative agent in docetaxel, cisplatin, and 5-fluorouracil (5-FU)-related hypersensitivity in a patient with head-and-neck cancer. A significant increase in granulysin and granzyme B was observed for 5-FU rather than for docetaxel or cisplatin. Despite several limitations, we were still able to pinpoint 5-FU as the culprit drug in a chemotherapy combination without further drug rechallenge in our patient. In conclusion, an *in vitro* T-cell activation assay measuring granulysin and granzyme B can be a safe and alternative tool to determine the causative agent of hypersensitivity reactions in cancer patients who need combination chemotherapy.

Keywords: Docetaxel, cisplatin, and 5-fluorouracil, granulysin, granzyme B, hypersensitivity, *in vitro* T-cell activation assay

Introduction

The combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) (TPF) is commonly used as induction chemotherapy for patients with locally advanced head-and-neck cancer. The adverse effects of this regimen include myelotoxicity, stomatitis, nausea, vomiting, diarrhea, and less frequently, hypersensitivity reactions. The incidence of all grades of skin rash or itchiness has been reported to be ~ 20% despite the use of premedications.[1] Drug rechallenge is regarded to be the gold standard to determine the culprit drug in most circumstances; however, sometimes, it is not feasible owing to patient safety and ethical reasons.[2] Several previous studies have reported the use of an *in vitro* T-cell activation assay measuring granulysin, granzyme B, or interferon-γ (IFN-γ) to identify the causative drug in patients

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with severe cutaneous adverse reactions (SCARs).[3-6] Herein, we report the first clinical application of an *in vitro* T-cell activation assay measuring granulysin and granzyme B to determine the culprit drug in TPF-related hypersensitivity in a patient with head-and-neck cancer.

Case Report

A 48-year-old Taiwanese male was diagnosed with squamous cell carcinoma of the left tonsil, cT2N2bM0, and Stage IV A (AJCC 7th edition) in February 2017. He initially presented with the left neck Level III palpable, 5 cm × 4 cm, nontender mass which persisted for 1 month. Left tonsillectomy confirmed squamous cell carcinoma that was keratinizing and moderately differentiated. The results of immunohistochemistry staining for p16 were negative. 18-F fluorodeoxyglucose positron-emission tomography/computed tomography (CT) and head-and-neck CT revealed left tonsil cancer with left neck nodal metastasis, cT2N2bM0. A bone scan revealed no evidence of bony metastasis. He then started induction chemotherapy for the locally advanced disease, which consisted of docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and continuous infusion 5-FU 600 mg/m^2 on day 1 to 5.

One day after the completion of chemotherapy, he had a Grade 1 maculopapular rash over his face, Grade 3 oral mucositis, Grade 3 dysphagia, and Grade 3 hand-foot syndrome, according to the Common Terminology Criteria for Adverse Events version 4.0 (HHS/NHI/NCI, MD, USA). A physical examination revealed a maculopapular rash over his forehead and bilateral cheeks, multiple oral ulcers and blistering, and violaceous erythema plaques on his palms and soles [Figure 1]. No pustules or skin desquamation were observed. Laboratory tests revealed normal liver and renal function, with no leukocytosis or eosinophilia. The skin eruption progressed, and systemic corticosteroids were administered. Topical corticosteroids (i.e., clobetasol 0.05%), adequate pain control medications, and antihistamines were also prescribed. His symptoms resolved after 10 days of supportive treatment.

Due to the first episode of cutaneous adverse events involving the face and extremities immediately after finishing chemotherapy, the possibility of drug hypersensitivity was raised aside from hand-foot syndrome. We initially speculated that docetaxel was the causative drug based on the onset and timing of the dermatologic adverse events.[7] An *in vitro* T-cell activation test was performed to identify the culprit drug. We isolated peripheral blood mononuclear cells from the patient and cultured them with docetaxel, cisplatin, and 5-FU in RPMI-1640 medium (GIBCO Invitrogen, Life Technologies, Carlsbad, CA) supplemented with 10% human serum and IL-7 at 37°C in 5% CO_2 for 1 week.[4-6] Dimethyl sulfoxide was used as the negative control, and phytohemagglutinin was used as the positive control. The levels of granulysin and granzyme B in the culture supernatants were measured by the enzyme-linked immunosorbent assay after 1 week. The sensitivities of this assay for granulysin and granzyme B were 1.56 ng/mL and 10 pg/mL, respectively.[4,8] Significant fold changes of granulysin (6.4-fold) and granzyme B (29.2-fold) were observed in 5-FU compared to those in cisplatin and docetaxel [Table 1]. Therefore, the assay preliminarily identified 5-FU as the culprit drug. We stopped induction chemotherapy and proceeded to definitive concurrent chemoradiotherapy (CCRT) in this patient. However, we did not resume cisplatin in the following CCRT after discussion with the patient. Alternative bioradiotherapy with cetuximab was initiated in mid-April. He underwent complete treatment without further adverse effects. The most recent head-and-neck CT in March 2018 revealed the maintenance of complete remission.

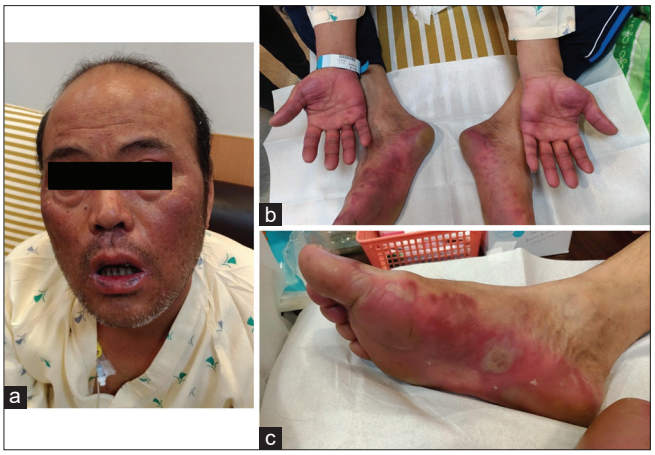

Figure 1: (a) Clinical features of Grade 1 maculopapular rash over the forehead and bilateral cheeks and Grade 3 oral mucositis. (b and c): Grade 3 hand-foot syndrome, erythema, and blistering of hands and feet interfering with normal activities after the first cycle of TPF chemotherapy

Table 1: Result of allergological investigation by *in vitro* T-cell activation assay

	Granulysin fold/(ng/mL)	Granzyme B fold/(pg/mL)
DMSO	1.00/2.01	1.00/359.28
5-fluorouracil	6.43/12.91	29.23/10500.40
Cisplatin	1.41/2.82	1.60/574.10
Docetaxel	0.87/1.79	0.78/284.24
PHA	13.2/26.53	3.06/1099.40

DMSO: Dimethyl sulfoxide, PHA: Phytohemagglutinin

Discussion

An *in vitro* T-cell activation assay measuring granulysin and granzyme B has been used to identify drug hypersensitivity in common causative drugs; however, hypersensitivity associated with chemotherapeutic drugs has not previously been reported.[4-6] The traditional method of drug rechallenge is time-consuming and risky, as it may lead to the recurrence of SCARs and even fatal consequences.[2] We used this assay because it can be performed *in vitro* is relatively safe and allows time for the patient to recover while awaiting the results.

Table 2: Comparison of cisplatin, docetaxel, and 5-fluorouracil-related hypersensitivity

	Cisplatin[10,11]	Docetaxel[7,12,13]	5-fluorouracil[14-18]
Incidence	5%-20%	5%	N/A
Onset	Mostly between 4th and 8th cycle	Onset at 1st or 2nd cycle	N/A
Risk factors	Increases with concurrent radiation	Taxane solvent (polysorbate 80) Atopy	DPD deficiency
Clinical presentation	Mostly immediate cutaneous symptoms, such as rash, flushing, urticaria, and pruritus Severe HSR included bronchospasm, chest pain, tachycardia, or hypertension	Immediate HSR: Flushing, bronchospasm, chest pain, and abdominal pain Delayed HSR: Rash, flushing, SJS/TEN, and pneumonitis	Case reports of delayed HSR, pneumonitis, and coronary vasospasm

HSR: Hypersensitivity reaction; SJS: Steven-Johnson syndrome; TEN: Toxic epidermal necrolysis; DPD: Dihydropyrimidine dehydrogenase, N/A: Not available

Both granulysin and granzyme B are cytotoxic molecules involved in skin eruptions that are immunologically induced by drugs, particularly in SCARs.[8,9] Single granulysin or granzyme B assays may provide a sensitivity of 30%–50% for common causative drugs.[3] Porebski *et al*. reported that a combination of granulysin, granzyme B, and IFN-γ assays may provide a sensitivity of 80% (confidence interval [CI]: 52%–96%) and specificity of 95% (CI: 80%–99%) for drug hypersensitivity.[3] Although our patient demonstrated less severe cutaneous adverse events, the culprit drug was able to induce concomitantly significant fold changes in granulysin and granzyme B in the assay.

Platinum and taxanes are two common classes of chemotherapeutic agents that cause hypersensitivity reactions [Table 2]. Cisplatin hypersensitivity is mostly IgE-mediated and often occurs within minutes after infusion.[10] Immediate hypersensitivity has also been observed with docetaxel; however, some patients may develop delayed skin reactions, occurring several days or up to 1 week after administration.[7,12] In comparison, few studies have investigated 5-FU hypersensitivity [Table 2].[14-16] Dihydropyrimidine dehydrogenase (DPD) deficiency, which is associated with DPYD gene mutations, has been reported to increase 5-FU-related adverse events by incompetent 5-FU degradation.[17] Different formulations, dosing, and route of administration of fluorouracil have been reported to result in diverse toxicities.[18-20] Whether our patient with hypersensitivity to 5-FU had cross-hypersensitivity to other formulations such as capecitabine, tegafur, and TS-1 is unknown.

There are several limitations to this case report. First, few studies have reported on 5-FU-related hypersensitivity, and therefore, more cases are needed to confirm our *in vitro* findings and to determine standardized cutoff values for hypersensitivity. Second, we lacked skin biopsies and skin patch tests for the second confirmation. In addition, we did not perform DPD deficiency tests in our patient. Nevertheless, the *in vitro* T-cell activation assay enabled the clinicians to avoid 5-FU and to select cisplatin or other efficacious drugs in the subsequent treatment of this patient. Our patient received cetuximab instead of cisplatin due to his preference.

Conclusion

We demonstrated a novel application of an *in vitro* T-cell activation assay which measured granulysin and granzyme B to pinpoint the culprit drug in a common chemotherapy combination in a patient with locally advanced head-and-neck cancer. This *in vitro* assay may provide clinicians with an alternative safe method to determine the causative agent of hypersensitivity in cancer patients who receive combination chemotherapy and possibly to resume other efficacious drugs.

Ethics approval and consent for publication

Local Institutional Review Board approval was obtained (No. 201801033B0). The patient provided informed consent for publication of this case.

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Conflicts of interest

There are no conflicts of interest.

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