

A Case of Fixed Drug Eruption Due to Doxycycline and Erythromycin Present in Food

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A fixed drug eruption (FDE) is not difficult to diagnose, given its clinical characteristics. However, the causative agent can be difficult to identify, particularly when the patient denies ingestion of any drugs. To the best of our knowledge, we present herein the first reported case of an FDE caused by antibiotics taken in food; doxycycline and erythromycin contained in pork and fish. A 57-year-old female experienced repeated episodes of well-demarcated erythematous patches covering her entire body. She denied taking any medications, but she thought that the lesions appeared after consuming pork and/or fish. An oral provocation test showed positive results for doxycycline and erythromycin, commonly used antibiotics in livestock farming and in the fishing industry. Because of the antibiotics' thermostability, cooking does not guarantee the elimination of residual drugs. From the patient's history, we concluded that doxycycline and erythromycin contained in the pork and fish that she ate were the cause of the FDE.

Key Words: Fixed drug eruption; doxycycline; erythromycin; residual antibiotics; food

INTRODUCTION

A fixed drug eruption (FDE) is a condition characterized by recurrent erythematous skin patches arising in the same location in response to drug ingestion. More than 100 drugs, including doxycycline and erythromycin, have been implicated in causing FDEs,¹ and the causative agent can be difficult to identify, particularly when the patient denies ingesting any medications. In such scenarios, there are two possibilities: either the causative agent is not a drug or the drug was contained in alternative vehicles such as food. Some FDEs resulting from food intake have been reported; the foods involved include liquorice, Japanese sand lance, and cashew nuts.²⁻⁴ However, FDEs caused by antibiotics contained in food have not been reported. We describe a patient who experienced an FDE due to doxycycline and erythromycin that occurred after ingestion of pork and/or fish.

CASE REPORT

A 57-year-old female patient visited our clinic with a 12-year history of repeated outbreaks of well-demarcated erythematous patches with hyperpigmentation over the entire body. She had no history of allergic disease or chronic medical illness. She de-

nied taking any medication before the lesion first developed or before the recurrences. The lesions developed every 2 or 3 months, at the same sites, when she ate pork or fish. She had therefore followed a nearly vegetarian diet for more than 10 years.

Patch tests were performed using acetaminophen, the nonsteroidal anti-inflammatory drug ibuprofen, and antibiotics, including cephalosporins, amoxicillin, sulfamethoxazole, gentamicin, neomycin, rifampin, doxycycline, and erythromycin. There were no definite reactions to these patch tests. Oral provocation tests with the same medications were then performed. When the patient ingested 10 mg of doxycycline as a single dose, she experienced an erythematous change on an existing pigmented lesion, accompanied by an itching sensation (Fig. 1A). One month after recovery from this lesion, the oral provocation testing was continued with the re-

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Fig. 1. (A) On the oral doxycycline provocation test, an erythematous change is observed in a hyperpigmented area of skin. (B) On the oral erythromycin provocation test, an erythema is observed at the site of the previous lesion.

maining drugs. After an erythromycin dose of 25 mg, she again experienced more intense pruritus and erythema at the site of a previous lesion (Fig. 1B).

Interestingly, the patient had no history of taking medication, including doxycycline or erythromycin. According to the Korea Food and Drug Administration, doxycycline and erythromycin are commonly used in livestock farming and sea farming in Korea. We did not know whether antibiotics in food cooked at high temperatures could induce an FDE, so we conducted a simple experiment to assess the heat stability of doxycycline and erythromycin. Using the disk-diffusion method, we found that doxycycline and erythromycin are stable at 100°C and even at autoclave temperatures reaching 121°C (Fig. 2).

DISCUSSION

FDEs usually appear as solitary or multiple pruritic, well-circumscribed, erythematous patches. These lesions typically recur at the same skin sites with re-exposure to the causative drug. They resolve spontaneously upon discontinuation of the medication, leaving behind hyperpigmentation. Intraepidermal clusters of differentiated CD8-positive T cells at the FDE lesion site contribute to localized tissue damage. Resting T cells are not cytolytic, but upon activation, they kill the surrounding keratinocytes and release cytokines such as interferon gamma. More CD8-positive T cells as well as CD4-positive T cells and neutrophils are recruited to the lesion, resulting in tissue damage.^{5,6}

In the patient, the diagnosis was not difficult; recurrent erythematous and hyperpigmented patches at the same skin sites indicated FDE. Although she did not take any medications, she had positive oral provocation tests for both doxycycline and erythromycin, which are not crosslinked. FDEs usually have a single causative drug, and polysensitivity involving two or more drugs is rare.⁷ Piroxicam and cotrimoxazole, tenoxicam and tri-

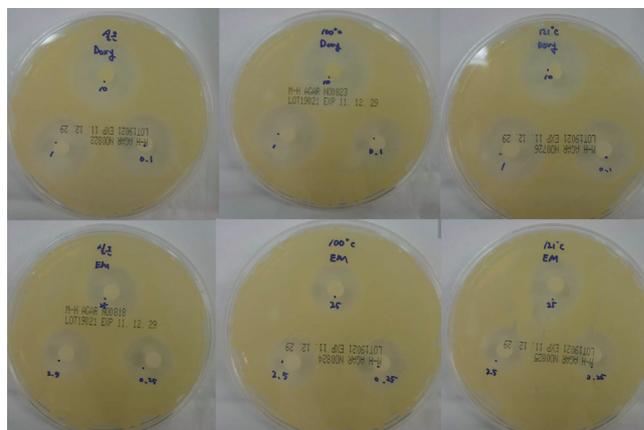


Fig. 2. The disk-diffusion method for doxycycline and erythromycin. There are no significant differences in the zones of inhibition at various temperatures or with the concentrations of doxycycline and erythromycin.

methoprim-sulfamethoxazole, and various anticonvulsants have been reported to cause polysensitive FDEs.⁷⁻⁹

The patient denied any history of using medication, including the two drugs that elicited her FDEs on oral challenge. We, therefore, considered the possibility of another source because there are some case reports of recurrent FDE exacerbations not linked to drug intake. Nonmedical factors such as food and ultraviolet radiation have been reported to precipitate FDE lesions.^{2-4,10} In the patient, it was possible that food might have caused the fixed eruptions, particularly as she thought that the lesions appeared after eating pork and/or fish. However, the lesions did not appear consistently with each of these meats ingested, and the patient refused additional provocation tests using pork or fish.

We hypothesized that pork and/or fish, acting as a vehicle, might have been the source of the causative drug. According to a document produced by the Korea Food and Drug Administration concerning the monitoring of antimicrobial resistance in food animals and their meat, tetracyclines such as doxycycline are commonly used veterinary antibiotics in Korea, as are macrolides such as erythromycin.^{11,12} The maximum residue limit (MRL) of doxycycline is 0.1 mg/kg for pig muscle and 0.5 mg/kg for fish; the MRL of erythromycin is 0.05 mg/kg for pig muscle and 0.2 mg/kg for fish.^{13,14} The MRLs of doxycycline and erythromycin are low; however, the dose represented by the MRL is the limit considered safe for public health and not the amount that might elicit an allergic reaction, which would presumably be a smaller dose. Although our patient ate only small amounts of pork and fish, the antibiotic residues might have been high enough to trigger an FDE in a sensitized individual. FDEs caused by antibiotics contained in food have not been previously reported, but there are some reports of hypersensitivity reactions caused by antibiotic residues, particularly of beta lactam and macrolide antibiotics, in food products.¹⁵ It is therefore conceivable that antibiotic residue in food can cause an FDE.

Although we had identified pork and fish as possible vehicles for our patient's drug ingestion, we still did not know whether antibiotics in these cooked meats could result in an FDE. By checking the thermostability of doxycycline and erythromycin, and by reviewing the literature, we found that doxycycline and erythromycin are heat stable, even during cooking.^{16,17} We propose that doxycycline and erythromycin contained in our patient's food caused her FDEs, even though the food was cooked at high temperatures. Some existing reports^{18,19} concerning the relationship between antibiotic residue and the cooking process state that, as we found through our experimentation, cooking does not guarantee full elimination of antibiotics present in animal tissues, particularly when it comes to doxycycline.

The limitation of the present case is that oral provocation tests for pork or fish were not performed to confirm the FDE. However, a reasonable explanation is that the patient's FDEs were elicited by residual antibiotics in food that she ate before the lesions developed.

Residual antibiotics in animal tissues are problematic in that adverse drug reactions may occur after ingestion of meat or fish, with concomitant unintended drug consumption. We report a rare case of an FDE resulting from residual antibiotics present in food. Physicians should keep in mind that drug reactions, including FDEs, can occur after eating food and without any patient history of medication use.

REFERENCES

1. Lee AY. Fixed drug eruptions. Incidence, recognition, and avoidance. *Am J Clin Dermatol* 2000;1:277-85.
2. Benomar S, Ismaili N, Koufane J, Senouci K, Hassam B. Fixed food eruption caused by liquorice. *Ann Dermatol Venereol* 2010;137:121-3.
3. Tsuruta D, Sowa J, Kobayashi H, Ishii M. Fixed food eruption caused by Japanese sand lance. *Clin Exp Dermatol* 2009;34:e309-10.
4. Fukushima S, Kidou M, Ihn H. Fixed food eruption caused by cashew nut. *Allergol Int* 2008;57:285-7.
5. Shiohara T. Fixed drug eruption: pathogenesis and diagnostic tests. *Curr Opin Allergy Clin Immunol* 2009;9:316-21.
6. Kim MH, Shim EJ, Jung JW, Sohn SW, Kang HR. A case of allopurinol-induced fixed drug eruption confirmed with a lymphocyte transformation test. *Allergy Asthma Immunol Res* 2012;4:309-10.
7. Ozkaya E. Polysensitivity in fixed drug eruption due to a novel drug combination-independent lesions due to piroxicam and cotrimoxazole. *Eur J Dermatol* 2006;16:591-2.
8. Chan HL, Tan KC. Fixed drug eruption to three anticonvulsant drugs: an unusual case of polysensitivity. *J Am Acad Dermatol* 1997;36:259.
9. Ozkaya-Bayazit E. Independent lesions of fixed drug eruption caused by trimethoprim-sulfamethoxazole and tenoxicam in the same patient: a rare case of polysensitivity. *J Am Acad Dermatol* 2004;51:S102-4.
10. del Río E, Guimaraens D, Aguilar A, Conde-Salazar L, Sánchez Yus E. Fixed exanthema induced by ultraviolet radiation. *Dermatology* 1996;193:54-5.
11. Animal, Plant and Fisheries Quarantine and Inspection Agency. Animal quarantine [Internet]. Anyang: Animal, Plant and Fisheries Quarantine and Inspection Agency; 2007. Available from: http://www.qia.go.kr/viewwebQiaCom.do?id=4266&type=1_23clyfy.
12. Shin HC. Veterinary drug residue monitoring [Internet]. Cheongwon: Korea Food & Drug Administration; 2006. Available from: <http://naver.nanet.go.kr/SearchDetailView.do?cn=MONO-1200710551>.
13. Korea Food & Drug Administration. Pig muscle. Veterinary drugs MRLs - sorted by food [Internet]. Cheongwon: Korea Food & Drug Administration; 2012. Available from: http://fse.foodnara.go.kr/residue/vd/food/popup_food_mrl.jsp?countryCode=KR&foodCode=vd101020006.
14. Korea Food & Drug Administration. Fish. Veterinary drugs MRLs - sorted by food [Internet]. Cheongwon: Korea Food & Drug Administration; 2012. Available from: http://fse.foodnara.go.kr/residue/vd/food/popup_food_mrl.jsp?countryCode=KR&foodCode=vd199010009.
15. Dewdney JM, Maes L, Raynaud JP, Blanc F, Scheid JP, Jackson T, Lens S, Verschuere C. Risk assessment of antibiotic residues of beta-lactams and macrolides in food products with regard to their immuno-allergic potential. *Food Chem Toxicol* 1991;29:477-83.
16. Hsieh MK, Shyu CL, Liao JW, Franje CA, Huang YJ, Chang SK, Shih PY, Chou CC. Correlation analysis of heat stability of veterinary antibiotics by structural degradation, changes in antimicrobial activity and genotoxicity. *Vet Med (Praha)* 2011;56:274-85.
17. Hassani M, Lázaro R, Pérez C, Condón S, Pagán R. Thermostability of oxytetracycline, tetracycline, and doxycycline at ultrahigh temperatures. *J Agric Food Chem* 2008;56:2676-80.
18. Croubels S, Baert K, De Busser J, De Backer P. Residue study of doxycycline and 4-epidoxycycline in pigs medicated via-drinking water. *Analyst* 1998;123:2733-6.
19. Rose MD, Bygrave J, Farrington WH, Shearer G. The effect of cooking on veterinary drug residues in food: 4. Oxytetracycline. *Food Addit Contam* 1996;13:275-86.